



Synthesis of Taurospongins A and Other Biologically Active Natural Products

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Trinity Term 2012

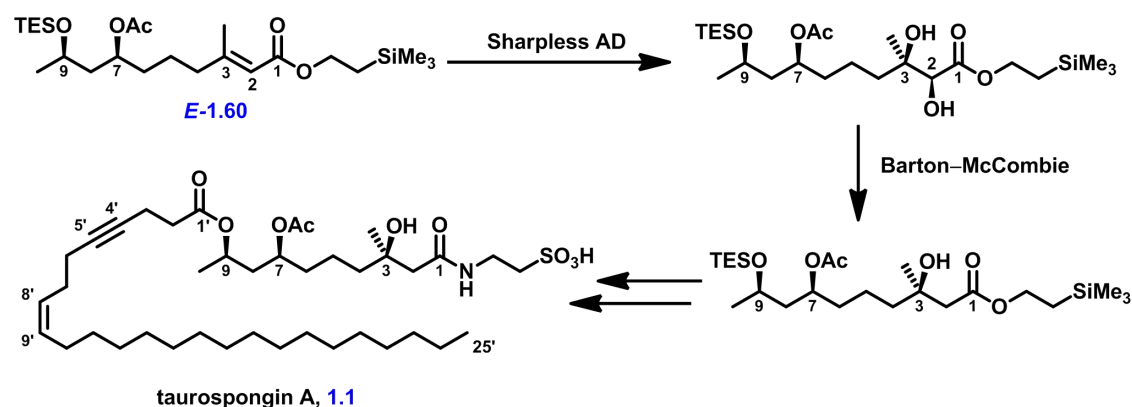
ASLIB Abstract

Synthesis of Taurospongins A and Other Biologically Active Natural Products

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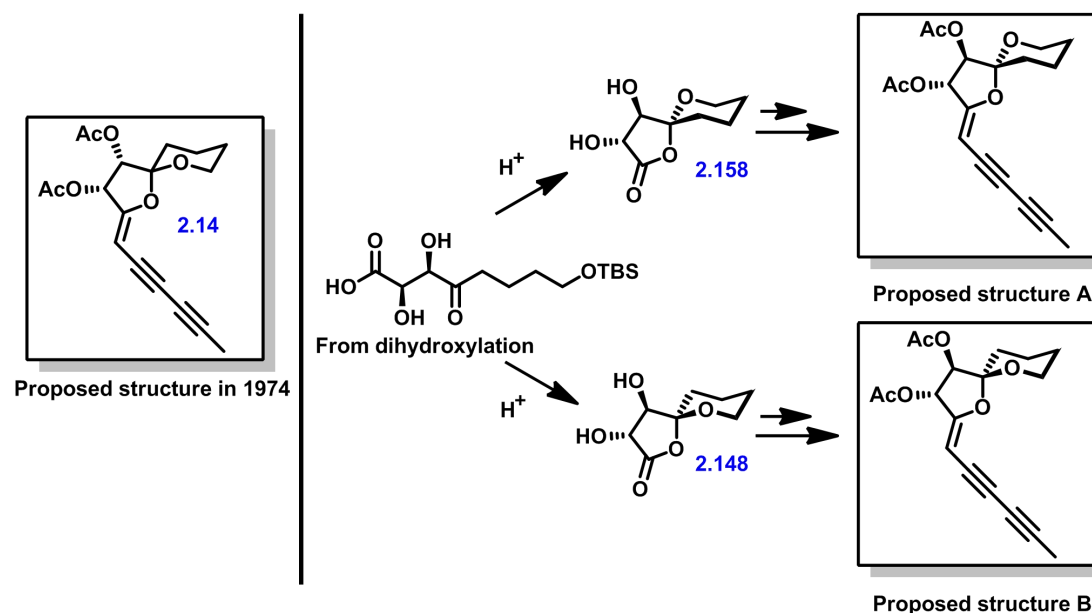
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This thesis firstly describes a synthesis of the natural product taurospongins A, a potent DNA polymerase β inhibitor. Sharpless asymmetric dihydroxylation on olefin **E-1.60** followed by selective deoxygenation at C(2) *via* Barton–McCombie reaction delivers the desired C(1)–C(10) carboxylic acid core. Subsequent esterification of the C(1)–C(10) fragment with C(1')–C(25') fatty acid furnishes the natural product in 13.5% yield.

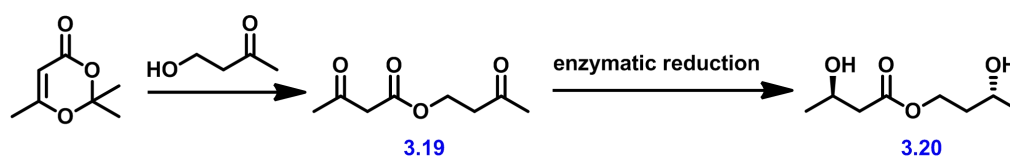


The structure of an unnamed natural product **2.14** isolated in 1974 is proven to be misassigned by previous studies within the Robertson group. As described in this thesis, two proposed structures **A** and **B** are obtained *via* total synthesis in order to reveal the identity of the natural product. A synthesis of key intermediate spirocycles **2.148** and **2.158** with desired *trans*- diol moiety is described by a dihydroxylation

reaction on an electron deficient γ -keto unsaturated acid with subsequent spirocyclisation reaction.



Finally, methodology for generating high-value synthetic intermediates by an asymmetric, one-pot enzymatic di/polycarbonyl reduction is described. The concept of such methodology is first proven by the synthesis of (3*R*)-hydroxybutyl (3*R*)-hydroxybutanoate **3.20**. This thesis then describes substrate scope studies and corresponding stereochemical proof to provide more information about this methodology.



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Abbreviations

Ac	acetyl
acac	acetylacetonate
AD	asymmetric dihydroxylation
ADH	alcohol dehydrogenase
ADH-LB	alcohol dehydrogenase from <i>Lactobacillus brevis</i>
ADP	adenosine-5'-diphosphate
AIBN	azobis(isobutyronitrile)
aq.	aqueous
ATP	adenosine-5'-triphosphate
BER	base excision repair
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-binaphthalene-2,2'-diol
Bn	benzyl
BOM	benzyloxymethyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
b.r.s.m.	based on recovered starting material
BSEH	<i>Bacillus subtilis</i> epoxide hydrolyase
Bu	butyl
BuLi	butyl lithium
Bz	benzoyl
ca.	approximately
cat.	catalytic
CDI	<i>N,N'</i> -carbonyldiimidazole
CI	chemical ionisation
CM	cross metathesis
¹³C NMR	carbon-13 nuclear magnetic resonance
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	day(s)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane

DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DET	diethyl tartrate
(DHQ)₂PHAL	dihydroquinine 1,4-phthalazinediyl diether
(DHQD)₂PHAL	dihydroquinidine 1,4-phthalazinediyl diether
DIBAL	diisobutylaluminium hydride
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DMAC	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
<i>d.r.</i>	diastereomeric ratio
dRP	5'-deoxyribose phosphate
EA	ethyl acetate
<i>e.e.</i>	enantiomeric excess
eq.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl

FAB	fast atom bombardment
FI	field ionisation
g	gram(s)
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
GDH	glucose dehydrogenase
h	hour(s)
Hal	halide
HATU	2-(7-aza-1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIV	human immunodeficiency virus
HIV-RT	human immunodeficiency virus reverse transcriptase
HKR	hydrolytic kinetic resolution
HMBC	heteronuclear multiple-bond correlation
HMQC	heteronuclear multiple-quantum correlation
HMPA	hexamethylphosphoric triamide
¹H NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HWE	Horner–Wadsworth–Emmons
Hz	hertz
<i>i</i>-Bu	isobutyl
imid.	imidazole
<i>i</i>-Pr	isopropyl
IR	infrared
<i>J</i>	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
KRED	ketoreductase
L	litre
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

LG	leaving group
lit.	literature value
M	molar
<i>m</i>-CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	mega hertz
min	minute(s)
mL	millilitre
mmol	millimole
MOM	methoxymethyl
mol	mole
m.p.	melting point
Ms	methane sulfonyl
MS	mass spectrometry
MTPA-Cl	α -methoxy- α -(trifluoromethyl)phenylacetyl chloride
MVK	methyl vinyl ketone
<i>m/z</i>	mass/charge ratio

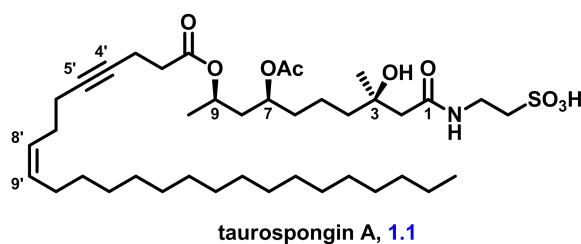
N/A	not applicable or not available
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -bromosuccinimide
NMM	<i>N</i> -methylmorpholine
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NR	no reaction
Nu	nucleophile
Ox	oxidation
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PHB	poly-(3 <i>R</i>)-hydroxybutyrate
pKa	acid dissociation constant
PMB	<i>para</i> -methoxybenzyl
pol-β	polymerase β
p.p.m.	parts per million
Pr	propyl
prod.	product
PTC	phase transfer catalyst
<i>p</i>-TSA	<i>para</i> -toluenesulfonic acid
py	pyridine
RD	racemic dihydroxylation
R_f	retention factor
RT	room temperature
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
Salen	2,2'-ethylenebis(nitrilomethylidene)diphenol
SAR	structure-activity relationship
sat.	saturated
SM	starting material
S_N2	bimolecular nucleophilic substitution
SuOH	1-hydroxypyrrolidine-2,5-dione

t	time
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBADH	<i>Thermoanaerobium brockii</i> alcohol dehydrogenase
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBME	<i>tert</i> -butyl methyl ether
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i>-Bu	<i>tert</i> -butyl
TCDI	thionocarbonyldiimidazole
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
TOF	time-of-flight
Tol.	toluene
TPA	12- <i>O</i> -tetradecanoylphorbol-13-acetate
TPAP	tetrapropylammonium perruthenate
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet

Chapter 1: Total synthetic study towards taurospongins A – a DNA polymerase β inhibitor

1.1 Total synthesis, the core of organic chemistry

Prior to Wöhler's synthesis of urea, the term 'organic matter' was generally believed to endow 'vital force'. According to chemists' beliefs of the day, these 'vital' matters, which were of animate origin, could only be produced within a life form, since they were too complicated to be artificially synthesised.¹ The total synthesis of urea from ammonium cyanate in 1828,² however, re-defined the term 'organic chemistry' and illuminated a path that has led to numerous achievements and discoveries in chemistry, biology, and medicine. Synthesis is one of the key issues that scientists will face sooner or later when they investigate the properties of molecules. There are various motives for the investigators: the demonstration of new synthetic methods through a total synthesis endeavour; the invention of efficient and robust methods for industrial production; the modification of the molecular structure in order to tune the properties of the substance; last but not least, the assignment of the identity of unknown compounds. Total synthesis can help scientists to discover new chemical methodologies, develop cost effective and flexible synthetic sequences, and provide a definite answer to the structural puzzles of unknown substances. As Nicolaou commented,³ 'as a practitioner of the art, one is filled with overwhelming pride to be part of such attractive and vigorous endeavours and apprehensive in being responsible for conveying its true meaning and value to society'. The following chapter illustrates the first key function of total synthesis, *i.e.*, developing a practical and flexible synthetic approach towards the marine natural product taurospongins A **1.1** (**Figure 1**).

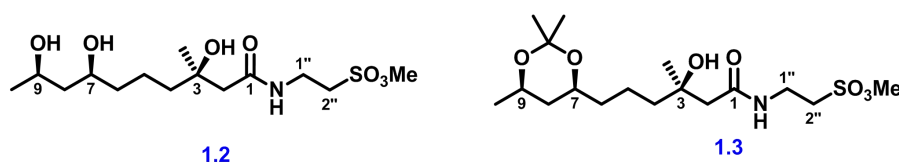
**Figure 1**

1.2 Taurospongins A – isolation, biological activity, and structural features

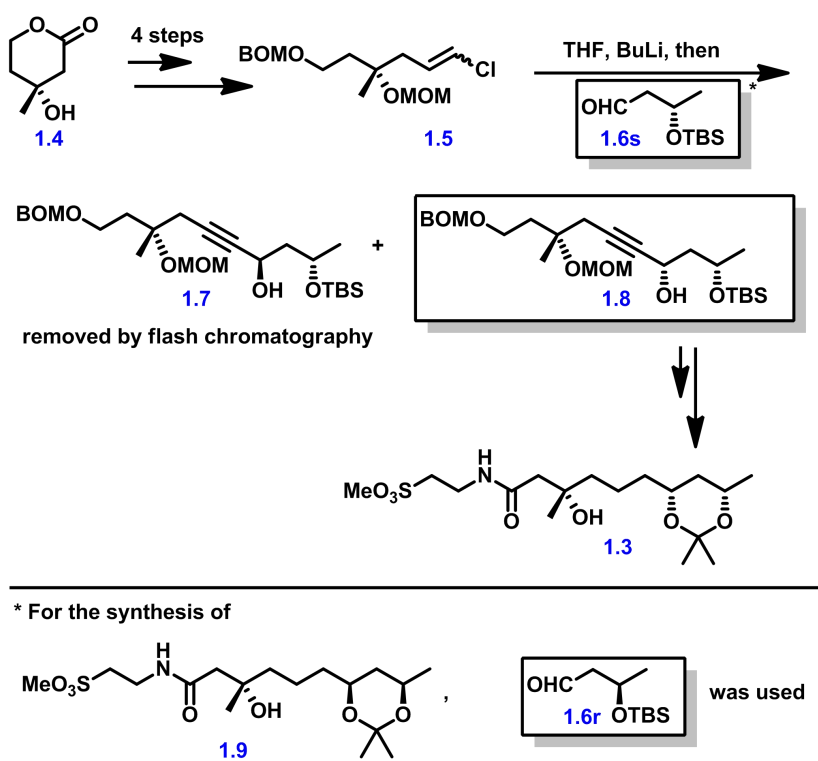
The *Hippospongia* sponge, indigenous to the sea around Okinawa Island in Japan, contains a novel taurine-containing acetylenic lipid that displays remarkable dual activities as a potent inhibitor of both DNA polymerase β (pol- β) and HIV reverse transcriptase (HIV-RT).⁴

As a target for total synthesis, taurosponin A (**Figure 1**) presents several challenges: an acetylene-containing fatty acid bearing a *Z*-alkene; a stereochemically defined tertiary alcohol at C(3), and differentially acylated secondary alcohols at C(7) and C(9). All stereogenic centres are located in the same taurine-bearing trihydroxy fatty acid amide, showing *3R,7S,9R* absolute stereochemistry.

In Kobayashi's original isolation and structural analysis article, the absolute stereochemistry of taurospongins A was established by a semi-synthesis of the trihydroxy fragment **1.2** (**Figure 2**). Rychnovsky ¹³C-acetonide analysis⁵ of acetonide **1.3** (from **1.2**) established the *syn*- relative stereochemistry of the 1,3-diol (**Figure 2**).

**Figure 2**

Kobayashi then synthesised diastereomers **1.3** and **1.9** starting from commercially available lactone **1.4** and aldehydes **1.6s^a** and **1.6r^b** (Scheme 1). After comparing the ¹H NMR spectra of this pair of diastereomers as acetonide derivatives **1.3** and **1.9**, the relative stereochemistry of the three stereogenic centres was proposed to be *3S,7R,9S* or *3R,7S,9R*. The specific rotation of **1.3** (+0.65) is close to zero, therefore, it has little practical value in absolute configuration assignment. Ultimately, Kobayashi applied Mosher's method to confirm the proposed stereochemistry.



Scheme 1

Most of the known pol-β inhibitors are not highly functionalised; therefore, chemical modifications of these inhibitors for SAR studies are difficult. Taurospongins A, in contrast, possesses three stereogenic centres for structural modification. In addition, its modular unsaturated fatty acid, chiral core **1.2** and its amide partners could be modified by rational

^a Compound numbers followed with *s* possess *S*- stereochemistry.

^b Compound numbers followed with *r* possess *R*- stereochemistry.

design. The structural features of taurospongins A, combined with its potent bioactivity, led the Robertson group to initiate a short and flexible total synthesis.

1.3 DNA polymerase β and cid-1: function and potential importance in antitumour treatment

The efficacy of anticancer agents is severely limited by cell resistance in the sense that these chemotherapeutics are not able to perform as well as they should. For DNA damaging agents, the ability of the cancer cell to repair its damaged DNA can result in resistance which greatly reduces the effectiveness of this type of chemotherapeutic.⁶

Pol- β is one of the enzymes that possesses DNA error correction function and it is a member of the X family of DNA polymerases.⁷ Pol- β has been identified as a key enzyme responsible for DNA repair mechanisms in cancer cells that have been exposed to DNA damaging agents like cisplatin,⁸⁻¹⁰ bleomycins,¹¹⁻¹⁴ monofunctional DNA alkylating agents¹⁵⁻¹⁷ and neocarzinostatin.¹⁸ The repair pathway for such processes is ‘base excision repair’ (BER), which is essential for repairing damaged bases in DNA.¹⁹ Pol- β makes two contributions in the BER process: removal of the 5'-deoxyribose phosphate (dRP) backbone of the abasic site; and subsequent single nucleotide gap-filling DNA synthesis.¹⁹

It is expected that inhibition of pol- β may lead logically to reduced cell resistance and enhancement of the efficacy of DNA damaging agents in chemotherapy. A number of pol- β inhibitors have been identified, and some of them have been investigated for their potential to synergise with conventional DNA damaging agents (**Figure 3**). Among all the highly

diverse structures against pol- β , taurospongins A stands out for two reasons as a synthetic target: 1) its extremely high potency (it has the lowest IC_{50} value among the inhibitors shown in **Figure 3**; 2) it has greater potential for structural modification compared to the other structurally similar compounds.

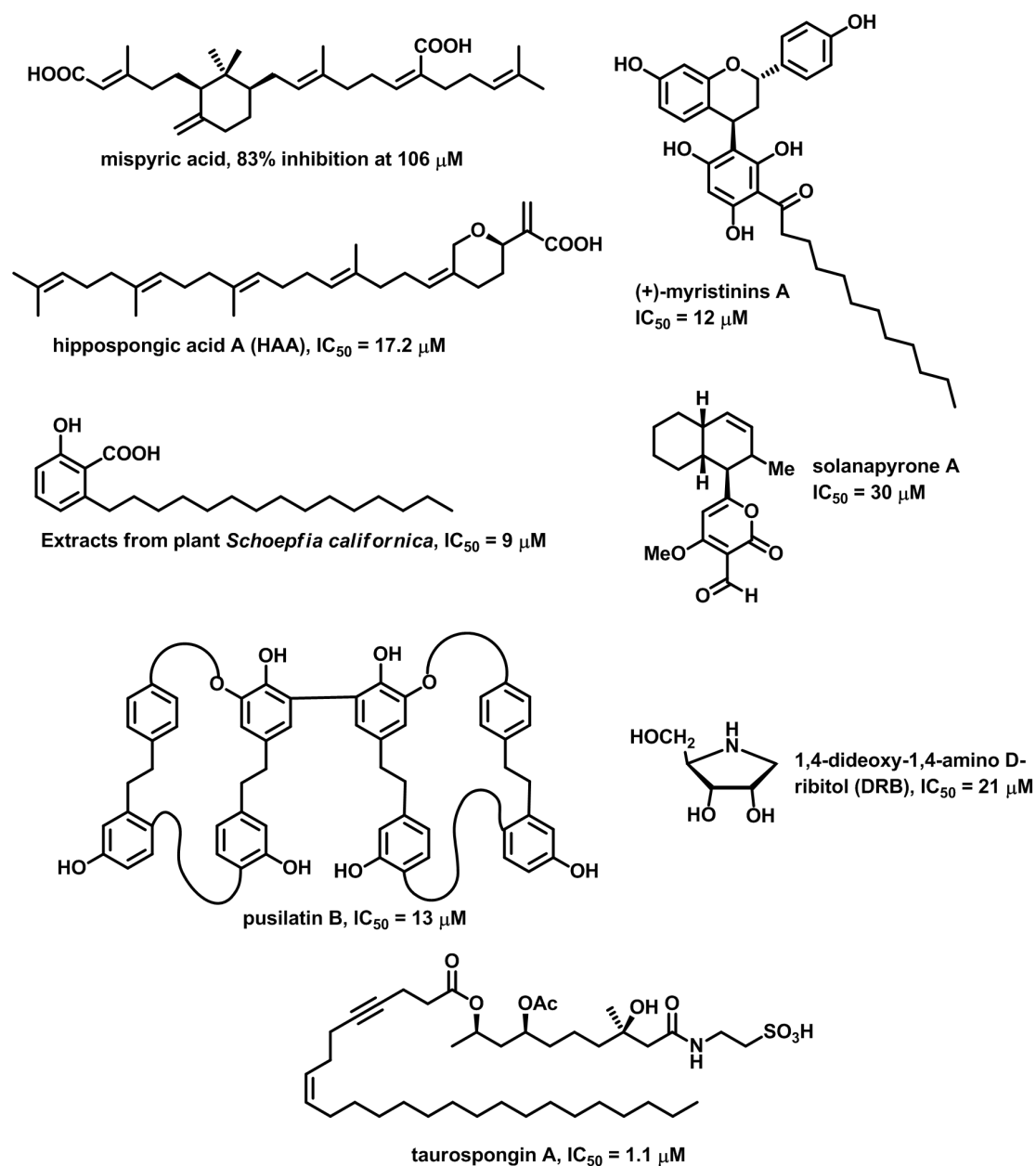


Figure 3

Yeast protein cid-1, discovered by Norbury, is a member of the pol- β superfamily.²⁰ It has been found that, instead of possessing BER function, cid-1 could potentially inhibit the replication of cancer cells by affecting intracellular checkpoint signaling.²⁰ It is anticipated that agents inhibiting pol- β would demonstrate similar activity against cid-1 and act synergistically with chemotherapeutics in cancer treatments through cellular checkpoint signaling interruptions.

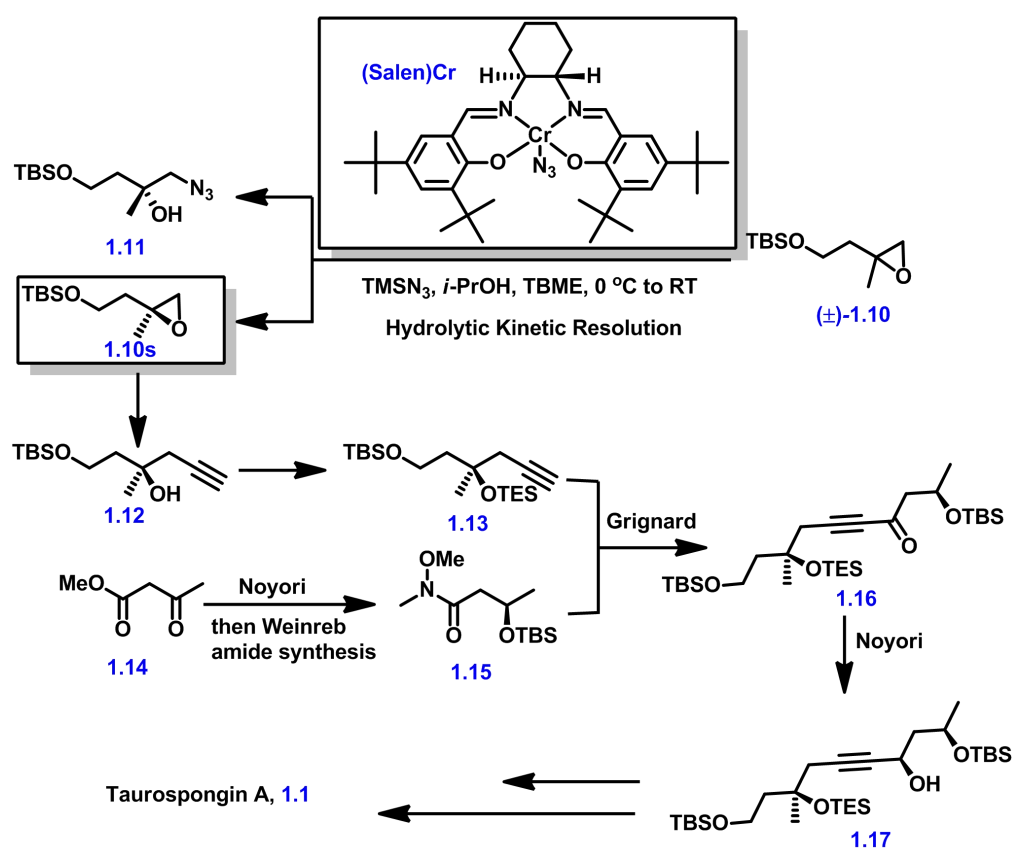
1.4 Aim of project – total synthesis of taurospongins A

The Robertson group became interested in taurospongins A because it inhibits DNA polymerase β (pol- β) and therefore is a likely inhibitor of cid-1.⁴ Due to its low extraction efficiency (0.02%), a practical and flexible synthesis of taurospongins A was needed to provide a sizeable amount of the substance and its analogues for biological SAR studies. The original aim of this project, therefore, was to develop a scalable, stereochemically controllable synthesis of taurospongins A and its analogues for SAR studies. This is a joint research project with Dr. Chris Norbury in the Dunn School of Pathology, University of Oxford who conducted the biological assays.

1.5 Previous synthetic studies towards taurospongins A

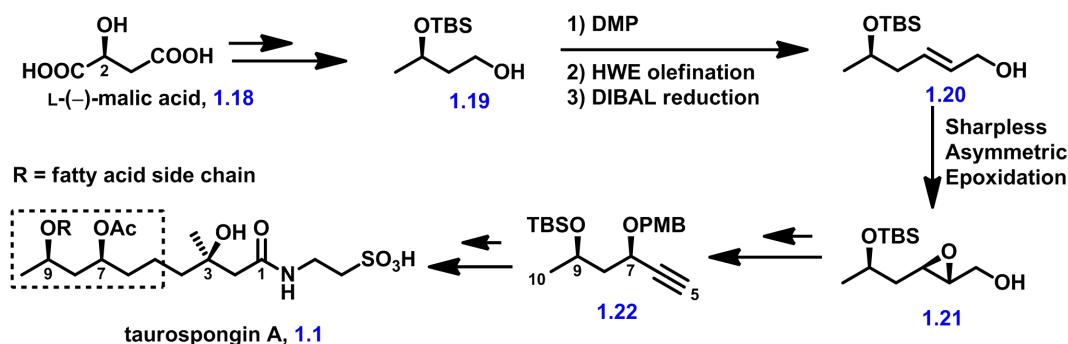
Prior to Robertson's synthesis of taurospongins A, Jacobsen²¹ and Ley^{22, 23} had separately completed the total synthesis of this natural product. Subsequently, three formal syntheses were reported by Ghosh,²⁴ Campagne,²⁵ and Sugai,²⁶ with a chiral fragment synthesis by Cai.^{27, 28}

Jacobsen achieved the first total synthesis of taurospongins A in 1998.²¹ A (Salen)Cr (Scheme 2) catalysed hydrolytic kinetic resolution was utilised to obtain enantiomerically pure 2,2-disubstituted epoxide **1.10s** (Scheme 2) which corresponded to the defined 3°-alcohol centre of the molecule. Further elaboration includes an epoxide ring-opening reaction with lithiated acetylene, followed by a Grignard reaction with chiral Weinreb amide **1.15** that originated from Noyori asymmetric hydrogenation of ketoester **1.14**.^{29, 30} The last stereocentre was set by another Noyori asymmetric hydrogenation.³¹



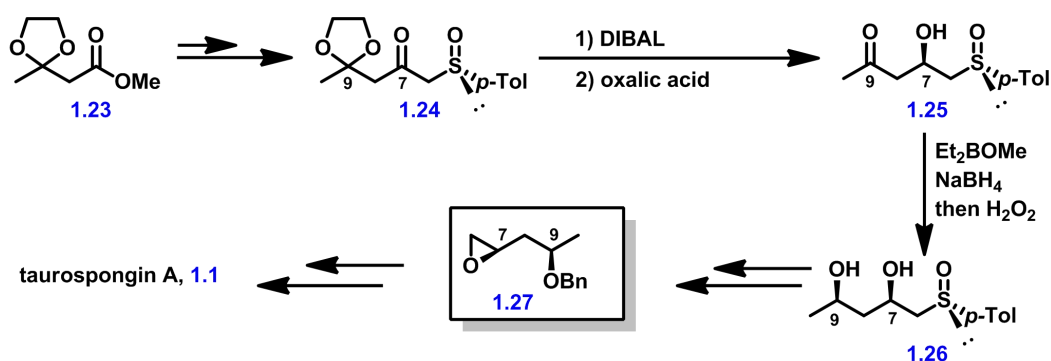
Scheme 2

In 2000, Cai synthesised a C(5)–C(10) fragment from L-(–)-malic acid **1.18**.²⁷ In this approach, the stereochemistry at C(9) in taurospongins A corresponds to C(2) of malic acid (Scheme 3). In order to obtain the desired configuration at C(7), an SAE reaction was conducted on allylic alcohol **1.20**, which came from a Dess–Martin oxidation–HWE olefination–DIBAL reduction sequence from **1.19**.



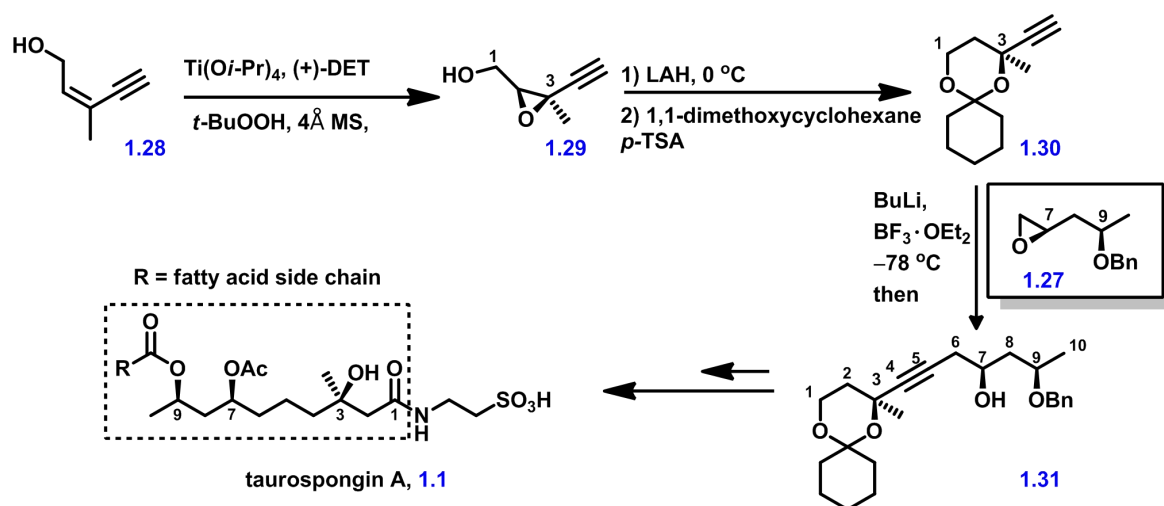
Scheme 3

Ghosh and co-workers assembled the C(1)–C(10) fragment of taurospongins A in a stereocontrolled fashion.²⁴ The three stereogenic centres were constructed in a stepwise manner (**Scheme 4**): the C(7) 2° alcohol was obtained *via* a stereoselective chelation-controlled reduction of optically active β -ketosulfoxide **1.24**. Using the same rationale, the 1,3-*syn* diol moiety was achieved by a chelation-controlled diastereoselective hydride reduction of hydroxyketone **1.25**. After further manipulation, the 1,3-diol was transformed into epoxide **1.27** ready for a nucleophilic attack.



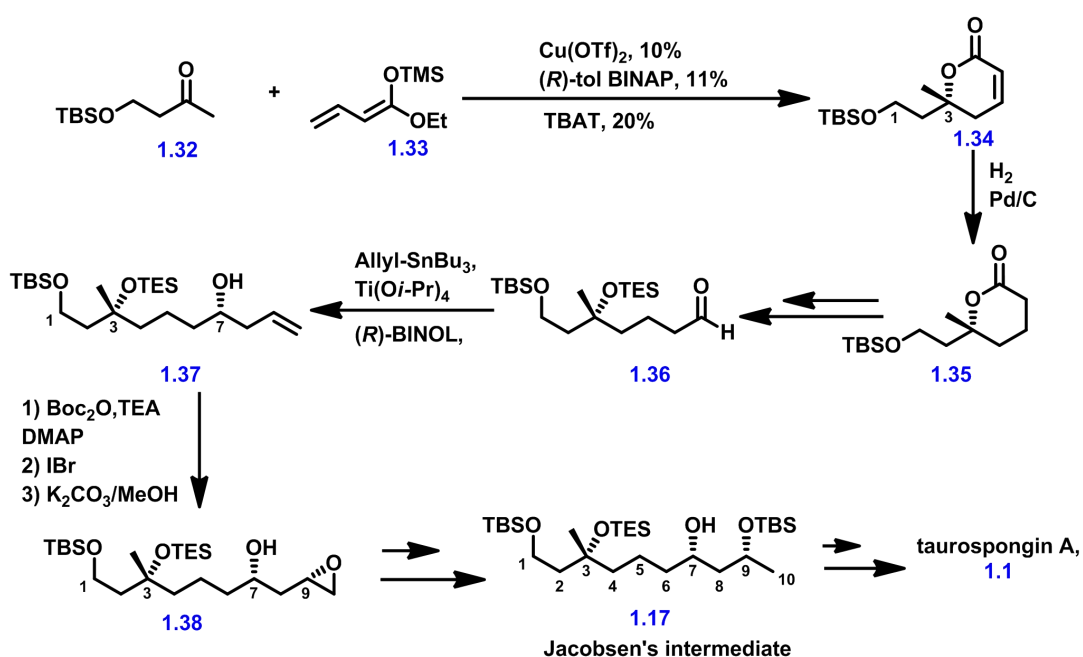
Scheme 4

To install the C(3) stereogenic centre, allylic alcohol **1.28** was subjected to SAE reaction to afford epoxide **1.29** (**Scheme 5**). LAH reduction of **1.29**, ketal formation, and coupling between epoxide **1.27** and lithiated **1.30** furnished the C(1)–C(10) framework of taurospongins A.



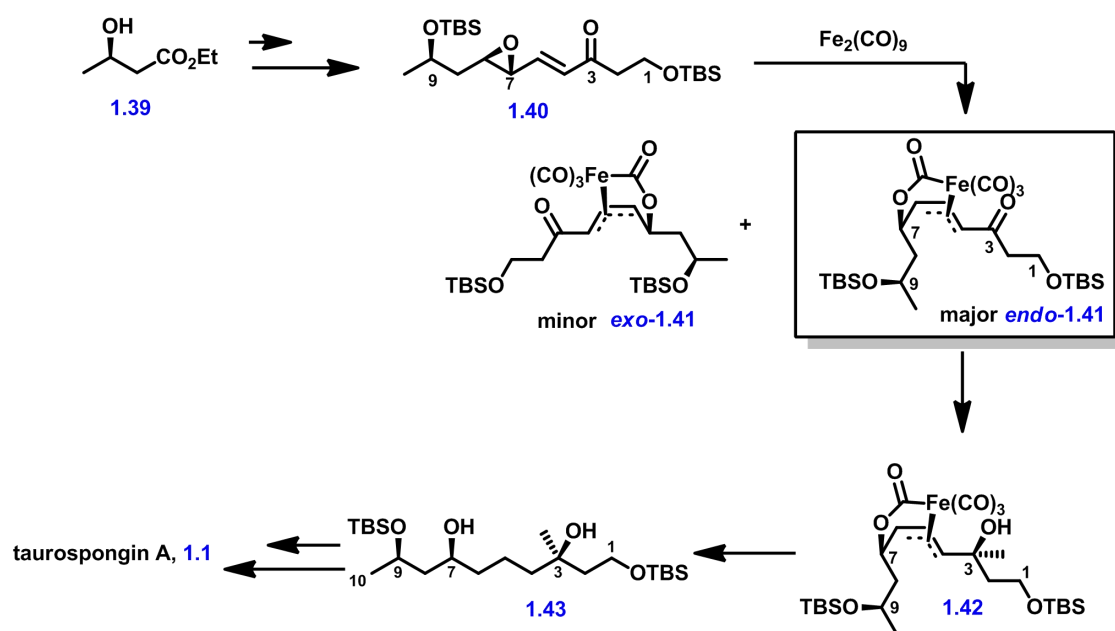
Scheme 5

A catalytic, asymmetric vinylogous Mukaiyama reaction is the key feature of Campagne's formal synthesis of taurospongins A.²⁵ Utilising this methodology, the stereogenic centre at C(3) was set with the desired configuration in the form of a protected δ -lactone (**Scheme 6**). This lactone was transformed into a corresponding aldehyde and subjected to a Keck asymmetric allylation³² to afford 2° alcohol at C(7). Treatment of homoallylic alcohol **1.37** with IBr and $\text{K}_2\text{CO}_3/\text{MeOH}$ furnished the last stereogenic centre at C(9), and further elaboration intercepted Jacobsen's intermediate and completed the formal synthesis.



Scheme 6

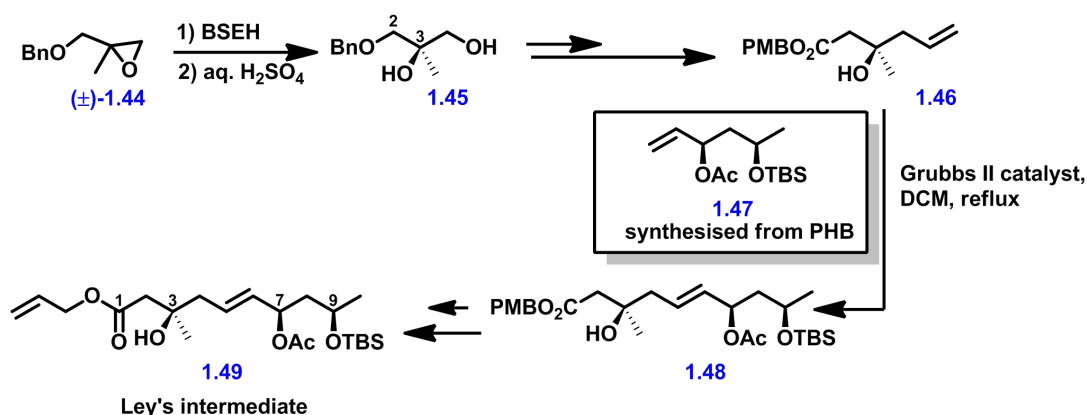
All the synthetic studies mentioned above tend to treat the C(3) and C(7,9) centres as separate stereochemical problems. Ley's synthesis^{22, 23} differs in this respect by using π -allyltricarbonyliron lactone complexes to direct the delivery of hydride (to generate the *syn*- C(7,9) diol moiety) or methyl group (to generate the C(3) centre). In Ley's synthesis (Scheme 7), epoxide **1.40** was generated *via* a highly efficient sequence, then this epoxide was treated with $\text{Fe}_2(\text{CO})_9$ to give separable π -allyltricarbonyliron lactone complexes in high yield. The major complex **endo-1.41** was then treated with trimethylaluminium, where the chiral information of the complex was successfully transferred to the 3° alcohol **1.42**. Reductive decomplexation and saturation of the double bond gave the C(1)–C(10) fragment of taurospongins A.



Scheme 7

The application of enzymatic reductions is featured in the Sugai synthesis²⁶ towards taurospongins A (Scheme 8). To access the tertiary alcohol at the β -position, Sugai utilised an over-expressed *Bacillus subtilis* epoxide hydrolyase (BSEH) to carry out enantioselective

hydrolysis of readily available racemic epoxide ($\pm$)-**1.44**. By means of carbon-chain elongation of the enantio-pure triol **1.45**, the PMB ester **1.46** was prepared and subjected to a cross metathesis reaction with **1.47**, which came from poly-(3*R*)-hydroxybutyrate (PHB). The cross metathesis gave the C(1)–C(10) framework **1.48**. Further transformation intercepted Ley's²³ intermediate **1.49** and completed a formal synthesis of taurospongine A.



1.6 Synthetic work within the Robertson group towards taurospongine A

1.6.1 Using PHB in total synthesis

PHB (**1.50**, **Figure 4**) is a naturally occurring, bio-degradable polymer which is a useful, renewable source of enantiomerically pure chiral intermediates such as (3*R*)-hydroxy esters. PHB is produced by certain microorganisms like *Ralstonia eutrophus* or *Bacillus megaterium*, feeding on saccharose from sugar cane.³³

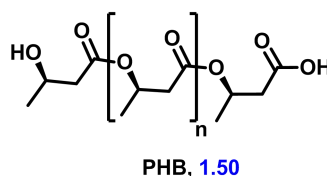
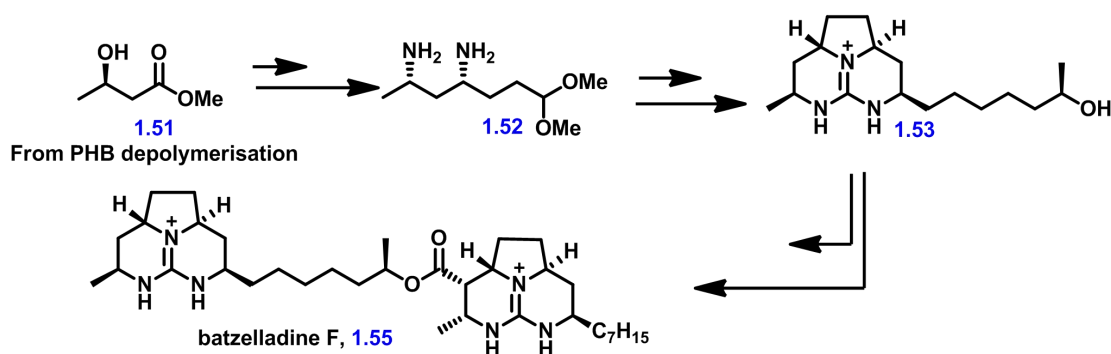


Figure 4

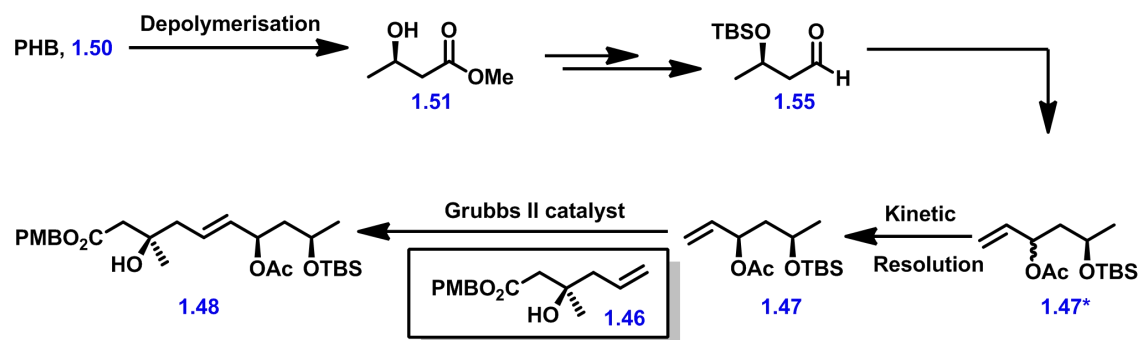
The main interest in PHB has been on its potential as a bioplastic. Compared to conventional plastics from non-renewable sources, the advantages of PHB are obvious: non-toxic, flexible, long lasting and most importantly, environment-friendly. Since 2001, most of the research on PHB has focused on producing from it an economically and environmentally sustainable bioplastic.

In terms of total synthesis, PHB has attracted much less attention. The depolymerisation of PHB into esters was previously investigated by Seebach,³⁴ and Overman utilised depolymerised methyl ester **1.51** in his batzelladine F synthesis³⁵ (**Scheme 9**).



Scheme 9

In Sugai's formal synthesis of taurospongine A (*cf.* page 22), PHB was utilised to prepare enantiomerically pure aldehyde **1.55**, which was then subjected to allylation and enzymatic kinetic resolution (**Scheme 10**).

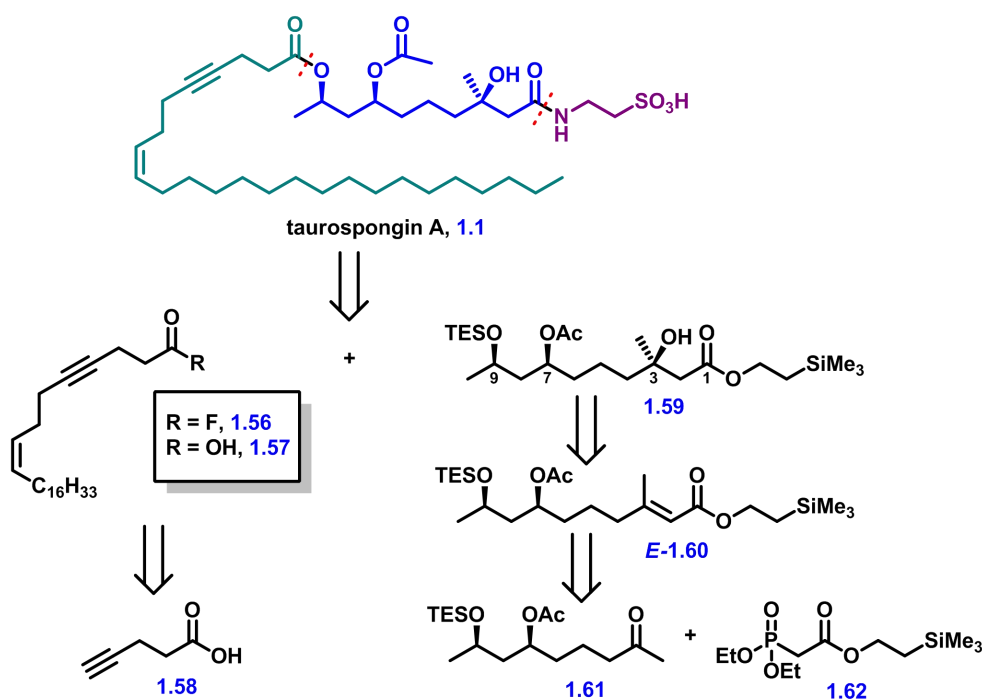


Scheme 10

Due to the fact that PHB can provide a useful building block with correct stereochemistry, this polymer was to be utilised in Robertson's taurospongins A synthesis.

1.6.2 Retrosynthetic analysis of taurospongins A

Taurospongins A was disconnected at the amide and ester bonds; three fragments were then identified: a fatty acid **1.59** with all stereogenic centres (in blue, **Scheme 11**), a fatty acid side-chain **1.57** with all unsaturations (in green, **Scheme 11**), and commercial taurine (in purple, **Scheme 11**).



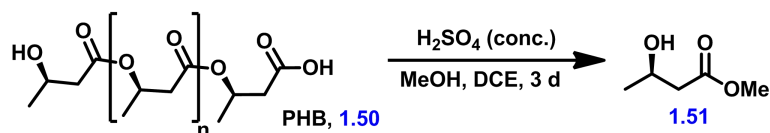
Scheme 11

In the original synthetic strategy, the aim was to achieve a catalytic process which combines deprotection of the C(9) silylated hydroxy group in **1.59**, esterification with acyl fluoride **1.56**, and removal of the silyl group at C(1) by adding a catalytic amount of fluoride. Bearing this design in mind, the carboxylic group at C(1) was protected as its 2-(trimethylsilyl)ethyl ester. To maximise the flexibility of the synthesis, which is a second feature of this approach, chiral fragment **1.59** was intended to be derived from a SAD reaction on α,β -unsaturated

ester **E-1.60** and subsequent selective α -deoxygenation. In such an approach, the α -hydroxy group can be retained for the preparation of analogues or even using asymmetric aminohydroxylation for obtaining 3-amino analogues. To synthesise unsaturated ester **E-1.60**, a Horner–Wadsworth–Emmons reaction would construct the double bond between methyl ketone **1.61** and its HWE partner **1.62**. As to fragment **1.57**, the double bond could be synthesised *via* a Wittig reaction, and commercially available pent-4-ynoic acid **1.58** bears the triple bond functionality from the outset of the synthesis.

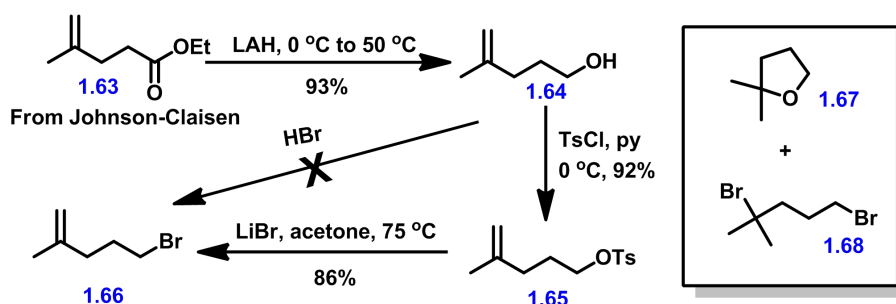
1.6.3 Preliminary synthetic study towards taurospingin A

Preliminary work in the Robertson group towards taurospingin A was undertaken by Reynolds.³⁶ In that study, PHB was depolymerised *via* methanolysis³⁴ to provide enantiomerically pure methyl (3*R*)-hydroxybutanoate for subsequent Grignard reaction (Scheme 12).



Scheme 12

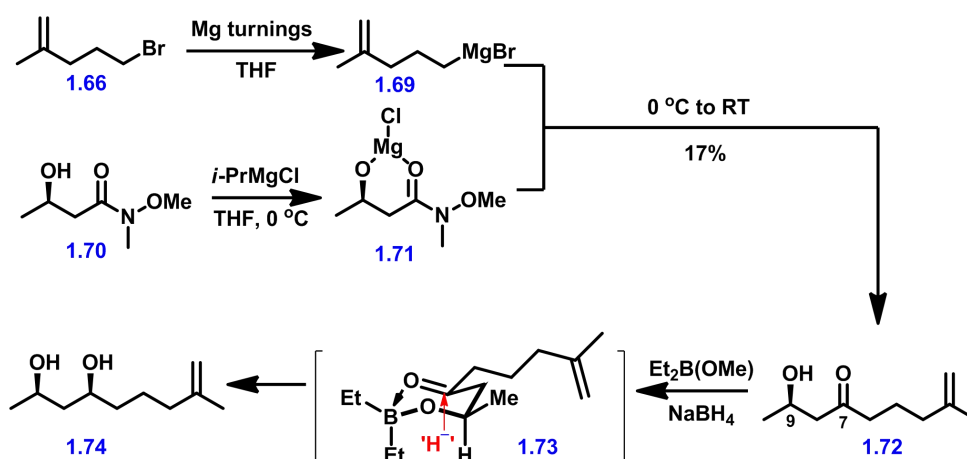
Grignard precursor 5-bromo-2-methyl-1-pentene **1.66** was prepared *via* a 4-step synthesis starting with a Johnson orthoester Claisen rearrangement of 2-methylprop-2-en-1-ol and triethyl orthoacetate. Constant removal of ethanol drove the reaction to completion, and an 82% yield of ester **1.63** was obtained. Subsequent reduction and tosylation followed by $\text{S}_{\text{N}}2$ reaction using LiBr resulted in alkene **1.66** efficiently (Scheme 13).



Scheme 13

A one-step shorter synthesis involves the direct bromination of alcohol **1.64** with HBr. Kraft³⁷ reported the infeasibility of this protocol due to acid-catalysed cyclisation ($\rightarrow$ **1.67**) and hydrohalogenation ($\rightarrow$ **1.68**).³⁸

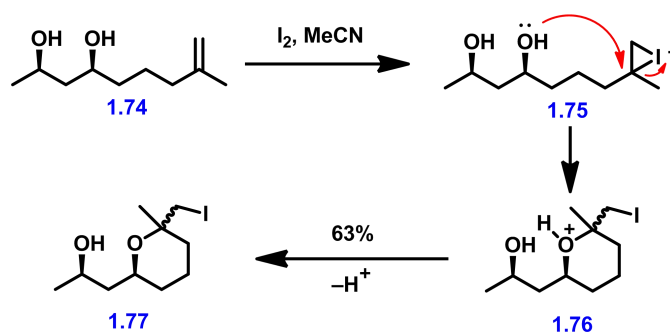
The reaction between Grignard reagent **1.69** and Weinreb amide **1.70** proceeded in only 17% yield. However, with the ketone in hand, 1,3-*syn*-reduction was carried out to set the stereochemistry at C(7). This method parallels Ghosh's approach to this portion of taurospongins A.²⁴ To explain the high diastereoselectivity in this step, it is proposed that axial delivery of hydride takes place on chelated intermediate **1.73** in **Scheme 14**.



Scheme 14

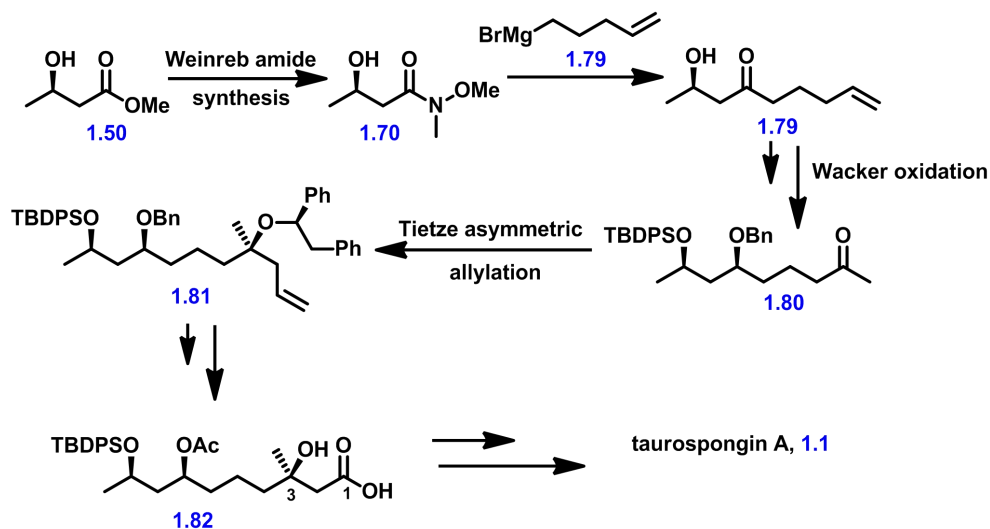
Differentiation of the two hydroxy groups in diol **1.74** was required in order to allow generation of taurospongins A analogues by functionalisation of either hydroxy group as

desired. To achieve this goal, iodoetherification was carried out by treating the diol with I_2 , in the expectation that attack of the iodonium intermediate by the hydroxyl at C(7) would be kinetically more favourable. Indeed, the desired compound was formed using Martín's conditions (**Scheme 15**).³⁹



Scheme 15

In parallel to this project, a second route was examined in the Robertson group by Dr. Mallinger.⁴⁰ The aim was to develop a more efficient route to ketone **1.80** by applying Wacker oxidation as a key step. In this approach, commercially available 5-bromo-1-pentene **1.79** was employed instead of bromide **1.66**, the synthesis of which was tedious. To install the 3° alcohol at C(3), diastereoselective Tietze allylation applied to methyl ketone **1.80** would deliver the desired motif with the correct stereochemistry. Terminal olefin oxidation and chiral auxiliary removal would furnish the C(1)–C(10) fragment (**Scheme 16**).



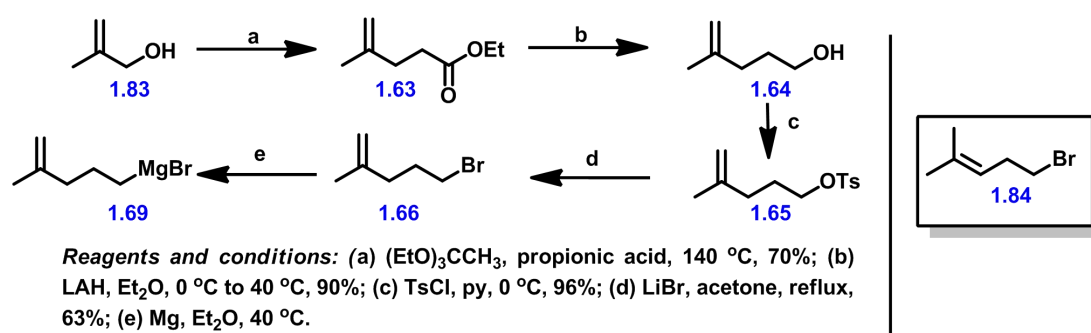
Scheme 16

1.7 Results and discussion

1.7.1 Chiral fragment synthesis

Reaction optimisation, large scale preparation of olefin 1.87

Following Reynold's work³⁶, the synthesis of bromide **1.66** required for the preparation of Grignard reagent **1.69** is shown in Scheme 17.

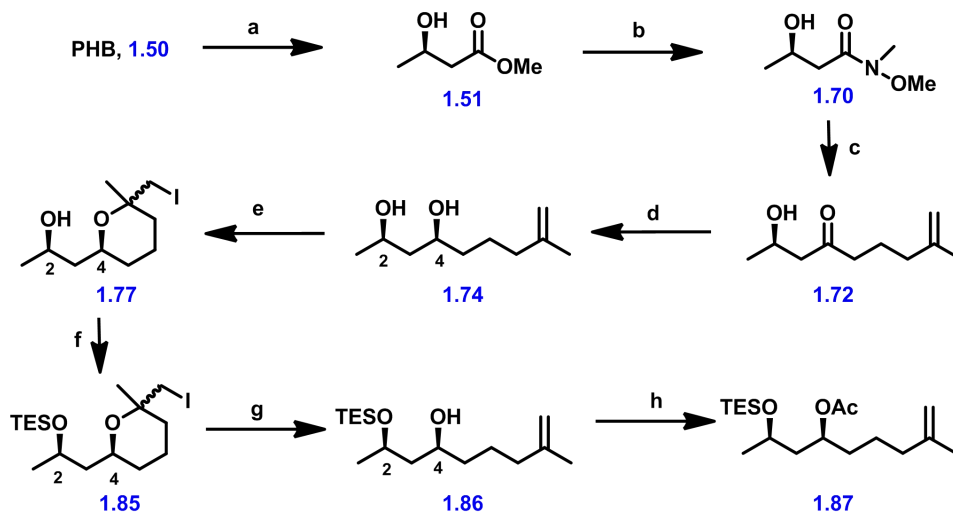


Scheme 17

The synthesis began with a Johnson orthoester Claisen rearrangement reaction.³⁷ The resulting ester **1.63** was subjected to reduction with LAH, giving alcohol **1.64** in 90% yield. Tosylation and bromination of **1.64** by Pirrung's protocol⁴¹ gave the desired bromide **1.66** in 63% yield over two steps. It was notable that up to 58% of olefin isomerisation of alkene **1.66** to product **1.84** was observed under prolonged reaction times. This unwanted side reaction was avoided by reducing the exposure time to LiBr to 2 h.

The Grignard reagent was prepared under standard conditions and Weinreb amide **1.70** was synthesised from PHB by methanolysis then reaction of the resulting methyl ester **1.51** with deprotonated *N,O*-dimethylhydroxylamine (Scheme 18). The Grignard reaction between **1.69** and **1.70** afforded a 70% yield of ketoalcohol **1.72**, which represents a significant improvement compared to previous work.³⁶ Directed reduction of hydroxyketone **1.72**

furnished *syn*-diol **1.74** in quantitative yield.³⁶ Subsequent iodoetherification of **1.74** allowed the two hydroxyl groups at C(2) and C(4) to be differentiated to afford **1.77** which was silylated to give iodide **1.85** as a mixture of diastereomers.

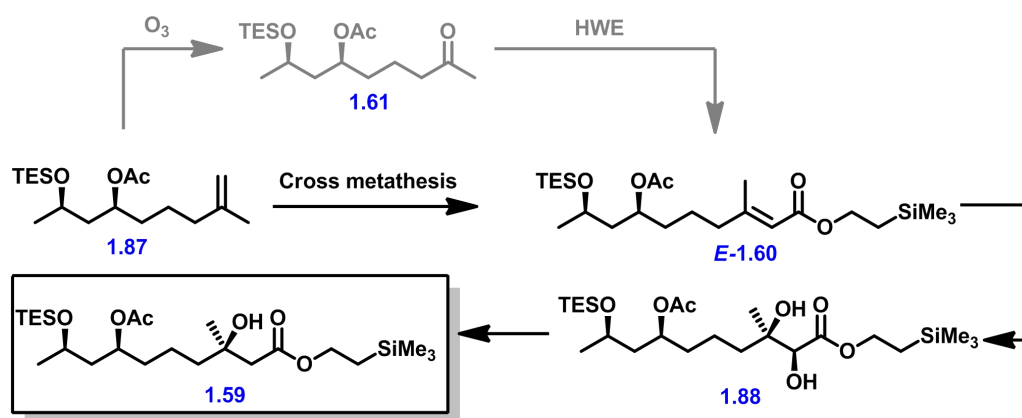


Scheme 18

The exposed hydroxyl in **1.77** was protected as triethylsilyl ether **1.85**, and Zn-mediated ring-opening released the hydroxy group at C(4) which was acylated quantitatively to give key intermediate **1.87** for subsequent reactions. Up to a 24% yield of olefin **1.87** could be achieved reproducibly after a 12-step synthetic sequence from PHB (89% yield per step on average).

Attempts towards *E*-configured ester *E*-1.60

In order to introduce the *E*-double bond of olefin *E*-**1.60** in the synthetic plan (Scheme 19), two different approaches were designed: a cross metathesis (CM) method or an ozonolysis–HWE pathway, both carried out in a parallel fashion on olefin **1.87** (Scheme 19).



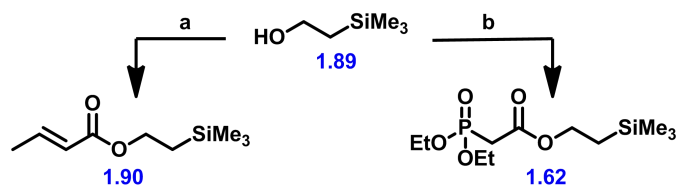
Scheme 19

The CM route could in principle provide a selective and convenient way to assemble key intermediate *E*-**1.60**,⁴² which would then be subjected to SAD and α -deoxygenation reactions. However, it was appreciated that the *E/Z* selectivity in the CM reaction might not be ideal in this case, since there was no clear difference in size between the methyl group and the methylene group on the olefin termini.⁴³

HWE olefination reaction is known to exhibit high *E*-selectivity.⁴⁴ However, to conduct HWE reaction to synthesise *E*-**1.60**, a methyl ketone **1.61** was required from olefin **1.87** via an oxidative cleavage (**Scheme 19**), which would lengthen the synthetic sequence compared to the direct CM approach.

Overall, given that the *E/Z* selectivity of the CM could potentially be acceptable,⁴² this approach was investigated first. The HWE approach was held in reserve should the *E/Z* selectivity be unsatisfactory.

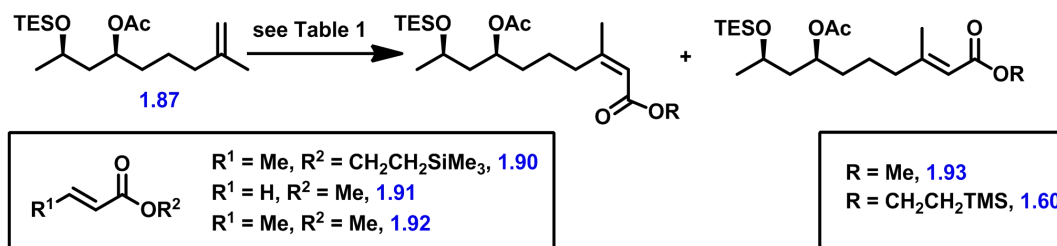
The partners of the CM and HWE reactions were prepared by employing transesterification and esterification reactions respectively as shown in **Scheme 20**.



Reagents and conditions: (a) methyl crotonate, Ti(Oi-Pr)₄, 100 °C, 86%; (b) (EtO)₂POCH₂CO₂H, BOPCl, TEA, DCM, 20 °C, 88%.

Scheme 20

Cross metathesis method



Scheme 21

The CM reaction between olefin **1.87** and crotonate **1.90** was first examined by using **1.93** as a model compound under a wide range of conditions between olefins **1.87** and **1.91** or **1.92** (Scheme 21). The metathesis reaction was first tested under mild conditions (Entry 1, Table 1), which resulted in the recovery of starting material. When the temperature was raised to 40 °C (Entry 2, Table 1), a 61% yield of the desired product **1.93** could be isolated as an inseparable *E/Z* mixture (*E/Z* = 2:1).

Entry	Ester	1.87 : Ester	Solvent	Catalyst (5 mol%)	T (°C)	Time (h)	Product	Yield ^c	<i>E</i> : <i>Z</i> ^d
1	1.92	4:1	DCM	Grubbs' II	RT	3	1.93	NR	N/A
2	1.92	4:1	DCM	Grubbs' II	40	24	1.93	61%	2:1
3	1.92	1.4:1	DCM	Grubbs' II	40	24	1.93	71%	2:1
4	1.91	1.4:1	DCM	Grubbs' II	40	24	1.93	20%	3:2
5	1.92	1.4:1	Toluene	Grubbs' II	40	60	1.93	Trace	1:1
6	1.92	1.4:1	DCM	Grubbs' II	40	48	1.93	60%	3:2
7	1.92	1.4:1	Toluene	Grubbs' II	110	3	1.93	NR	N/A
8	1.92	1.4:1	DCM	Hoveyda ^e	40	48	1.93	10%	5:4
9	1.90	1.4:1	DCM	Grubbs' II	40	24	1.60	70%	2:1

Table 1

It was proposed by Grubbs⁴² that a significant excess of type III olefin **1.87** (4 eq., **Entries 1, 2, Table 1**) was normally essential in order to compete efficiently with dimerisation of its Type II CM partner (**1.90–1.92, Scheme 21**) and ensure good yield. In the hope of decreasing the loading of **1.87**, the use of 1.4 equivalents of **1.87** was tested. This led to a 70% yield with the same level of *E*-selectivity (**Entry 3, Table 1**). When methyl acrylate **1.91** was tested, the yield dropped to 20% (**Entry 4, Table 1**), possibly due to fast homodimerisation of acrylate **1.91** compared to its β-capped counterpart **1.92**. When the metathesis was performed in toluene at 40 °C, only a trace amount of the desired product **1.93** was formed and no selectivity was apparent (**Entry 5, Table 1**).

It is known that in olefin metathesis reactions, a prolonged reaction time or a higher temperature can facilitate the equilibration of a thermodynamically less stable olefin, such as **Z-1.93**, to its more stable isomer, such as **E-1.93**. In the present case, these conditions either gave no improvement to the *E/Z* ratio (**Entry 6, Table 1**) or led to catalyst decomposition

^c Yield based on *E/Z* mixture.

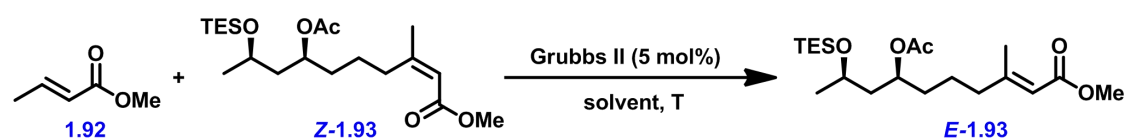
^d Determined by ¹H NMR, confirmed by NOE experiment.

^e Hoveyda–Grubbs' II catalyst.

(Entry 7, Table 1).

In summary, the cross metathesis reaction was shown to be less than ideal for the synthesis of model product **E-1.93**. Due to the possibility of substrate-dependent effects, crotonate **1.90** was subjected to a CM reaction with **1.87** using the optimal condition from model studies (Entry 9, Table 1). However, no significant improvement was obtained.

With a geometric mixture of olefin **1.93** in hand, three attempts were made to convert the *Z*- to its *E*- isomer (Schemes 22, 23, Table 2).



Scheme 22

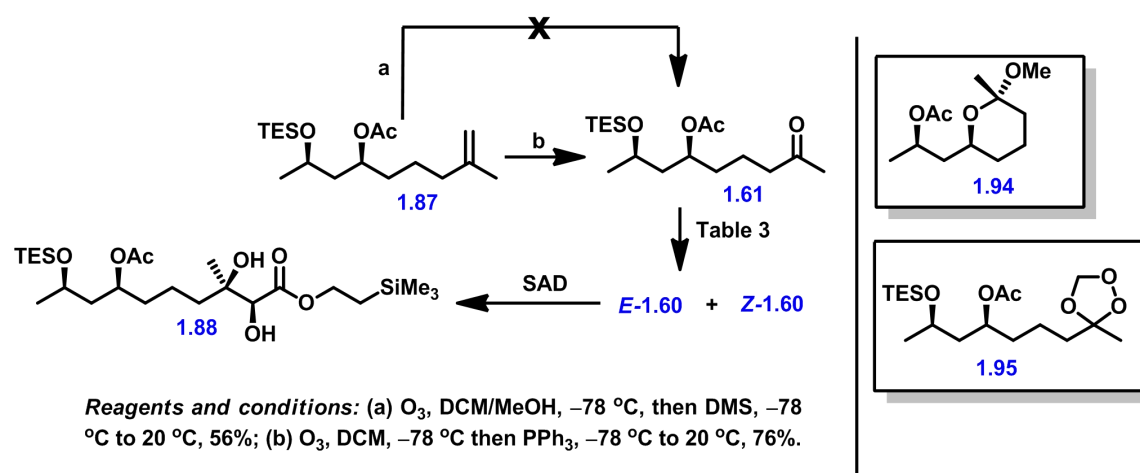
Entry	Conditions	Original <i>Z/E</i> ratio	Obtained <i>Z/E</i> ratio
1	Grubbs II, DCM, 40 °C	2:3	2:3
2	Grubbs II, Toluene, 110 °C	2:3	2:3
3	I ₂ (cat.), ether/benzene, <i>hν</i>	100:0	84:16

Table 2

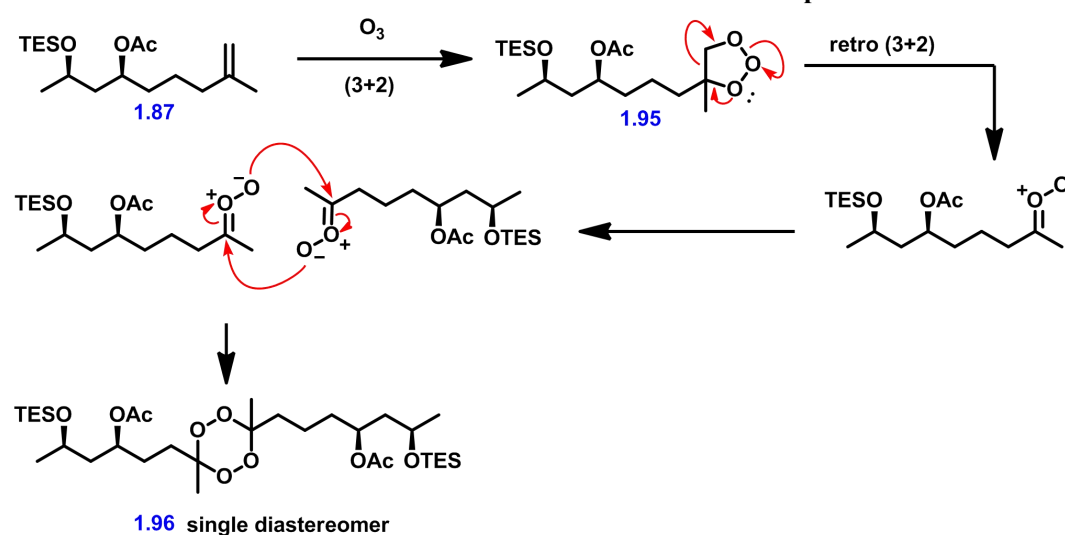
The CM reaction between the geometric mixture of **1.93** and methyl crotonate **1.92** was briefly employed as a pathway for *Z*-**1.93** to isomerise to its *E*-isomer **E-1.93** (Entries 1, 2, Table 2), however, an identical *E/Z* ratio was observed.

In a final attempt to obtain a sample enriched in the *E*-isomer, a small amount of the pure *Z*-isomer, obtained by preparative TLC, was irradiated in the presence of a catalytic amount of I₂ (Entry 3, Table 2). After 2.5 h, only a 16% conversion was observed.

Treatment of olefin **1.87** with O₃ followed by Me₂S in a mixture of DCM/MeOH resulted in ketal **1.94** as the main isolated product instead of the desired ketone **1.61** (**Scheme 24**). In order to avoid the cleavage of the TES group and prevent the formation of cyclic ketal **1.94**, MeOH was omitted from the solvent. In addition, the more nucleophilic PPh₃ was used to accelerate the reduction of ozonide **1.95** (which had been observed in up to 44% yield). When this reagent was tested, a 76% yield of ketone **1.61** was obtained.



An interesting structure **1.96**, isolated in 5% yield, was believed to derive from carbonyl oxide dimerisation according to Murray's proposal (**Scheme 25**).⁴⁵



Scheme 25

Having obtained ketone **1.61**, the HWE reaction for constructing the *E*-olefin was examined (Scheme 24, Table 3). The use of BuLi as base at 0 °C was found to be optimal in delivering a good yield and acceptable *E*-selectivity (Entries 1, 2, Table 3). Heathcock reported the effect of different cations on the *E/Z* selectivities in the HWE reaction.⁴⁶ However, when either NaHMDS or KHMDS were used as base, no improvement in *E*-selectivity was observed and the yield of **1.60** was reduced (Entries 3, 4, Table 3). Using DME instead of THF as solvent⁴⁶ did not change the *E*-selectivity (Entry 5, Table 3).

Entry	Molar ratio (1.61 : 1.62)	Base	Solvent	T (°C)	Time (h)	Yield ^f (%)	<i>E/Z</i> ^g
1	1:1.5	BuLi	THF	0 to RT	24	100	4:1
2	1:3	BuLi	THF	0 to RT	24	100	4:1
3	1:1.5	NaHMDS	THF	−78 to RT	24	71	4.5:1
4	1:3	KHMDS	THF	−78 to RT	24	43	4:1
5	1:3	BuLi	DME	0 to RT	24	78	4:1

Table 3

^f Based on recovered starting material.^g Determined by ¹H NMR, confirmed by NOE experiment.

Attempts towards diol 1.88 using SAD reaction

In order to install the correct C(3) configuration in taurospongins A (**Figure 1**), a SAD reaction was applied (**Figure 5**) for the following reasons:

1. SAD is a robust reaction for constructing stereo-defined diols. In addition, olefin **E-1.60** perfectly matched the mnemonic model proposed by Sharpless.⁴⁷

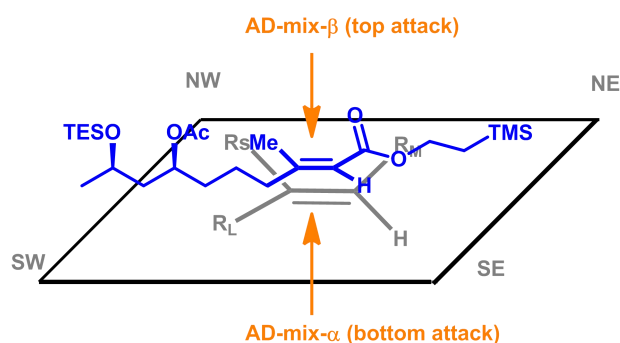
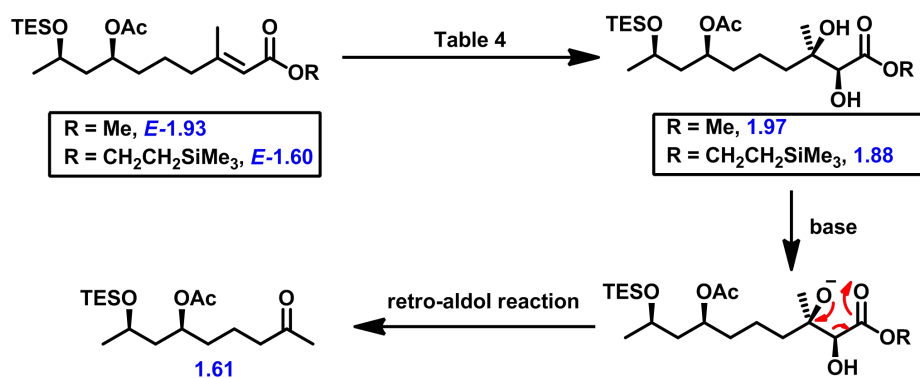


Figure 5

2. SAD on the double bond in **E-1.60** would allow access to a number of different derivatives of taurospongins A in a controllable fashion, which is flexible and beneficial for the projected synthesis of analogues.

When the dihydroxylation reaction was performed under standard conditions both on **E-1.93** as a model and **E-1.60** as a real system (**Scheme 26**),⁴⁷ compounds **1.97** and **1.88** were obtained in 59% and 56% yield respectively with excellent diastereoselectivities (**Entries 1, 2, Table 4**).



Scheme 26

Entry	Olefin	AD-mix type	Extra ligand (3 mol%)	MsNH ₂	Time (h)	Prod.	Yield (%)	d.r.
1	<i>E</i> -1.93	AD-mix- β	No	Yes	72	1.97 (2 <i>S</i> , 3 <i>R</i>)	59 ^h	>99:1
2	<i>E</i> -1.60	AD-mix- β	No	Yes	72	1.88 (2 <i>S</i> , 3 <i>R</i>)	56 ^h	>99:1
3	<i>E</i> -1.60	AD-mix- β	(DHQD) ₂ PHAL	Yes	24	1.88 (2 <i>S</i> , 3 <i>R</i>)	93	>99:1
4	<i>E</i> -1.60	AD-mix- β	(DHQD) ₂ PHAL	No	24	1.88 (2 <i>S</i> , 3 <i>R</i>)	60	>99:1
5	<i>E</i> -1.60	'RD'-mix ⁱ	No	Yes	24	1.88 (2 <i>S</i> , 3 <i>R</i>) 1.98 (2 <i>R</i> , 3 <i>S</i>)	51	1:1
6	<i>Z</i> -1.60	AD-mix- α	(DHQ) ₂ PHAL	Yes	48	1.99 (2 <i>R</i> , 3 <i>R</i>)	95 ^h	>99:1
7	<i>Z</i> -1.60	AD-mix- β	(DHQD) ₂ PHAL	Yes	24	1.100 (2 <i>S</i> , 3 <i>S</i>)	68	>99:1

Table 4

The addition of an extra 3 mol% of (DHQD)₂PHAL led to a significant acceleration of the SAD reaction with an enhanced yield (**Entry 3, Table 4**). This ligand acceleration effect was thought to be due to the binding of the ligand to the osmium species which facilitates the initial osmylation step.^{48, 49} Up to 5% of ketone **1.61** could be isolated as the main side

^h Based on recovered starting material.

ⁱ 'RD-mix' refers to a mixture of quinuclidine, K₃Fe(CN)₆, K₂CO₃, and OsCl₃•3H₂O.

product in the SAD protocol *via* a retro-aldol reaction (**Scheme 26**).

The hypothesis of Hormi⁵⁰ who suggested that methanesulfonamide might not be necessary in related dihydroxylation systems was also examined, aiming to prevent retro-aldol reaction. In the absence of methanesulfonamide, formation of **1.61** was still observed and the yield dropped to 60% (**Entry 4, Table 4**).

Product **1.88** showed only one set of ¹³C NMR signals, indicating the formation of a single diastereomer from the SAD reaction. For data comparison, a racemic dihydroxylation (RD)⁵¹ was performed on *E*-**1.60** (**Entry 5, Table 4**). Examination of the ¹³C NMR data from the SAD and RD reactions showed that high diastereoselectivities had been achieved (*d.r.* > 99:1) in the SAD reaction (**Figure 6**).

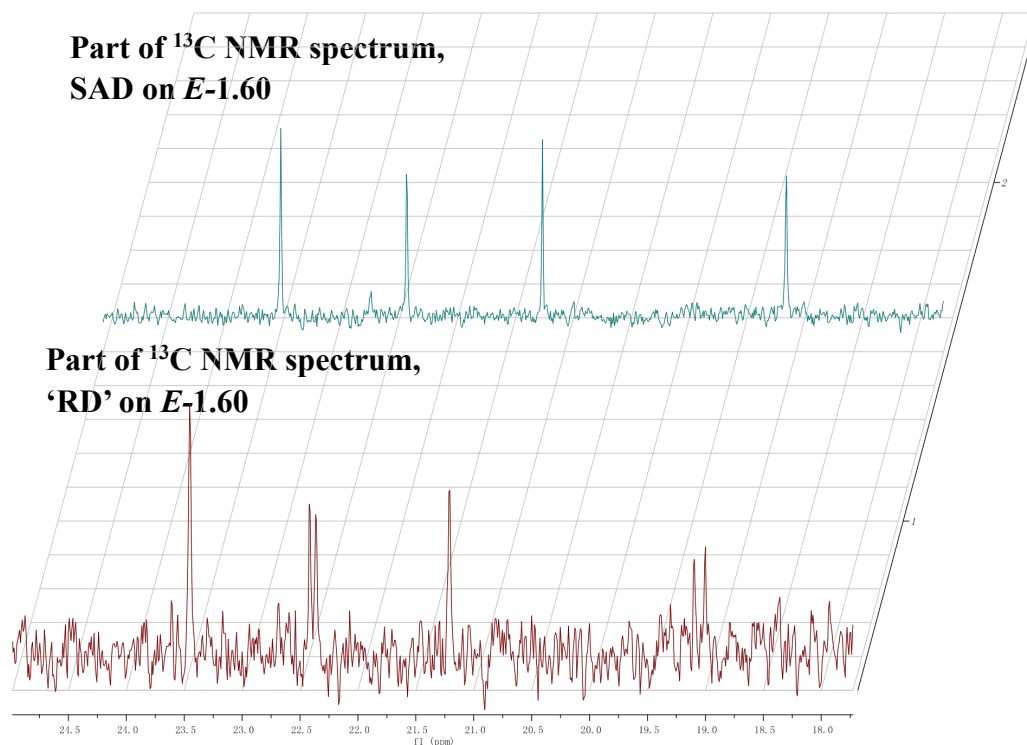
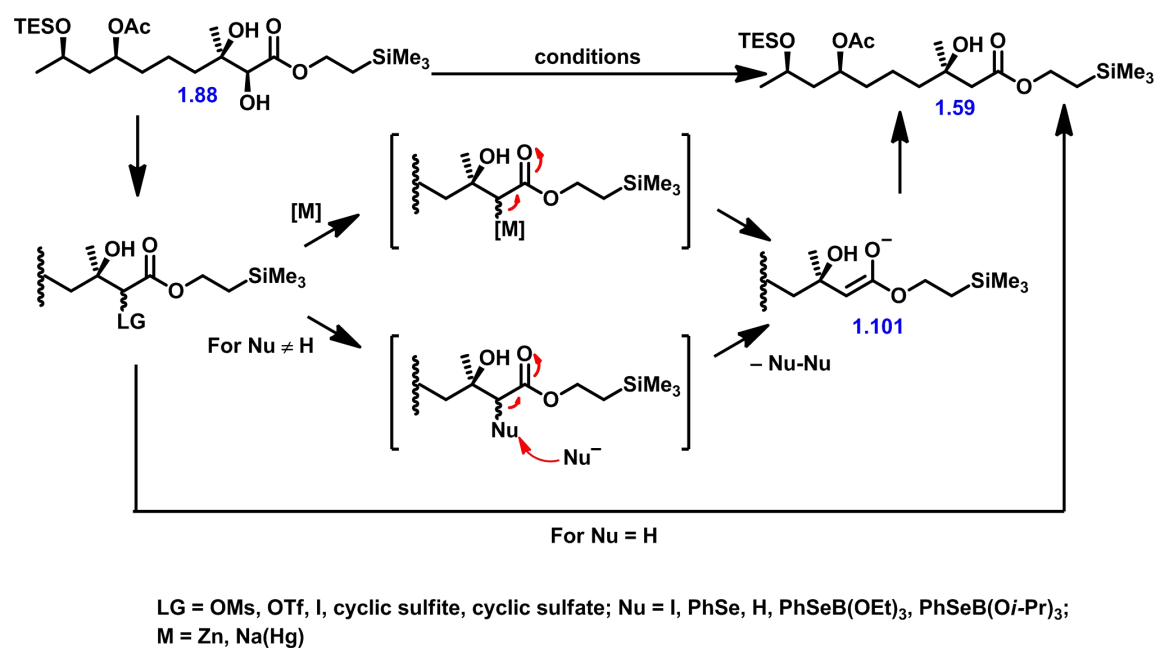


Figure 6

The dihydroxylation was also examined on **Z-1.60** (Entries 6, 7, Table 4). A high diastereoselectivity was also achieved even though the olefin did not perfectly match the Sharpless mnemonic model for *Z*-configured olefins.

Attempts towards selective α -deoxygenation; completion of chiral fragment synthesis

After the successful installation of the stereocentre at C(3), α -deoxygenation was the last step required to complete the synthesis of chiral fragment **1.59**. An ionic approach was first attempted. Three different ionic strategies were designed to conduct the α -deoxygenation process, as demonstrated in **Scheme 27**.



Scheme 27

1. [M] strategy

The first strategy would be to use a metallic reducing agent, such as Na or Zn, to displace the α -leaving group and produce enolate **1.101** that would be protonated *en route* to the desired product.

2. Nu strategy

The second idea would be to utilise a nucleophile to substitute the leaving group first, then the resulting adduct would be subjected to secondary attack by the same nucleophile to afford enolate **1.101** and thus complete overall deoxygenation.

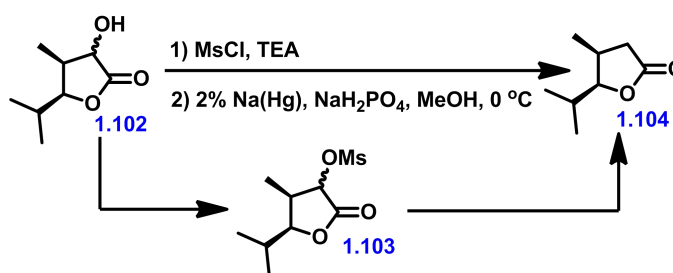
3. H⁻ strategy

The third idea would be to employ a direct displacement of the α -leaving group using a hydride source to complete the hydroxyl removal.

In the following section, each approach is discussed in detail.

Reduction of mesylate ([M] strategy)

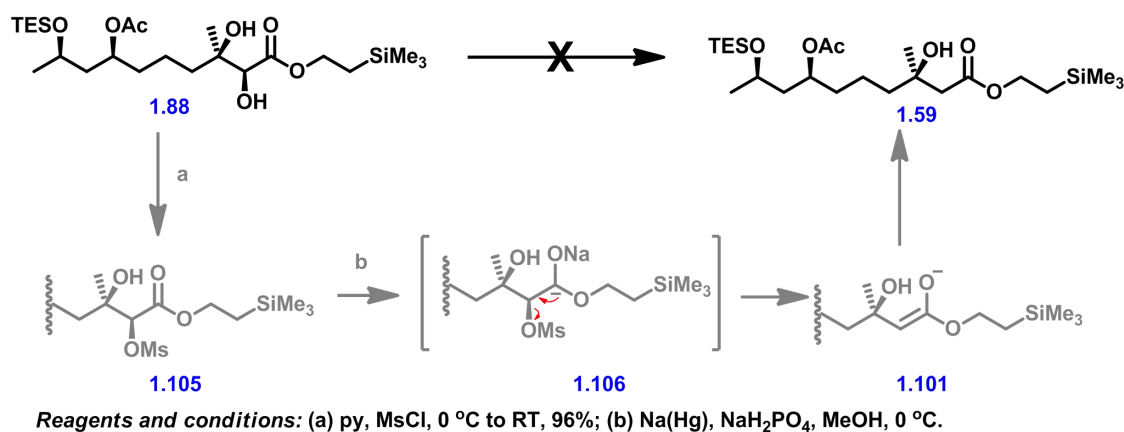
Stork⁵² reported deoxygenation of an α -hydroxy lactone (**Scheme 28**) *via* mesylate **1.103**.



Scheme 28

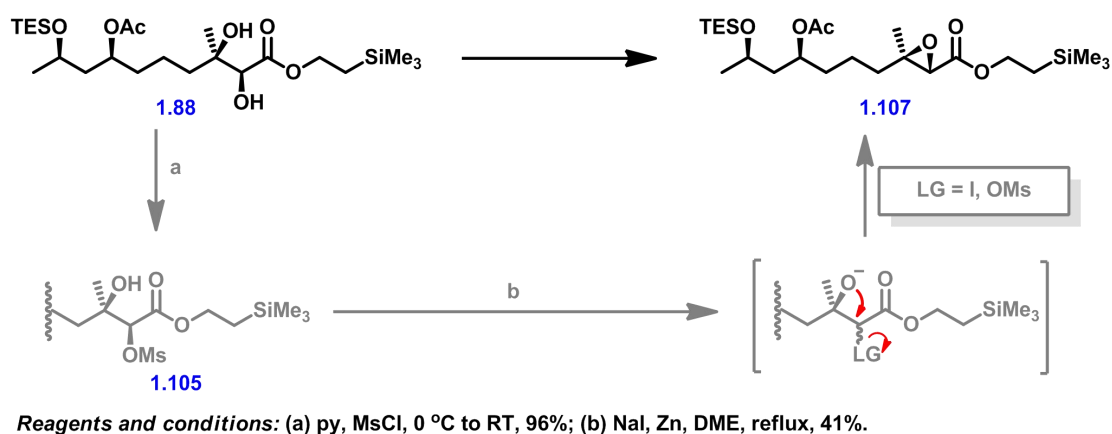
This approach was applied to mesylate **1.105**, which was prepared from diol **1.88**.

Unfortunately, decomposition of **1.105** was observed (**Scheme 29**).



Scheme 29

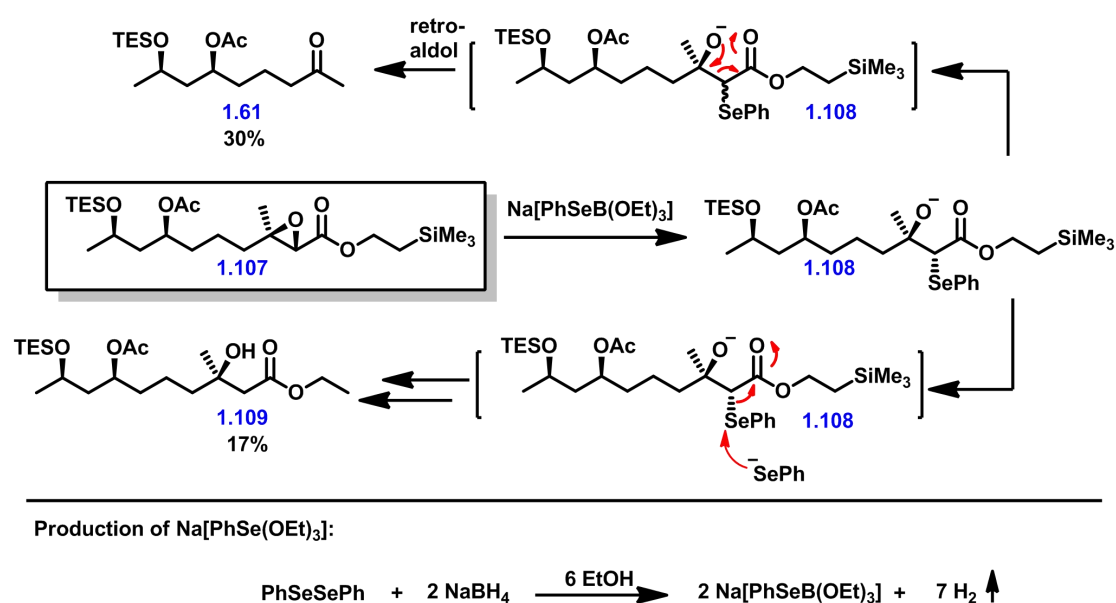
A similar reaction was attempted on mesylate **1.105** by treatment with activated Zn and NaI (Scheme 30).⁵³ However, epoxide **1.107** was isolated as the only observed product, the stereochemistry of which was proposed as shown in order to minimise steric interactions between the larger oxirane substituents. Apparently, intramolecular S_N2 attack by the neighboring hydroxyl onto a leaving group (iodide or mesylate) was rapid under the reaction conditions.



Scheme 30

Selenide reduction of the α,β -epoxide (Nu strategy)

Selenide sources have been reported to be excellent reducing reagents for α,β -epoxy esters.⁵⁴ Benzeneselenolate prepared by treating Na with diphenyldiselenide under sonication was the first reductant examined for the reduction of epoxide **1.107**. When **1.107** was treated with benzeneselenolate, a complex mixture was formed, but when the selenium nucleophile was changed to the bulky $\text{PhSeB}(\text{OEt})_3^-$, the desired deoxygenation of **1.107** was observed. However, this was accompanied by transesterification to give ethyl ester **1.109** (Scheme 31), and retro-aldol reaction was found to be a major side reaction in this process.



Scheme 31

In order to avoid the undesired transesterification reaction, increased bulk was introduced to the nucleophile but when $\text{Na}[\text{PhSeB}(\text{O}i\text{-Pr})_3]$ was applied, decomposition was observed.

