Synthetic Approaches to the Macrocyclic Natural Product Tripartilactam

A thesis submitted for the degree of
Doctor of Philosophy

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2012-2015 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

September, 2016 ----------

Yen Thi Hoang Vo

Acknowledgements

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Publication and Presentations

The following publications and presentations emerged from the research work undertaken during the course of the author's PhD studies.

Publication

Vo, Y., Banwell, M. G. and Willis, A. C. - *Chemoenzymatic Routes to Polyoxygenated Cyclooctenones Related to the Eastern Hemisphere of the Macrolactam Tripartilactam*. *Chem. Asian J*. **2014**, *9*, 67–70.

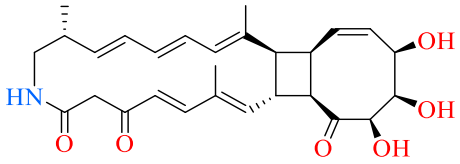
Poster Presentation

Vo, Y., Banwell, M. G. and Willis, A. C. - *Chemoenzymatic Routes to Polyoxygenated Cyclooctenones Related to the Eastern Hemisphere of the Macrolactam Tripartilactam*, 34th Annual Royal Australian Chemical Institute (NSW Branch) Organic Chemistry Symposium, Canberra, Australia 4th December 2013.

Vo, Y., Banwell, M. G. and Willis, A. C. - *Chemoenzymatic Routes to Polyoxygenated Cyclooctenones Related to the Eastern Hemisphere of the Macrolactam Tripartilactam*, Belgian Organic Synthesis Symposium XIV, Louvain-La-Neuve, Belgium13-18th July 2014.

Abstract

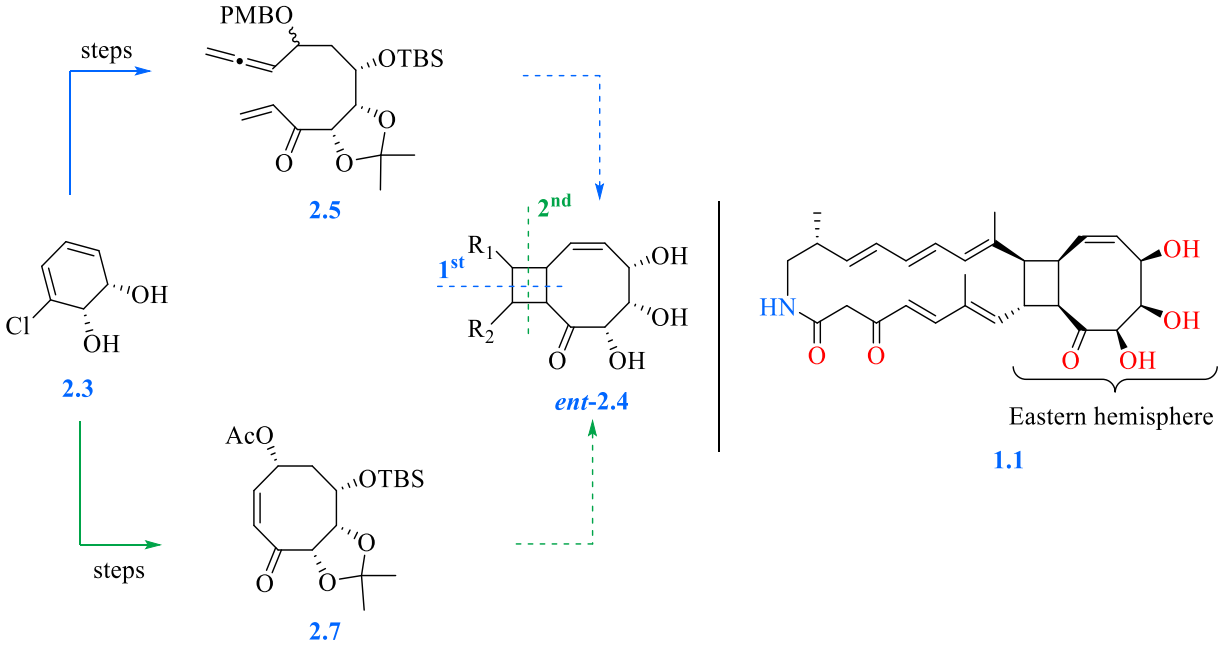
In 2012 Oh and co-workers reported the isolation of the tricyclic macrolactam tripartilactam **1.1** from a *Streptomyces sp.* found in the brood ball of the dung bettle *Copris tripartitus*. The compound proved to be a moderate inhibitor of Na^+/K^+ ATPase (IC_{50} of 16.6 μg/mL). The unique and rather complex structure embodies a cyclobutane fused, on its opposing faces, to both an 8- and an 18-membered ring. These architecturally novel features prompted the author to pursue a total synthesis of it.



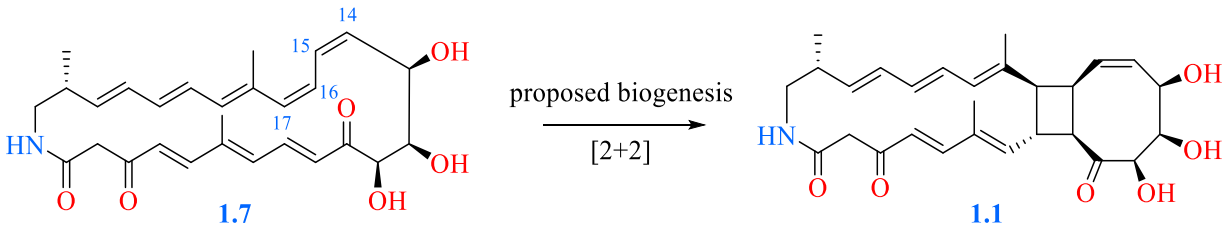
1.1

Chapter One provides a brief introduction to the isolation, structural elucidation and proposed biogenesis of tripartilactam. This section also provides details of selected organic reactions that played important roles in the synthetic studies of the author, in particular the Stille cross-coupling, olefin metathesis and olefination reactions.

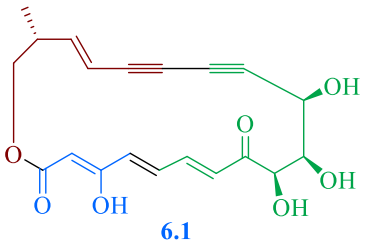
Chapter Two describes two distinct sets of manipulations of the enantiomerically pure chloro *cis*-1,2-dihydrocatechol **2.3**, readily obtained through the whole-cell biotransformation of chlorobenzene, into a terminal allene/carbonyl-conjugated alkene **2.5** and a polyoxygenated cyclooctenone **2.7** embodying the Eastern Hemisphere of the non-natural enantiomeric form of tripartilactam **1.1**. Attempts to elaborate intermediates **2.5** and **2.7** to the bicyclo[6.2.0]decane ***ent*-2.4** *via* both intra- and inter-molecular [2+2]-cycloaddition reactions are also discussed.



The research detailed in Chapters Three, Four and Five is focused on the synthesis of compound **1.7** that it was thought could engage in a transannular [2+2] cycloaddition reaction. If successful, this reaction would mimic the final step in the proposed biogenesis of tripartilactam **1.1**. Three different approaches were investigated and these involved masking the *Z*-double bonds between C14-C15 and/or C16-C17 as alkynes that could each be revealed *via* stereocontrolled (*Z*-selective) semi-reduction.



Macrolactone **6.1** was identified as a potential precursor to tripartilactam **1.1** and attempts to prepare the former compound are described in Chapter Six.



Glossary

°C	degrees Celsius
1,2-DCE	1,2-dichloroethane
ACN	acetonitrile
ADMET	acyclic diene metathesis polymerisation
BT	benzothiazoyl
CAN	ceric ammonium nitrate
cat.	catalytic amount
CM	cross metathesis
CoA	coenzyme A
COSY	correlation spectroscopy
(+)-CSA	(+)-camphor-10-sulfonic acid
CuTC	copper(I) thiophene-2-carboxylate
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
de	diastereomeric excess
DIAD	di-*iso*-propyl azodicarboxylate
DIBAl-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine (Hünig's base)
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
er	enantiomeric ratio
et al.	*et alia* (and others)
eV	electron volt
FVP	flask vacuum pyrolysis

g	gram
gem	*geminal*
h	hour(s)
hept	heptet
HMBC	heteronuclear multiple-bond correlation
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
hv	light
IR	Infrared spectroscopy
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
L	litre
LDA	lithium di-*iso*-propylamine
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molarity
m.p.	melting point
m/*z*	ratio of mass-to-charge
MeOH	methanol
mg	milligram
min	minute(s)
mL	millilitre
mmol	millimol
mol	mole
MS	mass spectrometry
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
pH	logarithm of the reciprocal of the hydrogen ion concentration
PGME	phenylglycine methyl ester
PMB	*para*-methoxybenzyl
PMBO-lepidine	2-(4-methoxybenyloxy)-4-methylquinoline

PMBTCA	*p*-methoxybenzyl trichloroacetimidate
ppm	parts per million
PT	phenyltetrazoyl
p-TsOH	*para*-toluensulfonic acid
q	quartet
RCM	ring-closing metathesis
Red-Al™	sodium bis(2-methoxyethoxy)aluminium hydride
ref.	reference
R_f	retardation factor
ROESY	Rotating Frame Overhauser Effect Spectroscopy
ROM	ring-opening metathesis
ROMP	ring-opening polymerisation metathesis
s	singlet
SEM	2-(trimethylsilyl)ethoxymethyl
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
TfO	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
™	trademark
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultra violet
v/*v*	unit volume per unit volume (ratio)
viz.	*videlicit* (that is, namely)
W	Watt
w/*v*	unit weight per unit volume (%)
δ	chemical shift (parts per million, ppm)
λ_{max}	wavelength (cm^{-1})

μL	microlitre
π	pi (denotes double bond)

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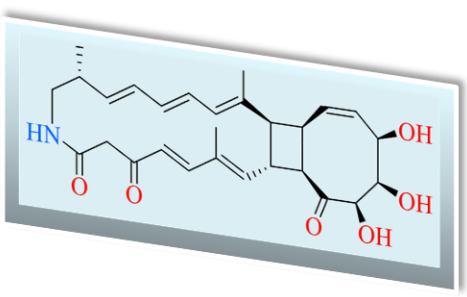
1. CHAPTER ONE

Introduction



1.1. The Macrocyclic Natural Product Tripartilactam

1.1.1. Isolation and Assignment of Structure to Tripartilactam

In recent years, investigations into the symbiotic relationships between insects and microbes have led to the discovery of natural products with pharmaceutical potential. Sceiliphrolactam, an antifungal polyene macrocyclic lactam, represents one natural product discovered in this way.[1] In 2012, Oh and co-workers investigated the selective isolation of actinomycete type microbes from the brood ball of dung beetle *Copris tripartitus*, a soil-dwelling insect, and showed both the diversity of the actinomycetes population and their potentially bioactive metabolites. Over the course of this study, Oh discovered a *Streptomyces* strain, SNA112, that produces a secondary metabolite displaying a distinctive UV spectrum (λ_{max} at 277 nm).[2] This yellowish powder was named tripartilactam and assigned structure **1.1** and thus embodying a cyclobutane core substituted on its opposing faces by an 8-membered carbocyclic ring and a 14-membered lactam.

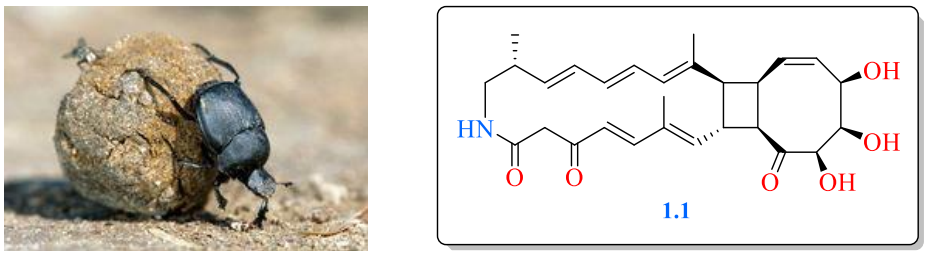


Figure 1.1. ***A Dung Beetle with a Brood Ball and the Structure of Tripartilactam 1.1.***

The molecular formula of tripartilactam was established through a combination of ^{1}H and ^{13}C NMR spectroscopic methods as well as mass spectrometry. A protonated molecular ion was observed at m/z = 482.2542 which corresponds to the molecular formula $C_{28}H_{35}NO_6$ (calculated m/z = 482.2543). Furthermore, the ^{13}C NMR spectrum showed twelve signals ranging from δ 147.0 to 121.7 ppm that were attributed to sp^2-hybridised and olefinic carbons. Three resonances due to carbonyl carbons appeared at δ 210.0, 191.2 and 164.4 ppm with the last of these arising from an amide carbon. The presence of an IR absorption band at 1677 cm^{-1} provided further evidence for the presence of such a unit. The three carbon resonances observed at δ 78.7, 74.2 and 70.2 ppm were attributed to oxygenated sp^3-hybridised carbons. The remaining ten resonances appeared in the up-field region of the ^{13}C NMR spectrum as would be expected for a compound with structure **1.1**. The ^{1}H NMR spectrum displayed signals

consistent with a poly-unsaturated compound containing ten olefinic protons with these resonating in the range δ 7.10 to 5.23 ppm. Two resonances due to the protons of allylic methyl groups appeared at δ 1.49 and 1.26 ppm and the signal due to the amide proton appeared at δ 7.99 ppm. The presence of three hydroxyl group protons was confirmed using deuterium exchange techniques while a broad absorption band appearing at 3361 cm^{-1} in the IR spectrum provided additional evidence for the presence of these moieties. Further analysis of the ^{1}H NMR spectrum revealed the presence of a secondary methyl group at δ 0.93 ppm (d, J = 6.5 Hz), as well as nine other proton resonances ranging from δ 3.54 to 2.32 ppm. Analyses of both NMR spectra as well as the IR spectrum led to the identification of six double bonds and three carbonyl groups. The remaining three degrees of "unsaturation" requires the presence of three rings. COSY correlations and an assessment of ^{1}H-^{1}H couplings led to the identification of a connectivity from C19 to the NH group of the lactam moiety as well as one between C28 and C24. The presence of a cyclobutane ring with two "pendant" alkenyl groups on C8 and C16 of the four-membered carbocycle was also supported by such studies. An isolated methylene (C2-H_2), a discrete double bond (C14/C15) and a triol moiety (C11/12/13) were also revealed in this way. The HMBC and ROESY correlations observed for the constituent atoms of both the four- and eight-membered rings are shown in **Figure 1.2** and these also served to reveal the details of the structure of tripartilactam.

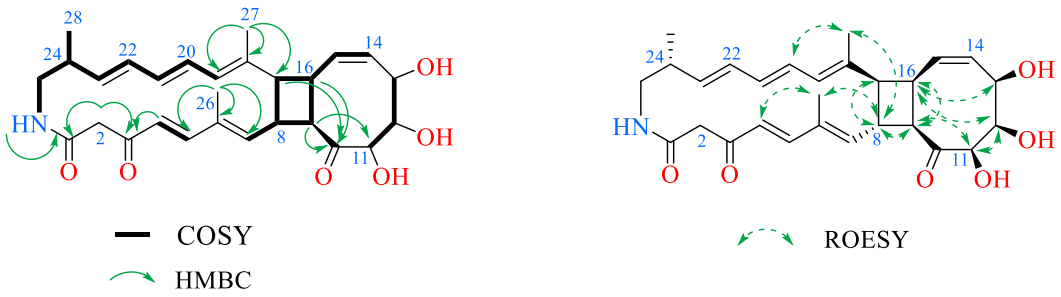
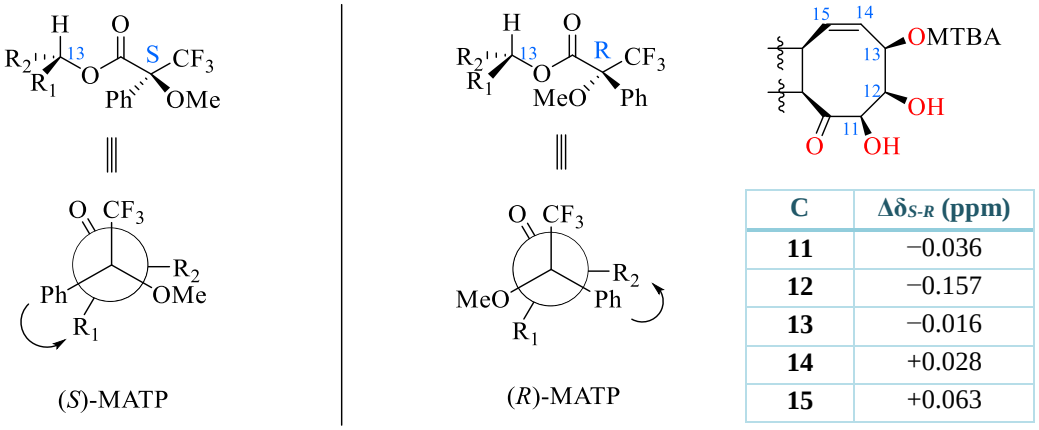


Figure 1.2. ***Key COSY, HMBC and ROESY Correlations Used to Establish the Structure of Tripartilactam.***

The configurations of the stereogenic centers on both the cyclobutane and the cyclooctene rings were determined *via* a modified Mosher method employing (*R*) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride as derivatizing agents. The preparation of the C13-MTPA ester led to the assignment of this center as *R* and from the relative configurations established using the ROESY experiments, the configurations at C8, C9, C11, C12, C16 and C17 were assigned as *R*, *R*, *R*, *R*, *R* and *S*, respectively. Indeed, it was observed that the difference in chemical shifts for the *R* and *S* diastereoisomers, as established using the

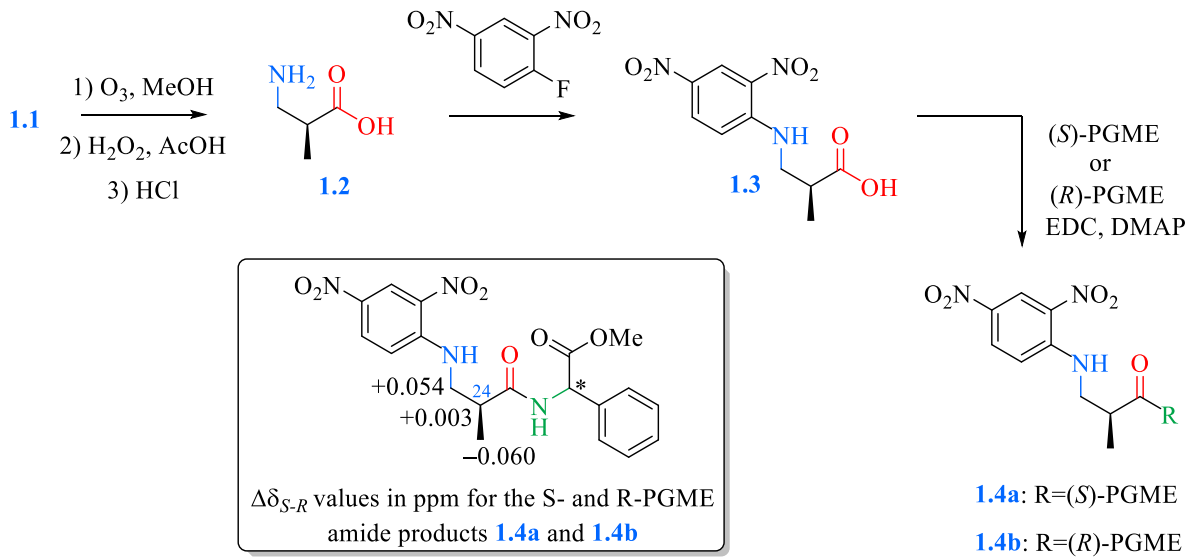
formula $\Delta\delta^{SR}$= δ (*S*-MTPA ester)-δ (*R*-MTPA ester), gave negative values for C11 and C12 while positive values were obtained for C14 and C15. This result strongly suggested that C11 was part of R_2 and C16 part of R_1 (**Figure 1.3**) and therefore led to the assignment of the *R* configuration at C13.



C	Δδ*S-R* (ppm)
11	−0.036
12	−0.157
13	−0.016
14	+0.028
15	+0.063

Figure 1.3. ***Application of the Mosher Ester Method in the Determination of the Absolute Configuration of C13 of Tripartilactam.***

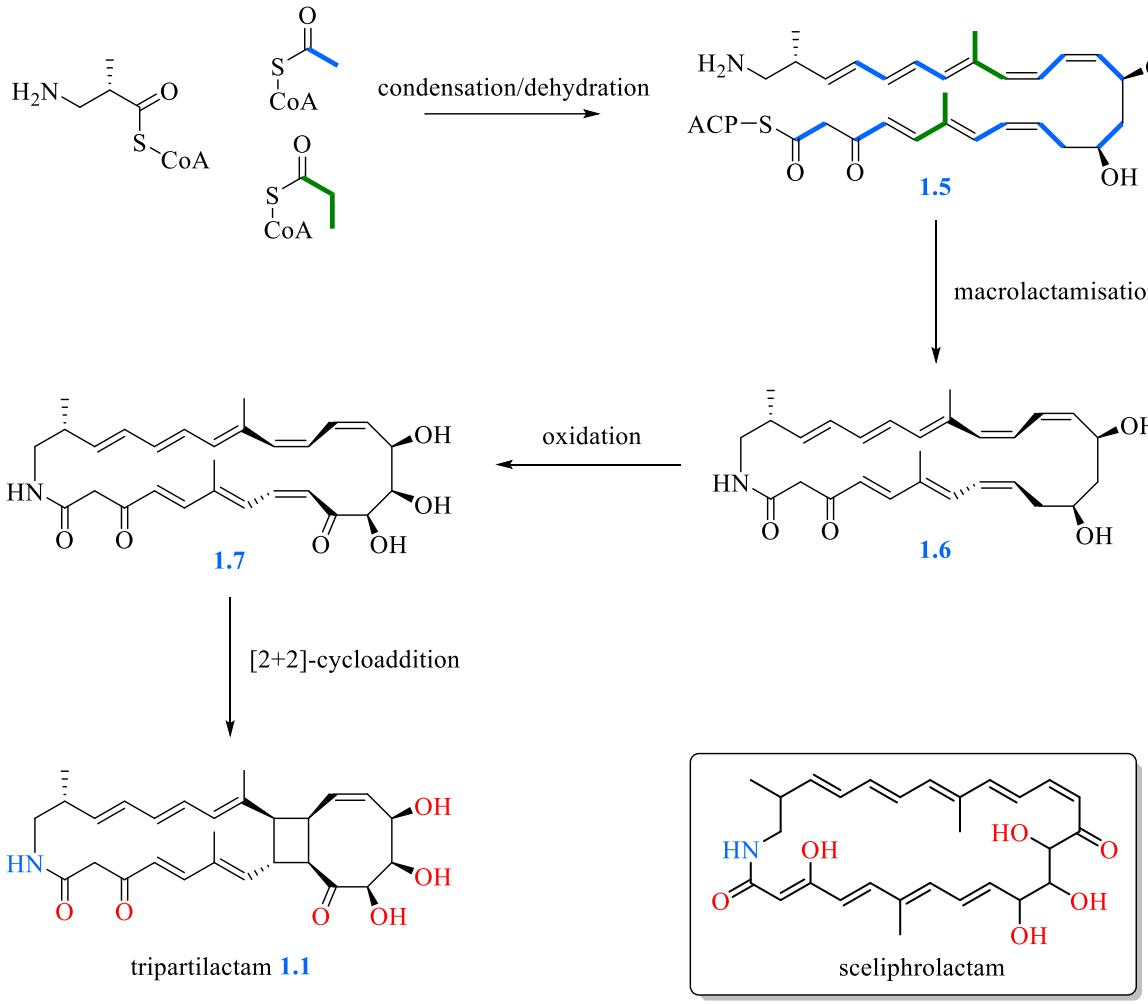
Finally, and as depicted in **Scheme 1.1**, the absolute stereochemistry at C24 was determined from β–amino-acid **1.2**, which was prepared through a multistep chemical degradation of tripartilactam that started with ozonolysis and acid hydrolysis steps. Reaction of this degradation product with the Sanger reagent followed by derivatisation using either (*S*)- or (*R*)-phenylglycine methyl ester (PGME) gave the amides **1.4a** and **1.4b**, respectively. ^{1}H NMR spectroscopic analyses of these products then led to assignment of *R*-stereochemistry at C24.



Scheme 1.1. ***Chemical Degradation Steps Applied to Tripartilactam that Led to the Assignment of the R-Configuration at C24.***

1.1.2. The Biogenesis of Tripartilactam

Oh and co-workers suggested that the biogenesis of tripartilactam occurs *via* an initial cascade of condensation/dehydration reactions involving one molecule of 3-amino-2-methylpropanoyl CoA, nine of acetyl-CoA and two of propionyl-CoA to afford the crucial acyclic precursor **1.5**. Lactamisation of this last species would then release the cofactor and lead to diol **1.6** that it was suggested would undergo oxidation to give the tricarbonyl compound **1.7**. A transannular and possibly photochemically promoted [2+2]-cycloaddition then takes place as illustrated and as the final chemical event to afford tripartilactam **1.1** (see **Scheme 1.2**). Support for such a proposal stems from the earlier isolation of sceiliphrolactam (see inset, stereochemistry undefined) from another insect-associated *Streptomyces* species reported by the Oh group.



Scheme 1.2. ***Proposed Biogenesis of Tripartilactam 1.1.***

1.2. Overview of the Contents of the Remaining Parts of this Thesis

The work described in this thesis was directed towards establishing a total synthesis of tripartilactam (**1.1**), a target natural product that has yet to be realised by any group. Two distinct strategies were investigated. The first sought to construct the cyclobutane-containing Eastern Hemisphere and then add the Western one to it. The other involved approaches to the assembly of macrolactam **1.7** with the intention of then effecting a transannular [2+2]-cycloaddition reaction in an effort to mimic the proposed bio-synthetic pathway. Chapter Two details the author's work involved in pursuing the former strategy, while the three different approaches to macrolactam **1.7** are presented in Chapters Three, Four and Five, respectively. A model macrolactone was also studied and the author's work in this area is described in Chapter Six. The remaining parts of this Chapter (One) highlight the general utilities and mechanisms that operate in key reactions used by the author in her studies. These include the Stille cross-coupling, olefin metathesis and olefination reactions.

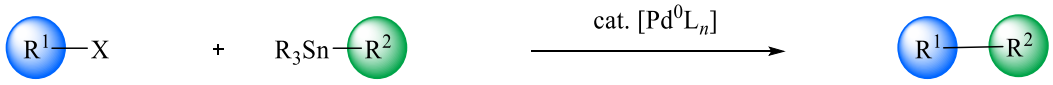
1.3. General Description of Key Organic Reactions Used in Synthetic Approaches to Tripartilactam

1.3.1. The Stille Cross-Coupling Reaction

1.3.1.1. Introduction

Carbon-carbon bond-forming reactions have played a pivotal role in the evolution of organic chemistry. Prominent classical examples of such processes include the Grignard, Diels-Alder cycloaddition and Wittig reactions. More recently, palladium-catalysed cross-coupling reactions have emerged as powerful tools in the assembly of complex molecular frameworks. The reports of the first-generation variants of palladium-catalysed cross-coupling reactions emerged in the mid-1970s.[3] In the intervening period, such processes have become widely known, especially in the forms of the Heck,[4] Sonogashira,[5] Stille,[6] Suzuki,[7] and Negishi[8] cross-coupling reactions. This section focuses on the Stille reaction due to its utility in the author's studies as delineated in certain of the following chapters.

The first example of a palladium-catalysed cross-coupling reaction involving organotin compounds was reported by Eaborn in 1976.[9] A year later, Kosugi and Migita described the reaction of an allyltin compound with either an aromatic halide or acyl chloride in the presence of a palladium catalyst.[6a,b] This process was studied both synthetically and mechanistically in 1978 by Stille and co-workers as part of their establishment of a new route to ketones.[6c,d] By the early 1980s Stille was recognised as a pioneer in the use of this method. Over the years, the Migita-Kosugi-Stille reaction, the name originally given to palladium-catalysed couplings of organostannanes with organic electrophiles to form a new carbon-carbon bond, has become known as the Stille cross-coupling reaction, the general form of which is shown in **Scheme 1.3**.



R^1 = alkyl, alkynyl, allyl, aryl, benzyl, vinyl
R^2 = alkyl, alkynyl, aryl, vinyl
X = Br, Cl, I, OAc, $OP(=O)(OR)_2$, OTf

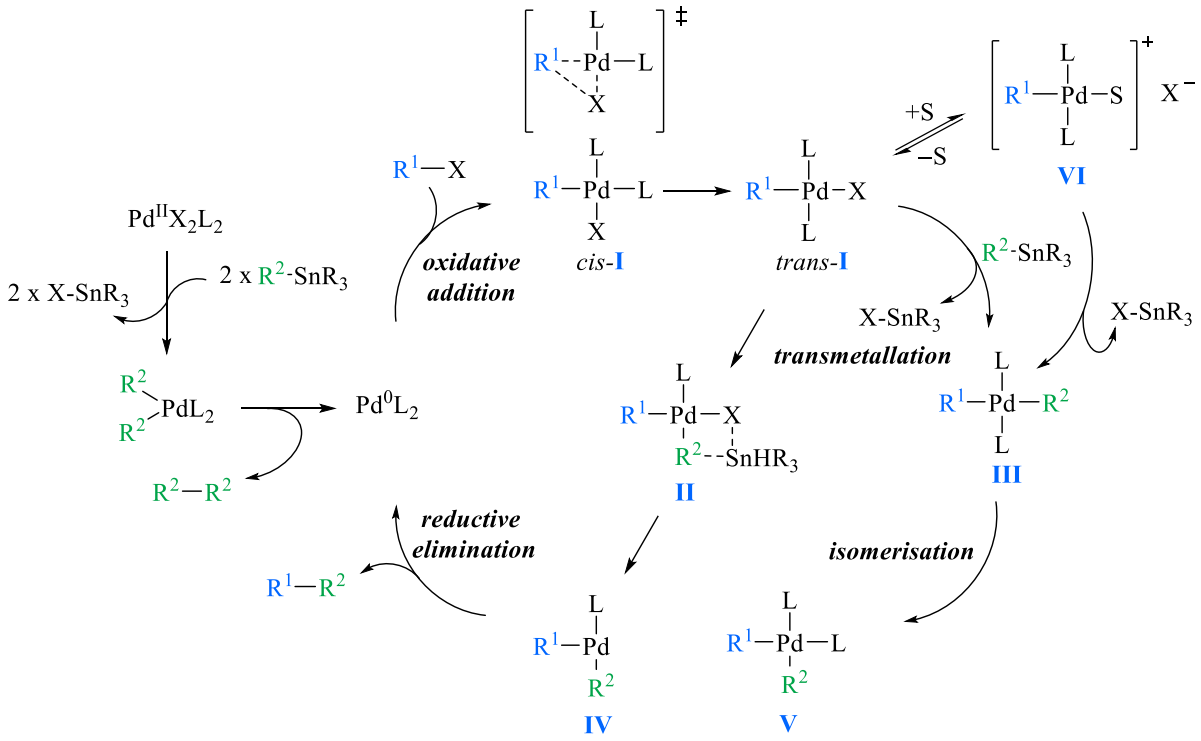
Scheme 1.3. ***The Stille Cross-Coupling Reaction.***

Almost forty years later, this reaction remains one of the most widely applied methods for the formation of carbon-carbon bonds due to the normally mild reaction conditions involved and its tolerance to the presence of various sensitive functionalities as well as air and moisture. The ease of handling of organotin compounds compared to other organometallic substrates is a further attraction of the process.

1.3.1.2. Mechanism

A mechanistic rationalisation of the Stille cross-coupling reaction was first proposed by its namesake in 1979.[6d] More detailed information has since emerged including a knowledge of the geometry of the palladium center in the relevant intermediates and the roles of the different ligands employed as part of the catalytic system. In the case of chiral halides, the matter of inversion *versus* retention of configuration at the relevant stereogenic center(s) is dictated by the nature of the oxidative addition step and shown to depend on the nature of both the solvent and the metal-bound ligand.[10] In those instances involving chiral stannanes, the transmetalation step dictates whether retention or inversion of the configuration is observed.[11] In general, the catalytic cycle proceeds as illustrated in **Scheme 1.4**.[12] The active catalytic species is believed to be a Pd^0L_2 complex that can be generated *in situ* from a pre-catalyst, for example, a preformed palladium(0) system [such as tetrakis(triphenylphosphine)palladium or bis(dibenzylideneacetone)palladium] or from a palladium(II) complex [such as palladium acetate or bis(triphenylphosphine)palladium(II) chloride]. These latter complexes are reduced to the relevant Pd(0) species by the organostannanes. The first step, namely the oxidative addition, involves reaction of a PdL_2 complex with an organic electrophile R^1-X in a three-atom centered transition state to form complex **I**. The *cis*-[R^1PdXL_2] complex is believed to form initially and then isomerise to the more stable *trans*-isomer. The latter species is the only observable intermediate in the catalytic cycle, a feature that suggests the next (transmetalation) step involving reaction with the organostannane is the slow or rate limiting one. Two possible transition states for this process have been proposed and involve either a cyclic or open-chain species.[13] In the former pathway, the generation of the Pd-X-Sn-containing species is assisted by the exchange of one ligand (L) for R^2 to give the complex **II** that then delivers a *cis* R^1/R^2 arrangement as shown in the *cis* T-shaped **IV** species. The open mechanism proceeds *via* an exchange of X for R^2 to form the *trans*-complex **III** that itself isomerises to the *cis*-complex **V**. Both *cis* complexes **IV** and **V** would be expected to undergo reductive elimination to deliver

the observed product. A study by Amatore and Jutand[14] showed that in a coordinating solvent, the replacement of X by a solvent molecule could occur to form the stabilised complex **VI** from the dominant *trans*-[R^1PdXL_2] species. It is noteworthy that this pathway also leads to the generation of *trans*-complex **III**.



Scheme 1.4. ***Generally Accepted Mechanism for the Stille Cross-Coupling Reaction.***

1.3.1.3. Effects of Added Copper

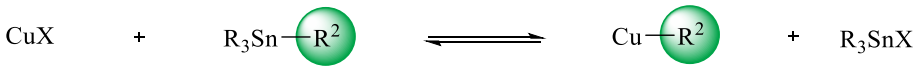
Several significant variations on the original Stille cross-coupling protocol have been developed. Perhaps the most remarkable of these involves the recognition of the co-catalytic effect encountered upon addition of copper(I) salts. This phenomenon was first studied by Liebeskind[15] who suggested two reasons for the observed and highly valuable rate accelerations:

i. Copper(I) acts as a free-ligand scavenger such that when strong ones (such as PPh_3) are present it helps dissociation of *trans*-[PdR^1XL_2] in the transmetalation step. Specifically, the copper "captures" the neutral ligand released during the oxidative addition of PdL_4 to *trans*-[PdR^1XL_2] and so reducing the concentration of free

ligand in the solution. The addition of a copper(I) salt results in minimal rate enhancements when a soft ligand (such as $AsPh_3$) is involved as these are readily dissociated from palladium(II) anyway.

ii. In polar solvents, tin-to-copper transmetalation of the tin reagents takes place to give the more nucleophilic organocopper species.

In 1996, Corey[16] described the beneficial exploitation of a tetrakis(triphenylphosphine)-palladium/copper chloride/lithium chloride combination in a Stille cross-coupling reaction between a range of sterically hindered 1-substituted alkenyl stannanes and aryl perfluoroalkane sulfonates or halides. These reactions were conducted at 60 °C in dimethyl sulfoxide. Lithium chloride was presumed to suppress the homocoupling of the alkenyl copper intermediate. Again, the rate enhancement was attributed to the conversion of alkenyl stannanes into the alkenylcopper(I) species $R^2CuLiCl$ that themselves react rapidly with R^1PdXL_2. The tin/copper exchange was thought to be reversible and, therefore, an increased reversion would delay the positive influence of copper due to the accumulation of R_3SnX in the reaction medium (**Scheme 1.5**). This hypothesis was supported by Liebeskind's observations[17] that the reaction was initially rapid but slowed as it approached 50% conversion.



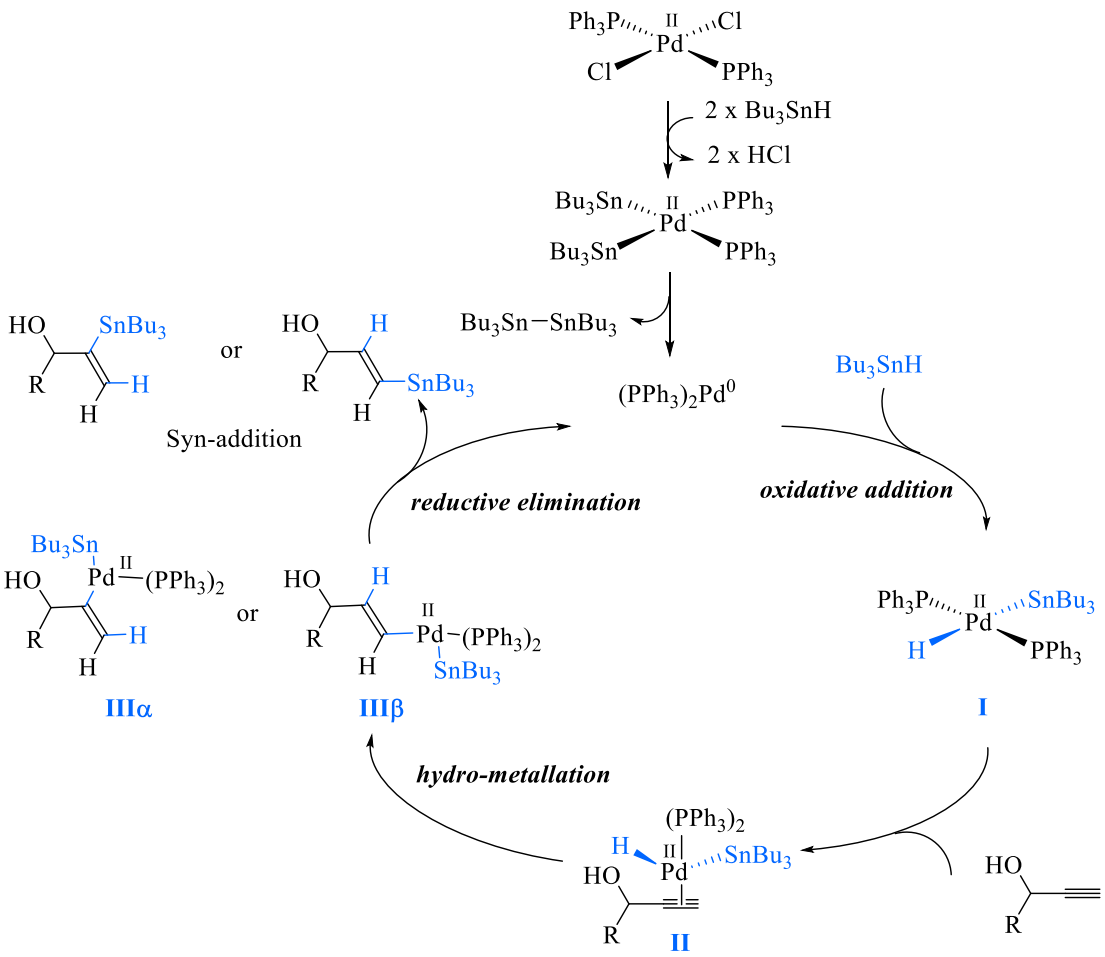
Scheme 1.5. ***Co-Catalytic Effect of Copper Additive in Polar Media - the Formation of a More Nucleophilic Organocopper Species***.

Several methods have been devised to ensure the desired effect of the added copper is actually observed. Those involve either choosing the type of copper(I) salt so that the R_3SnX would be less prone to participate in the reverse process or removing the R_3SnX from the equilibrium. Copper(I) thiophene-2-carboxylate[17] (CuTC) was recommended for the first purpose. In 2005, Baldwin reported the use of either tetra-*n*-butylammonium fluoride (TBAF) or cesium fluoride as a fluoride source to remove the R_3SnX by-product from the equilibrium mixture as polymeric R_3SnF and so shifting the equilibrium towards the more reactive organocopper species. However, using such fluoride additives was found to be incompatible with some late-stage Stille coupling reactions associated with natural product syntheses due to their basicities and their capacity to effect unwanted desilylation reactions. As a result, Fürstner[18] attempted to use the neutral tin scavenging phosphinate salt $[Ph_2PO_2][NBu_4]$ instead and in combination with copper(I) thiophene-2-carboxylate as the copper(I) source. This

protocol proved very effective in all the reactions involved, with the desired reaction often going to completion in less than an hour at ambient temperatures and providing the requisite products in good yield.

1.3.1.4. Preparation of Alkenyl Stannanes via *a Hydrostannylation Reaction*

The hydrostannylation of alkynes is perhaps the most straightforward method for preparing alkenyl stannanes required in Stille cross-coupling reactions. This palladium-catalysed process proceeds under mild conditions and two commonly used catalysts are tetrakis(triphenylphosphine)palladium and bis(triphenylphosphine)palladium(II) chloride, the latter being reduced *in situ* to give the palladium(0) species as illustrated in **Scheme 1.6**.[a]

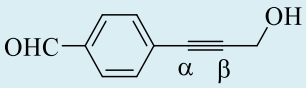
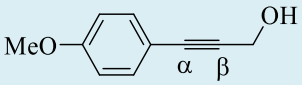
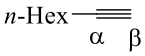
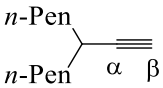
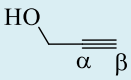
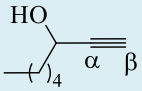
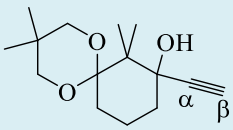
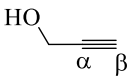
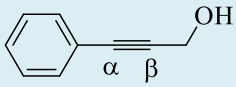
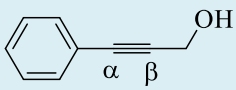


Scheme 1.6. ***Proposed Mechanism for the Palladium-Catalysed Hydrostannylation Reaction.***

[a] A propargylic alcohol was chosen as a substrate in this mechanistic illustration because of its relevant to the work detailed in Chapter Four and Five.

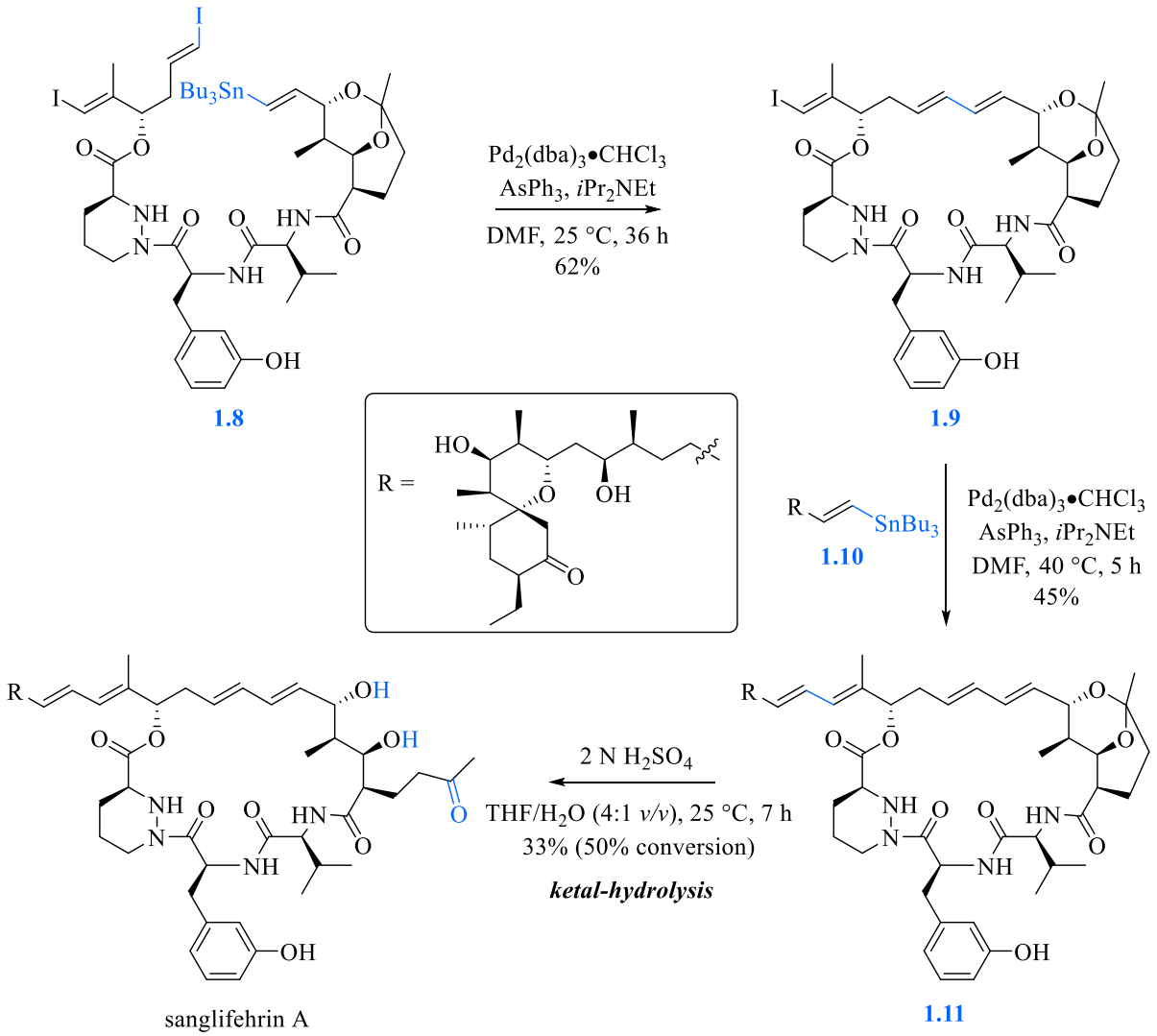
Thus, the catalytic cycle starts with the oxidative addition of tri-*n*-butyltin hydride to the metal center (complex **I**) and this is followed by coordination of the triple bond to form complex **II** that itself undergoes hydrometallation to give one or both of the regio-isomeric hydrostannylation products **IIIα** and **IIIβ**.[19] As a consequence of the operation of a *syn*-addition process, reductive elimination within these two alkenyl complexes will lead to the *E*-isomeric form of organostannanes. The relative steric bulk as well as the electronic nature of R will dictate the mode of addition (the *n*-Bu_3Sn fragment can attach to either the sp-hybridised carbon proximal or distal to R). In an overall sense, then, the regioselectivity of this transformation is dictated by the nature of the substrate. **Table 1.1** provides some examples of the variation in regioselectivity that can be observed in such processes. In 1999, Alami[20] reported an extensive study involving aryl-substituted alkyne substrates and found that an electron-withdrawing group in the *para*-position gave exclusively the α-isomer (entry 1) while the regioselectivity decreased when an electron-donating group was present at the same position (entry 2). Little selectivity was found for 1-octyne (entry 3), but the β-isomer was obtained exclusively upon increasing the steric bulk at the sp^3-hybridised carbon attached to the sp-carbon of the alkyne.[21] So, the primary propargylic alcohol[22] gave a 62:38 ratio of α/β isomers while the secondary alcohol began to show some preference for formation of the β-isomer (25:75 α/β ratio of products).[21] Complete selectivity for β-isomer formation was observed for tertiary alcohols, such as shown in entry 7.[23] Kazmaier[24] developed a molybdenum-based catalyst that could improve the selectivity for the α-isomer as shown in entry 8 with the α/β ratio rising to 91:9 as compared with the 62:38 ratio observed earlier (entry 5). Alami[20] also noticed that the reverse selectivity was engendered by changing the solvent. So, for example, switching from dichloromethane to tetrahydrofuran led to a change in the α/β ratio from 33:67 to 80:20, respectively.

Table 1.1. ***Controlling the Regioselectivity of the Hydrostannylation Reaction of Substituted Alkynes.***

Entry	Substrate	Catalyst	Ratio		Ref.
			α-isomer	β-isomer	
1		$Pd(PPh_3)_2Cl_2$	100	-	20
2		$Pd(PPh_3)_2Cl_2$	76	24	20
3		$Pd(PPh_3)_2Cl_2$	57	43	21
4		$Pd(PPh_3)_2Cl_2$	0	100	21
5		$Pd(PPh_3)_4$	62	38	22
6		$Pd(PPh_3)_2Cl_2$	25	75	21
7		$Pd(PPh_3)_2Cl_2$	-	100	23
8		$Mo(CO)_3(tBuNC)_3$	91	9	24
9		$Pd(PPh_3)_2Cl_2$, DCM	33	67	20
10		$Pd(PPh_3)_2Cl_2$, THF	80	20	20

1.3.1.5. Application in Natural Product Synthesis

Stille cross-coupling reactions have provided particularly reliable means for effecting both inter- and intra-molecular carbon-carbon bond formation (the latter mode leading to carbocyclic ring-formation). A wide variety of ring sizes is available *via* such means. Besides being tolerant of the presence of a range of functional groups that are often present in the complex substrates required for natural product synthesis, the reaction provides remarkable levels of chemo- and stereo-selectivity. The synthesis of novel immunosuppressant agent sanglifehrin A reported by Nicolaou[25] (**Scheme 1.7**) emphasises such matters.

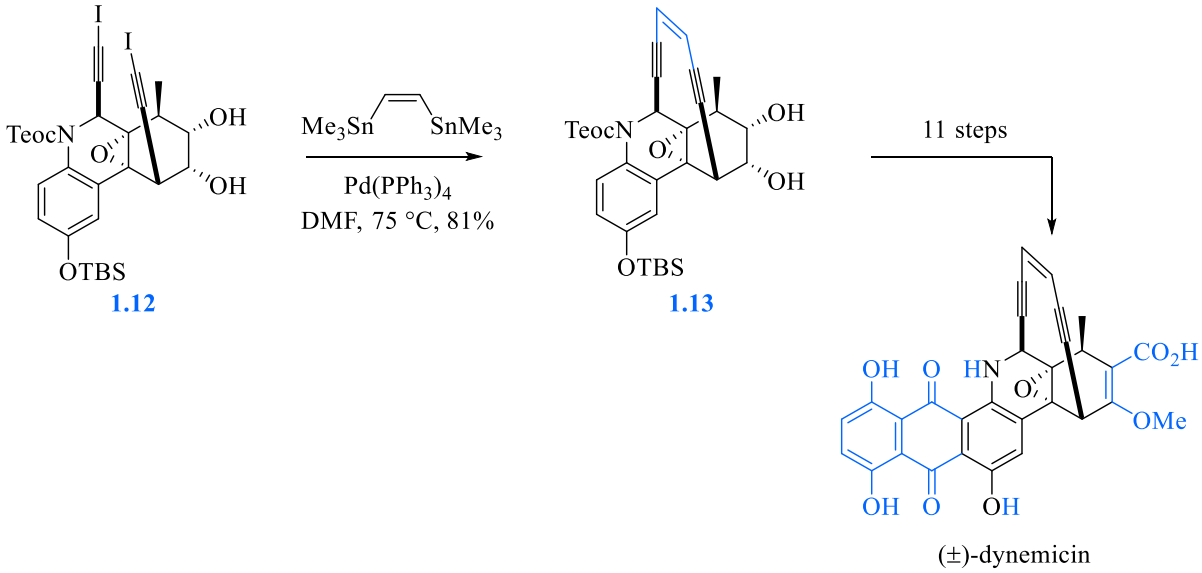


Scheme 1.7. ***Chemoselective Intra- and Inter-molecular Stille Cross-Coupling Reactions in a Total Synthesis of Sanglifehrin A.***

The late-stage and regio-selective intramolecular Stille cross-coupling reaction involving the alkenyl stannane and alkenyl iodide residues within substrate **1.8** provided the

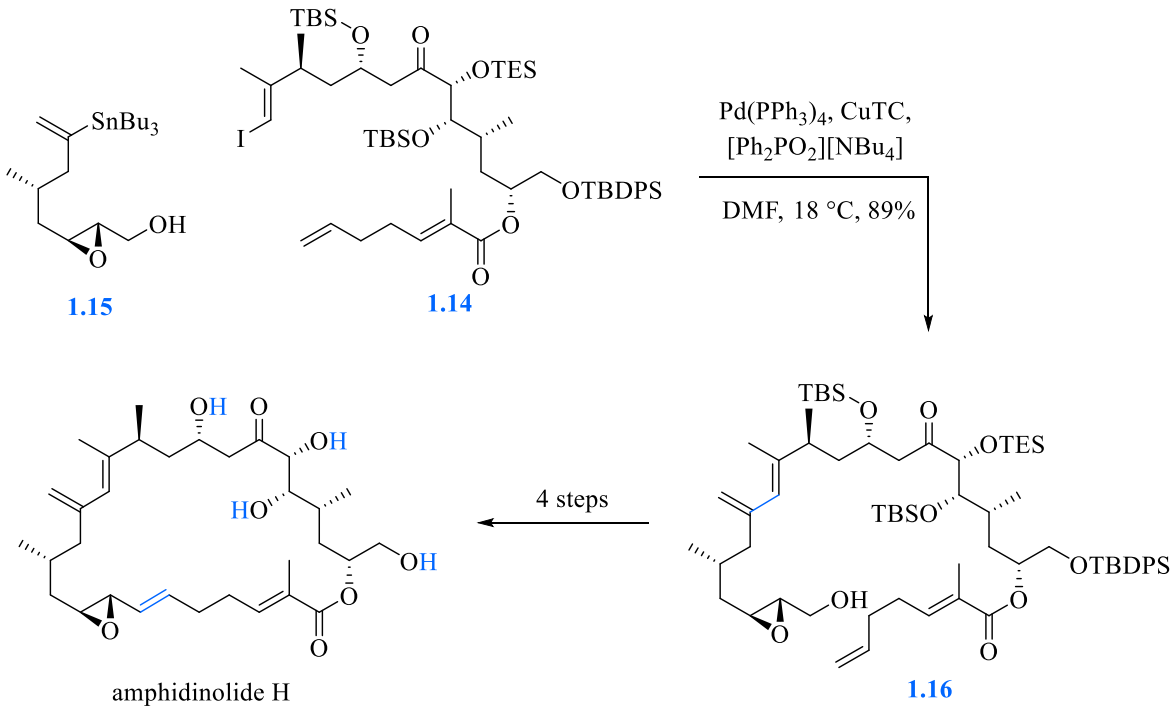
22-membered macrocycle **1.9** in 62% yield. A subsequent intermolecular Stille cross-coupling reaction between the hindered alkenyl iodide embodied within this product and alkenyl stannane **1.10** delivered compound **1.11** incorporating the full carbon framework of the target natural product. Indeed, when this last compound was subjected to acetal-deprotection, sanglifehrin A was obtained.

A so-called "stitching" cyclisation strategy featuring a double Stille cross-coupling reaction has also been employed by various research groups including those of Nicolaou[26] (in the total synthesis of rapamycin), Panek[27] (in the construction of (+)-mycotrienol and (+)-mycotrienin I) and Danishefsky[28] [in the preparation of the racemic modification of the enediyne anticancer antibiotic dynemicin (**Scheme 1.8**)]. The pivotal step in this last synthesis was the coupling of bis(iodoalkyne) **1.12** with the *cis*-1,2-distannyl ethylene thus leading to formation of the highly strained 10-membered ring-containing compound **1.13** in 81% yield.



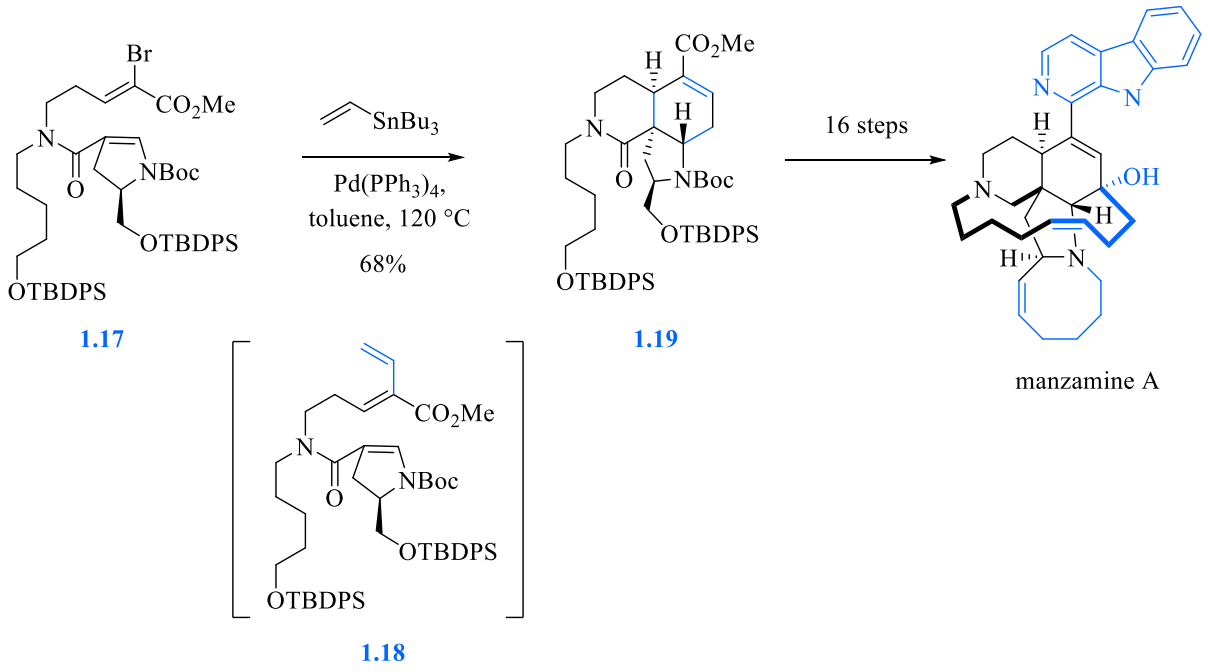
Scheme 1.8. ***Double-Stille Cross-Coupling Strategy Leading to the Enediyne Core Associated with the Danishefsky's Synthesis of Dynemicin.***

In 2007, Fürstner[29] reported formal total syntheses of amphidinolides H and G in which the crucial intermolecular Stille cross-coupling reaction between alkenyl iodide **1.14** and the hindered stannane **1.15** was performed with the assistance of copper(I) thiophene-2-carboxylate and conducted in presence of the neutral tin scavenger phosphinate salt [Ph_2PO_2][NBu_4] (**Scheme 1.9**). The desired product **1.16** was obtained in 89% yield at ambient temperatures and, notably, in the presence of an unprotected alcohol residue, a sensitive β-hydroxyketone unit and various *O*-silyl groups.



Scheme 1.9. ***Crucial Stille Cross-Coupling Reaction Used in a Synthesis of Amphidinolide H.***

The Stille reaction has the capacity to generate species that can engage, *in situ*, in the next step of a reaction cascade. Thus, in Martin's synthesis of manzamine A,[30] **Scheme 1.10**, treatment of bromide **1.17** with vinyl stannane in refluxing toluene using a catalytic amount of tetrakis(triphenylphosphine)palladium provided the coupling product **1.18** that underwent an *in situ* and intramolecular Diels-Alder reaction to furnish the tricyclic core containing compound **1.19** in 68% yield. This process delivered three new carbon-carbon bonds and three new stereocenters with full control. Over sixteen additional steps, product **1.19** was carried forward to manzamine A.



Scheme 1.10. ***Tandem Intermolecular Stille Coupling/Intramolecular Diels-Alder Cycloaddition Processes Leading to the Tricyclic Core of Manzamine A.***

It is clear from the foregoing that, the Stille cross-coupling reaction has become one of the most popular and effective transition metal-catalysed processes available for carbon-carbon bond formation. It has evolved, since its inception, from a relatively demanding method into an extremely mild and flexible one. Its versatility has been increased tremendously through the discovery of the co-catalytic effect of copper and the optimisation of the ligand set used. There is even a palladium-free method available now involving the use of copper(I) thiophene-2-carboxylate.[17] This reaction proceeds at room temperature.

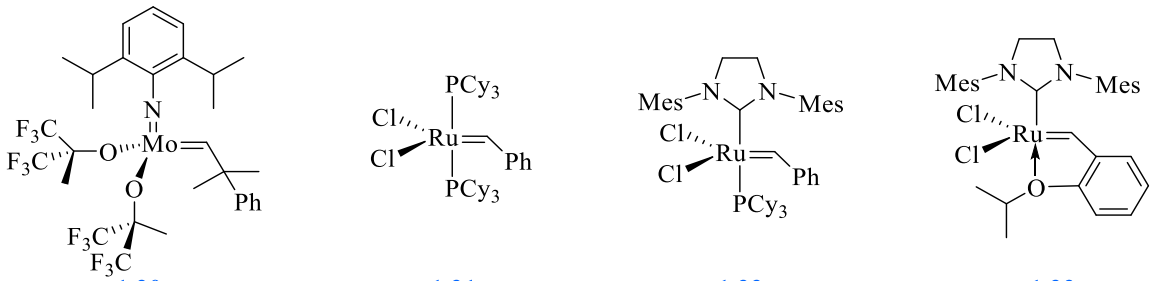
1.3.2. Metathesis Reactions

In recent decades, metathesis reactions have also contributed dramatically to the repertoire of carbon-carbon bond forming processes now available, particularly by allowing the reorganisation-transformation of simple molecules into target systems that are often structurally complex, highly functionalised and difficult to obtain by other means. This section highlights some of the features and applications of such processes in total syntheses. Metathesis reactions are no longer restricted to olefins. Now they can also involve enynes and alkynes as substrates. In fact, the rate of development in this area has been rather dramatic, especially in regards to the matter of catalyst design. As a result, synthetic chemists now have access to transformations that would have, until recently, been thought almost impossible. Furthermore, such processes often show exceptional tolerance for a broad range of substrates.

1.3.2.1. Alkene Metathesis

The alkene metathesis reaction has a fascinating history, starting with its discovery in 1955.[31] Its potential utility has attracted global attention. As a result, a wide range of readily available catalyst systems with high activity and functional group tolerance have led it to becoming the most commonly used method among the metathesis-based carbon-carbon bond forming processes. **Figure 1.4** shows the most commonly utilised, commercially available catalysts. The molybdenum-based complex **1.20** was introduced by Schrock[32] in 1990 and represents the first advanced catalyst containing a tetra-coordinated alkylidene species with bulky substituents on the imido and alkoxide ligands. The complex is a well behaved metathesis initiator even for sterically hindered systems.[33] It is, however, quite sensitive to oxygen and moisture as well as being relatively intolerant of the presence of protons on heteroatoms (such as encountered in carboxylic acids, alcohols, amines, amides, *etc*). In 1995 Grubbs[34] disclosed the ruthenium carbene complex **1.21** as initiator system exhibiting greater functional group tolerance. Although less reactive than Schrock's molybdenum alkylidene **1.20**, this so-called first-generation Grubbs' catalyst is reasonably stable to oxygen, water and minor impurities in the reaction solvent. The replacement of one of the phosphine ligands with an *N*-heterocyclic carbene (NHC) ligand provides complex **1.22** which is known as the second-generation Grubbs' catalyst.[35] The introduction of this last catalyst expanded the scope of the olefin/alkene metathesis process significantly. It is not only stable and tolerant of various functional groups but also more reactive with sterically demanding substrates. Another remarkable contribution to the field of ruthenium-based catalysts involved the introduction of *iso*-propoxystyrene-

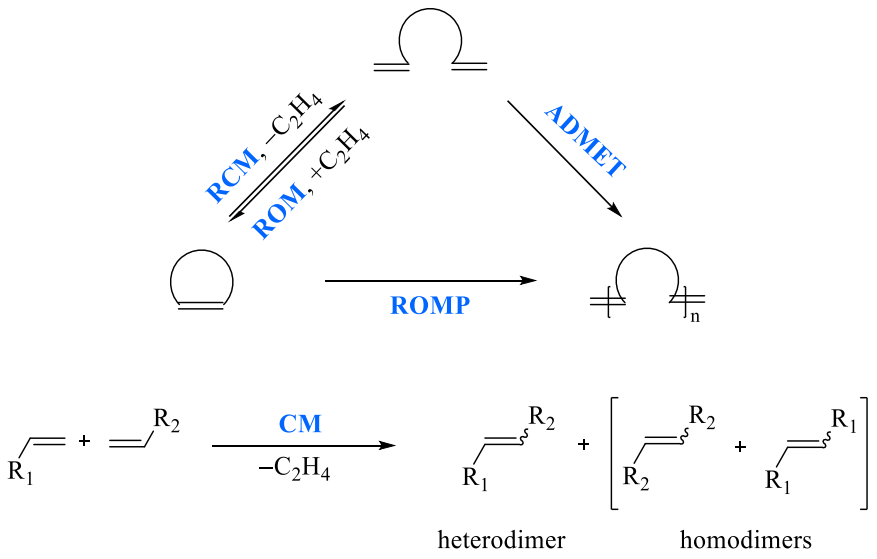
coordinated complex **1.23** by Hoveyda[36] in 2000. This system is now known as the second-generation Hoveyda-Grubbs' catalyst. The complex contains an NHC ligand that imparts significant reactivity and a styrenyl ether residue that allows the recovery of the catalyst by conventional flash chromatography. The origin of such useful features is the presence of the *iso*-propoxy group on the phenylcarbene unit. This stabilises the complex while continuing to provide an accessible coordination site for the substrate. Despite these significant innovations, the search for increasingly efficient, as well as selective catalysts continues unabated.[37]



1.20 **1.21** **1.22** **1.23**

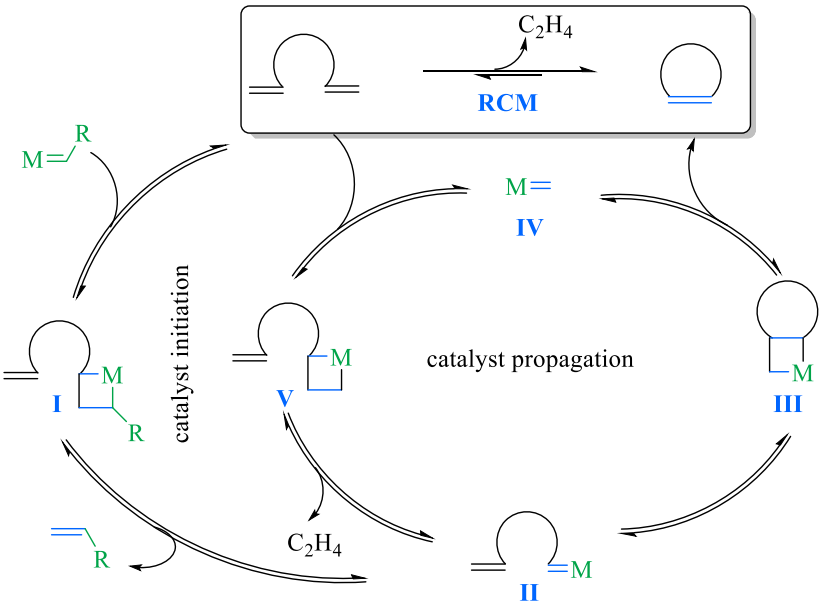
Figure 1.4. ***Commonly Used Alkene Metathesis Catalysts.***

Alkene metatheses can be divided in five important subtypes. As shown in **Scheme 1.11** these are the ring-closing metathesis (RCM), ring-opening metathesis (ROM), ring-opening polymerisation metathesis (ROMP), acyclic diene metathesis polymerisation (ADMET) and cross metathesis (CM) processes.[38]



Scheme 1.11. ***Five Different Types of Alkene Metathesis Reaction.***

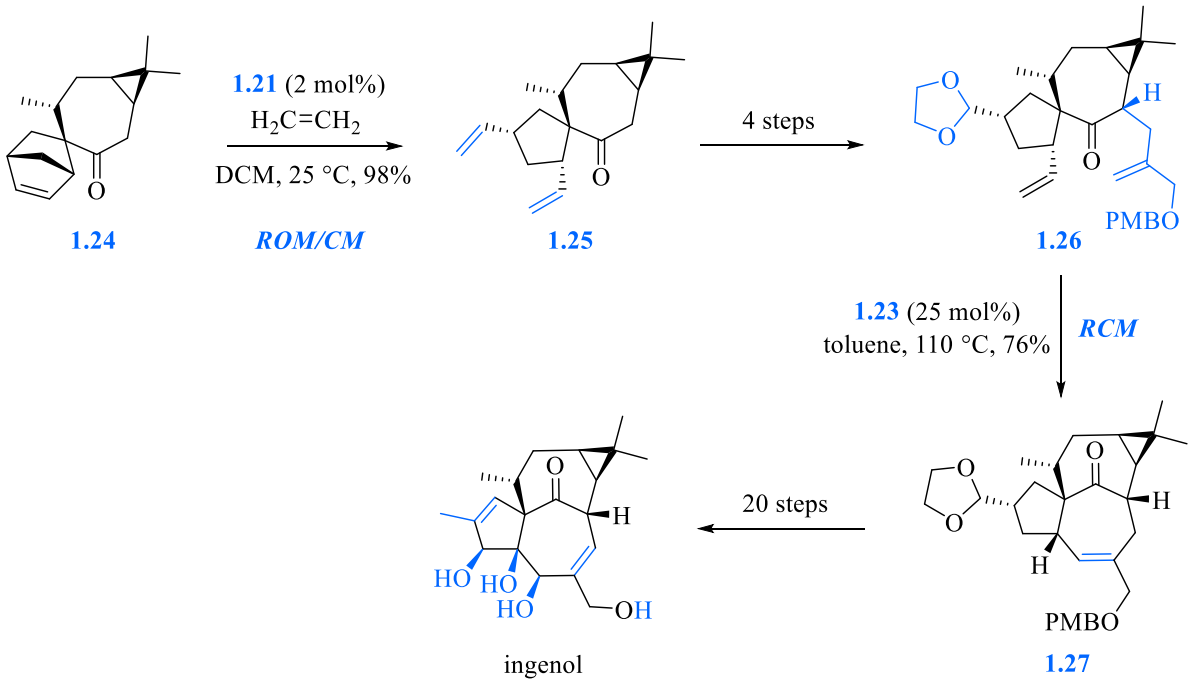
Among them, the ring-closing metatheses of acyclic dienes have probably received the greatest attention as they provide a highly effective method for the construction of medium to large carbocycles and heterocycles. Ring-opening polymerisation metatheses provide the capacity to prepare functionalised polymers. Cross metatheses, on the other hand, are found to be the most challenging processes because of the frequent lack of selectivity between those reactions leading to the desired "heterodimer" and those producing the normally undesired "homodimers". **Scheme 1.12** shows the mechanism that most likely operates in the ring-closing metathesis process. Thus, the now generally accepted mechanism for alkene metathesis was first proposed by Chauvin[39] in 1970. It proceeds through coordination of the alkene with a metal alkylidene to generate a metallacyclobutane intermediate that then fragments in the reverse manner to that by which it was formed. As such, it involves sequential [2+2]-cycloaddition and cycloreversion events. Since all the individual steps of the catalytic cycle are reversible, it is important to shift the equilibrium in one direction in order to obtain a productive outcome. For example, in the case of the ring-closing metathesis, the catalytic cycle commences with an initiation phase involving a [2+2]-cycloaddition reaction between the catalyst and one of the two olefins present in the substrate so as to deliver the metallacyclobutane **I** which then ruptures to furnish the active alkylidene metal **II**. Formation of the second metallacyclobutane **III** and its disintegration generates the cyclic product and the metal carbene **IV**, that serves as the active complex to promote the next catalytic cycle. The release of the volatile ethylene by-product formed at this stage is the driving force that allows for the complete formation of the desired cycloalkene product (provided the ethylene is vented properly).



Scheme 1.12. ***General Catalytic Cycle Associated with the Ring-Closing Metathesis of Dienes.***

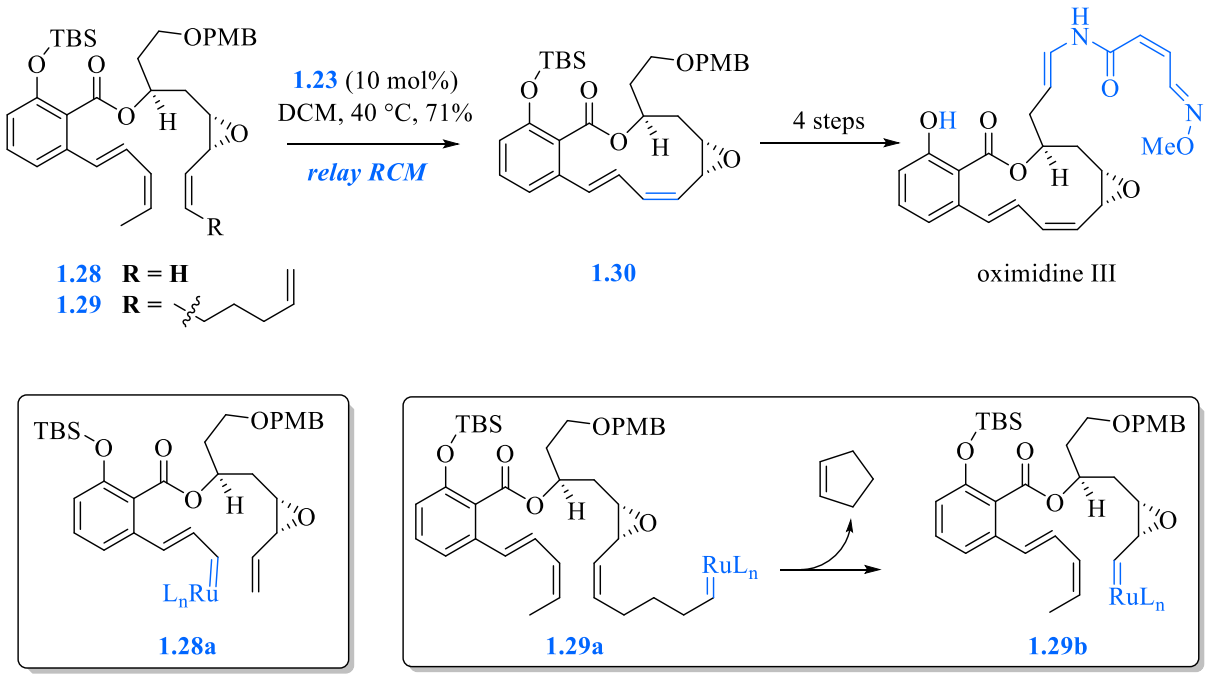
The situation is different for ring-opening metatheses or ring-opening polymerisation metatheses. Ring-strain release is normally the driving force for these transformations. Any potential competition between ring-closing metathesis and acyclic diene metathesis polymerisation events can be controlled through the application of high-dilution techniques.

The total synthesis of ingenol reported by Wood and co-workers represents a remarkable application of the alkene metathesis reaction.[40] Ingenol is the parent compound associated with a class of naturally occurring compound called ingenanes. They all share the same carbon framework. Ingenol has attracted the attention of synthetic chemists not only because of its highly oxygenated polycyclic structure, which features a distinctive bridged ring system, but also because of its interesting biological profile. By using a ring-opening/cross metathesis tactic involving the first-generation Grubbs' catalyst, the authors were able to convert the spiro compound **1.24** into diene **1.25** in almost quantitative yield under an ethylene atmosphere (**Scheme 1.13**).[41] The derived diene **1.26** itself served as the substrate for the pivotal ring-closing metathesis step. Delightfully, it was found that by using the second-generation Hoveyda-Grubbs' catalyst **1.23** then compound **1.27** could be generated (in 76% yield) and then elaborated to ingenol, albeit over a further twenty steps.



Scheme 1.13. ***Ring-Opening/Cross Metathesis and Ring-Closing Metathesis Reactions Used in a Total Synthesis of Ingenol.***

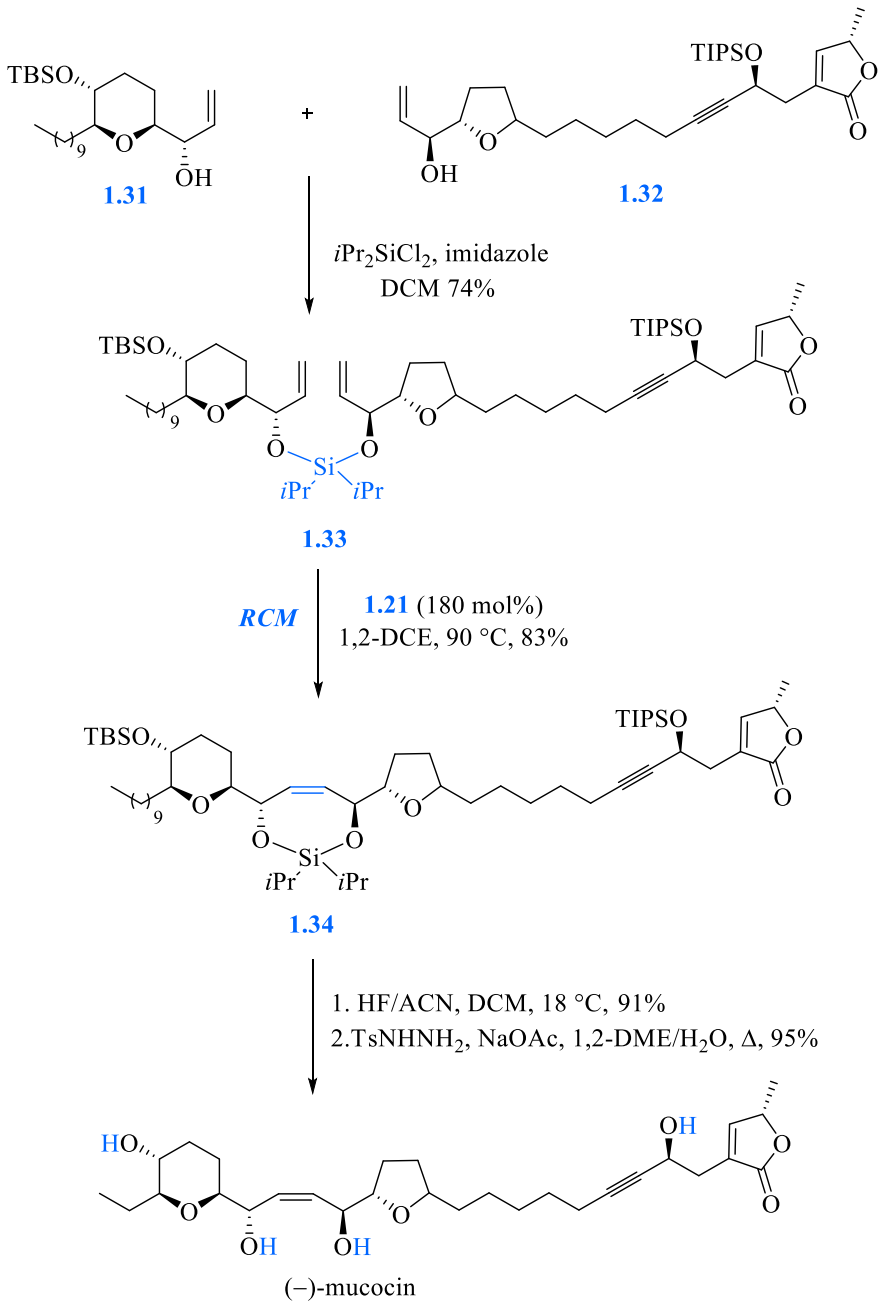
Difficulties sometimes encountered with steric hindrance and/or electronic deactivation within a substrate can be circumvented through the application of a "relay ring-closing metathesis" approach. Since such problems often derive from a difficult initiation process, a solution would be the installation of a temporary tether containing a sterically unencumbered alkene that would initiate the catalytic cycle. One such an example is illustrated in **Scheme 1.14** and involves the synthesis of oximidine III by the Porco group.[42] Thus, on submitting diene **1.28** to conventional ring-closing metathesis only a 15% yield of the desired product **1.30** was obtained. It was presumed that the stabilised alkylidene **1.28a** did not undergo ready reaction with the hindered alkenyl epoxide. Accordingly, a so-called relay moiety was introduced as seen in compound **1.29** and its presence allowed the ruthenium alkylidene catalyst to react, initially, with this less hindered terminal double bond to form intermediate **1.29a**. The kinetically favorable ring-closing metathesis then occurred to form, through the extrusion of a molecule of cyclopentene, complex **1.29b** that itself underwent another ring-closing metathesis reaction to afford the target macrolactone **1.30** in 71% yield.



Scheme 1.14. ***Relay Ring-Closing Metathesis in a Total Synthesis of Oximidine III.***

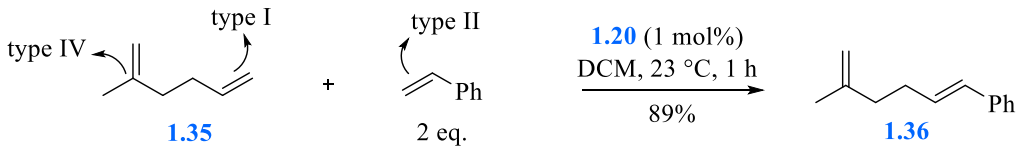
Alkene cross metatheses are also important processes and could be considered, in some instances, as useful alternatives to cross-coupling reactions. The most challenging issue in this type of metathesis is the chemo- and stereo-selective formation of the desired heterodimeric product. An interesting tactic involves temporary connection through silicon-based tethers so

as to enable a ring-closing metathesis reaction to be employed instead. Such an approach was employed in the total synthesis of the antitumor agent (−)-mucocin by Evans and co-workers (**Scheme 1.15**).[43] Since, the cross metathesis of allylic alcohols **1.31** and **1.32** did not seem to be a promising approach for a selective "heterodimerisation" process, a temporary silicon tether as seen in substrate **1.33**, was installed and a ring-closing metathesis reaction then took place to provide alkene **1.34** in 83% yield although an excess of catalyst (180 mol%) was required to drive the reaction to completion. Finally, sequential global deprotection and diimide reduction steps revealed the natural product (−)-mucocin.



Scheme 1.15. ***Use of a Temporary Silicon Tether in a Synthesis of (−)-Mucocin.***

In 2003, Grubbs and co-workers described a general model for predicting the outcomes of alkene cross metatheses.[44] Their investigations revealed that olefins can be ranked (in terms of their reactivity in cross-metatheses) by considering their relative ability to undergo homodimerisation and examining the reactivity of these "homodimers" in a secondary metathesis process. As a result, four different olefin types were identified as shown in **Scheme 1.16**. The selectivity of such reactions can be tuned by decreasing the rate of "homodimerisation" of one component, something that can be achieved by altering either the steric or electronic properties of the substituents near the reacting alkenes. In other words, selective cross metatheses would be achieved by engaging two different types of olefins. So, for example, Crowe and Zhang[45] showed a chemoselective cross metathesis could be achieved between a type I terminal olefin **1.35** and so-called type II styrene to form product **1.36** possessing the *E*-configuration about the newly established double bond (normally the products of such reactions are mixtures of *E*- and *Z*-isomers). High *Z*-selectivities are realised when the coupling partner bears a substituent incorporating an sp-hybridised carbon as seen, for example, in acrylonitrile.[46]



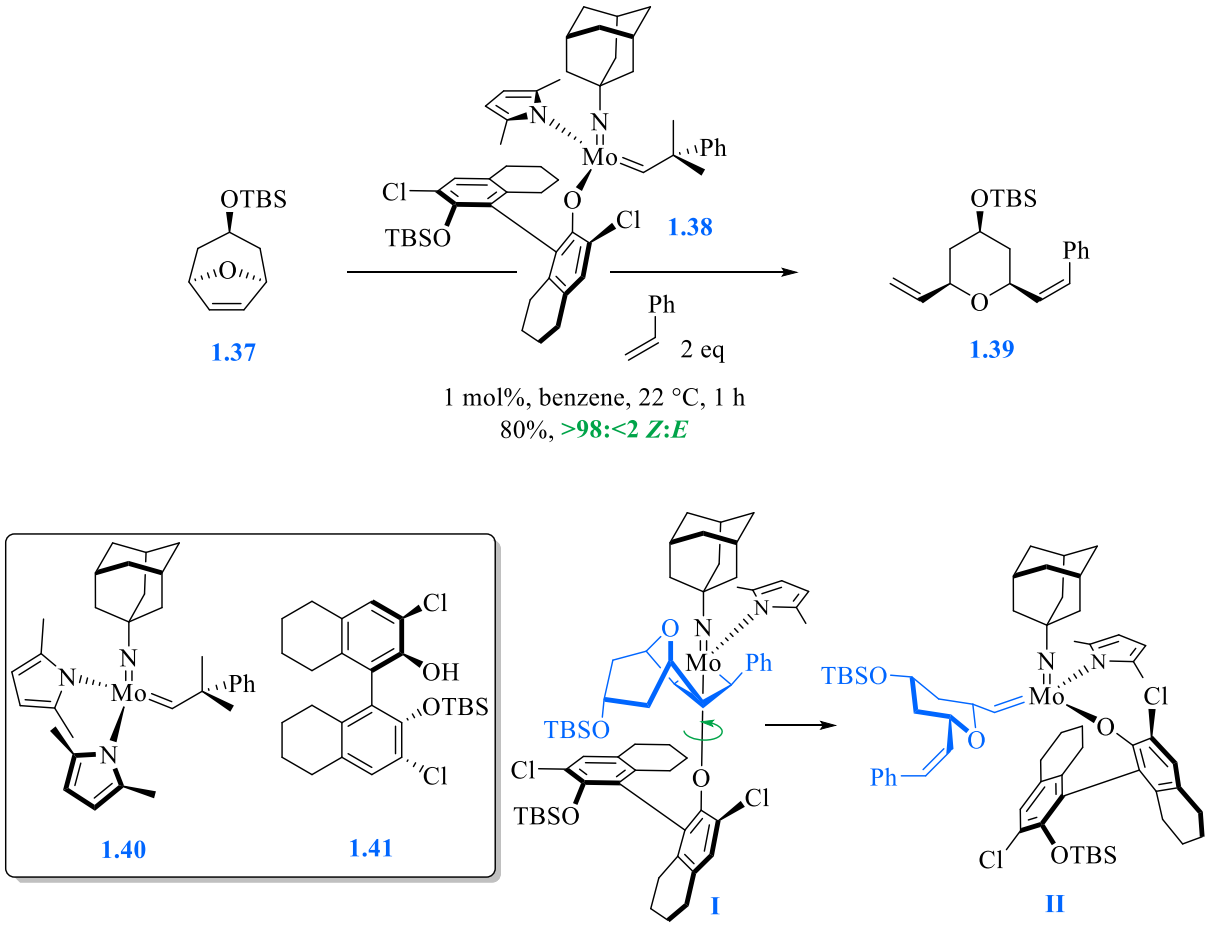
olefin reactivity ↑

Type I	Rapid homodimerisation, consumable homodimers
Type II	Slow homodimerisation, sparingly consumable homodimers
Type III	No homodimerisation
Type IV	Olefins inert to cross metathesis, but do not deactivate catalyst

Scheme 1.16. ***Chemoselective Cross Metathesis Using Schrock's Catalyst 1.20.***

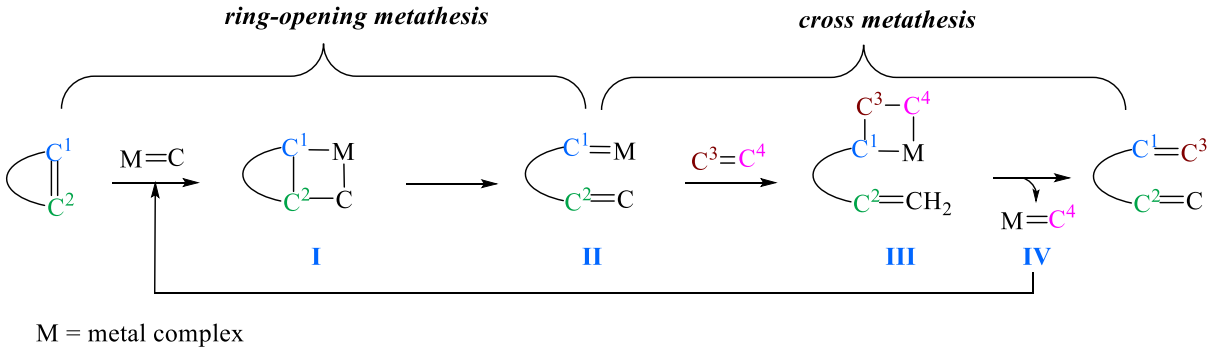
The lack of methods that selectively furnish *Z*-alkenes captured the attention of Hoveyda (a pioneer in the field) who developed structurally distinct catalysts to address this matter (**Scheme 1.17**). So, the *Z*-olefin **1.39** was obtained upon treatment of oxabicycle **1.37** with styrene and 1 mol% molybdenum catalyst **1.38** (generated *in situ* from adamantylimido bispyrolide **1.40** and alcohol **1.41**).[47] The ring-opening/cross metathesis sequence proceeded within an hour to afford the desired product in 80% yield. It is presumed that the sterically demanding but fully rotatable around Mo-O bond to the aryloxide ligand, together with a smaller imido substituent (relative to the aryloxide), allows for the formation of the key *cis*-

metallacyclobutane **I**, that likely involves in the formation of the *Z*-configured product. The bromo-derivative of complex **1.38** also proved to be an efficient and highly stereoselective catalyst for reactions involving enol ethers.[48]



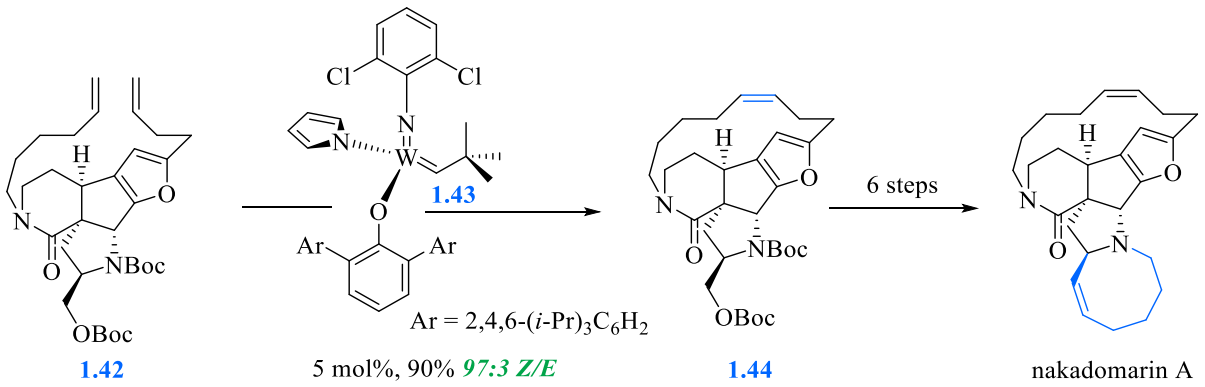
Scheme 1.17. ***Selective Z-Alkene Formation Using a Molybdenum Catalyst.***

A general accepted mechanism for the ring-opening/cross metathesis process is shown in **Scheme 1.18**. First, a [2+2]-cycloaddition reaction between the cyclo-olefinic substrate and the alkylidene catalyst generates metallacyclobutane **I** that collapses to form the ring-opened metal complex **II**. This intermediate then participates in a cross metathesis reaction with another acyclic olefin to yield an acyclic metallacyclobutane **III**, that itself ruptures to deliver both the product and the active metal-carbene **IV**, the latter being capable of participating in subsequent catalytic cycles.



Scheme 1.18. ***General Mechanism for Catalytic Ring-Opening/Cross Metathesis***.

Although *Z*-alkenes are generated exclusively when small or medium rings are formed in ring-closing metatheses, this is not the case for larger rings wherein mixtures of *E*- and *Z*-isomers are observed in most cases. Further investigations of ring-closing metathesis reactions show that the use of tungsten alkylidene **1.43** delivers even higher *Z*-alkene selectivity than the molybdenum-based systems, as seen, for example in the synthesis of the 15-membered ring of nakadomarin A.[49] Thus, the desired pentacycle, **1.44**, was isolated in 90% yield by exposing substrate **1.42** to 5 mol% of catalyst **1.43** (**Scheme 1.19**). Only 3% of the corresponding *E*-isomer was obtained.



Catalyst	Schrock's cat. **1.20** (5 mol%)	2nd-Grubbs' cat. **1.22** (10 mol%)	2nd-Hoveyda-Grubbs' cat. **1.23** (10 mol%)	Molybdenum cat. **1.38** (Br derivative) (6 mol%)
Yield	67%	70%	66%	71%
Z/*E*	38:62	38:62	36:64	69:31

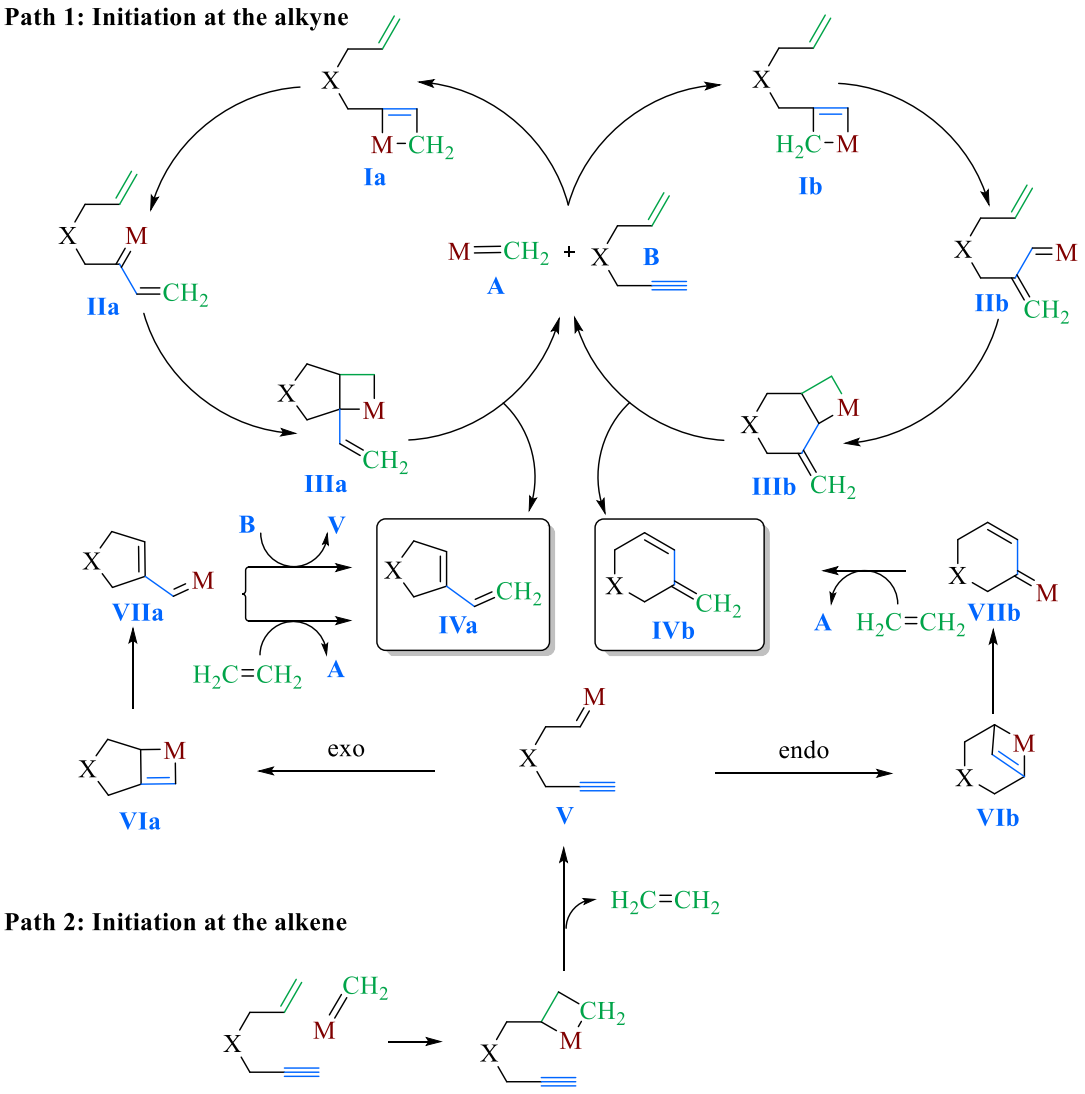
Scheme 1.19. ***Z-Selective Ring-Closing Metathesis Reaction Employed as the Key Step in a Synthesis of Nakadomarin A and Results Using Other Catalysts.***

Examination of the ability of different catalysts to promote the *Z*-selective ring-closing metathesis of substrate **1.42** revealed that some of the *E*-isomer was normally obtained with most catalysts. The bromine analogue of the molybdenum-based catalyst **1.38** provided a 69:31 ratio of *Z*- and *E*-isomers. Another advantage of catalyst **1.43** is its high stability towards air and moisture compared with its molybdenum-based counterpart. Ruthenium based-catalysts have been studied by Grubbs and found to deliver useful *Z*/*E* ratios.[50] These catalysts are also found to be more functional group tolerant than molybdenum- and tungsten-based systems and capable of *ca.* 1000 turnovers in several cross metathesis reactions at low loadings and without requiring low pressures or high temperatures. As such, they offer significant advantages from an industrial point-of-view. Nevertheless, the search for even better catalyst continues.

1.3.2.2. Enyne Metathesis

Although less-studied than alkene metatheses, enyne metatheses, especially intramolecular variants, have proven to be a powerful method for the construction of 1,3-dienes. This enyne reorganisation reaction involves the migration of the terminal alkylidene moiety from an alkene to an alkyne carbon and delivers a semi-cyclic diene product.[51] The first use of a ruthenium carbene complex in such a transformation was reported by Mori (**Scheme 1.20**).[52] This author proposed a mechanism in which the active metal alkylidene **A** first associates with the terminal alkyne **B**. This pathway would lead to two metallacyclobutenes, **Ia** and **Ib**, that collapse to the ring-opened metal complexes **IIa** and **IIb**, respectively. A ring-closing metathesis of the latter species would then deliver the 1,2-disubstituted product **IVa** and the 1,3-disubstituted product **IVb**. It was later noted that it was advantageous to effect the enyne-metathesis macrocyclisation under an atmosphere of ethylene.[53] Such observations suggested a second mechanistic pathway could be operational wherein the active metal alkylidene first reacts with the alkene moiety. The ensuing metal carbene intermediate **V** can then engage in two different modes of ring closure, namely either an *exo* or an *endo* one, to generate the metallacyclobutenes **VIa** and **VIb**, respectively. The alkylidene complexes derived from these intermediates would then react with ethylene to produce the same products, **IVa** and **IVb**, arising from the operation of the other pathway. Indeed, intermediate **VIIa** can participate in a cross metathesis reaction with another enyne substrate **B** to afford the *exo* product and, simultaneously, release the metal carbene **V**. A systematic study by Lee *et al.*[54]

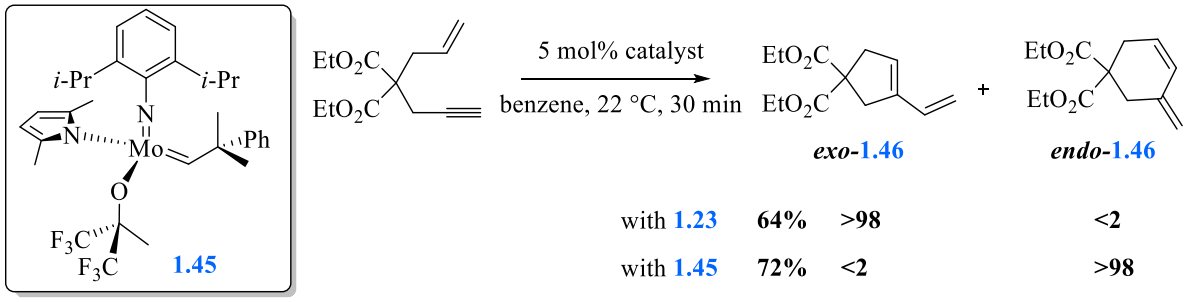
based on the analysis of literature data[55] revealed a correlation between the ring size and the *exo*/*endo* selectivity. The authors showed that the *exo*-products predominated for ring-closing metatheses of enynes leading to ten-membered and smaller rings, while *endo*-products were obtained preferentially when the formation of twelve-membered or larger rings was involved. For eleven-membered rings 1:1 mixtures of *exo* and *endo* products were observed.



Scheme 1.20. ***Two Possible Mechanistic Pathways Associated with Intramolecular Enyne Metatheses.***

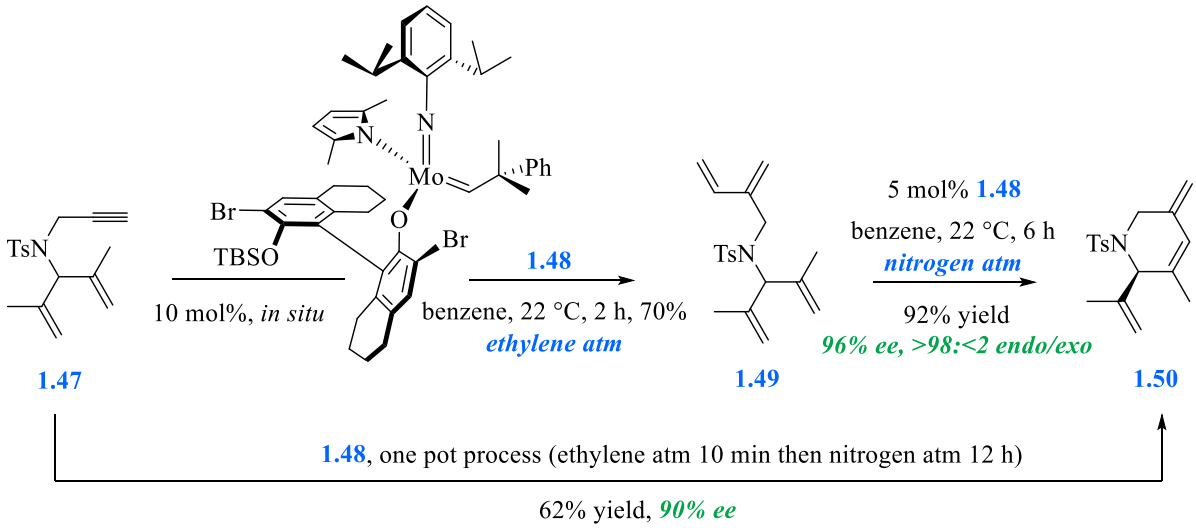
In 2009, Schrock and Hoveyda demonstrated the capacity of the stereogenic-at-Mo complex **1.45** (**Scheme 1.21**) to promote the formation of *endo*-products for five-, six-, and seven-membered rings.[56] The reaction is presumed to proceed through initial catalyst association with the alkyne and, given the preference of the sterically demanding molybdenum centre to form the metallacyclobutene **Ib**, thus leading to the selective formation of 1,3-

disubstituted and *endo*, ring-closed metathesis products. As illustrated, the formation of *exo*-**1.46** and *endo*-**1.46** could be controlled by appropriate choice of catalysts.



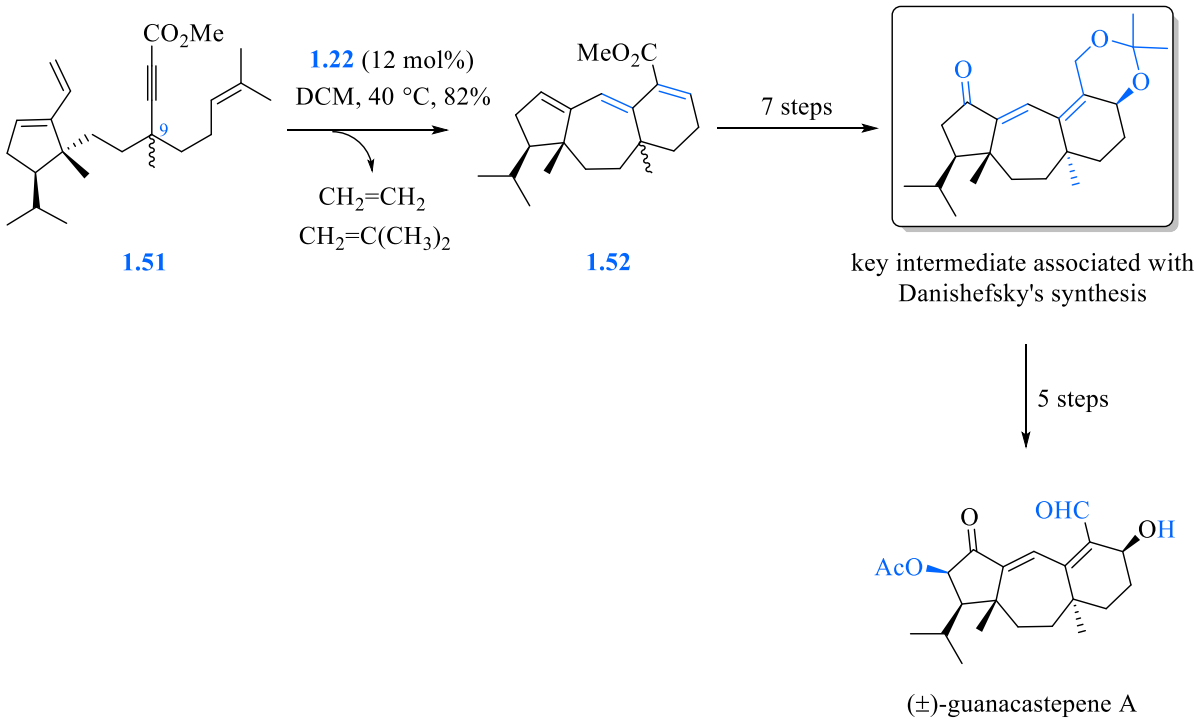
Scheme 1.21. ***Catalyst Control of the* Endo/Exo *Nature of the Ring-Closing Enyne Metathesis Reaction.***

Further investigations have led to several new catalysts that not only promote efficient *endo*-selective reactions but also provide enantiomerically enriched products. For example, the cyclic triene **1.50** (**Scheme 1.22**) is obtained in 96% ee by exposing compound **1.47** to the chiral catalyst **1.48**. The isolation of tetraene **1.49** in the course of this reaction revealed the first association of an alkylidene complex with the alkyne moiety that subsequently participates in enyne cross metathesis with ethylene. Exposure of compound **1.49** to catalyst **1.48** under a nitrogen atmosphere gave rise to product **1.50** in 92% yield. In fact, this two-step sequence could be performed as a one-pot process wherein treatment of substrate **1.47** with 10 mol% of catalyst **1.48** under ethylene atmosphere for ten minutes was followed by stirring for twelve hours after the ethylene atmosphere was removed. Under such conditions, product **1.50** was obtained in 62% yield and 90% ee.



Scheme 1.22. ***An Example of* endo*-Selective Ring-Closing Enyne Metathesis Reaction.***

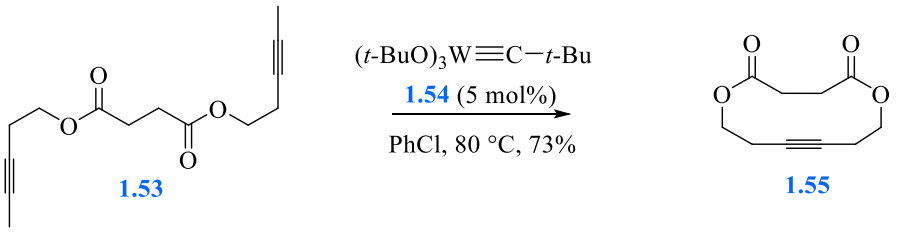
The use of enyne metatheses in cascade processes is one of the most powerful applications of this type of reaction. The metal carbenoid arising from the initial ring-closing metathesis reaction can participate in a second intramolecular event with an appropriately tethered olefin to generate another ring and a new metal carbene species. So, for example, during the course of the formation of key intermediate associated with Danishefsky's guanacastepene A synthesis[57a] (**Scheme 1.23**), Hanna's group[57b] reported that exposure of enyne **1.51** (as a 1:1 mixture of epimers at C9) to the second-generation Grubbs' catalyst (**1.22**) afforded the tricyclic core **1.52** in 82% yield. The selectivity of this cascade process was due to the programed initiation at the least hindered (substituted) alkene in precursor **1.51** which ensured the correct regiochemical outcome. Indeed, the initially formed metal carbene directed the first enyne ring-closing metathesis so as to generate the seven-membered ring and the co-produced metal carbene that participated in the second ring-closing metathesis with the more hindered alkene.[38b]



Scheme 1.23. ***Tandem Ring-Closing Metathesis Reaction Used in a Total Synthesis of Guanacastepene A.***

1.3.2.3. Alkyne Metathesis

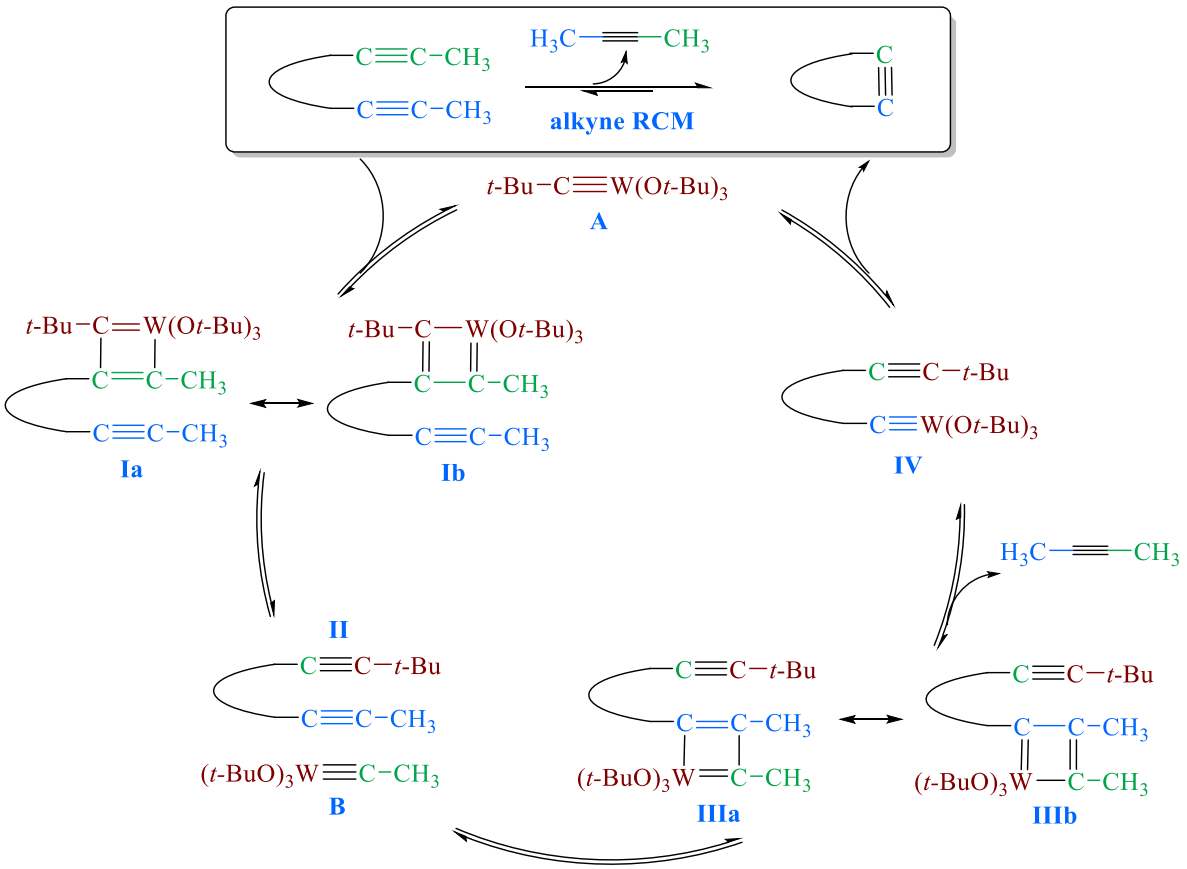
The first alkyne metathesis reaction was reported in 1968 by Penella and catalysed by a heterogeneous mixture of tungsten oxide and silica at very high temperatures (200-450 °C).[58] Following this observation, Mortreux and Blanchard reported that a combination of molybdenum hexacarbonyl and resorcinol was able to effect the disproportionation of *p*-tolylphenylacetylene to diphenylacetylene.[59] Ten years later, the report of the well-defined tungsten alkylidyne catalyst **1.54** by Schrock was considered as the major breakthrough in catalyst design.[60] Reactions involving terminal alkynes, however, suffered from catalyst deactivation and polymerisation. As such, this type of metathesis has found only rather limited application in organic synthesis. In 1998, the first ring-closing alkyne metathesis (**Scheme 1.24**) between two methyl-substituted alkyne moieties was reported by Fürstner[61] and heralded a new era for this process. So, treatment of diyne **1.53** with Schrock's catalyst (**1.54**) in chlorobenzene at 80 °C smoothly generated macrocycle **1.55** in 73% yield.



Scheme 1.24. ***First Example of an Alkyne Ring-Closing Metathesis***.

The favoured mechanism for alkyne ring-closing metatheses is shown in **Scheme 1.25** and follows the "logic" of the Chauvin cycle for alkene metathesis.[62] So, the catalytic cycle starts with the combining of the metal alkylidyne **A** and one of the methyl-capped alkyne units of the substrate *via* a [2+2]-cycloaddition reaction so as to form the metallacyclobutadiene **Ia** that is converted into isomer **Ib**. Cycloreversion of the latter complex releases intermediate **II** and another competent metal species **B**. The steric hindrance associated with substrate **II** directs the association of **B** to the remaining methyl-capped alkyne to deliver a second metallacyclobutadiene, **IIIa**, that itself isomerises to congener **IIIb** that, in turn, ruptures to give the metal-carbon triple bond complex **IV** and 2-butyne. In line with events proposed for the alkene ring-closing metathesis, the release of this volatile product (*viz* 2-butyne) is the driving force for the reaction. Finally, a [2+2]-cycloaddition reaction of intermediate **IV** and

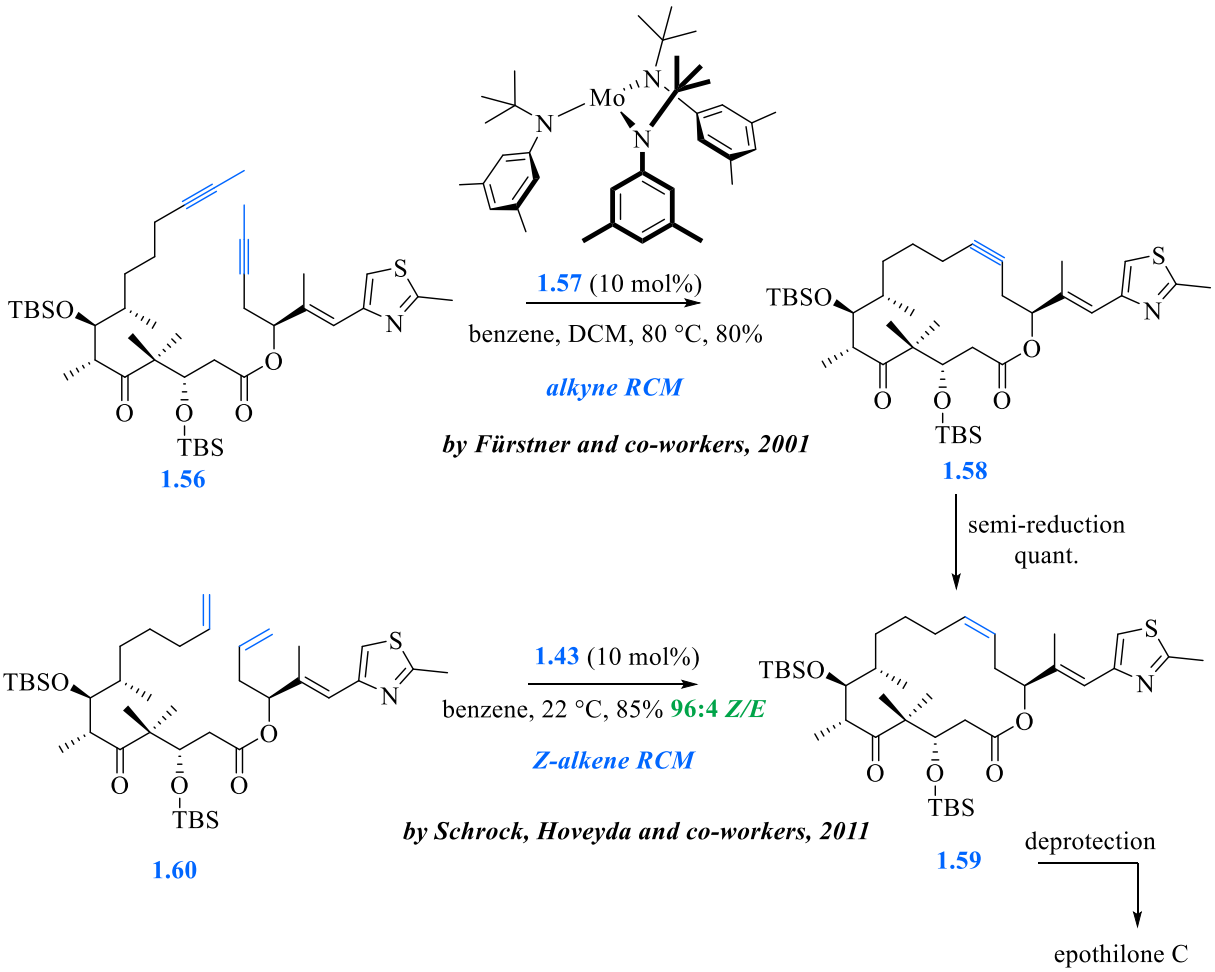
cycloreversion within the resulting adduct would deliver the product cycloalkyne and regenerate catalyst **A**.



Scheme 1.25. ***General Catalytic Cycle Associated with Alkyne Ring-Closing Metathesis reaction.***

The most interesting application of this transformation, however, was the stereoselective semi-reduction of the product cycloalkyne to generate either naturally occurring *E*- or *Z*-configured cycloalkenes. As already noted, alkene ring-closing metatheses usually provide an unpredictable and often uncontrollable mixture of geometrical isomers. This situation was highlighted in the first three syntheses of epothilones A and C by Nicolaou,[63] Danishefski,[64] and Schinzer[65] wherein the alkene metathesis was successfully exploited despite suffering from little or no selectivity for the required *Z*-isomer. Upon revisiting the issue, in 2001, Fürstner's group[66] reported the first stereoselective synthesis through alkyne ring-closing metathesis of diyne **1.56** (**Scheme 1.26**) followed by semi-reduction of the cycloalkyne product using hydrogen in the presence of Lindlar's catalyst so as to generate the *Z*-configured alkene **1.59**, which was itself converted into epothilone C by cleavage of the associated silyl ether. The 16-membered cycloalkyne was isolated in 80% yield upon exposure to molybdenum amido catalyst precursor **1.57** that was converted, *in situ*, into the active species through

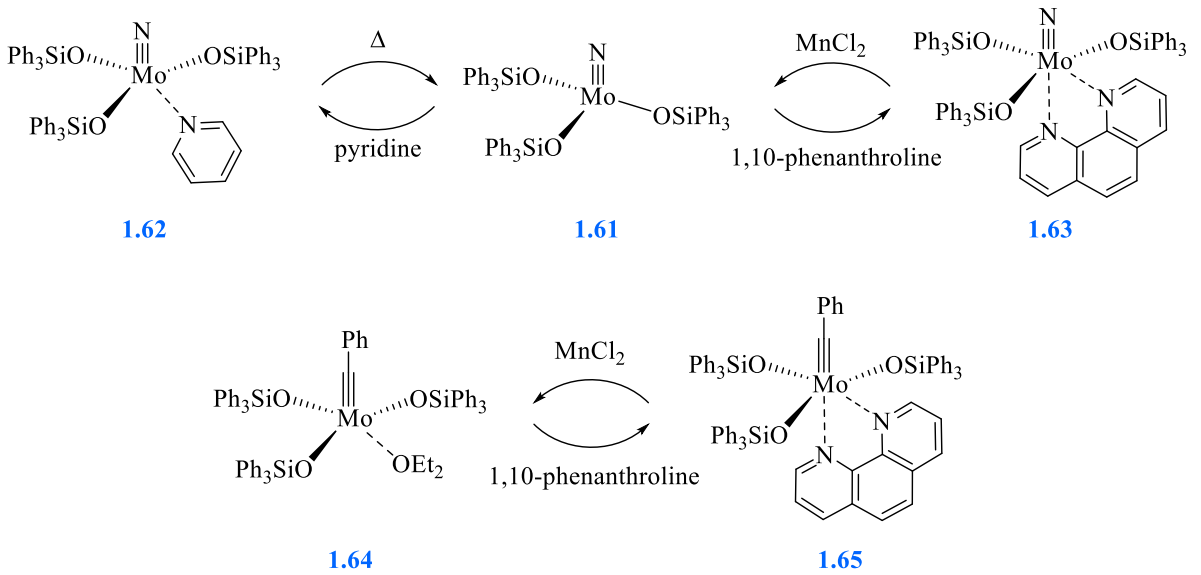
reaction with *gem*-dihalides, for example, dichloromethane.[67] Ten years later, Schrock and Hoveyda[49] were able to obtain macrolactone **1.59** in a highly *Z*-selective alkene ring-closing metathesis reaction (85% yield with a 96:4 *Z*/*E* ratio) by treating diene **1.60** with the tungsten-based catalyst **1.43**.