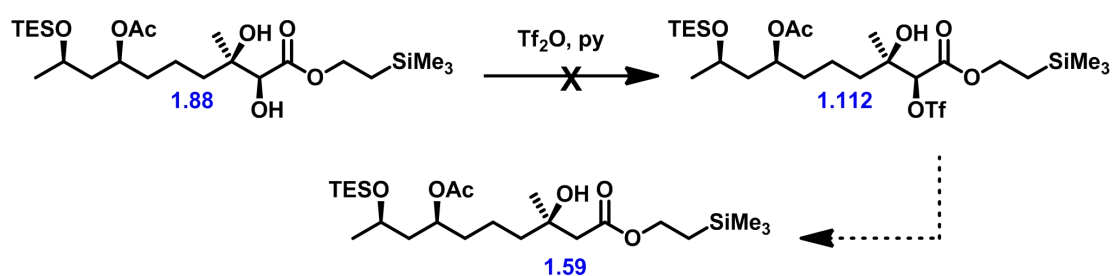
Iodide-mediated reduction of α -triflate (Nu strategy)

Fleet reported the deoxygenation of an α -hydroxy lactone **1.110** *via* its triflate derivative **1.111** by applying LiI as reducing agent^{55, 56} (Scheme 32).



Scheme 32

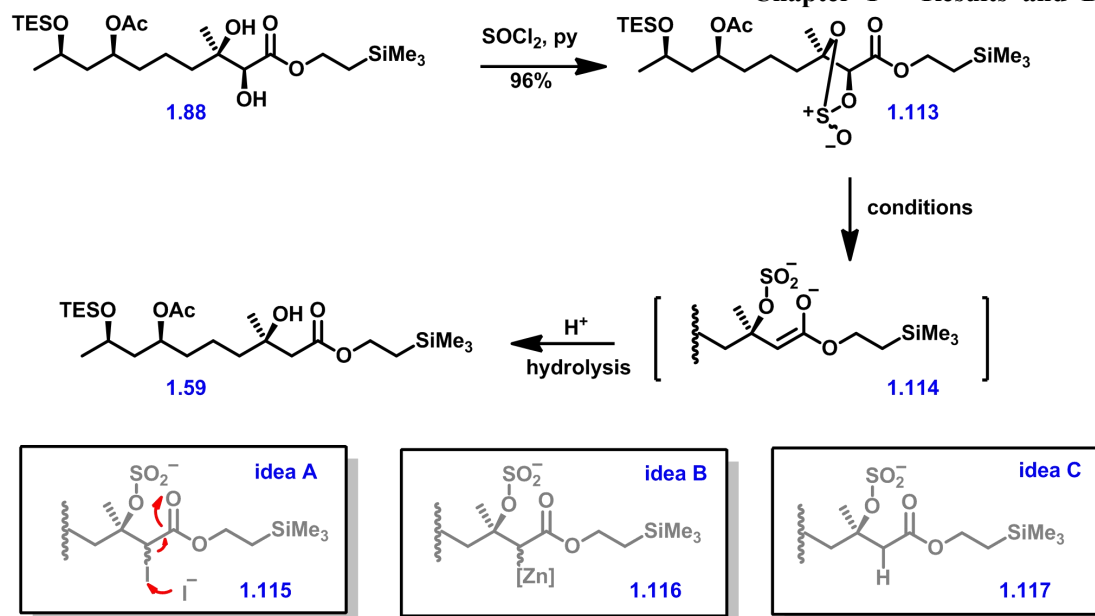
Attempts to prepare α -triflate **1.112** from diol **1.88** resulted only in decomposition (Scheme 33).



Scheme 33

Reduction of cyclic sulfite/sulfate ([M], Nu, H^- strategy)

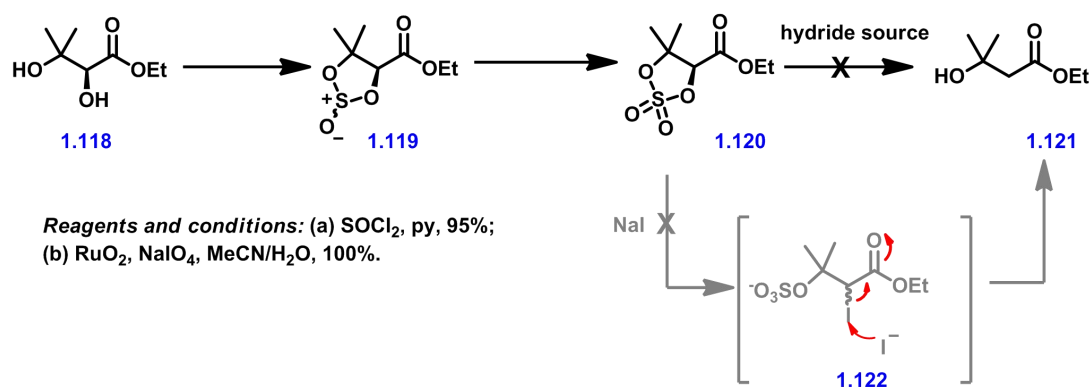
It was reported that cyclic sulfites⁵⁷ and cyclic sulfates⁵⁸ behave similarly to the corresponding epoxides in their susceptibility to nucleophilic attack. Three ideas were examined on cyclic sulfite **1.113**, which was synthesised in 96% yield from diol **1.88** (Scheme 34).



Scheme 34

In practice, I⁻, Zn, and NaBH₄ were utilised as nucleophile, metal source, and hydride source respectively, aiming to afford the ring-opened enolate intermediate **1.114** (Scheme 34). All of these attempts failed, either giving complex mixtures or leaving the starting material (cyclic sulfite).

A cyclic sulfate model substrate was then prepared (Scheme 35). When the model sulfate **1.120** was subjected to either borohydride reduction or NaI conditions, the desired deoxygenated product **1.121** was not observed. Therefore, ionic methods were not further investigated.



Scheme 35

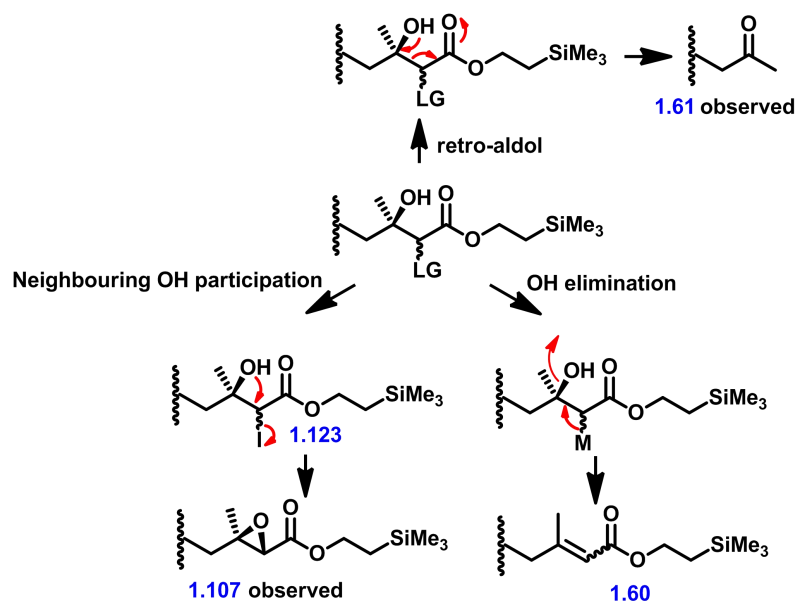
All the ionic methods examined are summarised in **Table 5**.

Entry	LG	Deoxygenation conditions	Product(s)	Strategy
1	OMs	Na(Hg), NaH ₂ PO ₄ , MeOH	Decomposition	[M]
2	OMs	NaI, Zn*, DME, reflux	1.107	[M]
3	OTf	LiI•3H ₂ O, THF	SM decomposed	Nu
4	cyclic sulfite	NaBH ₄ , DMAC, 10% H ₂ SO ₄	Decomposition	H ⁻
5	cyclic sulfite	NaI, Zn*, DME, reflux	SM	[M] and Nu
6	1.107	NaSePh, THF	Decomposition	Nu
7	1.107	Na[PhSeB(OEt) ₃], EtOH	1.61 + 1.109	Nu
8	1.107	Na[PhSeB(Oi-Pr) ₃], EtOH	Decomposition	Nu

Table 5

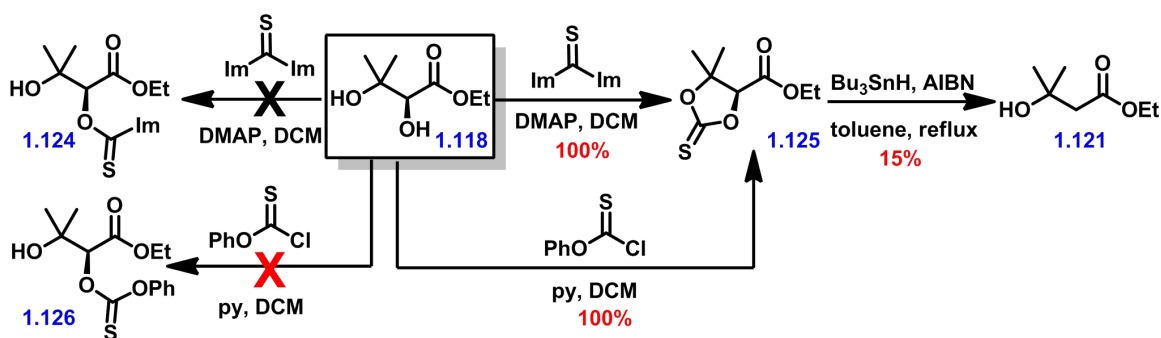
Barton–McCombie deoxygenation: completion of chiral fragment synthesis

After the lack of success with ionic deoxygenation strategies, a new approach for α -hydroxyl removal in **1.88** was required. The most obvious problem in the ionic methods is that many competing pathways could be envisaged that would lead to side product formation or compound decomposition. For example, neighbouring group participation by the β -hydroxyl could lead to epoxide **1.107** formation, as observed during the reaction; in addition, when a metal source displaces the leaving group, the so-formed enolate could eliminate the β -hydroxyl to yield an olefin; retro-aldol to yield methyl ketone **1.61** was also observed (**Scheme 36**).



Scheme 36

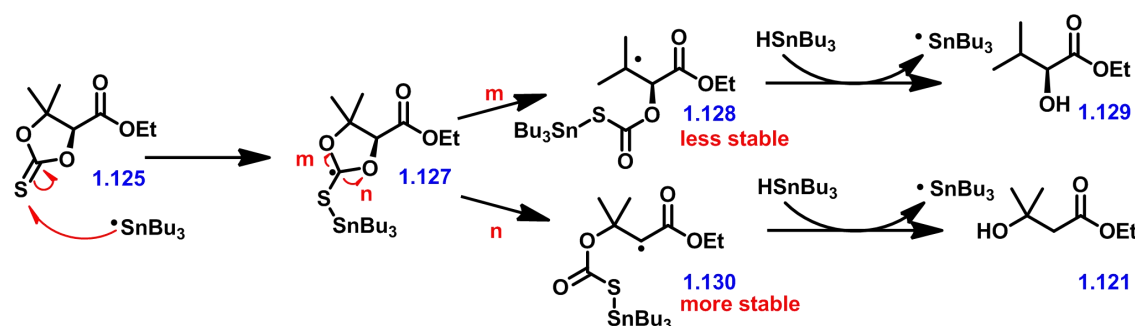
In contrast, rearrangement processes for homolytic pathways are relatively limited compared to ionic approaches. Therefore, a radical reaction was thought to be a suitable alternative for the deoxygenation and the Barton–McCombie reaction⁵⁹ is well-known for such a process. A model substrate was prepared before the deoxygenation of **1.88** was examined (**Scheme 37**).



Scheme 37

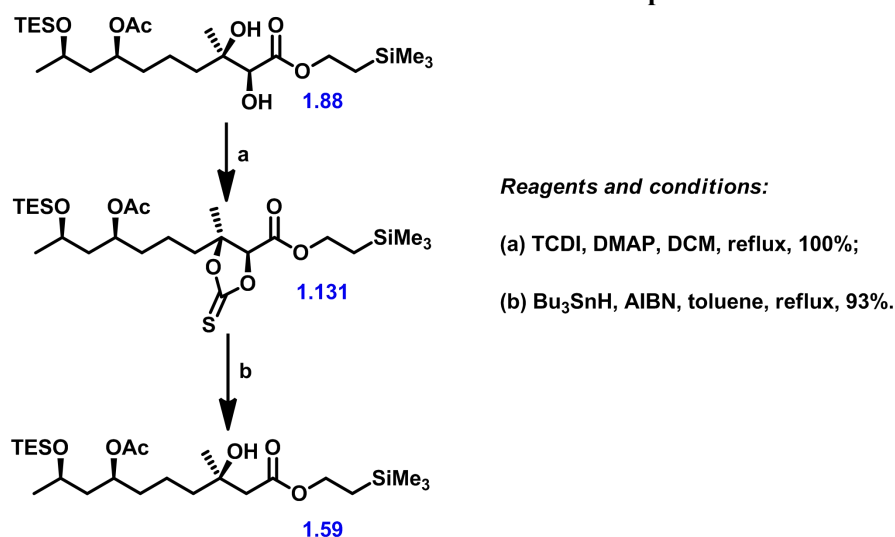
Initially, functionalisation of the α -hydroxyl group was attempted so that eventual deoxygenation would be necessarily selective. Two different conditions^{60, 61} for derivatisation both led to the quantitative formation of thionocarbonate **1.125** instead of the desired products **1.124** and **1.126**, as shown in **Scheme 37**. However, according to Rho's precedent,⁶²

this cyclised product was a likely substrate selective for deoxygenation. When the thionocarbonate **1.125** was subjected to the radical reduction conditions, a 15% yield of deoxygenated product **1.121** was obtained; promisingly, only α -deoxygenation occurred. Due to the fact that the deoxygenated product **1.121** shared an identical R_f value with starting material **1.125**, this led to an unnecessarily prolonged exposure of deoxygenated product **1.121** to heat which caused decomposition and the low yield.



Scheme 38

When intermediate **1.127** is formed in this reaction, fragmentation *via* pathway **n** is preferred due to preferential stabilisation of the forming radical centre by the carbonyl group (Scheme 38), thus, the α -deoxygenated product was observed as the only product. When the same deoxygenation conditions were applied to diol **1.88**, a 93% of chiral fragment **1.59** was obtained (Scheme 39).

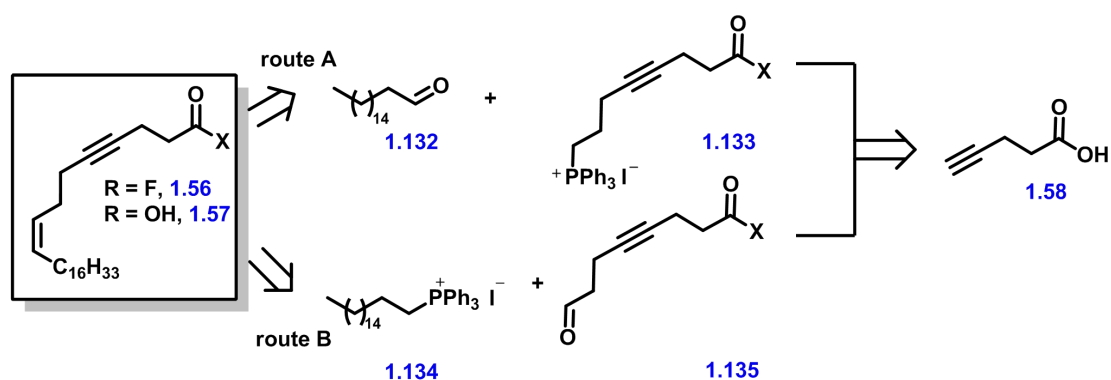


Scheme 39

In summary, the chiral fragment **1.59** was synthesised from PHB depolymerisation in 13 steps with a yield of 15.8% (*ca.* 87% per step on average).

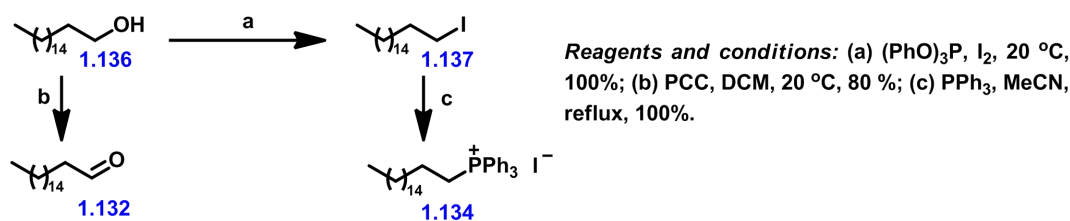
1.7.2 Fatty acid side-chain synthesis

As mentioned earlier (*cf.* page 25), a Wittig reaction was chosen for the construction of the *Z*-double bond in fatty acid **1.57**. Two strategies were considered (**Scheme 40**).



Scheme 40

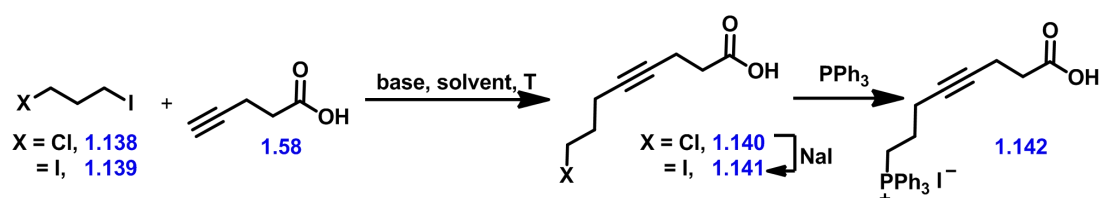
The Wittig partners for both routes were synthesised from 1-heptadecanol **1.136** as shown in **Scheme 41**.



Scheme 41

Route A

In **route A**, it was envisaged that fatty acid ($\text{X} = \text{OH}$) could be obtained by treating the doubly deprotonated phosphonium salt from **1.142** with 1-heptadecanal **1.132**. In order to prepare the corresponding halides **1.140** or **1.141**, a precursor to phosphonium salt **1.142**, the alkylation of pent-4-ynoic acid **1.58** was investigated (Scheme 42, Table 6).



Scheme 42

Entry	Dihalide	Solvent	Base	Temp ($^\circ\text{C}$)	Product	Conversion ^j
1	1.138	THF/DMPU (1 eq.)	BuLi	-78 to RT	1.140	Less than 5%
2	1.138	THF/DMPU (2 eq.)	BuLi	-78 to RT	1.140	ca. 35%
3	1.138	THF/HMPA ^k	BuLi	-45 to RT	1.140	ca. 35%
4	1.139	THF/DMPU (4 eq.)	BuLi	-78 to RT	1.141	ca. 15%
5	1.139	THF/DMPU (2 eq.)	<i>i</i> -PrMgCl	0 to 50	1.141	0
6	1.139	THF/HMPA (2 eq.)	BuLi	-78 to RT	1.141	ca. 35%
7	1.139	THF/HMPA ^k	BuLi	-45 to RT	1.141	ca. 50%

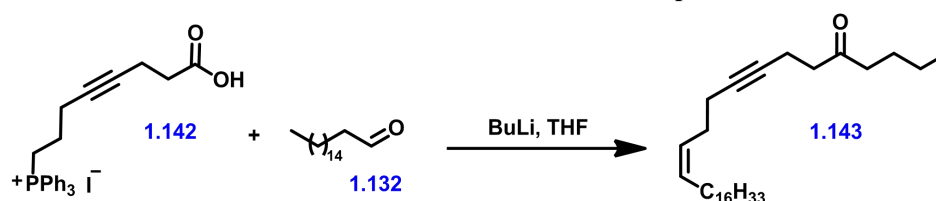
Table 6

^j Determined by ^1H NMR.^k 1:1 THF/HMPA.

1-Chloro-3-iodopropane **1.138** was first used as the alkylating agent, expecting the alkylation to occur selectively on the 3-position. Two problems arose in terms of reaction conversion and product purification. Less than 5% conversion was observed when 1 equivalent of DMPU was used as additive (**Entry 1, Table 6**). Increasing the amount of DMPU led to a significant increase in conversion and a reasonable improvement in yield (**Entry 2, Table 6**). When a mixed solvent of 1:1 THF/HMPA and a higher temperature were employed, only 35% conversion was observed (**Entry 3, Table 6**). What is more, it was found that the alkylated product **1.140** had the same retention factor as starting material **1.58** on TLC, hampering product purification.

The alkylating reagent was then changed to diiodide **1.139** in the hope that the alkylated product **1.141** could be utilised without purification. Even with low yield, the resulting phosphonium salt **1.142** (**Scheme 42**) would be easily separated from other substances, which would be soluble in organic solvents through several washes. Not surprisingly, no significant improvement was observed after screening different additives, bases and temperatures (**Entries 4–7, Table 6**). Eventually, sufficient phosphonium salt **1.142** was accumulated and the subsequent Wittig reaction was examined.

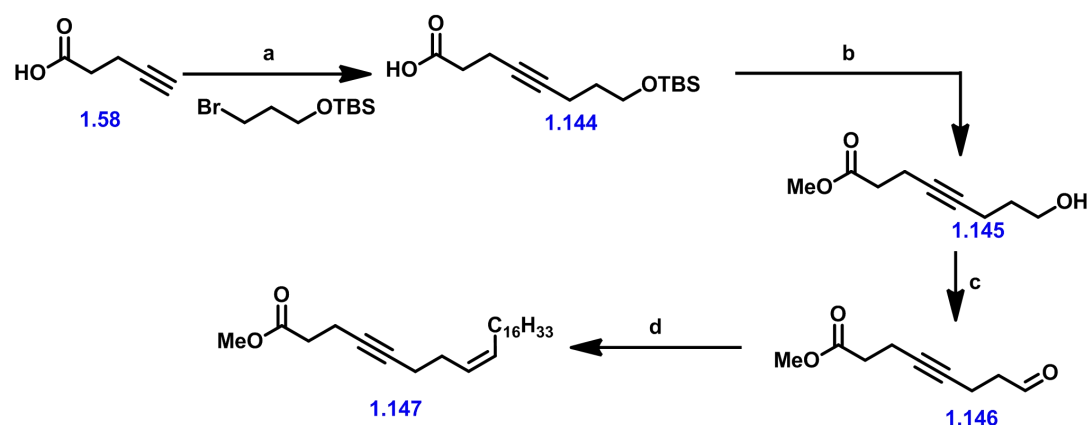
Wittig reaction between **1.142** and 1-heptadecanal **1.132** was attempted using BuLi in THF. However, instead of the desired fatty acid **1.57**, a trace amount of ketone **1.143** was obtained (**Scheme 43**).



Scheme 43

Route B

Due to the low conversion during the alkylation and difficulty in purifying the alkylated product, the synthetic strategy was changed to **route B** in which aldehyde **1.135** was required (Scheme 40, page 49). Jacobsen's taurospongins A synthesis²¹ adopted such a strategy (Scheme 44). However, when Jacobsen's route was repeated, an extremely low yield of **1.144** was observed in the alkylation step. When the Wittig reaction was attempted, just a trace amount of ester **1.147** was observed in the ¹H NMR spectrum of the crude product.



Reagents and conditions: (a) BuLi, HMPA/THF; (b) *p*-TSA, MeOH, reflux, 10% for two steps; (c) PDC, Celite, 4 Å MS, DCM, 74%; (d) NaHMDS, **1.134**, THF, trace.

Scheme 44

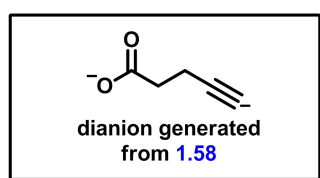
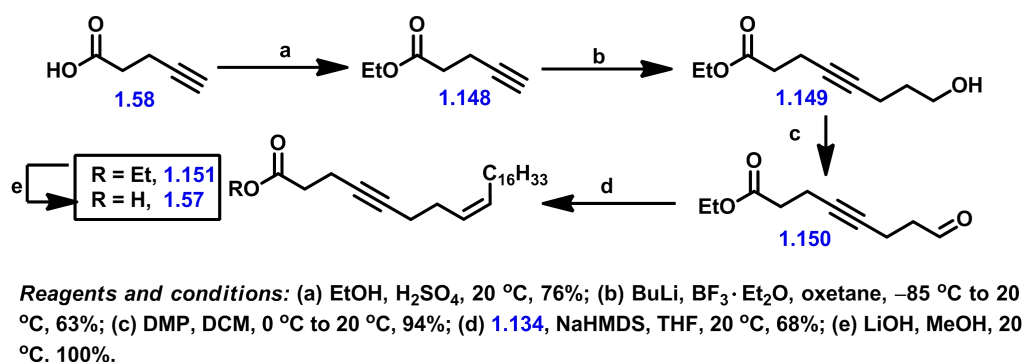


Figure 7

It was envisaged that the dianion derived from alkyne-alkynoic acid **1.58** (Figure 7) might be the cause of the alkylation problem. In order to solubilise the dianion, the addition of highly

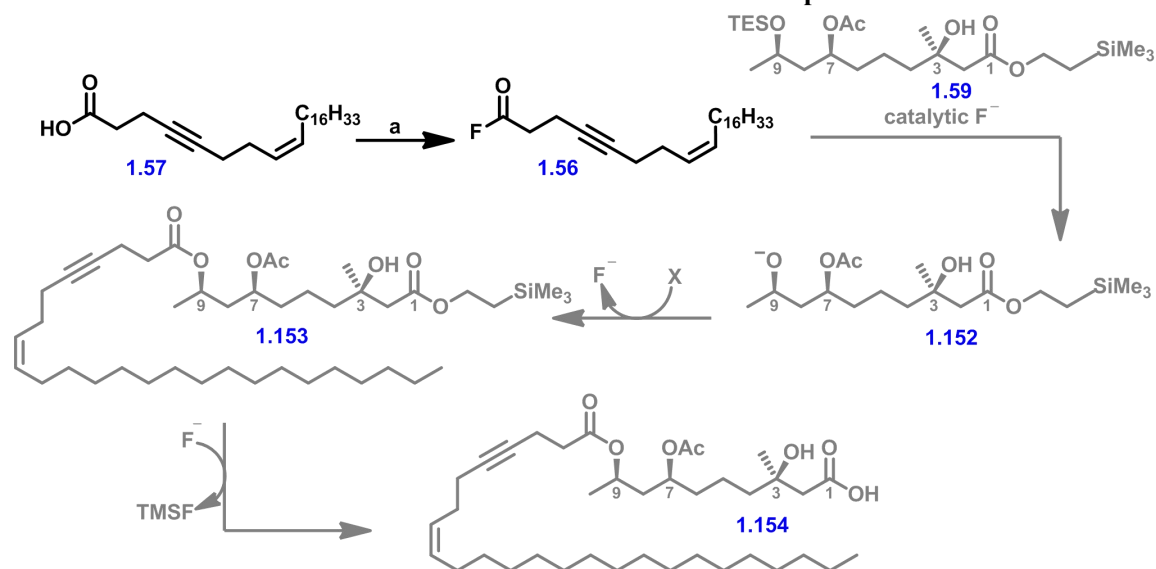
polar DMPU or HMPA was required. Thus, ester **1.148** was chosen (**Scheme 45**) to avoid this problem. One major concern for this reaction was that the pK_a value difference between the terminal acetylene C-H and the α -proton of the carbonyl group was expected to be small although values are unavailable for THF. In practice, when the alkylation reaction was conducted between ester **1.148** and oxetane, a 63% yield of alkylated product **1.149** was isolated, which proved to be a feasible alkylation protocol for the fatty acid synthesis.



Scheme 45

From hydroxyester **1.149**, the remaining fatty acid skeleton was assembled as shown in **Scheme 45**. In summary, fatty acid **1.57** was obtained in 22.4% yield after a 5-step synthetic sequence (75% yield per step on average).

According to the original synthesis plan, an acyl fluoride **1.56** was required to telescope the TES deprotection at C(9), acylation at C(9), and the silyl group removal at C(1) (**Scheme 46**). When fatty acid **1.57** was treated with cyanuric fluoride,⁶³ a 75% of acyl fluoride **1.56** was obtained, ready for the final stage of the synthesis.

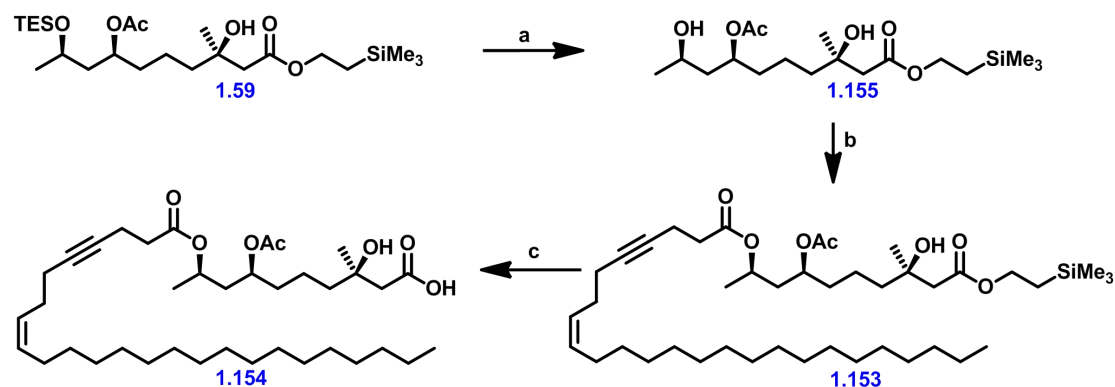


Scheme 46

1.7.3 Completion of Synthesis

Stepwise completion of taurospongins A

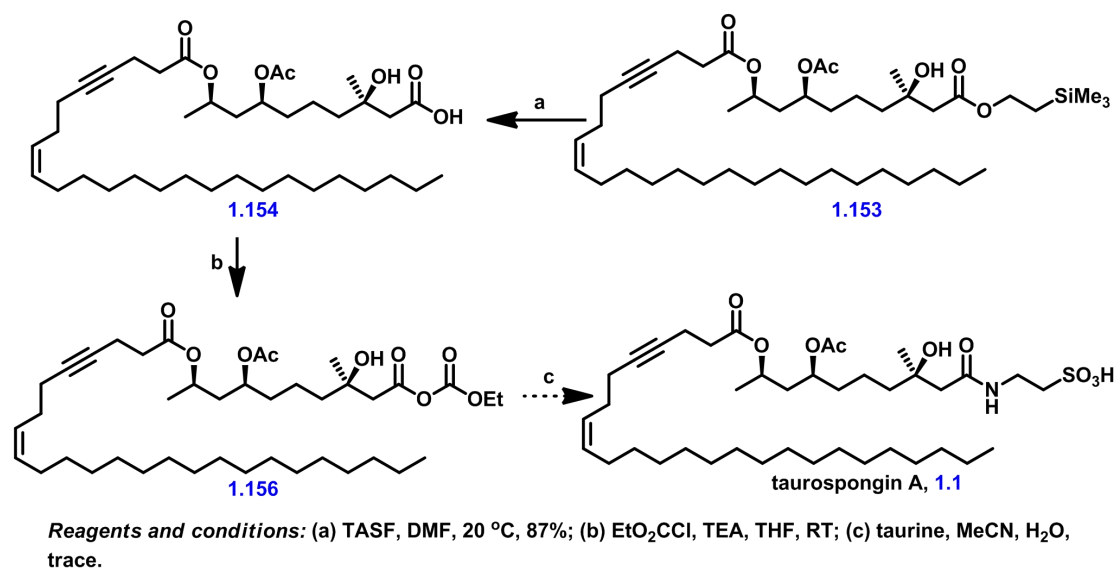
Before the telescoping process was examined, a stepwise process was first conducted (Scheme 47) to afford acid **1.154** for the last taurine coupling reaction.



Scheme 47

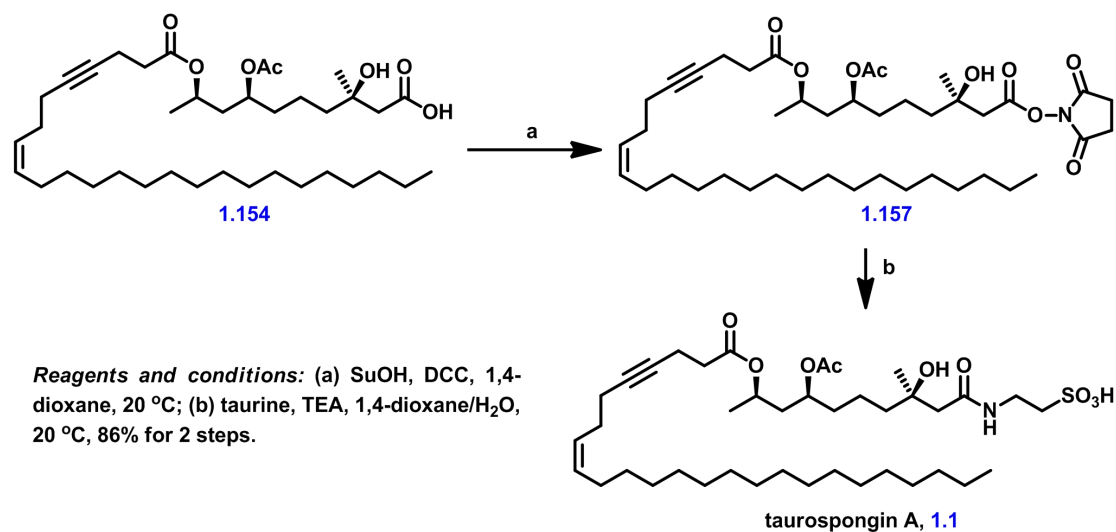
Removal of the 2-(trimethylsilyl)ethyl group proceeded poorly with TBAF but the TASF procedure⁶⁴ produced the acid very cleanly. To complete the taurospongins A synthesis,

repetition of the final step in Jacobsen's synthesis,²¹ through a mixed anhydride intermediate **1.156**, led only to a trace amount of the natural product. One of the problems for this reaction is that the intermediate mixed anhydride could not be purified by silica gel chromatography, and hence subsequent taurine coupling of the crude anhydride turned out to be inconclusive (Scheme 48).



Scheme 48

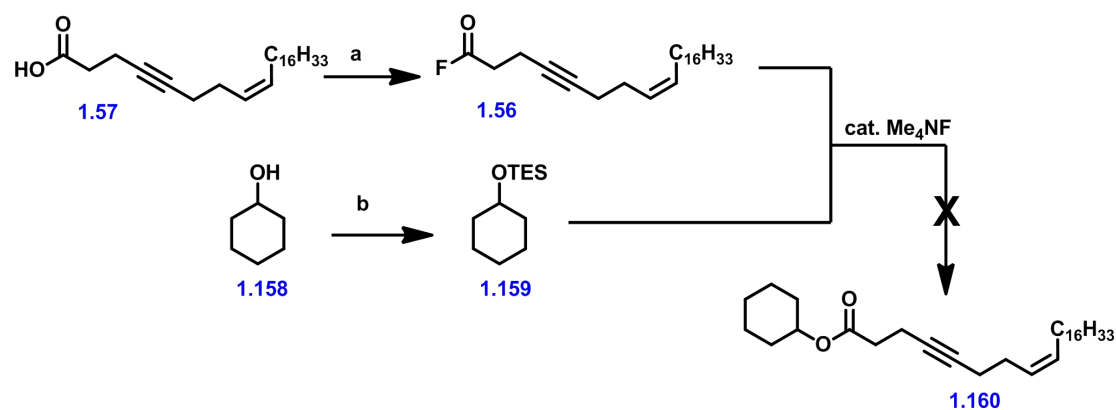
Finally, it turned out that the *N*-hydroxysuccinimide method described by Ley,²³ who followed Kobayashi's protocol,⁴ worked very well to complete the total synthesis of taurospongins A (Scheme 49).



Scheme 49

Telescoping process towards taurospongins A

A model substrate was tested for the acylation before the actual system was tackled. TES protected cyclohexanol **1.159** was prepared in quantitative yield and coupling was attempted with acyl fluoride **1.56** (Scheme 50).



Reagents and conditions: (a) cyanuric fluoride, py, MeCN, 75%; (b) TESCl, py, 100%

Scheme 50

When the telescoping process was tested by treating freshly prepared acyl fluoride **1.56** with silyl ether **1.159** in the presence of a catalytic amount of tetramethylammonium fluoride according to Natalia's protocol,⁶⁵ the formation of a complex mixture was observed. Due to the failure of the test reaction, this approach was not further examined.

1.7.4. NMR study of taurospongins A

Interestingly, although the NMR data in CDCl_3 matched those reported in the literature (Tables 7, 8), some of the signals were shown to be weak and broadened. In CD_3OD , however, all ^{13}C and ^1H NMR resonances were sharp (Figures 8, 9).

	Robertson	Kobayashi	Ley	Jacobsen	Robertson
Solvent	CDCl_3	CDCl_3	CDCl_3	CD_3OD	CD_3OD
H-2	2.24–2.51 ¹ (m)	2.26 (d)	2.31 (br.s)	2.28 (d)	2.30 (d)
		2.35 (d)		2.34 (d)	2.36 (d)
H-11	1.19 (br.s)	1.18 (s)	1.18 (br.s)	1.19 (s)	1.21 (s)
H-1''	3.13 (br.s)	3.02 (m)	3.13 (br.s)	2.96 (t)	2.99 (t)
H-2''	3.66 (br.s)	3.59 (m)	3.66 (br.s)	3.60 (t)	3.63 (t)

Table 7

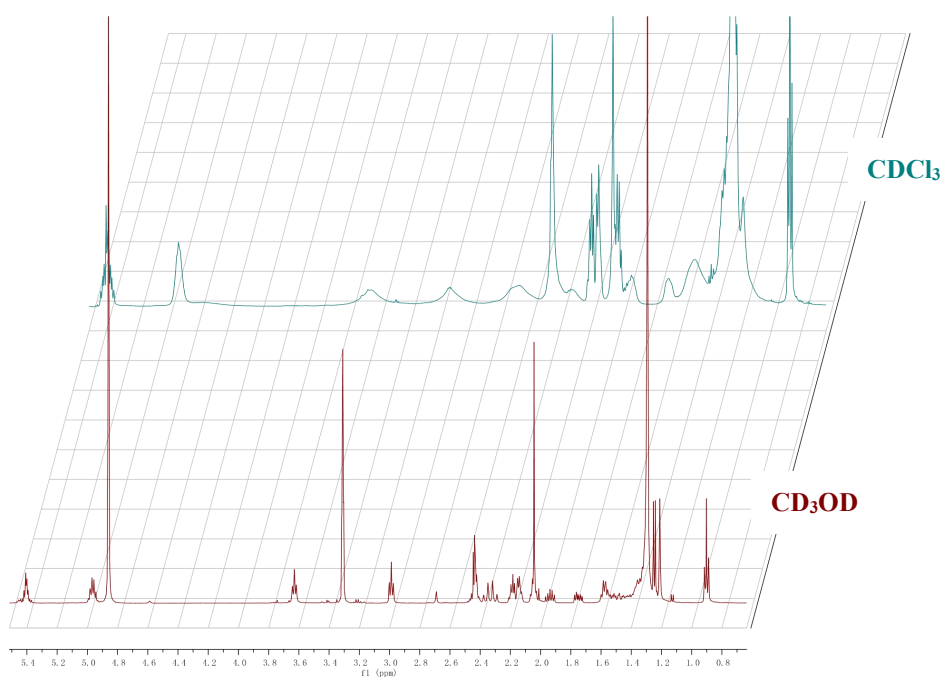


Figure 8

¹ Overlapping with resonances of H-2', H-3'.

	Robertson	Kobayashi	Ley	Jacobsen	Robertson
Solvent	CDCl ₃	CDCl ₃	CDCl ₃	CD ₃ OD	CD ₃ OD
C-1	173.1 (br.)	172.3	173.2	NA	174.2
C-2	46.5 (br.)	47.1	46.5	NA	47.8
C-3	71.8 (br.)	missing	71.8	NA	72.6
C-4	42.2 (br.)	missing	42.2	NA	43.0
C-5	19.6 (br.)	missing	19.6	NA	20.7
C-6	34.9 (br.)	missing	34.9	NA	35.9
C-8	40.4 (br.)	missing	40.4	NA	41.4
C-11	26.1 (br.)	missing	26.1	NA	26.8
C-1''	50.0 (br.)	50.4	50.0	NA	51.5
C-2''	35.2 (br.)	35.2	35.2	NA	36.5

Table 8

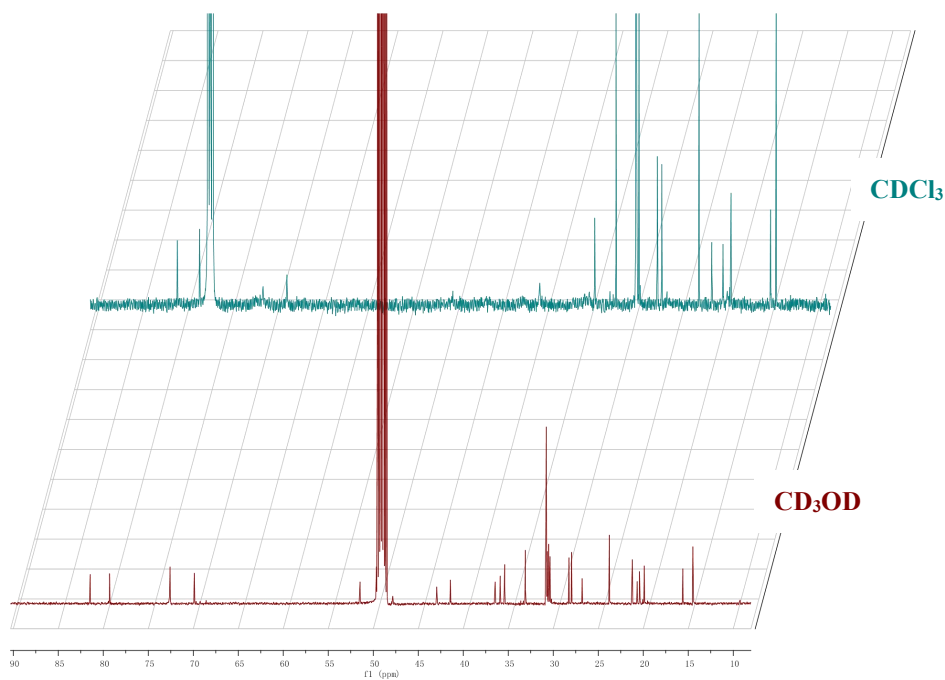


Figure 9

A substantial number of ^{13}C resonances listed in Ley's publication were missing in Kobayashi's data. It was suggested that in a non-polar solvent, molecular aggregation, such as reverse micelle formation, may be responsible for this phenomenon. In polar, protic solvents, such as CD_3OD , taurospongins A is sufficiently solvated, and sharp NMR resonances are seen.

1.8 Conclusion of the project

The Robertson total synthesis of taurospongins A required 15 steps from Weinreb amide **1.70** and was achieved in *ca.* 13.5% overall yield (average *ca.* 88% per step). Compared to the reported syntheses (**Table 9**), the Robertson synthesis possessed the highest yield (overall yield and yield per step) and the equal shortest synthetic sequence.

Research Group	Jacobsen	Ley	Robertson
Completion year	1998	2002	2010
Overall Yield	6.8%	3.8%	13.5%
Yield per step	83%	86%	88%
Total Steps	15	21	15
Longest linear sequence	13	16	13

Table 9

The original aim of this synthesis, *i.e.* to develop a practical and flexible synthetic approach towards taurospongins A, had been met. With this synthetic route in hand, the next goal was to prepare analogues of taurospongins A and to examine the structure-activity relationships of these compounds which was taken up by Dr. Mallinger and is currently ongoing.

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Chapter 2: The identity of a spirocyclic bis(acetylene) enol ether isolated from *Chrysanthemum boreale* via total synthesis

2.1 Using total synthesis to elucidate the structure of natural products

Historically, total synthesis served a crucial role in the structural elucidation of unknown compounds.¹ However, with the rapid advancement of spectroscopic techniques, this role diminished.¹ Scientists rely increasingly on advanced spectroscopic methods, such as NMR, IR, and mass spectrometry, but these techniques still sometimes mislead, and can result in erroneous structural assignment. Therefore, total synthesis, combined with state-of-the-art spectroscopic techniques, can aid reliable identification of molecules in doubt. The following synthesis is an example in this regard.

2.2 Spiroacetal enol ethers in Nature

The spiroacetal motif is one of the most common structural moieties in natural products²⁻⁴ (Figure 1).

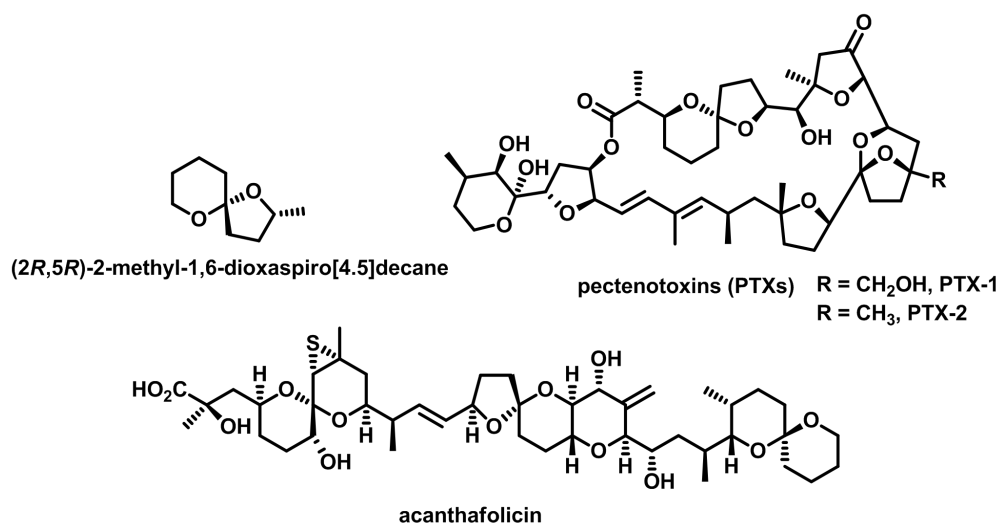


Figure 1

Among these natural products, Bohlmann reported the isolation of many spiroketal enol ethers with a [4,5] ring framework and a bis(acetylenic) side-chain from the *Asteraceae*,⁵⁻⁷ the largest family of flowering plants⁸ (**Figure 2**); an example is AL-1 **2.5**, a potential antitumour agent from *Artemisia lactiflora*.^{9, 10}

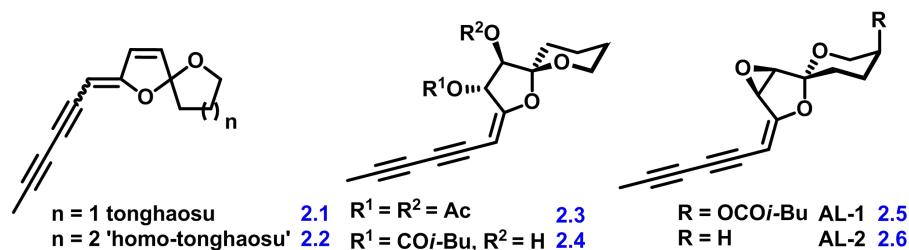


Figure 2

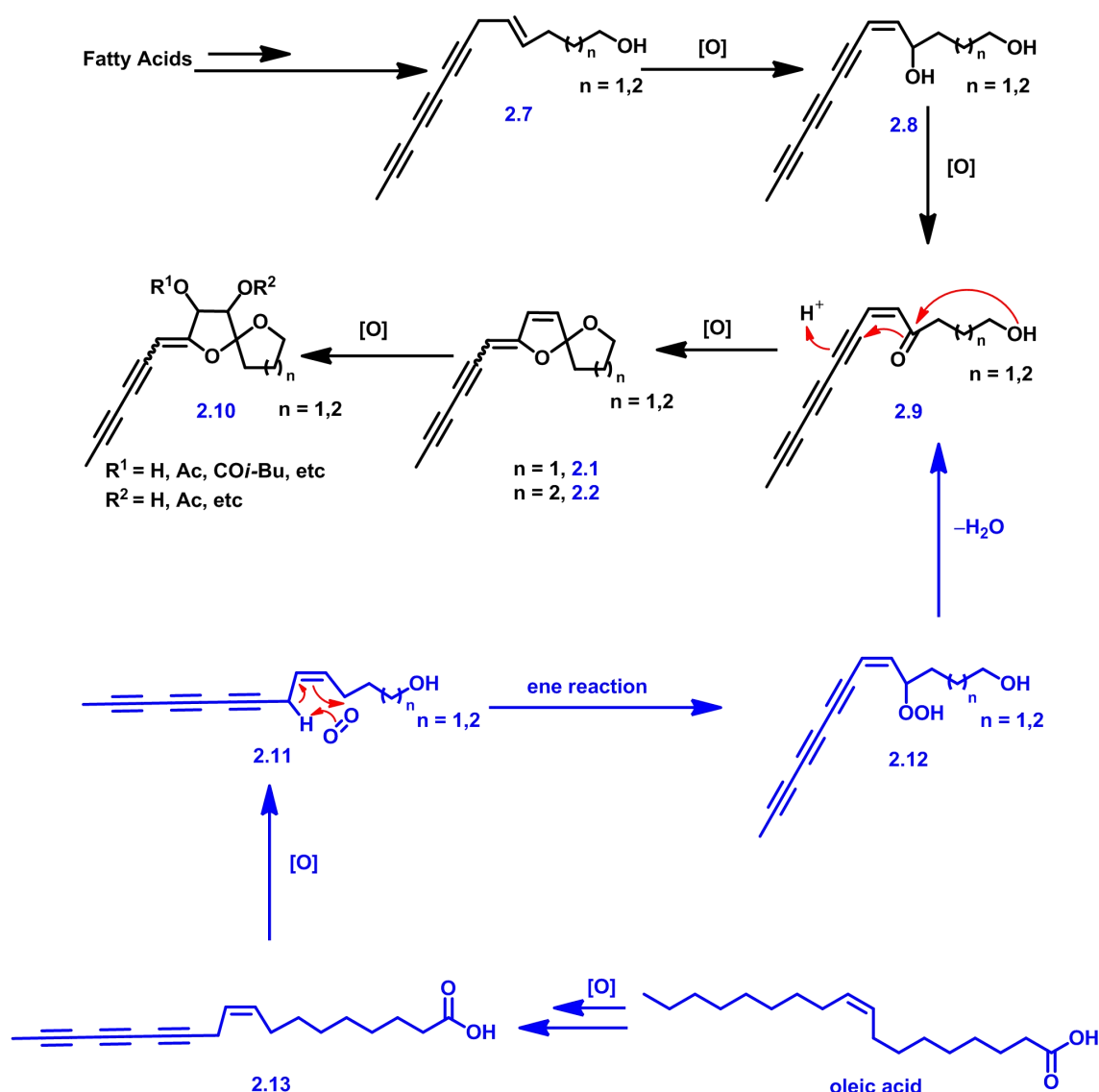
Spiroketal natural products have attracted a lot of attention as synthetic targets due to their interesting structures and their wide range of biological activities;²⁻⁴ compounds from the *Artemisia* and *Chrysanthemum* genera serve as good examples.

2.3 Biosynthesis, biological activity and structural elucidation of spiroketal enol ethers from *Artemisia* and *Chrysanthemum* genera

2.3.1 Biosynthesis

The biosynthesis of *Artemisia* and *Chrysanthemum* spirocyclic natural products is not fully understood. Bohlmann¹¹⁻¹³ suggested that the biosynthesis proceeds *via* an acyclic tris(acetylene) structure such as **2.7**, which could originate from fatty acids (**Scheme 1**). After oxidation, ketone **2.9** can undergo spirocyclisation under acidic conditions. Further oxidation and esterifications would give rise to structures such as **2.10** (**Scheme 1**). More recent literature¹⁴ proposed that oleic acid is subjected to an oxidative sequence including an ene reaction between olefin **2.11** and oxygen to intercept common intermediate **2.9** that can

undergo spirocycle formation and further manipulations (shown in blue, **Scheme 1**).



Scheme 1

2.3.2 Biological activity

Tada found that tonghaosu (**Figure 2**) shows antifeeding properties towards fifth instar larvae of male *Bombyx mori* (silk worm).¹⁵ Structurally related compounds have also shown antifeeding effects towards the large white butterfly (*Pieris brassicae* L.).¹⁶ Nakamura and co-workers^{9, 10} found that AL-1 strongly inhibited tumour progression induced by TPA, a tumour promoter, both *in vitro* and *in vivo*. The mechanism for this inhibition is unclear, but

it is possible that AL-1 either prevents the generation of $O_2^{\bullet-}$ or acts as an $O_2^{\bullet-}$ scavenger. The structurally related compound AL-2 (**2.6** in **Figure 2**) also showed antitumour activity, although much less pronounced than AL-1, towards TPA-induced tumour progression, indicating that the axial subsistent substituent on C(8) in AL-1 (**2.5** in **Figure 2**) is important for its biological activity (**Figure 3**).

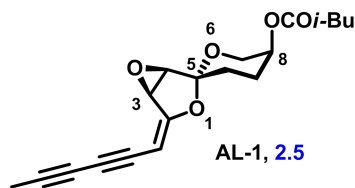


Figure 3

In 1974, Matsuo isolated an unnamed compound from *Chrysanthemum boreale*.¹⁷ This compound contains the characteristic [4,5]-spiroketal and bis(acetylene) side-chain as mentioned above, and a *cis*-diacetate motif in ring A was also reported (**Figure 4**). The biological activity of this molecule is unknown, but its structural similarity to AL-1 and potentially similar bioactivity makes it an interesting synthetic target for further SAR studies.

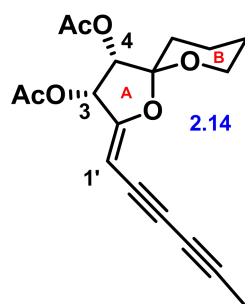
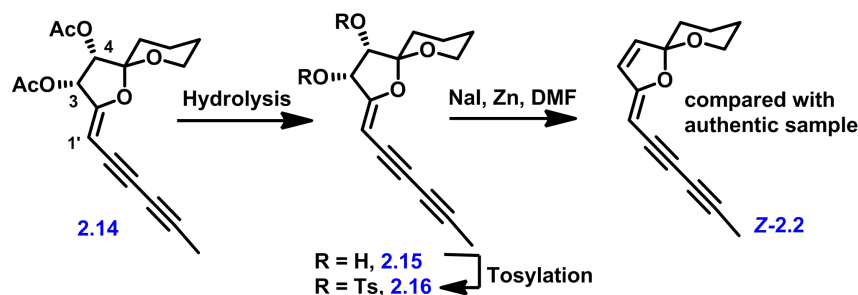


Figure 4

2.3.3 Structural elucidation of compound 2.14

The structural assignment of compound **2.14** (**Figure 4**) was based largely on 1H NMR spectroscopic analysis. The diacetate moiety was reported as *cis*- on the basis of the vicinal coupling constant (7.5 Hz) between H(3) and H(4). The exocyclic double bond was assigned as *Z*- on the basis of the allylic proton coupling constant (2.0 Hz) between H(1') and H(3).

The stereochemistry of the spiro-centre, however, was not assigned.

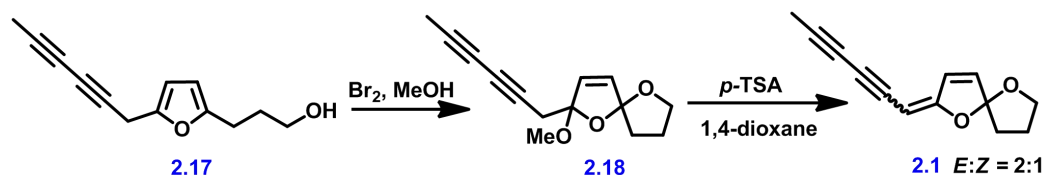


Scheme 2

A chemical correlation experiment was conducted to confirm the olefin geometry (**Scheme 2**). From **2.14**, hydrolysis and double tosylation furnished the bis-tosylate **2.16**. Treatment of **2.16** with NaI and Zn¹⁸ gave deoxygenated homo-tonghaosu **Z-2.2** that was compared with an authentic sample obtained from Fukuoka University of Education to confirm the double bond geometry.¹⁹

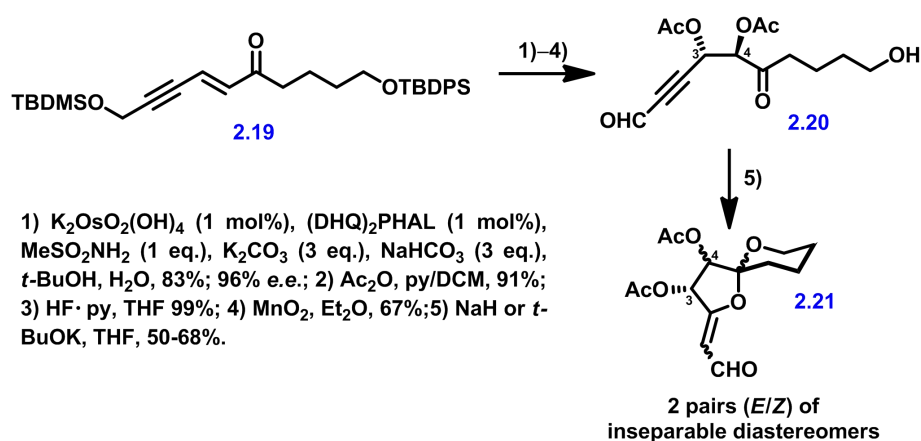
2.4 Previous work towards the synthesis of spiroketals isolated from the *Artemisia* and *Chrysanthemum* genera

Spiroketals from the *Artemisia* and *Chrysanthemum* genera have not drawn much attention as synthetic targets except for Bohlmann's pioneering tonghaosu synthesis in 1964.²⁰ In his synthesis, disubstituted furan **2.17** underwent a bromoetherification, in effect, an intramolecular Clauson–Kaas reaction, to achieve spirocyclisation. Acid-catalysed elimination of methanol furnished both *E*- and *Z*- isomers of tonghaosu in a 2:1 ratio (**Scheme 3**).



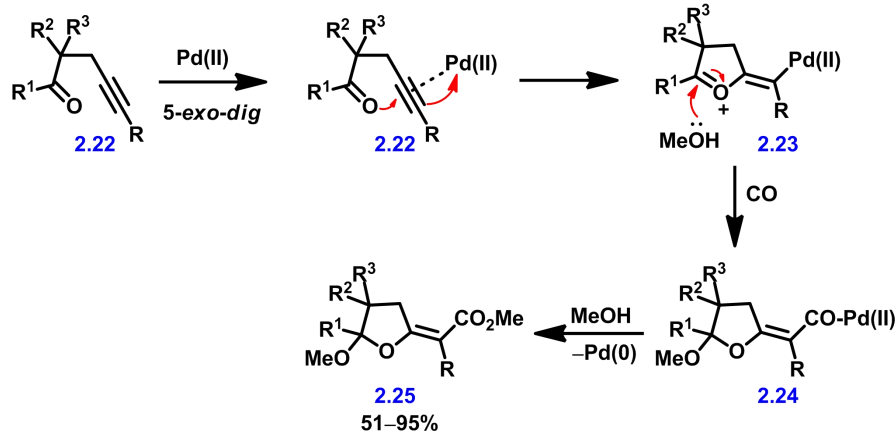
Scheme 3

From the mid-1990s, these spiro-skeletons re-emerged as attractive synthetic targets.²¹⁻²⁶ In 1999, Toshima proposed a biomimetic approach to assemble the spirocyclic system *via* an intramolecular conjugate addition on an acyclic keto-alcohol **2.20** bearing an unsaturated aldehyde functionality²⁴ (**Scheme 4**). In this synthesis, stereocontrol arose from a SAD reaction.



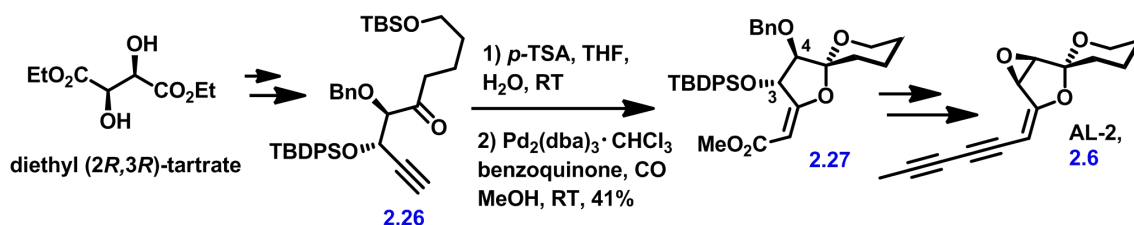
Scheme 4

Mukai's synthesis of AL-2²³ is based on palladium mediated chemistry reported by Kato and Akita.^{27, 28} Initial 5-*exo-dig* cyclisation is followed by CO insertion, esterification and catalyst regeneration (by oxidation) to complete the catalytic cycle, giving the desired tetrahydrofuran core in high yield (**Scheme 5**).



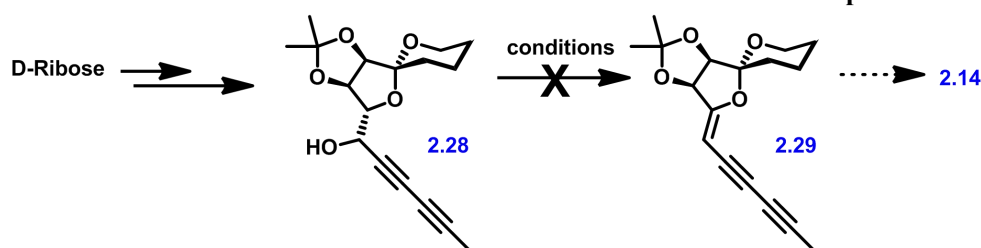
Scheme 5

The synthesis of AL-2 started from either (*R,R*)- or (*S,S*)- diethyl tartrate, within which the diol motif at C(3) and C(4) of intermediate **2.27** was set with correct absolute stereochemistry. By applying Kato and Akita's approach,^{27, 28} the 1,6-dioxaspiro[4.5]decane framework in **2.27** was prepared in 41% yield under optimised conditions. Further transformation of **2.27** led to the first synthesis of AL-2 (**Scheme 6**).



Scheme 6

In 2007, Koviach²⁹ published a synthetic approach towards this natural product **2.14** (**Scheme 7**) with the aim to establish the absolute configuration of the molecule, especially the spirocentre. The synthesis began with D-ribose, but intermediate **2.28** surprisingly could not be dehydrated to give the desired enol ether. Prior to the Robertson group synthesis of this compound,³⁰ no successful synthesis had been published.



Scheme 7

2.5 Previous work in the Robertson group towards natural product 2.14 from

Chrysanthemum boreale

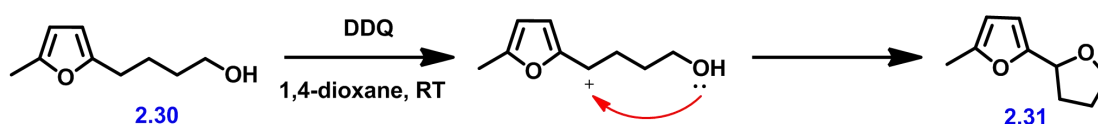
2.5.1 Furan-based spirocyclisation strategies towards the spiroketal moiety

Spirocyclisation triggered by furan oxidation

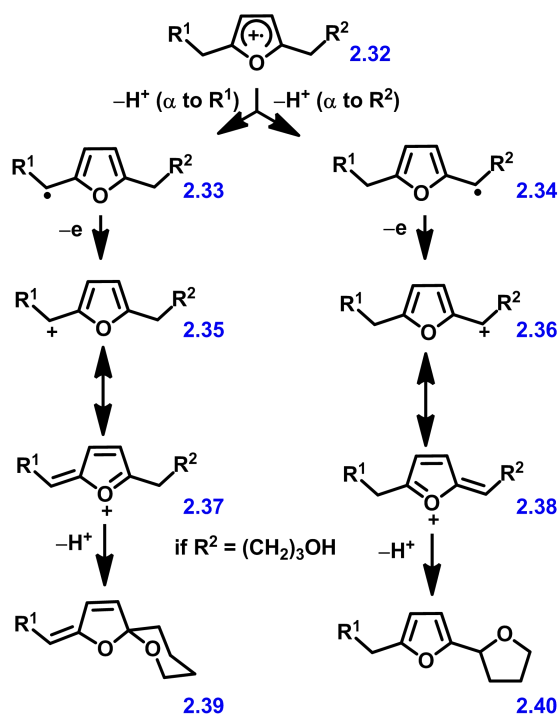
Furan derivatives are versatile synthetic intermediates which may be transformed, usually by oxidation, into a large variety of structures for total synthesis.³¹⁻³⁷

Spirocyclisation *via* single electron transfer oxidation reaction

Treatment of furan derivatives with oxidising agents such as DDQ³⁸ can lead to single electron transfer, resulting in overall hydride loss at the α - position allowing nucleophilic attack of a tethered nucleophile. Harwood³⁹ in 1987 discovered a method of synthesising cyclic ether 2.31 using this principle (Scheme 8).



Scheme 8

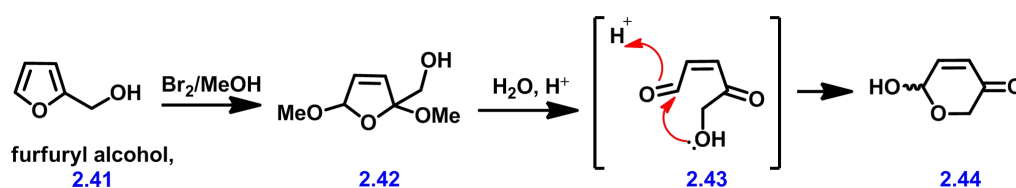


Scheme 9

Mechanistically, electron-transfer from the electron-rich furan ring occurs rapidly to DDQ, resulting in delocalised radical-cation **2.32** (Scheme 9). This radical cation is then activated, by proton abstraction and a second electron transfer to generate α -carbocations **2.35** and **2.36**. The regiochemistry of cation formation in this process depends on the relative levels of α -radical stabilisation on either side of the furan moiety. The regiochemistry of this process can be probed by a tethered nucleophile present in either R^1 or R^2 . For instance, if $R^2 = (CH_2)_3OH$, two cyclisation products **2.39** and **2.40** can form depending on the regioselectivity of carbocation formation. If a more effective radical stabilising functionality, such as a double bond or aromatic group is incorporated in R^1 , then cation formation should be preferred on the other side of the tethered nucleophile, resulting in spirocyclic products.

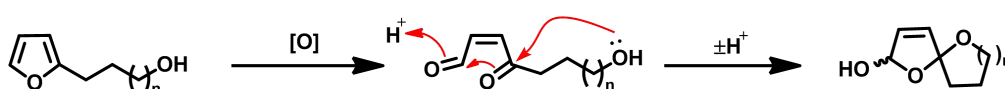
***m*-CPBA mediated spirocyclisation**

The Achmatowicz reaction⁴⁰ and its aza-counterpart,^{41, 42} conducted classically with Br₂ in methanol and then acidic conditions, transforms furfuryl alcohols and α -aminomethyl furans into hydroxypyrones and hydroxypyridones respectively. These transformations involve a ring-opened ene-dione intermediate which is trapped at the distal carbonyl by the tethered hydroxyl or amino nucleophile (Scheme 10).



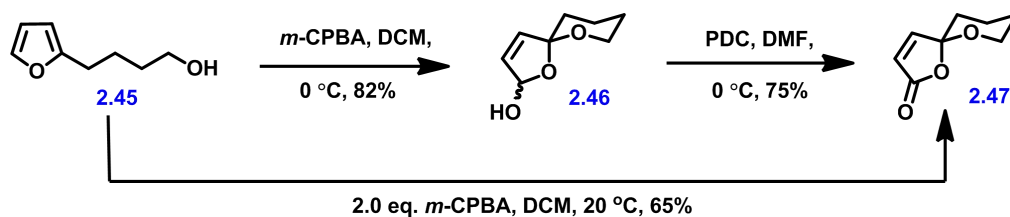
Scheme 10

By tethering more remote nucleophiles, related oxidative conditions can lead to spirocyclisation (Scheme 11). A range of oxidants have been used for this purpose, including Br₂, NBS, ¹O₂ and *m*-CPBA.⁴³⁻⁴⁶



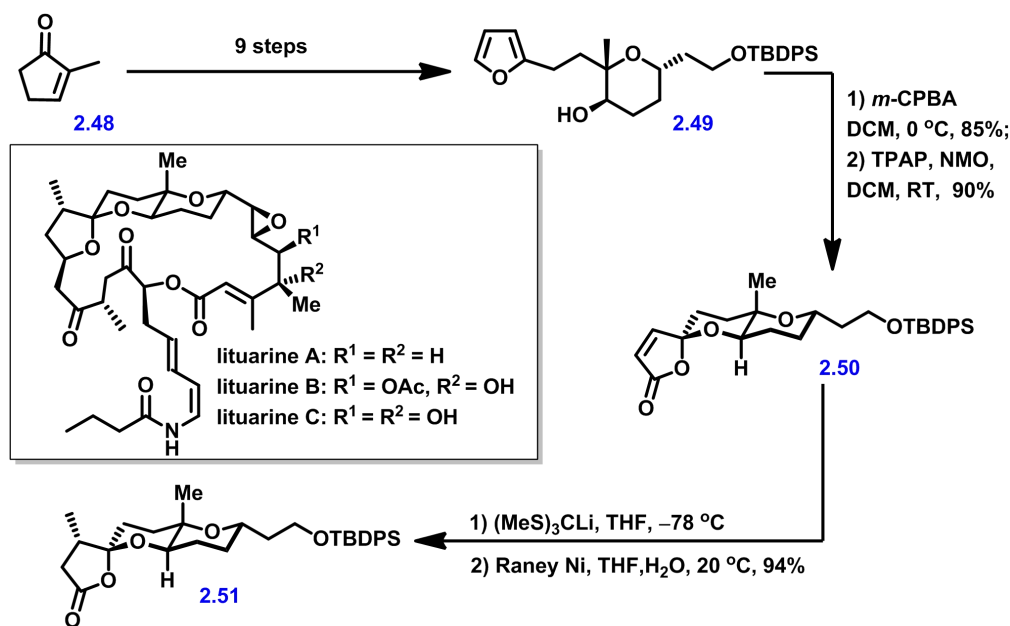
Scheme 11

The Robertson group demonstrated that *m*-CPBA oxidised δ -hydroxy alkyl furans as shown in Scheme 12; spirocyclisation proceeded smoothly in 82% yield and subsequent oxidation led to butenolide 2.47. Further investigation showed that this two-step sequence could be truncated into one step by using excess *m*-CPBA at a higher temperature (20 °C).⁴⁷



Scheme 12

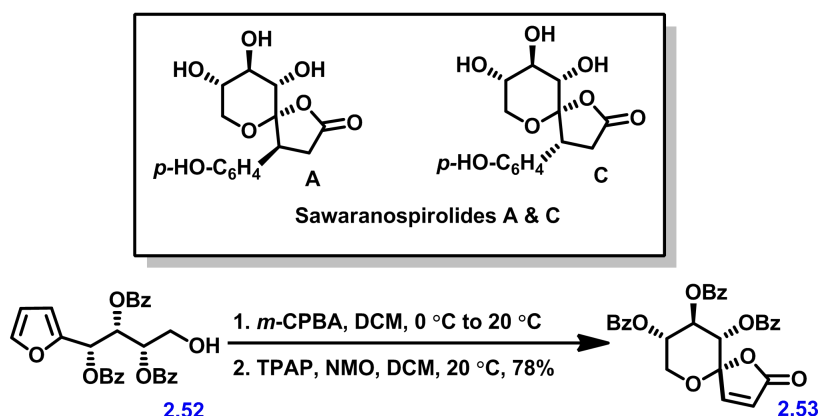
In Robertson's plan for the synthesis of lituarines A–C,⁴⁷ this oxidative cascade was utilised to synthesise the tricyclic core (**Scheme 13**). The functionalised 2(4-hydroxybutyl)furan precursor **2.49** was synthesised in 9 steps starting with asymmetric reduction of 2-methyl-cyclopentenone **2.48**. Spirocyclisation of **2.49** using *m*-CPBA, followed by a TPAP oxidation afforded spirobutenolide **2.50** in 90% yield. Further work⁴⁸ showed high *anti*-stereoselectivity, with respect to the tetrahydropyran ring oxygen, for the conjugate addition of tris(methylthio)methyl lithium as a methyl equivalent.



Scheme 13

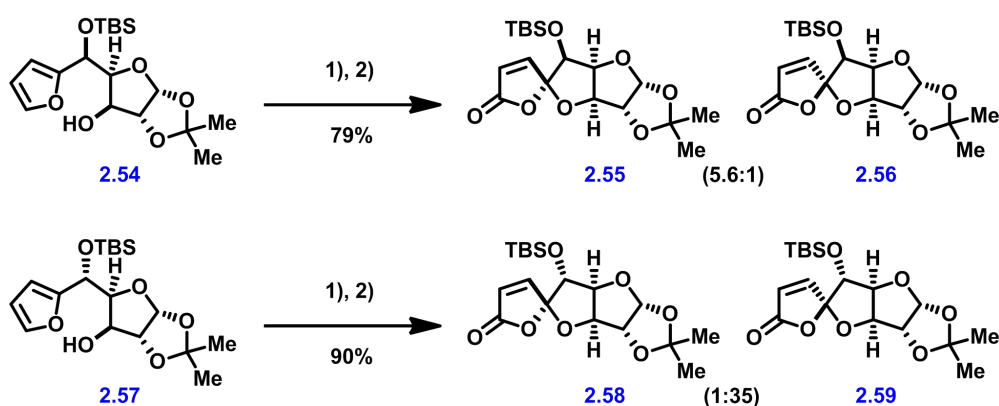
The *m*-CPBA-mediated cyclisation was also applied to other natural product syntheses within the Robertson group. Sawaranospirolides A and C⁴⁹ were isolated from the acetone-soluble components of the heartwood of the Japanese tree 'Sawara', *Chamaecyparis pisifera*. The synthetic approach towards the sawaranospirolides included an *m*-CPBA

oxidation of intermediate **2.52**, followed by a TPAP oxidation (Scheme 14).



Scheme 14

Similarly, in a synthesis of four analogues of pyrenolide D,⁵⁰ *m*-CPBA oxidation of **2.54** and **2.57** and subsequent PDC oxidation gave a pair of diastereomers, *e.g.* **2.55** and **2.56**, in each case. NOE studies showed that in the major diastereomer of each pair, the butenolide ring oxygen possessed an *anti*-relationship with respect to the TBS-protected hydroxy group (Scheme 15).

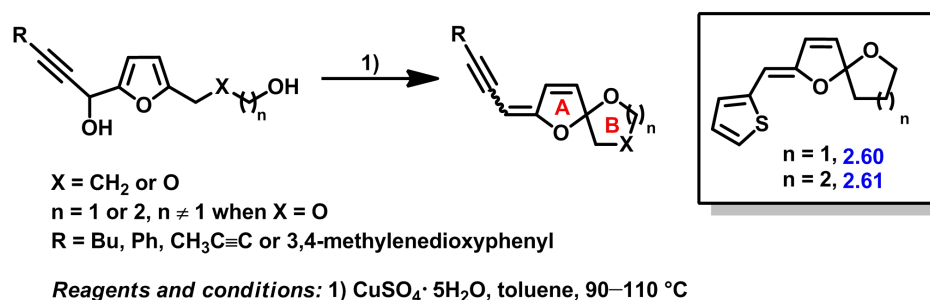


Reagents and conditions: 1) *m*-CPBA, DCM; 2) PDC, 4 Å MS, DMF.

Scheme 15

Non-oxidative spirocyclisation of furan derivatives

In a separate work, Wu¹⁶ developed a non-oxidative, Lewis acid-catalysed process to synthesise spirocyclic enol ethers. Cyclisation and dehydration were achieved in a single step using CuSO₄ at high temperature (90–110 °C). Wu also applied this method in the synthesis of thiophenyl tonghaosu variants, such as **2.60** and **2.61**²² (Scheme 16).

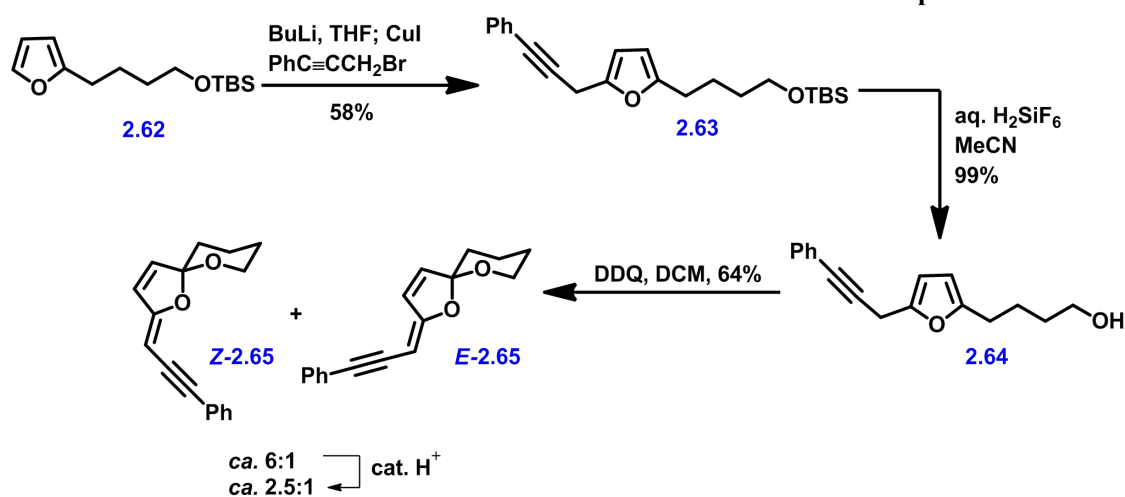


Scheme 16

2.5.2 Synthetic efforts in the Robertson group towards the unnamed natural product isolated from *Chrysanthemum boreale*

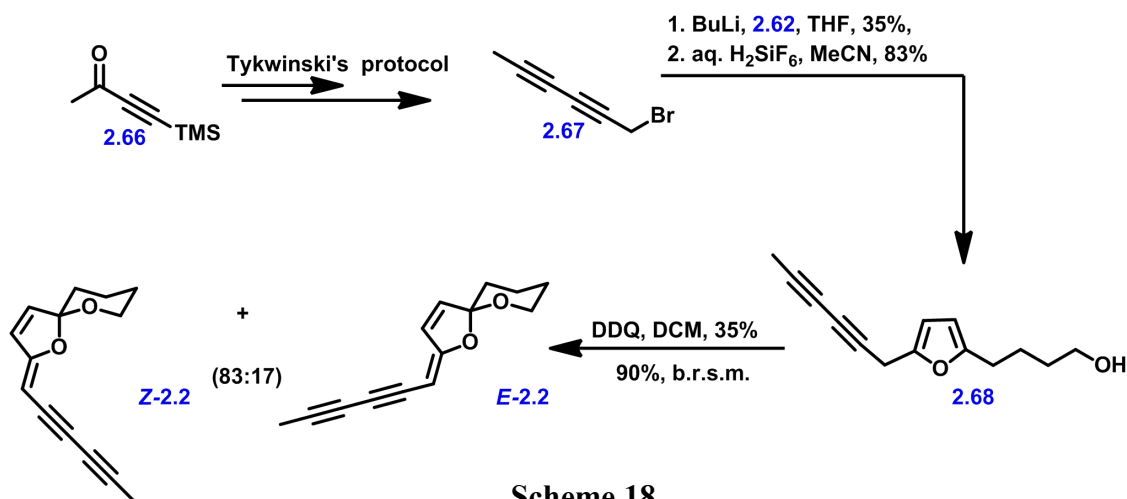
Single electron transfer spirocyclisation approach (cf. page 71)

Before testing that the penta-1,3-diynyl side-chain is a suitable radical stabilising substituent for the DDQ mediated cyclisation, a model system was investigated. TBS-protected cyclisation precursor **2.64** was prepared efficiently from furan derivative **2.62** through a short synthesis (Scheme 17).³⁰ Under the optimised conditions using DDQ as oxidant, precursor **2.64** was converted to spirocycle **2.65** in an *E/Z* ratio of *ca.* 1:6. Prolonged exposure of **2.65** to a catalytic amount of CSA in CDCl₃ led to *E/Z* equilibration to a final ratio of *ca.* 1:2.5.



Scheme 17

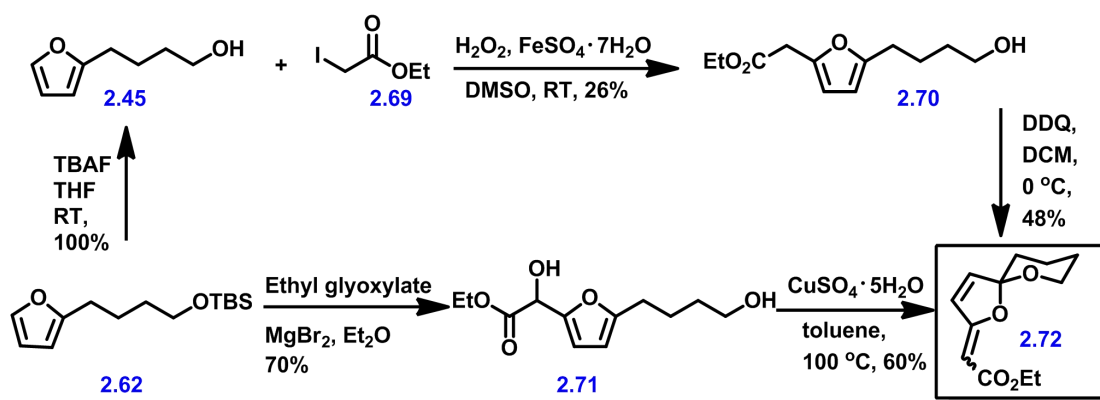
With this positive result that the *Z*-configured isomer could be synthesised selectively, the bis(acetylene) side-chain of precursor **2.68** was synthesised by applying Tykwinski's protocol.⁵¹ Bromide **2.67** was coupled with furan **2.62**, then DDQ oxidative cyclisation afforded 'homo-tonghaosu' **2.2** as a mixture of *E*/*Z* isomers (17:83). Exposure of this mixture to catalytic CSA led to a 1:1 *E*/*Z* ratio after a few days³⁰ (Scheme 18).



Scheme 18

It was expected that the exocyclic double bond in **2.2** would be more electron rich than the endocyclic double bond and hence more prone to oxidation. In order to de-tune the electronic properties of the exocyclic double bond, another spriocyclisation precursor **2.70** was

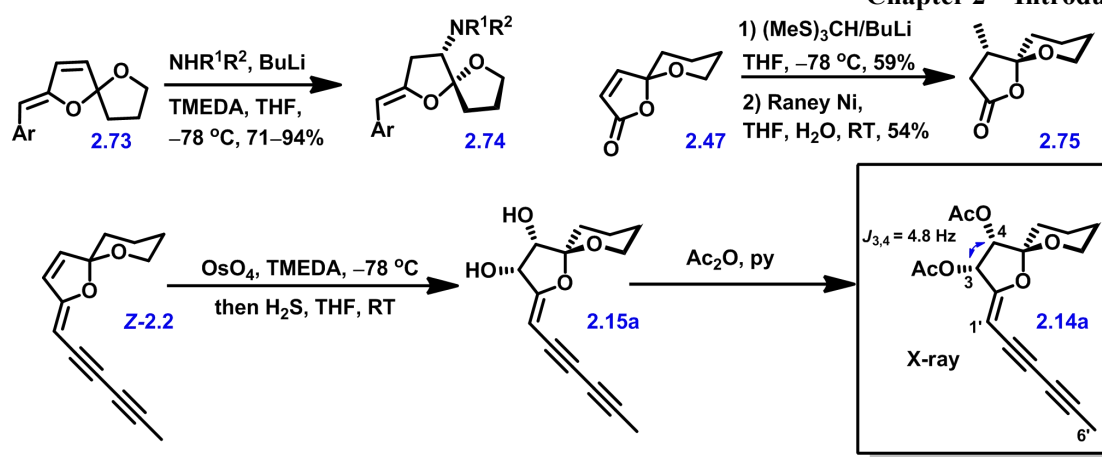
prepared. Using Bacchiocci's protocol⁵² as a key step, precursor **2.70** was prepared by a two-step synthesis. Treating **2.70** with DDQ afforded the desired ring system (**Scheme 19**) but in low overall yield (*ca.* 13% yield for 2 steps). In order to address the low yield in synthesising spirocycle **2.72**, Wu's protocol was applied (*cf.* page 76), which allowed a more efficient 2-step synthesis of spirocycle **2.72** for further investigations (**Scheme 21**).



Scheme 19

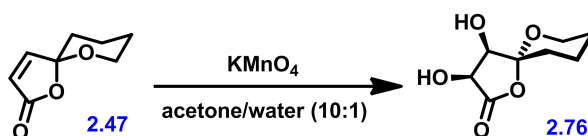
Although the exocyclic double bond is generally more reactive towards oxidation, there is precedent for an increased reactivity of the endocyclic double.⁵ For example, tonghaosu analogues can be hydroaminated in a highly regio- and diastereoselective manner^{53, 54} (**Scheme 20**). The authors attributed the observed high level of *syn*-diastereoselectivity with respect to the THP oxygen to chelation control of the THP oxygen. In contrast, the Robertson group found high *anti*-selectivity during the conjugate addition of carbon nucleophiles to butenolide **2.47** (**Scheme 20**).⁴⁸ To ascertain the sense of diastereoselectivity of dihydroxylation on the endocyclic double bond, the corresponding diol was synthesised. After acetylation, X-ray analysis of **2.14a**ⁿ revealed an *anti*-relationship of the diol relative to the THP oxygen (**Scheme 20**).³⁰

ⁿ Compound numbers followed with **a** possess *anti*- stereochemistry between the THP oxygen and the neighbouring functionality in the THF ring, in this case the C(4)OAc group.



Scheme 20

Similarly, butenolide **2.47** bearing a deactivated olefin was dihydroxylated with KMnO_4 to give diol **2.76** as a single diastereomer with an *anti*-relationship with respect to the THP oxygen, again, confirmed by X-ray analysis (Scheme 21).⁵⁵



Scheme 21

The synthesis of **2.14a** revealed significant chemical shift deviations in the NMR spectrum between the synthesised compound and the natural product (Scheme 20, Table 1).

Position	Reported data ^a	Data obtained ^b	δ Difference (ppm)
H-3	6.07 (dd, J 7.5, 2.0)	5.82 (dd, J 4.7, 1.8)	-0.25
H-4	4.99 (d, J 7.5)	4.98 (d, J 4.7)	-0.01
H-1'	5.03 (dq, J 2.0, 1.0)	4.42 (app.s)	-0.61
H-6'	1.97 (d, J 1.0)	1.98 (s)	+0.01

Table 1

The most notable difference is the coupling constant between H(3) and H(4). In the synthesised compound, the J value was 4.8 ± 0.2 Hz (in CDCl_3 , C_6D_6 , and CCl_4) whereas the

^a Data obtained from CCl_4 .

reported coupling constant was 7.5 Hz in CCl₄. This deviation could mean that the natural product possesses the opposite configuration at the spirocentre,⁵⁶ but a difference of this magnitude more likely indicates that the natural product possesses a *trans*-diacetate.

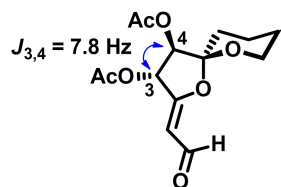


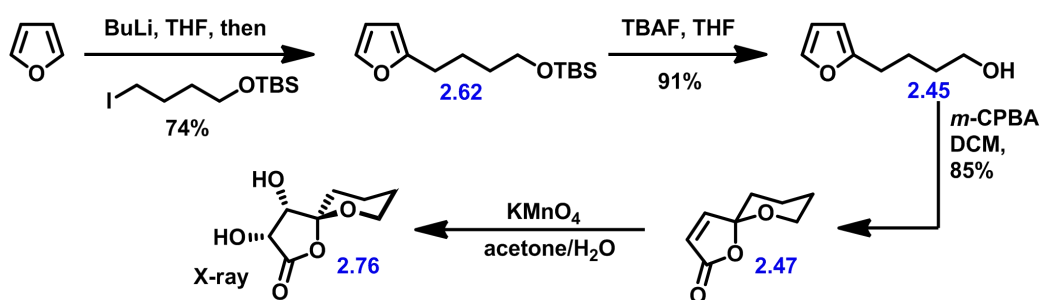
Figure 5

Indeed, the corresponding coupling constant reported for a similar *trans*-diacetate²⁴ is 7.8 Hz (**Figure 5**). Additionally, a *trans*-diacetate is more reasonable according to the proposed

biosynthetic pathway which involves nucleophilic attack on a corresponding 3,4-epoxide.¹¹⁻¹³

m-CPBA mediated spirocyclisation approach

The synthesis (**Scheme 22**) commenced with the alkylation of furan; subsequent deprotection furnished precursor **2.45** in 67% yield over 2 steps. Oxidation of **2.45** with *m*-CPBA gave butenolide **2.47** which was then dihydroxylated with *anti*-selectivity relative to the THP oxygen as shown by X-ray crystallography (**Scheme 22**).

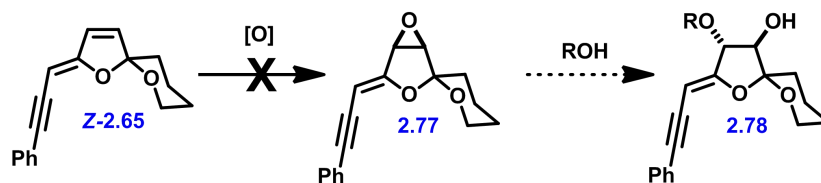


Scheme 22

2.5.3 Attempts to introduce a *trans*-diacetate

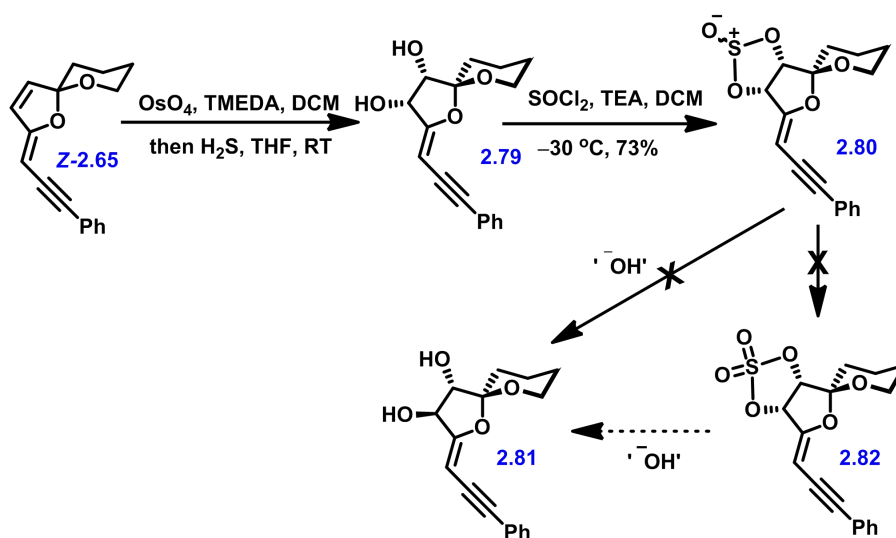
The original plan to introduce the *trans*-diacetate was based on its proposed biosynthesis, *i.e.* nucleophilic ring-opening of the epoxide (**Scheme 23**). Numerous efforts had been made in the Robertson group to conduct the epoxidation of the endocyclic double bond in ‘tonghaosu’

analogue **Z-2.65**. However, all attempts were unsuccessful, all tested reagents either reacting preferentially at the exocyclic double bond or giving starting material only⁵⁷ (**Scheme 23**).



Scheme 23

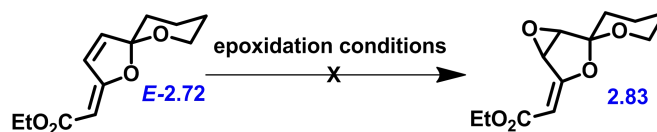
An alternative strategy was to take advantage of the successful dihydroxylation of the endocyclic double, giving *cis*-diol **2.79**. Conversion of diol **2.79** into cyclic sulfite **2.80** would allow opening by nucleophilic attack.⁵⁸ However, all attempts again proved to be unsuccessful (**Scheme 24**). Further attempts using cyclic sulfates, which are more susceptible to nucleophilic attack than corresponding sulfites,⁵⁹ failed because sulfite **2.80** was reluctant to react cleanly under ruthenium-catalysed oxidation⁶⁰ (**Scheme 24**).



Scheme 24

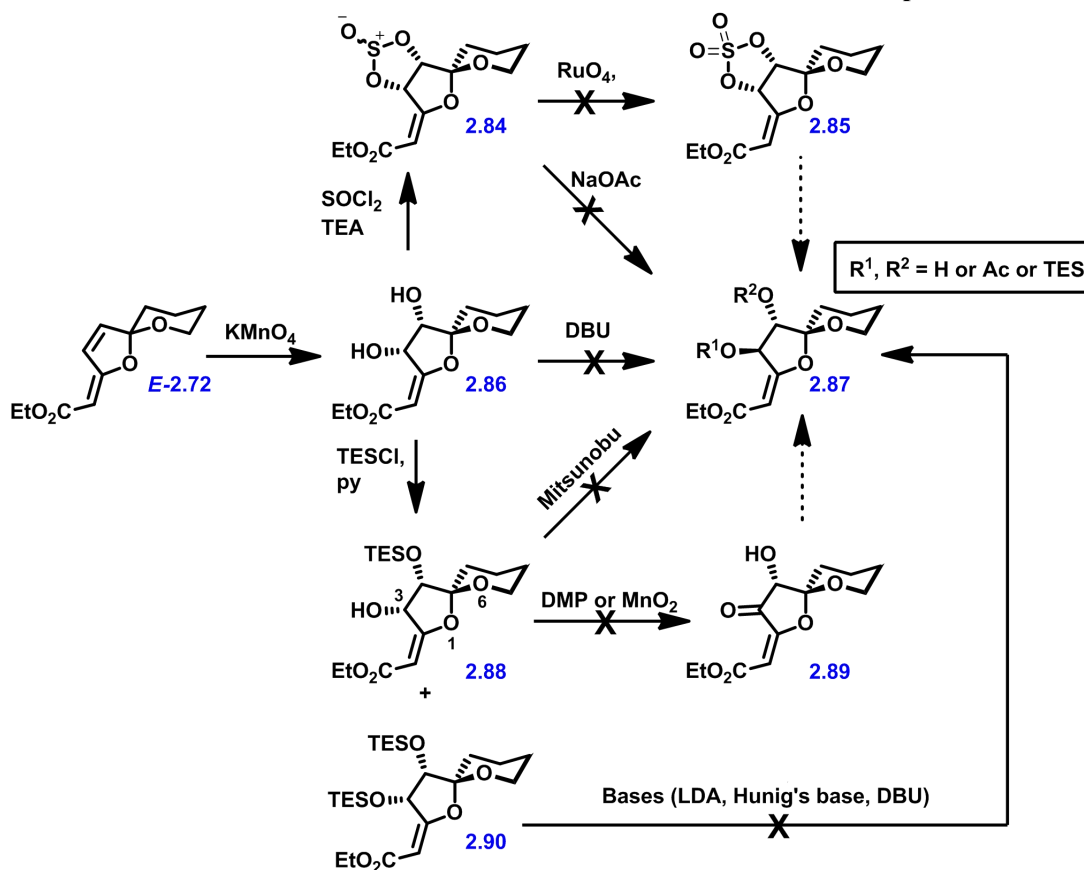
In order to address the problem of reactivity of the exocyclic olefin, ester **2.72** was synthesised (*cf.* page 78). However, when epoxidation reactions⁵⁵ were attempted on **E-2.72**,

no reaction was observed. (Scheme 25).



Scheme 25

Dihydroxylation of **E-2.72** led to diol **2.86** which was then subjected to a range of transformations aiming to provide *trans*-diol derivative **2.87**. Attempted ring opening of cyclic sulfite **2.84** with NaOAc⁵⁸ only resulted in recovery of starting material;⁵⁵ the oxidation of cyclic sulfite **2.84** to cyclic sulfate **2.85** led to over-oxidation at the exocyclic double bond; Mitsunobu conditions⁶¹ were next scrutinised to try to invert the C(3) hydroxyl on the mono-silylated alcohol **2.88**, but no reaction was observed;⁵⁵ and base mediated epimerisation of bis-silylated diol **2.90** resulted in either decomposition or gave only starting material.⁵⁵ It was envisaged that stereoselective reduction of ketone **2.89** would install the *trans*- diol motif in the spirocycle but oxidation of **2.88** using Dess–Martin periodinane or MnO₂ led to decomposition⁵⁵ (Scheme 26).



Scheme 26

2.6 Aim of project

The aim of this project was to build on previous work and prepare either or both of the two diastereomers of *trans*-diacetate **2.91** or **2.92** (Figure 6). Completion of the synthesis and comparison of analytical data should reveal the identity of the natural product.

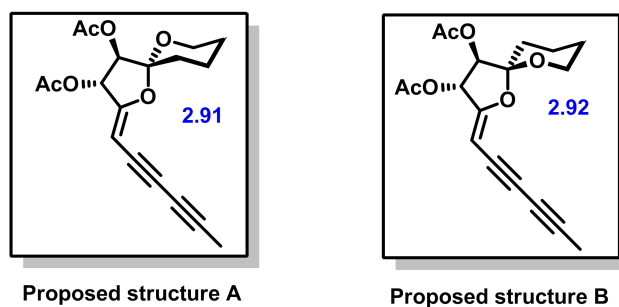
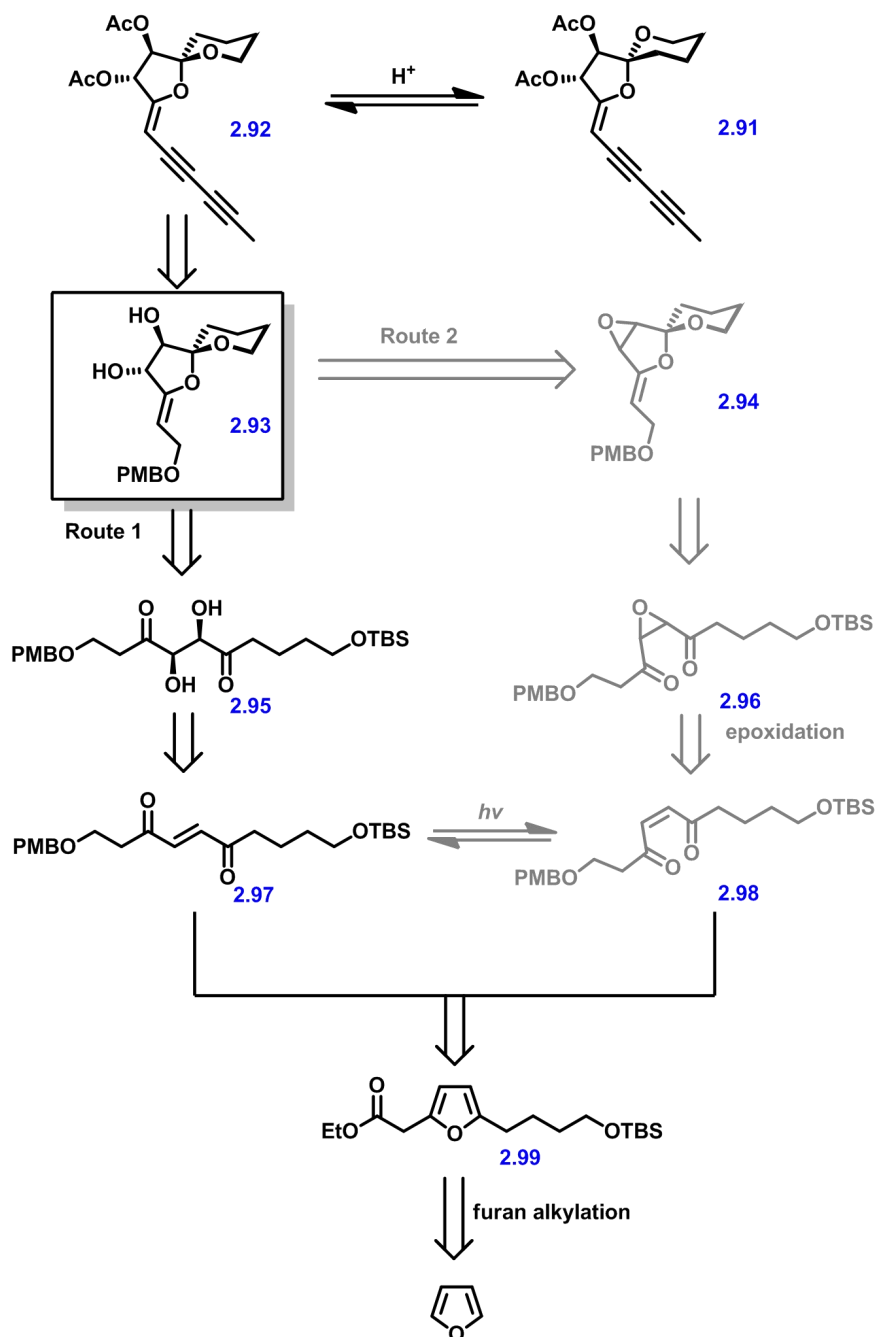


Figure 6

2.7. Results and discussion

2.7.1 Retrosynthetic analysis towards product 2.91 and 2.92

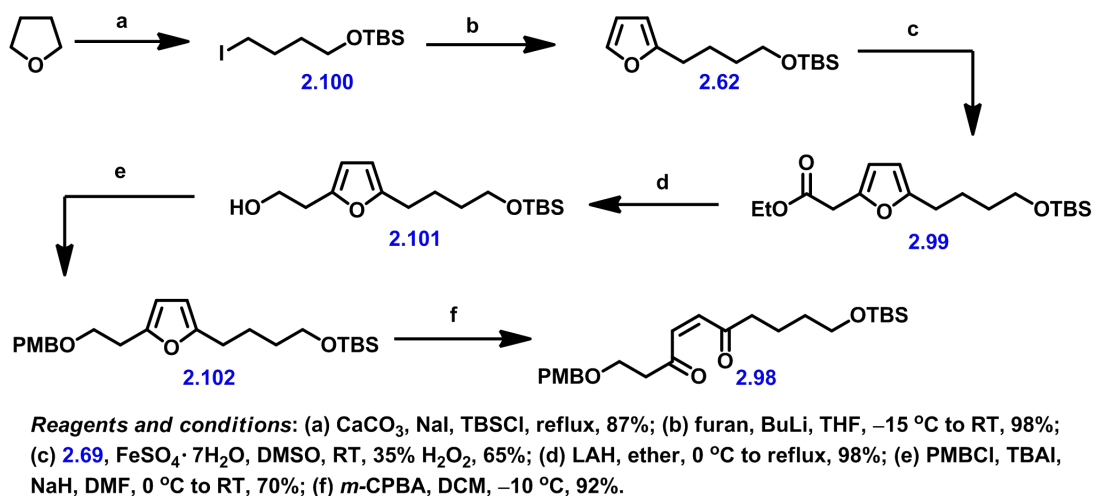


Scheme 27

Two initial strategies were outlined for the synthesis of **2.91** and **2.92** (Scheme 27). It was envisaged that enediones **2.97** and **2.98** would be the key intermediates for either dihydroxylation or epoxidation prior to spirocyclisation of **2.95** or **2.96**.

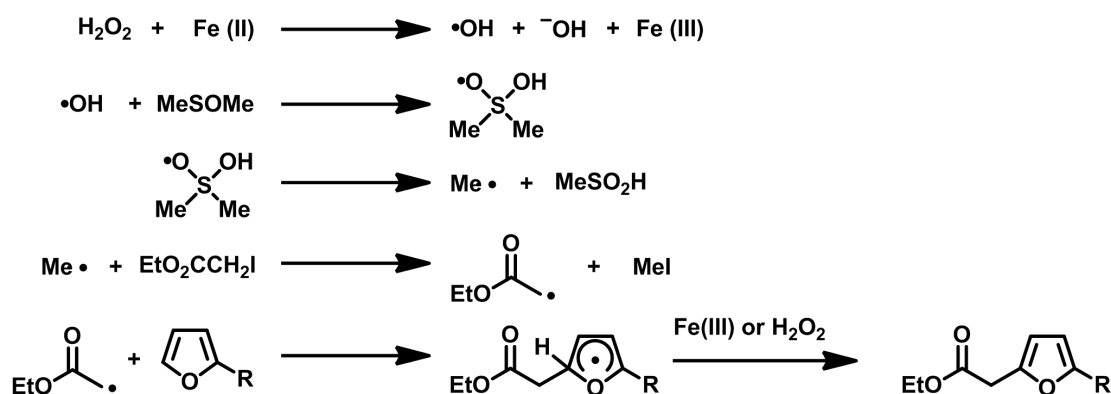
Thus, either dihydroxylation of *E*- enedione **2.97** (Route 1) or epoxidation of its *Z*-isomer **2.98** (Route 2) could lead to the key spirocycle **2.93** after elaboration. Further side-chain elongation and final acetylation would lead to the desired *trans*-diacetates **2.91** and **2.92** (Scheme 27).

2.7.2 Attempt towards *Z*-enedione 2.98



Scheme 28

The synthesis commenced with furan alkylation with iodide **2.100**, which was prepared in 87% yield by ring-opening of THF (Scheme 28). Radical coupling under Baciocchi's⁵² conditions afforded disubstituted furan **2.99** in 65% yield.



Scheme 29

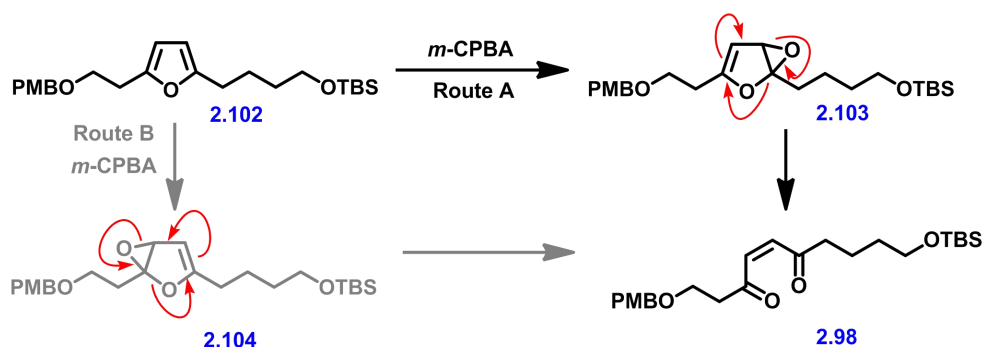
The proposed mechanism for this reaction is summarised in **Scheme 29**. When this reaction was initially applied, a low yield (28%) of the desired product **2.99** was obtained (**Entry 1, Table 2**), as had been found in the Robertson group by Smith.⁶⁰ A range of conditions were screened in order to try to increase the reaction efficiency and understand the reason for the low yield (**Table 2**):

Entry	SM Conc. (M)	t (h)	Open air? (Y/N)	Yield (%)	TBS deprotection (%)
1	0.03	1	N	28	30
2	0.03	0.5	N	65	8
3	0.15	1	N	40	13
4	0.15	0.5	N	44	10
5	0.15	0.5	Y	4	11

Table 2

The main side reaction in this process was TBS deprotection. When the pH was monitored, a decrease in pH from 6 to 4 was observed over the course of the reaction; therefore, the reaction time was reduced, thus affording a much improved 65% yield (**Entry 2, Table 2**). Furthermore, a higher concentration of starting material **2.62** was found to be beneficial (**Entry 3, Table 2**) and when the reaction was open to air (**Entry 5, Table 2**), a significant drop of yield to only 4% was observed.

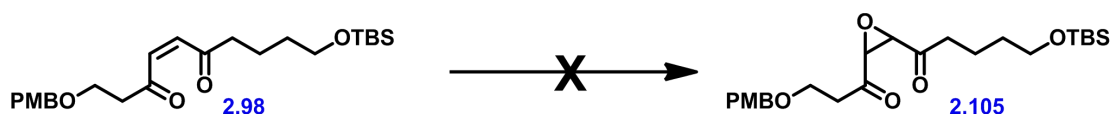
LAH reduction of disubstituted furan **2.99** and subsequent PMB protection furnished substrate **2.102**, which was subjected to the *m*-CPBA mediated oxidation, resulting in *Z*-enedione **2.98** in 92% yield (Scheme 28) through the process mentioned earlier (Scheme 30).



Scheme 30

2.7.3 Attempts to epoxidise *Z*-enedione **2.98**

Having obtained *Z*-enedione **2.98**, the key epoxidation reaction was investigated. Despite few precedents for the epoxidation of enediones,⁶²⁻⁶⁵ four conditions were examined on enedione **2.98** (Scheme 31, Table 3) but none of these delivered the desired product.

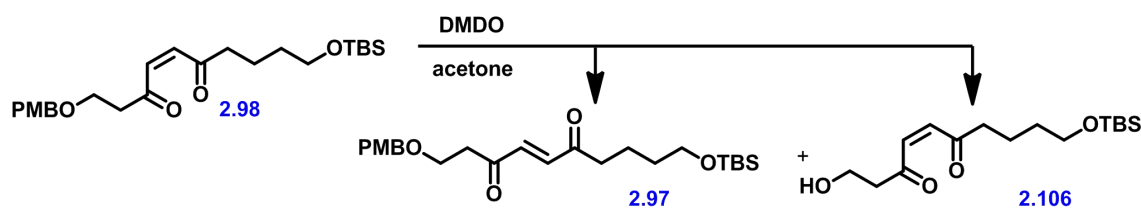


Scheme 31

Entry	Conditions	Result
1	<i>m</i> -CPBA, DCM, RT	NR
2	DMDO, acetone, 0 °C	see text
3	Mo(O ₂) ₂ O·H ₂ O·HMPA, DCM, RT	decomposition
4	H ₂ O ₂ , TBAI (cat.), THF, 0 °C to RT	NR

Table 3

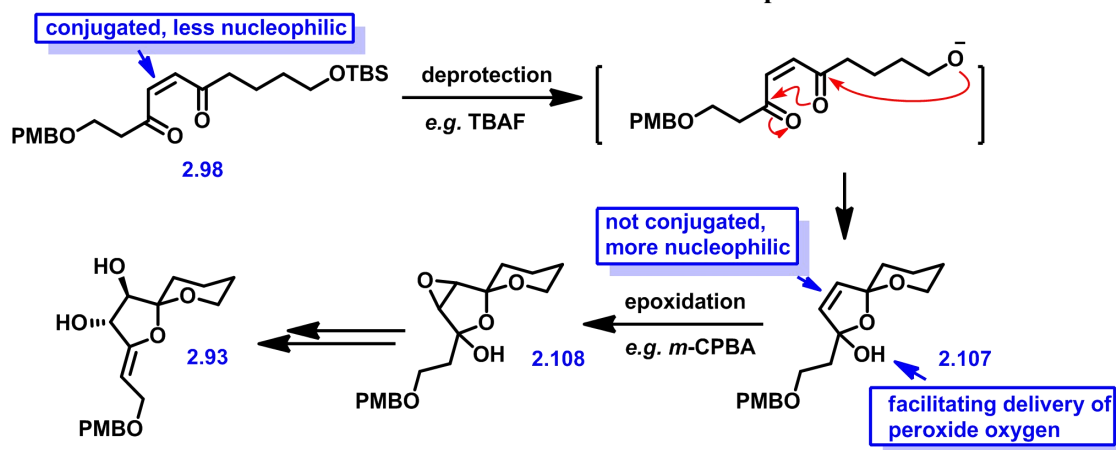
Although notprecedented, a large excess of *m*-CPBA was used in the hope that the excess reagent could effect the epoxidation in the same reaction as the furan oxidation. However, when disubstituted furan **2.102** was treated with excess *m*-CPBA, enedione **2.98** was the only isolated product (**Entry 1, Table 3**). Use of DMDO⁶⁶ led to isomerisation of the double bond and deprotection of the PMB group (**Entry 2, Table 3, Scheme 32**).



Scheme 32

Sakamoto reported that molybdenum(VI) species were effective for enedione epoxidation⁶³ but when these conditions were applied to substrate **2.98**, only decomposition was observed. A final attempt with H₂O₂, and TBAI⁶² as a phase transfer catalyst (PTC), led only to the recovery of the starting material **2.98**.

Next, it was envisaged that if the epoxidation reaction was conducted on the cyclised compound **2.107**, the tertiary alcohol in **2.107** could facilitate the delivery of the oxidant *via* hydrogen-bonding; and more importantly, the C=C would not be conjugated and should therefore be much more nucleophilic compared to enedione **2.98** (**Scheme 33**).

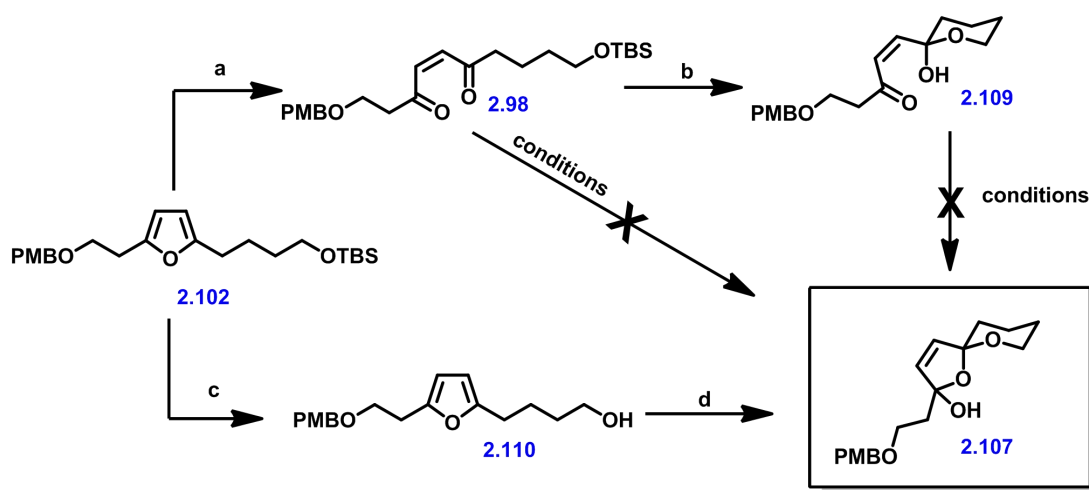


Scheme 33

Three different conditions were examined for spirocyclisation (**Scheme 34**, **Table 4**). TBAF removed the TBS group but only the mono-cyclisation product **2.109** was obtained (**Entry 1**, **Table 4**). Apparently, the basic conditions did not favour the formation of spirocycle **2.107**. Therefore, acid catalysis was attempted but with hemiketal **2.109**, *p*-TSA gave only recovered starting material, and CSA resulted in a complex product mixture.

Acidic deprotection conditions (**Entries 2, 3**, **Table 4**) resulted in decomposition. In summary, the stepwise furan oxidation–deprotection–cyclisation strategy did not deliver spirocycle **2.107**.

The synthetic sequence was then modified to allow a potential deprotection–furan oxidation–spirocyclisation strategy. In this variant, the free hydroxy group would trap the enedione *in situ* to give spirocycle **2.107**. Indeed, after TBS group removal by TBAF, spirocycle **2.107** was obtained in 96% yield after *m*-CPBA oxidation (**Scheme 34**).



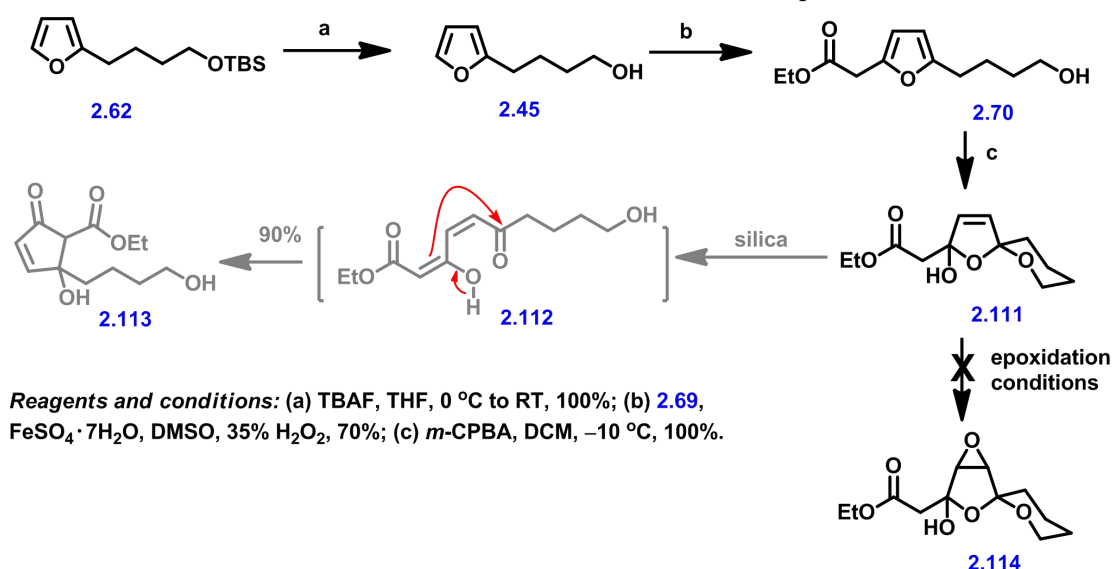
Reagents and conditions: (a) *m*-CPBA, DCM, $-10\text{ }^{\circ}\text{C}$, 92%; (b) TBAF, THF, $0\text{ }^{\circ}\text{C}$ to RT, 17%; (c) TBAF, THF, RT, 100%; (d) *m*-CPBA, DCM, $-10\text{ }^{\circ}\text{C}$, 96%.

Scheme 34

Entry	Conditions	Result
1	TBAF, THF, $0\text{ }^{\circ}\text{C}$ to RT	monocyclisation (5% yield)
2	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM, RT	decomposition
3	H_2SiF_6 , MeCN	decomposition

Table 4

To preserve the precious key intermediate **2.107** (Scheme 34), a model substrate for the epoxidation reaction was prepared from **2.62** (Scheme 35), again using the one-pot furan oxidation–spirocyclisation process. It is notable that under acidic conditions, such as exposure to silica gel, compound **2.111** unravelled and then underwent aldol reaction to afford cyclopentenone derivative **2.113**, indicated by a singlet at 3.46 ppm (1 H) in ^1H NMR spectrum.



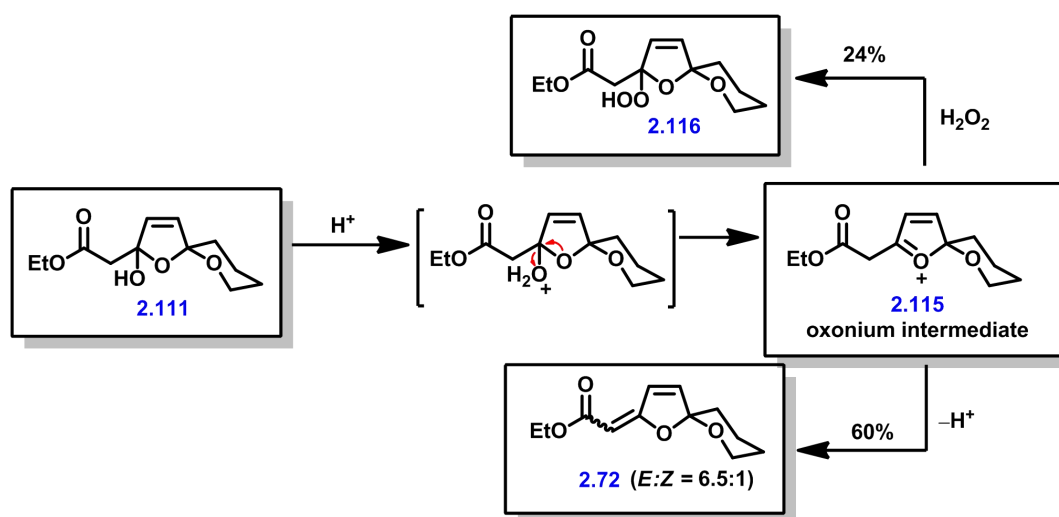
Scheme 35

As shown in **Table 5**, different epoxidation conditions were attempted on spirocycle **2.111**.

Entry	Conditions	Result
1	<i>m</i> -CPBA, DCM, RT	NR
2	<i>m</i> -CPBA, DCM, NaHCO_3 (solid), RT	NR
3	DMDO, acetone, 0 °C	Decomposition
4	35% H_2O_2 , TFAA, DCM, 0 °C to RT	see text

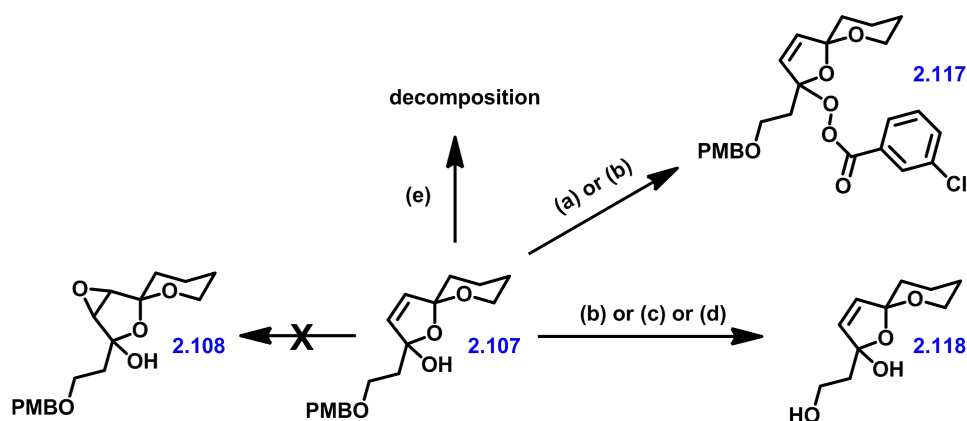
Table 5

Normal *m*-CPBA epoxidation conditions (**Entry 1, Table 5**) gave only starting material, and buffering with NaHCO_3 proved unfruitful (**Entry 2, Table 5**). Treating **2.111** with DMDO in acetone (**Entry 3, Table 5**) led to the formation of a complex mixture, and an attempt to use trifluoroperacetic acid led to either elimination ($\rightarrow$ **2.72**) or the introduction of a hydroperoxide group onto the THF ring *via* oxonium intermediate **2.115** (**Scheme 36**).



Scheme 36

Similarly, on the real system, a range of conditions (*m*-CPBA, DMDO, and *t*-BuOOH/ $VO(acac)_2$) led to no positive results (Scheme 37) and the epoxidation route was finally abandoned.

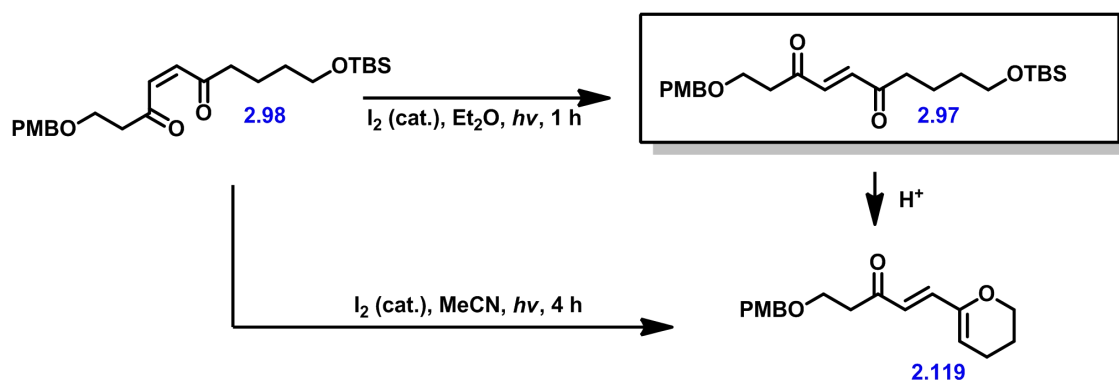


Reagents and conditions: (a) *m*-CPBA, DCM, 0 °C to reflux; (b) *m*-CPBA, DCM, $NaHCO_3$ (solid), RT; (c) *m*-CPBA, DCM, $NaHCO_3$ (solution), RT; (d) DMDO, acetone; (e) $VO(acac)_2$, *t*-BuOOH, DCM.

Scheme 37

2.7.4 Dihydroxylation attempts with *E*-enedione 2.97

Attention was then turned to the dihydroxylation of *E*-enedione **2.97**. To access *E*-enedione **2.97**, an isomerisation reaction was conducted by UV irradiation (Philips 300 W light bulb) with a catalytic amount of I_2 (Scheme 38, Table 6).



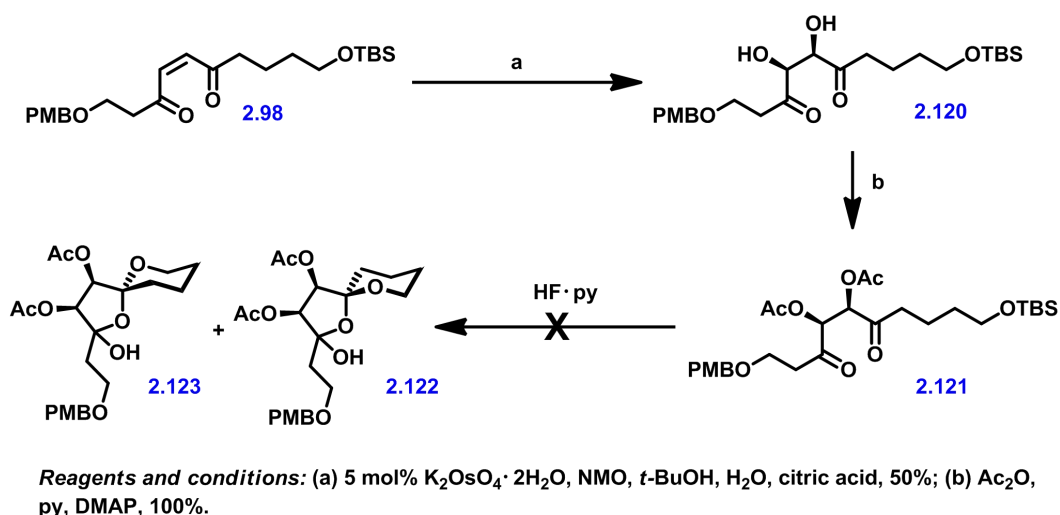
Scheme 38

Entry	Solvent	I_2 (mol%)	Distance	Time (h)	Conversion	Note
1	MeCN	5	45 cm	4	100%	only 2.119
2	Et_2O	2.5	45 cm	4	25%	no 2.119
3	Et_2O	2.5	30 cm	1	100%	only 2.97

Table 6

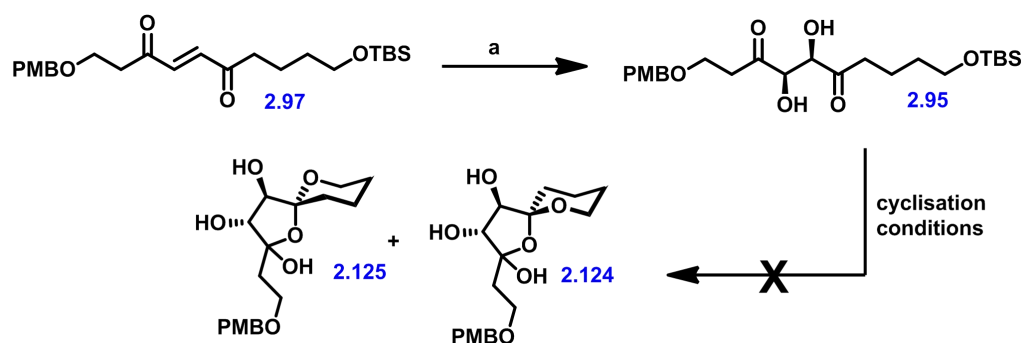
The polar aprotic solvent MeCN was first tested for the isomerisation (**Entry 1, Table 6**). It was found that in MeCN, TBS cleavage and subsequent cyclisation and dehydration competed to give compound **2.119** only. In ether (**Entries 2, 3, Table 6**), no side product **2.119** was observed and when the distance between the reaction flask and the light source was reduced to 30 cm, a quantitative conversion of *Z*-enedione **2.98** to its *E*-isomer **2.97** was achieved. Unsurprisingly, prolonged exposure of **2.97** to an acidic environment (*e.g.* silica gel) caused the conversion of **2.97** to **2.119**.

Before subjecting key intermediate **2.97** to further transformations, *Z*-enedione **2.98** was used as a model substrate to investigate the possibility of effecting dihydroxylation on the electron-deficient double bond.



Scheme 39

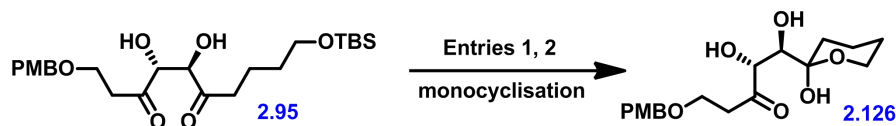
Taking advantage of Sharpless' acidic dihydroxylation conditions,⁶⁷ *Z*-enedione **2.98** was successfully dihydroxylated (**Scheme 39**) and double acylation of diol **2.120** was completed in good overall yield. Subsequent cyclisation, in principle, would give spirocycles **2.122** and **2.123** but treatment of **2.121** with HF·pyridine⁶⁸ led to the formation of a complex product mixture (**Scheme 39**). No further conditions were examined since by then most of the *Z*-enedione **2.98** had been converted to its *E*-isomer **2.97**. Attention was then turned to the dihydroxylation of *E*-enedione **2.97** and subsequent spirocyclisation.



Scheme 40

Again, application of Sharpless' conditions to alkene **2.97** gave a 50% yield of diol **2.95** after purification (**Scheme 40**). Having installed the diol with the correct relative configuration,

spirocyclisation was next examined. Three silyl group removal conditions were attempted but desired spirocycles **2.124** and **2.125** were not observed (Table 7, Scheme 41)

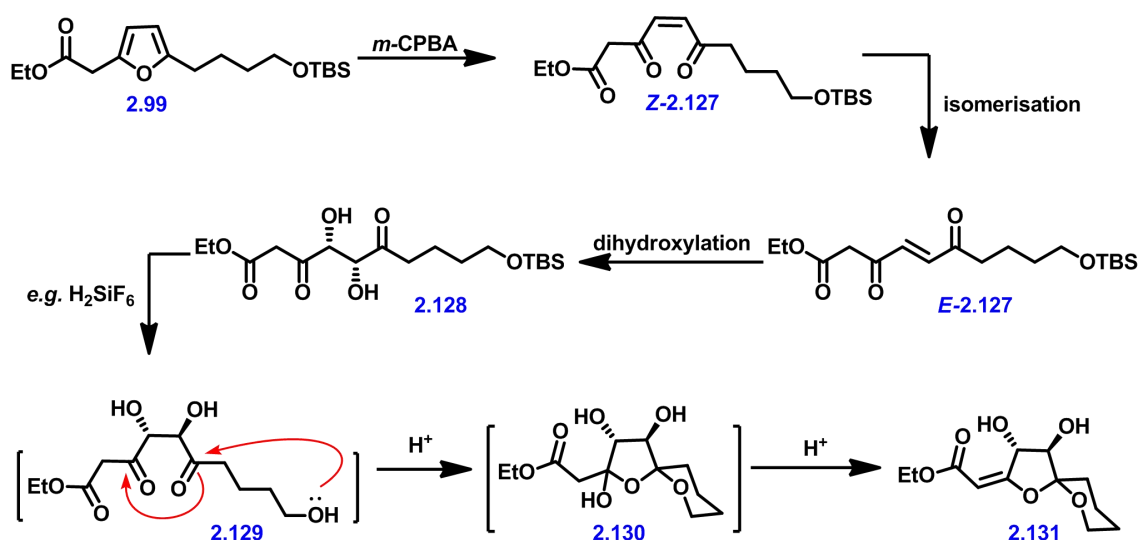


Scheme 41

Entry	Conditions	Result
1	H ₂ SiF ₆ , MeCN	monocyclisation observed ^p
2	HF·py, THF	monocyclisation observed ^c
3	BF ₃ ·Et ₂ O, DCM	decomposition

Table 7

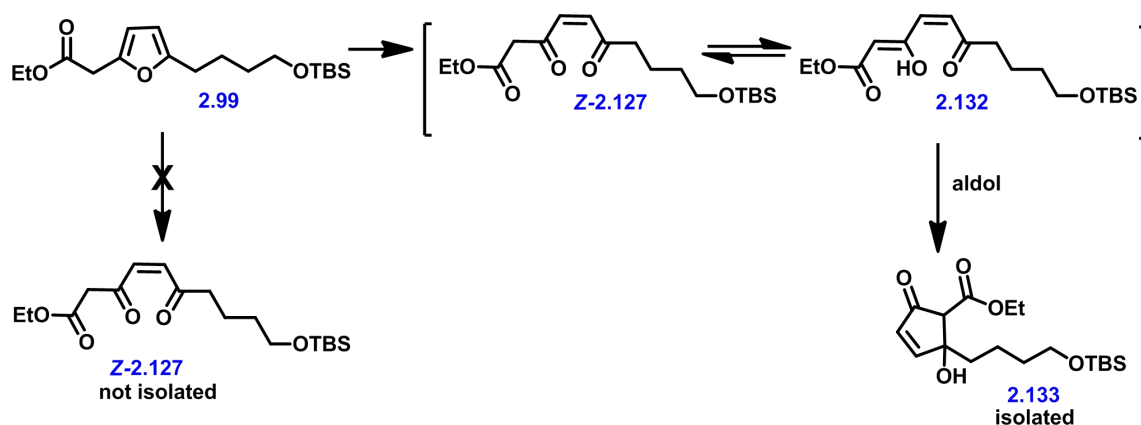
As indicated in Scheme 42, spirocyclisation was expected to be favoured with an ester group (CO₂Et) in place of the CH₂OPMB side-chain. Here, conjugation between the ester group and the double bond formed after dehydration would provide a thermodynamic sink to accumulate a spirocyclic product **2.131**. Indeed, if this idea was proven to be feasible, further investigation might lead to a cascade dihydroxylation, deprotection, spirocyclisation, and dehydration sequence in a single operation (Scheme 42).



Scheme 42

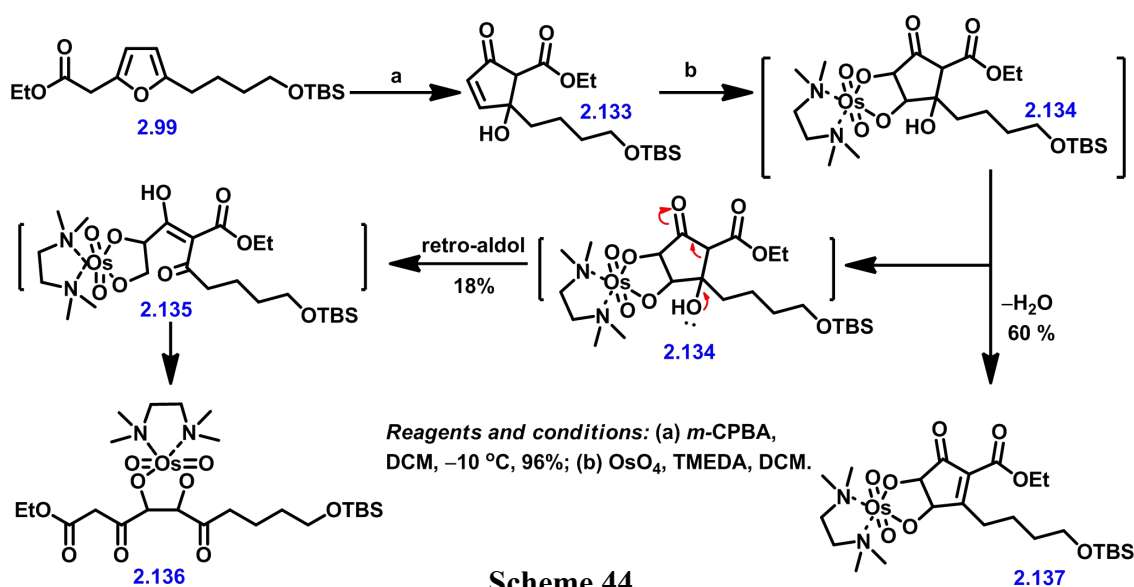
^p Indicated by ¹H NMR analysis of reaction mixture, compound **2.126** was not isolated.

It was found that when the furan oxidation was employed to prepare *Z*-enedione **Z-2.127** as a model substrate for dihydroxylation, spontaneous aldol reaction competed as before (*cf.* **Scheme 35**, page 91).



Scheme 43

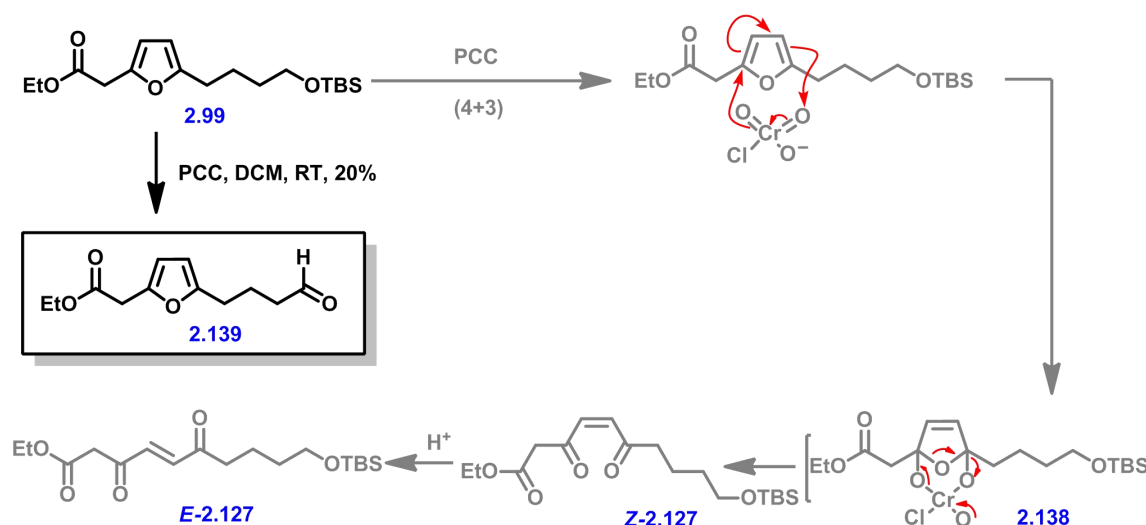
Two solutions were proposed to overcome this aldol reaction. First, if reaction conditions could be found to reverse the aldol cyclisation (retro-aldol process) then enedione **Z-2.127** could be dihydroxylated (**Scheme 44**). When this idea was examined by treating **2.133** with OsO_4 under basic conditions, 18% of the desired product **2.136** was isolated, together with 60% of osmate diester **2.137** (**Scheme 44**).



Scheme 44

This result was promising, but not helpful for the original goal of dihydroxylating the *E*-enedione **E-2.127**. Therefore, a strategy that afforded the *E* enedione **E-2.127** was sought since then aldol condensation could not occur.

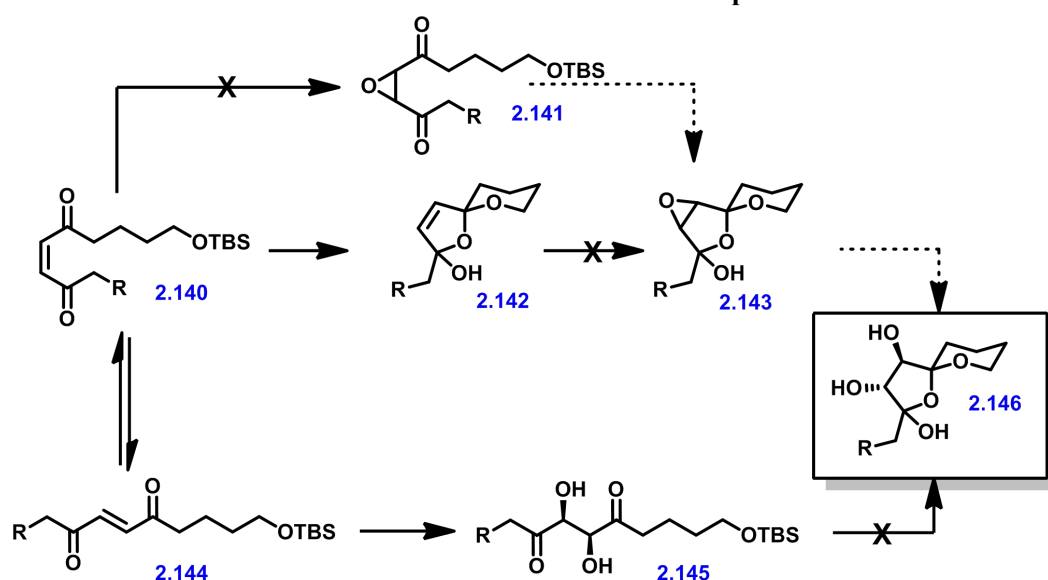
Piancatelli reported that PCC oxidation of furans can give *E*-enedione products.⁶⁹ The authors suggested that the reaction proceeds *via* a formal (4+3) adduct, such as **2.138** (Scheme 45), which then collapses to give the *Z*-enedione, such as **Z-2.127**. Then, under the mildly acidic conditions provided by PCC, the newly formed **Z-2.127** is then isomerised to its *E*-isomer **E-2.127**. When such conditions were tested, aldehyde **2.139** was isolated as the only product, the acidity of PCC leading to TBS deprotection and oxidation (Scheme 45).



Scheme 45

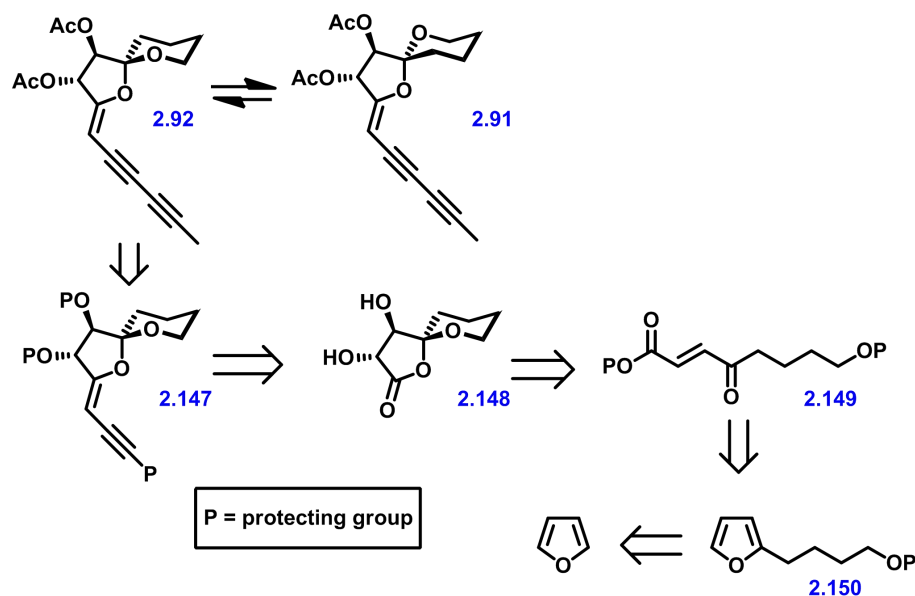
2.7.5. Towards γ -lactone *via* spirocyclisation

This work raised fundamental problems with the synthesis of intermediate **2.146** (Scheme 46). For the spirocycles derived from *Z*-enediones, attempted epoxidations were unsuccessful; however, whilst *E*-enediones could be successfully dihydroxylated, the corresponding diols could not be induced to undergo spirocyclisation (Scheme 46).



Scheme 46

As mentioned earlier, much fruitless effort had been expended to epoxidise spirocyclic systems^{55, 57, 60} but the key dihydroxylation step was found to be feasible, and therefore a modified retrosynthetic strategy was developed to make the 2nd cyclisation step irreversible in order to fix the spirocyclic structure (**Scheme 47**).

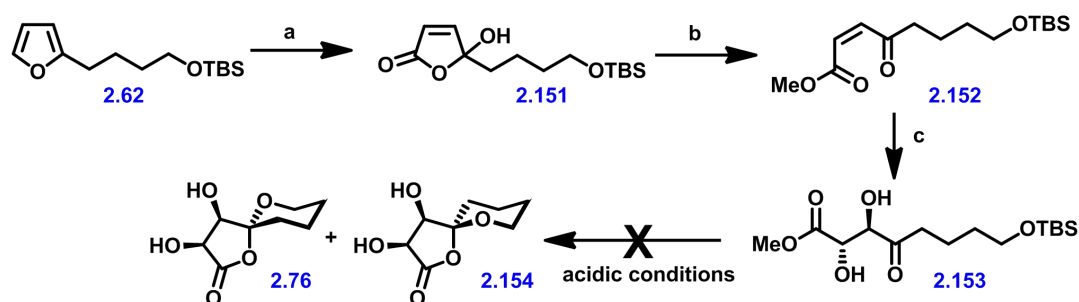


Scheme 47

In this modified scheme, γ -lactone **2.148** was identified as the key intermediate, and this would be synthesised from a γ -keto- α,β -unsaturated ester **2.149** by employing Sharpless' protocol⁶⁷ followed by spirocyclisation under appropriate conditions. The ester would in turn

derive from substituted furan **2.150**.

The new route began with oxidation of substituted furan **2.62** (**Scheme 48**), and butenolide **2.151** was prepared in 98% yield using Salomon's protocol.⁷⁰

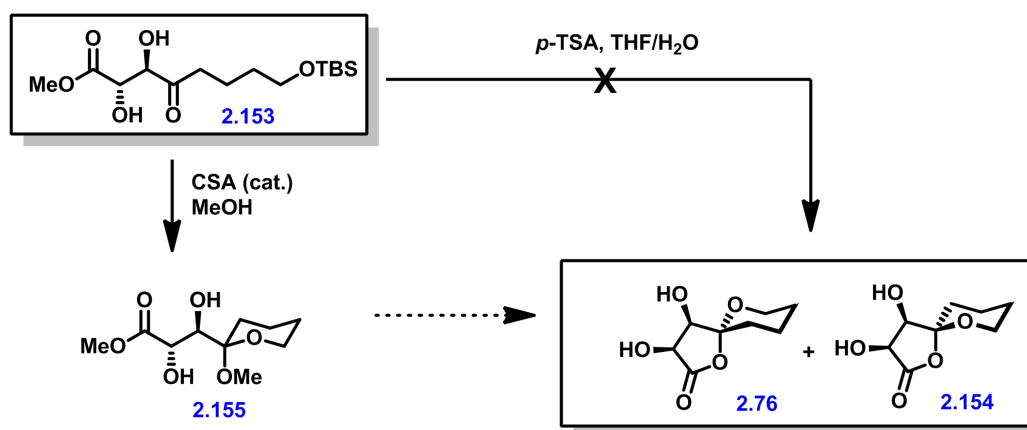


Reagents and conditions: (a) NaClO_2 , NaH_2PO_4 , *t*-BuOH, H_2O , RT, 98%; (b) Cs_2CO_3 , MeI, DMF, 67%; (c) $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, citric acid, NMO, *t*-BuOH, H_2O , RT, 61%.

Scheme 48

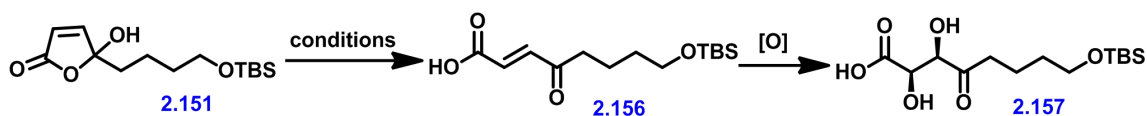
Problems were encountered during the purification of butenolide **2.151** as this compound showed a strong tailing effect on silica, which hindered the purification of **2.151** from the baseline contaminants. However, simply by adding 1% acetic acid to the eluent (petrol/ether 80:20), the desired product could be easily purified using conventional silica gel chromatography.

Esterification of **2.151** was achieved by methylation under basic conditions, and subsequent dihydroxylation was successful using Sharpless' protocol. Cyclisation attempts were unsuccessful under acidic conditions (**Scheme 49**); ^1H NMR analysis of the reaction mixture showed that CSA gave monocyclised product **2.155**, and the *p*-TSA conditions were inconclusive. No further attempts were made to convert **2.153** into the desired products **2.76** or **2.154**.



Scheme 49

Since hydroxy *ester* **2.153** was reluctant to cyclise, it was envisaged that the *acid* would be a better substrate for the spirocyclisation reaction. Thus, dihydroxylation was to be attempted on *E*-unsaturated acid **2.156** (Scheme 50).



Scheme 50

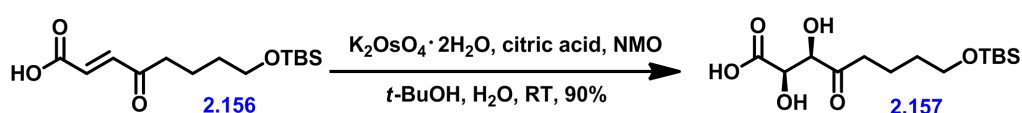
Acid **2.156** was prepared *via* double bond isomerisation of butenolide **2.151** under nucleophilic catalysis. A range of isomerisation conditions were examined during optimisation (Scheme 50, Table 8).

Entry	Catalyst	Catalyst loading (mol%)	T (°C)	t (h)	Substrate concentration	Conversion ^q (%)
1	pyridine	1	RT	2	1 M	40
2	pyridine	1	RT	2	5 M	90
3	pyridine	1	40	2	1 M	85
4	pyridine	5	RT	2	1 M	87
5	pyridine	10	RT	2	1 M	90
6	DMAP	1	RT	2	5 M	0

Table 8

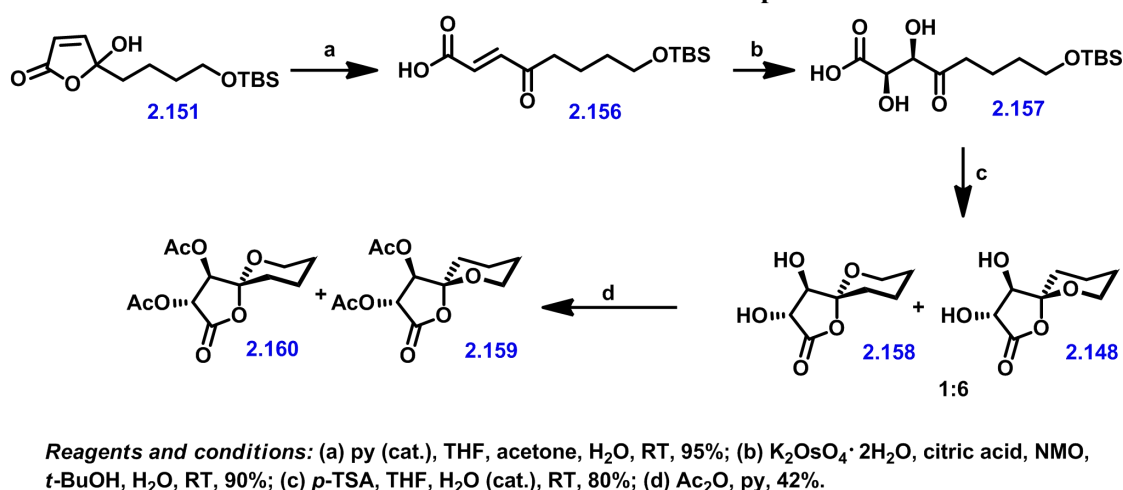
^q Determined by ¹H NMR of reaction mixture.

Treatment of butenolide **2.151** with 1 mol% pyridine led to 40% of isomerisation (**Entry 1, Table 8**). It was found that higher conversion could be achieved either by increasing the substrate concentration (**Entry 2, Table 8**) or elevating the temperature (**Entry 3, Table 8**). Increasing the catalyst loading also led to higher conversion (**Entries 4, 5, Table 8**). Although DMAP is more nucleophilic than pyridine, no conversion was observed with this catalyst (**Entry 6, Table 8**). In practice, 1 mol% pyridine under a relatively high substrate concentration (5 M) was chosen to prepare **2.156** on gram-scale. Pleasingly, a 90% yield of dihydroxy acid **2.157** was obtained by Sharpless' protocol⁶⁷ which would then be subjected to spirocyclisation (**Scheme 51**).



Scheme 51

The purity of dihydroxy acid **2.157** was found to have a profound effect on the spirocyclisation process. Excess NMO and its related by-products such as NMM that could destroy the acidic environment in the spirocyclisation step had to be avoided to synthesise spirolactones **2.158** and **2.148** (**Scheme 52**) successfully. By applying conventional silica gel chromatography with 3% acetic acid in the eluent (methanol/DCM, 10:90), dihydroxy acid **2.157**, pure by NMR, could be obtained reliably. Spirocycle formation was found to be successful by utilising 20 mol% *p*-TSA in THF/ H_2O . Through this route, the desired lactone with correct stereochemistry installed was finally prepared as a mixture of two inseparable isomers **2.158** and **2.148** in a diastereomeric ratio of approximately 1:6.



Scheme 52

Having the spirocycles in hand, it was interesting to examine the proton J value between H(3) and H(4) of **2.159** and **2.160** even without the bis(acetylene) side-chain attached. Double acylation was conducted in an unoptimised 42% yield. The $J_{3,4}$ values for each diastereomer was large in both cases, 9.1 Hz and 6.4 Hz (**Figure 7**). This result was promising since the J values were significantly larger than 4.8 ± 0.2 Hz for *cis*-diacetate **2.14a**, which had been synthesised previously in the Robertson group (*cf.* **Scheme 20**, page 79).

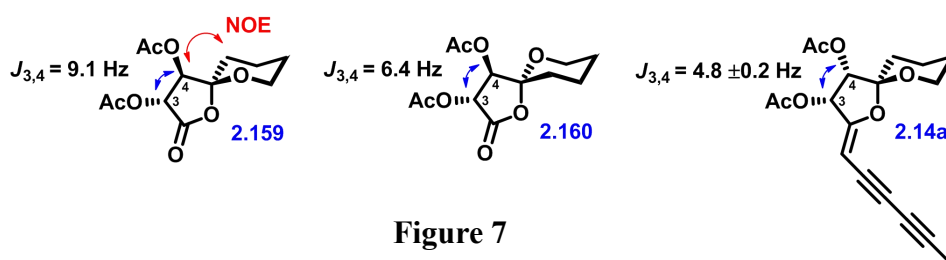
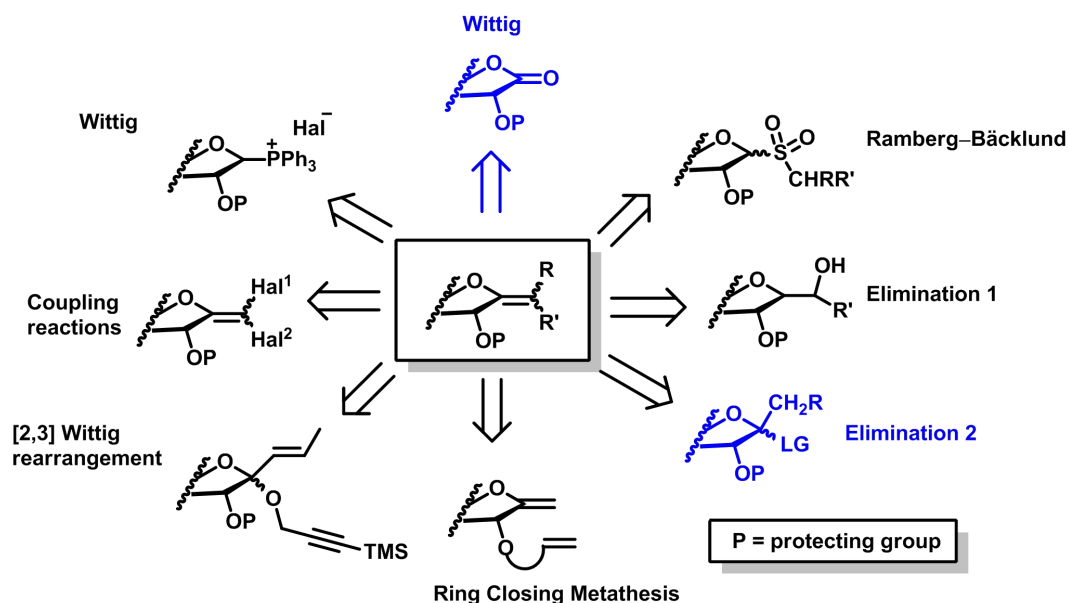


Figure 7

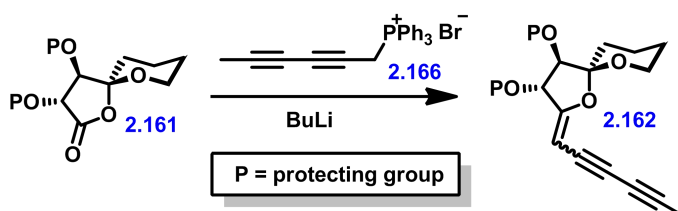
2.7.6 Installation of the bis(acetylene) side-chain and completion of synthesis

The next challenge for the synthesis was the installation of the bis(acetylene) side-chain. Gómez and López have extensively reviewed the construction of exocyclic enol double bond systems (**Scheme 53**).⁷¹ Among all the methods mentioned, Wittig olefination and alkylation–elimination processes were chosen as direct methods from the lactone (shown in blue, **Scheme 53**).



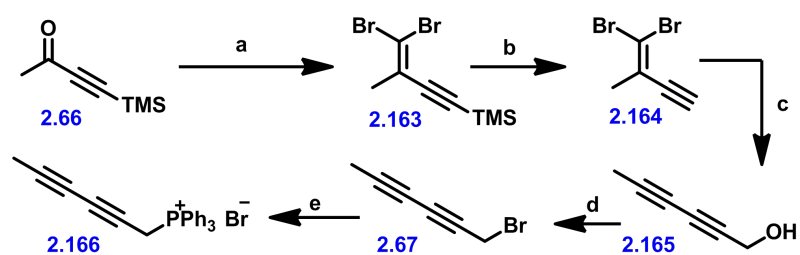
Scheme 53

Wittig olefination was first examined. The idea was to apply the established method in the Robertson group to prepare phosphonium salt **2.166**.³⁰ It was anticipated that the ylid generated from **2.166** could react with lactone **2.161** to deliver spirocycle **2.162** directly (Scheme 54).



Scheme 54

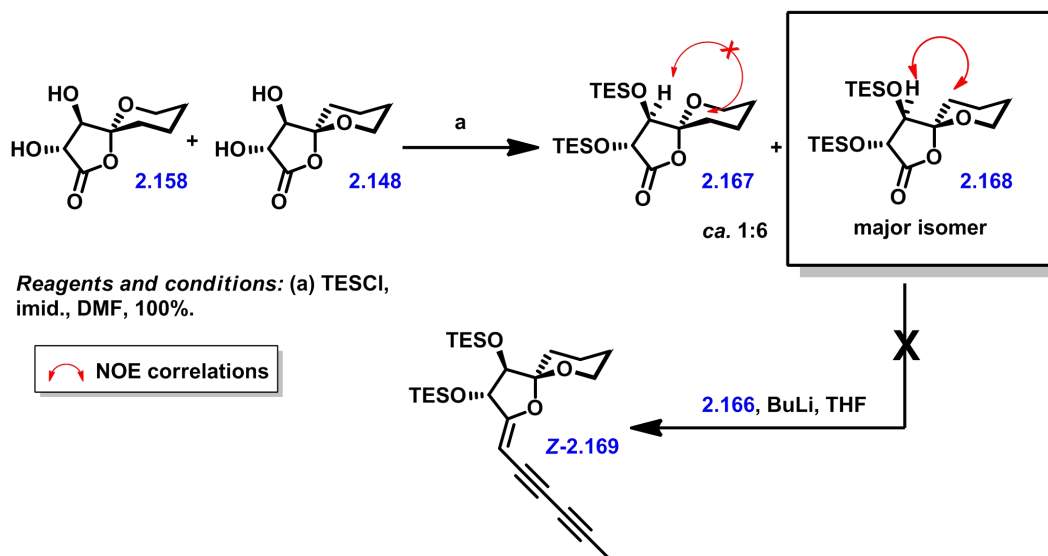
The synthesis of phosphonium salt **2.166** started from ketone **2.66** (Scheme 55). Compared to the published protocol,³⁰ only a moderate yield (59%) was observed in the key Fritsch–Buttenberg–Wiechell rearrangement, possibly due to the quality of BuLi.



Reagents and conditions: (a) CBr_4 , PPh_3 , DCM, 98%; (b) K_2CO_3 , THF, MeOH, 100%; (c) BuLi, $(\text{CH}_2\text{O})_n$, toluene, ether, 59%; (d) py, PBr_3 , ether, 60%; (e) PPh_3 , benzene, 53%.

Scheme 55

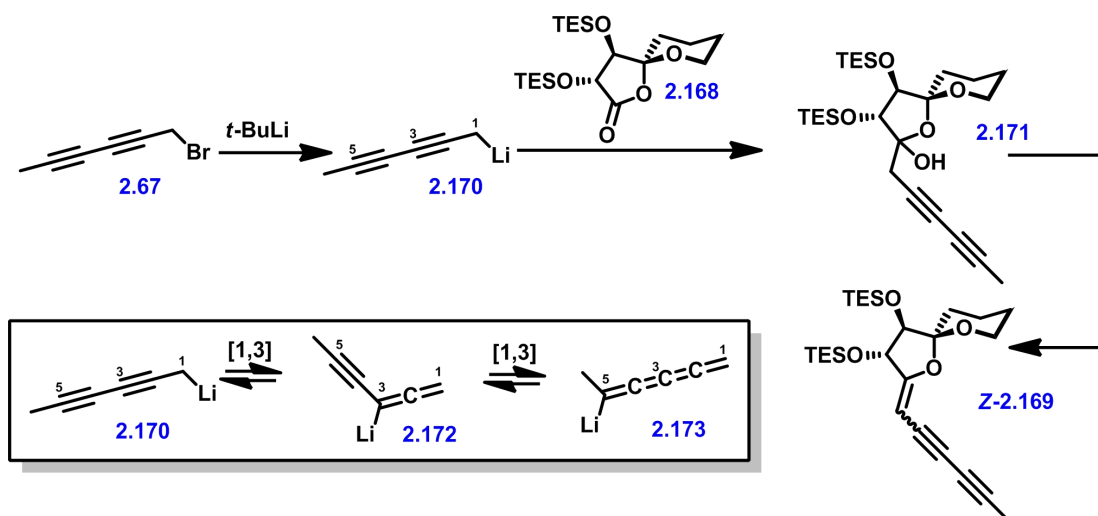
With phosphonium salt **2.166** prepared, the Wittig reaction was next examined (**Scheme 56**). Instead of conducting the olefination directly on diols **2.148** and **2.158**, the hydroxy groups were protected as silyl ethers. The original diol mixture was found to be separable after silylation which allowed the relative stereochemistry of each bis-silyl ether to be determined by NOE experiments (**Scheme 56**). When the Wittig reaction was carried out between major isomer **2.168** and phosphonium salt **2.166**, only starting material **2.168** was recovered.



Scheme 56

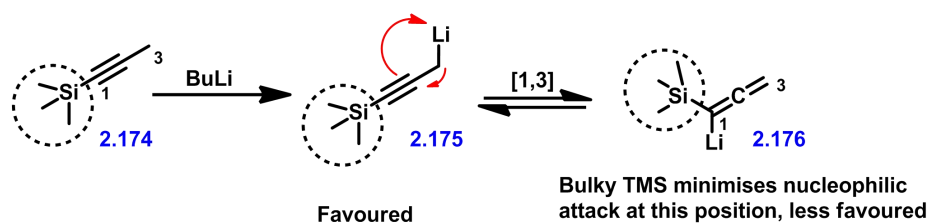
Thus the strategy was changed to an alkylation–elimination process. The idea was to effect nucleophilic addition to lactone such as **2.168** then dehydrate the so-formed lactol **2.171**. It was thought that organolithium **2.170** might be a viable nucleophile in this context (**Scheme**

57). However, 1,3- isomerisations were envisaged to complicate the alkylation process.⁷²



Scheme 57

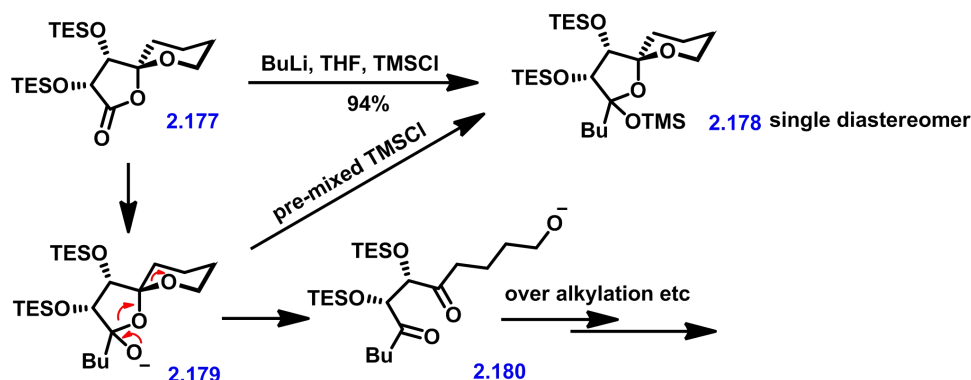
Corey had reported that alkyne **2.174** was an effective reagent for propargyl transfer in contrast to allenyl transfer.⁷³ The reason lies in the bulk of TMS group that prevents C(1) attack even if isomerisation does occur (Scheme 58).



Scheme 58

Double alkylation of the lactone was a potential concern in this strategy^r. To minimise this, TMSCl was used to trap the alkoxide and avoid unraveling the heterocycle and subsequent secondary alkylation. As planned, in a test reaction using BuLi as a nucleophile, lactone **2.177** was successfully monoalkylated in 94% yield as a single diastereomer. No double alkylation product was observed (Scheme 59).

^r For more information, see 'Miscellaneous compounds' section in experimental, page 340.



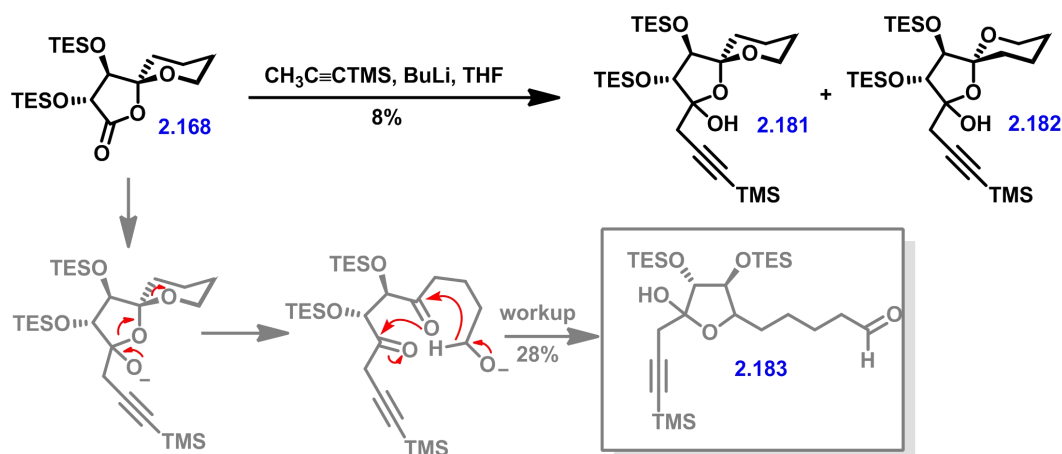
Scheme 59

When the same conditions were applied using deprotonated alkyne **2.175** as a nucleophile, a complex mixture was observed (Entry 1, Table 9)

Entry	Conditions	Result	Note
1	BuLi , $-78\text{ }^{\circ}\text{C}$, TMSCl , 1 h	decomposition	N/A
2	BuLi , $-78\text{ }^{\circ}\text{C}$, 1 h	8% product	rearrangement
3	BuLi , $-78\text{ }^{\circ}\text{C}$, TMEDA , 10 min	45% product	100% b.r.s.m.
4	BuLi , $-78\text{ }^{\circ}\text{C}$, TMEDA , 20 min	46% product	92% b.r.s.m.
5	BuLi , $-78\text{ }^{\circ}\text{C}$, TMEDA , 30 min	54% product	87% b.r.s.m.

Table 9

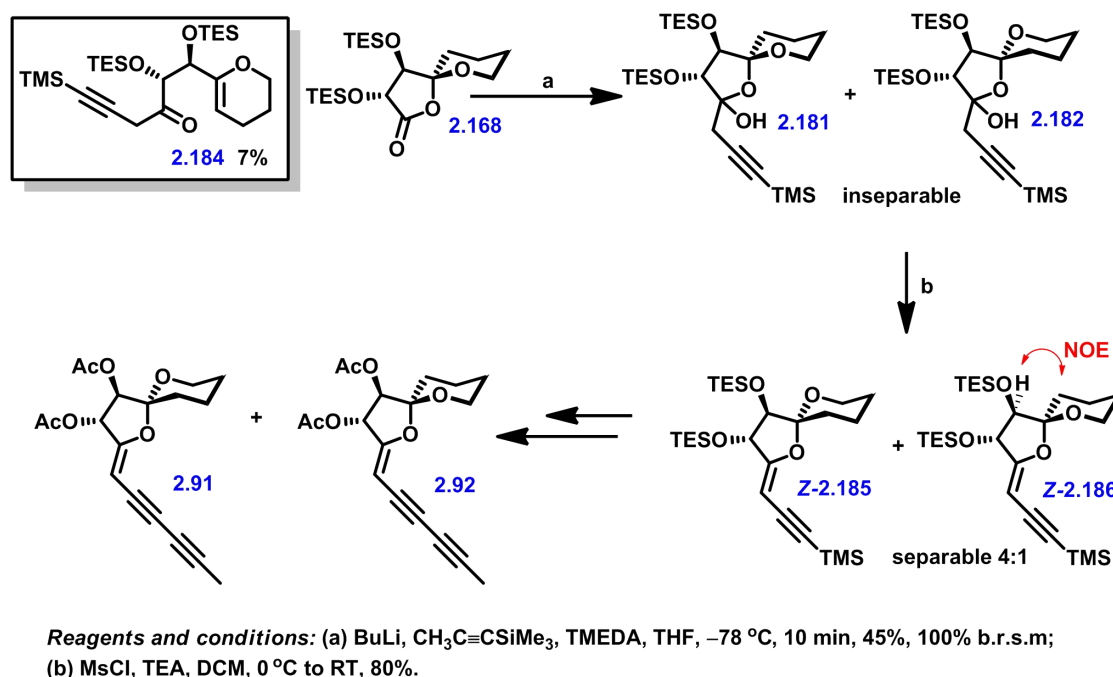
Alonso reported that mono-alkylation of γ -lactones could be achieved without the use of TMSCl .⁷⁴ Application of these conditions resulted in the formation of aldehyde **2.183** as the main product (Scheme 60), together with desired lactols **2.181** and **2.182** in only 8% yield (Entry 2, Table 9). The formation of aldehyde **2.183** as a side product was explained by hydride transfer as shown (Scheme 60).



Scheme 60

It was envisaged that a shortened reaction time would avoid the undesired hydride shift and optimise the yield of **2.181** and **2.182**. To enhance the rate of this alkylation, additives such as TMEDA⁷⁵ were considered since this would increase the reactivity of the organometallic by chelating lithium.

A 45% yield of desired products **2.181** and **2.182** (100% b.r.s.m.), as an inseparable mixture of four diastereomers, were obtained when the alkylation was conducted in the presence of TMEDA (**Entry 3, Table 9**). The reaction was quenched after 10 minutes to avoid side reactions. Longer reaction times were also attempted (**Entries 4, 5, Table 9**) and although the yield was improved by up to 9% (**Entry 5, Table 9**), these conditions were not considered as ideal since unreacted starting material could not be recovered completely.



Scheme 61

The inseparable lactols **2.181** and **2.182** were next subjected to dehydration (**Scheme 61**).

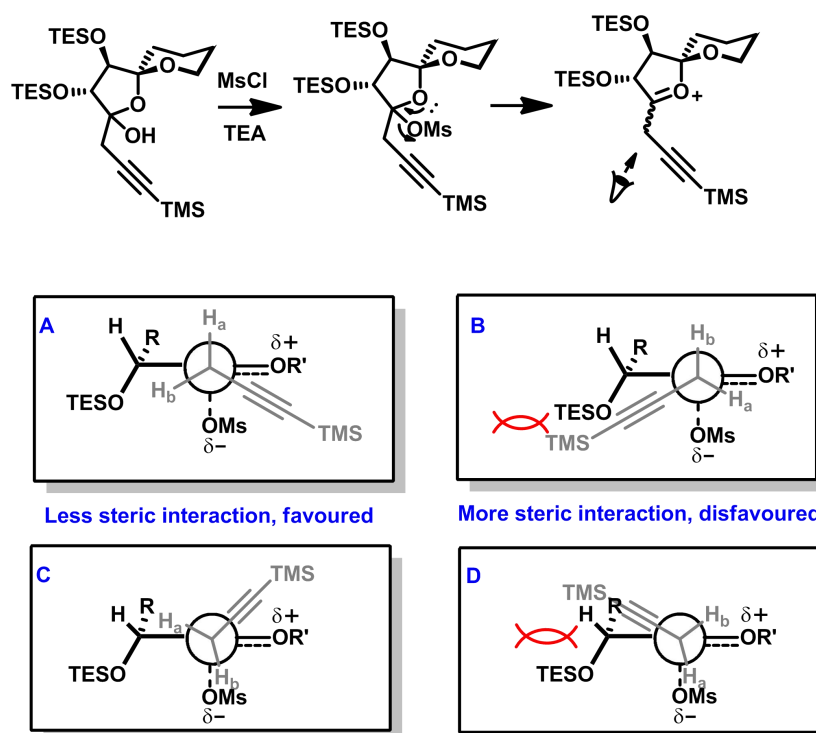
Two conditions were investigated (**Table 10**) and the MsCl/TEA/DCM method was chosen

as the suitable.

Entry	Conditions	Result
1	POCl ₃ , py	NR
2	MsCl/TEA/DCM	80% yield

Table 10

The diastereomeric ratio had changed from 1:6 between lactones **2.167** and **2.168** to 4:1 between enol ethers **Z-2.185** and **Z-2.186**, both of which possessed a *Z*-exocyclic double bond geometry (**Scheme 61**). It was proposed that the heterocycle unraveled during or following the alkylation reaction, which was supported by the isolation of a side product **2.184** in 7% yield. The explanation for the high *Z*-selectivity may lie in the steric preferences of different configured oxonium intermediates (**Scheme 62**) and the elimination transition states leading to them.



Scheme 62

Significant steric repulsion between the acetylene side-chain and the bulky silyl group (TES) may occur in conformations **B** and **D** whereas little interaction between functionalities would occur in **A** and **C**, which would result in the formation of a *Z*-configured product after loss of OMs^- then proton (H_a or H_b as shown). The geometry and relative stereochemistry in the products **Z-2.185** and **Z-2.186** were supported by NOE studies (**Figure 8**).

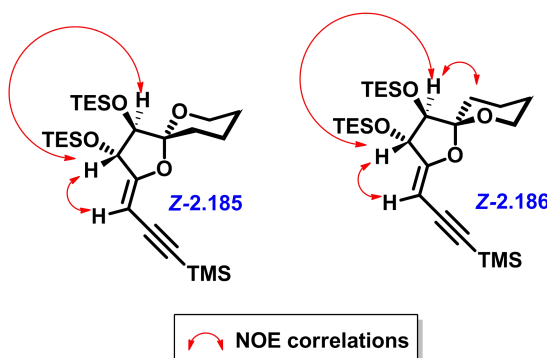
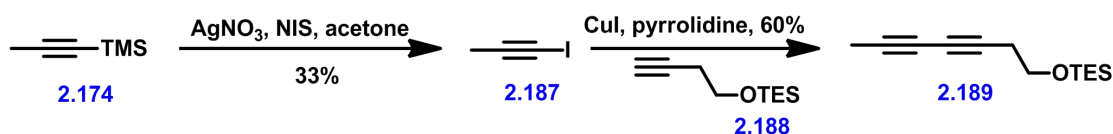


Figure 8

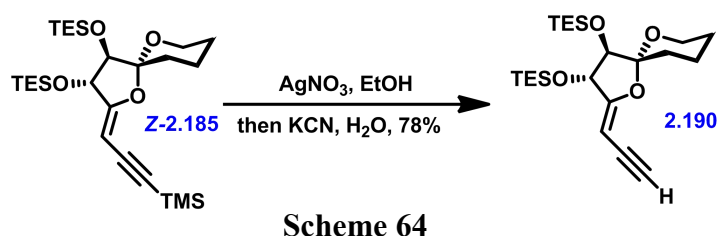
To complete the synthesis, a Cadiot–Chodkiewicz^{76, 77} alkyne cross coupling reaction was chosen.

A model reaction between **2.187** and **2.188** was conducted (**Scheme 63**) and since the cost of 1-iodopropyne **2.187** is high (£170/g), this reagent was prepared by following the procedure developed by Nishikawa.⁷⁸ The yield of this latter reaction was moderate (33%), partly due to the volatility of iodide **2.187**. Despite this shortcoming, Nishikawa's approach was chosen due to its reliability. Eventually, the desired coupled product **2.189** was obtained in 60% yield using Cadiot–Chodkiewicz conditions, paralleling the end stages of Mukai's route to AL-2 and related molecules (**Scheme 63**).²³



Scheme 63

Before subjecting siprocyclic **Z-2.185** to the established Cadiot–Chodkiewicz conditions,²³ selective deprotection of the TMS group was required. Use of K_2CO_3 in absolute methanol is a popular choice for this purpose⁷⁹⁻⁸¹ but this reaction was attempted, global deprotection occurred and a complex mixture resulted; 1.0 equivalent of TBAF⁷⁹ gave the same result. Finally, treatment of **Z-2.185** with $AgNO_3$ then aqueous KCN was found to be suitable^{82, 83} and a 78% yield of terminal alkyne **2.190** was achieved, which was ready for the key Cadiot–Chodkiewicz coupling (**Scheme 64**).



Scheme 64

Established conditions for the Cadiot–Chodkiewicz reaction—treating terminal alkyne **2.190** with freshly prepared 1-iodopropyne **2.187**—gave a 71% isolated yield of the desired product **Z-2.191** (**Scheme 65**). This chemistry had established the full carbon skeleton of the target. To complete the synthesis, TBAF was used to conduct a global deprotection, and double acylation furnished the final product **2.91**. The relative configuration of each stereogenic centre was ascertained by X-ray crystallography (**Scheme 65**).

2.7.7 Comparison of data

Having obtained both proposed structures, their spectroscopic data were compared. As to the proposed structure A, deviations were apparent in both chemical shift and coupling constant (Table 11).

Position	Reported data ^s	Proposed structure A ^f	δ Difference (ppm)
H-3	6.07 (dd, J 7.5, 2.0)	5.32 (s)	-0.75
H-4	4.99 (d, J 7.5)	4.90 (s)	-0.09
H-1'	5.03 (dq, J 2.0, 1.0)	4.71 (s)	-0.32
H-6'	1.97 (d, J 1.0)	1.95 (s)	-0.02

Table 11

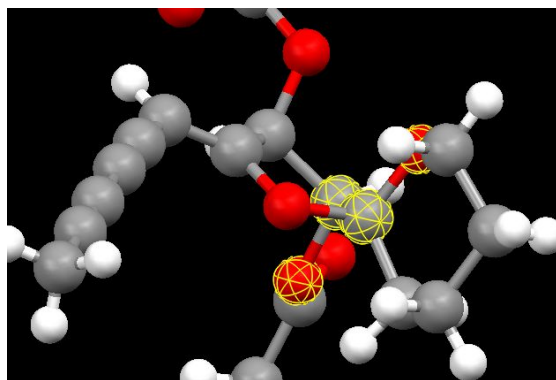


Figure 9

inspection of the crystal structure, the dihedral angle of H(4)–C(4)–C(3)–H(3) was 93° (Figure 10).

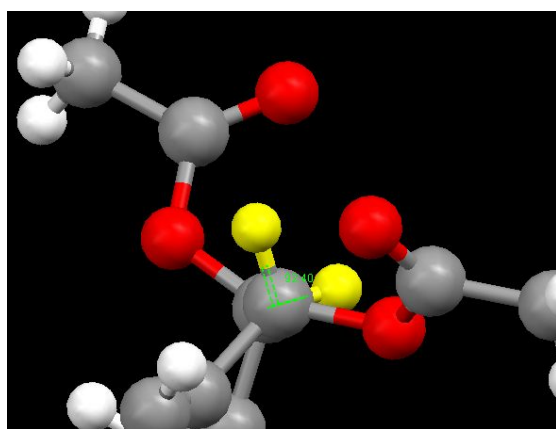


Figure 10

C(4)–O and C(5)–O bonds (highlighted in Figure 9) are *trans*- to each other, the C(5)–O also

The chemical shift of H(3) and H(1') were significantly upfield (0.75 ppm and 0.32 ppm) compared to the original data. In addition, the coupling constant between H(3) and H(4) (close to 0 Hz) was surprisingly small. From close

Despite the difference in conformation between the solid and solution states, a hypothesis was proposed as follows: to minimise dipolar repulsion between the C(4)–O and C(5)–O bonds (as highlighted in Figure 9), the C(4)–O bond adopts a pseudo axial site. Then the

^s Data obtained from CCl₄.

adopts a pseudo axial position, and dipolar repulsion is minimised. Consequently, H(4) and H(3) must adopt pseudo equatorial positions. Therefore, the dihedral angle of H(4)–C(4)–C(3)–H(3) ends up about 90°, as seen in the crystal (**Figure 10**, H(3) and H(4) are highlighted in yellow).

Comparisons between proposed structure **B** and the original data are listed in **Table 12**.

Position	Reported data ^t	Proposed structure B ^g	δ Difference (ppm)
H-3	6.07 (dd, <i>J</i> 7.5, 2.0)	5.77 (d, <i>J</i> 7.5)	–0.30
H-4	4.99 (d, <i>J</i> 7.5)	4.92 (d, <i>J</i> 7.5)	–0.07
H-1'	5.03 (dq, <i>J</i> 2.0, 1.0)	4.53 (s)	–0.50
H-6'	1.97 (d, <i>J</i> 1.0)	1.94 (s)	–0.03

Table 12

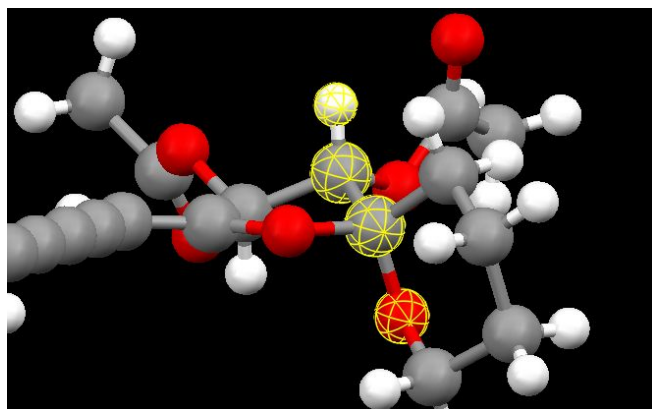


Figure 11

Despite the coupling constant between H(3) and H(4) (7.5 Hz) being identical to that reported, a significant chemical shift deviation (0.50 ppm) was found for H(1'). In summary, neither **2.91** nor **2.92** corresponds structurally to the unnamed

natural product isolated in 1974.

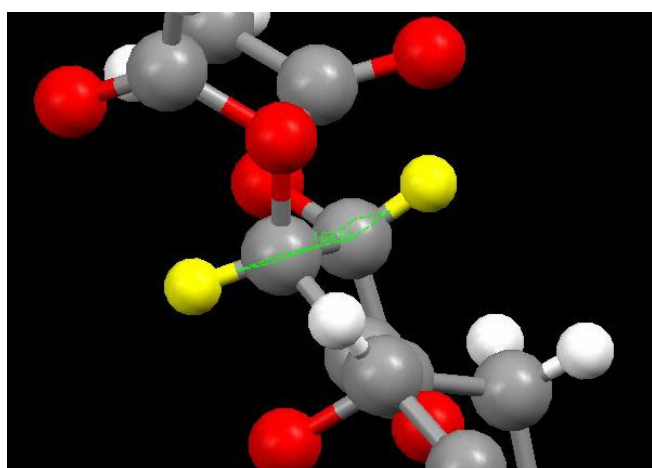


Figure 12

position, it can not minimise dipolar interactions to the same extent as in proposed structure

^t Data obtained from CCl₄.

A. As a result, H(4) is pseudo axial perhaps to enhance C(4)–H σ orbital overlap with C(5)–O σ^* (highlighted in **Figure 11**). Similarly, due to the *trans*-relationship of H(3) and H(4), H(3) must also adopt a pseudo axial position. Therefore, the dihedral angle of H(4)–C(4)–C(3)–H(3) lies near to 180° , as seen in the crystal (**Figure 12**, H(3) and H(4) are highlighted in yellow), resulting in a large *J* value.

In summary, neither of the proposed structures corresponds to the unnamed natural product. In particular, significant chemical shift differences were found at H(1') between proposed structures **2.91** and **2.92** and the natural product, indicating that the double bond might be *E*- in the natural product. Indeed, a more recently reported natural product **2.3**⁸⁴ bearing an *E*-configured olefin (**Figure 13**) corresponds the most closely in the characterisation data (**Table 13**). Therefore, this natural product is proposed for the true identity of the unnamed natural product.