Scheme 1.26. ***Alkyne Ring-Closing Metathesis/Semi-Reduction and Z-Selective Alkene Ring-Closing Metathesis in the Syntheses of Epothilone C.***

The alkyne ring-closing metathesis/semi-reduction tactic developed by Fürstner was rapidly applied to the synthesis of various other natural products.[68] Although it might never reach the breadth of alkene metatheses, the potential of this reaction is significant. Therefore, it is important to note the recent development of more stable, reactive, and functional group tolerant catalysts. Although the Schrock alkylidyne **1.54** and the molybdenum complex **1.57** were found to be reactive and surprisingly functional group tolerant, they are very air and moisture sensitive. Inspired by the work of John *et al*,[69] that had focused on novel nitride molybdenum and tungsten complexes capable of generating active alkylidynes *in situ*, further investigations by Fürstner's group resulted in the identification of the highly active species

1.61 (**Scheme 1.27**), one that is compatible with many polar groups save for epoxides, aldehydes and acid chlorides [due to the reactions with the nitride residue of the catalyst].[70] Although this complex requires handling in an inert atmosphere, it can be generated by heating the corresponding pyridine adduct **1.62**, which is sufficiently stable to be weighed in air, and used at temperatures up to 80 °C. Inert atmosphere storage is, however, still required for catalyst **1.62** because of its eventual hydrolysis. Gratifyingly, replacement of the pyridine ligand with 1,10-phenanthroline provided an indefinitely air stable and crystalline pre-catalyst **1.63** that delivers, *in situ*, the reactive species on treatment with manganese chloride or related salts. At the present time, a molybdenum alkylidyne complex carrying ancillary silanolate ligands is considered the most effective catalyst. It is possible to choose between the air sensitive ether form **1.64**, which is superbly active and selective at ambient temperature, or the more robust phenanthroline adduct **1.65** (inert gas storage required), which can be activated by treatment with manganese chloride at 80 °C for thirty minutes. For example, by using 2 mol% of catalyst **1.64**, the product macrolactone **1.58** (**Scheme 1.26**) was obtained in 91% yield at room temperature and thus providing ready access to a key intermediate associated with a new route to epothilone C.[70]



1.62 **1.61** **1.63**

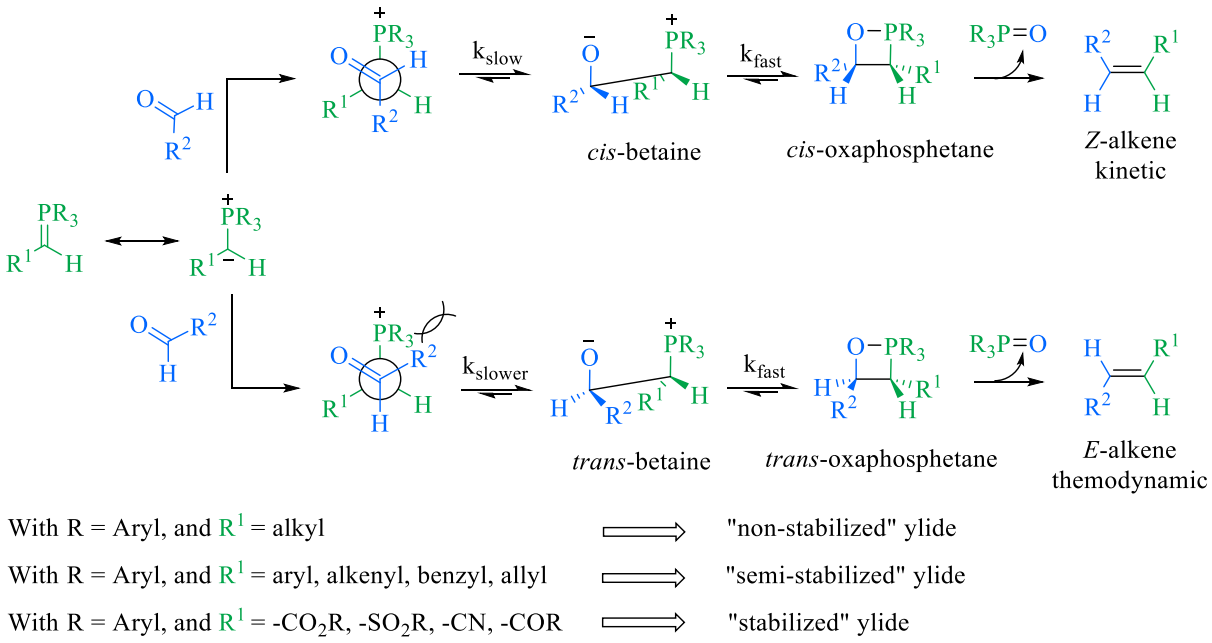
1.64 **1.65**

Scheme 1.27. ***Molybdenum Nitride/Alkylidyne Complexes with Ancillary Silanolate Ligands and their Precursors.***

1.3.3. Some Stereoselective Olefination Reactions

1.3.3.1. The Wittig Reaction

The "classic" Wittig reaction between a phosphorous ylide and an aldehyde or ketone to afford the corresponding alkene and phosphine oxide was first described in 1953.[71] Since then, it has become one of the most important methods for carbon-carbon bond formation. A number of investigations have sought to understand and control the *E*- and *Z*-stereoselectivity of such reactions. This has, in turn, led to diverse modifications.[72] The active species in this reaction is the phosphorous ylide, which is usually prepared from triphenylphosphine and a primary or secondary halide followed by deprotonation with a suitable base. The ylide chemoselectively and rapidly reacts with aldehydes and more slowly with ketones while the other carbonyl-containing functionalities such as esters, amides and acids *etc*. remain unaffected. Generally, there are two pathways by which the aldehyde can approach the ylide (in the rate limiting step) and so leading to either the *cis*- or *trans*-oxaphosphetanes that engage in a cycloreversion process to afford the corresponding *Z*- and *E*- alkenes, respectively (**Scheme 1.28**).



Scheme 1.28. ***General Mechanism for the Wittig Reaction.***

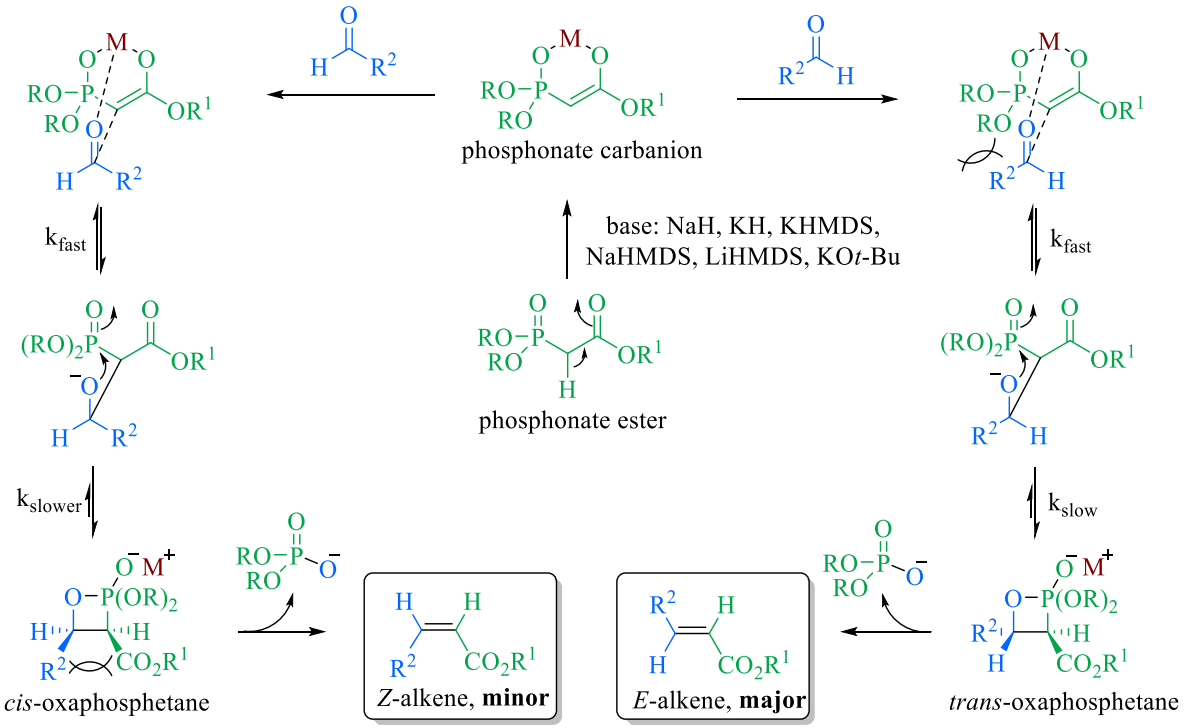
The *Z*-product is normally the kinetically favoured one, while the *E*-isomer, although initially suffering from steric clashes between the R^2 of the aldehyde and the triphenylphosphonium

group is favoured under thermodynamic conditions due to the formation of the more stable *trans*-oxaphosphetane. The selectivity of the Wittig reaction can be tuned through careful choice of the particular ylide and the solvent. Indeed, in polar aprotic solvents, the less reactive, stabilised ylides, formed by treatment with an alkali metal hydroxide, usually react with an aldehyde to afford *E*-alkenes under conditions of thermodynamic control. In contrast, when non-stabilised ylides are involved (and thus requiring the use of strong bases such as *n*-butyllithium for their formation) they react with either aldehydes or ketones to produce the corresponding *Z*-alkenes. Furthermore, the addition of lithium salts and a second equivalent of a strong base, such as an alkyl lithium, followed by quenching with a proton source under kinetic control facilitates the formation of the *E*-alkene from non-stabilised ylides. This important procedure is known as Schlosser's modification of the Wittig reaction.[73]

1.3.3.2. The Horner-Wadsworth-Emmons Reaction

The olefination reaction involving a phosphonate stabilised carbanion and an aldehyde/ketone is referred to as the Horner-Wadsworth-Emmons (HWE) reaction.[74] The starting alkyl phosphonates are easily prepared by using a Michaelis-Arbuzov reaction between a trialkylphosphite and an organic halide. The phosphonate carbanions generated by deprotonation of the resulting phosphonates are more nucleophilic than the corresponding phosphorous ylides and produce water-soluble dialkyl phosphates as by-products that are, therefore, much easier to remove than the triphenylphosphine oxide by-product produced in the Wittig reaction. Generally, this HWE olefination reaction proceeds with high *E*-selectivity when stabilizing groups are attached to the phosphonate-substituted carbon (COO^-, CO_2R, CN, aryl, vinyl, SO_2R, OR, NR_2). The non-stabilised phosphonates result in low yields of the desired products due to the formation of β-hydroxyphosphonates.[75] The commonly accepted mechanism for such reactions is depicted in **Scheme 1.29**. Thus, as with the Wittig reaction, there are two possible modes of the addition of the carbanion to the carbonyl group although this is not the rate limiting step due to the higher activity of phosphonate carbanions compared to phosphorous ylides (this is rate limiting step in Wittig reaction). The *cis*- and *trans*-oxaphosphetanes are in equilibrium with one another and, as a result, the elimination reaction normally provides the *E*-alkene as the major product. However, high *Z*-selectivity can be achieved using the Still-Gennari modification that involves a stabilised bis(trifluoroalkyl)-phosphonate with a well-dissociated base such as potassium bis(trimethylsilyl)amide.[76]

Subsequently, Masamune and Roush[77] reported a protocol employing both lithium chloride and an amine base that proceeds at ambient temperature and thus allows for the olefination of relatively base-sensitive substrates. The reaction also proceeds with high *E*-selectivity when stabilised phosphonates (*viz*. those carrying electron withdrawing groups at the phosphonate substituted-carbon) are used. Relevant examples from the author's own work are presented in Chapter Four.



Scheme 1.29. ***Mechanism for the Horner-Wadsworth-Emmons Reaction.***

1.3.3.3. The Julia Reaction

The Julia olefination reaction involves the condensation of an aryl sulfone with an aldehyde or ketone. The initial protocol, reported in 1973, involved a three-step sequence starting with the addition of an α-metalated phenylsulfone to a carbonyl group, followed by trapping of the resulting β-alkoxysulfone as an acetate, benzylate, mesylate or tosylate and, finally, a reductive elimination of the resulting β-acyloxysulfone, or equivalent, with a one-

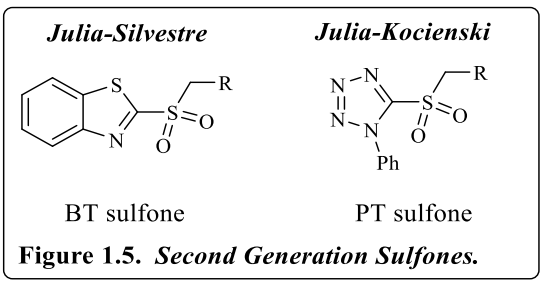
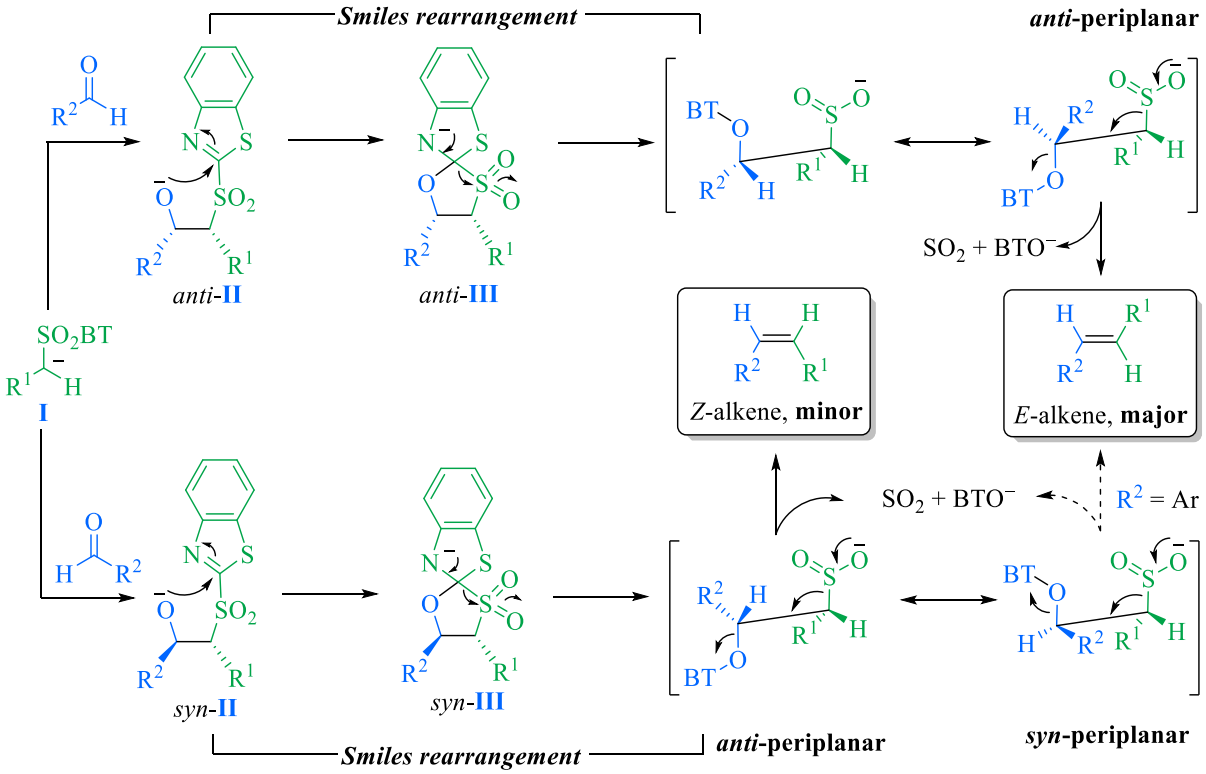


Figure 1.5. ***Second Generation Sulfones.***

electron donor such as samarium iodide to yield the alkene.[78] Although the reaction proceeds with high *E*-selectivity, the classic procedure is quite a tedious one. Second generation variants involving a heteroarylsulfone, benzothiazoyl (BT)[79] or phenyltetrazoyl (PT)[80] sulfone (**Figure 1.5**) provide a more convenient process. Indeed, they allow for a one-pot reaction that proceeds *via* an *in situ* reductive elimination reaction involving a Smiles rearrangement. The widely accepted mechanism involving the BT-sulfone is shown in **Scheme 1.30**.



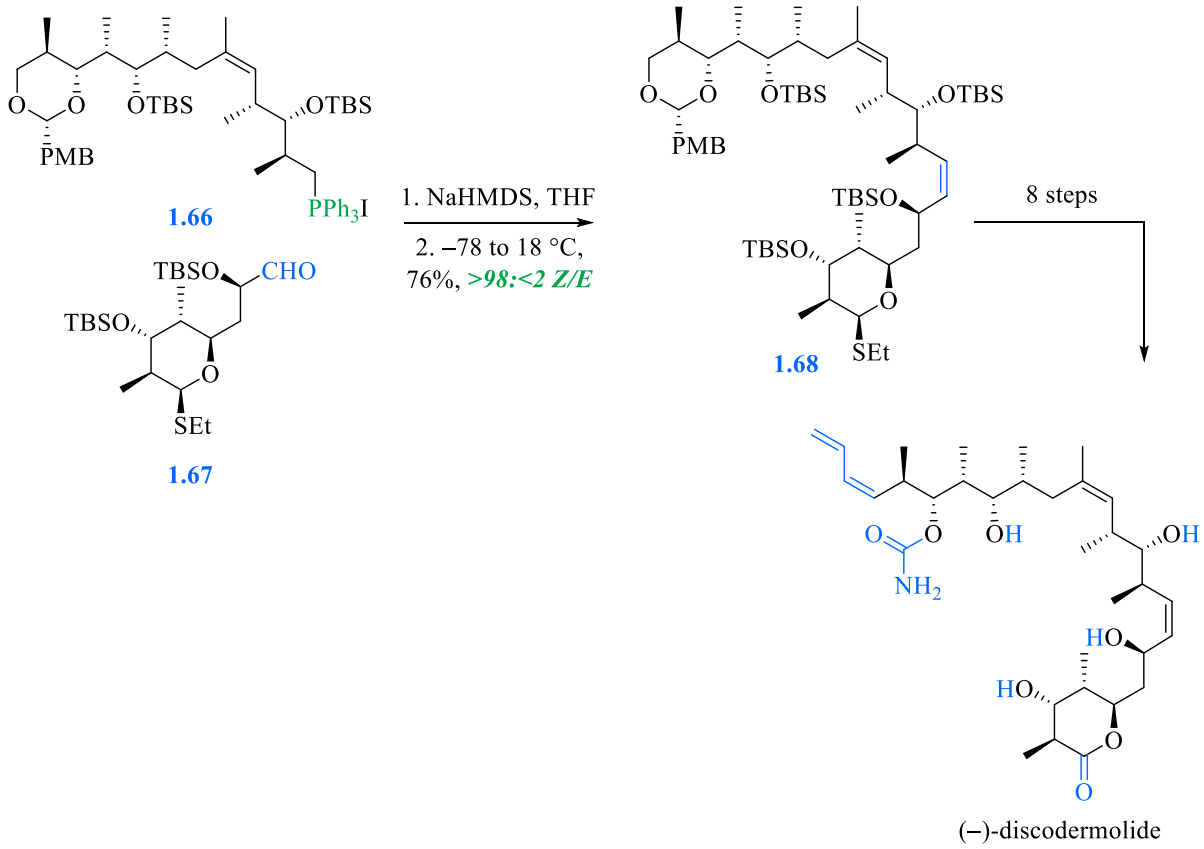
Scheme 1.30. ***General Accepted Mechanism for Julia Olefination Reaction.***

There are two possible modes of addition of carbanion **I** to the carbonyl-containing substrate and thus affording either or both of the *anti*-**II** and *syn*-**II** adducts, which then undergo a series of transformations, including Smiles rearrangement and elimination, to release sulphur dioxide and a metal derivative of 1,3-benzothiazol-2-one. Concomitant alkene production also takes place. The elimination reaction is presumed to occur through a concerted, *anti*-periplanar process to give the *E*- or *Z*-olefin from the corresponding *anti*- or *syn*-sulfinate, respectively. Generally, the stereochemical outcome is highly dependent on the nature of the reactants as well as the solvent and the counter-ion to the base. Although reactions with aliphatic aldehydes furnish the corresponding alkenes with almost no stereochemical bias, aromatic aldehydes show some *E*-selectivity. Robiette and Pospíšil[81] demonstrated that with aromatic aldehydes *syn*-periplanar elimination reaction occurred preferentially within the *syn*-sulfinate to afford

the *E*-olefin. Kocienski also reported the influence of the solvent and the base on the stereoselectivity of the reaction, most particularly in those variants involving a large counter-ion (potassium) in a polar solvent (1,2-dimethoxyethane). In such circumtances, the *E*-alkene product predominates.[80]

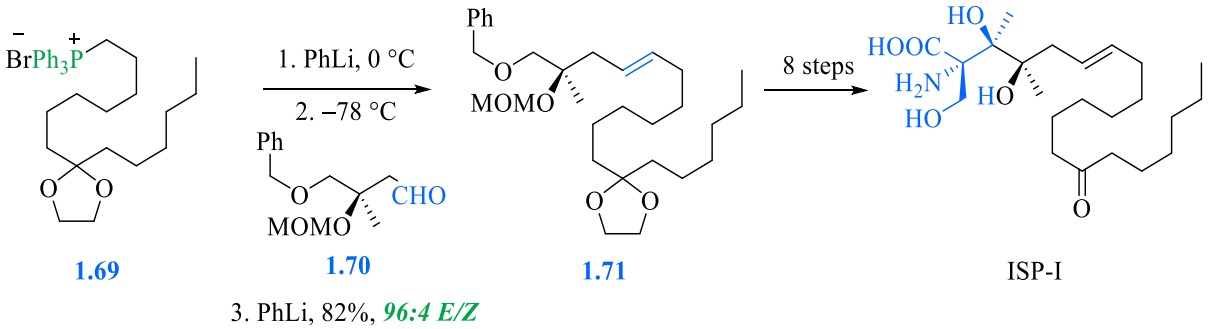
1.3.3.4. Applications of Olefination Reactions to the Syntheses of Natural Products

Olefinations have been used extensively as early steps in preparing many compounds for natural product synthesis. A proper choice among the different types of olefination reactions, in addition to proper substrate design, can provide the required product with high stereoselectivity. For example, in their synthesis of unnatural or (−)-discodermolide, Smith and co-workers were able to effect a highly *Z*-selective Wittig reaction between phosphonium salt **1.66** and the hindered aldehyde **1.67** (**Scheme 1.31**).[82] Product **1.68** was thus obtained in 76% yield (with 98:2 ratio of *Z*- and *E*-isomers) when sodium bis(trimethylsilyl)amide was used as a base.



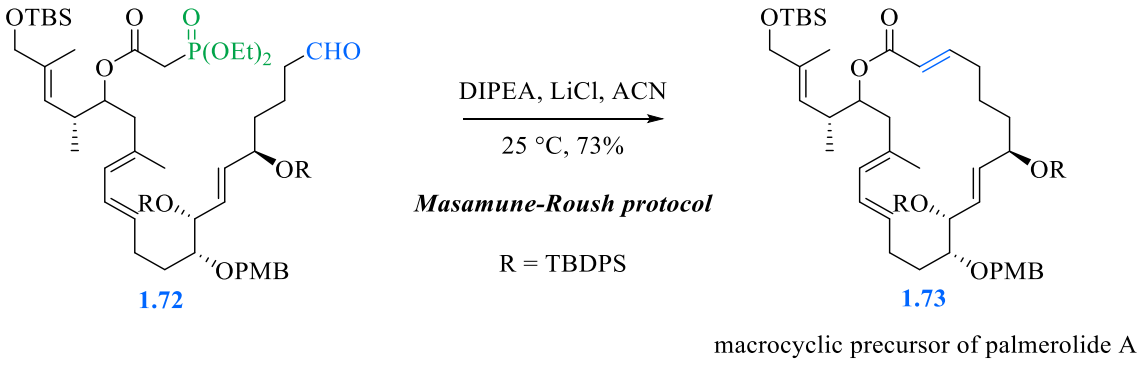
Scheme 1.31. ***Highly Z-Selective Wittig Reaction in a Synthesis of (−)-Discodermolide.***

In contrast, *en route* to establishing an asymmetric total synthesis of ISP-I, as a potent immunosuppressive compound (**Scheme 1.32**), [83] on applying the Schlosser modification of the Wittig reaction to substrates **1.69** and **1.70** in the presence of phenyllithium, compound **1.71** was obtained in 82% yield with high *E*-selectivity (with 96:4 ratio of *E*- and *Z*- isomers)



Scheme 1.32. ***Use of a Highly* E-*Selective Wittig-Schlosser Modification Reaction in a Synthesis of ISP-I.***

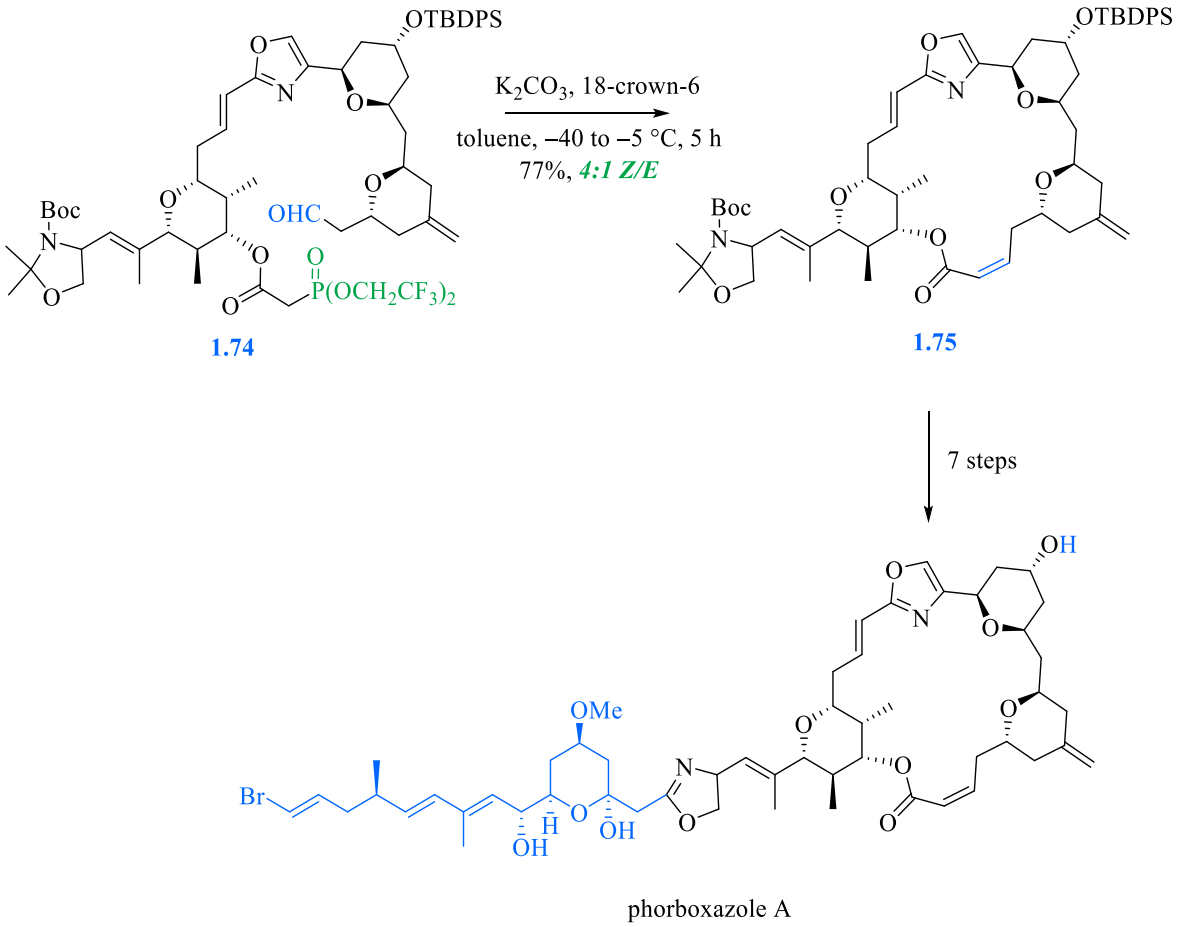
In 2007, Nicolaou and co-workers[84] reported a highly convergent and flexible strategy for the construction of the key precursor, **1.73**, associated with a synthesis of palmerolide A (**Scheme 1.33**). Under the appropriate conditions (namely those involved in applying the Masamune-Roush protocol) the desired *E*-alkene was obtained from substrate **1.72** in 73% yield.



Scheme 1.33. ***The Highly* E-*Selective HWE Reaction with Massamune-Rouch Protocol for the Macrocylisation Step in a Synthesis of Palmerolide A.***

In contrast, in the synthesis of phorboxazole reported by Forsyth,[85] an intramolecular Horner-Wadsworth-Emmons (involving the Still-Gennari modification) was employed using bis(trifluoroethoxy)phosphonate-aldehyde **1.74** as substrate (**Scheme 1.34**) and the desired intermediate macrolactone **1.75** was obtained in 77% yield (with 4:1 ratio of *Z*- and *E*-isomers)

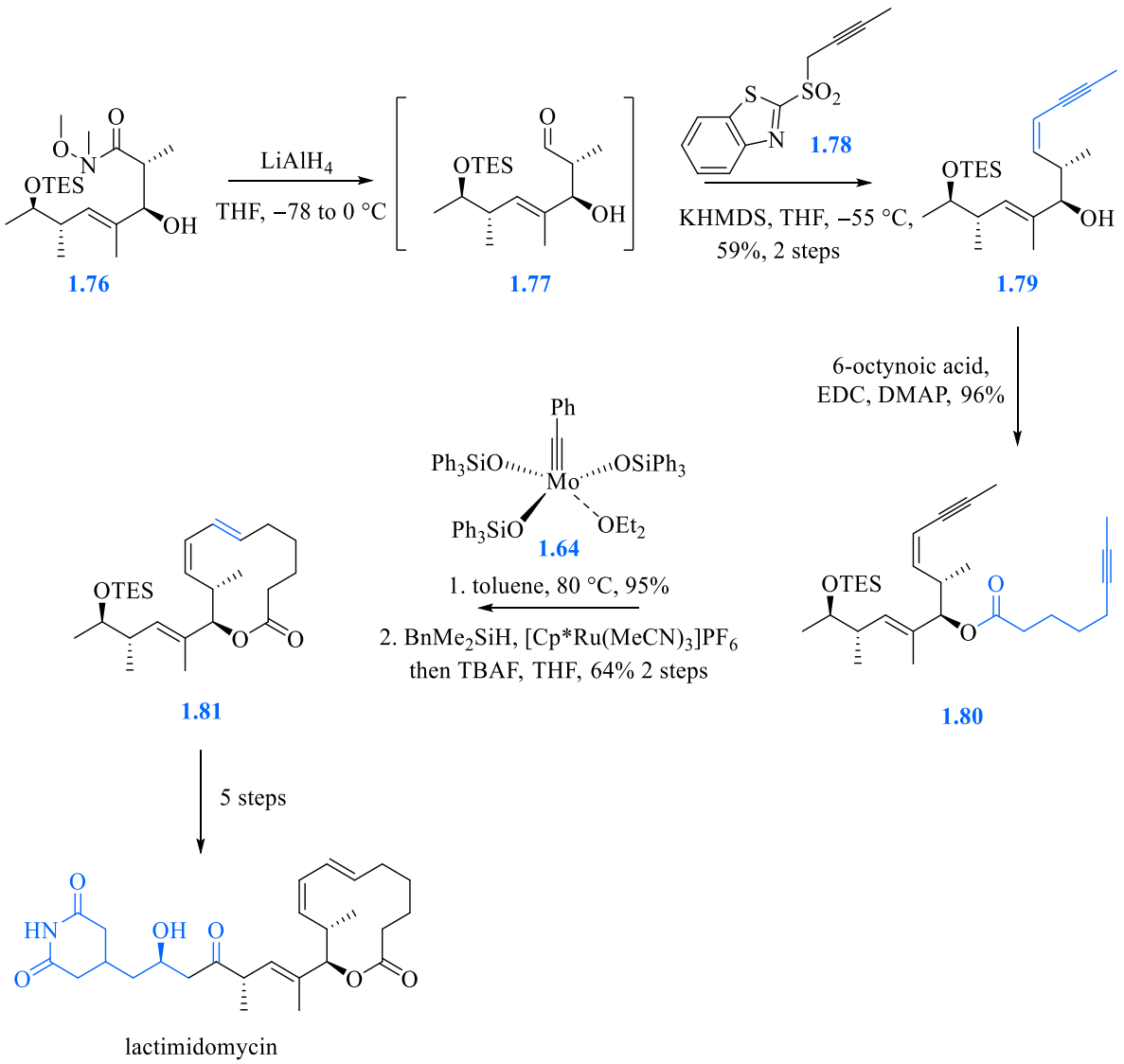
upon exposure to potassium carbonate and 18-crown-6 in toluene for five hours at −40 to −5 °C.



Scheme 1.34. ***Z-Selective HWE Reaction (Still-Gennari Modification) Used in Forsyth's Synthesis of Phorboxazole A.***

In 2006, Bonini[86] reported using a benzothiazol TMS-propargylic sulfone in a one-pot Julia olefination reaction to effect a predominantly *Z*-selective process when a variety of aliphatic and aromatic aldehydes was employed. The tactic was then applied in the synthesis of lactimidomycin by Fürstner[87] wherein reduction of amide **1.76** with lithium aluminum hydride followed by reaction of the product aldehyde with sulfone **1.78** under the one-pot Julia olefination reaction conditions gave the product *Z*-**1.79** in isomerically pure form and in 59% yield over the two steps (**Scheme 1.35**). Esterification of this last compound with 2-octynoic acid provided the ester diyne **1.80** (in high yield), and this was then subjected to alkyne ring-closing metathesis and so-forming the cyclic enyne in 95% yield. Selective semi-reduction of this cycloalkyne using a *trans*-hydrosilylation/protodesilylation protocol then delivered the required *E*,*Z*-configured diene **1.81**, a key intermediate associated with a synthesis of

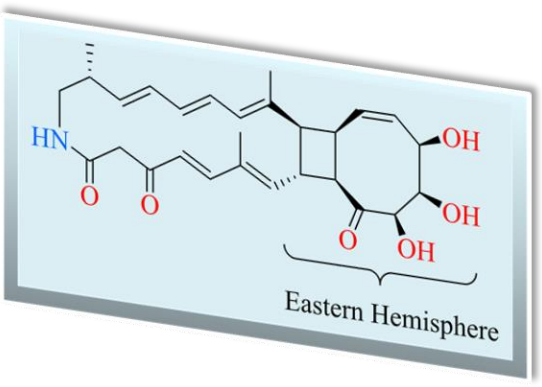
lactimidomycin. This one-pot Julia olefination and alkyne ring-closing metathesis strategy served as an inspiration for the author's pursuit of a tripartilactam synthesis by the pathway detailed in Chapter Four.



Scheme 1.35. ***Application of the Z-Selective Julia Reaction to a Synthesis of Lactimidomycin.***

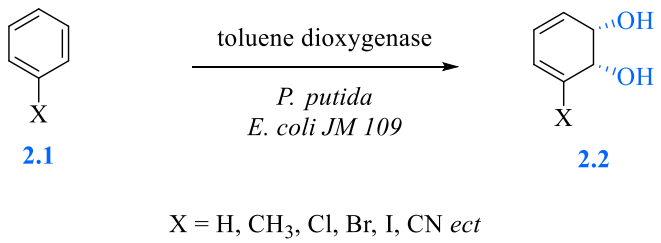
2. CHAPTER TWO

Synthetic Approaches to the Eastern Hemisphere of Tripartilactam



2.1. cis-*1,2-Dihydrocatechols*

Enzymes have been exploited in the production, through fermentation, of food and beverages such as cheese, bread, vinegar, soy sauce, beer, and wine for more than a thousand years. The first modern enzyme study was conducted around 1833 by Payen and Persoz[88] and involved the isolation of a substance from malt extract that has since been shown to be a mixture of lipases. In 1857 the reducing nature of yeast was first noted by Pasteur during the production of alcohol by fermentation then in 1874, by Duma, during the conversion of sulfur to hydrosulfide and by Lintner and von Liebig in 1911 during the reduction of furfural to furfuryl alcohol.[88] Today, biocatalysis provides a remarkable means for conducting chemical syntheses, especially in an enantioselective manner. These capacities were recognised some one hundred years ago. In 1908, for example, Störmer *et al.*[88] established that aromatic compounds such as toluene and xylene could be consumed by *Bacillus hexacarovorum*. Then, in 1968 Gibson *et al.*[89] described the enzymatic dihydroxylation of *p*-chlorotoluene to the corresponding *cis*-dihydrocatechol by toluene dioxygenase, an enzyme obtained from the soil bacterium *Pseudomonas putida* F1. Further studies established that the lack of catechol dehydrogenase expression in Gibson's chemically-induced mutant *Pseudomonas putida* 39D[90] results in the accumulation of the *cis*-1,2-dihydrocatechol in the fermentation broth. The recombinant strain of *Escherichia coli* JM 109 (pDTG601), which harbors encoding genes for toluene dioxygenase, is now the most widely used biocatalyst for this purpose and allows for the production, in high enantiomeric purity (> 98% ee), of up to 35 g of metabolite **2.2** per litre of fermentation broth (**Scheme 2.1**).[91]



Scheme 2.1. ***Generation of* cis-*1,2-Dihydrocatechol Derivatives through the Biotransformation of the Corresponding Arene***.

cis-1,2-Dihydrocatechols have been recognised as versatile building blocks for the enantioselective synthesis of a range of complex and homochiral natural products. Several groups have highlighted the utility of these metabolites as seen, for example, in Taylor's polyphenylene[92] synthesis in 1983, Ley's synthesis of racemic (±)-pinitol[93] in 1987, Hudlicky's

enantioselective syntheses of prostaglandin $E_{2\alpha}$[94] ($PGE_{2\alpha}$) in 1988, zeylena[95] in 1989 and specionin[96] in 1992 (**Figure 2.1**).

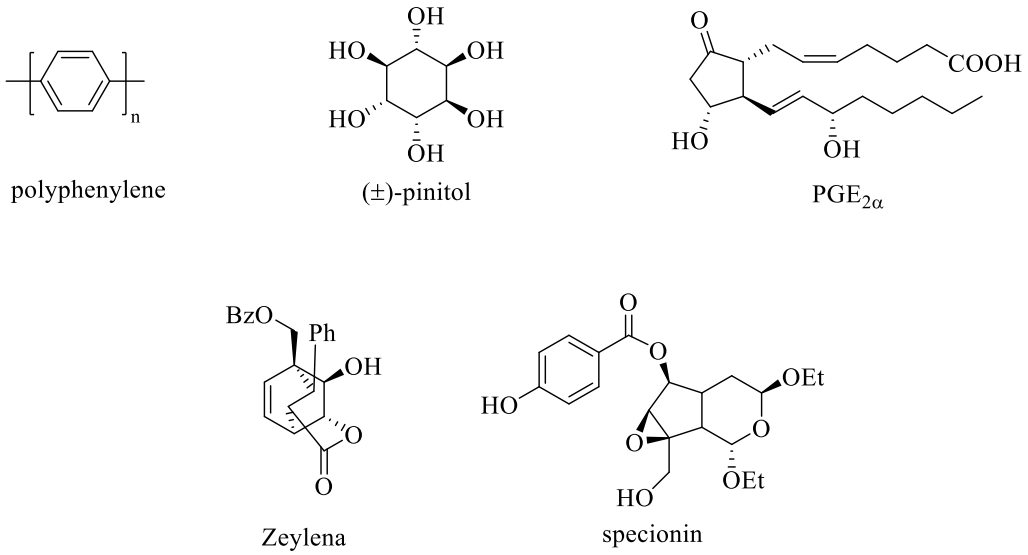


Figure 2.1. ***Early Examples of Compounds Prepared from Enzymatically-Derived* cis-*1,2-Dihydrocatechols.***

The novel combination of functionalities and reactive sites associated with the *cis*-1,2-dihydrocatechols have been exploited in the Banwell group over the years to prepare a variety of target compounds (**Figure 2.2**). Among the notable functionalities associated with these compounds, the 1,3-diene unit often readily participates in intermolecular Diels-Alder cycloaddition reactions to deliver enantiomerically pure bicyclo[2.2.2]octenes that can, for example, be elaborated into linear triquinanes such as (+)-connatusin B[97] or the non-natural or (−)-enantiomer of hirsutene.[98] In the case of the halogenated *cis*-1,2-dihydrocatechols, the more electron-rich (non-halogenated) double bond can be selectively converted, *via* electrophilic addition process, into the corresponding bromohydrin and this then engaged in a 3-*exo*-tet cyclisation reaction, or a vinylogous variant, to afford a single epoxide, a process exploited during the course of the formation of (+)-hexacyclinol,[99] an inhibitor of *Plasmodium falciparum* (and thus a possible lead compound for the development of new antimalarial drugs). When the halogenated double bond is oxidatively cleaved by treatment with ozone, then various open-chain compounds are obtained, as highlighted in the total synthesis of (−)-cladospolide A.[100] These halogenated systems can also engage in palladium(0)-catalysed cross-coupling reactions with organometallic species or participate in transmetallation process that can then followed by halide couplings. The successful completion of the total synthesis of (−)-platencin[101] provides an illustrative example in which a Negishi cross-coupling reaction then a thermally-promoted and intramolecular Diels-Alder (IMDA) reaction were performed to

deliver the tricyclic framework of this important new antibiotic. When 3-chloro-*cis*-1,2-dihydrocatechol (**2.1**, X = Cl) was employed as the starting material, it was possible to accomplish the first total synthesis of the alkaloid (+)-nangustine[102] using, as a pivotal step, an unusual radical addition-elimination process.

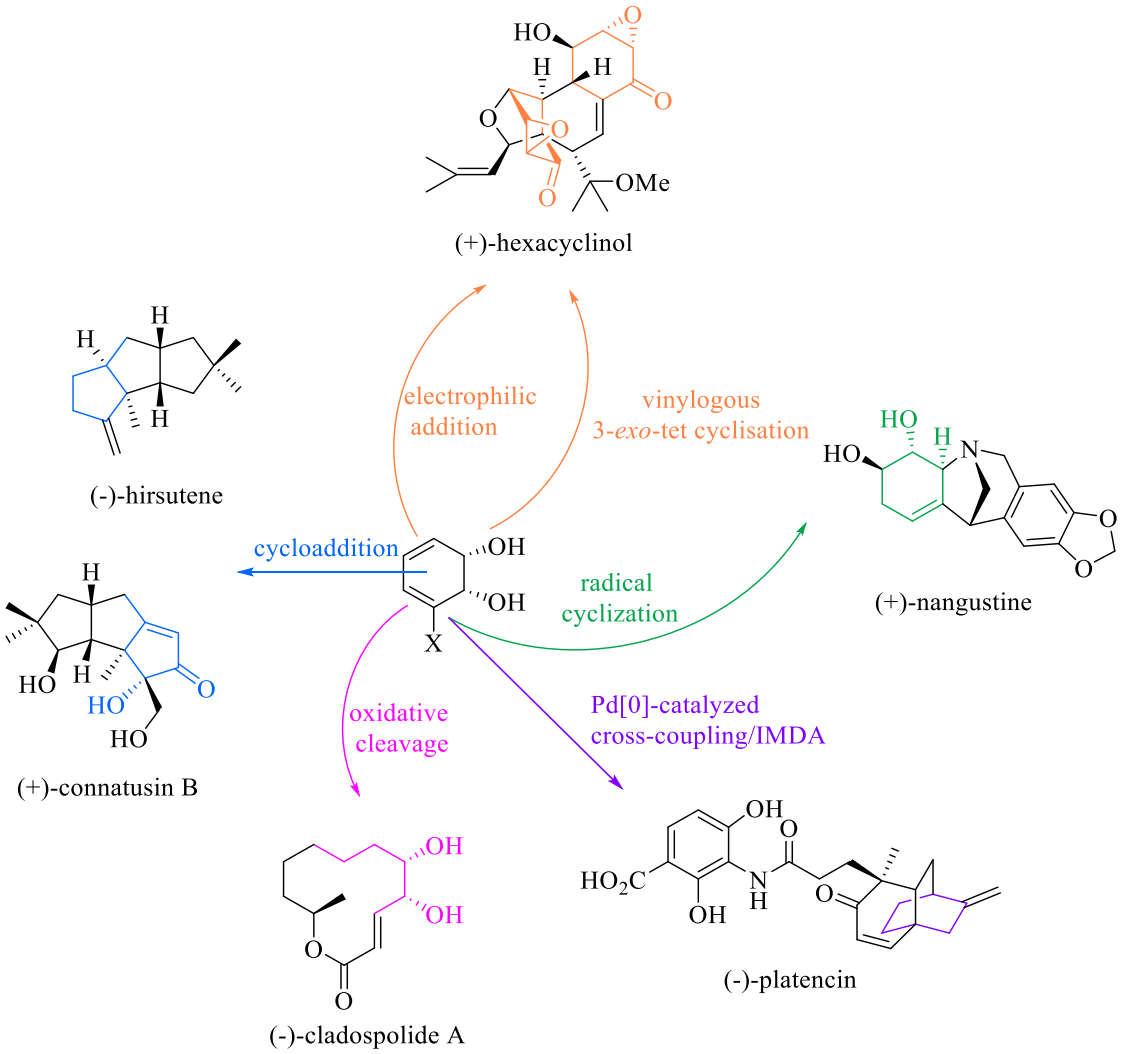


Figure 2.2. ***Selective Manipulations of the* cis-*1,2-Dihydrocatechols Leading to Natural Products Undertaken in the Banwell Group.***

On the basis of such examples, it was envisioned that 3-chloro-*cis*-1,2-dihydrocatechol could be used as an effective starting material in developing approaches to the synthesis of the Eastern Hemisphere of tripartilactam.

2.2. Synthetic Strategy Leading to a Substructure of ent-*Tripartilactam*

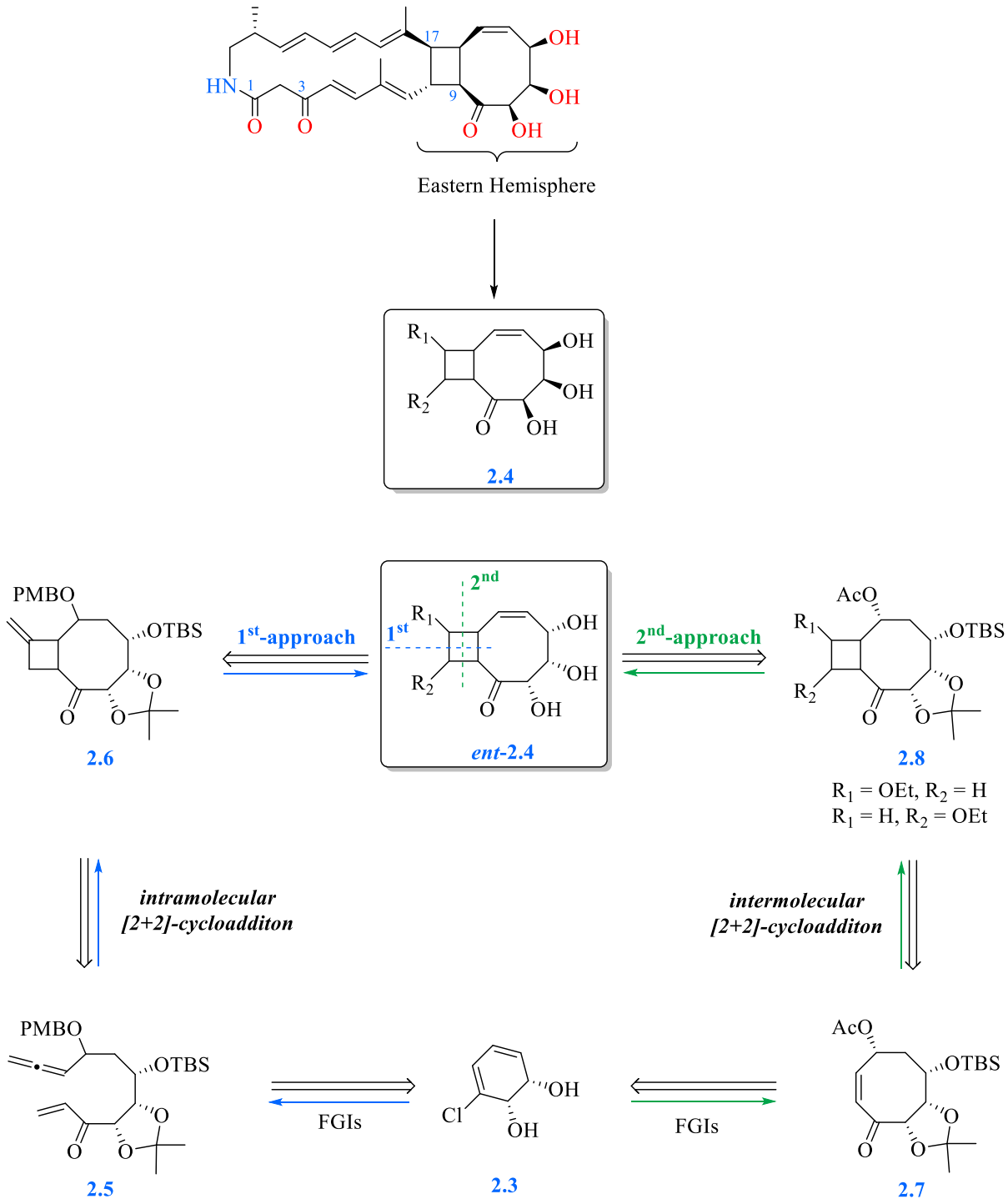
The synthesis of highly functionalised eight-membered carbocycles is known to be challenging owing to strain induced by transannular interactions.[103] An even more challenging objective, then, would be the assembly of an eight-membered ring fused to a cyclobutane as encountered in the Eastern Hemisphere of tripartilactam. Thus, the author's first efforts in this area focused on the synthesis of the chiral polyoxygenated bicyclo[6.2.0]decane **2.4**. The retrosynthetic plan shown in **Scheme 2.2** highlights two distinct approaches, both of which exploit the enantiomerically pure 3-chloro-*cis*-1,2-dihydrocatechol **2.3** as the starting material. The use of this readily available compound in the reaction sequence would lead to the optical antipodes of the relevant substructures, namely ***ent*-2.4**, in the first instance. However, since the enantiomer of compound **2.3** is also available any successful synthetic sequence automatically allows for access to the equivalent "natural" enantiomeric forms of the relevant compounds.

In the first approach, an intramolecular [2+2]-cycloaddition reaction between a terminal allene and an enone as embodied in compound **2.5** was expected to deliver adduct **2.6** in which the associated eight- and four-membered rings would have been assembled in a biomimetic fashion through simultaneous formation of the C8–C17 and C9–C16 bonds. The choice of an allene moiety was inspired by the recently reported approaches to the synthesis of various cyclobutane-containing compounds,[104] most notably bielschowskysin.[105] Although, according to the Woodward-Hoffmann rules, [2+2]-cycloaddition reactions of allenes are "forbidden" under thermal conditions, these processes have been effected both thermally and photochemically. Diradical intermediates are presumed to be involved. More recently, transition metal catalysts have been employed for the same purpose.[105] In addition, an intramolecular process could be more effective in terms of providing a capacity to control the regio- and/or stereo-selectivities of these reactions. In this approach the tether was designed to include an acetonide and a bulky TBS-ether protecting group on the basis that these would favourably influence the entropics of the process.

In the contrasting second approach, it was envisaged that an intermolecular [2+2]-cycloaddition reaction between cyclooctenone **2.7** and a suitable alkene would allow for the formation of the requisite four-membered ring as embodied within adduct **2.8**. The key eight-membered ring-containing compound **2.7** could be constructed using a ring closing metathesis reaction as the pivotal step.[106] Once again, the formation of this challenging medium-sized ring

would be assisted by the presence of both the acetonide and a bulky TBS-ether protecting groups.

The outcomes of the relevant sets of studies are presented in the following sections.

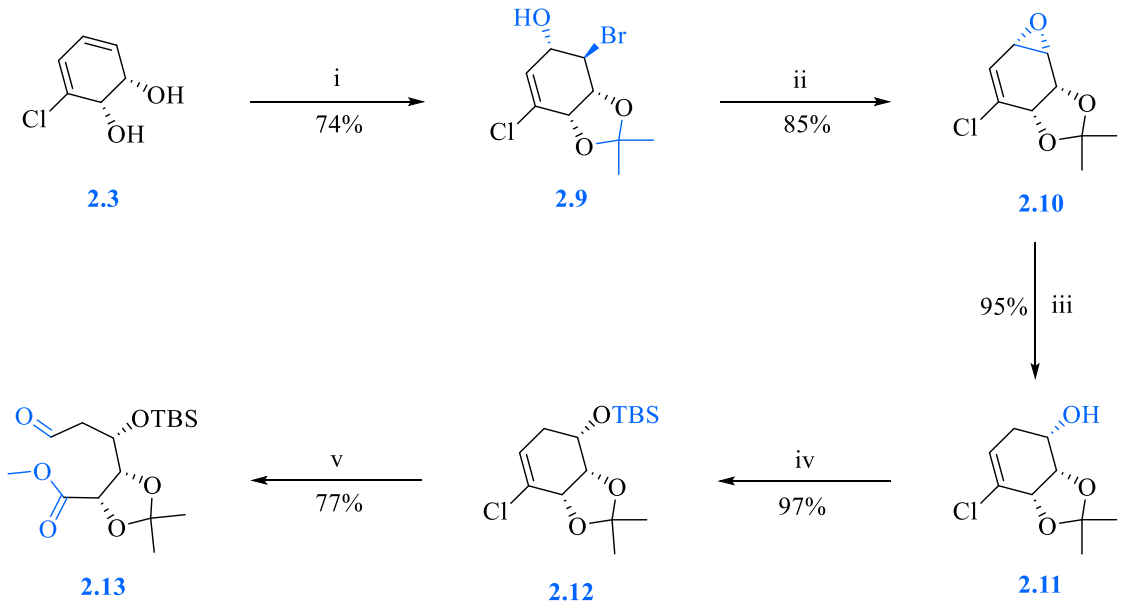


Scheme 2.2. ***Synthetic Approaches to the Eastern Hemisphere of* ent-*Tripartilactam***.

2.3. Exploring an Intramolecular [2+2]-Cycloaddition Approach

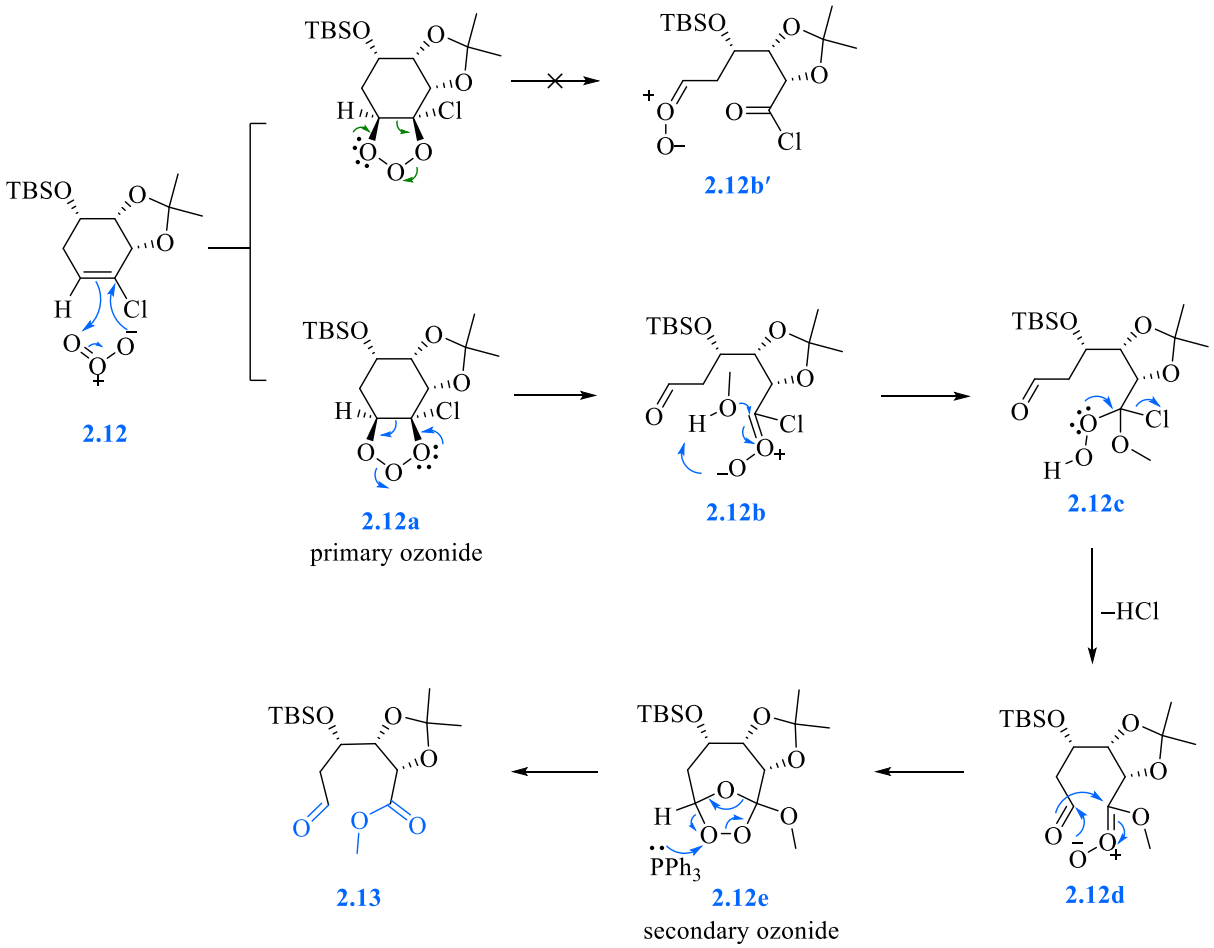
2.3.1. Preparation of an Allene Precursor

In order to investigate the possibility of performing an intramolecular [2+2]-cycloaddition reaction as the means for obtaining the bicyclo[6.2.0]decane moiety associated with the Eastern Hemisphere of tripartilactam, the necessary substrates were prepared as delineated in **Schemes 2.3**–**2.5** shown immediately below. First, 3-chloro-*cis*-1,2-dihydrocatechol **2.3** was treated (**Scheme 2.3**) with *N*-bromosuccinimide in aqueous tetrahydrofuran and the resulting bromotriol converted into the corresponding acetonide **2.9**[107] (74% from **2.3**) by treating it with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid. Reaction of bromohydrin **2.9** thus formed with sodium hydride then provided epoxide **2.10**[107] in 85% yield. Regioselective reductive cleavage of this epoxide using di-*iso*-butylaluminium hydride (DIBAl-H), wherein hydride added to the allylic carbon, afforded the homoallylic alcohol **2.11** (95%) as a crystalline solid, the structure of which was secured by single-crystal X-ray analysis (**Figure 2.3**). Protection of this alcohol as the corresponding TBS-ether **2.12** (using *tert*-butyldimethylsilyl chloride and imidazole, 97%) and submission of the latter to oxidative cleavage through exposure to ozone in the presence of methanol then reductive work-up (with triphenylphosphine) provided the ω-oxo-ester **2.13** in 77% yield.



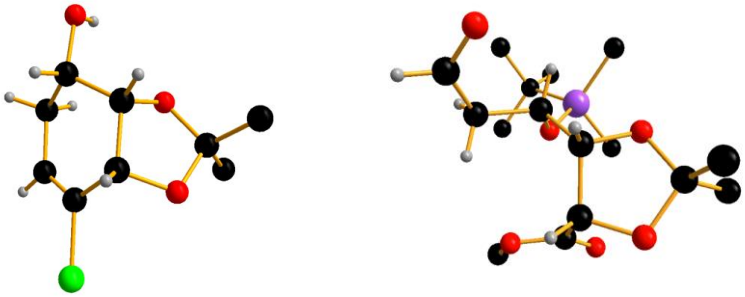
Scheme 2.3. ***Reagents and Conditions*** (i) a) NBS, THF/H_2O (4:1 *v*/*v*), 0 to 18 °C, 4 h; b) $(MeO)_2CMe_2$, *p*-TsOH, THF, 18 °C , 2 h; (ii) NaH, THF, 0 to 18 °C, 2 h; (iii) DIBAl-H, Et_2O, −40 to 0 °C, 3 h; (iv) TBS-Cl, imidazole, DMF, 18 °C, 4 h; (v) O_3, pyridine, DCM/MeOH (4:1 *v*/*v*) then PPh_3, 18 °C, 2 h.

The manner in which the ozonolytic cleavage of unsaturated compounds proceeds was originally suggested by Criegee[108] and involves three discrete steps. In the case of compound **2.13**, 1,3-dipolar cycloaddition of ozone to the double bond (**Scheme 2.4**) results in the primary ozonide (molozonide) **2.12a**. Due to the presence of the chlorine atom, the fragmentation of the molozonide probably occurs through the indicated pathway to give carbonyl oxide **2.12b**. In the presence of methanol, this last species reacts to give hyperoxide **2.12c** and elimination of the elements of hydrochloric acid from this then gives intermediate **2.12d**. An intramolecular 1,3-dipolar cycloaddition reaction of the carbonyl oxide moiety to the tethered aldehyde then affords the secondary ozonide **2.12e**. Finally, on treatment with triphenylphosphine this ozonide fragments to give the observed ω-oxo-ester **2.13**.



Scheme 2.4. ***Reaction Pathway for the Ozonolytic Cleavage of Chlorocyclohexene 2.12 to give Product 2.13.***

A single-crystal X-ray analysis of ω-oxo-ester **2.13** served to confirm the assigned structure. The derived ORTEP is shown in **Figure 2.3**.



2.11 **2.13**

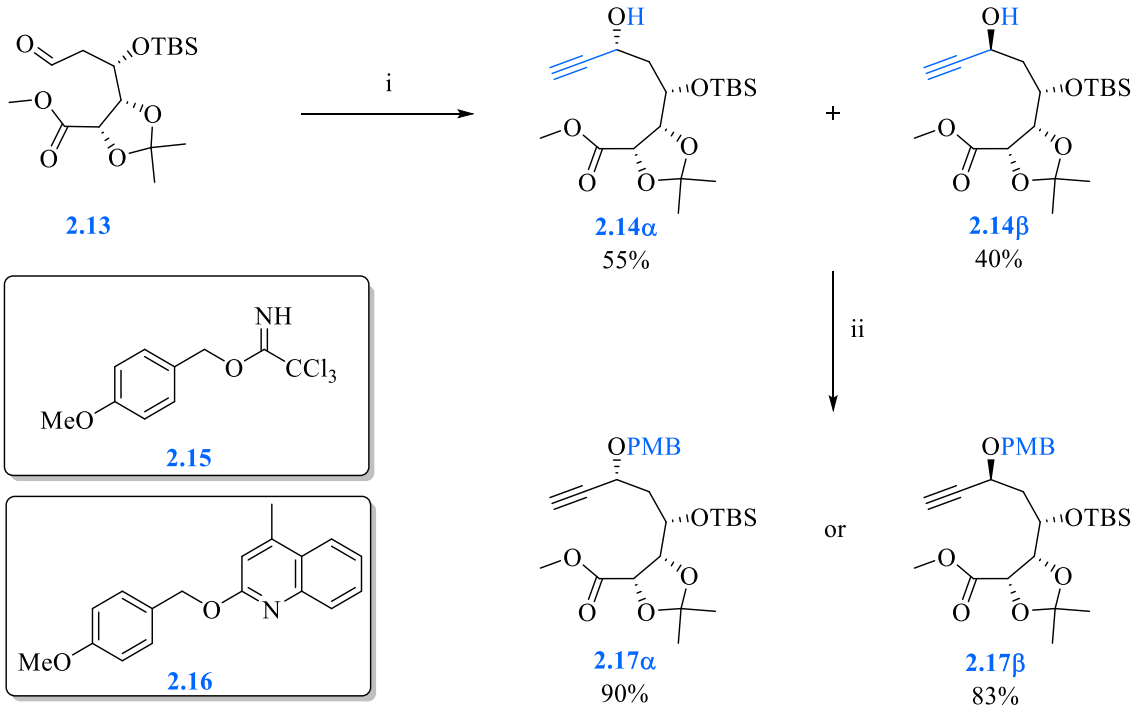
(black = C, red = O, purple = Si, green = Cl, grey = H)

Figure 2.3. ***Plots Arising from the Single-Crystal X-ray Analyses of Alcohol 2.11 and ω-oxo-Ester 2.13.***

Treatment of compound **2.13** with ethynylmagnesium bromide at −78 °C (**Scheme 2.5**) gave a 1:0.4 mixture of the epimeric and chromatographically separable α- and β- forms of propargylic alcohol **2.14** in 95% combined yield. An increase in the reaction temperature from −78 to −15 °C led to an erosion of the preference for the formation of epimer **2.14α** (1:0.7 ratio of α/β epimers). Further increases in temperature were not investigated due to the possibility of the newly formed alcohol adding to the pendant methyl ester given that such a lactonisation process was observed in the reaction of this aldehyde with vinylmagnesium bromide.[b] On the basis that each of these epimers could, in principle, be exploited in the proposed synthetic sequence (since the alcohol would be oxidised to the corresponding ketone at a later stage) subsequent studies were carried out on each of the diastereomerically pure compounds **2.14α** and **2.14β**. This needed to commence with protection of the propargylic alcohol residue. The protecting group to be used had to be orthogonal to the ones already present and not exceedingly bulky as it might otherwise inhibit the foreshadowed cycloaddition process. Furthermore, this same group should be capable of installation without the need to use a strong base (in order to prevent lactonisation and/or the isomerisation of the acetonide moiety). The *p*-methoxybenzyl ether (PMB) group was thus chosen as it could be installed under mild conditions using *p*-methoxybenzyl trichloroacetimidate (**2.15**, PMBTCA)[109] in combination with catalytic amounts of $Ph_3C^+BF_4^-$. Unfortunately, the reaction proved to be very slow and low yielding (25–30%) at 18 °C and the temperature could not be increased to accelerate the process due to the instability of the reagent. In contrast, when 2-(4-methoxybenyloxy)-4-methylquinoline **2.16** (PMBO-lepidine)[110] (**Scheme 2.6**) was used in combination with (+)-

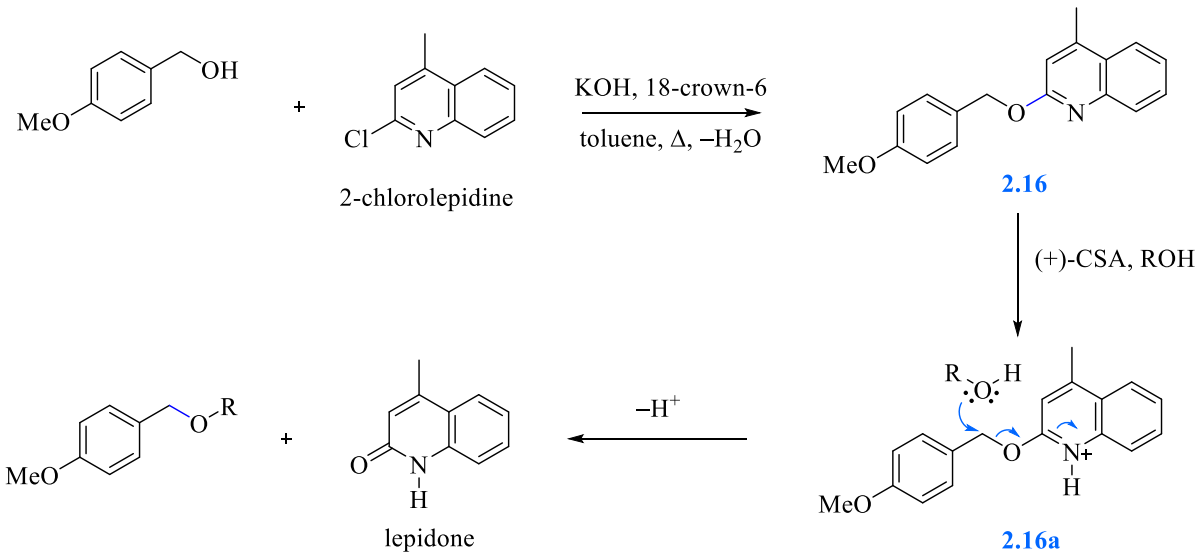
[b] Such lactonisation processes are discussed in Section **3.4**

camphor-10-sulfonic acid (CSA) (cat.) in refluxing dichloromethane, the desired and protected alcohol **2.17** was readily obtained (in 90% yield for **2.17α** and 83% yield for **2.17β**).



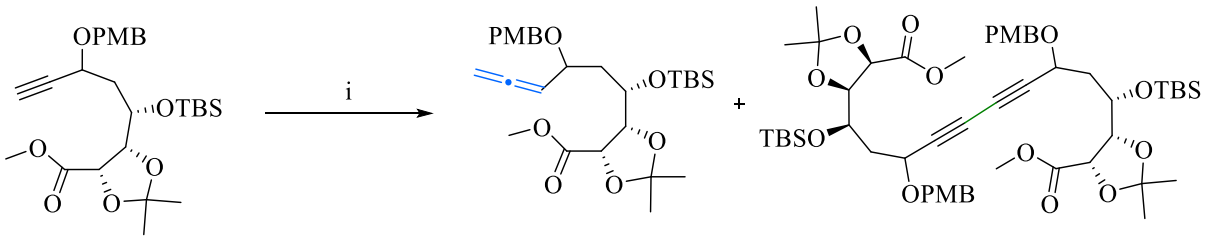
Scheme 2.5. ***Reagents and Conditions*** (i) HC≡CMgBr, Et_2O, −78 to −15 °C, 1 h; (ii) PMBO-lepidine (**2.16**), CSA (cat.), DCM, 40 °C, 16 h.

The use of 2-((4-methoxybenzyl)oxy)-4-methylquinoline (PMBO-lepidine), **2.16**, (**Scheme 2.6**) as an acetimidate surrogate for transferring the *p*-methoxybenzyl protecting group onto an hydroxyl center was established by Dudley[110] in 2006. The reagent is easily prepared by heating (at reflux for one hour) a mixture of *p*-methoxybenzyl alcohol, 2-chlorolepidine and potassium hydroxide with accompanying (azeotropic) removal of water. Lepidine ether **2.16** is more stable and easier to handle than its PMBTCA-containing counterpart **2.15**. The *in situ* activation of PMBO-lepidine **2.16** (into **2.16a**) is effected in the presence of a catalytic amount of camphorsulfonic acid, an event that is followed by nucleophilic substitution of the alcohol to provide the desired product (along with lepidone that can be easily removed by flash chromatography).



Scheme 2.6. ***Preparation of PMBO-Lepidine (2.16) and the Likely Mechanism for its Use in the Introduction of PMB-Ether Protecting Group***.

To advance the synthesis, each of the terminal alkynes **2.17α** and **2.17β** was subjected to the Searles-Crabbé allene-forming protocol[111] (**Scheme 2.7**) using paraformaldehyde, copper(I) iodide and di-*iso*-propylamine and so providing the target allenes **2.18α** and **2.18β** in 78% and 85% yields, respectively. Interestingly, the use of copper(I) bromide led to dimeric coupling of the terminal alkyne starting material and thus giving diyne **2.19α**/**2.19β** as the major product under such conditions.[112]



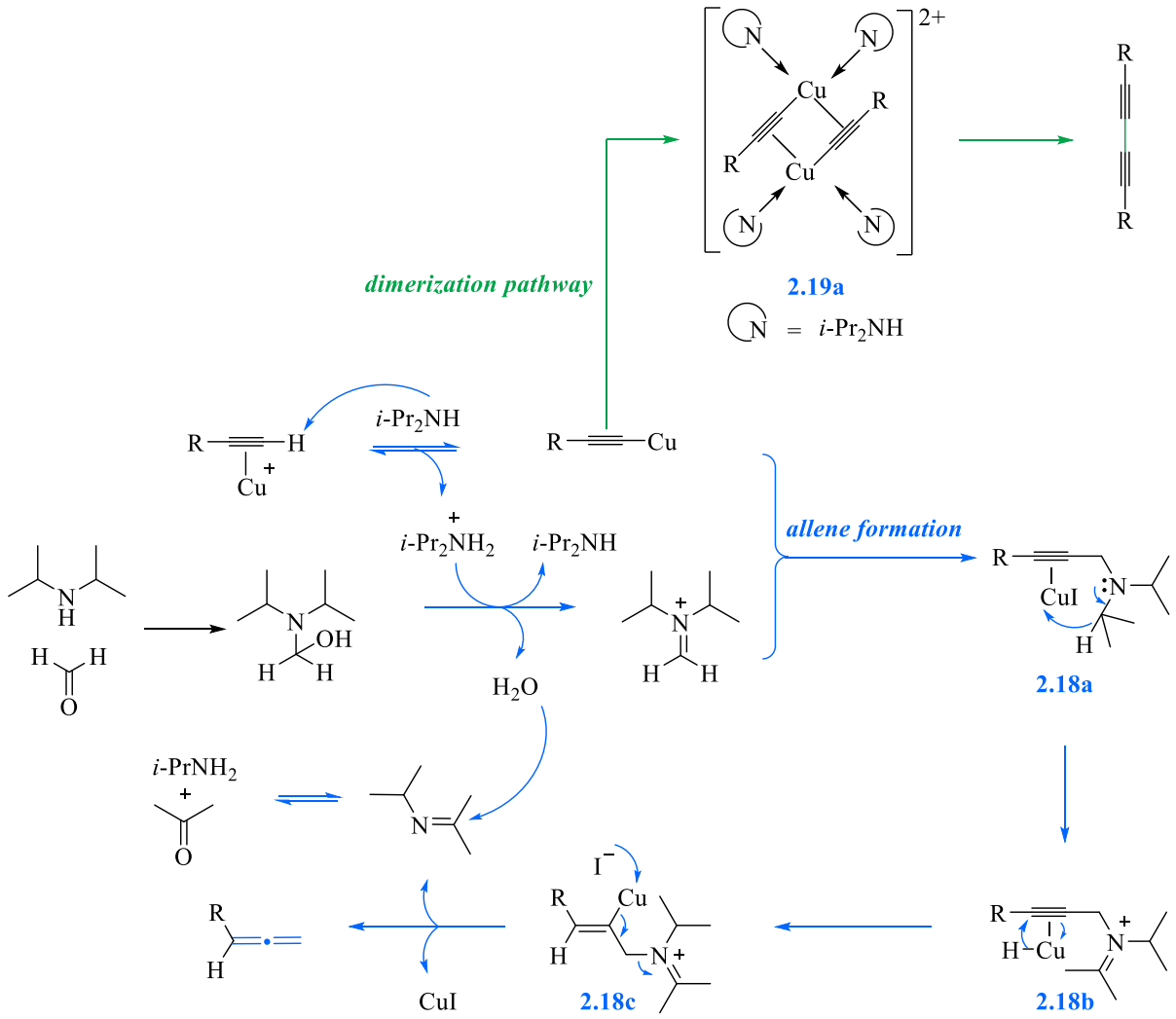
2.17α/**2.17β**

CuBr	**2.18α**	21%	**2.19α**	47%
	2.18β	19%	**2.19β**	44%
CuI	**2.18α**	78%	**2.19α**	trace
	2.18β	85%	**2.19β**	trace

Scheme 2.7. ***Reagents and Conditions*** (i) $(CHO)_n$, CuI, *i*-Pr_2NH, dioxane, 100 °C, 24 h.

Although the mechanism for such dimerisation reactions is not fully understood, the one proposed by Bohlmann *et al*. is the most widely accepted.[113] This pathway starts with the copper(I) ion activation of the terminal alkyne through deprotonation to form a monomeric π-

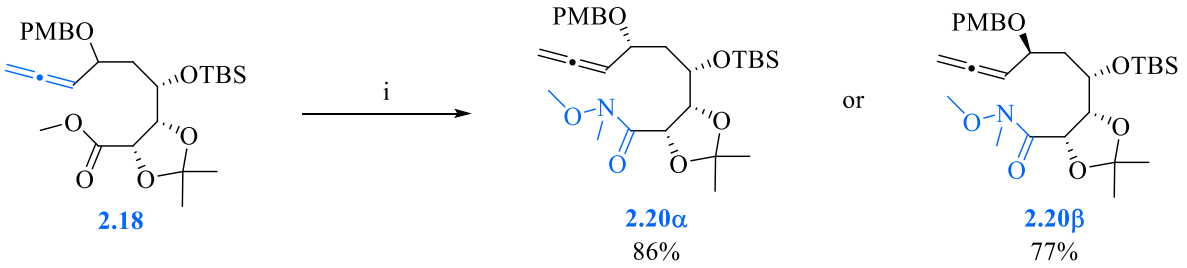
complex. The combination of two of these gives dimer **2.19a** (**Scheme 2.8**) that, while stabilised by the added amine, eventually collapses to the homocoupled product. By using copper(I) iodide that is minimally contaminated with a copper(II) species, allene formation occurs, presumably *via* the illustrated two-step mechanism (**Scheme 2.8**). The first step involves reaction of the cuprous acetylene with the iminium ion derived from the reaction of di-*iso*-propylamine with paraformaldehyde and so affording intermediate **2.18a**. Next, a 1,5-sigmatropic shift of the α-hydrogen from the *N*-isopropyl group onto the π-complexed copper(I) **2.18b** takes place and this is converted into intermediate **2.18c** that itself fragments in the indicated manner to give the observed allene.



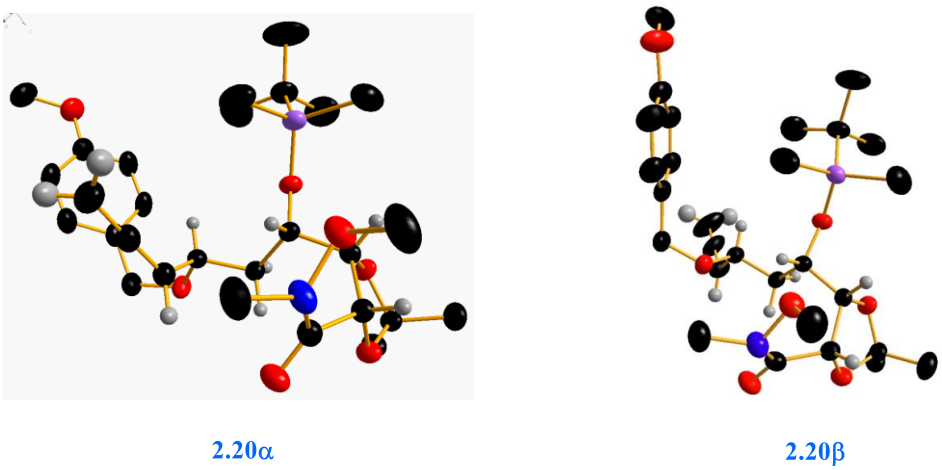
Scheme 2.8. ***Mechanism for the Formation of Dimerisation and Allene Products.***

Separate treatment of the methyl esters **2.18α** and **2.18β** with *N,O*-dimethylhydroxylamine hydrochloride salt in the presence of *iso*-propylmagnesium chloride at −15 °C (**Scheme 2.9**) produced the corresponding and crystalline Weinreb amides **2.20α** (86%)

and **2.20β** (77%) and the structures of both of these were confirmed by single-crystal X-ray analyses (**Figure 2.4**).



Scheme 2.9. ***Reagents and Conditions*** (i) HCl•HN(OMe)Me, *i*-PrMgCl, THF, −15 to 0 °C, 1 h.

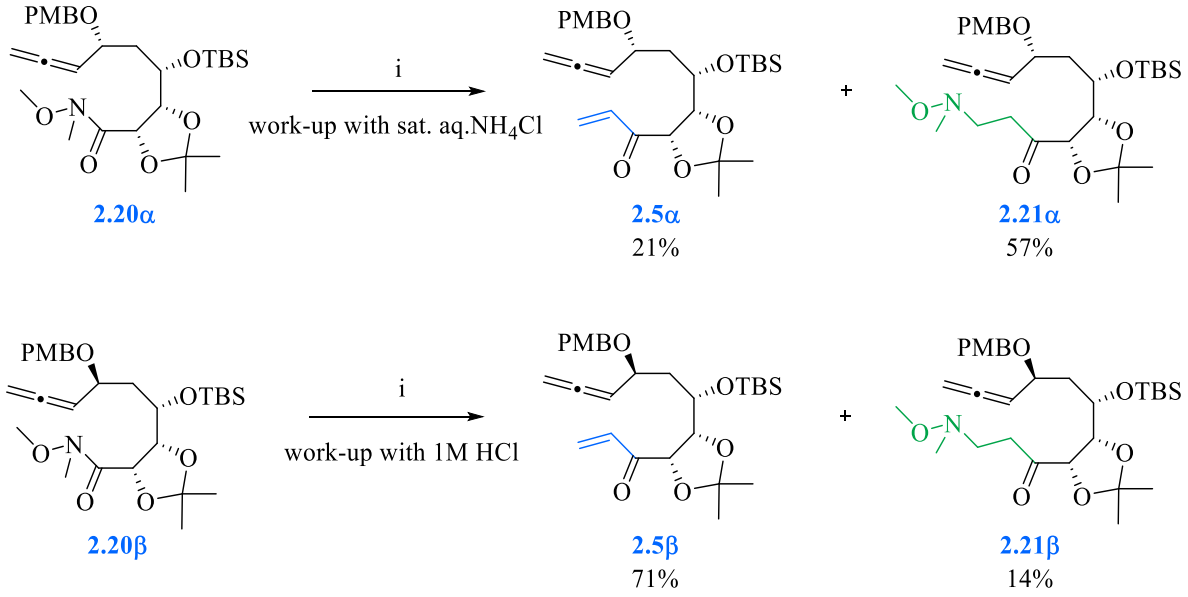


2.20α **2.20β**

(black = C, red = O, purple = Si, blue = N, grey = H)

Figure 2.4. ***Plots Arising from the Single-Crystal X-ray Analyses of Weinreb Amides 2.20α and 2.20β.***

Reaction of Weinreb amide **2.20α** with vinyl magnesium bromide (**Scheme 2.10**) delivered, after work up of the reaction mixture with a saturated aqueous solution of ammonium chloride, the target enone **2.5α** (21%) as a minor product, the major one being β-aminoketone **2.21α** which was isolated in 57% yield. The latter product is no doubt formed through the conjugate addition of the *N*,*O*-dimethylhydroxylamine by-product to the enone moiety of the initially produced enone. Consistent with this, when the epimeric amide **2.20β** was submitted to the same reaction conditions but 1.0 M aqueous hydrochloric acid was now used in the work-up, then the desired enone **2.5β** (71%) was isolated as the major product, although the related aminoketone **2.21β** was still obtained in 14% yield.



Scheme 2.10. ***Reagents and Conditions*** (i) H_2C=CHMgBr, THF, −78 °C, 1 h.

Figure 2.5 provides a comparison of the ^{1}H NMR spectra of compounds **2.5α** and **2.5β**. These epimers share the same characteristic signals (four CH protons in the aromatic region and two germinal protons with large coupling constant, around 11.0 Hz) due to the presence of PMB-ether residues, the enone systems (three mutually coupling protons with two distinct coupling constant corresponding for *trans* coupling around 17.4 Hz and *cis* coupling around 10.5 Hz), and the allene moieties (wherein the C16-H appeared as a quartet and the two germinal protons coupled around 11.0 Hz). The major differences between the two spectra are in the regions associated with the resonances arising from C15-H and C14-H_2 (appearing as a quartet and an overlapped doublet of triplets, respectively, for **2.5α** and appearing as a doublet of triplets and doublet of doublets of doublets, respectively, for **2.5β**).

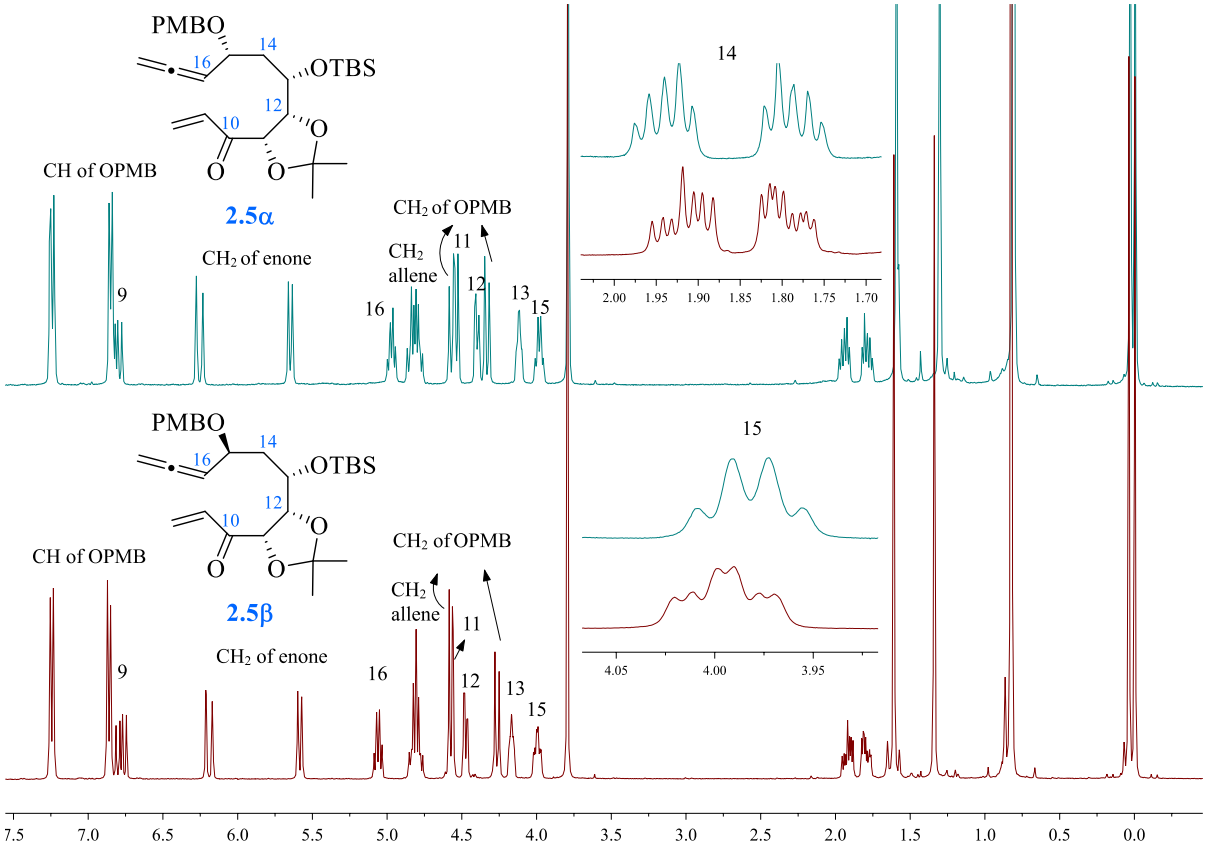


Figure 2.5. ***400 MHz ^{1}H NMR Spectra of Enones 2.5α above and 2.5β below (each recorded in* d-*chloroform)***.

2.3.2. Attempts to Effect an Intramolecular [2+2]-Cycloaddition Reaction

With allene-enone **2.5** finally in hand, the foreshadowed intramolecular [2+2]-cycloaddition reaction was attempted under various conditions. However, all of these failed to produce the desired bicyclo[6.2.0]decane. Instead, when compound **2.5α** was submitted to heating at 150 °C in *N*,*N*-dimethylformamide some decomposition was observed while a significant quantity of starting material was recovered. Microwave irradiation of an acetonitrile solution of substrate **2.5β** failed to effect any reaction at 150 °C even after four hours while heating at 180 °C only led to decomposition. Successful thermally induced [2+2]-cycloaddition reactions of allenes have been rationalised as proceeding *via* a stepwise, diradical mechanism[104] and these usually require high temperatures (160 to 200 °C) as well as long reaction times in order to proceed. In the present case, due to the complex nature of the substrate, decomposition occurred when the temperatures normally required for the desired transformation were reached. Upon irradiation with a high-pressure mercury lamp, compound **2.5α** remained unchanged while decomposition was observed for congener **2.5β** under the same conditions. When

compound **2.5α** was treated with Echavarren's gold catalyst the associated PMB group was cleaved and the secondary alcohol so-formed cyclized to give the corresponding dihydrofuran.

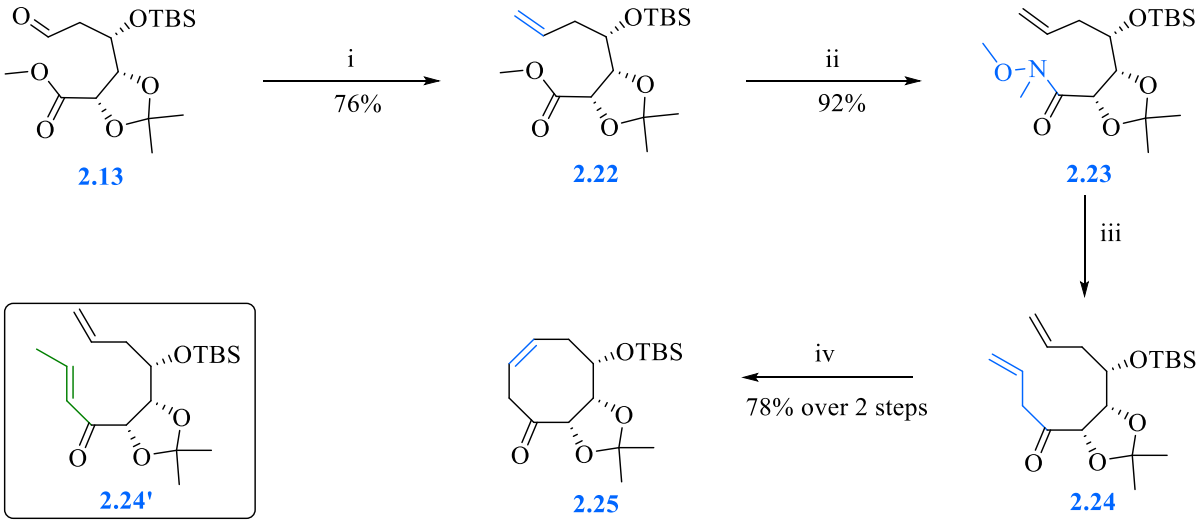
2.4. Exploring an Intermolecular [2+2]-Cycloaddition Approach

Although compounds **2.5α**/**2.5β** bear some resemblance to the Eastern Hemisphere of the putative biogenetic precursor, **1.7**,[c] of tripartilactam, neither epimer could be elaborated, through an intramolecular [2+2]-cycloaddition reaction, to the targeted bicyclo[6.2.0]decane ***ent*-2.4**. Therefore, an alternate route to a chiral, polyoxygenated cyclooctenone incorporating the Eastern Hemisphere of tripartilactam was pursued wherein the eight-membered ring would be assembled first, and the cyclobutane ring then annulated *via* an intermolecular [2+2]-cycloaddition process (see **Scheme 2.2**).

2.4.1. Preparation of Cyclooctenone 2.25

The starting point for this new approach to the Eastern Hemisphere began with the readily prepared ω-oxo-ester **2.13** obtained as described earlier (see **Scheme 2.3**). Thus, compound **2.13** was first subjected to Wittig olefination reaction (**Scheme 2.11**) with the ylide obtained by deprotonation of methyl triphenylphosphonium bromide and so affording the unsaturated ester **2.22** (76%) that was then converted into the corresponding Weinreb amide **2.23** (92%) under standard conditions (as described in Section **2.3.1**). Treatment of this amide with allylmagnesium bromide provided the rather sensitive β,γ-unsaturated ketone **2.24** which was partially isomerised to its conjugated counterpart **2.24'** during the course of attempted flash chromatographic purification. Accordingly, the crude ketone **2.24** was immediately engaged in a ring closing metathesis reaction (RCM) by treating it with the second-generation Grubbs' catalyst,[114] and so affording the expected cyclooctenone **2.25** (78% from **2.23**). The illustrated assignments of the signals observed in the ^{1}H NMR spectrum of **2.25** (**Figure 2.6**) were established using ^{1}H/^{1}H correlation spectroscopic (COSY) techniques while the ^{13}C NMR spectrum (**Figure 2.7**) shows the expected eight signals corresponding to cyclooctenone moiety as well as the resonances arising from the protecting groups. The structure of this eight-membered ring-containing compound was finally confirmed by single-crystal X-ray analysis (**Figure 2.8**).

[c] Described in **Scheme 1.2**, Chapter One.



Scheme 2.11. ***Reagents and Conditions*** (i) $(Ph_3P^+CH_3)Br^-$, LiHMDS, THF, 0 to 18 °C, 2 h; (ii) HCl•HN(OMe)Me, *i*-PrMgCl, THF, −15 to 0 °C, 1 h; (iii) $H_2C{=}CHCH_2MgBr$, THF, −78 °C., 1h; (iv) Grubbs' (II) cat., DCM, 40 °C, 16 h.

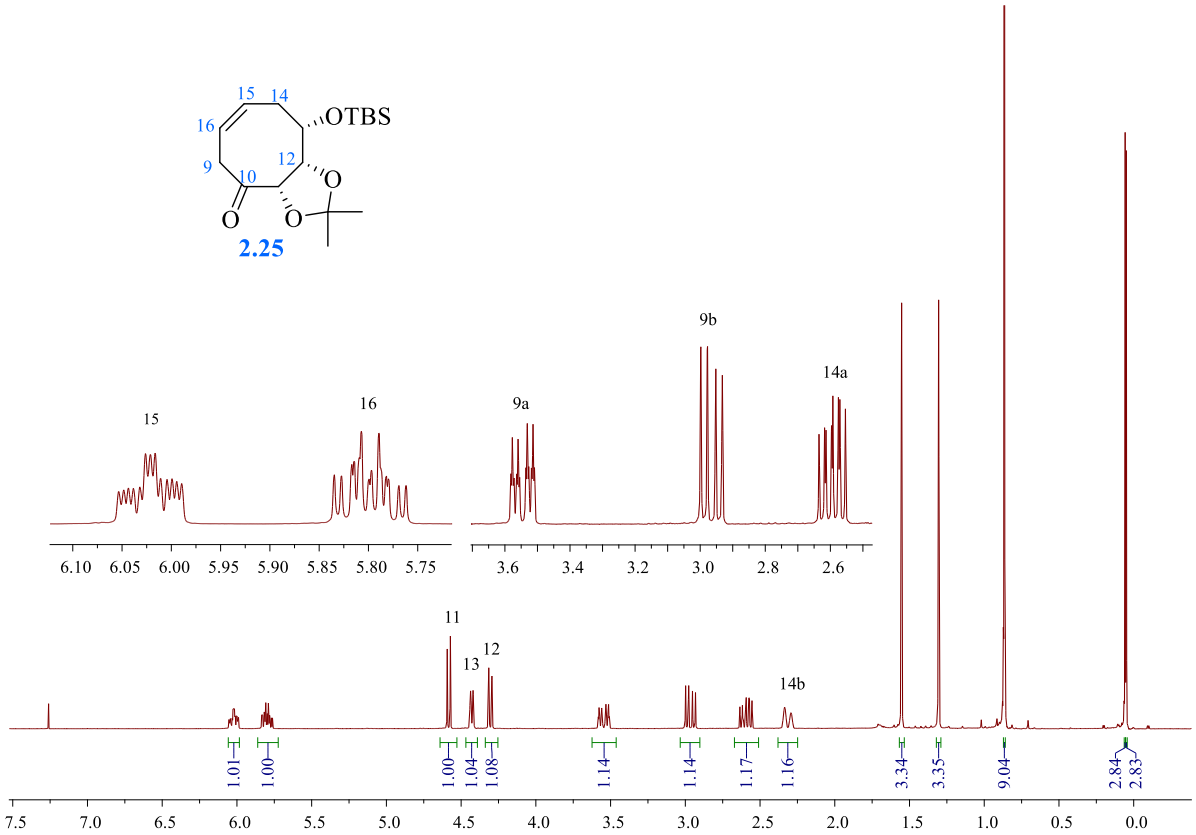


Figure 2.6. ***400 MHz ^{1}H NMR Spectrum of Compound 2.25 (recorded in* d*-chloroform)***.

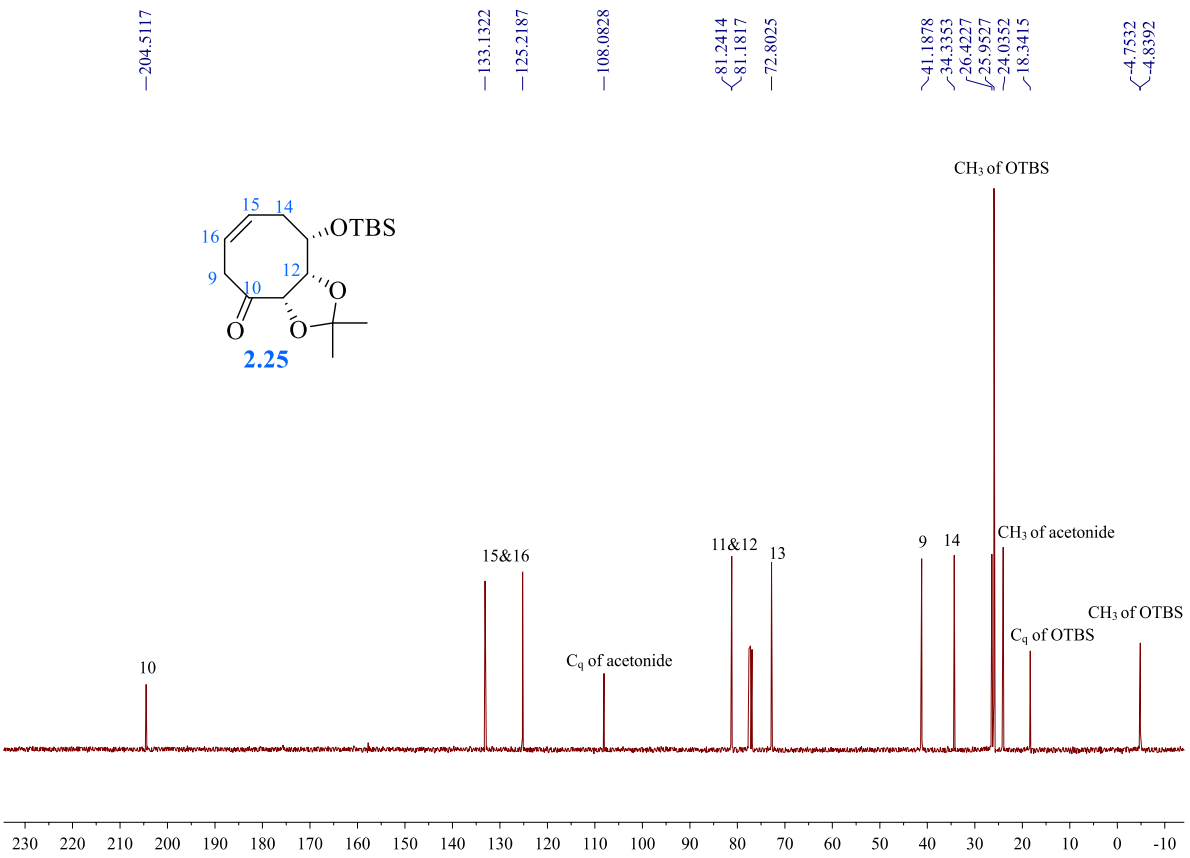


Figure 2.7. ***100 MHz ^{13}C NMR Spectrum of Compound 2.25 (recorded in* d*-chloroform)***.

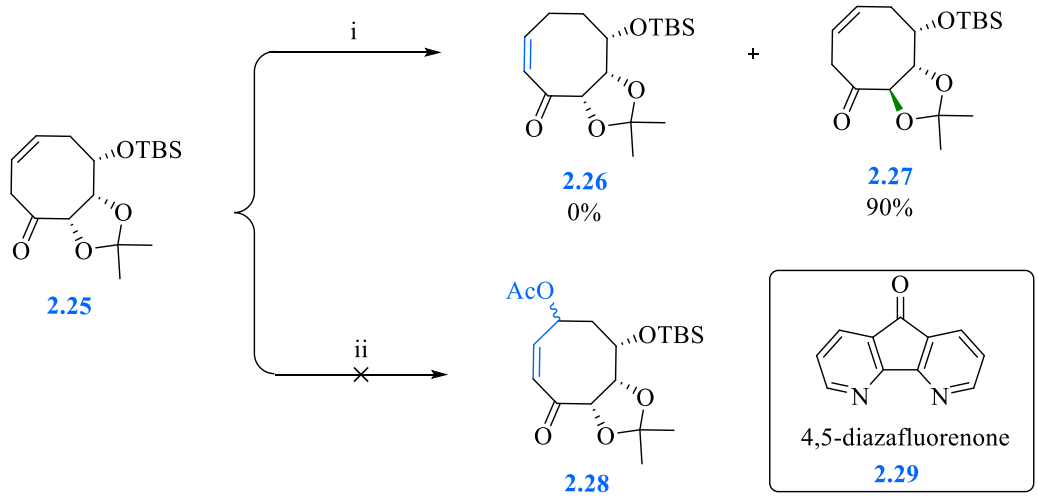
(black = C, red = O, purple = Si, grey = H)

Figure 2.8. ***Plots Derived from the Single-Crystal X-ray Analyses of Cyclooctenone 2.25.***

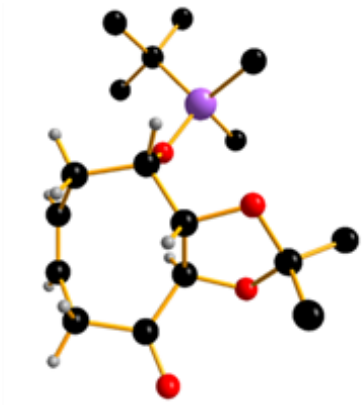
Having successfully established the polyoxygenated cyclooctenone core of tripartilactam, attention was now turned toward the elaboration of this material into a desired substrate for the pivotal [2+2]-cycloaddition reaction.

2.4.2. Elaboration of Cyclooctenone 2.25

The substrate required for the [2+2]-cycloaddition reaction was sought by a two-step reaction sequence involving isomerisation of the β,γ-unsaturated ketone **2.25** to the conjugated enone **2.26** (**Scheme 2.12**) followed by allylic oxidation with selenium oxide to install a hydroxyl group at the γ-carbon. This hydroxyl group would eventually be eliminated so as to form the corresponding (*Z*)-alkene, a motif that would be retained in the final product. Unfortunately, treatment of ketone **2.25** with lithium hydroxide only led, in 90% yield, to an epimerisation product, namely compound **2.27**,[115] the structure of which was confirmed by single-crystal X-ray analysis (**Figure 2.9**).



Scheme 2.12. ***Reagents and Conditions*** (i) (LiOH, MeOH, 18 °C, 2 h; (ii) $Pd(OAc)_2$, $NaBO_3.4H_2O$, Ac_2O, ACN or **2.29**, NaOAc, AcOH, $Pd(OAc)_2$, O_2, dioxane, 60 °C, 2 d.

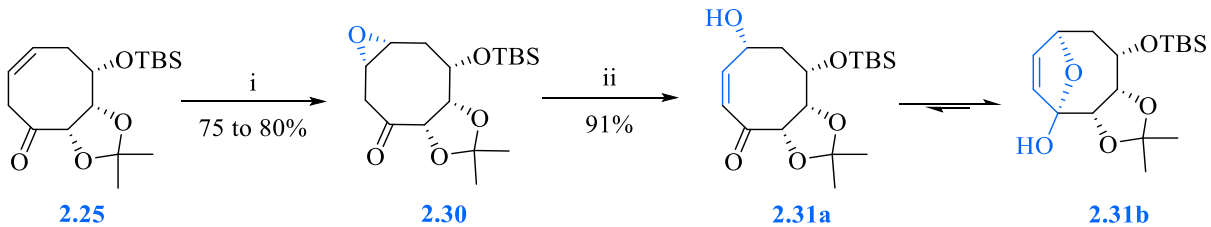


(black = C, red = O, purple = Si, grey = H)

Figure 2.9. ***Plots Derived from the Single-Crystal X-ray Analyses of Cyclooctenone 2.27.***

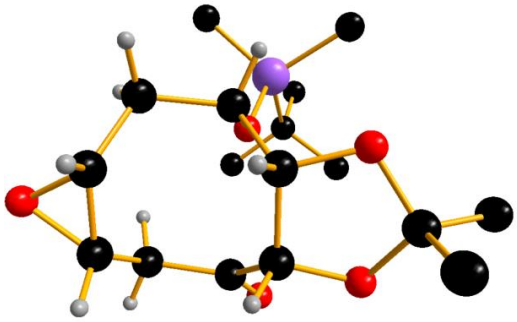
As a result, palladium-acetate catalysed allylic C-H acetoxylation was attempted in the hope of obtaining the γ-acetate enone **2.28** (**Scheme 2.12**). However, no reaction occurred upon using sodium perborate as an oxidant and acetic anhydride as the source of nucleophile.[116] Furthermore, following the procedure of Stahl,[117] using 4,5-diazafluorenone (**2.29**) as ligand, oxygen as the oxidant and a catalytic amount of sodium acetate, the epimerised product **2.27** was once again the only observable product even after heating substrate **2.25** at 60 °C for two days.

In order to prevent the unwanted epimerisation described above, a new route was pursued, this being inspired by a literature reports[118] describing the formation of an epoxide from the alkene and then effecting its opening with a base. It was postulated that the opening of epoxide would be more favourable than the epimerisation of the acetonide. However, efforts to apply this process to compound **2.25** by subjecting it to various epoxidation conditions, only met with limited success. So, for example, epoxidation with *m*-chloroperoxybenzoic acid only gave 25 to 30% of the desired epoxide. Purification of the *m*-chloroperoxybenzoic acid before use or attempts to carry out the reaction in buffered media using sodium hydrogencarbonate also failed to improve matters. The use of hydrogen peroxide was also investigated but this only led to decomposition of the starting material.[119] Gratifyingly, when cyclooctenone **2.25** was treated (**Scheme 2.13**) with freshly prepared dimethyldioxirane (DMDO)[120] a completely stereoselective and substrate-directed reaction ensued to give epoxide **2.30** (80%), the structure of which was confirmed by single-crystal X-ray analysis (**Figure 2.10**). Exposure of this epoxide to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted, presumably *via* an $E1_{cb}$ reaction pathway, in a fully regiocontrolled cleavage of the epoxide ring to form the γ-hydroxy-α,β-unsaturated enone **2.31a**. This product existed almost exclusively as the lactol **2.31b** (as judged by the derived spectral data). Significantly, no epimerisation at the α-carbon appeared to have taken place during the conversion of epoxide **2.30** into lactol **2.31b**.



2.25 **2.30** **2.31a** **2.31b**

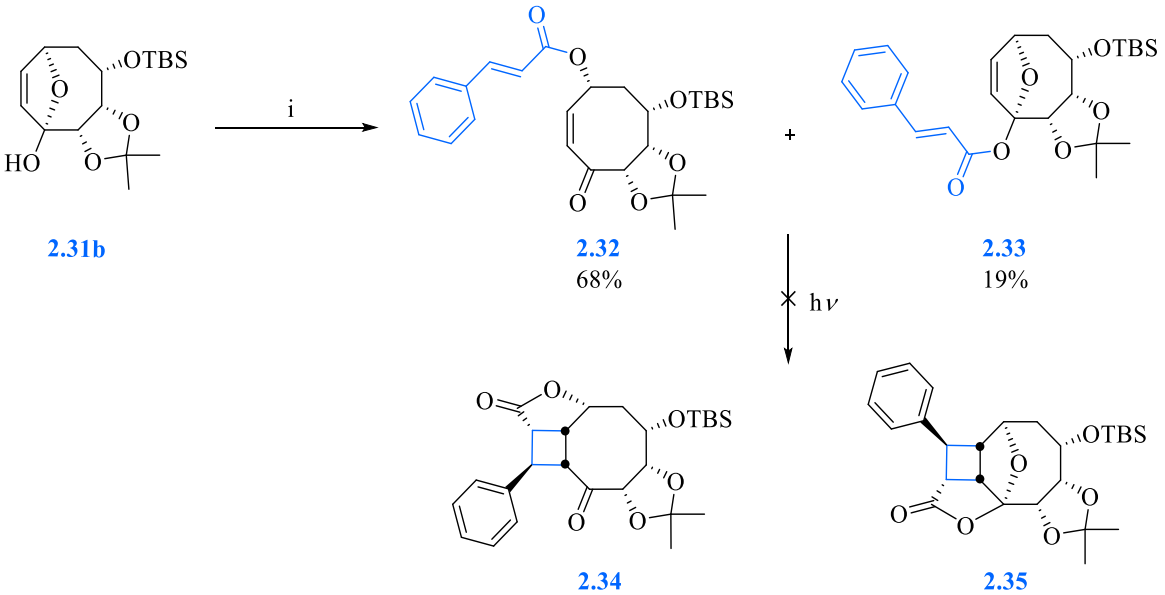
Scheme 2.13. ***Reagents and Conditions*** (i) DMDO, DCM, 0 to 18 °C, 16 h; (ii) DBU, DCM, 18 °C, 4 h.



(black = C, red = O, purple = Si, grey = H)

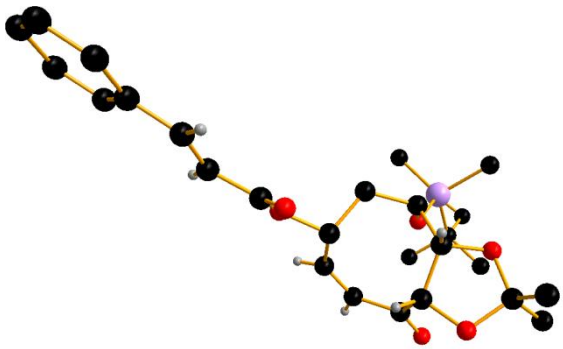
Figure 2.10. ***Plots Derived from the Single-Crystal X-ray Analysis of Epoxide 2.30.***

It was envisioned that lactol **2.31b** would serve as a precursor to a model substrate for an intramolecular photolysis reaction if it could be opened to reveal the enone moiety concurrently with derivatisation of the γ-hydroxyl group so as to install a chromophore. Accordingly, the lactol was heated in dichloromethane with cinnamoyl chloride and pyridine in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) for two days. As hoped, the desired enone **2.32** (68%) (**Scheme 2.14**) was obtained as a major product (its structure was confirmed by single-crystal X-ray analysis - see **Figure 2.11**), although it was accompanied by the related acetal **2.33** (19%). Disappointingly, separate irradiation of each of these products in degassed acetonitrile in a quartz flask using a commercially available UV-C lamp for two hours did not afford any of the desired [2+2]-cycloaddition products. Decomposition was observed when enone **2.32** was used as the substrate and recovered starting material was obtained in the case of acetal **2.33**.



2.31b **2.32** 68% **2.33** 19% **2.34** **2.35**

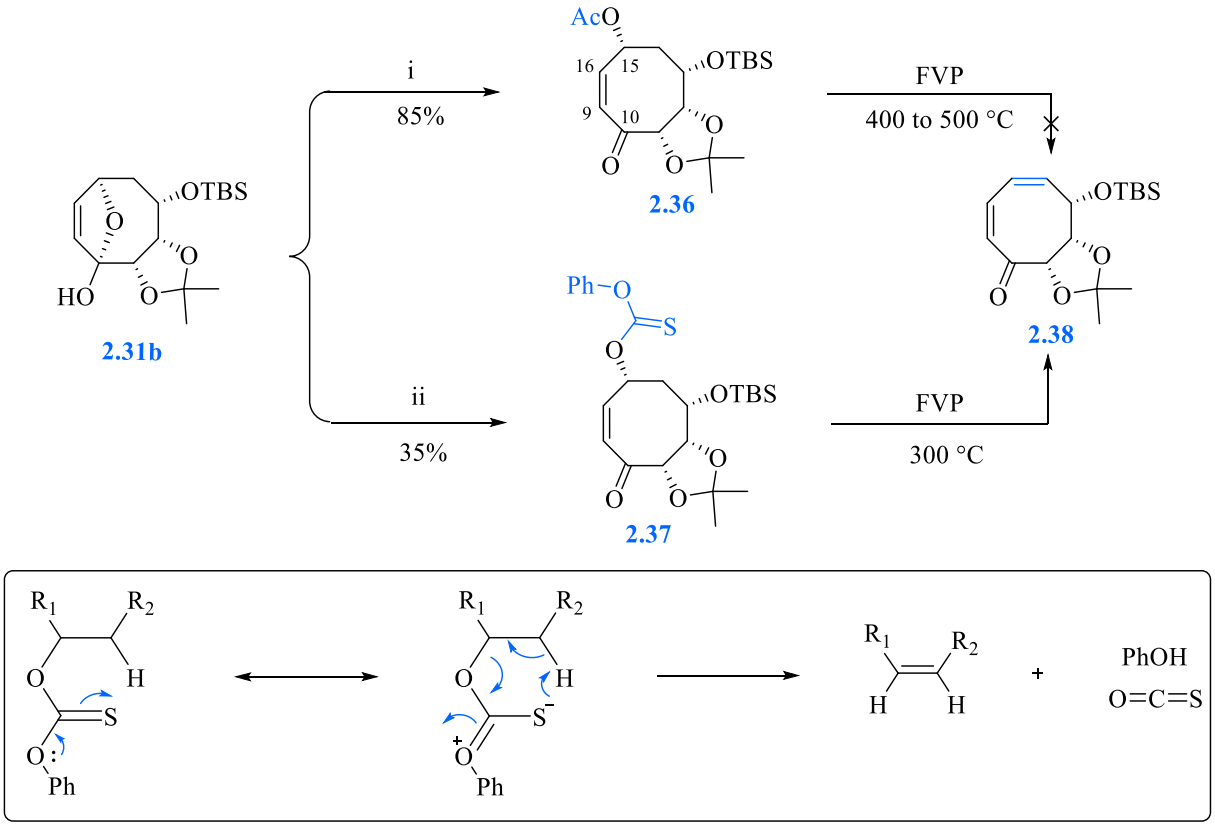
Scheme 2.14. ***Reagents and Conditions*** (i) cinnamoyl chloride, DMAP, pyridine, DCM, 40 °C, 48 h; (ii) UV-C, 18 °C, ACN, 2 h.



(black = C, red = O, purple = Si, grey = H)

Figure 2.11. ***Plot Derived from the Single-Crystal X-ray Analysis of Enone 2.32.***

For the purpose of preparing a substrate suitable for an intermolecular [2+2]-cycloaddition reaction, lactol **2.31b** was converted into acetate **2.36** (85%) (**Scheme 2.15**) under the same conditions as used for the formation of compound **2.32**. The most significant features observed in the ^{1}H NMR spectrum of compound **2.36** (**Figure 2.12**) were the resonances associated with the enone moiety. The lower field resonance was attributed to C16-H and appeared at δ 6.24 as a doublet of doublets (J = 12.9 and 5.9 Hz) while the other doublet of doublets resonating at δ 6.05 (J = 12.9 and 2.2 Hz) was assigned to C9-H. The signal at δ 5.85 was assigned to C15-H as expected for an oxymethine proton on an sp^{3}-hybridised carbon bearing an acetate group. The ^{13}C NMR spectrum (**Figure 2.13**) also provided strong evidence for the assigned structure, which was finally confirmed by single-crystal X-ray analysis. The derived ORTEP is shown in **Figure 2.14**. The possibility of effecting a thermal *syn*-elimination within compound **2.36** so as to generate the (*Z*)-alkene **2.38** was explored.[121] However, the use of flash vacuum pyrolytic (FVP) techniques at 400 °C only led to the recovery of the starting material while raising the temperature to 500 °C resulted in the onset of decomposition processes. In an effort to investigate other modes of thermally-induced elimination, lactol **2.31b** was treated with phenyl thionochloroformate. Although only a small amount of the anticipated thiocarbonate **2.37** was obtained this could be submitted to FVP at 300 °C. The product mixture obtained appeared to contain the desired dienenone **2.38** (as judged by ^{1}H NMR analysis) and this is presumably formed by the pathway shown in the inset associated with **Scheme 2.15**.[122] Although this product could not be completely characterised, the possibility of installing the (*Z*)-olefin by such means had been established. Efforts were then undertaken to test the intermolecular [2+2]-cycloaddition reaction.



Scheme 2.15. ***Reagents and Conditions*** (i) $(CH_3CO)_2O$, DMAP, pyridine, DCM, 40 °C, 24 h; (ii) thionochloroformate, DMAP, pyridine, DCM, 40 °C, 48 h.

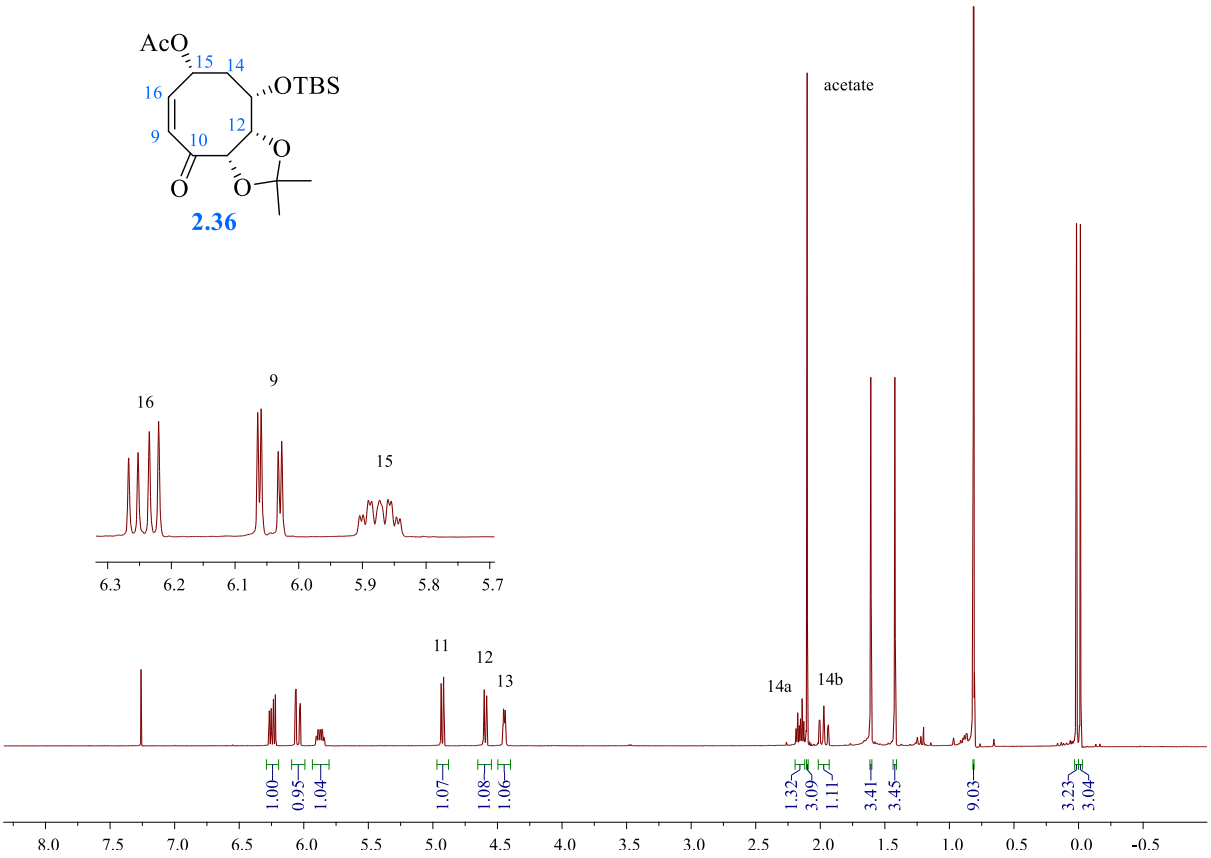


Figure 2.12. ***400 MHz ^{1}H NMR Spectrum of Acetate 2.36 (recorded in* d*-chloroform).***

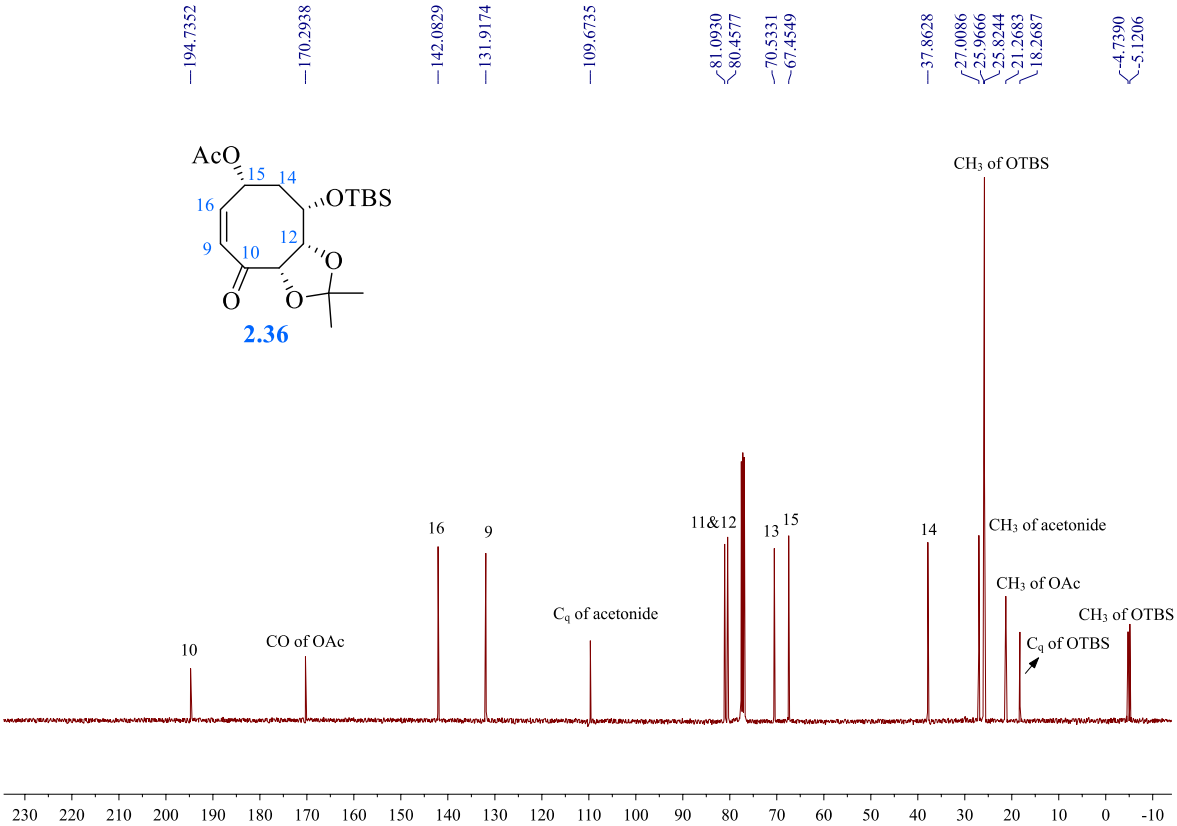
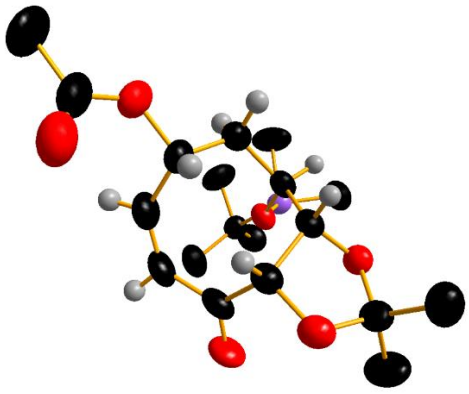


Figure 2.13. ***100 MHz ^{13}C NMR Spectrum of Acetate 2.36 (recorded in* d*-chloroform).***

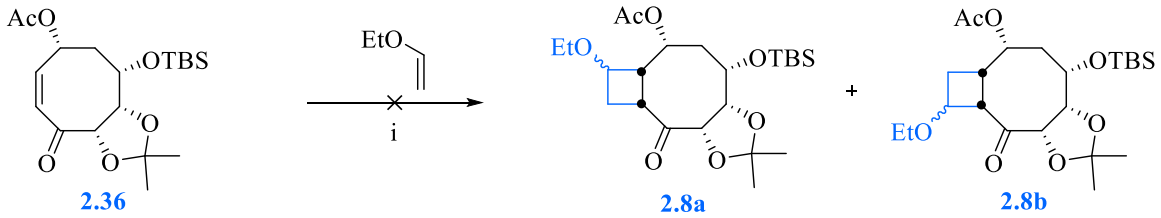


(black = C, red = O, purple = Si, grey = H)

Figure 2.14. ***Plots Derived from the Single-Crystal X-ray Analysis of Acetate 2.36.***

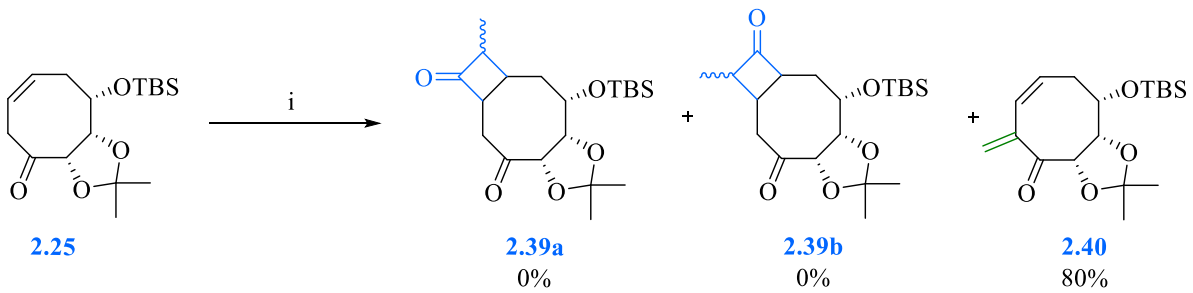
2.4.3. Attempts to Effect an Intermolecular [2+2]-Cycloaddition Reaction

Notwithstanding the failure to effect an intramolecular [2+2]-cycloaddition as described in previous sections, an intermolecular photocycloaddition reaction was explored. To such ends, a solution of acetate **2.36** and ethyl vinyl ether in degassed acetonitrile contained in a quartz flask (**Scheme 2.16**) was irradiated with high-pressure mercury lamp (UV-C) for two hours. Disappointingly, neither of the hoped-for photoproducts **2.8a** or **2.8b** was detected. The substrate enone simply decomposed under the reaction conditions used.



Scheme 2.16. ***Reagents and Conditions*** (i) UV-C, 18 °C, ACN, 2 h.

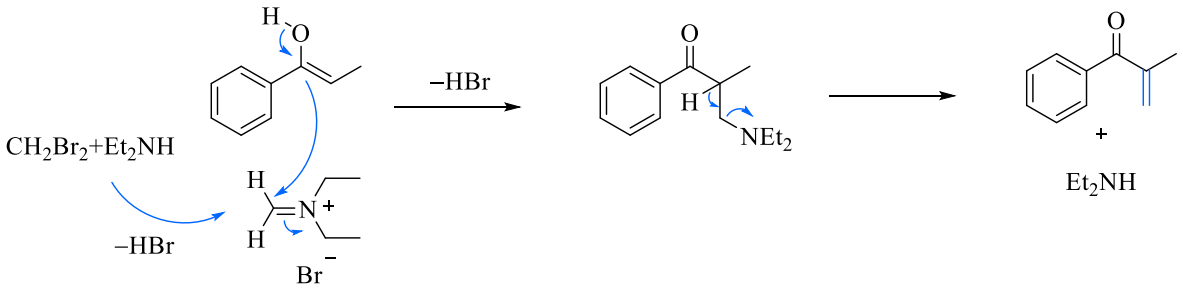
At this stage, it was decided to investigate the possibility of effecting a [2+2]-cycloaddition reaction between an unconjugated alkene and a ketene. Cyclooctenone **2.25** was chosen as the substrate with which to explore this possible transformation. On heating at 110 °C with propionyl chloride and triethylamine in toluene, no reaction was observed, even after a full day. When the same reagent/reactant combination was submitted to microwave irradiation in dichloromethane, the *exo*-methylenated product **2.40** (80%) was, rather unexpectedly, isolated instead of the desired adducts **2.39a** or **2.39b** (**Scheme 2.17**). A control experiment was undertaken in the absence of propionyl chloride and compound **2.40** was again obtained, this time in 87% yield.



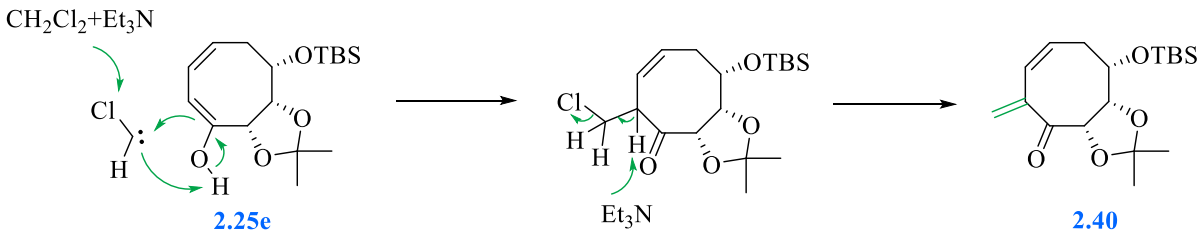
Scheme 2.17: ***Reagents and Conditions*** (i) propionyl chloride, Et_3N, DCM, 100 °C, µW, 4 h.

There is some literature precedent for this methylenation reaction. Hon and co-workers have shown that on using 1,2-dibromomethane (CH_2Br_2) and diethylamine (Et_2NH) in dichloromethane the α-methylenation of a range of substrates takes place in varying yields.[123] They rationalised this outcome as shown in **Scheme 2.18** and wherein initial formation of an iminium ion, through reaction of diethylamine with dibromomethane occurs and this ion, in turn, reacts with the added and enolizable carbonyl compound to form a Mannich base. Following deamination of the resulting β-diethylamino ketone, the α-methylenated products are finally formed. Presumably a somewhat related but new pathway, involving formation of chlorocarbene (rather than an iminium ion), applies in the case of the conversion **2.25** → **2.40**.

Mechanism proposed by Hon



Related pathway for the conversion 2.25 → 2.40



Scheme 2.18. ***Proposed Mechanism for the Formation Methylenation Product.***

2.5. Conclusion

The eight-membered ring-containing compounds **2.25**, **2.32** and **2.36** (**Figure 2.15**), each of which embodies the polyoxygenated cyclooctene-containing Eastern Hemisphere of *ent*-tripartilactam, were synthesised from a readily available and homochiral 3-chloro-*cis*-1,2-dihydrocatechol. Several X-ray structures were obtained to confirm the structures of these compounds. In light of the lack of the participation of these compounds, and the acyclic congener **2.5**, in any productive inter- or intra-molecular [2+2]-cycloaddition process, an alternative strategy was required for the assembly of the Eastern Hemisphere of tripartilactam. Details of such a new approach are presented in the following Chapters.

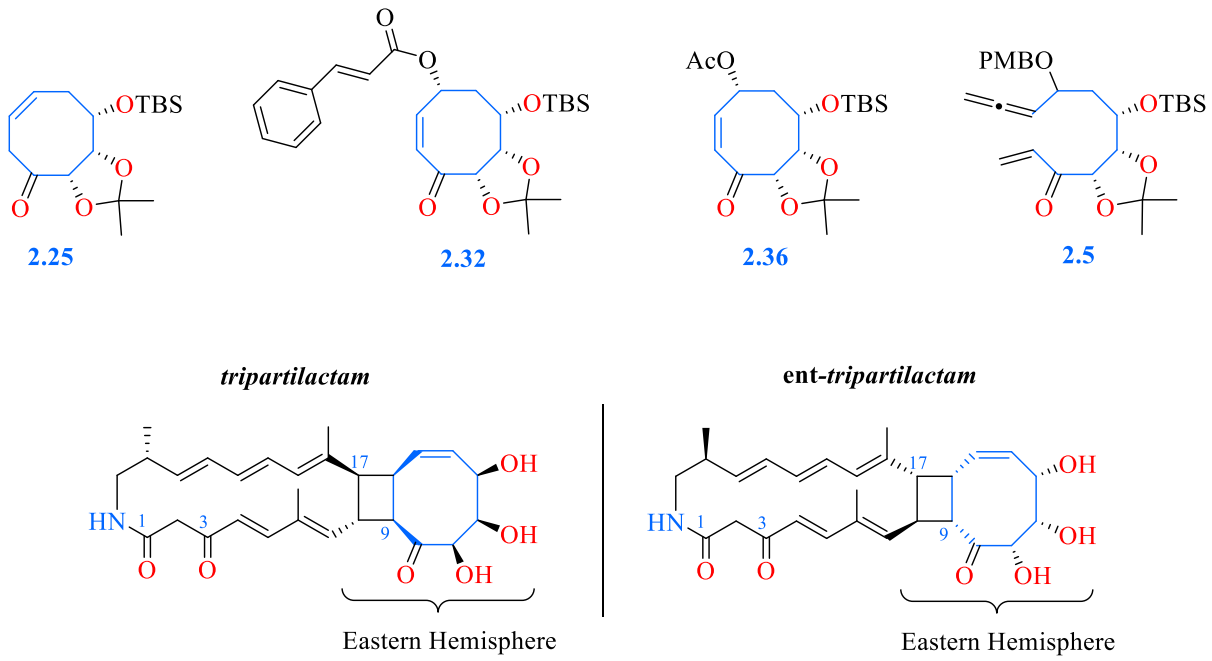
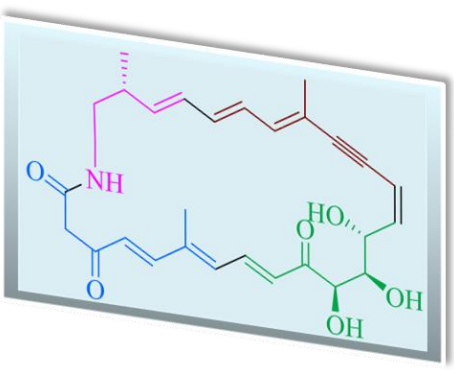


Figure 2.15. ***Eight-Membered Ring-Containing Compounds Embodying Eastern Hemisphere of* ent-*Tripartilactam.***

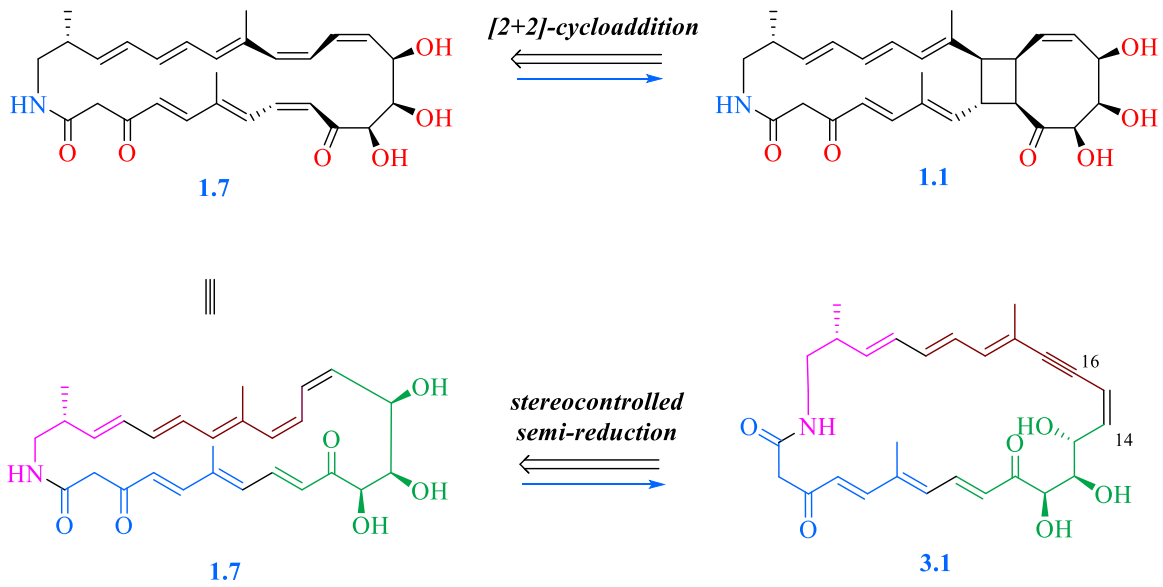
3. CHAPTER THREE

First-Generation Approach to a Substrate for Macrolactamisation



3.1. The Basic Strategy

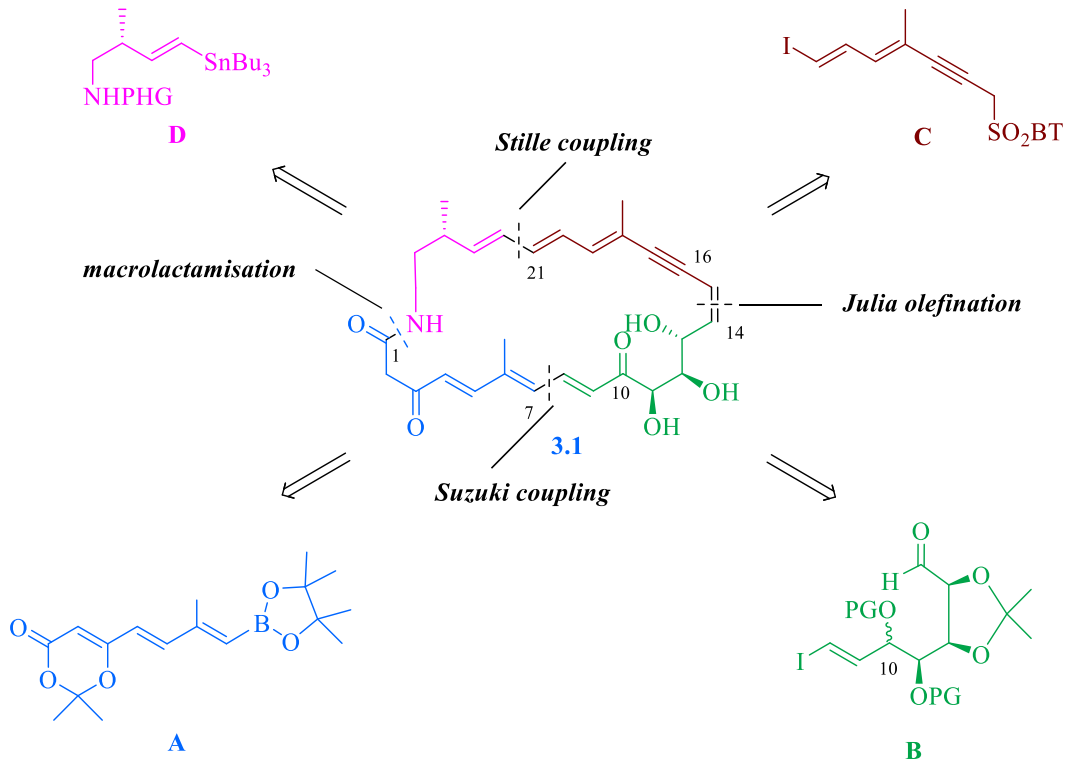
Owing to the difficulties encountered with the approach to tripartilactam outlined in the preceding Chapter, a new one was considered necessary. The proposal that the macrolactam **1.7** is transformed, during the course of the biogenesis of tripartilactam **1.1**, through a transannular [2+2]-cycloadditon reaction into the natural product prompted the author to attempt to mimic this process.[2] On this basis, the alkyne-containing lactam **3.1** (**Scheme 3.1**) was thought to be a logical precursor to macrolactam **1.7** in that semi-reduction of the alkyne moiety associated with the former compound (**3.1**) would deliver its dihydro-counterpart (**1.7**).



Scheme 3.1. ***Revised Synthetic Approach to Tripartilactam that Exploits a Transannular [2+2]-Cycloaddition Reaction***.

3.2. Retrosynthetic Analysis and Identification of Key Fragments

The retrosynthetic plan formulated for the generation of compound **3.1** is outlined in **Scheme 3.2**. Disconnections of the lactam bond, the C7–C8 σ-bond, the C14–C15 (*Z*)-olefinic bond and the C21–C22 σ-bond reveal four sub-structures **A**, **B**, **C** and **D**. It was envisioned that a Suzuki cross-coupling reaction could be used to connect fragments **A** and **B**, thus providing a compound that embodies the Southern Hemisphere of the macrolactam **3.1**. The $\Delta^{14,15}$-(*Z*)-olefin associated with this target would be installed along with fragment **C** by employing a Julia olefination reaction,[124] and the complete but uncyclised form of macrolactam **3.1** would finally arise from a Stille cross-coupling reaction involving fragment **D** and this would be followed by a thermally induced macrolactamisation reaction. In this plan, it is important to note that by using the same starting material as featured in the previous approach, namely the 3-chloro-*cis*-1,2-dihydrocatechol **2.3**, for the formation of fragment **B** then the natural enantiomeric form of macrolactam **3.1** should be accessible. It is also noteworthy that the configuration at C10 (in **B**) is not relevant as the alcohol at this position would be oxidised to the corresponding ketone at a later stage. The preparations of synthons **A**, **B**, **C** and **D** central to this approach are described in the following sections.



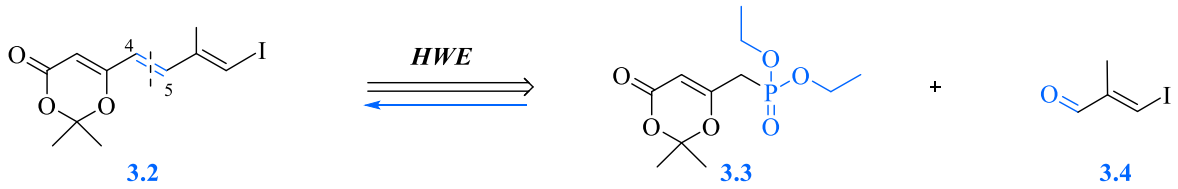
Scheme 3.2. *Key Building Blocks (Fragments) Associated with the Assembly of Macrolactam **3.1**.*

3.3. Synthesis of Fragment A

3.3.1. Synthesis of the Corresponding Alkenyl Iodide 3.2

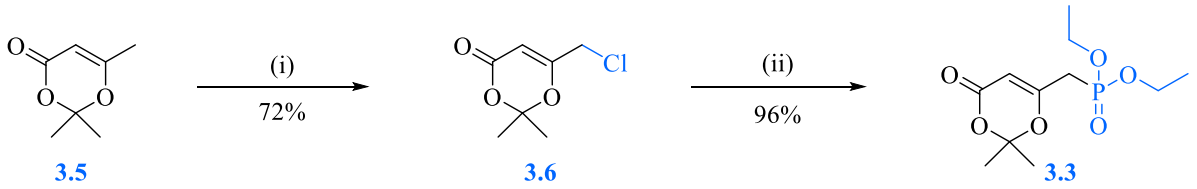
The convergent assembly of this first key subunit appeared straightforward and was thought achievable *via* a Horner-Wadsworth-Emmons (HWE) olefination reaction between phosphonate **3.3** and aldehyde **3.4** (**Scheme 3.3**) so as to install the (*E*)-configured double bond between C4 and C5. Borylation of the alkenyl iodide **3.2** would then deliver fragment **A**. The 1,3-dioxinone moiety associated with target **3.2** was chosen in the construction of this coupling partner because:

i. the carbonyl moieties are protected in a manner that should allow for the use of lithium di-*iso*-propylamine to effect the necessary lithiation and chlorination steps required for the preparation of phosphonate **3.3**.
ii. thermolysis of this functionalised 1,3-dioxinone would generate, *in situ*, a highly reactive acylketene species that could be trapped by either added or internal nucleophiles.[125]



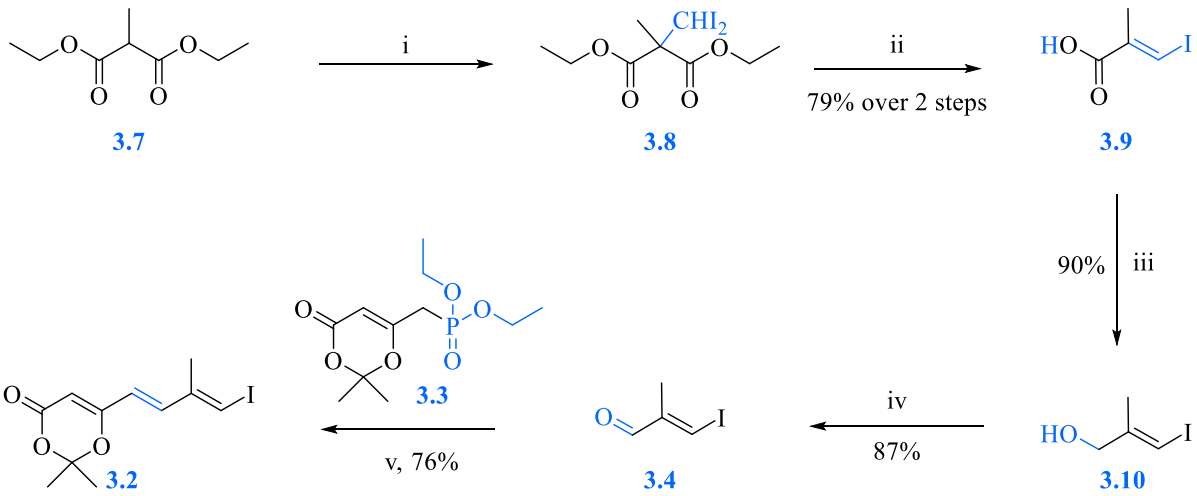
Scheme 3.3: ***Retrosynthetic Analysis of Alkenyl Iodide 3.10.***

The synthesis began with the preparation of phosphonate **3.3** following the procedure of Boeckman and Thomas (**Scheme 3.4**).[126] So, the known dioxinone **3.5** was deprotonated with lithium di-*iso*-propylamine (LDA) at −78 °C and the resulting anion quenched with hexachloroethane at −50 °C to afford chloride **3.6** in 72% yield. This last compound was converted into the corresponding phosphonate **3.3** (96%) by treating it with the sodium salt of diethyl phosphite at room temperature.



Scheme 3.4. ***Reagents and Conditions*** (i) LDA, C_2Cl_6, THF, −78 to −50 °C; (ii) NaH, $(EtO)_2P(O)H$, THF, DMF, 0 to 18 °C.

The aldehyde **3.4** (**Scheme 3.5**) to be coupled with phosphonate **3.3** was prepared by first treating diethyl 2-methylmalonate (**3.7**) with diiodocarbene (generated *in situ* by reaction of iodoform and sodium hydride) in refluxing ether.[127] The resulting carbene insertion product, namely diethyl di-iodomethylmethylmalonate (**3.8**), was itself converted into (*E*)-3-iodo-2-methylacrylic acid (**3.9**) (79% over 2 steps) through successive saponification (with potassium hydroxide) and decarboxylation reactions, the latter being effected by refluxing the intermediate acid in ethanol-water. Reduction of compound **3.9** with lithium aluminium hydride furnished the allylic alcohol **3.10** (90%) that was oxidised with manganese dioxide to 3-iodomethacrolein (**3.4**). This was obtained in 87% yield. The foreshadowed Horner-Wadsworth-Emmons (HWE) olefination reaction involved generating the anion of phosphonate **3.3** (through reaction with sodium hydride) and then treating this with acrolein **3.4** and so generating the alkenyl iodine **3.2** (76%). This product was obtained exclusively as the (*E*)-isomer, as evident from a 15.5 Hz coupling observed between C4-H and C5-H in the ^{1}H NMR spectrum (**Figure 3.1**).



Scheme 3.5. ***Reagents and Conditions*** (i) NaH, CHI_3, Et_2O, 35 °C, 20 h; (ii) KOH, EtOH-H_2O, 100 °C, 16 h; (iii) $LiAlH_4$, Et_2O, 0 to 18 °C, 4 h; (iv) MnO_2, DCM, 18 °C, 4 h; (v) NaH, THF, −78 to 18 °C, 1 h.

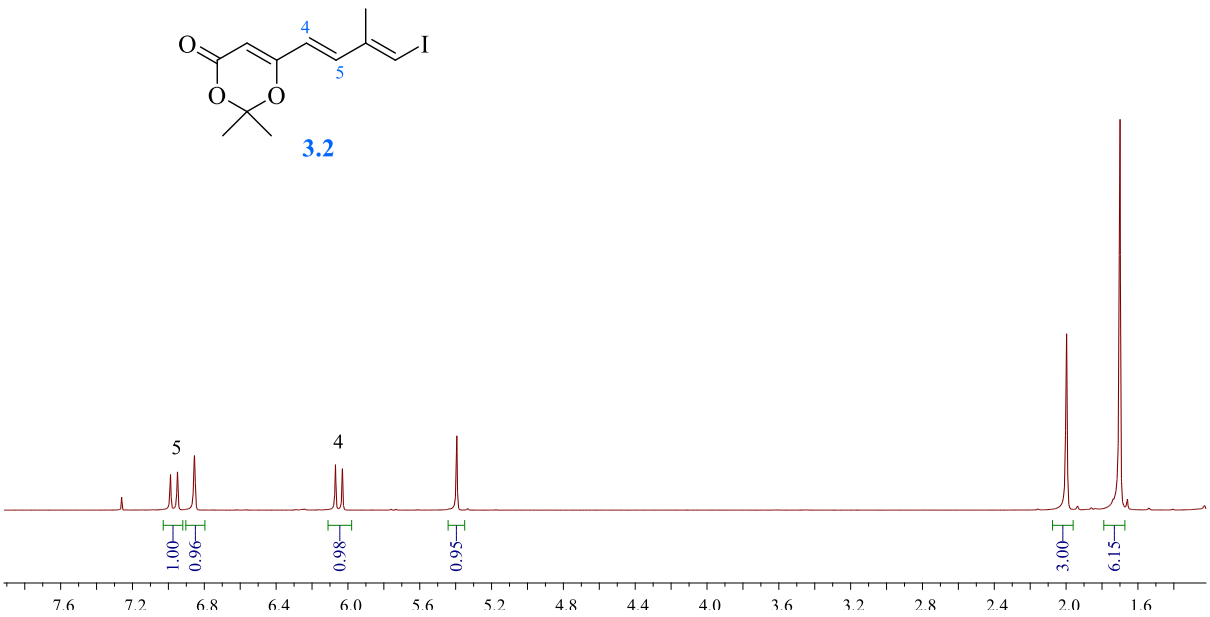
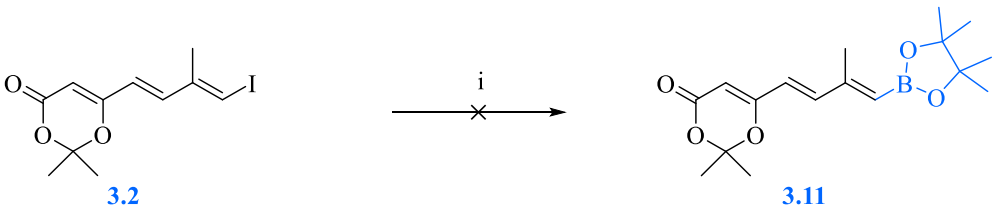


Figure 3.1. ***400 MHz ^{1}H NMR Spectrum of Alkenyl Iodide 3.2 (recorded in* d*-chloroform).***

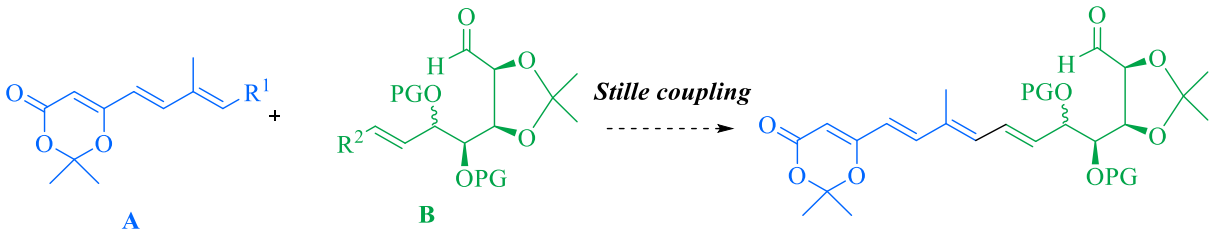
3.3.2. Borylation of Alkenyl Iodide 3.2

With alkenyl iodide **3.2** in hand, the Miyaura borylation of this material was investigated in efforts to prepare fragment **A**, namely **3.11**, (**Scheme 3.6**) required in the Suzuki cross-coupling reaction planned for the assembly of the Southern Hemisphere of macrolactam **3.1**. This transformation turned out to be challenging. So, for example, heating a mixture of compound **3.2**, pinacol borane, triethylamine, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)-dichloride dichloromethane complex in dioxane at 80 °C for sixteen hours did not provide the desired product. Rather, a complex reaction mixture was observed. Similarly, using bis(pinacolato)-diboron and potassium acetate[128] also only led to complex reaction mixtures under the same conditions. These outcomes may result from the sensitivity of the 1,3-dioxinone moiety to both base and heat.



Scheme 3.6. ***Reagents and Conditions*** (i) pinacol borane, $PdCl_2(dppf)•CH_2Cl_2$, Et_3N, dioxane, 80 °C, 16 h; or bis(pinacolato)diboron, $PdCl_2(dppf)•CH_2Cl_2$, KOAc, dioxane, 80 °C, 16 h.

In light of these difficulties, it was concluded that the Suzuki-Miyaura cross-coupling reaction could not be used to connect fragments **A** and **B**. As such, a Stille cross-coupling reaction was planned instead and wherein a stannane moiety could be associated with either fragment **A** or **B** (both options shown in **Scheme 3.7**). Accordingly, attention turned to the preparation of stannane **B** (see option 1) in the first instance.

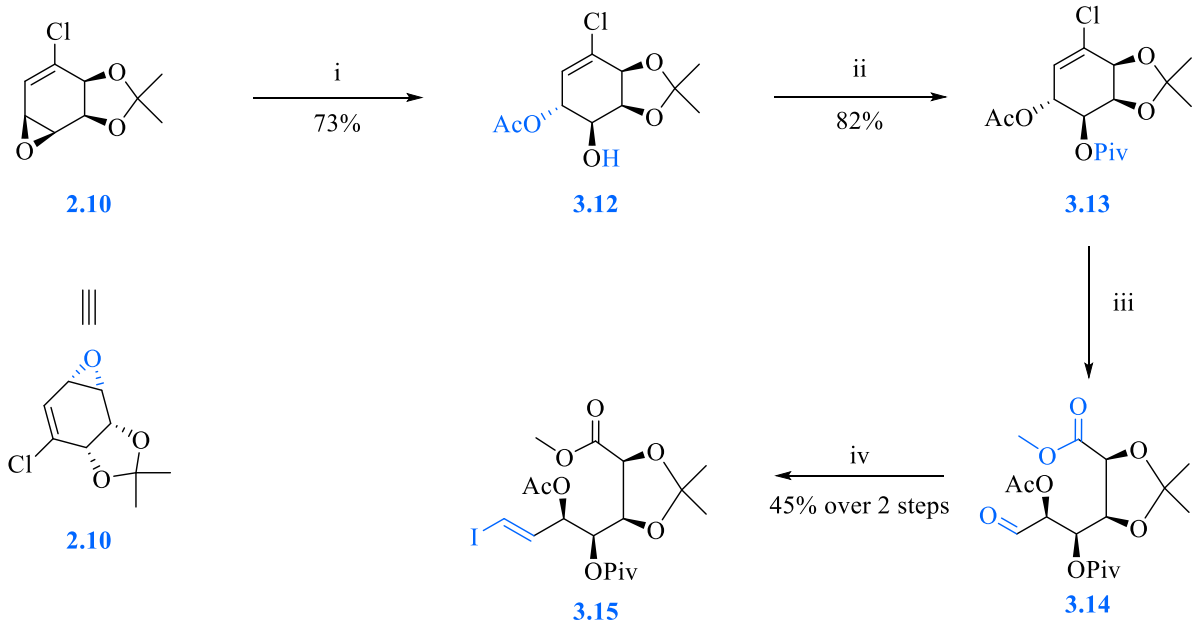


Scheme 3.7. ***Stille Cross-Coupling Reaction for Connection of Fragments A and B.***

3.4. Synthesis of Fragment B

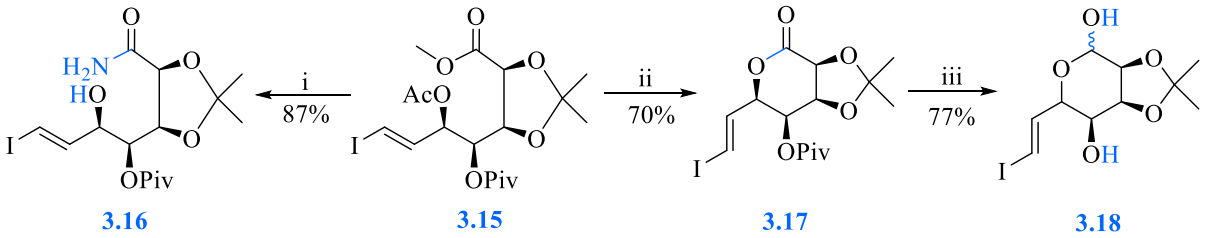
3.4.1. Preparation of the Pivaloate-Protected Fragment B

The synthesis of the revised form of fragment **B** started with the readily accessible epoxide **2.10** (prepared as described in Section **2.3.1**) that was regioselectively opened with acetic acid and a catalytic amount of phosphoric acid to deliver diol mono-acetate **3.12** (73%) (**Scheme 3.8**). The associated alcohol was protected as a pivaloate **3.13** (82%) under conventional conditions and this was subjected to ozonolysis in the presence of methanol. After reductive work-up with triphenylphosphine the rather unstable aldehyde **3.14** was obtained. Immediate submission of this aldehyde to a Takai olefination reaction using anhydrous chromium chloride and iodoform then afforded the alkenyl iodide **3.15** in 45% yield (over the two steps from precursor **3.13**).



Scheme 3.8. ***Reagents and Conditions*** (i) H_3PO_4 cat., acetic acid, 18 °C, 4 h; (v) Piv-Cl, DMAP, Et_3N, DCM, −0 to 18 °C, 16 h; (vi) ozone, pyridine, DCM/MeOH (4:1 *v/v*), −78 °C, then PPh_3, 18 °C, 1 h; (vii) $CrCl_2$, CHI_3, THF, 18 °C, 16 h.

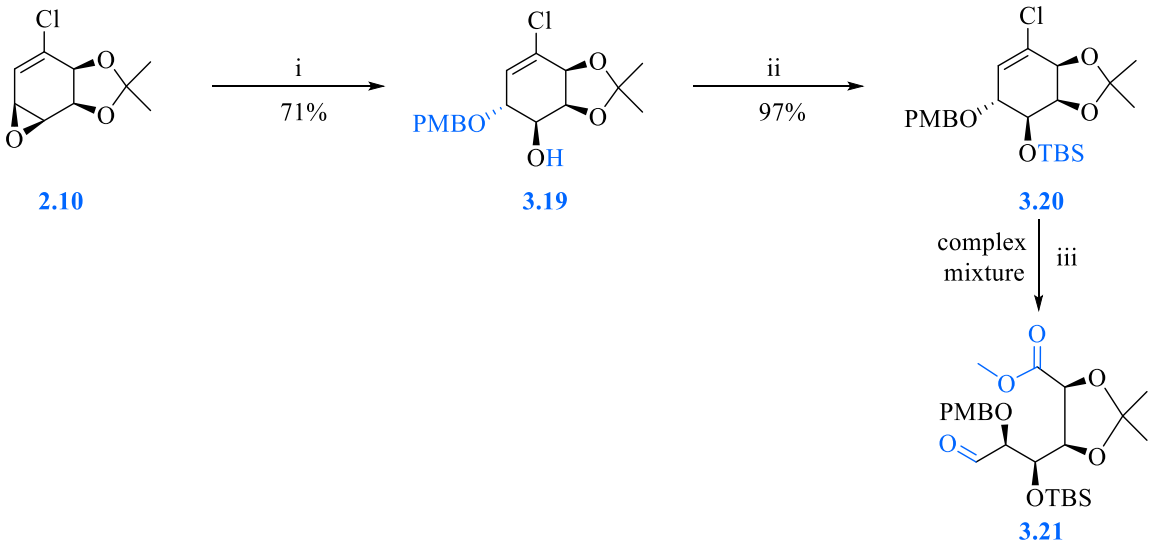
With compound **3.15** in hand, it was decided to pursue a method for the formation of the $\Delta^{14,15}$-(*Z*)-olefinic residue within target **3.1** (see **Scheme 3.1**) before converting the alkenyl iodide into the alkenyl stannane. In order to do so, the methyl ester moiety within compound **3.15** had to be reduced to the corresponding aldehyde, perhaps by using di-*iso*-butylaluminium hydride. Prior to carrying out such an operation, the acetate residue within compound **3.15** needed to be replaced by another protecting group that was stable to the reducing conditions being contemplated. However, treatment of acetate **3.15** (**Scheme 3.9**) with potassium carbonate in methanol failed to give the selectively deprotected alcohol. Indeed, both the acetate and pivaloate ester units were cleaved when this reagent was employed and lactonisation then followed. While the use of aqueous ammonia led to the desired alcohol, the formation of this was accompanied by amide formation to give compound **3.16** (87%). Gratifyingly, it was found that using magnesium methoxide allowed for cleavage of the acetyl group, although this newly formed alcohol then cyclised to give lactone **3.17** in 70% yield and reaction of this lactone with di-*iso*-butylaluminium hydride led to the deprotected lactol **3.18** (77%). The generation of lactone **3.17** and lactol **3.18** as just described established that the pivaloate could not serve as a suitable protecting group in this particular instance. Accordingly, the use of the TBS-ether was explored as an alternative.



Scheme 3.9. ***Reagents and Conditions*** (i) NH_4OH, MeOH, 18 °C, 4 h; (ii) $Mg(OMe)_2$, THF, 18 °C, 4 h; (iii) DIBAl-H, DCM, −78 °C, 30 min.

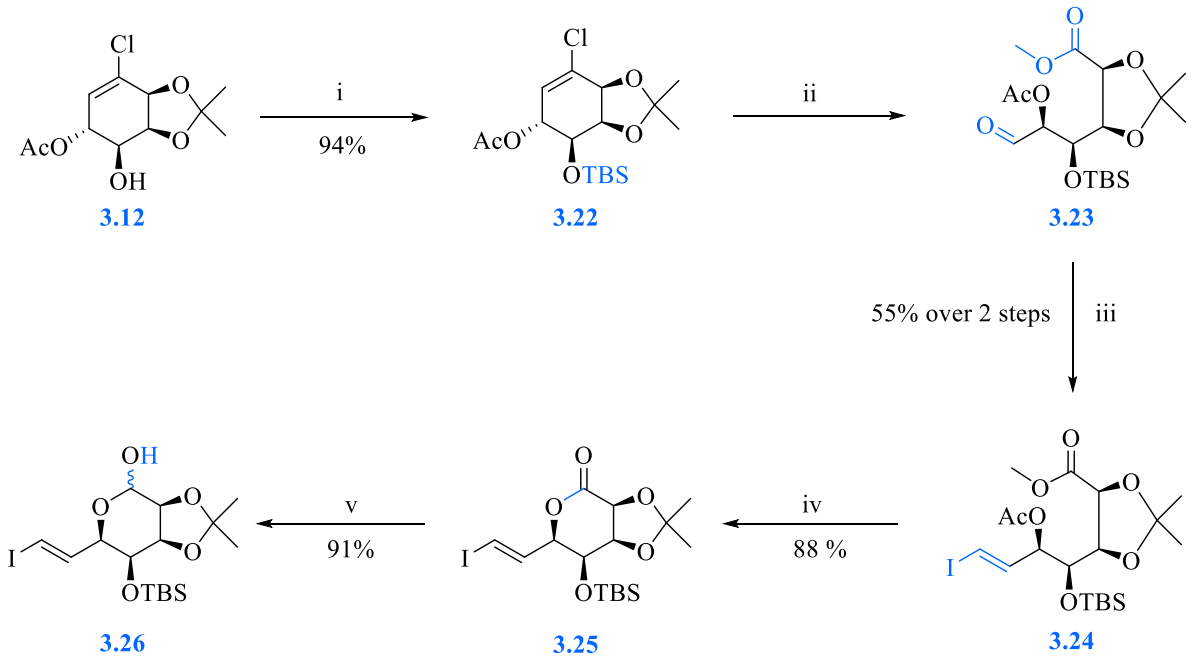
3.4.2. Preparation of the TBS-Ether-Protected Fragment B

It was thought the lactonisation "issue" encountered during the course of the studies described immediately above could be circumvented by switching from an acetate to a PMB-ether protecting group. Accordingly, regioselective ring-opening of the epoxide **2.10** (**Scheme 3.10**) with *p*-methoxybenzyl alcohol and a catalytic amount of copper(II) tetrafluoroborate was carried out and the alcohol **3.19** (71%) so obtained was then protected as the TBS-ether **3.20** (97%) under conventional conditions. Disappointingly, exposure of compound **3.20** to ozone only gave a complex reaction mixture even when using Sudan III dye as indicator to detect the point at which oxidative cleavage of olefin had taken place without the benzyl ether beginning to react.[129]



Scheme 3.10. ***Reagents and Conditions*** (i) PMB-OH, $Cu(BF_4)_2$, DCM, 18 °C, 6 h; (ii) TBS-Cl, imidazole, DMF, 18 °C, 2 h; (iii) ozone, pyridine, DCM/MeOH (4:1 *v*/*v*), −78 °C, then PPh_3, 18 °C, 1 h.

Given the last result, it was decided to follow the previously established sequence starting with protection of the alcohol **3.12** (**Scheme 3.11**) as a TBS-ether **3.22** (94%) using conventional conditions. Submission of this product to ozonolysis followed by Takai olefination of the aldehyde so-formed furnished the alkenyl iodide **3.24** in 55% over the two steps. Finally, cleavage of the acetate followed by reduction of the ensuing lactone **3.25** afforded the lactol **3.26** as a 3:7 mixture of diastereomers which was obtained in 91% combined yield.

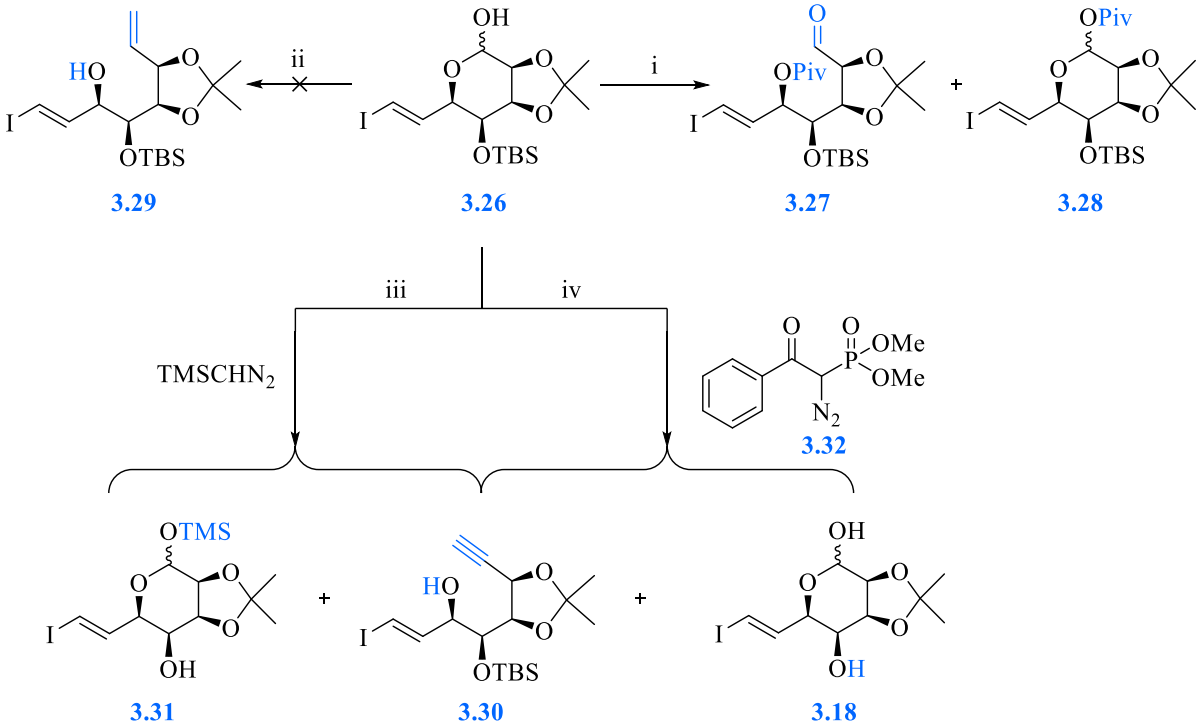


Scheme 3.11. ***Reagents and Conditions*** (i) TBS-Cl, imidazole, DMF, 18 °C, 2 h; (ii) ozone, pyridine, DCM/MeOH (4:1 *v/v*), −78 °C, then PPh_3, 18 °C, 1 h; (iii) $CrCl_2$, CHI_3, THF, 18 °C, 16 h; (iv) $Mg(OMe)_2$, THF, 18 °C, 4 h; (v) DIBAl-H, DCM, −78 °C, 30 min.

3.4.3. Attempts to Manipulate Lactol 3.26

Although the formation of lactol **3.26** was unexpected, it was still considered to have potential in the construction of fragment **B**. In particular, it could be deprotonated to reveal the corresponding alkoxy aldehyde that could then be quenched with pivaloyl chloride to provide compound **3.27** (**Scheme 3.12**). Unfortunately, when seemingly relevant conditions were employed only the "protected" lactol **3.28** (70%) was observed. Other attempts to open this lactol failed to give the desired product. For example, submission of it to a Wittig olefination reaction only led to the recovery of starting material rather than the formation of alkene **3.29**. Attempted homologation of the lactol using trimethylsilyldiazomethane[130] did not provide any

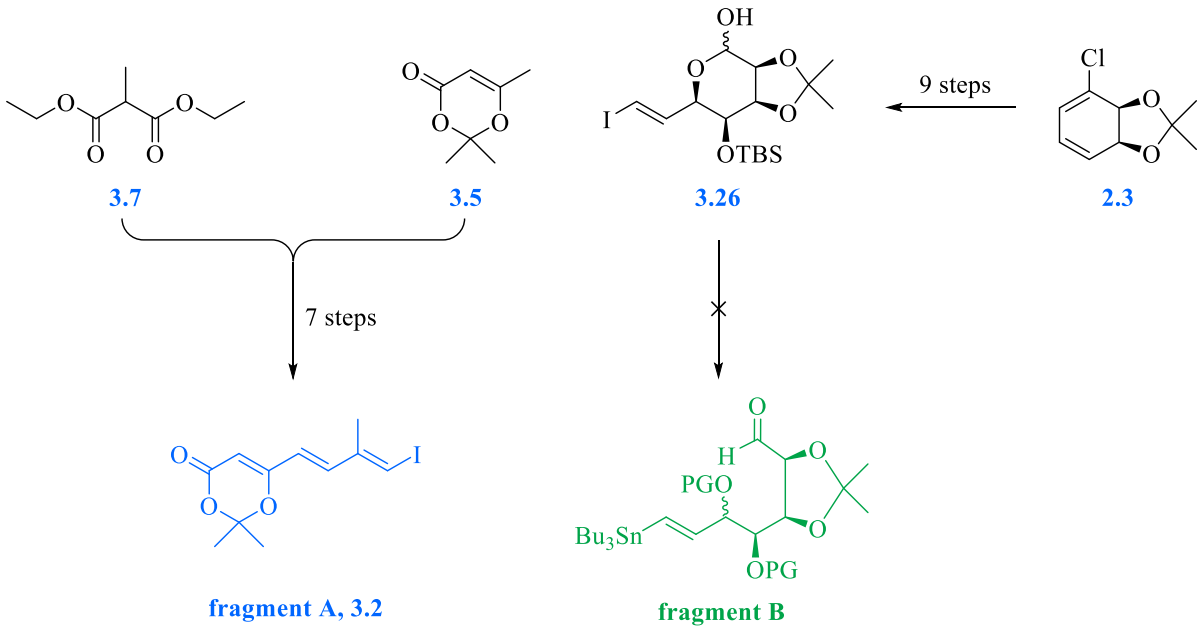
of the desired product, **3.30**. Only small amounts of TMS-protected lactol **3.31** were observed. Using the Bestmann-Ohira reagent **3.32** only provided a minor amount of the desired product **3.30**, the major one being TBS-deprotected lactol **3.18**.



Scheme 3.12. ***Reagents and Conditions*** (i) Piv-Cl, Et_3N, DMAP, DCM; (ii) $Ph_3P{=}CH_2$, *n*-BuLi; THF (iii) $TMSCHN_2$, LDA, THF; (iv) **3.32**, K_2CO_3, MeOH.

5. Conclusion

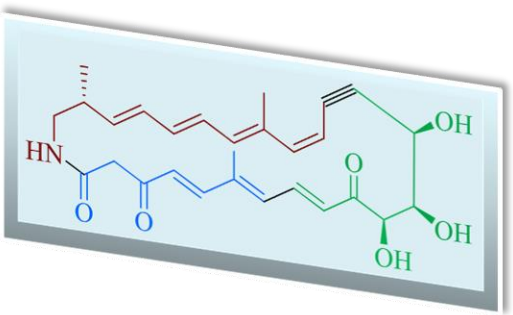
The alkenyl iodide **3.2** representing fragment **A** was successfully prepared by a straightforward sequence from two commercially available materials, namely dioxinone **3.5** and diethyl 2-methylmalonate **3.7** (**Scheme 3.13**). During the course of efforts to prepare fragment **B**, an unwanted lactonisation reaction thwarted efforts to secure the target compound. An alternate approach to this key building block was required and one is detailed in the next Chapter.



Scheme 3.13. ***Summary of Work Described in this Chapter (Three).***

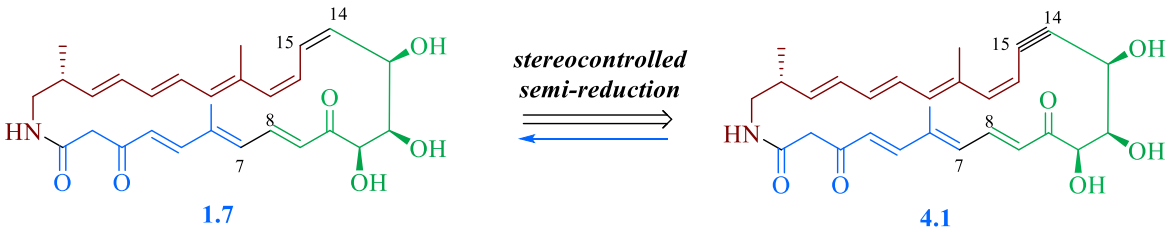
4. CHAPTER FOUR

Second-Generation Approach to a Substrate for Macrolactamisation



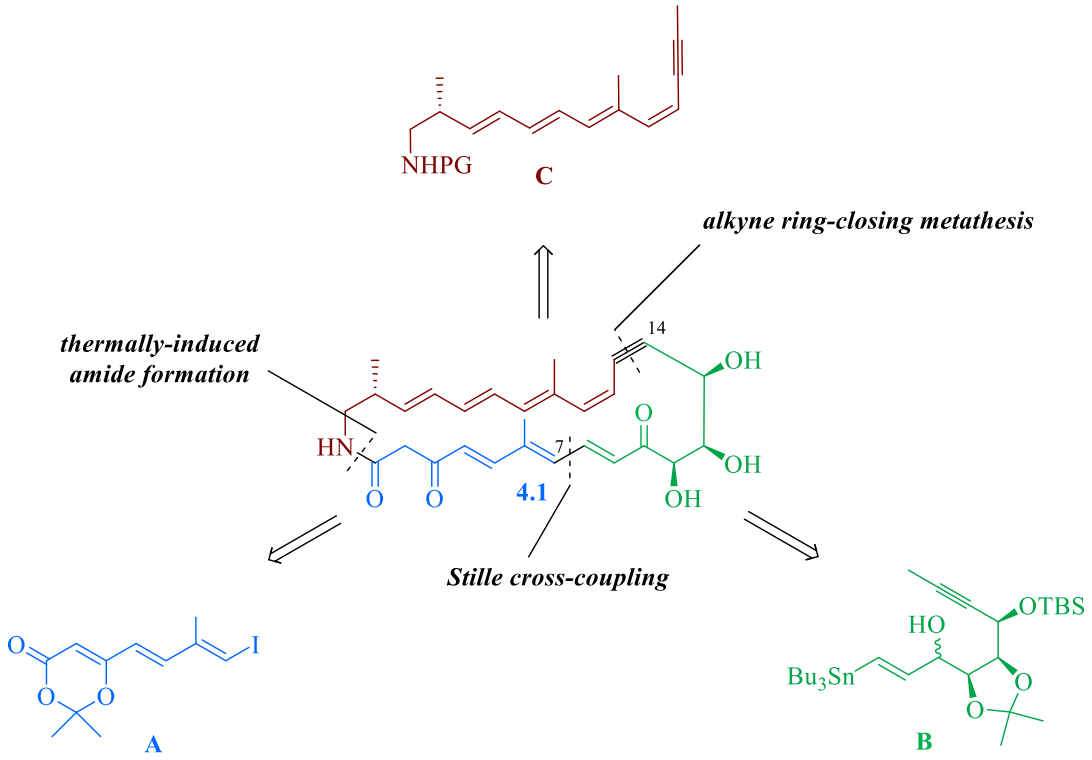
4.1. Retrosynthetic Analysis

The problems encountered during the course of the work described in Chapter Three prompted a re-evaluation of the approach to be taken in attempting to prepare lactam **1.7**. Specifically, it was now planned to synthesise macrolactam **1.7** by a pathway in which the C14-C15 (*Z*)-double bond, rather than the neighbouring (C16-C17) one, was obtained through a stereoselective semi-reduction of an acetylene linkage as seen, for example, in potential precursor **4.1** (**Scheme 4.1**). Such a step has some literature precedent.[131] As with the first approach, the (*Z*,*Z*)-diene **1.7** would be used as the substrate with which to perform the pivotal transannular and biomimetic [2+2]-cycloaddition reaction.



Scheme 4.1. ***Revised Strategy.***

A possible route to macrolactam **4.1** is shown in retrosynthetic form in **Scheme 4.2**. Thus, a Stille cross-coupling reaction would be used to establish the C7–C8 σ-bond and this would be followed by thermally-induced amide formation to attach fragment **C** and, finally, an alkyne ring-closing metathesis reaction to establish the macrocycle. This approach would require the synthesis of three key building blocks, namely alkenyl iodide **A**, alkenyl stannane **B**, and tetra-enyne **C**. The straightforward formation of fragment **A** (**3.2**) has already been described in Section **3.2.1**. It was decided to employ an inexpensive and readily available starting material, *D*-ribose, for the preparation of fragment **B** as a replacement for 3-chloro-*cis*-1,2-dihydrocatechol **2.3**. A major motivation for doing so is that the natural enantiomeric form of macrolactam **4.1** would be accessible by this means. The constructions of the crucial synthons **B** and **C** associated with this approach are described in the following sections.



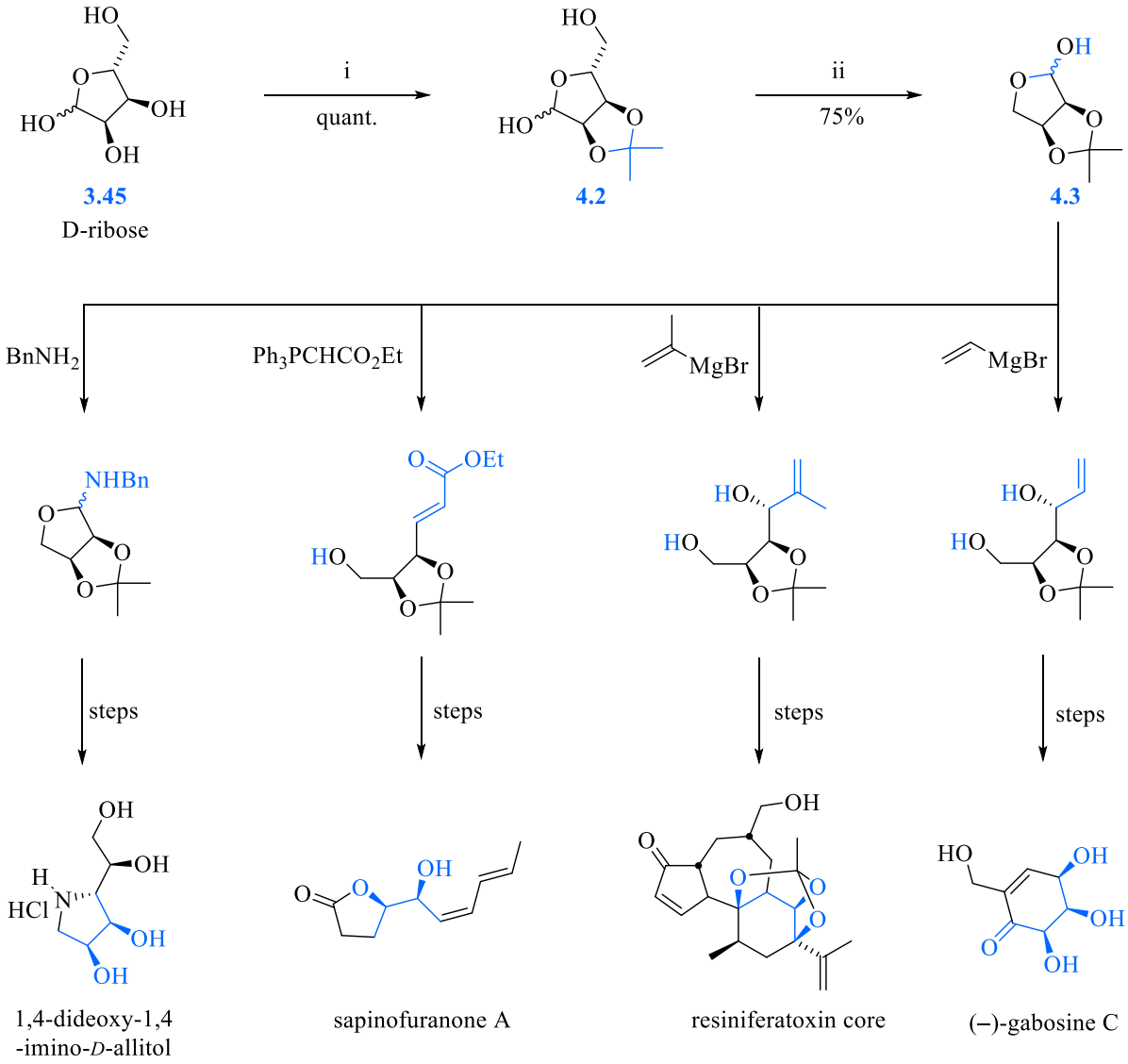
Scheme 4.2. ***Key Building Blocks (Fragments) Associated with the Assembly of Macrolactam 4.1.***

4.2. Synthesis of Fragment B and its Connection to A

4.2.1. From *D*-Ribose to Lactol 4.2

As noted above, it was anticipated that the stannane-containing fragment **B** could be synthesised from *D*-ribose. The reaction sequence started with treatment of this inexpensive starting material with acetone in the presence of catalytic quantity of sulfuric acid and so giving acetonide **4.2** in quantitative yield (**Scheme 4.3**). Reduction of this lactol with sodium borohydride followed by oxidative cleavage of the ensuing vicinal diol residue using sodium periodate then provided the lactol **4.3**[132] in 75% yield. Lactol **4.3** is a well-known chiron that reacts with a range of nucleophiles to give adducts of value in natural product synthesis.[133] It has, for example, been treated with vinylmagnesium bromide in the synthesis of (−)-gabosine C[133a] or with *iso*-propenylmagnesium bromide for the construction of tetracyclic core of resiniferatoxin.[133b] In addition, subjection of this masked aldehyde to Wittig olefination provided an intermediate employed in Bantu's synthesis of sapinofuranone A.[133c] Moreover, treatment of this lactol with *n*-butylamine delivered a lactamine that underwent nucleophilic

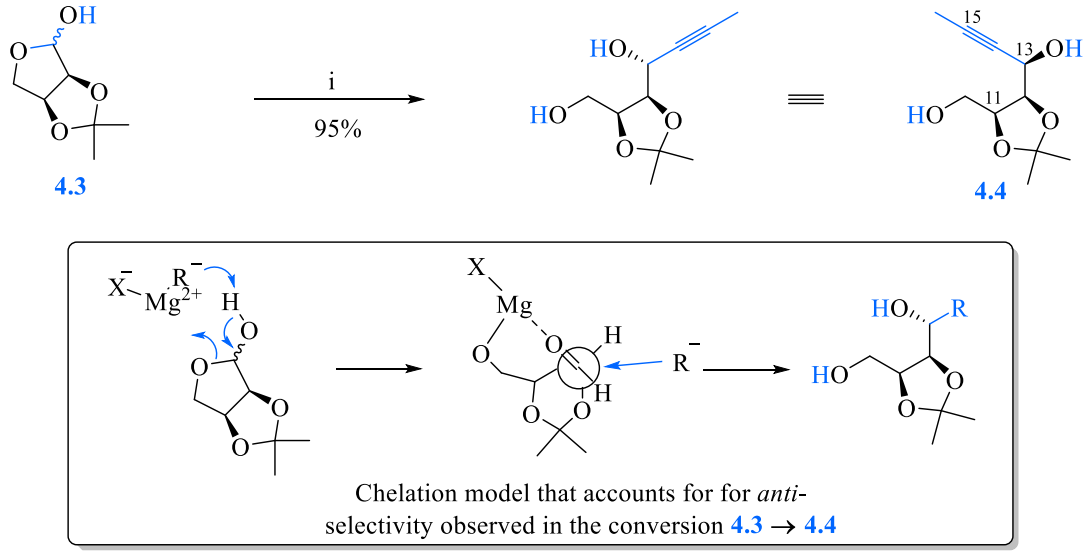
addition with vinylmagnesium bromide to give an alcohol that could be further elaborated to 1,4-dideoxy-1,4-imino-*D*-allitol.[133d]



Scheme 4.3. ***Preparation of Lactol 4.3 and Examples of its Application in Natural Product Synthesis. Reagents and Conditions*** (i) acetone, H_2SO_4 (cat.); 18 °C, 4 h (ii) a) $NaBH_4$, MeOH, 0 to 18 °C, 16 h; b) $NaIO_4$, *t*-BuOH-H_2O, 18 °C, 16 h.

4.2.2. Preparation of Alkenyl Stannane 4.9

As the first step in the synthesis of building block **4.9**, lactol **4.3** was reacted (**Scheme 4.4**) with 1-propynylmagnesium bromide to afford the ring-opened diol **4.4** as a single diastereoisomer. The newly generated stereocentre within compound **4.4** is *anti*-related to the adjacent acetonide-associated centre of chirality,[d] an outcome that can be accounted for by invoking the chelation-controlled addition process shown in the inset of Scheme **4.4**. Thus, the first equivalent of the Grignard reagent acts as a base to reveal the corresponding carbonyl and γ-alkoxy groups with the latter chelating to magnesium bromide. The second equivalent of the 1-propynyl anion attacks the carbonyl group from the less hindered face to deliver the observed diastereoisomer **4.4**. Related arguments have been advanced by Moon[134] and Rao[135] to account for the diastereoselective reactions they observed in similar systems.



Scheme 4.4. ***Reagents and Conditions*** (i) $H_3CC{\equiv}CMgBr$, THF, 0 °C, 1 h.

The ^{1}H NMR spectrum (**Figure 4.1**) of the product obtained from this reaction clearly indicated the formation of a single compound. The lowest field signal at δ 4.40 is a doublet of quartets (J = 6.7 and 2.2 Hz) and assigned to C13-H. This resonance couples to the signal at δ 4.13 (due to C12-H) that appears as a doublet of doublets (J = 6.7 and 6.5 Hz). The spectrum also displays the ABX spin system anticipated for the C10-H_2 methylene protons (J_{AB} = 11.7 Hz, J_{AX} = 4.8 Hz, J_{BX} = 6.5 Hz) which allowed for the assignment of the resonance at δ 4.30, that appears as a triplet of doublets (J = 6.5 and 4.8 Hz), to C11-H. The methyl doublet at δ

[d] The stereochemistry at this newly formed stereogenic center was confirmed by single-crystal X-ray analysis of derivative **5.3** (see Section **5.2.1**).

1.88 (J = 2.2 Hz, long range coupling to C13-H) was assigned to the methyl capped-alkyne unit. The protons of the diastereotopic acetonide methyl groups resonate as separate three-proton singlets at δ 1.49 and 1.40.

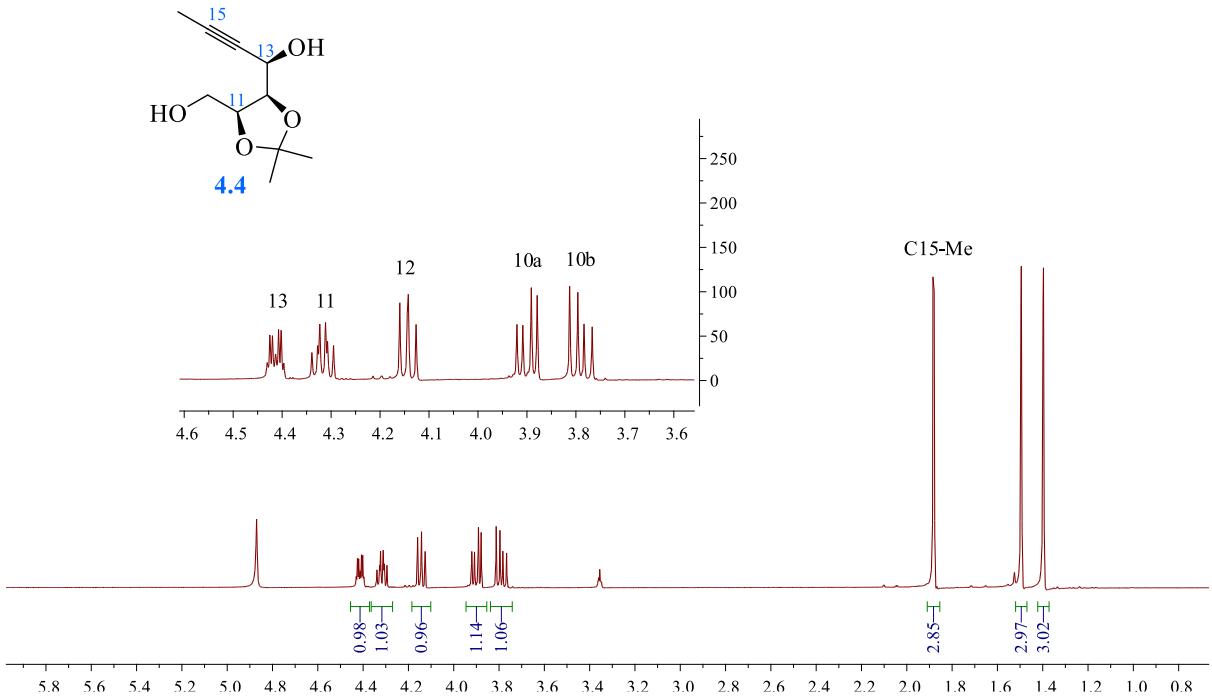
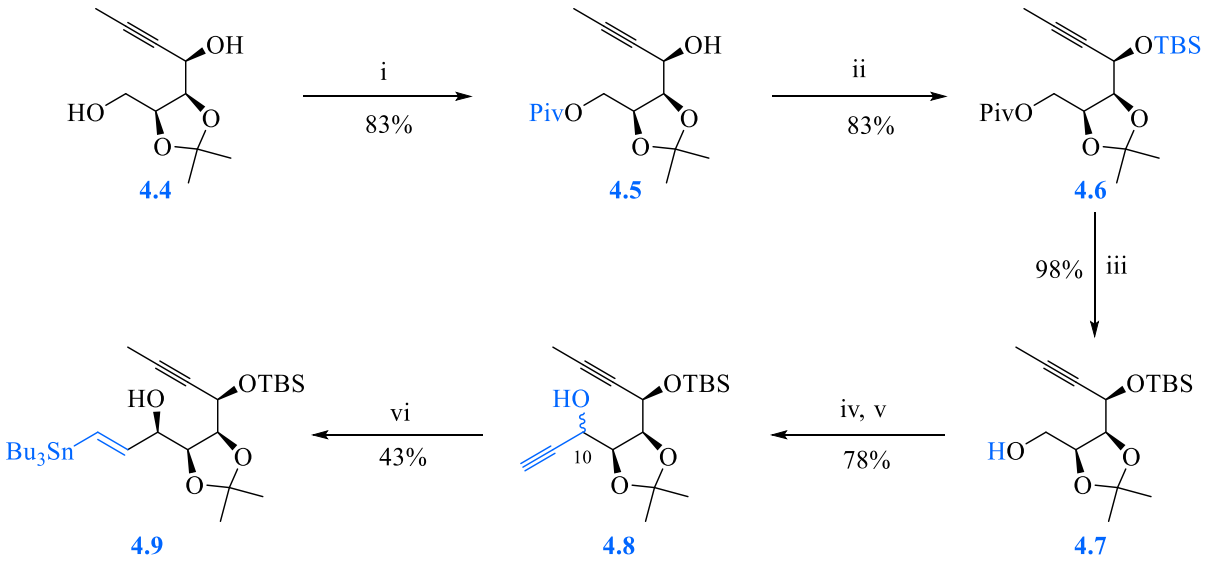


Figure 4.1. *400 MHz ^{1}H NMR Spectrum of Diol 4.4 (recorded in* d$_4$*-methanol).*

The primary alcohol residue within compound **4.4** was selectively protected (**Scheme 4.5**) as the corresponding pivaloate **4.5** [using pivaloate chloride, 4-(*N*,*N*)-dimethylamino-pyridine (DMAP) and trimethylamine, 83%] while the secondary alcohol was then converted into TBS-ether **4.6** (using *tert*-butyldimethylsilyl chloride and imidazole, 83%). Removal of the pivaloate protecting group was achieved by treating compound **4.6** with di-*iso*-butylaluminium hydride and so providing primary alcohol **4.7** in 98% yield. Compound **4.7** was subjected to Swern oxidation and the product aldehyde immediately reacted with ethynylmagnesium bromide to afford an inseparable epimeric mixture of the α- and β- forms of the propargylic alcohol **4.8** (23:77 α/β, 78%). Both epimers should be usefully carried forward in the synthetic sequence as the C10 alcohol would be oxidised to the corresponding ketone at a later stage. Thus, submission of this epimeric mixture of alkynes to a hydrostannylation reaction using bis(triphenylphosphine)palladium(II) dichloride as catalyst and tri-*n*-butyltin hydride as the source of tin gave a mixture of alkenyl stannanes from which the pure β-isomer **4.9** was isolated (as the major product) in 43% yield.[e]

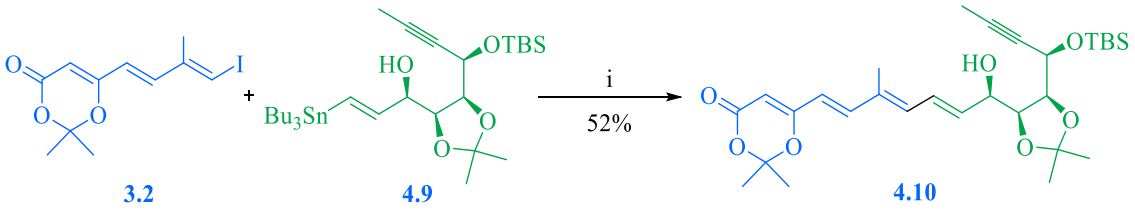
[e] An explanation for the selective formation of the β-epimer can be found in Section **5.3.2**.



Scheme 4.5. ***Reagents and Conditions*** (i) Piv-Cl, DMAP, Et_3N, DCM, −78 °C, 1 h; (ii) TBS-Cl, imidazole, DMF, 18 °C, 2 h; (iii) DIBAl-H, DCM, −78 °C, 30 min; (iv) $(COCl)_2$, DMSO, Et_3N, DCM, −78 to 0 °C, 1 h; (v) HC≡CMgBr, THF, −15 °C, 1 h; (vi) $Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH, DCM, −78 to 0 °C, 30 min.

4.2.3. The Stille Cross-Coupling Reaction

Having obtained the targeted alkenyl stannane **4.9** as described above, the Stille cross-coupling of this with the readily prepared alkenyl iodide fragment **A** (formed as described in Section **3.3.1**) was investigated. The reaction was performed using tetrakis(triphenylphosphine)palladium(0), in combination with triphenylphosphine, a large excess of copper(I) iodide and lithium chloride under anaerobic conditions at 40 °C in *N*,*N*-dimethylformamide (**Scheme 4.6**).[16] By such means, the desired product **4.10** was obtained in 52% yield.



Scheme 4.6. ***Reagents and Conditions*** (i) $Pd(PPh_3)_4$, PPh_3, CuI, LiCl, DMF, 40 °C, 16 h.

The ^1H and ^{13}C NMR spectral data obtained on the product arising from the union of fragments **A** and **B**, were consistent with the assigned structure **4.10** (**Table 4.1**). Thus, the ^1H NMR spectrum (**Figure 4.2**) exhibits six resonances due to olefinic protons as would be expected for a compound containing four *trans*-configured double bonds that bear two

branching substituents. The ^{13}C NMR spectrum (**Figure 4.3**) displays all of the expected twenty-nine signals, sixteen of which correspond to the carbons (C1-C15 and C26) of the Southern Hemisphere of macrolactam **4.1**.

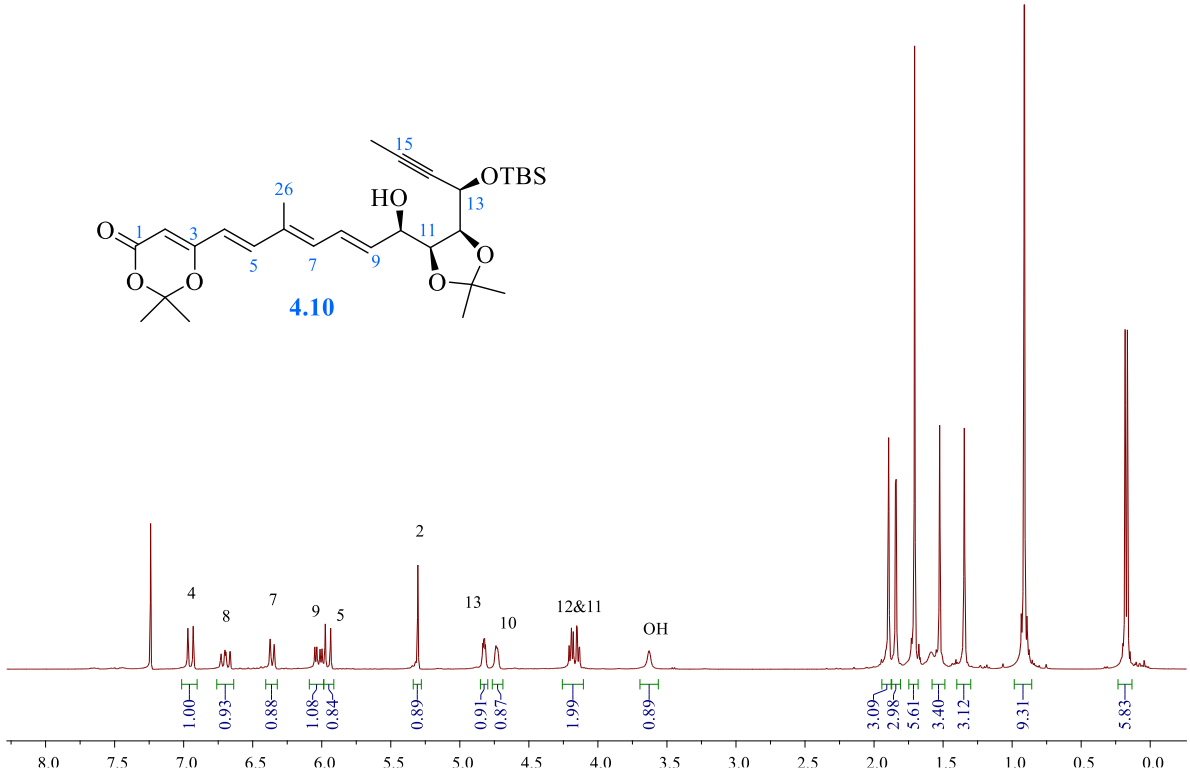


Figure 4.2. *400 MHz ^{1}H NMR Spectrum of Stille Coupling Product 4.10 (recorded in* **d**-*chloroform).*

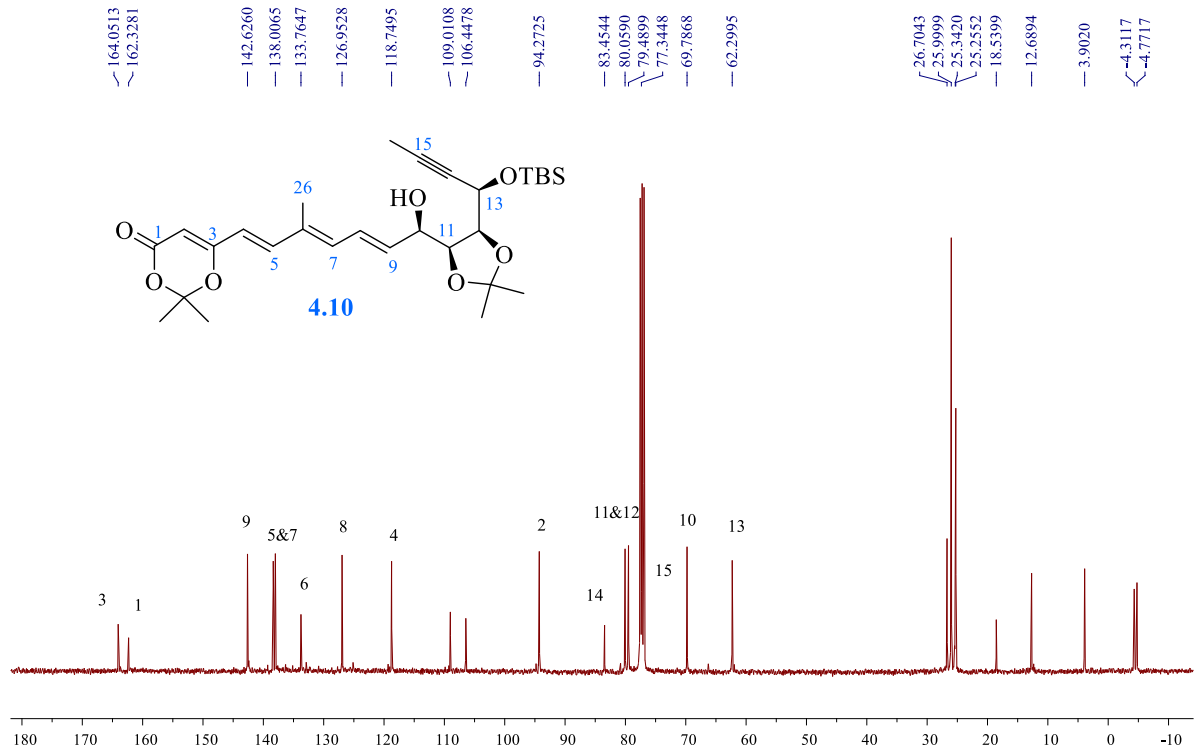


Figure 4.3. *100 MHz ^{13}C NMR Spectrum of Stille Coupling Product 4.10 (recorded in* **d**-*chloroform).*

Table 4.1. ***Assignment of ^{1}H and ^{13}C NMR Data for Compound 4.10*.***

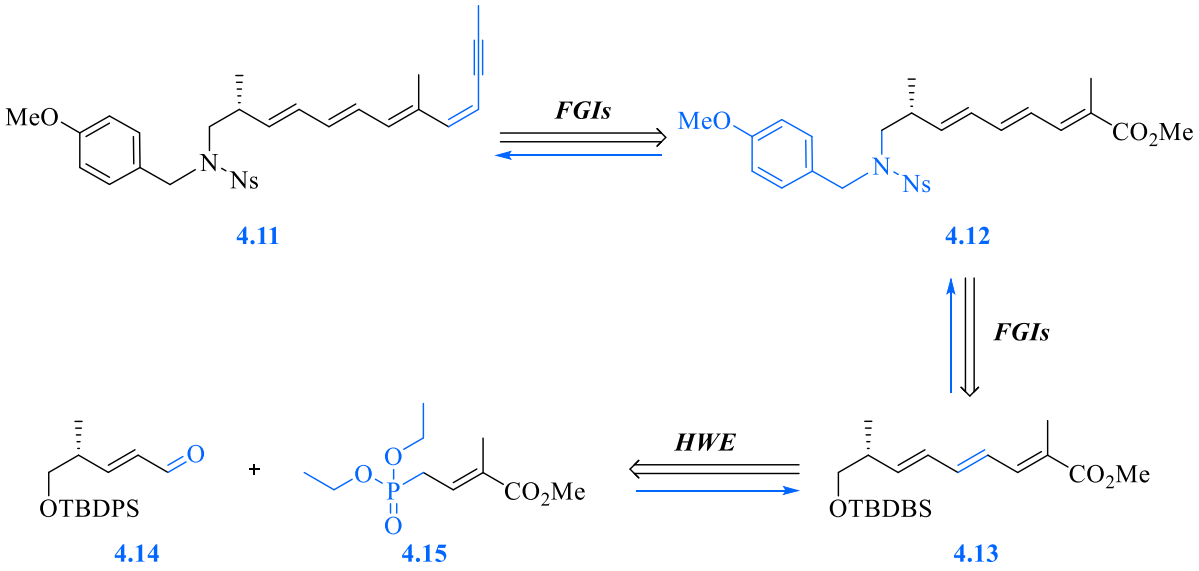
C/H	δ_H	mult (*J* in Hz)	δ_C	
1			162.3	C
2	5.30	s	94.3	CH
3			164.0	C
4	6.95	d (15.5)	118.7	CH
5	5.95	d (15.5)	138.4	CH
6			133.8	C
7	6.36	d (11.4)	138.0	CH
8	6.70	dd (15.0, 11.4)	126.9	CH
9	6.02	dd (15.0, 5.8)	142.6	CH
10	4.73	m	69.8	CH
10-OH	3.63	brs		
11, 12	4.14-4.17	m	80.1, 79.5	2 x CH
13	4.82	m	62.3	CH
14			83.4	C
15			77.3	C
15-methyl	1.84	d (2.2)	3.9	CH_3
26	1.89	s	12.7	CH_3
-TBS	0.91	m	26.0	3 x CH_3
	0.18, 0.16	s, s	−4.3, −4.8	2 x CH_3
			18.5	C
-acetonide	1.52, 1.35	s, s	26.7, 25.3	2 x CH_3
			109.0	C
-dioxinone	1.71	s	25.2	2 x CH_3
			106.4	C

* Data acquired in *d*-chloroform at 400 or 100 MHz (for ^{1}H and ^{13}C NMR data, respectively).

4.3. Synthesis of Fragment C

4.3.1. Retrosynthetic Analysis

The retrosynthetic analysis of polyenyne **4.11** shown below in **Scheme 4.7**, a specifically *N*-protected form of fragment **C** shown earlier (see **Scheme 4.2**), suggests this should be accessible from triene **4.12** through a sequence of standard functional group interconversions involving reduction, oxidation and Julia olefination steps. Sulfonamide **4.12** itself would be generated from the *tert*-butyldiphenylsilyl (TBDPS) ether **4.13** which could, in turn, be assembled from aldehyde **4.14** and phosphonate **4.15** *via* a Horner-Wadsworth-Emmons (HWE) olefination reaction. Attempts to implement this synthetic plan are detailed in the following sections.

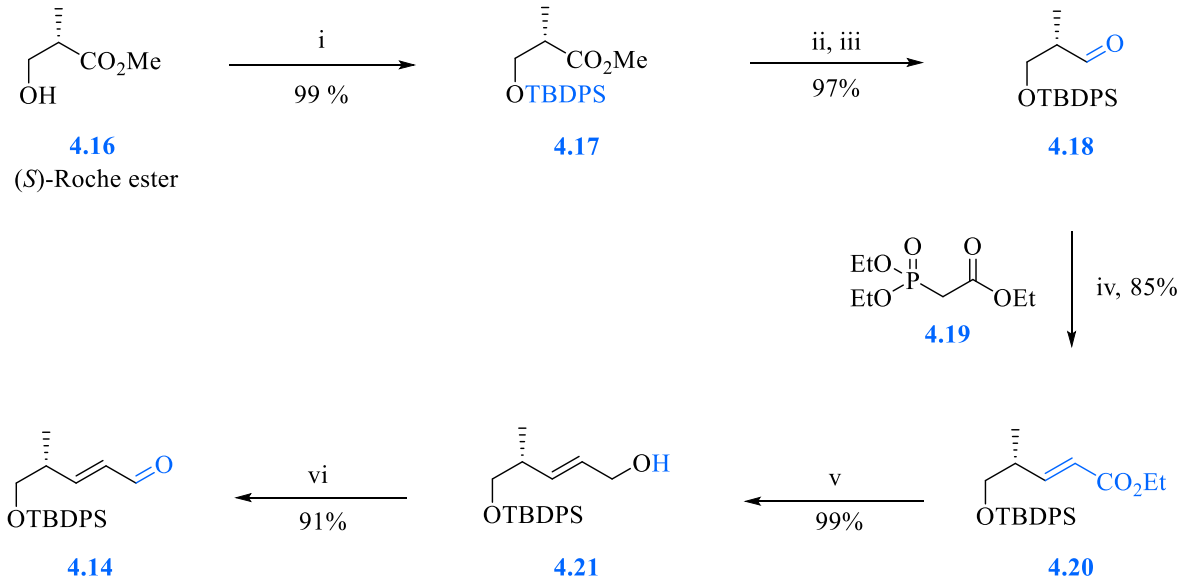


Scheme 4.7. ***Retrosynthetic Analysis of Fragment C.***

4.3.2. Preparation of Triene 4.13

The synthesis of sub-target **4.13** began with the preparation of aldehyde **4.14**. Thus, commercially available (*S*)-3-hydroxy-2-methylpropionate [(*S*)-Roche ester] **4.16** (**Scheme 4.8**) was first protected as the TBDPS-ether **4.17** (99%) by treating the alcohol with *tert*-butyldiphenylsilyl chloride and imidazole.[136] This product was converted into the corresponding aldehyde **4.18** (82%) through a DIBAl-H mediated reduction of the ester motif

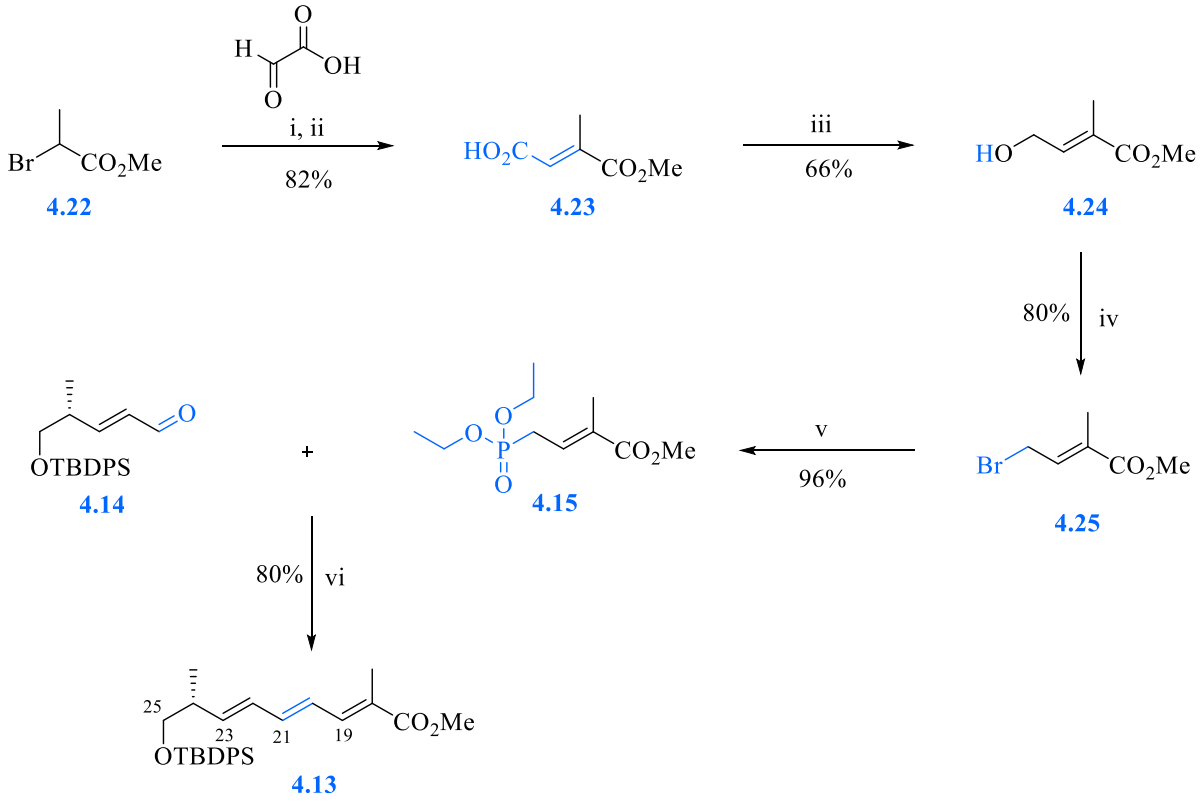
using hexane as solvent. A slightly higher yielding, two-step sequence starting with a reduction using lithium borohydride and submission of the crude product to the Swern oxidation also delivered aldehyde **4.18**, this time in 97% yield. A Horner-Wadsworth-Emmons reaction involving compound **4.18** and triethyl phosphonoacetate **4.19** was effected using the Masamune-Roush's protocol[77] [involving lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the key reagents] and so affording the conjugated ester **4.20**[137] (85%). This was converted, in 99% yield, into alcohol **4.21** by treating it with di-*iso*-butylaluminium hydride. Allylic oxidation of product **4.21** using manganese dioxide then provided the desired aldehyde **4.14** in 91% yield.



Scheme 4.8. ***Reagents and Conditions*** (i) TBDPS-Cl, imidazole, DMF, 0 to 18 °C, 16 h; (ii) $LiBH_4$, MeOH-Et_2O, 0 to 18 °C, 2 h; (iii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 to 0 °C, 1 h; (iv) LiCl, DBU, acetonitrile, 18 °C, 16 h; (v) DIBAl-H, hexane, −78 °C, 2 h; (vi) MnO_2, DCM, 18 °C, 3 h.

The four-step synthetic sequence used to produce the previously reported[138] phosphonate **4.15** (**Scheme 4.9**) commenced with the commercially available methyl 2-bromopropionate (**4.22**). Heating this material in acetonitrile with triphenylphospine generated a stabilised Wittig reagent that was condensed with glyoxylic acid monohydrate to deliver the *E*-configured acid **4.23** in 82% yield. Selective reduction of the carboxylic acid residue associated with this product (in the presence of the associated methyl ester) could be effected using the borane-tetrahydrofuran complex and this generated allylic alcohol **4.24** in 66% yield. An Apel reaction was employed to convert the latter alcohol into allylic bromide **4.25** which was obtained in 80% yield. Heating this bromide in neat triethyl phosphite, so as to effect a Michaelis-Arbuzov reaction, then gave the phosphonate **4.15**[139] in 96% yield. Finally,

condensation of this phosphonate and aldehyde **4.14** in the presence of *n*-butyl lithium furnished the all-*E*-triene **4.13** (80%).



Scheme 4.9. ***Reagents and Conditions*** (i) PPh_3, ACN, 65 °C, 16 h; (ii) DIPEA, glyoxylic acid monohydrate, 0 to 18 °C, 16 h; (iii) BH_3.THF, THF, −15 to 18 °C, 16 h; (iv) CBr_4, PPh_3, DCM, 0 to 18 °C, 30 min; (v) $P(OEt)_3$, 110 °C, 2 h; (vi) *n*-BuLi, THF, −78 to 18 °C, 3.5 h.

The most notable features observed in the ^{1}H NMR spectrum of compound **4.13** (**Figure 4.4**) were the resonances associated with the triene moiety. The signal appearing at δ 7.22 was assigned to C19-H (tripartilactam numbering) and this is coupled (J = 11.0 Hz) with the signal due to the C20-H which appears at δ 6.40. This resonance, in turn, shows a coupling to the resonance at δ 6.50 that is attributed to C21-H. The other doublet of doublets (for C22- and C23-H) are centered at δ 6.21 and 5.85, respectively. The observed coupling constants of 14.8 Hz (between C21- and C20-H) and 15.3 Hz (between C22- and C23-H)

Table 4.2. ***^{1}H NMR Data for the Triene Moiety of Compound 4.13***

C/H	δ_H	mult (J in Hz)
19	7.22	d (11.0)
20	6.40	dd (14.8, 11.0)
21	6.50	dd (14.8, 10.2)
22	6.21	dd (15.3, 10.2)
23	5.85	dd (15.3, 7.4)

indicate an *E*-configuration about each of the associated double bonds. **Table 4.2** shows the mutual couplings between these relevant protons.

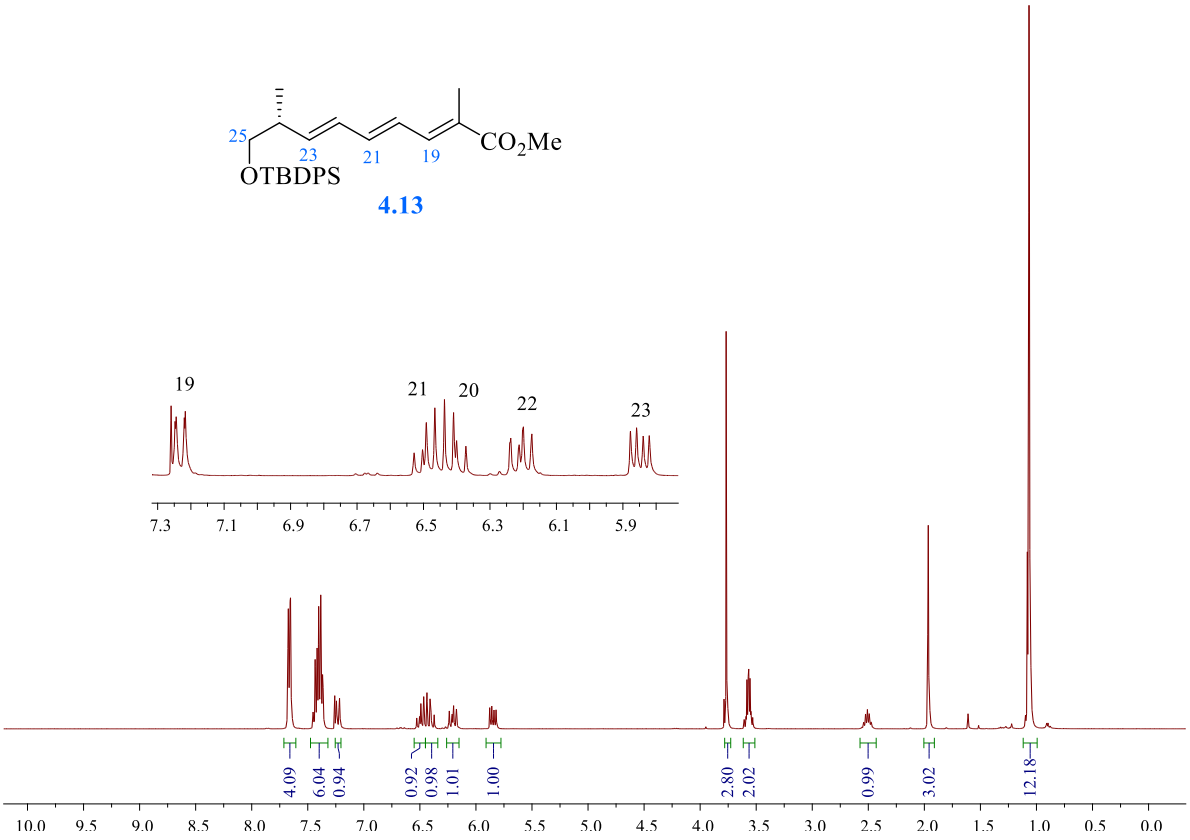
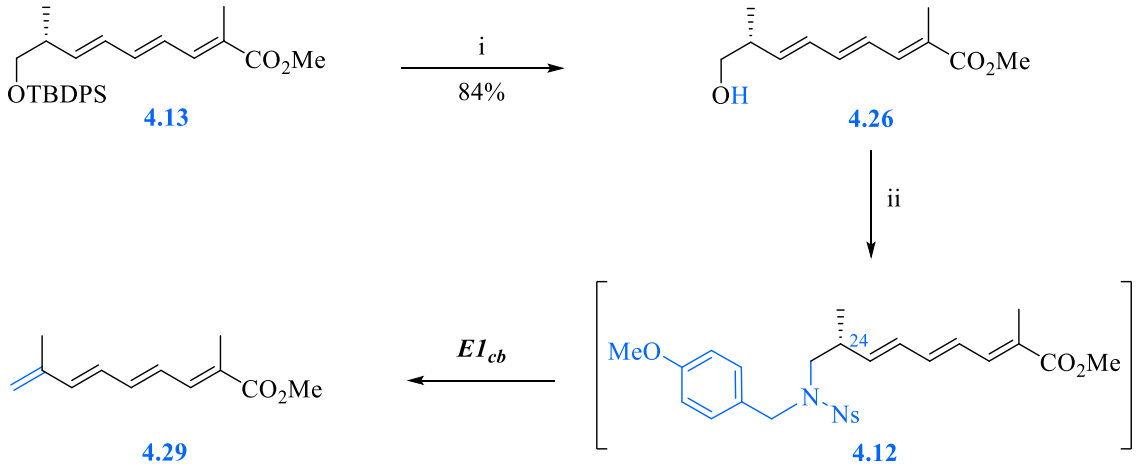
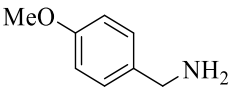
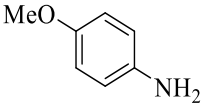
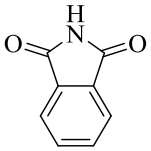
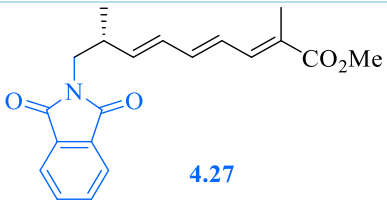
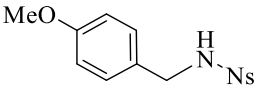
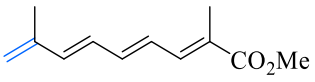


Figure 4.4. *400 MHz ^{1}H NMR Spectrum of Triene 4.15 (recorded in* **d**-*chloroform).*

In order to install the amine residue required in fragment **C**, a tetra-*n*-butylammonium fluoride (TBAF)-mediated desilylation reaction was used to convert ether **4.13** into the free alcohol **4.26** (84%) (**Scheme 4.10**). Then, with this alcohol in hand, instead of following a three-step sequence involving conversion of the alcohol into the corresponding azide, reduction of this to the amine and, finally, protecting this amine (with possibility of over protection to form a tertiary amine with the same protecting group), Mitsunobu reactions using various different amine derivatives as nucleophiles were explored as a means of introducing a protected amine directly. Thus, a solution of alcohol **4.26**, the relevant nitrogen-based nucleophile and triphenylphosphine in tetrahydrofuran was treated with di-*iso*-propyl azodicarboxylate (DIAD). The outcomes of these types of reactions are shown in **Scheme 4.10**. Unfortunately, no reaction was observed when using a primary amine such as *p*-methoxybenzylamine or *p*-methoxyaniline as a nucleophile - only starting material was recovered. However, when the more acidic nitrogen-centred nucleophile phthalimide (pK_a = 8.3) was used then product **4.27** was obtained in 87% yield. Unfortunately, attempts to manipulate this product in various ways

only led to intractable mixtures. Accordingly, Fukuyama's method[140] was employed using *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** (prepared from *p*-methoxybenzylamine and 2-nitrobenzenesulfonyl chloride) as the nucleophile. Disappointedly, only the elimination product **4.29** was observed under these conditions.

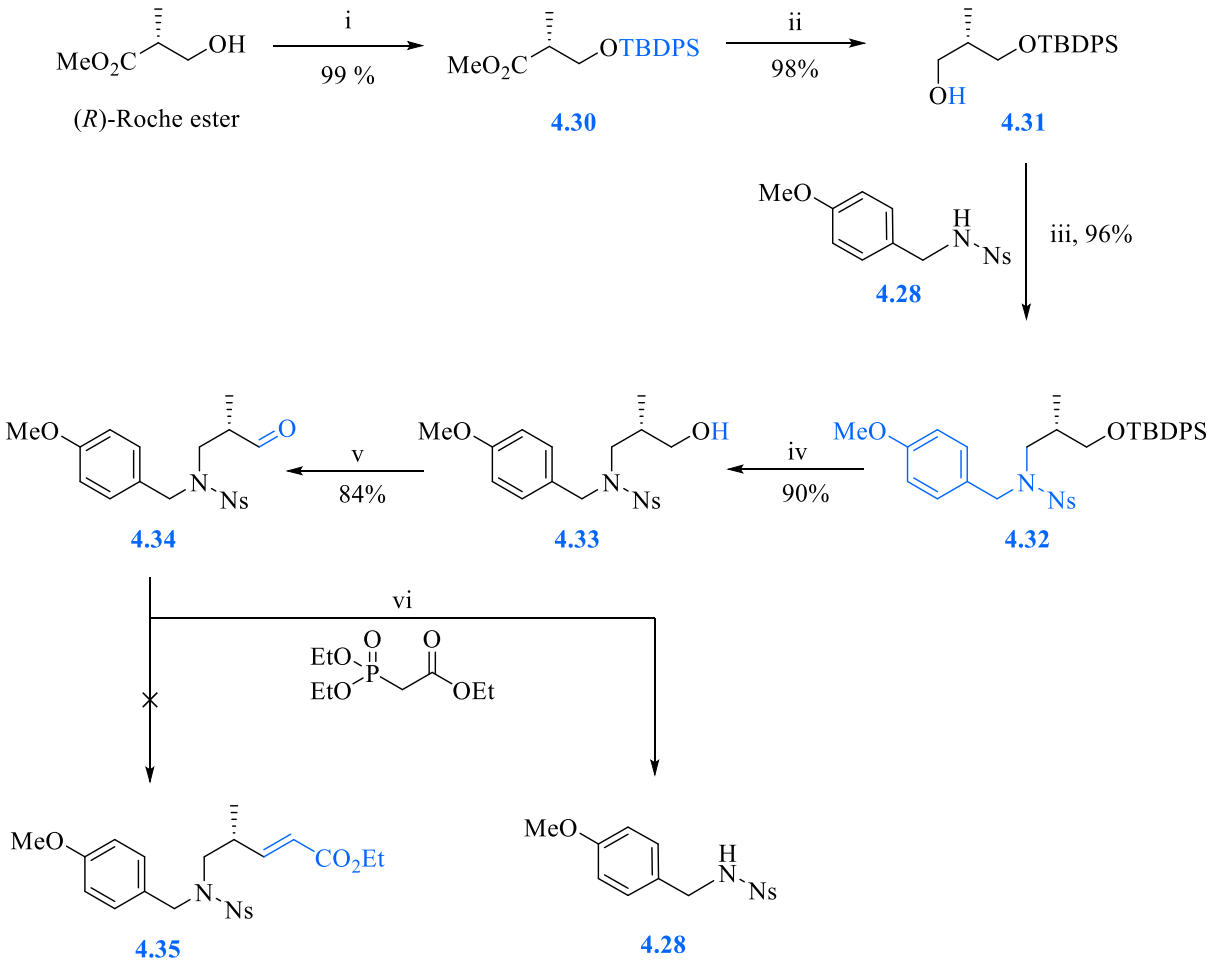


Entry	Nucleophile	Result/Product
1		No reaction, recovered SM
2		No reaction, recovered SM
3		 **4.27**
4	 **4.28**	 **4.29**

Scheme 4.10. ***Reagents and Conditions*** (i) TBAF, THF, 18 °C, 2 h; (ii) nucleophile, DIAD, PPh_3, THF, 18 °C, 16 h.

In light of the outcomes defined above, the reaction sequence shown in **Scheme 4.11** was followed. Thus, the (*R*)-Roche ester was protected as the TBDPS-ether **4.30**[141] (99%) and this was reduced with lithium borohydride in the presence of an equivalent amount of methanol to provide alcohol **4.31** (98%). Submission of this alcohol to a Mitsunobu reaction with sulfonamide **4.28** then gave the desired sulfonamide **4.32** in 96% yield. Fluoride-mediated deprotection of silyl-ether **4.32** provided alcohol **4.33** (90%) that was oxidised to the

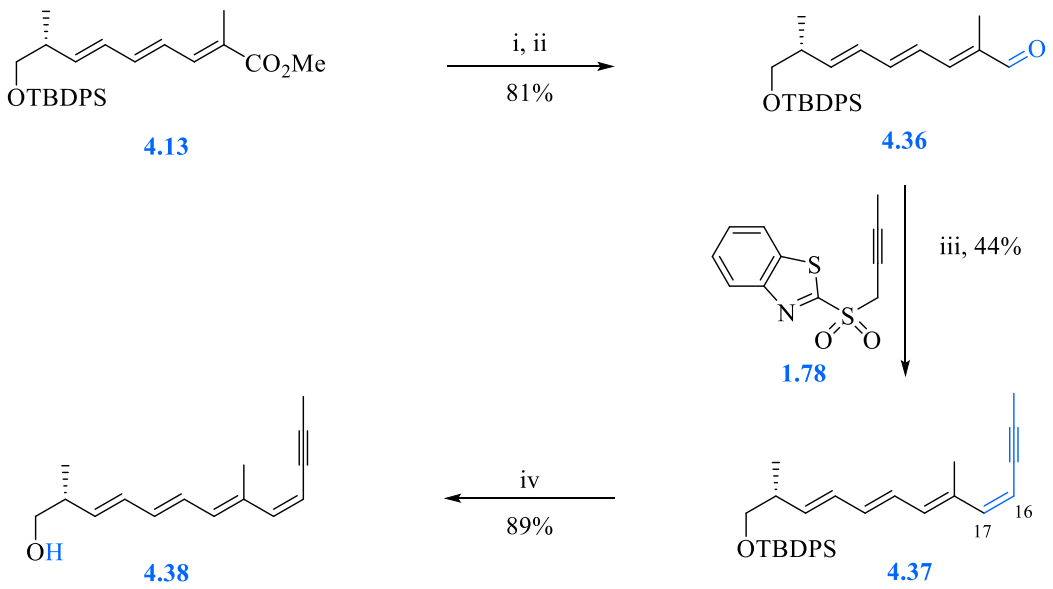
corresponding aldehyde **4.34** (84%) using the Dess-Martin periodinane (DMP). Disappointingly, upon submission of compound **4.34** to reaction with triethyl phosphonoacetate, lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (as used successfully in the formation of compound **4.20**), only the simple sulfonamide **4.28** (almost certainly the product of an $E1_{cb}$ reaction) was isolated. None of the hoped-for ester **4.35** was obtained.



Scheme 4.11. ***Reagents and Conditions*** (i) TBDPS-Cl, imidazole, DMF, 0 to 18 °C, 16 h; (ii) $LiBH_4$, MeOH-Et_2O, 0 to 18 °C, 2 h; (iii) DIAD, PPh_3, THF, 18 °C, 16 h; (iv) TBAF, THF, 18 °C, 2 h; (v) DMP, pyridine, DCM, 18 °C, 3 h; (vi) triethylphosphonoacetate, LiCl, DBU, acetonitrile, 18 °C, 16 h.

4.3.3. The Julia Olefination Reaction

In order to address the difficulties detailed immediately above, ester **4.13** was reduced (**Scheme 4.12**), with di-*iso*-butylaluminium hydride, to the corresponding alcohol that was immediately oxidised to the corresponding aldehyde **4.36** (81% yield over two steps) using manganese dioxide. A Julia olefination reaction was then performed so as to install the key *Z*-configured double bond (C16-C17) associated with fragment **C**. So. following the procedure of Bonini,[86] which was later used by Fürstner[87] as a part of total synthesis of lactimidomycin, sulfone **1.78** and potassium bis(trimethylsilyl)amide (KHMDS) were reacted with aldehyde **4.36** at −55 °C and the desired product **4.37** was obtained, after two days, in 44% yield as an inseparable mixture with the corresponding *E*-isomer (85:15 *Z*/*E*). As observed by Bonini, the *Z*-isomer is favored in this case.[f] The ^{1}H NMR spectrum of the mixture of tetra-ene **4.37** and its *E*-isomer is shown in **Figure 4.5**. The resonances due to both geometric isomers are quite evident. Thus, the signals at δ 5.58 (*J* = 15.9 and 2.5 Hz) and δ 5.39 (*J* = 11.8 and 2.8 Hz) were assigned to the C16 protons associated with the *E*- and *Z*- isomeric forms, respectively. Each is coupled, as a doublet, with C17-H. Coupling to the protons of the methyl "cap" of the alkyne was also observed in each instance. While deprotection of the TBDPS-ether **4.37** could be achieved using tetra-*n*-butylammonium fluoride, and thus providing alcohol **4.38** in 89% yield, additional proportions of the *E*-isomer were formed (*Z*/*E* ratio now 75:25).



Scheme 4.12. ***Reagents and Conditions*** (i) DIBAl-H, hexane, −78 °C, 2 h; (ii) MnO_2, DCM, 18 °C, 3 h; (iii) KHMDS, THF, −55 °C, 48 h; (iv) TBAF, THF, 18 °C, 2 h.

[f] See Section **1.3.3.4** for more information.

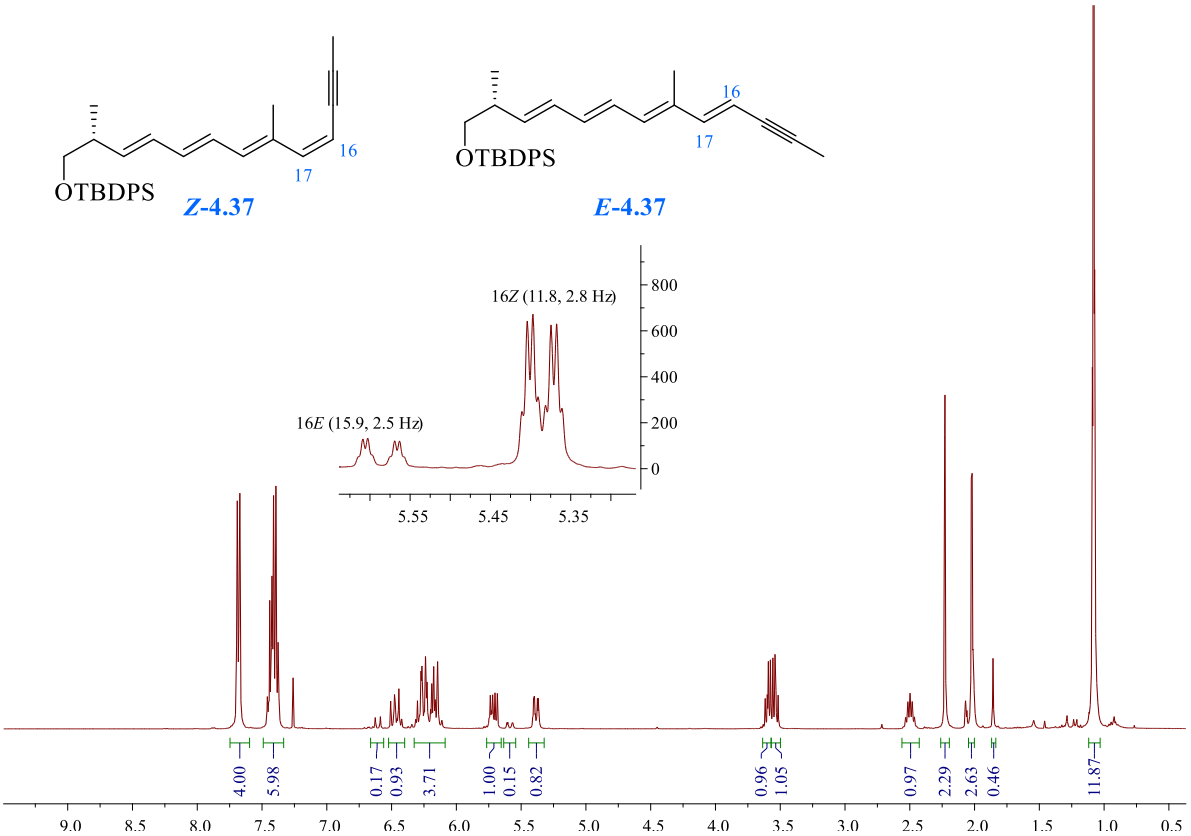
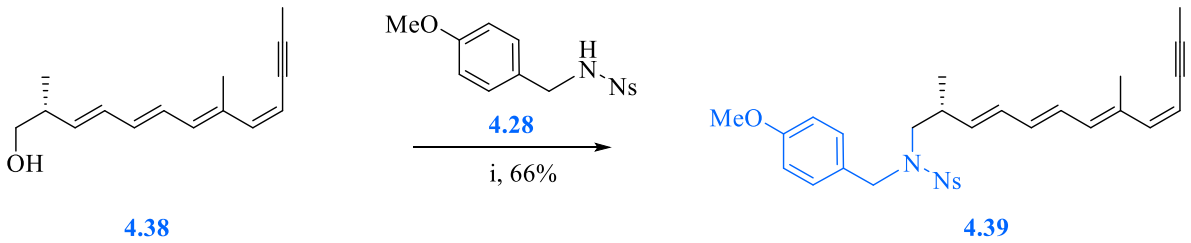


Figure 4.5. ***400 MHz ^{1}H NMR Spectrum of Tetraenyne 4.37 (recorded in* d*-chloroform).***

Reaction of *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** with alcohol **4.38** (**Scheme 4.13**) in the presence of triphenylphosphine and di-*iso*-propyl azodicarboxylate (DIAD) provided the sulfonamide **4.39** in 66% yield. Unfortunately, even more *Z*- to *E*-isomerisation was observed during this reaction as revealed by inspection of ^{1}H NMR spectrum (**Figure 4.6**) of the product mixture. Specifically, the *Z*/*E* ratio was now 60:40 and thus constituting a synthetically unacceptable situation. It was envisioned that these difficulties could be addressed by replacing of the double bonds between C14-C15 and C16-C17 in lactam **1.7** by triple bonds, a possibility that was now pursued as detailed in the following Chapter.



Scheme 4.13. ***Reagents and Conditions*** (i) DIAD, PPh_3, THF, 18 °C, 16 h.

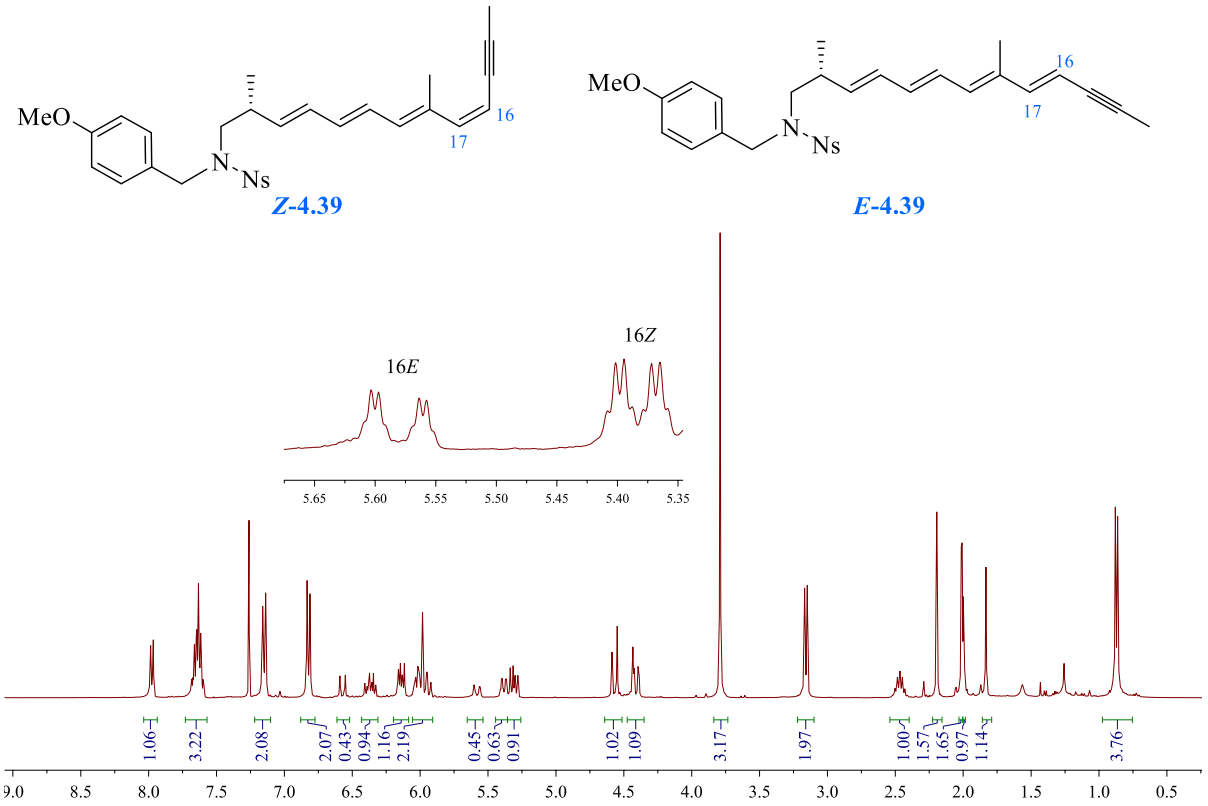
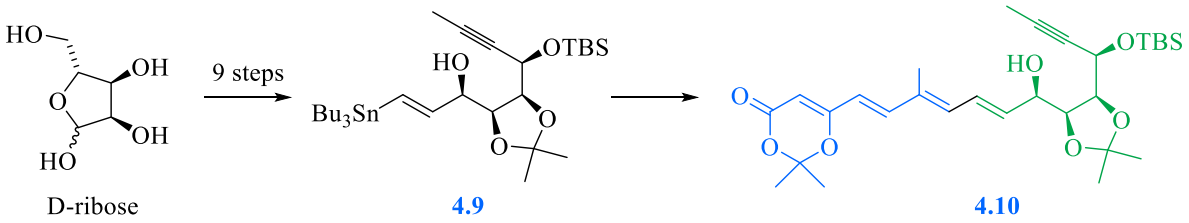


Figure 4.6. ***400 MHz ^{1}H NMR Spectrum of the* E- *and* Z-*Isomeric Forms of Sulfonamide 4.39 (recorded in* d-*chloroform).***

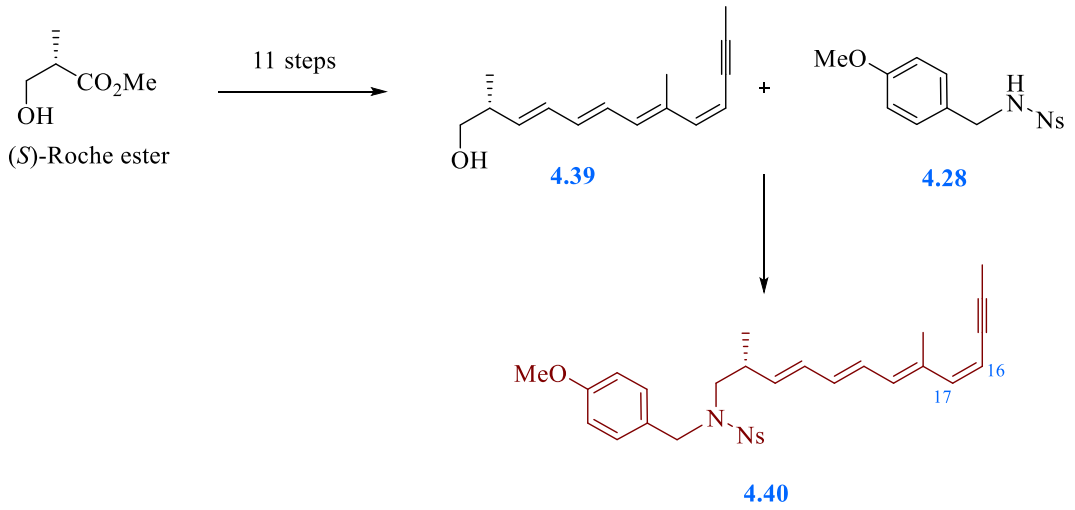
4.4. Conclusion

In the work described in this Chapter (Four), a synthetic sequence leading to the Southern Hemisphere of macrolactam **4.1** (as embodied in compound **4.10**) has been established. The Stille cross-coupling reaction used for the connection of fragments **A** and **B** proved effective in generating polyene **4.10** (**Scheme 4.14**), even if only in modest yield. Attempts to enhance the effectiveness of this reaction are presented in the next Chapter.



Scheme 4.14. ***Summary of the Formation of Southern Hemisphere of Macrolactam 4.1.***

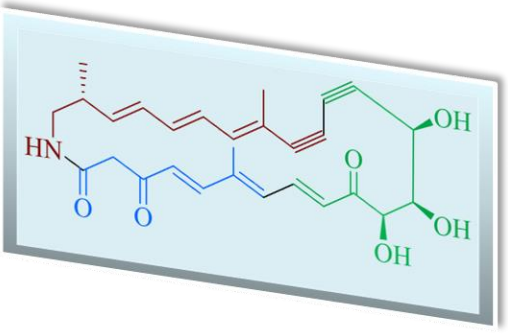
The polyene fragment **C** as manifest in compound **4.40**, which embodies the Northern Hemisphere of macrolactam **4.1**, was also constructed from the enantiomerically pure (*S*)-Roche ester (**Scheme 4.15**). The use of *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** as a nucleophile in Mitsunobu reaction allowed for the conversion of a primary alcohol into a protected amine in one step. Unfortunately, the ready isomerisation of the (*Z*)-configured $\Delta^{16,17}$-double bond within tetraene **4.40** to its *E*-isomer undermined the utility of this reaction sequence.