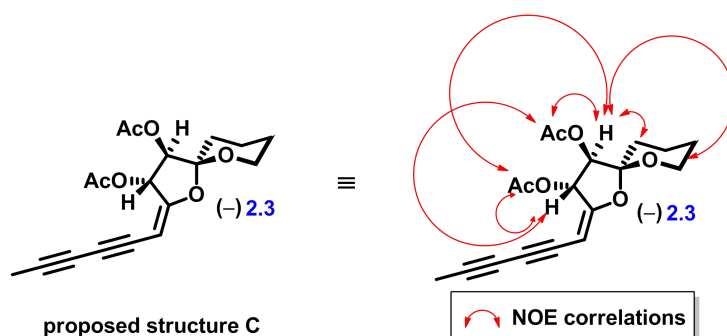


Figure 13

Position	Reported data ^u	Proposed structure C ^v	δ Difference (ppm)
H-3	6.07 (dd, <i>J</i> 7.5, 2.0)	6.25 (dd, <i>J</i> 7.5, 2.0)	+0.18
H-4	4.99 (d, <i>J</i> 7.5)	5.16 (d, <i>J</i> 7.5)	+0.17
H-1'	5.03 (dq, <i>J</i> 2.0, 1.0)	5.14 (dq, <i>J</i> 2.0, 1.0)	+0.11
H-6'	1.97 (d, <i>J</i> 1.0)	1.96 (d, <i>J</i> 1.0)	+0.01

Table 13

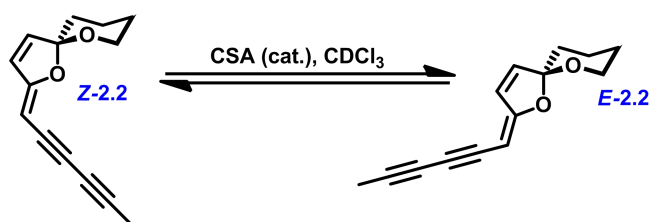
^u Data obtained from CCl₄.

^v Data obtained from CDCl₃.

The absolute configuration of proposed structure **C** was established by NOE⁸⁴, the Horeau method⁸⁵ and CD spectrum analysis⁸⁵ (**Figure 13**). It is notable that the NMR data in Marco's article are reported in CDCl₃ instead of CCl₄, therefore, the small systematic deviation is reasonable. To further support this hypothesis, attempts were made to isomerise proposed structure **B** (**2.92**) to **C** (**2.3**), so that NMR data in CCl₄ could be obtained.

2.7.8 Attempts to effect *E/Z* isomerisation

As mentioned earlier, *Z*- 'homo tonghaosu' **Z-2.2** has been shown in the Robertson group and by others to undergo isomerisation to its *E*-isomer by treatment with CSA³⁰ (**Scheme 67**).



Scheme 67

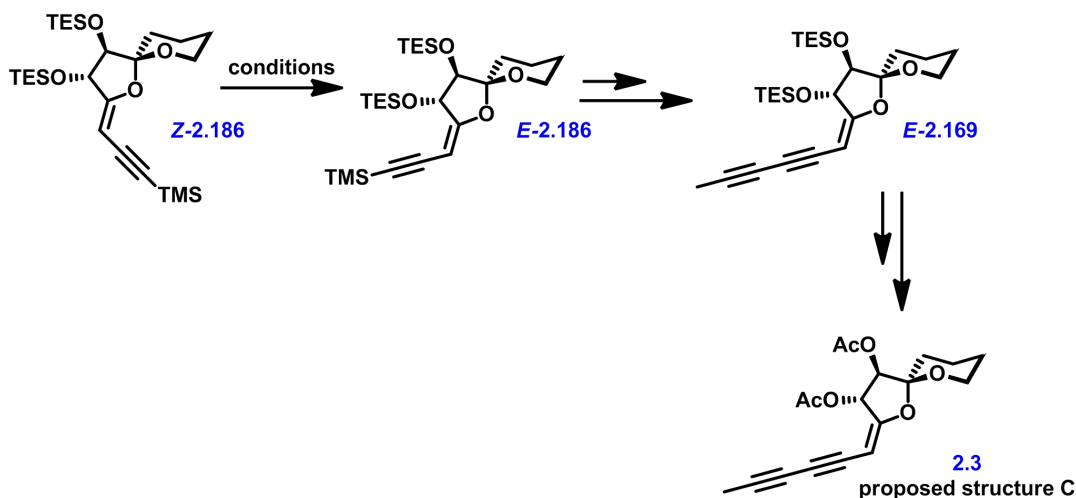
When **2.92** was treated with CSA in CDCl₃, no isomerisation was observed even after 6 days (**Entry 1, Table 14**). *p*-TSA was also examined for the isomerisation (**Entry 2, Table 14**), however, the same result was obtained. Finally, when a strong acid (HI) was used (**Entry 3, Table 14**), the starting material decomposed.

Entry	Conditions	Result
1	CSA (cat.), CDCl ₃	NR (6 days)
2	<i>p</i> -TSA (cat.), CDCl ₃	NR (2 days)
3	HI (cat.), CDCl ₃	decomposition

Table 14

Having exhausted all starting material **2.92** in these attempts, attention was turned to isomerising intermediate **Z-2.186**. If spirocycle **E-2.186** could be obtained, then it could be

subjected to the established sequence to synthesise **2.3** (Scheme 68).



Scheme 68

In order to preserve the precious intermediate **Z-2.186**, its diastereomeric isomer **Z-2.185** was first used to establish feasible conditions (Scheme 69). Seven different conditions were attempted, and the results are listed in Table 15.



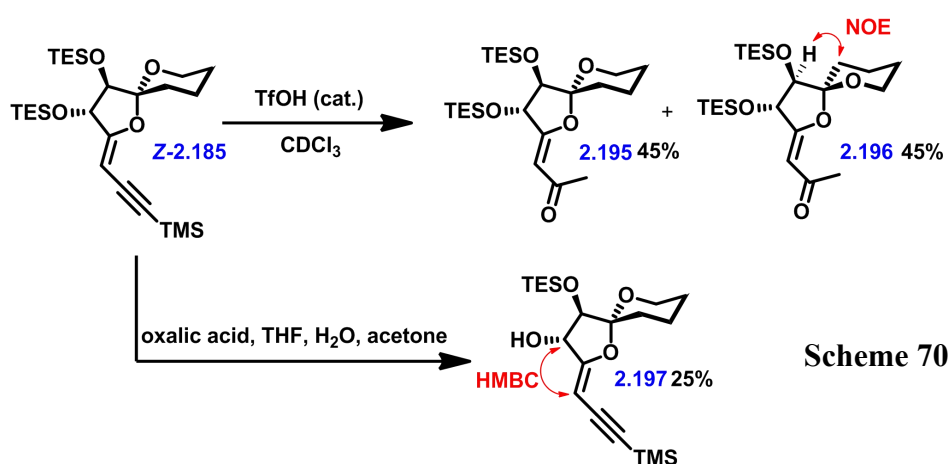
Scheme 69

Entry	Conditions	Result
1	MsOH (cat.), CD ₂ Cl ₂ , 10 h	decomposition
2	TfOH (cat.), CDCl ₃ , 30 min	See text
3	Oxalic acid, THF/H ₂ O/acetone, 2 h	See text
4	Oxalic acid, THF/H ₂ O/acetone, 2 d	decomposition
5	I ₂ , DCM, 5 h	decomposition
6	hν, CD ₂ Cl ₂ , 6 h	NR
7	I ₂ (cat.), hν, CD ₂ Cl ₂ , 2 h	NR

Table 15

Either decomposition (Entries 1, 4, 5, Table 15) or no reaction (Entries 6, 7, Table 15) were

observed except two cases (**Entries 2, 3, Table 15**). When a catalytic amount of TfOH was used (**Entry 2, Table 15**), hydration of the triple bond occurred, yielding α,β -unsaturated ketones **2.195** and **2.196** (**Scheme 76**). Application of a reported protocol,⁸⁶ using oxalic acid as a catalyst in a mixed solvent system (**Entry 3, Table 15**), resulted in selective TES group deprotection at the C(3) oxygen as proven by an HMBC NMR experiment (**Scheme 70**). Due to time constraints, no further conditions were examined.



Scheme 70

2.8 Conclusions

Two proposed structures of the unnamed natural product isolated from *Chrysanthemum boreale* were successfully synthesised. From data comparison, it is apparent that *none* of the synthesised compounds in the Robertson group corresponds structurally to the natural product (**Figure 14**).

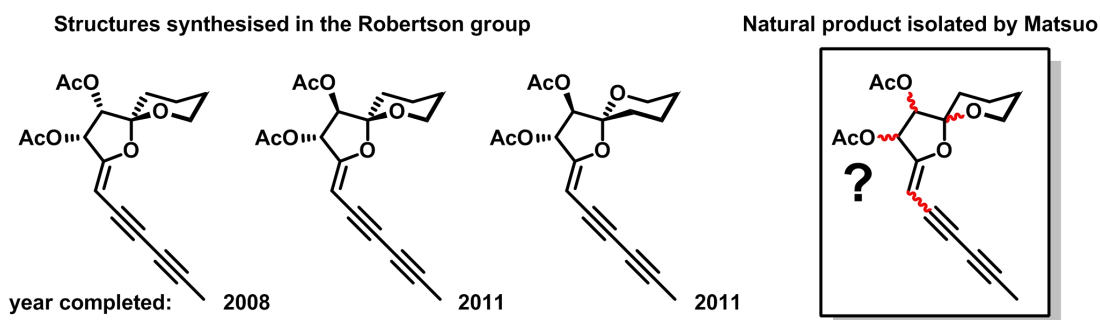


Figure 14

However, through this endeavour, much knowledge has been gained on the properties of this class of compounds. Now it becomes fairly evident that the structural assignments by Matsuo probably are incorrect at all stereogenic centres. In addition, it is likely that the ‘new’ natural product reported in 1992 by Marco is identical to Matsuo’s 1974 structure. It would be useful to have a sample from either Macro or Matsuo group to confirm the structural proposal.

This project has demonstrated the power of total synthesis combined with modern analytical techniques, which together act as a reliable way to elucidate complex structures of interest. Whilst chemists rely increasingly on advanced spectroscopy alone, it is time to recall the original role of total synthesis: tackling the structural puzzles in the arena of natural products identification.

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Chapter 3: Logical synthesis using enzymatic reduction as a key step

3.1 An ideal total synthesis

With the dramatic advancement of synthetic technologies including new methodologies and rational retrosynthetic designs, synthetic chemists today can say confidently that any molecule of interest can be synthesised given enough time and effort. Take Kishi's palytoxin (Figure 1) synthesis¹ as an example. The natural product contains 64 stereogenic centres and was synthesised by coupling seven key fragments together in 39 steps. Besides these 39 'building block coupling' reactions, the synthesis required more than 140 steps to produce all the building blocks.^{1,2}

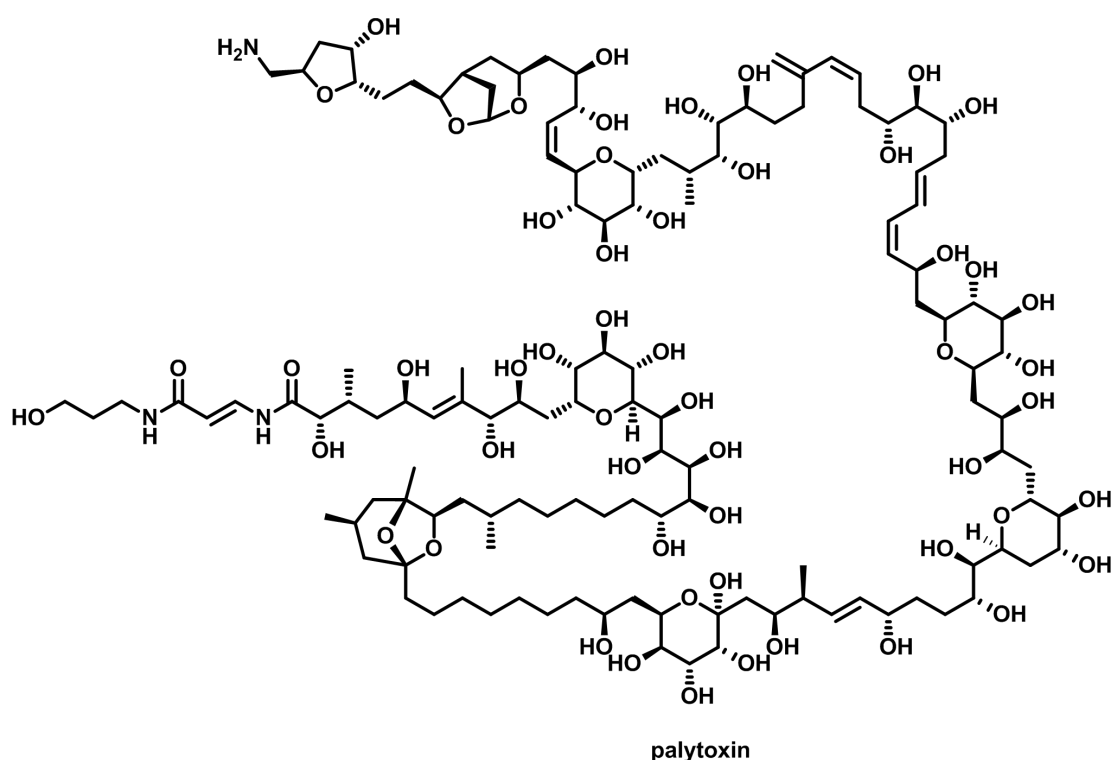


Figure 1

‘Aiming for a better synthesis’ is a central focus in natural product synthesis.³ As early as 1975, Hendrickson commented that an ideal synthesis ‘creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalisations, and leading directly to the target, not only its skeleton but also its correctly placed functionality’.⁴ Subsequently, various concepts of ‘economies of synthesis’ have been addressed in different contexts by Hoffmann, Baran,^{5, 6} Trost^{7, 8} and Wender⁹⁻¹¹ as ‘redox economy’, ‘atom economy’, and ‘step economy’. The following section attempts to demonstrate that using strategic redox manipulation, *i.e.* di/polyketone synthesis followed by one-pot enzymatic multiple reduction can dramatically enhance synthetic efficiency and allow chemists to assemble target molecules through rational substrate selection, enzyme design, and subsequent C–O bond activation and manipulation.

3.2 Enzymes in total synthesis

3.2.1 Background

Catalysis is an efficient way to provide cost-effective processes in organic synthesis. Chemists apply chemical catalysis in order to obtain improved conversions, higher yields or enhanced selectivities (chemo-, regio- or stereo-selectivity), but biological catalysis using various enzymes to conduct chemical transformations has received much more limited attention. This is surprising because enzymes offer many advantages including high turnover rates¹² and selectivities. Thanks to recombinant DNA technology,¹³ during the last decade, there has been a burst of applications of biological catalysis, especially in industrial processes.¹⁴ Partly, this is due to the development of bio-technologies (including bioinformatics, genome sequencing and gene synthesis), but also due to the fact that

biocatalysis is environmentally friendly, sustainable, controllable, and highly selective and efficient.

3.2.2 Ways to design appropriate enzymes

There are three main ways to engineer suitable enzymes: rational design, directed evolution, and a combination of the two (**Figure 2**).¹⁵

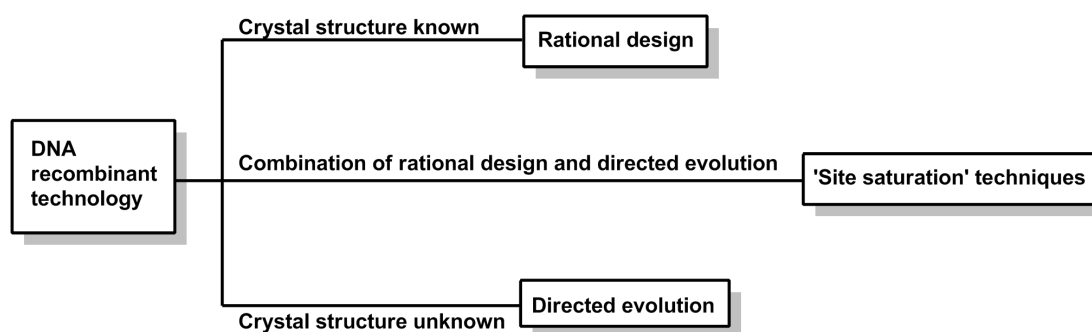


Figure 2

If the enzyme of interest is structurally characterised by its crystal structure, rational design of enzymes can be applied especially when the crystallography is conducted with co-crystallisation of the substrate of interest, the product, or substrate-like inhibitors. Such a process consists of identifying the active site of the enzyme and the amino acids involved in the catalysis, then exchanging amino acid residues by design to adjust substrate compatibility,^{16, 17} reactivity, and its function.¹⁸

In most cases, full structural information for the enzyme of interest is not accessible to enzyme engineers and therefore the ‘directed evolution’ approach is the method of choice. In this process, two steps are involved: random mutagenesis then subsequent screening for the desired property. When the mutation process is complete, the best mutants are selected. These first-generation mutants can either serve as a sufficient enzyme library for certain

organic syntheses, or they can be subjected to further mutagenesis by providing ‘hot spot’ information to enzyme engineers.¹⁹

The aforementioned approaches identify amino acid residues that should be modified in order to obtain desired enzymatic function, but it is hard to know whether the optimum amino acid for the desired property has been found without fully exchanging with all possible natural amino acids. As a result, ‘site-saturation mutagenesis’ has arisen to address this problem. This technique combines both the concepts of rational design and directed evolution in the sense that the active site of the enzyme is firstly recognised, followed by full mutation on a specific site with subsequent screening for function.²⁰

The choice of different enzyme design is currently a case-by-case issue; the philosophy is to gain access to a suitable enzyme with the proper functionality to conduct the desired transformations.

3.3 Application of designed redox-active enzymes in total synthesis

3.3.1 Background

Major effort has been invested in developing asymmetric synthetic methodologies. Among all these available methods, countless articles have been published on redox transformations; however, synthetic chemists tend to rely largely on just a few robust and well-tested asymmetric redox transformations such as the SAE²¹/SAD²² reactions, Noyori hydrogenation²³ in their syntheses, especially in the case of industrial production. Thus, on one hand the majority of synthetic chemists apply only a limited number of procedures to

generate a relatively limited range of intermediates (epoxyalcohols; 1,2-*syn* diols; chiral 2° alcohol etc); on the other hand, there is a huge number of specific procedures that generate highly diverse motifs, but they are not yet widely accepted and tested. To address this problem, a robust methodology is required that leads to a wide range of motifs asymmetrically, and applying designed enzymes to conduct multiple reductions is a possible solution (**Figure 3**).

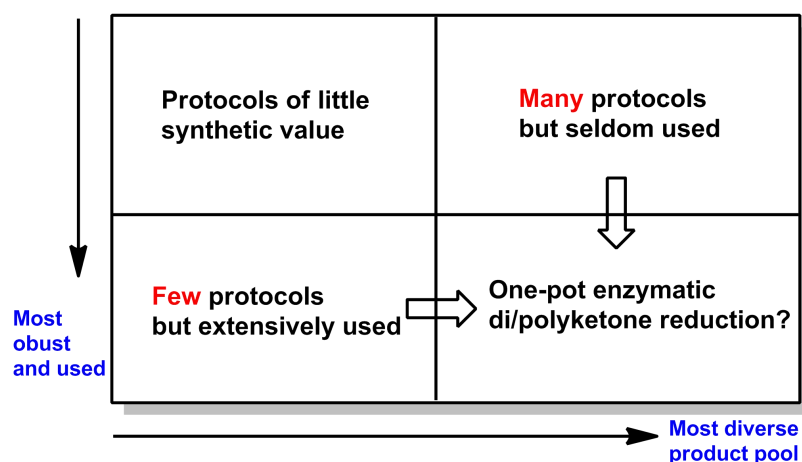
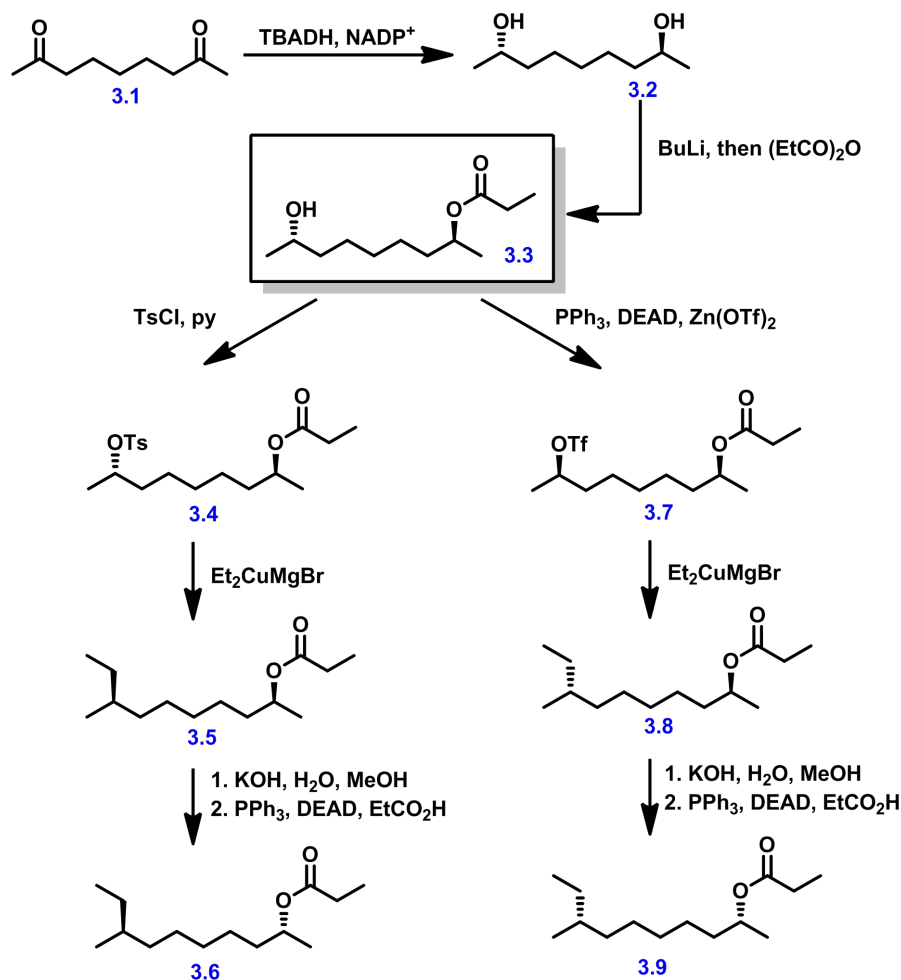


Figure 3

Consider the synthesis of 1,*n*-diols. It is well-known that 1,2-diols are available by SAD reaction;²² however, since the SAD reaction is a *syn*-stereospecific process, the olefinic substrate has to have a defined geometry in order to afford the desired stereochemistry of the diol. This can present a limitation to the methodology. No analogous transformation is available to yield a stereochemically defined 1,3-diol directly. Generally, one of the hydroxyls in the 1,3-diol moiety has to be present before the second hydroxyl is installed. The ‘pre-existing’ alcohol can either be present in the chiral starting material (*e.g.* the (*R*)-configured alcohol in PHB) or be introduced *e.g.* by asymmetric ketone reduction. The newly introduced alcohol can then be produced with a *syn*- or *anti*- 1,3 relationship *via* different chelation models mediated by metals for *syn* reduction²⁴⁻²⁷ or *anti* reduction.²⁸⁻³⁰

Diols with general 1,n-relationships are generally considered as separate synthetic problems which may give rise to poor stereoselectivity and long synthetic sequences. This, of course, does not match the criterion of ‘ideal synthesis’ as mentioned above.³ For a general access to a 1,n-diol or even polyalcohols, a one-pot enzymatic reduction of di/polycarbonyl compounds is a potentially powerful candidate solution with careful selection of substrates and enzymes.

The multiple enzymatic reduction is not limited to the synthesis of diols and other poly-alcohols. The power of this process is to generate a broad spectrum of chiral intermediates towards synthetic targets—structurally complex and unique natural products or drug-like lead compounds with subsequent C–O activation processes. There are few total synthesis examples that employ a systematic enzymatic reduction approach on di/polyketone substrates. In one example,³¹ diol **3.2** was formed *via* a *Thermoanaerobium Brockii* alcohol dehydrogenase (TBADH) catalysed reduction on *symmetric* diketone **3.1**; monoacylation left an alcohol free for C–O activation. Further chemical transformations set the required stereochemistry of all stereogenic centres for the synthesis of all stereoisomers of a sex pheromone of the female western corn rootworm *Diabrotica virgifera* LeConte (**Scheme 1**).



Scheme 1

3.3.2 Biocatalytic precedents for the one-pot reduction on *non-symmetric* di/polyketones

Among enzymatic transformations that have been reviewed,³²⁻³⁸ enzyme-catalysed mono-reduction of non-symmetrical diketone substrates followed by a second, separate, ketone reduction are well-precedented;³⁹ examples are also established for one-pot double enzymatic reduction on *symmetrical* diketones.⁴⁰ The use of a single enzyme to reduce two chemically and spatially distinct ketones, however, has been rarely reported despite its potential as a methodology for the assembly of molecules bearing multiple stereogenic centers. Examples of substrates that *have* been studied in this regard are listed in **Figure 4**.⁴¹⁻⁵¹ Within these substrates, diketone **3.14** or **3.15** exemplifies a biocatalytic double ketone

reduction with relevance to drug production on industrial scale (*Lipitor*).

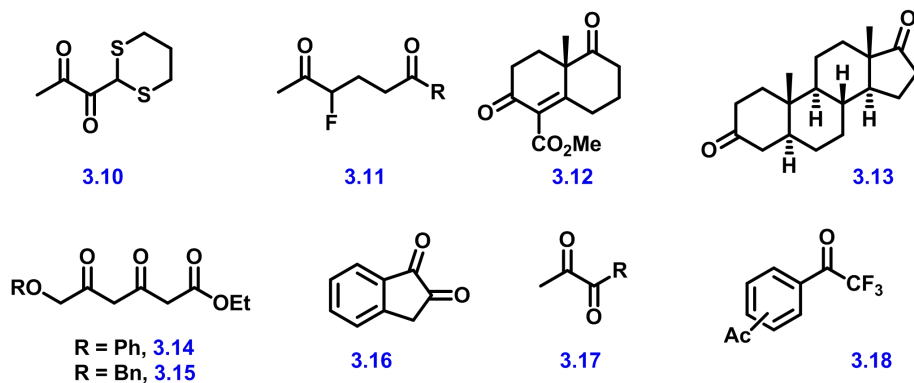
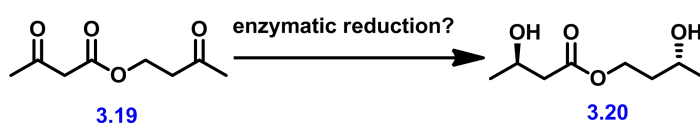


Figure 4

3.3.3 Robertson's development of the synthesis of a palatable food additive *via* an enzymatic double reduction of a non-symmetric diketone

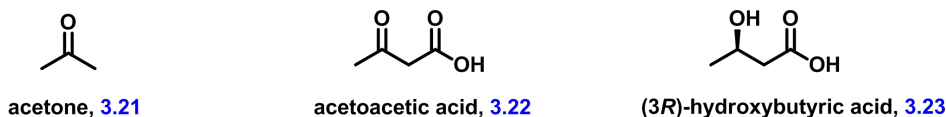
To use and extend the above-mentioned concept, through a collaboration project, the Robertson group became involved in the synthesis of a potential food additive **3.20** due to its biological activities and its potential to examine the enzymatic reduction on diketone- substrate **3.19** as shown in **Scheme 2**.



Scheme 2

Function of ester **3.20**

'Ketone bodies' are water-soluble, metabolic equivalents of fatty acids in humans. The three ketone bodies produced endogenously are acetone, acetoacetic acid, and (3*R*)-hydroxybutyric acid⁵² (**Figure 5**).

**Figure 5**

Ketone bodies are by-products that arise when fatty acids are broken down for energy in the liver and kidneys. They can substitute for glucose as a source of energy in the heart, skeletal muscle and, most importantly, the brain due to their ability to cross the blood-brain barrier.⁵³

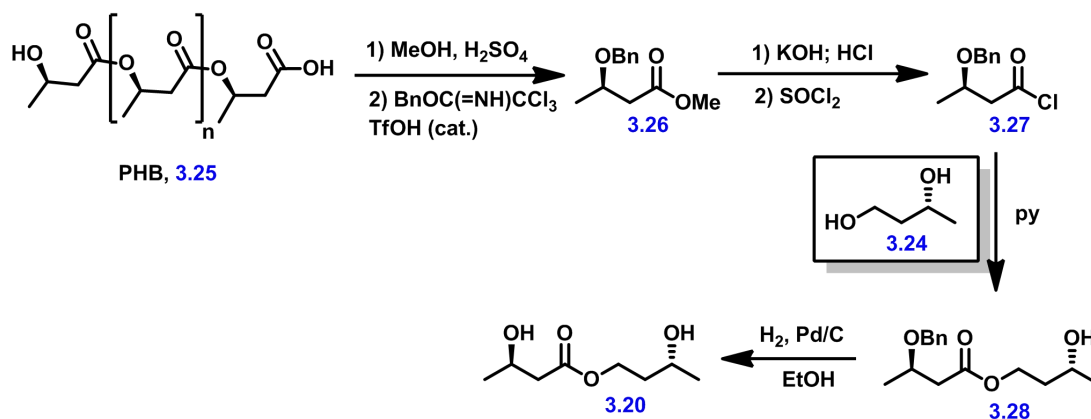
While the brain utilises only glucose for energy under normal conditions, when glucose becomes less available (*e.g.* fasting, prolonged exercise, low carbohydrate or ‘ketogenic’ diets), the brain gradually switches its energy supply from glucose to ketone bodies. Hasselbalch⁵⁴ established that after 3 days of starvation, the human brain obtains 25% of its energy from ketone bodies; in fact, Cahill showed that at least 60% of energy for the human brain can be supplied by ketone bodies.⁵⁵

Besides the metabolic function mentioned above, ketone bodies have several clinical benefits such as for treating refractory epilepsy,⁵⁶ insulin resistant type I diabetes,⁵⁷ Alzheimer’s disease,⁵⁸ and Parkinson’s disease.⁵⁹

Since the direct intake of ketone bodies can lead to acidosis or hypernatronemia,⁶⁰ a proper form of ketone bodies is needed for administration. As disclosed by Veech,⁶¹ (3R)-hydroxybutyl (3R)-hydroxybutanoate **3.20** can serve for this purpose. Moreover, hydrolysed diol **3.24** can be oxidised in the liver to generate further (3R)-hydroxybutyric acid for energy (**Scheme 3**). Indeed, Kashiwaya observed a significant increase of the concentration of ketone bodies in the brains of Wistar rats fed on ester **3.20**.⁶²

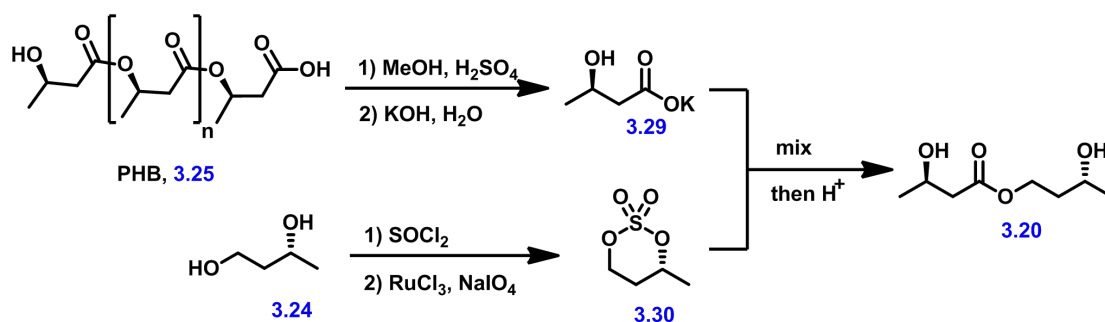
Intrigued by the biological activity and potential application of ester **3.20**, especially for its ability to enhance cognitive and physical performances, synthetic studies towards ester **3.20** were initiated in the Robertson group by Dr. Robertson and Dr. Tchabanenko in collaboration with Prof. Clarke from the Department of Physiology, University of Oxford and Dr. Veech from the National Institute of Alcohol Abuse & Alcoholism, U.S.A.

A classical Seebach type synthesis⁶³ starting from PHB (**Scheme 4**) allowed sufficient product accumulation of a 1st batch for preliminary biological testing. However, the long synthetic sequence and difficulty to scale up limited its potential for industrial application.



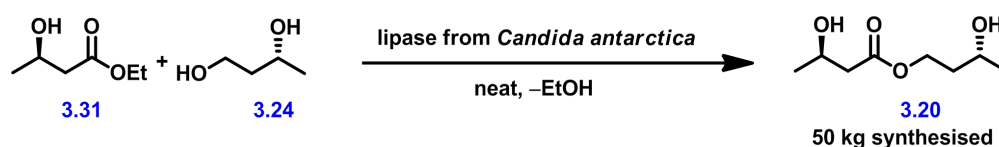
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Next, a novel route involving cyclic sulfate ring-opening in a more convergent synthetic strategy produced a 30 g batch of desired product to allow further testing (**Scheme 5**). However, even this short synthesis (three steps by longest linear route) was problematic at large scale.

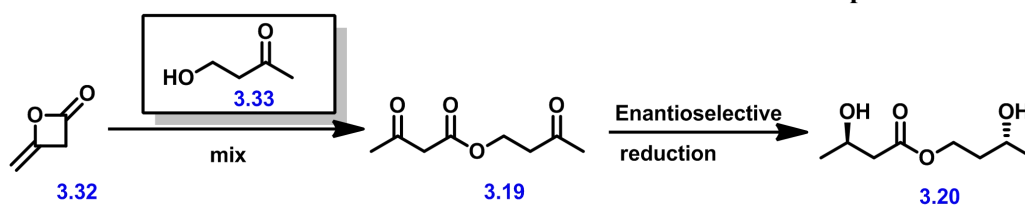


Enzymatic synthesis of ester 3.20

In order to solve the scalability problem mentioned above, a lipase catalysed transesterification was introduced (**Scheme 6**) to produce the ester on kilogram scales. Although this one-step synthesis provided fast and clean assembly of molecule, the cost for the ethyl ester **3.31** and diol **3.24** was too high (both at a cost of € 450/kg) for industrial production.



Finally, it was proposed that using a possible one-pot enzymatic reduction on diketoester **3.19** (**Scheme 7**) would be the best solution, since this might be achieved either with a single (engineered) ADH or two working consecutively or together.



Scheme 7

Through extensive investigation in the group by Dr. Tchabanenko in collaboration with Jülich Fine Chemicals GmbH and Biocatalytics, Inc., a suitable enzyme was identified together with its optimal cofactor, solvent system, substrate concentration and pH range for the double reduction⁶⁴ (**Table 1**). Up to a 76% yield of the desired product was obtained, HPLC analysis confirming that using this enzymatic method on diketone **3.19** provides a single enantiomer of product **3.20** (*e.e.* >99%).⁶⁴ Above all, it was envisaged to be the cheapest way to produce the potential food additive (\$ 10/kg).

Description	Conditions
Enzyme	Alcohol dehydrogenase from <i>Lactobacillus brevis</i> (ADH-LB)
Cofactor	NADPH
Cofactor recycling system	Glucose–Glucose Dehydrogenase (GDH)
Solvent	Phosphate buffer (pH = 7, 0.2 M)
Optimal pH range	5–6
pH maintaining reagent	5 M NaOH solution
Temperature	25–35 °C, typically 30 °C

Table 1

The success of the above-mentioned synthesis demonstrated the power of applying enzymatic approaches to produce polyalcohols that can be either retained as a final product (this case) or elaborated *via* C–O activation and subsequent chemical manipulations (**Scheme 1**, page 130). A general demonstration of systematic diketone reduction/manipulation is summarised as a flow chart shown in **Figure 6**. In practice, the simplest non-symmetric diketones would be explored in the first place to establish broad

substrate scope; with the concept proven to be feasible, further investigation of polyketones would then be initiated.

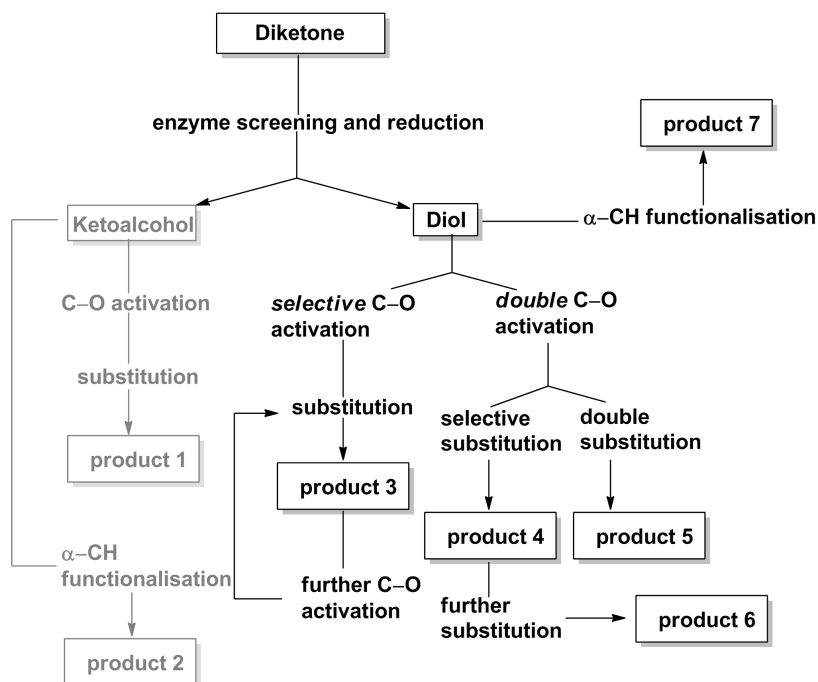


Figure 6

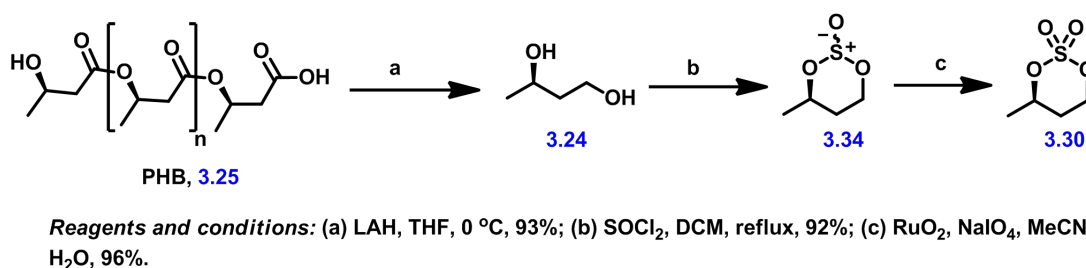
3.4 Aim of project

In this project, the cyclic sulfate route developed by Dr. Tchabanenko would be repeated to prepare, unambiguously, a standard sample for data comparison and characterisation. Next, the enzymatic approach would be repeated to confirm its feasibility. Last, when the enzymatic conditions were validated, a diketone substrate scope study, based on a monoester system, would be undertaken. This would provide a foundation for the use of other ketoreductases (KREDs) for cases found to be difficult with ADH-LB.

3.5 Results and discussion

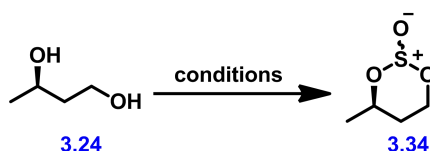
3.5.1 Classical approach towards (3*R*)-hydroxybutyl (3*R*)-hydroxybutanoate

The cyclic sulfate-opening strategy required the preparation of cyclic sulfate **3.30** as outlined in **Scheme 8**. Overall, a *ca.* 86% yield (95% per step on average) of the sulfate was synthesised for further transformation.



Scheme 8

The synthesis began with PHB, which was depolymerised reductively with LAH⁶⁵ to furnish the desired diol **3.24** in 93% yield on multigram scale. Two different conditions were tried for the preparation of cyclic sulfite **3.34** (**Scheme 9**, **Table 2**).

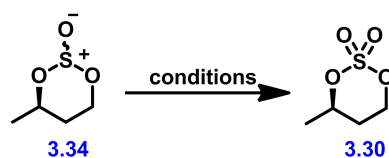


Scheme 9

Entry	Conditions	Yield
1	SOCl ₂ , pyridine, RT, 0.5 h	55% (<i>d.r.</i> = 10:1)
2	DCM, SOCl ₂ , reflux, 1 h	92% (<i>d.r.</i> = 13:1)

Table 2

The oxidation of cyclic sulfite **3.34** to the corresponding sulfate **3.30**⁶⁶ was then examined (**Scheme 10**, **Table 3**).



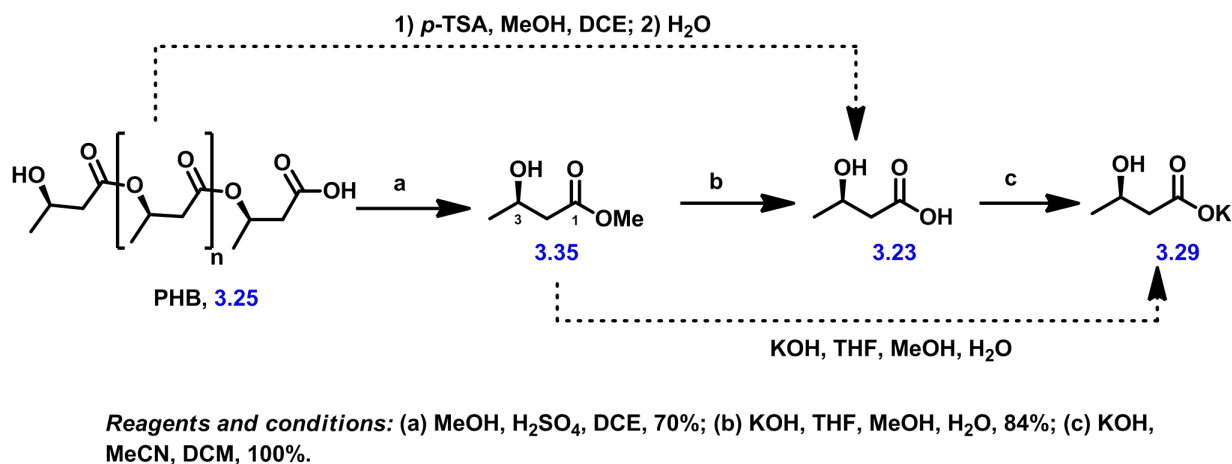
Scheme 10

Entry	Conditions	Yield
1	KMnO ₄ , H ₂ SO ₄ (aq.), DCM, 7 h	65%
2	RuCl ₃ (aq.), NaIO ₄ , CHCl ₃ (aq.), 3 h	95%
3	RuO ₂ , NaIO ₄ , CH ₃ CN (aq.), 10 min	96%

Table 3

By using 1.1 equivalents of KMnO₄ under acidic conditions (**Entry 1, Table 3**), unreacted sulfite **3.34** was found to persist after 2 h; addition of an extra 1.1 equivalents of oxidant drove the reaction to completion and the desired sulfate **3.30** was isolated in 65% yield. When the oxidant was changed to a ruthenium(VIII) source, an improved yield of sulfate **3.30** was achieved (**Entries 2, 3, Table 3**). Eventually, it was found that by using 30 mol% RuO₂ with NaIO₄ as the co-oxidant, cyclic sulfate **3.30** was prepared in 96% yield.

With electrophile **3.30** in hand, its nucleophile partner, potassium carboxylate **3.29**, was prepared following the sequence from PHB shown in **Scheme 11**.



Scheme 11

Although a one-pot procedure is available for the conversion of PHB to acid **3.23**,⁶⁷ the stepwise depolymerisation–hydrolysis procedure was chosen instead for two reasons: 1) at least 80 h of operation, including four distillations, was required to isolate desired acid **3.23** directly from PHB; 2) the optimised yield (53%) of the one-step process is far from excellent.

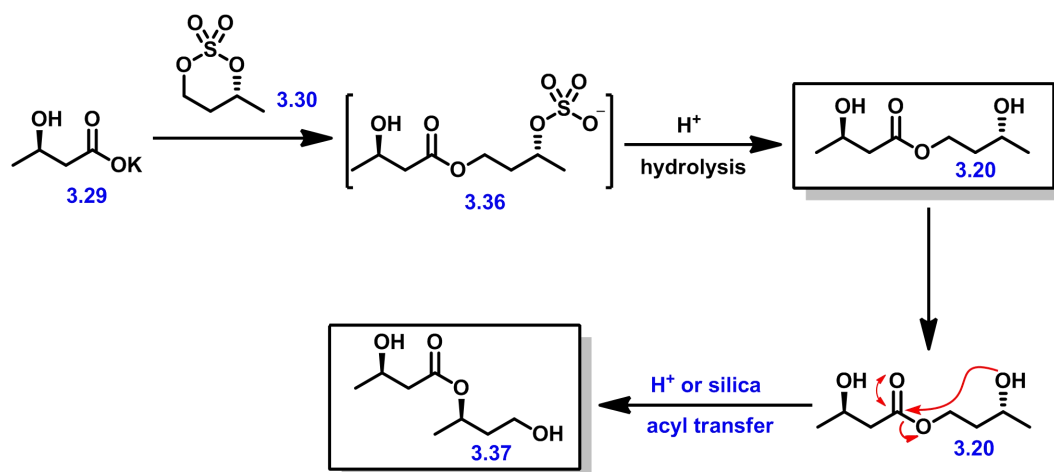
Compared to the one-step process, the depolymerisation protocol is easy to operate despite the methanolysis of PHB required 72 h for completion.⁶⁷ In addition, the subsequent hydrolysis step is fast and high yielding (84%). Applying the stepwise process, a 59% overall yield of carboxylate **3.29** (88% per step on average) was prepared for the subsequent key nucleophilic ring-opening reaction.

It is worth mentioning the conversion of methyl ester **3.35** to carboxylate **3.29**. In principle, a one-pot process can combine the hydrolysis step and carboxylate formation simply by concentrating the reaction mixture from the hydrolysis step (**Scheme 11**). However, in this one-pot procedure, the stoichiometry of base (KOH) is important since excess hydroxide ion would compete as a nucleophile for sulfate **3.30**, thus lowering the potential yield of the ring-opening reaction.

In principle, one equivalent of KOH should achieve conversion to the corresponding carboxylate. However, under such conditions, the reaction did not proceed to completion. Therefore, a stepwise procedure was applied that allows the KOH stoichiometry to be controlled.

It was intended that cyclic sulfate **3.30** would be opened by S_N2 attack of carboxylate **3.29**, and acidic hydrolysis of acyclic sulfate **3.36** would afford the target compound **3.20**. In the event, whilst ring-opening worked well, the acidic conditions of the sulfate hydrolysis led to up to 23% of acyl transfer. Moreover, the acyl transfer side product **3.37** could not be removed by chromatography since: 1) side product **3.37** shared the same retention factor as

the final target **3.20**; 2) silica gel catalyses the acyl transfer process (**Scheme 12**).



Scheme 12

Entry	Conditions	Yield (%)	Acyl transfer (%)
1	i) MeCN, reflux (90 °C), 1 h; ii) THF/H ₂ O/H ₂ SO ₄ (cat.), 1 h	100	23
2	i) MeCN, reflux (22 °C), 1 h; ii) THF/H ₂ O/H ₂ SO ₄ (cat.), 1 h	0	N/A
3	i) MeCN, reflux (40 °C), 2 h; ii) THF/H ₂ O/H ₂ SO ₄ (cat.), 1 h	0	N/A
4	i) DMF, RT, 1 h; ii) THF/H ₂ O/H ₂ SO ₄ (cat.), 1 h	91	14

Table 4

Four conditions were screened for the ring opening/hydrolysis process (**Table 4**). When acetonitrile was used as the solvent, the desired product **3.20** was furnished as a single diastereomer in quantitative yield (**Entry 1, Table 4**) but with 23% of the product converted into side product **3.37**. Although side product **3.37** and final product **3.20** had the same R_f value on TLC, attempts were made to separate them, in case the behavior of these two compounds on the column were different. However, silica gel chromatography achieved no separation. In addition, both the use of triethylamine (3%) deactivated silica gel and neutral alumina as the stationary phase were found to be ineffective for the separation. For this reason, the specific rotation obtained (-35.5) does not correspond to that of the pure product

3.20.

To tailor the reaction conditions to suit potential industrial production, lower temperatures were examined. When the reaction was attempted at room temperature using acetonitrile as the solvent (**Entry 2, Table 4**), a white heterogeneous suspension resulted and, probably due to the insolubility, the reaction led only to recovered starting material **3.30**. No improvement was observed when the temperature was raised to 40 °C (**Entry 3, Table 4**). Finally, DMF was examined as an alternative solvent that would provide a homogeneous mixture. Indeed, a 90% yield of product **3.20** was obtained in the solvent at room temperature (**Entry 4, Table 4**).

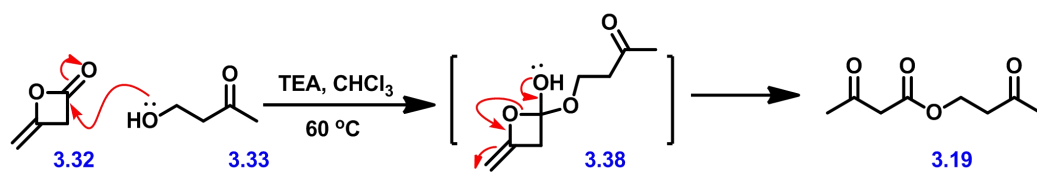
In summary, through the ‘classical approach’, the potential food additive **3.20** was prepared in 7 steps in 50% yield (92% per step on average) as a single enantiomer^x. Having a standard compound in hand, the one-pot enzymatic double reduction was investigated.

3.5.2 Enzymatic approach towards (3R)-hydroxybutyl (3R)-hydroxybutanoate**Production of diketoester 3.19 from 4-hydroxybutan-2-one and diketene**

As mentioned earlier,⁶⁴ a clean reaction between ketoalcohol **3.33** and diketene **3.32** was observed and the desired diketoester **3.19** was obtained in 77% yield. This reaction is supposed to proceed *via* a tetrahedral intermediate **3.28** which then collapses to give product **3.19** (**Scheme 13**). However, despite the fact that diketene is an inexpensive starting material, its transport and use are strictly controlled under recent regulations; therefore, to avoid

^x The *e.e.* of **3.20** was determined by HPLC in the literature (Robertson, J.; Clarke, K.; Veech, R. L., WO 2010/120300).

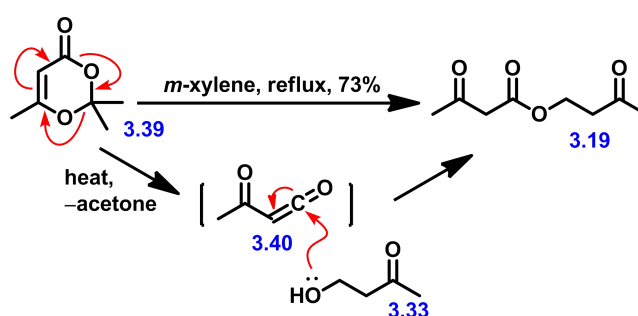
supply problems, an alternative route was sought.



Scheme 13

Production of diketoester 3.19 from 4-hydroxybutan-2-one and dioxinone 3.39

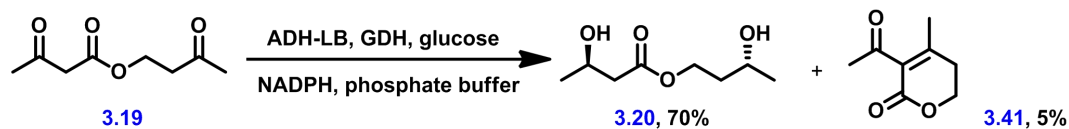
It was envisaged that treatment of 4-hydroxybutan-2-one 3.33 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one 3.39 would afford diketone 3.19 *via* a transesterification process. As expected, heating ketoalcohol 3.33 with dioxinone 3.39 in *m*-xylene at 150 °C for 30 minutes gave the desired product 3.19 in 73% yield. No side products were observed in this reaction and this protocol was applied as a general method for the synthesis of substrates for further explorations as discussed later in this chapter. Mechanistically, dioxinone 3.39 could undergo a thermal retro Diels–Alder reaction to form acyl ketene 3.40 that is immediately trapped by alcohol 3.33 to deliver product 3.19 (Scheme 14).



Scheme 14

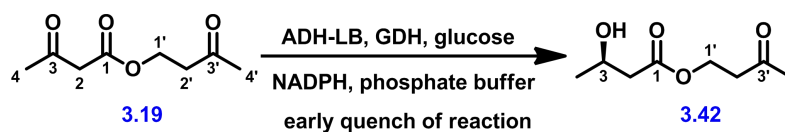
When diketoester 3.19 was subjected to the above-mentioned reduction conditions (*cf.* Table 1, page 135), a 70% yield of diol 3.20 was isolated after purification. A side product 3.41, isolated in 5% yield, derived from intramolecular aldol condensation, was produced,

probably as a result of a high local concentration of NaOH during the initial mixing process (Scheme 15).



Scheme 15

Interestingly, a single mono-reduction product was isolated when the reaction was quenched before completion. Since ADH-LB is known to recognise the β -ketoester moiety, it was expected that the first reduced carbonyl would be the C(3) carbonyl. Indeed, 3-oxobutyl (3*R*)-hydroxybutanoate **3.42** was isolated when an early quench was applied (Scheme 16).



Scheme 16

The pH of the system dropped from 7.0 to 4.4 over the course of 2 h as gluconic acid levels increased (Figure 7), and careful addition of 5 M NaOH solution maintained the pH within the proper range and minimised formation of the aldol product **3.41**.

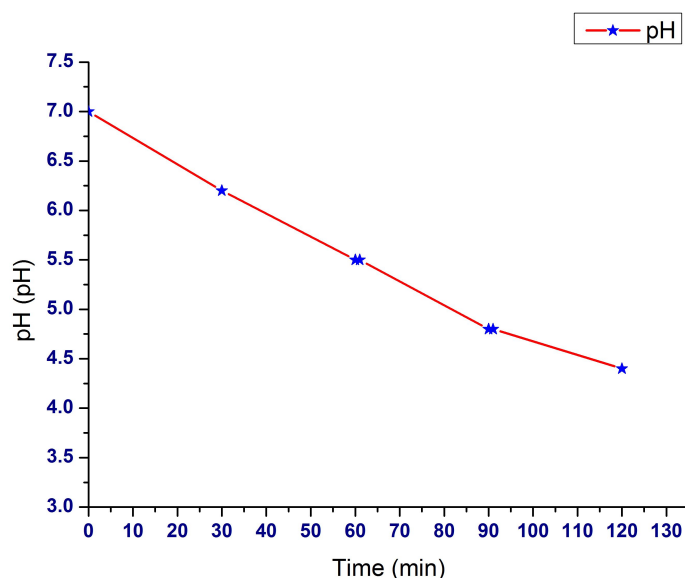


Figure 7

The *d.r.* of product **3.20** was determined by NMR spectroscopy. The ^{13}C NMR spectrum of **3.20** showed only one set of signals, identical to those for the product from the cyclic sulfate route, indicating that the formation of a single diastereomer had been achieved. The enantiomeric purity of **3.20** was ascertained by specific rotation (-54.6). This value is rather higher than that obtained (-35.5) from the product synthesised *via* the classical method (*cf.* page 140) in which acyl transfer product **3.37** would affect the $[\alpha]_{\text{D}}$ value.

Through repeating the two approaches towards diol **3.20**, double reduction of diketoester **3.19** was confirmed as a highly efficient, cost effective and scalable solution towards this palatable food additive. It also confirmed the concept of a ‘one-pot, one enzyme multi-reduction’.

3.5.3 Substrate scope in the ADH-LB multiple reduction

Substrate design

To gain more knowledge about the applicability of ADH-LB towards other di/polyketones, a preliminary exploration was conducted to obtain information on the following issues:

1. The relationship between enzyme reactivity and the distance between the two separated ketone functionalities. Three substrates were designed in which the chain connecting the two carbonyls varied from 5 to 7 bonds (**Figure 8**).

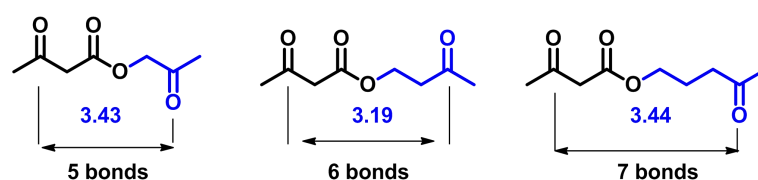


Figure 8

2. The requirement for a β -keto ester moiety in the reduction process. Three compounds were designed including an α -ketoester, a γ -ketoester and a mono-ketoester as shown in **Figure 9**.

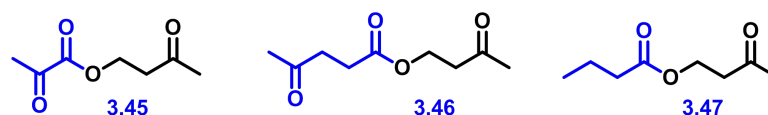


Figure 9

3. The electronic effect on the ketone towards the reduction process. Introducing substituted phenyl groups is the easiest way to modify the electronic demand of the adjacent ketone *via* conjugation. Two first substrates were selected (**Figure 10**).

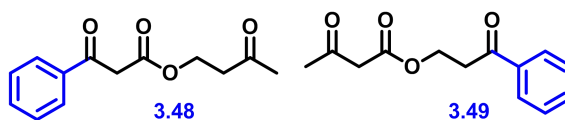


Figure 10

4. The steric effect on the ketone towards the reaction process. In this preliminary study, a cyclohexyl ring was introduced on either side of the molecule (**Figure 11**).

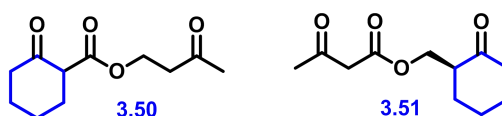


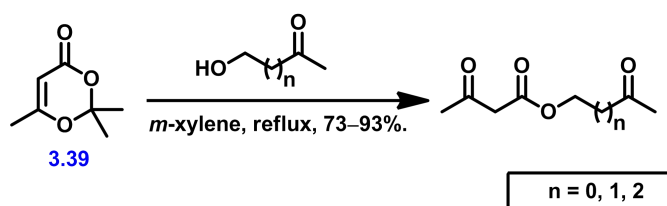
Figure 11

To synthesise the substrates, four different strategies were applied.

Synthesis of substrates

Series I

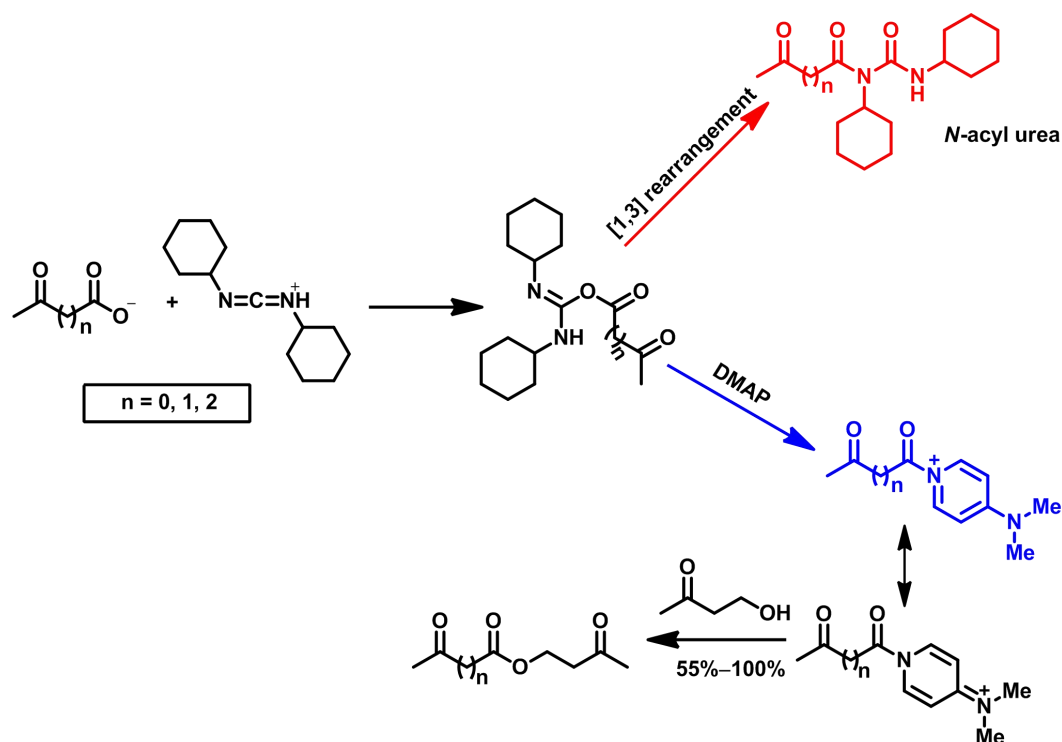
Although diketene was the first choice for the synthesis of this series of compounds, due to the new regulation problems, dioxinone **3.39** was used as a more accessible alternative. As discussed earlier, the reaction proceeds at relatively high temperature *via* a ketene intermediate which is trapped by the appropriate alcohols. For **series I**, high isolated yields (73–93%) were achieved with no observed side reactions (**Scheme 17**).



Scheme 17

Series II

Steglich esterification⁶⁸ conditions were applied to synthesise this series of compounds. Depending on the rate of formal [1,3]-rearrangement in the side reaction (shown in red)^y versus the rate of DMAP attack, the yield of coupled product varied from 55% to quantitative (Scheme 18).

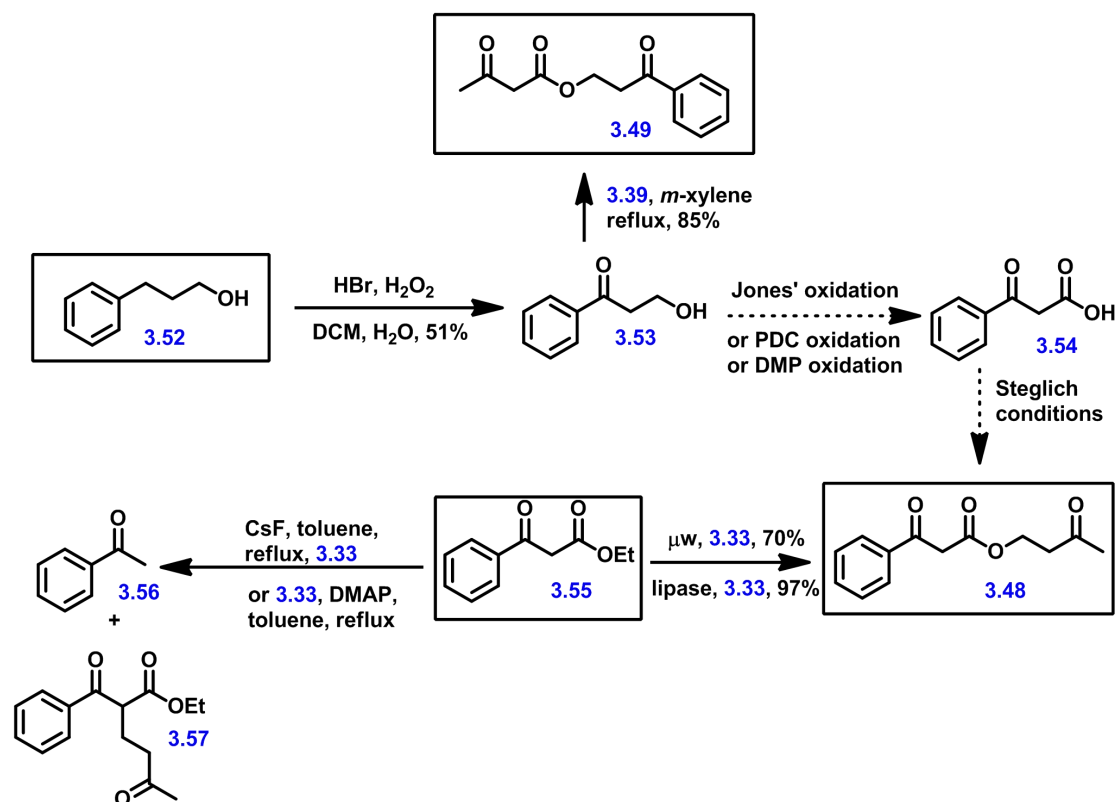


Scheme 18

Series III

For substrates **3.48** and **3.49**, 3-phenylpropan-1-ol **3.52** was used as the common starting material (Scheme 19).

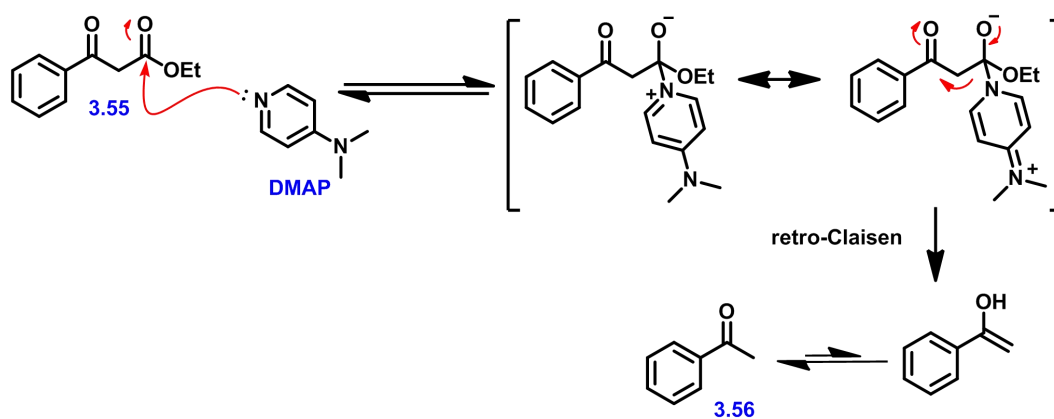
^y As an example, *N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)butyramide **3.89** was isolated as a side product during the synthesis of ester **3.47**, see page 365.



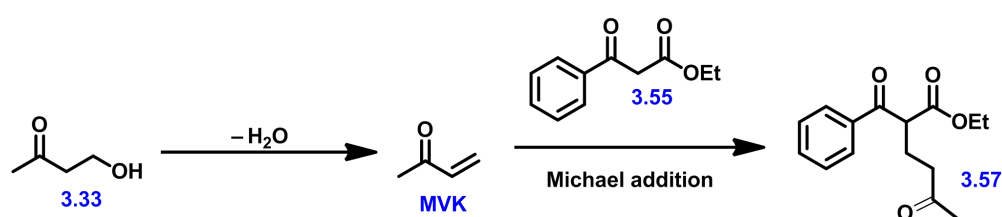
Scheme 19

Alcohol **3.52** was subjected to selective benzylic oxidation (HBr, H₂O₂),⁶⁹ but further oxidation towards carboxylic acid **3.54** led to complex mixtures (Scheme 19). Therefore, transesterification between ethyl ester **3.55** and 4-hydroxybutan-2-one **3.33** was attempted first using CsF⁷⁰ or a nucleophilic catalyst (DMAP).⁷¹ Surprisingly, when CsF or DMAP were introduced into the reaction mixture, acetophenone **3.56** (up to 93% with DMAP) and diketoester **3.57** (up to 61% with CsF) were isolated.

It was suspected that a retro-Claisen condensation process occurred under these conditions to give acetophenone (Scheme 20). To explain the formation of diketoester **3.57**, it was proposed that dehydration of hydroxyketone **3.33** gave MVK, and subsequent Michael addition furnished the adduct **3.57** in high yield (Scheme 21).



Scheme 20

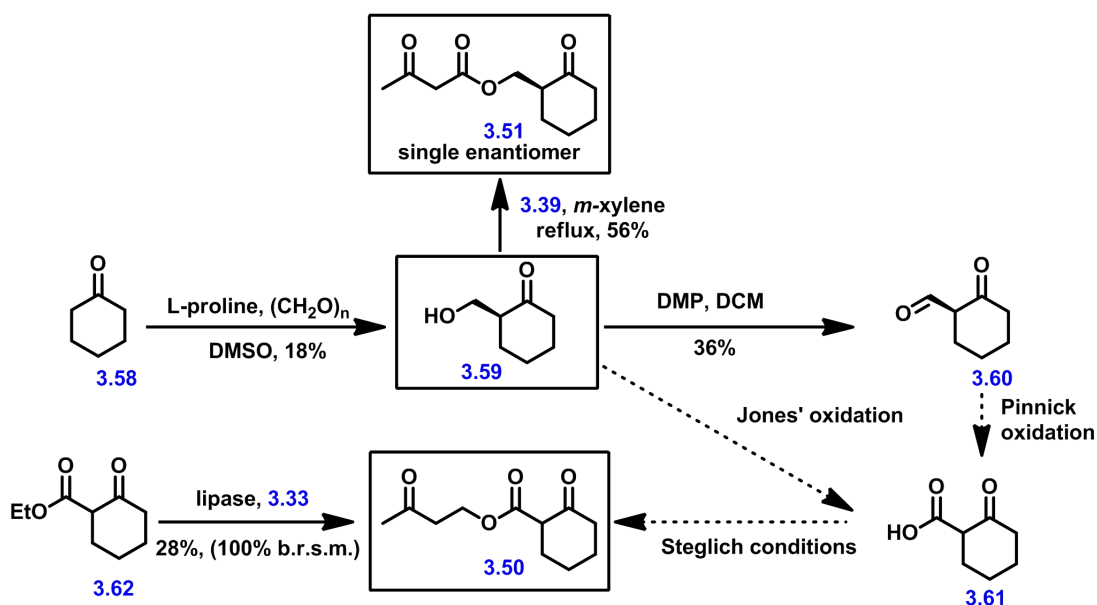


Scheme 21

Microwave conditions were investigated in the hope that brief intensive heating without a catalyst might facilitate transesterification. As planned, when microwave conditions were applied (130 °C, 10 min), a 70% yield of the desired product was isolated. Lipase catalysed transesterification was also tested, resulting in a 97% yield of the desired product **3.48** (Scheme 19).

Series IV

According to the synthetic plan, enantiomerically pure ester **3.51** and racemic ester **3.50** were selected to investigate steric effects on the enzyme ADH-LB. Chiral hydroxy ketone **3.59** was identified as the key intermediate for both substrate syntheses (Scheme 22).



Scheme 22

Córdova published a protocol using 10 mol% (*S*)-proline to effect asymmetric aldol reaction to afford the (*S*)-enantiomer **3.59** with up to 99% *e.e.*⁷² When the literature conditions were repeated, only an 18% yield of product was obtained (**Scheme 22**). Although the reported yield of this process is modest (47%), all attempts to improve the yield (using brand new and purified chemicals, or addition of formaldehyde *after* proline was completely dissolved in DMSO, or scaling up the reaction) were unsuccessful.

Next, transesterification was applied to prepare ester **3.50** using *Candida antarctica* lipase after all attempts to oxidise **3.59** to its corresponding acid **3.61** failed (**Scheme 22**). The yield by this process was modest (28%) but no side reactions were observed and the yield was quantitative based on recovered starting material. No further optimisation was attempted since sufficient material was accumulated for the enzymatic reductions to be tested.

Results of enzymatic reduction

With all substrates in hand, the enzymatic reductions were tested. The *d.r.* and *e.e.* values in these reductions were determined by NMR analysis including Mosher's ester derivatives. To ascertain the absolute stereochemistry of the reduced product, hydrolysis or further reduction^z of the reduced products was carried out. The absolute configuration of every stereogenic centre within each reduced product was determined based on the sign and magnitude of the specific rotation of each hydrolysed or further reduced fragment.

As an example, the reduced product from diketoester **3.44** (**Series I**, compound #3) was isolated in quantitative yield. Before the determination of the *d.r.* value of this product, characterisation of **3.63** showed that it had only one set of ¹³C signals, indicating that a single diastereomer had been obtained (**Figure 12**).

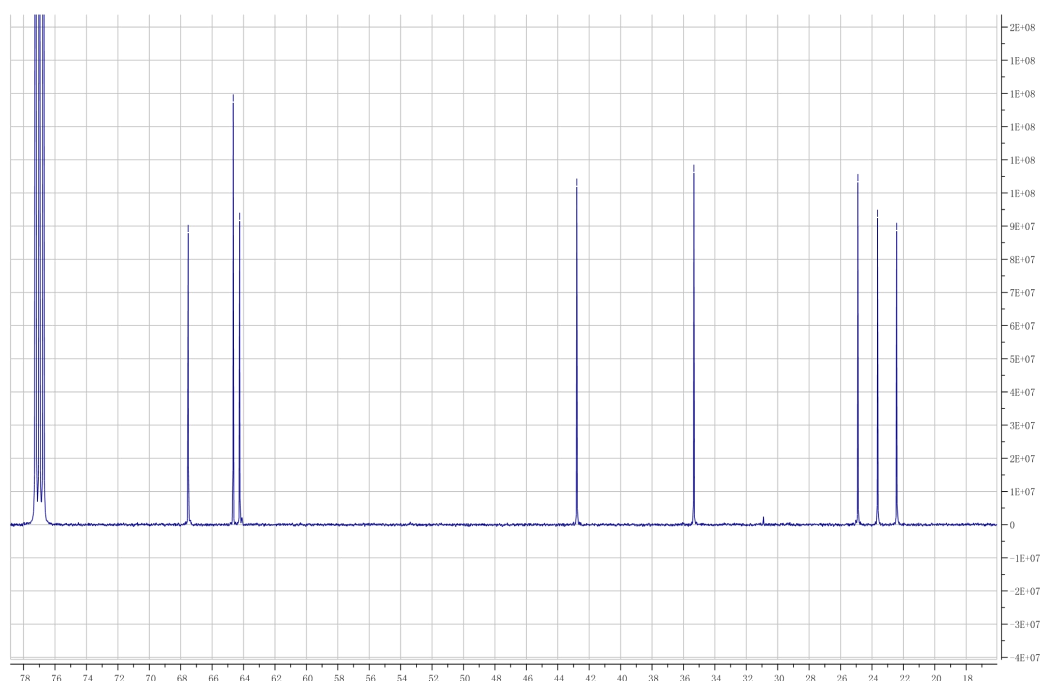
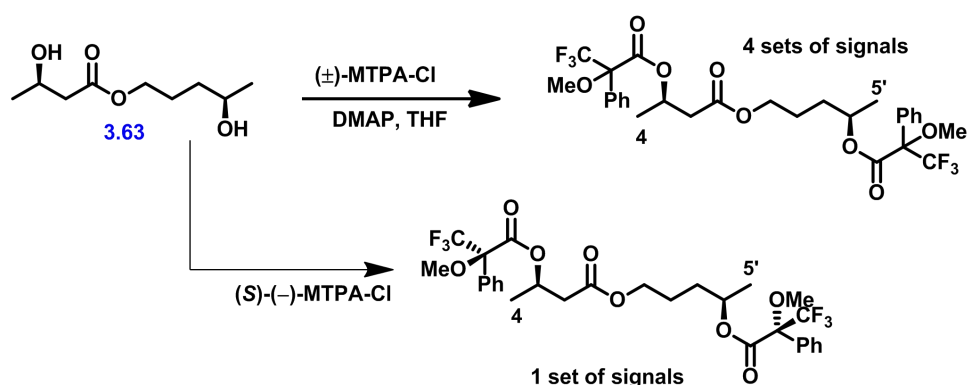


Figure 12

^z For more details of the reduction method, see 'Miscellaneous compounds' section in experimental, page 340.

With the knowledge that reduced product **3.63** was a single diastereomer, the enantioselectivity of the reduction was determined. Mosher's ester derivatives were synthesised as shown in **Scheme 23**. Diol **3.63** was first treated with *racemic* α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (MTPA-Cl)^{aa}. As expected, the ¹H NMR spectrum showed four sets of signals (**Figure 13**). Then diol **3.63** was treated with enantiomerically pure (*S*)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride ((*S*)-(-)-MTPA-Cl), giving one set of signals, which indicated high *e.e.* (**Figure 13**). The enantiomeric purity was further proven by ¹⁹F NMR analysis. Therefore, it was concluded that the enantiomeric excess of product **3.63** was more than 99%, *i.e.*, **3.63** was effectively obtained as a single enantiomer of a single diastereomer.



Scheme 23

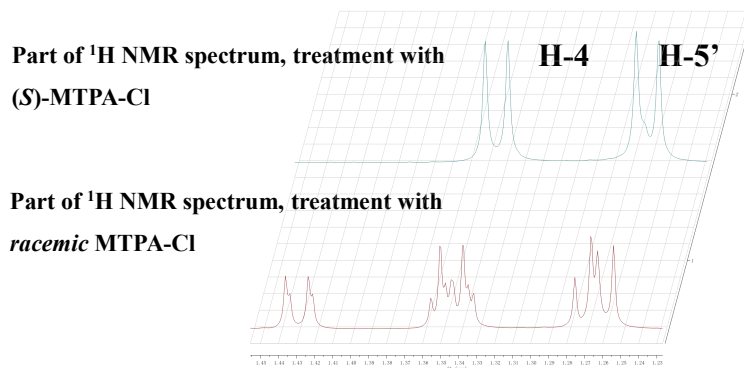
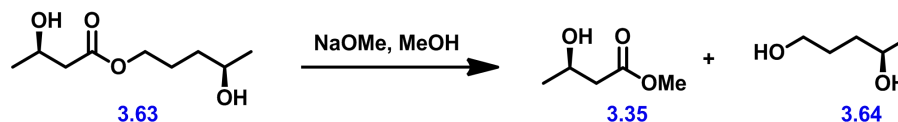


Figure 13

^{aa} The racemic MTPA-Cl treatment was done by adding 50% (*R*)-MTPA-Cl followed by 50% (*S*)-MTPA-Cl in the reaction mixture.

Subsequently, methanolysis was conducted on **3.63** to give ester **3.35** and diol **3.64** (Scheme 24).



Scheme 24

The specific rotations of the hydrolysed ester **3.35** and diol **3.64** were compared to their corresponding literature values^{73, 74} (Table 5) which confirmed the (*R*)- sense of reduction although the experimental magnitude of $[\alpha]_D$ was lower. It was concluded that diol **3.63** was obtained with more than 99:1 *d.r.* and more than 99% *e.e.* on the basis of Mosher's method.

	Reported data	Data obtained
 3.35	-25.7^{73} (c 1.00, CHCl ₃ , 22 °C)	-23.0 (c 1.00, CHCl ₃ , 24 °C)
 3.64	-13.1^{74} (c 1.02, MeOH, 20 °C)	-12.7 (c 1.00, MeOH, 24 °C)

Table 5

The results of the enzymatic reductions of various substrates are summarised in Tables 6 and 8–10.

Result of Series I

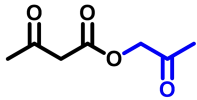
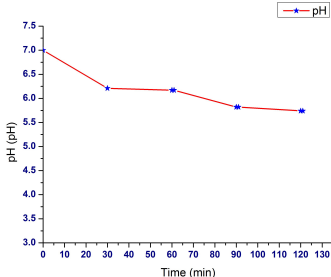
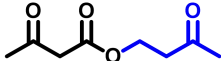
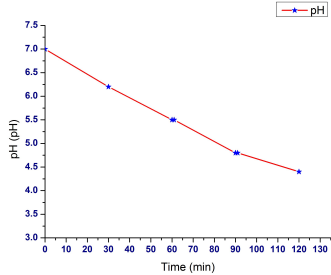
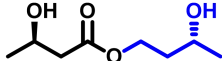
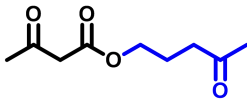
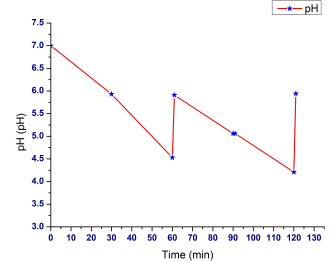
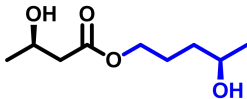
SM (synthetic yield)	pH value chart	Product	Yield <i>d.r. & e.e.</i>
 3.43 (77%)		Not identified	N/A N/A N/A
 3.19 (73%)		 3.20	70% >99:1 >99% ^{ab}
 3.44 (93%)		 3.63	100% >99:1 >99%

Table 6

The reductions of diketone **3.19** and **3.44** have been discussed earlier (pages 142 and 151), but enzymatic reduction of 2-oxopropyl 3-oxobutanoate **3.43** turned out to be interesting. Unlike the other enzymatic reductions, there was little decrease in pH during the reaction (Table 6). In addition, a dramatic colour change was observed: when diketone **3.43** was added to the phosphate buffer, the mixture became bright yellow, and within 30 minutes, it became dark green; if the reaction was left overnight, a light orange colour was observed.

^{ab} The *e.e.* of **3.20** was determined by HPLC in the literature (Robertson, J.; Clarke, K.; Veech, R. L., WO 2010/120300).

Two compounds, **A** and **B** ($M_A = 262$, $M_B = 252$), were isolated in this reaction^{ac}.

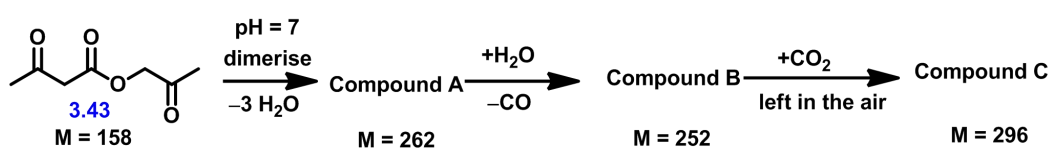
To find out the factors that affect this reaction, four other conditions were examined (**Table 7**). When otherwise identical conditions were tested but *without* adding any ADH-LB, the same result was observed (**Entry 2, Table 7**). Next, diketone **3.43** was added to the pure phosphate buffer *without* any additives (ADH, GDH, NADPH, glucose), which resulted in the same products (**Entry 3, Table 7**). Then, pure water was tested as the solvent (**Entry 4, Table 7**) and this time, no reaction was observed even when the reaction was left overnight. It was found that the initial pH of the water was 9.0, then it dropped to 2.85 after 18 h. These results suggested that pH was the only factor important to this reaction. Indeed, when the reaction was performed in a pH 9 phosphate buffer, the same result as for **Entries 1–3** was observed (**Entry 5, Table 7**).

Entry	Conditions	Result
1 (standard)	0.2 M Phosphate buffer (pH 7), ADH-LB, GDH, NADPH, glucose	A and B (1.3:1)
2	0.2 M Phosphate buffer (pH 7), GDH, NADPH, glucose	A and B (1.2:1)
3	0.2 M Phosphate buffer (pH 7)	A and B (1.3:1)
4	Distilled water (pH 9)	No reaction
5	0.2 M Phosphate buffer (pH 9)	A and B (1.3:1)

Table 7

^{ac} For the whole data set of compound **A** and **B**, see Appendix B, page 371.

From the MS data, it appeared that dimerisation of **3.43** occurred with loss of three H₂O molecules to form **A** (Scheme 25). The mass difference between **A** and **B** was 10, and it was proposed that overall loss of CO and addition of H₂O has occurred which was supported by ¹³C NMR analysis. It was also found that if **B** was left long enough in the air, a new compound **C** was formed in which the molecular weight increased by 44, indicating possible absorption of CO₂.



Scheme 25

There are many possibilities for ester **3.43** to dimerise and lose H₂O, and the structural identity of compounds **A** and **B** could not be fully resolved based solely on ¹H and ¹³C NMR analysis. On one hand, the ¹H NMR spectrum of compounds **A** and **B** provide limited information because most resonances for both compounds are singlets; on the other hand, ¹³C NMR showed there were 14 carbons in **A** and 13 carbons in **B** (Figures 13–17)^{ad}.

^{ad} For more details, see Appendix B, page 371.

NMR for Compound A

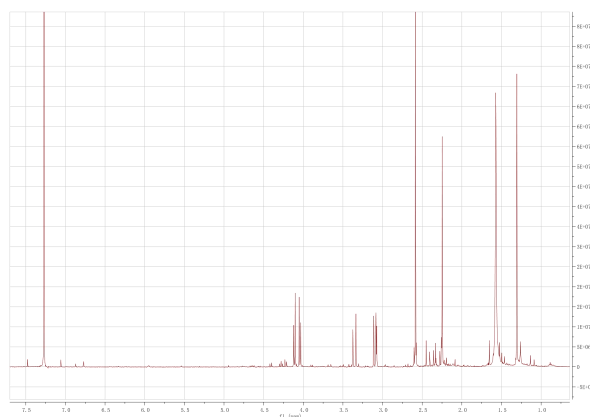


Figure 14

NMR for Compound B

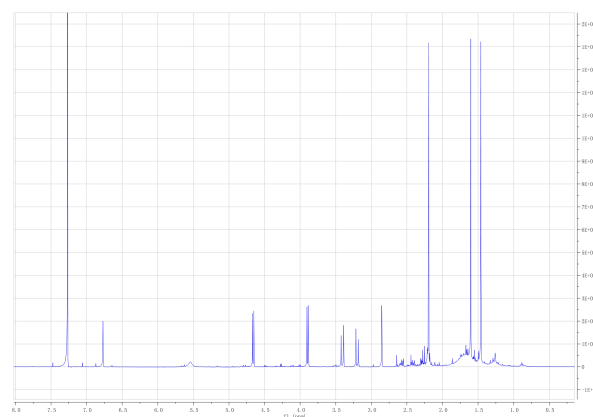


Figure 15

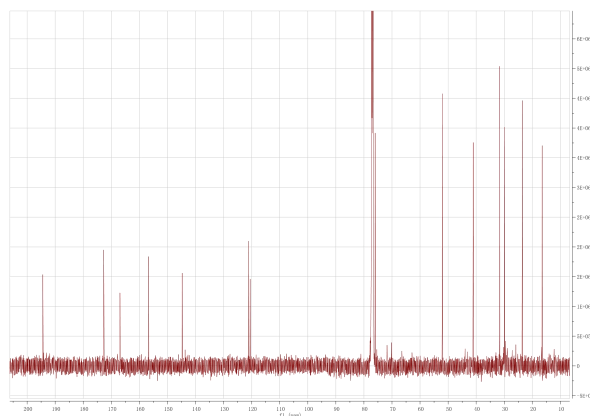


Figure 16

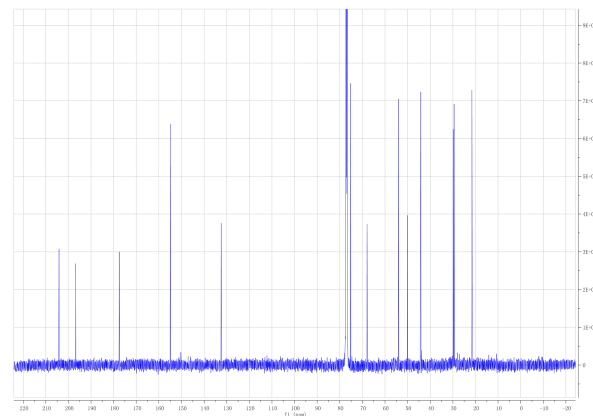


Figure 17

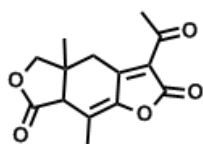


Figure 18

So far, a structure for **A** has been proposed (**Figure 18**). However, this suggested structure does not readily explain the conversion from **A** to **B**.

Attempts to crystallise **A** or **B** were unsuccessful because the newly-formed crystals were unstable.

Due to time constraints, further investigation of this reaction was paused, and focus was turned onto the enzymatic reduction of other substrates.

Result of Series II

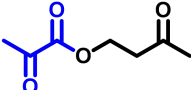
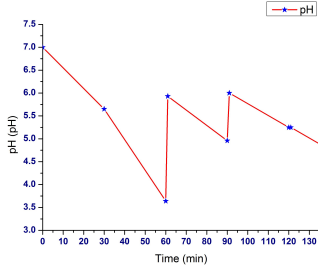
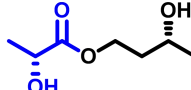
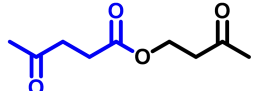
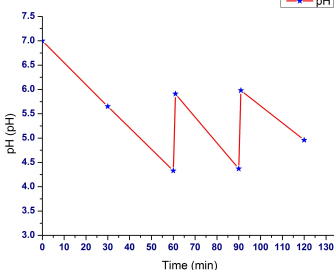
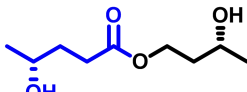
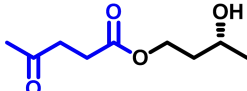
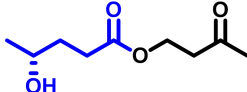
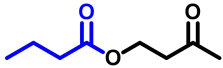
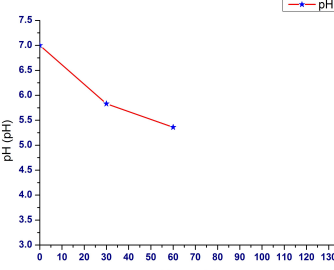
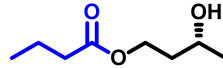
SM (synthetic yield)	pH value chart	Product	Yield <i>d.r. & e.e.</i>
 3.45 (55%)		 3.65	53% >99:1 >99%
 3.46 (100%)		 3.66  3.67  3.68	96% yield^{ae} <i>d.r.</i> >99:1 <i>e.e.</i> >99% 3% yield N/A <i>e.e.</i> >99% 3% yield N/A <i>e.e.</i> >99%
 3.47 (87%)		 3.69	83% N/A >99%

Table 8

All the substrates were reduced with excellent diastereo- and enantio- selectivity, implying that the β -ketoester moiety is *not* a prerequisite for this enzymatic reduction. Monoalcohols **3.67** and **3.68** could be isolated when early quench of reaction was applied on diketone **3.46**. Only a moderate yield (53%) of diol **3.65** was obtained by the enzymatic reduction but up to

^{ae} Yield of all reduction products is 102%, probably due to accuracy limit of balance; **3.67** and **3.68** were obtained as an inseparable mixture.

12% of (*R*)-butane-1,3-diol **3.24** was also isolated, indicating that hydrolysis had occurred during the process.

Result of Series III

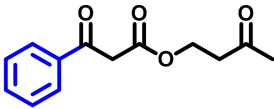
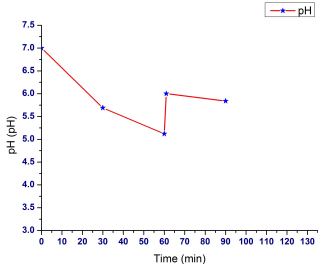
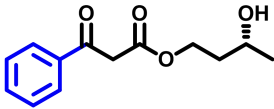
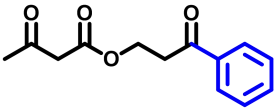
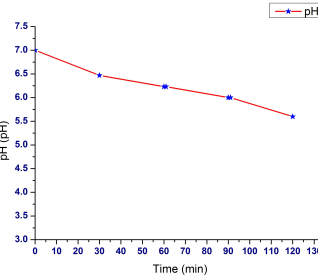
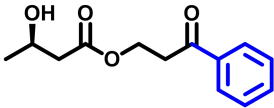
SM (synthetic yield)	pH value chart	Product	Yield <i>d.r. & e.e.</i>
 3.48 (97%)		 3.70	82% N/A >99%
 3.49 (85%)		 3.71	54% N/A >99%

Table 9

As shown in **Table 9**, only the methyl ketone was reduced in both cases. Perhaps the bulk of the phenyl group could not be accommodated by the enzyme, or conjugation from the phenyl group reduces the electrophilicity of this carbonyl group. The latter could be probed by introducing substituents into the phenyl rings in order to tune the electronic demand of the conjugated carbonyl.

Result of Series IV

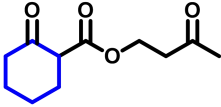
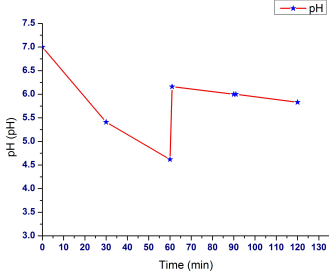
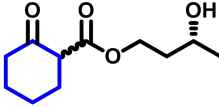
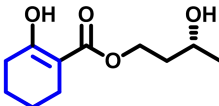
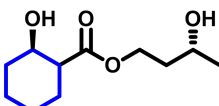
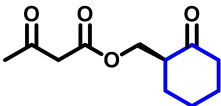
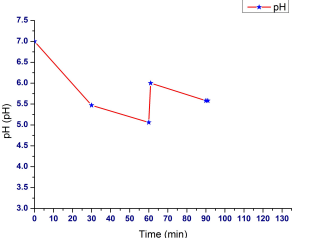
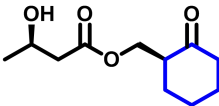
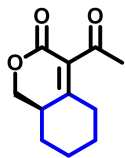
SM (synthetic yield)	pH value chart	Product	Yield <i>d.r.</i> & <i>e.e.</i>
 3.50 (28%, 100% b.r.s.m.)		 3.72a, 3.72b  3.72c  3.73	31% yield <i>d.r.</i> = 1:1 <i>e.e.</i> N/A 54% yield <i>d.r.</i> N/A <i>e.e.</i> — 3% yield <i>d.r.</i> — <i>e.e.</i> —
 3.51 (56%)		 3.74  3.75	88% yield <i>d.r.</i> >99:1 <i>e.e.</i> >99% 3% yield <i>d.r.</i> N/A <i>e.e.</i> —

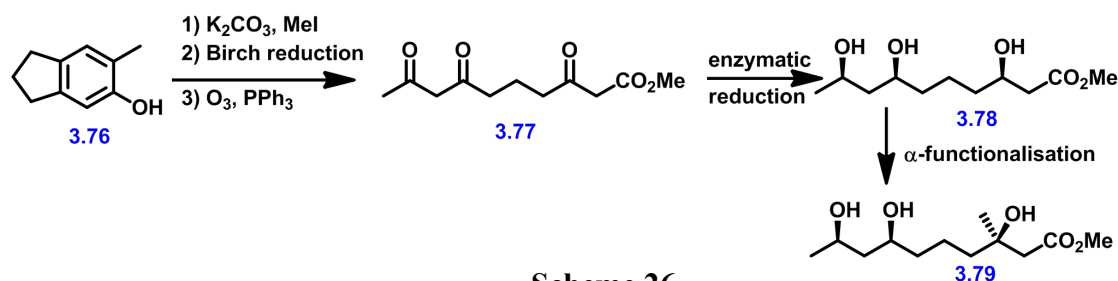
Table 10

When a cyclic system was introduced, the steric effect was apparent. The methyl ketone moiety was reduced first. In the case of diketone **3.50**, when the reduction reaction was left for 80 min, the doubly reduced product was isolated in 3% yield, implying that ADH-LB was tolerant to the bulk of the molecule to a certain extent. In the case of (*S*)-(2-oxocyclohexyl)methyl 3-oxobutanoate **3.51**, however, no diol formation was observed after 90 min, perhaps due to a stereochemical mismatch between the enzyme and the (*S*)-configured cyclohexanone, which could be tested with the (*R*)-enantiomer or the

racemate in the future. Further investigation of the steric effects towards ADH-LB could include introducing different ring size in the molecule and functionalising the ketone with acyclic bulky groups such as *tert*-butyl, isopropyl etc.