Scheme 4.15. ***Summary of the Synthetic Route to the Northern Hemisphere of Macrolactam 4.1.***

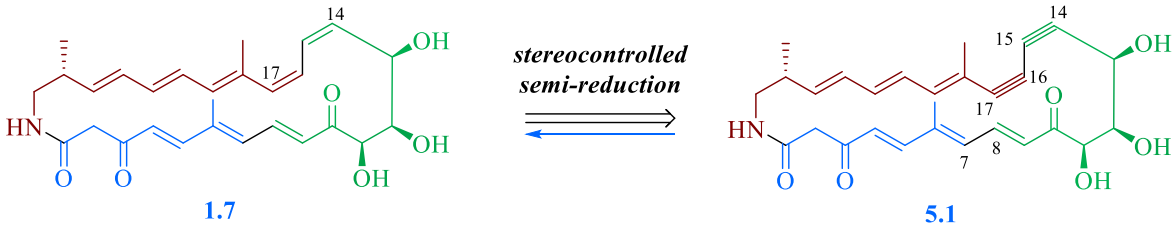
5. CHAPTER FIVE

Third-Generation Approach to a Substrate for Macrolactamisation



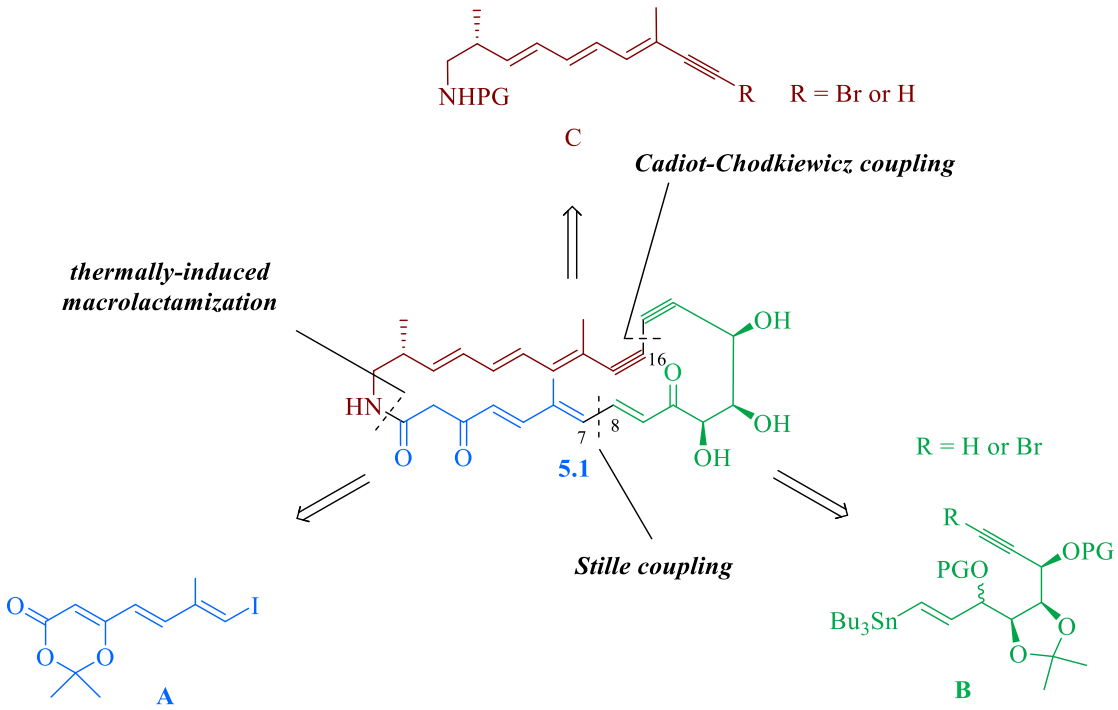
5.1. Retrosynthetic Analysis

In order to address the facile *Z*- to *E*-isomerisation process that had undermined the studies detailed in the preceding Chapter, another approach to macrolactam **1.7** was pursued wherein the stereo- and site-selective generation of the (*Z*,*Z*)-configured 1,3-diene moiety located between C14 and C17 would be established by semi-reduction of the corresponding 1,3-diyne moiety embedded within lactam **5.1** (**Scheme 5.1**).[142]



Scheme 5.1. ***Revised Strategy***.

In this third approach, the retrosynthetic analysis outlined in **Scheme 5.2** was applied in efforts to construct macrolactam **5.1**. A key feature would be to use a Cadiot-Chodkiewicz coupling reaction to connect C15 to C16 and wherein the precursor fragment **C** would contain either a terminal alkyne or a bromo-alkyne residue. Therefore, two possible routes to fragment **C** were pursued. As in the second approach detailed in the preceding Chapter, the truncated fragments **A** and **B** would be linked through a Stille cross-coupling reaction that establishes the C7–C8 σ-bond. The straightforward assembly of fragment **A** (**3.2**) has already been described (see Section **3.3.1**). The synthetic pathway leading to the formation of a compound closely related to fragment **B** from inexpensive and readily available *D*-ribose has also been described (see Section **4.2.2**). The modifications of these procedures for the purposes of constructing the "revised" fragments **B** and **C** are detailed in the following sections.

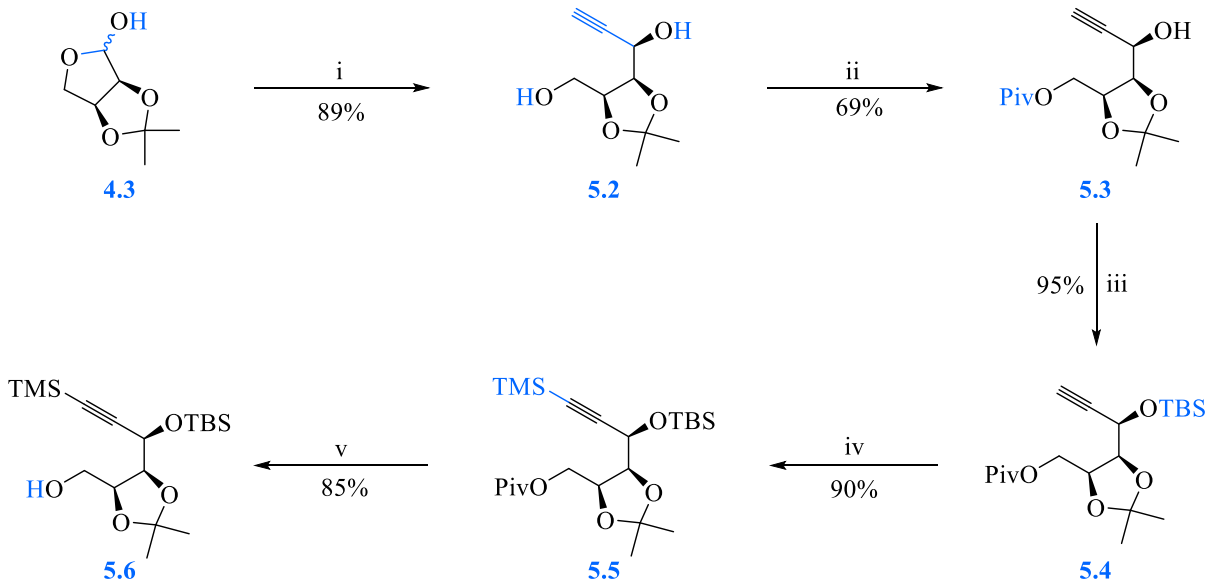


Scheme 5.2. ***Key Building Blocks (Fragments) Associated with the Assembly of Macrolactam 5.1.***

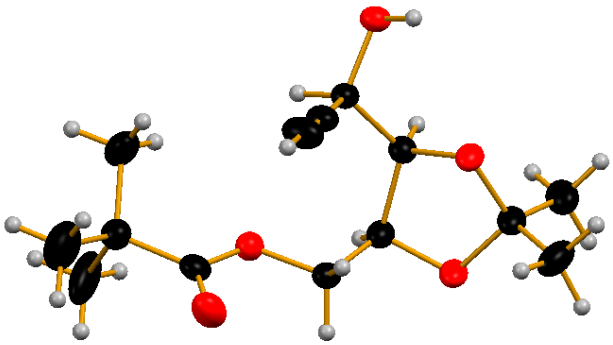
5.2. Synthesis of the TMS-Capped Variant of Fragment B and its Connection to Fragment A

5.2.1. Preparation of Alkenyl Stannane 5.8

Following the reaction sequence established as described in Section **4.2.2**, the known lactol **4.3** was treated (**Scheme 5.3**) with ethynylmagnesium bromide to afford the ring-opened diol **5.2** as a single-epimer in 89% yield. Confirmation of the illustrated configuration at the newly formed stereogenic center was obtained through the conversion of compound **5.2** into the corresponding pivaloate derivative **5.3** (69%), the structure of which was established by single-crystal X-ray crystallography (see **Figure 5.1** for derived plot). The secondary alcohol moiety within the latter compound was converted into the corresponding TBS-ether **5.4** (95%) under standard conditions. Upon treatment with *iso*-propylmagnesium chloride, deprotonation of terminal alkyne occured and the resulting anion was reacted with trimethylsilyl chloride (TMS-Cl) to afford the TMS-capped acetylene **5.5** in 90% yield. Reduction of this last compound with di-*iso*-butylaluminium hydride then gave the primary alcohol **5.6** in 85% yield.



Scheme 5.3. ***Reagents and Conditions*** (i) HC≡CMgBr, THF, 0 to 18 °C; (ii) Piv-Cl, DMAP, Et_3N, DCM, −78 °C, 1.5 h; (iii) TBS-Cl, imidazole, DMF, 18 °C, 2 h; (iv) *i*-PrMgCl, TMS-Cl, THF, 0 to 18 °C, 2 h; (v) DIBAl-H, hexane, −78 °C, 30 min.

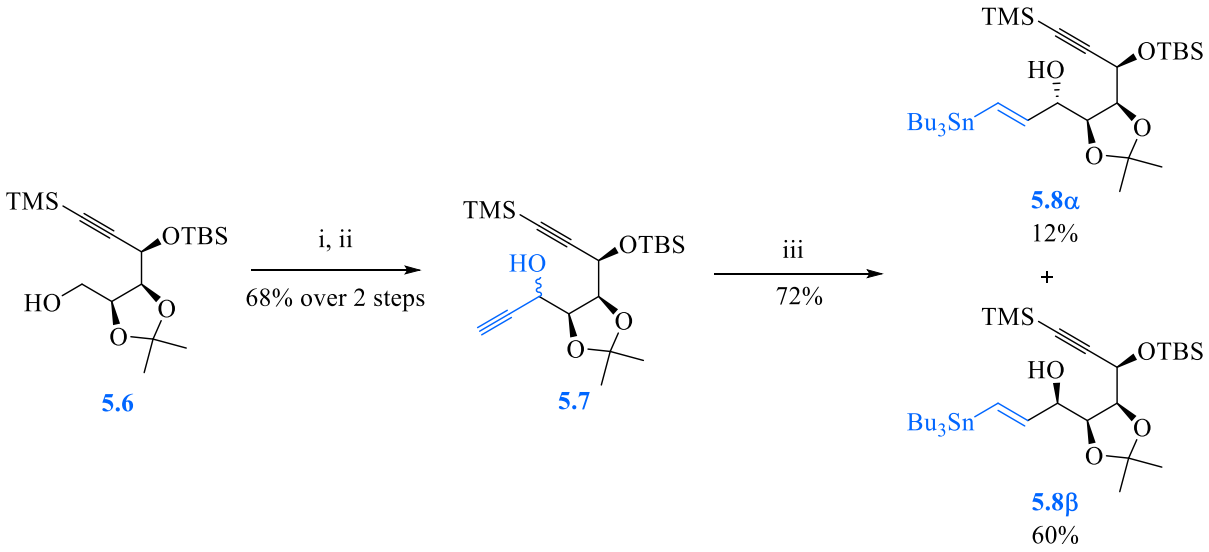


(black = C, red = O, grey = H)

Figure 5.1. ***Plot Derived from the Single-Crystal X-ray Analysis of Pivaloate 5.3.***

Oxidation of alcohol **5.6** using the Dess-Martin periodinane (**Scheme 5.4**) provided the corresponding aldehyde that was treated, without purification, with ethynylmagnesium bromide in the presence of zinc chloride at −15 °C and so delivering compound **5.7** as an inseparable 17:83 mixture of epimers. When the addition reaction was carried out at −40 °C a 10:90 mixture of epimers was obtained although the reaction rate was much slower. Notably, in the absence of zinc chloride the addition reaction proceeded with reduced selectivity, a 40:60 mixture of epimers being obtained, an outcome that could be attributed to the absence of chelation control. It is should be noted, at this point, that the two epimers are likely to be of equivalent value in the synthesis as each would eventually be oxidised to the corresponding

ketone. The mixture of the epimeric forms of alcohol **5.7** was subjected to hydrostannylation using bis(triphenylphosphine)palladium(II) dichloride and tri-*n*-butyltin hydride and thereby generating the corresponding and chromatographically separable alkenyl stannanes **5.8α** and **5.8β** in 12 and 60% yield, respectively.[g]



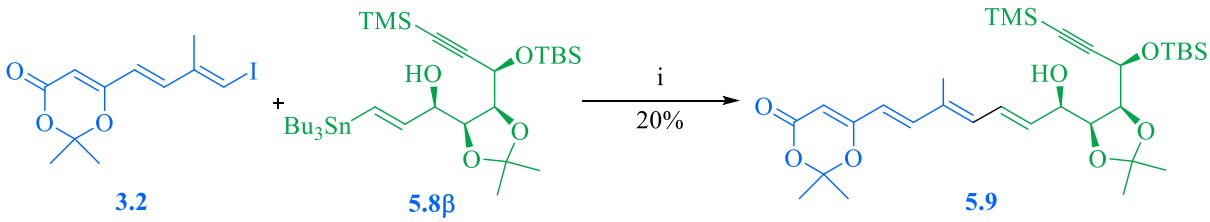
Scheme 5.4. ***Reagents and Conditions*** (i) DMP, pyridine, DCM, 18 °C, 3 h; (ii) HC≡CMgBr, $ZnCl_2$, THF, −15 °C, 4 h; (iii) $Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH, DCM, −78 to 0 °C, 30 min.

5.2.2. The Stille Cross-Coupling Reaction

With the more abundant alkenyl stannane **5.8β** readily to hand, the pivotal Stille coupling reaction with the easily prepared alkenyl iodide fragment **A** (as described in Section **3.3.1**) (**Scheme 5.5**) was undertaken in the presence of tetrakis(triphenylphosphine)-palladium(0), copper(I) iodide and lithium chloride. However, the desired coupling product **5.9** was only obtained in 20% yield when the same conditions as applied in the synthesis of the methyl-capped stannane **4.9** were used (see Section **4.2.3**). Various efforts to improve this outcome were pursued. These proved fruitless. For example, when a protocol reported by Fürstner[18] was employed, and involving the use of copper(I) thiophene-2-carboxylate and a phosphinate salt $[Ph_2PO_2][nBu_4]$ at room temperature, only a complex mixture of products was produced. These disappointing outcomes were attributed to the lability of TMS-capped alkyne

[g] An explanation for the selective formation of the β-epimer can be found in Section **5.3.2**.

moiety within compound **5.8β**. Accordingly, an equivalent synthetic sequence involving the TIPS-capped compound was investigated. Details are provided in the following section.



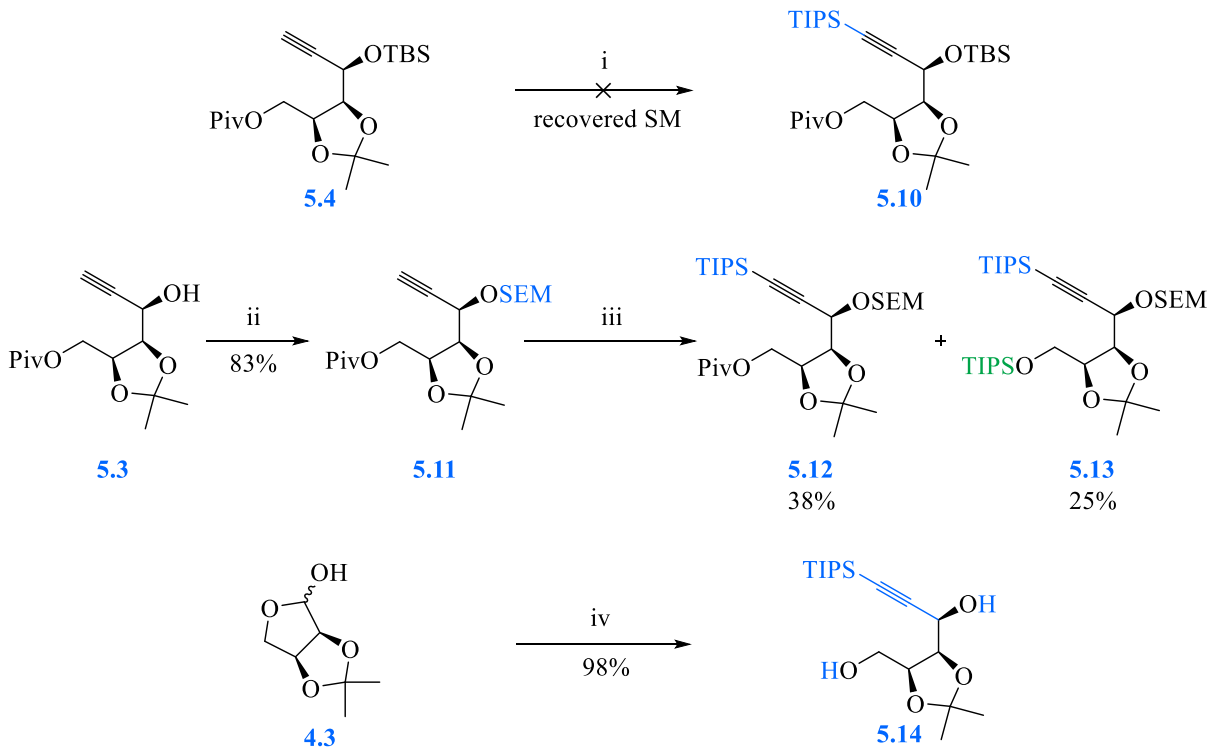
Scheme 5.5. ***Reagents and Conditions*** (i) $Pd(PPh_3)_4$, PPh_3, CuI, LiCl, DMF, 40 °C, 16 h.

5.3. Synthesis of the TIPS-Capped Variant of Fragment B and its Connection to Fragment A

5.3.1. Introduction of TIPS-Capped Alkyne

Upon treating compound **5.4** with *iso*-propylmagnesium chloride and tri-*iso*-propylsilyl chloride (TIPS-Cl) (**Scheme 5.6**) only starting material was recovered. As a result of considering various protecting group compatibilities, alcohol **5.3** was treated with di-*iso*-propylethylamine, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and 2-(trimethylsilyl)ethoxy-methyl chloride (SEM-Cl) to furnish the protected compound **5.11** (83%). However, upon exposure of this alkyne to *n*-butyl lithium and tri-*iso*-propylsilyl chloride (TIPS-Cl), the desired product **5.12** was only isolated in 38% yield and was accompanied by co-product **5.13** (25%). The conversion was found to be very slow at room temperature and the addition of an excess of tri-*iso*-propylsilyl chloride led to the formation of more of the TIPS-ether **5.13**. Therefore, a different route was pursued wherein the lactol **4.3** was treated with the metallated acetylene formed, *in situ*, upon exposure of TIPS-acetylene to *iso*-propylmagnesium chloride. As a result of the operation of a chelation-controlled addition reaction, diol **5.14** was obtained in 98% yield and 87% de.[h] The derived ^{1}H NMR spectrum of the product obtained from this reaction established that compound **5.14** was the major epimeric product (**Figure 5.2**).

[h] An explanation for the preferential formation of this diastereoisomer can be found in Section **4.2.2**.



Scheme 5.6. ***Reagents and Conditions*** (i) *i*-PrMgCl, TIPS-Cl, THF, 0 to 18 °C, 2 h; (ii) SEM-Cl, DIPEA, DMAP, DCM, reflux, 16 h; (iii) *n*-BuLi, TIPS-Cl, −78 to 18 °C, 16 h; (iv) *i*-PrMgCl, TIPS-C≡CH THF, 0 to 18 °C, 3 h.

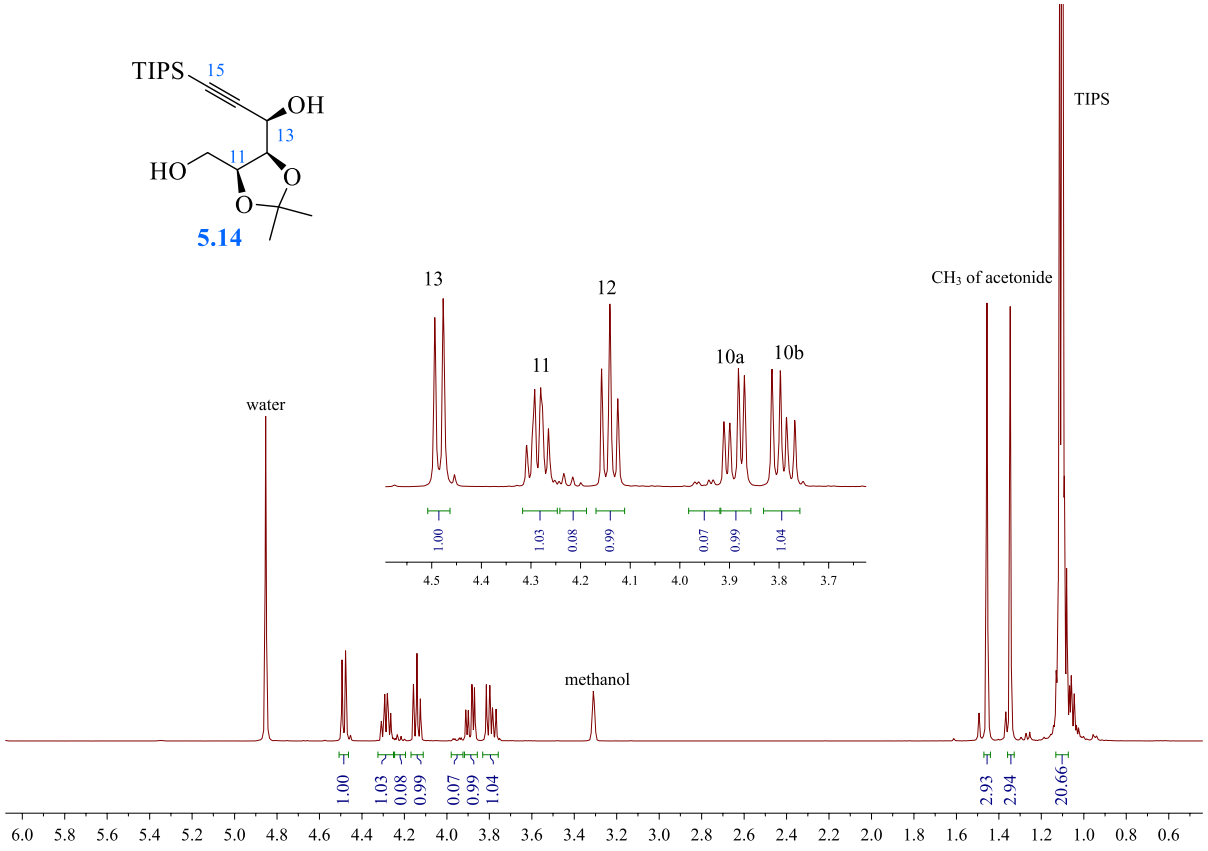
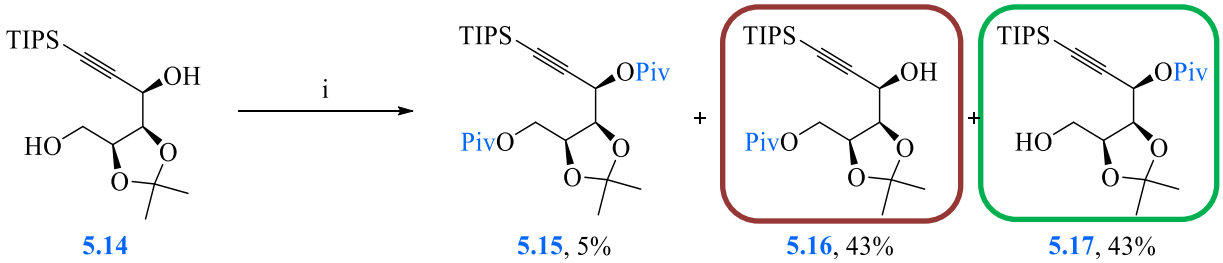


Figure 5.2. ***400 MHz ^{1}H NMR Spectrum of Diol 5.14 (recorded in* d$_4$*-methanol).***

Efforts to selectively protect the primary alcohol moiety within compound **5.14** (**Scheme 5.7**) as a pivaloate **5.16** (43%) were disappointingly low yielding because of the competitive formation of the secondary pivaloate **5.17** (43%). Changing the reaction temperature, equivalents of base used and/or the rates of addition of pivaloyl chloride to overcome the inherent bias in the formation of protected secondary alcohol failed to provide a workable solution to this problem. At this point, it was decided to carry the two products forward and, indeed, the pivaloate **5.17** was shown to be more useful as the two step protection and deprotection sequence originally envisaged for handling the protected primary alcohol **5.16** was no longer required.

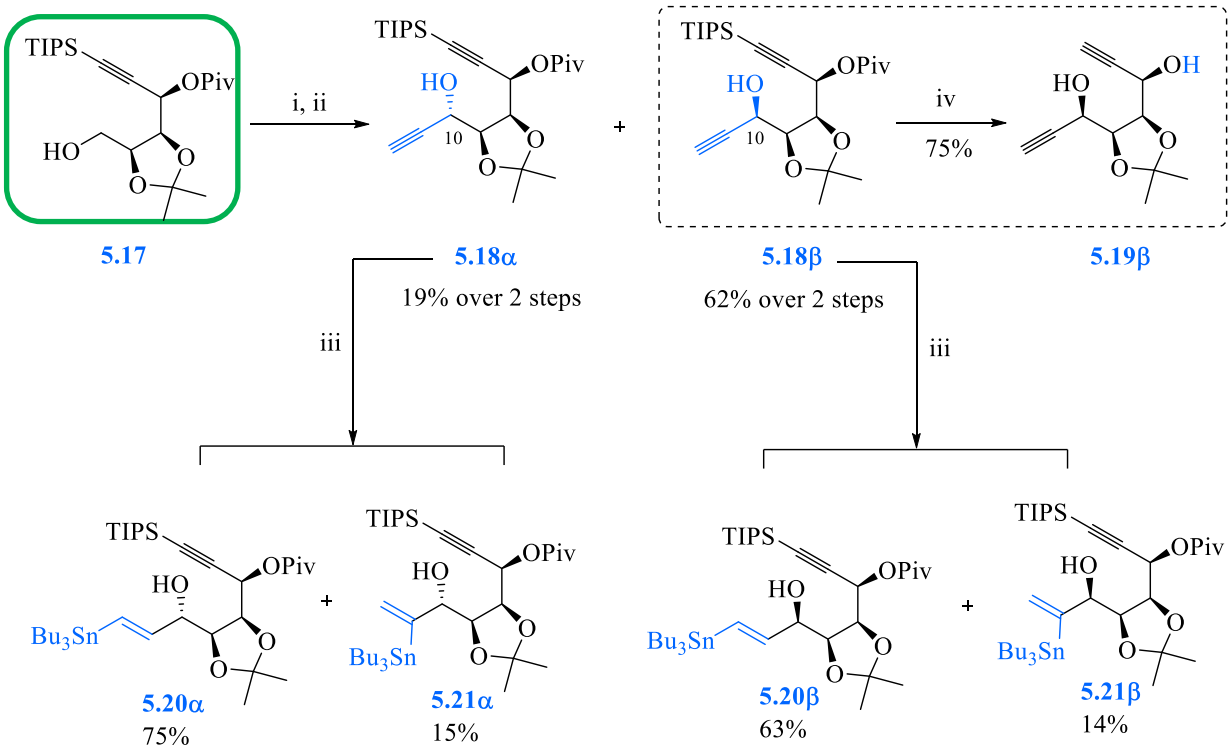


5.14 **5.15**, 5% **5.16**, 43% **5.17**, 43%

Scheme 5.7. ***Reagents and Conditions*** (i) Piv-Cl, DMAP, Et_3N, DCM, −78 °C, 1.5 h.

5.3.2. Advancing the Synthesis Using the Unprotected Propargylic Alcohol-Containing Fragment B

The liberated primary alcohol residue within compound **5.17** (**Scheme 5.8**) was subjected to oxidation with the Dess-Martin periodinane and the product aldehyde treated with ethynylmagnesium bromide in the presence of zinc chloride to provide a 23:77 mixture of the epimeric forms of compound **5.18**. This was obtained in 81% combined yield over the two steps involved. These two epimers could be separated by column chromatography and treatment of the major one with tetra-*n*-butylammonium fluoride provided an unsymmetrical and optically active diol **5.19β** and thus establishing (*R*)-configuration at C10 in its precursor. The ^{13}C NMR spectrum of diol **5.19β** is shown in **Figure 5.3**. Compounds **5.18α** and **5.18β** were independently submitted to the hydrostannylation reaction. The major, *β*-epimer **5.18β** provided the desired product **5.20β** and its regioisomer **5.21β** in 63 and 14% yields, respectively. The minor, *α*-epimer **5.18α**, was also submitted to the same reaction and, once again, both the desired product **5.20α** and its regioisomer **5.21α** were obtained in 75 and 15% yields, respectively.



Scheme 5.8. ***Reagents and Conditions*** (i) DMP, pyridine, DCM, 18 °C, 3 h then (ii) HC≡CMgBr, $ZnCl_2$, THF, −40 °C, 4 h; (iii) $Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH, DCM, −78 to 0 °C, 30 min; (iv) TBAF, THF, 18 °C, 4 h.

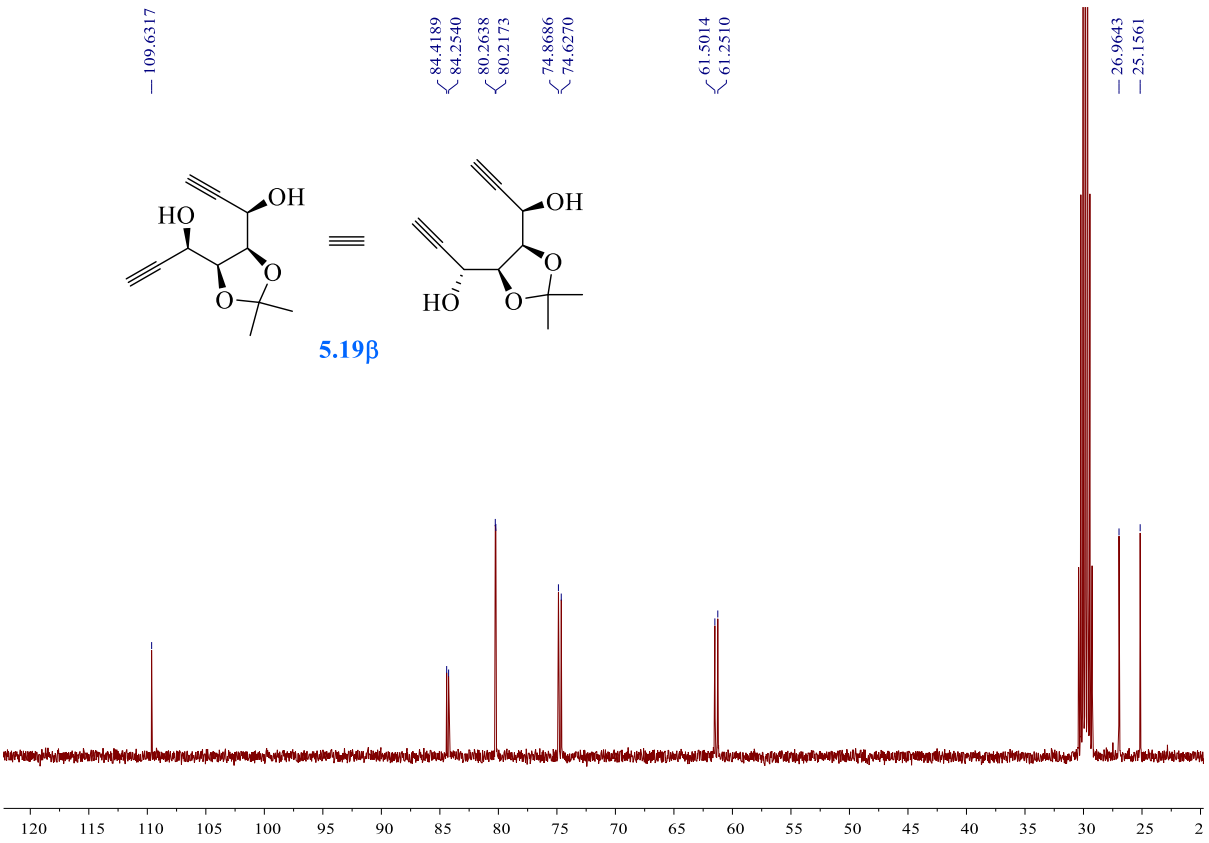
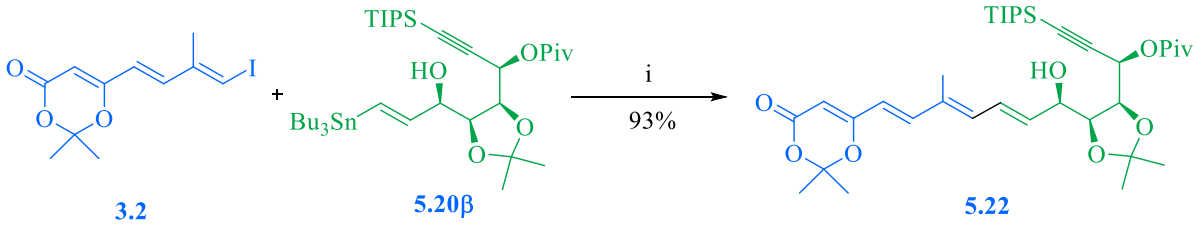


Figure 5.3: ***100 MHz ^{13}C NMR Spectrum of Diol 5.19β (recorded in d_6-acetone).***

The major isomer **5.20β** was used for the initial investigation of the Stille cross-coupling with fragment **A** (**Scheme 5.9**). Upon using Fürstner's conditions,[18] involving tetrakis(triphenylphosphine)palladium(0), triphenylphosphine, copper(I) thiophene and [Ph_2PO_2][nBu_4] (as a tin scavenger) under anaerobic conditions at ambient temperatures in *N*,*N*-dimethylformamide, the desired connection of fragments **A** and **B** took place to give, in 93% yield after thirty minutes, product **5.22**. The ^1H and ^{13}C NMR spectral data derived from this product were completely consistent with the assigned structure **5.22** (see **Figure 5.4**, **Figure 5.5** and **Table 5.1**).



Scheme 5.9. ***Reagents and Conditions*** (i) $Pd(PPh_3)_4$, PPh_3, [Ph_2PO_2][NBu_4], DMF, 18 °C, 30 min.

Polyene **5.22** was found to be unstable, even on storage at low temperature or after further manipulation. Means for addressing this matter are detailed below.

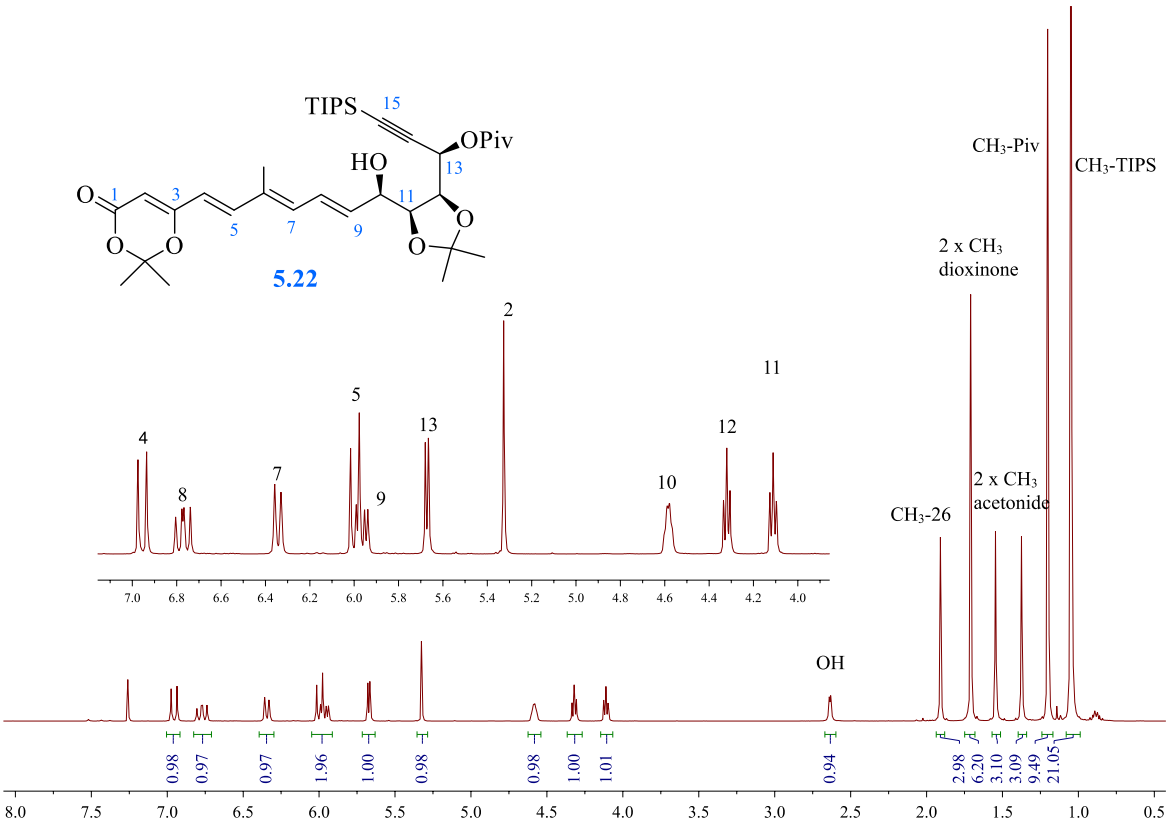


Figure 5.4. *400 MHz ^{1}H NMR Spectrum of Tetraenyne 5.22 (recorded in* **d**-*chloroform).*

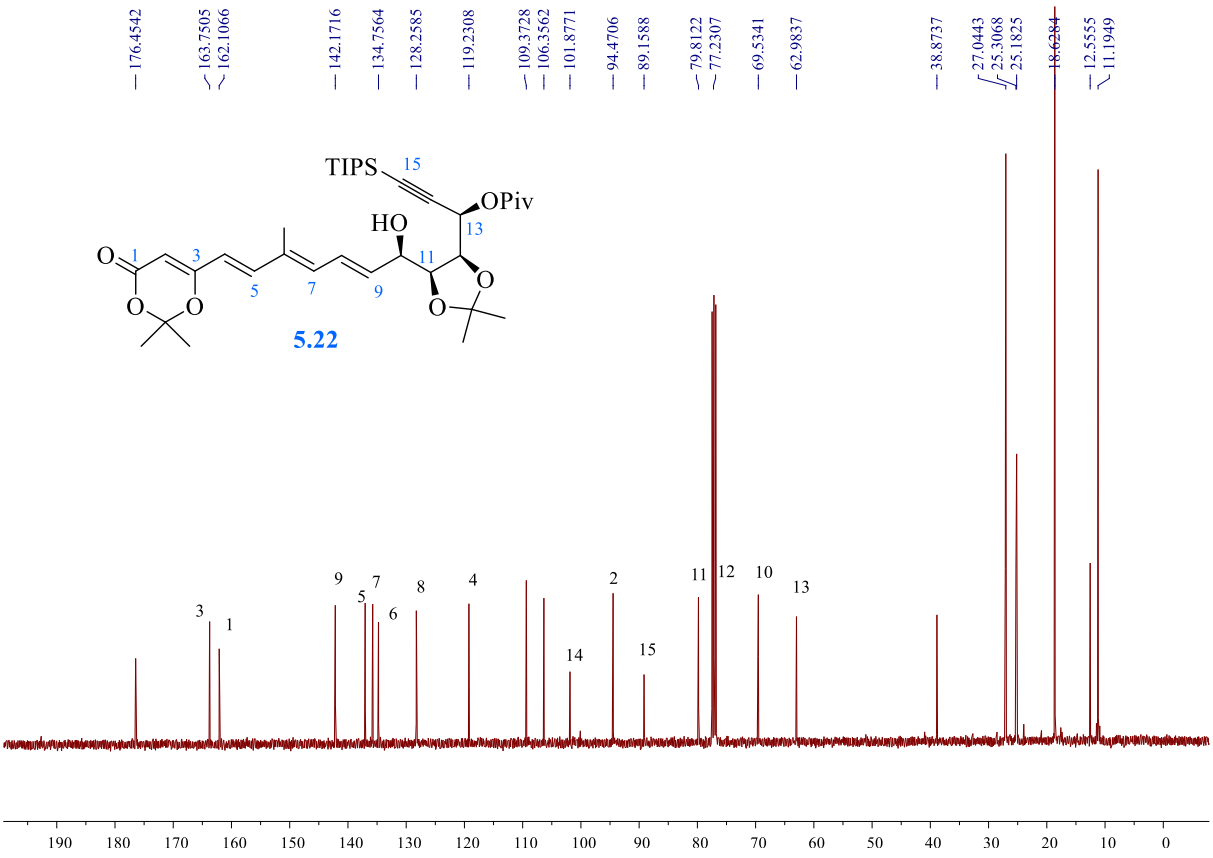


Figure 5.5. *100 MHz ^{13}C NMR Spectrum of Tetraenyne 5.22 (recorded in* **d**-*chloroform).*

Table 5.1. *Assignment of ^{1}H and ^{13}C NMR Data for Compound 5.22*.*

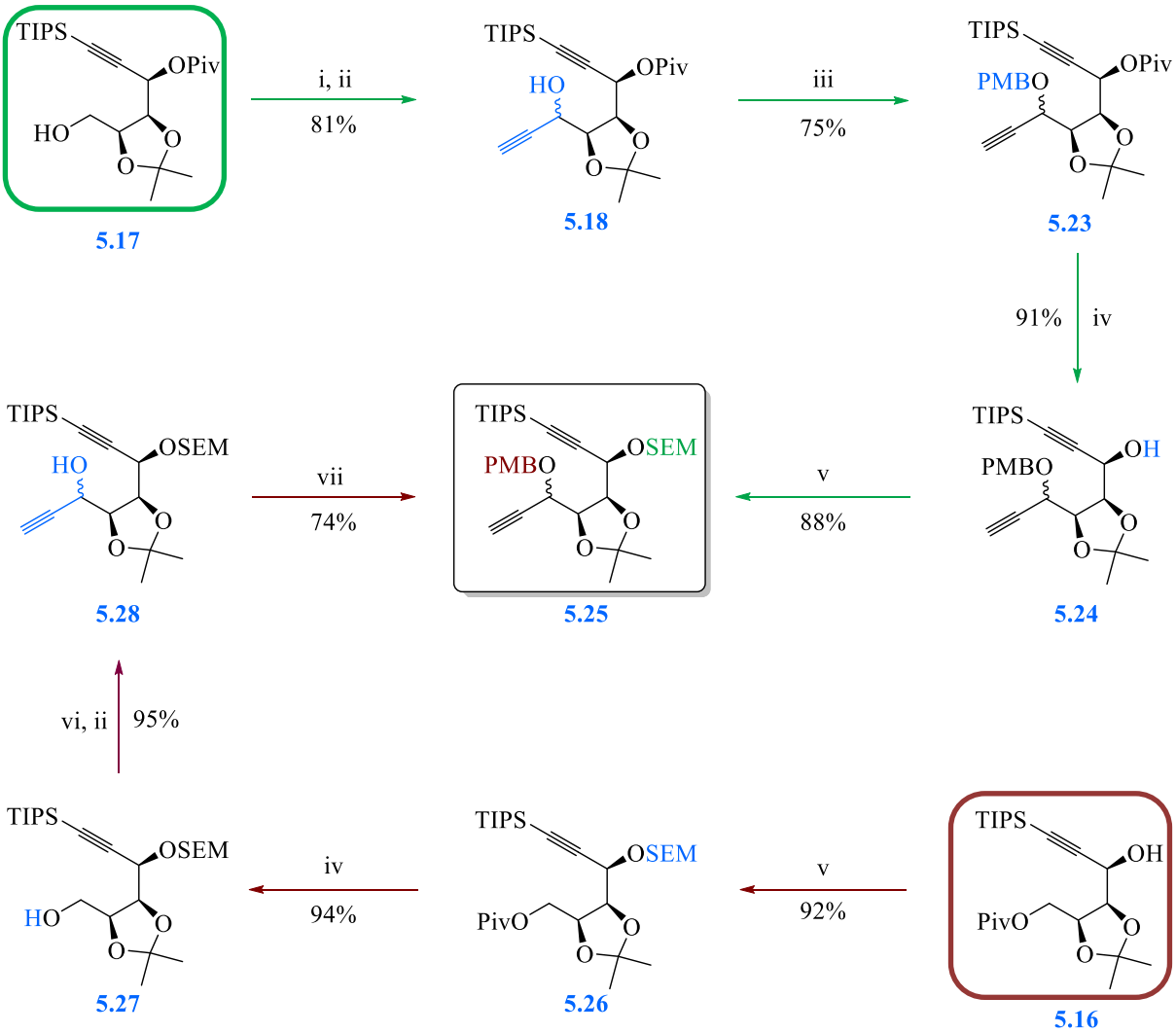
C/H	δ_H	mult (*J* in Hz)	δ_C	
1			162.1	C
2	5.33	s	94.5	CH
3			163.7	C
4	6.96	d (15.5)	119.2	CH
5	5.99	d (15.5)	137.0	CH
6			134.7	C
7	6.34	d (11.3)	135.8	CH
8	6.77	dd (15.0, 11.3)	128.3	CH
9	5.96	dd (15.0, 5.9)	142.2	CH
10	4.58	m	69.5	CH
10-OH	2.64	brd (3.8)		
11	4.11	t (5.5)	79.8	CH
12	4.32	t (5.5)	77.2	CH
13	5.67	d (5.5)	63.0	CH
14			101.9	C
15			89.1	C
26	1.91	s	12.6	CH_3
-TIPS	1.05	m	18.6	6 x CH_3
			11.2	3 x CH
-Piv	1.20	s	27.0	3 x CH_3
			38.9	C
			176.4	CO
-acetonide	1.55, 1.38	s, s	27.1, 25.3	2 x CH_3
			109.4	C
-dioxinone	1.71	s	25.2	2 x CH_3
			106.3	C

* Data acquired in *d*-chloroform at 400 or 100 MHz (for ^{1}H and ^{13}C NMR data, respectively).

5.3.3. Advancing the Synthesis Using the Protected Propargylic Alcohol-Containing Fragment B

A synthetic route to key intermediate **5.25** from both alcohols **5.16** and **5.17** (**Scheme 5.10**) was pursued as a means of obtaining a C-10 protected form of compound **5.22** that, in its OH unprotected form, was distinctly unstable. The route from alcohol **5.17** to sub-target **5.25** was straightforward and involved conventional steps through propagylic alcohol **5.18**, PMB-ether **5.23**, and alcohol **5.24**. By changing the order of reactions, alcohol **5.16** could also be converted into the same key compound **5.25** over the same number of conventional steps. The

only difference between the two routes rested in choosing the reaction conditions required for the protection of the newly installed propargylic alcohol as the PMB-ether. Indeed, in the case of compound **5.18** and owing to the presence of the pivaloate group, non-basic conditions were employed involving 2-(4-methoxybenyloxy)-4-methylquinoline (PMBO-lepidine) (**2.16**)[i] in the presence of (+)-camphor-10-sulfonic acid (cat.), while *p*-methoxybenzyl chloride and sodium hydride was the reagent combination applied to congener **5.28**.

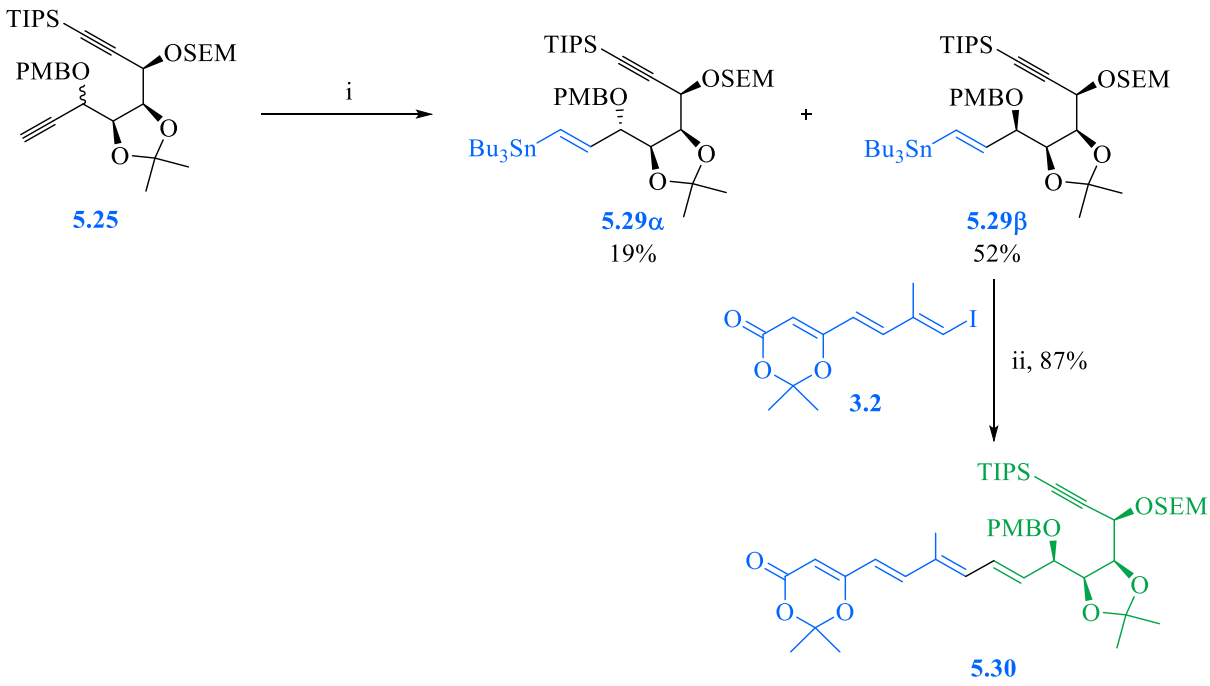


Scheme 5.10. ***Reagents and Conditions*** (i) DMP, pyridine, DCM, 18 °C, 3 h then (ii) HC≡CMgBr, $ZnCl_2$, THF, −40 °C, 4 h; (iii) PMBO-lepidine (**2.16**), CSA, DCM, 40 °C, 16 h; (iv) DIBAl-H, hexane, −78 °C, 30 min; (v) SEM-Cl, DIPEA, DMAP, DCM, reflux, 16 h; (vi) $(COCl)_2$, DMSO, Et_3N, DCM, −78 to 0 °C, 1 h then (ii) HC≡CMgBr, THF, −15 °C, 1 h, 95% over two steps; (vii) PMB-Cl, NaH, TBAI, THF, 18 °C, 16 h.

The PMB-protected analogue, **5.30**, (**Scheme 5.11**) of compound **5.22** was readily prepared from the epimeric mixture of ethers **5.25** by treating this with bis(triphenylphosphine)palladium(II) dichloride and tri-*n*-butyltin hydride and thus forming

[i] See **Scheme 2.6**, Section **2.3.1** for more information.

alkenyl stannanes **5.29α** and **5.29β** in 19 and 52% yields, respectively. Although the regioisomeric stannanes were not isolated and characterised, the presence of these by-products was detected by thin layer chromatography. When the major, β-epimer **5.29β** was submitted to the crucial Stille cross-coupling reaction with fragment **A**, **3.2**, using the same conditions as employed for the synthesis of congener **5.22**, then target **5.30** was obtained in 87% yield. The structure of this product was confirmed by both ^{1}H and ^{13}C NMR spectroscopies (see **Figure 5.6**, **Figure 5.7** and **Table 5.2**).



Scheme 5.11. ***Reagents and Conditions*** (i) $Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH, DCM, −78 to 0 °C, 30 min; (ii) $Pd(PPh_3)_4$, PPh_3, CuTC, $[Ph_2PO_2][NBu_4]$, DMF, 18 °C, 30 min.

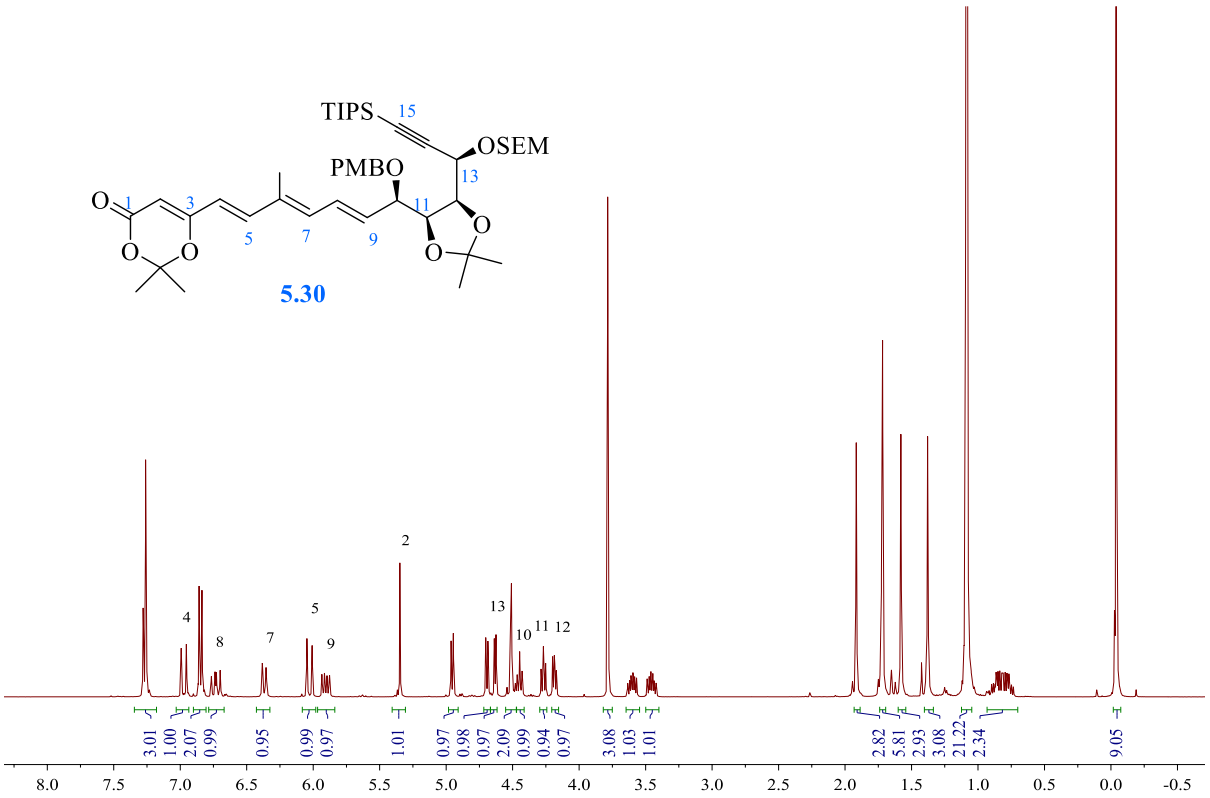


Figure 5.6. *400 MHz ^{1}H NMR Spectrum of Compound 5.30 (recorded in* **d**-*chloroform).*

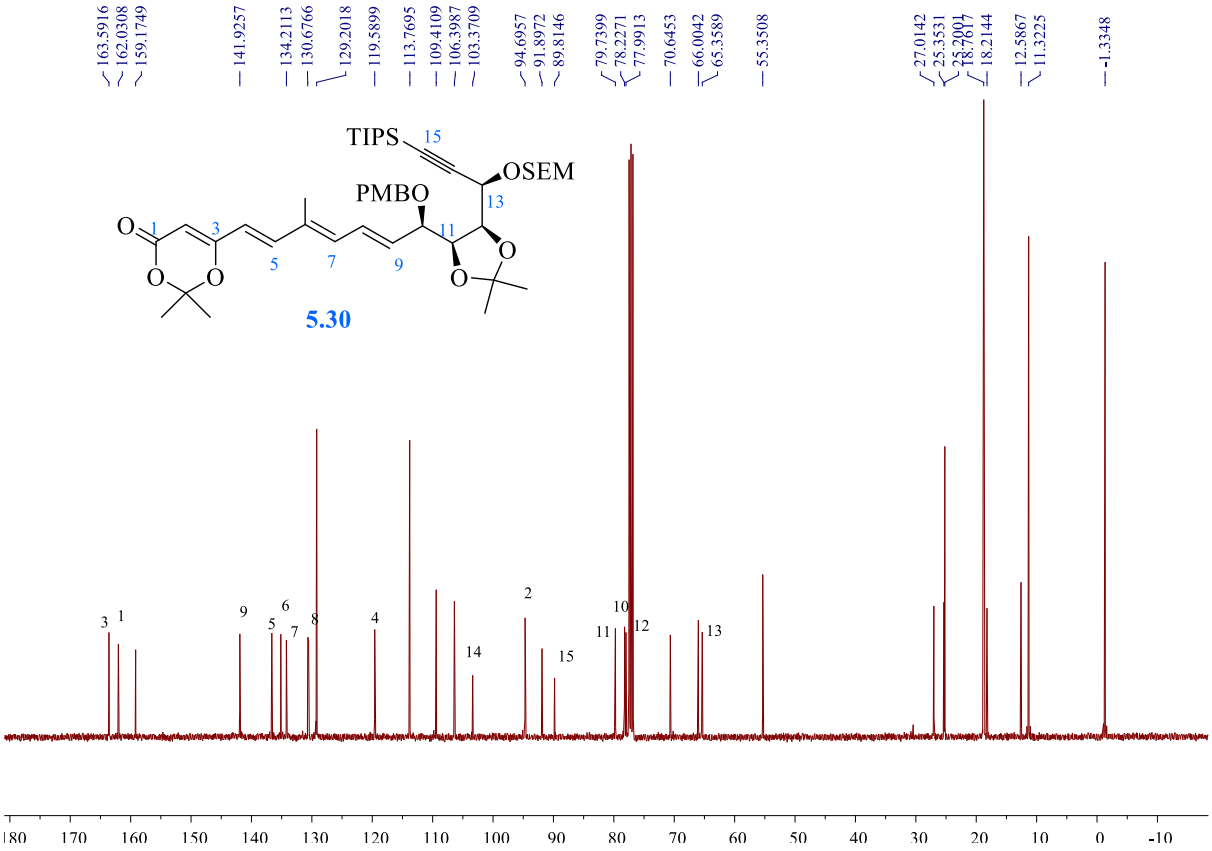


Figure 5.7. *100 MHz ^{1}H NMR Spectrum of Compound 5.30 (recorded in* **d**-*chloroform).*

Table 5.2. ***Assignment of ^{1}H and ^{13}C NMR Data for Compound 5.30*.***

C/H	δ_H	mult (*J* in Hz)	δ_C	
1			162.0	C
2	5.35	s	94.7	CH
3			163.6	C
4	6.97	d (15.5)	119.6	CH
5	6.03	d (15.5)	136.6	CH
6			135.1	C
7	6.37	d (11.3)	134.2	CH
8	6.73	dd (15.2, 11.3)	130.5	CH
9	5.91	dd (15.2, 7.7)	141.9	CH
10	4.45	t (7.7)	78.2	CH
11	4.27	t (6.8)	79.7	CH
12	4.19	dd (6.8, 5.0)	78.0	CH
13	4.63	d (5.0)	65.4	CH
14			103.4	C
15			89.8	C
26	1.91	s	12.6	CH_3
-TIPS	1.09	m	18.7	6 x CH_3
			11.3	3 x CH
-SEM	4.95, 4.69	d, d (6.7)	91.9	CH_2
	3.60, 3.55	ddd (11.1, 9.1, 5.8)	66.0	CH_2
	0.89–0.73	complex m	18.2	CH_2
	−0.04	s	−1.3	3 x CH_3
-acetonide	1.58, 1.38	s	27.0, 25.3	2 x CH_3
			109.4	C
-PMB	7.26, 6.58	d (8.6)	129.2, 113.8	4 x CH
	4.51	ABq (11.4)	70.6	CH_2
			159.2, 130.7	2 x C
	3.79	s	55.3	CH_3
-dioxinone	1.72, 1.71	s	25.2	2 x CH_3
			106.4	C

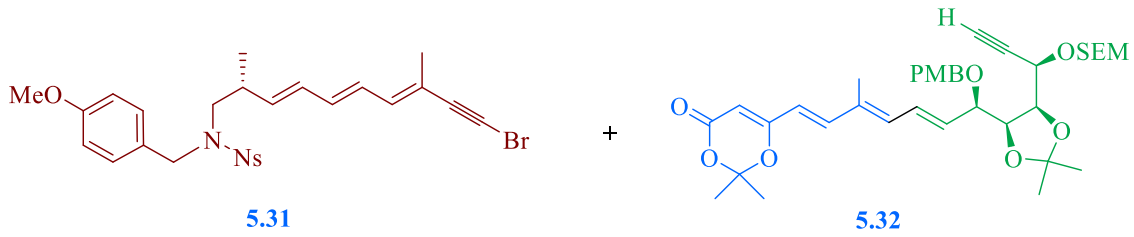
* Data acquired in *d*-chloroform at 400 or 100 MHz (for ^{1}H and ^{13}C NMR data, respectively).

5.4. Synthesis of Fragment C and its Cadiot-Chodkiewicz Coupling with Compound 5.30

5.4.1. Two Possible Means for Deploying the Cadiot-Chodkiewicz Coupling Reaction

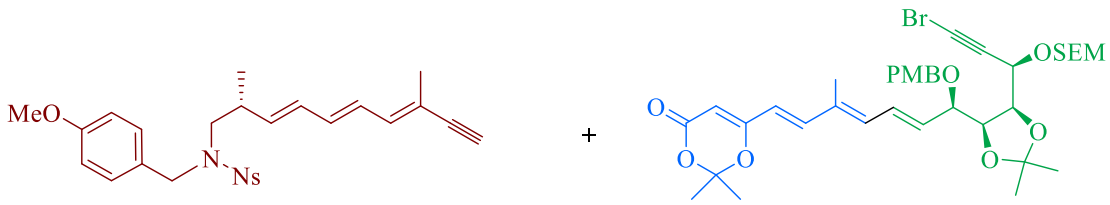
With compound **5.30** in hand, attention turned to the preparation of fragment **C** required for the Cadiot-Chodkiewicz coupling reaction. Two possibilities (**Figure 5.8**) were envisioned for effecting this pivotal step. In the first, fragment **C** would embody a bromo-alkyne moiety as seen in compound **5.31** and this would be coupled with the terminal alkyne **5.32** derived from precursor **5.30**, or, second, the diyne would be accessed from trienyne **5.33** and bromo-alkyne **5.34**. Attempts to prepare these polyenes from the aldehydes **4.36** or **4.18**, themselves readily generated from (*S*)-Roche ester (see **Schemes 4.12** and **4.8**), were undertaken as detailed in the following sections.

Possibility 1



5.31 **5.32**

Possibility 2

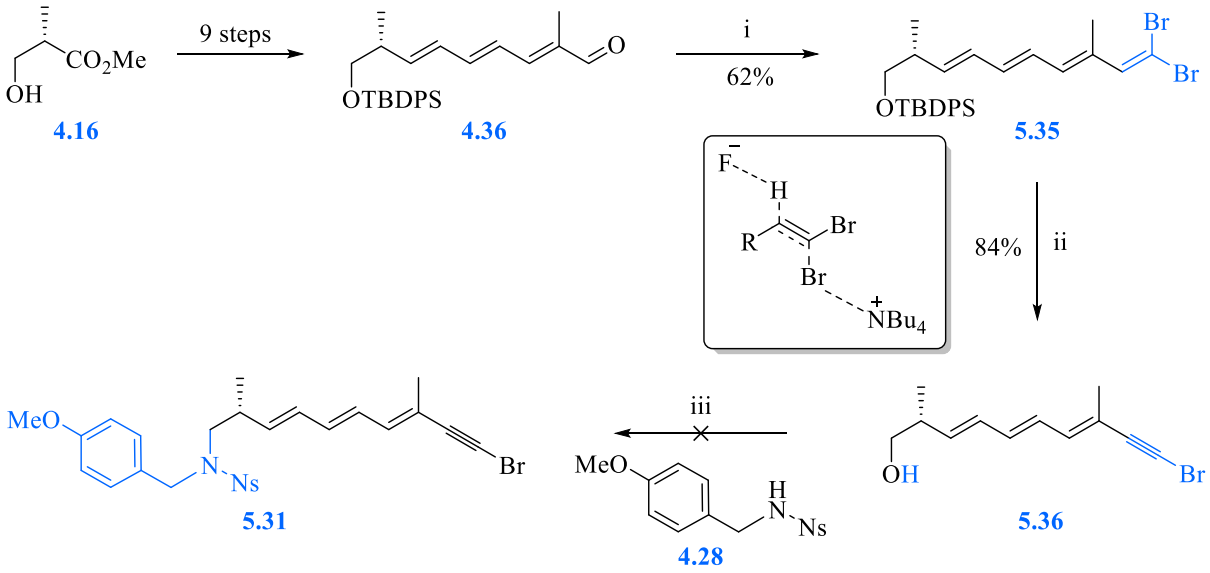


5.33 **5.34**

Figure 5.8. ***Two Possible Pairs of Fragment C-type Coupling Partners 5.31 and 5.33 to be Used in the Cadiot-Chodkiewicz Coupling Reaction.***

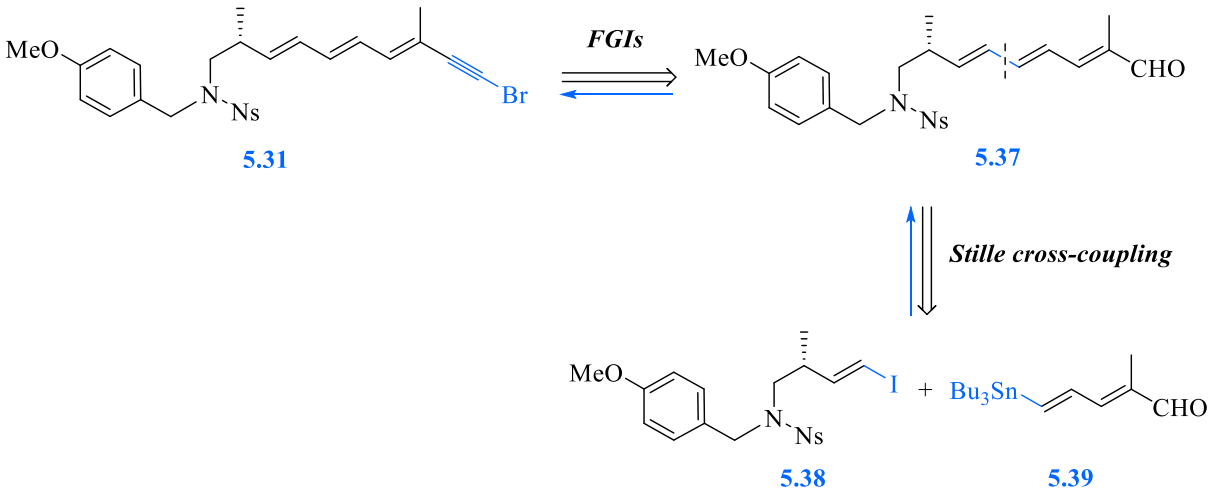
5.4.2. Preparation of the Bromo-Alkyne Variant of Fragment C

It was thought that compound **5.31** could be obtained from the corresponding alcohol *via* a Mitsunobu reaction using *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** as the nucleophile which had been exploited earlier in the preparation of compound **4.40** (see Section **4.3**). To such ends, subjection of aldehyde **4.36** (**Scheme 5.12**) obtained, as detailed in Chapter Four, in 9 steps from (*S*)-Roche ester **4.16**, to a Ramirez olefination reaction[143] with the ylide generated from carbon tetrabromide and triphenylphosphine gave the 1,1-dibromoalkene **5.35** in 62% yield. TBAF-mediated dehydrobromination of product **5.35** provided the desired bromoalkyne-containing primary alcohol **5.36** in 84% yield. This transformation, first reported by Mori,[144] probably proceeds *via* the anti-elimination pathway shown (see inset, **Scheme 512**). Unfortunately, compound **5.36** was extremely unstable and a complex mixture of products was observed on attempting to engage it in a Mitsunobu reaction with sulfonamide **4.28**.



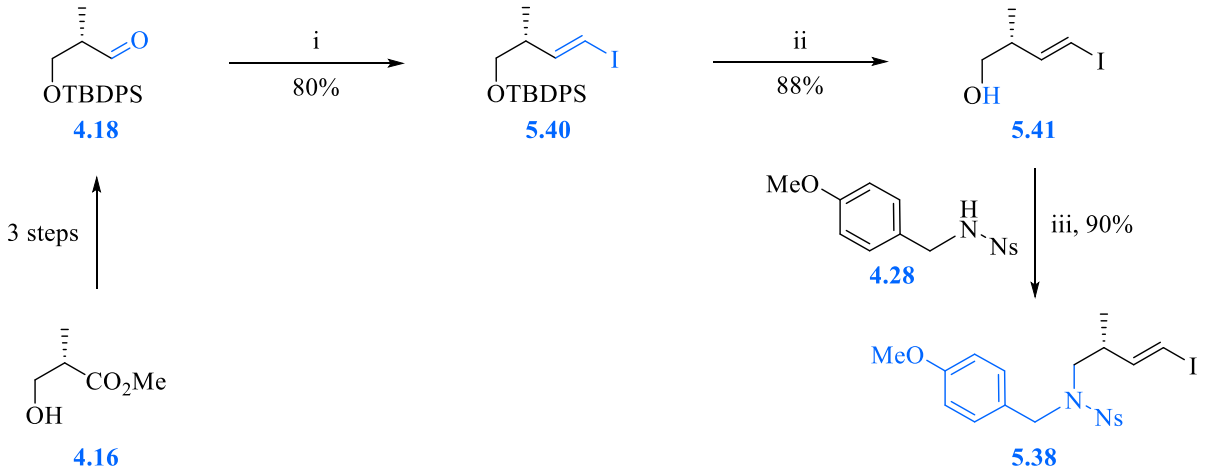
Scheme 5.12. ***Reagents and Conditions*** (i) CBr_4, PPh_3, DCM, 0 to 18 °C, 30 min; (ii) TBAF, THF, 18 °C, 6 h; (iii) DIAD, PPh_3, THF, 18 °C, 16 h.

Given the difficulties described immediately above the new approach shown in **Scheme 5.13** was pursued. The last stage in the preparation of target **5.31** would involve the relevant conversion of aldehyde **5.37** that could be obtained through a Stille cross-coupling reaction between alkenyl iodide **5.38** and stannane **5.39**.



Scheme 5.13. ***Revised Retrosynthetic Analysis of Target*** ***5.31***.

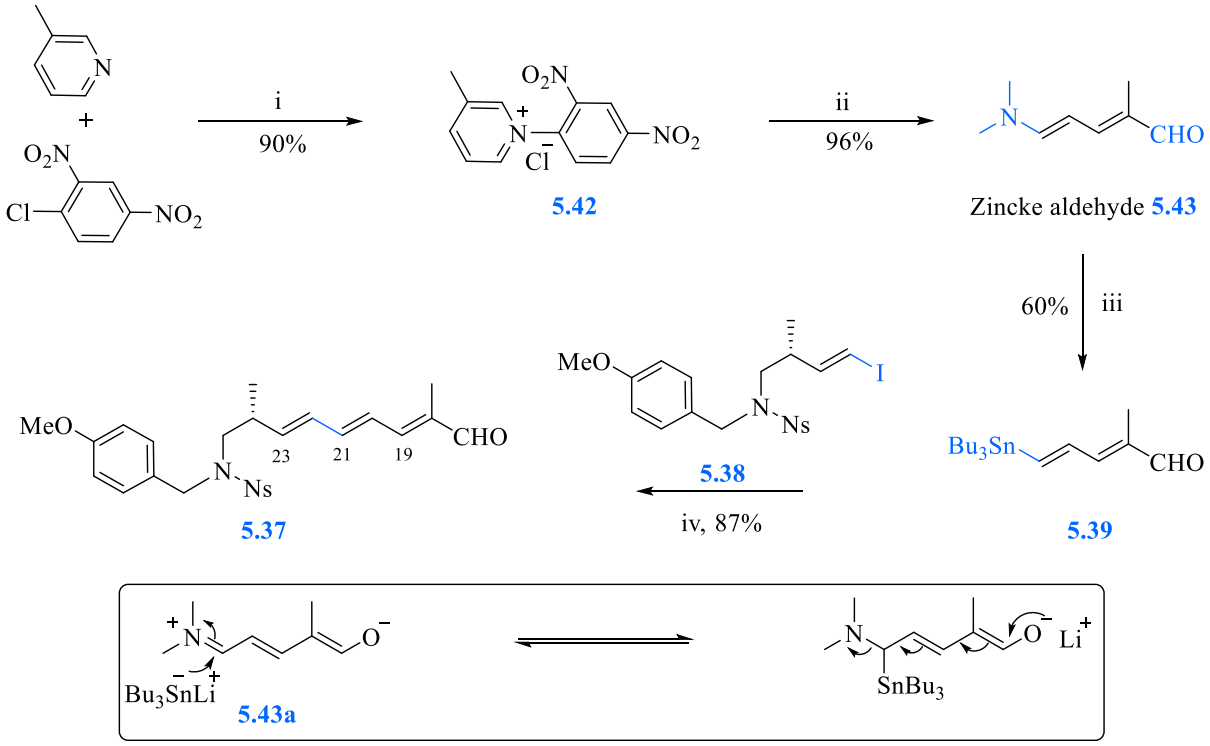
The left-hand side of fragment **C** (*viz*. the alkenyl iodide part) could be prepared from commercially available (*S*)-Roche ester **4.16** *via* the readily available aldehyde **4.18** as shown in **Scheme 5.14**. A Takai olefination reaction was used to convert this aldehyde into the corresponding alkenyl iodide **5.40**[145] (80%) which was itself submitted to a TBAF-mediated desilylation reaction to generate the alcohol **5.41**[146] (88%). With this last compound in hand, its Mitsunobu reaction with *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** was performed and this led to the sulfonamide **5.38** in 90% yield.



Scheme 5.14. ***Reagents and Conditions*** (i) $CrCl_2$, CHI_3, THF, 18 °C, 16 h; (ii) TBAF, THF, 18 °C, 2 h; (iii) DIAD, PPh_3, THF, 18 °C, 16 h.

The known stannylated dienal **5.39** embodying the right hand side of fragment **C** was synthesised from the Zincke aldehyde **5.43** as shown in **Scheme 5.15**.[147] Thus, heating a mixture of 3-methylpyridine and 2,4-dinitrochlorobenzene in acetone to 60 °C for thirty hours afforded the pyridinium or Zincke salt **5.42** (90%) which had a striking purple color. This salt

was heated under reflux with an excess of dimethylamine in ethanol and after the cooled reaction mixture was treated with sodium hydroxide the bifunctional Zincke aldehyde **5.43** was obtained in 96% yield. The electrophilic character of this Zincke aldehyde, as emphasised in the resonance structure **5.43a**, provided the "means" by which it could be converted into stannane **5.39** which was obtained in 60% yield. Cross-coupling of this compound with alkenyl iodide **5.38** under Fürstner's conditions[18] provided the desired product **5.37** in 87% yield.



Scheme 5.15. ***Reagents and Conditions*** (i) acetone, 60 °C, 30 h; (ii) Me_2NH, ethanol, 78 °C, 1 h, then 4 M NaOH; (iii) LDA, Bu_3SnH, THF, then CH_3COCl, 0 to 18 °C; (iv) $Pd(PPh_3)_4$, PPh_3, $[Ph_2PO_2][NBu_4]$, DMF, 18 °C, 30 min.

The spectral data obtained on trienal **5.37** indicated a successful union of the two coupling partners. The ^1H NMR spectrum displays four one-proton doublet of doublets arising from the *trans*-alkenyl protons, namely those located on C20 to C23. The characteristic peaks for the aldehyde, PMB- and nosyl- group protons were also assigned largely on the basis of their distinctive chemical shifts. The ^{13}C NMR spectrum exhibits, as expected, twenty-five distinct carbon resonances (see **Figure 5.9**, **Figure 5.10** and **Table 5.3**).

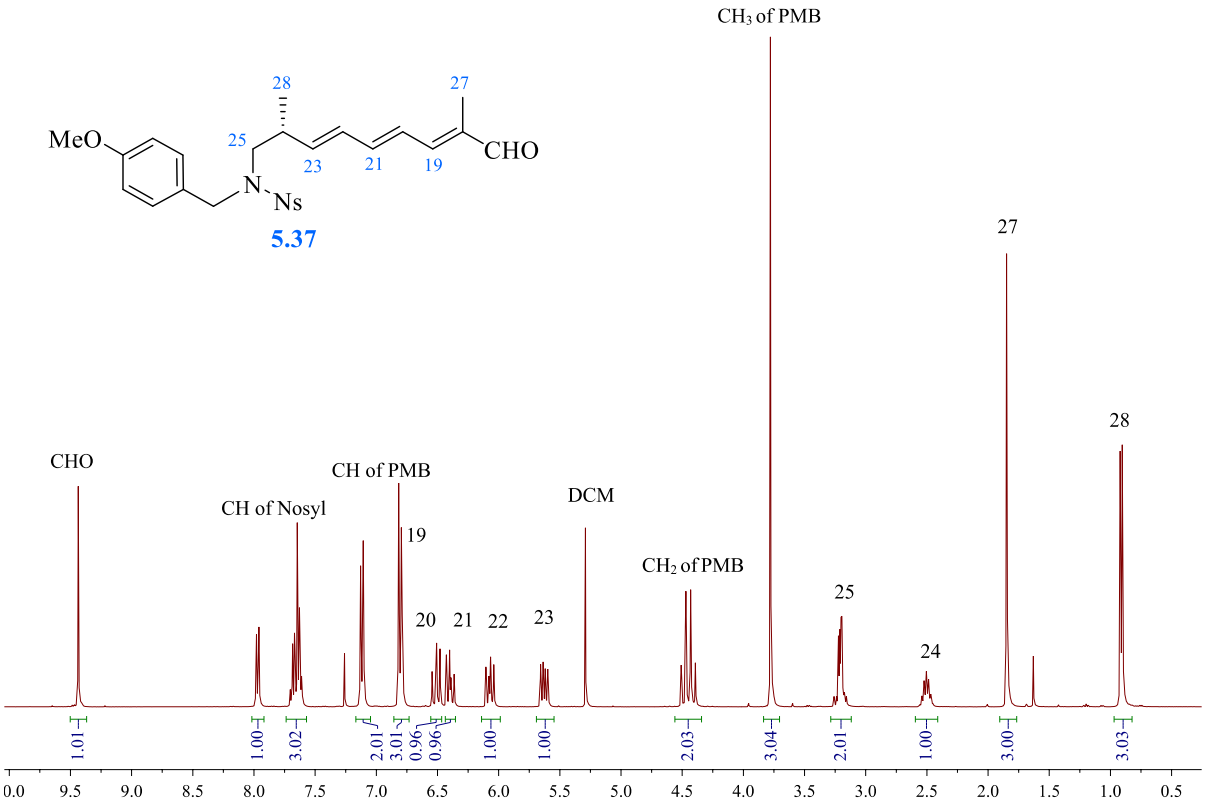


Figure 5.9. *400 MHz ^{1}H NMR Spectrum of Trienal 5.37 (recorded in* d*-chloroform).*

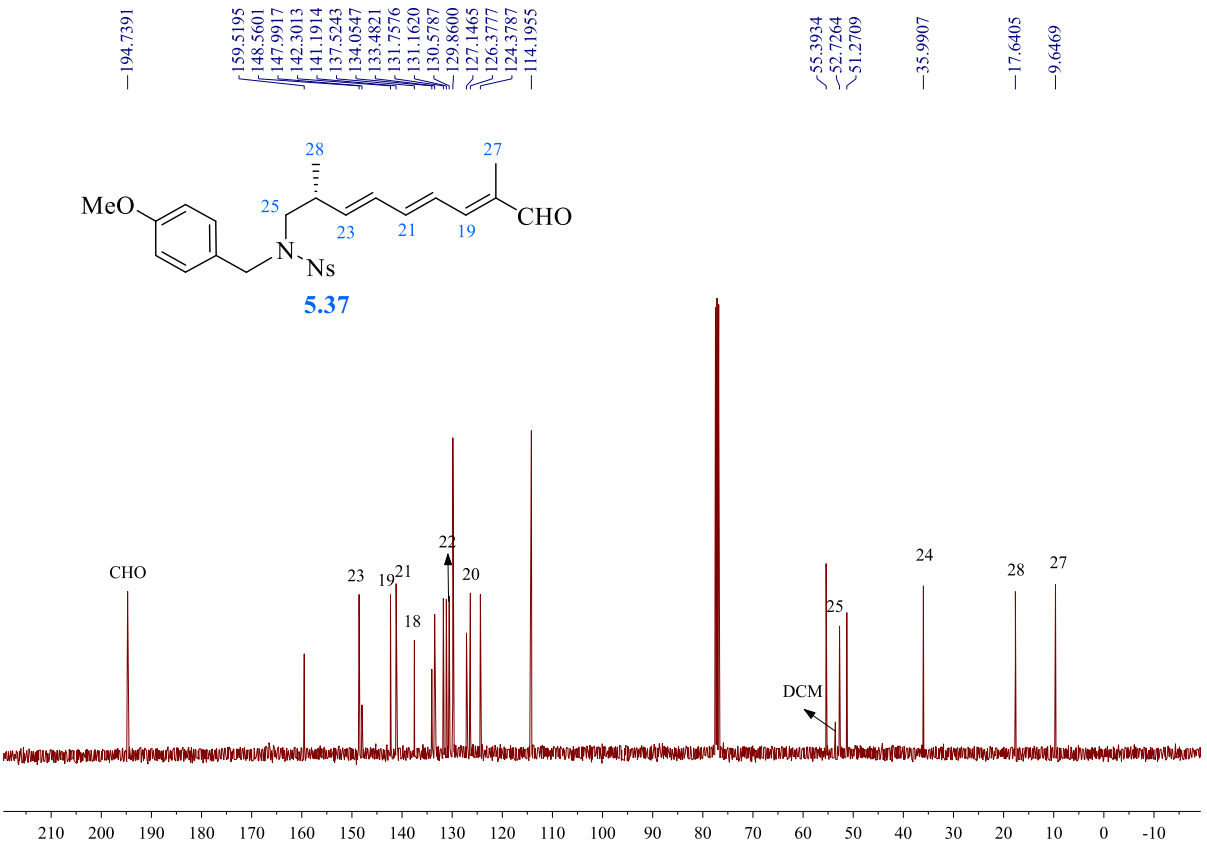


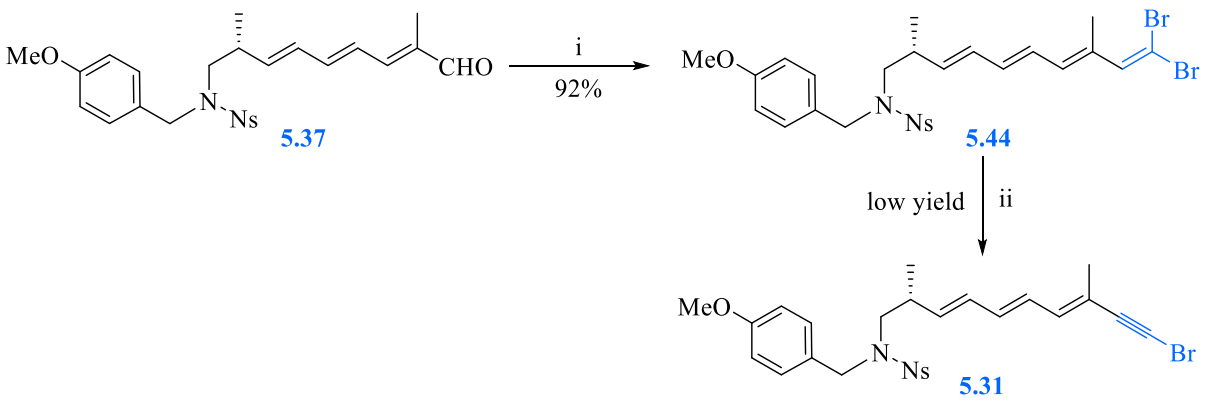
Figure 5.10. *100 MHz ^{13}C NMR Spectrum of Trienal 5.37 (recorded in* d*-chloroform).*

Table 5.3. *Assignment of ^{1}H and ^{13}C NMR Data for Trienal 5.37**.

C/H	δ_H	mult (*J* in Hz)	δ_C	
	9.44	s	194.7	CHO
18			137.5	C
19	6.81	partially obscured d	142.3	CH
20	6.51	dd (14.8, 11.1)	126.4	CH
21	6.40	dd (14.8, 10.5)	141.2	CH
22	6.07	dd (15.2, 10.5)	130.6	CH
23	5.63	dd (15.2, 8.2)	148.6	CH
24	2.50	hept (6.7)	36.0	CH
25-Ha	3.23	ABX (14.6, 8.3)	52.7	CH_2
25-Hb	3.18	ABX (14.6, 7.0)		
27	1.85	s	17.6	CH_3
28	0.91	d (6.7)	9.6	CH_3
-Nosyl	7.97, 7.74–7.57	d (7.7), complex m	133.5, 131.7,	4 x CH
			131.2, 124.4	
			148.0, 134.0	2 x C
-PMB	7.12, 6.81	d (8.6)	129.9, 114.2	4 x CH
	4.45	ABq (15.4)	51.3	CH_2
	3.78	s	55.4	CH_3
			159.6, 127.1	2 x C

* Data acquired in *d*-chloroform at 400 or 100 MHz (for ^{1}H and ^{13}C NMR data, respectively).

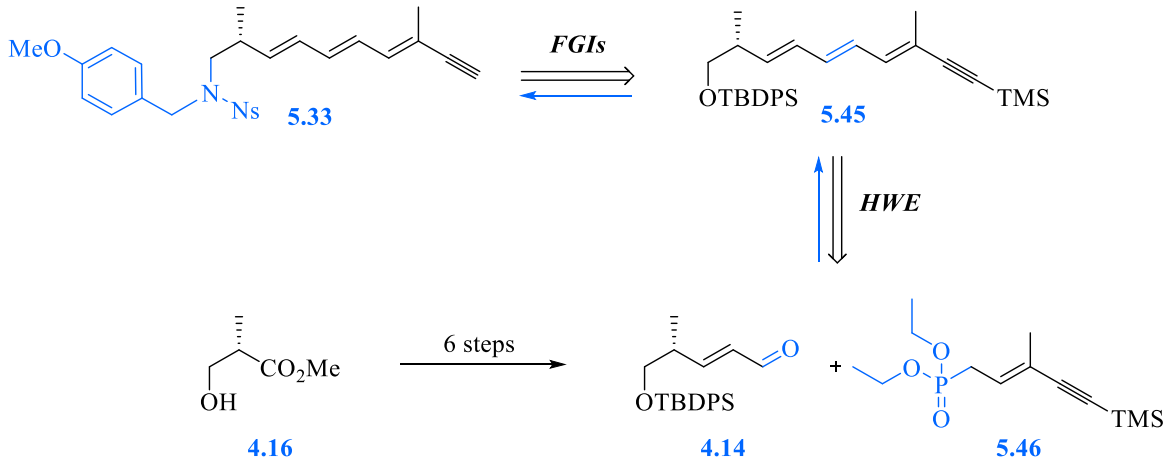
Treatment of aldehyde **5.37** with the ylide generated from carbon tetrabromide and triphenylphosphine (**Scheme 5.16**) gave the expected 1,1-dibromo tetraene **5.44** (92%). While dehydrobromination of product **5.44** with tetra-*n*-butylammonium fluoride did appear to lead to bromo-alkyne **5.31** this proved to be an exceptionally unstable material that rapidly decomposed on being dissolved in, for example, deuterated acetone. Accordingly, little useful spectroscopic data could be acquired on this compound and it was of no value from a synthetic point-of-view.



Scheme 5.16. ***Reagents and Conditions*** (i) CBr_4, PPh_3, DCM, 0 to 18 °C, 30 min; (ii) TBAF, THF, 18 °C, 6 h.

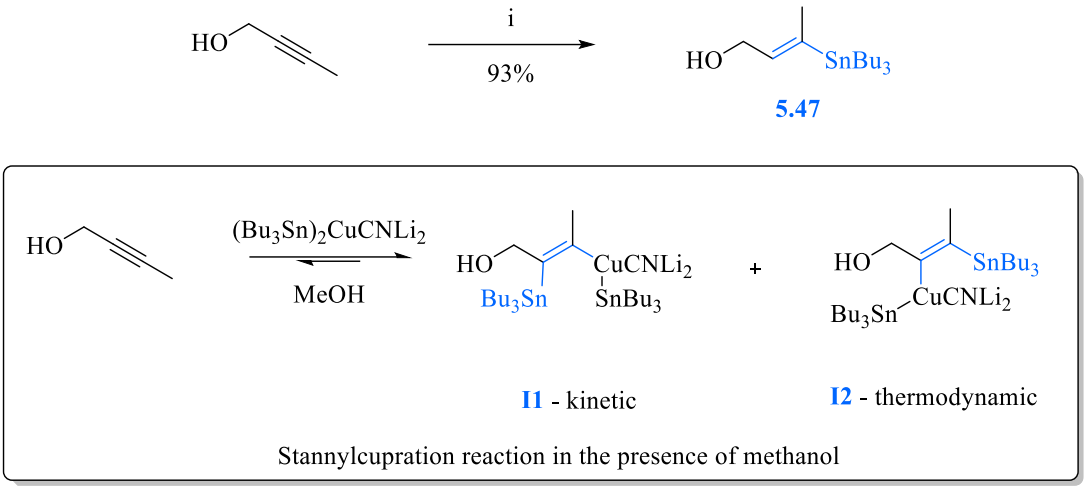
5.4.3. Preparation of the Terminal-Alkyne-Containing Fragment C

The instability of bromo-trienyne **5.31** prompted the development of a synthesis of its non-brominated counterpart **5.33** (**Scheme 5.17**). Thus, it was expected that a Horner-Wadsworth-Emmons olefination reaction involving aldehyde **4.14** [available in six steps from (*S*)-Roche ester **4.16**, see Section **4.3.2**] and phosphonate **5.46** would deliver the trienyne **5.45** that could be converted into the sulfonamide **5.33** *via* sequential Mitsunobu and desilylation reactions.



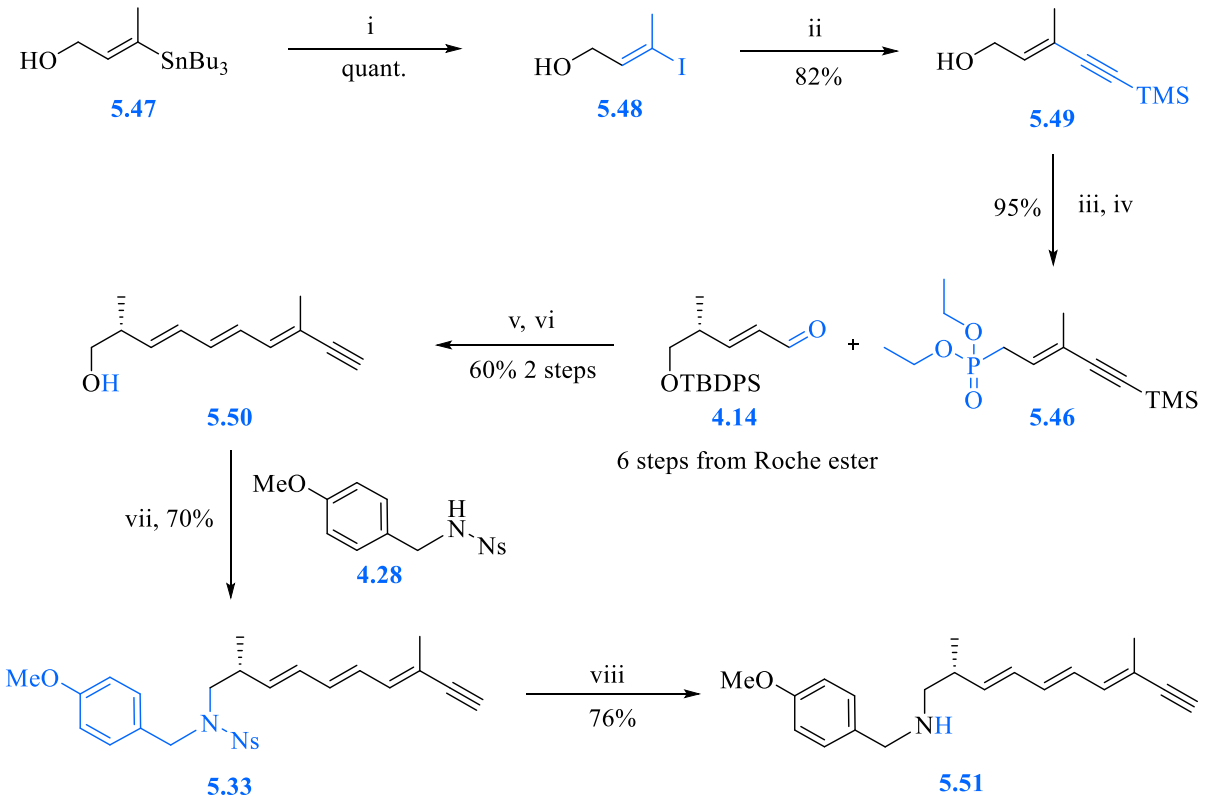
Scheme 5.17. ***Retrosynthesis Analysis of Trienyne 5.33.***

The first step in the proposed synthesis started with stannylcupration, using a high-order cuprate, of 2-butynol (**Scheme 5.18**) in the presence of methanol to obtain the thermodynamically favored *E*-configured alkenyl stannane **5.47** in 93% yield.[148] The use of a higher order cuprate [$(Bu_3Sn)_2CuCNLi_2$] is presumed to have given, in the initial step of the reaction, two regioisomeric intermediates **I1** and **I2** that result from a reversible *cis*-addition reaction. Hydrolysis of these cuprate residues provided the corresponding tin derivatives. The protic solvent methanol serves to methanolyse the alkenyl-copper adduct and drives the equilibrium toward the desired product. Under thermodynamic conditions (achieved at −10 °C), only the *E*-isomer was obtained.



Scheme 5.18. ***Reagents and Conditions*** (i) CuCN, *n*-BuLi, *n*-Bu_3SnH, MeOH, −78 to −10 °C, 2 h.

The alkenyl stannane **5.47** obtained as described above was treated with molecular iodine (**Scheme 5.19**) to furnish the corresponding iodide **5.48**[149] in quantitative yield and this was submitted to a Sonogashira coupling reaction with ethynyltrimethylsilane to deliver the known alcohol **5.49** (82%).[150] This alcohol could be converted into the corresponding bromide on treatment with carbon tetrabromide and triphenyl phosphine and heating of this product in neat triethyl phosphite (so as to effect a Michaelis-Arbuzov reaction) then gave the phosphonate **5.46** in 95% yield over the two steps. A Horner-Wadsworth-Emmons reaction between this phosphonate and aldehyde **4.14** using lithium bis(trimethylsilyl)amide as a base then gave, after global-deprotection (using tetra-*n*-butylammonium fluoride), the product alcohol **5.50** (60% over two steps). A Mitsunobu reaction between this last compound and *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (**4.28**) then provided the desired sulfonamide, **5.33** (70%), that embodies the Northern Hemisphere of lactam **5.1**. Reaction of this sulfonamide with 4-chlorothiophenol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in cleavage of the nosyl group and generation of the N-protected amine **5.51** that was obtained in 76% yield.

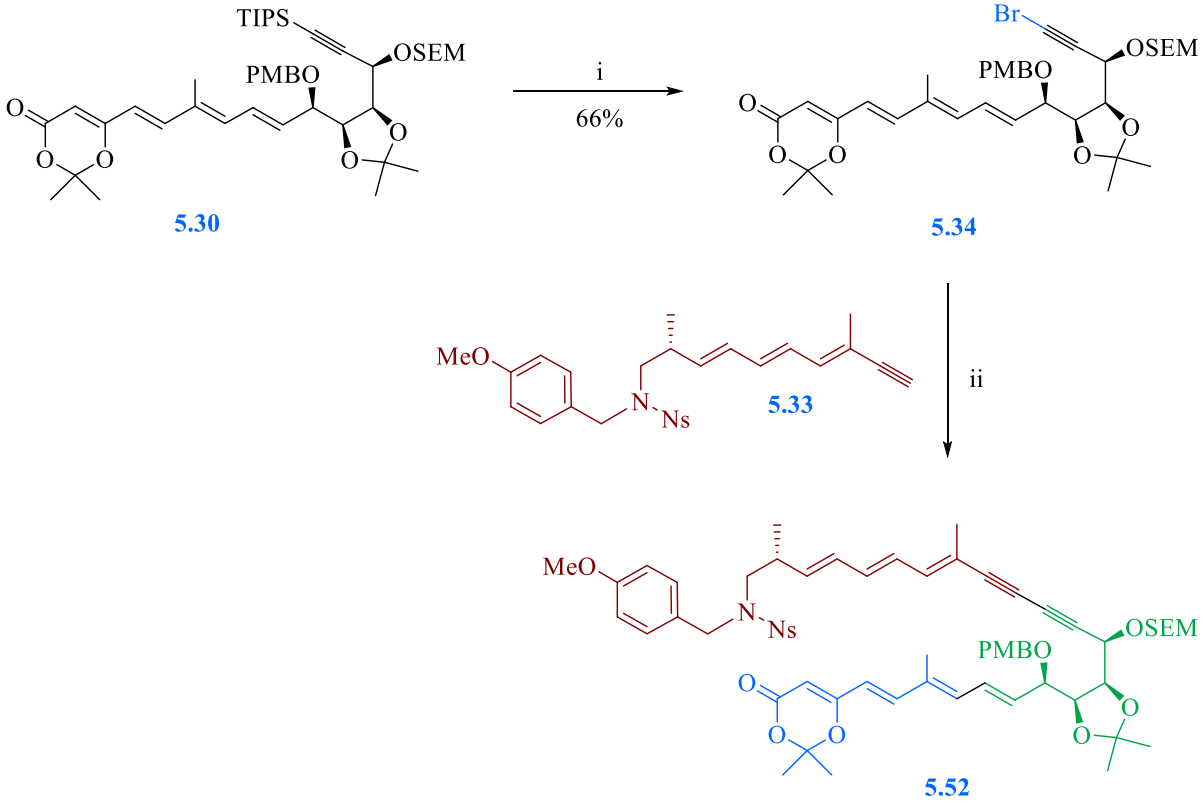


Scheme 5.19. ***Reagents and Conditions*** (i) iodine, THF, −78 to 18 °C, 0.5h; (ii) HC≡CTMS, $Pd(Ph_3P)_4$, PPh_3, CuI, DIPEA, DMF, 18 °C, 16 h; (iii) CBr_4, PPh_3, DCM, 0 to 18 °C, 2 h; (iv) triethylphosphite, 110 °C, 2h; (v) LiHMDS, THF, −78 to 18 °C, 4 h; (vi) TBAF, THF, 18 °C, 2 h; (vii) DIAD, PPh_3, THF, 18 °C, 16 h; (viii) 4-chlorothiophenol, DBU, THF, 18 °C, 4 h.

5.4.4. Cadiot-Chodkiewicz Coupling Reactions

With the terminal alkyne-containing form of fragment **C** in hand, a Cadiot-Chodkiewicz coupling reaction with the corresponding bromo-alkyne partner was pursued. In order to obtain this brominated coupling partner, the TIPS-capped alkyne **5.30** was desilylated *in situ* with silver fluoride (**Scheme 5.20**) and this was followed by treatment of the resulting terminal alkyne with *N*-bromosuccinimide.[151] By such means the bromo-alkyne **5.34** was obtained in 66% yield. Cadiot-Chodkiewicz coupling of compounds **5.34** and **5.33** was performed according to a literature[152] procedure using copper(I) chloride, *n*-butylamine and hydroxylamine hydrochloride. The reaction was monitored by thin layer chromatography which showed the disappearance of the two starting materials and the formation a single new and chromatographically less mobile product. The ^{1}H NMR spectrum of the isolated material suggested the presence of more than one product, although the expected molecular-associated ion [at *m/z* 1156 $(M+Na)^+$] was observed as the base peak in ESI mass spectrum. An accurate

mass measurement on this species established the molecular formula of the product to be $C_{62}H_{76}{}^{23}NaO_{14}SSi$, as expected for the desired product **5.52**. However, this material proved far too intractable for further development in the present context.



Scheme 5.20. ***Reagents and Conditions*** (i) NBS, AgF, acetonitrile, 18 °C, 4 h; (ii) CuCl, $NH_2OH.HCl$, *n*-$BuNH_2$, MeOH, Et_2O, 0 °C, 30 min.

5.6. Conclusion

The union of fragments **A** and **B** using Fürstner's modification of the Stille cross-coupling reaction proceeded effectively at room temperature to give, in good yield, the key compound **5.30** (**Figure 5.11**) that embodies the Southern Hemisphere of macrolactam **5.1**. The terminal alkyne **5.33**, representing the Northern Hemisphere of macrolactam **5.1** was also prepared. However, these key units could not be linked in a Cadiot-Chodkiewicz coupling reaction. Therefore, a simpler or model macrolactone was designed so as to study the amenability of such scaffolds to engage in the pivotal transannular [2+2]-cycloaddition reaction. Details of the relevant studies are presented in the following Chapter.

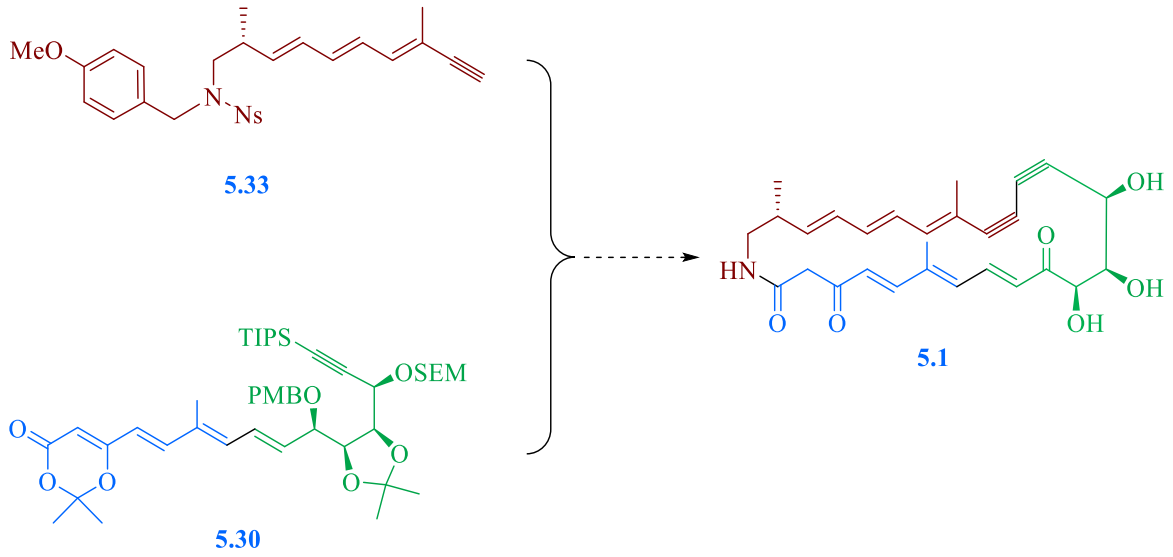
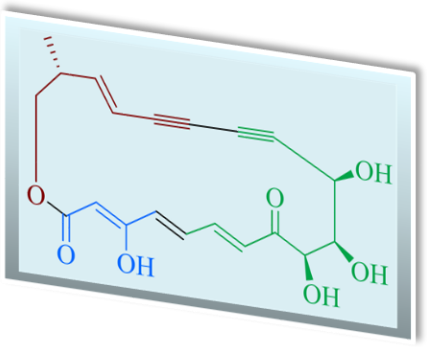


Figure 5.11. *The Advanced Intermediates **5.30** and **5.33** Prepared as Potential Precursors to Macrolactam **5.1**.*

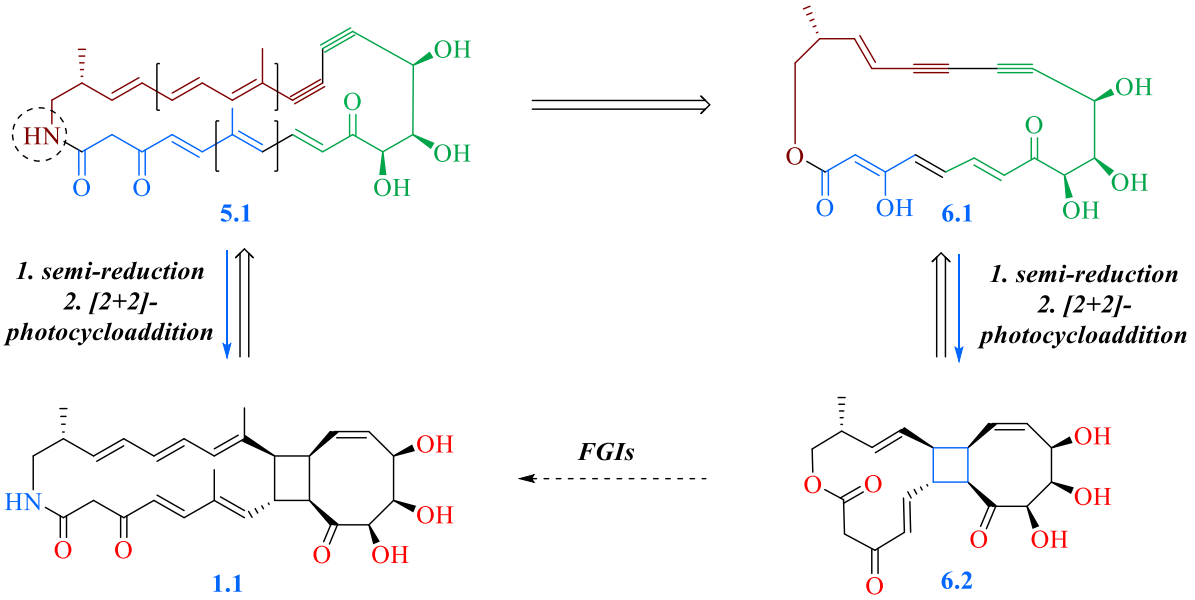
6. CHAPTER SIX

Seeking a Macrolactone as a Model for the Target Macrolactam



6.1. The Macrolactone Model and its Retrosynthetic Analysis

Due to the instability of the polyenyne **5.52** described in the preceding Chapter, the synthesis of macrolactone **6.1** was sought as a substrate with which to test the pivotal transannular [2+2]-photocycloaddition reaction. If successful, this would provide a model, **6.2**, of the Eastern Hemisphere of tripartilactam (**Scheme 6.1**). In this plan, the required substrate, **6.1**, for [2+2]-photocycloaddition reaction was expected to be delivered through a two-fold semi-reduction of the precursor diyne unit within macrolactone **6.1**. The anticipated photoproduct **6.2** could also serve as a potential precursor to the natural product itself through elaboration of its Western Hemisphere.

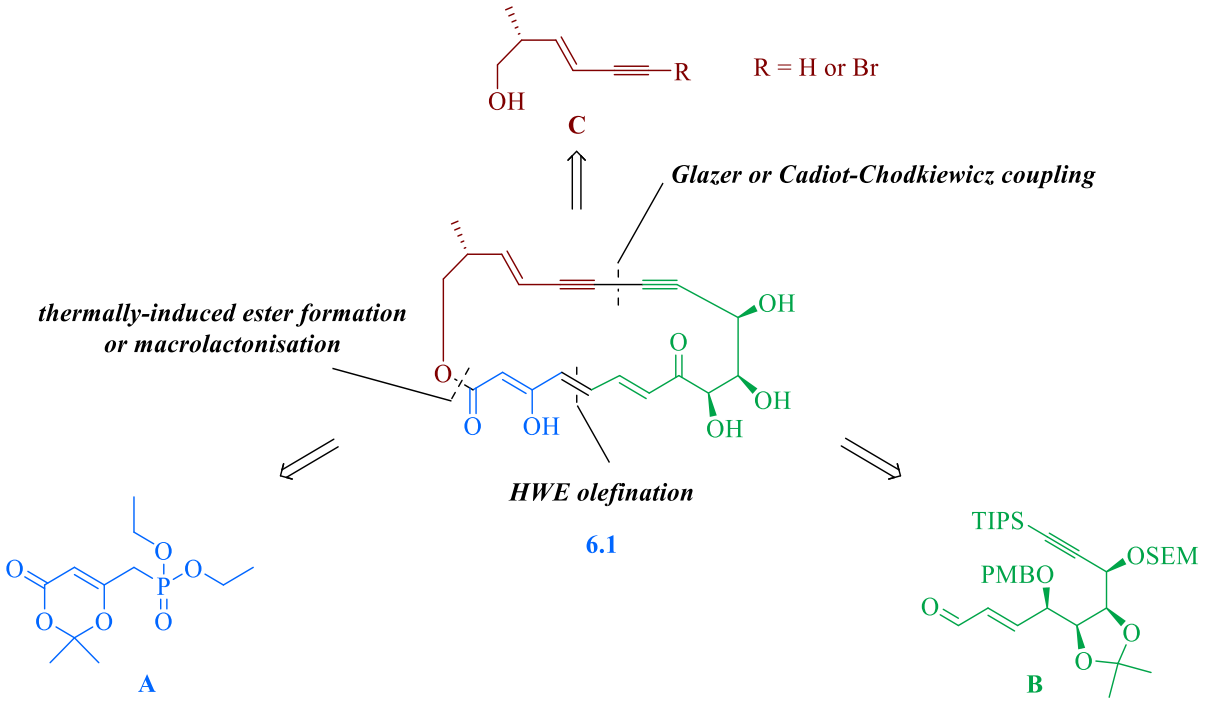


Scheme 6.1. ***Identification of Macrolactone 6.2 as a Model Substrate for the Transannular [2+2]-Cycloaddition Reaction.***

A convergent strategy for the synthesis of macrolactone **6.1** was devised exploiting, as much as possible, the already established protocols used in the assembly of fragments **A**, **B** and **C** (**Scheme 6.2**). Thus, it was anticipated that a Horner-Wadsworth-Emmons olefination could be employed to connect phosphonate **A** and fragment **B**, the latter itself being derived from compound **5.25** that was obtained as described earlier.[j] Two possibilities were considered for assembling fragment **C**. Either a thermally-induced ester forming process followed by an intramolecular Glaser type coupling reaction could be used or a Cadiot-Chodkiewicz coupling

[j] The preparation of this compound is described in Section **5.3.3**.

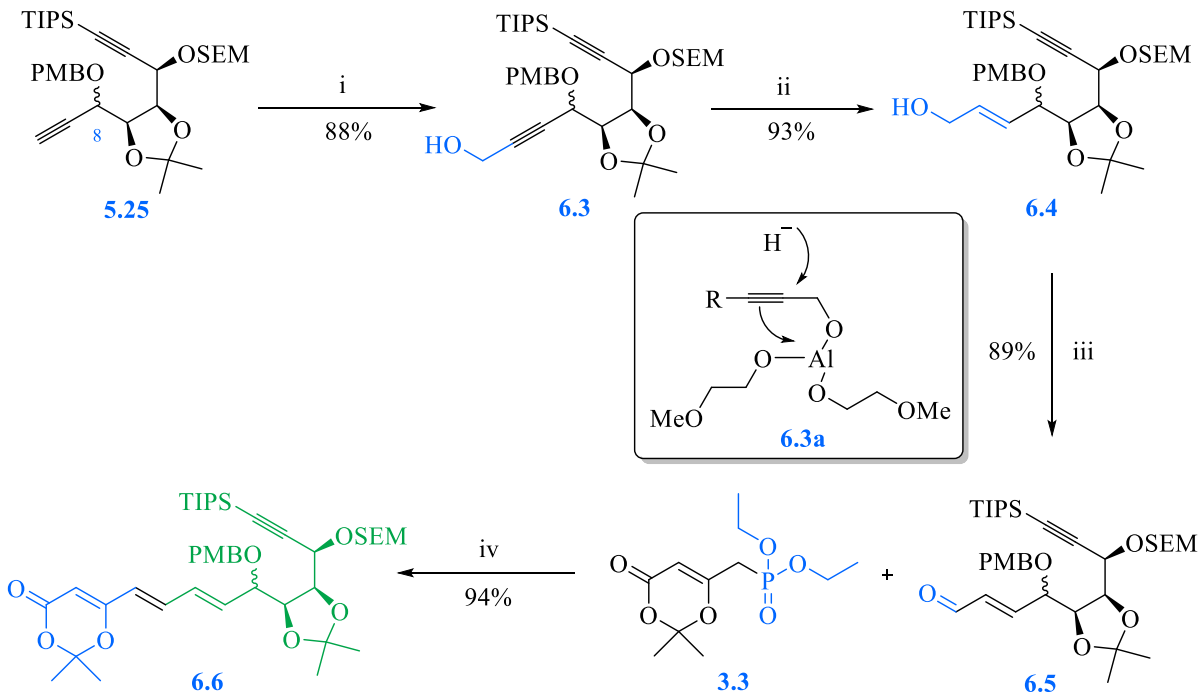
process could be engaged to establish the diyne linkage and this would then be followed by a thermally-induced lactonisation reaction to complete the macrocyclic ring.



Scheme 6.2. ***Key Building Blocks (Fragments) Targetted fot the Assembly of Macrolactone 6.1.***

6.2. Connection of Fragments A and B

Scheme 6.3 shows the synthetic route used to assemble the Southern part of macrolactone **6.1**. Thus, the synthesis started with compound **5.25** (obtained earlier as a mixture of epimers at C8), that was itself prepared from *D*-ribose in a ten-step sequence described in Section **5.3.3**. The terminal alkyne of this substrate was first deprotonated using *iso*-propylmagnesium chloride as a base and the acetylide anion thus formed condensed with paraformaldehyde to deliver propargylic alcohol **6.3** in 88% yield. Treatment of this alcohol with a solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al™) provided, after protic work-up, the desired *trans*-allylic alcohol **6.4** in 93% yield. This *trans*-hydroalumination reaction required the use of two equivalents of Red-Al™, the first being involved in coordination, through aluminium, to both a triple bond and a hydroxyl group and thus allowing the nucleophilic attack of a second hydride (from the second Red-Al™ molecule) as depicted in **6.3a**. Oxidation of the resulting allylic alcohol with manganese dioxide then furnished the unsaturated aldehyde **6.5** in 89% yield. A Horner-Wadsworth-Emmons olefination reaction between this epimeric mixture of aldehydes and phosphonate **3.3**[k] [using lithium bis(trimethylsilyl)amide as a base] finally provided the targeted compound **6.6** in 94% yield albeit as an inseparable mixture of epimers.



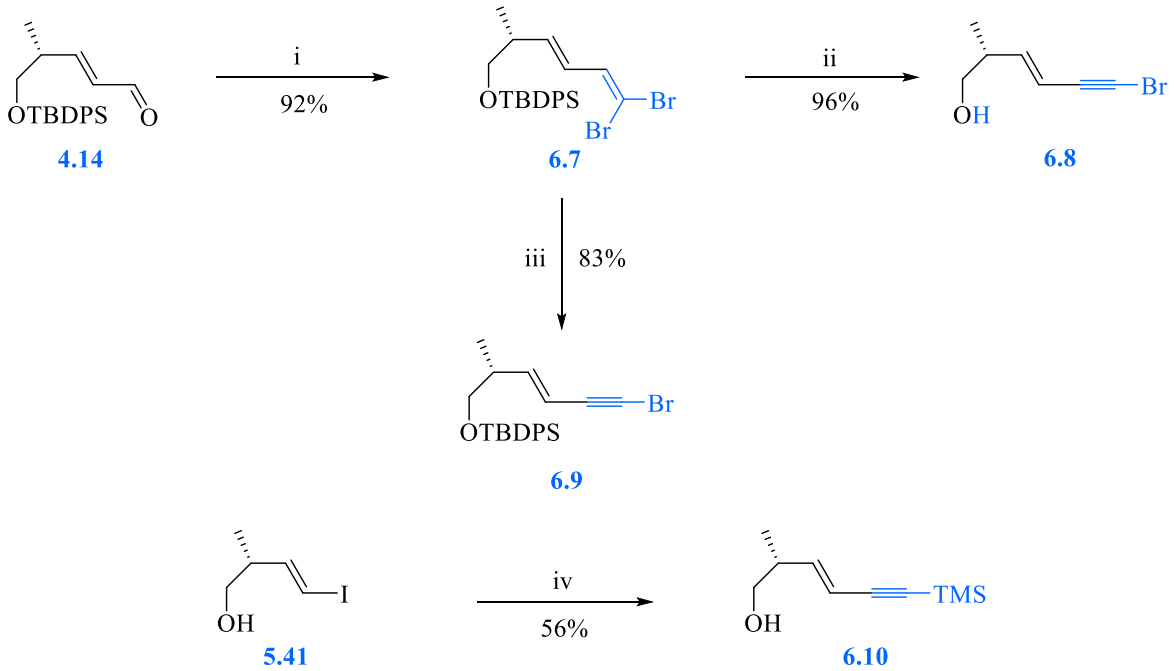
Scheme 6.3. ***Reagents and Conditions*** (i) *i*-PrMgCl, (CHO)n, THF, 18 °C, 16 h; (ii) Red-Al, 0 °C, 30 min; (iii) MnO_2, DCM, 18 °C, 4 h; (iv) LiHMDS, THF, −78 to 18 °C, 2 h.

[k] The preparation of this compound is described in Section **3.3.1**.

6.3. Preparation and Attachment of Fragment C and Attempts to Effect a Macrocyclisation Reaction

6.3.1. Preparation of Fragment C

As mentioned earlier, there were two options for the assembly of fragment **C** and for macrocyclisation. The macrolactone **6.1** could, in principle, be obtained through either a thermally-induced lactonisation process or an intramolecular cross-coupling reaction to form the diyne linkage. Both of these options were investigated experimentally and the outcomes are presented in the following sections. **Scheme 6.4** illustrates the preparation of the relevant alcohol-containing fragment employed in exploring both two options. Thus, the readily prepared aldehyde **4.14** [available in six steps from (*S*)-Roche ester][l] was reacted with the ylide generated from carbon tetrabromide and triphenylphosphine and the *gem*-dibromodiene **6.7** thus obtained in 92% yield. This dibromo-compound was exposed to either tetra-*n*-butylammonium fluoride to furnish the desilylated bromo-alkyne **6.8** (96%) or lithium bis(trimethylsilyl)amide to deliver the alcohol protected bromo-alkyne **6.9** (83%). On the other hand, alcohol **5.41** [obtained in a five-step sequence from (*S*)-Roche ester][m] was submitted to a Sonogashira coupling reaction with ethynyltrimethylsilane to give alcohol **6.10** (56%).

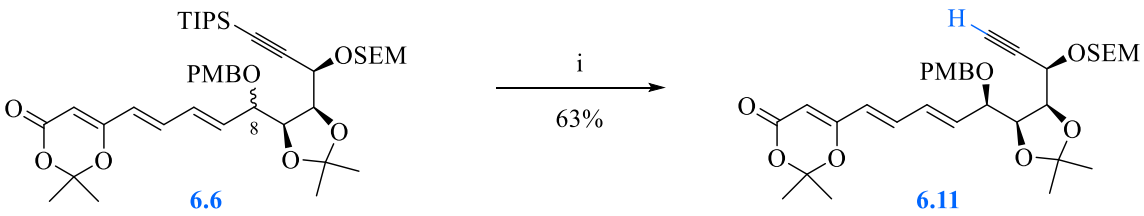


Scheme 6.4. ***Reagents and Conditions*** (i) CBr_4, PPh_3, DCM, 0 to 18 °C, 30 min; (ii) TBAF, THF, 18 °C, 6 h; (iii) LiHMDS, THF, 18 °C, 3 h; (iv) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, 18 °C, 16 h.

[l] The preparation of this compound is described in Section **4.3.2**.
[m] The preparation of this compound is described in Section **5.4.2**.

6.3.2. Macrocyclisation *via* a Thermally-Induced Lactonisation Process

In order to perform a thermally-induced lactonisation, the alcohols mentioned above needed to be connected to compound **6.6** *via* an intermolecular acetylene cross-coupling reaction. To this end, an epimeric mixture (at C8) of TIPS-capped alkyne **6.6** was first exposed to tetra-*n*-butylammonium fluoride and the desilylated and single epimeric form of product **6.11** was isolated in 63% yield after flash column chromatography (**Scheme 6.5**).



Scheme 6.5. ***Reagents and Conditions*** (i) TBAF, THF, 18 °C, 2 h.

Extensive analysis of the ^{1}H NMR and ^{13}C NMR spectra derived from this desilylation product led to the assignment of the illustrated structure for compound **6.11**. Various relevant assignments of the observed resonances are given in **Figure 6.1** and **Figure 6.2**.

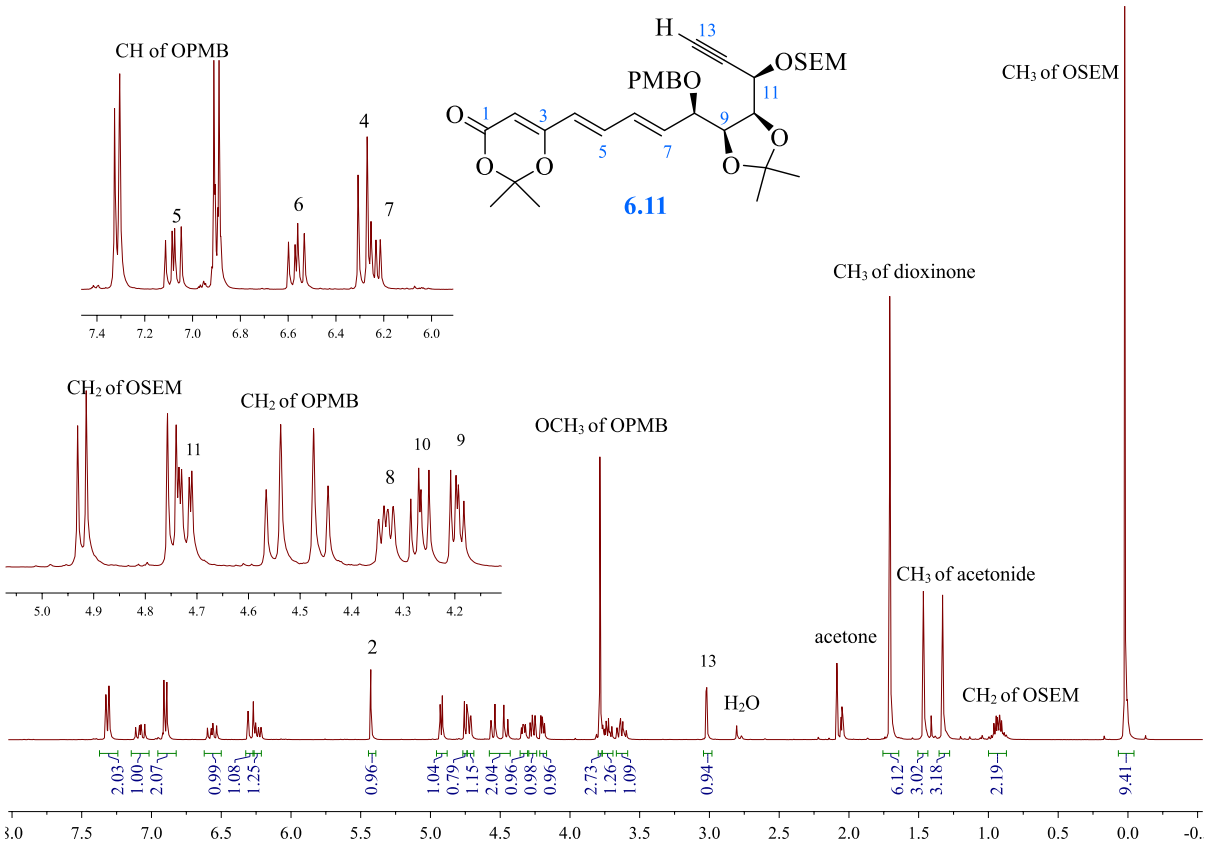


Figure 6.1. ***400 MHz ^{1}H NMR Spectrum of Compound 6.11 (recorded in d_6-acetone).***

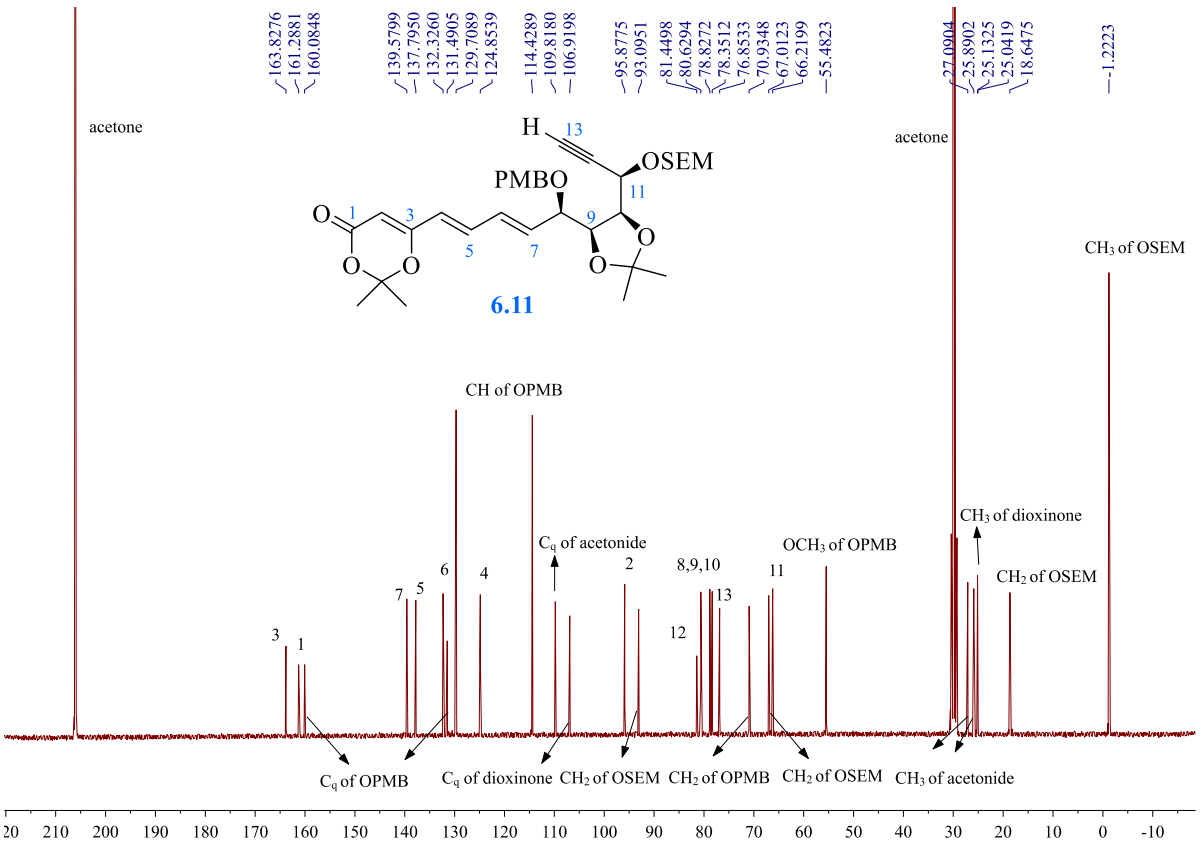
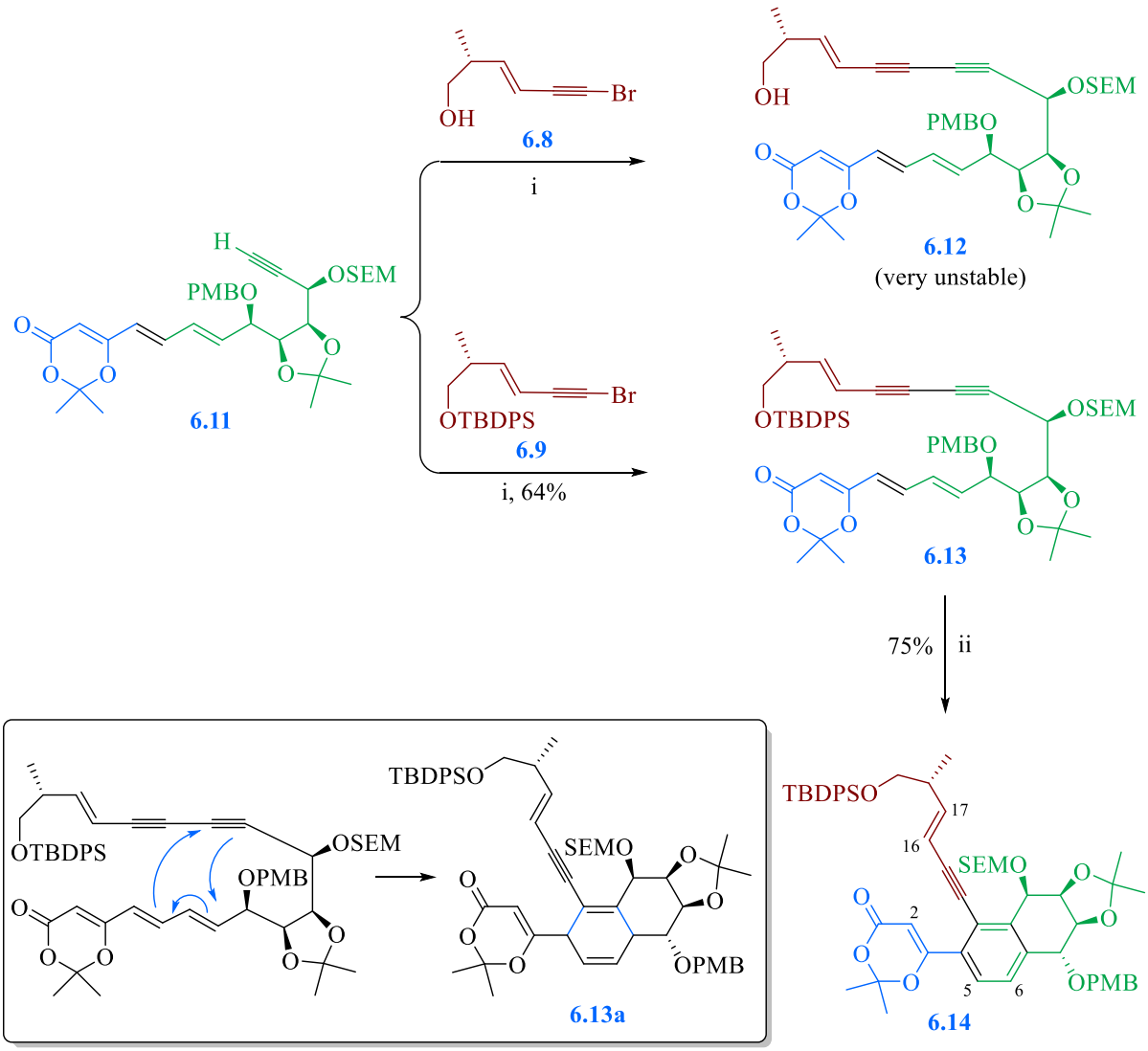


Figure 6.2. ***100 MHz ^{13}C NMR Spectrum of Compound 6.11 (recorded in d_6-acetone).***

The Cadiot-Chodkiewicz coupling of alkyne **6.11** (**Scheme 6.6**) with the unprotected alcohol **6.8** was conducted using the procedures employed earlier [using copper(I) chloride, *n*-butylamine and hydroxylamine hydrochloride as presented in Section **5.4.4**] and gave product **6.12** but this proved to be unstable as evidenced by the complexities of the derived ^1H NMR spectrum. Accordingly, the silylated alcohol **6.9** was examined as a possibly more suitable building block. By the simple means shown in **Scheme 6.6**, product **6.13** was obtained in 64% yield. However, while the preliminary spectroscopic data obtained on this material were in complete accord with the assigned structure as efforts were made to purify it then it began to engage in a transannular Diels-Alder cycloaddition reaction and thus providing, presumably after aromatisation of the intermediate dihydroaromatic compound, **6.13a**, the observed product **6.14**.



Scheme 6.6. ***Reagents and Conditions*** (i) CuCl, $NH_2OH.HCl$, *n*-$BuNH_2$, MeOH, Et_2O, 0 to 18 °C, 30 min; (ii) TBAF, THF, 18 °C, 2 h.

The ^{1}H NMR spectrum of compound **6.14** (**Figure 6.3**) displays only three signals in the olefinic region including a characteristic singlet for C2-H at δ 6.03 as well as two mutually coupled resonances at δ 5.94 (J = 16.0 Hz) and δ 6.49 (J = 16.0 and 7.7 Hz) that were assigned to C16-H and C17-H, respectively. The resonance appearing at δ 7.75 was attributed to the two protons attached to the newly established aromatic ring, namely C5-H and C6-H. The ^{13}C NMR spectrum (**Figure 6.4**) also shows the additional six aromatic resonances, the assignments of which were assisted through the use of DEPT experiments. The ESI mass spectrum displayed a molecular-associated ion at *m*/*z* 981 and accurate mass measurement on this species established that it had the expected molecular formula, *viz* $C_{56}H_{70}{}^{23}NaO_{10}Si_2$.

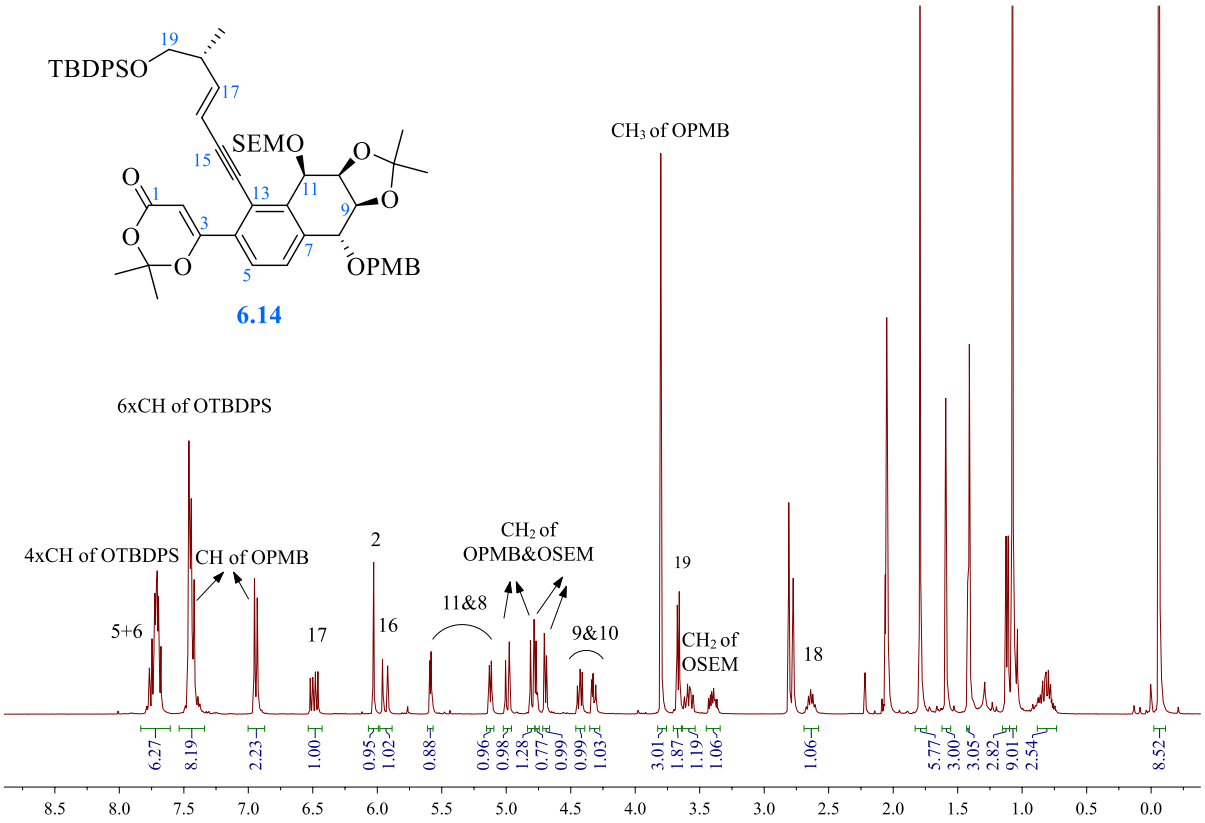


Figure 6.3. *400 MHz ^{1}H NMR Spectrum of Arene 6.14 (recorded in* d_6*-acetone).*

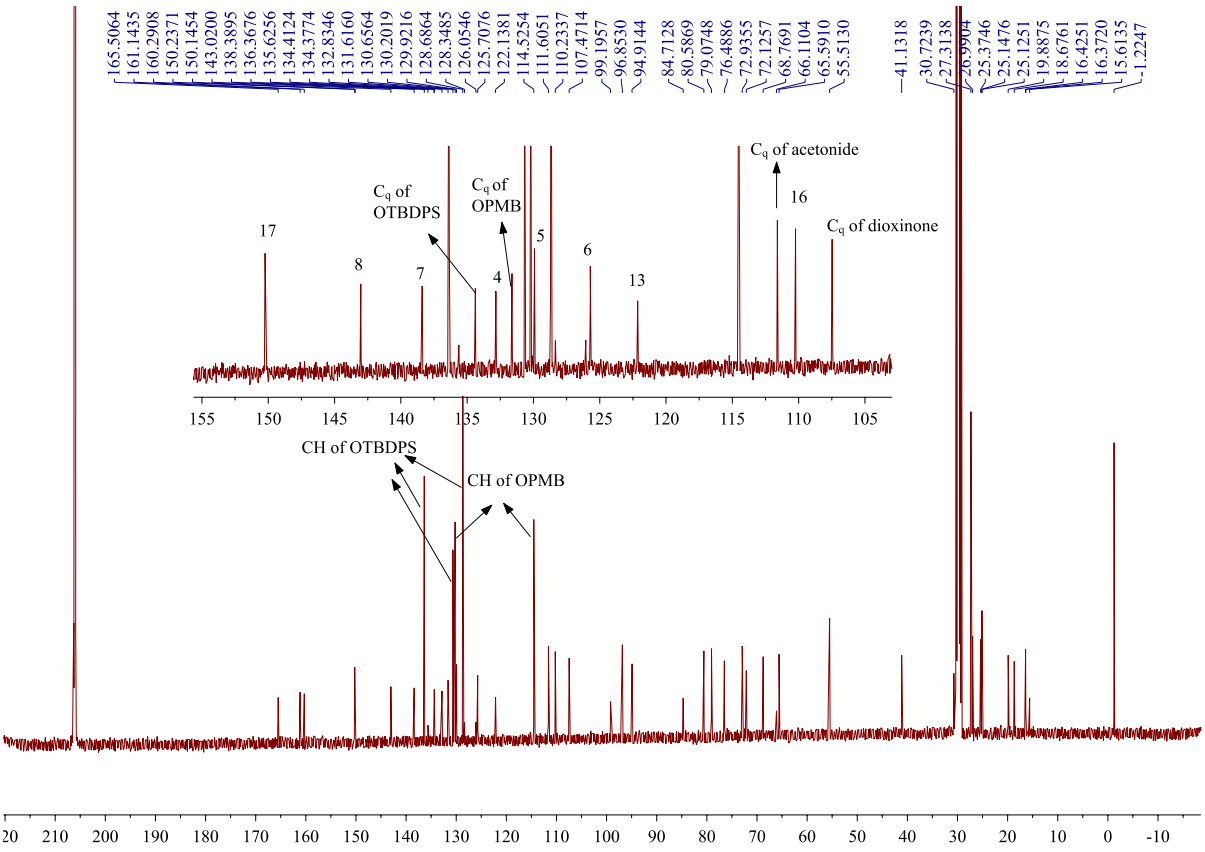
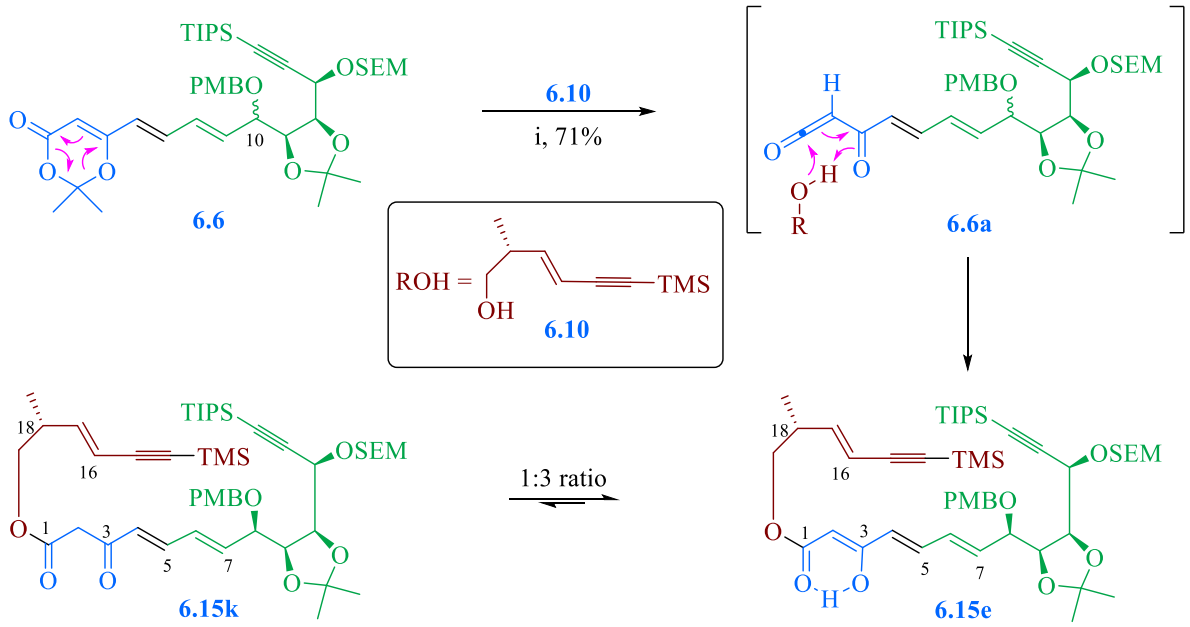


Figure 6.4. *100 MHz ^{13}C NMR Spectrum of Arene 6.14 (recorded in* d_6*-acetone).*

6.3.3. Attempts to Effect Macrocyclisation *via* an Intramolecular Cross-Coupling Reaction

As discussed earlier (see Section **3.3.1**), thermolysis of 1,3-dioxinone-containing compounds normally induces the loss of acetone so as to generate an acylketene that can be trapped by added nucleophiles.[125] Consistent with such expectations, heating equivalent quantities of compound **6.6** (as a mixture of epimers at C-10) and alcohol **6.10** (**Scheme 6.7**) to 120 °C in anhydrous toluene furnished the desired ester **6.15** in 71% yield. Although only the major epimer was isolated, the minor one was also being formed as evidenced by thin layer chromatographic analysis. Owing to the small scale of reaction, this minor isomer was not isolated. Careful maintenance of the anhydrous conditions was crucial to the success of this transformation as this prevented the transient acylketene reacting with adventitious water.



Scheme 6.7. ***Reagents and Conditions*** (i) toluene, 120 °C, 4 h.

The ^{1}H NMR spectrum of compound **6.15** is shown in **Figure 6.5** and clearly reveals the existence of a 3:1 mixture of both the enol, **6.15e**, and keto, **6.15k**, tautomeric forms of this esterification product. The major component gives rise to two singlets, at δ 11.71 and 5.09 that correspond to the OH and C2-H protons, respectively, for the enol form while a singlet at δ 3.61 arises from the C2-methylene protons of the minor or keto component. The spectrum also displays four distinct resonances arising from the protons of the two conjugated *trans*-double bonds of enol **6.15e**. These are a doublet for C4-H at δ 5.94 (J = 15.2 Hz) which shows a mutual coupling with C5-H at 7.06 [that appears as a doublet of doublets (J = 15.2 and 11.1 Hz)]. This

proton is also coupled with C6-H which appears at δ 6.46 as another doublet of doublets (J = 15.4 and 11.1 Hz). The resonance due to C7-H appears at δ 6.03 (J = 15.4 and 7.6 Hz). Evidence for the successful attachment of fragment **C** follows from the appearance of two additional signals in the olefinic region at δ 6.14 (dd, J = 16.0 and 7.7 Hz) and 5.58 (dd, J = 16.0 and 1.2 Hz). These are attributed to C17- and 16-H, respectively. The resonance due to C18-H appears at δ 2.62. An essentially equivalent set of signals with the same pattern was also observed for the minor or keto form, **6.15k**.

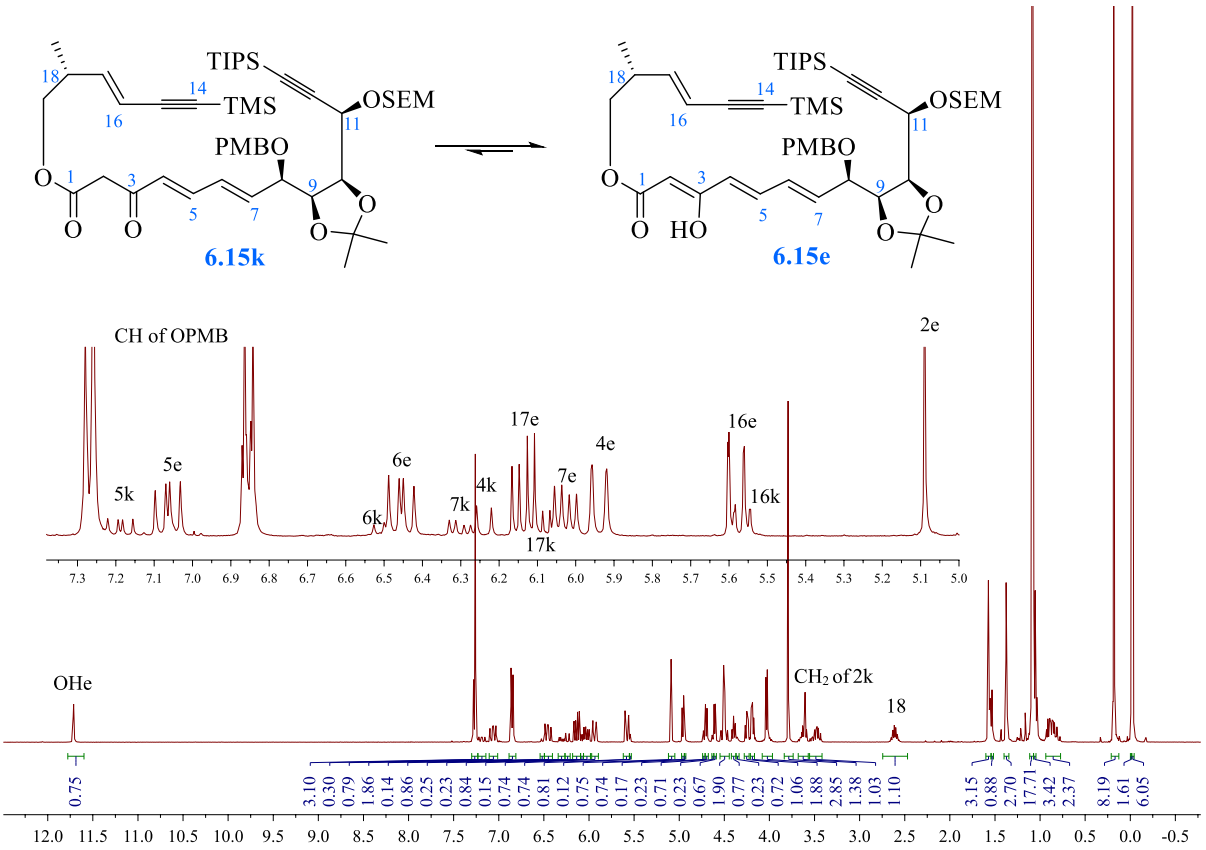
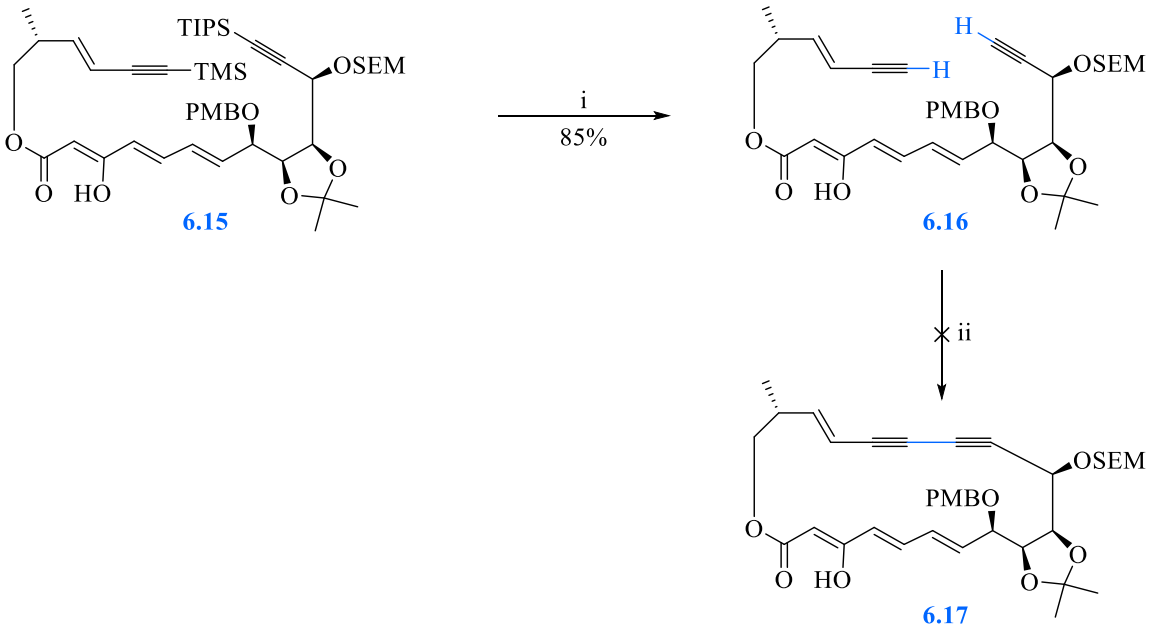


Figure 6.5. *400 MHz ^{1}H NMR Spectrum of 6.15e and 6.15k (recorded in* d*-chloroform).*

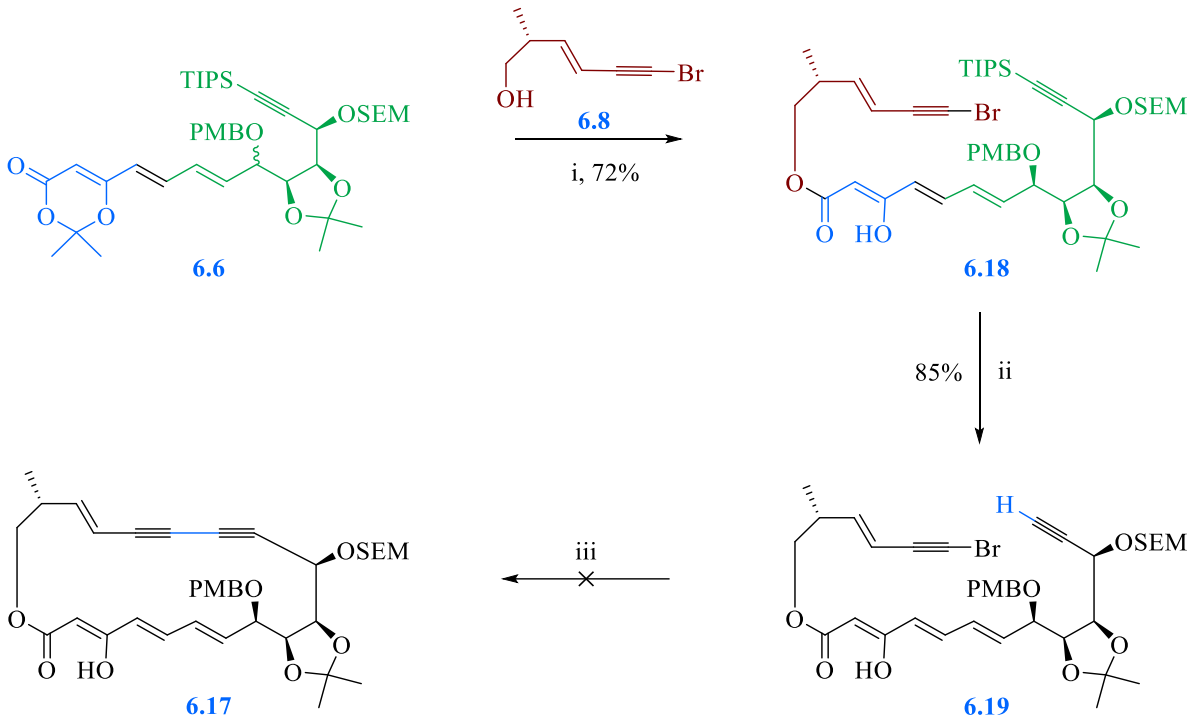
TBAF-mediated deprotection of the silyl-capped alkyne residue within substrate **6.15** (**Scheme 6.8**) furnished the desired diyne **6.16** (85%) that was to serve as the substrate for intramolecular cross-coupling reaction to create the macrocyclic ring. The Glaser-Hay oxidative coupling protocol was the first one examined, under high dilution conditions, and employed copper(I) chloride and the bidentate complexing ligand tetramethylethylenediamine (TMEDA) in dichloromethane. However, no coupling took place in a reaction flask open to the air at ambient temperatures while decomposition was observed at 40 °C under an oxygen atmosphere. A literature survey suggested that such intramolecular couplings of terminal diynes often requires heating (to above 80 °C) in basic media (eg. using pyridine as solvent) in

order to proceed. Such conditions could not be successfully applied to the rather sensitive substrate **6.16** without the outset of rapid decomposition.[153]



Scheme 6.8. ***Reagents and Conditions*** (i) TBAF, THF, 18 °C, 2 h; (ii) CuCl, TMEDA, O_2, DCM.

In effort to effect the desired intramolecular cross-coupling reaction, one of the two terminal alkynes was replaced by a notionally more reactive bromo-alkyne. Thus, alcohol **6.8**, instead of congener **6.10**, (**Scheme 6.9**) was used in the thermally-induced nucleophilic addition reaction with compound **6.6** so as to generate ester **6.18**. Once again, only the major epimer was isolated, this time in 72% yield. TBAF-mediated desilylation of compound **6.18** furnished the desired terminal alkyne **6.19** in 85% yield. Its intramolecular cross-coupling reaction was then attempted under either Sonogashira conditions or using the protocol recently reported by Lei.[154] Disappointingly, both sets of conditions failed to produce the 20-membered macrolactone **6.17**. Only decomposition was observed in each instance.



Scheme 6.9. ***Reagents and Conditions*** (i) toluene, 120 °C, 4 h; (ii) TBAF, THF, 18 °C, 2 h; (iii) $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 18 °C, 16 h; or $Pd(OAc)_2$, CuI, TBAB, *i*-Pr_2NH, 70 °C, 16 h.

6.4. Conclusion

A synthetic pathway leading to the advanced intermediates **6.6** and **6.11**, which embody the Southern region of model macrolactone **6.1**, has been established. Two means for introducing the corresponding enyne alcohols that, in principle, could allow for a macrocyclisation reaction to take place were investigated. The first involving an intermolecular Cadiot-Chodkiewicz coupling reaction between compound **6.11** and silyl ether **6.9** failed to deliver useful products in that treatment of the resulting intermediate with tetra-*n*-butylammonium fluoride resulted in the formation of the aromatised product **6.14** (**Figure 6.6**). The second pathway, employing a thermally-induced nucleophilic addition of either alcohol **6.10** or **6.8** to the 1,3-dioxinone-containing compound **6.6** followed by desilylation delivered the desired ester **6.16** and **6.19**, respectively, in good yield. Despite their lack of participation in intramolecular C_{sp}-C_{sp} Glaser-Hay or Cadiot-Chodkiewicz coupling reactions, the acquisition of these compounds demonstrated the capacity of the 1,3-dioxinone moiety to participate in desired β-keto-ester forming processes.

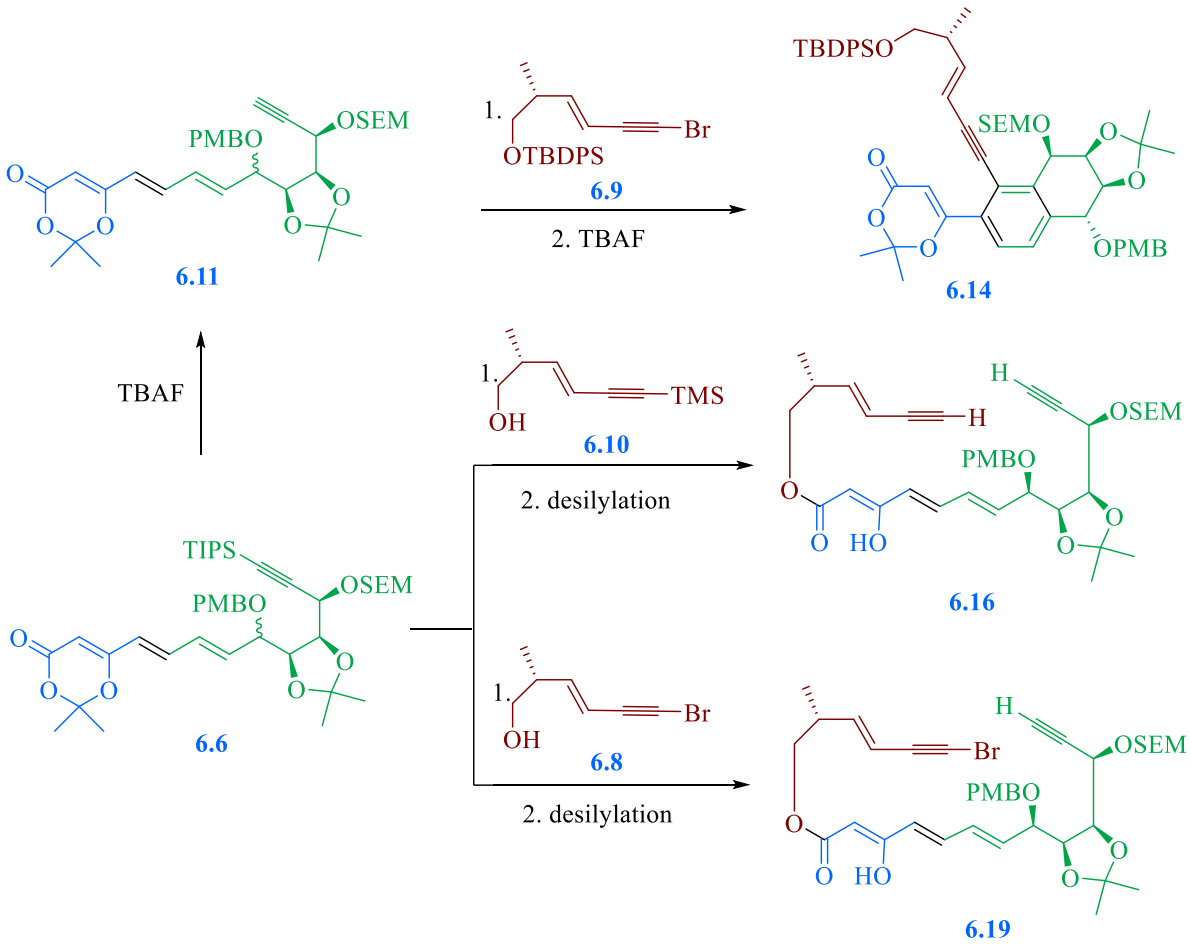
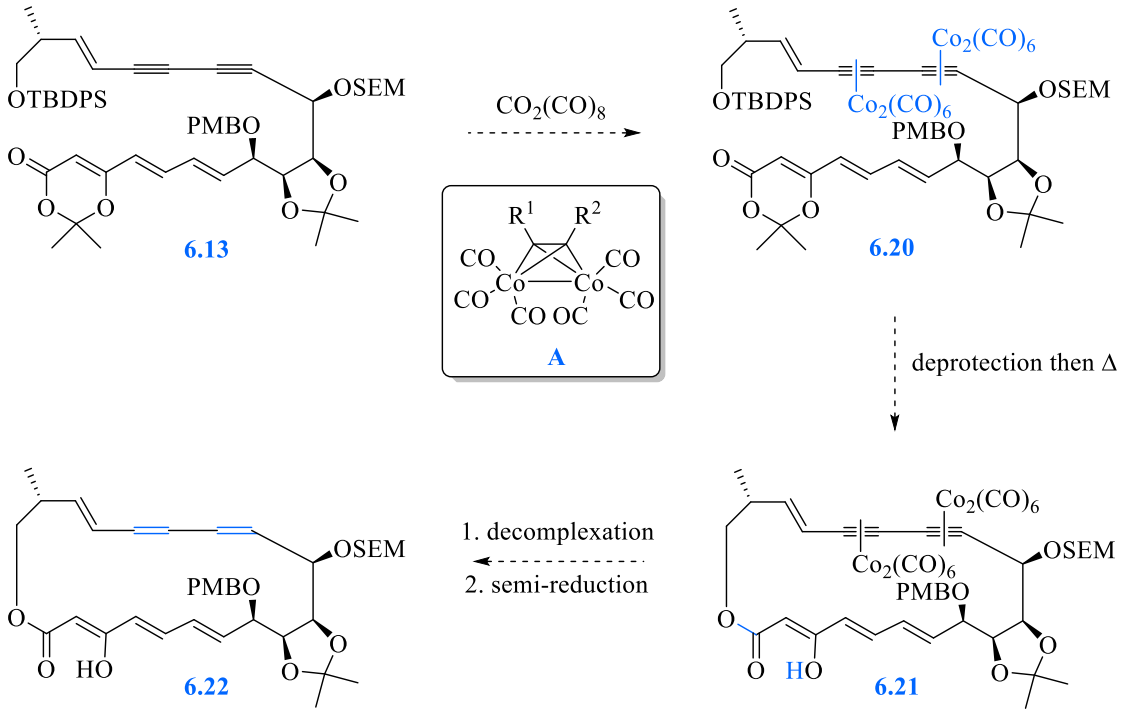


Figure 6.6. *Undesired compound 6.14 and Advanced Intermediates for Assembling Macrolactone 6.1.*

6.5. Future Research

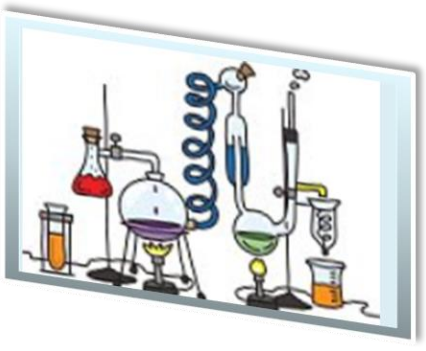
The undesired intramolecular Diels-Alder (IMDA) reaction occurring between the diyne linkage and the conjugated double bond within intermediate **6.13** could be prevented by a protection-deprotection strategy involving complexation of the alkyne residues as dicobalt-hexacarbonyl complex **A**[155] that can eventually be "liberated" by different oxidizing agents [such as ceric ammonium nitrate (CAN), or a tertiary amine oxide] or reducing agents (such as ethylenediamine).[156] As shown in **Scheme 6.10**, for example, treatment of diyne **6.13** with dicobalt-octacarbonyl, $Co_2(CO)_8$, would deliver the complex **6.20**. The 20-membered macrolactone **6.21** would arise through a thermally-induced macrocyclisation between the liberated alcohol and the dioxinone moiety. Decomplexation of compound **6.21** would then reveal the acetylene linkage that would deliver the likely delicate *Z,Z*-diene through a stereoselective semi-reduction effected by using hydrogenation in the presence of either Rieke zinc[157] or Lindlar catalyst.[158]



Scheme 6.10. ***Protection-Deprotection Strategy Leading to Macrolactone 6.13.***

7. CHAPTER SEVEN

Experimental Procedures



7.1. General Experimental Procedures

Starting materials and reagents were generally available from Sigma-Aldrich, Merck, TCI and/or AK Scientific and were used as supplied or, occasionally, recrystallised or distilled. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran, dichloromethane, *N*,*N*-dimethylformamide, diethyl ether, hexane and toluene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al*.[159]

All reaction mixtures were manipulated under a nitrogen atmosphere using standard Schlenk techniques and, unless otherwise specified, stirred magnetically. Deoxygenated solutions were obtained by bubbling nitrogen through the relevant solution for at least 15 min. Ambient temperature was assumed to be *ca*. 18 °C. Temperatures higher than ambient were attained using thermostated oil baths. To attain temperatures lower than ambient, a cooled, water-circulating bath (0 to 10 °C) or relevant cryostats [ice/water, 0 °C; ice/saturated aqueous ammonium chloride, −15 °C; dry-ice/acetonitrile, −40 °C; dry-ice/ethylene glycol:ethanol (1:1), −50 °C; dry-ice/acetone, −78 °C] were used.

Ozonolysis reactions were performed using a Model 500 Fischer portable ozone-generator with the luteinizing power and flow rate adjusted to 80 V and 50 L/h, respectively.

Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included: a) potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3g : 20g : 5 mL : 300mL); b) anisaldehyde : sulfuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL); c) phosphomolybdic acid : cerium sulfate : sulfuric acid (conc.) : water (15g : 2.5g : 15 mL : 485 mL); d) vanillin : sulfuric acid (conc.) : ethanol : water (18g : 3 mL : 285 mL : 15 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[160] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. Chemical shifts are recorded as δ values in

parts per million (ppm). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and proton-decoupled ^{13}C NMR spectra, respectively. For ^{13}C NMR spectra, the data are given as: chemical shift (δ), (protonicity), where protonicity is defined as: C = quaternary; CH = methane; CH_2 = methylene; CH_3 = methyl. The assignments of signals observed in proton and carbon NMR spectra were assisted by conducting complementary connectivity and/or proximity experiments. Connectivity experiments used included the homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) and/or heteronuclear (^{1}H/^{13}C) correlation spectroscopy [heteronuclear multiple quantum coherence (HMQC) and/or heteronuclear multiple-bond correlation (HMQC)].

Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed by IR spectroscopy (ν_{max}) as thin films on KBr plates. Samples for attenuated total reflectance (ATR) IR spectra were prepared by allowing a $CDCl_3$ solution of these to evaporate on the sampling plate before the spectrum was acquired.

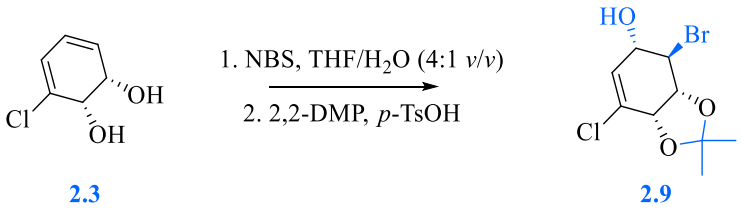
Mass spectrometry was performed by the Australian National University's Mass Spectrometric Services Unit located in the Research School of Chemistry, Canberra, Australia. Low-resolution ESI mass spectra were recorded on a single-quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution electron impact (EI) mass spectra were recorded on a magnetic-sector machine.

Optical rotations were measured between 17 to 20 °C with a Perkin-Elmer 241 polarimeter at the sodium-D line (λ = 589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in 10^{-1}.deg.cm^2.g^{-1}.

Melting points were recorded on an Optimelt automated melting point system and are uncorrected.

7.2 Experimental Procedures Related to Work Described in Chapter Two

(3a*R*,4*R*,5*S*,7a*S*)-4-Bromo-7-chloro-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (2.9)



2.3 2.9

A magnetically stirred solution of compound **2.3** (11.10 g, 75.73 mmol) in tetrahydrofuran/water (200 ml of a 4:1 *v/v* mixture) was cooled to 0 °C and then treated, in portions over 10 min, with *N*-bromosuccinimide (16.03 g, 90.06 mmol). The ensuing mixture was warmed to 18 °C, stirred at this temperature for 4 h then treated with sodium thiosulfate (6.00 g). Stirring was continued for a further 30 min then sodium chloride (6.00 g) was added and the separated aqueous layer was extracted with diethyl ether (3 x 60 mL). The combined organic phases were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was dissolved in 2,2-dimethoxypropane (150 mL) and the solution thus obtained treated with *p*-toluenesulfonic acid (1.43 g, 7.50 mmol). The mixture so-formed was stirred at 18 °C for 2 h then quenched with sodium hydrogen carbonate (50 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 x 100 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure and the light-yellow oil so formed subjected to flash chromatography (silica, 20:80 → 25:75 *v/v* diethyl ether/hexane gradient elution). Concentration of the appropriate fractions (R_f = 0.4 in 25:75 *v/v* diethyl ether/hexane) afforded compound **2.9**[107] (16.62 g, 78%) as a clear, colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 3.9 Hz, 1H), 4.53–4.47 (complex m, 2H), 4.26 (br t, *J* = 4.5 Hz, 1H), 4.10 (t, *J* = 6.0 Hz, 1H), 3.28 (br s, 1H), 1.43 (s, 3H), 1.33 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9 (C), 128.0 (CH), 111.9 (C), 77.9 (CH), 75.1 (CH), 70.0 (CH), 50.3 (CH), 27.9 (CH_3), 26.2 (CH_3);

IR (KBr) ν_{max} 3468, 2987, 2934, 1958, 1649, 1455, 1383, 1220, 1161, 1064, 1012, 980, 919, 866, 807 cm^{-1};

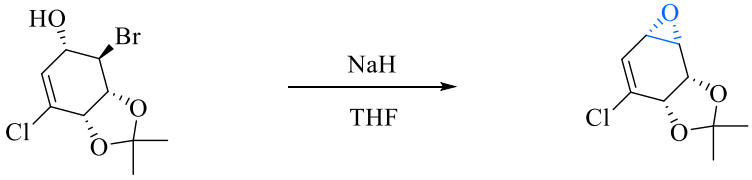
MS (EI, +70 eV) *m/z* 271, 269 and 267 [$(M-CH_3\bullet)^+$, 100, 80 and 22%], 209 and 207 (43 and 33), 131 (63), 128 (40);

HRMS (EI, +70 eV) Found: $(M-CH_3\bullet)^+$ 266.9417, $C_9H_{12}{}^{79}Br^{35}ClO_3$ requires 266.9424;

Specific rotation $[\alpha]^{25}_D = -1.3$ (*c* 1.0, $CHCl_3$).

These data matched those reported previously.[107]

(3a*S*,5a*S*,6a*S*,6b*S*)-4-Chloro-2,2-dimethyl-3a,5a,6a,6b-tetrahydrooxireno[2',3':3,4]benzo[1,2-*d*][1,3]dioxole (2.10)



2.9 **2.10**

A magnetically stirred solution of bromohydrin **2.9** (8.30 g, 29.27 mmol) in tetrahydrofuran (90 mL) maintained under nitrogen was cooled to 0 °C then treated with sodium hydride (1.75 g of 60% *w/w* dispersion in mineral oil, 43.75 mmol). After 1 h, the reaction mixture was filtered through a pad of Celite™ and the filtrate concentrated under reduced pressure to give pale-yellow oil. Subjection of this material to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4 in 25:75 *v/v* diethyl ether/hexane) afforded compound **2.10**[107] (5.10 g, 86%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 4.3 Hz, 1H), 4.60 (dd, *J* = 6.8 and 1.7 Hz, 1H), 4.54 (dd, *J* = 6.8 and 2.7 Hz, 1H), 3.64–3.61 (complex m, 1H), 3.50 (t, *J* = 4.1 Hz, 1H), 1.54 (s, 3H), 1.41 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (C), 125.9 (CH), 109.2 (C), 75.6 (CH), 74.1 (CH), 54.8 (CH), 49.9 (CH), 27.3 (CH_3), 25.5 (CH_3);

IR (KBr) ν_{max} 2986, 2935, 1958, 1648, 1455, 1429, 1371, 1246, 1213, 1162, 1078, 1062, 1003, 979, 873, 815 cm^{-1};

MS (ESI, +ve) *m/z* 227 and 225 $[(M+Na)^+$, 35 and 100%];

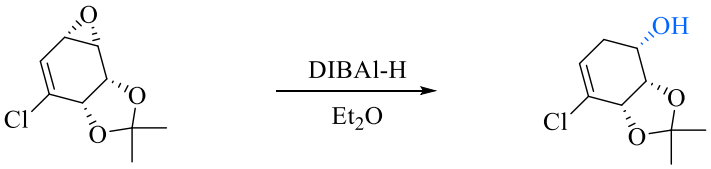
HRMS (ESI, +ve) Found: $(M+H)^+$ 203.0475, $C_9H_{12}{}^{35}ClO_3$ requires 203.0475;

Melting point 88–89 °C;

Specific rotation $[\alpha]^{25}_D = -91.3$ (*c* 1.0, $CHCl_3$).

These data matched those reported previously.[107]

(3a*S*,4*S*,7a*S*)-7-Chloro-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (2.11)



2.10 **2.11**

A magnetically stirred solution of epoxide **2.10** (4.27 g, 21.07 mmol) in diethyl ether (30 mL) was cooled to −78 °C then treated, dropwise, with di-*iso*-butylaluminium hydride (31.6 mL of a 1.0 M solution in hexane, 31.60 mmol). After addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h then treated with tartaric acid (60 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 30 min. The separated aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 30:70 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **2.11*** (3.90 g, 90%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 5.9 and 3.0 Hz, 1H), 4.56 (m, 1H), 4.46 (dd, *J* = 5.6 and 2.5 Hz, 1H), 3.95 (m, 1H), 2.46–2.32 (complex m, 2H), 2.06 (br s, 1H), 1.45 (s, 3H), 1.43 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4 (C), 124.2 (CH), 110.8 (C), 77.4 (CH), 77.0 (CH), 67.1 (CH), 29.9 (CH_2), 27.5 (CH_3), 26.6 (CH_3);

IR (KBr) ν_{max} 3436, 2986, 2934, 1650, 1372, 1227, 1163, 1085, 1049, 1034, 981, 922, 864, 811 cm^{-1};

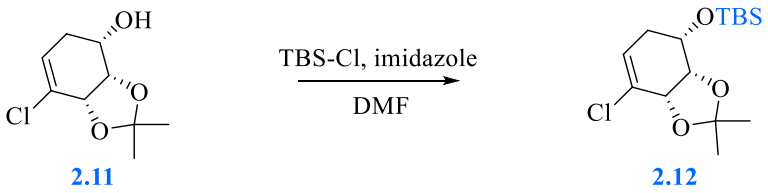
MS (ESI, +ve) *m/z* 229 and 227 [$(M+Na)^+$, 33 and 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 227.0449, $C_9H_{13}{}^{35}Cl^{23}NaO_3$ requires 227.0451;

Melting point 112–114 °C;

Specific rotation $[\alpha]^{25}_D$ = +29.8 (*c* 0.8, $CHCl_3$).

tert-Butyl(((3a*R*,4*S*,7a*S*)-7-chloro-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)oxy)dimethylsilane (2.12)



2.11 **2.12**

A magnetically stirred solution of alcohol **2.11** (3.89 g, 19.01 mmol) in *N*,*N*-dimethylformamide (30 mL) maintained at 20 °C was treated, sequentially, with *tert*-butyldimethylsilyl chloride (3.99 g, 26.47 mmol) then imidazole (2.40 g, 35.25 mmol). The ensuing mixture was stirred for 2 h then quenched with water (1 x 50 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with hydrochloric acid (1 x 100 mL of a 1.0 M aqueous solution) and brine (1 x 100 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.8) gave *compound **2.12*** (5.79 g, 98%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 6.7 and 2.0 Hz, 1H), 4.48 (dd, *J* = 5.1 and 2.7 Hz, 1H), 4.32 (m, 1H), 3.96 (ddd, *J* = 10.2, 5.3 and 2.0 Hz, 1H), 2.52 (m, 1H), 2.17 (dt, *J* = 12.1 and 5.8 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 0.90 (d, *J* = 0.6 Hz, 9H), 0.10 (s, 3H), 0.9 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6 (C), 124.6 (CH), 110.9 (C), 78.3 (CH), 77.5 (CH), 68.4 (CH), 30.0 (CH_2), 27.7 (CH_3), 26.9 (CH_3), 26.1 (3 x CH_3), 18.6 (C), −4.3 (CH_3), −4.5 (CH_3);

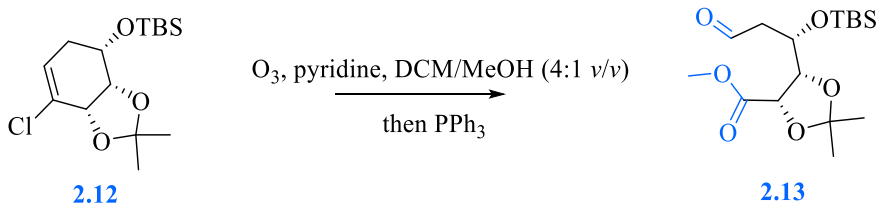
IR (KBr) ν_{max} 3401, 2987, 2954, 2931, 2888, 2858, 1647, 1472, 1382, 1371, 1253, 1237, 1170, 1120, 1065, 1039, 990, 936, 925, 837, 813 cm^{-1};

MS (ESI, +ve) *m/z* 341 [$(M + Na)^+$, 100%], 261 (10);

HRMS (ESI, +ve) Found: $(M+Na)^+$ 341.1316, $C_{15}H_{27}{}^{35}Cl^{23}NaO_3Si$ requires 341.1316;

Specific rotation $[\alpha]^{25}_D = -5.1$ (*c* 0.9, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-oxopropyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.13)



2.12 2.13

A magnetically stirred solution of alkene **2.12** (4.89 g, 15.33 mmol) in dichloromethane/methanol (125 mL of a 4:1 *v/v* mixture) was treated with pyridine (6.1 mL, 85.90 mmol) then cooled to −78 °C and ozone bubbled through it until a dark-blue colour persisted (*ca*. 30 min). At this point triphenylphosphine (4.92 g, 18.76 mmol) was added to the reaction mixture which was then warmed to 18 °C and kept at this temperature for 1 h before being concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 20:80 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4 in 25:75 *v/v* ethyl acetate/hexane) afforded *compound **2.13*** (4.55 g, 86%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, CHO), 4.60 (d, *J* = 7.1 Hz, 1H), 4.54 (m, 1H), 4.34 (dd, *J* = 7.0 and 3.9 Hz, 1H), 3.74 (s, 3H), 2.77–2.65 (complex m, 2H), 1.59 (s, 3H), 1.36 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (CHO), 170.5 (CO), 110.9 (C), 81.3 (CH), 75.1 (CH), 66.2 (CH), 52.3 (CH_3), 48.0 (CH_2), 26.5 (CH_3), 26.0 (3 x CH_3), 25.5 (CH_3), 18.3 (C), −4.3 (CH_3), −4.5 (CH_3);

IR (KBr) ν_{max} 2953, 2929, 2855, 2739, 1751, 1721, 1472, 1436, 1384, 1373, 1344, 1253, 1208, 1141, 1094, 1046, 1005, 966, 948, 864, 838, 809 cm^{-1};

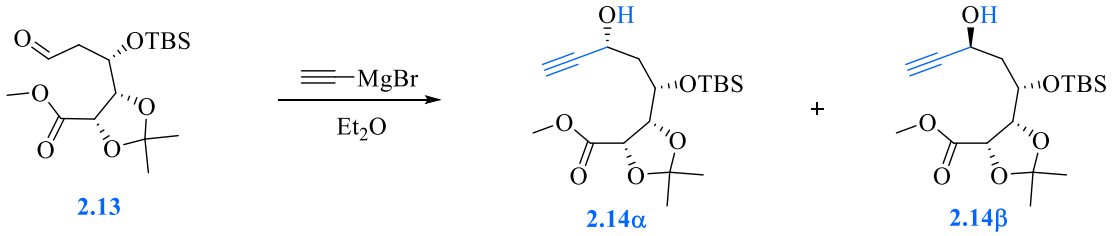
MS (ESI, +ve) *m/z* 401 [$(M+CH_3OH+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 369.1708, $C_{16}H_{30}{}^{23}NaO_6Si$ requires 369.1709;

Melting point 94–95 °C;

Specific rotation $[\alpha]^{25}_D$ = −29.8 (*c* = 0.8, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxypent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.14*α*) and Methyl (4*S*,5*R*)-5-((1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxypent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.14β)



2.13 2.14α 2.14β

A magnetically stirred solution of aldehyde **2.13** (1.77 g, 5.14 mmol) in diethyl ether (80 mL) maintained under nitrogen at −78 °C was treated with ethynylmagnesium bromide (30.8 mL of an 0.5 M solution in tetrahydrofuran, 15.40 mmol) and the ensuing mixture was stirred at −15 °C for a further 1 h then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 20:25:55 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and thus affording two fractions, A and B.

Concentration of fraction A (R_f = 0.4) gave *compound **2.14β*** (770 mg, 40%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, *J* = 7.2 Hz, 1H), 4.49 (d, *J* = 8.6 Hz, 1H), 4.34 (dd, *J* = 7.2 and 2.9 Hz, 1H), 4.29–4.23 (complex m, 1H), 3.71 (s, 3H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.39 (s, 1H), 2.07 (ddd, *J* = 14.6, 7.9 and 3.6 Hz, 1H), 1.79 (ddd, *J* = 14.6, 9.1 and 4.0 Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (CO), 110.7 (C), 85.1 (C), 81.5 (CH), 74.9 (CH), 73.1 (CH), 68.1 (CH), 59.2 (CH), 52.2 (CH_3), 40.9 (CH_2), 26.5 (CH_3), 26.1 (3 x CH_3), 25.4 (CH_3), 18.4 (C), −4.1 (CH_3), −4.5 (CH_3);

IR (KBr) ν_{max} 3474, 3309, 2953, 2932, 2888, 2857, 1762, 1472, 1463, 1437, 1381, 1323, 1251, 1209, 1138, 1092, 1004, 959, 868, 837, 780 cm^{-1};

MS (ESI, +ve) *m/z* 411 [$(M+K)^+$, 100%], 395 [$(M+Na)^+$, 12];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 395.1869, $C_{18}H_{32}{}^{23}NaO_6Si$ requires 395.1866;

Melting point 72–74 °C;

Specific rotation $[\alpha]^{25}_{D}$ = +12.8 (*c* 1.0, $CHCl_3$).

Concentration of fraction B (R_f = 0.3) gave *compound* ***2.14α*** (1.05 g, 55%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, *J* = 6.9 Hz, 1H), 4.56 (dd, *J* = 6.6 and 2.1 Hz, 1H), 4.37 (dd, *J* = 6.9 and 3.8 Hz, 1H), 4.26 (ddd, *J* = 6.4, 5.5 and 3.8 Hz, 1H), 3.73 (s, 3H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.21-2.12 (complex m, 1H), 1.93 (ddd, *J* = 14.2, 6.4 and 5.5 Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (CO), 110.6 (C), 84.6 (C), 81.4 (CH), 75.1 (CH), 73.7 (CH), 68.3 (CH), 59.9 (CH), 52.2 (CH_3), 41.5 (CH_2), 26.6 (CH_3), 26.1 (3 x CH_3), 25.6 (CH_3), 18.4 (C), −4.2 (CH_3), −4.4 (CH_3);

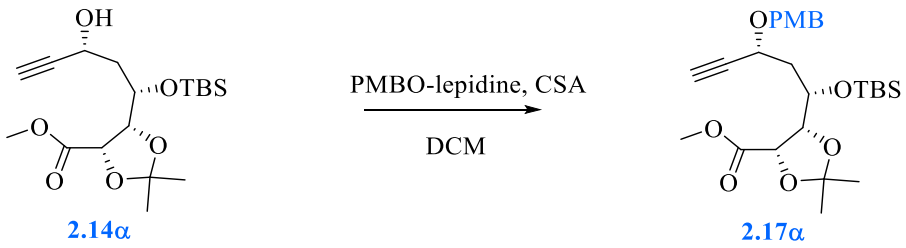
IR (KBr) ν_{max} 3472, 3309, 2953, 2932, 2889, 2857, 1762, 1472, 1463, 1437, 1382, 1317, 1251, 1208, 1138, 1092, 1031, 987, 959, 872, 837 cm^{-1};

MS (ESI, +ve) *m/z* 411 [$(M+K)^+$, 100%], 395 [$(M+Na)^+$, 17];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 395.1867, $C_{18}H_{32}{}^{23}NaO_6Si$ requires 395.1866;

Specific rotation $[\alpha]^{25}_{D}$ = + 22.3 (*c* 0.7, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-pent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.17α)



A magnetically stirred solution of alcohol **2.14α** (860 mg, 2.31 mmol) in dichloromethane (30 mL) was treated with 2-(4-methoxybenzyloxy)-4-methylquinoline (1.23 g, 4.62 mmol) and (+)-10-camphorsulfonic acid (54 mg, 0.23 mmol) and the ensuing mixture heated at 40 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4), *compound **2.17α*** (1.02 g, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 4.71 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 6.7 Hz, 1H), 4.43 (d, J = 11.5 Hz, 1H), 4.29 (t, J = 6.5 Hz, 2H), 4.17 (t, J = 6.5 Hz, 1H), 3.77 (d, J = 0.5 Hz, 3H), 3.67 (s, 3H), 2.50 (d, J = 0.9 Hz, 1H), 2.17–2.07 (complex m, 1H), 2.03–1.92 (complex m, 1H), 1.59 (s, 3H), 1.30 (s, 3H), 0.80 (d, J = 0.4 Hz, 9H), 0.04 (s, 3H), 0.02 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (CO), 159.5 (CH), 129.8 (2 x CH), 129.7 (C), 114.0 (2 x CH), 110.3 (C), 82.5 (C), 81.5 (CH), 75.0 (CH), 74.5 (CH), 70.3 (CH_2), 67.8 (CH), 65.5 (CH), 55.4 (CH_3), 51.9 (CH_3), 39.3 (CH_2), 26.7 (CH_3), 26.1 (3 x CH_3), 25.6 (CH_3), 18.4 (C), −4.1 (CH_3), −4.7 (CH_3);

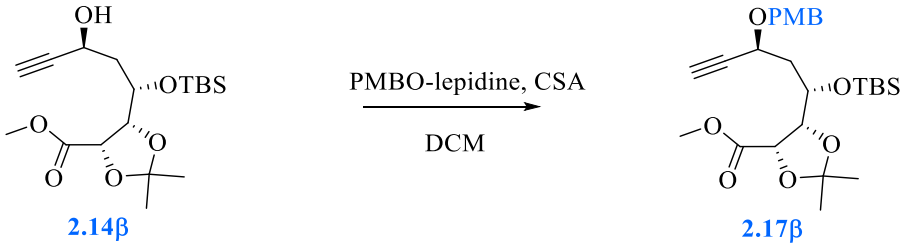
IR (KBr) ν_{max} 2933, 2857, 1763, 1612, 15145, 1249, 1093, 836 cm^{-1};

MS (ESI, +ve) *m/z* 531 [$(M+K)^+$, 100%]; 515 [$(M+Na)^+$, 5];

HRMS (ESI, +ve) Found: $(M+K)^+$ 531.2181, $C_{26}H_{40}{}^{39}KO_7Si$ requires 531.2180; $(M+Na)^+$ 515.2442, $C_{26}H_{40}{}^{23}NaO_7Si$ requires 515.2441;

Specific rotation $[\alpha]^{25}_D$ = +95.5 (*c* 0.9, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-pent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.17β)



Reaction of alcohol **2.14β** with 2-(4-methoxybenzyloxy)-4-methylquinoline and (+)-10-camphorsulfonic acid in the same manner as described immediately above for the conversion **2.14α** → **2.17α** afforded a light-yellow oil on work-up. Subjection of this material to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) afforded, after concentration of the relevant fractions (R_f = 0.4), *compound **2.17β*** (83%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.73 (d, J = 10.9 Hz, 1H), 4.52 (d, J = 7.1 Hz, 1H), 4.34 (d, J = 10.9 Hz, 1H), 4.31 (dd, J = 7.1 and 2.4 Hz, 1H), 4.25–4.17 (complex m, 2H), 3.78 (s, 3H), 3.59 (s, 3H), 2.48 (d, J = 1.4 Hz, 1H), 2.04 (complex m, 2H), 1.60 (s, 3H), 1.32 (s, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (CO), 159.5 (CH), 130.0 (2 x CH), 129.9 (C), 113.9 (2 x CH), 110.4 (C), 83.0 (C), 81.7 (CH), 74.5 (CH), 74.3 (CH), 70.5 (CH_2), 67.5 (CH), 65.2 (CH), 55.5 (CH_3), 52.0 (CH_3), 40.2 (CH_2), 26.6 (CH_3), 26.2 (3 x CH_3), 25.6 (CH_3), 18.5 (C), −4.0 (CH_3), −4.7 (CH_3);

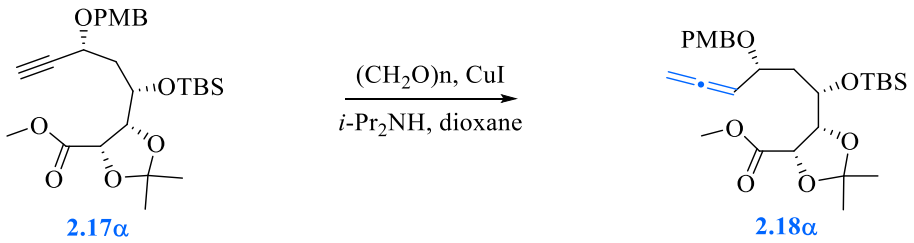
IR (KBr) ν_{max} 2953, 2857, 1763, 1515, 1250, 1204, 1092, 1036, 836, 779 cm^{-1};

MS (ESI, +ve) *m/z* 531 [$(M+K)^+$, 100%]; 515 [$(M+Na)^+$, 10];

HRMS (ESI, +ve) Found: $(M+K)^+$ 531.2183, $C_{26}H_{40}{}^{39}KO_7Si$ requires 531.2180; $(M+Na)^+$ 515.2449, $C_{26}H_{40}{}^{23}NaO_7Si$ requires 515.2441;

Specific rotation $[\alpha]^{25}_D$ = −21.8 (*c* 0.7, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy) hexa-4,5-dien-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.18α)



A magnetically stirred solution of compound **2.17α** (304 mg, 0.62 mmol), paraformaldehyde (53.5 mg, 1.85 mmol), di-*iso*-propylamine (130 µL, 0.93 mmol) and copper iodide (58.8 mg, 0.31 mmol) in 1,4-dioxane (10 mL) was heated to 100 °C for 24 h. The cooled reaction mixture was filtered through a pad of Celite™ and the filtrate treated with ammonium chloride (10 mL of a saturated aqueous solution) then water (20 mL). The ensuing mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic phases were then washed with brine (1 x 30 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 15:85 *v/v* of diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.5 in 30:70 *v/v* diethyl ether/hexane) gave *compound **2.18α*** (244 mg, 78%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.02 (dd, *J* = 14.7 and 6.6 Hz, 1H), 4.90–4.71 (complex m, 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 6.7 Hz, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.23–4.13 (complex m, 2H), 3.98 (dd, *J* = 14.4 and 7.0 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 1.96 (complex m, 2H), 1.59 (s, 3H), 1.27 (s, 3H), 0.82 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (C), 170.9 (CO), 159.3 (CH), 130.6 (C), 129.7 (2 x CH), 114.0 (2 x CH), 110.3 (C), 91.5 (CH), 81.2 (CH), 76.2 (CH), 74.6 (CH_2), 74.1 (CH), 69.8 (CH_2), 67.7 (CH), 55.4 (CH_3), 51.9 (CH_3), 40.4 (CH_2), 26.7 (CH_3), 26.2 (3 x CH_3), 25.7 (CH_3), 18.5 (C), −4.1 (CH_3), −4.5 (CH_3);

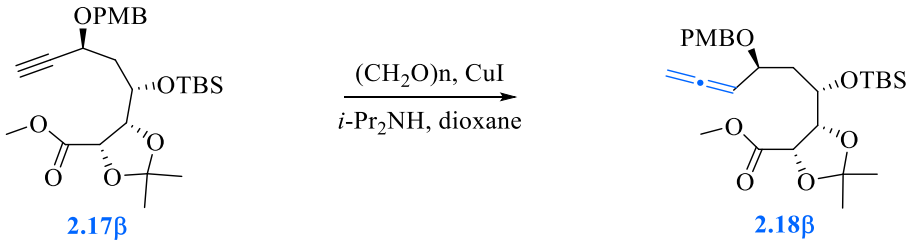
IR (KBr) ν_{max} 2952, 2931, 2857, 1954, 1765, 1736, 1613, 1513, 1249, 1201, 1093, 1038, 837, 779 cm^{-1};

Mass spectrum (ESI, +ve) *m/z* 545 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $[M+K]^+$ 545.2335, $C_{27}H_{42}{}^{39}KO_7Si$ requires 543.2337;

Specific rotation $[\alpha]^{25}_{D}$ = +32.5 (*c* 0.7, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy) hexa-4,5-dien-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.18β)



Reaction of alcohol **2.17β** with paraformaldehyde in the presence of di-*iso*-propylamine and copper iodide in the same manner as described immediately above for the conversion **2.17α** → **2.17α** afforded a light-yellow oil on work-up. Subjection of this material to flash chromatography (silica, 15:85 *v/v* diethyl ether/hexane elution) afforded, after concentration of the relevant fractions (R_f = 0.5 in 30:70 in *v/v* diethyl ether/hexane), *compound **2.18β*** (86%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.08 (dd, *J* = 14.7 and 6.6 Hz, 1H), 4.89–4.75 (complex m, 2H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 7.1 Hz, 1H), 4.33 (dd, *J* = 7.1 and 2.5 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.25–4.20 (m, 1H), 4.03 (dd, *J* = 13.0 and 8.1 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 1.98–1.82 (complex m, 2H), 1.62 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C), 170.9 (CO), 159.4 (CH), 130.7 (C), 129.8 (2 x CH), 113.9 (2 x CH), 110.2 (C), 91.9 (CH), 81.9 (CH), 76.1 (CH), 74.9 (CH_2), 74.5 (CH), 70.0 (CH_2), 68.1 (CH), 55.5 (CH_3), 51.9 (CH_3), 40.6 (CH_2), 26.7 (CH_3), 26.2 (3 x CH_3), 25.6 (CH_3), 18.5 (C), −3.9 (CH_3), −4.6 (CH_3);

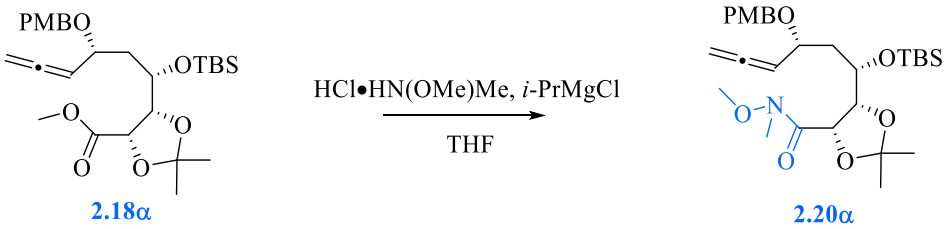
IR (KBr) ν_{max} 2952, 2932, 2856, 1954, 1764, 1613, 1514, 1249, 1203, 1092, 1036, 836 cm^{-1};

MS (ESI, +ve) *m/z* 529 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 529.2583, $C_{27}H_{42}{}^{23}NaO_7Si$ requires 529.2598;

Specific Rotation $[\alpha]^{25}_{D}$ = +9.3 (*c* 0.8, $CHCl_3$).

(4*S*,5*R*)-5-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)pent-4-yn-1-yl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (2.20α)



2.18α 2.20α

A magnetically stirred solution of methyl ester **2.18α** (344 mg, 0.68 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (267 mg, 2.73 mmol) in dry tetrahydrofuran (10 mL) maintained under nitrogen was cooled to −15 °C then treated, dropwise over 20 min *via* syringe pump, with *iso*-propylmagnesium chloride (2.0 mL of a 2.0 M solution in tetrahydrofuran, 4.00 mmol). The ensuing mixture was stirred at −15 °C for 1 h then quenched with ammonium chloride (5 mL of a saturated aqueous solution) and the separated aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure and the resulting light-yellow oil subjected to flash chromatography (silica, 70:30 *v/v* diethyl ether/hexane elution). Concentration of the relevant fractions (R_f = 0.2) afforded *compound **2.20α*** (314 mg, 86%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.01–4.90 (complex m, 1H), 4.83 (d, *J* = 7.8 Hz, 1H), 4.78 (dd, *J* = 10.9 and 6.7 Hz, 1H), 4.64 (dd, *J* = 10.9 and 6.5 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.43 (dd, *J* = 7.8 and 1.8 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 3.96 (m, 1H), 3.75 (s, 3H), 3.72 (s, 1H), 3.69 (s, 3H), 3.15 (s, 3H), 2.03–1.89 (complex m, 1H), 1.73–1.62 (complex m, 1H), 1.55 (s, 3H), 1.32 (s, 3H), 0.78 (s, 9H), −0.01 (s, 3H), −0.07 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (C), 169.1 (CO), 159.1 (C), 131.0 (C), 129.5 (2 x CH), 113.8 (2 x CH), 110.0 (C), 91.8 (CH), 81.5 (CH), 75.3 (CH), 74.9 (CH_2), 74.4 (CH), 69.4 (CH_2), 69.3 (CH), 61.2 (CH_3), 55.4 (CH_3), 38.9 (CH_2), 32.3 (CH_3), 26.4 (CH_3), 26.1 (3 x CH_3), 25.0 (CH_3), 18.2 (C), −4.0 (CH_3), −4.4 (CH_3);

IR (KBr) ν_{max} 2934, 2856, 1953, 1687, 1612, 1513, 1381, 1249, 1210, 1102, 1070, 993, 836 776 cm^{-1};

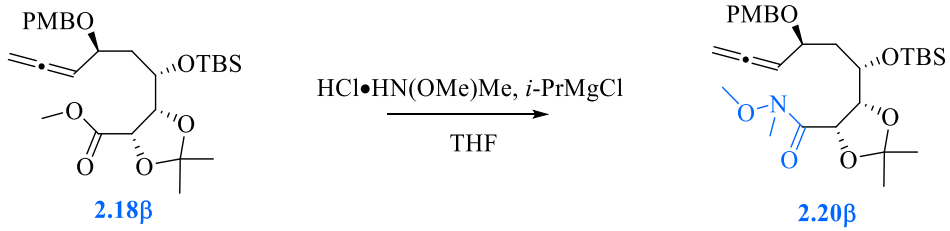
MS (ESI, +ve) *m/z* 558 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 558.2875, $C_{28}H_{45}{}^{23}NaNO_7Si$ requires 558.2863;

Melting point 137.5–138.4 °C;

Specific rotation $[\alpha]^{25}_D = -22.1$ (*c* 2.0, $CHCl_3$).

(4*S*,5*R*)-5-((1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)pent-4-yn-1-yl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (2.20β)



Reaction of ester **2.18β** with *N*,*O*-dimethylhydroxylamine hydrochloride and *iso*-propylmagnesium chloride in the same manner as described immediately above for the conversion **2.18α** → **2.20α** afforded a light-yellow oil on work-up. Subjection of this material to flash chromatography (silica, 70:30 *v/v* diethyl ether/hexane elution) afforded, after concentration of the relevant fractions (R_f = 0.2), *compound **2.20β*** (77%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.08 (m, 1H), 4.84 (d, *J* = 8.0 Hz, 1H), 4.80–4.70 (complex m, 2H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.17(d, *J* = 10.8 Hz, 1H), 4.05 (complex m, 2H), 3.79 (s, 3H), 3.63 (s, 3H), 2.82 (s, 3H), 1.73 (complex m, 2H), 1.60 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C), 169.7 (CO), 159.1 (C), 131.4 (C), 129.8 (2 x CH), 113.6 (2 x CH), 109.8 (C), 92.3 (CH), 82.2 (CH), 75.6 (CH), 74.8 (CH_2), 74.5 (CH), 69.7 (CH_2), 68.1 (CH), 61.0 (CH_3), 55.5 (CH_3), 38.6 (CH_2), 32.5 (CH_3), 26.4 (CH_3), 26.2 (3 x CH_3), 24.9 (CH_3), 18.4 (C), −4.1 (CH_3), −4.3 (CH_3);

IR (KBr) ν_{max} 2935, 2856, 1954, 1693, 1514, 1249, 1072, 995, 836 cm^{-1};

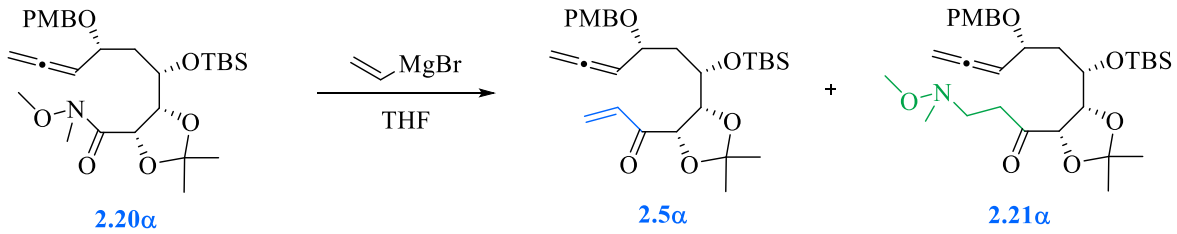
MS (ESI, +ve) *m/z* 558 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 558.2863, $C_{28}H_{45}{}^{23}NaNO_7Si$ requires 558.2863;

Melting point 78.4–79.3 °C;

Specific rotation $[\alpha]^{25}_{D} = -56.5$ (*c* 1.0, $CHCl_3$).

1-((4*S*,5*R*)-5-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)pent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-one (2.5α)



2.20α 2.5α 2.21α

A magnetically stirred solution of Weinreb amide **2.20α** (100 mg, 0.18 mmol) in dry tetrahydrofuran (2 mL) maintained at −78 °C under a nitrogen atmosphere was treated with vinylmagnesium bromide (0.93 mL of a 1.0 M solution in tetrahydrofuran, 0.93 mmol). After 1 h, the reaction mixture was quenched with ammonium chloride (5 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic phases were washed with brine (1 x 10 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 15:85 to 50:50 *v/v* of diethyl ether/hexane elution) and two fractions, A and B, thereby obtained.

Concentration of fraction A (R_f = 0.6 in 30:70 *v/v* diethyl ether/hexane) gave *compound **2.5α*** (20 mg, 21%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.83–6.75 (partially obscured d, *J* = 17.4 and 10.5 Hz, 1H), 6.25 (d, *J* = 17.4 Hz, 1H), 5.65 (d, *J* = 10.5 Hz, 1H), 4.97 (q, *J* = 7.0 Hz, 1H), 4.84 (dd, *J* = 11.0 and 7.0 Hz, 1H), 4.78 (dd, *J* = 11.0 and 7.0 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 8.2 Hz, 1H) 4.40 (dd, *J* = 8.2 and 3.1 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.12 (m, 1H), 3.98 (q, *J* = 7.0 Hz 1H), 3.79 (s, 3H), 1.94 (dt, *J* = 13.1 and 7.0 Hz, 1H), 1.78 (dt, *J* = 13.1 and 7.0 Hz, 1H), 1.59 (s, 3H), 1.30 (s, 3H), 0.81 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (C), 198.2 (CO), 159.3 (C), 133.3 (CH_2), 130.6 (C), 129.7 (2 x CH), 127.9 (CH), 113.9 (2 x CH), 109.7 (C), 91.3 (CH), 82.2 (CH), 80.4 (CH), 76.1 (CH), 74.3 (CH_2), 69.7 (CH_2), 68.3 (CH), 55.5 (CH_3), 40.0 (CH_2), 26.5 (CH_3), 26.2 (3 x CH_3), 24.6 (CH_3), 18.4 (C), −3.8 (CH_3), −4.3 (CH_3);

IR (KBr) ν_{max} 2930, 2856, 1953, 1698, 1612, 1513, 1249, 1211, 1172, 1070, 836 cm^{-1};

MS (ESI, +ve) *m/z* 541 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $[M+K]^+$ 541.2388, $C_{28}H_{42}{}^{39}KO_6Si$ requires 541.2388;

Specific rotation $[\alpha]^{25}_D$ = +48.2 (*c* 0.5, $CHCl_3$).

Concentration of fraction B (R_f = 0.6 in 50:50 *v/v* diethyl ether/hexane) gave *compound* ***2.21α*** (60 mg, 57%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.00 (dd, *J* = 14.4 and 6.8 Hz, 1H), 4.90–4.73 (complex m, 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.37–4.26 (complex m, 3H), 4.19 (m, 1H), 3.94 (m, 1H), 3.78 (s, 3H), 3.46 (s, 3H), 3.10–2.68 (complex m, 4H), 2.55 (s, 3H), 1.98–1.80 (complex m, 2H), 1.59 (s, 3H), 1.27 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1 (C), 209.2 (CO), 159.3 (C), 130.5 (C), 129.7 (2 x CH), 113.9 (2 x CH), 109.2 (C), 91.3 (CH), 81.7 (CH), 80.7 (CH), 76.2 (CH), 74.1 (CH_2), 69.7 (CH_2), 68.2 (CH), 60.1 (CH_3), 55.4 (CH_3), 55.0 (CH_2), 45.4 (CH_3), 39.9 (CH_2), 38.7 (CH_2), 26.5 (CH_3), 26.3 (3 x CH_3), 24.6 (CH_3), 18.6 (C), –3.9 (CH_3), –4.5 (CH_3);

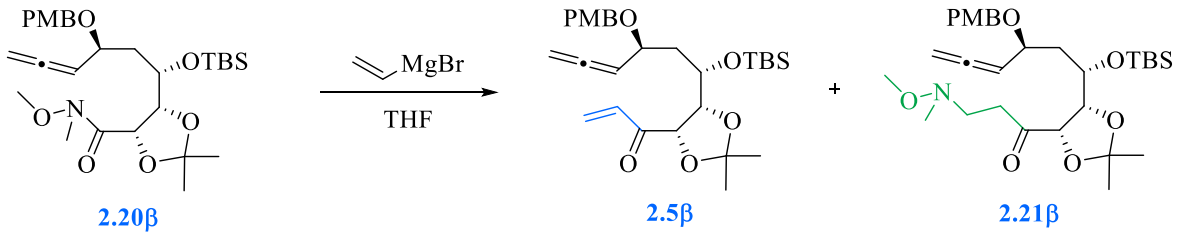
IR (KBr) ν_{max} 2934, 2856, 1954, 1714, 1613, 1513, 1381, 1250, 1059, 836 cm^{-1};

MS (ESI, +ve) *m/z* 586 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 586.3173, $C_{30}H_{49}{}^{23}NaNO_7Si$ requires 586.3176;

Specific rotation $[\alpha]^{25}_D$ = +27.6 (*c* 1.0, $CHCl_3$).

1-((4*S*,5*R*)-5-((1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)pent-4-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-one (2.5β)



2.20β 2.5β 2.21β

A magnetically stirred solution of Weinreb amide **2.20β** (210 mg, 0.39 mmol) in dry tetrahydrofuran (5 mL) maintained at −78 °C under a nitrogen atmosphere was treated with vinylmagnesium bromide (1.96 mL of a 1.0 M solution in tetrahydrofuran, 1.96 mmol). After 1 h, the reaction mixture was poured into hydrochloric acid (10 mL of a 1.0 M aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (1 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was purified by flash chromatography (silica, 15:85 → 50:50 *v/v* of diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 30:70 *v/v* diethyl ether/hexane) gave *compound **2.5β*** (140 mg, 71%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.78 (dd, *J* = 17.4 and 10.6 Hz, 1H), 6.19 (dd, *J* = 17.4 and 1.1 Hz, 1H), 5.58 (dd, *J* = 10.6 and 1.1 Hz, 1H), 5.06 (q, *J* = 6.7 Hz, 1H), 4.83 (dd, *J* = 11.0 and 6.7 Hz, 1H), 4.78 (dd, *J* = 11.0 and 6.7 Hz, 1H), 4.57 (partially obscured d, *J* = 8.1 Hz, 1H), 4.56 (partially obscured d, *J* = 11.2 Hz, 1H), 4.47 (dd, *J* = 8.1 and 2.5 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.79 (s, 3H), 1.98–1.74 (complex m, 2H), 1.61 (s, 3H), 1.34 (s, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C), 198.4 (CO), 159.3 (C), 133.4 (CH_2), 130.8 (C), 129.6 (2 x CH), 127.6 (CH), 113.9 (2 x CH), 109.6 (C), 91.8 (CH), 83.1 (CH), 80.3 (CH), 76.1 (CH), 75.0 (CH_2), 69.8 (CH_2), 68.9 (CH), 55.5 (CH_3), 40.8 (CH_2), 26.5 (CH_3), 26.3 (3 x CH_3), 24.7 (CH_3), 18.5 (C), −3.6 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 2931, 2856, 1953, 1698, 1613, 1514, 1382, 1248, 1212, 1071, 1037, 835 cm^{-1};

MS (ESI, +ve) *m/z* 525 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 525.2649. $C_{28}H_{42}{}^{23}NaO_6Si$ requires 525.2648;

Specific rotation $[\alpha]^{25}_D = -19.2$ (*c* 0.7, $CHCl_3$).

Concentration of fraction B (R_f = 0.6 in 50:50 *v/v* diethyl ether/hexane) gave *compound* ***2.21β*** (30 mg, 14%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.05 (m, 1H), 4.79 (complex m, 2H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.40 (s, 2H), 4.26 (d, *J* = 11.1 Hz, 1H), 4.15 (m, 1H), 3.97 (m, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 3.02 (m, 1H), 2.84–2.65 (complex m, 3H), 2.50 (s, 3H), 2.02–1.72 (complex m, 2H), 1.59 (s, 3H), 1.31 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1 (C), 208.8 (CO), 159.3 (C), 130.7 (C), 129.6 (2 x CH), 113.9 (2 x CH), 109.3 (C), 91.8 (CH), 82.9 (CH), 80.8 (CH), 76.1 (CH), 75.1 (CH_2), 69.9 (CH_2), 69.0 (CH), 60.1 (CH_3), 55.4 (CH_3), 55.0 (CH_2), 45.3 (CH_3), 40.7 (CH_2), 38.6 (CH_2), 26.5 (CH_3), 26.3 (3 x CH_3), 24.8 (CH_3), 18.62 (C), −3.68 (CH_3), −4.74 (CH_3);

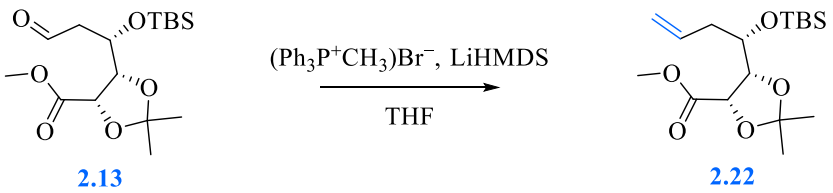
IR (KBr) ν_{max} 2934, 2856, 1954, 1714, 1613, 1514, 1464, 1381, 1302, 1250, 1212, 1172, 1072, 1048, 836 cm^{-1};

MS (ESI, +ve) *m/z* 564 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+H)^+$ 564.3345, $C_{30}H_{50}NO_7Si$ requires 564.3357;

Specific rotation $[\alpha]^{25}_D = -26.5$ (*c* 0.5, $CHCl_3$).

Methyl (4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.22)



2.13 **2.22**

A magnetically stirred solution of methyltriphenylphosphonium bromide (10.31 g, 28.9 mmol) in dry tetrahydrofuran (60 mL) maintained at 0 °C under a nitrogen atmosphere was treated with lithium bis(trimethylsilyl)amide (28.9 mL of a 1.0 M solution in tetrahydrofuran, 28.90 mmol). The resulting yellow mixture was allowed to warm to 20 °C, maintained at this temperature for 1 h then re-cooled to 0 °C and treated, *via* cannula, with a solution of aldehyde **2.13** (4.00 g, 11.54 mmol) in dry tetrahydrofuran (180 mL). The ensuing mixture was then warmed to 20 °C, stirred at this temperature for 2 h before being quenched with ammonium chloride (100 mL of a saturated aqueous solution) and then diluted with water (1 x 100 mL). The resulting mixture was extracted with diethyl ether (3 x 150 mL) and the combined organic phases were washed with water (1 x 100 mL) and brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.5 in 10:90 *v/v* diethyl ether/hexane) afforded *compound* ***2.22*** (3.02 g, 76%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88–5.76 (complex m, 1H), 5.16–5.04 (complex m, 2H), 4.52 (d, *J* = 6.6 Hz, 1H), 4.25 (dd, *J* = 6.6 and 4.2 Hz, 1H), 4.07 (m, 1H), 3.70 (s, 3H), 2.44 (complex m, 2H), 1.61 (s, 3H), 1.34 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (CO), 134.4 (CH), 117.9 (CH_2), 110.3 (C), 80.5 (CH), 74.9 (CH), 70.4 (CH), 52.0 (CH_3), 38.6 (CH_2), 26.8 (CH_3), 26.1 (3 x CH_3), 25.8 (CH_3), 18.5 (C), −4.2 (CH_3), −4.5 (CH_3);

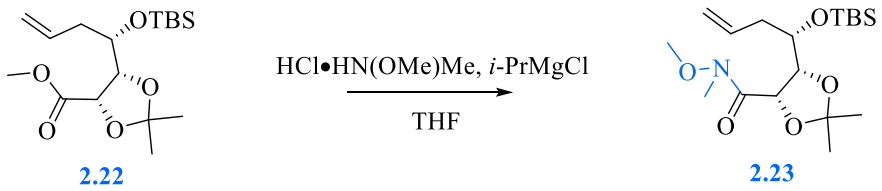
IR (KBr) ν_{max} 2953, 2929, 2857, 1766, 1641, 1472, 1436, 1384, 1370, 1249, 1199, 1094, 999, 957, 915, 870, 837 cm^{-1};

MS (ESI, +ve) *m/z* 345 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+H)^+$ 345.2097, $C_{17}H_{33}O_5Si$ requires 345.2097;

Specific rotation $[\alpha]^{25}_D$ = +41.6 (*c* 1.0, $CHCl_3$).

(4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)but-3-en-1-yl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (2.23)



2.22 2.23

A magnetically stirred solution of methyl ester **2.22** (1.11 g, 3.22 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (940 mg, 9.66 mmol) in dry tetrahydrofuran (25 mL) maintained at −15 °C under a nitrogen atmosphere was treated, dropwise over 20 min *via* syringe pump, with *i*so-propylmagnesium chloride (3.7 mL of a 2.0 M solution in tetrahydrofuran, 7.40 mmol). The resulting mixture was stirred at −15 °C for 1 h then quenched with ammonium chloride (25 mL of a saturated aqueous solution) before being diluted with water (1 x 10 mL). The resulting mixture was extracted with ethyl acetate (3 x 40 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 25:75 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3 in 25:75) afforded *compound **2.23*** (1.10 g, 92%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.74 (complex m, 1H), 5.06–4.97 (complex m, 2H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.34 (dd, *J* = 6.9 and 4.4 Hz, 1H), 3.96–3.90 (complex m, 1H), 3.70 (s, 3H), 3.15 (s, 3H), 2.35–2.20 (complex m, 2H), 1.52 (s, 3H), 1.34 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (CO), 135.4 (CH), 117.3 (CH_2), 110.1 (C), 80.8 (CH), 73.5 (CH), 71.4 (CH), 61.4 (OCH_3), 37.4 (CH_2), 32.4 (NCH_3), 26.6 (CH_3), 26.1 (3 x CH_3), 25.3 (CH_3), 18.3 (C), −4.0 (CH_3), −4.5 (CH_3);

IR (KBr) ν_{max} 2955, 2936, 2891, 2857, 1694, 1674, 1472, 1463, 1437, 1381, 1251, 1214, 1169, 1101, 1079, 1042, 1017, 995, 938, 913, 868, 835 cm^{-1};

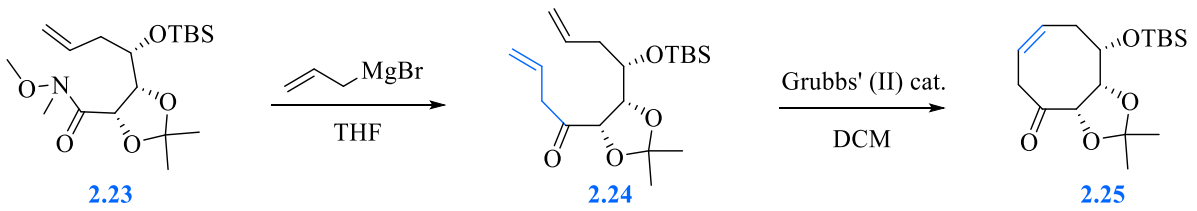
MS (ESI, +ve) *m/z* 396 [$(M+Na)^+$, 100%], 375 (10);

HRMS (ESI, +ve) Found: $[M+Na]^+$ 396.2183, $C_{18}H_{35}N^{23}NaO_5Si$ requires 396.2182;

Melting point 72–73 °C;

Specific rotation $[\alpha]^{25}_D$ = –7.5 (*c* 0.7, $CHCl_3$).

(3a*S*,9*S*,9a*R*,*Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-5,8,9,9a-tetrahydrocycloocta[*d*][1,3]dioxol-4(3a*H*)-one (2.25)



2.23 2.24 2.25

A magnetically stirred solution of Weinreb amide **2.23** (1.10 g, 2.95 mmol) in dry tetrahydrofuran (30 mL) maintained at −78 °C under a nitrogen atmosphere was treated with allylmagnesium bromide (7.4 mL of a 1.0 M solution in diethyl ether, 7.40 mmol) and after 1 h, the reaction mixture was quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phase washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the light-yellow oil presumed to contain diene **2.24**. A magnetically stirred solution of this material in dry dichloromethane (1000 mL) maintained at 20 °C was treated, *via* cannula, with a solution of Grubbs' second-generation catalyst (130 mg, 0.155 mmol) in dichloromethane (20 mL). The ensuing mixture was heated at reflux for 2 h then cooled and concentrated under reduced pressure. Subjection of this residue to flash chromatography (silica, 15:85 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5 with 25:75 *v/v* ethyl acetate/hexane) then gave *cyclooctenone* ***2.25*** (750 mg, 78%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.86–5.72 (complex m, 1H), 4.58 (d, *J* = 8.4 Hz, 1H), 4.43 (m, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 3.55 (ddt, *J* = 18.3, 7.0 and 1.8 Hz, 1H), 2.96 (dd, *J* = 18.3 and 8.1 Hz, 1H), 2.59 (ddd, *J* = 17.0, 8.6 and 6.7 Hz, 1H), 2.31 (m, 1H), 1.55 (s, 3H), 1.31 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5 (CO), 133.1 (CH), 125.2 (CH), 108.1 (C), 81.2 (CH), 81.2 (CH), 72.8 (CH), 41.2 (CH_2), 34.3 (CH_2), 26.4 (CH_3), 26.0 (3 x CH_3), 24.0 (CH_3), 18.3 (C), −4.7(5) (CH_3), −4.8(4) (CH_3);

IR (KBr) ν_{max} 2952, 2930, 2857, 1729, 1472, 1463, 1381, 1255, 1215, 1120, 1081, 1036, 958, 876, 837 cm^{-1};

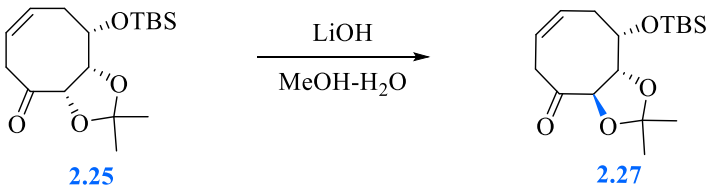
MS (ESI, +ve) *m/z* 349 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 349.1812, $C_{17}H_{30}{}^{23}NaO_4Si$ requires 349.1811;

Melting point 59–61 °C;

Specific rotation $[\alpha]^{25}_D$ = +108.1 (*c* 1.0, $CHCl_3$).

(3a*R*,9*S*,9a*R*,*Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-5,8,9,9a-tetrahydrocycloocta[*d*][1,3]dioxol-4(3a*H*)-one (2.27)



2.25 2.27

A magnetically stirred solution of compound **2.25** (65 mg, 0.20 mmol) in methanol/water (6 mL of a 2:1 *v/v* mixture) was treated with lithium hydroxide (0.4 mL of a 1.0 M aqueous solution, 0.40 mmol). The ensuing mixture was stirred at 18 °C for 2 h then treated successively with hydrochloric acid (0.4 mL of a 1.0 M aqueous solution) and brine (5 mL) before being extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure and the light-yellow oil thus obtained subjected to flash chromatography (silica, 25:75 *v/v* of ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.7) afforded *compound **2.27*** (58 mg, 90%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.72 (m, 1H), 5.12 (d, *J* = 8.2 Hz, 1H), 4.31 (dt, *J* = 7.6 and 2.0 Hz, 1H), 4.11 (dd, *J* = 8.2 and 2.0 Hz, 1H), 3.25 (ddd, *J* = 15.0, 8.5 and 1.0 Hz, 1H), 3.14 (dd, *J* = 15.0 and 7.6 Hz, 1H), 2.55 (m, 1H), 2.45 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (CO), 130.5 (CH), 124.3 (CH), 109.9 (C), 82.1 (CH), 79.1 (CH), 67.7 (CH), 40.4 (CH_2), 32.2 (CH_2), 26.6 (CH_3), 26.0 (3 x CH_3), 25.3 (CH_3), 18.4 (C), −4.3 (CH_3), −4.8 (CH_3);

IR (KBr) ν_{max} 2988, 2953, 2936, 2889, 2856, 1726, 1472, 1460, 1382, 1362, 1256, 1210, 1153, 1120, 1072, 998, 932, 914, 836 cm^{-1};

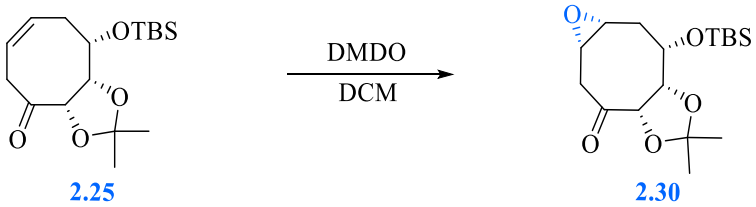
MS (ESI, +ve) *m/z* 675 [$(2M+Na)^+$, 100%], 349 [$(M+Na)^+$, 72];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 349.1799, $C_{17}H_{30}{}^{23}NaO_4Si$ requires 349.1811;

Melting point 75–77 °C;

Specific rotation $[\alpha]^{25}_{D} = -10.8$ (*c* 0.5, $CHCl_3$).

(3a*S*,5a*S*,6a*R*,8*S*,8a*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylhexahydrooxireno-[2',3':5,6]cycloocta[1,2-*d*][1,3]dioxol-4(3a*H*)-one (2.30)



2.25 2.30

A 100 mL round-bottomed flask was charged with the alkene **2.25** (480 mg, 1.47 mmol) and a stirring bar then cooled to 0 °C. Freshly prepared dimethyldioxirane (29.4 mL of a 0.06 M solution in acetone, 1.76 mmol) was added to the flask and the reaction mixture was then allowed to warm to 18 °C, maintained at this temperature for 16 h then concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *compound **2.30*** (378 mg, 75%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (complex m, 2H), 3.98 (br s, 1H), 3.30 (m, 1H), 3.20 (m, 1H), 2.82 (complex m, 2H), 2.45 (brd, *J* = 16.0 Hz, 1H), 1.85 (ddd, *J* = 16.0, 8.7 and 3.8 Hz, 1H), 1.61 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.06(5) (s, 3H), 0.06 (1) (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7 (CO), 110.2 (C), 82.3 (CH), 81.9 (CH), 69.0 (CH), 52.6 (CH), 51.5 (CH), 38.5 (CH_2), 33.9 (CH_2), 26.2 (CH_3), 25.9 (3 x CH_3), 24.1 (CH_3), 18.3 (C), –4.61 (2 x CH_3);

IR (KBr) ν_{max} 2930, 2858, 2895, 1725, 1472, 1463, 1382, 1258, 1212, 1166, 1124, 1102, 1075, 1031, 1003, 953, 914, 877, 837 cm^{-1};

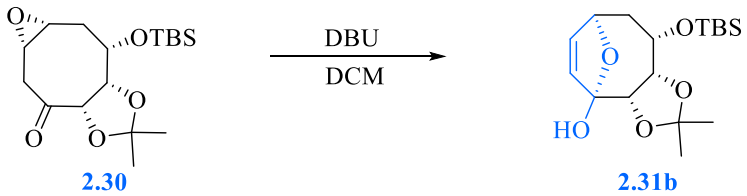
MS (ESI, +ve) *m/z* 365 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 365.1763, $C_{17}H_{30}{}^{23}NaO_5Si$ requires 365.1760;

Melting point 96–98 °C;

Specific rotation $[\alpha]^{25}_{D} = +43.5$ (*c* 0.4, $CHCl_3$).

(3a*S*,4*R*,7*R*,9*S*,9a*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-7,8,9,9a-tetrahydro-4,7-epoxycycloocta[*d*][1,3]dioxol-4(3a*H*)-ol (2.31b)



2.30 2.31b

A magnetically stirred solution of epoxide **2.30** (64 mg, 0.19 mmol) in dichloromethane (2 mL) maintained at 18 °C was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (56 μL, 0.37 mmol) and the ensuing mixture stirred for 6 h at this temperature then concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 25:75 *v/v* ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 25:75 *v/v* ethyl acetate/hexane elution), *compound **2.31b*** (58 mg, 91%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 5.9 and 1.9 Hz, 1H), 5.81 (dd, *J* = 5.9 and 1.1 Hz, 1H), 5.04–4.93 (complex m, 1H), 4.38 (br s, 1H), 4.29 (dd, *J* = 6.1 and 1.1 Hz, 1H), 4.07 (ddd, *J* = 11.1, 4.0 and 1.6 Hz, 1H), 3.91 (d, *J* = 6.1, 1H), 2.52 (m, 1H), 1.65 (ddd, *J* = 13.9, 4.0 and 2.2 Hz, 1H), 1.59 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (CH), 129.7 (CH), 108.9 (C), 107.9 (C), 81.0 (CH), 80.5 (CH), 77.8 (CH), 67.7 (CH), 36.2 (CH_2), 26.9 (CH_3), 26.1 (3 x CH_3), 25.8 (CH_3), 18.5 (C), −4.2 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 3502, 2931, 2856, 1471, 1403, 1380, 1324, 1290, 1248, 1222, 1168, 1099, 1075, 1037, 1014, 991, 922, 880, 836 cm^{-1};

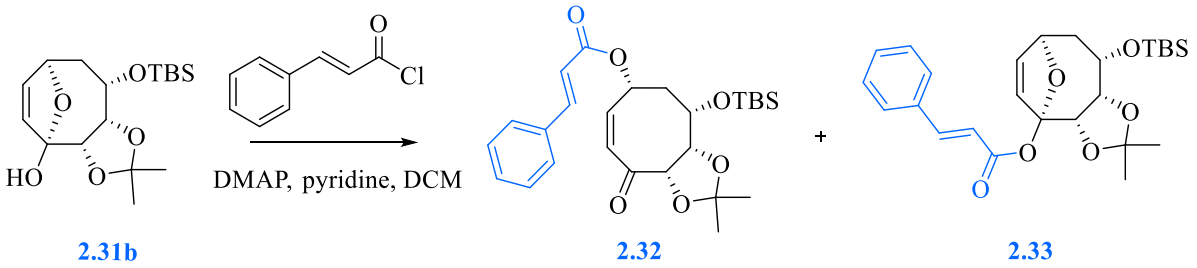
MS (ESI, +ve) *m/z* 365 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 365.1761, $C_{17}H_{30}{}^{23}NaO_5Si$ requires 365.1760;

Melting point 89–90 °C;

Specific rotation $[\alpha]^{25}_D$ = –20 (*c* 1.1, $CHCl_3$).

(3a*R*,4*S*,6*R*,9a*S*,*Z*)-4-((tert-Butyldimethylsilyl)oxy)-2,2-dimethyl-9-oxo-3a,4,5,6,9,9a-hexahydrocycloocta[*d*][1,3]dioxol-6-yl Cinnamate (2.32) and (3a*S*,4*S*,7*R*,9*S*,9a*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-7,8,9,9a-tetrahydro-4,7-epoxycycloocta[*d*][1,3]-dioxol-4(3a*H*)-yl Cinnamate (2.33)



2.31b 2.32 2.33

A magnetically stirred solution of lactol **2.31b** (41 mg, 0.12 mmol), pyridine (48µL, 0.59 mmol) and cinnamoyl chloride (82 µL, 0.59 mmol) in dichloromethane (5 mL) maintained under nitrogen was treated with 4-(*N*,*N*-dimethylamino)pyridine (73 mg, 0.59 mmol). The ensuing mixture was heated at 40 °C for 48 h then cooled and treated with ammonium chloride (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 15:85 *v/v* ethyl acetate/hexane elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 25:75 *v/v* ethyl acetate/hexane) gave *compound **2.33*** (10 mg, 19%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 16.0 Hz, 1H), 7.55–7.48 (complex m, 2H), 7.41–7.33 (complex m, 3H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.44 (dd, *J* = 6.0 and 1.1 Hz, 1H), 6.26 (dd, *J* = 6.0 and 1.7 Hz, 1H), 5.10 (br s, 1H), 4.69 (d, *J* = 6.0 Hz, 1H), 4.29 (d, *J* = 6.0 Hz, 1H), 4.05 (m, 1H), 2.60 (m, 1H), 1.71 (m, 1H), 1.58 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (CO), 145.7 (CH), 135.7 (CH), 134.6 (C), 130.6 (CH), 129.1 (2 x CH), 128.3(8) (2 x CH), 128.3(6) (CH), 118.3 (CH), 114.2 (C), 109.0 (C), 81.4 (CH), 80.8 (CH), 75.7 (CH), 67.6 (CH), 35.9 (CH_2), 26.7 (CH_3), 26.1 (3 x CH_3), 26.0 (CH_3), 18.6 (C), −4.3 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 2929, 2857, 1710, 1637, 1450, 1381, 1331, 1250, 1204, 1159, 1103, 1056, 1039, 926, 883 cm^{-1};

MS (ESI, +ve) *m/z* 495 [$(M+Na)^+$, 100%], 474 (8);

HRMS (ESI, +ve) Found: $(M+Na)^+$ 495.2173, $C_{26}H_{36}{}^{23}NaO_6Si$ requires 495.2179;

Specific rotation $[\alpha]^{25}_D = -73.8$ (*c* 0. 7, $CHCl_3$).

Concentration of fraction B (R_f = 0.5 in 25:75 *v/v* ethyl acetate/hexane) gave *compound* ***2.32*** (35 mg, 68%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 1H), 7.55 (complex m, 2H), 7.41 (complex m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.34 (m, 1H), 6.09 (m, 1H), 6.00 (m, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 4.65 (dd, *J* = 7.5 and 1.6 Hz, 1H), 4.49 (m, 1H), 2.26 (m, 1H), 2.06 (m, 1H), 1.63 (s, 3H), 1.45 (s, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (CO), 166.2 (CO), 146.2 (CH), 142.2 (CH), 134.3 (C), 131.9 (CH), 130.9 (CH), 129.2 (2 x CH), 128.4 (2 x CH), 117.4 (CH), 109.7 (C), 81.1 (CH), 80.5 (CH), 70.6 (CH), 67.5 (CH), 38.0 (CH_2), 27.0 (CH_3), 26.0 (CH_3), 25.9 (3 x CH_3), 18.3 (C), −4.7 (CH_3), −5.1 (CH_3);

IR (KBr) ν_{max} 2929, 2856, 1713, 1692, 1636, 1450, 1381, 1309, 1253, 1203, 1166, 1127, 1089, 1052, 1024, 991, 937 cm^{-1};

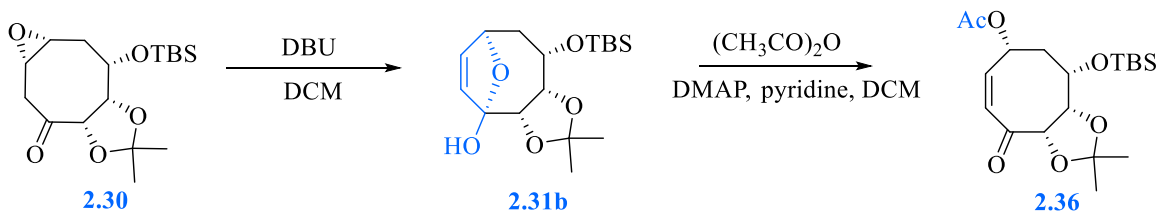
MS (ESI, +ve) *m/z* 511 [$(M+K)^+$, 100%], 495 [$(M+Na)^+$, 22];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 495.2175, $C_{26}H_{36}{}^{23}NaO_6Si$ requires 495.2179;

Melting point 139–140 °C;

Specific rotation $[\alpha]^{25}_D = -35$ (*c* 0.3, $CHCl_3$).

(3a*R*,4*S*,6*R*,9a*S*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-9-oxo-3a,4,5,6,9,9a-hexahydrocycloocta[*d*][1,3]dioxol-6-yl Acetate (2.36)



2.30 2.31b 2.36

A magnetically stirred solution of epoxide **2.30** (294 mg, 0.86 mmol) in dichloromethane (10 mL) maintained at 18 °C was treated with 1,8-diazabicyclo[5.4.0]undec-

7-ene (258 μL, 1.72 mmol) and the ensuing mixture stirred at this temperature for 6 h then filtered through a pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The resulting white solid (presumed to be lactol **2.31b**) was dissolved in dry dichloromethane (10 mL) and the ensuing solution treated with acetic anhydride (162 μL, 1.72 mmol), pyridine (207 μL, 2.57 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (104 mg, 0.86 mmol). The reaction mixture was heated at 40 °C for 24 h before being cooled then quenched with ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4 in 50:50 *v/v* diethyl ether/hexane) gave *compound **2.36*** (280.0 mg, 85%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 12.9 and 5.9 Hz, 1H), 6.05 (dd, *J* = 12.9 and 2.2 Hz, 1H), 5.87 (m, 1H), 4.93 (d, *J* = 7.4 Hz, 1H), 4.60 (dd, *J* = 7.4 and 1.7 Hz, 1H), 4.45 (m, 1H), 2.16 (dt, *J* = 13.8 and 5.1 Hz, 1H), 2.10 (s, 3H), 1.97 (m, 1H), 1.61 (s, 3H), 1.44 (s, 3H), 0.81 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7 (CO), 170.3 (CO), 142.1 (CH), 131.9 (CH), 109.7 (C), 81.1 (CH), 80.5 (CH), 70.5 (CH), 67.5 (CH), 37.9 (CH_2), 27.0 (CH_3), 26.0 (CH_3), 25.8 (3 x CH_3), 21.3 (CH_3), 18.3 (C), −4.7 (CH_3), −5.1 (CH_3);

IR (KBr) ν_{max} 2930, 2857, 1743, 1692, 1472, 1371, 1224, 1165, 1128, 1108, 1079, 1052, 1031, 991, 945, 838 cm^{-1};

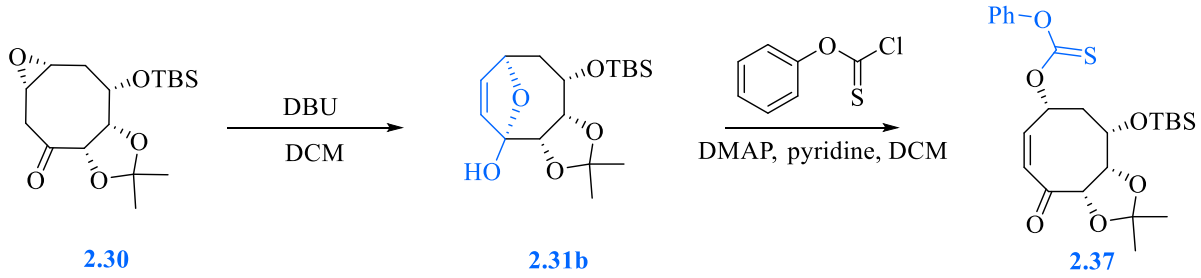
MS (ESI, +ve) *m/z* 423 [$(M+K)^+$, 100%], 407 [$(M+Na)^+$, 9], 385 [$(M+H)^+$, 13];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 407.1874, $C_{19}H_{32}{}^{23}NaO_6Si$ requires 407.1866;

Melting point 114–116 °C;

Specific rotation $[\alpha]^{25}_D$ = +11.7 (*c* 1.5, $CHCl_3$).

_O_-((3a_R_,4_S_,6_R_,9a_S_,_Z_)-4-((tert-Butyldimethylsilyl)oxy)-2,2-dimethyl-9-oxo-3a,4,5,6,9,9a-hexahydrocycloocta[_d_][1,3]dioxol-6-yl) _O_-Phenyl Carbonothioate (2.37)



2.30 **2.31b** **2.37**

A magnetically stirred solution of epoxide **2.30** (75 mg, 0.22 mmol) in dichloromethane (5 mL) maintained at 18 °C was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (66 μL, 0.44 mmol) and the ensuing mixture stirred at this temperature for 6 h before being filtered through a pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The white solid thus obtained was dissolved in dry dichloromethane (5 mL) and the resulting solution treated with phenyl thionocarbonate (59 mg, 0.44 mmol), pyridine (53 μL, 0.65 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (27 mg, 0.22 mmol). The ensuing mixture was heated at 40 °C for 48 h then cooled, quenched with ammonium chloride (5 mL of a saturated aqueous solution) and extracted with dichloromethane (3 x 5 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure and the light-yellow oil so-formed subjected to flash chromatography (silica, dichloromethane elution). Concentration of the relevant fractions (R_f = 0.7) then afforded *compound **2.37*** (37 mg, 35%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.39 (complex m, 2H), 6.13 (d, *J* = 10.9 Hz, 1H), 4.97 (d, *J* = 7.4 Hz, 1H), 4.63 (d, *J* = 7.4 Hz, 1H), 4.53 (d, *J* = 4.8 Hz, 1H), 2.45 (m, 1H), 2.18 (m, 1H), 1.63 (s, 3H), 1.44 (s, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4 (CO), 194.2 (CS), 153.4 (C), 140.6 (CH), 132.2 (CH), 129.9 (2 x CH), 127.1 (CH), 121.9 (2 x CH), 109.8 (C), 81.1 (CH), 80.6 (CH), 80.5 (CH), 67.3 (CH), 37.2 (CH_2), 27.0 (CH_3), 26.0 (CH_3), 25.8 (3 x CH_3), 18.3 (C), −4.7 (CH_3), −5.1 (CH_3);

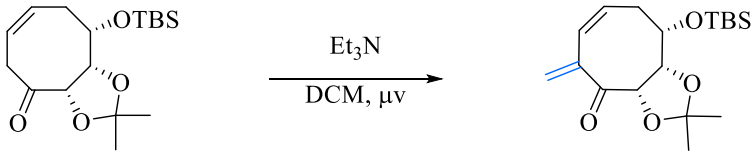
IR (KBr) ν_{max} 2929, 2856, 1692, 1490, 1290, 1255, 1217, 1124, 1079, 1051, 1019, 1003, 938, 853, 838 cm^{-1};

MS (ESI, +ve) *m/z* 479 [$(M+H)^+$, 60%], 325 (100);

HRMS (ESI, +ve) Found: $[M+Na]^+$ 501.1743, $C_{24}H_{34}{}^{23}NaO_6SSi$ requires 501.1743;

Specific rotation $[\alpha]^{25}_{D} = -39.8$ (*c* 0.5, $CHCl_3$).

(3a*S*,9*S*,9a*R*,*Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-5-methylene-5,8,9,9a-tetrahydrocycloocta[*d*][1,3]dioxol-4(3a*H*)-one (2.40)



2.25 2.40

A tube suitable for placement in a microwave reactor was charged with the alkene **2.25** (10 mg, 0.03 mmol), triethylamine (43 μL, 0.31 mmol) and dichloromethane (1 mL). The resulting yellow solution was immediately subjected to microwave irradiation (100 W, internal pressure of 200 psi) at 100 °C for 4 h then cooled and filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the yellow oil thus obtained subjected to flash chromatography (silica, 10:90 *v/v* ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.6 in 25:75 *v/v* ethyl acetate/hexane) afforded *compound **2.40*** (9 mg, 87%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (m, 1H), 6.17 (br s, 1H), 5.67–5.59 (complex m, 1H), 5.23 (s, 1H), 4.77 (d, *J* = 7.3 Hz, 1H), 4.37 (m, 1H), 4.33 (dd, *J* = 7.3 and 1.6 Hz, 1H), 2.64–2.39 (complex m, 2H), 1.68 (s, 3H), 1.36 (s, 3H), 0.79 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4 (CO), 142.9 (C), 129.0 (CH), 125.8 (CH), 125.5 (CH_2), 109.4 (C), 82.6 (CH), 79.7 (CH), 68.7 (CH), 35.9 (CH_2), 26.8 (CH_3), 26.1 (CH_3), 25.9 (3 x CH_3), 18.4 (C), −4.8 (CH_3), −5.2 (CH_3);

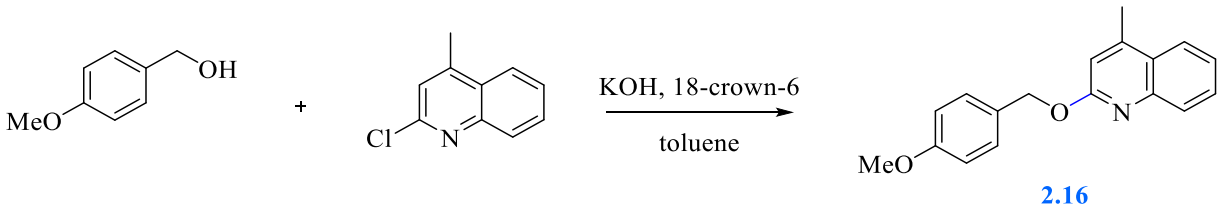
IR (KBr) ν_{max} 2930, 2896, 2856, 1713, 1581, 1472, 1378, 1244, 1220, 1164, 1133, 1090, 1068, 1025, 968, 941, 837 cm^{-1};

MS (ESI, +ve) *m/z* 377 [$(M+K)^+$, 100%], 361 [$(M+Na)^+$, 20];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 361.1811, $C_{18}H_{30}{}^{23}NaO_4Si$ requires 361.1811;

Specific rotation $[\alpha]^{25}_{D} = +85.7$ (*c* 0.7, $CHCl_3$).

2-((4-Methoxybenzyl)oxy)-4-methylquinoline (2.16)



2.16

A magnetically stirred mixture of 4-methoxybenzyl alcohol (8.4 mL, 67.56 mmol), 2-chlorolepidine (10.00 g, 56.30 mmol), finely ground potassium hydroxide (12.60 g, 0.22 mol) and 18-crown-6 (0.74 g, 2.80 mmol) in toluene (100 mL) was heated at reflux for 2 h with azeotropic removal of water (Dean-Stark trap). The reaction mixture was then cooled to 18 °C and partitioned between ethyl acetate (150 mL) and water (100 mL). The organic phase was washed with brine (1 x 100 mL) before being dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **2.16**[110] (15.00 g, 95%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4, 2H), 7.63 (t, *J* = 7.6, 1H), 7.46 (d, *J* = 8.6, 2H), 7.40 (t, *J* = 7.6, 1H), 6.92 (d, *J* = 8.6, 2H), 6.80 (s, 1H), 5.47 (s, 2H), 3.82 (s, 3H), 2.61 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (C), 159.6 (C), 147.0 (C), 146.7 (C), 130.3 (2 x CH), 129.8 (C), 129.5 (CH), 128.0 (CH), 125.7 (C), 124.0 (CH), 123.9 (CH), 114.1 (2 x CH), 113.5 (CH), 67.4 (CH_2), 55.5 (CH_3), 18.9 (CH_3);

IR (KBr) ν_{max} 1612, 1573, 1514, 1470, 1396, 1329, 1247, 1174, 1038, 1019 cm^{-1};

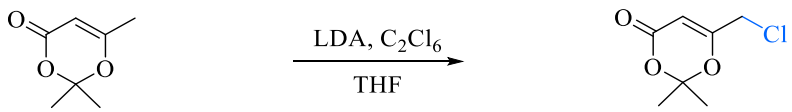
MS (ESI, +ve) *m/z* 302 [$(M+Na)^+$, 10%], 121 [$(C_8H_9O)^+$, 100];

HRMS (ESI, +ve) Found: $(M+H)^+$ 280.1339, $C_{18}H_{18}NO_2Si_2$ requires 280.1338.