3.6. Future work

These positive results lay the foundations for further investigations to widen substrate scope for ADH-LB as discussed earlier. However, *any* ADH/KRED could be explored in this application and when knowledge and experience grow by enzyme-substrate screening, targeted syntheses of structurally complex natural products will be possible. As an example, the chiral fragment of taurospongins A (**Chapter 1**) could, in principle, be realised by application of a systematic enzymatic reduction strategy (**Scheme 26**).



Commercially available dihydroindene derivative **3.76** will be subjected to a sequence of transformations (methylation, Birch reduction and ozonolysis) to obtain triketone **3.77** for the key reduction step. Ideally, the enzymatic reduction will proceed in a highly stereoselective fashion to yield triol **3.78**, which will then be subjected to a selective α -functionalisation to achieve the 3° alcohol centre in the triol fragment of taurospongins A. All published approaches to this fragment, including the Robertson synthesis,⁷⁵ require more than 11 steps. However, by utilising the enzymatic reduction–C–O activation strategy, the

synthesis should be approximately halved in length. Although selective α -functionalisation appears challenging, or even fanciful, precedents⁷⁶⁻⁸⁰ are available to show the potential of this transformation. Finally, by changing the enzyme for reduction or by adjusting subsequent chemical elaborations, highly diverse derivatives would be achieved.

In summary, systematic enzymatic multiple reduction combined with a selective C–O activation strategy could illuminate a new path for organic synthesis. Instead of relying on purely chemical-based transformations to achieve synthetic goals, a full investigation of enzyme mediated reactions (not only limited to reductions) can provide compelling advantages, among which the most important feature would be high selectivity and sustainability.

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Experimental

General Experimental Techniques

● Solvents

Solvents and commercially available reagents were dried and purified before use where appropriate, using standard procedures;¹ Benzene was distilled from sodium metal and stored over 4 Å molecular sieves; DMSO was degassed using the ‘freeze-pump-thaw’ procedure; DME was distilled from CaH₂ and stored over 4 Å molecular sieves; DMF, HMPA, DMPU were distilled from CaH₂ under reduced pressure and stored over 4 Å molecular sieves. Acetone was distilled from anhydrous K₂CO₃ and stored over 4 Å molecular sieves. Pyridine was distilled from KOH and stored over KOH. DCM, THF, ether, methanol, toluene, MeCN were obtained dry and oxygen free from Grubbs solvent dispenser units. All the other solvents (DCE, CHCl₃, ethanol, *t*-BuOH, 1,4-dioxane, ethyl acetate, *m*-xylene, pyrrolidine) were used as supplied without prior purification. ‘Petrol’ refers to the fraction of petroleum ether which boils in the range of 30–40 °C. ‘Ether’ refers to diethyl ether. ‘Brine’ refers to a saturated aqueous solution of NaCl. Unless otherwise specified, the term ‘solution’ refers to aqueous solution.

● Reagents

AD-mix- β refers to a mixture of (DHQD)₂PHAL, K₂CO₃, K₃Fe(CN)₆, and K₂OsO₄·2H₂O. Grubbs’ II catalyst refers to [1,3-*bis*-(2,4,6-trimethylphenyl)-2-imidazolidinylidene] (dichlorobenzylidene)-(tricyclohexylphosphine)ruthenium]. Hoveyda–Grubbs’ II catalyst refers to [(1,3-*bis*-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxy

phenylmethylene) ruthenium]. LiBr and NaI were heated to 150 °C under vacuum (0.05 Torr) for 16 h before use. Mg turnings were washed with HCl solution (10% in H₂O) and oven-dried before use. FeSO₄·7H₂O was recrystallised from H₂SO₄ solution (0.4 M in H₂O). CuI was purified by dissolving crude CuI in a boiling solution of NaI (sat.) over 30 min; pure CuI was obtained by cooling and diluting the solution with H₂O, followed by filtering and washing sequentially with H₂O, ethanol, ethyl acetate and ether, then drying under reduced pressure (0.05 Torr) for 24 h in the dark. Molecular sieves were activated by heating to 140 °C for 2 h under reduced pressure (0.05 Torr). All other reagents were used as supplied without prior purification.

● Reactions

For reactions requiring anhydrous conditions, experiments were carried out in oven-dried glassware under an argon atmosphere.

● Chromatography

Thin layer chromatography (TLC) was performed using Merck DC-Alufolien 60 F₂₅₄ 0.22 mm precoated plates. Spots on TLC were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) then stained and heated with either 5% anisaldehyde in ethanol, 5% KMnO₄ in 5% aqueous NaOH solution, or 5% H₃PMo₁₂O₄₀ in ethanol. Retention factors (R_f) are reported with the solvent system used in parentheses. Preparatory TLC was performed on Whatmann silica gel (60 Å) precoated glass plates (layer thickness 1 mm).

Flash chromatography was performed on Merck 60 silica with a particle size of 40–63 µm (pore diameter 60 Å) with the solvent system used in parentheses including graduated

solvent systems. The general method was adapted from the procedure reported by Still and co-workers.² The ‘KF silica column’ refers to the stationary phase composed of 90% silica and 10% KF.³ The resin of ion exchange column Amberlite® IR-120 (Na⁺ form) was activated by stirring it gently in a beaker with sufficient hydrochloric acid (1.0 M in H₂O) to cover it. After 45 min the resin was separated and washed repeatedly with distilled water until the washings were neutral. The wet resin was then transferred to the column (1.0 cm diameter, 8.5 cm bed depth) and washed through with distilled water (× 2) then eluent (× 4) prior to loading the sample.⁴

● Melting points & boiling points

Melting points were determined using a Griffin heated metal block apparatus and are uncorrected. Boiling points were measured using a short path distillation unit, Kugelrohr apparatus or Vigreux column assembly as indicated. The pressure (Torr) is specified in each case.

● Polarimetry

Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm with a path length of 1 dm, and are quoted in units of 10⁻¹ deg cm² g⁻¹. Concentrations are given in g/100 mL.

● Infrared spectroscopy

Infra-red spectra were recorded on a Brüker Tensor 27 Fourier Transform spectrometer as a thin film on NaCl plates or directly on a diamond ATR module. Absorption maxima ($\nu_{\max}$)

were recorded in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w) and broad (br).

● **Nuclear magnetic resonance spectroscopy**

Proton (^1H) NMR spectra were recorded on the following spectrometers: Brüker AVC 500 (500 MHz), Brüker AV 400 (400 MHz), Brüker DPX 400 (400 MHz) or Brüker DPX 200 (200 MHz) spectrometer. Chemical shifts (δ_{H}) are reported in parts per million (p.p.m.) downfield of tetramethylsilane using residual protonated solvent peak as the internal reference. Assignments were made on the basis of chemical shift, coupling constants, COSY, HMQC, HSQC, HMBC, NOE, NOESY data and comparison with spectra of related compounds. Abbreviations used in the description of multiplicities are singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), multiplet (m), app. (apparent) and broad (br). Coupling constants (J) are quoted to the nearest 0.5 Hz.

Carbon-13 (^{13}C) NMR spectra were recorded on the following spectrometers: Brüker AVC 500 (125 MHz) or Brüker AV 400 (100 MHz). Chemical shifts (δ_{C}) are reported in parts per million (p.p.m.) downfield of tetramethylsilane using deuterated chloroform as the internal reference. Assignments were made on the basis of DEPT-135, HMQC, HSQC and HMBC experiments where appropriate.

Fluorine (^{19}F) NMR spectra were recorded on a Brüker AVC 500 (470.4 MHz) or Brüker AV 400 (376.5 MHz) spectrometer. Trichlorofluoromethane was used as internal reference. Chemical shifts (δ_{F}) are reported in parts per million (p.p.m.).

● Mass spectrometry

Low resolution ESI mass spectra were recorded on a Waters Micromass LCT Premier spectrometer. Low resolution CI mass spectra were recorded by Dr. George C. Feast or by the author on a Micromass GCT – Agilent 6890 series GC platform. High resolution ESI or FI mass spectra were recorded by Robin Procter and co-workers at the Oxford Chemistry Research Laboratory, using a Brüker Daltronics microTOF spectrometer (ESI) or a temperature programmed Waters GC-TOF mass spectrometer (FI) where necessary. m/z values are given in Daltons with percentage abundances, and, where known, relevant fragment ions, given in parentheses. High resolution values are calculated to 4 decimal places from the molecular formula. The difference between measured and theoretical mass value is no more than 5 p.p.m.

● X-ray crystallography

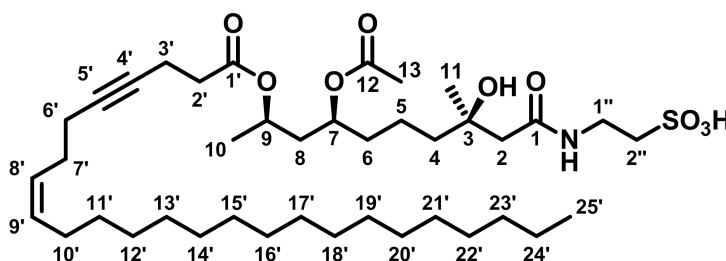
Single crystal X-ray crystallography was performed by Dr. Amber Thompson or Dr. George C. Feast. A single crystal was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073 \text{ \AA}$). Intensity data were processed using the DENZO-SMN package.⁵ Structures were solved using the direct-methods program SIR92 which located all non-hydrogen atoms.⁶ Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite.⁷ Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The ORTEP pictures of crystals were generated by CRYSTALMAKER software.

● **Useful information:**

1. The compounds are described in the numerical order (*e.g.* compound **1.1**, **1.2**, **1.3** etc), and this order does *not* necessarily correspond to the scheme order (*e.g.* **Scheme 1**, **Scheme 2**) and the order that compounds appear in a specific scheme.
2. The compounds are described with a diagram of the compound with atom numbers.
For a few cases, the atom numbers do not correspond to the number in the name of a compound.
3. For other compounds that are not mentioned in the main text in **Chapters 1, 2**, and **3** are described in the '**Miscellaneous compounds**' section.

Experimental Procedures and characterisation data for compounds in Chapter 1: Total synthetic study towards taurospongins A – a DNA polymerase β inhibitor

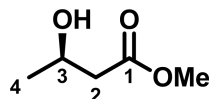
Taurospongins A (1.1)



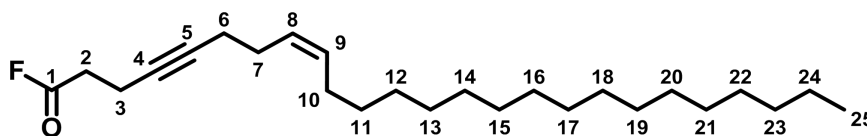
N-Hydroxysuccinimide (8 mg, 70.0 μmol) followed by dicyclohexylcarbodiimide (15 mg, 72.7 μmol) was added to a solution of acid **1.154** (15 mg, 23.6 μmol) in 1,4-dioxane (0.8 mL) at RT. The reaction mixture was stirred for 2 h before addition of ether (2 mL). The resulting white suspension was filtered and concentrated to furnish the desired *N*-hydroxysuccinic ester **1.157**, which was used immediately without further purification.

A solution of taurine (13 mg, 0.104 mmol), triethylamine (30 μL , 0.215 mmol), 1,4-dioxane (0.5 mL) and H_2O (0.4 mL) was added to the freshly prepared *N*-hydroxysuccinic ester **1.157**. The reaction mixture was stirred at RT for 1 h. Toluene (2 mL) was added and the reaction mixture was concentrated to remove H_2O azeotropically (repeated twice). The residue was purified by ion-exchange column (Amberlite® IR-120 Na^+ form, DCM/MeOH, 80:20) followed by flash chromatography on silica gel (DCM/MeOH, 80:20) to furnish the title compound (**1.1**) as a waxy solid (15 mg, 86% for two steps). R_f ($\text{CH}_3\text{Cl}/\text{MeOH}$; 80:20) = 0.30; $[\alpha]_{\text{D}}^{25} -3.40$ (c 1.00, CHCl_3), lit⁸ $[\alpha]_{\text{D}}^{25} -3.50$ (c 0.37, CHCl_3); ^1H NMR (500 MHz,

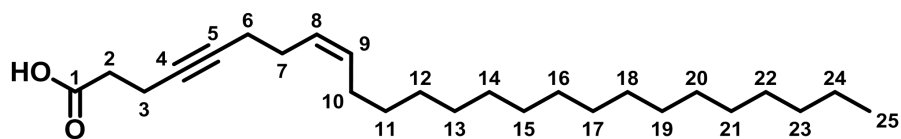
CD₃OD) δ 0.90 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 1.21 (3 H, s, H-11), 1.25 (3 H, d, $J_{10,9} = 6.5$ Hz, H-10), 1.29 (28 H, br.s, H-11'–H-24'), 1.33–1.60 (6 H, m, H-4, H-5, H-6), 1.75 (1 H, ddd, $J_{8,8} = 14.5$ Hz, $J_{8,7 \text{ or } 8,9} = 6.0$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, $1 \times$ H-8), 1.91–1.97 (1 H, m, $1 \times$ H-8), 2.01–2.07 (5 H, m, H-10', H-13), 2.13–2.15 (2 H, m, H-6'), 2.17–2.21 (2 H, m, H-7'), 2.30 (1 H, d, $J_{2,2} = 14.0$ Hz, $1 \times$ H-2), 2.36 (1 H, d, $J_{2,2} = 14.0$ Hz, $1 \times$ H-2), 2.40–2.48 (4 H, m, H-2', H-3'), 2.99 (2 H, t, $J_{1'',2''} = 6.5$ Hz, H-1''), 3.63 (2 H, t, $J_{2'',1''} = 6.5$ Hz, H-2''), 4.93–4.99 (2 H, m, H-7, H-9), 5.37–5.47 (2 H, m, H-8', H-9'); ¹H NMR (500 MHz, CDCl₃) δ 0.88 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 1.19 (3 H, br.s, H-11), 1.23–1.61 (37 H, m, H-4, H-5, H-6, H-10, H-11'–H-24'), 1.63–1.73 (1 H, m, H-8), 1.88–1.98 (1 H, m, H-8), 1.98–2.08 (5 H, m, H-10', H-13), 2.10–2.23 (4 H, m, H-6', H-7'), 2.24–2.51 (6 H, m, H-2, H-2', H-3'), 2.52–2.90 (3 H, br.s, NH, OH, SO₃H), 3.13 (2 H, br.s, H-1''), 3.66 (2 H, br.s, H-2''), 4.85–4.99 (2 H, m, H-7, H-9), 5.34–5.45 (2 H, m, H-8', H-9'); ¹³C NMR (125 MHz, CD₃OD) δ 14.5 (C-25'), 15.6 (C-3'), 19.9 (C-6'), 20.4 (C-10), 20.7 (C-5), 21.2 (C-13), 23.8 (C-24'), 26.8 (C-11), 28.0 (C-7'), 28.3 (C-10'), 30.4–33.1 (C-11'–C-23'), 35.4 (C-2'), 35.9 (C-6), 36.5 (C-2''), 41.4 (C-8), 43.0 (C-4), 47.8 (C-2), 51.5 (C-1''), 69.9 (C-9), 72.6 (C-3, C-7), 79.3 (C-4'), 81.5 (C-5'), 129.2 (C-8'), 132.0 (C-9'), 172.6 (C-12), 173.3 (C-1'), 174.2 (C-1); ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (C-25'), 14.8 (C-3'), 19.1 (C-6'), 19.6 (br, C-5), 20.0 (C-10), 21.2 (C-13), 22.7 (C-24'), 26.1 (br, C-11), 26.8 (C-7'), 27.3 (C-10'), 29.3–31.9 (C-11'–C-23'), 34.3 (C-2'), 34.9 (br, C-6), 35.2 (br, C-2''), 40.4 (br, C-8), 42.2 (br, C-4), 46.5 (br, C-2), 50.0 (br, C-1''), 68.5 (C-9), 71.1 (C-7), 71.8 (br, C-3), 78.2 (C-4'), 80.7 (C-5'), 127.8 (C-8'), 131.2 (C-9'), 171.0 (C-12), 171.6 (C-1'), 173.1 (br, C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3376 (br), 2918 (s), 2850 (s), 1734 (s), 1643 (m), 1375 (m), 1242 (s), 1050 (m); HRMS (ESI[−]) m/z calcd. for C₄₀H₇₀NO₉S[−] [M−H][−] 740.4777, found 740.4780.

Methyl (3*R*)-hydroxybutanoate (1.51)⁹

A 3 L round-bottom flask was charged with PHB (100 g, 1.16 mol) and absolute 1,2-dichloroethane (1 L). The flask was equipped with a reflux condenser, and the mixture was heated under reflux for 1 h. A solution of concentrated H₂SO₄ (20 mL) in absolute methanol (400 mL) was added and the reaction mixture was heated under reflux for 72 h. During this time, the mixture became homogeneous. The mixture was then cooled to RT. Half-saturated brine (200 mL) was added to the reaction mixture, then stirred for 15 min where layers were separated. The aqueous layer was extracted with CHCl₃ (3 × 400 mL), washed with brine (200 mL), NaHCO₃ solution (sat. aq., 200 mL), and brine (200 mL). The combined organic layers were dried (MgSO₄) and concentrated. The title compound (**1.51**) was obtained by distillation of the residue under reduced pressure as a colourless oil (61–62 °C, 18 Torr, 95.2 g, 70%). *R_f* (petrol/ethyl acetate; 50:50) = 0.49; [α]_D²⁰ –47.6 (*c* 1.00, CHCl₃), lit¹⁰ [α]_D²² –45.1 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.12 (3 H, d, *J*_{4,3} = 6.0 Hz, H-4), 2.34–2.36 (2 H, m, H-2), 3.35 (1 H, d, *J*_{OH,3} = 4.0 Hz, C(3)OH), 3.60 (3 H, s, OCH₃), 4.05–4.13 (1 H, m, H-3); ¹³C NMR (100 MHz, CDCl₃) δ 22.5 (C-4), 42.7 (C-2), 51.5 (OCH₃), 64.1 (C-3), 173.1 (C-1); IR (thin film) ν_{max} /cm^{–1} 3449 (br), 2974 (m), 1738 (s), 1439 (s), 1377 (m), 1295 (m), 1175 (s), 1125 (m), 1088 (m); HRMS (ESI⁺) *m/z* calcd. for C₅H₁₀NaO₃⁺ [MNa]⁺ 141.0522, found 141.0521.

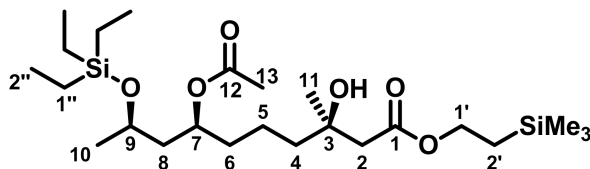
(Z)-Pentacos-8-en-4-ynoyl fluoride (1.56)

Acid **1.57** (16 mg, 42.6 μmol) and pyridine (3.43 μL , 42.5 μmol) were dissolved in MeCN (0.4 mL). To this solution was added cyanuric fluoride (11 μL , 0.128 mmol) at 0 $^{\circ}\text{C}$. The white suspension was warmed to RT and stirred for 60 min. Crushed ice was added slowly to this suspension to destroy excess cyanuric fluoride where layers were separated. The aqueous layer was extracted with ether (3×10 mL) and the combined organic layers were washed with ice-cold H_2O (5 mL), dried (MgSO_4) and concentrated to furnish the *title compound* (**1.56**) as a colourless liquid (12 mg, 75%). ^1H NMR (500 MHz, CDCl_3) δ 0.88 (3 H, t, $J_{25,24} = 7.0$ Hz, H-25), 1.25 (28 H, br.s, H-11–H-24), 2.02 (2 H, q, $J_{10,9} = J_{10,11} = 7.0$ Hz, H-10), 2.13–2.24 (4 H, m, H-6, H-7), 2.52 (2 H, t, $J_{3,2} = 7.5$ Hz, H-3), 2.71 (2 H, t, $J_{2,3} = 7.5$ Hz, H-2), 5.34–5.39 (1 H, m, H-8), 5.41–5.46 (1 H, m, H-9); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-25), 14.2 (d, $^3J_{\text{CF}} = 2.5$ Hz, C-3), 19.0 (C-6), 22.7 (C-24), 26.7 (C-7), 27.3 (C-10), 29.3–31.9 (C-11–C-23), 32.2 (d, $^2J_{\text{CF}} = 52.0$ Hz, C-2), 76.6 (C-4), 81.8 (C-5), 127.6 (C-8), 131.4 (C-9), 162.1 (d, $^1J_{\text{CF}} = 360.0$ Hz, C-1); ^{19}F NMR (470 MHz, CDCl_3) δ 44.5; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2924 (s), 2853 (s), 1847 (s), 1615 (w), 1466 (m), 1261 (m), 1092 (s); HRMS (FI^+) m/z calcd. for $\text{C}_{25}\text{H}_{43}\text{OF}^+$ $[\text{M}]^+$ 378.3298, found 378.3308.

(Z)-Pentacos-8-en-4-ynoic acid (1.57)¹¹

To a solution of ester **1.151** (13 mg, 32.1 μmol) in THF (0.3 mL) and methanol (0.1 mL) was added LiOH solution (1.0 M in H_2O , 0.1 mL, 0.1 mmol). The resulting mixture was stirred for 3 h at RT and white precipitate was formed. The reaction mixture was then poured into a mixture of CHCl_3 (5 mL) and hydrochloric acid (1.2 M in H_2O , 5 mL). Layers were separated and the aqueous layer was extracted with CHCl_3 (3×5 mL). The combined organic layers were dried (MgSO_4) and concentrated to furnish the title compound (**1.57**) as a white solid (12 mg, 100%). R_f (hexanes/ethyl acetate, 95:5) = 0.20; m.p. = 70–74 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 0.88 (3 H, t, $J_{25,24} = 7.0$ Hz, H-25), 1.25 (28 H, br.s, H-11–H-24), 2.02 (2 H, q, $J_{10,9} = J_{10,11} = 7.0$ Hz, H-10), 2.14–2.24 (4 H, m, H-6, H-7), 2.47 (2 H, t, $J_{3,2} = 7.0$ Hz, H-3), 2.56 (2 H, t, $J_{2,3} = 7.0$ Hz, H-2), 5.35–5.45 (2 H, m, H-8, H-9); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-25), 14.5 (C-3), 19.1 (C-6), 22.7 (C-24), 26.8 (C-7), 27.3 (C-10), 29.3–31.9 (C-11–C-23), 33.9 (br, C-2), 78.0 (C-4), 80.9 (C-5), 127.8 (C-8), 131.3 (C-9), 177.5 (br, C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3445 (br), 2916 (s), 2849 (s), 1695 (s), 1470 (m), 1260 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{25}\text{H}_{44}\text{NaO}_2^+ [\text{MNa}]^+$ 399.3234, found 399.3241.

(3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-3-hydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (1.59)

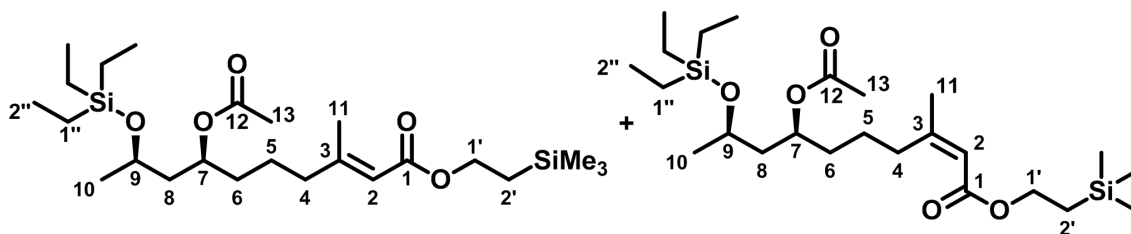


To a solution of thionocarbonate **1.131** (72 mg, 0.131 mmol) in degassed toluene (4.2 mL) under argon atmosphere was added Bu₃SnH (46 µL, 0.171 mmol) followed by addition of AIBN solution (0.12 M in toluene, 170 µL, 20.4 µmol). The resulting mixture was heated under reflux for 3 h and quenched with NH₄Cl solution (sat. aq., 5 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated. Slow flash chromatography (petrol/ether, 90:10 then 80:20) furnished the *title compound* (**1.59**) as a colourless oil (60 mg, 93%). *R_f* (petrol/ether; 50:50) = 0.58; [α]_D²¹ +1.90 (*c* 1.50, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.06 (9 H, s, SiCH₃), 0.59 (6 H, q, *J*_{1'',2''} = 8.0 Hz, H-1''), 0.96 (9 H, t, *J*_{2'',1''} = 8.0 Hz, H-2''), 0.99–1.03 (2 H, m, H-2'), 1.17 (3 H, d, *J*_{10,9} = 6.0 Hz, H-10), 1.22 (3 H, s, H-11), 1.29–1.67 (7 H, m, H-4, H-5, H-6, 1 × H-8), 1.82 (1 H, ddd, *J*_{8,8} = 14.0 Hz, *J*_{8,7} or *J*_{8,9} = 8.5 Hz, *J*_{8,9} or *J*_{8,7} = 5.0 Hz, 1 × H-8), 2.04 (3 H, s, H-13), 2.41 (1 H, d, *J*_{2,2} = 15.5 Hz, 1 × H-2), 2.47 (1 H, d, *J*_{2,2} = 15.5 Hz, 1 × H-2), 3.60 (1 H, br.s, OH), 3.79–3.86 (1 H, m, H-9), 4.20–4.23 (2 H, m, H-1'), 4.93–4.98 (1 H, m, H-7); ¹³C NMR (125 MHz, CDCl₃) δ –1.6 (SiCH₃), 4.9 (C-1''), 6.8 (C-2''), 17.3 (C-2'), 19.5 (C-5), 21.2 (C-13), 23.5 (C-10), 26.5 (C-11), 35.0 (C-6), 41.7 (C-4), 44.4 (C-8), 45.0 (C-2), 63.0 (C-1'), 65.4 (C-9), 70.8 (C-3), 71.6 (C-7), 170.7 (C-12), 173.2 (C-1); IR (thin film) ν_{max} /cm^{–1} 3509 (br), 2956 (s), 1736 (s), 1712 (s), 1458 (m),

1376 (m), 1249 (s), 1174 (m), 1065 (m); HRMS (ESI⁺) m/z calcd. for C₂₄H₅₀NaO₆Si₂⁺ [MNa]⁺ 513.3038, found 513.3036.

(7*S*,9*R*,*E*)-2-(Trimethylsilyl)ethyl 7-acetoxy-3-methyl-9-[(triethylsilyl)oxy]dec-2-enoate
(*E*-1.60) &

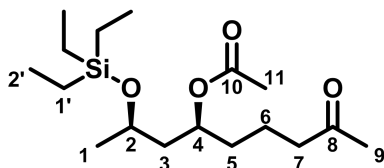
(7*S*,9*R*,*Z*)-2-(Trimethylsilyl)ethyl 7-acetoxy-3-methyl-9-[(triethylsilyl)oxy]dec-2-enoate
(*Z*-1.60)



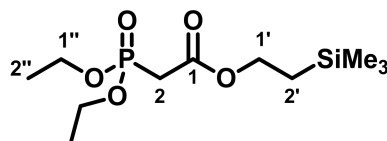
To a 0 °C solution of phosphonate **1.62** (250 mg, 0.845 mmol) in THF (3 mL) was added BuLi (1.6 M in hexanes, 0.55 mL, 0.880 mmol). The reaction mixture was stirred for 30 min at 0 °C and when a solution of ketone **1.61** (111 mg, 0.336 mmol) in THF (3 mL) was added. The ice bath was removed and the mixture was stirred for 24 h at RT. NH₄Cl solution (sat. aq., 15 mL) was added and the mixture was diluted with ether (20 mL) where phases were separated. The aqueous layer was extracted with ether (3 × 20 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 90:10 then 50:50) furnished the *title compounds* ***E*-1.60** and ***Z*-1.60** as a 4:1 *E/Z* mixture (117 mg, 75%, 100% b.r.s.m.) as a pale yellow oil. A pure sample of the *E*- or *Z*- isomer was obtained by preparative TLC (petrol/ether, 70:30). **Data for *E*-1.60:** R_f (petrol/ether; 90:10) = 0.14; $[\alpha]_D^{25} +87.0$ (c 0.83, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.04 (9 H, s, SiCH₃) 0.58 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.95 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 0.99–1.02 (2 H, m, H-2'), 1.16 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.44–1.60 (5 H, m, H-5, H-6, 1 × H-8), 1.81 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7}$ or $J_{8,9} =$

8.5 Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 2.03 (3 H, s, H-13), 2.10–2.14 (5 H, m, H-11, H-4), 3.78–3.84 (1 H, m, H-9), 4.16–4.19 (2 H, m, H-1'), 4.92–4.97 (1 H, m, H-7), 5.62 (1 H, s, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ -1.5 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.4 (C-2'), 18.5 (C-11), 21.2 (C-13), 22.9 (C-5), 23.5 (C-10), 34.1 (C-6), 40.5 (C-4), 44.3 (C-8), 61.6 (C-1'), 65.4 (C-9), 71.4 (C-7), 116.0 (C-2), 159.1 (C-3), 166.9 (C-1), 170.6 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954 (s), 2876 (s), 1743 (s), 1716 (s), 1651 (m), 1458 (m), 1374 (m), 1251 (s), 1019 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{48}\text{NaO}_5\text{Si}_2^+ [\text{MNa}]^+$ 495.2932, found 495.2944.

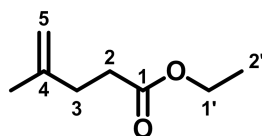
Data for Z-1.60: R_f (petrol/ether; 90:10) = 0.34; $[\alpha]_{\text{D}}^{25} +105.9$ (c 0.67, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.04 (9 H, s, SiCH_3), 0.58 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.95 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 0.98–1.00 (2 H, m, H-2'), 1.16 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.43–1.48 (2 H, m, H-5), 1.55–1.61 (3 H, m, H-6, 1 $\times$ H-8) 1.81 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 1.85 (3 H, d, $J_{11,2} = 1.0$ Hz, H-11), 2.03 (3 H, s, H-13), 2.57–2.67 (2 H, m, H-4), 3.77–3.83 (1 H, m, H-9), 4.14–4.18 (2 H, m, H-1'), 4.92–4.97 (1 H, m, H-7), 5.64 (1 H, d, $J_{2,11} = 1.0$ Hz, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ -1.5 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.3 (C-2'), 21.2 (C-13), 23.4 (C-10), 23.8 (C-5), 25.0 (C-11), 32.9 (C-4), 34.6 (C-6), 44.5 (C-8), 61.6 (C-1'), 65.4 (C-9), 71.7 (C-7), 116.6 (C-2), 159.6 (C-3), 166.4 (C-1), 170.7 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955 (s), 2916 (s), 1741 (s), 1716 (s), 1650 (m), 1460 (m), 1384 (m), 1250 (s), 1018 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{48}\text{O}_5\text{Si}_2^+ [\text{MNa}]^+$ 495.2932, found 495.2944.

(2*R*,4*S*)-8-Oxo-2-[(triethylsilyl)oxy]nonan-4-yl acetate (1.61)

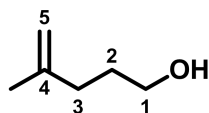
To a solution of alkene **1.87** (118 mg, 0.359 mmol) in anhydrous DCM (10 mL) was bubbled through O₃ until a blue colour persisted at -78°C . Then O₂ was bubbled through the reaction mixture to remove the excess O₃ as indicated by the disappearance of the blue colour. Triphenylphosphine (145 mg, 0.552 mmol) was added and the reaction mixture was allowed to warm to RT over 14 h. Most of the solvent was removed under reduced pressure. The residue was diluted with ether (20 mL) then washed with H₂O (5 mL) and brine (5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (petrol/ether, 90:10 then 80:20) to furnish the *title compound* (**1.61**) as a colourless oil (90 mg, 76%). R_f (petrol/ether; 70:30) = 0.32; $[\alpha]_{\text{D}}^{25} -0.59$ (c 1.00, CHCl₃); ¹H NMR (500 MHz) δ 0.59 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.96 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.17 (3 H, d, $J_{1,2} = 6.0$ Hz, H-1), 1.53–1.60 (5 H, m, H-5, H-6, 1 $\times$ H-3), 1.82 (1 H, ddd, $J_{3,3} = 13.5$ Hz, $J_{3,2}$ or $3,4} = 8.5$ Hz, $J_{3,2}$ or $3,4} = 5.0$ Hz, 1 $\times$ H-3), 2.04 (3 H, s, H-11), 2.13 (3 H, s, H-9), 2.38–2.50 (2 H, m, H-7), 3.79–3.85 (1 H, m, H-2), 4.92–4.97 (1 H, m, H-4); ¹³C NMR (125 MHz) δ 4.9 (C-1'), 6.8 (C-2'), 19.2 (C-6), 21.2 (C-11), 23.5 (C-1), 29.9 (C-9), 33.9 (C-5), 43.2 (C-7), 44.2 (C-3), 65.4 (C-2), 71.3 (C-4), 170.7 (C-10), 208.5 (C-8); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957 (s), 2878 (s), 1737 (s), 1720 (s), 1459 (m), 1416 (m), 1372 (s), 1243 (s), 1069 (s); HRMS (ESI⁺) m/z calcd. for C₁₇H₃₄O₄SiNa⁺ [MNa]⁺ 353.2119, found 353.2114.

2-(Trimethylsilyl)ethyl 2-(diethoxyphosphoryl)acetate (1.62)

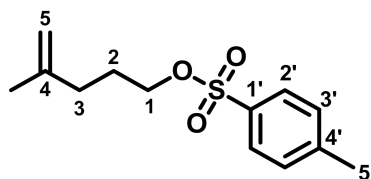
BOP-Cl (1.00 g, 3.93 mmol) was added to a solution of diethylphosphonoacetic acid (0.6 mL, 3.73 mmol), 2-(trimethylsilyl)ethanol (0.6 mL, 4.16 mmol) and triethylamine (1.1 mL, 7.89 mmol) in anhydrous DCM (10 mL). The suspension turned into a clear solution within minutes, and the mixture was stirred at RT for 4 h. Na₂CO₃ solution (5% in H₂O, 15 mL) was added and layers were separated. The aqueous layer was extracted with DCM (2 × 15 mL), and the combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 13:87) furnished the *title compound* (**1.62**) as a colourless oil (1.03 g, 88%). *R_f* (DCM/MeOH; 95:5) = 0.53; ¹H NMR (400 MHz, CDCl₃) δ 0.03 (9 H, s, SiCH₃), 0.98–1.02 (2 H, m, H-2'), 1.34 (6 H, t, *J*_{2'',1''} = 7.0 Hz, H-2''), 2.94 (2 H, d, ²*J*_{HP} = 21.5 Hz, H-2), 4.13–4.24 (6 H, m, H-1', H-1''); ¹³C NMR (100 MHz, CDCl₃) δ -1.6 (SiCH₃), 16.3 (d, ³*J*_{PC} = 6.5 Hz, C-2''), 17.3 (C-2'), 34.5 (d, ¹*J*_{PC} = 134.5 Hz, C-2), 62.6 (d, ²*J*_{PC} = 6.5 Hz, C-1''), 64.0 (C-1'), 166.0 (d, ²*J*_{PC} = 6.0 Hz, C-1); IR (thin film) *v*_{max}/cm⁻¹ 2993 (s), 2954 (s), 1746 (s), 1445 (s), 1392 (m), 1280 (s), 1248 (s), 1066 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₁H₂₅NaO₅Si⁺ [MNa]⁺ 319.1101, found 319.1101.

Ethyl 4-methylpent-4-enoate (1.63)¹²

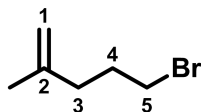
A mixture of alcohol **1.83** (40.0 g, 554 mmol), triethyl orthoacetate (270 mL, 1.45 mol), and propionic acid (2.4 mL, 33.4 mmol) was heated at 140 °C for 4 h with continuous removal of ethanol. The reaction mixture was then heated up to 165 °C to remove the excess triethyl orthoacetate. The mixture was cooled to RT, then ether (200 mL) was added to dilute the mixture. The mixture was washed successively with hydrochloric acid (1.0 M in H₂O, 2 × 100 mL), NaHCO₃ solution (sat. aq., 2 × 200 mL) and brine (2 × 200 mL). The combined organic layers were dried (MgSO₄) and concentrated. The residue (**1.63**) was used for further steps without purification (56.3 g, 70%). *R_f* (petrol/ethyl acetate; 83:17) = 0.73; ¹H NMR (400 MHz, CDCl₃) δ 1.21 (3 H, t, *J*_{2',1'} = 7.5 Hz, H-2'), 1.69 (3 H, s, C(4)CH₃), 2.26–2.30 (2 H, m, H-3), 2.38–2.42 (2 H, m, H-2), 4.08 (2 H, q, *J*_{1',2'} = 7.5 Hz, H-1'), 4.64 (1 H, s, 1 × H-5), 4.69 (1 H, s, 1 × H-5); ¹³C NMR (100 MHz, CDCl₃) δ 14.1 (C-2'), 22.4 (C(4)CH₃), 32.5 (C-3), 32.6 (C-2), 60.2 (C-1'), 110.2 (C-5), 144.0 (C-4), 173.2 (C-1); IR (thin film) *v*_{max}/cm⁻¹ 2981 (s), 1738 (s), 1651 (m), 1446 (s), 1373 (s), 1347 (m), 1031 (m). All the other data are as reported.

4-Methylpent-4-en-1-ol (1.64)¹²

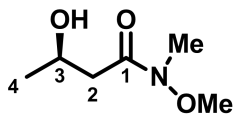
To a vigorously stirred solution of LiAlH_4 (14.0 g, 0.368 mol) in anhydrous ether (600 mL) was added dropwise a solution of ester **1.63** (40.0 g, 0.280 mol) in ether (100 mL) within 60 min while maintaining the internal temperature at 0 °C. The resulting suspension was heated under reflux for another 3 h then allowed to cool to RT. The reaction was quenched between 0–5 °C by careful addition of H_2O (14 mL), NaOH solution (15% in H_2O , 14 mL) and H_2O (40 mL). After the mixture was stirred for 1 h at RT, the resulting precipitate was filtered, and eluting with ether (1.2 L). The filtrate was dried (MgSO_4) and concentrated to furnish the title compound (**1.64**) for further steps without purification (25.3 g, 90%). R_f (petrol/ethyl acetate; 83:17) = 0.12; ^1H NMR (400 MHz, CDCl_3) δ 1.64–1.69 (2 H, m, H-2), 1.70 (3 H, s, C(4) CH_3), 2.05 (2 H, t, $J_{3,2}$ = 8.0 Hz, H-3), 2.49 (1 H, s, OH), 3.59 (2 H, t, $J_{1,2}$ = 6.5 Hz, H-1), 4.67–4.69 (2 H, m, H-5); ^{13}C NMR (100 MHz, CDCl_3) δ 22.3 (C(4) CH_3), 30.4 (C-2), 34.0 (C-3), 62.4 (C-1), 110.0 (C-5), 145.5 (C-4); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3396 (br), 2941 (s), 1650 (w), 1446 (m), 1376 (w), 1060 (m). All the other data are as reported.

4-Methylpent-4-enyl 4-methylbenzenesulfonate (1.65)¹²

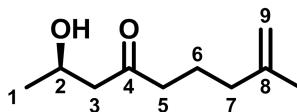
para-Toluenesulfonyl chloride (57.1 g, 0.300 mol) was dissolved in pyridine (60 mL) and added to a solution of alcohol **1.64** (20.0 g, 0.200 mol) in pyridine (40 mL). The mixture was stirred for 3 h at RT before being poured into toluene (160 mL). To this mixture was added hydrochloric acid (6.0 M in H₂O, 420 mL) with stirring below 10 °C. Layers were separated and the aqueous layer was extracted with ether (3 × 200 mL). The combined organic layers were washed with H₂O (2 × 200 mL), Na₂CO₃ solution (sat. aq., 2 × 200 mL), and brine (2 × 200 mL). After being dried (MgSO₄), the residue was concentrated to furnish the title compound (**1.65**) as a yellow liquid for further steps without purification (48.6 g, 96%). *R_f* (petrol/ethyl acetate; 83:17) = 0.48; ¹H NMR (400 MHz, CDCl₃) δ 1.66 (3 H, s, C(4)CH₃), 1.73–1.80 (2 H, m, H-2), 2.03 (2 H, t, *J*_{3,2} = 8.0 Hz, H-3), 2.45 (3 H, s, ArCH₃), 4.03 (2 H, t, *J*_{1,2} = 6.5 Hz, H-1), 4.58 (1 H, s, 1× H-5), 4.68 (1 H, s, 1× H-5), 7.35 (2 H, d, *J*_{3',2'} = 8.0 Hz, H-3'), 7.78 (2 H, d, *J*_{2',3'} = 8.0 Hz, H-2'); ¹³C NMR (100 MHz, CDCl₃) δ 21.6 (C-5'), 22.2 (C(4)CH₃), 26.7 (C-2), 33.3 (C-3), 70.1 (C-1), 110.9 (C-5), 127.9, 129.8, 133.1 (arom), 143.8 (C-4), 144.8 (C-1'); IR (thin film) *v*_{max}/cm⁻¹ 2972 (s), 1599 (m), 1495 (m), 1360 (s), 1098(m); HRMS (ESI⁺) *m/z* calcd. for C₁₃H₁₈NaO₃S⁺ [MNa]⁺ 277.0869, found 277.0869.

5-Bromo-2-methylpent-1-ene (1.66)¹³

A solution of tosylate **1.65** (5.26 g, 20.7 mmol) and LiBr (8.50 g, 97.9 mmol) in anhydrous acetone (50 mL) was heated under reflux for 2 h. The mixture was then poured into Na₂CO₃ solution (sat. aq., 40 mL) at 0 °C. The white precipitate was filtered with ether eluting (50 mL), and the filtrate was diluted with ether (20 mL). The aqueous layer was extracted with ether (3 × 60 mL). The combined organic layers were dried (MgSO₄), filtered, and most amount of ether was removed by distillation under ambient atmosphere. The residual ether was removed under reduced pressure to furnish the title compound (**1.66**) for further steps without purification (2.12 g, 63%). *R_f* (petrol) = 0.71; ¹H NMR (400 MHz, CDCl₃) δ 1.73 (3 H, s, C(2)CH₃), 1.99 (2 H, qn, *J*_{4,3} = *J*_{4,5} = 7.0 Hz, H-4), 2.18 (2 H, t, *J*_{3,4} = 7.0 Hz, H-3), 3.41 (2 H, t, *J*_{5,4} = 7.0 Hz, H-5), 4.72 (1 H, s, 1 × H-1), 4.76 (1 H, s, 1 × H-1); ¹³C NMR (100 MHz, CDCl₃) δ 22.3 (C(2)CH₃), 30.6 (C-4), 32.8 (C-3), 36.0 (C-5), 111.0 (C-1), 143.9 (C-2); IR (thin film) *v*_{max}/cm⁻¹ 2967 (s), 2938 (s), 1650 (s), 1439 (s), 1375 (m), 1244 (m). All the other data are as reported.

(3*R*)-Hydroxy-*N*-methoxy-*N*-methylbutanamide (1.70)¹⁴

To a stirred solution of ester **1.51** (1.00 g, 8.47 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (2.00 g, 20.5 mmol) in THF (25 mL) at $-30\text{ }^{\circ}\text{C}$ was added dropwise isopropylmagnesium chloride (2.0 M solution in THF, 21.2 mL, 42.4 mmol). The solution was stirred at $-30\text{ }^{\circ}\text{C}$ for a further 30 min then at $0\text{ }^{\circ}\text{C}$ for 4 h. The solution was quenched with hydrochloric acid (0.5 M in H_2O , 100 mL) and layers were separated. The aqueous layer was extracted with ethyl acetate ($10 \times 30\text{ mL}$) and the combined organic layers were dried (MgSO_4) then concentrated. The title compound (**1.70**) was used for further steps without purification as a yellow oil (1.25 g, 100%). R_f (ethyl acetate) = 0.34; $[\alpha]_{\text{D}}^{20} -68.0$ (c 1.00, CHCl_3), lit¹⁴ $[\alpha]_{\text{D}}^{20} -74.5$ (c 1.10, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.15 (3 H, d, $J_{4,3} = 6.5\text{ Hz}$, H-4), 2.39 (1 H, dd, $J_{2,2} = 16.5\text{ Hz}$, $J_{2,3} = 9.5\text{ Hz}$, $1 \times \text{H-2}$), 2.57 (1 H, app. d, $J_{2,2} = 16.5\text{ Hz}$, $1 \times \text{H-2}$), 3.10 (3 H, s, NCH_3), 3.60 (3 H, s, OCH_3), 4.09–4.17 (1 H, m, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ 22.2 (C-4), 31.6 (C-2), 39.5 (NCH_3), 61.0 (OCH_3), 63.9 (C-3), 173.5 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3432 (br), 2972 (s), 1737 (m), 1644 (s), 1389 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_6\text{H}_{13}\text{NNaO}_3^+ [\text{MNa}]^+$ 170.0788, found 170.0788.

(2*R*)-Hydroxy-8-methylnon-8-en-4-one (1.72)¹⁴

- **Synthesis of Grignard reagent 1.69**

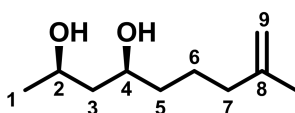
Dry Mg turning (974 mg, 40.0 mmol) in anhydrous ether (1.5 mL) was vigorously stirred when 10 drops of bromide **1.66** (3.27 g, 20.0 mmol) was added. The reaction was initiated easily and begun to reflux. The mixture was diluted with ether (15 mL) while bromide **1.66** was added dropwise within 3 min. The reaction was heated gently to keep refluxing for 15 min then left at RT before use.

- **Synthesis of ketone 1.72**

Isopropyl magnesium bromide (2.0 M in THF, 4.0 mL, 8.00 mmol) was added dropwise to solution of Weinreb amide **1.70** (1.18 g, 8.00 mmol) in anhydrous ether (25 mL) at 0 °C, white precipitate could be seen during addition. The mixture was stirred at 0 °C for 10 min then left at RT for 30 min before the freshly prepared Grignard reagent **1.69** was added dropwise *via* cannula at 0 °C. The mixture was stirred at 0 °C for 30 min then allowed to warm to RT over 4 h. The mixture was poured into NH₄Cl solution (sat. aq., 135 mL) at 0 °C and extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the title compound (**1.72**) as a pale yellow liquid (2.32 g, 70%). *R_f* (petrol/ethyl acetate;

50:50) = 0.24; $[\alpha]_{\text{D}}^{20}$ -42.1 (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.16 (3 H, d, $J_{1,2}$ = 6.5 Hz, H-1), 1.65–1.74 (5 H, m, C(8) CH_3 , H-6), 2.01 (2 H, t, $J_{7,6}$ = 7.5 Hz, H-7), 2.40 (2 H, t, $J_{5,6}$ = 7.5 Hz, H-5), 2.45–2.60 (2 H, m, H-3), 3.17 (1 H, br.s, OH), 4.16–4.23 (1 H, m, H-2), 4.64 (1 H, s, 1 $\times$ H-9), 4.70 (1 H, s, 1 $\times$ H-9); ^{13}C NMR (125 MHz, CDCl_3) δ 21.1 (C-6), 22.1 (C(8) CH_3), 22.3 (C-1), 36.9 (C-7), 42.7 (C-5), 50.5 (C-3), 63.8 (C-2), 110.7 (C-9), 144.8 (C-8), 212.1 (C-4); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3509 (br), 2973 (m), 1703 (s), 1632 (m), 1378 (m); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{10}\text{H}_{18}\text{NaO}_2^+ [\text{MNa}]^+$ 193.1199, found 193.1193.

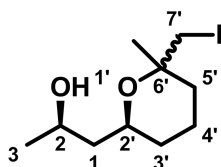
(2*R*,4*S*)-8-Methylnon-8-ene-2,4-diol (1.74)¹⁴



To a stirred solution of ketone **1.72** (2.32 g, 13.6 mmol) in anhydrous THF (107 mL) and anhydrous methanol (27.6 mL) was added dropwise diethylmethoxyborane (2.1 mL, 16.0 mmol) at -78 °C. The resulting mixture was stirred for 15 min before careful addition of NaBH_4 (600 mg, 15.9 mmol). The mixture was stirred for another 3 h before quenching by careful addition of acetic acid (14.3 mL). The mixture was diluted with ethyl acetate (150 mL) and washed with NaHCO_3 solution (sat. aq., 100 mL). The resulting organic layers were dried (MgSO_4), filtered, and concentrated. The residue was azeotroped several times with methanol (5×25 mL) to furnish the title compound (**1.74**) as a colourless oil (2.35 g, 100%). R_f (petrol/ethyl acetate; 50:50) = 0.16; $[\alpha]_{\text{D}}^{20}$ -1.40 (c 0.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.21 (3 H, d, $J_{1,2}$ = 6.2 Hz, H-1), 1.42–1.63 (6 H, m, H-3, H-5, H-6), 1.71 (3 H, s, C(8) CH_3), 2.09 (2 H, t, $J_{7,6}$ = 6.0 Hz, H-7), 2.76–2.82 (2 H, m, 2 $\times$ OH), 3.86–3.91 (1 H, m,

H-4), 4.03–4.10 (1 H, m, H-2), 4.67–4.68 (1 H, m, 1 × H-9), 4.71–4.72 (1 H, m, 1 × H-9); ^{13}C NMR (125 MHz, CDCl_3) δ 22.3 (C(8)CH₃), 23.2 (C-6), 24.1 (C-1), 37.6 (C-5), 38.9 (C-7), 44.4 (C-3), 69.1 (C-4), 72.8 (C-2), 110.0 (C-9), 145.7 (C-8); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3384 (br), 2968 (m), 2935 (m), 1650 (s), 1454 (s), 1377 (m), 1262 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{10}\text{H}_{20}\text{NaO}_2^+ [\text{MNa}]^+$ 195.1356, found 195.1359.

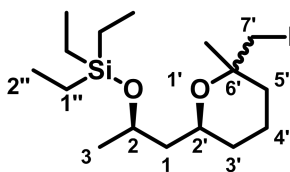
(2*R*)-1-[(2'*S*,6'*RS*)-6'-(Iodomethyl)-6'-methyltetrahydro-2'*H*-pyran-2'-yl] propan-2-ol
(1.77)¹⁴



To a stirred suspension of diol **1.74** (2.5 g, 14.5 mmol) and NaHCO_3 (3.65 g, 43.5 mmol) in MeCN (30 mL) was added dropwise a solution of I_2 (11.1 g, 43.5 mmol) in MeCN (110 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and diluted with ether (600 mL). The resulting mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution (10% in H_2O , 3 × 200 mL), NaHCO_3 solution (sat. aq., 3 × 200 mL), and brine (2 × 200 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated. The residue (**1.77**) was used for further steps without purification as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (4.34 g, 100%) as a yellow oil. R_f (petrol/ethyl acetate; 70:30) = 0.21; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (6 H, d, $J_{3,2} = 6.5$ Hz, 2 × H-3, **A** and **B**), 1.28 (3 H, s, C(6')CH₃, **A**), 1.35 (3 H, s, C(6')CH₃, **B**), 1.40–1.79 (16 H, m, 2 × H-1, 2 × H-3', 2 × H-4', 2 × H-5', **A** and **B**), 3.17–3.28 (3 H, m, 3 of 2 × H-7', **A** and **B**), 3.60–3.69 (1 H, m, H-2', **A** or **B**), 3.77–3.83 (2

H, m, H-2', **A** or **B**; 1 of 2 $\times$ H-7', **A** or **B**), 3.92 (1 H, br.s, OH, **A** or **B**), 3.98–4.06 (2 H, m, OH, **A** or **B**; H-2, **A** or **B**), 4.12–4.20 (1 H, m, H-2, **A** or **B**); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (1 $\times$ C-7', **A** or **B**), 19.4, 20.4, 21.1, 21.5, 23.2, 23.4, 30.1, 31.2, 31.7, 32.3, 33.3 (2 $\times$ C-3, 2 $\times$ C-3', 2 $\times$ C-4', 2 $\times$ C-5', 2 $\times$ C(6')CH₃, **A** and **B**; 1 $\times$ C-7', **A** or **B**), 44.5, 45.0 (2 $\times$ C-1, **A** and **B**), 68.0, 68.5 (2 $\times$ C-2, **A** and **B**), 71.7, 72.0 (2 $\times$ C-6', **A** and **B**), 72.5, 73.4 (2 $\times$ C-2', **A** and **B**); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3492 (br), 2937 (s), 1459 (m), 1378 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{10}\text{H}_{19}\text{NaO}_2^+ [\text{MNa}]^+$ 321.0322, found 321.0317.

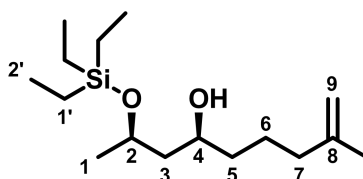
***O*-Triethylsilyl (2*R*)-1-[(2'*S*,6'*RS*)-6'-(Iodomethyl)-6'-methyltetrahydro-2'*H*-pyran-2'-yl]propan-2-ol (1.85)**



To a solution of alcohol **1.77** (360 mg, 1.21 mmol) in anhydrous pyridine (6 mL) was added chlorotriethylsilane (0.6 mL, 3.58 mmol). The mixture was stirred at 60 °C for 14 h, diluted with ether (20 mL), then poured into CuSO_4 solution (sat. aq., 20 mL) at 0 °C. The aqueous layer was extracted with ether (3 $\times$ 30 mL) and the combined organic layers were washed with CuSO_4 solution (sat. aq., 3 $\times$ 20 mL), H_2O (1 $\times$ 20 mL), dried (MgSO_4) and concentrated. Flash chromatography (petrol) furnished the *title compound* (**1.85**) as a mixture of two diastereomers (**A**:**B** = 2:1) as a pale yellow oil (413 mg, 84%). R_f (petrol/ethyl; 90:10) = 0.80; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2936 (s), 1458 (m), 1374 (m), 1237 (m), 1036 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{16}\text{H}_{33}\text{IO}_2\text{NaSi}^+ [\text{MNa}]^+$ 435.1187, found 435.1184. **NMR data for**

diastereomer A: ^1H NMR (400 MHz, CDCl_3) δ 0.61 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.20 (3 H, d, $J_{3,2} = 6.0$ Hz, H-3), 1.25 (3 H, s, C(6')CH₃), 1.35–1.82 (8 H, m, H-1, H-3', H-4', H-5'), 3.21–3.27 (1 H, m, 1 $\times$ H-7'), 3.38–3.45 (1 H, m, H-2'), 3.64 (1 H, d, $J_{7',7''} = 10.5$ Hz, 1 $\times$ H-7'), 4.04–4.15 (1 H, m, H-2); ^{13}C NMR (100 MHz, CDCl_3) δ 4.9 (C-1''), 7.0 (C-2''), 14.4 (C-7'), 19.8 (C-3' or C-4' or C-5'), 24.0 (C-3), 30.3 (C(6')CH₃), 31.1 (C-3' or C-4' or C-5'), 32.6 (C-3' or C-4' or C-5'), 47.2 (C-1), 65.0 (C-2), 67.8 (C-2') 71.1 (C-6'); **NMR data for diastereomer B:** ^1H NMR (400 MHz, CDCl_3) δ 0.61 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.15 (3 H, d, $J_{3,2} = 6.0$ Hz, H-3), 1.27 (3 H, s, C(6')CH₃), 1.35–1.82 (8 H, m, H-1, H-3', H-4', H-5'), 3.21–3.27 (2 H, m, H-7'), 3.52–3.58 (1 H, m, H-2'), 4.04–4.15 (1 H, m, H-2); ^{13}C NMR (100 MHz, CDCl_3) δ 4.9 (C-1''), 7.0 (C-2''), 20.4 (C(6')CH₃), 20.6 (C-3' or C-4' or C-5'), 22.1 (C-7'), 23.3 (C-3), 31.6 (C-3' or C-4' or C-5'), 33.6 (C-3' or C-4' or C-5'), 46.6 (C-1), 65.1 (C-2), 68.4 (C-2') 71.0 (C-6').

(2*R*,4*S*)-8-Methyl-2-[(triethylsilyl)oxy]non-8-en-4-ol (1.86)



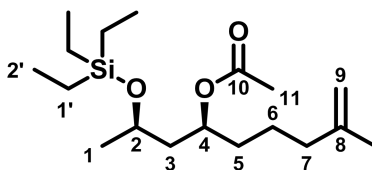
● **Activation of zinc**

The commercial Zn powder (2.00 g, 30.8 mmol) was put into a conical flask when hydrochloric acid (3.0 M in H₂O, 5 mL) was added. The mixture was stirred for 1 min before

it was filtered, then successively washed with hydrochloric acid (3.0 M in H₂O, 3 × 20 mL), H₂O (3 × 20 mL), acetone (3 × 20 mL) and ether (3 × 20 mL). The powder was then dried under reduced pressure.

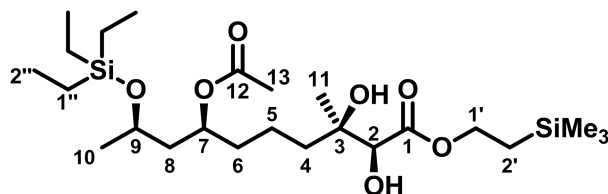
● Synthesis of alcohol **1.86**

Iodide **1.85** (300 mg, 0.728 mmol) was dissolved in ethanol (12 mL) before freshly activated Zn powder (708 mg, 10.9 mmol) was added. The mixture was heated under reflux for 3 h before cooled to RT. NH₄Cl (1.16 g, 21.7 mmol) and ether (60 mL) was added followed by stirring for 5 min to give a grey suspension. Then the suspension was filtered through a short pad of Celite[®] and concentrated. Flash chromatography (petrol/ether, 90:10) furnished the *title compound* (**1.86**) as a colourless liquid (200 mg, 97%). *R_f* (petrol/ethyl acetate; 90:10) = 0.33; [α]_D²⁵ –21.1 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.65 (6 H, q, *J*_{1',2'} = 8.0 Hz, H-1'), 0.98 (9 H, t, *J*_{2',1'} = 8.0 Hz, H-2'), 1.20 (3 H, d, *J*_{1,2} = 6.0 Hz, H-1), 1.35–1.62 (6 H, m, H-3, H-5, H-6), 1.72 (3 H, s, C(8)CH₃), 2.03 (2 H, t, *J*_{7,6} = 7.0 Hz, H-7), 3.70 (1 H, br.s, OH), 3.76–3.82 (1 H, m, H-2), 4.07–4.15 (1 H, m, H-4), 4.68 (1 H, s, 1 × H-9), 4.70 (1 H, s, 1 × H-9); ¹³C NMR (100 MHz, CDCl₃) δ 5.1 (C-1'), 6.8 (C-2'), 22.4 (C(8)CH₃), 23.4 (C-6), 24.7 (C-1), 37.4 (C-7), 37.9 (C-5), 45.7 (C-3), 70.4 (C-2), 71.7 (C-4), 109.8 (C-9), 146.0 (C-8); IR (thin film) ν_{max} /cm^{–1} 3529 (br), 2968 (s), 1650 (w), 1458 (m), 1375 (m), 1261 (m), 1103 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₆H₃₄NaO₂Si [MNa]⁺ 309.2220, found 309.2213.

(2*R*,4*S*)-8-Methyl-2-[(triethylsilyl)oxy]non-8-en-4-yl acetate (1.87)

Acetic anhydride (160 μ L, 1.69 mmol) was added to a solution of alcohol **1.86** (263 mg, 0.920 mmol), triethylamine (180 μ L, 1.30 mmol) and DMAP (18 mg, 0.150 mmol) in anhydrous DCM (7 mL) at 0 $^{\circ}$ C. The reaction was then allowed to warm to RT and stirred for 4 h. The reaction mixture was concentrated and the residue was then purified by flash chromatography (petrol) to furnish the *title compound* (**1.87**) as a colourless oil (302 mg, 100%). R_f (petrol/ether; 90:10) = 0.60; $[\alpha]_D^{25} +2.40$ (c 0.85, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.59 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.97 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.18 (3 H, d, $J_{1,2} = 6.0$ Hz, H-1), 1.41–1.62 (5 H, m, H-5, H-6, 1 $\times$ H-3), 1.70 (3 H, s, C(8)CH₃), 1.82 (1 H, ddd, $J_{3,3} = 14.0$ Hz, $J_{3,2 \text{ or } 3,4} = 8.5$ Hz, $J_{3,4 \text{ or } 3,2} = 5.0$ Hz, 1 $\times$ H-3), 2.01 (2 H, t, $J_{7,6} = 7.5$ Hz, H-7), 2.04 (3 H, s, H-11), 3.79–3.86 (1 H, m, H-2), 4.67 (1 H, s, 1 $\times$ H-9) 4.71 (1 H, s, 1 $\times$ H-9), 4.92–4.99 (1 H, m, H-4); ^{13}C NMR (100 MHz, CDCl_3) δ 4.9 (C-1') 6.8 (C-2'), 21.2 (C-11), 22.2 (C(8)CH₃), 23.1 (C-6), 23.5 (C-1), 34.2 (C-7), 37.5 (C-5), 44.4 (C-3), 65.4 (C-2), 71.8 (C-4), 110.2 (C-9), 145.4 (C-8), 170.7 (C-10); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2969 (s), 2876 (s), 1743 (s), 1650 (w), 1469 (s), 1375 (s), 1243 (s), 1065 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{18}\text{H}_{36}\text{NaO}_3\text{Si}^+$ [MNa]⁺ 351.2326, found 351.2323.

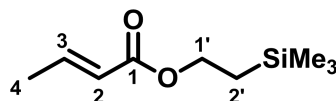
(2*S*,3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (1.88)



To a stirred mixture of H₂O and *t*-BuOH (1:1, 3 mL) at RT was added AD-mix- β (355 mg, 1 mol% osmium) and (DHQD)₂PHAL (2.5 mg, 2.88 μ mol). Once the two phases became clear after 15 min, the mixture was cooled at 0 °C and solid methanesulfonamide (10 mg, 0.105 mmol) was added in one portion. After 20 min at 0 °C, a solution of alkene **E-1.60** (50 mg, 0.106 mmol) in toluene (0.5 mL) was added and the slurry was stirred vigorously for 24 h at RT. After dilution with ethyl acetate (25 mL) and H₂O (25 mL) at 0 °C and addition of Na₂SO₃ (160 mg, 1.27 mmol) portionwise, the mixture was stirred further for 1 h at RT. The aqueous layer was then extracted with ethyl acetate (3 $\times$ 25 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.88**) as a colourless oil (50 mg, 93%). *R_f* (petrol:ether; 50:50) = 0.23; [α]_D²⁵ +9.00 (*c* 0.17, CHCl₃); ¹H NMR (500 MHz, CHCl₃) δ 0.07 (9 H, s, SiCH₃), 0.59 (6 H, q, *J*_{1'',2''} = 8.0 Hz, H-1''), 0.97 (9 H, t, *J*_{2'',1''} = 8.0 Hz, H-2''), 1.05–1.09 (2 H, m, H-2'), 1.16 (3 H, s, H-11), 1.18 (3 H, d, *J*_{10,9} = 6.0 Hz, H-10), 1.43–1.70 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.83 (1 H, ddd, *J*_{8,8} = 14.0 Hz, *J*_{8,7} or *J*_{8,9} = 8.5 Hz, *J*_{8,9} or *J*_{8,7} = 5.0 Hz, 1 $\times$ H-8), 2.04 (3 H, s, H-13), 2.48 (1 H, br s, C(3)OH), 3.12 (1 H, d, *J*_{OH,2} = 6.5 Hz, C(2)OH), 3.80–3.86 (1 H, m, H-9), 3.96 (1 H, d, *J*_{2,OH} = 6.5 Hz, H-2), 4.30–4.34 (2 H, m, H-1'), 4.94–4.99 (1 H, m, H-7); ¹³C NMR (125MHz, CHCl₃) δ -1.6

(SiCH₃), 4.9 (C-1''), 6.8 (C-2''), 17.6 (C-2'), 19.1 (C-5), 21.2 (C-13), 22.4 (C-11), 23.5 (C-10), 35.1 (C-6), 38.0 (C-4), 44.4 (C-8), 64.6 (C-1'), 65.4 (C-9), 71.6 (C-7), 73.8 (C-3), 75.9 (C-2), 170.7 (C-12), 173.3 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3463 (br), 2956 (s), 1736 (s), 1459 (m), 1376 (m), 1250 (s), 1088 (m); HRMS (ESI⁺) m/z calcd. for C₂₄H₅₀NaO₇Si₂⁺ [MNa]⁺ 529.2987, found 529.2994.

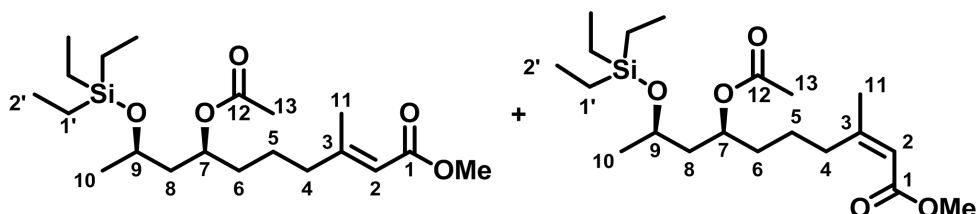
(E)-2-(Trimethylsilyl)ethyl but-2-enoate (1.90)



A solution of methyl crotonate (100 mg, 1.00 mmol), 2-(trimethylsilyl)ethanol (1.18 g, 10.0 mmol) and titanium(IV) isopropoxide (85 mg, 0.296 mmol) was heated at 100 °C for 6 h. After cooling to RT, *n*-hexane (5 mL) was added to dilute the solution. Flash chromatography (petrol/ether, 95:5) furnished the *title compound* (**1.90**) as a colourless liquid (160 mg, 86%). R_f (petrol/ether; 80:20) = 0.78; ¹H NMR (400 MHz, CDCl₃) δ 0.04 (9 H, s, SiCH₃), 1.00 (2 H, t, $J_{2',1'} = 8.5$ Hz, H-2'), 1.86 (3 H, dd, $J_{4,3} = 7.0$ Hz, $J_{4,2} = 1.5$ Hz, H-4), 4.21 (2 H, t, $J_{1',2'} = 8.5$ Hz, H-1'), 5.82 (1 H, dq, $J_{2,3} = 15.5$ Hz, $J_{2,4} = 1.5$ Hz, H-2), 6.95 (1 H, dq, $J_{3,2} = 15.5$ Hz, $J_{3,4} = 7.0$ Hz, H-3); ¹³C NMR (100 MHz, CDCl₃) δ -1.5 (SiCH₃), 17.3 (C-2'), 17.9 (C-4), 62.3 (C-1'), 123.0 (C-2), 144.2 (C-3), 166.7 (C-4); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2955 (s), 1722 (s), 1660 (m), 1446 (m), 1379 (w), 1262 (s); HRMS (GCMS CI⁺) m/z calcd. for C₉H₂₂NO₂Si⁺ [MNH₄]⁺ 204.1420, found 204.1412.

(7*S*,9*R*,*E*)-Methyl 7-acetoxy-3-methyl-9-[(triethylsilyl)oxy]dec-2-enoate (*E*-1.93) &

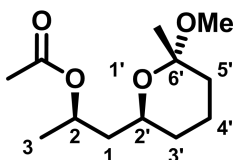
(7*S*,9*R*,*Z*)-Methyl 7-acetoxy-3-methyl-9-[(triethylsilyl)oxy]dec-2-enoate (*Z*-1.93)



To a solution of methyl crotonate **1.92** (40 μ L, 0.370 mmol), alkene **1.87** (170 mg, 0.517 mmol) in degassed DCM (2 mL) was added Grubbs' II catalyst (16 mg, 18.8 μ mol). The mixture was then heated under reflux for 24 h then the solvent was removed under reduced pressure. Flash chromatography (petrol/ether, 95:5) furnished the *title compounds* **E-1.93** and **Z-1.93** as a 2:1 *E/Z* mixture (85 mg, 71%) as a colourless oil. A pure sample of *E*- or *Z*-isomer was obtained by preparative TLC (petrol/ether, 90:10). **Data for E-1.93:** R_f (petrol/ether; 90:10) = 0.28; $[\alpha]_D^{25} +54.4$ (c 1.40, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.59 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.96 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.46–1.60 (5 H, m, H-5, H-6, 1 $\times$ H-8), 1.81 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7}$ or $8,9 = 8.5$ Hz, $J_{8,7}$ or $8,9 = 5.0$ Hz, 1 $\times$ H-8), 2.04 (3 H, s, H-13), 2.12–2.16 (5 H, m, H-4, H-11), 3.69 (3 H, s, OCH_3) 3.79–3.85 (1 H, m, H-9), 4.93–4.98 (1 H, m, H-7), 5.66 (1 H, s, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1'), 6.8 (C-2'), 18.6 (C-11), 21.2 (C-13), 22.9 (C-5), 23.5 (C-10), 34.1 (C-6), 40.5 (C-4), 44.3 (C-8), 50.8 (OCH_3), 65.4 (C-9), 71.4 (C-7), 115.4 (C-2), 159.7 (C-3), 167.1 (C-1), 170.6 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2972 (s), 1746 (s), 1710 (s), 1651 (m), 1460 (s), 1385 (m), 1254 (s), 1157 (s), 1019 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{20}\text{H}_{38}\text{NaO}_5\text{Si}^+ [\text{MNa}]^+$ 409.2381, found 409.2386. **Data for Z-1.93:** R_f (petrol/ether; 90:10)

= 0.21; $[\alpha]_{\text{D}}^{25} +39.2$ (c 1.90, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.59 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.96 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.44–1.51 (2 H, m, H-5), 1.56–1.62 (3 H, m, H-6, 1 $\times$ H-8), 1.82 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7}$ or $8,9 = 8.5$ Hz, $J_{8,9}$ or $8,7 = 5.0$ Hz, 1 $\times$ H-8), 1.87 (3 H, d, $J_{11,2} = 1.5$ Hz, H-11), 2.04 (3 H, s, H-13), 2.58–2.68 (2 H, m, H-4), 3.67 (3 H, s, OCH_3) 3.78–3.85 (1 H, m, H-9), 4.93–4.98 (1 H, m, H-7), 5.67 (1 H, d, $J_{2,11} = 1.5$ Hz, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1'), 6.8 (C-2'), 21.2 (C-13), 23.4 (C-10), 23.7 (C-5), 25.0 (C-11), 32.9 (C-4), 34.6 (C-6), 44.5 (C-8), 50.8 (OCH_3), 65.4 (C-9), 71.7 (C-7), 116.0 (C-2), 160.2 (C-3), 166.6 (C-1), 170.7 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968 (s), 1744 (s), 1719 (s), 1651 (m), 1465 (s), 1377 (s), 1250 (s), 1152 (s), 1019 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{20}\text{H}_{38}\text{NaO}_5\text{Si}^+ [\text{MNa}]^+ 409.2381$, found 409.2386.

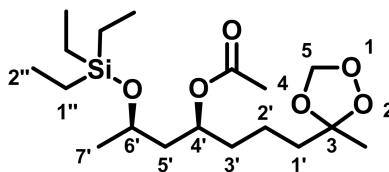
(2*R*)-1-[(2*S*,6*S*)-6-Methoxy-6-methyltetrahydro-2*H*-pyran-2-yl]propan-2-yl acetate
(1.94)



To a solution of alkene **1.87** (100 mg, 0.304 mmol) in anhydrous DCM (2 mL) and anhydrous methanol (2 mL) was bubbled through O_3 until a blue colour persisted at -78°C . O_2 was then bubbled through the reaction mixture to remove the excess O_3 as indicated by the disappearance of the blue colour. Dimethylsulfide (350 μL , 4.87 mmol) was added and the mixture was warmed to RT over 14 h. Most of the solvent was removed, and the residue was diluted with ether (20 mL) then washed with H_2O (5 mL) and brine (5 mL). The

combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**1.94**) as a colourless oil (56 mg, 56%). R_f (petrol/ether; 70:30) = 0.48; $[\alpha]_{\text{D}}^{25} +54.3$ (c 1.70, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.21 (1 H, m, $1 \times \text{H-3}'$), 1.26 (3 H, d, $J_{3,2} = 6.0$ Hz, H-3), 1.27 (3 H, s, C(6')CH_3), 1.43 (1 H, td, $J_{5'\text{ax},5'\text{eq}} = J_{5'\text{ax},4'\text{ax}} = 13.5$ Hz, $J_{5'\text{ax},4'\text{eq}} = 4.5$ Hz, H-5'_{ax}), 1.52–1.60 (3 H, m, $1 \times \text{H-1}$, $1 \times \text{H-4}'$, $1 \times \text{H-3}'$), 1.67–1.73 (1 H, m, H-5'_{eq}), 1.78–1.88 (2 H, m, $1 \times \text{H-1}$, $1 \times \text{H-4}'$), 2.03 (3 H, s, OC(O)CH_3), 3.20 (3 H, s, OCH_3), 3.58–3.64 (1 H, m, H-2') 5.08 (1 H, m, H-2); ^{13}C NMR (100 MHz, CDCl_3) δ 18.9 (C-4'), 20.3 (C-3), 21.4 (C(O)CH_3), 24.0 (C(6')CH_3), 30.7 (C-3'), 35.3 (C-5'), 42.4 (C-1), 47.8 (OCH_3), 67.2 (C-2'), 68.4 (C-2), 98.0 (C(6')CH_3), 170.7 (C(O)CH_3); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2941 (m), 1739 (s), 1456 (w), 1374 (m), 1245 (s), 1057 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{12}\text{H}_{22}\text{NaO}_4^+$ $[\text{MNa}]^+$ 253.1410, found 253.1411.

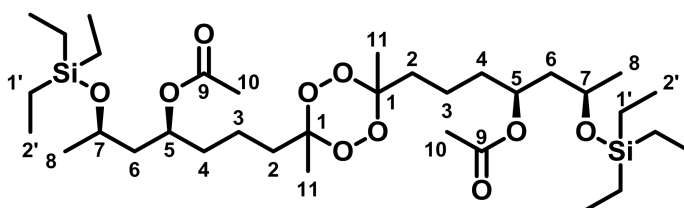
(4*S*,6*R*)-1-(3-Methyl-1,2,4-trioxolan-3-yl)-6-[(triethylsilyl)oxy]heptan-4-yl acetate (1.95**)**



To a solution of alkene **1.87** (1.10 g, 3.34 mmol) in anhydrous DCM (40 mL) was bubbled through O_3 until a blue colour persisted at -78°C , O_2 was then bubbled through the reaction mixture to remove the excess O_3 as indicated by the disappearance of the blue colour. Triphenylphosphine (1.30 g, 4.95 mmol) was added then the mixture was warmed to RT over 2 h. Most of the solvent was removed, and the residue was diluted with ether (200 mL), then washed with H_2O (50 mL) and brine (50 mL). The combined organic layers were dried

(MgSO₄) and concentrated. The residue was purified by flash chromatography (petrol/ether, 90:10) to furnish the *title compound* (**1.95**) as a colourless oil (462 mg, 44%) as a side product. R_f (petrol/ether; 70:30) = 0.68; $[\alpha]_D^{25} +0.68$ (c 0.89, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.17 (3 H, d, $J_{7',6'} = 6.0$ Hz, H-7'), 1.39–1.85 (11 H, m, H-1', H-2', H-3', H-5', C(3)CH₃), 2.04 (3 H, s, C(O)CH₃), 3.79–3.86 (1 H, m, H-6'), 4.91–4.98 (1 H, m, H-4'), 5.06 (1 H, d, $J_{5,5} = 2.0$ Hz, 1 $\times$ H-5), 5.13 (1 H, d, $J_{5,5} = 2.0$ Hz, 1 $\times$ H-5); ¹³C NMR (125 MHz, CDCl₃) δ 4.9 (C-1''), 6.8 (C-2''), 19.5 (C-2'), 21.2 (COCH₃), 22.4 (C(3)CH₃), 23.4 (C-7'), 34.6 (C-3'), 37.0 (C-1'), 44.3 (C-5'), 65.4 (C-6'), 71.5 (C-4'), 94.0 (C-5), 109.6 (C-3), 170.6 (C(O)CH₃); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2957 (m), 2878 (m), 1737 (s), 1377 (m), 1242 (s), 1138 (m), 1118 (m), 1018 (s); HRMS (ESI⁺) m/z calcd. for C₁₈H₃₆NaO₆Si⁺ [MNa]⁺ 399.2173, found 399.2174.

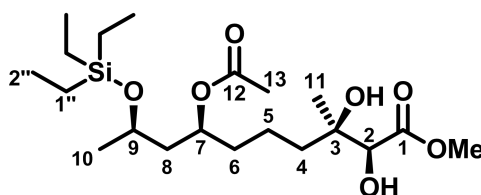
(2*R*,2'*R*,4*S*,4'*S*)-(3,6-Dimethyl-1,2,4,5-tetraoxane-3,6-diyl)bis{2-[(triethylsilyl)oxy]heptane-7,4-diyl} diacetate (1.96**)**



To a solution of alkene **1.87** (200 mg, 0.609 mmol) in anhydrous DCM (10 mL) was bubbled O₃ until a blue colour persisted at -78 °C, O₂ was then bubbled through the reaction mixture to remove excess O₃ as indicated by the disappearance of the blue colour. A solution of triphenylphosphine (240 mg, 0.915 mmol) in anhydrous DCM (2 mL) was added and warmed up to RT over 2.5 h. Most of the solvent was removed then the mixture was diluted

with ether (50 mL) and washed with brine (30 mL). The organic layer was dried (MgSO_4), concentrated and the residue was purified by flash chromatography (petrol/ether; 90:10 then 70:30) to furnish the *title compound* (**1.96**) as a colourless oil (10 mg, 4.7%) as a side product. R_f (petrol/ether; 70:30) = 0.63; ^1H NMR (500 MHz, CDCl_3) δ 0.59 (12 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.96 (18 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.17 (6 H, d, $J_{8,7} = 6.0$ Hz, H-8), 1.20–1.29 (4 H, m, H-3), 1.34–1.48 (4 H, m, $2 \times$ H-2, $2 \times$ H-4), 1.50–1.68 (8 H, m, H-11, $2 \times$ H-6), 1.68–1.77 (2 H, m, $2 \times$ H-4), 1.78–1.88 (2 H, m, $2 \times$ H-6), 2.03 (6 H, s, H-10), 2.13–2.27 (2 H, m, $2 \times$ H-2), 3.78–3.86 (2 H, m, H-7), 4.89–5.04 (2 H, m, H-5); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1'), 6.8 (C-2'), 19.8 (C-3), 21.2 (C-10), 23.5 (C-8), 29.7 (C-4), 32.1 (C-2), 32.6 (H-11), 44.4 (C-6), 65.4 (C-7), 71.4 (C-5), 109.1 (C-1), 170.6 (C-9); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957 (s), 1738 (s), 1376 (m), 1241 (s), 1018 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{34}\text{H}_{68}\text{NaO}_{10}\text{Si}_2^+ [\text{MNa}]^+$ 715.4243, found 715.4210.

(2*S*,3*R*,7*S*,9*R*)-Methyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate
(1.97)

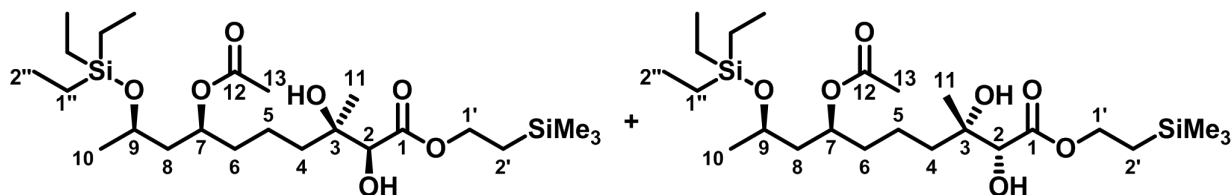


To a stirred mixture of H_2O and *t*-BuOH (1:1, 2 mL) at RT was added AD-mix- β (312 mg, 1 mol% osmium). Once the two phases were clear after about 15 min, the mixture was cooled to 0 °C and solid methanesulfonamide (9 mg, 93.1 μmol) was added in one portion. After 20 min at 0 °C, a solution of alkene **E-1.93** (36 mg, 93.1 μmol) in toluene (0.3 mL) was added

and the heterogeneous slurry was stirred vigorously for 72 h at RT. After dilution with ethyl acetate (10 mL) and H₂O (10 mL) at 0 °C and addition of Na₂SO₃ (98 mg, 0.770 mmol) portionwise, the mixture was stirred for 1 h at RT. The aqueous layer was then extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.97**) as a colourless oil (23 mg, 59%). *R_f* (petrol/ether; 50:50) = 0.10; [α]_D²⁵ –3.00 (*c* 0.17, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.59 (6 H, q, *J*_{1'',2''} = 8.0 Hz, H-1''), 0.97 (9 H, t, *J*_{2'',1''} = 8.0 Hz, H-2''), 1.16 (3 H, s, H-11), 1.18 (3 H, d, *J*_{10,9} = 6.0 Hz, H-10) 1.32–1.70 (7 H, m, H-4, H-5, H-6, 1 × H-8), 1.83 (1 H, ddd, *J*_{8,8} = 14.0 Hz, *J*_{8,7 or 8,9} = 8.5 Hz, *J*_{8,9 or 8,7} = 5.0 Hz, 1 × H-8), 2.04 (3 H, s, H-13), 3.83 (3 H, s, OCH₃), 3.81–3.84 (1 H, m, H-9), 4.01 (1 H, s, H-2), 4.71–4.90 (2 H, br.s, 2 × OH), 4.94–4.99 (1 H, m, H-7); ¹³C NMR (125 MHz, CDCl₃) δ 4.9 (C-1''), 6.8 (C-2''), 19.1 (C-5), 21.2 (C-13), 22.4 (C-10), 23.5 (C-11), 35.0 (C-6), 38.0 (C-4), 44.4 (C-8), 52.6 (OCH₃), 65.4 (C-9), 71.6 (C-7), 73.8 (C-3), 75.9 (C-2), 170.8 (C-12), 173.9 (C-1); IR (thin film) ν_{max} /cm^{–1} 3444 (br), 2962 (s), 2918 (s), 1735 (m), 1458 (w), 1376 (w), 1261 (s), 1095 (s); HRMS (ESI⁺) *m/z* calcd. for C₂₀H₄₀NaO₇Si⁺ [MNa]⁺ 443.2436, found 443.2437.

(2*S*,3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (**1.88**) &

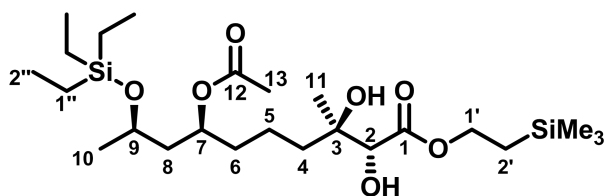
(2*R*,3*S*,7*S*,9*R*)-2-(trimethylsilyl)ethyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (**1.98**)



$\text{K}_3\text{Fe}(\text{CN})_6$ (40 mg, 0.120 mmol), K_2CO_3 (16.5 mg, 0.120 mmol), $\text{OsCl}_3 \cdot 3\text{H}_2\text{O}$ (1 mg, 3.33 μmol), quinuclidine (1.5 mg, 13.4 μmol) and methanesulfonamide (4 mg, 40.5 μmol) were dissolved in a mixture of H_2O and *t*-BuOH (1:1, 1.2 mL) by warming. The solution was cooled to RT then a solution of alkene **E-1.60** (20 mg, 40.5 μmol) in toluene (0.5 mL) was added. The reaction mixture was stirred vigorously for 24 h and Na_2SO_3 (60 mg, 0.480 mmol) was added portionwise. The mixture was stirred for another 1 h then DCM (15 mL) and H_2O (15 mL) were added to dilute the mixture. The aqueous layer was extracted with DCM (3 $\times$ 15 mL), and the combined organic layers were washed with brine (10 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compounds* **1.88** and **1.98** as a mixture of two diastereomers **A** and **B** (11 mg, 51%, **A**:**B** = 1:1) as a colourless oil. R_f (petrol/ether; 50:50) = 0.23; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3463 (br), 2956 (s), 2924 (s), 1736 (s), 1459 (m), 1376 (m), 1250 (s), 1088 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{50}\text{NaO}_7\text{Si}_2^+$ [MNa] $^+$ 529.2987, found 529.2994. **NMR data for 1.88:** see 196; **NMR data for diastereomer 1.98:** ^1H NMR (500 MHz, CDCl_3) δ 0.07 (9 H, s, SiCH_3), 0.59 (6 H,

q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.05–1.09 (2 H, m, H-2'), 1.16 (3 H, s, H-11), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10) 1.43–1.70 (7 H, m, H-4, H-5, H-6, 1 × H-8), 1.83 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 × H-8), 2.04 (3 H, s, H-13), 2.48 (1 H, br.s, C(3)OH), 3.12 (1 H, d, $J_{\text{OH},2} = 6.5$ Hz, C(2)OH), 3.80–3.86 (1 H, m, H-9), 3.96 (1 H, d, $J_{2,\text{OH}} = 6.5$ Hz, H-2), 4.30–4.34 (2 H, m, H-1'), 4.94–4.99 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH₃), 5.1 (C-1''), 6.8 (C-2''), 17.6 (C-2'), 19.0 (C-5), 21.2 (C-13), 22.4 (C-11), 23.4 (C-10), 35.0 (C-6), 37.7 (C-4), 44.4 (C-8), 64.6 (C-1'), 65.4 (C-9), 71.5 (C-7), 73.7 (C-3), 76.0 (C-2), 170.8 (C-12), 173.3 (C-1).

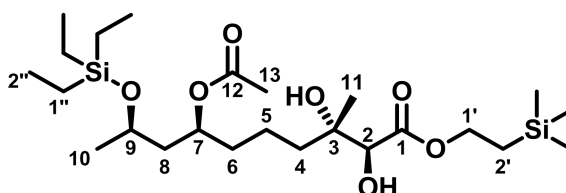
(2*R*,3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (1.99)



To a stirred mixture of H₂O and *t*-BuOH (1:1, 1.2 mL) at RT was added AD-mix- α (200 mg, 1 mol% osmium) and (DHQ)₂PHAL (1.5 mg, 3.26 μmol). Once the two phases became clear after 15 min, the mixture was cooled to 0 °C and solid methanesulfonamide (5.5 mg, 57.8 μmol) was added in one portion. After 20 min at 0 °C, a solution of alkene **Z-1.60** (28 mg, 58.9 μmol) in toluene (0.5 mL) was added and the slurry was stirred vigorously for 48 h at RT. After dilution with ethyl acetate (25 mL) and H₂O (25 mL) at 0 °C and addition of Na₂SO₃ (90 mg, 0.714 mmol) portionwise, the mixture was stirred for 1 h at RT. The aqueous layer was then extracted with ethyl acetate (3 × 25 mL), and the combined organic layers

were washed with brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.99**) as a colourless oil (5 mg, 16%, 95% b.r.s.m.). R_f (petrol/ether; 50:50) = 0.23; $[\alpha]_D^{25}$ -4.96 (c 0.63, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.06 (9 H, s, SiCH₃), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.06–1.09 (2 H, m, H-2') 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.20 (3 H, s, H-11), 1.39–1.62 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.82 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7}$ or $8,9 = 8.5$ Hz, $J_{8,9}$ or $8,7 = 5.0$ Hz, 1 $\times$ H-8), 2.04 (3 H, s, H-13), 2.57 (1 H, br.s, C(3)OH), 3.08 (1 H, d, $J_{OH,2} = 6.0$ Hz, C(2)OH), 3.79–3.85 (1 H, m, H-9), 3.98 (1 H, d, $J_{2,OH} = 6.0$ Hz, H-2), 4.31–4.35 (2 H, m, H-1'), 4.93–4.98 (1 H, m, H-7); ¹³C NMR (125 MHz, CDCl₃) δ -1.6 (SiCH₃), 4.9 (H-1''), 6.8 (H-2''), 17.6 (C-2'), 18.8 (C-5), 21.2 (C-13), 23.0 (C-11), 23.5 (C-10), 35.1 (C-6), 37.4 (C-4), 44.4 (C-8), 64.8 (C-1'), 65.4 (C-9), 71.7 (C-7), 73.7 (C-3), 76.3 (C-2), 170.7 (C-12), 173.5 (C-1); IR (thin film) ν_{max}/cm^{-1} 3463 (br), 2956 (s), 2924 (s), 1736 (s), 1459 (m), 1376 (m), 1250 (s), 1088 (w); HRMS (ESI⁺) m/z calcd. for C₂₄H₅₀NaO₇Si₂⁺ [MNa]⁺ 529.2987, found 529.2994.

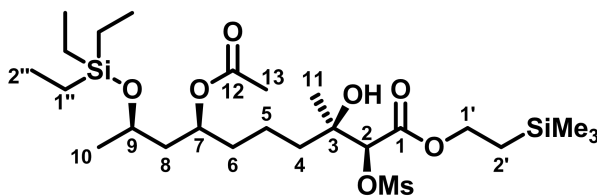
(2*S*,3*S*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-2,3-dihydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (1.100)



To a stirred mixture of H₂O and *t*-BuOH (1:1, 2.6 mL) at RT was added AD-mix- β (390 mg, 1 mol% osmium) and (DHQD)₂PHAL (2.5 mg, 3.20 μ mol). Once the two phases became

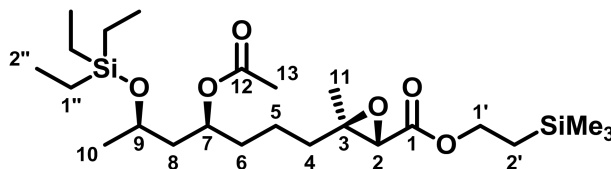
clear after 15 min, the mixture was cooled at 0 °C and solid methanesulfonamide (11 mg, 0.116 mmol) was added in one portion. After 20 min at 0 °C, a solution of alkene **Z-1.60** (55 mg, 0.116 mmol) in toluene (0.5 mL) was added and the slurry was stirred vigorously for 24 h at RT. After dilution with ethyl acetate (10 mL) and H₂O (10 mL) at 0 °C and addition of Na₂SO₃ (176 mg, 1.40 mmol) portionwise, the mixture was stirred for 1 h at RT. The aqueous layer was then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.100**) as a colourless oil (40 mg, 68%). R_f (petrol/ethyl acetate; 50:50) = 0.23; $[\alpha]_D^{21} +6.30$ (c 1.20, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.06 (9 H, s, SiCH₃), 0.58 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.04–1.09 (2 H, m, H-2'), 1.16 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.19 (3 H, s, H-11), 1.31–1.62 (7 H, m, H-4, H-5, H-6, 1 × H-8), 1.82 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 × H-8), 2.03 (3 H, s, H-13), 2.62 (1 H, br.s, C(3)OH), 3.13 (1 H, d, $J_{OH,2} = 6.5$ Hz, C(2)OH), 3.78–3.87 (1 H, m, H-9), 3.98 (1 H, d, $J_{2,OH} = 6.5$ Hz, H-2), 4.30–4.34 (2 H, m, H-1'), 4.92–4.98 (1 H, m, H-7) ¹³C NMR (100 MHz, CDCl₃) δ -1.6 (SiCH₃), 4.9 (C-1''), 6.8 (C-2''), 17.6 (C-2'), 18.8 (C-5), 21.2 (C-13), 22.8 (C-11), 23.4 (C-10), 35.0 (C-6), 37.3 (C-4), 44.4 (C-8), 64.7 (C-1'), 65.4 (C-9), 71.5 (C-7), 73.7 (C-3), 76.2 (C-2), 170.8 (C-12), 173.6 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3500 (br), 2956 (s), 1736 (s), 1460 (w), 1376 (m), 1250 (s); HRMS (ESI⁺) m/z calcd. for C₂₄H₅₀NaO₇Si₂⁺ [MNa]⁺ 529.2987, found 529.2984.