These data matched those reported previously.[110]

7.3 Experimental Procedures Related to Work Described in Chapter Three

6-(Chloromethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3.6)



3.5 3.6

A magnetically stirred solution of di-*iso*-propylamine (2.8 mL, 19.70 mmol) in tetrahydrofuran (50 mL) was treated, at −78 °C, with *n*-butyl lithium (12.7 mL of a 1.5 M solution in hexane, 18.99 mmol). The ensuing mixture was stirred for 30 min then 2,2-dimethyl-(4*H*)-1,3-dioxin-4-one **3.5** (2.0 mL, 14.07 mmol) was added dropwise over 5 min. The resulting mixture was stirred for another 5 min then the reaction temperature was gradually increased to −50 °C. A solution of hexachloroethane (5.83 g, 24.62 mmol) in tetrahydrofuran (10 mL) was then added dropwise over 1 h *via* syringe pump. After stirring for another 10 min, the reaction mixture was diluted with diethyl ether (40 mL) then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 30:70 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **3.6**[126] (1.81 g, 73%) as a light-yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H), 3.99 (s, 2H), 1.67 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C), 160.5 (C), 107.6 (C), 95.67 (CH), 41.1 (CH_2), 24.9 (2 x CH_3).

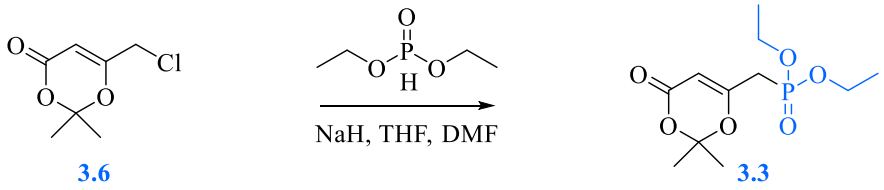
These data matched those reported previously.[126] The following additional data were acquired on this compound.

IR (ATR) ν_{max} 3000, 1726, 1640, 1391, 1376, 1272, 1201, 1014, 902 cm^{-1};

MS (ESI, +ve) *m/z* 121 and 119 [$(M–(CH_3)_2CO+H)^+$, 35 and 100%], 179 and 177 [$(M+H)^+$, 1.7 and 5];

HRMS (ESI, +ve) Found: $(M+H)^+$ 177.0316, $C_7H_{10}{}^{35}ClO_3$ requires 177.0318. $(M+H)^+$ 179.0287, $C_7H_{10}{}^{37}ClO_3$ requires 179.0289.

Diethyl ((2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl)phosphonate (3.3)



3.6 3.3

A magnetically stirred solution of sodium hydride (93 mg of 60% *w/w* dispersion in mineral oil, 2.31 mmol) in tetrahydrofuran (5 mL) and *N*,*N*-dimethylformamide (0.5 mL) was treated, at 18 °C, with diethyl phosphite (0.27 mL, 1.95 mmol). The ensuing mixture was stirred for 10 min and the resulting suspension then cooled to 0 °C. The reaction mixture thus formed was then treated, dropwise over 10 min with a solution of chloride **3.6** (314 mg, 1.78 mmol) in tetrahydrofuran (1 mL). After stirring for 15 min at 0 °C, the reaction temperature was gradually increased to 18 °C and stirring continued for a further 30 min. The reaction mixture was then filtered through a pad of Celite™ and the filter cake was washed with ethyl acetate (15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.1) afforded the phosphonate **3.3**[126] (478 mg, 96%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, *J* = 3.6 Hz, 1H), 4.09 (dq, *J* = 14.2 and 7.1 Hz, 4H), 2.75 (d, *J* = 22.1 Hz, 2H), 1.65 (s, 6H), 1.29 (t, *J* = 7.1 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, *J* = 9.9 Hz, C), 160.6 (d, *J* = 2.6 Hz, C), 107.2 (C), 96.2 (d, *J* = 8.0 Hz, CH), 62.7 (CH_2), 62.7 (CH_2), 32.5 (d, *J* = 137.6 Hz, CH_2), 25.0 (2 x CH_3), 16.5 (CH_3), 16.4 (CH_3).

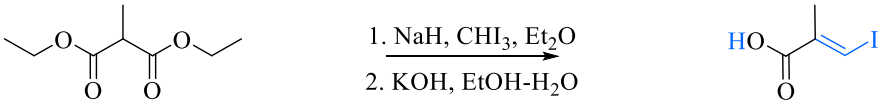
These data matched those reported previously.[126] The following additional data were acquired on this compound.

IR (KBr) ν_{max} 2988, 1728, 1633, 1376, 1269, 1204, 1023, 970 cm^{-1};

MS (ESI, +ve) *m/z* 301 [$(M+Na)^+$, 20%], 243 [$(M–2 \times C_2H_5+Na)^+$, 60], 221 [$(M–2 \times C_2H_5+H)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 301.0818, $C_{11}H_{19}{}^{23}NaO_6$ requires 301.0817.

(*E*)-3-Iodo-2-methylacrylic Acid (3.9)



3.7 3.9

A vigorously magnetically stirred solution of sodium hydride (2.75 g of 60% *w/w* dispersion in mineral oil, 68.88 mmol) in dry diethyl ether (100 mL) was treated, over 30 min, with a solution of diethyl methylmalonate (10.0 mL, 57.40 mmol) in diethyl ether (20 mL). The resulting slurry was heated at 35 ºC for 2.5 h before iodoform (22.60 g, 57.41 mmol) was added in one portion. Stirring was continued at 35 °C for another 20 h then the reaction mixture was cooled to 0 °C and the excess sodium hydride was quenched with hydrochloric acid (20 mL of a 1.0 M aqueous solution) (CAUTION: evolution of hydrogen gas). After stirring for 20 min, the aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (1 x 50 mL) then dried over magnesium sulfate and concentrated under reduced pressure. The residue was diluted with pentane (50 mL) and the precipitated iodoform was removed by filtration. The filtrate was concentrated under reduced pressure and the residue dissolved in ethanol (120 mL) then treated with a solution of potassium hydroxide (12.88 g, 0.23 mol) in water (40 mL). The ensuing mixture was then heated to 100 °C for 16 h and after cooling and evaporation of all volatile materials, the residue was dissolved in potassium carbonate (100 mL of a 10% aqueous solution). The basic solution was carefully acidified with concentrated hydrochloric acid at 0 °C then extracted with dichloromethane (4 x 100 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* ethyl acetate/hexane + 0.5% acetic acid elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the acid **3.9**[127] (9.61 g, 79%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.03 (d, *J* = 1.0 Hz, 1H), 2.06 (d, *J* = 1.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 139.2 (C), 102.3 (CH), 20.0 (CH_3);

IR (KBr) ν_{max} 3080, 2981, 2699, 2597, 2519, 1690, 1594, 1412, 1302, 1239, 1108, 992 cm^{-1};

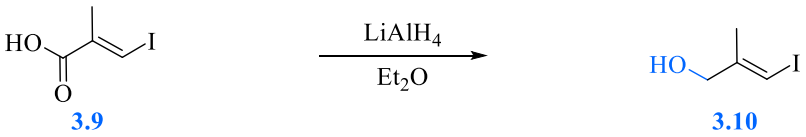
MS (EI, +ve, 70 eV) *m/z* 212 ($M^{+\bullet}$, 100%);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 211.9334, $C_4H_5{}^{127}IO_2$ requires 211.9334;

Melting point 45–46 °C.

These data matched those reported previously.[127]

(*E*)-3-Iodo-2-methylprop-2-en-1-ol (3.10)



3.9 **3.10**

A magnetically stirred suspension of lithium aluminium hydride (207 mg, 5.18 mmol) in diethyl ether (10 mL) maintained at 0 °C was treated, over 1 h *via* syringe pump, with a solution of acid **3.9** (1.00 g, 4.71 mmol) in diethyl ether (5 mL). The ensuing mixture was then stirred for an additional 1 h at 0 °C before being warmed to 18 °C and maintained at this temperature for a further 3 h. The reaction mixture was then cooled to 0 °C and the excess lithium aluminium hydride was quenched by the dropwise addition of ethyl acetate then tartaric acid (10 mL of a 1.0 M aqueous solution) (CAUTION: evolution of hydrogen gas). The reaction mixture was warmed to 18 °C and stirred for a further 30 min until two clear layers were formed. The separated aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were then washed with potassium carbonate (10 mL of a 10% aqueous solution) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **3.10**[127] (838 mg, 90%) as a clear, pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 0.9 Hz, 1H), 4.05 (s, 2H), 2.90 (s, 1H), 1.80 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2 (C), 77.4 (CH), 67.0 (CH_2), 21.5 (CH_3);

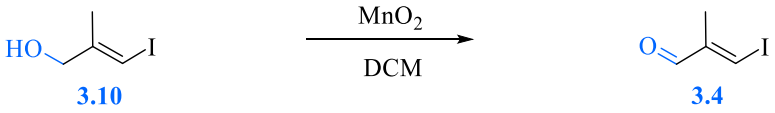
IR (KBr) ν_{max} 3307, 2914, 2852, 1621, 1444, 1377, 1276, 1068, 1012, 775, 666 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 198 ($M^{+\bullet}$, 45%), 165 (47), 71 (100);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 197.9542, $C_4H_7{}^{127}IO$ requires 197.9542.

These data matched those reported previously.[127]

(*E*)-3-Iodo-2-methylacrylaldehyde (3.4)



3.10 3.4

A vigorously magnetically stirred solution of alcohol **3.10** (500 mg, 2.52 mmol) in dichloromethane (10 mL) was treated, in two equal portions, with manganese dioxide (2.19 g, 25.25 mmol). A mildly exothermic reaction ensued. After 4 h, the reaction mixture was filtered through a pad of flame-dried then cooled Celite^{TM} and the pad rinsed with dichloromethane (3 x 20 mL). The combined filtrates were evaporated to give the aldehyde **3.4**[127] (430 mg, 87%) as a clear, pink oil (R_f = 0.5 in 20:80 *v/v* diethyl ether/hexane). This material was used, without purification, in the next step of the reaction sequence.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, CHO), 7.80 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 1.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6 (C), 151.0 (C), 109.6 (CH), 16.6 (CH_3);

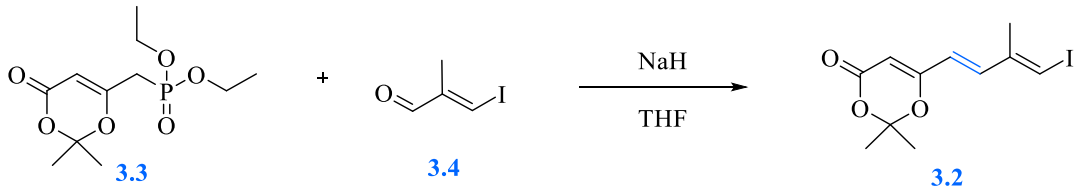
IR (KBr) ν_{max} 2919, 2849, 1686, 1593, 1374, 1292, 1045, 1011, 829 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 196 ($M^{+\bullet}$, 100%);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 195.9380, $C_4H_5{}^{127}IO$ requires 195.9385;

These data matched those reported previously.[127]

6-((1*E*,3*E*)-4-Iodo-3-methylbuta-1,3-dien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3.2)



3.3 3.4 3.2

A magnetically stirred solution of sodium hydride (83 mg of 60% *w/w* dispersion in mineral oil, 2.08 mmol) in tetrahydrofuran (5 mL) was treated, at 0 °C, with diethyl phosphonate **3.3** (580 mg, 2.08 mmol). The ensuing reaction was warmed to 18 °C and stirred at this temperature for another 30 min. The resulting suspension was cooled to −78 °C then treated, dropwise over 10 min, with a solution of aldehyde **3.4** (429 mg, 2.19 mmol) in tetrahydrofuran (5 mL). After stirring for another 15 min, the reaction mixture was warmed to 18 °C and stirring continued at this temperature for a further 1 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and quenched with water (15 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (1 x 30 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **3.2*** (510 mg, 76%) as an ivory to light-yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 15.5 Hz, 1H), 6.85 (s, 1H), 6.05 (d, *J* = 15.5 Hz, 1H), 5.39 (s, 1H), 2.00 (s, 3H), 1.70 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (C), 161.8 (C), 144.3 (C), 137.8 (CH), 120.1 (CH), 106.6 (C), 95.8 (CH), 92.6 (CH), 25.2 (2 x CH_3), −19.8 (CH_3);

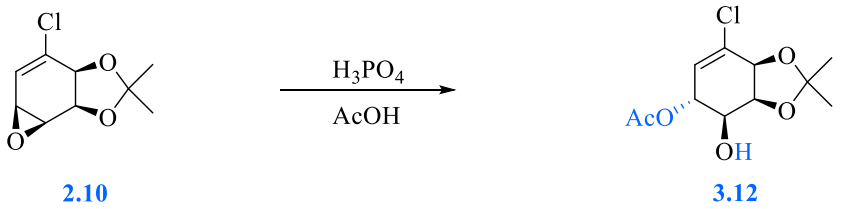
IR (KBr) ν_{max} 2998, 1714, 1629, 1560, 1391, 1377, 1275, 1204, 1026, 974, 904 cm^{-1};

MS (ESI, +ve) *m/z* 384 [$(M+Na+CH_3CN)^+$, 40%], 375 [$(M+Na+CH_3OH)^+$, 50], 343 [$(M+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 342.9807, $C_{11}H_{13}{}^{127}I^{23}NaO_3$ requires 342.9807. $(M+H)^+$ 320.9998, $C_{11}H_{14}IO_3$ requires 320.9988;

Melting point 129–131 °C.

(3a*S*,4*S*,5*R*,7a*S*)-7-Chloro-4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-5-yl Acetate (3.12)



2.10 **3.12**

A magnetically stirred solution of epoxide **2.10** (4.00 g, 20.00 mmol) in acetic acid (25 mL) was treated with phosphoric acid (0.08 mL). After stirring at 18 °C for 4 h, the reaction mixture was diluted with ethyl acetate (50 mL) then quenched with ammonium chloride (100 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) provided the *alcohol* ***3.12*** (3.80 g, 73%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, *J* = 2.1 Hz, 1H), 5.88–5.82 (m, 1H), 4.89 (complex m, 2H), 4.20 (m, 1H), 2.96 (br s, 1H), 2.46 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (CO), 133.8 (C), 124.8 (CH), 111.2 (C), 76.6 (2 x CH), 71.9 (CH), 71.0 (CH), 27.6 (CH_3), 26.5 (CH_3), 21.2 (CH_3);

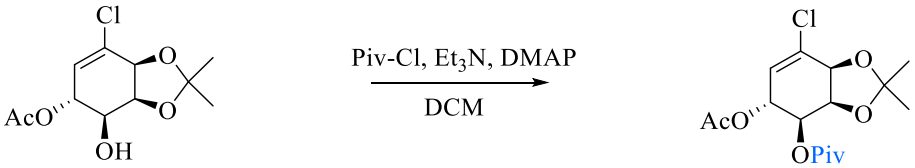
IR (ATR) ν_{max} 3458, 2988, 2937, 1743, 1372, 1222, 1038, 865 cm^{-1};

MS (ESI, +ve) *m/z* 287 and 285 [$(M+Na)^+$, 35 and 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 287.0476, $C_{11}H_{15}{}^{37}Cl^{23}NaO_5$ requires 287.0476. $(M+Na)^+$ 285.0506, $C_{11}H_{15}{}^{35}Cl^{23}NaO_5$ requires 285.0506;

Specific rotation $[\alpha]^{25}_D = -87.4$ (*c* 1.2, $CHCl_3$).

(3a*S*,4*S*,5*R*,7a*S*)-5-Acetoxy-7-chloro-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-4-yl Pivalate (3.13)



3.12 **3.13**

A magnetically stirred solution of alcohol **3.12** (3.70 g, 14.08 mmol), triethylamine (3.9 mL, 28.17 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (172 mg, 1.40 mmol) in dichloromethane (70 mL) maintained at 0 °C under a nitrogen atmosphere was treated with pivaloyl chloride (2.6 mL, 21.13 mmol). The ensuing mixture was allowed to warm to 18 °C then stirred at this temperature for 16 h before being poured into ammonium chloride (100 mL of a saturated aqueous solution). The separted aqueous layer was extracted with dicloromethane (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the desired *compound **3.13*** (4.00 g, 82%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (partially obscured s, 1H), 5.76 (partially obscured m, 1H), 5.11 (dd, *J* = 8.5 and 2.3 Hz, 1H), 4.59 (dd, *J* = 4.9 and 1.7 Hz, 1H), 4.50 (dd, *J* = 4.9 and 2.3 Hz, 1H), 2.04 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.21 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (CO), 170.2 (CO), 134.0 (C), 124.7 (CH), 111.5 (C), 76.7 (CH), 74.6 (CH), 70.9 (CH), 68.5 (CH), 39.1 (C), 27.7 (CH_3), 27.1 (3 x CH_3), 26.6 (CH_3), 21.0 (CH_3);

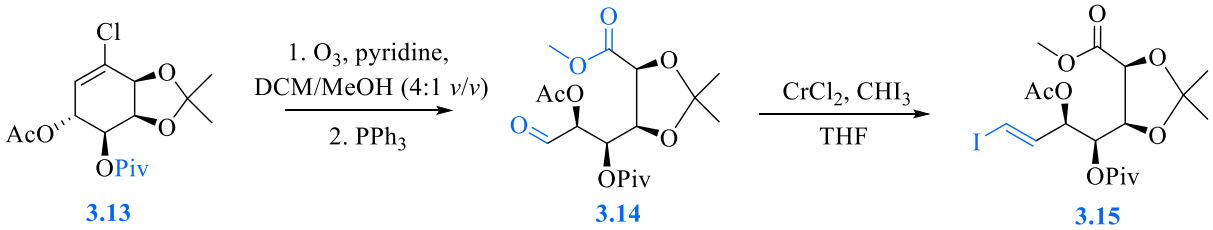
IR (KBr) ν_{max} 2984, 2937, 1751, 1734, 1481, 1372, 1224, 1150, 1040, 865 cm^{-1};

MS (ESI, +ve) *m/z* 387 and 385 [$(M+K)^+$, 35 and 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 387.0789, $C_{16}H_{23}{}^{37}Cl^{39}KO_6$ requires 387.0791. $(M+K)^+$ 385.0818, $C_{16}H_{23}{}^{35}Cl^{39}KO_6$ requires 385.0820;

Specific rotation $[\alpha]^{25}_D = -136.1$ (*c* 0.8, $CHCl_3$).

(4*S*,5*S*)-Methyl 5-((1*S*,2*R*,*E*)-2-Acetoxy-4-iodo-1-(pivaloyloxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (3.15)



3.13 **3.14** **3.15**

A magnetically stirred solution of alkene **3.13** (1.00 g, 2.9 mmol) in dichloromethane/methanol (50 mL of a 4:1 *v/v* mixture) was treated with pyridine (1.1 mL, 14.40 mmol) then cooled to −78 °C and ozone then bubbled through it until a dark-blue colour persisted (*ca*. 30 min). At this point triphenylphosphine (0.92 g, 3.50 mmol) was added to the reaction mixture which was warmed to 18 °C and kept at this temperature for 1 h before being concentrated under reduced pressure. The resulting light-yellow oil was filtered through a short pad of TLC-grade silica gel that was washed with diethyl ether/hexane (100 mL of a 2:3 *v/v* mixture). The combined filtrates were concentrated and dried under high vacuum and the residue thus obtained, and containing aldehyde **3.14**, was immediately subjected to the next step of the reaction sequence.

A solution of chromium chloride (1.97 g, 16.02 mmol), dispensed in a glove box, in dry tetrahydrofuran (25 mL) maintained at 18 ºC under an argon atmosphere was slowly treated, *via* cannula, with a solution of aldehyde **3.14** (1.00 g, 2.67 mmol) and iodoform (2.31 g, 5.87 mmol) in dry tetrahydrofuran (25 mL). The ensuing mixture was stirred for 16 h then filtered through a pad of Celite™. Water/diethyl ether (60 mL of a 1:1 *v/v* mixture) was added to the filtrate and the separated aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) afforded the *alkenyl iodide* ***3.15*** (0.65 g, 45%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46–6.30 (complex m, 2H), 5.58 (dd, *J* = 4.4 and 3.5 Hz, 1H), 5.11 (dd, *J* = 8.8 and 3.5 Hz, 1H), 4.57 (d, *J* = 6.4 Hz, 1H), 4.46 (dd, *J* = 8.8 and 6.4 Hz, 1H), 3.68 (s, 3H), 2.11 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H), 1.20 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 170.0 (CO), 169.3 (CO), 139.8 (CH), 111.7 (C), 80.2 (CH), 76.2 (CH), 75.5 (CH), 74.5 (CH), 69.8 (CH), 52.7 (CH_3), 39.1 (C), 27.2 (3 x CH), 26.8 (CH_3), 25.7 (CH_3), 20.8 (CH_3);

IR (KBr) ν_{max} 2979, 1743, 1372, 1226, 1138, 1094, 940, 865 cm^{-1};

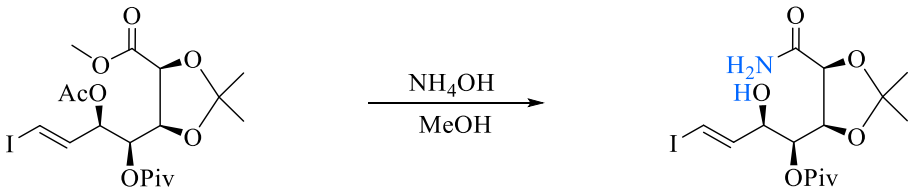
MS (ESI, +ve) *m/z* 537 [$(M+K)^+$, 40%], 521 [$(M+Na)^+$, 100];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 521.0649, $C_{18}H_{27}{}^{127}I^{23}NaO_8$ requires 521.0648;

Melting point 77–78 °C;

Specific rotation $[\alpha]^{25}_D$ = +9.1 (*c* 2.3, $CHCl_3$).

(1*S*,2*R*,*E*)-1-((4*S*,5*S*)-5-Carbamoyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxy-4-iodobut-3-en-1-yl Pivalate (3.16)



3.15 **3.16**

A magnetically stirred solution of acetate **3.15** (50 mg, 0.10 mmol) in methanol (2 mL) was treated with ammonia (0.17 mL of a 35% aqueous solution, 1.50 mmol). After 4 h, the reaction mixure was concentrated under reduced pressure and the residue dissolved in ethyl acetate (5 mL). The resulting solution was washed with ammonium chloride (5 mL of a saturated solution) and the separated aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:25:45 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded the *alcohol **3.16*** (40 mg, 87%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (br s, 1H), 6.71 (dd, *J* = 14.6 and 7.3 Hz, 1H), 6.50 (d, *J* = 14.6 Hz, 1H), 6.23 (br s, 1H), 5.34 (dd, *J* = 7.3 and 1.3 Hz, 1H), 4.68 (d, *J* = 3.1 Hz, 1H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.38 (dd, *J* = 9.3 and 7.4 Hz, 1H), 3.66 (d, *J* = 9.3 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H), 1.20 (s, 9H);

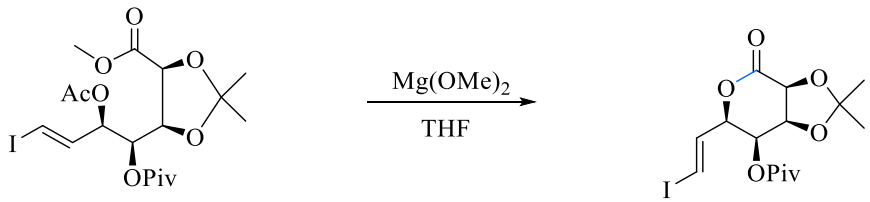
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (CO), 174.8 (CO), 140.9 (CH), 110.8 (C), 81.9 (CH), 77.0 (CH), 76.7 (CH), 74.7 (CH), 71.2 (CH), 39.2 (C), 27.3 (3 x CH_3), 27.1 (CH_3), 24.6 (CH_3);

IR (KBr) ν_{max} 3471, 3342, 2981, 2934, 1730, 1676, 1479, 1371, 1280, 1218, 1152, 1071 cm^{-1};

MS (ESI, +ve) *m/z* 464 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 464.0547, $C_{15}H_{24}{}^{127}I^{23}NaO_6$ requires 464.0546.

(3aS,6R,7S,7aS)-6-((E)-2-iodovinyl)-2,2-dimethyl-4-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl pivalate (3.17)



3.15 **3.17**

A magnetically stirred solution of acetate **3.15** (200 mg, 0.40 mmol) in tetrahydrofuran (5 mL) was treated with magnesium methoxide (0.62 mL of a 10% solution in methanol, 0.60 mmol). After 4 h, the reaction mixture was diluted with diethyl ether (5 mL) then quenched with ammonium chloride (5 mL of a saturated aqueous solution). The separted aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic phases were dried over magnesium sulfate, then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the *lactone **3.17*** (120 mg, 70%) as an ivory-colored solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 14.7 Hz, 1H), 6.57 (dd, *J* = 14.7 and 7.5 Hz, 1H), 5.37 (dd, *J* = 7.5 and 2.2 Hz, 1H), 4.69 (d, *J* = 5.8 Hz, 1H), 4.65 (d, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.20 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (CO), 173.1 (CO), 138.2 (CH), 114.1 (C), 84.7 CH), 82.5 (CH), 77.4 (CH), 74.9 (CH), 74.2 (CH), 39.1 (C), 27.1 (3 X CH_3), 26.7 (CH_3), 25.7(CH_3);

IR (KBr) ν_{max} 2981, 1791, 1738, 1610, 1480, 1376, 1275, 1175, 1132, 1086, 947 cm^{-1};

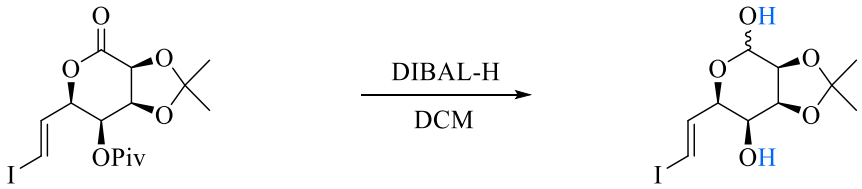
MS (ESI, +ve) *m/z* 495 [$(M+CH_3OH+K)^+$, 80%], 479 [$(M+CH_3OH+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 447.0282, $C_{15}H_{21}{}^{127}I^{23}NaO_6$ requires 447.0281;

Melting point 98.5–99.5 °C;

Specific rotation $[\alpha]^{25}_D = -55.7$ (*c* 1.1, $CHCl_3$).

(3aS,6R,7S,7aS)-6-((E)-2-iodovinyl)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4,7-diol (3.18)



3.17 **3.18**

A magnetically stirred solution of lactone **3.17** (40 mg, 0.09 mmol) in dichloromethane (5 mL) was cooled to −78 °C then treated, dropwise, with di-*iso*-butylaluminium hydride (0.11 mL of a 1.0 M solution in hexane, 0.11 mmol). After addition was complete, the reaction mixture was stirred for 30 min then treated with tartaric acid (5 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 30 min. The separated aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were then washed with brine (1 x 10 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:25:55 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *lactol **3.18*** (25 mg, 77%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*major isomer*) 1 6.65 (dd, *J* = 14.6 and 5.9 Hz, 1H), 6.48 (d, *J* = 14.6 Hz, 1H), 5.44 (s, 1H), 4.84 (d, *J* = 5.9 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 1H), 4.35 (d, *J* = 3.0 Hz, 1H), 4.19–4.14 (m, 1H), 3.57 (s, 2H), 1.48 (s, 3H), 1.32 (s, 3H); δ (*minor isomer*) 6.68 (dd, *J* = 14.6, 6.4 Hz, 1H), 6.54 (d, *J* = 14.6 Hz, 1H), 5.42 (d, *J* = 4.1 Hz, 1H), 4.72 (dd, *J* = 6.4 and 2.1 Hz, 1H), 4.63 (dd, *J* = 6.6 and 4.1 Hz, 1H), 4.12 (m, 1H), 4.07 (m, 1H), 3.57 (s, 2H), 1.56 (s, 3H), 1.39 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*major isomer*) 144.7 (CH), 112.6 (C), 103.2 (CH), 89.6 (CH), 86.5 (CH), 82.2 (CH), 79.6 (CH), 74.6 (CH), 26.5 (CH_3), 24.9 (CH_3); δ (*minor isomer*)143.9

(CH), 114.5 (C), 97.5 (CH), 82.9 (CH), 81.4 (CH), 80.7 (CH), 79.4 (CH), 75.0 (CH), 26.4 (CH_3), 24.9 (CH_3).

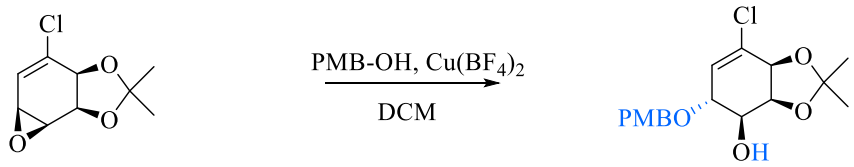
IR (KBr) ν_{max} 3351, 2985, 2939, 1609, 1374, 1209, 1158, 1059, 951, 859 cm^{-1};

MS (ESI, +ve) *m/z* 365 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 364.9871, $C_{10}H_{15}{}^{127}I^{23}Na\ O_5$ requires 364.9862;

Melting point 46.5–47.5 °C.

(3a*S*,4*S*,5*R*,7a*S*)-7-Chloro-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (3.19)



2.10 **3.19**

A magnetically stirred solution of epoxide **2.10** (1.00 g, 4.93 mmol) and *p*-methoxybenzyl alcohol (2.45 mL, 19.74 mmol) in dichloromethane (25 mL) was treated with copper(II) tetrafluoroborate (117 mg, 0.49 mmol) and the ensuing mixture stirred at 18 °C for 6 h then quenched with ammonium chloride (20 mL of a saturated solution). The separated aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate, then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.1) afforded *compound **3.19*** (1.20 g, 71%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.85 (m, 2H), 5.91 (d, *J* = 1.9 Hz, 1H), 4.56 (ABq, Δ δ_{AB} = 0.11, J_{AB} = 11.2 Hz, 2H), 4.47 (m, 2H), 4.18 (dt, *J* = 8.2 and 1.9 Hz, 1H), 3.78 (d, *J* = 2.3 Hz, 1H), 3.76 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (C), 132.6 (C), 129.8 (C), 129.7 (2 x CH), 125.8 (CH), 114.2 (2 x CH), 110.9 (C), 76.8 (CH), 76.4 (CH), 76.3 (CH), 72.2 (CH_2), 71.6 (CH), 55.4 (CH_3), 27.5 (CH_3), 26.4 (CH_3);

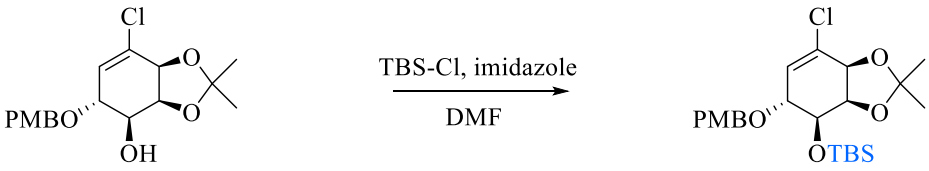
IR (KBr) ν_{max} 3462, 2987, 2934, 1613, 1514, 1371, 1248, 1174, 1102, 1042, 866 cm^{-1};

MS (ESI, +ve) *m/z* 381 and 379 [$(M+K)^+$, 35 and 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 381.0692, $C_{17}H_{21}{}^{37}Cl^{39}KO_5$ requires 381.0685. $(M+K)^+$ 379.0715, $C_{17}H_{21}{}^{35}Cl^{39}KO_5$ requires 379.0715;

Specific rotation $[\alpha]^{25}_D = -68.4$ (*c* 1.2, $CHCl_3$).

***tert*-Butyl(((3a*R*,4*S*,5*R*,7a*S*)-7-chloro-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)oxy)dimethylsilane (3.20)**



3.19 **3.20**

A magnetically stirred solution of alcohol **3.19** (1.00 g, 2.94 mmol) in *N*,*N*-dimethylformamide (15 mL) maintained at 18 °C was treated, sequentially, with *tert*-butyldimethylsilyl chloride (0.66 g, 4.41 mmol) then imidazole (0.40 g, 5.88 mmol). The ensuing mixture was stirred for 2 h then diluted with diethyl ether (30 mL) and quenched with water (30 mL). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with hydrochloric acid (50 mL of a 1.0 M aqueous solution), water (1 x 50 mL) and brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave *compound **3.20*** (1.30 g, 97%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.84 (d, *J* = 1.5 Hz, 1H), 4.62 (ABq, Δ δ_{AB} = 0.07, J_{AB} = 11.2 Hz, 2H), 4.47 (dd, *J* = 4.8 and 1.5 Hz, 1H), 4.38 (dd, *J* = 4.8 and 2.2 Hz, 1H), 4.21 (d, *J* = 8.1 Hz, 1H), 3.87 (dd, *J* = 8.1 and 2.2 Hz, 1H), 3.80 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 0.94 (s, 9H), 0.13 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C), 131.8 (C), 130.3 (C), 129.5 (2 x CH), 126.9 (CH), 113.9 (2 x CH), 110.7 (C), 77.9 (CH), 76.9 (CH), 76.6 (CH), 73.2 (CH), 73.1 (CH_2), 55.4 (CH_3), 27.7 (CH_3), 26.4 (CH_3), 26.0 (3 x CH_3), 18.4 (C), −4.09 (CH_3), −4.74 (CH_3);

IR (KBr) ν_{max} 2931, 2889, 2857, 1613, 1514, 1463, 1382, 1249, 1135, 1097, 1046, 838 cm^{-1};

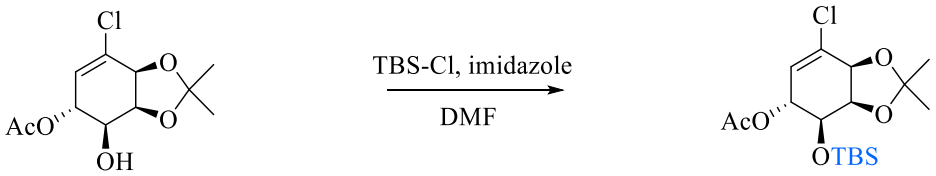
MS (ESI, +ve) *m/z* 479 and 477 [$(M+Na)^+$, 35 and 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 479.1810, $C_{23}H_{35}{}^{37}Cl^{23}NaO_5Si$ requires 479.1811. $(M+Na)^+$ 477.1840, $C_{23}H_{35}{}^{35}Cl^{23}NaO_5Si$ requires 477.1840;

Melting point 81–82 °C;

Specific rotation $[\alpha]^{25}_D = -46.3$ (*c* 1.1, $CHCl_3$).

(3a*R*,4*S*,5*R*,7a*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-7-chloro-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl Acetate (3.22)



3.12 3.22

A magnetically stirred solution of alcohol **3.12** (2.00 g, 7.61 mmol) in *N*,*N*-dimethylformamide (25 mL) maintained at 18 °C was treated, sequentially, with *tert*-butyldimethylsilyl chloride (1.72 g, 11.4 mmol) then imidazole (1.04 g, 1.52 mmol). The ensuing mixture was stirred for 2 h then diluted with diethyl ether (30 mL) and quenched with water (1 x 30 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with hydrochloric acid (1 x 50 mL of a 1.0 M aqueous solution), water (1 x 50 mL) and brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) gave *compound **3.22*** (2.70 g, 94%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 2.0 Hz, 1H), 5.53 (dt, *J* = 8.4 and 2.0 Hz, 1H), 4.50 (dd, *J* = 4.9 and 2.0 Hz, 1H), 4.38 (dd, *J* = 4.9 and 2.4 Hz, 1H), 3.95 (dd, *J* = 8.4 and 2.4 Hz, 1H), 2.08 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (CO), 133.4 (C), 125.2 (CH), 111.0 (C), 77.6 (CH), 76.8 (CH), 71.8 (CH), 71.3 (CH), 27.7 (CH_3), 26.5 (CH_3), 25.8 (3 X CH_3), 21.2 (CH_3), 18.2 (C), −4.4 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 2982, 2931, 2889, 2858, 1748, 1372, 1224, 1137, 1102, 1046, 838 cm^{-1};

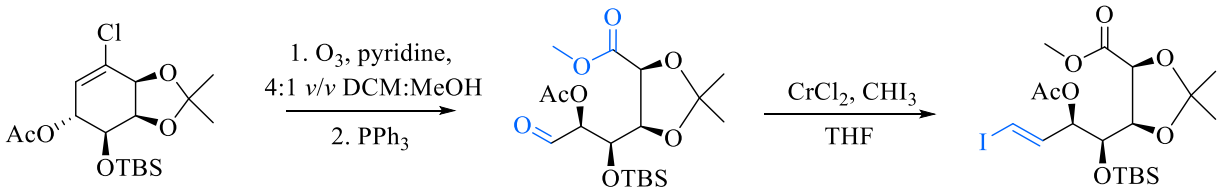
MS (ESI, +ve) *m/z* 401 and 399 $[(M+Na)^+$ 35 and 100%$)^+$;

HRMS (ESI, +ve) Found: $(M+Na)^+$ 401.1333, $C_{17}H_{29}{}^{37}Cl^{23}NaO_5Si$ requires 401.1341. $(M+Na)^+$ 399.1368, $C_{17}H_{29}{}^{35}Cl^{23}NaO_5Si$ requires 399.1371. $(M+H)^+$ 379.1522, $C_{17}H_{30}{}^{37}ClO_5Si$ requires 379.1522. $(M+H)^+$ 377.1553, $C_{17}H_{30}{}^{35}ClO_5Si$ requires 377.1551;

Melting point 43–44 °C;

Specific rotation $[\alpha]^{25}_D$ = −95.6 (*c* 1.0, $CHCl_3$).

(4*S*,5*R*)-Methyl 5-((1*S*,2*R*,*E*)-2-Acetoxy-1-((*tert*-butyldimethylsilyl)oxy)-4-iodobut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (3.24)



3.22 3.23 3.24

A magnetically stirred solution of alkene **3.22** (1.00 g, 2.65 mmol) in dichloromethane/methanol (50 mL of a 4:1 *v/v* mixture) was treated with pyridine (1.1 mL, 13.25 mmol) then cooled to −78 °C and ozone bubbled through it until a dark-blue colour persisted (*ca*. 30 min). At this point triphenylphosphine (0.85 g, 3.18 mmol) was added to the reaction mixture which was then warmed to 18 °C and kept at this temperature for 1 h before being concentrated under reduced pressure. The resulting light-yellow oil was filtered through a short pad of TLC-grade silica that was washed with diethyl ether/hexane (100 mL of a 2:3 *v/v* mixture). The combined filtrates were concentrated and dried under high vacuum and the

residue thus obtained, and containing aldehyde **3.23**, immediately used in the next step of the reaction sequence.

A solution of chromium chloride (1.64 g, 13.35 mmol), dispensed in a glove box, in dry tetrahydrofuran (25 mL) and dry *N*,*N*-dimethylformamide (1.0 mL) maintained at 18 ºC under an argon atmosphere was slowly treated, *via* cannula, with a solution of aldehyde **3.23** (0.90 g, 2.22 mmol) and iodoform (1.93 g, 4.89 mmol) in dry tetrahydrofuran (25 mL). The ensuing mixture was stirred for 16 h then filtered through a pad of Celite^{TM}. Water/diethyl ether (60 mL of a 1:1 *v/v* mixture) was added to the filtrate and the separated aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the *alkenyl iodide* ***3.24*** (780 mg, 55%) as a light-yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 14.6, 1H), 6.49 (dd, *J* = 14.6 and 8.0, 1H), 5.60 (t, *J* = 8.0, 1H), 4.41 (d, *J* = 6.5, 1H), 4.26 (dd, *J* = 8.0 and 3.0, 1H), 4.17 (dd, *J* = 6.5 and 3.0, 1H), 3.71 (s, 3H), 2.07 (s, 3H), 1.63 (s, 3H), 1.36 (s, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (CO), 169.8 (CO), 140.4 (CH), 110.3 (C), 83.8 (CH), 78.6 (CH), 76.5 (CH), 73.6 (CH), 71.6 (CH), 52.1 (CH_3), 26.7 (CH_3), 26.0 (3 x CH_3), 25.9 (CH_3), 21.5 (CH_3), 18.5 (C), −3.9 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 2932, 2857, 1766, 1745, 1609, 1473, 1371, 1227, 1145, 1096, 838 cm^{-1};

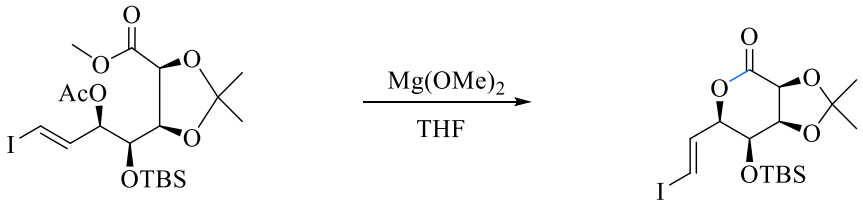
MS (ESI, +ve) *m/z* 567 [$(M+K)^+$, 100%], 551 [$(M+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+K)^+$ 567.0679, $C_{19}H_{33}{}^{127}I^{39}KO_7Si$ requires 567.0677. $(M+Na)^+$ 551.0939, $C_{19}H_{33}{}^{127}I^{23}Na\ O_7Si$ requires 551.0938;

Melting point 49–50 °C;

Specific rotation $[\alpha]^{25}_D$ = +36.9 (*c* 0.8, $CHCl_3$).

(3aS,6R,7S,7aR)-7-((tert-Butyldimethylsilyl)oxy)-6-((E)-2-iodovinyl)-2,2-dimethyltetra-hydro-4H-[1,3]dioxolo[4,5-c]pyran-4-one (3.25)



3.24 **3.25**

A magnetically stirred solution of acetate **3.24** (330 mg, 0.62 mmol) in tetrahydrofuran (10 mL) was treated with magnesium methoxide (2.6 mL of a 10% solution in methanol, 2.46 mmol). After 4 h, the reaction mixture was diluted with diethyl ether (10 mL) then quenched with ammonium chloride (10 mL of a saturated solution). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate, then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the *lactone **3.25*** (250 mg, 88%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 14.7 and 7.2 Hz, 1H), 6.51 (d, *J* = 14.7 Hz, 1H), 4.68 (d, *J* = 5.8 Hz, 1H), 4.62 (d, *J* = 5.8 Hz, 1H), 4.47 (s, 1H), 4.30 (d, *J* = 7.2 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 (CO), 143.6 (CH), 113.6 (C), 84.7 (CH), 81.0 (CH), 77.9 (CH), 75.4 (CH), 75.3 (CH), 26.9 (CH_3), 25.9 (3 x CH_3), 25.8 (CH_3), 18.2 (C), −4.1 (CH_3), −4.6 (CH_3);

IR (KBr) ν_{max} 2955, 2931, 2858, 1787, 1609, 1472, 1376, 1256, 1175, 1100, 942, 838 cm^{-1};

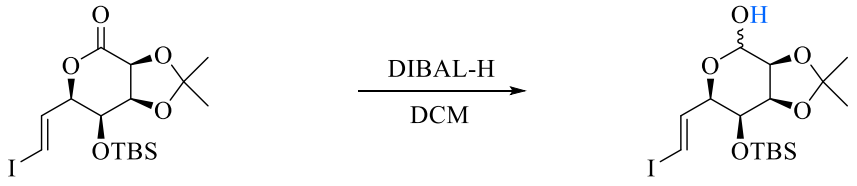
MS (ESI, +ve) *m/z* 493 [$(M+K)^+$, 15%], 477 [$(M+Na)^+$, 40], 472 [$(M-CO_2+Na+K)^+$, 100], 397 [$(M-(CH_3)_2CO+H)^+$, 40];

HRMS (ESI, +ve) Found: $(M+K)^+$ 493.0313, $C_{16}H_{27}{}^{127}I^{39}KO_5Si$ requires 567.0677. $(M+Na)^+$ 477.0572, $C_{16}H_{27}{}^{127}I^{23}NaO_5Si$ requires 477.0570;

Melting point 90–92 °C;

Specific rotation $[\alpha]^{25}_D$ = −71.9 (*c* 1.7, $CHCl_3$).

(3aS,6R,7S,7aR)-7-((tert-Butyldimethylsilyl)oxy)-6-((E)-2-iodovinyl)-2,2-dimethyltetra-hydro-4H-[1,3]dioxolo[4,5-c]pyran-4-ol (3.26)



3.25 **3.26**

A magnetically stirred solution of lactone **3.25** (60.mg, 0.13 mmol) in dichloromethane (5 mL) was cooled to −78 °C then treated dropwise with di-*iso*-butylaluminium hydride (0.14 mL of a 1.0 M solution in hexane, 0.14 mmol). After addition was complete, the reaction mixture was stirred at this temperature for 30 min then treated with tartaric acid (5 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 30 min. The separated aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were then washed with brine (1 x 10 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, 7.5:20:72.5 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *lactol* ***3.26*** (55 mg, 91%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*major isomer*) 6.69 (dd, *J* = 14.8 and 8.0 Hz, 1H), 6.43 (d, *J* = 14.8, 1H), 5.31 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 4.64 (br s, 1H), 4.51 (d, *J* = 5.9 Hz, 1H), 4.27 (d, *J* = 5.9 Hz, 1H), 4.23 (dd, *J* = 8.0 and 2.0 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); δ (*minor isomer*) 6.68 (dd, *J* = 14.6 and 7.5 Hz, 1H), 6.30 (d, *J* = 14.6, 1H), 5.47 (br s, 1H), 4.67 (partially obscured m, 1H), 4.54 (dd, *J* = 6.3 and 4.0 Hz, 1H), 4.15 (dd, *J* = 7.5 and 1.8 Hz, 1H), 4.07 (d, *J* = 1.8 Hz, 1H), 3.90 (br s, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*major isomer*) 145.5 (CH), 112.5 (C), 103.9 (CH), 89.9 (CH), 87.4 (CH), 82.1 (CH), 79.8 (CH), 76.9 (CH), 26.7 (CH_3), 25.9 (3 x CH_3), 25.3 (CH_3), 18.4 (C), −4.08 (CH_3), −4.7 (CH_3); δ (*minor isomer*) 145.3 (CH), 113.3 (C), 98.4 (CH), 84.1 (CH), 82.0 (CH), 79.3 (CH), 79.1 (CH), 77.4 (CH), 26.4 (CH_3), 26.0 (3 x CH_3), 24.9 (CH_3), 18.2 (C), −4.1 (CH_3), −4.73 (CH_3);

IR (KBr) ν_{max} 3415, 2934, 2859, 1608, 1471, 1382, 1258, 1160, 1074, 836 cm^{-1};

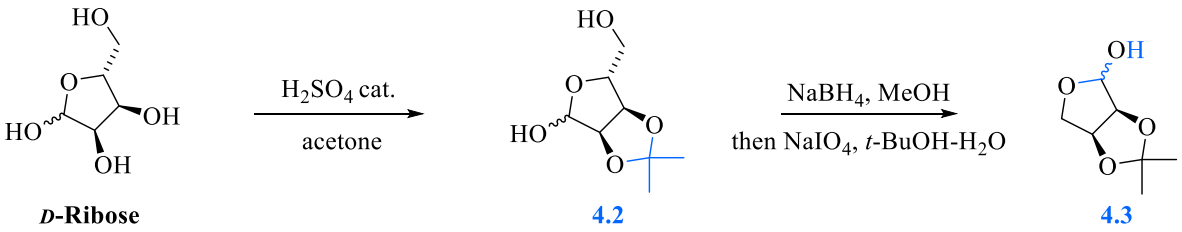
MS (ESI, +ve) *m/z* 520 [$(M+Na+CH_3CN)^+$, 100%], 479 [$(M+Na)^+$, 65], 495 [$(M+K)^+$, 20];

HRMS (ESI, +ve) Found: $(M+K)^+$ 495.0467, $C_{16}H_{29}{}^{127}I^{39}KO_5$ requires 495.0466. $(M+Na)^+$ 479.0727, $C_{16}H_{29}{}^{127}I^{23}NaO_5$ requires 479.2727;

Melting point 66–68 °C.

7.4 Experimental Procedures Related to Work Described in Chapter Four

(3a*S*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (4.3)



D-Ribose 4.2 4.3

A magnetically stirred solution of *D*-ribose (5.00 g, 33.30 mmol) in acetone (120 mL) was cooled to 0 °C and then treated dropwise with sulfuric acid (0.10 mL of a 98% aqueous solution). The resulting mixture was warmed to 18 °C and stirred at this temperature for 5 h (or until thin layer chromatographic analysis showed complete consumption of starting material). The reaction mixture was treated with sodium hydrogen carbonate (2.00 g) then filtered through a pad of Celite™. The filter cake was washed with acetone (100 mL) and the combined filtrates concentrated under reduced pressure. The residue thus obtained was dissolved in methanol (100 mL) and the resulting solution cooled to 0 °C then sodium borohydride (2.52 g, 66.61 mmol) was added in portions. The ensuing mixture was warmed to 18 °C and stirring continued for 16 h then the solvent was removed under reduced pressure. The residue thus obtained was dissolved in *tert*-butanol/water (100 mL of a 3:2 *v/v* mixture) then sodium periodide (28.49 g, 133.21 mmol) was added at 0 ºC. The resulting mixture was stirred at 18 °C for 16 h then diethyl ether (100 mL) was added and the pH adjusted to 7 by addition of sodium hydrogen carbonate (saturated aqueous solution). The solid was filtered off and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 → 50:50 *v/v* diethyl ether/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.3 in 40:60 *v/v* diethyl ether/hexane) afforded compound **4.3**[133b,c] (4.00 g, 75%) as a clear, colourless oil and as an inseparable (16:84) mixture of α/β isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-isomer*) 4.97 (d, *J* = 3.5 Hz, 1H), 4.74 (dd, *J* = 6.2 and 3.8 Hz, 1H), 4.47 (dd, *J* = 6.2 and 3.6 Hz, 1H), 3.95 (d, *J* = 11.1, 1H), 3.52 (dd, *J* = 11.0 and 3.7 Hz, 1H), 3.26 (br s, 1H), 1.52 (s, 3H), 1.35 (s, 3H); δ (*β-isomer*) 5.39 (s, 1H), 4.81 (dd, *J* = 5.8 and 3.6 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.04 (dd, *J* = 10.4 and 3.5 Hz, 1H), 3.99 (d, *J* = 10.4 Hz, 1H), 3.26 (br s, 1H), 1.44 (s, 3H), 1.29 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-isomer*) 113.6 (C), 97.6 (CH), 79.7 (CH), 78.4 (CH), 67.8 (CH_2), 26.1 (CH_3), 25.0 (CH_3); δ (*β-isomer*) 112.5 (C), 101.9 (CH), 85.3 (CH), 80.1 (CH), 72.0 (CH_2), 26.3 (CH_3), 24.9 (CH_3);

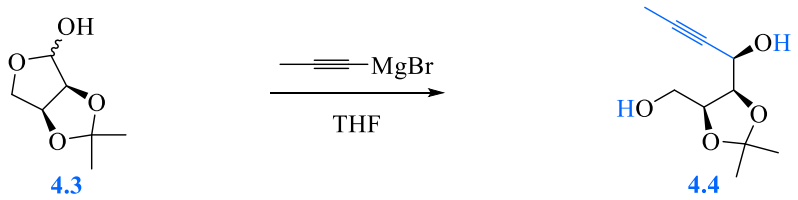
IR (KBr) ν_{max} 3433, 2945, 1458, 1383, 1330, 1210, 1160, 1075, 983, 907, 855 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 145 [$(M-CH_3\bullet)^+$, 75%], 85 (50), 59 (100);

HRMS (EI, +ve, 70 eV) Found: $(M-CH_3\bullet)^+$ 145.0502, $C_7H_{12}O_4$ requires 145.0501.

These data matched those reported previously.[133b,c]

(*R*)-1-((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (4.4)



4.3 **4.4**

A magnetically stirred solution of lactol **4.3** (2.93 g, 18.30 mmol) in tetrahydrofuran (50 mL) maintained at 0 °C under a nitrogen atmosphere was treated with 1-propynylmagnesium bromide (109.8 mL of an 0.5 M solution in tetrahydrofuran, 54.90 mmol). The ensuing mixture was allowed to stir at this temperature for 1 h then poured into ammonium chlodride (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 50:50 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **4.4*** (3.50 g, 95%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 4.40 (dq, *J* = 6.7 and 2.2 Hz, 1H), 4.30 (td, *J* = 6.5 and 4.8 Hz, 1H), 4.13 (dd, *J* = 6.7 and 6.5 Hz, 1H), 3.88 (ABX, J_{AB} = 11.7 Hz, J_{AX} = 4.8 Hz, 1H), 3.77 (ABX, J_{AB} = 11.7 Hz, J_{BX} = 6.5 Hz, 1H), 1.87 (d, *J* = 2.2 Hz, 3H), 1.48 (s, 3H), 1.38 (s, 3H) (signal due to hydroxyl group protons not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 110.6 (C), 83.2 (C), 81.6 (CH), 80.2 (CH), 80.1 (C), 63.0 (CH), 62.3 (CH_2), 28.7 (CH_3), 26.3 (CH_3), 4.1 (CH_3);

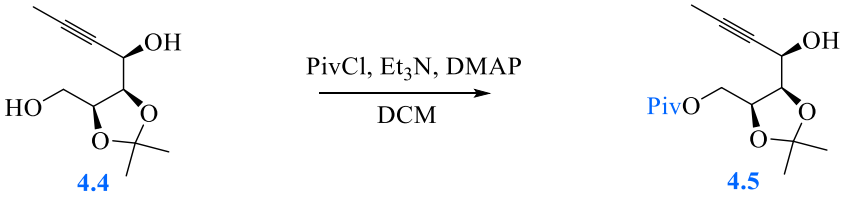
IR (KBr) ν_{max} 3384, 2985, 2936, 2234, 1453, 1382, 1218, 1166, 1077, 1043, 859 cm^{-1};

MS (ESI, +ve) *m/z* 239 [(M+K)$^+$, 100%], 223 [(M+Na)$^+$, 40];

HRMS (ESI, +ve) Found: (M+K)$^+$ 239.0686, $C_{10}H_{16}{}^{39}KO_4$ requires 239.0686. (M+Na)$^+$ 223.0946, $C_{10}H_{16}{}^{23}NaO_4$ requires 223.0946;

Specific rotation $[\alpha]^{25}_D$ = +20.6 (*c* 1.0, $CHCl_3$).

((4*S*,5*R*)-5-((*R*)-1-Hydroxybut-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivaloate (4.5)



A magnetically stirred solution of diol **4.4** (3.18 g, 15.88 mmol), triethylamine (5.5 mL, 39.70 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (194 mg, 1.58 mmol) in dichloromethane (100 mL) maintained at −78 °C under a nitrogen atmosphere was treated, over 30 min *via* syringe pump, with pivaloyl chloride (2.1 mL, 17.47 mmol). The ensuing mixture was stirred for a further 1 h then poured into water (100 mL). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **4.5*** (3.70 g, 83%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (ABX, J_{AB} = 11.5 Hz, J_{AX} = 4.6 Hz, 1H), 4.46 (m, 1H), 4.39 (td, *J* = 6.4 and 4.6 Hz, 1H), 4.29 (ABX, J_{AB} = 11.2 Hz, J_{BX} = 6.7 Hz, 1H), 4.19 (t, *J* = 5.8 Hz, 1H), 2.55 (s, OH), 1.86 (d, *J* = 1.2 Hz, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.21 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (CO), 109.4 (C), 83.3 (C), 79.3 (CH), 77.5 (C), 75.3 (CH), 62.9 (CH), 61.8 (CH_2), 38.9 (C), 27.6 (CH_3), 29.3 (3 x CH_3), 25.4 (CH_3), 3.9 (CH_3);

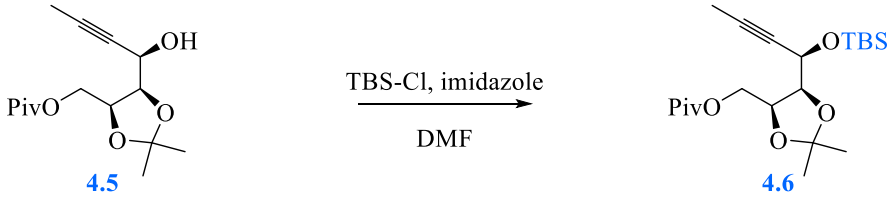
IR (KBr) ν_{max} 3462, 2980, 2938, 2237, 1733, 1481, 1382, 1284, 1218, 1150, 1081, 1035, 869 cm^{-1};

MS (ESI, +ve) *m/z* 323 [(M+K)$^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 323.1261, $C_{15}H_{24}{}^{39}KO_5$ requires 323.1261. $(M+Na)^+$ 307.1522, $C_{15}H_{24}{}^{23}NaO_5$ requires 307.1521. $(M+H)^+$ 285.1702, $C_{15}H_{25}O_5$ requires 285.1702;

Specific rotation $[\alpha]^{25}_D$ = +1.6 (*c* 0.6, $CHCl_3$).

((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivaloate (4.6)



A magnetically stirred solution of alcohol **4.5** (3.60 g, 12.66 mmol) in *N*,*N*-dimethylformamide (30 mL) maintained at 18 °C was treated, sequentially, with *tert*-butyldimethylsilyl chloride (2.86 g, 18.99 mmol) then imidazole (2.15 g, 31.65 mmol). The ensuing mixture was stirred for 2 h then diluted with diethyl ether (100 mL) and quenched with water (100 mL). The separated aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were washed with hydrochloric acid (1 x 100 mL of a 1.0 M aqueous solution), water (1 x 100 mL) and brine (1 x 100 mL) then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 7.5:92.5 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave *compound **4.6*** (4.20 g, 83%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (m, 2H), 4.33 (m, 1H), 4.19 (dd, *J* = 11.8 and 8.2 Hz, 1H), 4.11 (t, *J* = 6.3 Hz, 1H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.21 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (CO), 109.1 (C), 82.9 (C), 79.7 (CH), 78.2 (C), 75.9 (CH), 64.1 (CH), 62.5 (CH_2), 38.9 (C), 27.8 (CH_3), 27.4 (3 x CH_3), 26.0 (3 x CH_3), 25.6 (CH_3), 18.3 (C), 3.9 (CH_3), −4.0 (CH_3), −4.7 (CH_3);

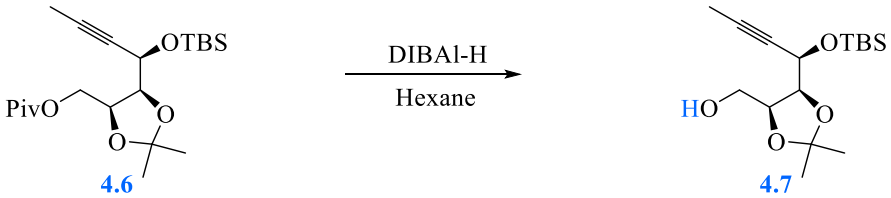
IR (KBr) ν_{max} 3524, 2959, 2932, 2859, 2298, 2230, 1732, 1481, 1381, 1283, 1253, 1155, 1083, 1033, 838 cm^{-1};

MS (ESI, +ve) *m/z* 437 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 437.2126, $C_{21}H_{38}{}^{39}KO_5Si$ requires 437.2126;

Specific rotation $[\alpha]^{25}_{D} = -35.8$ (*c* 1.2, $CHCl_3$).

((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (4.7)



A magnetically stirred solution of pivaloate **4.6** (2.00 g, 5.02 mmol) in dichloromethane (50 mL) was cooled to −78 °C then treated, dropwise, with di-*iso*-butylaluminium hydride (10.0 mL of a 1.0 M solution in hexane, 10.00 mmol). After addition was complete, the reaction mixture was stirred for 30 min then treated with tartaric acid (60 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 30 min. The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 20:80 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **4.7*** (1.55 g, 98%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 4.59 (m, 1H), 4.31 (ddd, *J* = 8.5, 6.5 and 3.2 Hz, 1H), 4.14 (dd, *J* = 6.5 and 5.5 Hz, 1H), 3.95 (ABX, J_{AB} = 11.8, J_{AX} = 3.2 Hz, 1H), 3.80 (ABX, J_{AB} = 11.8 Hz, J_{BX} = 8.0, 1H), 1.86 (d, *J* = 2.2 Hz, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 0.96 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 109.7 (C), 83.6 (C), 80.9 (CH), 79.9 (CH), 78.9 (C), 63.7 (CH_2), 62.5 (CH), 27.9 (CH_3), 26.3 (3 x CH_3), 25.5 (CH_3), 19.0 (C), 3.2 (CH_3), −4.1 (CH_3), −4.7 (CH_3);

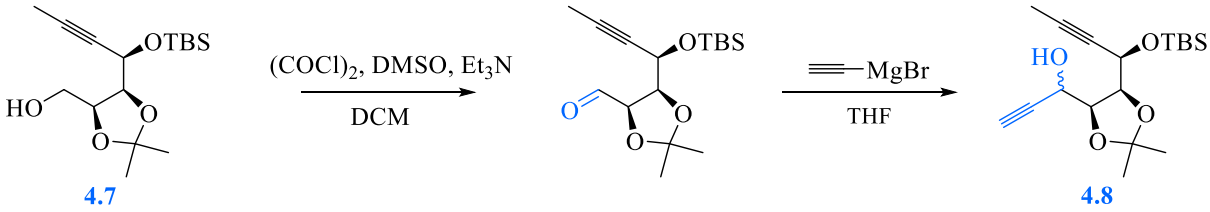
IR (KBr) ν_{max} 3497, 2931, 2858, 2231, 1472, 1380, 1252, 1148, 1075, 838 cm^{-1};

MS (ESI, +ve) *m/z* 353 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 353.1551, $C_{16}H_{30}{}^{39}KO_4Si$ requires 353.1550;

Specific rotation $[\alpha]^{25}_{D} = -28.6$ (*c* 0.8, $CHCl_3$).

1-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (4.8)



A magnetically stirred solution of oxalyl chloride (0.86 mL, 10.03 mmol) in dichloromethane (40 mL) was treated, at −78 °C, with dimethyl sulfoxide (1.8 mL, 25.08 mmol). The ensuing mixture was stirred for 10 min then treated with a solution of alcohol **4.7** (1.55 g, 4.93 mmol) in dichloromethane (10 mL). The resulting mixture was stirred −78 °C for another 1 h then treated with triethylamine (4.9 mL, 35.12 mmol) before being warmed to 0 °C and stirred for 1 h then quenched with water (100 mL). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried over magnesium sulfate, filtered, concentrated under reduced pressure to afford the anticipated *aldehyde* (1.30 g, 84%) as a clear, colorless oil. This material was immediately used without purification in the next step of the reaction sequence.

A magnetically stirred solution of the aldehyde (390 mg, 1.25 mmol), formed as described above, in tetrahydrofuran (10 mL) maintained at −15 °C under a nitrogen atmosphere was treated with ethynylmagnesium bromide (6.2 mL of an 0.5 M solution in tetrahydrofuran, 3.12 mmol). The ensuing mixture was stirred for a further 1 h then poured into ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were then washed with brine (1 x 10 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow residue was subjected to flash chromatography (silica, 15:85 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **4.8*** (392 mg, 93%) as a clear, colourless oil and as an inseparable (23:77) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 4.79 (m, 1H), 4.59 (dd, *J* = 7.9 and 2.2 Hz, 1H), 4.23 (d, *J* = 5.4, 1H), 4.17 (t, *J* = 5.4 Hz, 1H), 3.82 (s, OH), 2.48 (d, *J* = 2.2 Hz, 1H), 1.84 (d, *J* = 2.2 Hz, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); (*β-epimer*) 4.90 (m, 1H), 4.85 (m, 1H), 4.29 (dd, *J* = 6.8 and 1.8 Hz, 1H), 4.22 (dd, *J* = 6.9 and 5.5 Hz,

1H), 3.64 (s, OH), 2.45 (d, *J* = 2.3 Hz, 1H), 1.84 (d, *J* = 2.2 Hz, 3H), 1.57 (s, 3H), 1.40 (s, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H);

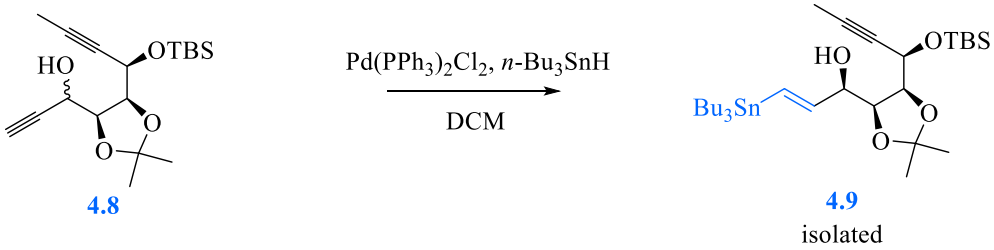
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*) 109.2 (C), 83.8 (C), 82.9 (C), 79.7 (CH), 79.6 (CH), 77.3 (C), 73.7 (CH), 62.5 (CH), 61.6 (CH), 27.9 (CH_3), 25.9 (3 x CH_3), 25.8 (CH_3), 18.4 (C), 3.9 (CH_3), −4.3 (CH_3), −4.6 (CH_3); (*β-epimer*) 109.6 (C), 83.7 (C), 83.1 (C), 79.8 (CH), 79.4 (CH), 77.1 (C), 72.8 (CH), 62.0 (CH), 61.2 (CH), 26.6 (CH_3), 25.9 (3 x CH_3), 25.3 (CH_3), 18.5 (C), 3.8 (CH_3), −4.3 (CH_3), −4.8 (CH_3);

IR (KBr) ν_{max} 3447, 3310, 2930, 2858, 2232, 2114, 1472, 1382, 1252, 1215, 1066, 838 cm^{-1};

MS (ESI, +ve) *m/z* 377 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 377.1550, $C_{18}H_{30}{}^{39}KO_4Si$ requires 377.1550.

(*R*,*E*)-1-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tributylstannyl)prop-2-en-1-ol (4.9)



A magnetically stirred solution of bis(triphenylphosphine)palladium(II) dichloride (10 mg, 0.014 mmol) and compound **4.8** (100 mg, 0.25 mmol) in dry dichloromethane (5 mL) maintained at 0 °C under an argon atmosphere was treated, dropwise over 2 min, with tri-*n*-butyltin hydride (95 mg, 0.35 mmol). The ensuing mixture was stirred for 10 min then warmed to 18 ºC and maintained at this temperature for a further 30 min. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica which was pre-deactivated with 1% triethylamine in hexane, 10:90 *v/v* diethylether/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded the *compound **4.9*** (80 mg, 43%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 19.1 Hz, 1H), 6.09 (dd, *J* = 19.1 and 5.1 Hz, 1H), 4.78 (m, 1H), 4.54 (m, 1H), 4.15 (m, 2H), 3.16 (d, *J* = 5.1 Hz, 1H), 1.83 (d, *J* = 2.2 Hz, 3H),

1.51 (s, 3H), 1.50–1.41 (complex m, 6H), 1.34 (s, 3H), 1.32–1.23 (complex m, 6H), 0.97–0.77 (complex m, 24H), 0.17 (s, 3H), 0.15 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2 (CH), 129.2 (CH), 108.6 (C), 83.2 (C), 80.3 (CH), 79.8 (CH), 78.6 (C), 72.4 (CH), 62.8 (CH), 29.3 (3 x CH_2), 27.5 (3 x CH_3), 26.9 (CH_3), 26.1 (3 x CH_3), 25.1 (CH_3), 18.5 (C), 13.9 (3 x CH_3), 9.7 (3 x CH_2), 3.9 (CH_3), −4.1 (CH_3), −4.6 (CH_3);

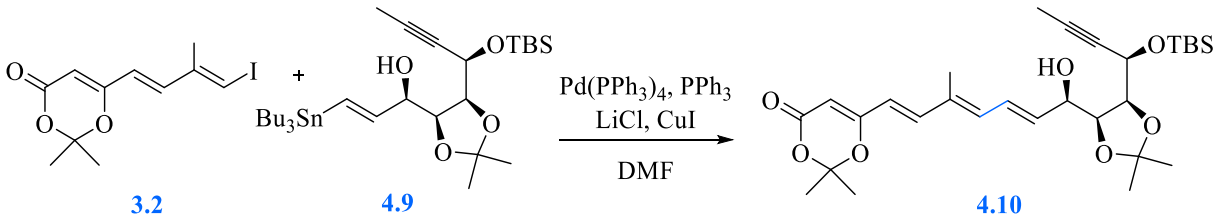
IR (KBr) ν_{max} 3482, 2956, 2928, 2856, 2232, 1463, 1378, 1250, 1213, 1147, 1071, 837 cm^{-1};

MS (ESI, +ve) *m/z* 669 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 669.2764, $C_{30}H_{58}{}^{39}KO_4Si^{120}Sn$ requires 669.2763. $[M+H]^+$ 631.3201, $C_{30}H_{59}O_4Si^{120}Sn$ requires 631.3205;

Specific rotation $[\alpha]^{25}_D = -22.4$ (*c* 1.3, $CHCl_3$).

6-((*R*,1*E*,3*E*,5*E*)-7-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-hydroxy-3-methylhepta-1,3,5-trien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4.10)



A two-neck round bottom flask equipped with a condenser and a rubber septum was charged with stannane **4.9** (45 mg, 0.07 mmol), alkenyl iodine **3.2** (23 mg, 0.07 mmol), tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.01 mmol), triphenylphosphine (5 mg, 0.01 mmol), lithium chloride (18 mg, 0.43 mmol) and copper iodide (68 mg, 0.36 mmol). The flask was evacuated at low pressure then filled with argon. The reaction mixture was dissolved in degassed *N*,*N*-dimethylformamide (2 mL) and the resulting solution heated to 40 ºC for 16 h. After cooling, potassium fluoride (5 mL of a 10% aqueous solution) was added and the reaction mixture stirred at 18 ºC for 30 min before being filtered and the filtrate extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl

acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound* ***4.10*** (20 mg, 52%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 15.5 Hz, 1H), 6.70 (ddd, *J* = 15.0, 11.4 and 1.2 Hz, 1H), 6.36 (d, *J* = 11.4 Hz, 1H), 6.02 (dd, *J* = 15.0 and 5.8 Hz, 1H), 5.95 (d, *J* = 15.5 Hz, 1H), 5.30 (s, 1H), 4.82 (m, 1H), 4.73 (m, 1H), 4.17 (m, 1H), 4.14 (m, 1H), 3.63 (br s, OH), 1.89 (s, 3H), 1.84 (d, *J* = 2.2 Hz, 3H), 1.71 (s, 6H), 1.52 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) 164.0 (C), 162.3 (C), 142.6 (CH), 138.4 (CH), 138.0 (CH), 133.8 (C), 126.9 (CH), 118.7 (CH), 109.0 (C), 106.4 (C), 94.3 (CH), 83.4 (C), 80.1 (CH), 79.5 (CH), 77.3 (C), 69.8 (CH), 62.3 (CH), 26.7 (CH_3), 26.0 (3 x CH_3), 25.3 (CH_3), 25.2 (2 x CH_3), 18.5 (C), 12.7 (CH_3), 3.9 (CH_3), −4.3 (CH_3), −4.8 (CH_3);

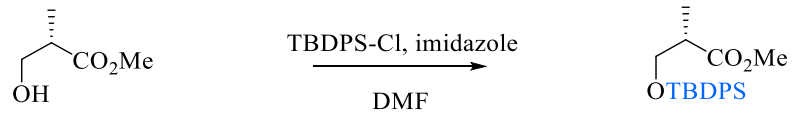
IR (KBr) ν_{max} 3450, 2930, 2858, 2237, 1723, 1613, 1383, 1273, 1250, 1208, 1147, 1068, 1024, 901, 838 cm^{-1};

MS (ESI, +ve) *m/z* 571 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 571.2497, $C_{29}H_{44}{}^{39}KO_7Si$ requires 571.2493. $(M+Na)^+$ 555.2757, $C_{29}H_{44}{}^{23}NaO_7Si$ requires 555.2754. $(M+H)^+$ 533.2937, $C_{29}H_{45}O_7Si$ requires 533.2935;

Specific rotation $[\alpha]^{25}_D$ = −39.9 (*c* 0.8, $CHCl_3$).

(*S*)-Methyl 3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanoate (4.17)



(*S*)-Roche ester **4.17**

A magnetically stirred solution of methyl (*S*)-3-hydroxy-2-methylpropionate (5.00 g, 42.32 mmol) in dry *N*,*N*-dimethylformamide (50 mL) maintained at 0 °C was treated, sequentially, with *tert*-butyldiphenylsilyl chloride (12.11 g, 46.56 mmol) then imidazole (3.17 g, 46.56 mmol). The resulting solution was warmed to 18 °C and stirred at this temperature for 16 h then diluted with diethyl ether (100 mL) and quenched by the addition of water (50 mL). The separated aqueous layer was extracted with diethyl ether (3 x 75 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.17**[136] (14.90 g, 99%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (complex m, 4H), 7.46–7.38 (complex m, 6H), 3.86 (ABX, J_{AB} = 9.7, J_{AX} = 6.9 Hz, 1H), 3.75 (ABX, J_{AB} = 9.7, J_{BX} = 5.8 Hz, 1H), 3.70 (s, 3H), 2.74 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.06 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (CO), 135.8 (4 x CH), 133.7 (C), 133.6 (C), 129.8 (2 x CH), 127.8 (4 x CH), 66.1 (CH_2), 51.7 (CH_3), 42.6 (CH), 26.9 (3 x CH_3), 19.4 (C), 13.7 (CH_3);

IR (KBr) ν_{max} 3071, 2933, 2858, 1741, 1472, 1428, 1199, 1112, 823, 702 cm^{-1};

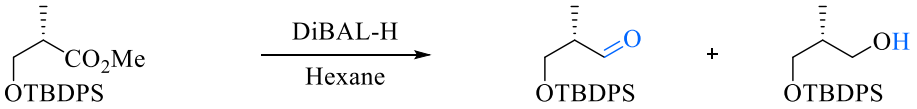
MS (ESI, +ve) *m/z* 379 [$(M+Na)^+$, 100%], 279 [$(M-C_6H_5)^+$, 55];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 379.1706, $C_{21}H_{28}{}^{23}NaO_3Si$ requires 379.1705. $(M+H)^+$ 357.1898, $C_{21}H_{29}O_3Si$ requires 357.1886;

Specific rotation $[\alpha]^{25}_D$ = +16.7 (*c* 1.8, $CHCl_3$).

These data matched those reported previously.[136]

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanal (4.18), and (*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (4.18b)



4.17 **4.18** **4.18b**

A magnetically stirred solution of ester **4.17** (1.00 g, 2.80 mmol) in dry hexane (20 mL) maintained at −78 °C under a nitrogen atmosphere was treated, dropwise, with di-*iso*-butylaluminium hydride (3.1 mL of 1.0 M solution in hexane, 3.10 mmol). The ensuing mixture was stirred at −78 °C for 1 h then quenched with tartaric acid (20 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for further 30 min. The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) then the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 to 20:80 *v/v* diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 5:95 *v/v* diethyl ether/hexane) afforded compound **4.18**[136](750 mg, 82%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, CHO), 7.68–7.66 (complex m, 4H), 7.48–7.39 (complex m, 6H), 3.90 (m, 2H), 2.60 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6 (CHO), 135.8 (4 x CH), 133.4 (2 x C), 130.0 (2 x CH), 128.0 (4 x CH), 64.3 (CH_2), 49.0 (CH), 27.0 (3 x CH_3), 19.4 (C), 10.5 (CH_3);

IR (KBr) ν_{max} 3071, 2932, 2858, 1737, 1472, 1428, 1112, 823, 702 cm^{-1};

MS (ESI, +ve) *m/z* 381 [$(M+CH_3OH+Na)^+$, 50%], 365 [$(M+K)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 349.1602, $C_{20}H_{26}{}^{23}NaO_3Si$ requires 349.1600;

Specific rotation $[\alpha]^{25}_D$ = +20.9 (*c* 1.1, $CHCl_3$).

Concentration of fraction B (R_f = 0.2 in 20:80 *v/v* diethyl ether/hexane) afforded compound **4.18b**[136] (100 mg, 11%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (complex m, 4H), 7.47–7.39 (complex m, 6H), 3.74 (ABX, J_{AB} = 10.0, J_{AX} = 4.5 Hz 1H), 3.68 (d, *J* = 6.0 Hz, 2H), 3.61 (ABX, J_{AB} = 10.0, J_{BX} = 7.7 Hz, 1H), 2.36 (s, 1H), 2.00 (m, 1H), 1.07 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (2 x CH), 135.7 (2 x CH), 133.4 (C), 133.3 (C), 130.0 (2 x CH), 128.0 (4 x CH), 68.9 (CH_2), 68.0 (CH_2), 37.5 (CH), 27.0 (3 x CH_3), 19.4 (C), 13.4 (CH_3);

IR (KBr) ν_{max} 3368, 3071, 2930, 2858, 1472, 1427, 1112, 823, 701 cm^{-1};

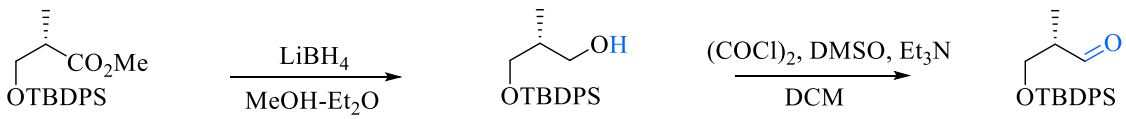
MS (ESI, +ve) *m/z* 351 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 351.1758, $C_{20}H_{28}{}^{23}NaO_2Si$ requires 351.1756. $(M+H)^+$ 329.1937, $C_{20}H_{29}O_2Si$ requires 329.1937;

Specific rotation $[\alpha]^{25}_D$ = +6.0 (*c* 1.3, $CHCl_3$).

These data matched those reported previously.[136]

Aldehyde **4.18** can also be prepared by the following procedure:



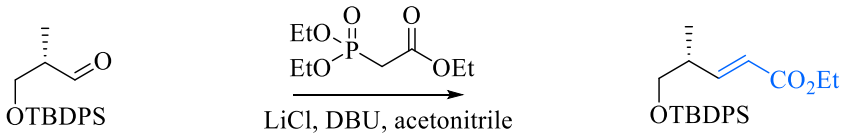
4.17 **4.18b** **4.18**

A magnetically stirred solution of ester **4.17** (1.00 g, 2.80 mmol) in dry diethyl ether (30 mL) containing dry methanol (0.17 mL, 4.21 mmol) maintained at 0 °C was carefully treated with lithium borohydride (92 mg, 4.21 mmol). After 15 min, the reaction mixture was warmed to 18 °C and stirred for 1 h before being cooled to 0 °C and slowly quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The alcohol **4.18b** was used without further purification in the next step of the reaction sequence.

A magnetically stirred solution of oxalyl chloride (325 µL, 6.04 mmol) in dichloromethane (25 mL) was treated, at −78 °C, with dimethyl sulfoxide (590 µL, 8.31 mmol). The ensuing mixture was stirred for 10 min then treated with a solution of alcohol **4.18b**, formed as described above, in dichloromethane (15 mL). The resulting mixture was stirred at −78 °C for another 1 h then treated with triethylamine (2.3 mL, 16.16 mmol) before being warmed to 0 °C, stirred for 1 h then quenched with water (30 mL). The separated aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash

chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded aldehyde **4.18** (890 mg, 97%) as a clear, colorless oil. This material was identical, in all respects, with that obtained by the first method.

(*R*,*E*)-Ethyl 5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-2-enoate (4.20)



4.18 **4.20**

A magnetically stirred solution of anhydrous lithium chloride (370 mg, 8.73 mmol) in dry acetonitrile (80 mL) was treated, at 18 °C, with triethyl phosphonoacetate (1.73 mL, 8.73 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.2 mL, 8.15 mmol). A mildly exothermic reaction followed and a clear solution obtained after *ca*.15 min. After 30 min, a solution of aldehyde **4.18** (1.90 g, 5.82 mmol) in acetonitrile (40 mL) was added and the reaction mixture was stirred for a further 16 h. The ensuing mixture was diluted with diethyl ether (50 mL) then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.20**[137] (1.95 g, 88%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (complex m, 4H), 7.45–7.37 (complex m, 6H), 6.97 (dd, *J* = 15.8 and 7.2 Hz 1H), 5.84 (d, *J* = 15.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.62–3.55 (complex m, 2H), 2.57 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (CO), 151.5 (CH), 135.8(1) (2 x CH), 135.8(0) (2 x CH), 133.7(8) (C), 133.7(4) (C), 129.9 (2 x CH), 127.9 (4 x CH), 121.3 (CH), 67.8 (CH_2), 60.4 (CH_2), 39.3 (CH), 27.0 (3 x CH_3), 19.4 (C), 15.8 (CH_3), 14.5 (CH_3);

IR (KBr) ν_{max} 3068, 2960, 2932, 2858, 1720, 1654, 1428, 1268, 1112, 823, 702 cm^{-1};

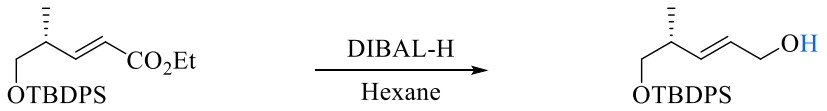
MS (ESI, +ve) *m/z* 419 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(2M+Na)^+$ 815.4146, $C_{48}H_{64}{}^{23}Na\ O_6Si_2$ requires 815.4139. $(M+Na)^+$ 419.2020, $C_{24}H_{32}{}^{23}Na\ O_3Si$ requires 419.2018;

Specific rotation $[\alpha]^{25}_D$ = +3.1 (*c* 1.1, $CHCl_3$).

These data matched those reported previously.[137]

(*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-2-en-1-ol (4.21)



4.20 **4.21**

A magnetically stirred solution of ester **4.20** (1.50 g, 3.92 mmol) in dry hexane (40 mL) maintained at −78 °C under a nitrogen atmosphere was treated with di-*iso*-butylaluminium hydride (8.6 mL of 1.0 M solution in hexane, 8.60 mmol). The ensuing mixture was stirred at −78 °C for 2 h then quenched with tartaric acid (40 mL of a 1.0 M aqueous solution). The resulting mixture was stirred for 1 h and the separated aqueous layer extracted with diethyl ether (2 x 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.21**[137] (1.37 g, 99%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (complex m, 4H), 7.45–7.36 (complex m, 6H), 5.69–5.59 (complex m, 2H), 4.07 (d, *J* = 4.9 Hz, 2H), 3.58 (ABX, J_{AB} = 9.8, J_{AX} = 6.3 Hz, 1H), 3.52 (ABX, J_{AB} = 9.8, J_{BX} = 6.6 Hz, 1H), 2.42 (m, 1H), 1.36 (br s, OH), 1.07 (s. 9H), 1.05 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (4 x CH), 135.7 (CH), 134.1 (2 x C), 129.8 (2 x CH), 128.9 (CH), 127.8 (4 x CH), 68.7 (CH_2), 64.1 (CH_2), 39.1 (CH), 27.1 (3 x CH_3), 19.5 (C), 16.6 (CH_3);

IR (KBr) ν_{max} 3336, 3071, 2959, 2931, 2858, 1427, 1111, 701 cm^{-1};

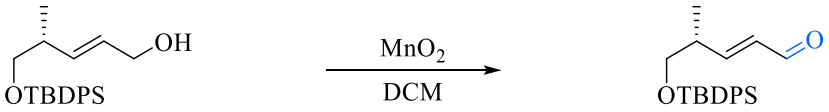
MS (ESI, +ve) *m/z* 377 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 393.1652, $C_{22}H_{30}{}^{39}KO_2Si$ requires 393.1652. $(M+Na)^+$ 377.1915, $C_{22}H_{30}{}^{23}NaO_2Si$ requires 377.1913. $(M+H)^+$ 355.2093, $C_{22}H_{31}O_2Si$ requires 3355.2093;

Specific rotation $[\alpha]^{25}_D$ = +3.2 (*c* 1.5, $CHCl_3$).

These data matched those reported previously.[137]

(*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-2-enal (4.14)



4.21 **4.14**

A magnetically stirred solution of alcohol **4.21** (1.37 g, 3.96 mmol) in dichloromethane (40 mL) was treated, in two portions, with manganese dioxide (6.37 g, 46.37 mmol). A slightly exothermic reaction was took place. The ensuing mixture was stirred for 3 h then filtered through a pad of Celite™ and the pad rinsed with dichloromethane (2 x 30 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.5) afforded aldehyde **4.14**[137] (1.20 g, 91%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.8 Hz, CHO), 7.66–7.64 (complex m, 4H), 7.46–7.37 (complex m, 6H), 6.83 (dd, *J* = 15.8 and 6.9 Hz, 1H), 6.14 (ddd, *J* = 15.8, 7.8 and 1.3 Hz, 1H), 3.69 (ABX, J_{AB} = 9.9, J_{AX} = 5.7 Hz, 1H), 3.63 (ABX, J_{AB} = 9.9, J_{BX} = 6.7 Hz, 1H), 2.69 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4 (CHO), 161.2 (CH), 135.7(9) (2 x CH), 135.7(7) (2 x CH), 133.5(8) (C), 133.5(5) (C), 132.6 (CH), 130.0 (2 x CH), 127.9 (4 x CH), 67.5 (CH_2), 39.8 (CH), 27.0 (3 x CH_3), 19.5 (C), 15.6 (CH_3);

IR (KBr) ν_{max} 3071, 2960, 2931, 2858, 1693, 1427, 1111, 702 cm^{-1};

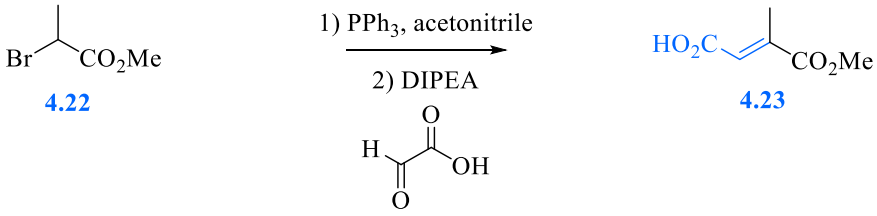
MS (ESI, +ve) *m/z* 375 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 375.1756, $C_{22}H_{28}{}^{23}NaO_2Si$ requires 375.1756;

Specific rotation $[\alpha]^{25}_D$ = +12.3 (*c* 1.9, $CHCl_3$).

These data matched those reported previously.[137]

(*E*)-4-Methoxy-3-methyl-4-oxobut-2-enoic Acid (4.23)



A magnetically stirred solution of 2-bromopropionate **4.22** (10.00 g, 59.88 mmol) in acetonitrile (120 mL) was treated with triphenylphosphine (15.70 g, 59.88 mmol). After stirring at 65 °C for 16 h, the reaction mixture was cooled to 0 °C then treated with a solution of di-*iso*-propylethylamine (9.39 mL, 53.89 mmol) and glyoxylic acid monohydrate (4.96 g, 53.89 mmol) in acetonitrile (40 mL). The solution thus formed was stirred for a further 2 h then warmed to 18 °C and stirred at this temperature for 16 h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL). The solution thus obtained was extracted with sodium hydrogen carbonate (3 x 50 mL of a saturated aqueous solution) and the combined aqueous phases were acidified to pH 1–2 with hydrochloric acid (cont.) then extracted with ethyl acetate (3 x 100 mL). The combined organic phases were concentrated under reduced pressure then filtered through a pad of TLC-grade silica gel that was washed with ethyl acetate. The combined filtrates were evaporated under reduced pressure to afford compound **4.23**[138] (6.40 g, 82%) as a white, crystalline solid (R_f = 0.1 in 50:50 *v/v* ethyl acetate/hexane).

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.73 (m, 1H), 3.79 (s, 3H), 2.24 (d, *J* = 1.6 Hz, 3H) (signal due to the acid proton not observed);

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 168.0 (CO), 167.0 (CO), 144.1 (C), 127.4 (CH), 52.8 (CH_3), 14.3 (CH_3).

These data matched those reported previously.[138] The following additional data were acquired on this compound.

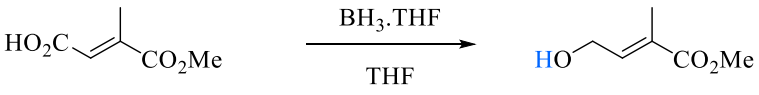
IR (KBr) ν_{max} 3006, 2960, 1723, 1699, 1645, 1436, 1241, 1121, 905 cm^{-1};

MS (ESI, −ve) *m/z* 99 [$(M-COOH-H)^-$, 100%], 143 [$(M-H)^-$, 50];

HRMS (ESI, −ve) Found: $(M-H)^-$ 143.0344, $C_6H_7O_4$ requires 143.0344;

Melting point 76–77 °C.

(*E*)-Methyl 4-Hydroxy-2-methylbut-2-enoate (4.24)



4.23 4.24

A magnetically stirred solution of acid **4.23** (6.17 g, 42.81 mmol) in dry tetrahydrofuran (90 mL) maintained at −15 °C was treated, dropwise, with borane-tetrahydrofuran complex (47.1 mL of 1.0 M solution in tetrahydrofuran, 47.10 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h then treated, dropwise, with water (50 mL) and potassium carbonate (10.00 g). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 60:40 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded compound **4.24**[138] (4.00 g, 72%) as a clear, colourless oil.

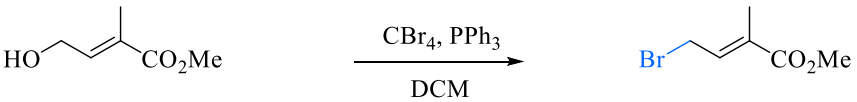
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (td, *J* = 6.0, 1.3 Hz, 1H), 4.33 (dd, *J* = 6.0 and 0.8 Hz, 2H), 3.73 (s, 3H), 2.21 (s, OH), 1.82 (d, *J* = 1.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (CO), 140.6 (CH), 128.5 (C), 59.8 (CH_2), 52.1 (CH_3), 12.9 (CH_3);

IR (KBr) ν_{max} 3420, 2954, 1716, 1653, 1645, 1438, 1266, 1131, 730 cm^{-1};

These data matched those reported previously.[138]

(*E*)-Methyl 4-Bromo-2-methylbut-2-enoate (4.25)



4.24 4.25

A magnetically stirred solution of alcohol **4.24** (3.10 g, 23.82 mmol) and carbon tetrabromide (9.48 g, 28.58 mmol) in dry dichloromethane (100 mL) maintained at 0 °C was

treated, in one portion, with triphenylphosphine (7.50 g, 28.58 mmol). The ensuing mixture was warmed to 18 °C and treated with methanol (0.3 mL). After a further 30 min, the solvent was removed by evaporation and the residue filtered through a pad of TLC-grade silica gel that was eluted with diethyl ether/pentane (100 mL of a 3:7 *v/v* mixture). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/pentane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.25**[138] (3.70 g, 80%) as a clear, colourless liquid.

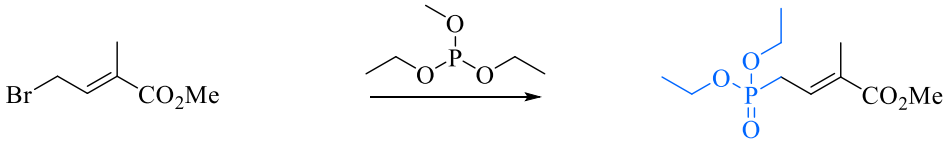
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H), 4.03 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 1.92 (d, *J* = 1.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (CO), 135.3 (CH), 132.1 (C), 52.1 (CH_3), 26.1 (CH_2), 12.4 (CH_3);

IR (KBr) ν_{max} 2952, 1718, 1647, 1436, 1268, 1194, 1104, 749 cm^{-1};

These data matched those reported previously.[138]

(*E*)-Methyl 4-(Diethoxyphosphoryl)-2-methylbut-2-enoate (4.15)



4.25 **4.15**

A magnetically stirred solution of bromide **4.25** (2.80 g, 14.50 mmol) and triethylphosphite (3.73 g, 21.76 mmol) was heated to 110 °C for 2 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 70:30 *v/v* ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.15**[139] (3.50 g, 96%) as a clear, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (m, 1H), 4.09–4.02 (complex m, 4H), 3.69 (s, 3H), 2.69 (dd, *J* = 23.4 and 8.2 Hz, 2H), 1.83 (d, *J* = 3.7 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 6H);

IR (KBr) ν_{max} 3469, 2985, 1716, 1651, 1438, 1254, 1166, 1050, 1026, 966 cm^{-1}.

These data matched those reported previously.[139] The following additional data were acquired on this compound.

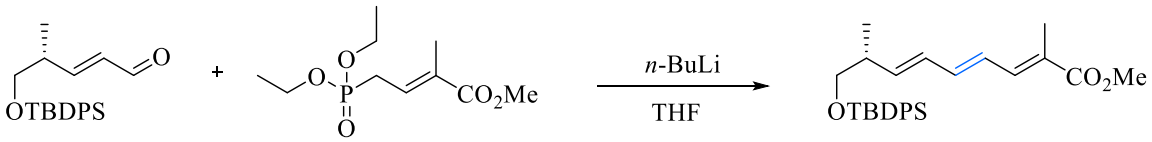
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (d, *J* = 3.4 Hz, CO), 131.7 (d, *J* = 13.8 Hz, C), 130.5 (d, *J* = 11.3 Hz, CH), 62.3(3) (CH_2), 62.3(2) (CH_2), 52.0 (CH_3), 27.7 (d, *J* = 140.0 Hz, CH_2–PO), 16.5(5) (CH_3), 16.5(0) (CH_3), 12.7 (d, *J* = 2.5 Hz, CH_3);

^{31}P NMR (162 MHz, $CDCl_3$) δ 25.4 (PO);

MS (ESI, +ve) *m/z* 273 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 273.0868, $C_{10}H_{19}{}^{23}NaO_5P$ requires 273.0868. $(M+H)^+$ 251.1048, $C_{10}H_{20}O_5P$ requires 251.1048.

(*R*,2*E*,4*E*,6*E*)-Methyl 9-((*tert*-Butyldiphenylsilyl)oxy)-2,8-dimethylnona-2,4,6-trienoate (4.13)



4.14 **4.15** **4.13**

A magnetically stirred solution of phosphonate **4.15** (1.76 g, 7.06 mmol) in dry tetrahydrofuran (30 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *n*-butyllithium (4.5 mL of 1.5 M solution in tetrahydrofuran, 6.70 mmol). The ensuing mixture was stirred at 0 °C for 10 min then cooled to –78 °C and treated with a solution of aldehyde **4.14** (1.24 g, 3.53 mmol) in tetrahydrofuran (30 mL). The resulting mixture was stirred at −78 °C for 30 min then warmed to 18 °C and stirred for a further 3.5 h. The reaction was quenched with ammonium chloride (50 mL of a saturated aqueous solution) and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried over magnesium sulfate, then filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 4:96 *v/v* diethylether/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) afforded *compound **4.13*** (1.27 g, 80%) as a clear, colourless oil and as an inseparable (94:6) mixture of *E*/*Z* isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*E-isomer*) 7.68–7.65 (complex m, 4H), 7.45–7.36 (complex m, 6H), 7.22 (dd, *J* = 11.0 and 1.4 Hz, 1H), 6.50 (dd, *J* = 14.8 and 10.2 Hz, 1H), 6.40 (dd, *J* =

14.8 and 11.0 Hz, 1H), 6.21 (dd, *J* = 15.3 and 10.2 Hz, 1H), 5.85 (dd, *J* = 15.3 and 7.4 Hz, 1H), 3.77 (s, 3H), 3.61–3.53 (complex m, 2H), 2.51 (m, 1H), 1.96 (s, 3H), 1.08 (d, *J* = 5.6 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*E-isomer*) 169.1 (CO), 141.8 (CH), 140.1 (CH), 138.8 (CH), 135.8(4) (2 x CH), 135.8(2) (2 x CH), 134.0 (C), 133.9(8) (C), 130.1 (CH), 129.8 (2 x CH), 127.8 (4 x CH), 126.3 (CH), 126.2 (C), 68.5 (CH_2), 52.0 (CH_3), 39.8 (CH), 27.1 (3 x CH_3), 19.5 (C), 16.5 (CH_3), 12.9 (CH_3);

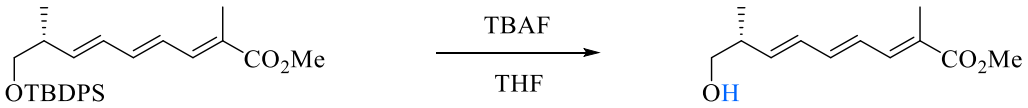
IR (KBr) ν_{max} 2955, 2858, 1707, 1614, 1428, 1235, 1111, 701 cm^{-1};

MS (ESI, +ve) *m/z* 471 [$(M+Na)^+$, 100%], 449 [$(M+H)^+$, 20];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 471.2331, $C_{28}H_{36}{}^{23}NaO_3Si$ requires 471.2331. $(M+H)^+$ 449.2525, $C_{28}H_{37}O_3Si$ requires 449.2513;

Specific rotation $[\alpha]^{25}_D$ = +2.6 (*c* 0.9, $CHCl_3$).

(*R*,2*E*,4*E*,6*E*)-Methyl 9-Hydroxy-2,8-dimethylnona-2,4,6-trienoate (4.26)



4.13 **4.26**

A magnetically stirred solution of silyl ether **4.13** (1.02 g, 2.27 mmol) in tetrahydrofuran (25 mL) was treated with tetra-*n*-butylammonium fluoride (4.6 mL of a 1.0 M solution in tetrahydrofuran, 4.60 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (25 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *alcohol **4.26*** (400 mg, 84%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 10.6 and 1.5 Hz, 1H), 6.50 (dd, *J* = 14.7 and 9.6 Hz, 1H), 6.44 (dd, *J* = 14.7 and 10.6 Hz, 1H), 6.28 (dd, *J* = 15.3 and 9.6 Hz, 1H), 5.79 (dd, *J* = 15.3 and 7.7 Hz, 1H), 3.75 (s, 3H), 3.56 (ABX, J_{AB} = 10.5, J_{AX} = 5.7 Hz, 1H), 3.49 (ABX, J_{AB} = 10.5, J_{AX} = 7.3 Hz, 1H), 2.47 (m, 1H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.64 (s, OH), 1.05 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (CO), 140.7 (CH), 139.4 (CH), 138.5 (CH), 131.0 (CH), 126.8 (CH), 126.6 (C), 67.3 (CH_2), 51.9 (CH_3), 40.0 (CH), 16.3 (CH_3), 12.8 (CH_3);

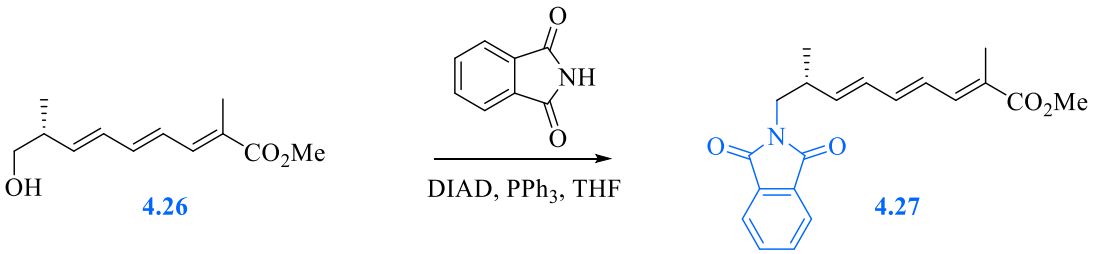
IR (KBr) ν_{max} 3419, 2953, 2873, 1705, 1613, 1436, 1253, 1109, 992 cm^{-1};

MS (ESI, +ve) *m/z* 265.4 [$(M+CH_3OH+Na)^+$, 50%], 233 [$(M+Na)^+$, 70], 186 (100);

HRMS (ESI, +ve) Found: $(M+Na)^+$ 233.1155, $C_{12}H_{18}{}^{23}NaO_3$ requires 233.1154;

Specific rotation $[\alpha]^{25}_D$ = +17.8 (*c* 0.9, $CHCl_3$).

(*R*,2*E*,4*E*,6*E*)-Methyl 9-(1,3-Dioxoisoindolin-2-yl)-2,8-dimethylnona-2,4,6-trienoate (4.27)



A magnetically stirred solution of alcohol **4.26** (100 mg, 0.47 mmol) and phthalimide (140 mg, 0.95 mmol) in tetrahydrofuran (2 mL) maintained at 0 °C was treated, sequentially, with triphenylphosphine (187 mg, 0.71 mmol) then di-*iso*-propyl azodicarboxylate (0.17 mL, 0.86 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h, then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:30:65 *v/v/v* diethyl ether/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *phtalimide* ***4.27*** (140 mg, 87%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.4 and 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4 and 3.1 Hz, 2H), 7.13 (d, *J* = 11.4 Hz, 1H), 6.42 (dd, *J* = 14.8 and 10.5 Hz, 1H), 6.30 (dd, *J* = 14.8 and 11.4 Hz, 1H), 6.13 (dd, *J* = 15.1 and 10.5 Hz, 1H), 5.76 (dd, *J* = 15.1 and 8.4 Hz, 1H), 3.73 (s, 3H), 3.65 (ABX, J_{AB} = 13.6, J_{AX} = 8.4 Hz, 1H), 3.60 (ABX, J_{AB} = 13.6, J_{BX} = 7.0 Hz, 1H), 2.81 (hept, *J* = 7.0 Hz, 1H), 1.88 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (CO), 168.5 (2 x CO), 140.3 (CH), 139.2 (CH), 138.4 (CH), 134.1 (2 x CH), 132.1 (2 x C), 130.9 (CH), 126.8 (CH), 126.6 (C), 123.4 (2 x CH), 51.9 (CH_3), 43.5 (CH_2), 37.1 (CH), 18.1 (CH_3), 12.8 (CH_3);

IR (KBr) ν_{max} 3468, 2952, 1773, 1713, 1614, 1434, 1396, 1352, 1282, 1244, 1101, 1046, 993, 917 cm^{-1};

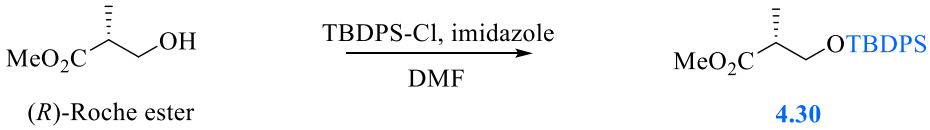
MS (ESI, +ve) *m/z* 394 [$(M+CH_3OH+Na)^+$, 95%], 362 [$(M+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 362.1369, $C_{20}H_{21}N^{23}NaO_4$ requires 362.1368;

Melting point 84–85 °C;

Specific rotation $[\alpha]^{25}_D$ = +87.9 (*c* 1.2, $CHCl_3$).

(*R*)-Methyl 3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanoate (4.30)



(*R*)-Roche ester **4.30**

A magnetically stirred solution of methyl (*R*)-3-hydroxy-2-methylpropionate (1.00 g, 8.46 mmol) in dry *N*,*N*-dimethylformamide (10 mL) maintained at 0 °C was treated, sequentially, with *tert*-butyldiphenylsilyl chloride (2.42 g, 9.31 mmol) then imidazole (634 mg, 9.31 mmol). The resulting solution was warmed to 18 °C and stirred at this temperature for 16 h then diluted with diethyl ether (20 mL) before being quenched by addition of water (30 mL). The separated aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic phases were washed with brine (1 x 30 mL), then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded compound **4.30**[141] (2.90 g, 96%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (complex m, 4H), 7.45–7.39 (complex m, 6H), 3.87 (ABX, J_{AB} = 9.7, J_{AX} = 6.9 Hz, 1H), 3.76 (ABX, J_{AB} = 9.7, J_{BX} = 5.8 Hz, 1H), 3.71 (s, 3H), 2.75 (hept, *J* = 7.0 Hz, 1H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (CO), 135.8 (4 x CH), 133.7 (C), 133.6 (C), 129.8 (2 x CH), 127.8 (4 x CH), 66.1 (CH_2), 51.7 (CH_3), 42.6 (CH), 26.9 (3 x CH_3), 19.4 (C), 13.7 (CH_3);

IR (KBr) ν_{max} 3071, 2932, 2858, 1741, 1472, 1428, 1199, 1112, 823, 702 cm^{-1};

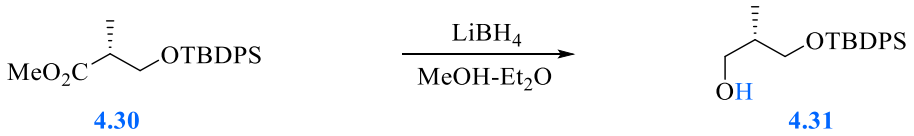
MS (ESI, +ve) *m/z* 379 [$(M+Na)^+$, 100%], 279 [$(M-C_6H_5)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 379.1707, $C_{21}H_{28}{}^{23}NaO_3Si$ requires 379.1705. $(M+H)^+$ 357.1887, $C_{21}H_{29}O_3Si$ requires 357.1886,

Specific rotation $[\alpha]^{25}_D = -16.7$ (*c* 1.5, $CHCl_3$).

These data matched those reported previously.[141]

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (4.31)



4.30 **4.31**

A magnetically stirred solution of methyl ester **4.30** (1.30 g, 3.64 mmol) in dry diethyl ether (30 mL) containing dry methanol (0.22 mL, 5.47 mmol) maintained at 0 °C was carefully treated with lithium borohydride (120 mg, 5.47 mmol). After 15 min, the reaction mixture was warmed to 18 °C and stirred for 2 h before being cooled to 0 °C then slowly quenched with ammonium chloride (30 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (1 x 30 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded alcohol **4.31**[141] (1.19 g, 99%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (complex m, 4H), 7.47–7.38 (complex m, 6H), 3.74 (ABX, J_{AB} = 10.1, J_{AX} = 4.5 Hz, 1H), 3.68 (complex m, 2H), 3.61 (ABX, J_{AB} = 10.1, J_{BX} = 7.7 Hz, 1H), 2.48 (s, OH), 2.01 (m, 1H), 1.07 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7(2) (2 x CH), 135.7(0) (2 x CH), 133.3(0) (C), 133.2(8) (C), 129.9 (2 x CH), 127.9 (4 x CH), 68.8 (CH_2), 67.8 (CH_2), 37.5 (CH), 26.9 (3 x CH_3), 19.3 (C), 13.3 (CH_3);

IR (KBr) ν_{max} 3351, 3071, 2958, 2930, 2858, 1589, 1472, 1427, 1390, 1361, 1112, 1039, 823, 740, 701 cm^{-1};

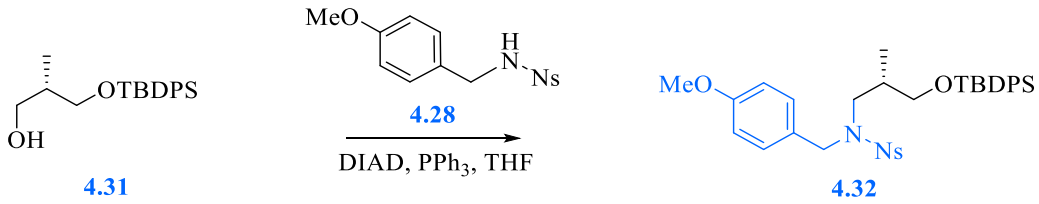
MS (ESI, +ve) *m/z* 392 $[(M+CH_3CN+Na)^+$, 30%], 351 $[(M+Na)^+$, 100],

HRMS (ESI, +ve) Found: $(M+Na)^+$ 351.1758, $C_{20}H_{28}{}^{23}NaO_2Si$ requires 351.1756. $(M+H)^+$ 329.1935, $C_{20}H_{29}O_2Si$ requires 329.1937;

Specific rotation $[\alpha]^{25}_{D}$ = +5.3 (*c* 1.9, $CHCl_3$).

These data matched those reported previously.[141]

(*S*)-*N*-(3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropyl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (4.32)



A magnetically stirred solution of alcohol **4.31** (1.05 g, 3.19 mmol) and *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** (1.55 g, 4.79 mmol) in tetrahydrofuran (50 mL) maintained at 0 °C was treated, sequentially, with triphenylphosphine (1.09 g, 4.15 mmol) then di-*iso*-propyl azodicarboxylate (0.84 mL, 4.15 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h, before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:30:67 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **4.32*** (1.95 g, 96%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8 and 1.2 Hz, 1H), 7.65–7.49 (complex m, 7H), 7.47–7.33 (complex m, 6H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.43 (ABq, $\Delta\delta_{AB}$= 0.07, J_{AB} =15.5 Hz, 2H), 3.77 (s, 3H), 3.37 (ABX, J_{AB} = 10.1, J_{AX} = 5.9 Hz, 1H), 3.31 (ABX, J_{AB} = 14.5, J_{AX} = 5.6 Hz, 1H), 3.27 (ABX, J_{AB} = 10.1, J_{BX} = 6.1 Hz, 1H), 3.17 (ABX, J_{AB} = 14.5, J_{BX} = 9.0 Hz, 1H), 1.91 (m, 1H), 0.99 (s, 9H), 0.74 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 147.9 (C), 135.6(9) (2 x CH), 135.6(7) (2 x CH), 134.1 (C), 133.5(8) (C), 133.5(6) (C), 133.3 (CH), 131.6 (CH), 131.2 (CH), 129.8(0) (3 x CH), 129.7(8) (CH), 127.7(9) (2 x CH), 127.7(7) (2 x CH), 127.5 (C), 124.3 (CH), 114.1 (2 x CH), 66.7 (CH_2), 55.4 (CH_3), 50.7 (CH_2), 50.2 (CH_2), 33.9 (CH), 26.9 (3 x CH_3), 19.3 (C), 14.5 (CH_3);

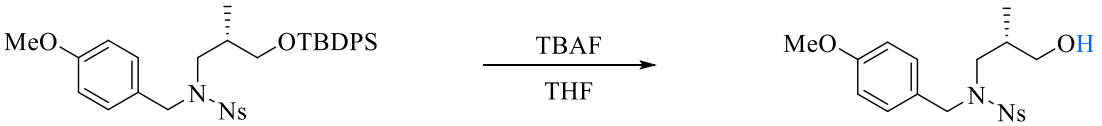
IR (KBr) ν_{max} 2931, 2857, 1588, 1544, 1513, 1462, 1427, 1370, 1251, 1159, 1112, 1034, 703 cm^{-1};

MS (ESI, +ve) *m/z* 671 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 671.2017, $C_{34}H_{40}{}^{39}KN_2O_6SSi$ requires 671.2013;

Specific rotation $[\alpha]^{25}_D$ = +18.9 (*c* 0.9, $CHCl_3$).

(*S*)-*N*-(3-Hydroxy-2-methylpropyl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (4.33)



4.32 **4.33**

A magnetically stirred solution of silyl ether **4.32** (1.95 g, 3.08 mmol) in tetrahydrofuran (50 mL) was treated with tetra-*n*-butylammonium fluoride (4.6 mL of 1.0 M solution in tetrahydrofuran, 4.62 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (50 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:30:30 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *alcohol **4.33*** (1.10 g, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8 and 1.2 Hz, 1H), 7.73–7.62 (complex m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.46 (ABq, $\Delta\delta_{AB}$= 0.14, J_{AB} =15.2 Hz, 2H), 3.79 (s, 3H), 3.58 (ABX, J_{AB} = 11.4, J_{AX} = 4.1 Hz, 1H), 3.44 (ABX, J_{AB} = 14.7, J_{AX} = 9.1 Hz, 1H), 3.37 (ABX, J_{AB} = 11.4, J_{AX} = 4.2 Hz, 1H), 3.01 (ABX, J_{AB} = 14.7, J_{AX} = 6.2 Hz, 1H), 1.93 (s, OH), 1.89–1.66 (complex m, 1H), 0.82 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C), 148.0 (C), 133.6 (CH), 133.5 (C), 131.8 (CH), 130.8 (CH), 129.9 (2 x CH), 127.4 (C), 124.4 (CH), 114.2 (2 x CH), 63.9 (CH_2), 55.4 (CH_3), 51.8 (CH_2), 50.7 (CH_2), 33.8 (CH), 14.5 (CH_3);

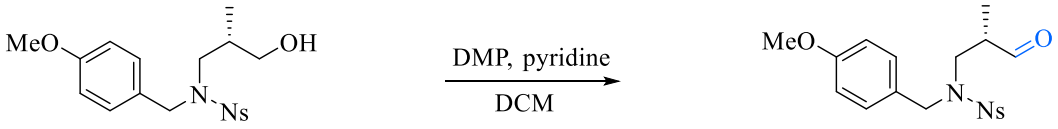
IR (KBr) ν_{max} 3557, 2933, 1612, 1544, 1513, 1463, 1371, 1248, 1162, 1032, 911, 778 cm^{-1};

MS (ESI, +ve) *m/z* 417 [$(M+Na)^+$, 100%], 395 [$(M+H)^+$, 25];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 417.1103, $C_{18}H_{22}N_2{}^{23}NaO_6S$ requires 417.1096;

Specific rotation $[\alpha]^{25}_D$ = −7.1 (*c* 1.4, $CHCl_3$).

(*S*)-*N*-(4-Methoxybenzyl)-*N*-(2-methyl-3-oxopropyl)-2-nitrobenzenesulfonamide (4.34)



4.33 **4.34**

A magnetically stirred solution of alcohol **4.33** (1.50 g, 3.80 mmol) in dichloromethane (50 mL) maintained at 0 ºC was treated with the Dess-Martin periodinane (2.26 g, 5.32 mmol) and pyridine (1.4 mL, 17.11 mmol). The ensuing mixture was warmed to 18 ºC and stirred for 3 h then quenched by addition of a mixture of sodium thiosulfate (25 mL of a 10% aqueous solution) and sodium hydrogen carbonate (25 mL of a saturated aqueous solution). The resulting slurry was filtered through Celite^{TM} and the separated aqueous layer associated with the filtrate was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:25:55 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *aldehyde **4.34*** (1.25 g, 84%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 1.7 Hz, CHO), 7.96 (m, 1H), 7.73–7.63 (complex m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.44 (s, 2H), 3.78 (s, 3H), 3.61 (ABX, J_{AB} = 15.0, J_{AX} = 7.3 Hz, 1H), 3.29 (ABX, J_{AB} = 15.0, J_{AX} = 6.9 Hz, 1H), 2.54 (m, 1H), 0.96 (d, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (CO), 159.6 (C), 148.1 (C), 133.8 (CH), 133.5 (C), 131.8 (CH), 130.8 (CH), 129.9 (2 x CH), 127.4 (C), 124.4 (CH), 114.2 (2 x CH), 55.4 (CH_3), 52.0 (CH_2), 47.9 (CH_2), 45.4 (CH), 12.0 (CH_3);

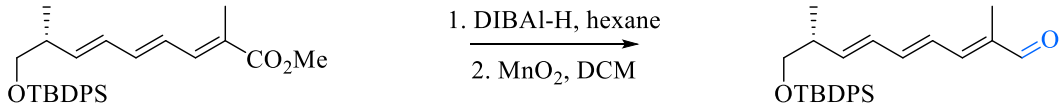
IR (KBr) ν_{max} 3096, 2936, 2838, 1724, 1612, 1544, 1513, 1458, 1372, 1250, 1164, 1031, 851, 777 cm^{-1};

MS (ESI, +ve) *m/z* 447 [$(M+CH_3OH+Na)^+$, 100%], 393 [$(M+H)^+$, 20];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 415.0941, $C_{18}H_{20}N_2{}^{23}NaO_6S$ requires 415.0940. $(M+H)^+$ 393.1121, $C_{18}H_{21}N_2O_6S$ requires 393.1120;

Specific rotation $[\alpha]^{25}_D$ = +1.5 (*c* 1.6, $CHCl_3$).

(*R*,2*E*,4*E*,6*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-2,8-dimethylnona-2,4,6-trienal (4.36)



4.13 4.36

A magnetically stirred solution of ester **4.13** (659 mg, 1.47mmol) in dry hexane (20 mL) maintained at −78 °C was treated with di-*iso*-butylaluminium hydride (3.3 mL of 1.0 M solution in hexane, 3.30 mmol). The ensuing reaction mixture was stirred for 2 h then quenched with tartaric acid (20 mL of a 1 M aqueous solution) and stirring was continued for a further 1 h. The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in dichloromethane (20 mL) and the solution thus formed was treated, in three portions, with manganese dioxide (2.94 g, 21.39 mmol). A slightly exothermic reaction occured. The ensuing mixture was stirred for 3 h then filtered through a pad of Celite^{TM} that was rinsed with dichloromethane (3 x 20 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane). Concentration of the appropriate fractions (R_f = 0.2) afforded *compound **4.36*** (500 mg, 81%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.68–7.66 (complex m, 4H), 7.52–7.31 (complex m, 6H), 6.87 (dd, *J* = 10.8, 1.1 Hz, 1H), 6.62 (partially obscured d, *J* = 14.8 and 9.9 Hz, 1H), 6.57 (partially obscured d, *J* = 14.8 and 10.8 Hz, 1H), 6.25 (dd, *J* = 15.3 and 9.9 Hz, 1H), 5.97 (dd, *J* = 15.3 and 7.4 Hz, 1H), 3.59 (d, *J* = 6.2 Hz, 2H), 2.54 (m, 1H), 1.87 (s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (CO), 149.0 (CH), 143.8 (CH), 142.0 (CH), 137.1 (C), 135.7(4) (2 x CH), 135.7(3) (2 x CH), 133.8(6) (C), 133.8(4) (C), 129.9 (CH), 129.8 (2 x CH), 127.8 (4 x CH), 125.8 (CH), 68.3 (CH_2), 39.9 (CH), 27.0 (3 x CH_3), 19.4 (C), 16.3 (CH_3), 9.6 (CH_3);

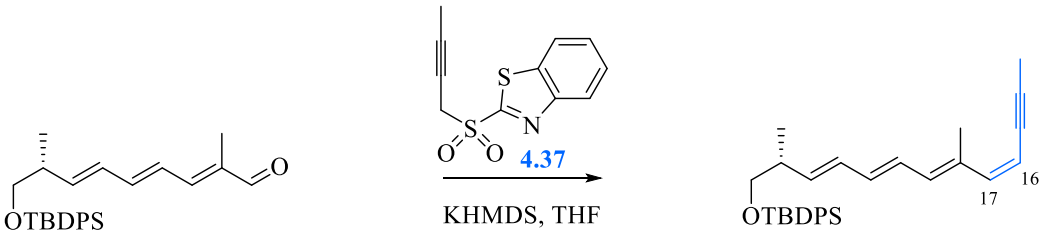
IR (KBr) ν_{max} 2930, 2857, 1679, 1611, 1427, 1190, 1112, 998, 702 cm^{-1};

MS (ESI, +ve) *m/z* 457 [$(M+K)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 457.1967, $C_{27}H_{34}{}^{39}KO_2Si$ requires 457.1965;

Specific rotation $[\alpha]^{25}_D$ = +3.5 (*c* 1.4, $CHCl_3$).

***tert*-Butyl(((*R*,3*E*,5*E*,7*E*,9*Z*)-2,8-dimethyltrideca-3,5,7,9-tetraen-11-yn-1-yl)oxy)diphenylsilane (4.38)**



A magnetically stirred solution of sulfone **4.37** (360 mg, 1.43 mmol) in tetrahydrofuran (10 mL) maintained at −55 °C was treated, dropwise, with potassium bis(trimethylsilyl)amide (2.87 mL of an 0.5 M solution in toluene, 1.43 mmol). The resulting dark-red solution was stirred at this temperature for 30 min then slowly treated with a solution of aldehyde **4.36** (200 mg, 0.47 mmol) in tetrahydrofuran (5 mL). The ensuing mixture was stirred at −55 °C for a further 16 h then warmed to 18 ºC for 1 h before being diluted with diethyl ether (15 mL) and washed with water (20 mL). The separated aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic phases were washed with brine (1 x 20 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:98 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded *compound **4.38*** (95 mg, 44%) as a clear, yellow oil and as an inseparable (85:15) mixture of 16*Z*/16*E* isomers containing starting material (40 mg, 20% recovery).

^{1}H NMR (400 MHz, $CDCl_3$) δ (*Z-isomer*) 7.69–7.67 (complex m, 4H), 7.49–7.33 (complex m, 6H), 6.52–6.40 (complex m, 1H), 6.33–6.09 (complex m, 4H), 5.72 (dd, *J* = 14.5 and 7.4 Hz, 1H), 5.39 (dq, *J* = 11.8 and 2.8 Hz, 1H), 3.60 (ABX, J_{AB} = 9.7, J_{AX} = 6.2 Hz, 1H), 3.54 (ABX, J_{AB} = 9.7, J_{BX} = 6.6 Hz, 1H), 2.50 (m, 1H), 2.23 (s, 3H), 2.02 (d, *J* = 2.8 Hz, 3H), 1.08(2) (d, *J* = 6.7, 3H), 1.08(1) (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*Z-isomer*) 142.1 (CH), 138.3 (CH), 135.9 (C), 135.7(8) (2 x CH), 135.7(7) (2 x CH), 134.8 (CH), 134.0(3) (C), 134.0(1) (C), 133.7 (CH), 130.6 (CH), 129.7 (2 x CH), 127.7 (4 x CH), 127.4 (CH), 106.4 (CH), 93.0 (C), 79.4 (C), 68.6 (CH), 39.7 (CH), 27.0 (3 x CH_3), 19.5 (C), 16.6 (CH_3), 15.1 (CH_3), 4.9 (CH_3);

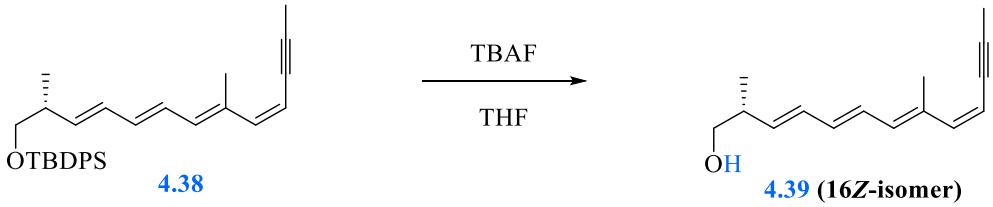
IR (KBr) ν_{max} 3025, 2958, 2857, 1958, 1471, 1427, 1112, 1082, 986, 701 cm^{-1};

MS (ESI, +ve) *m/z* 493 $[(M+K)^+$, 100%], 477 $[(M+Na)^+$, 20];

HRMS (ESI, +ve) Found: $(M+K)^+$ 493.2336, $C_{31}H_{38}{}^{39}KOSi$ requires 493.2329;

Specific rotation $[\alpha]^{25}_D = -2.0$ (*c* 1.0, $CHCl_3$).

(*R*,3*E*,5*E*,7*E*,9*Z*)-2,8-Dimethyltrideca-3,5,7,9-tetraen-11-yn-1-ol (4.39)



4.38 **4.39 (16*Z*-isomer)**

A magnetically stirred solution of silyl ether **4.38** (130 mg, 0.29 mmol) in tetrahydrofuran (5 mL) was treated with tetra-*n*-butylammonium fluoride (0.58 mL of a 1.0 M solution in tetrahydrofuran, 0.58 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (5 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic phases were then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *alcohol **4.39*** (55 mg, 89%) as a clear, yellow oil and as an inseparable (72:25) mixture of 16*Z*/16*E* isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*Z-isomer*) 6.49 (m, 1H), 6.33–6.19 (complex m, 3H), 6.13 (d, *J* = 11.9 Hz, 1H), 5.63 (m, 1H), 5.37 (dq, *J* = 11.9 and 2.8 Hz, 1H), 3.53 (ABX, J_{AB} = 10.5, J_{AX} = 5.7 Hz, 1H), 3.45 (ABX, J_{AB} = 10.5, J_{BX} =7.5 Hz, 1H), 2.44 (hept, *J* = 6.8 Hz, 1H), 2.20 (s, 3H), 2.00 (d, *J* = 2.8 Hz, 3H), 1.46 (s, OH), 1.04 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*Z-isomer*) 141.9 (CH), 137.2 (CH), 136.4 (C), 134.1 (CH), 133.3 (CH), 131.9 (CH), 128.2 (CH), 106.7 (CH), 93.2 (C), 79.4 (C), 67.5 (CH_2), 40.2 (CH), 16.5 (CH_3), 15.1 (CH_3), 4.9 (CH_3);

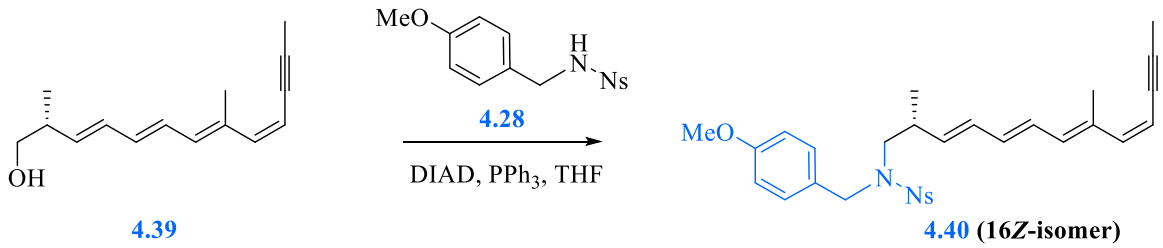
IR (KBr) ν_{max} 3351, 3024, 2958, 2914, 2871, 1956, 1439, 1376, 1030, 987 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 216 ($M^{+\bullet}$, 100%), 185 (50), 157 (75), 142 (60). 128 (50);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 216.1515, $C_{15}H_{20}O$ requires 215.1514;

Specific rotation $[\alpha]^{25}_D = +11.7$ (*c* 2.3, $CHCl_3$).

_N_-((_R_,3_E_,5_E_,7_E_,9_Z_)-2,8-Dimethyltrideca-3,5,7,9-tetraen-11-yn-1-yl)-_N_-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (4.40)



4.39 **4.40 (16*Z*-isomer)**

A magnetically stirred solution of alcohol **4.39** (18 mg, 0.08 mmol) and *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** (54 mg, 0.17 mmol) in tetrahydrofuran (2 mL) maintained at 0 °C was treated, sequentially, with triphenylphosphine (33 mg, 0.12 mmol) then di-*iso*-propyl azodicarboxylate (0.03 mL, 0.15 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:25:65 *v/v/v* ethyl acetate/dichloromethane/hexane) and concentration of the appropriate fractions (R_f = 0.4 in 20:25:55 *v/v/v* ethyl acetate/dichloromethane/hexane) afforded *compound **4.40*** (35 mg, 66%) as a clear, yellow oil and as an inseparable (60:40) mixture of 16*Z*/16*E* isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*Z-isomer*) 7.98 (d, *J* = 7.9 Hz, 1H), 7.73–7.57 (m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.37 (partially obscured d, *J* = 11.8 Hz, 1H), 6.35 (partially obscured m, 1H), 6.14 (dd, *J* = 11.7 and 6.0 Hz, 1H), 6.01–5.92 (complex m, 2H), 5.38 (dq, *J* = 11.8 and 2.8 Hz, 1H), 5.31 (dd, *J* = 14.1 and 8.2 Hz, 1H), 4.57 (d, *J* = 15.4 Hz, 1H), 4.41 (dd, *J* = 15.4 and 3.4 Hz, 1H), 3.79 (s, 3H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.47 (m, 1H), 2.19 (s, 3H), 2.01 (d, *J* = 2.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*Z-isomer*) 159.5 (C), 147.9 (C), 141.8 (CH), 137.0 (CH), 136.5 (C), 134.0 (C), 133.3 (CH), 133.2 (CH), 131.7 (CH), 131.4 (CH), 131.2 (CH), 129.9 (2 x CH), 128.1 (CH), 128.0 (C), 127.3 (CH), 124.5 (CH), 114.2 (2 x CH), 106.8 (CH), 93.3 (C), 79.4 (C), 55.4 (CH_3), 52.5 (CH_2), 50.1 (CH_2), 35.6 (CH), 17.9 (CH_3), 15.1 (CH_3), 4.9 (CH_3);

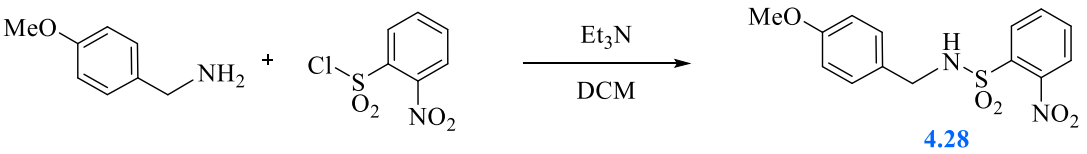
IR (KBr) ν_{max} 2960, 2916, 1612, 1543, 1513, 1455, 1440, 1371, 1303, 1248, 1162, 1125, 1030, 989 cm^{-1};

MS (ESI, +ve) *m/z* 543 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 543.1936, $C_{29}H_{32}N_2{}^{23}NaO_5S$ requires 543.1930;

Specific rotation $[\alpha]^{25}_D = -2.9$ (*c* 1.7, $CHCl_3$).

N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide (4.28)



4.28

A magnetically stirred solution of 4-methoxybenzylamine (2.00 g, 15.31 mmol) in dichloromethane (100 mL) was treated with triethylamine (3.2 mL, 22.96 mmol). The ensuing mixture was cooled to 0 °C and treated with 2-nitrobenzenesulfonyl chloride (3.73 g, 16.84 mmol). After 5 min, the reaction mixture was warmed to 18 °C, stirred at this temperature for 1 h then quenched with hydrochloric acid (100 mL of a 1.0 M aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were washed with brine (1 x 50 mL) then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded compound **4.28**[140] (4.70 g, 95%) as a white, crystalline solid.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.95 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.89 (dd, *J* = 7.8 and 1.4 Hz, 1H), 7.83 (td, *J* = 7.7 and 1.5 Hz, 1H), 7.75 (td, *J* = 7.7 and 1.4 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.07 (s, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.29 (s, 2H), 3.74 (s, 3H);

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 160.1 (C), 148.9 (C), 134.9 (C), 134.5 (CH), 133.3 (CH), 131.3 (CH), 130.1 (2 x CH), 129.9 (C), 125.5 (CH), 114.5 (2 x CH), 55.5 (CH_3), 47.5 (CH_2);

IR (KBr) ν_{max} 3304, 1609, 1537, 1510, 1404, 1362, 1333, 1244, 1154, 1028, 835, 783 cm^{-1};

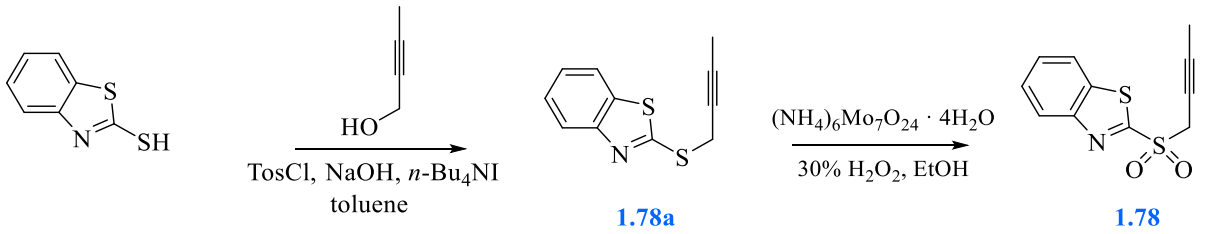
MS (ESI, +ve) *m/z* 345 [$(M+Na)^+$, 100%], 340 [$(M+NH_4)^+$, 30];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 345.0523, $C_{14}H_{14}{}^{23}NaN_2O_5S$ requires 345.0521;

Melting point 120 °C.

These data matched those reported previously.[140]

2-(But-2-yn-1-ylsulfonyl)benzo[*d*]thiazole (1.78)



A magnetically stirred solution of 2-butynol (1.00g, 14.27 mmol) and tetra-*n*-butyl ammonium iodide (527 mg, 1.42 mmol), in toluene (20 mL) maintained at 0 ºC was treated, sequentially, with sodium hydroxide (35 mL of a 2.0 M aqueous solution) then, dropwise, with a solution of *p*-toluenesulfonyl chloride (2.85 g, 14.98 mmol) in toluene (5 mL). The ensuing mixture was warmed to 18 °C and stirring was continued at this temperature for 3 h. 2-Mercaptobenzothiazole (2.58 g, 15.41 mmol) was then added to the reaction mixture in one portion. After another 2 h, the separated aqueous layer was extracted with ethyl acetate (3 x 25 mL) and the combined organic phases were washed with water (1 x 50 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded sulfide **1.78a**[86,87] (2.30 g, 73%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.43 (m, 1H), 7.31 (m, 1H), 4.10 (q, *J* = 2.5 Hz, 2H), 1.83 (t, *J* = 2.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C), 153.2 (C), 135.5 (C), 126.2 (CH), 124.5(CH), 121.8 (CH), 121.1 (CH), 80.8 (C), 73.2 (C), 22.6 (CH_2), 3.9 (CH_3);

IR (KBr) ν_{max} 3061, 2916, 2236, 1456, 1427, 1309, 1238, 1077, 1001 cm^{-1}.

These data matched those reported previously.[86,87]

A magnetically stirred solution of sulfide **1.78a** (1.00 g, 4.55 mmol) in ethanol (25 mL) maintained at 0 °C was treated, dropwise, with a pre-mixed solution of ammonium molybdate tetrahydrate (2.25 g, 1.82 mmol) and hydrogen peroxide (15.5 mL of a 30% *w*/*w* in aqueous solution, 0.15 mol). The resulting mixture was slowly warmed to 18 °C and stirred at this temperature for 16 h before being diluted with diethyl ether (50 mL) and washed with sodium hydrogen carbonate (1 x 20 mL of a saturated aqueous solution). The separated aqueous layer

was washed with diethyl ether (2 x 20 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduce pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl acetate/dichloromethane /hexane) and concentration of the appropriate fractions (R_f = 0.2) afforded sulfone **1.78**[86,87] (2.30 g, 73%) as a light-yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.7 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.62 (m, 2H), 4.34 (q, *J* = 2.5 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (C), 152.6 (C), 137.2 (C), 128.2 (CH), 127.8 (CH), 125.6 (CH), 122.4 (CH), 86.0 (C), 65.1 (C), 47.7 (CH_2), 3.8 (CH_3).

These data matched those reported previously.[86,87] The following additional data were acquired on this compound.

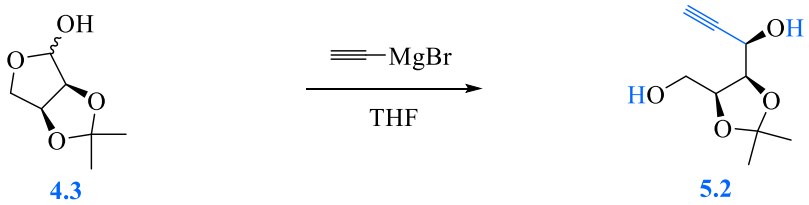
IR (KBr) ν_{max} 3086, 2903, 2245, 1461, 1339, 1316, 1153, 853 cm^{-1};

MS (ESI, +ve) *m/z* 315 [$(M+CH_3CN+Na)^+$, 95%,], 290 [$(M+K)^+$, 100];

HRMS (ESI, +ve) Found: $(M+K)^+$ 289.9713, $C_{11}H_9{}^{39}KNO_2S_2$ requires 289.9712. $(M+Na)^+$ 273.9973, $C_{11}H_9{}^{23}NaNO_2S_2$ requires 273.9972.

7.5 Experimental Procedures Related to Work Described in Chapter Five

(*R*)-1-((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (5.2)



4.3 5.2

A magnetically stirred solution of lactol **4.3** (1.25 g, 7.80 mmol) in tetrahydrofuran (20 mL) maintained at 0 °C under a nitrogen atmosphere was treated with ethynylmagnesium bromide (62.4 mL of an 0.5 M solution in tetrahydrofuran, 31.20 mmol). The ensuing mixture was stirred at this temperature for 2 h then poured into ammonium chloride (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The light-yellow residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound* ***5.2*** (1.29 g, 89%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 4.45 (dd, *J* = 7.2 and 2.2 Hz, 1H), 4.33 (td, *J* = 6.5 and 4.6 Hz, 1H), 4.17 (dd, *J* = 7.2 and 6.5 Hz, 1H), 3.91 (ABX, J_{AB} = 11.8, J_{AX} = 4.6 Hz, 1H), 3.80 (ABX, J_{AB} = 11.8, J_{BX} = 6.5 Hz, 1H), 2.89 (d, *J* = 2.2 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H) (signal due to hydroxyl group protons not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 109.9 (C), 84.0 (C), 80.3 (CH), 79.3 (CH), 74.9 (CH), 61.9 (CH), 61.3 (CH_2), 27.9 (CH_3), 25.5 (CH_3);

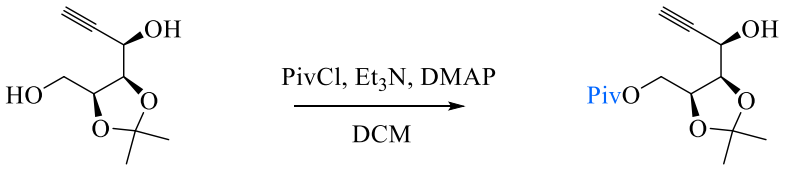
IR (KBr) ν_{max} 3380, 3285, 2987, 2937, 2109, 1383, 1219, 1166, 1054 cm^{-1};

MS (ESI, +ve) *m/z* 209 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 209.0793, $C_9H_{14}{}^{23}NaO_4$ requires 209.0790;

Specific rotation $[\alpha]^{25}_D$ = +29.7 (*c* 1.6, $CHCl_3$).

((4*S*,5*R*)-5-((*R*)-1-Hydroxyprop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivaloate (5.3)



5.2 5.3

A magnetically stirred solution of diol **5.2** (1.29 g, 6.92 mmol), triethylamine (2.4 mL, 17.32 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (85 mg, 0.70 mmol) in dichloromethane (100 mL) maintained at −78 °C under a nitrogen atmosphere was treated, over 30 min *via* syringe pump,with pivaloyl chloride (0.94 mL, 7.62 mmol). The ensuing mixture was stirred at −78 °C for a further 1 h then poured into ammonium chloride (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:25:55 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the desired *compound **5.3*** (1.30 g, 69%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (ABX, J_{AB} = 11.6, J_{AX} = 4.3 Hz, 1H), 4.48 (dd, J = 6.5 and 2.1 Hz, 1H), 4.41 (td, J = 6.5 and 4.3 Hz, 1H), 4.28 (ABX, J_{AB} = 11.6, J_{BX} = 6.5 Hz, 1H), 4.22 (t, J = 6.5 Hz, 1H), 2.73 (s, OH), 2.55 (d, J = 2.1 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 3H), 1.20 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (CO), 109.5 (C), 82.1 (C), 78.8 (CH), 75.2 (CH), 75.0 (CH), 62.6 (CH_2), 61.6 (CH), 38.9 (C), 27.5 (CH_3), 27.3 (3 x CH_3), 25.4 (CH_3);

IR (KBr) ν_{max} 3374, 3227, 2974, 2936, 2115, 1726, 1463, 1382, 1219, 1166, 1023, 912 cm^{-1};

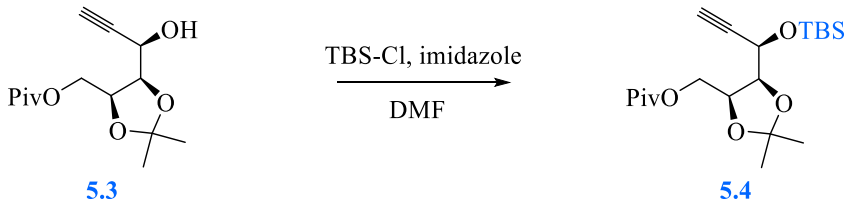
MS (ESI, +ve) *m/z* 334 [$(M+CH_3CN+Na)^+$, 100%], 293 [$(M+Na)^+$, 55];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 293.1365, $C_{14}H_{22}{}^{23}NaO_5$ requires 293.1365;

Melting point 102 °C;

Specific rotation $[\alpha]^{25}_D$ = +3.6 (*c* 1.2, $CHCl_3$).

((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivalate (5.4)



5.3 5.4

A magnetically stirred solution of alcohol **5.3** (1.00 g, 3.70 mmol) in *N*,*N*-dimethylformamide (20 mL) maintained at 18 °C was treated, sequentially, with *tert*-butyldimethylsilyl chloride (0.84 g, 5.55 mmol) then imidazole (0.63 g, 9.25 mmol). The ensuing mixture was stirred for 2 h then diluted with diethyl ether (30 mL) and quenched with water (30 mL). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with hydrochloric acid (1 x 50 mL of a 1.0 M aqueous solution), water (1 x 50 mL) and brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **5.4*** (1.40 g, 98%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (partially obscured dd, *J* = 6.3 and 2.2 Hz, 1H), 4.52 (partially obscured dd, *J* = 11.8 and 2.6 Hz, 1H), 4.37 (ddd, *J* = 8.1, 6.3 and 2.6 Hz, 1H), 4.20 (partially obscured dd, *J* = 11.8 and 8.1 Hz, 1H), 4.18 (partially obscured t, *J* = 6.3 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.21 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (CO), 109.2 (C), 82.7 (C), 79.3 (CH), 75.8 (CH), 74.8 (CH), 63.9 (CH_2), 62.2 (CH), 38.9 (C), 27.7 (CH_3), 27.3 (3 x CH_3), 25.9 (3 x CH_3), 25.4 (CH_3), 18.2 (C), −4.1 (CH_3), −4.7 (CH_3);

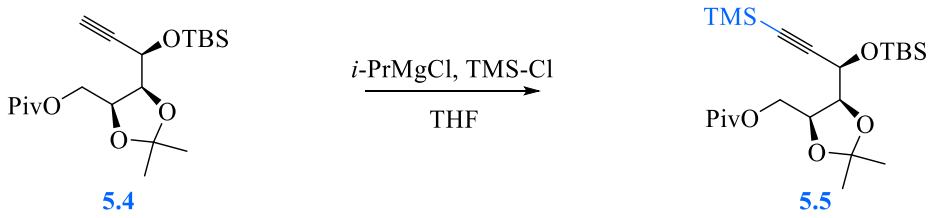
IR (KBr) ν_{max} 3264, 2959, 2933, 2859, 2118, 1732, 1481, 1463, 1382, 1371, 1255, 1158, 1089, 839, 780 cm^{-1};

MS (ESI, +ve) *m/z* 407 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 407.2231, $C_{20}H_{36}{}^{23}NaO_5Si$ requires 407.2230. $(M+H)^+$ 385.2416, $C_{20}H_{37}O_5Si$ requires 385.2410;

Specific rotation $[\alpha]^{25}_D$ = −41.2 (*c* 1.4, $CHCl_3$).

((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivalate (5.5)



A magnetically stirred solution of terminal alkyne **5.4** (1.40 g, 3.64 mmol) in tetrahydrofuran (40 mL) maintained at 0 °C was treated, dropwise, with *iso*-propylmagnesium chloride (3.6 mL of a 2.0 M solution in tetrahydrofuran, 7.28 mmol). After 30 min, the reaction mixture was warmed to 18 °C for 10 min then cooled to 0 °C again before being treated with trimethylsilyl chloride (0.69 mL, 5.26 mmol). After stirring at this temperature for a further 30 min, the reaction mixture was warmed to 18 °C for 1 h then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound* ***5.5*** (1.50 g, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (partially obscured d, J = 5.2 Hz, 1H), 4.54 (ABX, J_{AB} = 11.8, J_{AX} = 2.8 Hz, 1H), 4.37 (ddd, J = 8.2, 6.4 and 2.8 Hz, 1H), 4.22 (ABX, J_{AB} = 11.8, J_{BX} = 8.2 Hz, 1H), 4.16 (dd, J = 6.4 and 5.2 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.22 (s, 9H), 0.91 (s, 9H), 0.17 (s, 3H), 0.16 (s, 9H), 0.14 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (CO), 109.1 (C), 104.2 (C), 91.8 (C), 79.4 (CH), 75.9 (CH), 64.1 (CH_2), 62.9 (CH), 38.9 (C), 27.7 (CH_3), 27.4 (3 x CH_3), 25.9 (3 x CH_3), 25.5 (CH_3), 18.2 (C), −0.22 (3 x CH_3), −4.1 (CH_3), −4.6 (CH_3);

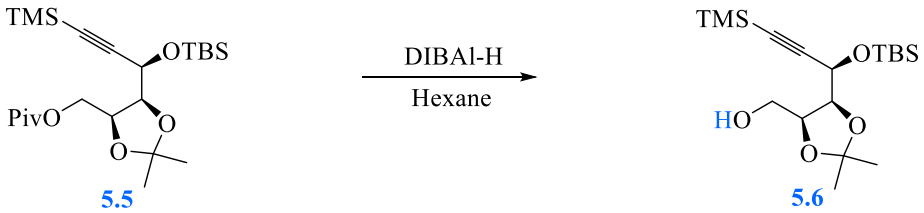
IR (KBr) ν_{max} 2959, 2933, 2900, 2859, 2176, 1732, 1480, 1463, 1382, 1370, 1251, 1157, 1090, 842, 779 cm^{-1};

MS (ESI, +ve) *m/z* 479 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 479.2617, $C_{23}H_{44}{}^{23}NaO_5Si_2$ requires 479.2625;

Specific rotation $[\alpha]^{25}_D$ = −40.0 (*c* 1.0, $CHCl_3$).

((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.6)



A magnetically stirred solution of pivaloate **5.5** (1.50 g, 3.28 mmol) in hexane (50 mL) maintained at −78 °C was treated, dropwise, with di-*iso*-butylaluminium hydride (6.6 mL of a 1.0 M solution in hexane, 6.60 mmol). After addition was complete, the reaction mixture was stirred for 1 h then treated with tartaric acid (60 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 1 h. The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 25:75 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.6*** (1.15 g, 94%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 4.63 (d, *J* = 5.2 Hz, 1H), 4.34 (ddd, *J* = 7.9, 6.6 and 3.4 Hz, 1H), 4.17 (dd, *J* = 6.6 and 2.2 Hz, 1H), 3.98 (ABX, J_{AB} = 11.8, J_{AX} = 3.4 Hz, 1H), 3.84 (ABX, J_{AB} = 11.8, J_{BX} = 7.9 Hz, 1H), 1.50 (s, 3H), 1.39 (s, 3H), 0.97 (s, 9H), 0.23 (s, 3H), 0.20 (s, 9H), 0.19 (s, 3H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 109.8 (C), 105.8 (C), 92.3 (C), 80.6 (CH), 79.8 (CH), 64.2 (CH_2), 62.3 (CH_2), 27.8 (CH_3), 26.3 (3 x CH_3), 25.4 (CH_3), 19.0 (C), −0.3 (3 x CH_3), −4.0 (CH_3), −4.5 (CH_3);

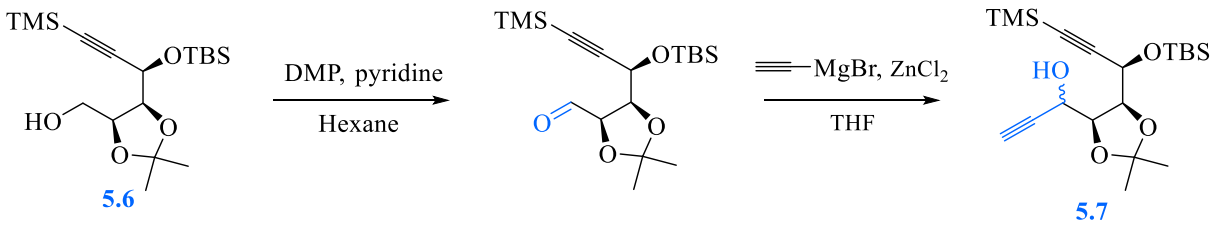
IR (KBr) ν_{max} 3500, 2958, 2932, 2897, 2859, 2176, 1472, 1380, 1251, 1084, 841, 779 cm^{-1};

MS (ESI, +ve) *m/z* 395 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 395.2051, $C_{18}H_{36}{}^{23}NaO_4Si_2$ requires 395.2050;

Specific rotation $[\alpha]^{25}_D$ = −27.4 (*c* 1.2, $CHCl_3$).

1-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (5.7)



A magnetically stirred solution of alcohol **5.6** (200 mg, 0.54 mmol) in dichloromethane (5 mL) maintained at 0 ºC was treated with the Dess-Martin periodinane (341 mg, 0.80 mmol) and pyridine (0.22 mL, 2.68 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 3 h then quenched with sodium thiosulfate (5 mL of a 10% aqueous solution) and sodium hydrogen carbonate (5 mL of a saturated aqueous solution). The resulting slurry was filtered through Celite™ and the separated aqueous phase associated with the filtrate was extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was immediately submitted, without purification, to the next step of the reaction sequence.

A magnetically stirred solution of zinc chloride (0.77 mL of a 1.0 M solution in diethyl ether, 0.77 mmol) maintained at 0 °C was treated with ethynylmagnesium bromide (5.2 mL of a 0.5 M solution in tetrahydrofuran, 2.60 mmol). The ensuing mixture was cooled to −15 °C and treated with a solution of aldehyde (160 mg, 0.43 mmol), formed as described above, in tetrahydrofuran (5 mL). After 4 h, the reaction mixture was poured into ammonium chloride (10 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with brine (1 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) afforded *compound* ***5.7*** (140 mg, 68%) as a clear, colourless oil and as an inseparable (17:83) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*β-epimer*) 4.92 (br s, 1H), 4.85 (d, *J* = 4.7 Hz, 1H), δ 4.29 (dd, *J* = 6.8 and 1.9 Hz, 1H), 4.25 (dd, *J* = 6.8 and 4.7 Hz, 1H), 3.63 (br s, OH), 2.45 (d, *J* = 2.3 Hz, 1H), 1.57 (s, 3H), 1.39 (s, 3H), 0.92 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.16 (s, 9H);

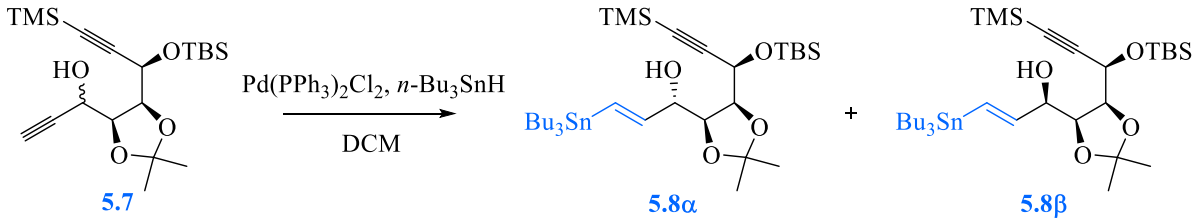
^{13}C NMR (100 MHz, $CDCl_3$) δ (*β-epimer*) 109.7 (C), 102.9 (C), 92.8 (C), 82.7 (C), 79.8 (CH), 78.9 (CH), 72.8 (CH), 62.2 (CH), 61.1 (CH), 26.5 (CH_3), 25.8 (3 x CH_3), 25.3 (CH_3), 18.4 (C), −0.3 (3 x CH_3), −4.5 (CH_3), −4.9 (CH_3);

IR (KBr) ν_{max} 3467, 3312, 3279, 2957, 2858, 2176, 1472, 1382, 1251, 1215, 1080, 841 cm^{-1};

MS (ESI) *m/z* 419 [$(M+Na)^+$, 100%];

HRMS (ESI) Found: $(M+Na)^+$ 419.2054, $C_{20}H_{36}{}^{23}NaO_4Si$ requires 419.2050.

(*R*,*E*)-1-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tributylstannyl)prop-2-en-1-ol (5.8β)



A magnetically stirred solution of bis(triphenylphosphine)palladium(II) dichloride (10 mg, 0.02 mmol) and compound **5.7** (119 mg, 0.30 mmol) in dry dichloromethane (5 mL) maintained at −78 °C under an argon atmosphere was treated, dropwise over 2 min, with tri-*n*-butyltin hydride (0.97 mL, 0.35 mmol). The ensuing mixture was stirred for 30 min then warmed to 0 ºC and maintained at this temperature for a further 30 min. After being warmed to 18 ºC the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica deactivated with 1% triethylamine in hexane, 3:97 *v/v* diethylether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded *compound **5.8α*** as a clear, colourless oil (24 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 19.2 and 1.2 Hz, 1H), 6.31 (dd, *J* = 19.2 and 4.7 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 4.34 (m, 1H), 4.12 (dd, *J* = 6.5 and 5.2 Hz, 1H), 3.99 (dd, *J* = 9.0 and 5.2 Hz, 1H), 3.37 (d, *J* = 3.5 Hz, 1H), 1.54 (s, 3H), 1.52–1.46 (complex m, 6H), 1.33 (s, 3H), 1.31–1.25 (complex m, 6H), 0.93 (s, 9H), 0.91–0.86 (complex m, 15H), 0.24 (s, 3H), 0.21 (s, 3H), 0.17 (s, 9H);

Concentration of fraction B (R_f = 0.2) afforded *compound* ***5.8β*** as a clear, colourless oil (125 mg, 60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 19.2 Hz, 1H), 6.12 (dd, *J* = 19.2 and 5.5 Hz, 1H), 4.81 (d, *J* = 4.7 Hz, 1H), 4.61 (m, 1H), 4.24–4.13 (complex m, 2H), 3.38 (d, *J* = 4.0 Hz, 1H), 1.54 (s, 3H), 1.51–1.43 (complex m, 6H), 1.36 (s, 3H), 1.34–1.25 (complex m, 6H), 0.93 (s, 9H), 0.91–0.86 (complex m, 15H), 0.20 (s, 3H), 0.18 (s, 3H), 0.17 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2 (C), 129.5 (C), 108.8 (C), 103.8 (C), 92.2 (C), 80.6 (CH), 79.3 (CH), 72.8 (CH), 62.8 (CH), 29.2 (3 x CH_2), 27.4 (3 x CH_2), 26.7 (CH_3), 25.9 (3 x CH_3), 25.2 (CH_3), 18.5 (C), 13.9 (3 x CH_3), 9.6 (3 x CH_2), −0.2 (3 x CH_3), −4.4 (CH_3), −4.7 (CH_3);

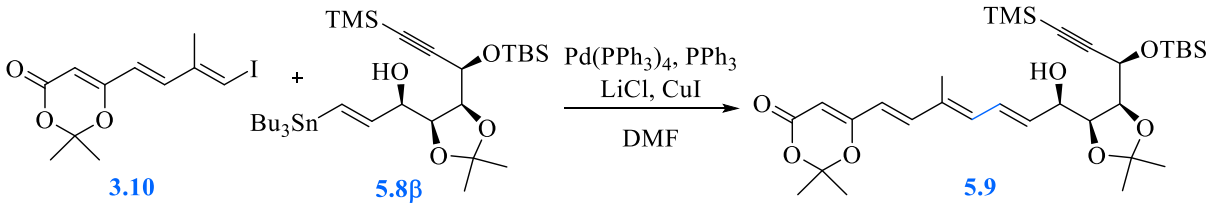
IR (KBr) ν_{max} 3496, 2957, 2929, 2857, 2177, 1464, 1379, 1250, 1214, 1079, 841 cm^{-1};

MS (ESI, +ve) *m/z* 711 [$(M+Na)^+$, 100%]; 597 {[M–(2xC_4H_9)+Na]$^+$, 50};

HRMS (ESI, +ve) Found: $(M+Na)^+$ 711.3279, $C_{32}H_{64}{}^{23}NaO_4Si_2{}^{120}Sn$ requires 711.3263;

Specific rotation $[\alpha]^{25}_D = -29.5$ (*c* 0.9, $CHCl_3$).

6-((*R*,1*E*,3*E*,5*E*)-7-((4*S*,5*S*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-hydroxy-3-methylhepta-1,3,5-trien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (5.9)



A two-neck round bottom flask equipped with a condenser and a rubber septum was charged with stannane **5.8β** (100 mg, 0.14 mmol), alkenyl iodine **3.10** (46 mg, 0.14 mmol), tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.01(4) mmol), triphenylphosphine (9 mg, 0.03 mmol), lithium chloride (37 mg, 0.87 mmol) and cooper iodide (138 mg, 0.73 mmol). The flask was evacuated at low pressure then filled with argon. The resulting mixture was dissolved in degassed *N*,*N*-dimethylformamide (5 mL) and the solution so formed was heated to 40 ºC for 16 h. After cooling, potassium fluoride (5 mL of a 10% aqueous solution) was added and the reaction mixture was stirred at 18 ºC for 30 min before being filtered and the filtrate then extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with water

(2 x 20 mL) and brine (1 x 10 mL) then dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound* ***5.9*** (16 mg, 20%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 15.5 Hz, 1H), 6.70 (dd, *J* = 15.0 and 11.3 Hz, 1H), 6.38 (d, *J* = 11.3 Hz, 1H), 6.06 (dd, *J* = 15.0 and 6.1 Hz, 1H), 5.97 (d, *J* = 15.5 Hz, 1H), 5.32 (s, 1H), 4.86 (d, *J* = 4.6 Hz, 1H), 4.80 (d, *J* = 5.1 Hz, 1H), 4.24 (dd, *J* = 6.8 and 5.1 Hz 1H), 4.16 (d, *J* = 6.8 Hz, 1H), 3.74 (s, OH), 1.90 (s, 3H), 1.72 (s, 6H), 1.55 (s, 3H), 1.36 (s, 3H), 0.94 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.18 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (C), 162.2 (C), 142.5 (CH), 138.2 (CH), 137.9 (CH), 133.7 (CH), 126.9 (CH), 118.7 (CH), 109.2 (C), 106.4 (C), 103.1 (C), 94.2 (CH), 92.5 (C), 80.3 (CH), 79.0 (CH), 70.0 (CH), 62.3 (CH), 26.5 (CH_3), 25.9 (3 x CH_3), 25.3 (CH_3), 25.3 (CH_3), 25.2 (CH_3), 18.5 (C), 12.5 (CH_3), −0.3 (3 x CH_3), −4.6 (CH_3), −4.9 (CH_3);

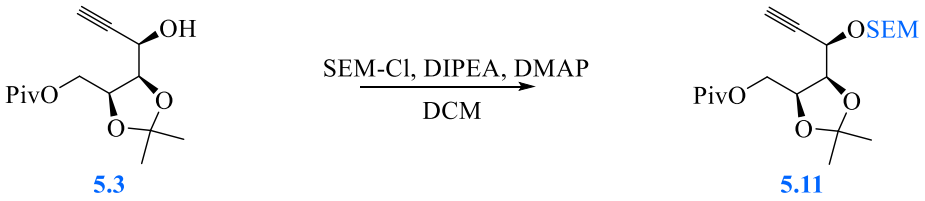
IR (KBr) ν_{max} 3467, 2956, 2929, 2858, 1726, 1614, 1383, 1273, 1250, 1210, 1074, 1024, 971, 842 cm^{-1};

MS (ESI, +ve) *m/z* 613 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 613.2994, $C_{31}H_{50}{}^{23}NaO_7Si$ requires 613.2993. $[M+H]^+$ 591.3179, $C_{31}H_{51}O_7Si_2$ requires 591.3173;

Specific rotation $[\alpha]^{25}_D$ = −41.6 (*c* 0.6, $CHCl_3$).

((4*S*,5*R*)-2,2-Dimethyl-5-((*R*)-1-((2-(trimethylsilyl)ethoxy)methoxy)prop-2-yn-1-yl)-1,3-dioxolan-4-yl)methyl Pivaloate (5.11)



5.3 5.11

A magnetically stirred solution of alcohol **5.3** (0.65 g, 2.40 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (147 mg, 1.20 mmol) in dichloromethane (20 mL) maintained at 0 °C under a nitrogen atmosphere was treated, sequentially, with di-*iso*-propylethylamine (1.3 mL, 7.21 mmol) then, dropwise, with 2-(trimethylsilyl)ethoxymethyl chloride (1.3 mL, 7.21 mmol). After stirring for a further 30 min, the reaction mixture was heated at reflux for 16 h before being cooled to 18 °C and poured into ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.11*** (800 mg, 83%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.50 (partially obscured dd, *J* = 5.9 and 2.1 Hz, 1H), 4.50 (partially obscured ABX, J_{AB} = 11.7 Hz, J_{AX} = 4.2 Hz, 1H), 4.40 (m, 1H), 4.28 (t, *J* = 5.9 Hz, 1H), 4.23 (ABX, J_{AB} = 11.7 Hz, J_{BX} = 7.4 Hz, 1H), 3.71 (td, *J* = 9.9, 7.0 Hz, 1H), 3.56 (td, *J* = 9.9, 6.8 Hz, 1H), 2.50 (d, *J* = 2.1 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 1.20 (s, 9H), 0.95–0.90 (complex m, 2H), −0.01 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) 178.2 (CO), 109.5 (C), 92.5 (CH_2), 79.6 (C), 77.9 (CH), 75.9 (CH), 75.2 (CH), 66.4 (CH_2), 65.0 (CH), 62.7 (CH_2), 38.8 (C), 27.4 (CH_3), 27.3 (3 x CH_3), 25.3 (CH_3), 18.2 (CH_2), −1.3 (3 x CH_3);

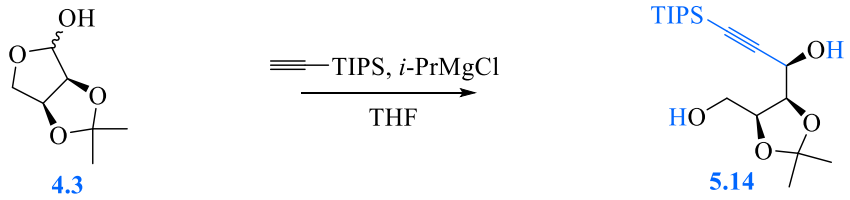
IR (ATR) ν_{max} 3265, 2956, 2895, 1730, 1481, 1371, 1248, 1156, 1022, 834 cm^{-1};

MS (ESI, +ve) *m/z* 423 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 423.2180, $C_{20}H_{36}{}^{23}NaO_6Si$ requires 423.2179;

Specific rotation $[\alpha]^{25}_D$ = −70.3 (*c* 1.2, $CHCl_3$).

(*R*)-1-((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl) prop-2-yn-1-ol (5.14)



4.3 **5.14**

A magnetically stirred solution of *iso*-propylmagnesium chloride (9.4 mL of a 2.0 M solution in tetrahydrofuran, 18.80 mmol) in tetrahydrofuran (5 mL) maintained at 0 °C was treated with tri-*iso*-propylsilylacetylene (4.2 mL, 18.72 mmol). The ensuing mixture was stirred for a further 30 min then warmed to 18 °C for 1 h before being cooled to 0 °C and treated with a solution of lactol **4.3** (1.00 g, 6.24 mmol) in tetrahydrofuran (10 mL). After 3 h the reaction mixture was warmed to 18 ºC and stirred for a further 16 h then treated with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:30:50 *v/v/v* diethyl ether/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.14*** (2.10 g, 98%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 4.49 (d, J = 6.7 Hz, 1H), 4.28 (m, 1H), 4.14 (t, J = 6.7 Hz, 1H), 3.89 (ABX, J_{AB} = 11.8 Hz, J_{AX} = 4.7 Hz, 1H), 3.79 (ABX, J_{AB} = 11.8 Hz, J_{BX} = 6.7 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.13–1.07 (complex m, 21H) (signal due to hydroxyl group protons not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 109.8 (C), 108.4 (C), 86.8 (C), 80.6 (CH), 79.4 (CH), 62.5 (CH), 61.5 (CH_2), 28.0 (CH_3), 25.6 (CH_3), 19.0 (6 x CH_3), 12.4 (3 x CH);

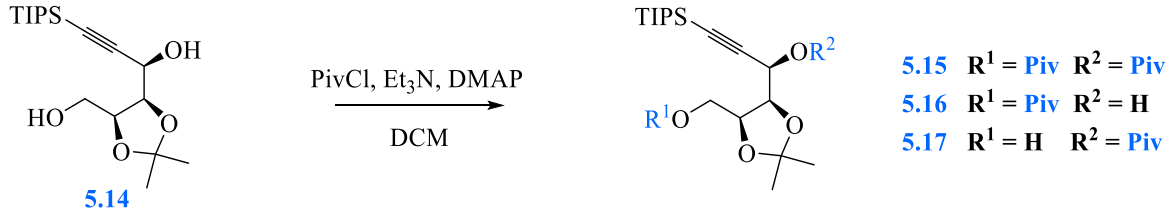
IR (KBr) ν_{max} 3368, 2943, 2866, 2173, 1463, 1382, 1245, 1219, 1073, 883 cm^{-1};

MS (ESI, +ve) *m/z* 365 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 365.2125, $C_{18}H_{34}O_4Si^{23}Na$ requires 365.2124;

Specific rotation $[\alpha]^{25}_D$ = +1.9 (*c* 1.3, $CHCl_3$).

((4*S*,5*R*)-2,2-Dimethyl-5-((*R*)-1-(pivaloyloxy)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl)-1,3-dioxolan-4-yl)methyl Pivalate (5.15), ((4*S*,5*R*)-5-((*R*)-1-Hydroxy-3-(tri-*iso*-propylsilyl) prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivalate (5.16), and (*R*)-1-((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivalate (5.17)



A magnetically stirred solution of diol **5.14** (0.86 g, 2.51 mmol), triethylamine (0.38 mL, 2.76 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (31 mg, 0.25 mmol) in dichloromethane (50 mL) maintained at −78 °C was treated with pivaloyl chloride (0.32 mL, 2.63 mmol). The ensuing mixture was stirred at −78 °C for a further 1.5 h then poured into ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were washed with brine (1 x 100 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:80 to 30:70 *v/v* diethyl ether/hexane elution) to afford three fractions, A, B, and C.

Concentration of fraction A (R_f = 0.6 in 20:80 *v/v* diethyl ether/hexane) afforded *compound **5.15*** (70 mg, 5%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, J = 4.4 Hz, 1H), 4.52 (ABX, J_{AB} = 11.6, J_{AX} = 3.2 Hz, 1H), 4.45 (ddd, J = 8.0, 6.6 and 3.2 Hz, 1H), 4.36 (dd, J = 6.6 and 4.4 Hz, 1H), 4.29 (ABX, J_{AB} = 11.6, J_{BX} = 8.0 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.24 (s, 9H), 1.22 (s, 9H), 1.04 (s, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (CO), 176.8 (CO), 109.5 (C), 101.3 (C), 89.4 (C), 77.1 (CH), 75.7 (CH), 63.8 (CH_2), 62.4 (CH), 38.9 (2 x C), 27.6 (CH_3), 27.3 (3 x CH_3), 27.2 (3 x CH_3), 25.4 (CH_3), 18.6 (6 x CH_3), 11.2 (3 x CH);

IR (ATR) ν_{max} 2960, 2942, 2867, 2180, 1734, 1480, 1462, 1381, 1279, 1131, 882 cm^{-1};

MS (ESI, +ve) *m/z* 533 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 533.3280, $C_{28}H_{50}{}^{23}NaO_6Si$ requires 533.3274;

Specific rotation $[\alpha]^{25}_D$ = −60.7 (*c* 1.3, $CHCl_3$).

Concentration of fraction B (R_f = 0.4 in 30:70 *v/v* diethyl ether/hexane) afforded *compound* ***5.16*** (460 mg, 43%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (t, *J* = 5.7 Hz, 1H), 4.44 (dd, *J* = 10.9 and 3.8 Hz, 1H), 4.37–4.26 (complex m, 2H), 4.18 (t, *J* = 5.7 Hz, 1H), 2.26 (d, *J* = 5.7 Hz, OH), 1.44 (s, 3H), 1.30 (s, 3H), 1.14 (s, 9H), 1.00 (s, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (CO), 109.4 (C), 104.9 (C), 88.7 (C), 79.1 (CH), 75.4 (CH), 63.0 (CH_2), 62.0 (CH), 38.9 (C), 27.6 (CH_3), 27.3 (3 x CH_3), 25.5 (CH_3), 18.7 (6 x CH_3), 11.3 (3 x CH);

IR (ATR) ν_{max} 3463, 2943, 2866, 2173, 1733, 1481, 1463, 1381, 1284, 1222, 1162, 882 cm^{-1};

MS (ESI, +ve) *m/z* 449 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 449.2702, $C_{23}H_{42}{}^{23}NaO_5Si$ requires 449.2699;

Specific rotation $[\alpha]^{25}_D$ = −3.7 (*c* 0.8, $CHCl_3$).

Concentration of fraction C (R_f = 0.2 in 30:70 *v/v* diethyl ether/hexane) afforded *compound* ***5.17*** (460 mg, 43%) as a clear, colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (d, *J* = 4.5 Hz, 1H), 4.43–4.31 (complex m, 2H), 3.97 (ddd, *J* = 11.9, 8.2 and 3.5 Hz, 1H), 3.86 (ddd, *J* = 11.9, 7.2 and 4.5 Hz, 1H), 2.00 (dd, *J* = 8.2 and 4.5 Hz, OH), 1.47 (s, 3H), 1.37 (s, 3H), 1.22 (s, 9H), 1.05 (s, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) 176.7 (CO), 109.2 (C), 101.7 (C), 89.2 (C), 78.3 (CH), 77.1 (CH), 62.7 (CH), 61.8 (CH_2), 38.9 (C), 27.6 (CH_3), 27.2 (3 x CH_3), 25.4 (CH_3), 18.6 (6 x CH_3), 11.2 (3 x CH);

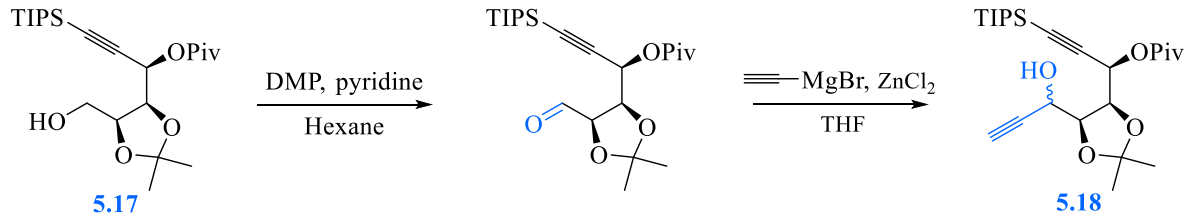
IR (ATR) ν_{max} 3491, 2942, 2866, 2178, 1742, 1463, 1381, 1277, 1138, 1045, 882 cm^{-1};

MS (ESI, +ve) *m/z* 449 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 449.2701, $C_{23}H_{42}{}^{23}NaO_5Si$ requires 449.2699;

Specific rotation $[\alpha]^{25}_D$ = −62.4 (*c* 1.2, $CHCl_3$).

(*R*)-1-((4*R*,5*S*)-5-((*S*)-1-Hydroxyprop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivalate (5.18α) and (*R*)-1-((4*R*,5*S*)-5-((*R*)-1-Hydroxyprop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivaloate (5.18β)



A magnetically stirred solution of alcohol **5.17** (1.00 g, 2.34 mmol) in dichloromethane (50 mL) maintained at 0 ºC was treated with the Dess-Martin periodinane (1.99 g, 4.69 mmol) and pyridine (0.94 mL, 11.72 mmol). The ensuing mixture was warmed to 18 °C and stirred for 3 h then quenched with sodium thiosulfate (25 mL of 10% aqueous solution) and sodium hydrogen carbonate (25 mL of a saturated aqueous solution). The resulting slurry was filtered through Celite™ and the separated aqueous layer associated with the filtrate was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was immediately submitted, without purification, to the next step of the reaction sequence.

A magnetically stirred solution of zinc chloride (4.7 mL of 1.0 M solution in diethyl ether, 4.70 mmol) maintained at 0 °C was treated with ethynylmagnesium bromide (28.0 mL of 0.5 M solution in tetrahydrofuran, 14.00 mmol). The ensuing mixture was cooled to −40 ºC and treated with a solution of the aldehyde, formed as described above, in tetrahydrofuran (10 mL). After 4 h, the reaction mixture was poured into ammonium chloride (50 mL of a saturated aqueous solution) and the separated aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 20:80 to 30:70 *v/v* diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2(7) in 30:70 *v/v* diethyl ether/hexane) afforded ***5.18α*** (0.17 g, 19%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 5.78 (d, *J* = 4.6 Hz, 1H), 4.77 (dd, *J* = 8.2 and 2.1 Hz, 1H), 4.36 (dd, *J* = 6.5 and 4.6 Hz, 1H), 4.26 (dd, *J* = 8.2 and 6.5 Hz, 1H), 2.85 (d, *J* = 2.1 Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.24 (s, 9H), 1.13–1.10 (complex m, 21H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 178.0 (CO), 110.7 (C), 104.3 (C), 89.2 (C), 84.2 (C), 80.1 (CH), 78.7 (CH), 74.8 (CH), 64.7 (CH), 61.3 (CH), 39.7 (C), 27.5 (CH_3), 27.4 (3 x CH_3), 25.23 (CH_3), 19.0 (6 x CH_3), 12.4 (3 x CH);

IR (KBr) ν_{max} 3467, 3313, 3279, 2943, 2867, 2175, 1740, 1463, 1382, 1280, 1217, 1146, 1047, 882 cm^{-1};

MS (ESI, +ve) *m/z* 473 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 473.2699, $C_{25}H_{42}{}^{23}NaO_5Si$ requires 473.2699;

Specific rotation $[\alpha]^{25}_D$ = −51.2 (*c* 1.6, $CHCl_3$).

Concentration of fraction B (R_f = 0.3(2) in 30:70 *v/v* diethyl ether/hexane) afforded ***5.18β*** (0.56 g, 62%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 5.86 (d, *J* = 4.4 Hz, 1H), 4.71 (dd, *J* = 7.2 and 2.2 Hz, 1H), 4.43–4.29 (complex m, 2H), 3.04 (d, *J* = 2.2 Hz, 1H), 1.60 (s, 3H), 1.43 (s, 3H), 1.25 (s, 9H), 1.13–1.11 (complex m, 21H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 178.0 (CO), 110.8 (C), 104.2 (C), 89.4 (C), 82.9 (C), 81.1 (CH), 78.4 (CH), 76.4 (CH), 64.9 (CH), 61.2 (CH), 39.7 (C), 27.5 (CH_3), 27.4 (3 x CH_3), 25.3 (CH_3), 19.0 (6 x CH_3), 12.3 (3 x CH);

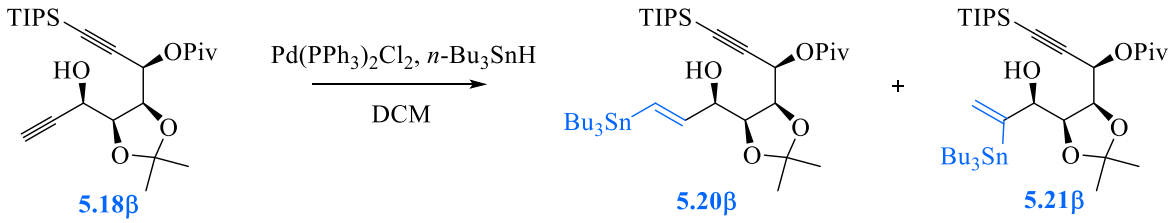
IR (ATR) ν_{max} 3475, 3313, 3271, 2942, 2866, 2183, 1738, 1462, 1382, 1216, 1120, 1047, 880 cm^{-1};

MS (ESI, +ve) *m/z* 473 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 473.2694, $C_{25}H_{42}{}^{23}NaO_5Si$ requires 473.2699. $(M+H)^+$ 451.2882, $C_{25}H_{43}O_5Si$ requires 451.2880;

Specific rotation $[\alpha]^{25}_D$ = −23.8 (*c* 1.3, $CHCl_3$).

(*R*)-1-((4*R*,5*S*)-5-((*R*,*E*)-1-Hydroxy-3-(tributylstannyl)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivalate (5.20β)



A magnetically stirred solution of bis(triphenylphosphine)palladium(II) dichloride (33 mg, 0.05 mmol) and terminal alkyne **5.18β** (430 mg, 0.95 mmol) in dry dichloromethane (20 mL) maintained at −78 ºC under an argon atmosphere was treated, dropwise over 2 min, with tri-*n*-butyltin hydride (0.39 mL, 1.43 mmol). The ensuing mixture was stirred at −78 ºC for 30 min then warmed to 0 ºC and maintained at this temperature for a further 30 min. After being warmed to 18 ºC, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica deactivated with 1% triethylamine in hexane, 10:90 *v/v* diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5) afforded *compound **5.21β*** (100 mg, 14%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, $J_{H\text{-}Sn}$= 64.2 Hz, 1H), 5.70 (d, J = 5.4 Hz, 1H), 5.35 (s, $J_{H\text{-}Sn}$= 31.3 Hz, 1H), 4.54 (dd, J = 5.6 and 4.0 Hz, $J_{H\text{-}Sn}$= 22.0 Hz, 1H), 4.27 (dd, J = 6.6 and 5.4 Hz, 1H), 4.19 (dd, J = 6.6 and 4.0 Hz, 1H), 2.43 (d, J = 5.6 Hz, OH), 1.56 (s, 3H), 1.50–1.43 (complex m, 6H), 1.37 (s, 3H), 1.35–1.26 (complex m, 6H), 1.21 (s, 9H), 1.07–1.05 (complex m, 21H), 0.94–0.86 (complex m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 156.8 (C), 126.4 (CH_2), 109.0 (C), 102.6 (C), 88.6 (C), 79.8 (CH), 77.6 (CH), 75.6 (CH), 63.9 (CH), 38.9 (C), 29.2 (3 x CH_2), 27.6 (3 x CH_2), 27.1 (3 x CH_3), 26.9 (CH_3), 25.1 (CH_3), 18.7 (6 x CH_3), 13.8 (3 x CH_3), 11.3 (3 x CH), 10.6 (3 x CH_2).

Concentration of fraction B (R_f = 0.3) afforded *compound **5.20β*** (450 mg, 63%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J = 19.1 Hz, $J_{H\text{-}Sn}$= 33.4 Hz, 1H), 6.04 (dd, J = 19.1 and 5.7 Hz, $J_{H\text{-}Sn}$= 31.0 Hz, 1H), 5.67 (d, J = 6.0 Hz, 1H), 4.41 (m, 1H), 4.27 (t, J = 6.0 Hz,

1H), 4.15 (dd, *J* = 6.0 and 5.0 Hz, 1H), 2.35 (d, *J* = 5.0 Hz, OH), 1.56 (s, 3H), 1.52–1.44 (complex m, 6H), 1.37 (s, 3H), 1.34–1.25 (complex m, 6H), 1.21 (s, 9H), 1.06 (br s, 21H), 0.92–0.85 (complex m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (CO), 146.4 (CH), 132.3 (CH), 109.2 (C), 102.5 (C), 88.6 (C), 79.8 (CH), 77.3 (CH), 72.3 (CH), 63.6 (CH), 38.9 (C), 29.2 (3 x CH_2), 27.4 (3 x CH_2), 27.1 (3 x CH_3), 27.1 (CH_3), 25.3 (CH_3), 18.7 (6 x CH_3), 13.8 (3 x CH_3), 11.3 (3 x CH), 9.6 (3 x CH_2);

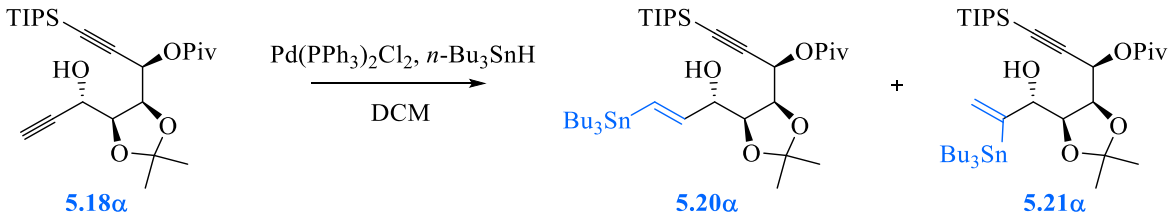
IR (ATR) ν_{max} 3516, 2956, 2926, 2866, 1739, 1463, 1376, 1276, 1215, 1139, 1071, 1045, 881, 677 cm^{-1};

MS (ESI, +ve) *m/z* 765 [$(M+Na)^+$, 45%], 743 [$(M+H)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 765.3913, $C_{37}H_{70}{}^{23}NaO_5Si^{120}Sn$ requires 765.3912. $(M+H)^+$ 743.4093, $C_{37}H_{71}O_5Si^{120}Sn$ requires 743.4093;

Specific rotation $[\alpha]^{25}_D = -2.0$ (*c* 1.0, $CHCl_3$).

(*R*)-1-((4*R*,5*S*)-5-((*S*,*E*)-1-Hydroxy-3-(tributylstannyl)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivalate (5.20α)



Reaction of terminal alkyne **5.18α** with bis(triphenylphosphine)palladium(II) dichloride and tri-*n*-butyltin hydride in the same manner as described immediately above for the conversion **5.18β** → **5.20β** afforded a dark-yellow oil on work-up. Subjection of this material to flash chromatography (silica, 10:90 *v/v* diethyl ether/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.4) afforded *compound* **5.21α** (15%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, $J_{H\text{-}Sn}$= 65.0 Hz, 1H), 5.81 (d, *J* = 3.6 Hz, 1H), 5.35 (s, $J_{H\text{-}Sn}$= 31.5 Hz, 1H), 4.64 (dd, *J* = 9.3 and 3.2 Hz, $J_{H\text{-}Sn}$= 24.4 Hz, 1H), 4.34 (dd, *J* = 6.2 and 3.6 Hz, 1H), 4.02 (dd, *J* = 9.3 and 6.2 Hz, 1H), 2.31 (d, *J* = 3.2 Hz, OH), 1.53–1.51 (complex m, 9H), 1.33–1.26 (complex m, 9H), 1.23 (s, 9H), 1.06 (s, 21H), 0.95–0.86 (complex m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 155.8 (C), 127.1 (CH_2), 109.4 (C), 103.1 (C), 89.2 (C), 79.3 (CH), 78.3 (CH), 76.3 (CH), 64.5 (CH), 38.9 (C), 29.2 (3 x CH_2), 27.6 (3 x CH_2), 27.2 (CH_3), 27.2 (3 x CH_3), 25.2 (CH_3), 18.7 (6 x CH_3), 13.8 (3 x CH_3), 11.3 (3 x CH), 10.5 (3 x CH_2).

Concentration of fraction B (R_f = 0.2) afforded *compound* **5.20α** (75%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 19.2 Hz, $J_{H\text{-}Sn}$= 35.2 Hz, 1H), 6.11 (dd, *J* = 19.2 and 4.7 Hz, $J_{H\text{-}Sn}$= 30.8 Hz, 1H), 5.80 (d, *J* = 3.7 Hz, 1H), 4.55 (dt, *J* = 8.8 and 4.7 Hz, 1H), 4.32 (dd, *J* = 6.0 and 3.7 Hz, 1H), 4.01 (dd, *J* = 8.8 and 6.0 Hz, 1H), 2.14 (d, *J* = 4.7 Hz, 1H), 1.58–1.42 (complex m, 9H), 1.35–1.26 (complex m, 9H), 1.22 (s, 9H), 1.06 (s, 21H), 0.92–0.86 (complex m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (CO), 146.4 (CH), 132.3 (CH), 109.2 (C), 102.5 (C), 88.6 (C), 79.8 (CH), 77.3 (CH), 72.3 (CH), 63.6 (CH), 38.9 (C), 29.2 (3 x CH_2), 27.4 (3 x CH_2), 27.1 (3 x CH_3), 27.1 (CH_3), 25.3 (CH_3), 18.7 (6 x CH_3), 13.8 (3 x CH_3), 11.3 (3 x CH), 9.6 (3 x CH_2);

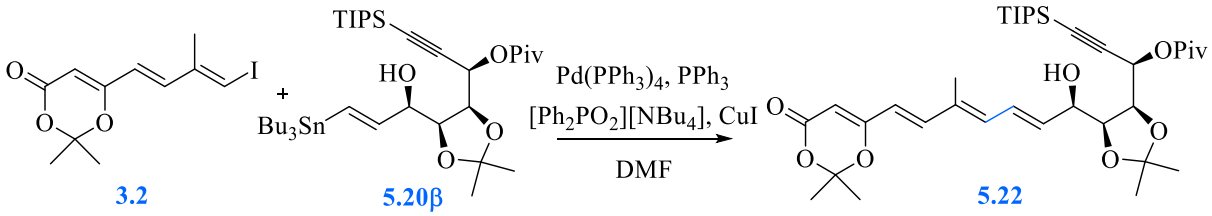
IR (ATR) ν_{max} 3512, 2957, 2927, 2867, 1741, 1721, 1464, 1379, 1281, 1214, 1147, 1071, 881, 678 cm^{-1};

MS (ESI, +ve) *m/z* 765 [$(M+Na)^+$, 40%], 743 [$(M+H)^+$, 25], 56 ($C_4H_8^+$, 100);

HRMS (ESI, +ve) Found: $(M+Na)^+$ 765.3914, $C_{37}H_{70}{}^{23}NaO_5Si^{120}Sn$ requires 765.3912;

Specific rotation $[\alpha]^{25}_D = -36.4$ (*c* 1.6, $CHCl_3$).

(*R*)-1-((4*R*,5*S*)-5-((*R*,2*E*,4*E*,6*E*)-7-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-1-hydroxy-5-methylhepta-2,4,6-trien-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivaloate (5.22)



A Schlenk flask was charged with tetra-*n*-butylammonium diphenylphosphinate (369 mg, 0.80 mmol) that was melted then cooled to ambient temperature (twice) under high vacuum. Thereafter, tetrakis(triphenylphosphine)palladium(0) (33 mg, 0.03 mmol), triphenylphosphine (19 mg, 0.06 mmol) and copper thiophene-2-carboxylate (153 mg, 0.80 mmol) were introduced under an argon atmosphere, followed by addition of a degassed solution of stannane **5.20β** (425 mg, 0.57 mmol) and alkenyl iodide **3.2** (165 mg, 0.52 mmol) in *N*,*N*-dimethylformamide (10 mL). After 30 min, the reaction mixture was diluted with diethyl ether (10 mL) then quenched with water (10 mL) and filtered through a short pad of Celite™. The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were then washed with water (2 x 20 mL) and brine (1 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound* ***5.22*** (310 mg, 93%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 15.5 Hz, 1H), 6.77 (dd, *J* = 15.0 and 11.4 Hz, 1H), 6.34 (d, *J* = 11.3 Hz, 1H), 5.99 (d, *J* = 15.5 Hz, 1H), 5.96 (dd, *J* = 15.0 and 5.9 Hz, 1H), 5.67 (d, *J* = 5.8 Hz, 1H), 5.33 (s, 1H), 4.58 (m, 1H), 4.32 (t, *J* = 5.8 Hz, 1H), 4.11 (t, *J* = 5.8 Hz, 1H), 2.64 (d, *J* = 3.8 Hz, OH), 1.91 (s, 3H), 1.71 (s, 6H), 1.55 (s, 3H), 1.38 (s, 3H), 1.20 (s, 9H), 1.05 (s, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (CO), 163.7 (C), 162.1 (CO), 142.2 (CH), 137.0 (CH), 135.8 (CH), 134.7 (C), 128.3 (CH), 119.2 (CH), 109.4 (C), 106.4 (C), 101.9 (C), 94.5 (CH), 89.2 (C), 79.8 (CH), 77.2 (CH), 69.5 (CH), 63.0 (CH), 38.9 (C), 27.1 (CH_3), 27.0 (3 x CH_3), 25.3 (CH_3), 25.2 (2 x CH_3), 18.6 (6 x CH_3), 12.6 (CH_3), 11.2 (3 x CH);

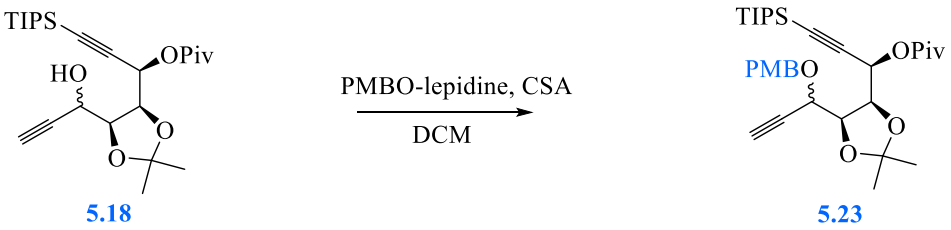
IR (ATR) ν_{max} 3445, 2960, 2943, 2866, 1724, 1613, 1382, 1273, 1248, 1138, 1025, 972 cm^{-1};

MS (ESI, +ve) *m/z* 667 [$(M+Na)^+$, 100%], 645 [$(M+H)^+$, 80], 627 [$(M-H_2O+H)^+$, 50];

HRMS (ESI, +ve) Found: $[M+Na]^+$ 667.3646, $C_{36}H_{56}{}^{23}NaO_8Si$ requires 667.3642. $[M+H]^+$ 645.3829, $C_{36}H_{57}O_8Si$ requires 645.3823;

Specific rotation $[\alpha]^{25}_D$ = +27.7 (*c* 1.1, $CHCl_3$).

(1*R*)-1-((4*R*,5S)-5-(1-((4-Methoxybenzyl)oxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-yl Pivalate (5.23)



A magnetically stirred solution of alcohol **5.18** (1.00 g, 2.22 mmol) in dichloromethane (50 mL) was treated with 2-(4-methoxybenzyloxy)-4-methylquinoline (1.23 g, 4.44 mmol) and (+)-10-camphorsulfonic acid (258 mg, 0.23 mmol) and the ensuing mixture was heated at 40 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 15:85 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 30:70 v/v diethyl ether/hexane), *compound **5.23*** (0.95 g, 75%) as a clear, colourless oil and as an inseparable (25:75) mixture of α/β epimers. A small fraction of an earlier eluting fraction containing a single epimer was used for characterisation.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.73 (d, *J* = 3.8 Hz, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.60 (dt, *J* = 6.2 and 2.0 Hz, 1H), 4.52 (d, *J* = 10.5 Hz, 1H), 4.29–4.24 (complex m, 2H), 3.80 (s, 3H), 2.57 (d, *J* = 2.0 Hz, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.16 (s, 9H), 1.06–1.04 (complex m, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C), 159.6 (C), 130.7 (2 x CH), 129.0 (C), 114.0 (2 x CH), 109.8 (C), 102.6 (C), 88.7 (C), 80.5 (C), 77.6 (CH), 77.4 (CH), 75.5 (CH), 70.6 (CH_2), 67.2 (CH), 63.1 (CH), 55.4 (CH_3), 38.7 (C), 27.3 (CH_3), 27.0 (3 x CH_3), 25.3 (CH_3), 18.7 (6 x CH_3), 11.3 (3 x CH);

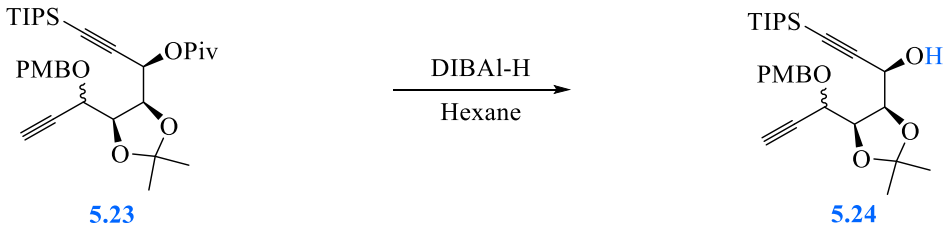
IR (ATR) ν_{max} 3274, 2942, 2866, 2178, 1737, 1612, 1515, 1463, 1318, 1250, 1144, 1071, 881 cm^{-1};

MS (ESI, +ve) *m/z* 593 [$(M+Na)^+$, 85%], 588 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 593.3266, $C_{33}H_{50}{}^{23}NaO_6Si$ requires 593.3274;

Specific rotation $[\alpha]^{25}_D$ = +8.4 (*c* 1.4, $CHCl_3$).

(1*R*)-1-((4*R*,5*S*)-5-(1-((4-Methoxybenzyl)oxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tri-*iso*-propylsilyl)prop-2-yn-1-ol (5.24)



5.23 5.24

A magnetically stirred solution of pivaloate **5.23** (500 mg, 0.87 mmol) in hexane (20 mL) maintained at −78 °C was treated, dropwise, with di-*iso*-butylaluminium hydride (1.8 mL of a 1.0 M solution in hexane, 1.80 mmol). After addition was complete, the reaction mixture was stirred for 30 min then treated with tartaric acid (20 mL of a 1.0 M aqueous solution) and stirring continued at 18 °C for a further 1h. The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were then washed with brine (1 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **5.24*** (390 mg, 91%) as a clear, colourless oil and as an inseparable (25:75) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 7.30 (partially obscured d, *J* = 8.6 Hz, 2H), 6.86 (partially obscured d, *J* = 8.6 Hz, 2H), 4.80 (partially obscured d, *J* = 10.7 Hz, 1H), 4.52 (partially obscured d, *J* = 10.7 Hz, 1H), 4.49–4.43 (complex m, 2H), 4.26 (m, 2H), 3.80 (s, 3H), 3.12 (d, *J* = 5.3 Hz, OH), 2.61 (d, *J* = 2.0 Hz, 1H), 1.48 (s, 3H), 1.36 (s, 3H), 1.07 (complex partially obscured m, 21H); δ (*β-epimer*) 7.30 (partially obscured d, *J* = 8.6 Hz, 2H), 6.86 (partially obscured d, *J* = 8.6 Hz, 2H), 4.91 (t, *J* = 6.3 Hz, 1H), 4.80 (partially obscured d, *J* = 10.7 Hz, 1H), 4.65 (dd, *J* = 4.6 and 2.2 Hz, 1H), 4.52 (partially obscured d, *J* = 10.7 Hz, 1H),

4.39–4.32 (complex m, 2H), 3.79 (s, 3H), 3.57 (d, *J* = 6.4 Hz, OH), 2.63 (d, *J* = 2.2 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H), 1.07 (complex partially obscured m, 21H);

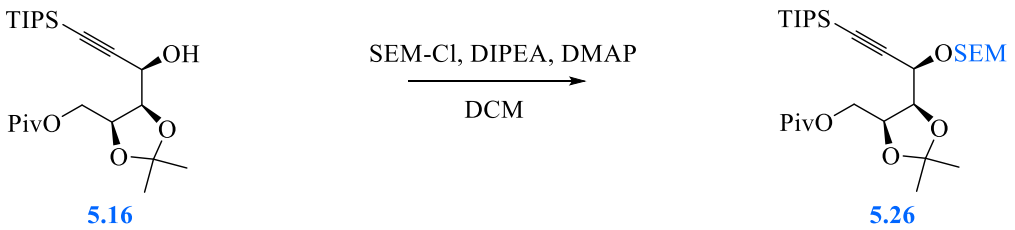
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*)159.9 (C), 130.5 (2 x CH), 128.2 (C), 114.2 (2 x CH), 109.6 (C), 105.8 (C), 87.6 (C), 80.3 (CH), 80.2 (C), 77.4 (CH), 75.8 (CH), 70.8 (CH_2), 67.4 (CH), 61.5 (CH), 55.3 (CH_3), 27.6 (CH_3), 25.3 (CH_3), 18.7 (6 x CH_3), 11.3 (3 x CH); δ (*β-epimer*) δ 159.8 (C), 130.3 (2 x CH), 128.5 (C), 114.0 (2 x CH), 109.8 (C), 106.1 (C), 87.5 (C), 79.9 (CH), 79.1 (C), 78.2 (CH), 76.9 (CH), 71.1 (CH_2), 67.6 (CH), 61.6 (CH), 55.3 (CH_3), 26.7 (CH_3), 25.3 (CH_3), 18.7 (6 x CH_3), 11.3 (3 x CH);

IR (ATR) ν_{max} 3451, 3274, 2941, 2865, 2172, 1612, 1514, 1463, 1381, 1248, 1066, 881 cm^{-1};

MS (ESI, +ve) *m/z* 509 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 509.2692, $C_{28}H_{42}{}^{23}NaO_5Si$ requires 509.2699.

((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl Pivaloate (5.26)



5.16 5.26

A magnetically stirred solution of alcohol **5.16** (1.58 g, 3.70 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (226 mg, 1.85 mmol) in dichloromethane (30 mL) maintained at 0 °C was treated, sequentially, with di-*iso*-propylethylamine (3.9 mL, 22.23 mmol) then, dropwise, with 2-(trimethylsilyl)ethoxymethyl chloride (3.3 mL, 18.5 mmol). After stirring for a further 30 min, the ensuing mixture was heated at reflux for 16 h before being cooled to 18 °C and poured into ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **5.26*** (1.90 g, 92%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 4.6 Hz, 1H), 4.50 (dd, *J* = 11.3 and 4.2 Hz, 1H), 4.40 (td, *J* = 6.9 and 4.2 Hz, 1H), 4.35–4.25 (complex m, 2H), 3.74 (td, *J* = 10.0 and 6.6 Hz, 1H), 3.54 (td, *J* = 10.0 and 6.6 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 1.21 (s, 9H), 1.06 (s, 21H), 0.96–0.91 (complex m, 2H), 0.00 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) 178.1 (CO), 109.4 (C), 102.7 (C), 92.2 (CH_2), 89.7 (C), 78.3 (CH), 75.3 (CH), 66.2 (CH_2), 65.2 (CH), 63.2 (CH_2), 38.8 (C), 27.5 (CH_3), 27.3 (3 x CH_3), 25.4 (CH_3), 18.7 (6 x CH_3), 18.2 (CH_2), 11.3 (3 x CH), −1.3 (3 x CH_3);

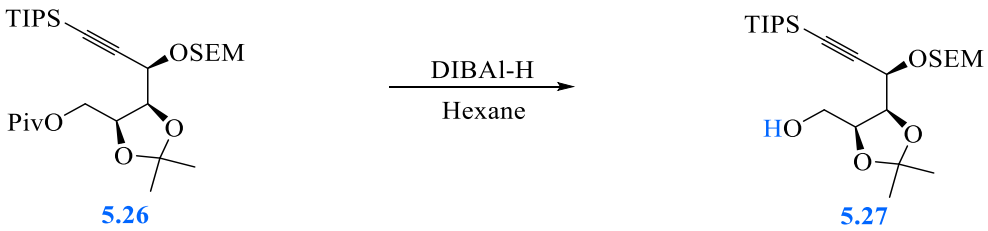
IR (ATR) ν_{max} 2957, 2866, 1732, 1462, 1381, 1248, 1156, 1022, 835 cm^{-1};

MS (ESI, +ve) *m/z* 579 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 579.3512, $C_{29}H_{56}{}^{23}NaO_6Si_2$ requires 579.3513;

Specific rotation $[\alpha]^{25}_D = -73.3$ (*c* 1.2, $CHCl_3$).

((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.27)



5.26 5.27

A magnetically stirred solution of pivaloate **5.26** (1.62 g, 2.90 mmol) in hexane (50 mL) maintained at −78 °C was treated, dropwise, with di-*iso*-butylaluminium hydride (5.8 mL of a 1.0 M solution in hexane, 5.82 mmol). After addition was complete, the reaction mixture was stirred for 30 min then treated with tartaric acid (50 mL of a 1.0 M aqueous solution) and stirring was continued at 18 °C for a further 1 h. The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 100 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 25:75 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.27*** (1.3 g, 94%) as a clear, colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 5.02 (d, *J* = 6.6 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 5.5 Hz, 1H), 4.36 (ddd, *J* = 7.6, 6.6 and 4.1 Hz, 1H), 4.28 (dd, *J* = 6.6 and 5.5 Hz, 1H), 3.97 (ABX, J_{AB} = 11.6 Hz, J_{AX} = 4.1 Hz, 1H), 3.83 (partially obscured ABX, J_{AB} = 11.6 Hz, J_{BX} = 7.6 Hz, 1H), 3.80 (partially obscured m, 1H), 3.65 (td, *J* = 9.1 and 7.4 Hz, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 1.14 (s, 3H), 1.13 (s, 18 H), 1.00–0.96 (complex m, 2H), 0.06 (s, 9H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ 109.9 (C), 104.8 (C), 93.4 (CH_2), 89.9 (C), 79.6 (CH), 79.4 (CH), 67.2 (CH_2), 66.8 (CH), 61.8 (CH_2), 27.9 (CH_3), 25.5 (CH_3), 19.1 (6 x CH_3), 18.9 (CH_2), 12.4 (3 x CH), −1.2 (3 x CH_3);

IR (ATR) ν_{max} 3505, 2944, 2866, 2171, 1463, 1381, 1249, 1027, 836 cm^{-1};

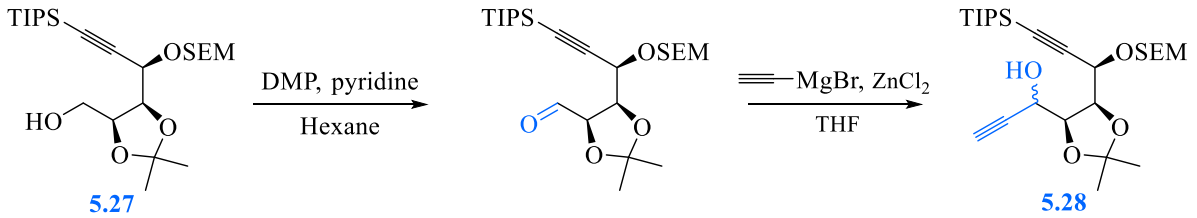
MS (ESI, +ve) *m/z* 495 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 495.2936, $C_{24}H_{48}{}^{23}NaO_5Si_2$ requires 495.2938;

Specific rotation $[\alpha]^{25}_D = -76.7$ (*c* 1.2, $CHCl_3$).

1-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (5.28)

Method A



A magnetically stirred solution of alcohol **5.27** (647 mg, 1.36 mmol) in dichloromethane (30 mL) maintained at 0 ºC was treated with the Dess-Martin periodinane (1.16 g, 2.72 mmol) and pyridine (0.55 mL, 6.84 mmol). The ensuing mixture was warmed to 18 °C and stirred for 3 h then quenched by addition of a mixture of sodium thiosulfate (15 mL of a 10% aqueous solution) and sodium hydrogen carbonate (15 mL of a saturated aqueous solution). The resulting slurry was filtered through Celite^{TM} and the separated aqueous layer associated with the filtrate was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried over magnesium sulfate, filtered and

concentrated under reduced pressure. The residue thus obtained was immediately submitted, without purification, to the next step of the reaction sequence.

A magnetically stirred solution of zinc chloride (2.55 mL of 1.0 M solution in diethyl ether, 2.55 mmol) maintained at 0 °C was treated with ethynylmagnesium bromide (15.3 mL of a 0.5 M solution in tetrahydrofuran, 7.65 mmol). The ensuing solution was cooled to −40 ºC and treated with a solution of aldehyde, formed as described above, in tetrahydrofuran (10 mL). After 4 h, the reaction mixture was poured into ammonium chloride (50 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave *compound* ***5.28*** (490 mg, 72% over 2 steps) as a clear, colourless oil and as an inseparable (25:75) mixture of α/β epimers.

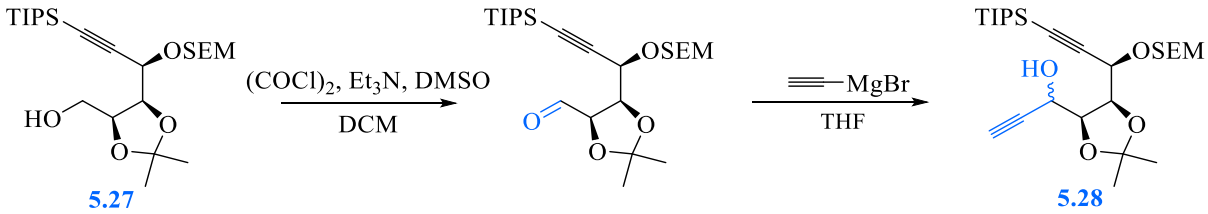
^{1}H NMR (400 MHz, CD_3OD) δ (*α-epimer*) 5.05 (d, *J* = 6.7 Hz, 1H), 4.92 (d, *J* = 4.6, 1H), 4.85 (partially obscured m, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.37–4.26 (complex partially obscured m, 2H), 3.89 (partially obscured m, 1H), 3.66 (partially obscured m, 1H), 2.88 (d, *J* = 2.1 Hz, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.16 (br s, 21H), 0.95–0.89 (complex m, 2H), 0.07 (s, 9H) (signal due to hydroxyl group proton not observed); δ (*β-epimer*)5.04 (d, *J* = 6.7 Hz, 1H), 4.94 (d, *J* = 4.2 Hz, 1H), 4.82 (dd, *J* = 6.6 and 2.1 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.37–4.26 (complex partially obscured m, 2H), 3.89 (partially obscured m, 1H), 3.66 (partially obscured m, 1H), 2.98 (d, *J* = 2.1 Hz, 1H), 1.58 (s, 3H), 1.42 (s, 3H), 1.15 (br s, 21H), 1.00–0.97 (complex m, 2H), 0.07 (s, 9H) (signal due to hydroxyl group proton not observed);

^{13}C NMR (100 MHz, CD_3OD) δ (*α-epimer*) 110.5 (C), 105.0 (C), 93.0 (CH_2), 90.3 (C), 84.4 (C), 80.3 (CH), 79.7 (CH), 74.9 (CH), 67.0(7) (CH_2), 66.5(0) (CH), 61.5 (CH), 27.2(6) (CH_3), 25.1(7) (CH_3), 19.1 (6 x CH_3), 18.9 (CH_2), 12.4 (3 x CH), −1.2 (3 x CH_3); δ (*β-epimer*) 110.6 (C), 104.8 (C), 93.1 (CH_2), 90.5 (C), 83.3 (C), 81.2 (CH), 79.5 (CH), 75.7 (CH), 67.1(5) (CH_2), 66.5(5) (CH), 61.4 (CH), 27.3(0) (CH_3), 25.2 (CH_3), 19.1 (6 x CH_3), 18.9 (CH_2), 12.4 (3 x CH), −1.2 (3 x CH_3); **IR** (ATR) ν_{max} 3471, 3313, 2944, 2866, 2176, 1463, 1381, 1249, 1025, 835 cm^{-1};

MS (ESI, +ve) *m/z* 519 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 519.2938, $C_{26}H_{48}{}^{23}NaO_5Si_2$ requires 519.2938.

Method B

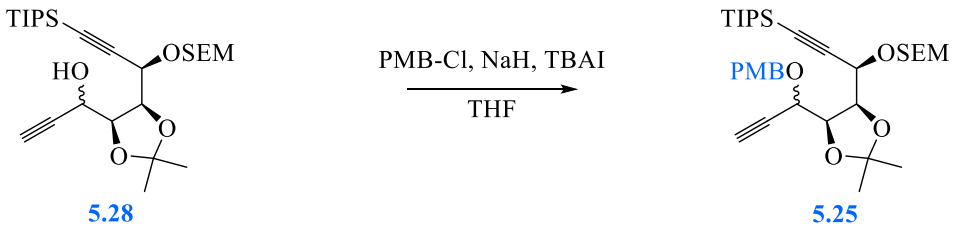


A magnetically stirred solution of oxalyl chloride (0.40 mL, 4.65 mmol) in dichloromethane (20 mL) maintained at −78 ºC was treated with dimethyl sulfoxide (0.60 mL, 8.46 mmol). The ensuing mixture was stirred for 30 min, then treated with the solution of alcohol **5.27** (1.00 g, 2.11 mmol) in dichloromethane (10 mL). The resulting mixture was stirred at −78 °C for another 30 min then treated with triethylamine (1.8 mL, 12.69 mmol) before being warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched with water (50 mL) and the separated aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried over magnesium sulfate, concentrated under reduced pressure. The residue thus obtained was used, without purification, in the next step of the reaction sequence.

A magnetically stirred solution of aldehyde, formed as described above, in tetrahydrofuran (50 mL) maintained at −15 °C was treated with ethynylmagnesium bromide (8.5 mL of 0.5 M solution in tetrahydrofuran, 4.23 mmol). The ensuing mixture was stirred for a further 1 h then poured into ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave *compound **5.28*** (1.00 g, 95% over 2 steps) as a clear, colourless oil and as an inseparable (30:70) mixture of α/β epimers. This material was identical, in all respects, with that obtained by method A.

(8*R*)-11,11-Di-*iso*-propyl-8-((4*R*,5*S*)-5-(1-((4-methoxybenzyl)oxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yne (5.25)

Method A



A magnetically stirred solution of alcohol **5.28** (1.00 g, 2.01 mmol) in dry tetrahydrofuran (25 mL) maintained at 0 °C was treated with sodium hydride (402 mg of 60% *w/w* dispersion in mineral oil, 10.06 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for a further 30 min then treated with *p*-methoxybenzyl chloride (0.57 mL, 5.03 mmol) and tetra-*n*-butyl ammonium iodide (372 mg, 1.01 mmol). After 16 h, the reaction mixture was quenched by dropwise addition of water (until no more gas evolution observed) then ammonium chloride (30 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 15:85 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.25*** (920 mg, 74%) as a clear, colourless oil and as an inseparable (30:70) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 7.32 (partially obscured d, *J* = 8.6 Hz, 2H), 6.86 (partially obscured d, *J* = 8.6 Hz, 2H), 5.02 (d, *J* = 6.9 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.85 (partially obscured m, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.46 (partially obscured m, 1H), 4.39–4.29 (complex partially obscured m, 2H), 3.79 (s, 3H), 3.68 (partially obscured m, 1H), 3.51 (partially obscured m, 1H), 2.57 (d, *J* = 2.0 Hz, 1H), 1.58 (s, 3H), 1.39 (s, 3H), 1.12–0.98 (complex partially obscured m, 21H), 0.98–0.80 (complex partially obscured m, 2H), −0.02 (s, 9H); δ (*β-epimer*) 7.32 (partially obscured d, *J* = 8.6 Hz, 2H), 6.86 (partially obscured d, *J* = 8.6 Hz, 2H), 4.97 (d, *J* = 6.9 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.63 (dd, *J* = 8.1 and 2.0 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.49–4.42 (complex partially obscured m, 1H), 4.39–4.29 (complex partially obscured m, 1H), 3.79 (s, 3H), 3.68 (partially obscured m, 1H), 3.51 (partially obscured m, 1H), 2.56 (d, *J* = 2.0

Hz, 1H), 1.58 (s, 3H), 1.39 (s, 3H), 1.12–0.98 (complex partially obscured m, 21H), 0.98–0.80 (complex partially obscured m, 2H), 0.01 (s, 9H);

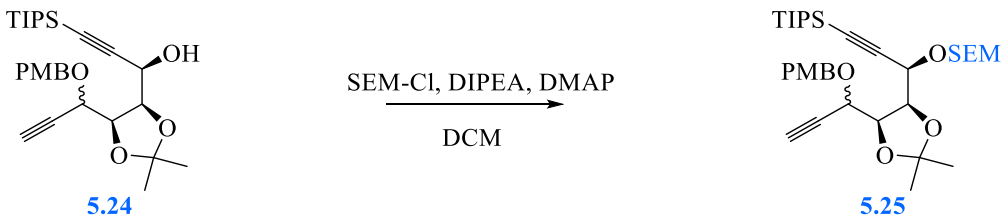
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*)159.6 (C), 130.4 (2 x CH), 129.2 (C), 114.0 (2 x CH), 109.8 (C), 103.1 (C), 91.7 (CH_2), 90.0 (C), 80.9 (C), 78.6 (CH), 77.3 (CH), 75.12 (CH), 70.7 (CH_2), 67.7 (CH), 65.6 (CH_2), 64.8 (CH), 55.3 (CH_3), 26.9 (CH_3), 24.8 (CH_3), 18.7 (6 x CH_3), 18.2 (CH_2), 11.4 (3 x CH), −1.3 (3 x CH_3); δ (*β-epimer*) 159.4 (C), 129.7(1) (2 x CH), 129.7(0) (C), 113.8 (2 x CH), 110.2 (C), 103.2 (C), 91.9 (CH_2), 89.9 (C), 80.1 (C), 78.7 (CH), 78.5 (CH), 76.3 (CH), 70.7 (CH_2), 67.5 (CH), 65.9 (CH_2), 65.2 (CH), 55.3 (CH_3), 26.9 (CH_3), 25.2 (CH_3), 18.7 (6 x CH_3), 18.3 (CH_2), 11.3 (3 x CH), −1.3 (3 x CH_3);

IR (ATR) ν_{max} 3310, 2943, 2865, 2172, 1613, 1514, 1380, 1248, 1027, 860, 834 cm^{-1};

MS (ESI, +ve) *m/z* 639 [$(M+Na)^+$, 100%], 634 [$(M+NH_4)^+$, 50];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 639.3515, $C_{34}H_{56}{}^{23}NaO_6Si_2$ requires 639.3513.

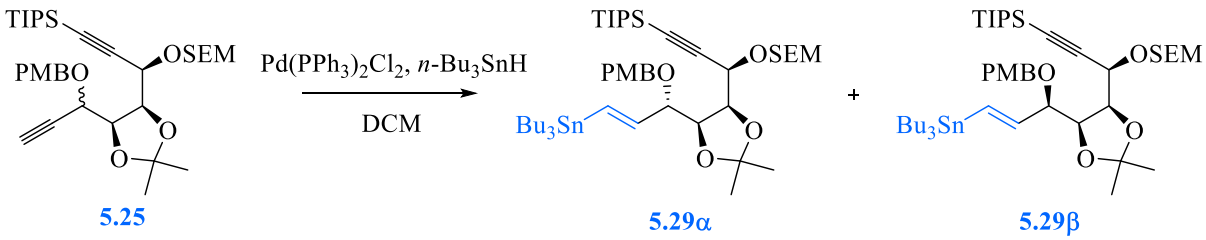
Method B



A magnetically stirred solution of alcohol **5.24** (0.90 g, 1.85 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (113 mg, 0.92 mmol) in dichloromethane (20 mL) maintained at 0 °C was treated, sequentially, with di-*iso*-propylethylamine (1.9 mL, 11.09 mmol) then, dropwise, with 2-(trimethylsilyl)ethoxymethyl chloride (1.6 mL, 9.25 mmol). After stirring for a further 30 min, the reaction mixture was heated at reflux for 16 h before being cooled to 18 °C and poured into ammonium chloride (30 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **5.25*** (1.00 g, 88%) as a clear, colourless oil

and as an inseparable (25:75) mixture of α/β epimers. This material was identical, in all respects, with that obtained by method A.

(*R*)-11,11-Di-*iso*-propyl-8-((4*R*,5*S*)-5-((*S*,*E*)-1-((4-methoxybenzyl)oxy)-3-(tributylstannyl)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yne (5.29α) and (*R*)-11,11-Di-*iso*-propyl-8-((4*R*,5*S*)-5-((*R*,*E*)-1-((4-methoxybenzyl)oxy)-3-(tributylstannyl)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yne (5.29β)



A magnetically stirred solution of bis(triphenylphosphine)palladium(II) dichloride (20 mg, 0.028 mmol) and compound **5.25** (350 mg, 0.57 mmol) in dry dichloromethane (15 mL) maintained at −78 ºC under an argon atmosphere was treated, dropwise over 2 min, with tri-*n*-butyltin hydride (0.33 mL, 1.13 mmol). The ensuing mixture was stirred for 30 min at −78 ºC then warmed to 0 ºC and maintained at this temperature for a further 30 min. After being warmed to 18 ºC, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica deactivated with 1% triethylamine in hexane, 10:90 *v/v* diethylether/hexane elution) and thus affording two fractions, A and B.

Concentration of fractions A (R_f = 0.3) afforded ***5.29β*** (270 mg, 52%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 19.2 Hz, $J_{H\text{-}Sn}$= 35.9 Hz, 1H), 6.06 (dd, *J* = 19.2 and 7.0 Hz, $J_{H\text{-}Sn}$= 29.5 Hz, 1H), 4.94 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 4.52 (ABq, Δ δ_{AB} = 0.09, J_{AB} = 11.4 Hz, 2H), 4.27–4.24 (complex m, 2H), 4.19 (m, 1H), 3.79 (s, 3H), 3.67 (td, *J* = 10.4 and 6.1 Hz, 1H), 3.53 (td, *J* = 10.4 and 6.1 Hz, 1H), 1.58 (s, 3H), 1.55–1.47 (complex m, 6H), 1.38 (s, 3H), 1.36–1.27 (complex m, 6H), 1.10–1.07 (complex m, 21H), 0.94–0.87 (complex m, 17H), 0.00 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C), 144.6 (CH), 135.8 (CH), 131.1 (C), 129.2 (2 x CH), 113.7 (2 x CH), 109.1 (C), 103.9 (C), 92.0 (CH_2), 89.2 (C), 81.2 (CH), 79.6 (CH), 78.3 (CH), 69.9 (CH_2), 66.0 (CH and CH_2), 55.3 (CH_3), 29.3 (3 x CH_2), 27.4 (3 x CH_2), 27.0 (CH_3), 25.4 (CH_3), 18.8 (6 x CH_3), 18.2 (CH_2), 13.9 (3 x CH_3), 11.4 (3 x CH), 9.7 (3 x CH_2), −1.3 (3 x CH_3);

IR (ATR) ν_{max} 2955, 2926, 2866, 1614, 1514, 1464, 1377, 1248, 1025, 860, 835 cm^{-1};

MS (ESI, +ve) *m/z* 931 (^{120}Sn) [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 931.4731, $C_{46}H_{84}{}^{23}NaO_6Si_2{}^{120}Sn$ requires 931.4726. $(M+H)^+$ 909.4905, $C_{46}H_{85}O_6Si_2{}^{120}Sn$ requires 909.4907;

Specific rotation $[\alpha]^{25}_D = -21.5$ (*c* 1.7, $CHCl_3$).

Concentration of fractions B (R_f = 0.2) afforded ***5.29α*** (100 mg, 19%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.43–6.13 (d, *J* = 19.1 Hz, $J_{H\text{-}Sn}$= 35.9 Hz, 1H), 6.02–5.74 (dd, *J* = 19.1 and 7.0 Hz, $J_{H\text{-}Sn}$= 31.0 Hz, 1H), 5.07 (d, *J* = 7.0 Hz, 1H), 4.90 (d, *J* = 1.9 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.45 (partially obscured m, 1H), 4.38 (ABq, Δ δ_{AB} = 0.15, J_{AB} = 10.3 Hz, 2H), 4.36 (dd, *J* = 7.2 and 2.0 Hz, 1H), 4.15 (dd, *J* = 9.3 and 7.2 Hz, 1H), 3.78 (s, 3H), 3.69 (ddd, *J* = 11.5, 10.0 and 5.7 Hz, 1H), 3.50 (ddd, *J* = 11.5, 10.0 and 5.7 Hz, 1H), 1.57–1.50 (complex m, 9H), 1.35–1.30 (complex m, 9H), 1.10 (br s, 21H), 0.95–0.88 (complex m, 17H), −0.20 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 145.8 (CH), 134.1 (CH), 130.2 (C), 130.1 (2 x CH), 114.0 (2 x CH), 109.2 (C), 103.8 (C), 91.6 (CH_2), 89.5 (C), 81.0 (CH), 79.2 (CH), 77.7 (CH), 69.9 (CH_2), 65.5 (CH_2), 65.4 (CH), 55.3 (CH_3), 29.3 (3 x CH_2), 27.3 (3 x CH_2), 26.9 (CH_3), 24.9 (CH_3), 18.8 (6 x CH_3), 18.2 (CH_2), 13.9 (3 x CH_3), 11.5 (3 x CH), 9.8 (3 x CH_2), −1.3 (3 x CH_3);

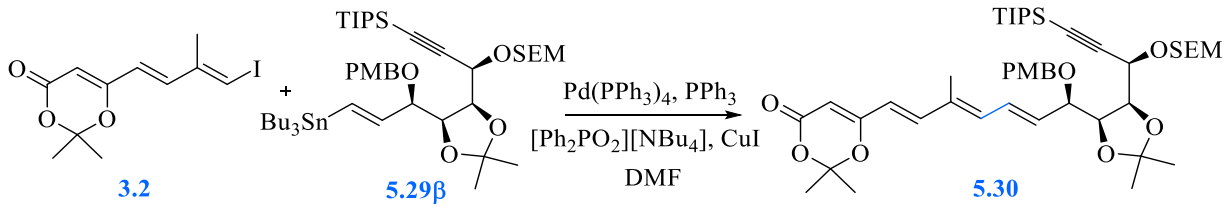
IR (ATR) ν_{max} 2954, 2926, 2866, 1613, 1515, 1464, 1378, 1249, 1031, 860, 835 cm^{-1};

MS (ESI, +ve) *m/z* 931 [$(M+Na)^+$, 50%], 926 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 931.4709, $C_{46}H_{84}{}^{23}NaO_6Si_2{}^{120}Sn$ requires 931.4726;

Specific rotation $[\alpha]^{25}_D = -50.5$ (*c* 1.0, $CHCl_3$).

6-((*R*,1*E*,3*E*,5*E*)-7-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-((4-methoxybenzyl)oxy)-3-methylhepta-1,3,5-trien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (5.30)



A Schlenk flask was charged with tetra-*n*-butylammonium diphenylphosphinate (262 mg, 0.57 mmol). This was melted then cooled to ambient temperature (twice) under high vacuum. Thereafter, tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol), copper thiophene-2-carboxylate (109 mg, 0.57 mmol) and triphenylphosphine (10.7 mg, 0.04mmol) were introduced under an argon atmosphere, followed by addition of a degassed solution of stannane **5.29β** (370 mg, 0.41 mmol) and alkenyl iodide **3.2** (117 mg, 0.37 mmol) in *N*,*N*-dimethylformamide (10 mL). After 30 min, the reaction mixture was diluted with diethyl ether (20 mL) then quenched with water (10 mL) and filtered through a short pad of Celite™. The separated aqueous layer associated with the filtrate was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with water (2 x 30) and brine (1 x 20 mL) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 10:30:60 *v/v/v* diethyl ether/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.1) afforded *compound **5.30*** (260 mg, 87%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.73 (dd, *J* = 15.2 and 11.3 Hz, 1H), 6.37 (d, *J* = 11.3 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 5.91 (dd, *J* = 15.2 and 7.7 Hz, 1H), 5.35 (s, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 4.51 (ABq, Δ δ_{AB} = 0.02, J_{AB} = 11.4 Hz, 2H), 4.45 (t, *J* = 7.7 Hz, 1H), 4.27 (t, *J* = 6.8 Hz, 1H), 4.19 (dd, *J* = 6.8 and 5.0 Hz, 1H), 3.79 (s, 3H), 3.60 (ddd, *J* = 11.1, 9.9 and 5.8 Hz, 1H), 3.55 (ddd, *J* = 11.1, 9.9 and 5.8 Hz, 1H), 1.9 1(s, 3H), 1.72 (s, 3H), 1.71 (s, 3H), 1.58 (s, 3H), 1.38 (s, 3H), 1.12–1.05 (complex m, 21H), 0.89–0.73 (complex m, 2H), −0.04 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C), 162.0 (C), 159.2 (C), 141.9 (CH), 136.6 (CH), 135.1 (C), 134.2 (CH), 130.7 (C), 130.5 (CH), 129.2 (2 x CH), 119.6 (CH), 113.8 (2 x CH), 109.4 (C), 106.4 (C), 103.4 (C), 94.7 (CH), 91.9 (CH_2), 89.8 (C), 79.7 (CH), 78.2 (CH), 78.0 (CH),

70.6 (CH_2), 66.0 (CH_2), 65.4 (CH), 55.3 (CH_3), 27.0 (CH_3), 25.3 (CH_3), 25.2 (2 x CH_3), 18.7 (6 x CH_3), 18.2 (CH_2), 12.6 (CH_3), 11.3 (3 x CH), −1.3 (3 x CH_3);

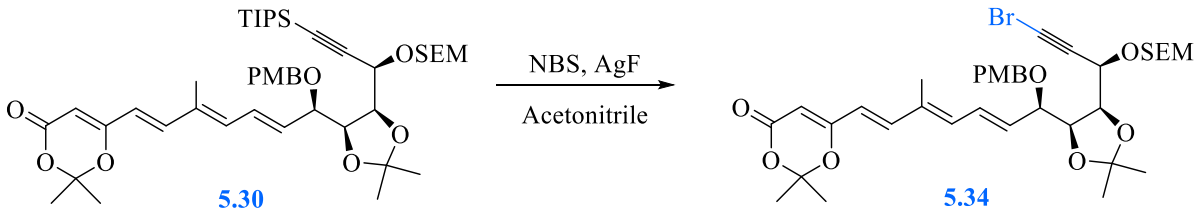
IR (ATR) ν_{max} 2944, 2865, 1725, 1613, 1514, 1380, 1248, 1024, 836 cm^{-1};

MS (ESI, +ve) *m/z* 833 [$(M+Na)^+$, 50%], 828 [$(M+NH_4)^+$, 70], 811 [$(M+H)^+$, 65], 82 [$(C_3H_8O+Na)^+$, 90], 55 [$(CH_3OH+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 833.4465, $C_{45}H_{70}{}^{23}NaO_9Si_2$ requires 833.4456. $(M+H)^+$ 811.4634, $C_{45}H_{71}O_9Si_2$ requires 811.4637;

Specific rotation $[\alpha]^{25}_D$ = +38.0 (*c* 1.1, $CHCl_3$).

6-((*R*,1*E*,3*E*,5*E*)-7-((4*S*,5*R*)-5-((*R*)-3-Bromo-1-((2-(trimethylsilyl)ethoxy)methoxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-((4-methoxybenzyl)oxy)-3-methylhepta-1,3,5-trien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (5.34)



A magnetically stirred solution of alkyne **5.30** (58 mg, 0.07 mmol) in acetonitrile (3 mL) was treated, sequentially, with *N*-bromosuccinimide (15 mg, 0.08 mmol) then silver fluoride (11 mg, 0.08 mmol). The ensuing mixture was protected from light and stirred for 4 h at ambient temperatures then filtered through a pad of Celite™ that was washed with ether (1 x 10 mL). The combined filtrates were washed with water (1 x 10 mL) then dried over magnesium sulfate and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.34*** (35 mg, 67%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 15.5 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.65 (dd, *J* = 15.2 and 11.3 Hz, 1H), 6.36 (d, *J* = 11.3 Hz, 1H), 6.04 (d, *J* = 15.5 Hz, 1H), 5.86 (dd, *J* = 15.2 and 7.1 Hz, 1H), 5.36 (s, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 4.9 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.28 (complex m, 2H), 4.18 (m, 1H), 3.80 (s, 3H), 3.56 (ddd, *J* = 11.3, 9.7 and 5.8 Hz, 1H),

3.49 (ddd, *J* = 11.3, 9.7 and 5.8 Hz, 1H), 1.93 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.58 (s, 3H), 1.41 (s, 3H), 0.86–0.76 (complex m, 2H), −0.03 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C), 162.1 (C), 159.2 (C), 141.9 (CH), 136.5 (CH), 135.3 (C), 133.9 (CH), 130.9 (C), 130.3 (CH), 129.3 (2 x CH), 119.8 (CH), 113.9 (2 x CH), 109.9 (C), 106.5 (C), 94.8 (CH), 92.5 (CH_2), 79.5 (CH), 78.4 (CH), 77.4 (CH), 76.6 (C), 70.2 (CH_2), 66.2 (CH), 66.1 (CH_2), 55.4 (CH_3), 47.7 (C), 26.9 (CH_3), 25.5 (CH_3), 25.3 (CH_3), 25.2 (CH_3), 18.2 (CH_2), 12.7 (CH_3), −1.3 (3 x CH_3);

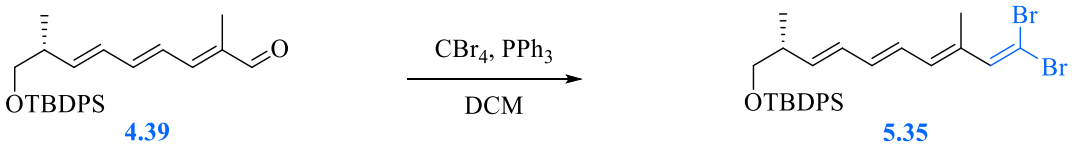
IR (ATR) ν_{max} 2992, 2942, 1723, 1612, 1514, 1380, 1248, 1023, 836 cm^{-1};

MS (ESI, +ve) *m/z* 805 and 803 [$(M+CH_3OH+K)^+$, both 40%], 757 and 755 [$(M+Na)^+$, both 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 757.2207, $C_{36}H_{49}{}^{81}Br^{23}NaO_9Si$ requires 757.2206. $(M+Na)^+$ 755.2220, $C_{36}H_{49}{}^{79}Br^{23}NaO_9Si$ requires 755.2227;

Specific rotation $[\alpha]^{25}_D = -1.0$ (*c* 1.0, $CHCl_3$).

***tert*-Butyl(((*R*,3*E*,5*E*,7*E*)-10,10-dibromo-2,8-dimethyldeca-3,5,7,9-tetraen-1-yl)oxy)diphenylsilane (5.35)**



4.39 5.35

A magnetically stirred solution of carbon tetrabromide (554 mg, 1.67 mmol) in dry dichloromethane (10 mL) maintained at 0 °C was treated with triphenylphosphine (877 mg, 3.34 mmol). After 15 min, the ensuing mixture was slowly treated with a solution of aldehyde **4.39** (350 mg, 0.84 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 15 min then warmed to 18 °C and maintained at this temperature for a further 30 min. The reaction solvent was removed by evaporation and the residue was filtered through a pad of TLC-grade silica gel that was eluted with diethyl ether/hexane (2 x 30 mL of 1:4 *v/v* mixture). The combined filtrates were concentrated under reduced pressure to give the *compound **5.35*** (400 mg, 83%) as a clear, yellow oil (R_f = 0.6 in 5:95 *v/v* diethyl ether/hexane). This material was used, without purification, in the next step of reaction sequence.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (complex m, 4H), 7.45–7.37 (complex m, 6H), 7.05 (s, 1H), 6.40 (dd, *J* = 14.3 and 10.6 Hz, 1H), 6.32 (dd, *J* = 14.3 and 10.0 Hz, 1H), 6.26 (d, *J* = 10.6 Hz, 1H), 6.17 (dd, *J* = 15.2 and 10.0 Hz, 1H), 5.77 (dd, *J* = 15.2 and 7.4 Hz, 1H), 3.59 (ABX, J_{AB} = 9.7, J_{AX} = 6.3 Hz, 1H), 3.54 (ABX, J_{AB} = 9.7, J_{BX} = 6.6 Hz, 1H), 2.48 (hept, *J* = 6.5 Hz, 1H), 2.08 (s, 3H), 1.08 (s, 9H), 1.07 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9 (CH), 139.4 (CH), 136.0 (CH), 135.8 (2 x CH), 135.8 (2 x CH), 134.7 (CH), 134.0 (C), 134.0 (C), 132.2 (C), 130.4 (CH), 129.7 (2 x CH), 127.7 (4 x CH), 126.6 (CH), 85.9 (C), 68.5 (CH_2), 39.8 (CH), 27.0 (3 x CH_3), 19.5 (C), 16.6 (CH_3), 15.6 (CH_3);

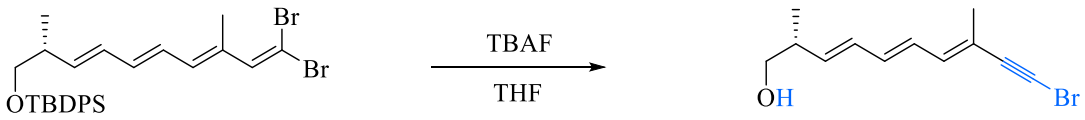
IR (KBr) ν_{max} 3028, 2959, 2930, 2857, 1471, 1427, 1112, 987, 701 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 519 [$(M-HBr+Na)^{+\bullet}$, 30%], 517 (60), 515 (30), 239 (35), 199 (80), 135 (100);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 576.0692, $C_{28}H_{34}{}^{81}Br_2OSi$ requires 576.0705. $M^{+\bullet}$ 574.0714, $C_{28}H_{34}{}^{79}Br^{81}BrOSi$ requires 574.0725. $M^{+\bullet}$ 572.0741, $C_{28}H_{34}{}^{79}Br_2OSi$ requires 572.0746;

Specific rotation $[\alpha]^{25}_D$ = +1.6 (*c* 1.6, $CHCl_3$).

(*R*,3*E*,5*E*,7*E*)-10-Bromo-2,8-dimethyldeca-3,5,7-trien-9-yn-1-ol (5.36)



5.35 5.36

A magnetically stirred solution of silyl ether **5.35** (350 mg, 0.61 mmol) in tetrahydrofuran (10 mL) was treated with tetra-*n*-butylammonium fluoride (3.3 mL of 1.0 M solution in tetrahydrofuran, 3.30 mmol). After 6 h, the reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* diethyl ether/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *alcohol **5.36*** (130 mg, 84%) as a clear, yellow oil. As the compound was found to be unstable, only the following data were acquired on it.

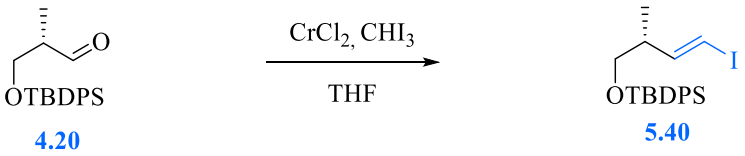
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48–6.31 (complex m, 2H), 6.31–6.15 (complex m, 2H), 5.68 (dd, *J* = 14.5 and 7.9 Hz, 1H), 3.53 (ABX, J_{AB} = 10.5, J_{AX} = 5.6 Hz, 1H), 3.47 (ABX, J_{AB} = 10.5, J_{BX} = 6.1 Hz, 1H), 2.44 (hept, *J* = 6.6 Hz, 1H), 2.08 (s, 3H), 1.47 (br s, OH), 1.04 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (CH), 137.1 (CH), 134.6 (CH), 131.4 (CH), 127.0 (CH), 118.0 (C), 84.0 (C), 67.4 (CH_2), 49.5 (C), 40.0 (CH), 17.4 (CH_3), 16.4 (CH_3);

IR (KBr) ν_{max} 3367, 3026, 2960, 2923, 2872, 2175, 1602, 1455, 1382, 1031, 987 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 254 and 256 ($M^{+\bullet}$, both 20%), 223 and 225 (both 18%), 199 (100), 129 (70).

(*R*,*E*)-*tert*-Butyl((4-iodo-2-methylbut-3-en-1-yl)oxy)diphenylsilane (5.40)



4.20 5.40

A magnetically stirred solution of chromium chloride (1.03 g, 8.42 mmol), dispensed in a glove box, in dry tetrahydrofuran (20 mL) maintained at 18 ºC under an argon atmosphere was slowly treated, *via* cannula, with a solution of aldehyde **4.20** (500 mg, 1.53 mmol) and iodoform (1.50 g, 3.82 mmol) in dry tetrahydrofuran (20 mL). The ensuing mixture was stirred for 16 h then filtered through a pad of Celite^{TM}. Water/diethyl ether (60 mL of a 1:1 *v/v* mixture) was added to the filtrate and the separated aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried over magnesium sulfate, then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2.5:97.5 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) afforded the alkenyl iodide **5.40**[145] (470 mg, 68%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (complex m, 4H), 7.30–7.24 (complex m, 6H), 6.37 (dd, *J* = 14.5 and 7.6 Hz, 1H), 5.93 (d, *J* = 14.5 Hz, 1H), 3.39 (d, *J* = 6.3 Hz, 2H), 2.29 (hept, *J* = 6.8 Hz, 1H), 0.94 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (CH), 135.8 (2 x CH), 135.7 (2 x CH), 133.8 (C), 133.7 (C), 129.8 (2 x CH), 127.8 (4 x CH), 75.4 (CH), 67.7 (CH_2), 43.2 (CH), 27.0 (3 x CH_3), 19.4 (C), 15.7 (CH_3);

IR (ATR) ν_{max} 2959, 2930, 2857, 1471, 1427, 1110, 1084, 823, 738, 699 cm^{-1};

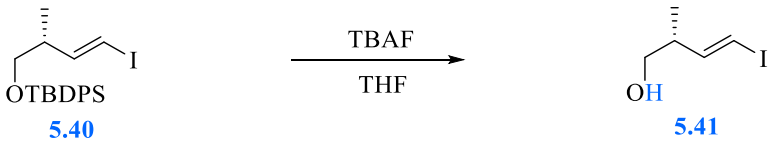
MS (ESI, +ve) *m/z* 473 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 473.0777, $C_{21}H_{27}{}^{127}I^{23}NaOSi$ requires 473.0774;

Specific rotation $[\alpha]^{25}_D$ = +10.6 (*c* 0.8, $CHCl_3$).

These data matched those reported previously.[145]

(*R*,*E*)-4-Iodo-2-methylbut-3-en-1-ol (5.41)



5.40 5.41

A magnetically stirred solution of silyl ether **5.40** (470 mg, 1.04 mmol) in tetrahydrofuran (10 mL) was treated with tetra-*n*-butylammonium fluoride (1.6 mL of 1.0 M solution in tetrahydrofuran, 1.60 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded alcohol **5.41**[146] (195 mg, 88%) as a clear, light-pink oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 14.5 and 7.9 Hz, 1H), 6.15 (dd, *J* = 14.5 and 1.1 Hz, 1H), 3.50 (ABX, J_{AB} = 10.6, J_{AX} = 5.8, 1H), 3.46 (ABX, J_{AB} = 10.6, J_{BX} = 7.3 Hz, 1H), 2.40 (hept, *J* = 6.8 Hz, 1H), 1.57 (br s, OH), 1.02 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (CH), 76.1 (CH), 66.6 (CH_2), 43.5 (CH), 15.7 (CH_3).

These data matched those reported previously.[146] The following additional data were acquired on this compound.

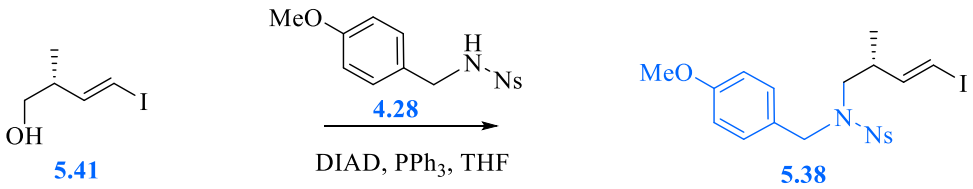
IR (ATR) ν_{max} 3325, 2959, 2927, 2871, 1603, 1455, 1379, 1229, 1181, 1031, 947 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 212 ($M^{+\bullet}$, 25%), 199 (50), 181 (95), 85 (82), 55 (100);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 211.9709, $C_5H_9{}^{127}IO$ requires 211.9698;

Specific rotation $[\alpha]^{25}_D$ = +24.7 (*c* 0.7, $CHCl_3$).

(*R*,*E*)-*N*-(4-Iodo-2-methylbut-3-en-1-yl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (5.38)



A magnetically stirred solution of alcohol **5.41** (300 mg, 1.41 mmol) and *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** (730 mg, 2.26 mmol) in tetrahydrofuran (20 mL) maintained at 0 °C was treated, sequentially, with triphenylphosphine (482 mg, 1.84 mmol) then di-*iso*-propyl azodicarboxylate (0.36 mL, 1.84 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound **5.38*** (660 mg, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.75–7.61 (complex m, 3H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.15 (dd, *J* = 14.4 and 8.3 Hz, 1H), 5.96 (d, *J* = 14.4 Hz, 1H), 4.44 (ABq, Δ δ_{AB} = 0.09, J_{AB} = 15.3 Hz, 2H), 3.79 (s, 3H), 3.15 (d, *J* = 7.8 Hz, 2H), 2.41 (hept, *J* = 6.8 Hz, 1H), 0.86 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C), 148.1 (CH), 148.0 (C), 133.9 (C), 133.7 (CH), 131.9 (CH), 131.1 (CH), 129.9 (2 x CH), 127.0 (C), 124.6 (CH), 114.3 (2 x CH), 76.5 (CH), 55.4 (CH_3), 51.8 (CH_2), 51.3 (CH_2), 39.3 (CH), 17.0 (CH_3);

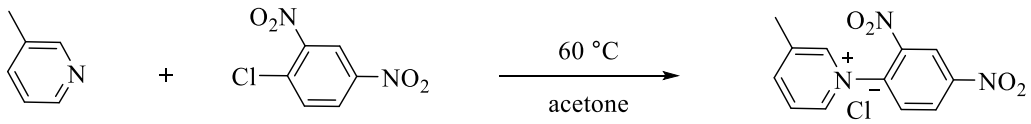
IR (KBr) ν_{max} 2963, 2931, 1611, 1540, 1512, 1455, 1342, 1245, 1160, 1027, 910, 728 cm^{-1};

MS (ESI, +ve) *m/z* 539 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 539.0112, $C_{19}H_{21}{}^{127}IN_2{}^{23}NaO_5S$ requires 539.0114;

Specific rotation $[\alpha]^{25}_D$ = +23.7 (*c* 1.1, $CHCl_3$).

1-(2,4-Dinitrophenyl)-3-methylpyridin-1-ium chloride (5.42)



5.42

A magnetically stirred solution of 3-methylpyridine (2.00 mL, 20.55 mmol) in acetone (20 mL) was treated, in one portion, with 2,4-dinitrochlorobenzene (4.12 g, 20.35 mmol). The ensuing mixture was heated to 60 °C for 30 h then the reaction solvent was removed under vacuum. The solid associated with the residue was removed by filtration and washed several times (hexane) to afford pyridinium salt **5.42**[147] (5.50 g, 90%) as a purple powder.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.32 (s, 1H), 9.24 (d, *J* = 6.2 Hz, 1H), 9.11 (d, *J* = 2.6 Hz, 1H), 8.95 (dd, *J* = 8.7, 2.6 Hz, 1H), 8.79 (d, *J* = 8.2 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 8.32 (dd, *J* = 8.2, 6.2 Hz, 1H), 2.59 (s, 3H).

These data matched those reported previously.[147] The following additional data were acquired on this compound.

^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ 149.6 (C), 149.5 (CH), 145.7 (CH), 143.7 (CH), 143.4 (C), 139.4 (CH), 139.1 (C), 132.3 (CH), 130.7 (CH), 127.8 (CH), 122.0 (CH), 18.4 (CH_3);

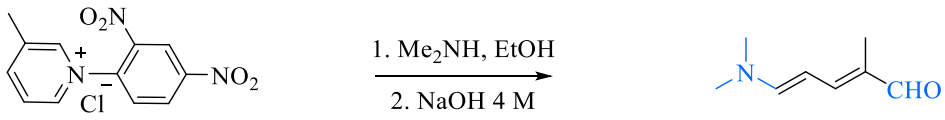
IR (ATR) ν_{max} 3392, 2916, 1603, 1531, 1342, 1123, 1084, 834, 818 cm^{-1};

MS (ESI, +ve) *m/z* 260 [$(M–Cl^–)^+$, 100%], 214 [$(M–Cl^––NO_2)^+$, 50];

HRMS (ESI, +ve) Found: $(M–Cl^–)^+$ 260.0672, $C_{12}H_{10}N_3O_4$ requires 260.0671;

Melting point 187–189 °C.

(2*E*,4*E*)-5-(Dimethylamino)-2-methylpenta-2,4-dienal (5.43)



5.42 Zincke aldehyde 5.43

A magnetically stirred solution of pyridinium salt **5.42** (1.00 g, 3.38 mmol) in ethanol (20 mL) was treated, dropwise, with dimethylamine (0.95 mL of a 40% *w/w* solution in water, 8.46 mmol). The ensuing mixture was heated to 78 °C for 1 h and solvent then removed, under reduced pressure from the cooled reaction mixture. The residue thus obtained was dissolved in sodium hydroxide (20 mL of a 4 M aqueous solution) and the ensuing solution transferred to a separatory funnel containing dichloromethane (20 mL). The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, diethyl ether elution) and concentration of the appropriate fractions (R_f = 0.2) afforded aldehyde **5.43**[147] (0.45 g, 96%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 6.80 (d, *J* = 12.1 Hz, 1H), 6.73 (d, *J* = 12.1, Hz, 1H), 5.20 (t, *J* = 12.1 Hz, 1H), 2.91 (s, 6H), 1.71 (s, 3H).

These data matched those reported previously[147] The following additional data were acquired on this compound.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6 (CO), 153.7 (CH), 151.5 (CH), 125.7 (C), 94.9 (CH), 40.8 (2 x CH_3), 9.1 (CH_3);

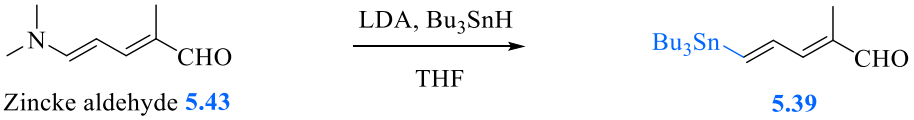
IR (ATR) ν_{max} 3467, 2910, 1547, 1375, 1221, 1180, 1102, 998, 817 cm^{-1};

MS (ESI, +ve) *m/z* 162 [$(M+Na)^+$, 100%], 140 [$(M+H)^+$, 95];

HRMS (ESI, +ve) Found: $(M+H)^+$ 140.1071, $C_8H_{14}NO$ requires 140.1075;

Melting point 74 °C.