(2*S*,3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-3-hydroxy-3-methyl-2-[(methanesulfonyl)oxy]-9-[(triethylsilyl)oxy]decanoate (1.105)



To a stirred solution of diol **1.88** (20 mg, 39.5 μmol) in freshly distilled pyridine (0.5 mL) was added methanesulfonyl chloride (3.67 μL , 47.3 μmol) at 0 °C. When TLC showed there was no starting material left in the reaction mixture, ether (20 mL) was added to dilute the solution. The mixture was then washed with CuSO_4 solution (sat. aq., 2×10 mL), and the aqueous layer was extracted with ether (2×10 mL). The combined organic layers were dried (MgSO_4) then concentrated to furnish the *title compound* (**1.105**) for further steps without any purification (22 mg, 96%). R_f (petrol/ether; 50:50) = 0.15; $[\alpha]_D^{25} -10.0$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.07 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.06–1.10 (2 H, m, H-2'), 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.27 (3 H, s, H-11), 1.36–1.66 (7 H, m, H-4, H-5, H-6, $1 \times$ H-8), 1.83 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, $1 \times$ H-8), 2.03 (3 H, s, H-13), 3.15 (3 H, s, SCH_3), 3.77–3.88 (1 H, m, H-9), 4.32 (2 H, t, $J_{1',2'} = 9.0$ Hz, H-1'), 4.82 (1 H, s, H-2), 4.92–4.98 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.5 (C-2'), 18.7 (C-5), 21.2 (C-13), 22.9 (C-11), 23.4 (C-10), 34.9 (C-6), 38.0 (C-4), 39.0 (SCH_3), 44.3 (C-8), 64.9 (C-1'), 65.4 (C-9), 71.4 (C-7), 73.3 (C-3), 82.4 (C-2), 167.8 (C-1), 170.7 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3508 (br), 2959 (s), 1736 (s), 1364 (s), 1260 (s), 1178 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{25}\text{H}_{52}\text{NaO}_9\text{SSi}_2^+ [\text{MNa}]^+$ 607.2763, found 607.2738.

**(2*S*,3*R*)-2-(Trimethylsilyl)ethyl 3-{(4*S*,6*R*)-4-acetoxy-6-[(triethylsilyl)oxy]heptyl}-
3-methyloxirane-2-carboxylate (1.107)**



● **Activation of Zinc**

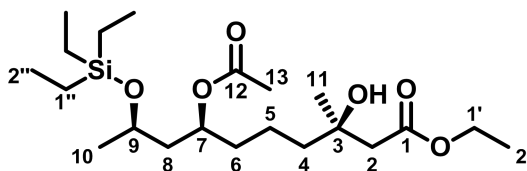
Commercial Zn powder (500 mg, 6.16 mmol) was put into a conical flask and hydrochloric acid (3.0 M in H₂O, 1 mL) was added. The mixture was stirred for 1 min before it was filtered, then successively washed with hydrochloric acid (3.0 M in H₂O, 3 × 4 mL), H₂O (3 × 4 mL), acetone (3 × 4 mL) and ether (3 × 4 mL). The powder was then dried under reduced pressure.

● **Synthesis of epoxide 1.107**

To a solution of mesylate **1.105** (22 mg, 37.6 μmol) in DME (2.5 mL) was added NaI (28 mg, 0.187 mmol) and activated Zn (25 mg, 0.382 mmol). The mixture was heated under reflux for 3 h then cooled to RT. The mixture was filtered through a short pad of Celite® and washed with ether (50 mL), then the filtrate was washed successively with NH₄Cl solution (sat. aq., 20 mL), Na₂S₂O₃ solution (sat. aq., 20 mL) and brine (20 mL). The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (petrol/ether; 80:20) to furnish the *title compound* (**1.107**) as a colourless oil (8 mg, 41%). *R_f* (petrol/ether; 50:50) = 0.74; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (9 H, s, SiCH₃), 0.58 (6 H, q, *J*_{1'',2''} = 8.0 Hz, H-1''), 0.95 (9 H, t, *J*_{2'',1''} = 8.0 Hz, H-2''), 1.03 (2 H, t, SiCH₃), 0.58 (6 H, q, *J*_{1'',2''} = 8.0 Hz, H-1''), 0.95 (9 H, t, *J*_{2'',1''} = 8.0 Hz, H-2''), 1.03 (2 H, t, SiCH₃).

$J_{2',1'} = 8.5$ Hz, H-2'), 1.16 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.38 (3 H, s, H-11), 1.44–1.70 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.80 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7}$ or $8,9 = 8.5$ Hz, $J_{8,9}$ or $8,7 = 5.1$ Hz, 1 $\times$ H-8), 2.03 (3 H, s, H-13), 3.29 (1 H, s, H-2), 3.77–3.84 (1 H, m, H-9), 4.20–4.32 (2 H, t, $J_{1',2'} = 8.5$ Hz, H-1'), 4.91–4.95 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.5 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.5 (C-2'), 21.2 (C-5, C-13), 21.4 (C-11), 23.5 (C-10), 31.7 (C-4), 34.6 (C-6), 44.5 (C-8), 59.6 (C-2), 62.6 (C-3), 63.8 (C-1'), 65.4 (C-9), 71.5 (C-7), 168.5 (C-1), 170.6 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (s), 2877 (m), 1737 (s), 1460 (w), 1416 (w), 1378 (w), 1249 (s), 1188 (m), 1018 (w); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{48}\text{NaO}_6\text{Si}_2^+$ $[\text{MNa}]^+ 511.2882$, found 511.2868.

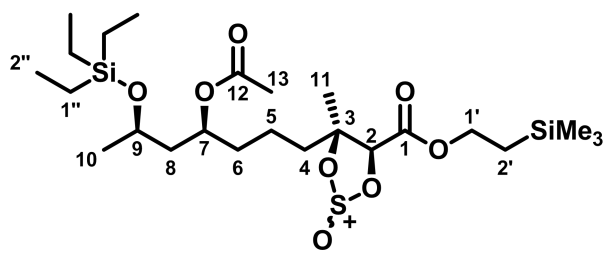
(3*R*,7*S*,9*R*)-Ethyl 7-acetoxy-3-hydroxy-3-methyl-9-[(triethylsilyl)oxy]decanoate (1.109)



To a solution of epoxide **1.107** (7 mg, 14.3 μmol) in ethanol (0.5 mL) was added $\text{Na}[\text{PhSeB}(\text{OEt})_3]$ (14 mg, 43 μmol) at RT under argon. The mixture was stirred for 20 min before dilution with ethyl acetate (5 mL). The solution was washed with brine (5 mL), and the aqueous layer was extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic layers were dried (MgSO_4) then concentrated, and the residue was purified by flash chromatography (petrol/ether, 80:20) to furnish the *title compound* (**1.109**) as a colourless oil (1 mg, 17%). R_f (petrol/ether; 50:50) = 0.60; $[\alpha]_{\text{D}}^{25} -33.0$ (c 0.09, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.58 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2',1''} = 8.0$ Hz, H-2''), 1.17 (3

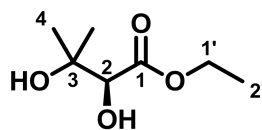
H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.21 (3 H, s, H-11), 1.28 (3 H, t, $J_{2',1'} = 7.0$ Hz, H-2'), 1.30–1.61 (7 H, m, H-4, H-5, H-6, $1 \times$ H-8), 1.81 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7}$ or $8,9 = 8.5$ Hz, $J_{8,9}$ or $8,7 = 5.0$ Hz, $1 \times$ H-8), 2.03 (3 H, s, H-13), 2.42 (1 H, d, $J_{2,2} = 15.5$ Hz, $1 \times$ H-2), 2.48 (1 H, d, $J_{2,2} = 15.5$ Hz, $1 \times$ H-2), 3.54 (1 H, br.s, OH), 3.79–3.85 (1 H, m, H-9), 4.18 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'), 4.92 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1''), 6.8 (C-2''), 14.2 (C-2'), 19.5 (C-5), 21.2 (C-13), 23.5 (C-10), 26.5 (C-11), 35.0 (C-6), 41.7 (C-4), 44.4 (C-8), 44.8 (C-2), 60.7 (C-1'), 65.4 (C-9), 70.8 (C-3), 71.6 (C-7), 170.7 (C-12), 173.0 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3527 (br), 2963 (s), 1738 (m), 1447 (w), 1375 (w), 1261 (s), 1095 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{21}\text{H}_{42}\text{NaO}_6\text{Si}_2^+ [\text{MNa}]^+ 441.2643$, found 441.2641.

(4*S*,5*R*)-2-(Trimethylsilyl)ethyl 5-{(4*S*,6*R*)-4-acetoxy-6-[(triethylsilyl)oxy]heptyl}-5-methyl-1,3,2-dioxathiolane-4-carboxylate 2-oxide (1.113)

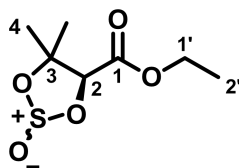


To a stirred solution of diol **1.88** (20 mg, 39.5 μmol) in freshly distilled pyridine (0.5 mL) was added thionyl chloride (3.16 μL , 43.3 μmol) at -30 $^{\circ}\text{C}$. When TLC showed there was no starting material left in the reaction mixture, ether (20 mL) was added to dilute the solution. The mixture was then washed with CuSO_4 solution (sat. aq., 2×10 mL) and the aqueous layer was extracted with ether (2×10 mL). The combined organic layers were dried (MgSO_4) then concentrated to furnish the *title compound* (**1.113**) for further steps without

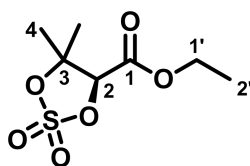
any purification as a mixture of two diastereomers **A** and **B** (25 mg, 96%, **A**:**B** = 2:1) as a colourless oil. R_f (petrol/ether; 50:50) = 0.83; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2958 (s), 1763 (s), 1736 (s), 1459 (m), 1380 (m), 1251 (s), 1177 (s), 1019 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{24}\text{H}_{48}\text{NaO}_8\text{SSi}_2^+ [\text{MNa}]^+$ 575.2501, found 575.2499. **NMR data for diastereomer A:** ^1H NMR (500 MHz, CDCl_3) δ -0.07 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.05–1.10 (2 H, m, H-2'), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.27 (3 H, s, H-11), 1.45–1.78 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.83 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 2.04 (3 H, s, H-13), 3.80–3.87 (1 H, m, H-9), 4.31–4.36 (2 H, m, H-1'), 4.95–5.01 (1 H, m, H-7), 5.02 (1 H, s, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.5 (C-2'), 19.5 (C-5), 21.0 (C-11), 21.2 (C-13), 23.5 (C-10), 34.4 (C-6), 39.3 (C-4), 44.4 (C-8), 65.0 (C-1'), 65.4 (C-9), 71.1 (C-7), 81.6 (C-2), 93.2 (C-3), 166.0 (C-1), 170.7 (C-12); **NMR data for diastereomer B:** ^1H NMR (500 MHz, CDCl_3) δ -0.07 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.05–1.10 (2 H, m, H-2'), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.25 (3 H, s, H-11), 1.45–1.78 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.83 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 2.04 (3 H, s, H-13), 3.80–3.87 (1 H, m, H-9), 4.31–4.36 (2 H, m, H-1'), 4.61 (1 H, s, H-2), 4.95–5.01 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.5 (C-2'), 19.2 (C-5), 21.0 (C-11), 21.2 (C-13), 22.9 (C-10), 34.4 (C-6), 39.6 (C-4), 44.3 (C-8), 65.0 (C-1'), 65.4 (C-9), 71.1 (C-7), 85.5 (C-2), 91.9 (C-3), 166.6 (C-1), 170.6 (C-12).

(2S)-Ethyl 2,3-dihydroxy-3-methylbutanoate (1.118)¹⁵

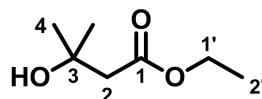
To a stirred mixture of H₂O and *t*-BuOH (1:1, 44 mL) at RT was added AD-mix-β (14.4 g, 1 mol% Osmium). Once the two phases became clear after about 15 min, the mixture was cooled to 0 °C and solid methanesulfonamide (409 mg, 4.29 mmol) was added in one portion. After 20 min, a solution of alkene **1.164** (550 mg, 4.29 mmol) in toluene (2 mL) was added and the heterogeneous slurry was stirred vigorously for 6 h at RT. After dilution with ethyl acetate (20 mL) at 0 °C and addition of Na₂SO₃ (6.52 g, 51.6 mmol) portionwise, the mixture was stirred for 1 h at RT. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine (15 mL), dried (MgSO₄), then concentrated. Flash chromatography (petrol/ether, 70:30) furnished the title compound (**1.118**) as a colourless oil (544 mg, 80 %). *R_f* (petrol/ether; 50:50) = 0.21; [*α*]_D²⁵ +19.6 (*c* 1.10, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.21 (3 H, s, H-4 or C(3)CH₃), 1.29 (3 H, s, C(3)CH₃ or H-4), 1.32 (3 H, t, *J*_{2',1'} = 7.0 Hz, H-2'), 2.73 (1 H, br.s, C(3)OH), 3.29 (1 H, d, *J*_{OH,2} = 6.5 Hz, C(2)OH), 3.96 (1 H, d, *J*_{2,OH} = 6.5 Hz, H-2), 4.23–4.35 (2 H, m, H-1'); ¹³C NMR (100 MHz, CDCl₃) δ 14.2 (C-2'), 24.9 (C-4 or C(3)CH₃), 25.7 (C(3)CH₃ or C-4), 62.0 (C-2, C-1'), 72.0 (C-3), 173.2 (C-1); IR (thin film) *v*_{max}/cm⁻¹ 3444 (br), 2981 (s), 1732 (s), 1469 (m), 1373 (s), 1271 (s), 1094 (s); HRMS (ESI⁺) *m/z* calcd. for C₇H₁₄NaO₄⁺ [MNa]⁺ 185.0784, found 185.0786.

(2S)-Ethyl 5,5-dimethyl-1,3,2-dioxathiolane-4-carboxylate 2-oxide (1.119)

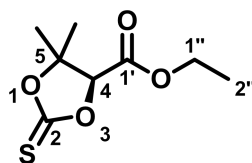
To a solution of diol **1.118** (30 mg, 0.188 mmol) in anhydrous pyridine (1 mL) at 0 °C was added thionyl chloride (20 μ L, 0.282 mmol). After 2 h, the reaction mixture was diluted with ether (20 mL). The mixture was washed with CuSO₄ solution (sat. aq., 3 $\times$ 10 mL) and the organic layer was dried (MgSO₄) then concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**1.119**) as an mixture of two diastereomers (**A**:**B** = 2.8:1, 37 mg, 95%) as a colourless oil. R_f (petrol/ether; 50:50) = 0.62; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2989 (m), 1763 (s), 1738 (m), 1376 (m), 1211 (s), 1139 (m), 1052 (s); HRMS (ESI⁺) m/z calcd. for C₇H₁₂NaO₅S⁺ [MNa]⁺ 231.0298, found 231.0296. **NMR data for diastereomer A:** ¹H NMR (500 MHz, CDCl₃) δ 1.31–1.38 (6 H, m, H-2', 1 $\times$ C(3)CH₃), 1.81 (3 H, s, 1 $\times$ C(3)CH₃), 4.32 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'), 5.06 (1 H, s, H-2); ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (C-2'), 23.3 (1 $\times$ C(3)CH₃), 27.7 (1 $\times$ C(3)CH₃), 62.3 (C-1'), 82.6 (C-2), 90.8 (C-3), 165.9 (C-1); **NMR data for diastereomer B :** ¹H NMR (500 MHz, CDCl₃) δ 1.31–1.38 (3 H, m, H-2'), 1.64 (3 H, s, 1 $\times$ C(3)CH₃), 1.65 (3 H, s, 1 $\times$ C(3)CH₃), 4.32 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'), 4.61 (1 H, s, H-2); ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (C-2'), 24.7 (1 $\times$ C(3)CH₃), 27.1 (1 $\times$ C(3)CH₃), 62.3 (C-1'), 86.3 (C-2), 89.7 (C-3), 166.2 (C-1).

(2S)-Ethyl 5,5-dimethyl-1,3,2-dioxathiolane-4-carboxylate 2,2-dioxide (1.120)

To a solution of cyclic sulfite **1.119** (30 mg, 0.144 mmol) and RuO₂ (6 mg, 0.045 mmol) in MeCN (1.3 mL) was added a solution of NaIO₄ (62 mg, 0.29 mmol) in H₂O (0.3 mL) at 0 °C. The reaction mixture was stirred vigorously at RT until a green colour appeared. After the colour appeared for 10 min, the reaction mixture was diluted with ethyl acetate (5 mL) and H₂O (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried (MgSO₄), then concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**1.120**) as a colourless oil (37 mg, 100%). *R_f* (petrol/ether; 50:50) = 0.50; [α]_D²⁵ -28.5 (*c* 1.40, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.36 (3 H, t, *J*_{2',1'} = 7.0 Hz, H-2'), 1.58 (3 H, s, 1 × C(3)CH₃), 1.80 (3 H, s, 1 × C(3)CH₃), 4.36 (2 H, q, *J*_{1',2'} = 7.0 Hz, H-1'), 5.03 (1 H, s, H-2); ¹³C NMR (125 MHz, CDCl₃) δ 14.0 (C-2'), 22.1 (1 × C(3)CH₃), 26.1 (1 × C(3)CH₃), 63.1 (C-1'), 83.8 (C-2), 91.8 (C-3), 163.5 (C-1); IR (thin film) ν_{max} /cm⁻¹ 2992 (m), 1768 (s), 1743 (m), 1379 (s), 1214 (s); HRMS (ESI⁺) *m/z* calcd. for C₇H₁₂NaO₆S⁺ [MNa]⁺ 247.0247, found 247.0243.

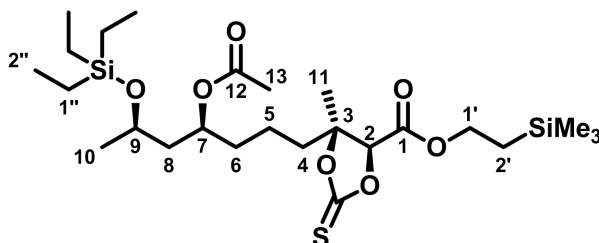
Ethyl 3-hydroxy-3-methylbutanoate (1.121)¹⁶

To a solution of thionocarbonate **1.125** (40 mg, 0.196 mmol) in degassed toluene (4 mL) under argon was added Bu₃SnH (65 μ L, 0.24 mmol) followed by AIBN solution (0.12 M in degassed toluene, 0.15 mL, 0.03 mmol). The resulting mixture was heated under reflux for 3 h and quenched with NH₄Cl solution (sat. aq., 10 mL). The mixture was extracted with ethyl acetate (3 $\times$ 10 mL), and the combined organic layers were dried (MgSO₄) then concentrated. Flash chromatography (KF-silica gel, petrol/ether, 70:30) furnished the title compound (**1.121**) as a colourless oil (4 mg, 15 %). R_f (petrol/ether; 70:30) = 0.67; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (9 H, m, H-2', H-4, C(3)CH₃), 2.45 (2 H, s, H-2), 3.59 (1 H, s, OH), 4.15 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'); ¹³C NMR (100 MHz, CDCl₃) δ 14.1 (C-2'), 29.1 (C-4 and C(3)CH₃), 46.3 (C-2), 60.5 (C-1'), 68.9 (C-3), 172.9 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3385 (br), 2933 (s), 1730 (s), 1463 (m), 1378 (m), 1263 (m); HRMS (ESI⁺) m/z calcd. for C₇H₁₄NaO₃⁺ [MNa]⁺ 169.0835 found 169.0834.

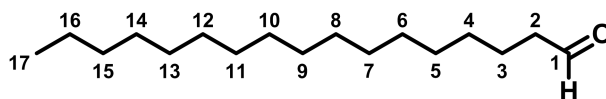
(2S)-Ethyl 5,5-dimethyl-2-thioxo-1,3-dioxolane-4-carboxylate (1.125)

A solution of diol **1.118** (30 mg, 0.188 mmol), 1,1'-thionodiimidazole (50 mg, 0.28 mmol), and DMAP (30 mg, 0.246 mmol) in anhydrous DCM (9.4 mL) was heated under reflux under argon for 5 h. The mixture was then cooled to RT and concentrated. The residue was purified by flash chromatography (petrol/ether, 80:20) to furnish the *title compound* (**1.125**) as a colourless oil (39 mg, 100%). R_f (petrol/ether; 50:50) = 0.47; $[\alpha]_D^{25} -5.70$ (c 0.70, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.35 (3 H, t, $J_{2'',1''} = 7.0$ Hz, H-2''), 1.48 (3 H, s, 1 $\times$ C(5)CH₃), 1.70 (3 H, s, 1 $\times$ C(5)CH₃), 4.34 (2 H, q, $J_{1'',2''} = 7.0$ Hz, H-1''), 4.86 (1 H, s, H-4); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (C-2''), 21.9 (1 $\times$ C(5)CH₃), 26.8 (1 $\times$ C(5)CH₃), 62.7 (C-1''), 84.7 (C-4), 89.2 (C-5), 165.1 (C-1'), 189.5 (C-2); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2986 (m), 1758 (s), 1467 (s), 1378 (s), 1268 (s), 1199 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_8\text{H}_{12}\text{NaO}_4\text{S}^+ [\text{MNa}]^+$ 227.0349, found 227.0349.

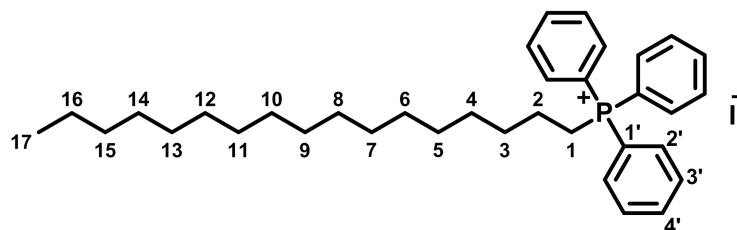
2-(Trimethylsilyl)ethyl (2*S*,3*R*,7*S*,9*R*)-7-acetoxy-3-methyl-2,3-thiocarbonyldioxy-9-[(triethylsilyl)oxy]decanoate (1.131)



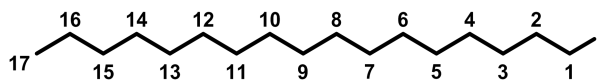
A stirred solution of diol **1.88** (30 mg, 59.3 μmol), 1,1'-thiocarbonyldiimidazole (16 mg, 89.8 μmol), and DMAP (10 mg, 81.4 μmol) in anhydrous DCM (3 mL) was refluxed under argon atmosphere for 5 h. The reaction mixture was then cooled to RT and concentrated. The residue was purified by flash chromatography (petrol/ether, 90:10 then 80:20) to furnish the *title compound* (**1.131**) as a colourless oil (33 mg, 100%). R_f (petrol/ether; 50:50) = 0.82; $[\alpha]_D^{20} +9.60$ (c 0.83, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.07 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.04–1.11 (2 H, m, H-2'), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.44 (3 H, s, H-11), 1.46–1.53 (2 H, m, H-5), 1.56–1.66 (3 H, m, H-6, 1 $\times$ H-8), 1.80–1.88 (2 H, m, 1 $\times$ H-4, 1 $\times$ H-8), 1.92–1.98 (1 H, m, 1 $\times$ H-4), 2.06 (3 H, s, H-13), 3.81–3.87 (1 H, m, H-9), 4.31–4.39 (2 H, m, H-1'), 4.85 (1 H, s, H-2), 4.95–5.00 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.6 (C-2'), 18.8 (C-5), 19.9 (C-11), 21.2 (C-13), 23.5 (C-10), 34.3 (C-6), 39.5 (C-4), 44.2 (C-8), 65.3 (C-9, C-1'), 70.8 (C-7), 83.7 (C-2), 91.3 (C-3), 165.4 (C-1), 170.7 (C-12), 189.5 (C=S); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (s), 2877 (s), 1760 (s), 1737 (s), 1458 (m), 1309 (s), 1249 (s), 1177 (s), 1047 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{25}\text{H}_{48}\text{NaO}_7\text{SSi}_2^+$ [MNa]⁺ 571.2551, found 571.2549.

1-Heptadecanal (1.132)¹⁷

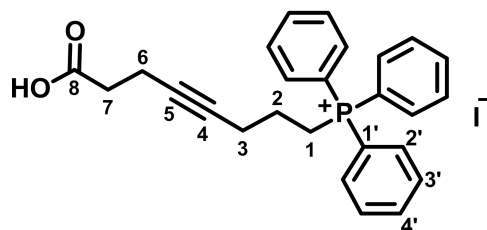
To a suspension of PCC (530 mg, 2.46 mmol) in DCM (20 mL) was added a solution of 1-heptadecanol **1.136** (420 mg, 1.64 mmol) in DCM (10 mL). The mixture was stirred vigorously at RT until TLC showed no starting material was left. DCM (20 mL) was added and the mixture was passed through a short pad of Celite[®] and washed with DCM (20 mL). The filtrate was concentrated and flash chromatography (petrol/ether, 95:5) furnished the title compound (**1.132**) as a white solid (333 mg, 80%). R_f (petrol/ether; 85:15) = 0.79; m.p. 32–33 °C; ^1H NMR (400 MHz, CDCl_3) δ 0.87 (3 H, t, $J_{17,16} = 7.0$ Hz, H-17), 1.22–1.32 (26 H, m, H-4–H-16), 1.62 (2 H, m, H-3), 2.41 (2 H, td, $J_{2,3} = 7.5$ Hz, $J_{2,1} = 2.0$ Hz, H-2), 9.76 (1 H, t, $J_{1,2} = 2.0$ Hz, H-1); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (C-17), 22.1 (C-16), 22.7 (C-15), 29.2–29.7 (C-4–C-14), 31.9 (C-3), 43.9 (C-2), 202.9 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954 (m), 2915 (s), 2849 (s), 1727 (s), 1470 (s); HRMS (GCMS, CI^+) m/z calcd. for $\text{C}_{17}\text{H}_{34}\text{NO}^+ [\text{MNH}_4]^+$ 272.2953, found 272.2940.

Heptadecyltriphenylphosphonium iodide (1.134)¹¹

A suspension of iodide **1.137** (545 mg, 1.50 mmol) and triphenylphosphine (473 mg, 1.80 mmol) in anhydrous MeCN (5 mL) was heated under reflux for 20 h. The mixture was cooled to RT and concentrated. The title compound (**1.134**) was used for further steps without purification (1.14 g, 100%) as a white solid. R_f (ethyl acetate/hexanes; 20:80) = 0; m.p. 86–87 °C; ^1H NMR (400 MHz, CDCl_3) δ 0.88 (3 H, t, $J_{17,16} = 7.0$ Hz, H-17), 1.20–1.32 (26 H, m, H-4–H-16), 1.63–1.68 (4 H, m, H-2, H-3), 3.67–3.74 (2 H, m, H-1), 7.68–7.73 (6 H, m, arom), 7.78–7.85 (9 H, m, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (C-17), 22.57, 22.61, 22.67, 29.19, 29.34, 29.53, 29.58, 29.64, 29.68, 30.37, 30.53, 31.90 (C-1–C-16), 118.2 (d, $^1J_{\text{PC}} = 85.0$ Hz, C-1'), 130.5 (d, $^2J_{\text{PC}} = 12.5$ Hz, C-2'), 133.7 (d, $^3J_{\text{PC}} = 10.0$ Hz, C-3'), 135.0 (d, $^4J_{\text{PC}} = 3.0$ Hz, C-4'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2924 (s), 2853 (s), 1587 (w), 1437 (s); HRMS (FAB⁺) m/z calcd. for $\text{C}_{35}\text{H}_{50}\text{P}^+ [\text{M}]^+$ 501.3650, found 501.3645

1-Iodoheptadecane (1.137)¹¹

To 1-heptadecanol **1.136** (380 mg, 1.50 mmol) at 0 °C was added triphenylphosphite (5 mL, 19.1 mmol) followed by I₂ (1.50 g, 6.00 mmol). The resulting heterogeneous mixture was warmed to RT and stirred over 14 h. The mixture was diluted with ether (25 mL), and the brown mixture was poured over ice. Two layers were separated and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with NaHCO₃ solution (sat. aq., 20 mL), brine (20 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol) furnished the title compound (**1.137**) as a white solid (550 mg, 100%). *R_f*(ethyl acetate/ hexanes; 1:99) = 0.90; m.p. 34–35 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.88 (3 H, t, *J*_{17,16} = 7.0 Hz, H-17), 1.25 (26 H, br.s, H-4–H-16), 1.30–1.40 (2 H, m, H-3), 1.82 (2 H, qn, *J*_{2,1} = *J*_{2,3} = 7.0 Hz, H-2), 3.19 (2 H, t, *J*_{1,2} = 7.0 Hz, H-1); ¹³C NMR (100 MHz, CDCl₃) δ 7.4 (C-1), 14.2 (C-17), 22.8 (C-16), 28.6, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 30.6, 32.0, 33.6 (C-2–C-15); IR (thin film) *v*_{max}/cm⁻¹ 2917 (s), 2849 (s), 1472 (m), 1463 (m); HRMS (ESI⁺) *m/z* calcd. for C₁₇H₃₅I⁺ [M]⁺ 366.1784, found 366.1779.

(7-Carboxyhept-4-ynyl)triphenylphosphonium iodide (1.142)

- **Synthesis of 8-chlorooct-4-ynoic acid 1.140**

To a solution of alkyne **1.58** (500 mg, 5.09 mmol) in THF (12.5 mL) was added BuLi (1.6 M in hexanes, 6.4 mL, 10.2 mmol) dropwise over a period of 5 min at -78°C . The mixture was stirred for 1 h, and anhydrous DMPU (1.3 mL, 10.7 mmol) was added. The resulting mixture was stirred for 30 min and 1-chloro-3-iodopropane (0.7 mL, 6.52 mmol) was added quickly. The resulting mixture was warmed to RT over 14 h. Most of the solvent was removed under reduced pressure then hydrochloric acid (1.0 M in H_2O , 20 mL) and ethyl acetate (20 mL) were added to dilute the mixture. The aqueous layer was extracted with ethyl acetate (8×20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), and concentrated. The residue was passed through a pad of silica, eluting with 1:1 petrol/ether (100 mL). The filtrate was concentrated to give a crude residue (862 mg) containing the desired product for further steps without any purification.

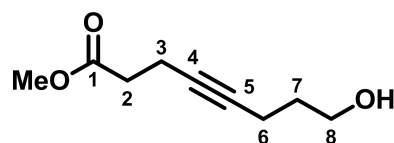
- **Synthesis of 8-iodooct-4-ynoic acid 1.141**

A solution of crude acid **1.140** (274 mg from previous step) and NaI (3.50 g, 23.6 mmol) in

acetone (15 mL) was heated under reflux for 14 h. The mixture was cooled to RT and concentrated. Hydrochloric acid (1 M in H₂O, 10 mL) was added and the mixture was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with Na₂S₂O₃ solution (sat. aq., 15 mL), brine (15 mL), then dried (MgSO₄) and concentrated to give crude (372 mg) containing the desired product for next steps without any purification.

● Synthesis of phosphonium salt **1.142**

A solution of crude acid **1.141** (372 mg, crude from previous step) and triphenylphosphine (368 mg, 1.40 mmol) in toluene (10 mL) was heated under reflux for 24 h. The mixture was cooled to RT and concentrated. The residue was recrystallised from DCM/ether and washed with ether (6 × 10 mL) to furnish the *title compound* (**1.142**) as a white solid (113 mg, 4%). m.p. 178 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.81 (2 H, m, H-2), 2.47–2.49 (4 H, m, H-3, H-6), 2.62 (2 H, t, *J*_{7,6} = 6.5 Hz, H-7), 3.68–3.74 (2 H, m, H-1), 7.73–7.76 (6 H, m, arom), 7.81–7.85 (9 H, m, arom); ¹³C NMR (125 MHz, CDCl₃) δ 15.0 (C-6), 19.4 (d, ³*J*_{PC} = 17.5 Hz, C-3), 21.7 (d, ¹*J*_{PC} = 82.0 Hz, C-1), 21.9 (d, ²*J*_{PC} = 25.0 Hz, C-2), 34.1 (C-7), 78.7 (C-5), 81.4 (C-4), 118.0 (d, ¹*J*_{PC} = 86.5 Hz, C-1'), 130.6 (d, ²*J*_{PC} = 12.5 Hz, C-2'), 133.7 (d, ³*J*_{PC} = 10.0 Hz, C-3'), 135.1 (d, ⁴*J*_{PC} = 2.5 Hz, C-4'), 174.4 (C-8); IR (thin film) ν_{max}/cm⁻¹ 3053 (m), 2918 (m), 1731 (s), 1641 (w), 1587 (w), 1438 (s), 1340 (w); HRMS (ESI⁺) *m/z* calcd. for C₂₆H₂₆O₂P⁺ [M-I]⁺ 401.1665, found 401.1670.

Methyl 8-hydroxyoct-4-ynoate (1.145)¹¹

- **Synthesis of 8-(*tert*-butyldimethylsilyloxy)oct-4-ynoic acid 1.144**

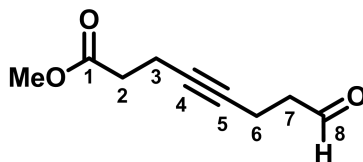
To a solution of alkyne **1.58** (450 mg, 4.60 mmol) in THF and HMPA (1:1, 18 mL) at $-45\text{ }^{\circ}\text{C}$ was slowly added BuLi (1.6 M in hexanes, 6.9 mL, 11.0 mmol) while maintaining the internal temperature below $-30\text{ }^{\circ}\text{C}$. After stirring the yellow solution for 5 min at $-45\text{ }^{\circ}\text{C}$, a solution of (3-bromopropoxy)-*tert*-butyldimethylsilane (1.6 mL, 7.00 mmol) in HMPA (4.5 mL) was added dropwise *via* cannula. The resulting mixture was stirred for 1 h at $-40\text{ }^{\circ}\text{C}$, then warmed to $0\text{ }^{\circ}\text{C}$ over 2 h. After another 1 h of stirring at $0\text{ }^{\circ}\text{C}$, NH_4Cl solution (sat. aq., 50 mL) was used to quench the reaction. The mixture was then diluted with ether (250 mL) and hydrochloric acid (1.2 M in H_2O , 25 mL) and the aqueous layer was extracted with ether ($2 \times 50\text{ mL}$). The combined organic layers were washed with hydrochloric acid (1.2 M in H_2O , 250 mL), brine (250 mL), dried (MgSO_4), then concentrated to furnish residue (2.32 g) containing the desired acid for further steps without purification.

- **Synthesis of alcohol 1.145**

A solution of crude acid **1.144** (2.32 g from previous step) and *para*-toluenesulfonic acid monohydrate (390 mg, 2.00 mmol) in methanol (60 mL) was heated under reflux for 4 h. After cooling to RT, the mixture was concentrated and NH_4Cl solution (sat. aq., 100 mL) and ether (250 mL) were added to dilute the mixture. Two layers were separated and the organic

layer was washed with NH_4Cl solution (sat. aq., 100 mL), NaHCO_3 solution (sat. aq., 100 mL), brine (1000 mL), then dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 50:50) furnished the title compound (**1.145**) as a colourless oil (75 mg, 10%). R_f (ethyl acetate/hexanes; 50:50) = 0.40; ^1H NMR (400 MHz, CDCl_3) δ 1.62 (1 H, br.s, OH), 1.73 (2 H, qn, $J_{7,6} = J_{7,8} = 6.0$ Hz, H-7), 2.23–2.28 (2 H, m, H-6), 2.44–2.51 (4 H, m, H-2, H-3), 3.70 (3 H, s, OCH_3), 3.75 (2 H, t, $J_{8,7} = 6.0$ Hz, H-8); ^{13}C NMR (100 MHz, CDCl_3) δ 14.7 (C-3), 15.3 (C-6), 31.4 (C-7), 33.8 (C-2), 51.8 (OCH_3), 61.9 (C-8), 78.8 (C-4), 80.3 (C-5), 172.6 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3410 (br), 2950, 2230, 1740, 1440, 1370, 1260; HRMS (CI^+) m/z calcd. for $\text{C}_9\text{H}_{14}\text{O}_3\text{N}^+ [\text{MNH}_4]^+$ 188.1287, found 188.1291.

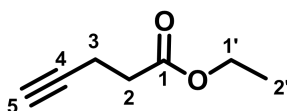
Methyl 8-oxooct-4-ynoate (**1.146**)¹¹



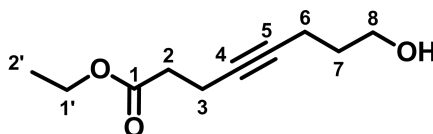
To a solution of alcohol **1.145** (45 mg, 0.300 mmol) in anhydrous DCM (5 mL) was added Celite® (200 mg), powdered MS 4Å (200 mg) and PDC (220 mg, 0.600 mmol). The resulting brown mixture was stirred for 2 h at RT then diluted with ether (10 mL). The mixture was filtered through a short pad of Celite® with ether eluting (50 mL), and the filtrate was washed successively with hydrochloric acid (1.2 M in H_2O , 20 mL), NaHCO_3 solution (sat. aq., 20 mL), brine (20 mL), dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 80:20) furnished the title compound (**1.146**) as a colourless liquid (33 mg, 74%). R_f (ethyl acetate/hexanes; 20:80) = 0.27; ^1H NMR (400 MHz, CDCl_3) δ 2.42–2.50 (6 H, m, H-2, H-3,

H-6), 2.59–2.62 (2 H, m, H-7), 3.68 (3 H, s, OCH₃), 9.76–9.77 (1 H, m, H-8); ¹³C NMR (100 MHz, CDCl₃) δ 12.0 (C-6), 14.6 (C-3), 33.6 (C-2), 42.8 (C-7), 51.7 (OCH₃), 78.8 (C-4), 79.3 (C-5), 172.5 (C-1), 200.8 (C-8); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2956 (m), 1737 (s), 1438 (m), 1366 (m), 1260 (m), 1039 (m); HRMS (ESI⁺) *m/z* calcd. for C₉H₁₂NaO₃⁺ [MNa]⁺ 191.0679, found 191.0678.

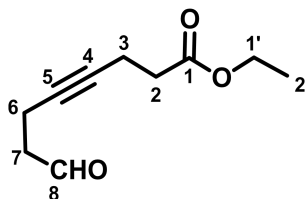
Ethyl pent-4-ynoate (**1.148**)¹⁸



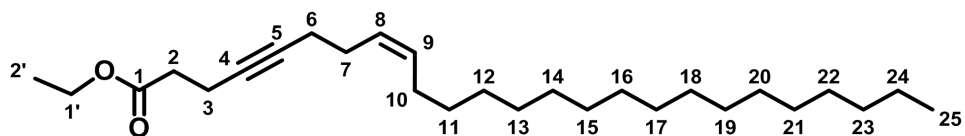
Concentrated H₂SO₄ (1 mL) was added to a solution of acid **1.58** (1.00 g, 10.2 mmol) in ethanol (12 mL). The reaction mixture was stirred at RT for 24 h. H₂O (20 mL), NaOH solution (5% in H₂O, 3 mL) were added, and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated. Flash chromatography (petrol/ether, 90:10) furnished the title compound (**1.148**) as a colourless oil (978 mg, 76%). *R_f* (petrol/ether; 60:40) = 0.91; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3 H, t, *J*_{2',1'} = 7.0 Hz, H-2'), 1.97 (1 H, t, *J*_{5,3} = 2.0 Hz, H-5), 2.47–2.57 (4 H, m, H-2, H-3), 4.16 (2 H, q, *J*_{1',2'} = 7.0 Hz, H-1'); ¹³C NMR (100 MHz, CDCl₃) δ 14.2 (C-2'), 14.3 (C-3), 33.3 (C-2), 60.7 (C-1'), 68.9 (C-5), 82.5 (C-4), 171.7 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3296 (s), 2984 (m), 2122 (w), 1737 (s), 1466 (s), 1375 (s), 1287 (m), 1042 (m); HRMS (GCMS, CI⁺) *m/z* calcd. for C₇H₁₄O₂N⁺ [MNH₄]⁺ 144.1024, found 144.1019.

Ethyl 8-hydroxyoct-4-ynoate (1.149)

To a solution of alkyne **1.148** (500 mg, 3.96 mmol) in THF (3.5 mL) was added BuLi (1.6 M in hexanes, 2.5 mL, 4.00 mmol) at -85°C . Stirring was continued for 15 min when $\text{BF}_3\cdot\text{OEt}_2$ (490 μL , 3.96 mmol) was added. The mixture was stirred for another 15 min when oxetane (130 μL , 1.99 mmol) was added. The mixture was stirred for 3 h and the mixture was then slowly warmed to RT over 30 min. The mixture was then poured into NaHCO_3 solution (sat. aq., 15 mL) and the mixture was extracted with ether (3×25 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ ether, 80:20) furnished the *title compound* (**1.149**) as a colourless oil (230 mg, 63%). R_f (petrol/ether; 50:50) = 0.30; ^1H NMR (500 MHz, CDCl_3) δ 1.27 (3 H, t, $J_{2',1'} = 7.0$ Hz, H-2'), 1.56 (1 H, br.s, OH), 1.73 (2 H, qn, $J_{7,6} = J_{7,8} = 6.5$ Hz, H-7), 2.27 (2 H, t, $J_{6,7} = 6.5$ Hz, H-6), 2.46–2.52 (4 H, m, H-2, H-3), 3.75 (2 H, t, $J_{8,7} = 6.5$ Hz, H-8), 4.16 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'); ^{13}C NMR (125MHz, CDCl_3) δ 14.2 (C-2'), 14.7(C-3), 15.3 (C-6), 31.4 (C-7), 34.0 (C-2), 60.6 (C-1'), 61.9 (C-8), 78.9 (C-4), 80.2 (C-5), 172.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3409 (m), 2937 (m), 1735 (s), 1436 (m), 1375 (m), 1256 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{10}\text{H}_{16}\text{NaO}_3^+ [\text{MNa}]^+$ 207.0992, found 207.0992.

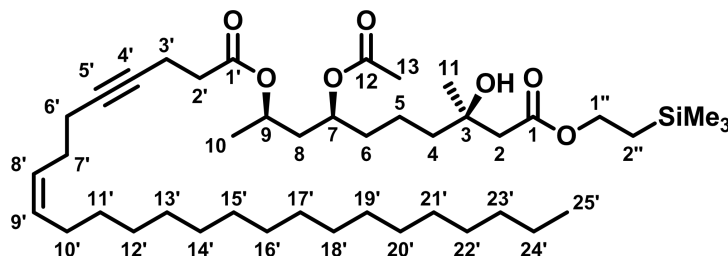
Ethyl 8-oxooct-4-ynoate (1.150)

To a solution of alcohol **1.149** (50 mg, 0.271 mmol) in anhydrous DCM (6 mL) was added Dess–Martin periodinane (345 mg, 0.815 mmol) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C, then allowed to warm to RT. After stirring at RT for 5 h, the mixture was diluted with ether (10 mL). Aqueous buffer [10 mL of a solution made from Na₂S₂O₃ (*ca.* 100–158 g/L) and Na₂CO₃ (*ca.* 100 g/L)], was added and the resulting mixture was stirred for 15 min where layers were separated. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.150**) as a colourless oil (46 mg, 94%). *R_f* (petrol/ether; 50:50) = 0.47; ¹H NMR (500 MHz, CDCl₃) δ 1.27 (3 H, t, *J*_{2',1'} = 7.0 Hz, H-2'), 2.46–2.48 (6 H, m, H-2, H-3, H-6), 2.62 (2 H, t, *J*_{7,6} = 7.0 Hz, H-7), 4.16 (2 H, q, *J*_{1',2'} = 7.0 Hz, H-1'), 9.79 (1 H, s, H-8); ¹³C NMR (125 MHz, CDCl₃) δ 12.0 (C-6), 14.2 (C-2'), 14.7 (C-3), 33.8 (C-2), 42.8 (C-7), 60.6 (C-1'), 78.7 (C-5), 79.4 (C-4), 172.0 (C-1), 200.8 (C-8); IR (thin film) *v*_{max}/cm⁻¹ 2982 (m), 2918 (m), 1732 (s), 1375 (m), 1166 (m), 1043 (m); HRMS (ESI⁺) *m/z* calcd. for C₁₀H₁₄NaO₃⁺ [MNa]⁺ 205.0835, found 205.0832.

(Z)-Ethyl pentacos-8-en-4-ynoate (1.151)

A solution of NaHMDS (1.0 M in THF, 2 mL, 2.00 mmol) was added to a suspension of phosphonium salt **1.134** (1.38 g, 2.19 mmol) in THF (9 mL) at 0 °C. The resulting orange solution was allowed to warm to RT, stirred for 60 min, then cooled to –20 °C. A solution of aldehyde **1.150** (200 mg, 1.10 mmol) in THF (4.5 mL) was added to the orange solution and the resulting mixture was warmed to RT and stirred for 3 h. The mixture was poured into a mixture of ether (60 mL) and NH₄Cl solution (sat. aq., 32 mL) where layers were separated. The organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (petrol then petrol/ether, 99:1) to furnish the *title compound* (**1.151**) as a colourless oil (300 mg, 68%). *R_f* ((hexanes/ethyl acetate, 95:5) = 0.52; ¹H NMR (500 MHz, CDCl₃) δ 0.88 (3 H, t, *J*_{25,24} = 7.0 Hz, H-25), 1.25 (31 H, br.s, H-2', H-11–H-24), 2.02 (2 H, q, *J*_{10,9} = *J*_{10,11} = 7.0 Hz, H-10), 2.11–2.24 (4 H, m, H-6, H-7), 2.43–2.52 (4 H, m, H-2, H-3), 4.15 (2 H, q, *J*_{1',2'} = 7.0 Hz, H-1'), 5.35–5.45 (2 H, m, H-8, H-9); ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (C-25), 14.2 (C-2'), 14.8 (C-3), 19.1 (C-6), 22.7 (C-24), 26.9 (C-7), 27.3 (C-10), 29.3–31.9 (C-11–C-23), 34.1 (C-2), 60.5 (C-1'), 78.3 (C-4), 80.6 (C-5), 127.8 (C-8), 131.3 (C-9), 172.2 (C-1); IR (thin film) *v*_{max}/cm^{–1} 2924 (s), 2854 (s), 1741 (s), 1466 (m), 1373 (m), 1046 (w); HRMS (ESI⁺) *m/z* calcd. for C₂₇H₄₈NaO₂⁺ [MNa]⁺ 427.3547, found 427.3551.

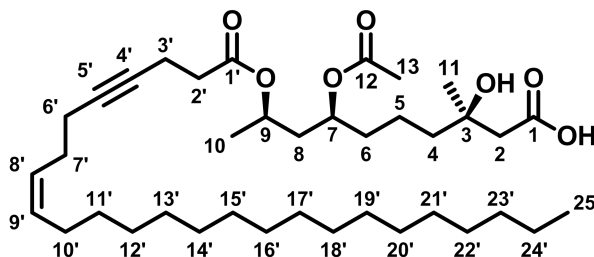
2-(Trimethylsilyl)ethyl (3*R*,7*S*,9*R*)-7-acetoxy-3-hydroxy-3-methyl-9-[(*Z*)-pentacos-8'-en-4'-ynoxy]decanoate (1.153)



To a solution of alcohol **1.155** (27 mg, 71.8 μmol) and acid **1.57** (54 mg, 0.143 mmol) in DCM (5 mL) was added successively added *N,N*-diisopropylethylamine (62.5 μL , 0.359 mmol), DMAP (9 mg, 73.6 μmol) and *N,N'*-diisopropylcarbodiimide (56 μL , 0.361 mmol). The resulting mixture was stirred for 15 h at RT then poured into a mixture of NH_4Cl solution (sat. aq., 5 mL) and ether (20 mL). Layers were separated and the organic layer was washed with hydrochloric acid (1.2 M in H_2O , 5 mL), NaHCO_3 solution (sat. aq., 5 mL), and brine (5 mL). The organic layer was dried (MgSO_4), and concentrated. Flash chromatography (petrol/ether, 85:15) furnished the *title compound* (**1.153**) as a colourless oil (42 mg, 80%). R_f (petrol/ether; 50:50) = 0.60; $[\alpha]_{\text{D}}^{25} -1.60$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.06 (9 H, s, SiCH_3), 0.89 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 1.00–1.03 (2 H, m, H-2''), 1.22 (3 H, s, H-11), 1.25 (3 H, d, $J_{10,9} = 6.5$ Hz, H-10), 1.26 (28 H, br.s, H-11'–H-24'), 1.38–1.58 (6 H, m, H-4, H-5, H-6), 1.68 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 6.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 1.95 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 8.0$ Hz, $J_{8,9 \text{ or } 8,7} = 6.5$ Hz, 1 $\times$ H-8), 2.01–2.04 (2 H, m, H-10'), 2.05 (3 H, s, H-13), 2.15–2.23 (4 H, m, H-6', H-7'), 2.41 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 2.47 (4 H, app.s, H-2', H-3'), 2.48 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 3.61 (1 H, s, OH), 4.20–4.24 (2 H, m, H-1''), 4.92–4.99 (2 H, m, H-7, H-9), 5.36–5.45

(2 H, m, H-8', H-9'); ^{13}C NMR (125 MHz, CDCl_3) δ -1.5 (SiCH_3), 14.1 (C-25'), 14.8 (C-3'), 17.3 (C-2''), 19.1 (C-6'), 19.4 (C-5), 20.0 (C-10), 21.2 (C-13), 22.7 (C-24'), 26.5 (C-11), 26.8 (C-7'), 27.3 (C-10'), 29.3-31.9 (C-11'–C-23'), 34.3 (C-2'), 34.6 (C-6), 40.1 (C-8), 41.6 (C-4), 45.0 (C-2), 63.0 (C-1''), 68.3 (C-9), 70.7 (C-7), 70.9 (C-3), 78.2 (C-4'), 80.7 (C-5'), 127.8 (C-8'), 131.2 (C-9'), 170.6 (C-12), 171.5 (C-1'), 173.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3520 (br), 2925 (s), 2854 (s), 1737 (s), 1459 (m), 1374 (m), 1249 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{43}\text{H}_{78}\text{NaO}_7\text{Si}^+ [\text{MNa}]^+$ 757.5409, found 757.5415.

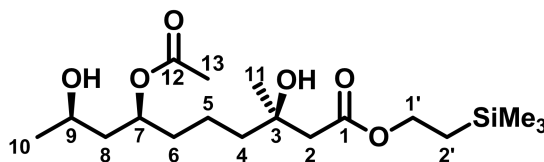
(3*R*,7*S*,9*R*)-7-Acetoxy-3-hydroxy-3-methyl-9-[(*Z*)-pentacos-8-en-4-ynoyloxy]decanoic acid (1.154)



To a solution of ester **1.153** (20 mg, 27.2 μmol) in DMF (0.3 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate in DMF (0.145 M in DMF, 380 μL , 55.1 μmol) at RT. The resulting mixture was stirred for 60 min; then ethyl acetate (20 mL) was added to dilute the mixture. The solution was washed with hydrochloric acid (1.2 M in H_2O , 5 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20 then ethyl acetate) furnished the *title compound* (**1.154**) as a colourless oil (15 mg, 87%). R_f (DCM/MeOH; 95:5) = 0.33; $[\alpha]_{\text{D}}^{25}$ -2.20 (c 0.37, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.87 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 1.23–1.60 (40 H, m, H-4, H-5, H-6, H-10,

H-11, H-11'–H-24'), 1.65–1.70 (1 H, m, 1 × H-8), 1.92–1.98 (1 H, m, 1 × H-8), 1.99–2.05 (5 H, m, H-13, H-10'), 2.12–2.23 (4 H, m, H-6', H-7'), 2.41–2.62 (6 H, m, H-2, H-2', H-3'), 4.91–5.00 (2 H, m, H-7, H-9), 5.35–5.44 (2 H, m, H-8', H-9'); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-25'), 14.8 (C-3'), 19.1 (C-6'), 19.4 (br, C-5), 20.0 (C-10), 21.2 (C-13), 22.7 (C-24'), 26.7 (br, C-11), 26.8 (C-7'), 27.3 (C-10'), 29.3–31.9 (C-11'–C-23'), 34.3 (C-2'), 34.5 (C-6), 40.2 (C-8), 41.5 (br, C-4), 44.7 (br, C-2), 68.3 (C-9), 70.7 (C-7), 71.0 (br, C-3), 78.2 (C-4'), 80.7 (C-5'), 127.8 (C-8'), 131.3 (C-9'), 170.9 (C-12), 171.5 (C-1'), 176.0 (br, C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3445 (br), 2924 (s), 2853 (s), 1737 (s), 1463 (m), 1375 (m), 1260 (s), 1092 (m); HRMS (ESI) m/z calcd. for $\text{C}_{38}\text{H}_{66}\text{NaO}_7^+ [\text{MNa}]^+$ 657.4701, found 657.4695.

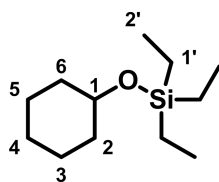
(3*R*,7*S*,9*R*)-2-(Trimethylsilyl)ethyl 7-acetoxy-3,9-dihydroxy-3-methyldecanoate (1.155)



To a stirred solution of silyl ether **1.59** (35 mg, 71.4 μmol) in MeCN (1.6 mL) was added hydrofluoric acid solution (1% in H_2O , 0.15 mL, 71.4 μmol). The reaction mixture was stirred for 60 min before being quenched with NaHCO_3 solution (sat. aq., 4.5 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with NH_4Cl solution (sat. aq., 6 mL), dried (MgSO_4), and concentrated. The residue (**1.155**) was used for further steps without purification (27 mg, 100%). R_f (ether) = 0.48; $[\alpha]_{\text{D}}^{25} -1.20$ (c 1.30, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.06 (9 H, s, SiCH_3), 1.00–1.03 (2 H, m, H-2'), 1.21 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.22 (3 H, s, H-11), 1.35–1.67 (7 H, m, H-4, H-5, H-6, 1 ×

H-8), 1.76–1.83 (1 H, m, 1 × H-8), 2.06 (3 H, s, H-13), 2.41 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 × H-2), 2.48 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 × H-2), 3.62 (1 H, br.s, 1 × OH), 3.84–3.92 (1 H, m, H-9), 4.20–4.24 (2 H, m, H-1'), 4.98–5.03 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.5 (SiCH_3), 17.3 (C-2'), 19.5 (C-5), 21.3 (C-13), 23.8 (C-10), 26.5 (C-11), 35.0 (C-6), 41.6 (C-4), 43.7 (C-8), 45.0 (C-2), 63.0 (C-1'), 65.8 (C-7), 70.8 (C-3), 72.5 (C-9), 171.0 (C-12), 173.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3418 (br), 2955 (s), 1732 (s), 1461 (m), 1375 (m), 1249 (s), 1174 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{18}\text{H}_{36}\text{NaO}_6\text{Si}^+[\text{MNa}]^+$ 399.2173, found 399.2175.

(Cyclohexyloxy)triethylsilane (1.159)¹⁹



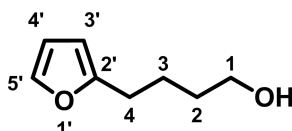
To a solution of cyclohexanol **1.158** (210 μL , 1.99 mmol) in pyridine (10 mL) was added chlorotriethylsilane (1 mL, 5.95 mmol). The mixture was then stirred at 60 °C for 14 h then it was poured into a mixture of ether (20 mL) and CuSO_4 solution (sat. aq., 20 mL) at 0 °C. The aqueous layer was extracted with ether (3 × 20 mL), washed with CuSO_4 solution (2 × 10 mL), dried (MgSO_4) then concentrated. Flash chromatography (petrol) furnished the title compound (**1.159**) as a colourless oil (432 mg, 100%). R_f (petrol) = 0.73; ^1H NMR (400 MHz, CDCl_3) δ 0.58 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.95 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.07–1.35 (5 H, m, 1 × H-2, 1 × H-3, 1 × H-4, 1 × H-5, 1 × H-6), 1.46 (1 H, m, 1 × H-4), 1.67–1.82 (4 H, m, 1 × H-2, 1 × H-3, 1 × H-5, 1 × H-6), 3.51–3.59 (1 H, m, H-1); ^{13}C NMR

Experimental – Chapter 1 Compounds

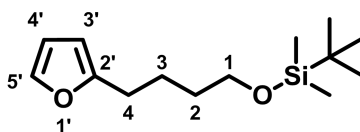
(100 MHz, CDCl₃) δ 4.9 (C-1'), 6.9 (C-2'), 24.4 (C-3, C-5), 25.6 (C-4), 36.1 (C-2, C-6), 70.9 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934 (s), 2877 (s), 2858 (s), 1451 (m), 1373 (m), 1238 (m), 1096 (s), 1016 (s); HRMS (FI⁺) m/z calcd. for C₁₂H₂₆OSi⁺ [M]⁺ 214.1753, found 214.1757.

Experimental Procedures and characterisation data for compounds in Chapter 2: The identity of a spirocyclic bis(acetylene) enol ether isolated from *Chrysanthemum boreale* via total synthesis

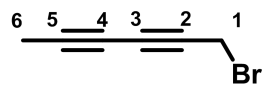
4-(Furan-2-yl)butan-1-ol (2.45**)²⁰**



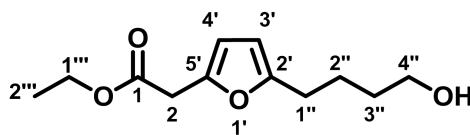
To a solution of silyl ether **2.62** (3.00 g, 11.8 mmol) in THF (60 mL) was added TBAF solution (1.0 M in THF, 17.7 mL, 17.7 mmol) at 0 °C. The resulting solution was stirred at RT for 4 h before dilution with ether (100 mL). The mixture was washed with H₂O (50 mL), dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 50:50) furnished the title compound (**2.45**) as a colourless oil (1.66 g, 100%). *R_f* (petrol/ether; 50:50) = 0.25; ¹H NMR (400 MHz, CDCl₃) δ 1.56 (1 H, br.s, OH), 1.61–1.65 (2 H, m, H-2), 1.70–1.75 (2 H, m, H-3), 2.67 (2 H, t, *J*_{4,3} = 7.0 Hz, H-4), 3.67 (2 H, t, *J*_{1,2} = 6.5 Hz, H-1), 6.00 (1 H, dd, *J*_{3',4'} = 3.0 Hz, *J*_{3',5'} = 1.0 Hz, H-3'), 6.29 (1 H, dd, *J*_{4',3'} = 3.0 Hz, *J*_{4',5'} = 2.0 Hz, H-4'), 7.27–7.30 (1 H, m, H-5'); ¹³C NMR (100 MHz, CDCl₃) δ 24.3 (C-3), 27.7 (C-4), 32.1 (C-2), 62.6 (C-1), 104.8 (C-3'), 110.1 (C-4'), 140.8 (C-5'), 156.0 (C-2'); IR (thin film) *v*_{max}/cm⁻¹ 3346 (br), 2940 (s), 1596 (m), 1508 (s), 1457 (s), 1384 (m), 1063 (s). All the other data are as reported.

***tert*-Butyl[4-(furan-2-yl)butoxy]dimethylsilane (**2.62**)²¹**

To a solution of furan (10.7 mL, 147 mmol) in THF (150 mL) was added BuLi (1.6 M in hexanes, 83.5 mL, 133.6 mmol) at $-15\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-15\text{ }^{\circ}\text{C}$ for 1 h, $0\text{ }^{\circ}\text{C}$ for 1 h, then RT for 1.5 h. The reaction mixture was cooled to $-15\text{ }^{\circ}\text{C}$ and a solution of iodide **2.100** (21.0 g, 66.8 mmol) in THF (150 mL) was added dropwise over 30 min. The resulting yellow solution was stirred at $-15\text{ }^{\circ}\text{C}$ for 2 h then warm to RT over 14 h. The mixture was diluted with ether (500 mL) and NH_4Cl solution (sat. aq., 250 mL), and the aqueous layer was extracted with ether ($3 \times 250\text{ mL}$). The combined organic layers were washed with brine (250 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ether, 98:2) furnished the title compound (**2.62**) as a pale yellow oil (16.7 g, 98%). R_f (petrol/ether; 98:2) = 0.62; ^1H NMR (400 MHz, CDCl_3) δ 0.07 (6 H, s, SiCH_3), 0.92 (9 H, s, SiCCH_3), 1.54–1.63 (2 H, m, H-2), 1.67–1.76 (2 H, m, H-3), 2.66 (2 H, t, $J_{4,3} = 7.5\text{ Hz}$, H-4), 3.65 (2 H, t, $J_{1,2} = 6.5\text{ Hz}$, H-1), 6.00 (1 H, app.s, H-3'), 6.29 (1 H, app.s, H-4'), 7.31 (1 H, app.s, H-5'); ^{13}C NMR (100 MHz, CDCl_3) δ -5.3 (SiCH_3), 18.3 (SiCCH_3), 24.4 (C-3), 26.0 (SiCCH_3), 27.7 (C-4), 32.3 (C-2), 62.8 (C-1), 104.7 (C-3'), 110.0 (C-4'), 140.7 (C-5'), 156.3 (C-2'). All the other data are as reported.

1-Bromohexa-2,4-diyne (2.67)²²

To a solution of propargylic alcohol **2.165** (120 mg, 1.28 mmol) in ether (1 mL) at 0 °C was added successively pyridine (10.3 μ L, 0.128 mmol) and PBr₃ (48 μ L, 0.512 mmol). The reaction mixture was warmed to RT, stirred for 14 h, and then diluted with ether (10 mL) and washed with Na₂CO₃ solution (sat. aq., 2 $\times$ 5 mL). The aqueous layer was extracted with ether (3 $\times$ 5 mL) and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 95:5) furnished the title compound (**2.67**) as a yellow oil (120 mg, 60%). R_f (petrol) = 0.45; ¹H NMR (400 MHz, CDCl₃) δ 1.96 (3 H, s, H-6), 3.96 (2 H, s, H-1); ¹³C NMR (100 MHz, CDCl₃) δ 4.4 (C-6), 14.7 (C-1), 63.6, 69.4, 71.8 and 78.9 (C-2, C-3, C-4, C-5). All the other data are as reported.

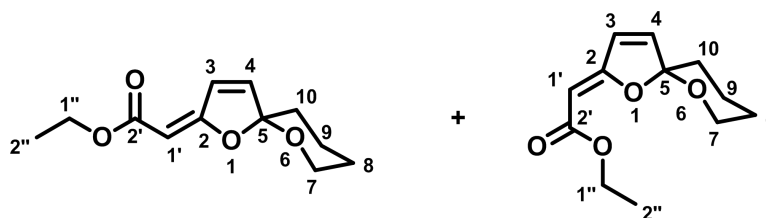
Ethyl 2-[5-(4-hydroxybutyl)furan-2-yl]acetate (2.70)²⁰

To a dark green solution of FeSO₄·7H₂O (600 mg, 2.14 mmol) and furan derivative **2.45** (100 mg, 0.714 mmol) in DMSO (10 mL) was added a solution of ethyl 2-iodoacetate **2.69** (169 μ L, 1.43 mmol) in DMSO (2 mL). The resulting mixture was stirred at RT for 5 min and H₂O₂ solution (35% in H₂O, 0.85 mL, 8.67 mmol) was added dropwise. The resulting

red mixture was stirred at RT for 14 h before dilution with H₂O (15 mL) and ether (15 mL). The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the title compound (**2.70**) as a colourless oil (113 mg, 70%, 100% b.r.s.m.). R_f (petrol/ethyl acetate; 50:50) = 0.25; ¹H NMR (500 MHz, CDCl₃) δ 1.27 (3 H, t, $J_{2''',1'''} = 7.0$ Hz, H-2'''), 1.59–1.65 (2 H, m, H-3''), 1.68–1.75 (2 H, m, H-2''), 2.63 (2 H, t, $J_{1'',2''} = 7.5$ Hz, H-1''), 3.63 (2 H, s, H-2), 3.65 (2 H, t, $J_{4',3'} = 6.0$ Hz, H-4'), 4.18 (2 H, q, $J_{1''',2'''} = 7.0$ Hz, H-1'''), 5.93 (1 H, d, $J_{4',3'} = 3.0$ Hz, H-4'), 6.10 (1 H, d, $J_{3',4'} = 3.0$ Hz, H-3'); ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (C-2'''), 24.2 (C-2''), 27.7 (C-1''), 32.1 (C-3''), 34.2 (C-2), 61.1 (C-1'''), 62.6 (C-4''), 105.8 (C-4'), 108.4 (C-3'), 145.9 (C-2'), 155.5 (C-5'), 169.7 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3419 (br), 2940 (m), 1739 (s), 1566 (m), 1226 (w), 1031 (s); HRMS (ESI⁺) m/z calcd. for C₁₂H₁₈NaO₄⁺ [MNa]⁺ 249.1097, found 249.1097.

(E)-Ethyl 2-(1,6-dioxaspiro[4.5]dec-3-en-2-ylidene)acetate (*E*-2.72)²¹ &

(Z)-ethyl 2-(1,6-dioxaspiro[4.5]dec-3-en-2-ylidene)acetate (*Z*-2.72)²¹



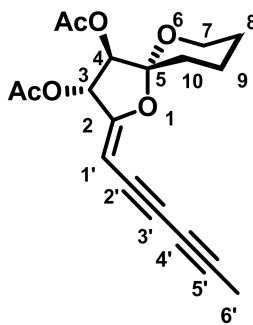
Pertrifluoroacetic acid was prepared *in situ* by addition of TFAA (30 μL, 0.207 mmol) to a stirred mixture of H₂O₂ solution (35% in H₂O, 60 μL) and DCM (0.5 mL) at 0 °C. This

solution was subsequently added dropwise to a stirred mixture of NaH₂PO₄ (60 mg, 0.443 mmol) and spiroketal **2.111** [a mixture of two diastereomers (*d.r.* = 1:1), 25 mg, 0.103 mmol] in DCM (1.5 mL). The mixture was stirred at RT for 2 h before dilution with H₂O (10 mL) and DCM (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with H₂O (10 mL), NaHCO₃ solution (sat. aq., 10 mL), brine (10 mL), then dried (MgSO₄) and concentrated. Preparative TLC (petrol/ethyl acetate, 70:30) furnished the title compounds **E-2.72** (13 mg, 52 %) and **Z-2.72** (2 mg, 8%), both as a colourless oils as side products. **Data for E-2.72:** *R_f* (petrol/ether; 90:10) = 0.20; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3 H, t, *J*_{2'',1''} = 7.0 Hz, H-2''), 1.62–2.00 (6 H, m, H-8, H-9, H-10), 3.84–3.88 (1 H, m, H-7_{eq}), 4.00 (1 H, td, *J*_{7ax,7eq} = *J*_{7ax,8ax} = 11.5 Hz, *J*_{7ax,8eq} = 3.5 Hz, H-7_{ax}), 4.16 (2 H, q, *J*_{1'',2''} = 7.0 Hz, H-1''), 5.32–5.33 (1 H, m, H-1'), 6.43 (1 H, dd, *J*_{3,4} = 6.0 Hz, *J*_{3,1'} = 1.5 Hz, H-3), 7.36 (1 H, d, *J*_{4,3} = 6.0 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 14.4 (C-2''), 19.2 (C-9), 24.3 (C-8), 32.2 (C-10), 59.6 (C-1''), 64.5 (C-7), 91.2 (C-1'), 111.4 (C-5), 125.7 (C-4), 141.9 (C-3), 167.6 (C-2), 170.5 (C-2'); IR (thin film) *v*_{max}/cm⁻¹ 2949 (s), 1702 (s), 1647 (s), 1584 (m), 1444 (m); HRMS (ESI⁺) *m/z* calcd. for C₁₂H₁₆NaO₄⁺ [MNa]⁺ 247.0941, found 247.0938. **Data for Z-2.72:** *R_f* (petrol/ether; 80:20) = 0.30; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3 H, t, *J*_{2'',1''} = 7.0 Hz, H-2''), 1.63–1.68 (5 H, m, H-8, H-9, 1 × H-10), 2.01–2.13 (1 H, m, 1 × H-10), 3.85–3.89 (1 H, m, H-7_{eq}), 4.13 (1 H, td, *J*_{7ax,7eq} = *J*_{7ax,8ax} = 12.0 Hz, *J*_{7ax,8eq} = 3.5 Hz, H-7_{ax}), 4.18 (2 H, q, *J*_{1'',2''} = 7.0 Hz, H-1''), 4.96 (1 H, s, H-1'), 6.23 (1 H, d, *J*_{3,4} = 5.5 Hz, H-3), 6.39 (1 H, d, *J*_{4,3} = 5.5 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 14.4 (C-2''), 19.4 (C-9), 24.4 (C-8), 32.3 (C-10), 59.4 (C-1''), 64.6 (C-7), 90.8 (C-1'), 114.1 (C-5), 128.0 (C-4), 141.1 (C-3), 165.8 (C-2), 167.3 (C-2'); IR (thin film) *v*_{max}/cm⁻¹ 2950 (s), 1711 (s), 1648 (s), 1590 (w), 1444 (w); HRMS (ESI⁺) *m/z* calcd. for C₁₂H₁₆NaO₄⁺ [MNa]⁺

247.0941, found 247.0943.

(3*R,4*R**,5*R**,*Z*)-3,4-Diacetoxy-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane**

(2.91)

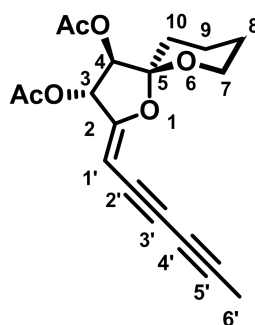


To a stirred solution of diol **2.192** (30 mg, 0.121 mmol) in pyridine (7.5 mL) at RT was added acetic anhydride (115 μ L, 1.21 mmol). The reaction mixture was stirred for 14 h at RT before dilution with ether (50 mL) and washed with CuSO₄ solution (sat. aq., 3 $\times$ 20 mL). The combined aqueous layers were extracted with ether (3 $\times$ 50 mL), and the combined organic layers were dried (MgSO₄) then concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the *title compound* (**2.91**) as a pale yellow solid (35 mg, 88%). *R_f* (petrol/ethyl acetate; 80:20) = 0.42; ¹H NMR (500 MHz, CDCl₃) δ 1.52–2.00 (6 H, m, H-8, H-9, H-10), 2.00 (3 H, d, $J_{6',1'} = 1.0$ Hz, H-6'), 2.11 (3 H, s, 1 $\times$ COCH₃), 2.12 (3 H, s, 1 $\times$ COCH₃), 3.78 (1 H, dd, $J_{7eq,7ax} = 11.5$ Hz, $J_{7eq,8ax} = 4.5$ Hz, H-7_{eq}), 3.98 (1 H, td, $J_{7ax,7eq} = J_{7ax,8ax} = 11.5$ Hz, $J_{7ax,8eq} = 3.5$ Hz, H-7_{ax}), 4.88 (1 H, app.t, $J_{1',3} = J_{1',6'} = 1.0$ Hz, H-1'), 5.11 (1 H, d, $J_{4,3} = 1.0$ Hz, H-4), 5.52 (1 H, t, $J_{3,1'} = J_{3,4} = 1.0$ Hz, H-3); ¹H NMR (500 MHz, CCl₄) δ 1.47–1.77 (6 H, m, H-8, H-9, H-10), 1.95 (3 H, s, H-6'), 2.02 (3 H, s, 1 $\times$ COCH₃), 2.04 (3 H, s, 1 $\times$ COCH₃), 3.69 (1 H, br.d, $J_{7eq,7ax} = 11.5$ Hz, H-7_{eq}), 3.91 (1 H, td, $J_{7ax,7eq} = J_{7ax,8ax} = 11.5$

Hz, $J_{7\text{ax},8\text{eq}} = 3.5$ Hz, H-7_{ax}), 4.71 (1 H, s, H-1'), 4.90 (1 H, s, H-4), 5.32 (1 H, s, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ 4.7 (C-6'), 18.7 (C-9), 20.6, 20.9 ($2 \times \text{COCH}_3$), 24.5 (C-8), 29.7 (C-10), 62.9 (C-7), 64.8 (C-4'), 68.7 (C-2'), 75.5 (C-3), 78.6 (C-4), 78.8 (C-3'), 80.3 (C-5'), 83.7 (C-1'), 109.1 (C-5), 164.3 (C-2), 169.2, 170.0 ($2 \times \text{COCH}_3$); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970 (m), 2143 (w), 1741 (s), 1659 (m), 1437 (m), 1367 (m), 1230 (s), 1103 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{NaO}_6^+ [\text{MNa}]^+$ 355.1152, found 355.1143.

(3*R,4*R**,5*S**,*Z*)-3,4-Diacetoxy-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane**

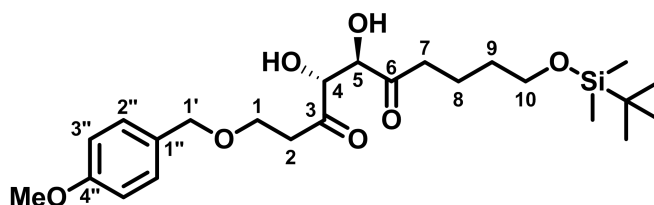
(2.92)



To a stirred solution of diol **2.194** (5 mg, 20.1 μmol) in pyridine (1 mL) at RT was added acetic anhydride (19 μL , 0.201 mmol). The reaction mixture was stirred for 14 h at RT before dilution with ether (10 mL) and washed with CuSO_4 solution (sat. aq., 3×5 mL). The combined aqueous layers were extracted with ether (3×10 mL), and the combined organic layers were dried (MgSO_4) then concentrated. Preparative TLC (petrol/ethyl acetate, 80:20) furnished the *title compound* (**2.92**) as a pale yellow solid (5 mg, 75%). R_f (petrol/ethyl acetate; 80:20) = 0.37; m.p. not determined; ^1H NMR (500 MHz, CDCl_3) δ 1.50–1.86 (6 H, m, H-8, H-9, H-10), 2.00 (3 H, d, $J_{6',1'} = 1.0$ Hz, H-6'), 2.10 (3 H, s, $1 \times \text{COCH}_3$), 2.15 (3 H, s, $1 \times \text{COCH}_3$), 3.83 (1 H, dd, $J_{7\text{eq},7\text{ax}} = 12.0$ Hz, $J_{7\text{eq},8\text{ax}} = 4.5$ Hz, H-7_{eq}), 3.96 (1 H, td, $J_{7\text{ax},7\text{eq}} =$

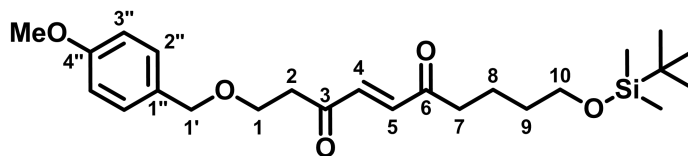
$J_{7ax,8ax} = 12.0$ Hz, $J_{7ax,8eq} = 3.0$ Hz, H-7_{ax}), 4.70 (1 H, app.t, $J_{1',3} = J_{1',6'} = 1.0$ Hz, H-1'), 5.13 (1 H, d, $J_{4,3} = 7.5$ Hz, H-4), 5.98 (1 H, dd, $J_{3,4} = 7.5$ Hz, $J_{3,1'} = 1.0$ Hz, H-3); ^1H NMR (500 MHz, CCl_4) δ 1.59–1.81 (6 H, m, H-8, H-9, H-10), 1.94 (3 H, s, H-6'), 2.00 (3 H, s, $1 \times \text{COCH}_3$), 2.04 (3 H, s, $1 \times \text{COCH}_3$), 3.72 (1 H, dd, $J_{7eq,7ax} = 11.5$ Hz, $J_{7eq,8ax} = 2.5$ Hz, H-7_{eq}), 3.90 (1 H, td, $J_{7ax,7eq} = J_{7ax,8ax} = 11.5$ Hz, $J_{7ax,8eq} = 3.0$ Hz, H-7_{ax}), 4.53 (1 H, s, H-1'), 4.92 (1 H, d, $J_{4,3} = 7.5$ Hz, H-4), 5.77 (1 H, d, $J_{3,4} = 7.5$ Hz, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ 4.7 (C-6'), 18.7 (C-9), 20.76, 20.83 ($2 \times \text{COCH}_3$), 24.2 (C-8), 30.7 (C-10), 63.2 (C-7), 64.8 (C-4'), 68.3 (C-2'), 74.3 (C-3), 77.4 (C-4), 78.5 (C-3'), 80.2 (C-5'), 81.7 (C-1'), 104.5 (C-5), 162.2 (C-2), 170.1, 170.4 ($2 \times \text{COCH}_3$); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954 (m), 2145 (w), 1748 (s), 1665 (m), 1440 (m), 1371 (m), 1239 (s), 1115 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{NaO}_6^+$ $[\text{MNa}]^+$ 355.1152, found 355.1142.

(4*R,5*R**)-10-(*tert*-Butyldimethylsilyloxy)-4,5-dihydroxy-1-(4-methoxybenzyloxy)decane-3,6-dione (2.95)**

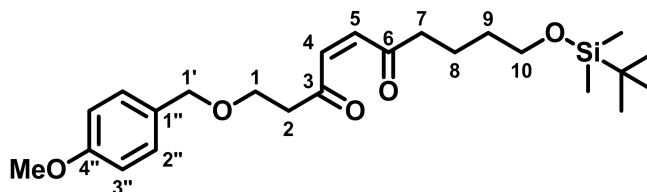


Citric acid (29.5 mg, 0.154 mmol) and enedione **2.97** (88 mg, 0.203 mmol) were dissolved in a mixture of *t*-BuOH and H_2O (1:1, 6.6 mL). $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (3.5 mg, 9.5 μmol) was then added followed by NMO solution (50% in H_2O , 8 μL , 38 μmol). The resulting mixture was stirred at RT for another 2 h. Ethyl acetate (10 mL) and H_2O (10 mL) was used to dilute the reaction mixture and Na_2SO_3 (19 mg, 0.151 mmol) was used to quench the reaction. The

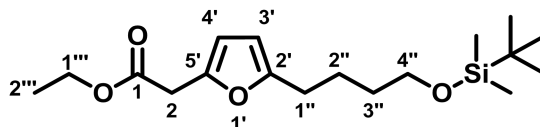
aqueous layer was extracted with ethyl acetate (3×10 mL), and the combined organic layers were dried (MgSO_4) then concentrated. Flash chromatography (petrol/ethyl acetate, 70:30 then 60:40) furnished the *title compound* (**2.95**) as a colourless oil (48 mg, 50%). R_f (petrol/ethyl acetate; 70:30) = 0.32; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.90 (9 H, s, SiCCH_3), 1.50–1.56 (2 H, m, H-9), 1.68–1.75 (2 H, m, H-8), 2.52 (1 H, dt, $J_{7,7} = 17.5$ Hz, $J_{7,8} = 7.5$ Hz, $1 \times \text{H-7}$), 2.64 (1 H, dt, $J_{7,7} = 17.5$ Hz, $J_{7,8} = 7.5$ Hz, $1 \times \text{H-7}$), 2.84–2.94 (2 H, m, H-2), 3.62 (2 H, t, $J_{10,9} = 6.5$ Hz, H-10), 3.66 (1 H, d, $J_{\text{OH},4} \text{ or } \text{OH},5 = 5.5$ Hz, $1 \times \text{OH}$), 3.74 (1 H, d, $J_{\text{OH},5} \text{ or } \text{OH},4 = 5.5$ Hz, $1 \times \text{OH}$), 3.76–3.84 (2 H, m, H-1), 3.81 (3 H, s, OCH_3), 4.45 (1 H, d, $J_{1',1'} = 11.5$ Hz, $1 \times \text{H-1'}$), 4.47 (1 H, d, $J_{1',1'} = 11.5$ Hz, $1 \times \text{H-1'}$), 4.57–4.61 (2 H, m, H-4, H-5), 6.89 (2 H, d, $J_{3'',2''} = 8.5$ Hz, $2 \times \text{H-3''}$), 7.24 (2 H, d, $J_{2'',3''} = 8.5$ Hz, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ –5.3 (SiCH_3), 18.3 (SiCCH_3), 19.9 (C-8), 25.9 (SiCCH_3), 32.0 (C-9), 37.7 (C-7), 38.8 (C-2), 55.3 (OCH_3), 62.7 (C-10), 65.0 (C-1), 73.2 (C-1'), 77.8 (C-4, C-5), 113.9 (C-3''), 129.5 (C-2''), 129.6 (C-1''), 159.4 (C-4''), 207.0 (C-3), 207.8 (C-6); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3458 (br), 2954 (s), 1719 (s), 1613 (m), 1514 (s), 1250 (s), 1099 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{40}\text{NaO}_7\text{Si}^+ [\text{MNa}]^+$ 491.2436, found 491.2436.

(E)-10-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)dec-4-ene-3,6-dione (2.97)

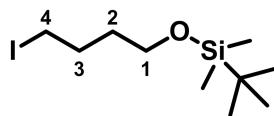
To a stirred solution of enedione **2.98** (88 mg, 0.202 mmol) in ether (4 mL) was added a solution of I₂ (1.5 mg, 5.93 μmol) in benzene (1.5 mL) at RT. The resulting solution was irradiated with UV light (Philips light bulb, 300W, at a distance of 30 cm). After 1 h of irradiation, the reaction mixture was diluted with ether (20 mL) and the solution was washed with Na₂S₂O₃ solution (sat. aq., 20 mL). The organic layer was dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**2.97**) as a colourless oil (88 mg, 100%). *R_f* (petrol/ethyl acetate; 70:30) = 0.73; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.89 (9 H, s, SiCCH₃), 1.51–1.58 (2 H, m, H-9), 1.67–1.73 (2 H, m, H-8), 2.67 (2 H, t, *J*_{7,8} = 7.5 Hz, H-7), 2.92 (2 H, t, *J*_{2,1} = 6.0 Hz, H-2), 3.63 (2 H, t, *J*_{10,9} = 6.5 Hz, H-10), 3.78 (2 H, t, *J*_{1,2} = 6.0 Hz, H-1), 3.81 (3 H, s, OCH₃), 4.46 (2 H, s, H-1'), 6.87–6.89 (4 H, m, H-4, H-5, 2 × H-3''), 7.24 (2 H, d, *J*_{2'',3''} = 8.5 Hz, 2 × H-2''); ¹³C NMR (125 MHz, CDCl₃) δ –5.3 (SiCH₃), 18.3 (SiCCH₃), 20.2 (C-8), 25.9 (SiCCH₃), 32.0 (C-9), 41.3 (C-7), 41.7 (C-2), 55.3 (OCH₃), 62.7 (C-10), 64.6 (C-1), 73.0 (C-1'), 113.8 (C-3''), 129.4 (C-2''), 130.0 (C-1''), 136.2 (C-4), 136.6 (C-5), 159.3 (C-4''), 198.8 (C-3), 200.4 (C-6); IR (thin film) *v*_{max}/cm^{–1} 2955 (s), 1686 (s), 1614 (m), 1514 (s), 1463 (m), 1362 (m), 1250 (s); HRMS (ESI⁺) *m/z* calcd. for C₂₄H₃₈NaO₅Si⁺ [MNa]⁺ 457.2381 found 457.2383.

(Z)-10-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)dec-4-ene-3,6-dione (2.98)

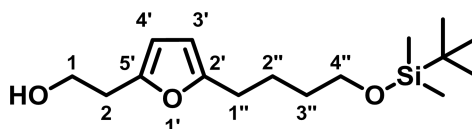
To a solution of furan derivative **2.102** (44 mg, 0.105 mmol) in DCM (3.5 mL) at $-10\text{ }^{\circ}\text{C}$ was added *m*-CPBA (60%, 37 mg, 0.128 mmol) in one portion. The resulting mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 3 h before dilution with ether (10 mL) and H_2O (10 mL). The aqueous layer was extracted with ether ($3 \times 10\text{ mL}$), and the combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**2.98**) as an amorphous solid (42 mg, 92%). R_f (petrol/ether; 50:50) = 0.35; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.90 (9 H, s, SiCCH_3), 1.50–1.58 (2 H, m, H-9), 1.65–1.72 (2 H, m, H-8), 2.57 (2 H, t, $J_{7,8} = 7.5\text{ Hz}$, H-7), 2.85 (2 H, t, $J_{2,1} = 6.5\text{ Hz}$, H-2), 3.62 (2 H, t, $J_{10,9} = 6.5\text{ Hz}$, H-10), 3.76 (2 H, t, $J_{1,2} = 6.5\text{ Hz}$, H-1), 3.81 (3 H, s, OCH_3), 4.44 (2 H, s, H-1'), 6.30 (1 H, d, $J_{4,5} = 12.0\text{ Hz}$, H-4), 6.32 (1 H, d, $J_{5,4} = 12.0\text{ Hz}$, H-5), 6.88 (2 H, d, $J_{3'',2''} = 8.5\text{ Hz}$, $2 \times \text{H-3''}$), 7.24 (2 H, d, $J_{2'',3''} = 8.5\text{ Hz}$, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH_3), 18.3 (SiCCH_3), 20.0 (C-8), 25.9 (SiCCH_3), 32.1 (C-9), 42.3 (C-7), 42.8 (C-2), 55.3 (OCH_3), 62.8 (C-10), 64.9 (C-1), 72.9 (C-1'), 113.8 (C-3''), 129.4 (C-2''), 130.0 (C-1''), 134.9 (C-4), 136.4 (C-5), 159.2 (C-4''), 201.7 (C-3), 202.5 (C-6); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3384 (br), 2931 (s), 2857 (s), 1698 (s), 1613 (s), 1514 (s), 1463 (m), 1392 (m), 1250 (s), 1098 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{38}\text{NaO}_5\text{Si}^+ [\text{MNa}]^+$ 457.2381, found 457.2379.

Ethyl 2-{5-[4-(*tert*-butyldimethylsilyloxy)butyl]furan-2-yl}acetate (**2.99**)²¹

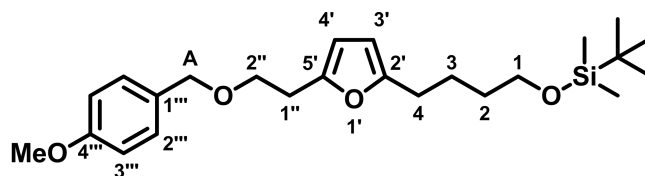
To a stirred solution of furan derivative **2.62** (200 mg, 0.786 mmol), ethyl 2-iodoacetate (46.5 μ L, 0.393 mmol) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (55 mg, 0.196 mmol) in DMSO (26 mL) was added H_2O_2 solution (35% in H_2O , 114 μ L, 1.18 mmol). The resulting solution was stirred for 0.5 h before dilution with ether (50 mL) and brine (25 mL). The aqueous layer was extracted with ether (3 $\times$ 50 mL) and the combined organic layers were washed with brine (20 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ether, 98:2 then 95:5) furnished the title compound (**2.99**) as a colourless oil (73 mg, 65%). R_f (petrol/ether; 90:10) = 0.57; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.90 (9 H, s, SiCCH_3), 1.27 (3 H, t, $J_{2''',1'''} = 7.0$ Hz, H-2'''), 1.53–1.59 (2 H, m, H-3''), 1.64–1.71 (2 H, m, H-2''), 2.61 (2 H, t, $J_{1'',2''} = 7.5$ Hz, H-1''), 3.62–3.64 (4 H, m, H-2, H-4''), 4.18 (2 H, q, $J_{1''',2''} = 7.0$ Hz, H-1'''), 5.92 (1 H, d, $J_{4',3'} = 3.0$ Hz, H-4'), 6.10 (1 H, d, $J_{3',4'} = 3.0$ Hz, H-3'); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH_3), 14.1 (C-2'''), 18.3 (SiCCH_3), 24.3 (C-2''), 25.9 (SiCCH_3), 27.8 (C-1''), 32.2 (C-3''), 34.3 (C-2), 61.0 (C-1'''), 62.9 (C-4''), 105.6 (C-4'), 108.3 (C-3'), 145.8 (C-2'), 155.8 (C-5'), 169.7 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954 (s), 2931 (s), 2858 (s), 1744 (s), 1567 (w), 1256 (m), 1033 (w); HRMS (ESI⁺) m/z calcd. for $\text{C}_{18}\text{H}_{32}\text{NaO}_4\text{Si}^+$ [MNa]⁺ 363.1962, found 363.1962.

***tert*-Butyl(4-iodobutoxy)dimethylsilane (2.100)²¹**

To a stirred suspension of CaCO_3 (1.28 g, 12.7 mmol) and NaI (19.1 g, 12.7 mmol) in THF (80 mL) was added *tert*-butyldimethylsilyl chloride (19.2 g, 12.7 mmol). The resulting mixture was then heated under reflux for 48 h. After cooling to RT, $\text{Na}_2\text{S}_2\text{O}_3$ solution (sat. aq., 50 mL) and ether (600 mL) were added to the suspension where layers were separated. The organic layer was washed with brine (150 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol) furnished the title compound (**2.100**) as a colourless oil (34.7 g, 87%). R_f (petrol) = 0.92; ^1H NMR (400 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.89 (9 H, s, SiCCH_3), 1.62 (2 H, qn, $J_{2,3} = J_{2,1} = 6.5$ Hz, H-2), 1.91 (2 H, qn, $J_{3,2} = J_{3,4} = 6.5$ Hz, H-3), 3.23 (2 H, t, $J_{4,3} = 6.5$ Hz, H-4), 3.64 (2 H, t, $J_{1,2} = 6.5$ Hz, H-1); ^{13}C NMR (100 MHz, CDCl_3) δ -5.4 (SiCH_3), 7.1 (C-4), 18.3 (SiCCH_3), 25.9 (SiCCH_3), 30.2 (C-3), 33.5 (C-2), 61.9 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955 (br), 2738 (s), 1472 (s), 1388 (s), 1361 (s), 1256 (br); HRMS (GCMS- CI^+) m/z calcd. for $\text{C}_{10}\text{H}_{24}\text{IOSi}^+ [\text{MH}]^+$ 315.0641, found 315.0643.

2-{5-[4-(*tert*-Butyldimethylsilyloxy)butyl]furan-2-yl}ethanol (2.101)

LiAlH₄ (10 mg, 0.267 mmol) was stirred vigorously in anhydrous ether (2 mL) when a solution of ester **2.99** (70 mg, 0.206 mmol) in anhydrous ether (4 mL) was added dropwise within 1 min at 0 °C. The resulting suspension was heated under reflux for additional 3 h then it was cooled to RT. The reaction was quenched by adding H₂O (7 mL), NaOH solution (15% in H₂O, 7 mL) and H₂O (7 mL) carefully. After the resulting mixture was stirred for another 1 h at RT, the white precipitate was filtered, eluting with ether (70 mL). The filtrate was dried (MgSO₄) and concentrated. Flash Chromatography (petrol/ether, 70:30) furnished the *title compound* (**2.101**) as a colourless oil (68 mg, 98%). *R_f* (petrol/ether; 70:30) = 0.28; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.90 (9 H, s, SiCCH₃), 1.54–1.62 (2 H, m, H-3''), 1.65–1.71 (2 H, m, H-2''), 2.60 (2 H, t, *J*_{1'',2''} = 7.5 Hz, H-1''), 2.86 (2 H, t, *J*_{2,1} = 6.0 Hz, H-2), 3.63 (2 H, t, *J*_{4'',3''} = 6.5 Hz, H-4''), 3.82–3.88 (2 H, m, H-1), 5.89 (1 H, d, *J*_{4',3'} = 3.0 Hz, H-4'), 5.99 (1 H, d, *J*_{3',4'} = 3.0 Hz, H-3'); ¹³C NMR (125 MHz, CDCl₃) δ –5.3 (SiCH₃), 18.3 (SiCCH₃), 24.4 (C-2''), 25.9 (SiCCH₃), 27.8 (C-1''), 31.7 (C-2), 32.3 (C-3''), 61.2 (C-1), 62.9 (C-4''), 105.3 (C-4'), 107.0 (C-3'), 150.7 (C-2'), 155.4 (C-5'); IR (thin film) *v*_{max}/cm^{–1} 3357 (br), 2953 (s), 2930 (s), 2858 (s), 1567 (w), 1255 (m), 1103 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₆H₃₀NaO₃Si⁺ [MNa]⁺ 321.1856, found 321.1856.