(2*E*,4*E*)-2-Methyl-5-(tributylstannyl)penta-2,4-dienal (5.39)



Zincke aldehyde **5.43** **5.39**

A magnetically stirred solution of di-*iso*-propylamine (0.42 mL, 3.02 mmol) and tetrahydrofuran (10 mL) maintained at 0 °C was treated, dropwise, with *n*-butyllithium (2.60 mL of a 1.3 M solution in hexane, 2.60 mmol). After 5 min, tri-*n*-butyltin hydride (0.64 mL, 2.38 mmol) was introduced, and the ensuing mixture was stirred for a further 10 min before being treated, dropwise, with a solution of aldehyde **5.43** (0.30 g, 2.15 mmol) in tetrahydrofuran (2 mL). The reaction mixture was then warmed to 18 °C and treated with acetyl chloride (0.46 mL, 6.46 mmol). After stirring for 10 min, sodium hydrogen carbonate (20 mL of a saturated aqueous solution) was added to the reaction mixture and stirring was continued for a further 15 min. The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:97 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the title compound **5.39**[147] (500 mg, 60%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.14-6.90 (complex m, 2H), 6.74 (dd, *J* = 9.2 and 0.9 Hz, 1H), 1.88 (s, 3H), 1.62–1.47 (complex m, 6H), 1.42–1.25 (complex m, 6H), 1.08-0.94 (complex m, 6H), 0.90 (t, *J* = 7.3 Hz, 9H).

These data matched those reported previously.[147] The following additional data were acquired on this compound.

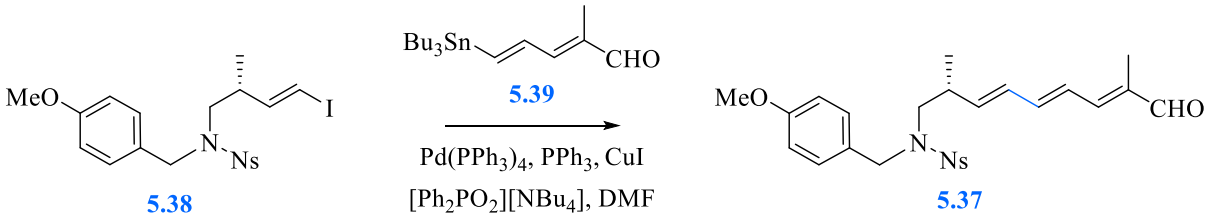
^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8 (CO), 150.3 (CH), 149.8 (CH), 141.5 (CH), 135.9 (C), 29.2 (3 x CH_2), 27.4 (3 x CH_2), 13.8 (3 x CH_3), 9.9 (3 x CH_2), 9.6 (CH_3);

IR (ATR) ν_{max} 2955, 2923, 2852, 1675, 1619, 1463, 1395, 1377, 1354, 1237, 1159, 997 cm^{-1};

MS (ESI, +ve) *m/z* 450 [$(M+CH_3CN+Na)^+$, 100%], 441 [$(M+CH_3OH+Na)^+$, 80], 409 [$(M+Na)^+$, 85], 387 [$(M+H)^+$, 20];

HRMS (ESI, +ve) Found: $(M+H)^+$ 387.1711, $C_{18}H_{35}O^{120}Sn$ requires 387.1710.

_N_-((_R_,3_E_,5_E_,7_E_)-2,8-Dimethyl-9-oxonona-3,5,7-trien-1-yl)-_N_-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (5.37)



A Schlenk flask was charged with tetra-*n*-butylammonium diphenylphosphinate (593 mg, 1.29 mmol) that was melted then cooled to ambient temperature (twice) under high vacuum. Thereafter, tetrakis(triphenylphosphine)palladium(0) (53 mg, 0.05 mmol), triphenylphosphine (25 mg, 0.09 mmol) and copper thiophene-2-carboxylate (246 mg, 1.29 mmol) were introduced under an argon atmosphere, followed by addition of a degassed solution of stannane **5.39** (355 mg, 0.92 mmol) and alkenyl iodide **5.38** (452 mg, 0.87 mmol) in *N*,*N*-dimethylformamide (10 mL). After 30 min, the reaction mixture was diluted with diethyl ether (20 mL) then quenched with water (10 mL) and filtered through a short pad of Celite™. The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were then washed with water (2 x 20) and brine (1 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **5.37*** (370 mg, 87%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, CHO), 7.97 (d, *J* = 7.7 Hz, 1H), 7.74–7.57 (complex m, 3H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (partially obscured d, *J* = 8.6 Hz, 3H), 6.51 (dd, *J* = 14.8 and 11.1 Hz, 1H), 6.40 (dd, *J* = 14.8 and 10.5 Hz, 1H), 6.07 (dd, *J* = 15.2 and 10.5 Hz, 1H), 5.63 (dd, *J* = 15.2 and 8.2 Hz, 1H), 4.45 (ABq, Δ δ_{AB} = 0.07, J_{AB} = 15.4 Hz, 2H), 3.78 (s, 3H), 3.23 (ABX, J_{AB} = 14.6, J_{AX} = 8.3 Hz, 1H), 3.18 (ABX, J_{AB} = 14.6, J_{BX} = 7.0 Hz, 1H), 2.50 (hept, *J* = 6.7 Hz, 1H), 1.85 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7 (CO), 159.6 (C), 148.6 (CH), 148.0 (C), 142.3 (CH), 141.2 (CH), 137.5 (C), 134.0 (C), 133.5 (CH), 131.7 (CH), 131.2 (CH), 130.6 (CH), 129.9 (2 x CH), 127.1 (C), 126.4 (CH), 124.4 (CH), 114.2 (2 x CH), 55.4 (CH_3), 52.7 (CH_2), 51.3 (CH_2), 36.0 (CH), 17.6 (CH_3), 9.6 (CH_3);

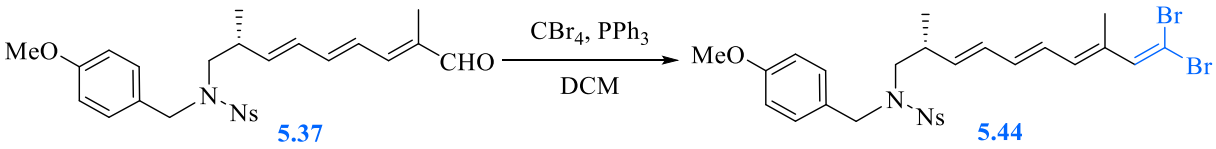
IR (KBr) ν_{max} 2970, 2930, 1666, 1610, 1542, 1513, 1352, 1248, 1161, 1004 cm^{-1};

MS (ESI, +ve) *m/z* 507 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 507.1555, $C_{25}H_{28}N_2{}^{23}NaO_6S$ requires 507.1566;

Specific rotation $[\alpha]^{25}_D$ = +9.4 (*c* 3.5, $CHCl_3$).

N-((*R*,3*E*,5*E*,7*E*)-10,10-Dibromo-2,8-dimethyldeca-3,5,7,9-tetraen-1-yl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (5.44)



A magnetically stirred solution of carbon tetrabromide (137 mg, 0.41 mmol) in dry dichloromethane (5 mL) maintained at 0 °C was treated with triphenyl phosphine (217 mg, 0.83 mmol). After 15 min, the ensuing mixture was slowly treated with a solution of aldehyde **5.37** (100 mg, 0.21 mmol) in dry dichloromethane (5 mL). The reaction mixture was stirred for 15 min then warmed to 18 °C and maintained at this temperature for a further 30 min. The reaction solvent was removed by evaporation and the residue thus obtained was filtered through a pad of TLC-grade silica gel that was eluted with diethyl ether/hexane (2 x 30 mL of a 1:1 *v/v* mixture). The combined filtrates were concentrated under reduced pressure to give *compound **5.44*** (119 mg, 90%) as a clear, light-yellow oil (R_f = 0.3 in 50:50 *v/v* diethyl ether/hexane). This material was used, without purification, in the next step of reaction sequence.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 8.09 (dd, *J* = 7.8 and 1.2 Hz, 1H), 7.93–7.81 (complex m, 3H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.19 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.42 (dd, *J* = 13.6 and 11.4 Hz, 1H), 6.33 (d, *J* = 11.4 Hz, 1H), 6.15 (dd, *J* = 13.6 and 10.8 Hz, 1H), 6.06 (dd, *J* = 14.5 and 10.4 Hz, 1H), 5.46 (dd, *J* = 14.5 and 8.3 Hz, 1H), 4.52 (ABq, Δ δ_{AB} = 0.10, J_{AB} = 15.3 Hz, 2H), 3.79 (s, 3H), 3.23 (ABX, J_{AB} = 14.4, J_{AX} = 8.4 Hz, 1H), 3.18 (ABX, J_{AB} = 14.4, J_{BX} = 7.3 Hz, 1H), 2.50 (hept, *J* = 6.7 Hz, 1H), 2.07 (s, 3H), 0.86 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 160.4 (C), 148.9 (C), 141.9 (CH), 139.1 (CH), 136.7 (CH), 135.8 (CH), 134.9 (CH), 134.2 (C), 133.1 (C), 132.9 (CH), 131.9 (CH), 131.5 (CH), 130.7 (2 x CH), 128.6 (CH), 127.7 (CH), 125.2 (CH), 114.8 (2 x CH), 85.9 (C), 55.5 (CH_3), 53.3 (CH_2), 51.5 (CH_2), 36.3 (CH), 17.8 (CH_3), 15.5 (CH_3);

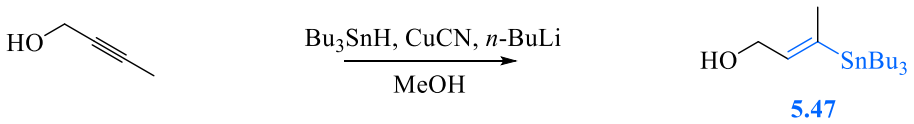
IR (KBr) ν_{max} 2962, 2929, 1611, 1542, 1512, 1359, 1248, 1161, 1027, 989, 777 cm^{-1};

MS (ESI, +ve) *m/z* 663 [$(M+Na)^+$, 40%], 658 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 664.9962, $C_{26}H_{28}{}^{81}Br_2N_2{}^{23}NaO_5S$ requires 664.9942. $(M+Na)^+$ 662.9957, $C_{26}H_{28}{}^{79}Br{}^{81}Br{}^{23}NaN_2O_5S$ requires 662.9963. $(M+Na)^+$ 660.9964, $C_{26}H_{28}{}^{79}Br_2{}^{23}NaN_2O_5S$ requires 660.9983;

Specific rotation $[\alpha]^{25}_D$ = +3.5 (*c* 1.7, $CHCl_3$).

(*E*)-3-(Tributylstannyl)but-2-en-1-ol (5.47)



5.47

A magnetically stirred solution of copper cyanide (2.39 g, 26.70 mmol) in tetrahydrofuran (100 mL) maintained at –78 °C was treated with *n*-butyllithium (35.7 mL of a 1.5 M solution in hexane, 53.55 mmol). After 5 min, the reaction mixture was warmed to −40 °C and stirred for a further 10 min. The by now almost clear solution was cooled to −78 °C and tri-*n*-butyltin hydride (14.3 mL, 53.55 mmol) was added, dropwise, resulting in an immediate formation of a turbid yellow solution. Evolution of gas was also observed. After stirring for an additional 10 min at −78 °C, the reaction mixture was warmed to −40 °C for 5 min giving an almost clear golden-yellow solution. The reaction mixture was then re-cooled to −78 °C before being treated with methanol (60 mL, 1.47 mol) while maintaining vigorous stirring. After a further 10 min, the reaction mixure was warmed to −40 °C and stirring was continued for an additional 15 min to afford a clear, red coloured solution. The reaction mixture was then treated with 2-butynol (1.00 g, 13.40 mmol) before being warmed to −10 °C and stirred at this temperature for 1 h. The reaction mixture was then quenched with methanol (20 mL), ammonium chloride (40 mL of a saturated solution) and ammonium hydroxide (40 mL of a 30% aqueous solution). Stirring was then continued for a further 20 min. The separated aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:90 *v/v* ethyl acetate/hexane with 1% triethylamine elution) and concentration of the appropriate fractions (R_f = 0.2) afforded alcohol **5.47**[148] (4.50 g, 93%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 7.8, 4.2 and 1.8 Hz, $J_{H\text{-}Sn}$= 32.9 Hz, 1H), 4.24 (t, *J* = 5.6 Hz, 2H), 1.88 (s, $J_{H\text{-}Sn}$= 22.1 Hz, 3H), 1.54–1.43 (complex m, 6H), 1.30 (dd, *J* = 14.7 and 7.3 Hz, 7H), 0.91–0.86 (complex m, 15H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (C), 139.5 (CH), 59.1 (CH_2), 29.3 (3 x CH_2), 27.6 (3 x CH_2), 19.6 (CH_3), 13.9 (3 x CH_2), 9.3 (3 x CH_3);

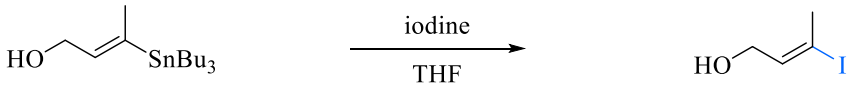
IR (KBr) ν_{max} 3308, 2956, 2924, 2872, 2853, 1464, 1376, 1059, 1002 cm^{-1};

MS (ESI, +ve) *m/z* 385 [$(M+Na)^+$, 12%], 179 [$(M-C_{12}H_{25}O+H)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 385.1527, $C_{16}H_{34}{}^{23}NaO^{120}Sn$ requires 385.1529.

These data matched those reported previously.[148]

(*E*)-3-Iodobut-2-en-1-ol (5.48)



5.47 5.48

A magnetically stirred solution of alkenyl tin **5.47** (2.00 g, 5.53 mmol) in tetrahydrofuran (30 mL) maintained at −78 °C was treated, dropwise over 10 min *via* an addition funnel, with a solution of iodine (1.69 g, 6.64 mmol) in tetrahydrofuran (10 mL). After addition was complete, the reaction mixture was warmed to 18 °C and stirrred for a further 30 min at this temperature then quenched with a mixture of sodium thiosulfate (30 mL of a saturated aqueous solution) and sodium bicarbonate (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were treated with potassium fluoride (50 mL of a 10% aqueous solution). The resuling mixture was vigorously stirred for 30 min before being filtered through Celite™. The separated aqueous layer associated with the filtrate was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded alkenyl iodide **5.48**[149] (1.10 g, quant.) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (t, *J* = 6.9 Hz, 1H), 4.04 (t, *J* = 6.9 Hz, 2H), 2.53 (s, 1H), 2.53 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (CH), 98.5 (C), 59.8 (CH_2), 28.2 (CH_3);

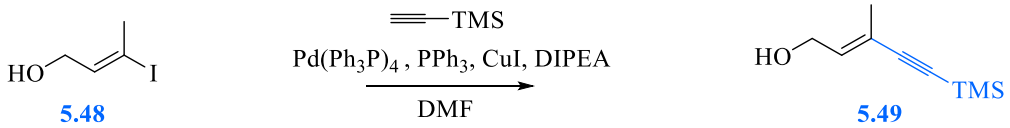
IR (KBr) ν_{max} 3304, 2916, 1636, 1424, 1376, 1219, 1099, 1059, 1002 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 198 [($M^{+\bullet}$, 70%], 155 (40), 121 (100);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 197.9543, $C_4H_7{}^{127}IO$ requires 197.9542.

These data matched those reported previously.[149]

(*E*)-3-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (5.49)



5.48 5.49

A magnetically stirred solution of alkenyl iodide **5.48** (1.00 g, 5.05 mmol), tetrakis(triphenylphosphine)palladium(0) (292 mg, 0.25 mmol), triphenylphosphine (132 mg, 0.50 mmol) and copper iodide (96 mg, 0.50 mmol) in *N*,*N*-dimethylformamide (20 mL) maintained under an argon atmosphere was treated with diethyl-*iso*-propylamine (1.8 mL, 10.10 mmol). The ensuing mixture was cooled to 0 °C, flushed with argon for a further 10 min then treated with ethynyltrimethylsilane (1.07 mL, 7.57 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h before being quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic phases were then washed with water (2 x 25 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded alkyne iodide **5.49**[150] (690 mg, 81%) as a clear, colourless oil.

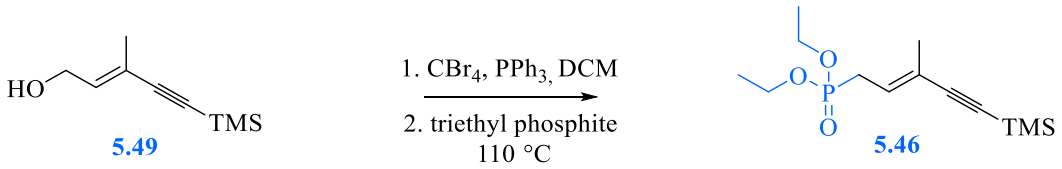
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (td, *J* = 6.8 and 1.4 Hz, 1H), 4.19 (d, *J* = 6.8 Hz, 2H), 1.81 (s, 3H), 1.72 (s, OH), 0.17 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (CH), 120.8 (C), 107.5 (C), 92.3 (C), 59.2 (CH_2), 17.5 (CH_3), 0.1 (3 x CH_3);

IR (KBr) ν_{max} 3307, 2959, 2145, 1630, 1409, 1377, 1249, 1009, 842 cm^{-1};

These data matched those reported previously.[150]

(*E*)-Diethyl (3-methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)phosphonate (5.46)



A magnetically stirred solution of alcohol **5.49** (750 mg, 4.46 mmol) and carbon tetrabromide (1.63 g, 4.90 mmol) in dichloromethane (10 mL) maintained at 0 °C was treated with triphenylphosphine (1.29 g, 4.90 mmol). The ensuing mixture was warmed to 18 °C and stirring was continued for 2 h. The reaction solvent was removed under reduced pressure and the residue thus obtained filtered through a pad of TLC-grade silica gel that was eluted with diethyl ether/hexane (30 mL of a 3:7 *v/v* mixture). The combined filtrates were concentrated under reduced pressure to afford the anticipated bromide that was used, without purification, in the next step of the reaction sequence. NMR spectral data were recorded on the bromide.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (m, 1H), 4.00 (d, *J* = 8.7 Hz, 2H), 1.87 (d, *J* = 1.5 Hz, 3H), 0.18 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5 (CH), 124.3 (C), 106.8 (C), 94.9 (C), 27.4 (CH_2), 17.1 (CH_3), 0.04 (3 x CH_3)];

The bromide, formed as described above, was treated with triethyl phosphite (0.96 mL, 5.00 mmol) and the resulting mixture was heated to 110 ºC for 2 h. After cooling to 18 ºC the residue was subjected to flash chromatography (silica, ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.4) afforded *phosphonate* ***5.46*** (1.10 g, 95%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 4.17–3.91 (complex m, 4H), 2.57 (dd, *J* = 23.1 and 8.2 Hz, 2H), 1.76 (d, *J* = 3.6 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.11 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 126.8 (d, *J* = 12.3 Hz, CH), 122.3 (d, *J* = 15.6 Hz, C), 107.4 (d, *J* = 5.9 Hz, C), 91.9 (d, *J* = 2.8 Hz, C), 62.1(7) (CH_2), 62.1(0) (CH_2), 27.3 (d, *J* = 141.0 Hz, CH_2–PO), 17.5 (d, *J* = 2.6 Hz, CH_3), 16.5(8) (CH_3), 16.5(2) (CH_3), 0.1 (3 x CH_3);

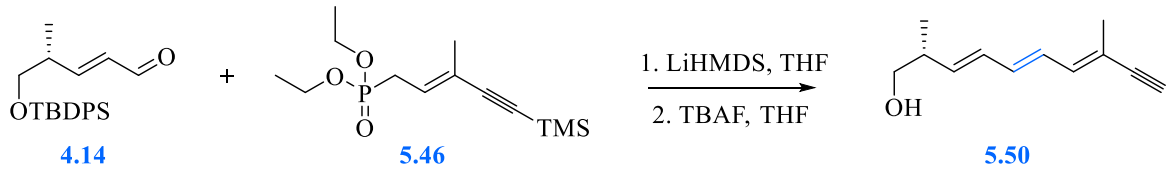
^{31}P NMR (162 MHz, $CDCl_3$) δ 26.2 (PO);

IR (KBr) ν_{max} 3468, 2961, 2904, 2146, 1444, 1392, 1250, 1163, 1050, 1027, 964, 842 cm^{-1};

MS (ESI, +ve) *m/z* 311 [$(M+Na)^+$, 100%], 289 [$(M+H)^+$, 30];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 311.1211, $C_{13}H_{25}{}^{23}NaO_3PSi$ requires 311.1208. $(M+H)^+$ 289.1389, $C_{13}H_{26}O_3PSi$ requires 289.1389.

(*R*,3*E*,5*E*,7*E*)-2,8-Dimethyldeca-3,5,7-trien-9-yn-1-ol (5.50)



4.14 5.46 5.50

A magnetically stirred solution of phosphonate **5.46** (736 mg, 2.55 mmol) in dry tetrahydrofuran (20 mL) maintained at –78 °C under a nitrogen atmosphere was treated with lithium bis(trimethylsilyl)amide (2.38 mL of a 1.0 M solution in tetrahydrofuran, 2.38 mmol). The ensuing mixture was stirred at this temperature for 1 h then treated with a solution of aldehyde **4.14** (600 mg, 1.70 mmol) in dry tetrahydrofuran (10 mL). After 30 min, the reaction mixture was warmed to 18 °C, stirred at this temperature for a further 3.5 h then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (2 x 30 mL) and the combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in tetrahydrofuran (20 mL) and the resulting solution was treated with tetra-*n*-butylammonium fluoride (2.9 mL of a 1.0 M solution in tetrahydrofuran, 2.90 mmol). After 2 h the reaction mixture was quenched with ammonium chloride (20 mL of a saturated aqueous solution) and the separated aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *alcohol **5.50*** (180 mg, 60%) as a clear, colourless oil and as an inseparable (90:10) mixture of *E*/*Z* isomers.

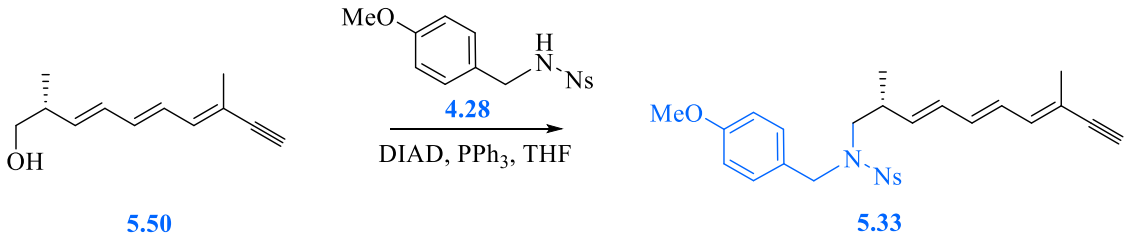
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 11.2 and 1.1 Hz, 1H), 6.37 (dd, *J* = 13.6 and 11.2 Hz, 1H), 6.29–6.16 (complex m, 2H), 5.67 (dd, *J* = 14.4 and 7.9 Hz, 1H), 3.52 (dd, *J* = 10.5 and 5.7 Hz, 1H), 3.45 (dd, *J* = 10.5 and 7.3 Hz, 1H), 2.99 (s, 1H), 2.45 (m, 1H), 1.91 (s, 3H), 1.54 (s, OH), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (CH), 137.2 (CH), 134.6 (CH), 131.3 (CH), 127.0 (CH), 117.4 (C), 87.7 (C), 77.2 (CH), 67.4 (CH_2), 40.0 (CH), 17.5 (CH_3), 16.4 (CH_3);

IR (KBr) ν_{max} 3367, 3296, 3027, 2961, 2925, 2873, 2084, 1605, 1454, 1031, 988 cm^{-1};

Specific rotation $[\alpha]^{25}_D$ = +34.5 (*c* 1.1, $CHCl_3$).

N-((*R*,3*E*,5*E*,7*E*)-2,8-Dimethyldeca-3,5,7-trien-9-yn-1-yl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (5.33)



5.50 **5.33**

A magnetically stirred solution of alcohol **5.50** (120 mg, 0.68 mmol) and *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide **4.28** (329 mg, 1.02 mmol) in tetrahydrofuran (10 mL) maintained at 0 °C was treated, sequentially, with triphenylphosphine (232 mg, 0.88 mmol) then di-*iso*-propyl azodicarboxylate (0.17 mL, 0.88 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:30:67 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *sulfonamide* ***5.33*** (230 mg, 70%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.73–7.58 (complex m, 3H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 11.6 Hz, 1H), 6.27 (dd, *J* = 13.8 and 11.6 Hz, 1H), 6.04–5.88 (complex m, 2H), 5.34 (dd, *J* = 14.3 and 8.2 Hz, 1H), 4.48 (ABq, Δ δ_{AB} = 0.17, J_{AB} = 15.4 Hz, 2H), 3.79 (s, 3H), 3.16 (d, *J* = 7.6 Hz, 2H), 3.01 (s, 1H), 2.47 (m, 1H), 1.91 (s, 3H), 0.87 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C), 147.9 (C), 138.3 (CH), 137.1 (CH), 134.5 (CH), 134.3 (C), 133.4 (CH), 131.7 (CH), 131.2 (CH), 130.9 (CH), 129.9 (2 x CH), 127.3 (C), 126.9 (CH), 124.4 (CH), 117.5 (C), 114.2 (2 x CH), 87.7 (C), 77.3 (CH), 55.4 (CH_3), 52.4 (CH_2), 50.9 (CH_2), 35.6 (CH), 17.8 (CH_3), 17.6 (CH_3);

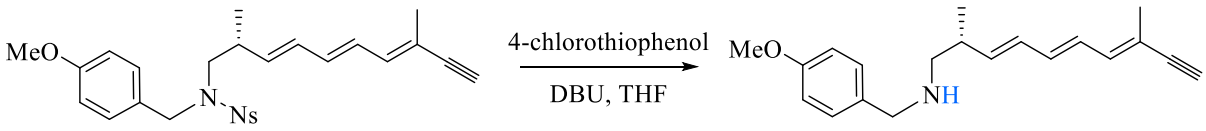
IR (KBr) ν_{max} 3289, 2930, 2083, 1611, 1543, 1513, 1455, 1371, 1248, 1162, 990 cm^{-1};

MS (ESI, +ve) *m/z* 503 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 503.1619, $C_{26}H_{28}N_2{}^{23}NaO_5S$ requires 503.1617;

Specific rotation $[\alpha]^{25}_D$ = +13.4 (*c* 1.2, $CHCl_3$).

(*R*,3*E*,5*E*,7*E*)-*N*-(4-Methoxybenzyl)-2,8-dimethyldeca-3,5,7-trien-9-yn-1-amine (5.51)



5.33 5.51

A magnetically stirred solution of 4-chlorothiophenol (90 mg, 0.62 mmol) in tetrahydrofuran (2 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (124 µL, 0.62 mmol). After 15 min, the reaction mixture was treated, dropwise, with a solution of sulfonamide **5.33** (150 mg, 0.31 mmol) in tetrahydrofuran (3 mL) and stirring was the continued for 4 h before it was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *amine **5.51*** (70 mg, 76%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.46 (dd, *J* = 11.2 and 1.6 Hz, 1H), 6.34 (dd, *J* = 13.9 and 11.2 Hz, 1H), 6.29–6.11 (complex m, 2H), 5.65 (dd, *J* = 14.5 and 7.6 Hz, 1H), 3.80 (s, 3H), 3.72 (d, *J* = 3.3 Hz, 2H), 2.98 (s, 1H), 2.62–2.40 (complex m, 3H), 1.91 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H) (signal due to amine proton not observed);

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 (C), 140.5 (C), 137.3 (CH), 134.9 (CH), 130.6 (CH), 129.6 (2 x CH), 126.7 (CH), 117.1 (C), 113.9 (3 x CH), 87.8 (CH), 83.1 (C), 55.4 (CH_3), 54.8 (CH_2), 53.2 (CH_2), 37.5 (CH), 18.6 (CH_3), 17.5 (CH_3);

IR (KBr) ν_{max} 3292, 2953, 2924, 2083, 1610, 1512, 1454, 1300, 1246, 1175, 1036, 989 cm^{-1};

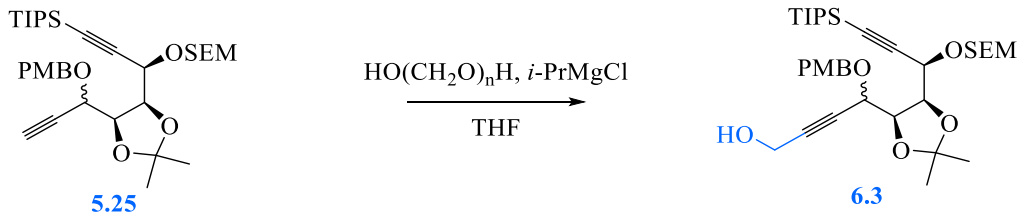
MS (ESI, +ve) *m/z* 296 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+H)^+$ 296.2014, $C_{20}H_{26}NO$ requires 296.2014;

Specific rotation $[\alpha]^{25}_D$ = −6.2 (*c* 0.6, $CHCl_3$).

7.6 Experimental Procedures Related to Work Described in Chapter Six

4-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxybenzyl)oxy)but-2-yn-1-ol (6.3)



A magnetically stirred solution of terminal alkyne **5.25** (930 mg, 1.51 mmol) in tetrahydrofuran (50 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *iso*-propylmagnesium chloride (1.5 mL of a 2 M solution in tetrahydrofuran, 3.00 mmol). The ensuing mixture was stirred for a further 15 min then treated with formaldehyde (181 mg, 6.03 mmol). The reaction mixture was warmed to 18 °C and stirred at this temperature for 16 h then quenched with ammonium chloride (30 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were then washed with brine (1 x 50 mL) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound* ***6.3*** (858 mg, 88%) as a clear, colourless oil and as an inseparable (3:7) mixture of α/β epimers along with recovered starting material (100 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 7.32 (partially obscured d, *J* = 8.7 Hz, 2H), 6.87 (partially obscured d, *J* = 8.7 Hz, 2H), 5.01 (d, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 2.6 Hz, 1H), 4.84 (partially obscured d, *J* = 7.8 Hz, 1H), 4.73 (partially obscured d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.46 (partially obscured d, *J* = 10.5 Hz, 1H), 4.36 (partially obscured d, *J* = 1.5 Hz, 2H), 4.38–4.34 (complex partially obscured m, 2H), 3.78 (s, 3H), 3.65 (ddd, *J* = 11.0, 10.1 and 5.9 Hz, 1H), 3.49 (ddd, *J* = 11.0, 10.1 and 5.9 Hz, 1H), 2.17 (partially obscured s, OH), 1.57 (s, 3H), 1.37 (s, 3H), 1.08–1.03 (complex partially obscured m, 21H), 0.98–0.80 (complex partially obscured m, 2H), −0.02 (s, 9H); (*β-epimer*) 7.30 (partially obscured d, *J* = 8.7 Hz, 2H), 6.85 (partially obscured d, *J* = 8.7 Hz, 2H), 4.97 (d, *J* = 3.3 Hz, 1H), 4.92 (d, *J* = 7.0 Hz, 1H), 4.73 (partially obscured d, *J* = 7.0 Hz, 1H), 4.72 (partially obscured d, *J* = 11.5 Hz, 1H), 4.66 (dt, *J* = 8.4 and 1.8 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.45 (partially obscured d, *J* = 8.4

and 7.1 Hz 1H), 4.36 (partially obscured m, 1H), 4.32 (partially obscured m, 1H), 4.27 (partially obscured d, *J* = 1.7 Hz, 1H), 3.79 (s, 3H), 3.73 (ddd, *J* = 11.5, 10.1 and 5.9 Hz, 1H), 3.58 (ddd, *J* = 11.5, 10.1 and 5.9 Hz, 1H), 2.17 (partially obscured s, OH), 1.59 (s, 3H), 1.38 (s, 3H), 1.08–1.03 (complex partially obscured m, 21H), 0.98–0.80 (complex partially obscured m, 2H), 0.01 (s, 9H);

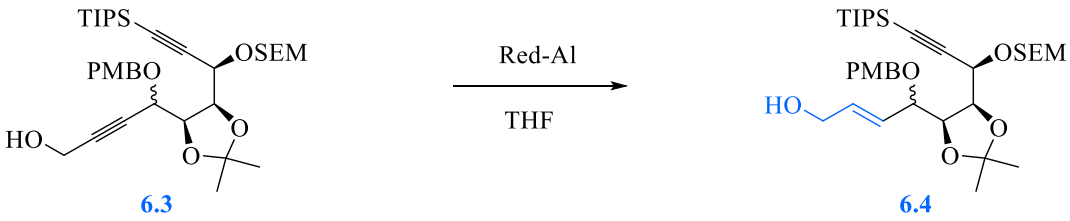
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*) 159.5 (C), 130.2 (2 x CH), 129.4 (C), 114.0 (2 x CH), 109.7 (C), 103.3 (C), 91.8 (CH_2), 89.9 (C), 85.4 (C), 82.7 (C), 78.6 (CH), 77.4 (CH), 70.7 (CH_2), 67.9 (CH), 65.7 (partially obscured, CH_2), 64.9 (CH), 55.3 (CH_3), 51.3 (CH_2), 26.9 (CH_3), 25.0 (CH_3), 18.7 (6 x CH_3), 18.2 (CH_2), 11.4 (3 x CH), −1.3 (3 x CH_3); (*β-epimer*) 159.4 (C), 129.8 (C), 129.7 (2 x CH), 113.8 (2 x CH), 110.3 (C), 103.2 (C), 92.2 (CH_2), 89.9 (C), 86.9 (C), 81.8 (C), 78.9 (CH), 78.5 (CH), 70.9 (CH_2), 67.8 (CH), 66.2 (CH_2), 65.7 (partially obscured, CH), 55.3 (CH_3), 50.9 (CH_2), 26.8 (CH_3), 25.2 (CH_3), 18.8 (6 x CH_3), 18.2 (CH_2), 11.3 (3 x CH), −1.4 (3 x CH_3);

IR (ATR) ν_{max} 3452, 2944, 2892, 2865, 2172, 1613, 1514, 1380, 1249, 1027, 835 cm^{-1};

MS (ESI, +ve) *m/z* 669 [$(M+Na)^+$, 100%], 664 [$(M+NH_4)^+$, 25];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 669.3619, $C_{35}H_{58}{}^{23}NaO_7Si_2$ requires 669.3619.

(*E*)-4-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxybenzyl)oxy)but-2-en-1-ol (6.4)



6.3 6.4

In a 100 mL flame-dried round bottom flask, a magnetically stirred solution of propargylic alcohol **6.3** (858 mg, 1.32 mmol) in dry tetrahydrofuran (50 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise, with Red-Al™ (sodium bis(2-methoxyethoxy)aluminium hydride) (0.86 mL of 65% *w/w* solution in toluene, 2.64 mmol). After 30 min, the reaction mixture was quenched by dropwise addition of methanol until no further gas evolution occurred then by the addition of tartaric acid (50 mL of a 1.0 M aqueous solution). The ensuing mixture was warmed to 18 °C and stirring was continued for an

additional 1 h. The separated aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were then washed with potassium carbonate (1 x 50 mL of a 10% aqueous solution) before being dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:30:50 *v/v/v* ethyl acetate/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded *compound* ***6.4*** (800 mg, 93%) as a clear, colourless oil and as an inseparable (30:70) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 7.32 (partially obscured d, *J* = 8.7 Hz, 2H), 6.87 (partially obscured d, *J* = 8.7 Hz, 2H), 5.94 (partially obscured dt, *J* = 15.6, 5.3 Hz, 1H), 5.67 (partially obscured d, *J* = 15.6 and 7.7 Hz, 1H), 5.07 (d, *J* = 7.0 Hz, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.55 (dd, *J* = 7.8 and 7.6 Hz, 1H), 4.48 (d, *J* = 10.3 Hz, 1H), 4.38 (dd, *J* = 7.2 and 2.0 Hz, 1H), 4.33 (partially obscured d, *J* = 10.3 Hz, 1H), 4.24 (partially obscured d, *J* = 5.2 and 1.0 Hz, 1H), 4.19–4.13 (complex partially obscured m, 2H), 3.78 (s, 3H), 3.67 (partially obscured m, 1H), 3.50 (partially obscured m, 1H), 1.77 (partially obscured s, OH), 1.55 (s, 3H), 1.33 (s, 3H), 1.10–1.06 (complex partially obscured m, 21H), 0.92–0.82 (complex partially obscured m, 2H), −0.02 (s, 9H); (*β-epimer*) 7.30 (partially obscured d, *J* = 8.7 Hz, 2H), 6.85 (partially obscured d, *J* = 8.7 Hz, 2H), 6.00 (dt, *J* = 15.6, 5.3 Hz, 1H), 5.70 (partially obscured d, *J* = 15.6 and 8.0 Hz, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 4.9 Hz, 1H), 4.50 (ABq, Δ δ_{AB} = 0.03, J_{AB} = 11.4 Hz, 2H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.27 (partially obscured t, *J* = 6.6 Hz, 1H), 4.19–4.13 (partially obscured m, 3H), 3.79 (s, 3H), 3.72–3.63 (partially obscured m, 1H), 3.57–3.44 (partially obscured m, 1H), 1.77 (partially obscured s, OH), 1.58 (s, 3H), 1.38 (s, 3H), 1.10–1.06 (complex partially obscured m, 21H), 0.92–0.82 (complex partially obscured m, 2H), 0.00 (s, 9H);

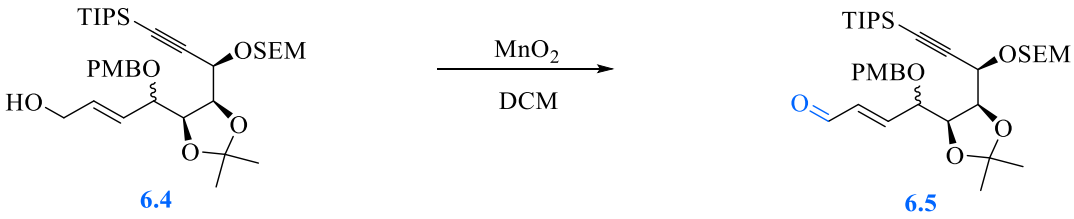
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*) 159.5 (C), 134.6 (CH), 130.1 (2 x CH), 129.9 (C), 129.3 (CH), 114.0 (2 x CH), 109.4 (C), 103.6 (C), 91.6 (CH_2), 89.7 (C), 79.1 (CH), 77.8 (CH), 77.6 (CH), 70.0 (CH_2), 65.5 (CH_2), 65.2 (CH), 63.1 (CH_2), 55.3 (CH_3), 26.8 (CH_3), 24.8 (CH_3), 18.8 (6 x CH_3), 18.2 (CH_2), 11.4 (3 x CH), −1.3 (3 x CH_3); (*β-epimer*) 159.2 (C), 135.3 (CH), 130.9 (C), 129.2 (2 x CH), 128.2 (CH), 113.8 (2 x CH), 109.4 (C), 103.5 (C), 92.1 (CH_2), 89.5 (C), 79.7 (CH), 78.3 (CH), 77.8 (CH), 70.3 (CH_2), 66.3 (CH_2), 65.7 (CH), 63.0 (CH_2), 55.4 (CH_3), 26.9 (CH_3), 25.4 (CH_3), 18.7 (6 x CH_3), 18.3 (CH_2), 11.3 (3 x CH), −1.3 (3 x CH_3);

IR (ATR) ν_{max} 3446, 2945, 2866, 1613, 1514, 1379, 1249, 1030, 835 cm^{-1};

MS (ESI, +ve) *m/z* 671 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 671.3775. $C_{35}H_{60}{}^{23}NaO_7Si_2$ requires 671.3775.

(*E*)-4-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxybenzyl)oxy)but-2-enal (6.5)



6.4 6.5

A magnetically stirred solution of alcohol **6.4** (800 mg, 1.23 mmol) in dichloromethane (50 mL) was treated, in three portions, with manganese dioxide (1.69 g, 12.32 mmol). A slightly exothermic reaction occured. The ensuing mixture was stirred for 4 h at ambient temperatures then filtered through a pad of flame-dried Celite™ that was rinsed with dichloromethane (2 x 30 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 20:80 *v/v* ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.6) afforded *aldehyde* ***6.5*** (710 mg, 89%) as a clear, colourless oil and as an inseparable (30:70) mixture of α/β epimers.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ (*α-epimer*) 9.68 (d, *J* = 7.7 Hz, 1H), 7.34 (partially obscured d, *J* = 8.5 Hz, 2H), 6.96 (dd, *J* = 15.8 and 6.4 Hz, 1H), 6.90 (partially obscured d, *J* = 8.5 Hz, 2H), 6.25 (dd, *J* = 15.8 and 7.7 Hz, 1H), 5.02 (d, *J* = 6.5 Hz, 1H), 4.96 (d, *J* = 2.7 Hz, 1H), 4.84 (partially obscured m, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.51 (ABq, Δ δ_{AB} = 0.04, J_{AB} = 10.3 Hz, 2H), 4.43 (dd, *J* = 6.9 and 2.7 Hz, 1H), 4.25 (partially obscured m, 1H), 3.80 (s, 3H), 3.73 (partially obscured m, 1H), 3.60 (partially obscured m, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 1.14–1.10 (complex partially obscured m, 21H), 0.92–0.82 (complex partially obscured m, 2H), −0.01 (s, 9H); (*β-epimer*) 9.65 (d, *J* = 7.9 Hz, 1H), 7.34 (partially obscured d, *J* = 8.5 Hz, 2H), 7.08 (dd, *J* = 15.8 and 5.7 Hz, 1H), 6.90 (partially obscured d, *J* = 8.5 Hz, 2H), 6.33 (ddd, *J* = 15.8, 7.9 and 1.1 Hz, 1H), 5.02 (d, *J* = 6.5 Hz, 1H), 4.80 (d, *J* = 6.5 Hz, 1H), 4.79 (d, *J* = 8.1 Hz, 1H), 4.58 (s, 2H), 4.53 (partially obscured m, 1H), 4.31 (dd, *J* = 8.1 and 5.8 Hz, 1H), 4.25 (partially obscured m, 1H), 3.79 (s, 3H), 3.73 (partially obscured m, 1H), 3.60 (partially obscured m, 1H), 1.48 (s, 3H), 1.34 (s, 3H), 1.14–1.10 (complex partially obscured m, 21H), 0.92–0.82 (complex partially obscured m, 2H), −0.01 (s, 9H);

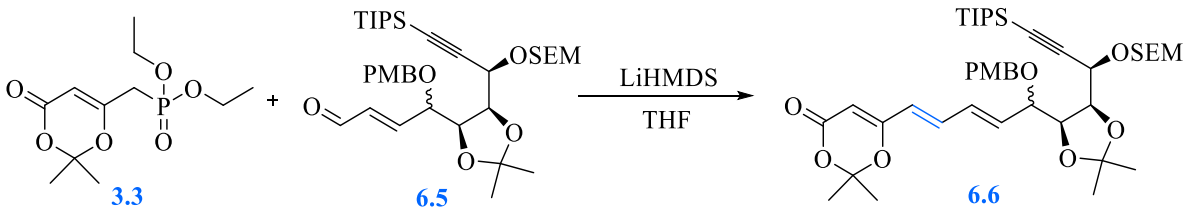
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ (*α-epimer*) 193.7 (CO), 160.5 (C), 154.9 (CH), 134.8 (CH), 130.7 (2 x CH), 130.3 (C), 114.6 (2 x CH), 109.8 (C), 105.1 (C), 92.4 (CH_2), 89.8 (C), 79.6 (CH), 78.4 (CH), 77.3 (CH), 71.6 (CH_2), 66.1 (CH_2), 65.8 (CH), 55.5 (CH_3), 27.3 (CH_3), 25.0 (CH_3), 19.1 (6 x CH_3), 18.6 (CH_2), 12.0 (3 x CH), −1.3 (3 x CH_3); (*β-epimer*) 193.8 (CO), 160.2 (C), 154.7 (CH), 134.3 (CH), 131.2 (C), 129.7 (2 x CH), 114.5 (2 x CH), 109.8 (C), 105.4 (C), 93.7 (CH_2), 88.7 (C), 80.1 (CH), 78.9 (CH), 77.7 (CH), 71.8 (CH_2), 67.2 (CH_2), 66.7 (CH), 55.5 (CH_3), 27.3 (CH_3), 25.9 (CH_3), 19.1 (6 x CH_3), 18.9 (CH_2), 11.9 (3 x CH), −1.2 (3 x CH_3);

IR (ATR) ν_{max} 2944, 2866, 2171, 1695, 1514, 1248, 1026, 835 cm^{-1};

MS (ESI, +ve) *m/z* 701 [$(M+CH_3OH+Na)^+$, 70%], 669 [$(M+Na)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 669.3602, $C_{35}H_{58}{}^{23}NaO_7Si_2$ requires 669.3619.

6-((1*E*,3*E*)-5-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-((4-methoxybenzyl)oxy)penta-1,3-dien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (6.6)



A magnetically stirred solution of phosphonate **3.3** (458 mg, 1.65 mmol) in dry tetrahydrofuran (30 mL) maintained at −78 °C under a nitrogen atmosphere was treated with lithium bis(trimethylsilyl)amide (1.54 mL of 1.0 M solution in tetrahydrofuran, 1.54 mmol). The ensuing mixture was stirred at −78 °C for 1 h then treated with a solution of aldehyde **6.5** (710 mg, 1.10 mmol) in tetrahydrofuran (15 mL). After 30 min, the reaction mixture was warmed up to 18 °C and stirred for a further 3.5 h at this temperature then quenched with ammonium chloride (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (2 x 50 mL) and the combined organic phases were then dried over magnesium sulfate before being filtered, concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave *compound* **6.6** (800 mg, 94%) as a clear, colourless oil and as an inseparable (30:70) mixture of α/β epimers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*α-epimer*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.04 (dd, *J* = 15.2 and 11.1 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.39 (dd, *J* = 15.4 and 11.1 Hz, 1H), 6.07–6.00 (complex partially obscured m, 2H), 5.36 (s, 1H), 5.07 (d, *J* = 7.0 Hz, 1H), 4.92 (d, *J* = 2.1 Hz, 1H), 4.73 (partially obscured d, *J* = 7.0 Hz, 1H), 4.68 (partially obscured m, 1H), 4.44 (d, *J* = 10.2 Hz, 1H), 4.39–4.36 (complex partially obscured m, 2H), 4.16 (partially obscured m, 1H), 3.79 (partially obscured s, 3H), 3.63 (partially obscured td, *J* = 10.2, 6.1 Hz, 1H), 3.50 (partially obscured td, *J* = 10.2, 6.1 Hz, 1H), 1.71 (s, 6H), 1.55 (s, 3H), 1.32 (s, 3H), 1.01 (s, 21H), 0.96–0.76 (complex partially obscured m, 2H), −0.02 (s, 9H); (*β-epimer*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 6.95 (dd, *J* = 15.2 and 11.0 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.46 (dd, *J* = 15.4 and 11.0 Hz, 1H), 6.12 (dd, *J* = 15.4 and 7.1 Hz, 1H), 6.03 (partially obscured d, *J* = 15.2 Hz, 1H), 5.34 (s, 1H), 4.95 (d, *J* = 6.6 Hz, 1H), 4.72 (d, *J* = 6.6 Hz, 1H), 4.61 (m, 1H), 4.50 (m, 2H), 4.38 (partially obscured m, 1H), 4.21–4.18 (complex partially obscured m, 2H), 3.79 (partially obscured s, 3H), 3.63 (partially obscured td, *J* = 10.2, 6.1 Hz, 1H), 3.50 (partially obscured td, *J* = 10.2, 6.1 Hz, 1H), 1.71 (s, 6H), 1.55 (s, 3H), 1.37 (s, 3H), 1.09 (s, 21H), 0.96–0.76 (complex partially obscured m, 2H), −0.02 (s, 9H);

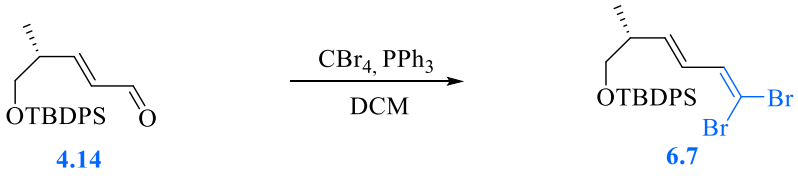
^{13}C NMR (100 MHz, $CDCl_3$) δ (*α-epimer*) 163.2 (C), 161.9 (C), 159.6 (C), 139.5 (CH), 137.3 (CH), 132.0 (CH), 130.1 (2 x CH), 129.4 (C), 123.8 (CH),114.1 (2 x CH), 109.5 (C), 106.5 (C),103.5 (C), 95.1 (CH), 91.6 (CH_2), 90.0 (C), 79.0 (CH), 77.8 (CH), 77.3 (CH), 70.6 (CH_2), 65.6 (CH_2), 65.1 (CH), 55.3 (CH_3), 26.8 (CH_3), 25.3 (CH_3),25.1 (CH_3), 24.7 (CH_3) 18.7 (6 x CH_3), 18.2 (CH_2), 11.4 (3 x CH), −1.3 (3 x CH_3); (*β-epimer*) 163.0 (C), 161.8 (C), 159.2 (C), 138.1 (CH), 137.0 (CH), 132.0 (CH), 130.5 (C), 129.1 (2 x CH), 124.2 (CH), 113.8 (2 x CH), 109.5 (C), 106.5 (C), 103.4 (C), 95.3 (CH), 92.2 (CH_2), 89.6 (C), 79.8 (CH), 78.2 (CH), 77.3 (CH), 70.8 (CH_2), 66.4 (CH_2), 65.7 (CH), 55.3 (CH_3), 27.0 (CH_3), 25.5 (CH_3), 25.3 (CH_3), 25.1 (CH_3), 18.7 (6 x CH_3), 18.3 (CH_2), 11.3 (3 x CH), −1.3 (3 x CH_3);

IR (ATR) ν_{max} 2944, 2865, 2173, 1726, 1628, 1514, 1377, 1248, 1018, 859, 835 cm^{-1};

MS (ESI, +ve) *m/z* 793 [$(M+Na)^+$, 100%], 788 [$(M+NH_4)^+$, 80];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 793.4125, $C_{42}H_{66}{}^{23}NaO_9Si_2$ requires 793.4143.

(*R*,*E*)-*tert*-Butyl((6,6-dibromo-2-methylhexa-3,5-dien-1-yl)oxy)diphenylsilane (6.7)



4.14 6.7

A magnetically stirred solution of carbon tetrabromide (734 mg, 2.21 mmol) in dry dichloromethane (15 mL) maintained at 0 °C was treated with triphenylphosphine (1.16 g, 4.42 mmol). After 15 min, the ensuing mixture was slowly treated with a solution of aldehyde **4.14** (390 mg, 1.11 mmol) in dichloromethane (15 mL). The ensuing mixture was stirred for 15 min then warmed to 18 °C and maintained at this temperature for a further 30 min. The solvent was removed under reduced pressure and the residue thus obtained was filtered through a pad of TLC-grade silica gel that was eluted with diethyl ether/hexane (2 x 30 mL of a 1:4 *v/v* mixture). The combined filtrates were concentrated under reduced pressure to give *compound **6.7*** (520 mg, 92%) as a clear, colourless oil (R_f = 0.7 in 5:95 *v/v* diethyl ether/hexane). This material was used, without purification, in the next step of reaction sequence

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (complex m, 4H), 7.49–7.33 (complex m, 6H), 6.88 (d, *J* = 10.1 Hz, 1H), 6.12 (ddd, *J* = 15.4, 10.1 and 1.0 Hz, 1H), 5.84 (dd, *J* = 15.4 and 7.5 Hz, 1H), 3.58 (ABX, J_{AB} = 9.9, J_{AX} = 6.2 Hz, 1H), 3.55 (ABX, J_{AB} = 9.9, J_{BX} = 6.4 Hz, 1H), 2.46 (hept, *J* = 6.8 Hz, 1H), 1.07 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9 (CH), 137.3 (CH), 135.8 (2 x CH), 135.7 (2 x CH), 133.9 (CH), 133.8 (CH), 129.8 (2 x CH), 127.8 (4 x CH), 126.9 (CH), 89.1 (C), 68.1 (CH_2), 39.9 (CH), 27.0 (3 x CH_3), 19.5 (C), 16.3 (CH_3);

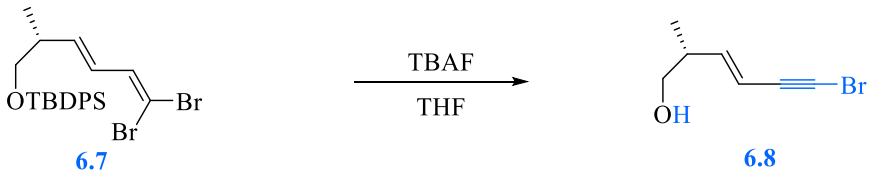
IR (ATR) ν_{max} 3073, 2959, 2930, 2857, 1427, 1112, 701 cm^{-1};

MS (ESI, +ve) *m/z* 549, 547 and 545 [$(M+K)^+$, 50, 100 and 50%, respectively];

HRMS (ESI, +ve) Found: $(M+K)^+$ 548.9872, $C_{23}H_{28}{}^{81}Br_2{}^{39}KOSi$ requires 548.9872. $(M+K)^+$ 546.9888, $C_{23}H_{28}{}^{79}Br{}^{81}Br{}^{39}KOSi$ requires 546.9893. $(M+K)^+$ 544.9918, $C_{23}H_{28}{}^{79}Br_2{}^{39}KOSi$ requires 544.9913;

Specific rotation $[\alpha]^{25}_D = -2.0$ (*c* 1.0, $CHCl_3$).

(*R*,*E*)-6-Bromo-2-methylhex-3-en-5-yn-1-ol (6.8)



6.7 **6.8**

A magnetically stirred solution of silyl ether **6.7** (520 mg, 1.04 mmol) in tetrahydrofuran (10 mL) was treated with tetra-*n*-butylammonium fluoride (8.8 mL of a 1.0 M solution in tetrahydrofuran, 8.85 mmol). After 6 h, the reaction mixture was quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded *alcohol **6.8*** (200 mg, 96%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, *J* = 16.0, 7.8 Hz, 1H), 5.54 (dd, *J* = 16.0, 1.3 Hz, 1H), 3.52 (ABX, J_{AB} = 10.6, J_{AX} = 5.7 Hz, 1H), 3.47 (ABX, J_{AB} = 10.6, J_{BX} = 7.2 Hz, 1H), 2.43 (hept, *J* = 6.8 Hz, 1H), 1.57 (s, OH), 1.02 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2 (CH), 110.3 (CH), 78.6 (C), 66.9 (CH_2), 48.7 (C), 40.2 (CH), 15.9 (CH_3);

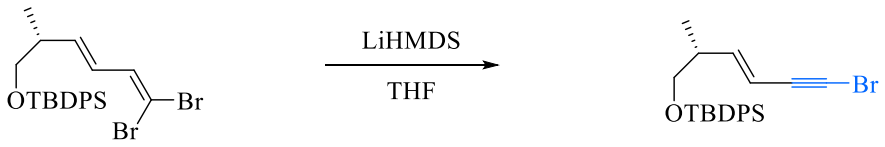
IR (ATR) ν_{max} 3336, 2966, 2930, 2874, 1457, 1381, 1032, 957 cm^{-1};

MS (EI, +ve, 70 eV) *m/z* 188 and 190 ($M^{+\bullet}$, both 20%), 159 and 157 [$(M-CH_3O\bullet)^+$, both 30], 78 (100);

HRMS (EI, +ve, 70 eV) Found: $M^{+\bullet}$ 189.9816, $C_7H_9{}^{81}BrO$ requires 189.9816. $M^{+\bullet}$ 187.9838, $C_7H_9{}^{79}BrO$ requires 187.9837;

Specific rotation $[\alpha]^{25}_D$ = +23 (*c* 1.5, $CHCl_3$).

(*R*,*E*)-((6-Bromo-2-methylhex-3-en-5-yn-1-yl)oxy)(*tert*-butyl)diphenylsilane (6.9)



6.7 6.9

A magnetically stirred solution of dibromoalkene **6.7** (200 mg, 0.39 mmol) in dry tetrahydrofuran (10 mL) maintained at −78 °C was treated with lithium bis(trimethylsilyl)amide (0.47 mL of a 1.0 M solution in tetrahydrofuran, 0.47 mmol). After 15 min, the reaction mixture was warmed to 18 °C and maintained at this temperature for 3 h then quenched with ammonium chloride (10 mL of a saturated aqueous solution). The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were dried over magnesium sulfate then filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.7) afforded *compound* ***6.9*** (140 mg, 83%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (complex m, 4H), 7.45–7.39 (complex m, 6H), 6.17 (dd, *J* = 16.0 and 7.5 Hz, 1H), 5.49 (d, *J* = 16.0 Hz, 1H), 3.54 (d, *J* = 6.3 Hz, 2H), 2.45 (hept, *J* = 6.8 Hz, 1H), 1.08 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0 (CH), 135.8 (2 x CH), 135.7 (2 x CH), 133.8 (2 x C), 129.8 (2 x CH), 127.8 (4 x CH), 109.2 (CH), 79.0 (C), 67.9 (CH_2), 47.9 (C), 40.0 (CH), 27.0 (3 x CH_3), 19.4 (C), 16.0 (CH_3);

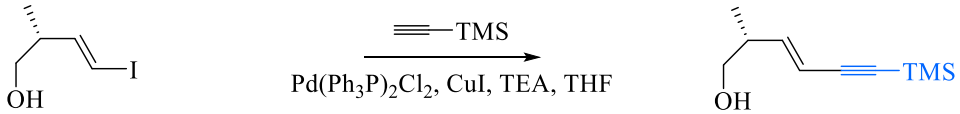
IR (ATR) ν_{max} 3071, 2959, 2931, 2858, 1471, 1427, 1109, 701 cm^{-1};

MS (ESI, +ve) *m/z* 467 and 465 [$(M+K)^+$, both 100%];

HRMS (ESI, +ve) Found: $(M+K)^+$ 465.0665, $C_{23}H_{27}{}^{79}Br^{39}KOSi$ requires 465.0652. $(M+K)^+$ 467.0644, $C_{23}H_{27}{}^{81}Br^{39}KOSi$ requires 467.0631;

Specific rotation $[\alpha]^{25}_D$ = +8.6 (*c* 1.2, $CHCl_3$).

(*R*,*E*)-2-Methyl-6-(trimethylsilyl)hex-3-en-5-yn-1-ol (6.10)



5.41 **6.10**

A magnetically stirred solution of alkenyl iodide **5.41** (540 mg, 2.55 mmol), bis(triphenylphosphine)palladium(II) dichloride (18 mg, 0.02 mmol) and copper iodide (10 mg, 0.02 mmol) in dry tetrahydrofuran (20 mL) maintained under an argon atmosphere was treated with triethylamine (0.71 mL, 5.09 mmol). The resulting solution was cooled to 0 °C and flushed with argon for further 10 min then treated with ethynyltrimethylsilane (0.54 mL, 3.82 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 16 h then quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* diethyl ether/dichloromethane/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *alcohol **6.10*** (260 mg, 56%) as a clear, light-brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, *J* = 16.0 and 7.9 Hz, 1H), 5.60 (d, *J* = 16.0 Hz, 1H), 3.57–3.38 (complex m, 2H), 2.43 (hept, *J* = 6.8 Hz, 1H), 1.42 (s, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.18 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6 (CH), 110.9 (CH), 103.7 (C), 93.9 (C), 67.0 (CH_2), 40.3 (CH), 15.9 (CH_3), 0.1 (3 x CH_3);

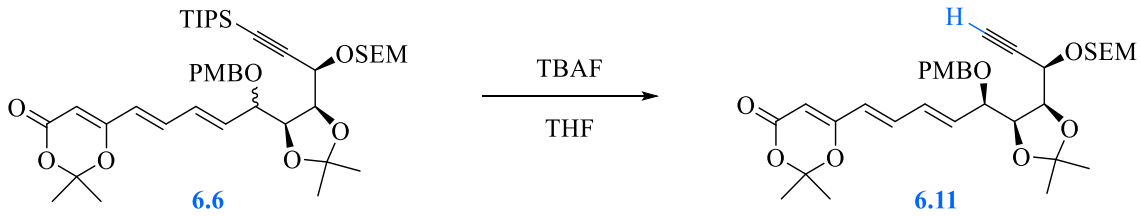
IR (ATR) ν_{max} 3339, 2960, 2874, 2154, 1248, 1033, 842 cm^{-1};

MS (ESI, +ve) *m/z* 205 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 205.1022, $C_{10}H_{18}{}^{23}NaOSi$ requires 205.1025;

Specific rotation $[\alpha]^{25}_D$ = +34.6 (*c* 1.2, $CHCl_3$).

6-((*R*,1*E*,3*E*)-5-((4*S*,5*R*)-2,2-Dimethyl-5-((*R*)-1-((2-(trimethylsilyl)ethoxy)methoxy)prop-2-yn-1-yl)-1,3-dioxolan-4-yl)-5-((4-methoxybenzyl)oxy)penta-1,3-dien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (6.11)



6.6 6.11

A magnetically stirred solution of compound **6.6** (300 mg, 0.39 mmol) in tetrahydrofuran (5 mL) was treated with tetra-*n*-butyl ammonium fluoride (0.77 mL of a 1.0 M solution in tetrahydrofuran, 0.77 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (5 mL of a saturated aqueous solution) and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:50 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the *terminal alkyne **6.11*** (150 mg, 63%) as a clear, yellow oil.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.32 (d, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 15.1 and 11.0 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.57 (dd, *J* = 15.5 and 11.0 Hz, 1H), 6.29 (d, *J* = 15.1 Hz, 1H), 6.24 (dd, *J* = 15.5 and 7.0 Hz, 1H), 5.43 (s, 1H), 4.92 (d, *J* = 6.7 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.72 (dd, *J* = 8.0 and 2.1 Hz, 1H), 4.50 (ABq, Δ δ_{AB} = 0.09, J_{AB} = 11.2 Hz, 2H), 4.33 (dd, *J* = 7.0 and 4.2 Hz, 1H), 4.27 (dd, *J* = 8.0 and 6.1 Hz, 1H), 4.20 (dd, *J* = 6.1 and 4.2 Hz, 1H), 3.79 (s, 3H), 3.73 (td, *J* = 9.8 and 6.6 Hz, 1H), 3.63 (td, *J* = 9.8 and 6.6 Hz, 1H), 3.02 (d, *J* = 2.1 Hz, 1H), 1.71 (s, 6H), 1.47 (s, 3H), 1.33 (s, 3H), 0.96–0.90 (complex m, 2H), 0.02 (s, 9H);

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 163.8 (C), 161.3 (C), 160.0 (C), 139.6 (CH), 137.8 (CH), 132.3 (CH), 131.5 (C), 129.7 (2 x CH), 124.8 (CH), 114.4 (2 x CH), 109.8 (C), 106.9 (C), 95.9 (CH), 93.1 (CH_2), 81.4 (C), 80.6 (CH), 78.8 (CH), 78.3 (CH), 76.8 (CH), 70.9 (CH_2), 67.0 (CH_2), 66.2 (CH), 55.5 (CH_3), 27.1 (CH_3), 25.9 (CH_3), 25.1 (CH_3), 25.0 (CH_3), 18.6 (CH_2), −1.2 (3 x CH_3).

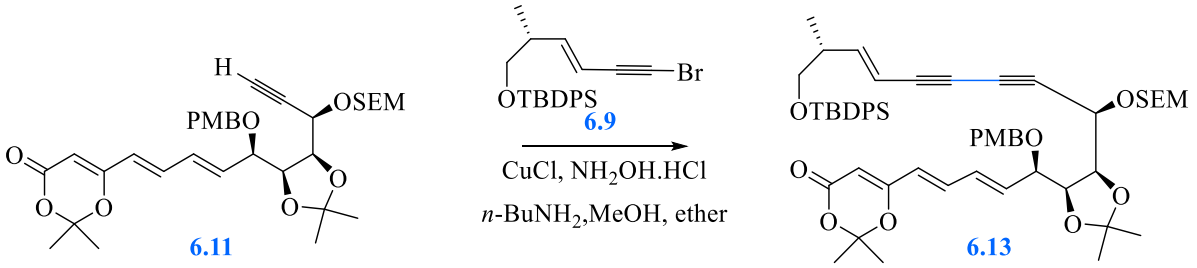
IR (ATR) ν_{max} 3264, 2948, 2894, 1724, 1628, 1514, 1379, 1249, 1019, 859, 836 cm^{-1};

MS (ESI, +ve) *m/z* 637 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 637.2808, $C_{33}H_{46}{}^{23}NaO_9Si$ requires 637.2809;

Specific rotation $[\alpha]^{25}_{D} = -46.5$ (*c* 1.0, $CHCl_3$).

6-((*R*,1*E*,3*E*)-5-((4*S*,5*R*)-2,2-Dimethyl-5-((8*R*,15*R*,*E*)-2,2,15,19,19-pentamethyl-18,18-diphenyl-5,7,17-trioxa-2,18-disilaicosa-13-en-9,11-diyn-8-yl)-1,3-dioxolan-4-yl)-5-((4-methoxybenzyl)oxy)penta-1,3-dien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (6.13)



In a two-neck round bottom flask, a degassed solution of copper iodide in *n*-butylamine (0.5 mL of 30% aqueous solution) was treated with hydroxylamine hydrochloride with the result that the original blue color was discharged. The reaction mixture was cooled to 0 °C then treated with a solution of alkyne **6.11** (40 mg, 0.06 mmol) in methanol (1 mL). The orange alkynide suspension thus formed was treated, dropwise, with a solution of bromoalkyne **6.9** (42 mg, 0.98 mmol) dissolved in the minimum volume of diethyl ether then warmed to 18 °C. More hydroxylamine hydrochloride was added as necessary throughout the reaction so as to prevent the solution from turning blue or green. After reaction was complete (*ca*. 30 min as judged by thin layer chromatography) then diethyl ether (5 mL) was added and the resulting mixture was washed with ammonium chloride (5mL of a saturated aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic phases were dried over magnesium sulfate, filtered, concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded *compound **6.13*** (40 mg, 64%) as a clear, light-yellow oil. As the compound was found to be unstable, only the following data were acquired on it.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.70–7.68 (complex m, 4H), 7.48–7.41 (complex m, 6H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 15.3 and 11.0 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.58 (dd, *J* = 15.4 and 11.0 Hz, 1H), 6.40 (dd, *J* = 16.0 and 7.6 Hz, 1H), 6.30 (d, *J* = 15.3 Hz, 1H), 6.23 (dd, *J* = 15.4 and 7.4 Hz, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 5.43 (s, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 7.4 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.51 (ABq, Δ δ_{AB} = 0.10, J_{AB} = 11.3 Hz, 2H), 4.34–4.26 (complex m, 2H), 4.23 (dd, *J* = 6.1 and 4.5 Hz, 1H), 3.78 (s, 3H), 3.71–

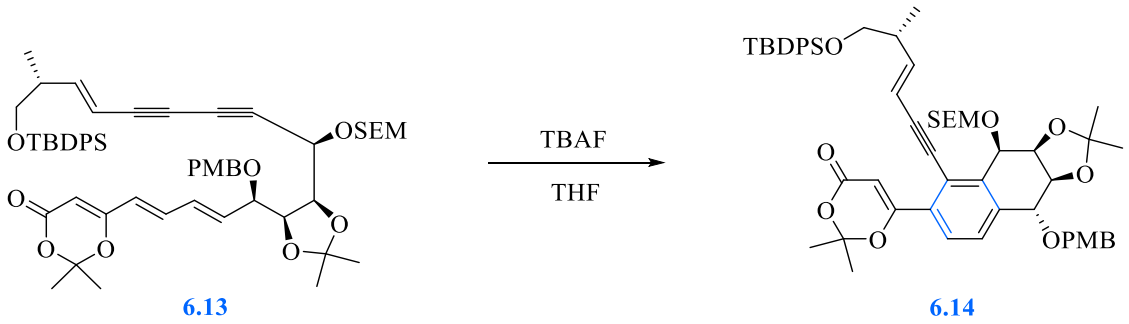
3.56 (complex m, 2 x 2H), 2.57 (hept, *J* = 6.8 Hz, 1H), 1.70 (s, 6H), 1.48 (s, 3H), 1.34 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 0.97–0.87 (complex m, 2H), 0.02 (s, 9H);

IR (ATR) ν_{max} 2953, 2932, 2859, 1726, 1628, 1514, 1377, 1247, 1006, 1018, 859, 834 cm^{-1};

MS (ESI, +ve) *m/z* 983 [$(M+Na)^+$, 50%], 978 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 983.4536, $C_{56}H_{72}{}^{23}NaO_{10}Si_2$ requires 983.4562.

6-((3a*R*,4*R*,9*S*,9a*S*)-5-((*R*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-5-methylhex-3-en-1-yn-1-yl)-9-((4-methoxybenzyl)oxy)-2,2-dimethyl-4-((2-(trimethylsilyl)ethoxy)methoxy)-3a,4,9,9a-tetrahydronaphtho[2,3-*d*][1,3]dioxol-6-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (6.14)



6.13 6.14

A magnetically stirred solution of compound **6.13** (20 mg, 0.02 mmol) in toluene (2 mL) maintained at ambient temperatures was treated with tetra-*n*-butylammonium fluoride (0.08 mL of 1.0 M solution in tetrahydrofuran, 0.08 mmol). After 16 h the reaction mixture was quenched with ammonium chloride (2 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 2 mL). The combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 40:60 *v/v* diethyl ether/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the aromatised *compound **6.14*** (15 mg, 75%) as a clear, colorless oil.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.83–7.61 (complex m, 6H), 7.54–7.34 (complex m, 8H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.49 (dd, *J* = 16.0 and 7.7 Hz, 1H), 6.03 (s, 1H), 5.94 (d, *J* = 16.0 Hz, 1H), 5.59 (d, *J* = 3.8 Hz, 1H), 5.12 (d, *J* = 6.2 Hz, 1H), 4.89 (ABq, Δ δ_{AB} = 0.19, J_{AB} = 11.4 Hz, 2H), 4.74 (ABq, Δ δ_{AB} = 0.08, J_{AB} = 6.4 Hz, 2H), 4.43 (dd, *J* = 8.5 and 6.2 Hz, 1H), 4.32 (dd, *J* = 8.5 and 3.8 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 6.3 Hz, 2H), 3.59 (td, *J* = 10.1, 6.7 Hz,

1H), 3.40 (td, *J* = 10.1, 6.7 Hz, 1H), 2.64 (hept, *J* = 6.8 Hz, 1H), 1.79 (s, 6H), 1.59 (s, 3H), 1.42 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 9H), 0.84–0.80 (m, 2H), −0.06 (s, 9H);

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 165.5 (C), 161.1 (C), 160.3 (C), 150.2 (CH), 143.0 (C), 138.4 (C), 136.4 (2 x CH), 136.4 (2 x CH), 134.4 (C), 134.4 (C), 132.8 (C), 131.6 (C), 130.7 (2 x CH), 130.2 (2 x CH), 129.9 (CH), 128.7 (4 x CH), 125.7 (CH), 122.1 (C), 114.5 (2 x CH), 111.6 (C), 110.2 (CH), 107.5 (C), 99.2 (C), 96.8 (CH), 94.9 (CH_2), 84.7 (C), 80.6 (CH), 79.1 (CH), 76.5 (CH), 72.9 (CH_2), 72.1 (CH), 68.8 (CH_2), 65.6 (CH_2), 55.5 (CH_3), 41.1 (CH), 27.3 (3 x CH_3), 26.9 (CH_3), 25.4 (CH_3), 25.2 (CH_3), 25.1 (CH_3), 19.9 (C), 18.7 (CH_2), 16.4 (CH_3), −1.2 (3 x CH_3);

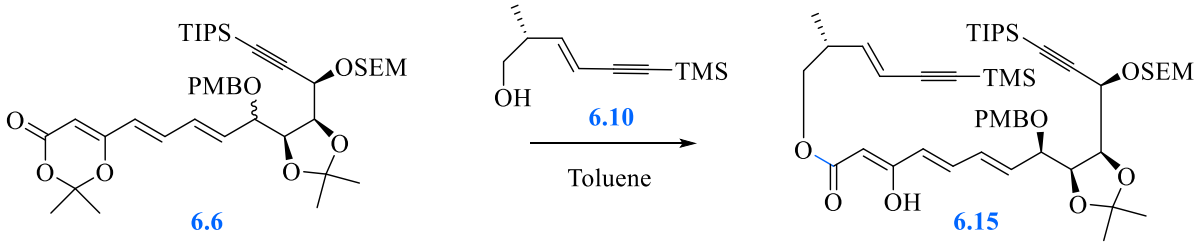
IR (ATR) ν_{max} 2954, 2894, 2859, 1730, 1614, 1514, 1377, 1249, 1207, 1111, 1023, 821 cm^{-1};

MS (ESI, +ve) *m/z* 981 [$(M+Na)^+$, 90%], 976 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 981.4415, $C_{56}H_{70}{}^{23}NaO_{10}Si_2$ requires 981.4405;

Specific rotation $[\alpha]^{25}_D$ = +66.2 (*c* 0.8, $CHCl_3$).

(*R*,*E*)-2-Methyl-6-(trimethylsilyl)hex-3-en-5-yn-1-yl (*R*,2*Z*,4*E*,6*E*)-8-((4*S*,5*R*)-5-((*R*)-11,11-Di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-8-((4-methoxybenzyl)oxy)octa-2,4,6-trienoate (6.15)



A magnetically stirred solution of dioxinone **6.6** (136 mg, 0.18 mmol) and alcohol **6.10** (48 mg, 0.26 mmol) in dry toluene (5 mL) was heated at 120 °C for 4 h. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 20:80 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) afforded the *β-epimeric* form of *compound **6.15*** (113 mg, 71%) as a clear, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*enol form*) 11.71 (s, OH), 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.06 (dd, *J* = 15.2 and 11.1 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.46

(dd, *J* = 15.4 and 11.1 Hz, 1H), 6.14 (dd, *J* = 16.0 and 7.7 Hz, 1H), 6.03 (dd, *J* = 15.4 and 7.6 Hz, 1H), 5.94 (d, *J* = 15.2 Hz, 1H), 5.58 (dd, *J* = 16.0 and 1.2 Hz, 1H), 5.09 (s, 1H), 4 .96 (partially obscured d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 5.3 Hz, 1H), 4.55–4.45 (complex partially obscured m, 2H), 4.40 (t, *J* = 7.3 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 1H), 4.18 (partially obscured m, 1H), 4.03 (partially obscured d, *J* = 6.6 Hz, 2H), 3.79 (s, 3H), 3.68–3.57 (complex partially obscured m, 1H), 3.55–3.42 (complex partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 1.57 (s, 3H), 1.37 (s, 3H), 1.09–1.05 (complex partially obscured m, 21H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.94–0.77 (complex partially obscured m, 2H), 0.18 (s, 9H), −0.01 (s, 9H); (*keto form*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.19 (dd, *J* = 15.5 and 11.0 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.51 (partially obscured d, *J* = 15.4 and 11.0 Hz, 1H), 6.30 (dd, *J* = 15.4 and 6.7 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 6.06 (dd, *J* = 16.0 and 7.6 Hz, 1H), 5.57 (dd, *J* = 16.0 and 1.2 Hz, 1H), 4.94 (partially obscured d, *J* = 6.7 Hz, 1H), 4.72 (partially obscured d, *J* = 6.7 Hz, 1H), 4.63 (partially obscured d, *J* = 5.3 Hz, 1H), 4.55–4.45 (complex partially obscured m, 2H), 4.35 (partially obscured m, 1H), 4.20–4.17 (complex partially obscured m, 2H), 4.03 (partially obscured d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.68–3.57 (partially obscured m, 1H), 3.61 (s, 2H), 3.55–3.42 (partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.09 (s, 21H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.94–0.77 (complex partially obscured m, 2H), 0.18 (s, 9H), −0.02 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*enol form*) 172.6 (C), 169.1 (C), 159.2 (C), 146.4 (CH), 136.3 (CH), 136.0 (CH), 132.9 (CH), 130.6 (C), 129.2 (2 x CH), 126.7 (CH), 113.8 (2 x CH), 110.6 (CH), 109.5 (C, partially obscured), 103.6 (C), 103.4 (C), 94.2 (C), 92.1 (CH), 92.0 (CH_2), 89.7 (C), 79.7 (CH), 78.3 (CH), 77.6 (CH), 70.7 (CH_2), 67.7 (CH_2), 66.2 (CH_2), 65.5 (CH), 55.4 (CH_3), 36.7 (CH), 27.0 (CH_3), 25.4 (CH_3), 18.8 (6 x CH_3), 18.3 (CH_2), 16.4 (CH_3), 11.4 (3 x CH), 0.07 (3 x CH_3), −1.3 (3 x CH_3); (*keto form*) 191.9 (C), 167.3 (C), 159.2 (C), 146.1 (CH), 143.4 (CH), 141.8 (CH), 131.2 (CH), 130.4 (C), 129.5 (CH), 129.1 (2 x CH), 113.9 (2 x CH), 110.8 (CH), 109.5 (C, partially obscured),103.5 (2 x C), 94.2 (C), 92.3 (CH_2), 89.4 (C), 79.8 (CH), 78.2 (CH), 77.4 (CH), 71.1 (CH_2), 68.7 (CH_2), 66.5 (CH_2), 65.8 (CH), 55.4 (CH_3), 47.3 (CH_2), 36.7 (CH), 27.1 (CH_3), 25.6 (CH_3), 18.8 (6 x CH_3), 18.7 (CH_2), 16.3 (CH_3), 11.3 (3 x CH), 0.07 (3 x CH_3), −1.2 (3 x CH_3);

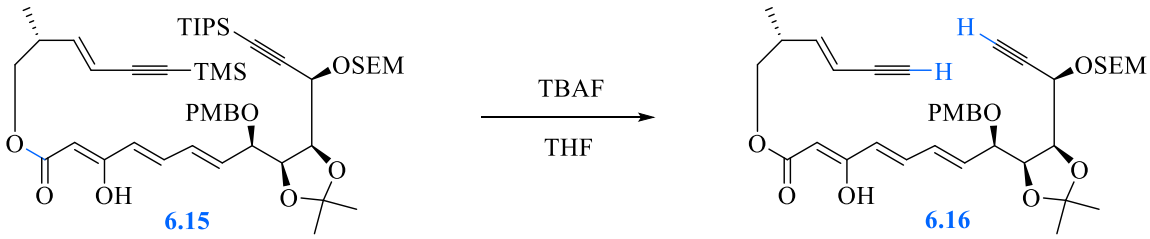
IR (ATR) ν_{max} 2945, 2893, 2866, 2159, 1633, 1580, 1514, 1464, 1419, 1248, 1026, 841 cm^{-1};

MS (ESI, +ve) *m/z* 917 [$(M+Na)^+$, 100%], 913 [$(M+NH_4)^+$, 50];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 917.4853, $C_{49}H_{78}{}^{23}NaO_9Si_3$ requires 917.4851. $(M+H)^+$ 895.5055, $C_{49}H_{79}O_9Si_3$ requires 895.5032;

Specific rotation $[\alpha]^{25}_{D}$ = +31.6 (*c* 0.9, $CHCl_3$).

(*R*,*E*)-2-Methylhex-3-en-5-yn-1-yl(*R*,2*Z*,4*E*,6*E*)-8-((4*S*,5*R*)-2,2-dimethyl-5-((*R*)-1-((2-(trimethylsilyl)ethoxy)methoxy)prop-2-yn-1-yl)-1,3-dioxolan-4-yl)-3-hydroxy-8-((4-methoxybenzyl)oxy)octa-2,4,6-trienoate (6.16)



A magnetically stirred solution of compound **6.15** (57 mg, 0.06 mmol) in tetrahydrofuran (2 mL) maintained at ambient temperatures was treated with tetra-*n*-butylammonium fluoride (0.16 mL of a 1.0 M solution in tetrahydrofuran, 0.16 mmol). After 2 h the reaction mixture was quenched with ammonium chloride (5 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) afforded *compound **6.16*** (36 mg, 85%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*enol form*) 11.71 (s, OH), 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.07 (dd, *J* = 15.2 and 11.0 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.42 (partially obscured d, *J* = 15.4 and 11.0 Hz, 1H), 6.17 (partially obscured d, *J* = 16.1 and 7.5 Hz, 1H), 6.03 (dd, *J* = 15.4 and 7.4 Hz, 1H), 5.94 (d, *J* = 15.2 Hz, 1H), 5.53 (ddd, *J* = 16.1, 2.2 and 1.3 Hz, 1H), 5.08 (s, 1H), 4.88 (partially obscured d, *J* = 6.7 Hz, 1H), 4.64 (partially obscured d, *J* = 6.7 Hz, 1H), 4.55 (partially obscured m, 1H), 4.51 (ABq, Δ δ_{AB} = 0.11, J_{AB} = 11.8 Hz, 2H), 4.29 (partially obscured d, *J* = 6.8 Hz, 1H), 4.27–4.16 (complex m, 2H), 4.04 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.66–3.56 (complex partially obscured m, 1H), 3.50 (partially obscured m, 1H), 2.83 (d, *J* = 2.2 Hz, 1H), 2.63 (hept, *J* = 6.9 Hz, 1H), 2.46 (d, *J* = 2.2 Hz, 1H), 1.57 (s, 3H), 1.40 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92–0.82 (complex partially obscured m, 2H), −0.02 (s, 9H); (*keto form*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 15.5 and 10.8 Hz, 1H), 6.88 (partially obscured d, *J* = 8.6 Hz, 2H), 6.48 (partially obscured d,

J = 15.4 and 10.8 Hz, 1H), 6.31 (dd, *J* = 15.4 and 6.8 Hz, 1H), 6.25 (d, *J* = 15.5 Hz, 1H), 6.12 (partially obscured d, *J* = 16.1 and 7.6 Hz, 1H), 5.50 (ddd, *J* = 16.1, 2.2 and 1.3 Hz, 1H), 4.87 (partially obscured d, *J* = 6.7 Hz, 1H), 4.69 (partially obscured d, *J* = 6.7 Hz, 1H), 4.59 (dd, *J* = 7.3 and 2.0 Hz, 1H), 4.51 (ABq, $\Delta\ \delta_{AB}$ = 0.11, J_{AB} = 11.8 Hz, 2H), 4.30 (partially obscured d, *J* = 6.0 Hz, 1H), 4.27–4.16 (complex m, 2H), 4.03 (d, *J* = 6.6, 2H), 3.80 (s, 3H), 3.61 (partially obscured m, 1H), 3.60 (s, 2H), 3.50 (partially obscured m, 1H), 2.83 (d, *J* = 2.2 Hz, 1H), 2.63 (hept, *J* = 6.9 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 1.55 (s, 3H), 1.40 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.92–0.82 (complex partially obscured m, 2H), 0.00 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*enol form*) 172.6 (C), 169.1 (C), 159.2 (C), 147.2 (CH), 136.3 (CH), 136.0 (CH), 132.9 (CH), 130.4 (C), 129.3 (2 x CH), 126.6 (CH), 113.8 (2 x CH), 109.9 (CH), 109.8 (C), 92.4 (CH_2), 91.9 (CH), 82.1 (CH), 80.2 (CH), 79.6 (CH), 78.1 (CH), 77.1 (CH), 76.9 (CH), 75.9 (CH), 70.3 (CH_2), 68.6 (CH_2), 66.4 (CH_2), 65.2 (CH), 55.4 (CH_3), 36.7 (CH), 26.9 (CH_3), 25.6 (CH_3), 18.2 (CH_2), 16.3 (CH_3), −1.4 (3 x CH_3); (*keto form*) 191.9 (C), 167.2 (C), 159.3 (C), 146.9 (CH), 143.4 (CH), 141.9 (CH), 131.2 (CH), 130.2 (C), 129.5 (CH), 129.1 (2 x CH), 113.9 (2 x CH), 109.7 (CH), 109.6 (C), 92.7 (CH_2), 82.1 (C), 80.3 (CH), 79.7 (CH), 78.0 (CH), 77.1 (CH), 76.6 (CH), 75.7 (CH), 70.7 (CH_2), 67.5 (CH_2), 66.6 (CH_2), 65.6 (CH), 55.4 (CH_3), 47.3 (CH_2), 36.7 (CH), 26.9 (CH_3), 25.6 (CH_3), 18.2 (CH_2), 16.2 (CH_3), −1.3 (3 x CH_3);

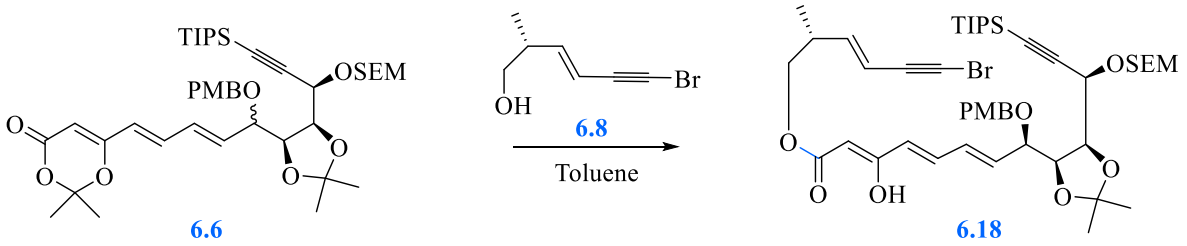
IR (ATR) ν_{max} 3288, 2954, 2894, 1741, 1634, 1514, 1420, 1248, 1025, 836 cm^{-1};

MS (ESI, +ve) *m/z* 689 [$(M+Na)^+$, 80%], 684 [$(M+NH_4)^+$, 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 689.3123, $C_{37}H_{50}{}^{23}NaO_9Si$ requires 689.3122. $(M+H)^+$ 667.3302, $C_{37}H_{51}O_9Si$ requires 667.3302;

Specific rotation $[\alpha]^{25}_D$ = −21.1 (*c* 2.3, $CHCl_3$).

(*R*,*E*)-6-Bromo-2-methylhex-3-en-5-yn-1-yl(*R*,2*Z*,4*E*,6*E*)-8-((4*S*,5*R*)-5-((*R*)-11,11-di-*iso*-propyl-2,2,12-trimethyl-5,7-dioxa-2,11-disilatridec-9-yn-8-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-8-((4-methoxybenzyl)oxy)octa-2,4,6-trienoate (6.18)



A magnetically stirred solution of dioxinone **6.6** (136 mg, 0.18 mmol) and alcohol **6.8** (100 mg, 0.13 mmol) in dry toluene (5 mL) was heated at 120 °C for 4 h. The ensuing mixture was concentrated under reduce pressure and the residue thus obtained subjected to flash column chromatography (silica, 30:70 *v/v* diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.6) afforded the *β-epimeric* form of *compound **6.18*** (85 mg, 72%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*enol form*) 11.70 (s, OH), 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.07 (dd, *J* = 15.2, 11.0 Hz, 1H), 6.85 (partially obscured d, *J* = 8.6 Hz, 2H), 6.45 (dd, *J* = 15.4, 11.0 Hz, 1H), 6.11 (dd, *J* = 16.0, 7.6 Hz, 1H), 6.04 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.94 (d, *J* = 15.2 Hz, 1H), 5.51 (dd, *J* = 16.0, 1.1 Hz, 1H), 5.08 (s, 1H), 4 .96 (partially obscured d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 5.3 Hz, 1H), 4.53–4.46 (complex partially obscured m, 2H), 4.38 (partially obscured m, 1H), 4.25 (t, *J* = 6.7 Hz, 1H), 4.19 (partially obscured m, 1H), 4.03 (partially obscured d, *J* = 6.6 Hz, 2H), 3.79 (s, 3H), 3.63 (partially obscured m, 1H), 3.49 (partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 1.57 (s, 3H), 1.37 (s, 3H), 1.08 (s, 21H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.93–0.80 (complex partially obscured m, 2H), −0.02 (s, 9H); (*keto form*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.19 (dd, *J* = 15.5, 10.8 Hz, 1H), 6.87 (partially obscured d, *J* = 8.6 Hz, 2H), 6.49 (partially obscured d, *J* = 15.4, 10.8 Hz, 1H), 6.31 (dd, *J* = 15.4, 6.7 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 6.08 (dd, *J* = 16.0, 7.6 Hz, 1H), 5.49 (dd, *J* = 16.0, 1.1 Hz, 1H), 4.95 (partially obscured d, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 5.3 Hz, 1H), 4.53–4.46 (complex partially obscured m, 2H), 4.38 (partially obscured m, 1H), 4.23–4.15 (complex partially obscured m, 2H), 4.03 (partially obscured d, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.63 (partially obscured m, 1H), 3.59 (s, 2H), 3.49 (partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H), 1.08 (s, 21H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93–0.80 (complex partially obscured m, 2H), −0.01 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*enol form*) 172.6 (C), 169.2 (C), 159.2 (C), 147.0 (CH), 136.3 (CH), 136.1 (CH), 132.9 (CH), 130.6 (C), 129.2 (2 x CH), 126.7 (CH), 113.8 (2 x CH), 110.1 (CH), 109.5 (C, partially obscured), 103.4 (C), 92.3 (CH), 92.0 (CH_2), 89.7 (C), 79.7 (CH), 78.5 (C), 78.3 (CH), 77.6 (CH), 70.7 (CH_2), 68.5 (CH_2), 66.2 (CH_2), 65.4 (CH), 55.4 (CH_3), 49.0 (C), 36.6 (CH), 27.0 (CH_3), 25.4 (CH_3), 18.8 (6 x CH_3), 18.3 (CH_2), 16.3 (CH_3), 11.3 (3 x CH), −1.4 (3 x CH_3); (*keto form*) 191.8 (C), 167.2 (C), 159.2 (C), 146.8 (CH), 143.5 (CH), 141.8 (CH), 131.2 (CH), 130.4 (C), 129.5 (CH), 129.1 (2 x CH), 113.9 (2 x CH), 110.3 (CH), 109.5 (C, partially obscured), 103.5 (C), 92.0 (CH_2), 89.4 (C), 79.8 (CH), 78.5 (C), 78.2 (CH), 77.3 (CH), 71.1 (CH_2), 67.5 (CH_2), 66.6 (CH_2), 65.8 (CH), 55.4 (CH_3), 49.1 (C), 47.3 (CH_2), 36.7 (CH), 27.1 (CH_3), 25.6 (CH_3), 18.8 (6 x CH_3), 18.3 (CH_2), 16.3 (CH_3), 11.3 (3 x CH), −1.3 (3 x CH_3);

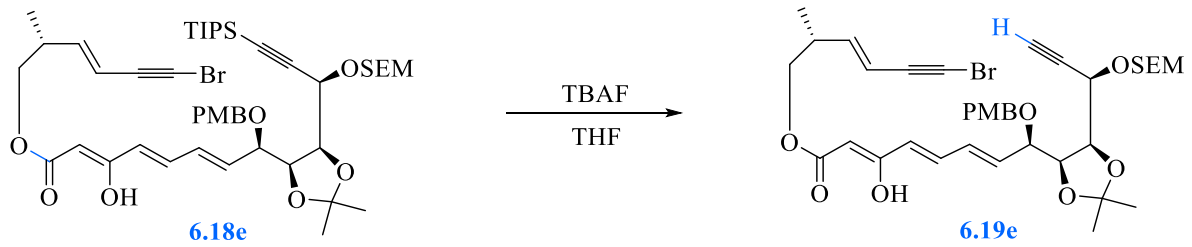
IR (ATR) ν_{max} 2944, 2865, 1743, 1633, 1580, 1514, 1420, 1248, 1026, 835 cm^{-1};

MS (ESI, +ve) *m/z* 925 and 923 [$(M+Na)^+$, both 90%], 920 and 918 [$(M+NH_4)^+$, both 100];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 925.3543, $C_{46}H_{69}{}^{81}Br^{23}NaO_9Si_2$ requires 925.3541. $(M+Na)^+$ 923.3568, $C_{46}H_{69}{}^{79}Br^{23}NaO_9Si_2$ requires 923.3561;

Specific rotation $[\alpha]^{25}_D$ = +16.5 (*c* 2.7, $CHCl_3$).

(*R*,*E*)-6-Bromo-2-methylhex-3-en-5-yn-1-yl (*R*,2*Z*,4*E*,6*E*)-8-((4*S*,5*R*)-2,2-Dimethyl-5-((*R*)-1-((2-(trimethylsilyl)ethoxy)methoxy)prop-2-yn-1-yl)-1,3-dioxolan-4-yl)-3-hydroxy-8-((4-methoxybenzyl)oxy)octa-2,4,6-trienoate (6.19)



A magnetically stirred solution of compound **6.18** (85 mg, 0.09 mmol) in tetrahydrofuran (2 mL) maintained at ambient temperatures was treated with tetra-*n*-butylammonium fluoride (0.11 mL of 1.0 M solution in tetrahydrofuran, 0.11 mmol). After 2 h, the reaction mixture was quenched with ammonium chloride (2 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with diethyl ether (3 x 2 mL). The combined organic phases were dried over magnesium sulfate before being filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 10:30:60 *v/v/v* diethyl ether/dichloromethane/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *compound **6.19*** (60 mg, 85%) as a clear, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (*enol form*) 11.71 (s, OH), 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.07 (dd, *J* = 15.1 and 11.0 Hz, 1H), 6.87 (partially obscured d, *J* = 8.6 Hz, 2H), 6.41 (dd, *J* = 15.4 and 11.0 Hz, 1H), 6.13 (dd, *J* = 16.1 and 7.5 Hz, 1H), 6.03 (dd, *J* = 15.4 and 7.4 Hz, 1H), 5.95 (d, *J* = 15.5 Hz, 1H), 5.52 (d, *J* = 16.1, 1H), 5.08 (s, 1H), 4.89 (partially obscured d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.56 (m, 1H), 4.52 (ABq, Δ δ_{AB} = 0.11, J_{AB} = 11.8 Hz, 2H), 4.30 (partially obscured m, 1H), 4.26–4.17 (complex m, 2H), 4.05–4.02 (partially obscured m, 2H), 3.80 (s, 3H), 3.61 (partially obscured m, 1H), 3.51 (partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 2.46 (d, *J* = 1.9 Hz, 1H), 1.58 (s, 3H), 1.40 (partially obscured s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92–0.82 (complex partially obscured m, 2H), −0.01 (s, 9H); (*keto form*) 7.27 (partially obscured d, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 15.5 and 10.8 Hz, 1H), 6.87 (partially obscured d, *J* = 8.6 Hz, 2H), 6.47 (partially obscured d, *J* = 15.5 and 10.8 Hz, 1H), 6.31 (dd, *J* = 15.5 and 6.9 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 6.08 (dd, *J* = 15.9 and 7.3 Hz, 1H), 5.49 (d, *J* = 15.9 Hz, 1H), 4.88 (partially obscured d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.61 (dd, *J* = 7.3 and 1.9 Hz, 1H), 4.51 (ABq, Δ δ_{AB} = 0.11, J_{AB} = 11.8 Hz, 2H), 4.30 (partially obscured m, 1H), 4.26–4.17 (complex m, 2H), 4.05–4.02 (complex partially obscured

m, 2H), 3.80 (s, 3H), 3.61 (partially obscured m, 1H), 3.60 (s, 2H), 3.51 (partially obscured m, 1H), 2.62 (hept, *J* = 6.9 Hz, 1H), 2.50 (d, *J* = 1.9 Hz 1H), 1.55 (s, 3H), 1.40 (partially obscured s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.92–0.82 (complex partially obscured m, 2H), 0.00 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (*enol form*) 172.6 (C), 169.2 (C), 159.2 (C), 147.1 (CH), 136.4 (CH), 136.1 (CH), 132.9 (CH), 130.4 (C), 129.3 (2 x CH), 126.6 (CH), 113.8 (2 x CH), 110.1 (CH), 109.8 (C), 92.4 (CH_2), 91.9 (CH), 80.2 (C), 79.6 (CH), 78.5 (C), 78.1 (CH), 76.6 (CH), 75.9 (CH), 70.3 (CH_2), 68.5 (CH_2), 66.4 (CH_2), 65.2 (CH), 55.4 (CH_3), 49.0 (C), 36.6 (CH), 26.9 (CH_3), 25.6 (CH_3), 18.3 (CH_2), 16.3 (CH_3), −1.3 (3 x CH_3); (*keto form*) 191.8 (C), 167.2 (C), 159.3 (C), 146.8 (CH), 143.4 (CH), 141.9 (CH), 131.2 (CH), 130.2 (C), 129.5 (CH), 129.1 (2 x CH), 113.9 (2 x CH), 110.3 (CH), 109.9 (C), 92.7 (CH_2), 80.4 (C), 79.7 (CH), 78.5 (C), 78.0 (CH), 76.8 (CH), 75.7 (CH), 70.7 (CH_2), 67.5 (CH_2), 66.6 (CH_2), 65.5 (CH), 55.4 (CH_3), 49.1 (C), 47.3 (CH_2), 36.6 (CH), 26.9 (CH_3), 25.7 (CH_3), 18.2 (CH_2), 16.2 (CH_3), −1.2 (3 x CH_3);

IR (ATR) ν_{max} 3283, 2954, 2923, 1741, 1633, 1514, 1420, 1248, 1027, 835 cm^{-1};

MS (ESI, +ve) *m/z* 769 and 767 [$(M+Na)^+$, both 100%], 689 [$(M-Br+H+Na)^+$, 80];

HRMS (ESI, +ve) Found: $(M+Na)^+$ 769.2219, $C_{37}H_{49}{}^{81}Br^{23}NaO_9Si$ requires 769.2206. $(M+Na)^+$ 767.2225, $C_{37}H_{49}{}^{79}Br^{23}NaO_9Si$ requires 767.2227;

Specific rotation $[\alpha]^{25}_D = -21.8$ (*c* 1.7, $CHCl_3$).

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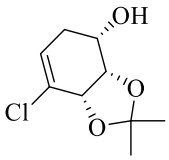
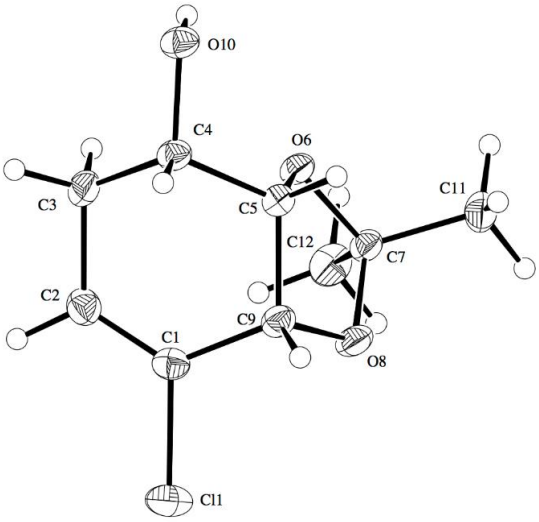
8. APPENDICES

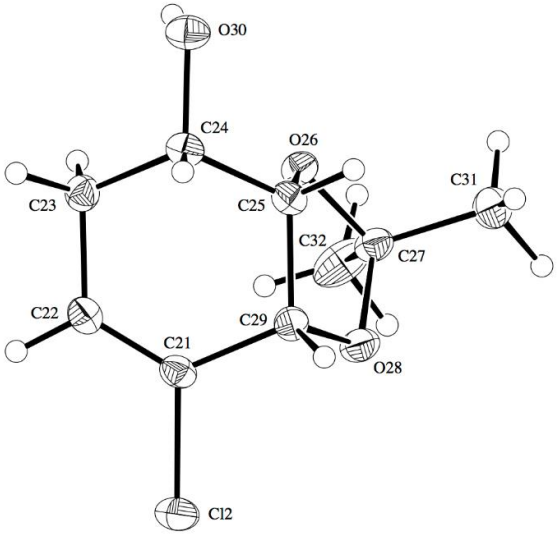
Appendix One: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.11*



2.11



Structure of molecule one of compound **2.11** (CCDC No. 956513) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

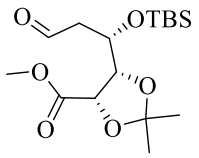


Structure of molecule two of compound **2.11** (CCDC No. 956513) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

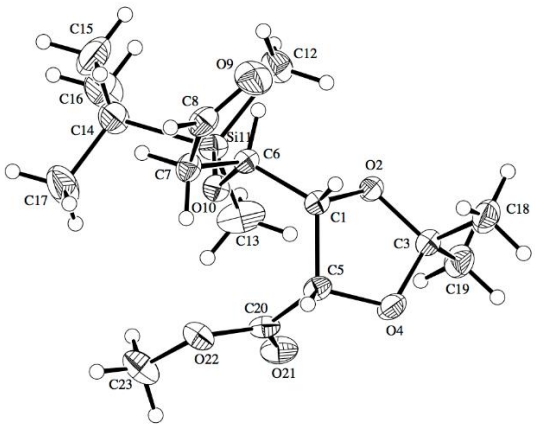
A full X-ray crystallographic report for compound **2.11** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.11.pdf

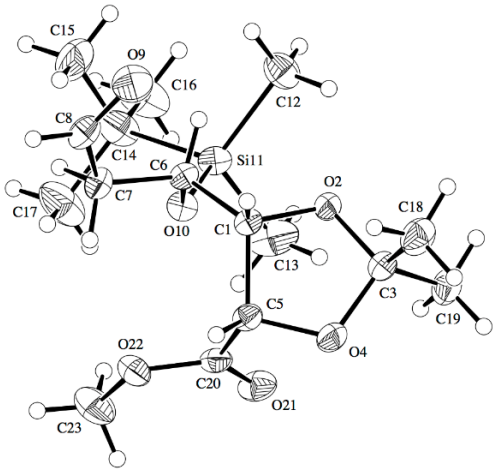
Appendix Two: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.13*



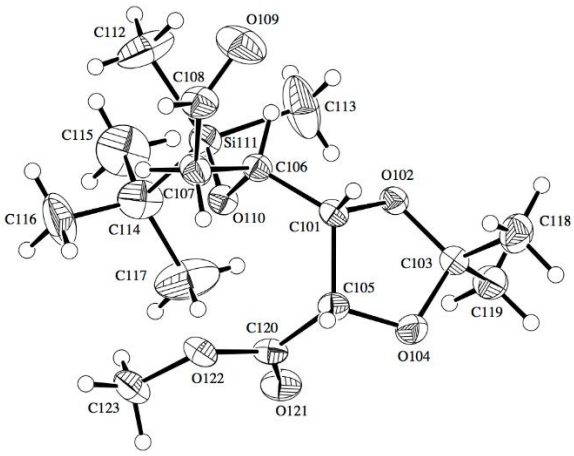
2.13

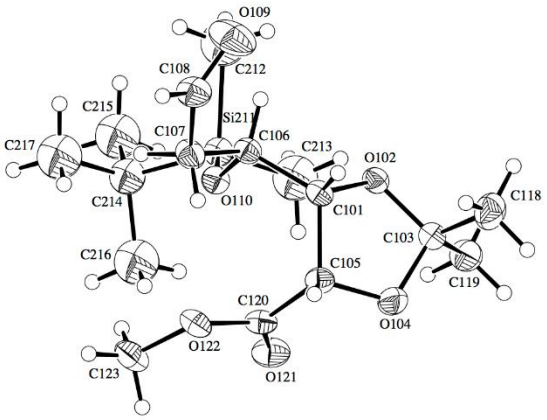


Structure of molecule one of compound **2.13** (CCDC No. 956514) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



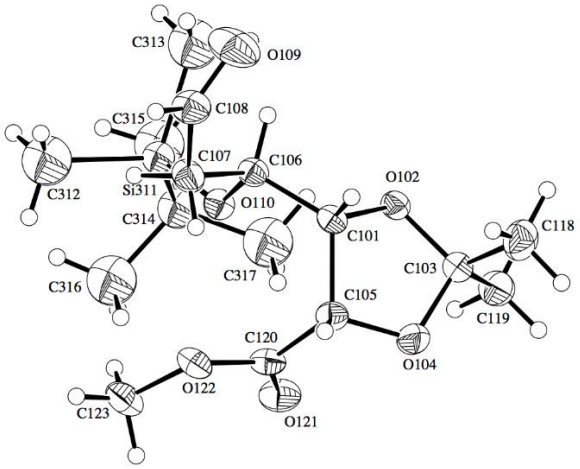
Structure of molecule one of compound **2.13** (CCDC No. 956514) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.





Structure of molecule two of compound **2.13** (CCDC No. 956514) with labelling of selected atoms, showing the dominant sites of disordered atoms (Si111, C112–C117, occupancy 0.742). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Structure of molecule two of compound **2.13** (CCDC No. 956514) with labelling of selected atoms, showing the dominant sites of disordered atoms (Si111, C112–C117, occupancy 0.742). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

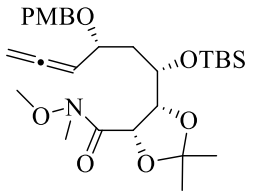


Structure of molecule three of compound **2.13** (CCDC No. 956514) with labelling of selected atoms, showing the dominant sites of disordered atoms (Si311, C312–C317, occupancy 0.080). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

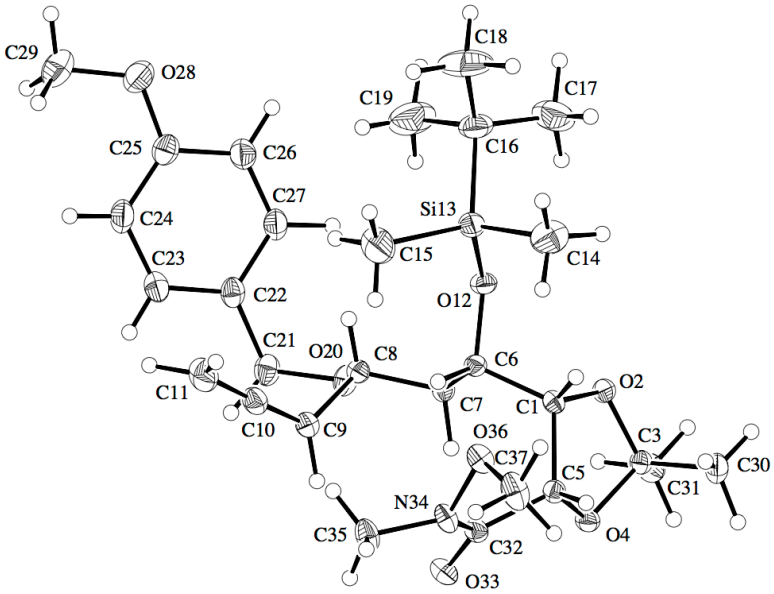
A full X-ray crystallographic report for compound **2.13** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.13.pdf

Appendix Three: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.20α*



2.20α

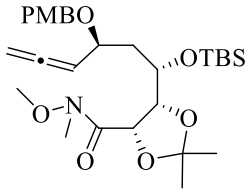


Structure of compound **2.20α** (CCDC No. 956515) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

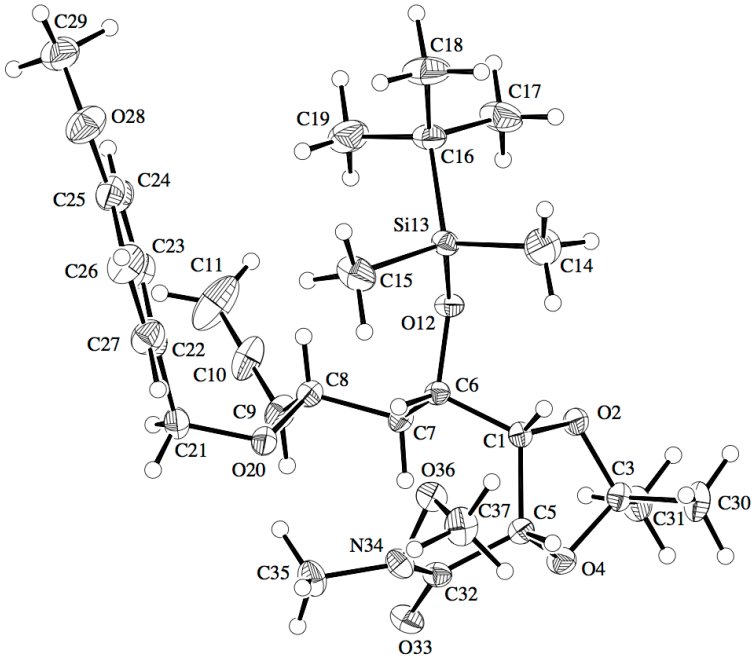
A full X-ray crystallographic report for compound **2.20α** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.20α.pdf

Appendix Four: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.20β*



2.20β

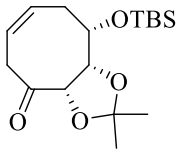


Structure of compound **2.20β** (CCDC No. 956516) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

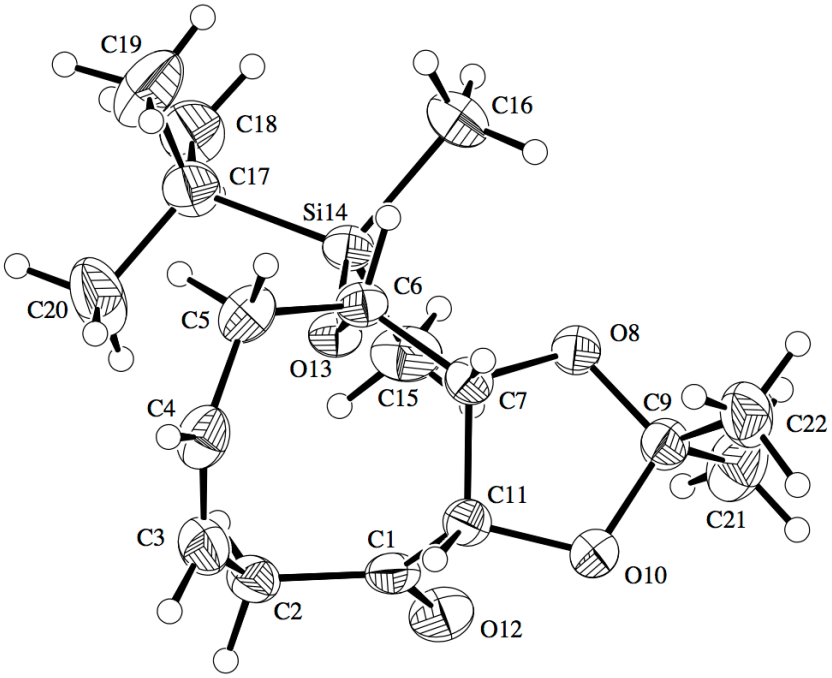
A full X-ray crystallographic report for compound **2.20β** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.20β.pdf

Appendix Five: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.25*



2.25

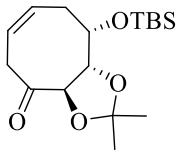


Structure of compound **2.25** (CCDC No. 956517) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

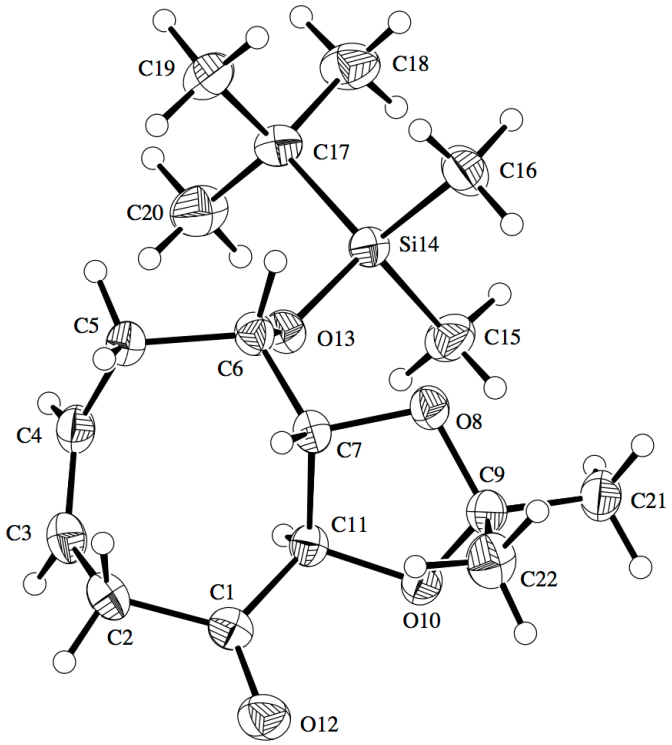
A full X-ray crystallographic report for compound **2.25** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.25.pdf

Appendix Six: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.27*



2.27

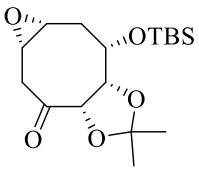


Structure of compound **2.27** (CCDC No. 956521) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

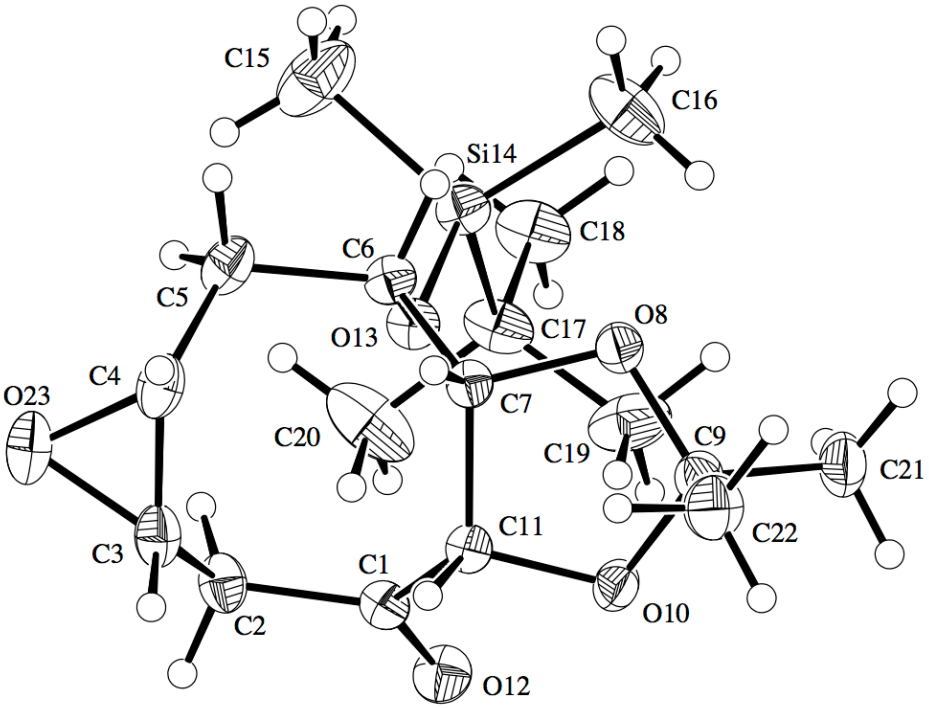
A full X-ray crystallographic report for compound **2.27** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.27.pdf

Appendix Seven: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.30*



2.30

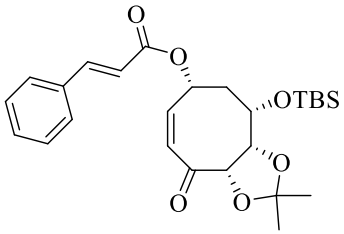


Structure of compound **2.30** (CCDC No. 956518) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

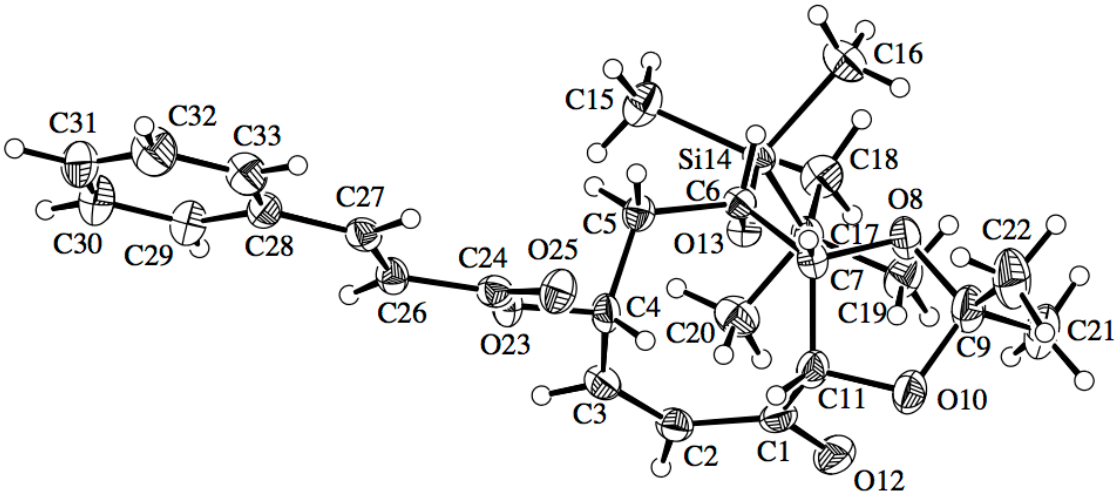
A full X-ray crystallographic report for compound **2.30** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.30.pdf

Appendix Eight: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.32*



2.32

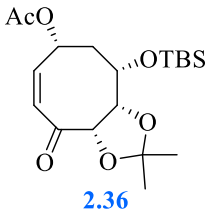


Structure of compound **2.32** (CCDC No. 956519) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

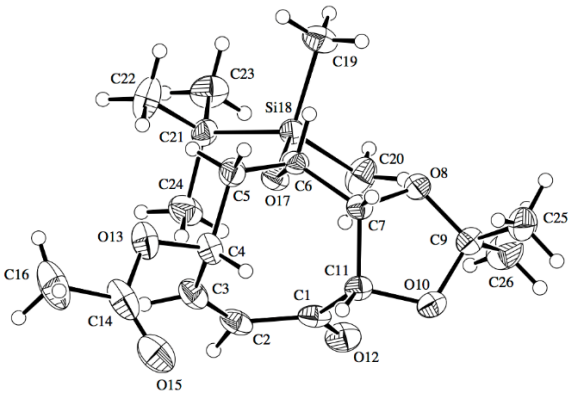
A full X-ray crystallographic report for compound **2.32** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.32.pdf

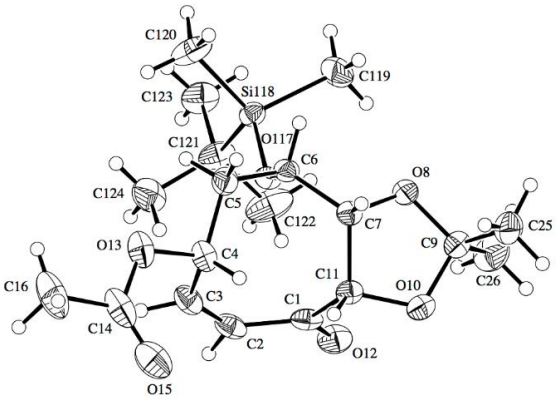
Appendix Nine: *ORTEPs and X-Ray Crystal Structure Report for Compound 2.36*



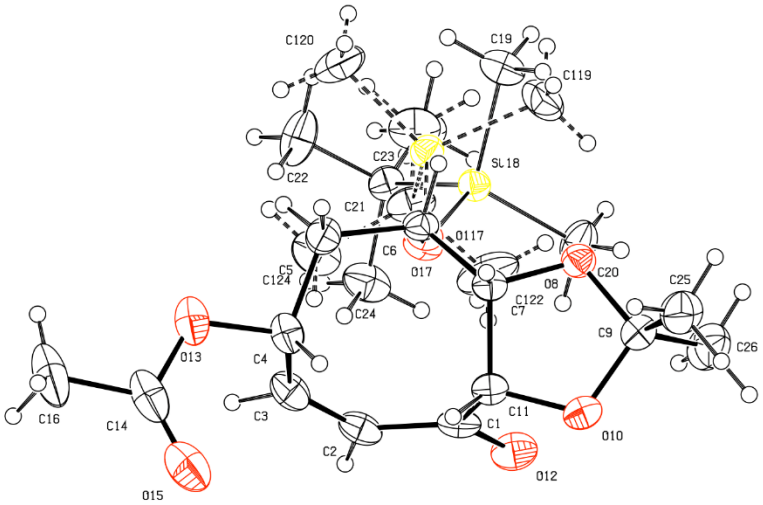
2.36



Structure of compound **2.36** (CCDC No. 956520) with labelling of selected atoms, showing the dominant sites of disordered atoms (O17, Si18, C19–C24, occupancy 0.679). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



Structure of compound **2.36** (CCDC No. 956520) with labelling of selected atoms, showing the dominant sites of disordered atoms (O117, Si118, C119–C124, occupancy 0.321). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

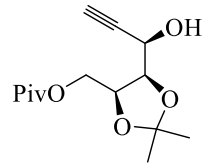


Structure of compound **2.36** (CCDC No. 956520) with labelling of selected atoms, showing both sites of each disordered atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

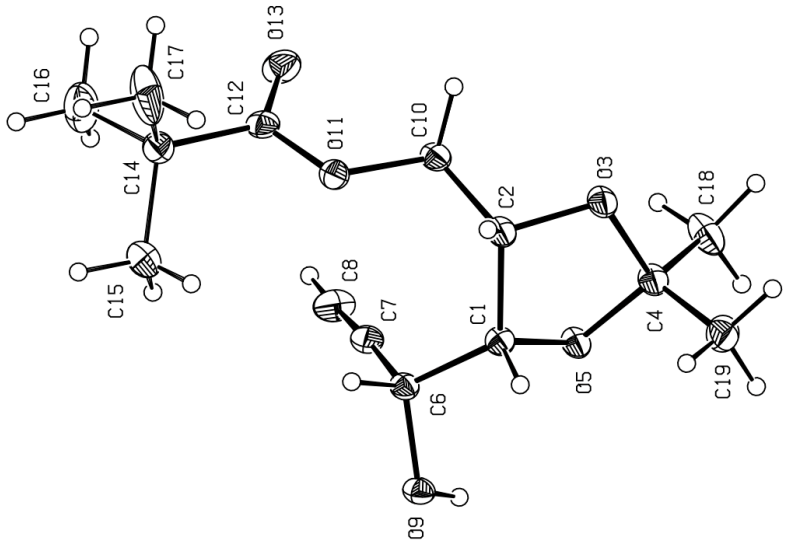
A full X-ray crystallographic report for compound **2.36** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 2.36.pdf

Appendix Ten: *ORTEPs and X-Ray Crystal Structure Report for Compound 5.3*



5.3



Structure of compound **5.3** with labelling of selected atoms. Only the major sites of disordered atoms are shown (C15, C16, C17, occupancy 0.829). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A full X-ray crystallographic report for compound **5.3** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 5.3.pdf

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