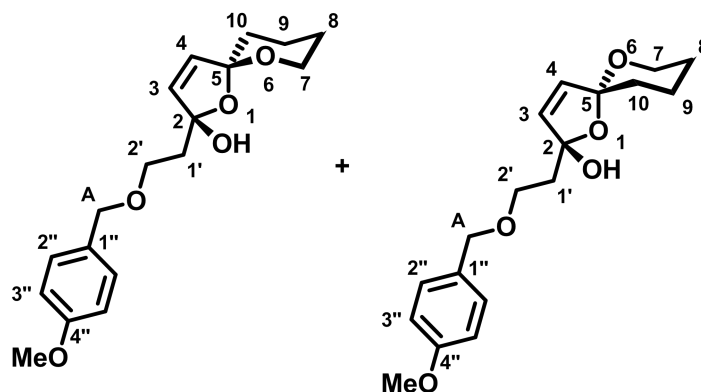
***tert*-Butyl(4-{5-[2-(4-methoxybenzyloxy)ethyl]furan-2-yl}butoxy)dimethylsilane (2.102)**

NaH (10 mg, 0.42 mmol) was added to a solution of alcohol **2.101** (60 mg, 0.200 mmol) and TBAI (3.5 mg, 9.4 μ mol) in anhydrous DMF (1.3 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 30 min before PMB-Cl (54 μ L, 0.40 mmol) was added. The resulting mixture was warmed to RT and stirred for another 1 h before methanol (0.3 mL) was added. After 30 min, the mixture was diluted with ether (10 mL) and H₂O (10 mL). The aqueous layer was extracted with ether (3 $\times$ 10 mL) and the combined organic layers were washed with brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 95:5) furnished the *title compound* (**2.102**) as a colourless oil (59 mg, 70%). R_f (petrol/ether; 90:10) = 0.69; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.90 (9 H, s, SiCCH₃), 1.54–1.60 (2 H, m, H-2), 1.64–1.70 (2 H, m, H-3), 2.59 (2 H, t, $J_{4,3}$ = 7.5 Hz, H-4), 2.90 (2 H, t, $J_{1'',2''}$ = 7.0 Hz, H-1''), 3.63 (2 H, t, $J_{1,2}$ = 6.5 Hz, H-1), 3.69 (2 H, t, $J_{2'',1''}$ = 7.0 Hz, H-2''), 3.81 (3 H, s, OCH₃), 4.47 (2 H, s, H-A), 5.87 (1 H, d, $J_{3',4'}$ = 3.0 Hz, H-3'), 5.94 (1 H, d, $J_{4',3'}$ = 3.0 Hz, H-4'), 6.88 (2 H, d, $J_{3''',2'''} = 8.5$ Hz, 2 $\times$ H-3'''), 7.25 (2 H, d, $J_{2''',3'''} = 8.5$ Hz, 2 $\times$ H-2'''); ¹³C NMR (125 MHz, CDCl₃) δ -5.3 (SiCH₃), 18.3 (SiCCH₃), 24.4 (C-3), 26.0 (SiCCH₃), 27.8 (C-4), 28.9 (C-1''), 32.3 (C-2), 55.3 (OCH₃), 62.9 (C-1), 68.2 (C-2''), 72.6 (C-A), 105.2 (C-3'), 106.2 (C-4'), 113.7 (C-3'''), 129.3 (C-2'''), 130.4 (C-1'''), 151.0 (C-5'), 154.8 (C-2'), 159.1 (C-4'''); IR (thin film) $\nu_{\max}$ /cm⁻¹ 2952 (s), 2931 (s), 2857 (s), 1614 (m), 1514 (s), 1249 (s), 1101 (s); HRMS (ESI⁺) m/z calcd. for C₂₄H₃₈NaO₄Si⁺ [MNa]⁺ 441.2432,

found 441.2430.

(2*R,5*S**)-2-[2-(4-Methoxybenzyloxy)ethyl]-1,6-dioxaspiro[4.5]dec-3-en-2-ol** &

(2*R,5*R**)-2-[2-(4-methoxybenzyloxy)ethyl]-1,6-dioxaspiro[4.5]dec-3-en-2-ol (2.107)**

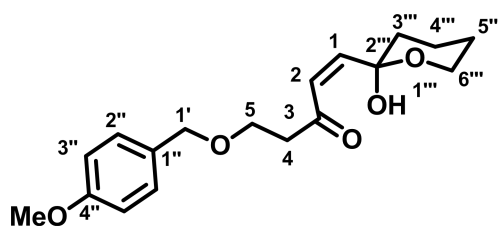


To a stirred solution of furan derivative **2.110** (110 mg, 0.361 mmol) in DCM (13 mL) at -10°C was added *m*-CPBA (60%, 80 mg, 0.464 mmol) in one portion. The resulting mixture was stirred for 3 h before dilution with ether (25 mL) and H_2O (25 mL). The aqueous layer was extracted with ether (3×25 mL) and the combined organic layers were dried (MgSO_4), filtered and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the *title compounds* (**2.107**) as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (110 mg, 96%). R_f (petrol/ethyl acetate; 50:50) = 0.44; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3406 (br), 2941 (s), 2968 (m), 1613 (m), 1514 (s), 1368 (m), 1248 (s), 1039 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{18}\text{H}_{24}\text{NaO}_5^+$ [MNa]⁺ 343.1516, found 343.1517. **¹H NMR data for both diastereomers:** ¹H NMR (500 MHz, CDCl_3) δ 1.50–2.30 (8 H, m, H-8, H-9, H-10, H-1'), 3.46–4.08 (7 H, m, H-7, H-2', OCH_3), 4.40–4.57 (2 H, m, H-A), 5.88–6.07 (2 H, m, H-3, H-4), 6.86–6.91 (2 H, m, $2 \times$ H-3''), 7.24–7.30 (2 H, m, $2 \times$ H-2''); **¹³C NMR data for**

diastereomer A: ^{13}C NMR (125 MHz, CDCl_3) δ 19.4 (C-9), 24.9 (C-8), 33.8 (C-10), 38.4 (C-1'), 55.3 (OCH_3), 63.2 (C-7), 66.1 (C-2'), 72.8 (C-A), 108.1 (C-5), 108.8 (C-2), 113.8 (C-3''), 129.3 (C-2''), 130.1 (C-1''), 133.1 (C-3), 134.5 (C-4), 159.2 (C-4''); ^{13}C NMR data for **diastereomer B:** ^{13}C NMR (125 MHz, CDCl_3) δ 19.4 (C-9), 25.0 (C-8), 35.1 (C-10), 39.5 (C-1'), 55.3 (OCH_3), 63.3 (C-7), 66.7 (C-2'), 73.0 (C-A), 109.1 (C-5), 110.3 (C-2), 113.8 (C-3''), 129.3 (C-2''), 129.7 (C-1''), 133.2 (C-3), 134.3 (C-4), 159.3 (C-4'').

(Z)-1-(2-Hydroxytetrahydro-2H-pyran-2-yl)-5-(4-methoxybenzyloxy)pent-1-en-3-one

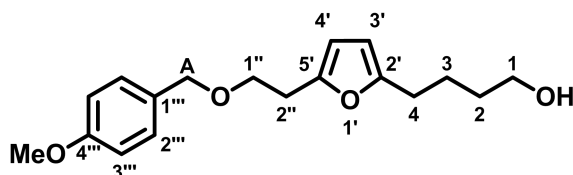
(2.109)



To a stirred solution of enedione **2.98** (24 mg, 0.055 mmol) in THF (1.7 mL) was added TBAF solution (1.0 M in THF, 170 μL , 0.17 mmol) at 0 $^{\circ}\text{C}$. The resulting solution was warmed to RT and stirred for another 3 h before dilution with ether (10 mL). The solution was washed with H_2O (5 mL), dried (MgSO_4), and concentrated. Preparative TLC (DCM/methanol, 95:5) furnished the *title compound* (**2.109**) as a pale yellow oil (3 mg, 17%). R_f (DCM/methanol; 95:5) = 0.31; ^1H NMR (500 MHz, CDCl_3) δ 1.43 (1 H, dt, $J_{4,4} = 14.5$ Hz, $J_{4,5} = 3.0$ Hz, 1 $\times$ H-4), 1.54–1.90 (6 H, m, H-3''', H-4''', H-5'''), 2.29–2.41 (1 H, m, 1 $\times$ H-4), 3.67–3.76 (4 H, m, H-5, H-6'''), 3.83 (3 H, s, OCH_3), 4.48 (1 H, d, $J_{1',1'} = 11.5$ Hz, 1 $\times$ H-1'), 4.56 (1 H, d, $J_{1',1'} = 11.5$ Hz, 1 $\times$ H-1'), 6.12 (1 H, d, $J_{2,1} = 6.0$ Hz, H-2), 6.92 (2 H, d, $J_{3'',2''} =$

8.5 Hz, $2 \times \text{H-3''}$), 7.28 (2 H, d, $J_{2'',3''} = 8.5$ Hz, $2 \times \text{H-2''}$), 7.47 (1 H, d, $J_{1,2} = 6.0$ Hz, H-1); ^{13}C NMR (125 MHz, CDCl_3) δ 20.3 (C-4'''), 31.1 (C-3'''), 36.9 (C-4), 55.3 (OCH_3), 62.7 (C-6'''), 66.9 (C-5), 73.4 (C-1'), 81.4 (C-2'''), 114.0 (C-3''), 129.1 (C-1''), 129.6 (C-2''), 131.9 (C-2), 159.6 (C-4''), 164.3 (C-1), 206.6 (C-3); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3406 (br), 2925 (s), 1711 (s), 1614 (m), 1514 (m), 1249 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{18}\text{H}_{24}\text{NaO}_5 + [\text{MNa}]^+$ 343.1516, found 343.1515.

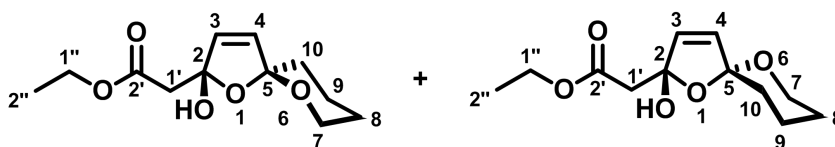
4-{5-[2-(4-Methoxybenzyloxy)ethyl]furan-2-yl}butan-1-ol (**2.110**)



To a stirred solution of silyl ether **2.102** (160 mg, 0.383 mmol) in THF (12.7 mL) was added TBAF solution (1.0 M in THF, 1.2 mL, 1.20 mmol) at 0 °C. The solution was warmed to RT and stirred for 1 h before dilution with ether (20 mL). The organic layer was washed with H_2O (10 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ethyl acetate, 70:30) furnished the *title compound* (**2.110**) as a colourless oil (117 mg, 100%). R_f (petrol/ethyl acetate; 70:30) = 0.42; ^1H NMR (500 MHz, CDCl_3) δ 1.59–1.65 (2 H, m, H-2), 1.67–1.73 (2 H, m, H-3), 2.61 (2 H, t, $J_{4,3} = 7.5$ Hz, H-4), 2.90 (2 H, t, $J_{2'',1''} = 7.0$ Hz, H-2''), 3.64–3.70 (4 H, m, H-1, H-1''), 3.81 (3 H, s, OCH_3), 4.47 (2 H, s, H-A), 5.88 (1 H, d, $J_{3',4'} = 3.0$ Hz, H-3'), 5.94 (1 H, d, $J_{4',3'} = 3.0$ Hz, H-4'), 6.88 (2 H, d, $J_{3'',2''} = 8.5$ Hz, $2 \times \text{H-3''}$), 7.25 (2 H, d, $J_{2'',3''} = 8.5$ Hz, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ 24.3 (C-3), 27.7 (C-4), 28.9 (C-2''), 32.2 (C-2), 55.3 (OCH_3), 62.6 (C-1), 68.1 (C-1'), 72.6 (C-A), 105.4

(C-3'), 106.3 (C-4'), 113.7 (C-3'''), 129.3 (C-2'''), 130.4 (C-1'''), 151.2 (C-5'), 154.5 (C-2'), 159.1 (C-4'''); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3406 (br), 2937 (s), 2864 (s), 1613 (m), 1514 (s), 1248 (s), 1096 (s), 1035 (s); HRMS (ESI⁺) m/z calcd. for C₁₈H₂₄NaO₄⁺ [MNa]⁺ 327.1567, found 327.1567.

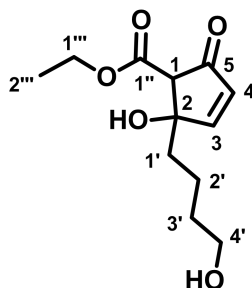
Ethyl 2-[(2*R,5*S**)-2-hydroxy-1,6-dioxaspiro[4.5]dec-3-en-2-yl]acetate &
ethyl 2-[(2*R**,5*R**)-2-hydroxy-1,6-dioxaspiro[4.5]dec-3-en-2-yl]acetate (2.111)**



To a stirred solution of furan derivative **2.70** (13 mg, 57.5 μmol) in DCM (1.9 mL) at $-10\text{ }^{\circ}\text{C}$ was added *m*-CPBA (60%, 20 mg, 69.5 μmol) in one portion. The resulting mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 2 h before dilution with DCM (10 mL). The solution was washed with aqueous buffer [$2 \times 10\text{ mL}$ of a solution made from Na₂S₂O₃ (*ca.* 100–158 g/L) and Na₂CO₃ (*ca.* 100 g/L)] and the aqueous layer was extracted with DCM ($2 \times 10\text{ mL}$). The combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the *title compounds* (**2.111**) as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (14 mg, 100%). R_f (petrol/ethyl acetate; 50:50) = 0.48; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2949 (w), 1738 (s), 1442 (s), 1370 (m), 1229 (m), 1094 (m), 1024 (m); HRMS (ESI⁺) m/z calcd. for C₁₂H₁₈NaO₅⁺ [MNa]⁺ 265.1046, found 265.1048. **¹H NMR data for both diastereomers:** ¹H NMR (500 MHz, CDCl₃) δ 1.25–1.35 (3 H, m, H-2''), 1.50–1.96 (6 H, m, H-8, H-9, H-10), 2.77–2.88 (2 H, m, H-1'), 3.68–3.79 (m, 1 H, 1 $\times$ H-7),

3.89–4.07 (1 H, m, 1 $\times$ H-7), 4.13–4.31 (2 H, m, H-1''), 5.93–6.21 (2 H, m, H-3, H-4); ^{13}C NMR data for diastereomer A: ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-2''), 19.2 (C-9), 24.7 (C-8), 33.6 (C-10), 44.0 (C-1'), 60.7 (C-1''), 63.3 (C-7), 107.3 (C-2), 108.6 (C-5), 133.4 (C-4), 134.1 (C-3), 170.1 (C-2'); ^{13}C NMR data for diastereomer B: ^{13}C NMR (125 MHz, CDCl_3) δ 13.9 (C-2''), 19.2 (C-9), 24.8 (C-8), 34.7 (C-10), 44.8 (C-1'), 61.0 (C-1''), 63.2 (C-7), 107.8 (C-2), 109.3 (C-5), 133.1 (C-4), 134.5 (C-3), 171.4 (C-2').

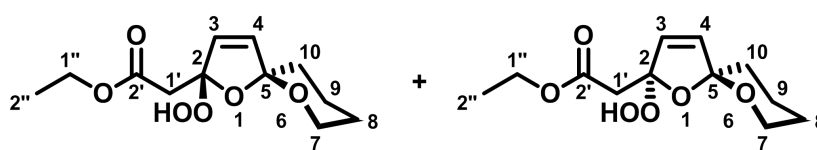
Ethyl 2-hydroxy-2-(4-hydroxybutyl)-5-oxocyclopent-3-enecarboxylate (2.113)



A suspension of spiroketal **2.111** [a mixture of two diastereomers (*d.r.* = 1:1), 10 mg, 0.041 mmol] and silica (3 mg) in ether (1.4 mL) was stirred at RT for 7 h. The silica gel was filtered and washed with ether (10 mL), and the filtrate was concentrated to furnish the *title compound* (**2.113**) as a colourless oil (9 mg, 90%). R_f (petrol/ethyl acetate; 20:80) = 0.23; ^1H NMR (500 MHz, CDCl_3) δ 1.32 (3 H, t, $J_{2''',1'''} = 7.0$ Hz, H-2'''), 1.47–1.65 (4 H, m, H-2', H-3'), 1.72–1.79 (1 H, m, 1 $\times$ H-1'), 1.82–1.89 (1 H, m, 1 $\times$ H-1'), 3.46 (1 H, s, H-1), 3.68 (2 H, t, $J_{4',3'} = 6.0$ Hz, H-4'), 3.81 (1 H, br.s, 1 $\times$ OH), 4.25 (2 H, q, $J_{1'',2''} = 7.0$ Hz, H-1''), 6.20 (1 H, d, $J_{4,3} = 6.0$ Hz, H-4), 7.54 (1 H, d, $J_{3,4} = 6.0$ Hz, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-2'''), 20.2 (C-2'), 32.5 (C-3'), 40.0 (C-1'), 60.9 (C-1), 62.2 (C-1'''), 62.4 (C-4'), 79.7

(C-2), 132.4 (C-4), 166.9 (C-3), 168.6 (C-1''), 199.8 (C-5); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3419 (br), 2940 (s), 1738 (s), 1706 (s), 1594 (w), 1037 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{NaO}_5^+$ [MNa]⁺ 265.1046, found 265.1054.

Ethyl 2-[(2*S,5*S**)-2-hydroperoxy-1,6-dioxaspiro[4.5]dec-3-en-2-yl]acetate & ethyl 2-[(2*R**,5*S**)-2-hydroperoxy-1,6-dioxaspiro[4.5]dec-3-en-2-yl]acetate (2.116)**



Pertrifluoroacetic acid was prepared *in situ* by addition of TFAA (30 μL , 0.207 mmol) to a stirred mixture of H_2O_2 solution (35% in H_2O , 60 μL) and DCM (0.5 mL) at 0 $^\circ\text{C}$. This solution was subsequently added dropwise to a stirred mixture of NaH_2PO_4 (60 mg, 0.443 mmol) and spiroketal **2.111** [a mixture of two diastereomers (*d.r.* = 1:1), 25 mg, 0.103 mmol] in DCM (2 mL). The mixture was stirred at RT for 2 h before dilution with H_2O (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 $\times$ 10 mL) and the combined organic layers were washed with H_2O (10 mL), NaHCO_3 solution (sat. aq., 10 mL), brine (10 mL), then dried (MgSO_4) and concentrated. Preparative TLC (petrol/ethyl acetate, 70:30) furnished the *title compounds* (**2.116**), a colourless oil (6 mg, 24%), as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as side products. R_f (petrol/ethyl acetate; 70:30) = 0.29; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3406 (br), 2945 (s), 1737 (s), 1443 (m), 1371 (m), 1095 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{NaO}_6^+$ [MNa]⁺ 281.0996, found 281.0996. **NMR data for diastereomer A:** ^1H NMR (500 MHz, CDCl_3) δ 1.24–1.29 (3 H, m, H-2''), 1.54–1.98 (6 H,

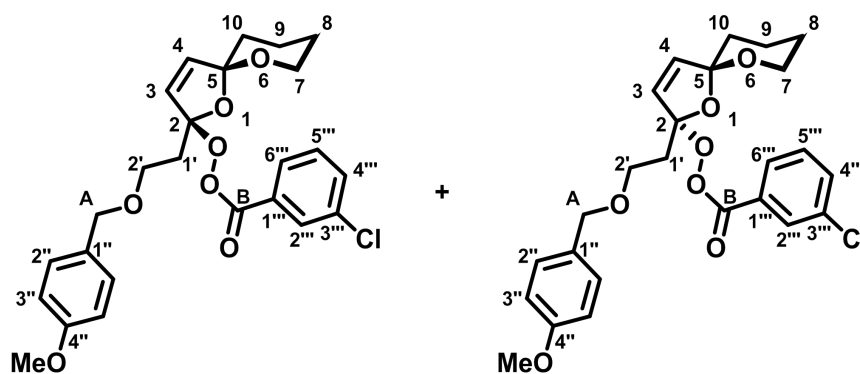
m, H-8, H-9, H-10), 2.80–3.16 (2 H, m, H-1'), 3.73–4.06 (2 H, m, H-7), 4.12–4.17 (2 H, m, H-1''), 6.05–6.18 (2 H, m, H-3, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-2''), 19.1 (C-9), 24.6 (C-8), 33.2 (C-10), 40.9 (C-1'), 60.9 (C-1''), 64.0 (C-7), 108.7 (C-5), 114.8 (C-2), 129.7 (C-4), 135.7 (C-3), 168.2 (C-2'); **NMR data for diastereomer B:** ^1H NMR (500 MHz, CDCl_3) δ 1.24–1.29 (3 H, m, H-2''), 1.54–1.98 (6 H, m, H-8, H-9, H-10), 2.80–3.16 (2 H, m, H-1'), 3.73–4.06 (2 H, m, H-7), 4.12–4.17 (2 H, m, H-1''), 6.05–6.18 (2 H, m, H-3, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-2''), 19.2 (C-9), 24.7 (C-8), 33.5 (C-10), 42.3 (C-1'), 60.9 (C-1''), 63.4 (C-7), 110.1 (C-5), 115.2 (C-2), 129.5 (C-4), 136.3 (C-3), 168.7 (C-2').

(2*S,5*S**)-2-[2-(4-Methoxybenzyloxy)ethyl]-1,6-dioxaspiro[4.5]dec-3-en-2-yl**

3-chlorobenzoperoxoate &

(2*R,5*S**)-2-[2-(4-methoxybenzyloxy)ethyl]-1,6-dioxaspiro[4.5]dec-3-en-2-yl**

3-chlorobenzoperoxoate (2.117)



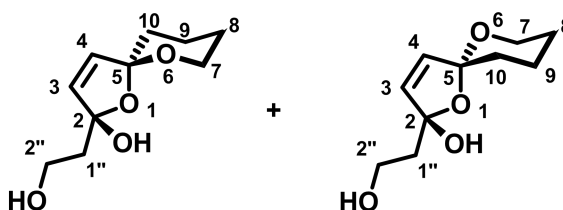
To a stirred suspension of spiroketal **2.107** [a mixture of two diastereomers (*d.r.* = 1:1), 20 mg, 63.0 μmol] and NaHCO_3 (26 mg, 0.310 mmol) in DCM (2 mL) was added *m*-CPBA (60%, 43 mg, 0.149 mmol) at 0 °C. After 30 min, the mixture was warmed to RT and stirred for another 2 h before dilution with DCM (10 mL). The mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$

solution (sat. aq., 10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated. Preparative TLC (petrol/ethyl acetate, 80:20) furnished the *title compounds* (**2.117**), two colourless oils (10 mg, 34%), as two separable diastereomers **A** and **B** (A:B = 1:1) as side products. **Data for Diastereomer A:** R_f (petrol/ethyl acetate; 50:50) = 0.78; ¹H NMR (500 MHz, CDCl₃) δ 1.47–1.63 (3 H, m, H-8, 1 × H-10), 1.65–1.77 (2 H, m, 1 × H-9, 1 × H-10), 1.83–1.97 (1 H, m, 1 × H-9), 2.22–2.36 (2 H, m, H-1'), 3.46 (1 H, dd, *J*_{eq,7ax} = 11.5 Hz, *J*_{eq,8ax} = 4.5 Hz, H-7_{eq}), 3.57 (1 H, dt, *J*_{2',2'} = 9.5 Hz, *J*_{2',1'} = 6.5 Hz, 1 × H-2'), 3.66 (1 H, dt, *J*_{2',2'} = 9.5 Hz, *J*_{2',1'} = 6.5 Hz, 1 × H-2'), 3.81 (3 H, s, OCH₃), 3.87 (1 H, td, *J*_{7ax,7eq} = *J*_{7ax,8ax} = 11.5 Hz, *J*_{7ax,8eq} = 3.0 Hz, H-7_{ax}), 4.41 (1 H, d, *J*_{A,A} = 11.5 Hz, 1 × H-A), 4.45 (1 H, d, *J*_{A,A} = 11.5 Hz, 1 × H-A), 6.02–6.06 (2 H, m, H-3, H-4), 6.88 (2 H, d, *J*_{3'',2''} = 8.5 Hz, 2 × H-3''), 7.25 (2 H, d, *J*_{2'',3''} = 8.5 Hz, 2 × H-2''), 7.36 (1 H, t, *J*_{5''',4'''} = *J*_{5''',6'''} = 8.0 Hz, H-5'''), 7.52 (1 H, ddd, *J*_{4''',5'''} = 8.0 Hz, *J*_{4''',2'''} = 1.5 Hz, *J*_{4''',6'''} = 1.0 Hz, H-4'''), 7.84 (1 H, dt, *J*_{6''',5'''} = 8.0 Hz, *J*_{6''',4'''} = *J*_{6''',2'''} = 1.0 Hz, H-6'''), 7.97 (1 H, dd, *J*_{2''',4'''} = 1.5 Hz, *J*_{2''',6'''} = 1.0 Hz, H-2'''); ¹³C NMR (125 MHz, CDCl₃) δ 19.2 (C-9), 24.6 (C-8), 33.9 (C-10), 35.3 (C-1'), 55.3 (OCH₃), 63.1 (C-7), 65.2 (C-2'), 72.7 (C-A), 109.2 (C-5), 113.8 (C-3''), 117.4 (C-2), 127.5 (C-6'''), 129.3 (C-2'''), 129.4 (C-2''), 129.5 (C-1''', C-4), 129.7 (C-5'''), 130.2 (C-1''), 133.2 (C-4'''), 134.5 (C-3'''), 136.0 (C-3), 159.2 (C-4''), 163.5 (C-B); IR (thin film) ν_{max}/cm⁻¹ 2942 (s), 2868 (m), 1765 (s), 1613 (w), 1514 (m), 1232 (s), 1102 (s), 1070 (m), 1044 (m); HRMS (ESI⁺) *m/z* calcd. for C₂₅H₂₇ClNaO₇ + [MNa]⁺ 497.1338 found 497.1336. **Data for Diastereomer B:** R_f (petrol/ethyl acetate; 50:50) = 0.68; ¹H NMR (500 MHz, CDCl₃) δ 1.51–1.71 (3 H, m, H-8, 1 × H-9), 1.71–1.82 (2 H, m, H-10), 1.83–1.91 (1 H, m, 1 × H-9), 2.30–2.40 (2 H, m, H-1'), 3.60–3.72 (2 H, m, 1 × H-2'), 3.72–3.77 (1 H, m, 1 × H-7), 3.81 (3 H, s, OCH₃), 3.95–4.01 (1

H, m, $1 \times \text{H-7}$), 4.41 (1 H, d, $J_{\text{A,A}} = 11.5$ Hz, $1 \times \text{H-A}$), 4.45 (1 H, d, $J_{\text{A,A}} = 11.5$ Hz, $1 \times \text{H-A}$), 6.02–6.04 (2 H, m, H-3, H-4), 6.88 (2 H, d, $J_{3'',2''} = 8.5$ Hz, $2 \times \text{H-3''}$), 7.26 (2 H, d, $J_{2'',3''} = 8.5$ Hz, $2 \times \text{H-2''}$), 7.40 (1 H, t, $J_{5''',4'''} = J_{5''',6'''} = 8.0$ Hz, H-5'''), 7.45 (1 H, ddd, $J_{4''',5'''} = 8.0$ Hz, $J_{4''',2'''} = 2.0$ Hz, $J_{4''',6'''} = 1.0$ Hz, H-4'''), 7.78 (1 H, dd, $J_{6''',5'''} = 8.0$ Hz, $J_{6''',4'''} = 1.0$ Hz, H-6'''), 7.88 (1 H, d, $J_{2''',4'''} = 2.0$ Hz, H-2'''); ^{13}C NMR (125 MHz, CDCl_3) δ 19.1 (C-9), 24.7 (C-8), 33.4 (C-10), 35.7 (C-1'), 55.3 (OCH_3), 63.3 (C-7), 65.3 (C-2'), 72.6 (C-A), 110.2 (C-5), 113.7 (C-3''), 118.8 (C-2), 127.2 (C-6'''), 129.3 (C-2'''), 129.3 (C-2''), 129.3 (C-1''', C-4), 130.0 (C-5'''), 130.4 (C-1''), 133.6 (C-4'''), 134.9 (C-3'''), 136.5 (C-3), 159.1 (C-4''), 162.9 (C-B); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2945 (m), 2871 (w), 1767 (s), 1613 (w), 1514 (m), 1231 (s), 1102 (m), 1069 (m), 1043 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{25}\text{H}_{27}\text{ClNaO}_7 + [\text{MNa}]^+$ 497.1338 found 497.1337.

(2*R,5*S**)-2-(2-Hydroxyethyl)-1,6-dioxaspiro[4.5]dec-3-en-2-ol &**

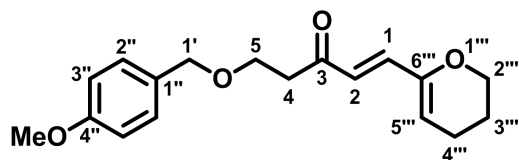
(2*R,5*R**)-2-(2-hydroxyethyl)-1,6-dioxaspiro[4.5]dec-3-en-2-ol (2.118)**



Spiroketal **2.107** [a mixture of two diastereomers (*d.r.* = 1:1), 14 mg, 43 μmol] was dissolved in DCM (1 mL) and treated with *m*-CPBA (60%, 17 mg, 59.1 μmol) and NaHCO_3 (19 mg, 0.226 mmol). The resulting mixture was stirred at 5 $^\circ\text{C}$ for 4 h. DCM (10 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ solution (sat. aq., 5 mL) were added and the organic layer was washed with NaHCO_3

solution (sat. aq., 5 mL). The organic layer was dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20 then 70:30 then 50:50) furnished the *title compounds* (**2.118**), a colourless oil (3 mg, 34%), as a mixture of two diastereomers **A** and **B** (**A:B** = 2:1) as side products. R_f (petrol/ethyl acetate; 50:50) = 0.10; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3396 (br), 2947 (s), 1693 (w), 1441 (w), 1370 (w), 1091 (m), 1069 (m), 1041 (m); HRMS (ESI⁺) m/z calcd. for C₁₀H₁₆NaO₄ + [MNa]⁺ 223.0941 found 223.0941. **NMR data for diastereomer A:** ¹H NMR (500 MHz, CDCl₃) δ 1.54–2.22 (8 H, m, H-8, H-9, H-10, H-1''), 3.72–4.16 (4 H, m, H-7, H-2''), 5.98 (1 H, d, $J_{4,3}$ = 6.0 Hz, H-4), 6.07 (1 H, d, $J_{3,4}$ = 6.0 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 19.3 (C-9), 24.7 (C-8), 33.5 (C-10), 40.0 (C-1''), 58.9 (C-2''), 63.4 (C-7), 108.4 (C-5), 110.3 (C-2), 134.0 (C-4), 134.4 (C-3); **NMR data for diastereomer B:** R_f (petrol/ethyl acetate; 50:50) = 0.10; ¹H NMR (500 MHz, CDCl₃) δ 1.54–2.22 (8 H, m, H-8, H-9, H-10, H-1''), 3.72–4.16 (4 H, m, H-7, H-2''), 5.97 (1 H, d, $J_{4,3}$ = 5.5 Hz, H-4), 6.04 (1 H, d, $J_{3,4}$ = 5.5 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 19.3 (C-9), 24.7 (C-8), 35.3 (C-10), 41.1 (C-1''), 59.2 (C-2''), 63.7 (C-7), 109.2 (C-5), 111.0 (C-2), 133.9 (C-4), 134.2 (C-3).

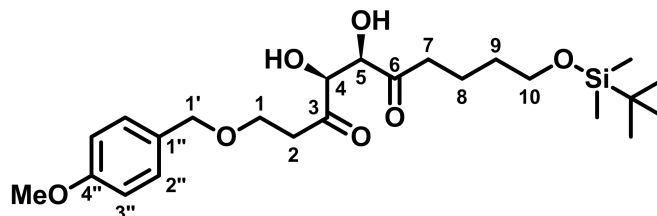
(E)-1-(3,4-Dihydro-2H-pyran-6-yl)-5-(4-methoxybenzyloxy)pent-1-en-3-one (2.119)



To a stirred solution of enedione **2.98** (87 mg, 0.202 mmol) in MeCN (4 mL) was added a solution of I₂ (2.5 mg, 9.9 μ mol) in benzene (1.5 mL) at RT. The resulting solution was

irradiated with UV light (Philips light bulb, 300W, at a distance of 45 cm). After 4 h of irradiation, the reaction mixture was diluted with ether (20 mL) and the solution was washed with Na₂S₂O₃ solution (sat. aq., 20 mL). The organic layer was dried (MgSO₄) and concentrated, flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**2.119**) as a colourless oil (64.9 mg, 100%). *R_f* (petrol/ethyl acetate; 70:30) = 0.57; ¹H NMR (500 MHz, CDCl₃) δ 1.85–1.92 (2 H, m, H-3'''), 2.20–2.25 (2 H, m, H-4'''), 2.87 (2 H, t, *J*_{4,5} = 6.5 Hz, H-4), 3.78 (2 H, t, *J*_{5,4} = 6.5 Hz, H-5), 3.81 (3 H, s, OCH₃), 4.10 (2 H, t, *J*_{2''',3'''} = 5.0 Hz, H-2'''), 4.47 (2 H, s, H-1'), 5.26 (1 H, t, *J*_{5''',4'''} = 4.5 Hz, H-5'''), 6.42 (1 H, d, *J*_{2,1} = 15.5 Hz, H-2), 6.84 (1 H, d, *J*_{1,2} = 15.5 Hz, H-1), 6.88 (2 H, d, *J*_{3'',2''} = 8.5 Hz, 2 × H-3''), 7.26 (2 H, d, *J*_{2'',3''} = 8.5 Hz, 2 × H-2''); ¹³C NMR (125 MHz, CDCl₃) δ 21.6 (C-4'''), 21.9 (C-3'''), 41.6 (C-4), 55.3 (OCH₃), 65.3 (C-5), 66.1 (C-2'''), 72.8 (C-1'), 112.5 (C-5'''), 113.8 (C-3''), 123.5 (C-2), 129.3 (C-2''), 130.3 (C-1''), 138.1 (C-1), 150.3 (C-6'''), 159.2 (C-4''), 198.6 (C-3); IR (thin film) *v*_{max}/cm⁻¹ 2915 (s), 2849 (s), 1686 (m), 1661 (m), 1625 (s), 1601 (s), 1513 (s), 1248 (s), 1175 (m); HRMS (ESI⁺) *m/z* calcd. for C₁₈H₂₂NaO₄⁺ [MNa]⁺ 325.1410, found 325.1408.

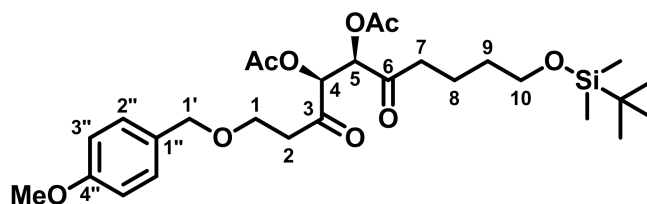
(4*S,5*R**)-10-(*tert*-Butyldimethylsilyloxy)-4,5-dihydroxy-1-(4-methoxybenzyloxy)decane-3,6-dione (2.120)**



Citric acid (5 mg, 0.75 mmol) and enedione **2.98** (15 mg, 34.5 μ mol) were dissolved in a mixture of *t*-BuOH and H₂O (1:1, 1 mL). K₂OsO₄·2H₂O solution (0.01 M in 1:1 *t*-BuOH and H₂O, 17 μ L, 0.17 μ mol) was then added followed by NMO solution (50% in H₂O, 8 μ L, 38 μ mol). The resulting mixture was stirred at RT for another 2 h. Ethyl acetate (10 mL) and H₂O (10 mL) was added to dilute the reaction mixture before quenching with Na₂S₂O₅ solution (sat. aq., 1 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate, 70:30 then 60:40) furnished the *title compound* (**2.120**) as a colourless oil (8 mg, 50%). *R_f* (petrol/ethyl acetate; 70:30) = 0.14; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.89 (9 H, s, SiCCH₃), 1.48–1.55 (2 H, m, H-9), 1.63–1.71 (2 H, m, H-8), 2.53 (1 H, dt, *J*_{7,7} = 18.0 Hz, *J*_{7,8} = 7.5 Hz, 1 $\times$ H-7), 2.69 (1 H, dt, *J*_{7,7} = 18.0 Hz, *J*_{7,8} = 7.5 Hz, 1 $\times$ H-7), 2.81 (1 H, *J*_{2,2} = 16.0 Hz, *J*_{2,1} = 6.0 Hz, 1 $\times$ H-2), 2.96 (1 H, *J*_{2,2} = 16.0 Hz, *J*_{2,1} = 6.0 Hz, 1 $\times$ H-2), 3.61 (2 H, t, *J*_{10,9} = 6.5 Hz, H-10), 3.68 (1 H, d, *J*_{OH,4} = 6.0 Hz, C(4)OH), 3.75 (2 H, t, *J*_{1,2} = 6.0 Hz, H-1), 3.81 (3 H, s, OCH₃), 3.93 (1 H, d, *J*_{OH,5} = 6.0 Hz, C(5)OH), 4.29–4.35 (2 H, m, H-4, H-5), 4.43 (1 H, d, *J*_{1',1'} = 11.5 Hz, 1 $\times$ H-1'), 4.46 (1 H, d, *J*_{1',1'} = 11.5 Hz, 1 $\times$ H-1'), 6.88 (2 H, d, *J*_{3'',2''} = 8.5 Hz, 2 $\times$ H-3''), 7.23 (2 H, d, *J*_{2'',3''} =

8.5 Hz, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH_3), 18.3 (SiCCH_3), 19.7 (C-8), 25.9 (SiCCH_3), 32.0 (C-9), 39.2 (C-7), 40.1 (C-2), 55.3 (OCH_3), 62.7 (C-10), 65.1 (C-1), 73.1 (C-1'), 78.1 (C-5), 78.6 (C-4), 113.9 (C-3''), 129.4 (C-2''), 129.6 (C-1''), 159.4 (C-4''), 209.1 (C-3), 209.6 (C-6); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3417 (br), 2953 (s), 1715 (s), 1613 (m), 1514 (s), 1463 (m), 1363 (m), 1250 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{24}\text{H}_{40}\text{NaO}_7\text{Si}^+ [\text{MNa}]^+$ 491.2436, found 491.2439.

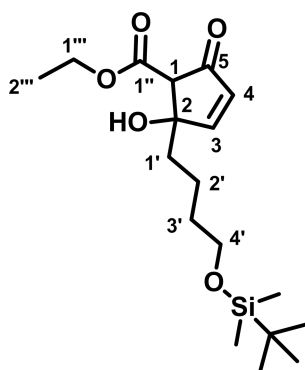
(4*S,5*R**)-10-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-3,6-dioxodecane-4,5-diyldiacetate (2.121)**



Acetic anhydride (5 μL , 52 μmol) was added to a solution of diol **2.120** (8 mg, 17 μmol) and DMAP (0.5 mg, 4.0 μmol) in pyridine (0.5 mL) at 0 $^\circ\text{C}$. The resulting mixture was warmed to RT over 1 h before dilution with ether (10 mL). The mixture was washed with CuSO_4 solution (sat. aq., 3×5 mL), dried (MgSO_4) and concentrated. Flash chromatography (petrol/ethyl acetate, 70:30) furnished the *title compound* (**2.121**) as a colourless oil (10 mg, 100%). R_f (petrol/ethyl acetate; 70:30) = 0.61; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.90 (9 H, s, SiCCH_3), 1.49–1.79 (4 H, m, H-8, H-9), 2.12 (3 H, s, $1 \times \text{COCH}_3$), 2.19 (3 H, s, $1 \times \text{COCH}_3$), 2.21–2.98 (4 H, m, H-2, H-7), 3.61–3.72 (2 H, m, H-10), 3.72–3.81 (2 H, m, H-1), 3.86 (3 H, s, OCH_3), 4.43–4.52 (2 H, m, H-1'), 5.55–5.70 (2 H, m, H-4, H-5), 6.89 (2 H, d, $J_{3'',2''} = 8.5$ Hz, $2 \times \text{H-3''}$), 7.26–7.31 (2 H, m, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz,

CDCl₃) δ -5.3 (SiCH₃), 18.5 (SiCCH₃), 19.6 (C-8), 20.3 (1 $\times$ COCH₃), 20.6 (1 $\times$ COCH₃), 25.9 (SiCCH₃), 32.0 (C-9), 39.1(C-7), 39.9 (C-2), 55.3 (OCH₃), 62.7 (C-10), 64.2 (C-1), 72.8 (C-1'), 76.1 (C-4), 76.4 (C-5), 113.8 (C-3''), 129.6 (C-2''), 130.2 (C-1''), 159.4 (C-4''), 167.5 (1 $\times$ COCH₃), 169.6 (1 $\times$ COCH₃), 202.7 (C-3), 203.2 (C-6); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2929 (s), 2856 (s), 1758 (s), 1760 (s), 1612 (s), 1514 (s), 1249 (s), 1215 (s), 1100 (s); HRMS (ESI⁺) m/z calcd. for C₂₈H₄₄NaO₉Si⁺ [MNa]⁺ 575.2647, found 575.2644.

Ethyl 2-[4-(*tert*-Butyldimethylsilyloxy)butyl]-2-hydroxy-5-oxocyclopent-3-enecarboxylate (2.133)

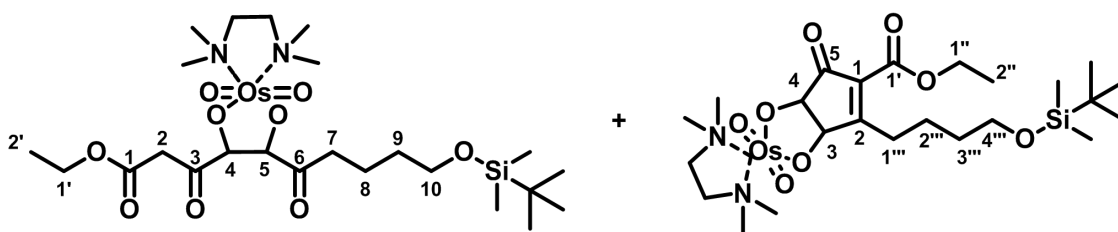


To a solution of furan derivative **2.99** (30 mg, 88.1 μmol) in DCM (3 mL) at $-10\text{ }^{\circ}\text{C}$ was added *m*-CPBA (60%, 30 mg, 0.105 mmol) in one portion. The resulting mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 3 h then ether (10 mL) and H₂O (10 mL) was added to dilute the mixture. The aqueous layer was extracted with ether (3 $\times$ 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**2.133**) as a colourless oil (18 mg, 58%). R_f (petrol/ethyl acetate; 80:20) = 0.48; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (3 H, t, $J_{2''',1'''} = 7.0\text{ Hz}$, H-2'''), 1.46-1.66 (4 H, m, H-2', H-3'), 1.74-1.81 (1 H, m, 1 $\times$ H-1'), 1.84-1.93 (1 H, m, 1 $\times$ H-1'), 3.50 (1 H, s, H-1), 3.67 (2 H, t, $J_{4',3'} = 6.0\text{ Hz}$, H-4'), 3.81 (1 H, br.s, OH), 4.29 (2 H, q, $J_{1'',2''} = 7.0\text{ Hz}$, H-1''),

6.24 (1 H, d, $J_{4,3} = 5.5$ Hz, H-4), 7.57 (1 H, d, $J_{3,4} = 5.5$ Hz, H-3); ^{13}C NMR, IR and HRMS are missing.

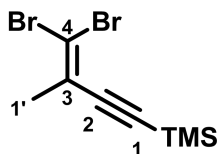
Ethyl 10-(*tert*-butyldimethylsilyloxy)-4,5-dihydroxy-3,6-dioxodecanoatato dioxo (*N,N,N'*, *N'*-tramethylethylenediamino) osmate diester (2.136) &

Ethyl 2-[4-(*tert*-butyldimethylsilyloxy)butyl]-3,4-dihydroxy-5-oxocyclopent-1-enecarboxylatato dioxo (*N,N,N'*, *N'*-tramethylethylenediamino) osmate diester (2.137)

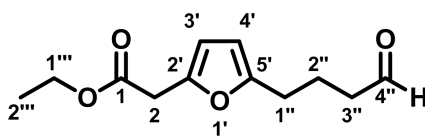


A solution of ketoester **2.133** (45 mg, 0.126 mmol) and TMEDA (22.7 μL , 0.152 mmol) in DCM (10 mL) was cooled to -78 $^{\circ}\text{C}$ under argon. A solution of OsO_4 (39 mg, 0.153 mmol) in DCM (3 mL) was added and the resulting solution was stirred at -78 $^{\circ}\text{C}$ for 30 min. The reaction mixture was warmed to RT and concentrated. The residue was purified by flash chromatography (DCM/MeOH, 97:3 then 95:5 then 90:10) to furnish the *title compounds* **2.136** (15 mg, 18%) and **2.137** (54 mg, 60%), both as brown oils. **Data for 2.136:** R_f (DCM/methanol; 90:10) = 0.55; ^1H NMR (500 MHz, CDCl_3) δ 0.04 (6 H, s, SiCH_3), 0.88 (9 H, s, SiCCH_3), 1.26 (3 H, t, $J_{2,1'} = 7.0$ Hz, H-2'), 1.48–1.57 (2 H, m, H-9), 1.59–1.70 (2 H, m, H-8), 2.64–2.69 (2 H, m, H-7), 2.90 (3 H, s, $1 \times \text{NCH}_3$), 2.91 (3 H, s, $1 \times \text{NCH}_3$), 2.92 (3 H, s, $1 \times \text{NCH}_3$), 2.93 (3 H, s, $1 \times \text{NCH}_3$), 3.10–3.16 (4 H, m, NCH_2), 3.49 (1 H, d, $J_{2,2} = 16.0$ Hz, $1 \times \text{H-2}$), 3.60 (2 H, t, $J_{10,9} = 6.5$ Hz, H-10), 4.01 (1 H, d, $J_{2,2} = 16.0$ Hz, $1 \times \text{H-2}$), 4.14–4.21

(2 H, m, H-1'), 4.89 (1 H, d, $J_{5,4} = 5.0$ Hz, H-5), 4.96 (1 H, d, $J_{4,5} = 5.0$ Hz, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH₃), 14.1 (C-2'), 18.3 (SiCCH₃), 19.6 (C-8), 26.0 (SiCCH₃), 32.6 (C-9), 39.0 (C-7), 47.3 (C-2), 51.9, 52.1, 52.3 ($4 \times \text{NCH}_3$), 60.7 (C-1'), 63.2 (C-10), 64.6, 64.7 ($2 \times \text{NCH}_2$), 94.6 (C-4), 96.6 (C-5), 168.3 (C-1), 204.6 (C-3), 210.2 (C-6); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2930 (s), 2857 (s), 1739 (s), 1715 (s), 1473 (m), 1463 (m), 1367 (m), 1257 (m), 1099 (s), 1038 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{24}\text{H}_{48}\text{N}_2\text{NaO}_9\text{OsSi}^+ [\text{MNa}]^+$ 751.2636, found 751.2629. **Data for 2.137:** R_f (DCM/methanol; 90:10) = 0.51; ^1H NMR (500 MHz, CDCl_3) δ 0.04 (6 H, s, SiCH₃), 0.89 (9 H, s, SiCCH₃), 1.32 (3 H, t, $J_{2'',1''} = 7.5$ Hz, H-2''), 1.59–1.65 (2 H, m, H-3'''), 1.68–1.85 (2 H, m, H-2'''), 2.71–2.77 (1 H, m, $1 \times \text{H-1}'''$), 2.82 (3 H, s, $1 \times \text{NCH}_3$), 2.84 (3 H, s, $1 \times \text{NCH}_3$), 2.88 (3 H, s, $1 \times \text{NCH}_3$), 2.92 (3 H, s, $1 \times \text{NCH}_3$), 2.90–2.96 (1 H, m, $1 \times \text{H-1}'''$), 3.01–3.15 (4 H, m, NCH₂), 3.63 (2 H, t, $J_{4''',3'''} = 6.5$ Hz, H-4'''), 4.24–4.30 (2 H, m, H-1''), 4.68 (1 H, d, $J_{3,4} = 5.5$ Hz, H-3), 5.25 (1 H, d, $J_{4,3} = 5.5$ Hz, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH₃), 14.2 (C-2''), 18.3 (SiCCH₃), 24.0 (C-2'''), 26.0 (SiCCH₃), 29.5 (C-1'''), 33.3 (C-3'''), 51.6, 52.0, 52.1, 52.5 ($4 \times \text{NCH}_3$), 60.7 (C-1''), 62.9 (C-4'''), 64.4, 64.5 ($2 \times \text{NCH}_2$), 90.9 (C-4), 91.6 (C-3), 130.8 (C-1), 163.3 (C-1'), 185.1 (C-2), 199.9 (C-5); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2931 (s), 2858 (s), 1741 (s), 1716 (s), 1473 (m), 1462 (m), 1372 (m), 1255 (m), 1099 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{24}\text{H}_{46}\text{N}_2\text{NaO}_8\text{OsSi}^+ [\text{MNa}]^+$ 733.2530, found 733.2527.

(4,4-Dibromo-3-methylbut-3-en-1-yn-1-yl)trimethylsilane (2.163)²²

To a solution of triphenylphosphine (3.07 g, 11.7 mmol) in DCM (3 mL) was added a solution of CBr_4 (1.98 g, 5.97 mmol) in DCM (3 mL) at 0 °C. After 10 min, ketone **2.66** (500 μL , 3.04 mmol) was added slowly. The reaction mixture was warmed to RT over 14 h then concentrated. Flash chromatography (petrol) afforded the title compound (**2.163**) as a colourless oil (873 mg, 98 %). R_f (petrol) = 0.57; ^1H NMR (400 MHz, CDCl_3) δ 0.22 (9 H, s, SiCH_3), 1.99 (3 H, s, H-1'); ^{13}C NMR (100 MHz, CDCl_3) δ -0.32 (SiCH_3), 23.5 (C-1'), 98.2, 102.3 and 103.4 (C-1, C-2, C-4), 125.9 (C-3). All the other data are as reported.

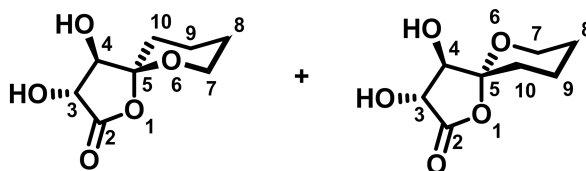
Ethyl 2-[5-(4-oxobutyl)furan-2-yl]acetate (2.139)

PCC (95 mg, 0.441 mmol) was added to a solution of furan derivative **2.99** (30 mg, 88.0 μmol) in DCM (3 mL). The resulting mixture was stirred at RT for 2 h then the brown mixture was filtered through a pad of Celite[®] with DCM eluting (30 mL). The filtrate was concentrated and flash chromatography (petrol/ethyl acetate, 80:20) furnished the *title compound* (**2.139**) as a pale yellow oil (4 mg, 20%). R_f (petrol/ethyl acetate; 80:20) = 0.41;

^1H NMR (500 MHz, CDCl_3) δ 1.27 (3 H, t, $J_{2''',1'''} = 7.0$ Hz, H-2'''), 1.97 (2 H, qn, $J_{2'',1''} = J_{2'',3''} = 7.5$ Hz, H-2''), 2.49 (2 H, td, $J_{3'',2''} = 7.5$ Hz, $J_{3'',4''} = 1.5$ Hz, H-3''), 2.66 (2 H, t, $J_{1'',2''} = 7.5$ Hz, H-1''), 3.63 (2 H, s, H-2), 4.19 (2 H, q, $J_{1''',2'''} = 7.0$ Hz, H-1'''), 5.95 (1 H, d, $J_{4',3'} = 3.0$ Hz, H-4'), 6.11 (1 H, d, $J_{3',4'} = 3.0$ Hz, H-3'), 9.76 (1 H, t, $J_{4'',3''} = 1.5$ Hz, H-4''); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-2'''), 20.6 (C-2''), 27.2 (C-1''), 34.2 (C-2), 43.0 (C-3''), 61.1 (C-1'''), 106.5 (C-4'), 108.5 (C-3'), 146.3 (C-2'), 154.4 (C-5'), 169.6 (C-1), 202.1 (C-4''); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2939 (m), 1739 (s), 1567 (w), 1227 (w), 1181 (w), 1032 (w); HRMS (ESI^+) m/z calcd. for $\text{C}_{12}\text{H}_{16}\text{NaO}_4^+ [\text{MNa}]^+$ 247.0941, found 247.0945.

(3*R,4*R**,5*S**)-3,4-Dihydroxy-1,6-dioxaspiro[4.5]decan-2-one (2.148) &**

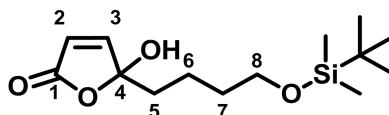
(3*R,4*R**,5*R**)-3,4-dihydroxy-1,6-dioxaspiro[4.5]decan-2-one (2.158)**



To a stirred solution of crude dihydroxyacid **2.157** (200 mg, 0.624 mmol) in a mixture of THF (6 mL) and H_2O (11.5 μL) was added *para*-toluenesulfonic acid monohydrate (60 mg, 0.315 mmol) at RT, some precipitation occurred. The resulting suspension was stirred at RT for 3 h then concentrated. Flash chromatography (DCM/ethyl acetate/acetic acid, 66:33:1) furnished the *title compounds* **2.148** and **2.158** as a mixture of two diastereomers ($d.r.$ = 6:1) as a white solid (94 mg, 80%). R_f (methanol/DCM/acetic acid; 10:90:3) = 0.44; m.p. = 120 $^\circ\text{C}$; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3406 (br), 2951 (m), 1784 (s), 1234 (m), 1148 (m), 1097 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_8\text{H}_{12}\text{NaO}_5^+ [\text{MNa}]^+$ 211.0577, found 211.0577. **^1H NMR for both**

diastereomers: ^1H NMR (500 MHz, d_6 -acetone) δ 1.58–2.03 (6 H, m, H-8, H-9, H-10), 3.81–3.85 (3 H, m, H-4, H-7), 4.43 (1 H, dd, $J_{3,4} = 9.0$ Hz, $J_{3,\text{OH}} = 5.0$ Hz, H-3), 4.48 (1 H, d, $J_{\text{OH},4} = 9.0$ Hz, C(4)OH), 5.12 (1 H, d, $J_{\text{OH},3} = 5.0$ Hz, C(3)OH); ^{13}C NMR for **diastereomer 2.148:** ^{13}C NMR (125 MHz, d_6 -acetone) δ 19.5 (C-9), 25.1 (C-8), 31.0 (C-10), 63.8 (C-7), 73.2 (C-3), 79.9 (C-4), 103.4 (C-5), 174.1 (C-2); ^{13}C NMR **diastereomer 2.158:** ^{13}C NMR (125 MHz, d_6 -acetone) δ 18.9 (C-9), 25.4 (C-8), 29.1 (C-10), 64.5 (C-7), 74.7 (C-3), 81.1 (C-4), 106.7 (C-5), 172.8 (C-2).

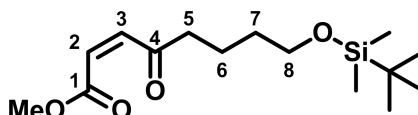
5-[4-(*tert*-Butyldimethylsilyloxy)butyl]-5-hydroxyfuran-2(5*H*)-one (2.151)²³



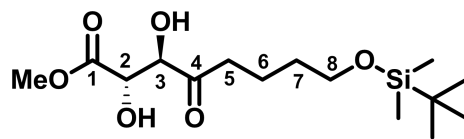
To a stirred solution of furan derivative **2.62** (2.00 g, 7.86 mmol) in *t*-BuOH and H_2O (5:1, 40 mL) was added $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (1.74 g, 12.6 mmol) and NaClO_2 (2.27 g, 25.1 mmol). The resulting mixture was stirred at RT for 4 h before dilution with H_2O (150 mL) and extracted with CHCl_3 (3×200 mL). The combined organic layers were washed with brine (200 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ether/acetic acid, 80:20:1) furnished the title compound (**2.151**) as a pale yellow oil (2.22 g, 98%). R_f (petrol/ethyl acetate; 80:20) = 0.37; ^1H NMR (400 MHz, CDCl_3) δ 0.04 (6 H, s, SiCH_3), 0.88 (9 H, s, SiCCH_3), 1.42–1.71 (4 H, m, H-6, H-7), 1.90–2.06 (2 H, m, H-5), 3.62 (2 H, t, $J_{8,7} = 6.0$ Hz, H-8), 4.52–5.43 (1 H, br.s, OH), 6.09 (1 H, d, $J_{2,3} = 5.5$ Hz, H-2), 7.21 (1 H, d, $J_{3,2} = 5.5$ Hz, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ -5.3 (SiCH_3), 18.3 (SiCCH_3), 20.2 (C-6), 25.9 (SiCCH_3), 31.8 (C-7), 36.9 (C-5), 62.9 (C-8), 108.0 (C-4), 123.1 (C-2), 154.2 (C-3), 170.3

(C-1); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3385 (br), 2955 (s), 2931 (s), 2859 (s), 1770 (s), 1256 (m), 1102 (s); HRMS (ESI⁺) m/z calcd. for C₁₄H₂₆NaO₄Si⁺ [MNa]⁺ 309.1493, found 309.1498.

(Z)-Methyl 8-(*tert*-butyldimethylsilyloxy)-4-oxooct-2-enoate (2.152)



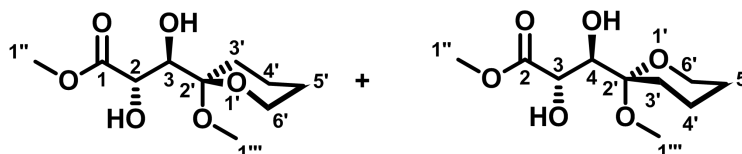
To a solution of butenolide **2.151** (20 mg, 69.9 μmol) in anhydrous DMF (0.7 mL) was added Cs₂CO₃ (17 mg, 52.5 μmol) followed by iodomethane (13 μL , 0.210 mmol). The resulting mixture was stirred at RT for 2 h. The mixture was then poured into a mixture of H₂O (10 mL) and ether (10 mL), and the aqueous layer was extracted with ether (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄) then concentrated. Flash chromatography (petrol/ethyl acetate, 90:10) furnished the *title compound* (**2.152**) as a colourless oil (14 mg, 67 %). R_f (petrol/ethyl acetate; 90:10) = 0.64; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.89 (9 H, s, SiCCH₃), 1.54–1.59 (2 H, m, H-7), 1.69–1.75 (2 H, m, H-6), 2.64 (2 H, t, $J_{5,6}$ = 7.5 Hz, H-5), 3.63 (2 H, t, $J_{8,7}$ = 6.5 Hz, H-8), 3.76 (3 H, s, OCH₃), 6.03 (1 H, d, $J_{2,3}$ = 12.0 Hz, H-2), 6.50 (1 H, d, $J_{3,2}$ = 12.0 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ –5.3 (SiCH₃), 18.3 (SiCCH₃), 19.8 (C-6), 26.0 (SiCCH₃), 32.1 (C-7), 42.4 (C-5), 52.1 (OCH₃), 62.8 (C-8), 124.4 (C-2), 141.8 (C-3), 165.7 (C-1), 203.5 (C-4); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3396 (br), 2960 (s), 2852 (s), 1732 (s), 1707 (s), 1634 (w), 1260 (s), 1098 (s); HRMS (ESI⁺) m/z calcd. for C₁₅H₂₈NaO₄Si⁺ [MNa]⁺ 323.1649 found 323.1651.

(2*S,3*R**)-Methyl 8-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxy-4-oxooctanoate (2.153)**

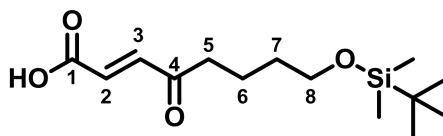
Unsaturated ester **2.152** (9 mg, 30.0 μmol) and citric acid (4.5 mg, 23.4 μmol) were dissolved in a mixture of *t*-BuOH and H_2O (1:1, 1 mL). To this solution was added $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ solution (0.01 M in 1:1 *t*-BuOH and H_2O , 152 μL , 1.52 μmol) followed by NMO solution (50% in H_2O , 13 μL , 62.6 μmol). The resulting mixture was stirred at RT for 3 h. Ethyl acetate (10 mL) and $\text{Na}_2\text{S}_2\text{O}_5$ solution (sat. aq., 10 mL) were added to dilute the solution and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried (MgSO_4) then concentrated, and flash chromatography (petrol/ethyl acetate, 70:30) furnished the *title compound* (**2.153**) as a pale brown oil (6 mg, 61%). R_f (petrol/ethyl acetate; 70:30) = 0.20; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (6 H, s, SiCH_3), 0.90 (9 H, s, SiCCH_3), 1.52–1.60 (2 H, m, H-6), 1.70–1.78 (2 H, m, H-7), 2.53–2.71 (2 H, m, H-5), 3.63 (2 H, t, $J_{8,7} = 6.0$ Hz, H-8), 3.76 (3 H, s, OCH_3), 4.45 (1 H, app.s, H-2), 4.63 (1 H, app.s, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ -5.3 (SiCH_3), 18.3 (SiCCH_3), 19.7 (C-7), 25.9 (SiCCH_3), 32.0 (C-6), 38.5 (C-5), 52.8 (OCH_3), 62.9 (C-8), 76.8 (C-3), 78.9 (C-2), 171.2 (C-1), 207.5 (C-4); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3443 (br), 2955 (s), 1745 (s), 1256 (m), 1102 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{15}\text{H}_{30}\text{NaO}_6\text{Si}^+ [\text{MNa}]^+$ 357.1704 found 357.1702.

(2*S,3*R**)-Methyl 2,3-dihydroxy-3-[(*R**)-2-methoxytetrahydro-2*H*-pyran-2-yl]propanoate &**

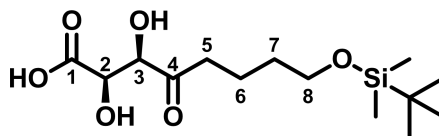
(2*S,3*R**)-methyl 2,3-dihydroxy-3-[(*S**)-2-methoxytetrahydro-2*H*-pyran-2-yl]propanoate (**2.155**)**



To a solution of silyl ether **2.153** (20 mg, 59.9 μmol) in methanol (2 mL) was added CSA (1.5 mg, 6.26 μmol) at 0 °C. The solution was warmed to RT and stirred for 4 h. The reaction was quenched with triethylamine (3 μL) then diluted with ether (10 mL) and H₂O (10 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate; 50:50) furnished the *title compounds* (**2.155**) as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (8 mg, 57%). R_f (petrol/ethyl acetate; 50:50) = 0.21; ¹H NMR (400 MHz, CDCl₃) δ 1.51–1.94 (12 H, m, H-3', H-4', H-5', **A** and **B**), 2.66–2.75 (2 H, m, OH, **A** and **B**), 3.37 (3 H, s, H-1''', **A** or **B**), 3.39 (3 H, s, H-1''', **B** or **A**), 3.72–4.06 (14 H, m, H-1'', H-3, H-6', OH, **A** and **B**), 4.36–4.42 (2 H, m, H-2, **A** and **B**); ¹³C NMR, IR and HRMS are missing.

(E)-8-(tert-Butyldimethylsilyloxy)-4-oxooct-2-enoic acid (2.156)²³

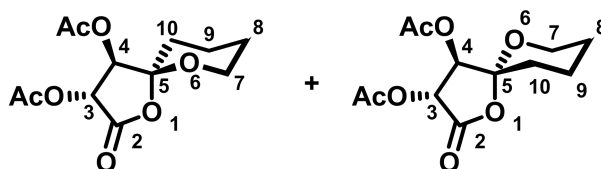
To a stirred solution of butenolide **2.151** (4.50 g, 15.7 mmol) in a mixture of THF, H₂O, and acetone (5:4:1, 3 mL) was added pyridine (12.6 μ L, 0.157 mmol) at RT. The resulting mixture was stirred at RT for 2 h then the solvent was removed. Flash chromatography (petrol/ether/acetic acid, 80:20:1) furnished the title compound (**2.156**) as a colourless oil (4.27 g, 95%). R_f (petrol/ether/acetic acid; 80:20:1) = 0.27; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃), 0.89 (9 H, s, SiCCH₃), 1.52–1.58 (2 H, m, H-7), 1.71 (2 H, qn, $J_{6,5} = J_{6,7} = 7.5$ Hz, H-6), 2.69 (2 H, t, $J_{5,6} = 7.5$ Hz, H-5), 3.63 (2 H, t, $J_{8,7} = 6.0$ Hz, H-8), 6.67 (1 H, d, $J_{3,2} = 16.0$ Hz, H-3), 7.13 (1 H, d, $J_{2,3} = 16.0$ Hz, H-2); ¹³C NMR (125 MHz, CDCl₃) δ –5.3 (SiCH₃), 18.3 (SiCCH₃), 20.2 (C-6), 25.9 (SiCCH₃), 32.0 (C-7), 41.4 (C-5), 62.7 (C-8), 129.6 (C-2), 141.0 (C-3), 170.0 (C-1), 199.4 (C-4); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3197 (br), 2955 (s), 1699 (s), 1256 (s), 1103 (s); HRMS (ESI⁺) m/z calcd. for C₁₄H₂₇O₄Si⁺ [MH]⁺ 287.1673, found 287.1676.

(2*R,3*R**)-8-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-4-oxooctanoic acid (2.157)**

To a stirred solution of unsaturated acid **2.156** (670 mg, 2.34 mmol) and citric acid (338 mg, 1.76 mmol) in a mixture of *t*-BuOH and H₂O (1:1, 5 mL) was added K₂OsO₄·2H₂O (43 mg, 0.117 mmol) followed by NMO solution (50% solution in H₂O, 580 μL, 2.81 mmol). The resulting mixture was stirred for 100 min then concentrated. Flash chromatography (methanol/DCM/acetic acid, 10:90:3) furnished the *title compound* (**2.157**) as a pale brown oil (673 mg, 90%) for further steps without purification. *R_f* (petrol/ether/acetic acid; 80:20:1) = 0.29; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (6 H, s, SiCH₃) 0.89 (9 H, s, SiCCH₃), 1.50–1.59 (2 H, m, H-6), 1.66–1.76 (2 H, m, H-7), 2.55–2.73 (2 H, m, H-5), 3.60–3.67 (2 H, m, H-8), 4.53–4.64 (1 H, app.s, H-2), 4.64–4.74 (1 H, app.s, H-3); ¹³C NMR (125 MHz, CDCl₃) δ –5.4 (SiCH₃), 18.3 (SiCCH₃), 19.9 (C-7), 25.9 (SiCCH₃), 31.9 (C-6), 37.7 (C-5), 62.8 (br, C-8), 71.4 (br, C-3), 77.3 (br, C-2), 175.4 (br, C-1), 208.1 (br, C-4); IR (film) ν_{max} /cm^{–1} 3420 (br), 2954 (s), 1720 (s), 1255 (s), 1101 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₄H₂₈NaO₆Si⁺ [MNa]⁺ 343.1547, found 343.1540.

(3*R**,4*R**,5*S**)-2-Oxo-1,6-dioxaspiro[4.5]decane-3,4-diyl diacetate (**2.159**) &

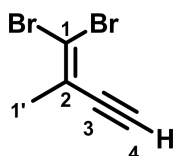
(3*R**,4*R**,5*R**)-2-oxo-1,6-dioxaspiro[4.5]decane-3,4-diyl diacetate (**2.160**)



To a solution of diols **2.148** and **2.158** [a mixture of 2 diastereomers (*d.r.* = 6:1), 10 mg, 53.2 μ mol] in pyridine (2 mL) was added acetic anhydride (50 μ L, 0.53 mmol) at 0 °C. The resulting mixture was stirred at RT for 14 h. Ether (20 mL) was added to dilute the mixture and washed with CuSO₄ solution (sat. aq., 3 $\times$ 5 mL). The organic layer was dried (MgSO₄) and concentrated, and flash chromatography (petrol/ethyl acetate, 80:20) furnished the *title compounds* **2.159** and **2.160** as a mixture of two diastereomers (*d.r.* = 6:1) as a colourless oil (6 mg, 42%). *R_f* (DCM/MeOH; 95:5) = 0.90; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953 (m), 1808 (s), 1759 (s), 1442 (m), 1373 (m), 1217 (s), 1080 (m); HRMS (ESI⁺) *m/z* calcd. for C₁₂H₁₆NaO₇⁺ [MNa]⁺ 295.0788, found 295.0796. **NMR data for 2.159:** ¹H NMR (500 MHz, d₆-acetone) δ 1.62–1.71 (2 H, m, H-8), 1.79–1.88 (2 H, m, H-9), 1.92–1.97 (2 H, m, H-10), 2.11 (3 H, s, 1 $\times$ COCH₃), 2.12 (3 H, s, 1 $\times$ COCH₃), 3.88–3.91 (2 H, m, H-7), 5.48 (1 H, d, *J*_{4,3} = 9.0 Hz, H-4), 5.69 (1 H, d, *J*_{3,4} = 9.0 Hz, H-3); ¹³C NMR (125 MHz, d₆-acetone) δ 19.3 (C-9), 20.4, 20.6 (2 $\times$ COCH₃), 24.7 (C-8), 31.6 (C-10), 64.3 (C-7), 71.9 (C-3), 75.7 (C-4), 103.9 (C-5), 168.5 (1 $\times$ COCH₃), 170.2 (1 $\times$ COCH₃), 170.7 (C-2); **NMR data for 2.160:** ¹H NMR (500 MHz, d₆-acetone) δ 1.62–1.71 (2 H, m, H-8), 1.79–1.88 (2 H, m, H-9), 1.92–1.97 (2 H, m, H-10), 2.13 (3 H, s, 1 $\times$ COCH₃), 2.15 (3 H, s, 1 $\times$ COCH₃), 3.88–3.91 (2 H, m, H-7), 5.34 (1

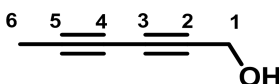
H, d, $J_{4,3} = 6.5$ Hz, H-4), 5.38 (1 H, d, $J_{3,4} = 6.5$ Hz, H-3); ^{13}C NMR (125 MHz, d_6 -acetone) δ 18.9 (C-9), 20.4, 20.6 ($2 \times \text{COCH}_3$), 24.9 (C-8), 31.6 (C-10), 64.9 (C-7), 73.3 (C-3), 78.3 (C-4), 106.7 (C-5), 168.2 ($1 \times \text{COCH}_3$), 169.8 ($1 \times \text{COCH}_3$), 170.7 (C-2).

1,1-Dibromo-2-methylbut-1-en-3-yne (**2.164**)²²



Dibromoalkene **2.163** (4.88 g, 16.6 mmol) was dissolved in a mixture of THF and methanol (1:1, 92 mL) when K_2CO_3 (550 mg, 3.98 mmol) was added. After 1 h, the solution was passed through a short pad of silica, eluting with petrol (100 mL). Concentration of the filtrate furnished the title compound (**2.164**) as a colourless oil (3.69 g, 100%). R_f (petrol) = 0.81; ^1H NMR (400 MHz, CDCl_3) δ 2.02 (3 H, s, H-1'), 3.48 (1 H, s, H-4); ^{13}C NMR (100 MHz, CDCl_3) δ 23.7 (C-1'), 82.6 (C-3), 84.3 (C-4), 98.6 (C-2), 125.2 (C-1). All the other data are as reported.

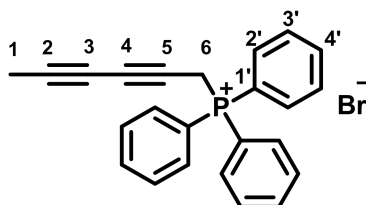
Hexa-2,4-diyne-1-ol (**2.165**)²²



BuLi (0.7 mL, 1.6 M in hexanes, 1.13 mmol) was added dropwise over 30 min to a stirred solution of dibromoalkene **2.164** (100 mg, 0.451 mmol) in toluene (2.3 mL) at -40 °C. The

reaction mixture was warmed to $-20\text{ }^{\circ}\text{C}$ over 30 min and a solution of paraformaldehyde (19 mg, 0.631 mmol) in ether (2.5 mL) was added. The reaction mixture was warmed slowly to RT and stirred for 14 h. Then the reaction mixture was quenched with NH_4Cl solution (sat. aq., 5 mL) and extracted with ether ($3 \times 5\text{ mL}$). The combined organic layers were dried (MgSO_4) then concentrated, and flash chromatography (petrol/ether, 80:20) furnished the title compound (**2.165**) as pale yellow needles (25 mg, 59%). R_f (petrol/ether; 80:20) = 0.26; ^1H NMR (400 MHz, CDCl_3) δ 1.92 (3 H, s, H-6), 2.76 (1 H, br.s, OH), 4.28 (2 H, s, H-1); ^{13}C NMR (100 MHz, CDCl_3) δ 4.2 (C-6), 51.2 (C-1), 63.6, 70.6, 73.0 and 77.3 (C-2, C-3, C-4, C-5). All the other data are as reported.

Hexa-2,4-diyn-1-yltriphenylphosphonium bromide (**2.166**)

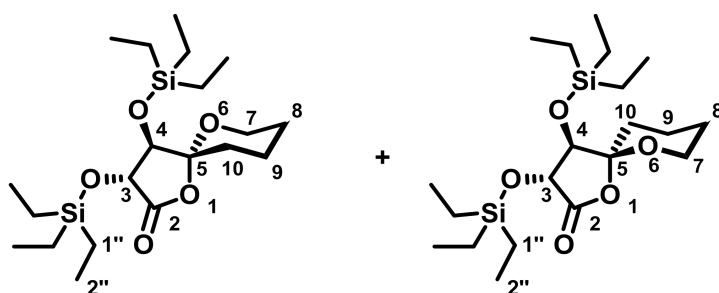


To a solution of bromide **2.67** (110 mg, 0.705 mmol) in anhydrous benzene (2 mL) was added triphenylphosphine (191 mg, 0.728 mmol) at RT. The resulting mixture was stirred at RT for 14 h, then ether (10 mL) was added to dilute the mixture and stirred for another 5 min. The white precipitate was isolated by filtration and dried under vacuum to give phosphonium salt (**2.166**) as a white powder (156 mg, 53%). ^1H NMR (500 MHz, CDCl_3) δ 1.85 (3 H, d, $^7J_{1,6} = 1.0\text{ Hz}$, H-1), 5.38 (2 H, dd, $^1J_{\text{HP}} = 15.5\text{ Hz}$, $^7J_{6,1} = 1.0\text{ Hz}$, H-6), 7.67–7.72 (6 H, m, $6 \times \text{H-3'}$), 7.77–7.83 (3 H, m, $3 \times \text{H-4'}$), 7.89–7.93 (6 H, m, $6 \times \text{H-2'}$); ^{13}C NMR (125 MHz,

CDCl₃) δ 4.3 (C-1), 19.2 (d, $^1J_{\text{PC}} = 55.0$ Hz, C-6), 62.6 (d, $^4J_{\text{PC}} = 14.5$ Hz, C-3), 63.6 (d, $^2J_{\text{PC}} = 7.5$ Hz, C-5), 73.0 (d, $^5J_{\text{PC}} = 10.0$ Hz, C-2), 77.2 (J value not available, overlapping with CDCl₃ peak, C-4), 117.4 (d, $^1J_{\text{PC}} = 87.5$ Hz, C-1'), 130.4 (d, $^3J_{\text{PC}} = 12.5$ Hz, C-3'), 134.0 (d, $^2J_{\text{PC}} = 10.5$ Hz, C-2'), 135.4 (d, $^4J_{\text{PC}} = 3.0$ Hz, C-4'); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2805 (w), 2732 (w), 2260 (w), 2180 (w), 1438 (s), 1112 (s); HRMS (ESI⁺) m/z calcd. for C₂₄H₂₀P⁺ [M–Br]⁺ 339.1297, found 339.1299.

(3*R,4*R**,5*R**)-3,4-Bis(triethylsilyloxy)-1,6-dioxaspiro[4.5]decan-2-one (2.167) &**

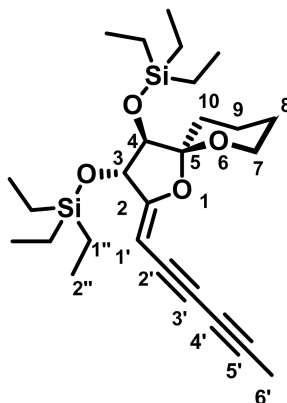
(3*R,4*R**,5*S**)-3,4-bis(triethylsilyloxy)-1,6-dioxaspiro[4.5]decan-2-one (2.168)**



To a stirred solution of diols **2.158** and **2.148** [a mixture of two diastereomers ($d.r. = 1:6$), 51 mg, 0.271 mmol] in anhydrous DMF (0.3 mL) was added imidazole (111 mg, 1.63 mmol) followed by chlorotriethylsilane (137 μL , 0.814 mmol) at 0 °C. The resulting mixture was warmed to RT and stirred for 3 h before dilution with H₂O (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (3 $\times$ 5 mL), the combined organic layers were dried (MgSO₄), and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compounds* **2.167** (18 mg, 15 %) and **2.168** (96 mg, 85%), both as colourless oils. **Data for 2.167:** R_f (petrol/ether; 95:5) = 0.60; ^1H NMR (500 MHz, CDCl₃) δ 0.63–0.76 (12 H, m,

H-1''), 0.96–1.02 (18 H, m, H-2''), 1.51–2.00 (6 H, m, H-8, H-9, H-10), 3.82 (1 H, dd, $J_{7eq,7ax} = 11.5$ Hz, $J_{7eq,8ax} = 4.5$ Hz, H-7eq), 3.98 (1 H, td, $J_{7ax,7eq} = J_{7ax,8ax} = 11.5$ Hz, $J_{7ax,8eq} = 3.0$ Hz, H-7ax), 4.04 (1 H, d, $J_{4,3} = 8.5$ Hz, H-4), 4.23 (1 H, d, $J_{3,4} = 8.5$ Hz, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ 4.7, 4.8 (C-1''), 6.6 (C-2''), 18.0 (C-9), 24.5 (C-8), 28.7 (C-10), 64.1 (C-7), 75.3 (C-3), 81.6 (C-4), 105.7 (C-5), 171.5 (C-2); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955 (s), 2878 (s), 1798 (s), 1459 (m), 1238 (m), 1166 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{20}\text{H}_{40}\text{NaO}_5\text{Si}_2^+$ [MNa]⁺ 439.2306, found 439.2305. **Data for 2.168:** R_f (petrol/ether; 95:5) = 0.42; ^1H NMR (500 MHz, CDCl_3) δ 0.65–0.77 (12 H, m, H-1''), 0.96–1.04 (18 H, m, H-2''), 1.57–1.93 (6 H, m, H-8, H-9, H-10), 3.85–3.92 (3 H, m, H-4, H-7), 4.56 (1 H, d, $J_{3,4} = 8.5$ Hz, H-3); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9, 5.0 (C-1''), 6.7 (C-2''), 18.7 (C-9), 24.3 (C-8), 30.8 (C-10), 63.4 (C-7), 73.7 (C-3), 80.2 (C-4), 102.9 (C-5), 173.1 (C-2); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (s), 2789 (s), 1802 (s), 1458 (m), 1239 (m), 1171 (s), 1103 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{20}\text{H}_{40}\text{NaO}_5\text{Si}_2^+$ [MNa]⁺ 439.2306, found 439.2303.

(3*R,4*R**,5*S**,*Z*)-3,4-Bis(triethylsilyloxy)-2-(hexa-2,4-diyne-1-ylidene)-1,6-dioxaspiro[4.5]decane (Z-2.169)**



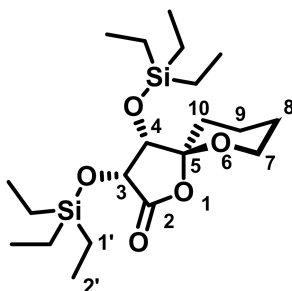
● **Synthesis of 1-iodoprop-1-yne 2.187**

To a stirred solution of trimethyl(prop-1-yn-1-yl)silane (250 μ L, 1.69 mmol) in freshly distilled acetone (12 mL) was added *N*-iodosuccinimide (490 mg, 2.18 mmol) and AgNO_3 (340 mg, 2.00 mmol) at RT. After stirring for 1 h in the dark, the white precipitate was filtered, and the filtrate was diluted with H_2O (40 mL) and petrol (40 mL). The layers were separated; the aqueous layer was extracted with petrol (3×40 mL), and the combined organic layers were dried (MgSO_4) then concentrated carefully. The crude (90 mg, 32%), an oil, was used for next step without any purification.

● **Synthesis of alkyne Z-2.169**

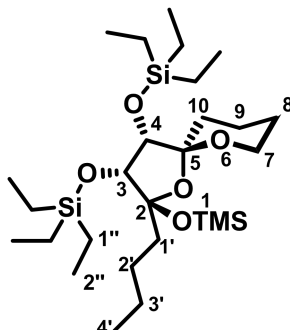
To a stirred solution of alkyne **2.193** (22 mg, 50.2 μ mol) and freshly prepared 1-iodoprop-1-yne (90 mg, 0.542 mmol) in degassed pyrrolidine (2.5 mL) was added CuI (3

mg, 18.0 μ mol) at RT. The solution became green immediately. After stirring for 1.5 h, the reaction mixture became yellow and was diluted with H₂O (10 mL). The mixture was extracted with ether (3 $\times$ 15 mL) and the combined organic layers were washed with H₂O (15 mL), brine (15 mL), then dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**Z-2.169**) as a pale yellow oil (17 mg, 72%). R_f (petrol/ether; 95:5) = 0.50; ¹H NMR (500 MHz, CDCl₃) δ 0.63–0.73 (12 H, m, H-1''), 0.95–1.03 (18 H, m, H-2''), 1.51–1.85 (6 H, m, H-8, H-9, H-10), 1.99 (3 H, d, $J_{6',1'} = 1.0$ Hz, H-6'), 3.70 (1 H, d, $J_{4,3} = 8.0$ Hz, H-4), 3.80 (1 H, dd, $J_{7eq,7ax} = 11.5$ Hz, $J_{7eq,8ax} = 4.5$ Hz, H-7eq), 3.92 (1 H, td, $J_{7ax,7eq} = J_{7ax,8ax} = 11.5$ Hz, $J_{7ax,8eq} = 3.5$ Hz, H-7ax), 4.60 (1 H, app.t, $J_{1',6'} = J_{1',3} = 1.0$ Hz, H-1'), 4.73 (1 H, dd, $J_{3,4} = 8.0$ Hz, $J_{3,1'} = 1.0$ Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 4.7 (C-6'), 5.1, 5.3 (C-1''), 6.8, 6.9 (C-2''), 18.9 (C-9), 24.5 (C-8), 31.1 (C-10), 62.7 (C-7), 65.1 (C-4'), 69.9 (C-2'), 76.3 (C-3), 77.2 (C-3'), 77.9 (C-1'), 79.3 (C-5'), 81.2 (C-4), 103.7 (C-5), 168.2 (C-2); IR (film) ν_{max}/cm^{-1} 2955 (s), 2144 (w), 1661 (m), 1458 (m), 1238 (m), 1155 (s); HRMS (ESI⁺) m/z calcd. for C₂₆H₄₄NaO₄Si₂⁺ [MNa]⁺ 499.2670, found 499.2660.

(3*R,4*S**,5*S**)-3,4-Bis(triethylsilyloxy)-1,6-dioxaspiro[4.5]decan-2-one (2.177)**

To a solution of (3*R*,4*S*,5*S**)-3,4-dihydroxy-1,6-dioxaspiro[4.5]decan-2-one (20 mg, 0.106 mmol) in pyridine (2 mL) was added chlorotriethylsilane (107 μ L, 0.64 mmol). The resulting mixture was heated to 60 $^{\circ}$ C for 3 h then it was cooled to RT. Ether (20 mL) and CuSO₄ solution (sat. aq., 10 mL) were used to dilute the mixture, and the organic layer was washed further with CuSO₄ solution (2 $\times$ 10 mL). The organic layer was dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 90:10) furnished the *title compound* (**2.177**) as a colourless oil (44 mg, 100%). *R*_f(petrol/ether; 95:5) = 0.60; ¹H NMR (500 MHz, CDCl₃) δ 0.58–0.78 (12 H, m, H-1'), 0.93–1.02 (18 H, m, H-2'), 1.50 (1 H, td, *J*_{10ax, 10eq} = *J*_{10ax, 9ax} = 13.5 Hz, *J*_{10ax, 9eq} = 5.0 Hz, H-10_{ax}), 1.56–1.70 (2 H, m, H-8), 1.73–1.80 (1 H, m, 1 $\times$ H-9), 1.81–1.91 (1 H, m, 1 $\times$ H-9), 2.07 (1 H, dt, *J*_{10eq, 10ax} = 13.5 Hz, *J*_{10eq, 9ax} = *J*_{10eq, 9eq} = 2.5 Hz, H-10_{eq}), 3.72–3.77 (1 H, m, H-7_{eq}), 3.85 (1 H, td, *J*_{7ax, 7eq} = *J*_{7ax, 8ax} = 11.5 Hz, *J*_{7ax, 8eq} = 3.5 Hz, H-7_{ax}), 4.01 (1 H, d, *J*_{4, 3} = 4.5 Hz, H-4), 4.64 (1 H, d, *J*_{3, 4} = 4.5 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 4.7, 5.0 (C-1'), 6.7, 6.8 (C-2'), 18.2 (C-9), 24.6 (C-8), 29.0 (C-10), 63.4 (C-7), 71.2 (C-3), 76.6 (C-4), 106.3 (C-5), 174.9 (C-2); IR (film) ν_{max} /cm⁻¹ 2955 (s), 2913 (s), 2878 (s), 1802 (s), 1459 (m); HRMS (ESI⁺) *m/z* calcd. for C₂₀H₄₀NaO₅Si₂⁺ [MNa]⁺ 439.2306, found 439.2313.

{[(2*S,3*R**,4*S**,5*S**)-2-Butyl-2-(trimethylsilyloxy)-1,6-dioxaspiro[4.5]decane-3,4-diyl]bis (oxy)}bis(triethylsilane) (2.178)**

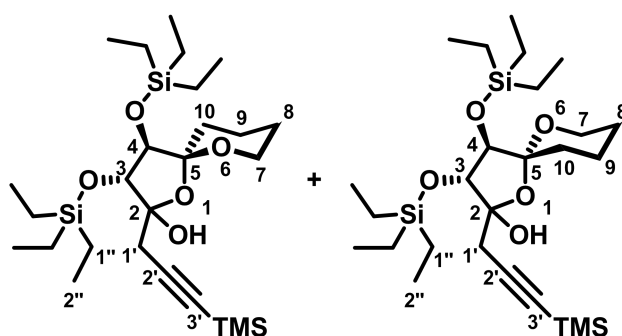


To a solution of lactone **2.177** (33 mg, 79.3 μmol) pre-mixed with TMSCl (10.2 μL , 80.3 μmol) in THF (2.6 mL) was added BuLi (1.6 M in hexanes, 50 μL , 80.0 μmol) at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h then was warmed to RT over 3 h. NH_4Cl solution (sat. aq., 10 mL) and ether (10 mL) were added to dilute the mixture and the aqueous layer was extracted with ether ($3 \times 10\text{ mL}$). The combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 95:5) furnished the *title compound* (**2.178**) as a colourless oil (41 mg, 94%). R_f (petrol/ether; 90:10) = 0.95; ^1H NMR (500 MHz, CDCl_3) δ 0.17 (9 H, s, SiCH_3), 0.60–0.71 (12 H, m, H-1''), 0.91 (3 H, t, $J_{4',3'} = 7.0\text{ Hz}$, H-4'), 0.93–1.01 (18 H, m, H-2''), 1.25–1.38 (5 H, m, H-2', H-3', 1 $\times$ H-8), 1.44–1.66 (4 H, m, 1 $\times$ H-1', 1 $\times$ H-8, 1 $\times$ H-9, 1 $\times$ H-10), 1.70–1.80 (3 H, m, 1 $\times$ H-1', 1 $\times$ H-9, 1 $\times$ H-10), 3.61–3.66 (1 H, m, 1 $\times$ H-7), 3.85–3.89 (1 H, m, 1 $\times$ H-7), 3.91 (1 H, d, $J_{3,4} = 4.5\text{ Hz}$, H-3), 4.09 (1 H, d, $J_{4,3} = 4.5\text{ Hz}$, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ 1.7 (SiCH_3), 4.9, 5.1 (C-1''), 6.9, 7.0 (C-2''), 14.1 (C-4'), 18.8 (C-9), 23.0 (C-3'), 25.5 (C-8), 25.8 (C-2'), 31.1 (C-10), 36.6 (C-1'), 63.0 (C-7), 78.8 (C-4), 79.3 (C-3), 105.9 (C-5), 108.2 (C-2); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (s), 2878 (s), 1459 (m), 1372 (m), 1249 (s), 1049 (m); HRMS (ESI^+) m/z

calcd. for $C_{27}H_{58}NaO_5Si_3^+ [MNa]^+$ 569.3484, found 569.3487.

(3*R,4*R**,5*S**)-3,4-Bis(triethylsilyloxy)-2-[3-(trimethylsilyl)prop-2-yn-1-yl]-1,6-dioxaspiro[4.5]decan-2-ol (2.181) &**

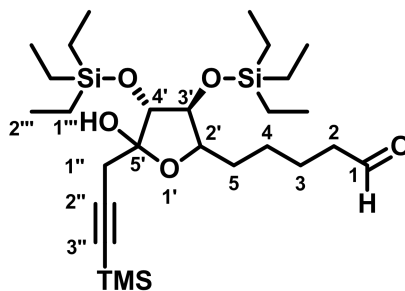
(3*R,4*R**,5*R**)-3,4-bis(triethylsilyloxy)-2-[3-(trimethylsilyl)prop-2-yn-1-yl]-1,6-dioxaspiro[4.5]decan-2-ol (2.182)**



To a stirred solution of 1-(trimethylsilyl)propyne (41 μ L, 0.277 mmol) and TMEDA (42 μ L, 0.280 mmol) in anhydrous, degassed THF (1.1 mL) was added BuLi (1.6 M in hexanes, 173 μ L, 0.277 mmol) at -78°C . After stirring for 1 h, a solution of lactone **2.168** (96 mg, 0.231 mmol) in anhydrous, degassed THF (5.8 mL) was added. The mixture was stirred at -78°C for 10 min before acetic acid (0.3 mL) was added to quench the reaction. Ether (15 mL) and H_2O (15 mL) were added and the layers were separated. The aqueous layer was extracted with ether (3×15 mL), and the combined organic layers were dried (MgSO_4) then concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compounds* **2.181** and **2.182**, a mixture of four diastereomers (*d.r.* not determined), as a colourless oil (54 mg, 45%, 100% b.r.s.m). R_f (petrol/ether; 70:30) = 0.58; ^1H NMR (500 MHz, CDCl_3) δ 0.14–0.17 (9 H, m, SiCH_3), 0.64–0.74 (12 H, m, H-1''), 0.96–1.03 (18 H, m, H-2''),

1.46–1.95 (6 H, m, H-8, H-9, H-10), 2.62–2.82 (2 H, m, H-1'), 3.60–4.31 (5 H, m, H-3, H-4, H-7, OH); ^{13}C NMR (125 MHz, CDCl_3) δ –0.08, 0.02, 0.04 (SiCH_3), 4.92, 4.95, 5.00, 5.15 (C-1''), 6.75, 6.80, 6.82, 6.90 (C-2''), 18.93, 19.18, 19.27 (C-9), 24.87, 24.93, 25.10, 25.18 (C-8), 28.29, 31.00 (C-1'), 29.58, 29.64, 29.68 (C-10), 61.88, 61.98, 62.03, 62.17 (C-7), 78.44, 78.71, 82.73, 83.01 (C-3), 82.49, 82.54 (C-4), 86.03, 86.18, 86.35 (C-3'), 99.89, 100.44, 102.13, 102.43, 102.60, 102.68, 102.72, 102.94, 104.19, 104.31, 105.53, 105.69 (C-2, C-5, C-2'); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3418 (br), 2957 (s), 2915 (s), 2181 (w), 1461 (m), 1249 (m), 1124 (s), 1091 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{26}\text{H}_{52}\text{NaO}_5\text{Si}_3^+$ $[\text{MNa}]^+$ 551.3015, found 551.3016.

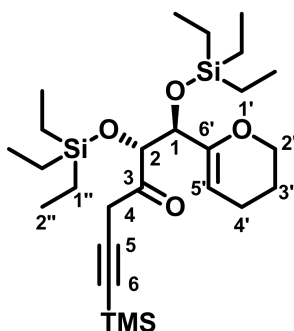
5-[(3*S,4*R**)-5-Hydroxy-3,4-bis(triethylsilyloxy)-5-[3-(trimethylsilyl)prop-2-yn-1-yl]tetrahydrofuran-2-yl]pentanal (2.183)**



To a stirred solution of 1-(trimethylsilyl)propyne (22 μL , 0.148 mmol) in anhydrous, degassed THF (0.35 mL) was added BuLi (1.6 M in hexanes, 0.1 mL, 0.16 mmol) at $-78\text{ }^\circ\text{C}$. After stirring for 1 h, a solution of lactone **2.168** (96 mg, 0.231 mmol) in anhydrous, degassed THF (0.75 mL) was added at $-78\text{ }^\circ\text{C}$. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h before NH_4Cl solution (1 mL) was added to quench the reaction. Ether (10 mL) and H_2O (10 mL) were added to dilute the solution where layers were separated. The aqueous layer was

extracted with ether (3×10 mL), and the combined organic layers were dried (MgSO_4) then concentrated. Flash chromatography (petrol/ether, 80:20) furnished the *title compound* (**2.183**) as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (5 mg, 8%). R_f (petrol/ether; 80:20) = 0.35; ^1H NMR (400 MHz, CDCl_3) δ 0.18 (9 H, s, SiCH_3 , **A** or **B**), 0.20 (9 H, s, SiCH_3 , **B** or **A**), 0.63–0.79 (24 H, m, H-1''', **A** and **B**), 0.98–1.08 (36 H, m, H-2''', **A** and **B**), 1.58–1.89 (8 H, m, H-3, H-4, **A** and **B**), 2.49–2.56 (4 H, m, H-2, **A** and **B**), 2.76–2.92 (4 H, m, H-1'', **A** and **B**), 3.72–3.79 (1 H, m, H-2', **A** or **B**), 3.83 (1 H, s, OH, **A** or **B**), 3.88 (1 H, t, $J_{3',2'} = J_{3',4'} = 2.0$ Hz, H-3', **A** or **B**), 4.00–4.03 (2 H, m, H-3', H-4', **B** or **A**), 4.05–4.11 (1 H, m, H-2', **B** or **A**), 4.20 (1 H, d, $J_{4',3'} = 2.0$ Hz, H-4', **A** or **B**), 4.52 (1 H, s, OH, **B** or **A**), 9.79–9.81 (2 H, m, H-1, **A** and **B**); ^{13}C NMR, IR and HRMS are missing.

(1*R,2*R**)-1-(3,4-Dihydro-2*H*-pyran-6-yl)-1,2-bis(triethylsilyloxy)-6-(trimethylsilyl)hex-5-yn-3-one (2.184)**

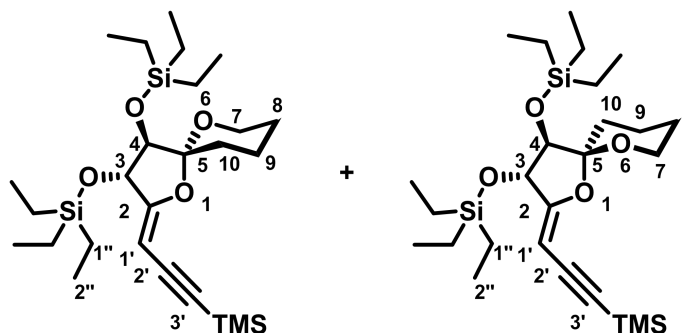


To a stirred solution of lactols **2.181** and **2.182** [a mixture of four diastereomers (*d.r.* not determined), 489 mg, 0.926 mmol] in DCM (27 mL) was added triethylamine (1 mL, 7.41 mmol) followed by methanesulfonyl chloride (289 μL , 3.74 mmol) at 0 °C. The resulting mixture was stirred at RT for 1 h then DCM (20 mL) and NaHCO_3 solution (sat. aq., 20 mL)

were added to dilute the solution. The aqueous layer was extracted with DCM (3×20 mL) and the combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**2.184**) as a side product as a colourless oil (32 mg, 6.7%). R_f (petrol/ether; 95:5) = 0.42; ^1H NMR (500 MHz, CDCl_3) δ 0.16 (9 H, s, SiCH_3), 0.58–0.63 (12 H, m, H-1''), 0.92–0.97 (18 H, m, H-2''), 1.73–1.81 (2 H, m, H-3'), 1.98–2.03 (2 H, m, H-4'), 3.51 (1 H, d, $J_{4,4} = 20.0$ Hz, $1 \times$ H-4), 3.63 (1 H, d, $J_{4,4} = 20.0$ Hz, $1 \times$ H-4), 3.82–3.95 (2 H, m, H-2'), 4.04 (1 H, d, $J_{1,2} = 4.5$ Hz, H-1), 4.21 (1 H, d, $J_{2,1} = 4.5$ Hz, H-2), 4.80 (1 H, t, $J_{5',4'} = 3.5$ Hz, H-5'); ^{13}C NMR (125 MHz, CDCl_3) δ 0.06 (SiCH_3), 4.7 (C-1''), 6.8 (C-2''), 19.8 (C-4'), 22.1 (C-3'), 32.1 (C-4), 65.7 (C-2'), 75.8 (C-1), 80.5 (C-2), 88.4 (C-6), 98.9 (C-5'), 99.3 (C-5), 151.5 (C-6'), 204.3 (C-3); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955 (s), 2877 (s), 2182 (m), 1733 (s), 1684 (m), 1460 (s), 1249 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{26}\text{H}_{50}\text{NaO}_4\text{Si}_3^+ [\text{MNa}]^+$ 533.2909, found 533.2907.

(3*R**,4*R**,5*R**,*Z*)-3,4-Bis(triethylsilyloxy)-2-[3-(trimethylsilyl)prop-2-yn-1-ylidene]-1,6-dioxaspiro[4.5]decane (**Z-2.185**) &

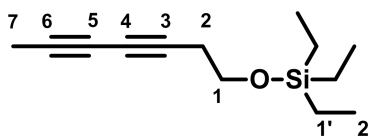
(3*R**,4*R**,5*S**,*Z*)-3,4-bis(triethylsilyloxy)-2-[3-(trimethylsilyl)prop-2-yn-1-ylidene]-1,6-dioxaspiro[4.5]decane (**Z-2.186**)



To a stirred solution of lactols **2.181** and **2.182** [a mixture of four diastereomers (*d.r.* not determined), 91 mg, 0.172 mmol] in DCM (5 mL) was added triethylamine (192 μ L, 1.38 mmol) followed by methanesulfonyl chloride (53.4 μ L, 0.688 mmol) at 0 °C. The resulting mixture was stirred at RT for 100 min then ether (5 mL) and NaHCO₃ solution (sat. aq., 5 mL) were added. The aqueous layer was extracted with ether (3 $\times$ 5 mL) and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 95:5) furnished the *title compounds* **Z-2.185** (56 mg, 64%) and **Z-2.186** (14 mg, 16%), both as colourless oils. **Data for Z-2.185:** *R_f* (petrol/ether; 95:5) = 0.79; ¹H NMR (500 MHz, CDCl₃) δ 0.20 (9 H, s, SiCH₃), 0.61–0.69 (12 H, m, H-1''), 0.94–1.00 (18 H, m, H-2''), 1.50–1.97 (6 H, m, H-8, H-9, H-10), 3.77 (1 H, dd, $J_{7eq,7ax}$ = 11.5 Hz, $J_{7eq,8ax}$ = 4.5 Hz, H-7_{eq}), 3.86 (1 H, d, $J_{4,3}$ = 7.5 Hz, H-4), 4.03 (1 H, td, $J_{7ax,7eq}$ = $J_{7ax,8ax}$ = 11.5 Hz, $J_{7ax,8eq}$ = 3.0 Hz, H-7_{ax}), 4.38 (1 H, dd, $J_{3,4}$ = 7.5 Hz, $J_{3,1'}$ = 1.5 Hz, H-3), 4.61 (1 H, d, $J_{1',3}$ = 1.5 Hz, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 0.17 (SiCH₃), 4.9, 5.0 (C-1''), 6.7, 6.8 (C-2''), 18.3 (C-9), 24.9 (C-8), 28.8 (C-10), 63.5 (C-7), 76.9 (C-3), 78.9 (C-1'), 82.3 (C-4), 97.2 (C-3'), 100.4 (C-2'),

107.1 (C-5), 166.2 (C-2); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2957 (s), 2879 (m), 2135 (w), 1665 (w), 1457 (m), 1247 (w), 1155 (m), 1116 (s), 1077 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{26}\text{H}_{50}\text{NaO}_4\text{Si}_3^+$ [MNa]⁺ 533.2909, found 533.2907. **Data for Z-2.186:** R_f (petrol/ether; 95:5) = 0.62; ¹H NMR (500 MHz, CDCl₃) δ 0.20 (9 H, s, SiCH₃), 0.63–0.73 (12 H, m, H-1''), 0.95–1.03 (18 H, m, H-2''), 1.55–2.02 (6 H, m, H-8, H-9, H-10), 3.72 (1 H, d, $J_{4,3}$ = 8.0 Hz, H-4), 3.81 (1 H, dd, $J_{7\text{eq},7\text{ax}}$ = 11.5 Hz, $J_{7\text{eq},8\text{ax}}$ = 4.0 Hz, H-7_{eq}), 3.95 (1 H, td, $J_{7\text{ax},7\text{eq}}$ = $J_{7\text{ax},8\text{ax}}$ = 11.5 Hz, $J_{7\text{ax},8\text{eq}}$ = 3.5 Hz, H-7_{ax}), 4.64 (1 H, d, $J_{1',3}$ = 2.0 Hz, H-1'), 4.73 (1 H, dd, $J_{3,4}$ = 8.0 Hz, $J_{3,1'}$ = 2.0 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 0.16 (SiCH₃), 5.1, 5.2 (C-1''), 6.8, 6.9 (C-2''), 19.0 (C-9), 24.7 (C-8), 31.2 (C-10), 62.7 (C-7), 76.1 (C-3), 79.0 (C-1'), 81.3 (C-4), 97.4 (C-3'), 100.2 (C-2'), 103.3 (C-5), 166.5 (C-2); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2956 (s), 2879 (s), 2136 (m), 1666 (m), 1458 (m), 1416 (m), 1247 (m), 1155 (m), 1128 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{26}\text{H}_{50}\text{NaO}_4\text{Si}_3^+$ [MNa]⁺ 533.2909, found 533.2910.

Triethyl(hepta-3,5-diyn-1-yloxy)silane (2.189)



● Synthesis of 1-iodoprop-1-yne 2.187

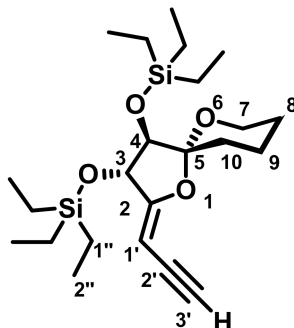
To a stirred solution of trimethyl(prop-1-yn-1-yl)silane (132 μL , 0.891 mmol) in freshly distilled acetone (9 mL) was added *N*-iodosuccinimide (260 mg, 1.16 mmol) and AgNO₃ (182 mg, 1.07 mmol) at RT. After stirring for 1 h in the dark, the white precipitate was filtered, and the filtrate was diluted with H₂O (15 mL) and petrol (15 mL). The layers were

separated; the aqueous layer was extracted with petrol (3×15 mL), and the combined organic layers were dried (MgSO_4) then concentrated carefully. The crude (50 mg, 33%), an oil, was used for next step without any purification.

● Synthesis of alkyne **2.189**

To a stirred solution of (but-3-yn-1-yloxy)triethylsilane (8.5 mg, 46.2 μmol) and freshly prepared 1-iodoprop-1-yne **2.187** (50 mg, 0.301 mmol) in degassed pyrrolidine (2.3 mL) was added CuI (2.5 mg, 13.1 μmol) at RT. The solution became green immediately. After stirring for 1.5 h, the reaction mixture became yellow and was diluted with H_2O (10 mL). The mixture was extracted with ether (3×20 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), then dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**2.189**) as a pale yellow oil (6 mg, 60%). R_f (petrol/ether; 97:3) = 0.66; ^1H NMR (500 MHz, CDCl_3) δ 0.61 (6 H, q, $J_{1',2'} = 8.0$ Hz, H-1'), 0.97 (9 H, t, $J_{2',1'} = 8.0$ Hz, H-2'), 1.91 (3 H, t, $J_{7,2} = 1.0$ Hz, H-7), 2.48 (2 H, tq, $J_{2,1} = 7.0$ Hz, $J_{2,7} = 1.0$ Hz, H-2), 3.73 (2 H, t, $J_{1,2} = 7.0$ Hz, H-1); ^{13}C NMR (125 MHz, CDCl_3) δ 4.3 (C-1'), 6.7 (C-2'), 23.6 (C-2), 29.7 (C-7), 61.2 (C-1), 64.3 (C-6), 66.4 (C-4), 73.3 (C-3), 73.5 (C-5); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2917 (s), 2251 (w), 1461 (m), 1383 (m), 1261 (s), 1102 (s), 1016 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{13}\text{H}_{22}\text{NaOSi}^+ [\text{MNa}]^+$ 245.1332, found 245.1333.

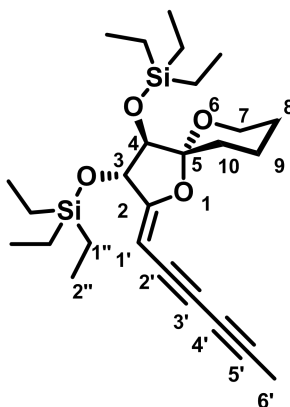
(3*R,4*R**,5*R**,*Z*)-3,4-Bis(triethylsilyloxy)-2-(prop-2-yn-1-ylidene)-1,6-dioxaspiro[4.5]decane (2.190)**



To a stirred solution of spiroketal **Z-2.185** (264 mg, 0.517 mmol) in absolute ethanol (8.8 mL) was added a solution of AgNO₃ (352 mg in 8.8 mL H₂O) at 0 °C. A white suspension formed immediately, and the mixture was stirred for 1 h in the dark. The reaction was diluted with DCM (100 mL) and transferred into a rapidly stirred solution of KCN (808 mg, 12.4 mmol in 176 mL H₂O). The mixture was extracted with DCM (3 × 100 mL), and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**2.190**) as a colourless oil (175 mg, 78%). *R_f* (petrol/ether; 95:5) = 0.87; ¹H NMR (500 MHz, CDCl₃) δ 0.63–0.70 (12 H, m, H-1''), 0.94–1.02 (18 H, m, H-2''), 1.54–1.98 (6 H, m, H-8, H-9, H-10), 3.05 (1 H, d, *J*_{3',1'} = 2.5 Hz, H-3'), 3.77 (1 H, dd, *J*_{7eq,7ax} = 11.5 Hz, *J*_{7eq,8ax} = 4.5 Hz, H-7eq), 3.86 (1 H, d, *J*_{4,3} = 7.0 Hz, H-4), 4.04 (1 H, td, *J*_{7ax,7eq} = *J*_{7ax,8ax} = 11.5 Hz, *J*_{7ax,8eq} = 3.0 Hz, H-7ax), 4.39 (1 H, dd, *J*_{3,4} = 7.0 Hz, *J*_{3,1'} = 1.5 Hz, H-3), 4.55–4.56 (1 H, m, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 4.9, 5.0 (C-1''), 6.7, 6.8 (C-2''), 18.3 (C-9), 24.8 (C-8), 28.8 (C-10), 63.4 (C-7), 76.8 (C-3), 77.7 (C-1'), 78.9 (C-2'), 80.1 (C-3'), 82.2 (C-4), 107.4 (C-5), 166.4 (C-2); IR (film) *v*_{max}/cm⁻¹ 3316 (w), 2955 (s), 2878 (s), 2103 (w), 1668 (m), 1458 (m), 1236 (s), 1114 (s); HRMS (ESI⁺) *m/z* calcd. for

$C_{23}H_{42}NaO_4Si_2^+ [MNa]^+$ 461.2514, found 461.2505.

(3*R,4*R**,5*R**,*Z*)-3,4-Bis(triethylsilyloxy)-2-(hexa-2,4-dyn-1-ylidene)-1,6-dioxaspiro[4.5]decane (Z-2.191)**



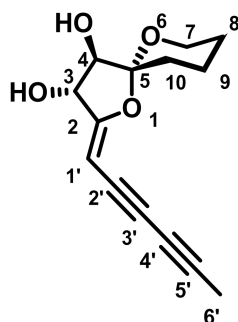
● Synthesis of 1-iodoprop-1-yne 2.187

To a stirred solution of trimethyl(prop-1-yn-1-yl)silane (1 mL, 6.75 mmol) in freshly distilled acetone (48 mL) was added *N*-iodosuccinimide (1.96 g, 8.71 mmol) and $AgNO_3$ (1.36 g, 8.00 mmol) at RT. After stirring for 1 h in the dark, the white precipitate was filtered, and the filtrate was diluted with H_2O (150 mL) and petrol (150 mL). The layers were separated; the aqueous layer was extracted with petrol (3×150 mL), and the combined organic layers were dried ($MgSO_4$) then concentrated carefully. The crude (346 mg, 31%), an oil, was used for next step without any purification.

● Synthesis of alkyne Z-2.191

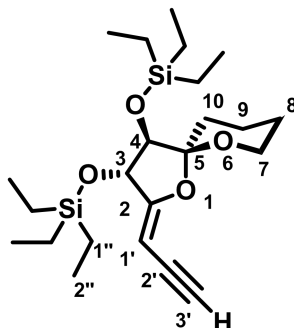
To a stirred solution of alkyne **2.190** (88 mg, 0.20 mmol) and freshly prepared 1-iodoprop-1-yne (346 mg, 2.08 mmol) in degassed pyrrolidine (10.1 mL) was added CuI

(11.5 mg, 60.5 μ mol) at RT. The solution became green immediately. After stirring for 1.5 h, the reaction mixture became yellow and was diluted with H₂O (50 mL). The mixture was extracted with ether (3 $\times$ 50 mL) and the combined organic layers were washed with H₂O (50 mL), brine (50 mL), then dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**Z-2.191**) as a pale yellow oil (68 mg, 71%). R_f (petrol/ether; 95:5) = 0.61; ¹H NMR (500 MHz, CDCl₃) δ 0.62–0.69 (12 H, m, H-1''), 0.95–1.00 (18 H, m, H-2''), 1.51–1.95 (6 H, m, H-8, H-9, H-10), 1.99 (3 H, s, H-6'), 3.76 (1 H, dd, $J_{7eq,7ax}$ = 11.5 Hz, $J_{7eq,8ax}$ = 4.5 Hz, H-7_{eq}), 3.85 (1 H, d, $J_{4,3}$ = 7.0 Hz, H-4), 4.04 (1 H, td, $J_{7ax,7eq}$ = $J_{7ax,8ax}$ = 11.5 Hz, $J_{7ax,8eq}$ = 3.0 Hz, H-7_{ax}), 4.38 (1 H, dd, $J_{3,4}$ = 7.0 Hz, $J_{3,1'}$ = 1.0 Hz, H-3), 4.57 (1 H, d, $J_{1',3}$ = 1.0 Hz, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 4.7 (C-6'), 4.8, 5.0 (C-1''), 6.7, 6.8 (C-2''), 18.2 (C-9), 24.8 (C-8), 28.7 (C-10), 63.5 (C-7), 65.2 (C-4'), 70.0 (C-2'), 77.1 (C-3'), 77.2 (C-3), 77.8 (C-1'), 79.1 (C-5'), 82.1 (C-4), 107.7 (C-5), 167.9 (C-2); IR (film) ν_{max}/cm^{-1} 2956 (s), 2144 (w), 1660 (m), 1458 (m), 1240 (m), 1155 (s); HRMS (ESI⁺) m/z calcd. for C₂₆H₄₄NaO₄Si₂⁺ [MNa]⁺ 499.2670, found 499.2662.

(3*R,4*R**,5*R**,*Z*)-2-(Hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane-3,4-diol (2.192)**

To a stirred solution of bis(silyl ether) **Z-2.191** (60 mg, 0.126 mmol) in THF (2.5 mL) was added TBAF solution (1.0 M in THF, 0.3 mL, 0.300 mmol) at 0 °C. The resulting mixture was warmed to RT and stirred for 1 h. H₂O (10 mL) and ether (15 mL) were added to the reaction mixture and the layers were separated. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were dried (MgSO₄) then concentrated. Flash chromatography (DCM/methanol, 95:5) furnished the *title compound* (**2.192**) as a colourless oil (31 mg, 100%). *R_f* (DCM/methanol; 95:5) = 0.34; ¹H NMR (500 MHz, CDCl₃) δ 1.62–2.04 (6 H, m, H-8, H-9, H-10), 2.00 (3 H, s, H-6'), 2.86 (1 H, d, *J*_{OH,3} = 11.5 Hz, C(3)OH), 3.73–3.78 (2 H, m, H-7_{eq}, C(4)OH), 3.93 (1 H, d, *J*_{4,OH} = 5.5 Hz, H-4), 4.01 (1 H, td, *J*_{ax,7eq} = *J*_{ax,8ax} = 11.0 Hz, *J*_{ax,8eq} = 4.0 Hz, H-7_{ax}), 4.24 (1 H, d, *J*_{3,OH} = 11.5 Hz, H-3), 4.91 (1 H, s, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 4.7 (C-6'), 18.5 (C-9), 24.6 (C-8), 27.4 (C-10), 62.9 (C-7), 64.9 (C-4'), 69.2 (C-2'), 77.6 (C-3), 78.2 (C-3'), 79.4 (C-4), 80.1 (C-5'), 82.8 (C-1'), 110.1 (C-5), 168.7 (C-2); IR (film) *v*_{max}/cm⁻¹ 3398 (br), 2950 (s), 2192 (m), 1739 (s), 1656 (s), 1217 (s), 1136 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₄H₁₆NaO₄⁺ [MNa]⁺ 271.0941, found 271.0941.

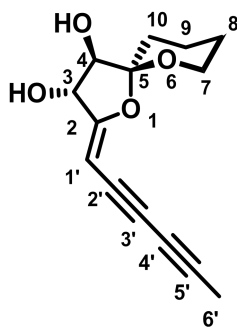
(3*R,4*R**,5*S**,*Z*)-3,4-Bis(triethylsilyloxy)-2-(prop-2-yn-1-ylidene)-1,6-dioxaspiro[4.5]decane (2.193)**



To a stirred solution of spiroketal **Z-2.186** (66 mg, 0.129 mmol) in absolute ethanol (2.2 mL) was added a solution of AgNO₃ (88 mg in 2.2 mL H₂O) at 0 °C. A white suspension formed immediately, and the mixture was stirred for 1 h in the dark. The reaction was diluted with DCM (20 mL) and transferred into a rapidly stirred solution of KCN (202 mg, 3.10 mmol in 44 mL H₂O). After 2 min, the mixture was extracted with DCM (3 × 20 mL), and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 97:3) furnished the *title compound* (**2.193**) as a colourless oil (44 mg, 79%). *R_f* (petrol/ether; 95:5) = 0.76; ¹H NMR (500 MHz, CDCl₃) δ 0.63–0.74 (12 H, m, H-1''), 0.96–1.04 (18 H, m, H-2''), 1.54–2.06 (6 H, m, H-8, H-9, H-10), 3.06 (1 H, d, *J*_{3',1'} = 1.5 Hz, H-3'), 3.72 (1 H, d, *J*_{4,3} = 8.0 Hz, H-4), 3.81 (1 H, dd, *J*_{7eq,7ax} = 11.5 Hz, *J*_{7eq,8ax} = 4.5 Hz, H-7_{eq}), 3.94 (1 H, td, *J*_{7ax,7eq} = *J*_{7ax,8ax} = 11.5 Hz, *J*_{7ax,8eq} = 3.0 Hz, H-7_{ax}), 4.59 (1 H, t, *J*_{1',3} = *J*_{1',3'} = 1.5 Hz, H-1'), 4.74 (1 H, dd, *J*_{3,4} = 8.0 Hz, *J*_{3,1'} = 1.5 Hz, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 5.1, 5.3 (C-1''), 6.8, 6.9 (C-2''), 19.0 (C-9), 24.6 (C-8), 31.1 (C-10), 62.7 (C-7), 76.1 (C-3), 77.8 (C-1'), 78.8 (C-2'), 80.2 (C-3'), 81.2 (C-4), 103.5 (C-5), 166.6 (C-2); IR (film) *v*_{max}/cm⁻¹ 3316 (m), 2956 (s), 2878 (s), 2104 (w), 1670 (m), 1459 (m), 1238 (m), 1127

(m), 1048 (m); HRMS (ESI⁺) m/z calcd. for C₂₃H₄₂NaO₄Si₂⁺ [MNa]⁺ 461.2514, found 461.2511.

(3*R,4*R**,5*S**,*Z*)-2-(Hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane-3,4-diol (2.194)**

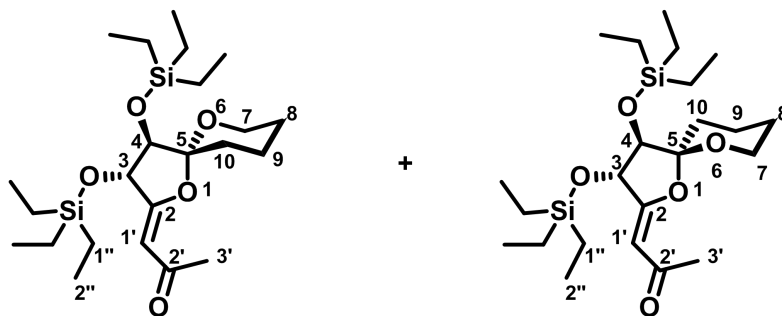


To a stirred solution of bis(silyl ether) **Z-2.169** (10 mg, 21.0 μ mol) in THF (0.4 mL) was added TBAF solution (1.0 M in THF, 52.5 μ L, 52.5 μ mol) at 0 °C. The resulting mixture was warmed to RT and stirred for 1 h. H₂O (5 mL) and ether (5 mL) were added to the reaction mixture and the layers were separated. The aqueous layer was extracted with ether (3 $\times$ 5 mL), and the combined organic layers were dried (MgSO₄) and concentrated. Preparative TLC (DCM/methanol, 95:5) furnished the *title compound* (**2.194**) as a colourless oil (5 mg, 100%). R_f (DCM/methanol; 95:5) = 0.37; ¹H NMR (500 MHz, CDCl₃) δ 1.54–2.05 (6 H, m, H-8, H-9, H-10), 2.00 (3 H, s, H-6'), 2.25–2.73 (2 H, br.s, 2 $\times$ OH), 3.63 (1 H, d, $J_{4,3}$ = 7.5 Hz, H-4), 3.81 (1 H, app.d, $J_{7eq,7ax}$ = 11.0 Hz, H-7_{eq}), 3.98 (1 H, td, $J_{7ax,7eq}$ = $J_{7ax,8ax}$ = 11.0 Hz, $J_{7ax,8eq}$ = 3.5 Hz, H-7_{ax}), 4.63 (1 H, d, $J_{3,4}$ = 7.5 Hz, H-3), 4.77 (1 H, s, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 4.7 (C-6'), 18.5 (C-9), 24.5 (C-8), 30.5 (C-10), 63.2 (C-7), 64.9 (C-4'), 69.1 (C-2'), 76.5 (C-3), 77.8 (C-3'), 79.2 (C-1'), 79.7 (C-5'), 80.8 (C-4), 103.5 (C-5), 168.7 (C-2); IR (film) ν_{max}/cm^{-1} 3398 (br), 2926 (s), 2182 (w), 1738 (s), 1662 (s), 1259 (m), 1131 (s),

1109 (s); HRMS (ESI⁺) m/z calcd. for C₁₄H₁₆NaO₄⁺ [MNa]⁺ 271.0941, found 271.0942.

(Z)-1-(3*R,4*R**,5*R**)-3,4-Bis(triethylsilyloxy)-1,6-dioxaspiro[4.5]decan-2-ylidenepropan-2-one (2.195) &**

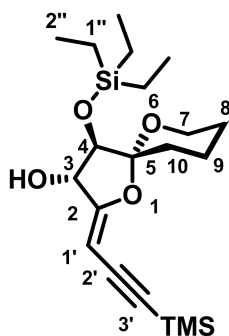
(Z)-1-(3*R,4*R**,5*S**)-3,4-bis(triethylsilyloxy)-1,6-dioxaspiro[4.5]decan-2-ylidenepropan-2-one (2.196)**



To a solution of spiroketal **Z-2.185** (5 mg, 9.8 μ mol) in CDCl₃ (0.7 mL) was added TfOH solution (0.5% in CDCl₃, 1 μ L, 0.06 μ mol). The resulting mixture was stored at RT until complete consumption of starting material, preparative TLC furnished the *title compounds* **2.195** (2 mg, 45%) and **2.196** (2 mg, 45%), both as colourless oils. **Data for 2.195:** R_f (petrol/ethyl acetate; 80:20) = 0.63; ¹H NMR (500 MHz, CDCl₃) δ 0.65–0.71 (12 H, m, H-1''), 0.97–1.01 (18 H, m, H-2''), 1.61–1.86 (6 H, H-8, H-9, H-10), 2.40 (3 H, s, H-3'), 3.85–3.90 (1 H, m, 1 $\times$ H-7), 3.93 (1 H, d, $J_{4,3}$ = 7.5 Hz, H-4), 3.96–3.99 (1 H, m, 1 $\times$ H-7), 4.46 (1 H, dd, $J_{3,4}$ = 7.5 Hz, $J_{3,1'}$ = 1.0 Hz, H-3), 5.18 (1 H, d, $J_{1',3}$ = 1.0 Hz, H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 4.8, 5.0 (C-1''), 6.7, 6.8 (C-2''), 18.3 (C-9), 24.7 (C-8), 28.6 (C-10), 31.1 (C-3'), 64.1 (C-7), 77.8 (C-3), 81.6 (C-4), 102.3 (C-1'), 109.1 (C-5), 167.9 (C-2), 197.4

(C-2'); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2970 (w), 1738 (s), 1436 (m), 1366 (s), 1229 (s), 1217 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{23}\text{H}_{44}\text{NaO}_5\text{Si}_2^+ [\text{MNa}]^+$ 479.2619, found 479.2605. **Data for 2.196:** R_f (petrol/ethyl acetate; 80:20) = 0.55; ¹H NMR (500 MHz, CDCl_3) δ 0.68–0.74 (12 H, m, H-1''), 0.98–1.04 (18 H, m, H-2''), 1.62–1.94 (6 H, m, H-8, H-9, H-10), 2.39 (3 H, s, H-3'), 3.81 (1 H, d, $J_{4,3} = 8.0$ Hz, H-4), 3.84–3.94 (2 H, m, H-7), 4.80 (1 H, d, $J_{3,4} = 8.0$ Hz, H-3), 5.22 (1 H, s, H-1'); ¹³C NMR (125 MHz, CDCl_3) δ 5.1, 5.3 (C-1''), 6.8 (C-2''), 19.2 (C-9), 24.4 (C-8), 31.1 (C-3'), 31.4 (C-10), 63.3 (C-7), 77.2 (C-3), 80.7 (C-4), 102.6 (C-1'), 105.1 (C-5), 168.4 (C-2), 197.5 (C-2'); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2970 (w), 1739 (s), 1436 (m), 1366 (s), 1229 (s), 1217 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{23}\text{H}_{44}\text{NaO}_5\text{Si}_2^+ [\text{MNa}]^+$ 479.2619, found 479.2602.

(3*R,4*R**,5*R**,*Z*)-4-(Triethylsilyloxy)-2-[3-(trimethylsilyl)prop-2-yn-1-ylidene]-1,6-dioxaspiro[4.5]decan-3-ol (2.197)**



A solution of spiroketal **Z-2.185** (30 mg, 58.8 μmol) in a mixture of H_2O , THF, and acetone (2:10:1, 3 mL) was treated with oxalic acid (5 mg, 55.5 μmol) and stirred for 14 h. Ether (10 mL) and NaHCO_3 solution (sat. aq., 10 mL) were added to dilute the solution and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were dried (MgSO_4) then concentrated, and flash chromatography (petrol/ethyl acetate, 95:5) furnished

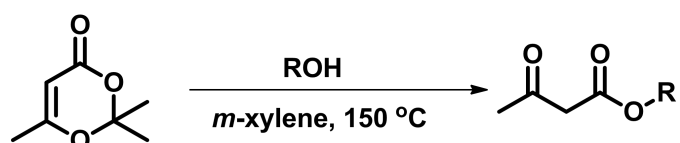
the *title compound* (**2.197**) as a colourless oil (5 mg, 25%). R_f (petrol/ethyl acetate; 95:5) = 0.36; ^1H NMR (500 MHz, CDCl_3) δ 0.21 (9 H, s, SiCH_3), 0.63 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.52–1.59 (1 H, m, H-10_{ax}), 1.60–1.70 (2 H, m, H-8), 1.73–1.81 (1 H, m, H-9_{eq}), 1.85–1.97 (1 H, m, H-9_{ax}), 2.04 (1 H, dt, $J_{10\text{eq},10\text{ax}} = 13.5$ Hz, $J_{10\text{eq},9\text{ax}} = 3.0$ Hz, H-10_{eq}), 2.73 (1 H, d, $J_{\text{OH},3} = 11.5$ Hz, C(3)OH), 3.73 (1 H, dt, $J_{7\text{eq},7\text{ax}} = 11.0$ Hz, $J_{7\text{eq},8\text{ax}} = 2.5$ Hz, H-7_{eq}), 3.85 (1 H, app.s, H-4), 4.00 (1 H, td, $J_{7\text{ax},7\text{eq}} = J_{7\text{ax},8\text{ax}} = 11.0$ Hz, $J_{7\text{ax},8\text{eq}} = 4.0$ Hz, H-7_{ax}), 4.10 (1 H, d, $J_{3,\text{OH}} = 11.5$ Hz, H-3), 4.88 (1 H, s, H-1'); ^{13}C NMR (125 MHz, CDCl_3) 0.09 (SiCH_3), 4.6 (C-1''), 6.7 (C-2''), 18.8 (C-9), 24.9 (C-8), 27.8 (C-10), 62.8 (C-7), 78.1 (C-3), 80.3 (C-4), 83.0 (C-1'), 98.1 (C-2'), 100.1 (C-3'), 110.3 (C-5), 167.9 (C-2); IR (film) 2955 (m), 2133 (w), 1739 (s), 1661 (w), 1366 (m), 1217 (m), 1120 (m), 1096 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{20}\text{H}_{36}\text{NaO}_4\text{Si}_2^+ [\text{MNa}]^+$ 419.2044, found 419.2033.

Experimental Procedures and characterisation data for compounds in Chapter 3:

Logical synthesis using enzymatic reduction as a key step

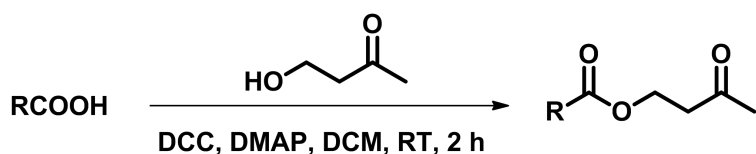
General procedures for substrate synthesis for enzymatic reduction

General procedure A



A mixture of dioxinone **3.39** (187 μ L, 1.41 mmol) and the corresponding alcohol (1.69 mmol) in *m*-xylene (1.4 mL) was heated under reflux with vigorous stirring for a total of 30 min then the mixture was cooled to RT. The product was obtained by flash chromatography (petrol/ethyl acetate, 70:30) as a colourless oil.

General procedure B



To a solution of the acid (1.36 mmol) and DMAP (84 mg, 0.686 mmol) in DCM (2 mL) was added a solution of alcohol **3.33** (100 mg, 1.14 mmol) in DCM (2 mL). A solution of DCC (282 mg, 1.36 mmol) in DCM (2 mL) was then added and the resulting mixture was stirred at RT for 2 h before being filtered, eluting with DCM (10 mL). The filtrate was washed with hydrochloric acid (1.0 M in H₂O, 5 mL), H₂O (5 mL), brine (5 mL), then dried (MgSO₄) and

concentrated. Flash chromatography (petrol/ethyl acetate, 70:30) furnished the product as a colourless oil.

General procedure for enzymatic reduction

General procedure C

To a solution of diketone (1 eq.) and D-glucose (3 eq.) in 0.2 M phosphate buffer* (diketone concentration = 0.2 M) was added alcohol dehydrogenase from *Lactobacillus brevis* (ADH-LB, 4.8 kU/mL, 100 U/mmol substrate), glucose dehydrogenase (GDH, 75 U/mg, 103 U/mmol substrate) and β -NADP disodium salt (2×10^{-3} eq.). The resulting mixture was stirred at 30 °C for 1–2 h depending on substrate. The pH value, monitored by pH probe, was maintained between 5.0 and 6.0 by dropwise addition of NaOH solution (5.0 M in H₂O) (Caution! The base should be added as slowly as possible to avoid decomposition or base-catalysed reactions of the starting material). Formation of a white precipitate/gel led to ‘milky’ of the solution. TLC analysis showed full conversion of the starting material and formation of product. The reaction mixture was diluted with H₂O (10 mL) and extracted with ethyl acetate (4 $\times$ 5 mL). The combined organic layers were dried (MgSO₄) and evaporated. Flash chromatography (petrol/ethyl acetate/triethylamine, 20:80:3) furnished the *title compounds* as colourless oils.

*0.2 M Phosphate buffer preparation: Na₂HPO₄ solution (0.2 M in H₂O) was added to a solution of NaH₂PO₄ (0.2 M in H₂O) until a pH of 7 was reached.

General procedure for Mosher's ester derivatisation**General procedure D**

To a solution of alcohol (1 eq.) and DMAP (1.6 eq. for each eq. of hydroxyl within the alcohol) in THF (alcohol concentration = 0.2 M) was added MTPA (racemic^{ag} or enantiomerically pure MTPA, 1.1 eq. for each eq. of hydroxyl within the alcohol) at 0 °C. The resulting white suspension was stirred at RT for 2 h before dilution with H₂O and DCM. The organic layer was washed with H₂O, dried (MgSO₄) and concentrated. The residue was passed through a short pad of silica with DCM eluting, and the filtrate was concentrated to furnish the Mosher's ester for NMR analysis.

General procedure for methanolysis of enzymatically reduced diketones**General procedure E**

To a solution of ester (1 eq.) in methanol (ester concentration = 0.2 M) was added NaOMe (0.6 eq.) at 0 °C and the resulting mixture was stirred at RT for 2 h. The reaction was quenched with NH₄Cl solution (sat. aq.), and the mixture was extracted with ethyl acetate. The combined organic layers were washed with H₂O and brine, then dried and concentrated. Flash chromatography furnished the product.

General procedure for further reduction of enzymatically reduced diketones**General procedure F**

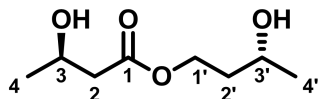
LiAlH₄ (2 eq.) was added to a solution of ester (1 eq.) in anhydrous ether (ester concentration = 0.1 M) at 0 °C. The resulting mixture was allowed to warm to RT and stirred for an

^{ag} The racemic MTPA-Cl treatment was done by adding 50% (*R*)-MTPA-Cl followed by 50% (*S*)-MTPA-Cl in the reaction mixture.

additional 30 min. The reaction was then carefully quenched at 0 °C with H₂O, NaOH solution (10% in H₂O), and H₂O. After the mixture was stirred for a further 20 min, the precipitate was filtered off and washed with ether. The filtrate was then washed with brine and the organic layer was dried (MgSO₄) and concentrated. Flash chromatography furnished the product.

3-Oxobutyl 3-oxobutanoate (3.19) &**(Z)-3-oxobutyl 3-hydroxybut-2-enoate (3.19 enol form)²⁴**

The title compounds were prepared by applying general procedure A to 4-hydroxybutan-2-one. The product (**3.19**), as a mixture of **keto** and **enol** forms (**keto:enol** = 9.5:1), was obtained as a colourless oil (177 mg, 73%). R_f (petrol/ether; 70:30) = 0.42; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3467 (w), 2970 (w), 1739 (s), 1720 (s), 1670 (w), 1365 (m), 1229 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_8\text{H}_{12}\text{NaO}_4$ $[\text{MNa}]^+$ 195.0628, found 195.0634. **NMR data for keto form:** ^1H NMR (500 MHz, CDCl_3) δ 2.19 (3 H, s, H-4'), 2.25 (3 H, s, H-4), 2.79 (2 H, t, $J_{2,1'} = 6.0$ Hz, H-2'), 3.43 (2 H, s, H-2), 4.40 (2 H, t, $J_{1',2'} = 6.0$ Hz, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 30.1 (C-4'), 30.2 (C-4), 41.9 (C-2'), 49.9 (C-2), 60.0 (C-1'), 166.9 (C-1), 200.4 (C-3), 205.3 (C-3'); **NMR data for enol form:** ^1H NMR (500 MHz, CDCl_3) δ 1.94 (3 H, s, H-4), 2.19 (3 H, s, H-4'), 2.79 (2 H, t, $J_{2',1'} = 6.0$ Hz, H-2'), 4.40 (2 H, t, $J_{1',2'} = 6.0$ Hz, H-1'), 4.95 (1 H, s, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ 21.2 (C-4), 30.2 (C-4'), 42.3 (C-2'), 58.7 (C-1'), 89.5 (C-2), 172.3 (C-1), 175.9 (C-3), 205.6 (C-3').

(3*R*)-Hydroxybutyl (3*R*)-hydroxybutanoate (3.20)²⁴**Method 1: DMF as solvent**

A mixture of cyclic sulfate **3.30** (50 mg, 0.33 mmol) and potassium carboxylate **3.29** (56 mg, 0.40 mmol) in DMF (0.5 mL) was stirred at RT to become a clear solution. Stirring was continued for 2 h until TLC analysis showed complete consumption of cyclic sulfate **3.30**. The reaction mixture was concentrated then THF (1 mL), H₂O (4 µL), and concentrated H₂SO₄ (10.5 µL) were added. The solution became cloudy. The mixture was stirred for 1 h at RT, followed by addition of solid NaHCO₃ (168 mg, 2.00 mmol). Stirring was continued for 20 min. Solids were filtered out and washed with ethyl acetate (20 mL). The combined filtrates were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate; 20:80) furnished the title compound (**3.20**) as a colourless oil (53 mg, 91%).

Method 2: MeCN as solvent

A mixture of cyclic sulfate **3.30** (50 mg, 0.33 mmol) and potassium carboxylate **3.29** (56 mg, 0.40 mmol) in MeCN (1.7 mL) was heated under reflux. Upon heating, the mixture became a clear solution. Stirring was continued until TLC analysis showed complete consumption of the cyclic sulfate **3.30**. The reaction mixture was concentrated then THF (1 mL), H₂O (4 µL), and concentrated H₂SO₄ (10.5 µL) were added. The solution became cloudy again. The mixture was stirred for 1 h at RT, followed by the addition of solid NaHCO₃ (168 mg, 2.00 mmol). Stirring was continued for 20 min. Solids were filtered out and washed with ethyl

acetate (20 mL). The combined filtrates were concentrated. Flash chromatography (petrol/ethyl acetate; 20:80) furnished the title compound (**3.20**) as a colourless oil (59 mg, 100%).

Method 3: Enzymatic method

To a solution of diketone **3.19** (160 mg, 0.920 mmol) and D-glucose (496 mg, 2.76 mmol) in 0.2 M phosphate buffer* (4 mL) was added alcohol dehydrogenase from *Lactobacillus brevis* (ADH-LB, 4.8 kU/mL, 19.2 μ L, 92.2 U), glucose dehydrogenase (GDH, 75 U/mg, 1.5 mg, 109 U) and β -NADP disodium salt (1.5 mg, 0.19 μ mol). The resulting mixture was stirred at 30 °C for 18 h. The pH value was maintained between 5.0 to 6.0 by dropwise addition of NaOH solution (5.0 M in H₂O) (Caution! The base should be added as slowly as possible to avoid decomposition or base-catalysed side reactions of the starting material). Formation of a white precipitate/gel led to 'milky' of the solution. TLC analysis showed full conversion of the starting material and formation of the product. The reaction mixture was diluted with H₂O (10 mL) and extracted with ethyl acetate (4 $\times$ 5 mL). The combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate/triethylamine, 20:80:3) furnished the title compound (**3.20**, 115 mg, 70%) as a colourless oil [*d.r.* > 99:1 (¹H NMR); *e.e.* >99%^{ah}] together with side product **3.41** (7 mg, 5%) as a colourless oil.

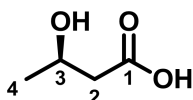
*0.2 M Phosphate buffer preparation: Na₂HPO₄ solution (0.2 M in H₂O) was added to a solution of NaH₂PO₄ (0.2 M in H₂O) until a pH of 7 was reached.

R_f (petrol/ethyl acetate; 20:80) = 0.29; [α]_D²⁵ –54.6 (*c* 0.92, CHCl₃); ¹H NMR (500 MHz,

^{ah} The *e.e.* of **3.20** was determined by HPLC in the literature (Robertson, J.; Clarke, K.; Veech, R. L., WO 2010/120300).

CDCl₃) δ 1.21–1.23 (6 H, m, H-4, H-4'), 1.69–1.82 (2 H, m, H-2'), 2.40–2.51 (2 H, m, H-2), 3.86–3.93 (1 H, m, H-3'), 4.16–4.23 (2 H, m, 1 $\times$ H-1', H-3), 4.32–4.37 (1 H, m, 1 $\times$ H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 22.5 (C-4'), 23.6 (C-4), 37.7 (C-2'), 43.0 (C-2), 62.1 (C-1'), 64.2 (C-3), 65.0 (C-3'), 173.0 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3390 (br), 2970 (w), 1737 (s), 1367 (m), 1217 (m), 1090 (w); HRMS (ESI⁺) m/z calcd. for C₈H₁₆NaO₄⁺ [MNa]⁺ 199.0941, found 199.0939.

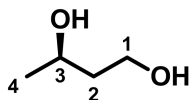
(3*R*)-Hydroxybutanoic acid (3.23)²⁵



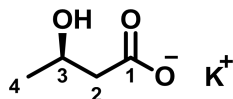
To a solution of ester **3.35** (590 mg, 0.500 mmol) in THF (37.5 mL) and MeOH (12.5 mL) was added aqueous KOH solution (1.0 M in H₂O, 15 mL, 15.0 mmol). The resulting mixture was stirred for 3 h at RT. When TLC analysis showed the completion of the reaction, the mixture was concentrated to half of the original volume under reduced pressure. The residue was poured into a mixture of ethyl acetate (50 mL) and hydrochloric acid (1.0 M in H₂O, 50 mL). The aqueous layer was extracted further with ethyl acetate (10 $\times$ 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (DCM/MeOH; 94:6) furnished the title compound (**3.23**) as a white solid (434 mg, 84%). R_f (DCM/MeOH/acetic acid; 95:5:3) = 0.31; $[\alpha]_D^{25}$ -48.3 (c 0.58, CHCl₃), lit²⁵ $[\alpha]_D^{22}$ -23.5 (c 2.20, MeOH); m.p. = 44–46 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (3 H, d, $J_{4,3}$ = 6.5 Hz, H-4), 2.45–2.57 (2 H, m, H-2), 4.20–4.28 (1 H, m, H-3), 7.15–7.46 (1 H, br.s, C(3)OH); ¹³C NMR (100 MHz, CDCl₃) δ 22.3 (C-4), 42.5 (C-2), 64.4 (C-3), 177.3 (C-1); IR (thin film)

$\nu_{\max}/\text{cm}^{-1}$ 2977 (m), 1710 (s), 1407 (m), 1293 (m), 1188 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_4\text{H}_7\text{Na}_2\text{O}_3^+ [\text{M}-\text{H}+2\text{Na}]^+$ 149.0185, found 149.0186.

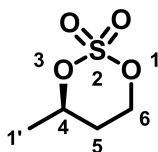
(3*R*)-Butane-1,3-diol (3.24)²⁶



To a suspension of LiAlH_4 (667 mg, 17.6 mmol) in anhydrous THF (30 mL) was added portionwise PHB (2.00 g, 23.3 mmol) at 15 °C. The reaction mixture was stirred at RT for 2 h, heated under reflux for 5 h, then cooled to RT and stirred for 14 h. The suspension was cooled to 0 °C, and successively treated with H_2O (0.7 mL), NaOH solution (10% in H_2O , 0.7 mL) and H_2O (2 mL). The mixture was stirred for 30 min until the grey suspension became white, then the solids were filtered through a short pad of Celite[®] and washed with ethyl acetate (50 mL). The filtrate was dried (MgSO_4) and concentrated to furnish the title compound **(3.24)** as a colourless oil (1.95 g, 93%). R_f (ethyl acetate) = 0.20; $[\alpha]_{\text{D}}^{25} -19.0$ (c 1.00, CHCl_3), lit²⁷ $[\alpha]_{\text{D}}^{22} -30.1$ (c 1.66, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.21 (3 H, d, $J_{4,3} = 6.5$ Hz, H-4), 1.64–1.70 (2 H, m, H-2), 3.25–3.42 (2 H, br.s, $2 \times \text{OH}$), 3.75–3.87 (2 H, m, H-1), 4.00–4.08 (1 H, m, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ 23.7 (C-4), 40.0 (C-2), 61.3 (C-1), 68.0 (C-3); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3316 (br), 2967 (m), 2932 (m), 1417 (m), 1375 (m), 1051 (s); HRMS (FI⁺) m/z calcd. for $\text{C}_4\text{H}_{10}\text{O}_2^+ [\text{M}]^+$ 90.0681, found 90.0679.

Potassium (3*R*)-hydroxybutanoate (3.29)²⁸

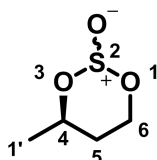
To a solution of acid **3.23** (395 mg, 3.79 mmol) in DCM (4.5 mL) and MeCN (4.5 mL) was added KOH solution (2.0 M in H₂O, 2 mL, 4.00 mmol). After vigorous stirring for 4 h at RT, the mixture was concentrated to furnish the title compound (**3.29**) as a white solid (538 mg, 100%). $[\alpha]_D^{22} -25.5$ (*c* 1.00, MeOH); m.p. = 46–48 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.20 (3 H, d, $J_{4,3} = 6.5$ Hz, H-4), 2.33 (2 H, d, $J_{2,3} = 6.5$ Hz, H-2), 4.08–4.14 (1 H, m, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 23.1 (C-4), 46.5 (C-2), 66.3 (C-3), 179.3 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3349 (br), 2482 (br), 2071 (m), 1568 (s), 1403 (m), 1120 (m); HRMS (ESI⁺) *m/z* calcd. for C₄H₇K₂O₃⁺ [M–H+2K]⁺ 180.9664, found 180.9666.

(4*R*)-Methyl-1,3,2-dioxathiane 2,2-dioxide (3.30)²⁹

To a stirred mixture of NaIO₄ (1.02 g, 4.77 mmol) in H₂O (2.3 mL) was added a solution of RuCl₃·3H₂O (0.1 M in H₂O, 740 μ L, 74.0 μ mol). The mixture was cooled to 0 °C, and a solution of cyclic sulfite **3.34** (500 mg, 3.67 mmol) in CHCl₃ (0.8 mL) was added. Stirring was continued for 3 h. The resulting suspension was filtered and washed with CHCl₃ (30 mL). The filtrate was washed with Na₂S₂O₃ solution (sat. aq., 15 mL), brine (15 mL), then

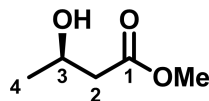
dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the title compound (**3.30**) as a colourless oil (533 mg, 96%). R_f (petrol/ether; 50:50) = 0.40; $[\alpha]_{\text{D}}^{25} +1.4$ (c 0.58, CHCl_3); m.p. = 28–30 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.49 (3 H, d, $J_{1',4} = 6.5$ Hz, H-1'), 1.87 (1 H, dddd, $J_{5\text{eq},5\text{ax}} = 15.0$ Hz, $J_{5\text{eq},4} = 2.5$ Hz, $J_{5\text{eq},6\text{ax}} = 2.0$ Hz, $J_{5\text{eq},6\text{eq}} = 1.5$ Hz, H-5_{eq}), 2.15 (1 H, dddd, $J_{5\text{ax},5\text{eq}} = 15.0$ Hz, $J_{5\text{ax},6\text{ax}} = 13.0$ Hz, $J_{5\text{ax},4} = 12.0$ Hz, $J_{5\text{ax},6\text{eq}} = 5.0$ Hz, H-5_{ax}), 4.57 (1 H, ddd, $J_{6\text{eq},6\text{ax}} = 11.5$ Hz, $J_{6\text{eq},5\text{ax}} = 5.0$ Hz, $J_{6\text{eq},5\text{eq}} = 1.5$ Hz, H-6_{eq}), 4.79 (1 H, ddd, $J_{6\text{ax},5\text{ax}} = 13.0$ Hz, $J_{6\text{ax},6\text{eq}} = 11.5$ Hz, $J_{6\text{ax},5\text{eq}} = 2.0$ Hz, H-6_{ax}), 5.06 (1 H, dqd, $J_{4,5\text{ax}} = 12.0$ Hz, $J_{4,1'} = 6.5$ Hz, $J_{4,5\text{eq}} = 2.5$ Hz, H-4); ^{13}C NMR (125 MHz, CDCl_3) δ 20.8 (C-1'), 30.8 (C-5), 71.8 (C-6), 82.5 (C-4); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2919 (w), 1388 (s), 1193 (s), 1051 (s), 1016 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_4\text{H}_8\text{NaO}_4\text{S}^+$ $[\text{MNa}]^+$ 175.0036, found 175.0034.

(4R)-4-Methyl-1,3,2-dioxathiane 2-oxide (3.34)²⁹

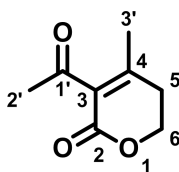


Diol **3.24** (500 mg, 5.55 mmol) was dissolved in anhydrous DCM (15 mL) under argon. Thionyl chloride (600 μL , 8.32 mmol) in DCM (0.8 mL) was added dropwise at 0 °C and the mixture was heated under reflux for 1 h. The reaction was then cooled and diluted with DCM (50 mL), washed with H_2O (3×20 mL), NaHCO_3 solution (sat. aq., 20 mL), then dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether; 70:30) furnished the title compound (**3.34**) as two separable diastereomers **A** and **B** (**A**:**B** = 13:1) as colourless oils (694 mg, 92%). **Data for Diastereomer A:** R_f (petrol/ether; 50:50) = 0.50; $[\alpha]_{\text{D}}^{25} +4.3$ (c

0.75, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.47 (3 H, d, $J_{1',4} = 6.5$ Hz, H-1'), 1.80 (1 H, dddd, $J_{5eq,5ax} = 14.0$ Hz, $J_{5eq,6eq} = 3.5$ Hz, $J_{5eq,6ax} = 3.0$ Hz, $J_{5eq,4} = 2.5$ Hz, H-5eq), 1.99 (1 H, dtd, $J_{5ax,5eq} = 14.0$ Hz, $J_{5ax,6ax} = J_{5ax,4} = 10.5$ Hz, $J_{5ax,6eq} = 5.0$ Hz, H-5ax), 4.35 (1 H, ddd, $J_{6ax,6eq} = 12.0$ Hz, $J_{6ax,5ax} = 10.5$ Hz, $J_{6ax,5eq} = 3.0$ Hz, H-6ax), 4.52 (1 H, ddd, $J_{6eq,6ax} = 12.0$ Hz, $J_{6eq,5ax} = 5.0$ Hz, $J_{6eq,5eq} = 3.5$ Hz, H-6eq), 4.56 (1 H, m, H-4); ¹³C NMR (125 MHz, CDCl₃) δ 21.6 (C-1'), 31.2 (C-5), 63.3 (C-6), 74.1 (C-4); IR (thin film) ν_{max}/cm^{-1} 2971 (w), 1739 (s), 1366 (s), 1228 (s); HRMS (ESI⁺) m/z calcd. for C₈H₁₆NaO₆S₂⁺ [M₂Na]⁺ 295.0281, found 295.0282. **Data for Diastereomer B:** R_f (petrol/ether; 50:50) = 0.60; $[\alpha]_D^{25} -9.3$ (c 0.67, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.29 (3 H, d, $J_{1',4} = 6.5$ Hz, H-1'), 1.69 (1 H, dddd, $J_{5eq,5ax} = 14.0$ Hz, $J_{5eq,4} = 2.5$ Hz, $J_{5eq,6ax} = 2.0$ Hz, $J_{5eq,6eq} = 1.5$ Hz, H-5eq), 2.20 (1 H, dddd, $J_{5ax,5eq} = 14.0$ Hz, $J_{5ax,6ax} = 13.0$ Hz, $J_{5ax,4} = 12.0$ Hz, $J_{5ax,6eq} = 5.0$ Hz, H-5ax), 3.90 (1 H, ddd, $J_{6eq,6ax} = 11.5$ Hz, $J_{6eq,5ax} = 5.0$ Hz, $J_{6eq,5eq} = 1.5$ Hz, H-6eq) 4.97 (1 H, ddd, $J_{6ax,5ax} = 13.0$ Hz, $J_{6ax,6eq} = 11.5$ Hz, $J_{6ax,5eq} = 2.0$ Hz, H-6ax), 5.10 (1 H, dqd, $J_{4,5ax} = 12.0$ Hz, $J_{4,1'} = 6.5$ Hz, $J_{4,5eq} = 2.5$ Hz, H-4); ¹³C NMR (125 MHz, CDCl₃) δ 21.2 (C-1'), 33.3 (C-5), 57.4 (C-6), 64.1 (C-4); IR (thin film) ν_{max}/cm^{-1} 2919 (m), 1738 (s), 1366 (m), 1216 (m); HRMS (FI⁺) m/z calcd. for C₄H₈O₃S⁺ [M]⁺ 136.0190, found 136.0194.

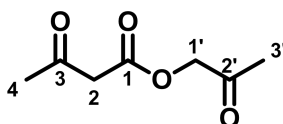
Methyl (3*R*)-hydroxybutanoate (3.35)⁹

A 3 L round-bottom flask was charged with PHB (100 g, 1.16 mol) and absolute 1,2-dichloroethane (1 L). The flask was equipped with a reflux condenser, and the mixture was heated under reflux for 1 h. A solution of concentrated H₂SO₄ (20 mL) in absolute methanol (400 mL) was added and the reaction mixture was heated under reflux for 72 h. During this time, the mixture became homogeneous. The mixture was then cooled to RT. Half-saturated brine (200 mL) was added to the reaction mixture, then stirred for 15 min where layers were separated. The aqueous layer was extracted with CHCl₃ (3 × 400 mL), washed with brine (200 mL), NaHCO₃ solution (sat. aq., 200 mL), and brine (200 mL). The combined organic layers were dried (MgSO₄) and concentrated. The title compound (**3.35**) was obtained by distillation of the residue under reduced pressure as a colourless oil (61–62 °C, 18 Torr, 95.2 g, 70%). *R_f* (petrol/ethyl acetate; 50:50) = 0.49; [α]_D²⁰ –47.6 (*c* 1.00, CHCl₃), lit¹⁰ [α]_D²² –45.1 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.12 (3 H, d, *J*_{4,3} = 6.0 Hz, H-4), 2.34–2.36 (2 H, m, H-2), 3.35 (1 H, d, *J*_{OH,3} = 4.0 Hz, C(3)OH), 3.60 (3 H, s, OCH₃), 4.05–4.13 (1 H, m, H-3); ¹³C NMR (100 MHz, CDCl₃) δ 22.5 (C-4), 42.7 (C-2), 51.5 (OCH₃), 64.1 (C-3), 173.1 (C-1); IR (thin film) ν_{max} /cm^{–1} 3449 (br), 2974 (m), 1738 (s), 1439 (s), 1377 (m), 1295 (m), 1175 (s), 1125 (m), 1088 (m); HRMS (ESI⁺) *m/z* calcd. for C₅H₁₀NaO₃⁺ [MNa]⁺ 141.0522, found 141.0521.

3-Acetyl-4-methyl-5,6-dihydro-2H-pyran-2-one (3.41)

Procedure see Method 3 for compound **3.20**. The *title compound* (**3.41**) was obtained as a side product as a colourless oil (7 mg, 5%).

R_f (petrol/ethyl acetate; 20:80) = 0.44; ^1H NMR (500 MHz, CDCl_3) δ 2.09 (3 H, s, H-2'), 2.45 (3 H, s, H-3'), 2.52 (2 H, t, $J_{5,6} = 6.0$ Hz, H-5), 4.38 (2 H, t, $J_{6,5} = 6.0$ Hz, H-6); ^{13}C NMR (125 MHz, CDCl_3) δ 21.1 (C-2'), 30.9 (C-5), 31.2 (C-3'), 65.1 (C-6), 130.2 (C-3), 158.1 (C-2), 162.5 (C-4), 200.2 (C-1'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2925 (w), 1700 (m), 1625 (w), 1308 (m), 1170 (m), 1093 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_8\text{H}_{10}\text{NaO}_3^+$ $[\text{MNa}]^+$ 177.0522, found 177.0518.

2-Oxopropyl 3-oxobutanoate (3.43)³⁰

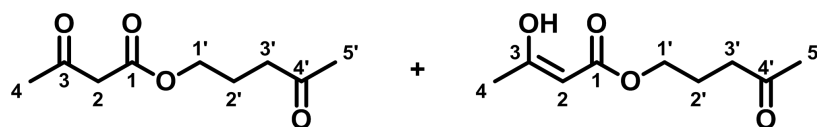
The title compound was prepared by applying general procedure A to 1-hydroxypropan-2-one.

The product (**3.43**) was obtained as a pale yellow oil (171 mg, 77%). R_f (petrol/ether; 50:50) = 0.14; ^1H NMR (500 MHz, CDCl_3) δ 2.19 (3 H, s, H-3'), 2.33 (3 H, s, H-4), 3.58 (2 H, s, H-2), 4.73 (2 H, s, H-1'), minor peaks for the enol form appeared at 1.98, 2.41, 2.54, 4.68,

4.75; ^{13}C NMR (125 MHz, CDCl_3) δ 26.0 (C-3'), 30.1 (C-4), 49.6 (C-2), 68.8 (C-1'), 174.2 (C-1), 200.0 (C-3), 200.7 (C-2'), minor peaks for the enol form appeared at 14.6, 67.8, 88.9, 125.0; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2971 (w), 2939 (w), 1749 (s), 1733 (s), 1717 (s), 1691 (m), 1626 (w), 1422 (m), 1364 (s); HRMS (FI^+) m/z calcd. for $\text{C}_7\text{H}_{10}\text{NaO}_4^+$ $[\text{MNa}]^+$ 158.0579, found 158.0578.

4-Oxopentyl 3-oxobutanoate (3.44) &

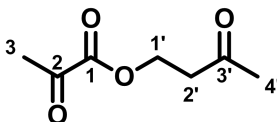
(Z)-4-oxopentyl 3-hydroxybut-2-enoate (3.44 enol form)



The *title compounds* were prepared by applying general procedure A to 5-hydroxypentan-2-one. The product (3.44), as a mixture of **keto** and **enol** forms (**keto:enol** = 15:1), was obtained as a colourless oil (243 mg, 93%). R_f (petrol/ether; 50:50) = 0.26; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3016 (w), 2970 (w), 2947 (w), 1739 (s), 1672 (w), 1435 (w), 1366 (s), 1229 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_9\text{H}_{14}\text{NaO}_4^+$ $[\text{MNa}]^+$ 209.0784, found 209.0788. **NMR data for keto form:** ^1H NMR (500 MHz, CDCl_3) δ 1.88–1.94 (2 H, m, H-2'), 2.14 (3 H, s, H-5'), 2.25 (3 H, s, H-4), 2.52 (2 H, t, $J_{3',2'} = 7.0$ Hz, H-3'), 3.44 (2 H, s, H-2), 4.14 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 22.6 (C-2'), 30.0 (C-5'), 30.2 (C-4), 39.6 (C-3'), 50.0 (C-2), 64.4 (C-1'), 167.0 (C-1), 200.5 (C-3), 207.6 (C-4'); **NMR data for enol form:** ^1H NMR (500 MHz, CDCl_3) δ 1.77 (3 H, s, H-4), 1.88–1.94 (2 H, m, H-2'), 2.14 (3 H, s, H-5'), 2.52 (2 H, t, $J_{3',2'} = 7.0$ Hz, H-3'), 4.14 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-1'), 4.95 (1 H, s,

H-2); ^{13}C NMR (125 MHz, CDCl_3) δ 21.2 (C-4), 22.6 (C-2'), 30.0 (C-5'), 39.6 (C-3'), 63.0 (C-1'), 89.5 (C-2), 167.0 (C-1 and C-3), 207.6 (C-4').

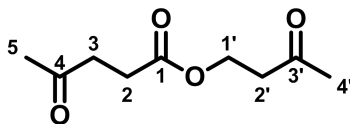
3-Oxobutyl 2-oxopropanoate (3.45)



The *title compound* was prepared by applying general procedure B to 2-oxopropanoic acid.

The product (**3.45**) was obtained as a colourless oil (100 mg, 55%). R_f (petrol/ethyl acetate; 60:40) = 0.36; ^1H NMR (500 MHz, CDCl_3) δ 2.21 (3 H, s, H-4'), 2.46 (3 H, s, H-3), 2.89 (2 H, t, $J_{2,1'} = 6.5$ Hz, H-2'), 4.50 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-2'); ^{13}C NMR (125 MHz, CDCl_3) δ 26.7 (C-3), 30.3 (C-4'), 41.6 (C-2'), 60.9 (C-1'), 160.6 (C-1), 191.5 (C-2), 204.7 (C-3'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970 (w), 1737 (s), 1424 (w), 1365 (m), 1229 (m); HRMS (FI^+) m/z calcd. for $\text{C}_7\text{H}_{10}\text{NaO}_4^+ [\text{MNa}]^+$ 158.0579, found 158.0583.

3-Oxobutyl 4-oxopentanoate (3.46)

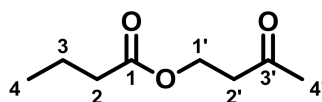


The *title compound* was prepared by applying general procedure B to 4-oxopentanoic acid.

The product (**3.46**) was obtained as a colourless oil (211 mg, 100%). R_f (petrol/ethyl acetate; 60:40) = 0.33; ^1H NMR (500 MHz, CDCl_3) δ 2.18 (3 H, s, H-5), 2.19 (3 H, s, H-4'), 2.54 (2

H, t, $J_{2,3} = 6.5$ Hz, H-2), 2.74 (2 H, t, $J_{3,2} = 6.5$ Hz, H-3), 2.76 (2 H, t, $J_{2',1'} = 6.5$ Hz, H-2'), 4.34 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 27.8 (C-2), 29.8 (C-4'), 30.2 (C-5), 37.9 (C-3), 42.1 (C-2'), 59.4 (C-1'), 172.6 (C-1), 205.7 (C-3'), 206.6 (C-4); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970 (w), 2926 (w), 1737 (s), 1717 (s), 1364 (m), 1229 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_9\text{H}_{14}\text{NaO}_4^+ [\text{MNa}]^+$ 209.0784, found 209.0784.

3-Oxobutyl butyrate (**3.47**)³¹



The title compound was prepared by applying general procedure B to butyric acid. The product (**3.47**) was obtained as a colourless oil (155 mg, 87%). R_f (petrol/ethyl acetate; 85:15) = 0.36; ^1H NMR (500 MHz, CDCl_3) δ 0.94 (3 H, t, $J_{4,3} = 7.5$ Hz, H-4), 1.63 (2 H, sext, $J_{3,4} = J_{3,2} = 7.5$ Hz, H-3), 2.19 (3 H, s, H-4'), 2.26 (2 H, t, $J_{2,3} = 7.5$ Hz, H-2), 2.76 (2 H, t, $J_{2',1'} = 6.5$ Hz, H-2'), 4.33 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 13.6 (C-4), 18.4 (C-3), 30.2 (C-4'), 36.0 (C-2), 42.3 (C-2'), 59.0 (C-1'), 173.5 (C-1), 205.7 (C-3'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968 (w), 2938 (w), 1732 (s), 1363 (s), 1184 (s), 1047 (m); HRMS (ESI^+) calcd. for $\text{C}_8\text{H}_{14}\text{NaO}_3^+ [\text{MNa}]^+$ 181.0835, found 181.0832.

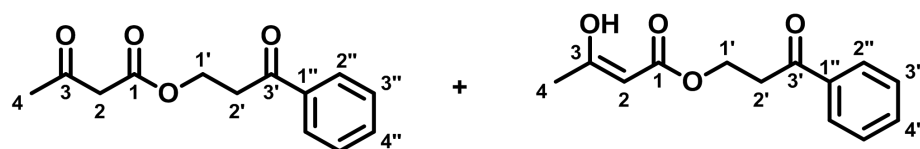
3-Oxobutyl 3-oxo-3-phenylpropanoate (3.48) &**(Z)-3-oxobutyl 3-hydroxy-3-phenyl acrylate (3.48 enol form)**

Ester **3.55** (484 μL , 2.80 mmol), alcohol **3.33** (172 μL , 2.00 mmol), and solid-supported *Candida Antarctica* lipase B (36 mg) were mixed in a round bottom flask which was then placed on a rotary evaporator. The system was evacuated to 8–10 Torr with rotation at 40–45 $^{\circ}\text{C}$ for 3 h. The reaction mixture was diluted with ether (10 mL), filtered, and concentrated. Flash chromatography (petrol/ether, 50:50) furnished the *title compounds* (**3.48**) as a mixture of **keto** and **enol** forms (**keto:enol** = 5:1) as a colourless oil (453 mg, 97%). R_f (petrol/ether; 70:30) = 0.29; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3016 (m), 2970 (m), 1739 (s), 1436 (m), 1367 (s), 1229 (s), 1216 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{13}\text{H}_{14}\text{NaO}_4^+$ [MNa]⁺ 257.0784, found 257.0790. **NMR data for keto form:** ^1H NMR (500 MHz, CDCl_3) δ 2.16 (3 H, s, H-4'), 2.78 (2 H, t, $J_{2,1'} = 6.0$ Hz, H-2'), 3.99 (2 H, s, H-2), 4.43 (2 H, t, $J_{1',2'} = 6.0$ Hz, H-1'), 7.49 (2 H, t, $J_{3'',2''} = J_{3'',4''} = 8.0$ Hz, $2 \times$ H-3''), 7.60 (1 H, t, $J_{4'',3''} = 8.0$ Hz, H-4''), 7.92 (2 H, d, $J_{2'',3''} = 8.0$ Hz, $2 \times$ H-2''); ^{13}C NMR (125 MHz, CDCl_3) δ 30.2 (C-4'), 41.9 (C-2'), 45.8 (C-2), 60.2 (C-1'), 128.4 (C-2''), 128.8 (C-3''), 133.8 (C-4''), 135.9 (C-1''), 167.4 (C-1), 192.4 (C-3), 205.4 (C-3'); **NMR data for enol form:** ^1H NMR (500 MHz, CDCl_3) δ 2.22 (3 H, s, H-4'), 2.84 (2 H, t, $J_{2,1'} = 6.0$ Hz, H-2'), 4.48 (2 H, t, $J_{1',2'} = 6.0$ Hz, H-1'), 5.65 (1 H, s, H-2), 7.42 (2 H, t, $J_{3'',2''} = J_{3'',4''} = 7.5$ Hz, $2 \times$ H-3''), 7.47 (1 H, t, $J_{4'',3''} = 7.5$ Hz, H-4''), 7.77 (2 H, d, $J_{2'',3''} = 7.5$ Hz, $2 \times$ H-2''); ^{13}C NMR (125 MHz, CDCl_3) δ 30.3 (C-4'), 42.3 (C-2'), 59.1 (C-1'), 87.0

(C-2), 126.1 (C-2''), 128.5 (C-3''), 131.4 (C-1''), 133.3 (C-4''), 171.8 (C-1), 172.9 (C-3), 205.6 (C-3').

3-Oxo-3-phenylpropyl 3-oxobutanoate (3.49) &

(Z)-3-oxo-3-phenylpropyl 3-hydroxybut-2-enoate (3.49 enol form)

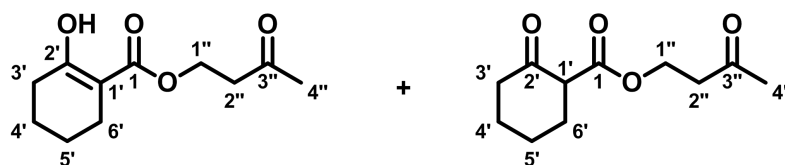


A mixture of dioxinone **3.39** (75 μ L, 0.560 mmol) and alcohol **3.53** (100 mg, 0.667 mmol) in *m*-xylene (5.6 mL) was heated under reflux with vigorous stirring. The heating was continued for a total of 30 min and cooled to RT. The crude was purified by flash chromatography (petrol/ethyl acetate; 70:30) to furnish the *title compounds* (**3.49**) as a mixture of **keto** and **enol** forms (**keto:enol** = 9:1) as a colourless oil (110 mg, 85%). R_f (petrol/ether; 70:30) = 0.31; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3063 (w), 2964 (w), 2920 (w), 1743 (s), 1716 (s), 1686 (s), 1598 (w), 1581 (w), 1218 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{13}\text{H}_{14}\text{NaO}_4^+$ [MNa]⁺ 257.0784, found 257.07873. **NMR data for keto form:** ¹H NMR (500 MHz, CDCl₃) δ 2.26 (3 H, s, H-4), 3.36 (2 H, t, $J_{2',1'} = 6.5$ Hz, H-2'), 3.45 (2 H, s, H-2), 4.61 (2 H, t, $J_{1',2'} = 6.5$ Hz, H-1'), 7.49 (2 H, t, $J_{3'',2''} = J_{3'',4''} = 7.5$ Hz, 2 $\times$ H-3''), 7.60 (1 H, t, $J_{4'',3''} = 7.5$ Hz, 2 $\times$ H-4''), 7.97 (2 H, d, $J_{2'',3''} = 7.5$ Hz, 2 $\times$ H-2''); ¹³C NMR (125 MHz, CDCl₃) δ 30.1 (C-4), 37.1 (C-2'), 50.0 (C-2), 60.5 (C-1'), 128.1 (C-2''), 128.7 (C-3''), 133.5 (C-4''), 136.4 (C-1''), 167.0 (C-1), 196.7 (C-3'), 200.4 (C-3); **NMR data for enol form:** ¹H NMR (500 MHz, CDCl₃) δ 1.95 (3 H, s, H-4), 3.36 (2 H, t, $J_{2',1'} = 6.5$ Hz, H-2'), 4.61 (2 H, t, $J_{1',2'} = 6.5$ Hz,

H-1'), 4.97 (1 H, s, H-2), 7.49 (2 H, t, $J_{3'',2''} = J_{3'',4''} = 7.5$ Hz, $2 \times$ H-3''), 7.60 (1 H, t, $J_{4'',3''} = 7.5$ Hz, H-4''), 7.97 (2 H, d, $J_{2'',3''} = 7.5$ Hz, $2 \times$ H-2''); ^{13}C NMR (125 MHz, CDCl_3) δ 21.2 (C-4), 37.4 (C-2'), 59.1 (C-1'), 89.6 (C-2), 126.5 (C-2''), 128.6 (C-3''), 133.4 (C-4''), 136.5 (C-1''), 172.4 (C-1), 175.8 (C-3), 197.0 (C-3').

3-Oxobutyl 2-hydroxycyclohex-1-enecarboxylate (**3.50**) &

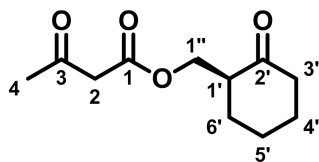
3-oxobutyl 2-oxocyclohexanecarboxylate (**3.50** keto form)



Ester **3.62** (448 μL , 2.80 mmol), alcohol **3.33** (172 μL , 2.00 mmol), and solid-supported *Candida Antarctica* lipase B (36 mg) were mixed in a round bottom flask that was then placed on a rotary evaporator. The system was evacuated to 8–10 Torr with rotation at 40–45 $^{\circ}\text{C}$ for 3 h. The crude was diluted with ether (10 mL), filtered, and concentrated. Flash chromatography (petrol/ether, 50:50) furnished the *title compounds* (**3.50**) as a mixture of **keto** and **enol** forms (**keto:enol** = 1:10) as a colourless oil (117 mg, 28%, 100% b.r.s.m). R_f (petrol/ether; 50:50) = 0.50; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2939 (w), 1715 (m), 1651 (m), 1616 (m), 1361 (m), 1260 (s), 1059 (w); HRMS (ESI^+) m/z calcd. for $\text{C}_{11}\text{H}_{16}\text{NaO}_4^+ [\text{MNa}]^+$ 235.0941, found 235.0942. **NMR data for keto form:** ^1H NMR (500 MHz, CDCl_3) δ 1.63–1.71 (1 H, m, $1 \times$ H-5'), 1.75–1.85 (1 H, m, $1 \times$ H-6'), 1.85–1.92 (1 H, m, $1 \times$ H-5'), 1.95–2.03 (1 H, m, $1 \times$ H-6'), 2.08–2.15 (2 H, m, H-4'), 2.21 (3 H, s, H-4''), 2.31–2.39 (1 H, m, $1 \times$ H-3'),

2.45–2.51 (1 H, m, 1 $\times$ H-3'), 2.73–2.87 (2 H, m, H-2''), 3.36 (1 H, t, $J_{1',6'} = 8.5$ Hz, H-1'), 4.36–4.49 (2 H, m, H-1''); ^{13}C NMR (125 MHz, CDCl_3) δ 21.8 (C-4'), 23.3 (C-5'), 27.1 (C-6'), 29.8 (C-4''), 41.6 (C-3'), 42.1 (C-2''), 57.1 (C-1'), 59.8 (C-1''), 169.9 (C-1), 205.7 (C-3''), 206.2 (C-2'); **NMR data for enol form:** ^1H NMR (500 MHz, CDCl_3) δ 1.56–1.62 (2 H, m, H-5'), 1.65–1.70 (2 H, m, H-4'), 2.17 (2 H, t, $J_{6',5'} = 6.0$ Hz, H-6'), 2.21 (3 H, s, H-4''), 2.27 (2 H, t, $J_{3',4'} = 6.5$ Hz, H-3'), 2.81 (2 H, t, $J_{2'',1''} = 6.5$ Hz, H-2''), 4.41 (2 H, t, $J_{1'',2''} = 6.5$ Hz, H-1''), 12.10 (1 H, s, OH); ^{13}C NMR (125 MHz, CDCl_3) δ 21.8 (C-4'), 22.3 (C-5', C-6'), 29.1 (C-3'), 30.3 (C-4''), 42.3 (C-2''), 59.1 (C-1''), 97.5 (C-1'), 172.4 (C-1), 172.6 (C-2'), 205.7 (C-3'').

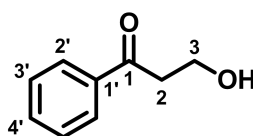
(S)-2-Oxocyclohexylmethyl 3-oxobutanoate (3.51)



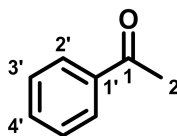
A mixture of dioxinone **3.39** (223 μL , 1.67 mmol) and alcohol **3.59** (258 mg, 2.00 mmol) in *m*-xylene (2 mL) was heated under reflux with vigorous stirring for a total of 30 min then cooled to RT. The crude was purified by flash chromatography (petrol/ether, 70:30 then 50:50) to furnish the *title compound* (**3.51**) as a colourless oil (198 mg, 56%). R_f (petrol/ether; 50:50) = 0.30; $[\alpha]_{\text{D}}^{20} -11.8$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.21–1.32 (1 H, m, 1 $\times$ H-6'), 1.62–1.76 (2 H, m, 1 $\times$ H-4', 1 $\times$ H-5'), 1.89–1.98 (1 H, m, 1 $\times$ H-5'), 2.07–2.15 (1 H, m, 1 $\times$ H-4'), 2.16–2.23 (1 H, m, 1 $\times$ H-6'), 2.27 (3 H, s, H-4), 2.29–2.38 (1 H, m, 1 $\times$ H-3'), 2.40–2.47 (1 H, m, 1 $\times$ H-3'), 2.67–2.74 (1 H, m, H-1'), 3.46 (2 H, s, H-2), 4.14 (1 H,

dd, $J_{1'',1'''} = 11.5$ Hz, $J_{1'',1'} = 6.0$ Hz, $1 \times \text{H-1}''$), 4.46 (1 H, dd, $J_{1'',1'''} = 11.5$ Hz, $J_{1'',1'} = 6.0$ Hz, $1 \times \text{H-1}''$); ^{13}C NMR (125 MHz, CDCl_3) δ 24.7 (C-5'), 27.6 (C-4'), 30.2 (C-4), 30.9 (C-6'), 42.0 (C-3'), 49.3 (C-1'), 50.0 (C-2), 64.1 (C-1'''), 167.0 (C-1), 200.5 (C-3), 210.1 (C-2'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2937 (m), 2864 (w), 1743 (m), 1713 (s), 1360 (m), 1152 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_{11}\text{H}_{16}\text{NaO}_4^+ [\text{MNa}]^+$ 235.0941, found 235.0941.

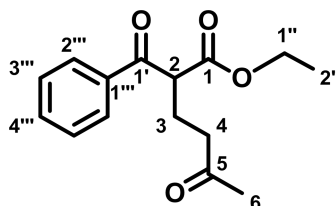
3-Hydroxy-1-phenylpropan-1-one (3.53)³²



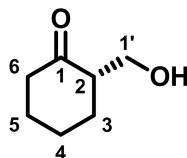
To a mixture of alcohol **3.52** (136 μL , 1.00 mmol) and HBr solution (48% in H_2O , 102 μL , 0.900 mmol) in DCM (1 mL) was added H_2O_2 solution (35% in H_2O , 450 μL , 5.14 mmol). The reaction mixture was stirred at RT for 14 h. $\text{Na}_2\text{S}_2\text{O}_5$ solution (sat. aq., 5 mL) was added and the mixture was extracted with DCM (3×5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), then dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 70:30 to 50:50) furnished the title compound **3.53** as a pale yellow oil (76 mg, 51%). R_f (petrol:ethyl acetate; 70:30) = 0.21; ^1H NMR (500 MHz, CDCl_3) δ 2.38–2.58 (1 H, br.s, C(3)OH), 3.24 (2 H, t, $J_{2,3} = 5.5$ Hz, H-2), 4.04 (2 H, t, $J_{3,2} = 5.5$ Hz, H-3), 7.48 (2 H, t, $J_{3',2'} = J_{3',4'} = 8.0$ Hz, $2 \times \text{H-3}'$), 7.59 (1 H, t, $J_{4',3'} = 8.0$ Hz, H-4'), 7.98 (2 H, d, $J_{2',3'} = 8.0$ Hz, $2 \times \text{H-2}'$); ^{13}C NMR (125 MHz, CDCl_3) δ 40.4 (C-2), 58.1 (C-3), 128.0 (C-2'), 128.7 (C-3'), 133.5 (C-4'), 136.6 (C-1'), 200.5 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3455 (w), 2970 (w), 1739 (s), 1679 (s), 1597 (w), 1449 (m), 1365 (s), 1216 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_9\text{H}_{10}\text{NaO}_2^+ [\text{MNa}]^+$ 173.0573, found 173.0573.

Acetophenone (3.56)³³

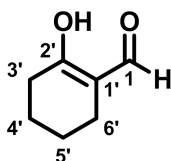
To a solution of alcohol **3.33** (103 μ L, 1.20 mmol) and DMAP (37 mg, 0.303 mmol) in toluene (2 mL) was added ester **3.55** (173 μ L, 1.00 mmol). The resulting mixture was heated under reflux for 4 h. The reaction was quenched with NH_4Cl solution (sat. aq., 10 mL) and extracted with ether (3×10 mL). The combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the title compound (**3.56**) as a colourless oil (111 mg, 93%) as well as Michael adduct **3.57** (25 mg, 11%) as a colourless oil as side products. **Data for 3.56:** R_f (petrol/ethyl acetate; 50:50) = 0.50; ^1H NMR (500 MHz, CDCl_3) δ 2.58 (3 H, s, H-2), 7.44 (2 H, t, $J_{3',2'} = J_{3',4'} = 7.5$ Hz, $2 \times$ H-3'), 7.54 (1 H, t, $J_{4',3'} = 7.5$ Hz, H-4'), 7.94 (2 H, d, $J_{2',3'} = 7.5$ Hz, $2 \times$ H-2'); ^{13}C NMR (125 MHz, CDCl_3) δ 26.6 (C-2), 128.3 (C-2'), 128.6 (C-3'), 133.1 (C-4'), 137.1 (C-1'), 198.1 (C-1). All the other data are as reported. **Data for 3.57:** see page 322.

Ethyl 2-benzoyl-5-oxohexanoate (3.57)

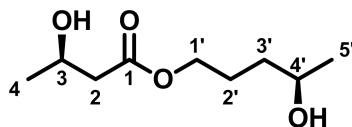
To a solution of alcohol **3.33** (103 μ L, 1.20 mmol) and ester **3.55** (173 μ L, 1.00 mmol) in toluene (5 mL) was added CsF (16 mg, 0.103 mmol). The resulting mixture was heated under reflux for 2 h, then it was cooled to RT. Solids was filtered out and the filtrate was concentrated. Flash chromatography (petrol/ether, 50:50) furnished the *title compound* (**3.57**) as a pale yellow oil (161 mg, 61%) together with MVK as a colourless oil (27 mg, 22%). R_f (petrol/ether; 50:50) = 0.48; ^1H NMR (500 MHz, CDCl_3) δ 1.18 (3 H, t, $J_{2'',1''} = 7.0$ Hz, H-2''), 2.14 (3 H, s, H-6), 2.18–2.31 (2 H, m, H-3), 2.53–2.67 (2 H, m, H-4), 4.12–4.18 (2 H, m, H-1''), 4.44 (1 H, dd, $J_{2,3} = 6.5$ Hz, $J_{2,3} = 8.0$ Hz, H-2), 7.49 (2 H, t, $J_{3''',4'''} = J_{3'',2''} = 7.5$ Hz, 2 $\times$ H-3'''), 7.60 (1 H, t, $J_{4''',3'''} = 7.5$ Hz, H-4'''), 8.03 (2 H, d, $J_{2''',3'''} = 7.5$ Hz, 2 $\times$ H-2'''); ^{13}C NMR (125 MHz, CDCl_3) δ 14.0 (C-2''), 22.7 (C-3), 30.0 (C-6), 40.5 (C-4), 52.6 (C-2), 61.4 (C-1''), 128.7 (C-2'''), 128.8 (C-3'''), 133.6 (C-4'''), 135.9 (C-1'''), 169.8 (C-1), 195.2 (C-1'), 207.8 (C-5); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970 (w), 1738 (s), 1683 (m), 1597 (w), 1581 (w), 1448 (m), 1367 (s), 1229 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{15}\text{H}_{18}\text{NaO}_4$ + $[\text{MNa}]^+$ 285.1099, found 285.1097.

(S)-2-Hydroxymethylcyclohexanone (3.59)

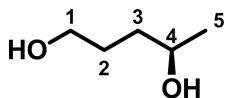
Formaldehyde solution (37% in H₂O, 111 μ L, 1.49 mmol) was added to a stirred solution of (S)-L-proline (17 mg, 0.147 mmol) and cyclohexanone (311 μ L, 3.00 mmol) in DMSO (4 mL) at RT. After 16 h, the reaction was quenched with brine (20 mL) and extracted with ethyl acetate (3 $\times$ 20 mL). The combined organic layers were concentrated and flash chromatography (petrol/ethyl acetate, 50:50) furnished the title compound **3.59** as a colourless oil (40 mg, 18%). R_f (petrol/ethyl acetate; 50:50) = 0.30; $[\alpha]_D^{23} +13.0$ (c 0.50, CHCl₃), lit³⁴ $[\alpha]_D^{22} +11.4$ (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.48 (1 H, qd, $J_{3ax,3eq} = J_{3ax,2} = J_{3ax,4ax} = 13.0$ Hz, $J_{3ax,4eq} = 3.5$ Hz, H-3_{ax}), 1.58–1.75 (2 H, m, 1 $\times$ H-4, 1 $\times$ H-6), 1.88–1.94 (1 H, m, 1 $\times$ H-4), 1.99–2.05 (1 H, m, H-3_{eq}), 2.07–2.13 (1 H, m, 1 $\times$ H-6), 2.27–2.43 (2 H, m, H-5), 2.46–2.56 (1 H, m, H-2), 2.66 (1 H, br.s, C(1')OH), 3.55–3.64 (1 H, m, 1 $\times$ H-1'), 3.68–3.77 (1 H, m, 1 $\times$ H-1'); ¹³C NMR (100 MHz, CDCl₃) δ 24.7 (C-4), 27.5 (C-6), 30.0 (C-3), 42.2 (C-5), 52.2 (C-2), 62.8 (C-1'), 214.8 (C-1); IR (thin film) ν_{max}/cm^{-1} 3245 (br), 2934 (m), 2864 (m), 1704 (s), 1450 (m), 1023 (s); HRMS (ESI⁺) m/z calcd. for C₇H₁₂NaO₂⁺ [MNa]⁺ 151.0730, found 151.0733.

2-Hydroxycyclohex-1-enecarbaldehyde (3.60)³⁵

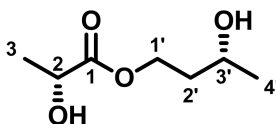
Dess–Martin periodinane (132 mg, 0.312 mmol) was added to a solution of alcohol **3.59** (20 mg, 0.156 mmol) in DCM (3 mL) at 0 °C. After 15 min, the ice bath was removed and stirring was continued for 1 h at RT. Aqueous buffer [5 mL of a solution made from Na₂S₂O₃ (*ca.* 100–158 g/L) and Na₂CO₃ (*ca.* 100 g/L)] was added and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ethyl acetate, 50:50) furnished the title compound **3.60** as a colourless oil (7 mg, 36%). *R_f* (petrol/ether; 50:50) = 0.84; ¹H NMR (500 MHz, CDCl₃) δ 1.66–1.74 (4 H, m, H-4', H-5'), 2.33–2.39 (4 H, m, H-3', H-6'), 8.65 (1 H, d, *J*_{1,6'} = 2.5 Hz, H-1), 14.4 (1 H, d, *J*_{OH,3'} = 3.0 Hz, C(2')OH); ¹³C NMR (125 MHz, CDCl₃) δ 21.2 (C-4'), 22.6 (C-5'), 23.1 (C-6'), 31.2 (C-3'), 108.9 (C-1'), 184.8 (C-1), 187.6 (C-2'); IR (thin film) *v*_{max}/cm⁻¹ 2926 (m), 1739 (s), 1366 (m), 1217 (m); HRMS (ESI⁺) *m/z* calcd. for C₈H₁₄NaO₃⁺ [M+Na+CH₃OH]⁺ 181.0835, found 181.0832.

(4*R*)-Hydroxypentyl (3*R*)-hydroxybutanoate (3.63)

The *title compound* was synthesised by applying general procedure C on diketone **3.44** (148 mg, 0.796 mmol). The product (**3.63**) was obtained as a colourless oil (162 mg, 100%). [*d*.*r*. > 99:1 (¹H NMR); *e.e.* > 99% (Mosher's analysis), see appendix D]. *R_f* (petrol/ethyl acetate; 20:80) = 0.42; [*α*]_D²⁴ −41.5 (*c* 0.92, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.21 (3 H, d, *J*_{5',4'} = 6.0 Hz, H-5'), 1.23 (3 H, d, *J*_{4,3} = 6.5 Hz, H-4), 1.48–1.54 (2 H, m, H-2'), 1.56 (1 H, br.s, 1 × OH), 1.67–1.83 (2 H, m, H-3'), 2.42 (1 H, dd, *J*_{2,2} = 16.5 Hz, *J*_{2,3} = 9.0 Hz, 1 × H-2), 2.50 (1 H, dd, *J*_{2,2} = 16.5 Hz, *J*_{2,3} = 3.5 Hz, 1 × H-2), 3.05 (1 H, br.s, 1 × OH), 3.81–3.87 (1 H, m, H-4'), 4.15 (2 H, t, *J*_{1',2'} = 6.5 Hz, H-1'), 4.18–4.24 (1 H, m, H-3); ¹³C NMR (125 MHz, CDCl₃) δ 22.4 (C-4), 23.7 (C-5'), 24.9 (C-3'), 35.3 (C-2'), 42.8 (C-2), 64.3 (C-3), 64.7 (C-1'), 67.5 (C-4'), 172.9 (C-1); IR (thin film) *v*_{max}/cm^{−1} 3376 (br), 2970 (m), 1736 (s), 1374 (m), 1217 (m), 1090 (m); HRMS (ESI⁺) *m/z* calcd. for C₉H₁₈NaO₄⁺ [MNa]⁺ 213.1097, found 213.1094.

(4*R*)-Pentane-1,4-diol (3.64)³⁶

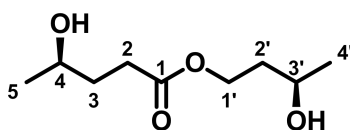
The title compound was synthesised by applying the general procedure E to ester **3.63** (34 mg, 0.179 mmol). Flash chromatography (petrol/ethyl acetate, 70:30) furnished the product (**3.64**) as a colourless oil (14 mg, 75%). R_f (petrol/ethyl acetate; 50:50) = 0.10; $[\alpha]_D^{24} -12.7$ (c 1.00, MeOH), lit³⁷ $[\alpha]_D^{20} -13.9$ (c 1.02, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 1.21 (3 H, d, $J_{5,4} = 6.0$ Hz, H-5), 1.40–1.84 (4 H, m, H-2, H-3), 3.60–3.76 (2 H, t, $J_{1,2} = 7.0$ Hz, H-1), 3.76–3.90 (1 H, m, H-4). All the other data were as reported.

(3*R*)-Hydroxybutyl (2*R*)-hydroxypropanoate (3.65)

The *title compound* was synthesised by applying general procedure C on diketone **3.45** (80 mg, 0.506 mmol). The product (**3.65**) was obtained as a colourless oil (43 mg, 53%). [$d.r.$ > 99:1 (^1H NMR); $e.e.$ > 99% (Mosher's analysis), see appendix D]. R_f (petrol/ethyl acetate; 20:80) = 0.32; $[\alpha]_D^{24} -15.5$ (c 0.58, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.25 (3 H, d, $J_{4',3'} = 6.5$ Hz, H-4'), 1.43 (3 H, d, $J_{3,2} = 7.0$ Hz, H-3), 1.65 (1 H, br.s, $1 \times \text{OH}$), 1.72–1.88 (2 H, m, H-2'), 2.86 (1 H, d, $J_{\text{OH},3'}$ or $J_{\text{OH},2} = 4.5$ Hz, $1 \times \text{OH}$), 3.87–3.94 (1 H, m, H-3'), 4.25–4.32 (2 H, m, $1 \times \text{H-1'}$, H-2), 4.44 (1 H, ddd, $J_{1',1} = 11.0$ Hz, $J_{1',2'} = 8.5$ Hz, $J_{1',2} = 5.5$ Hz, $1 \times \text{H-1'}$);

^{13}C NMR (125 MHz, CDCl_3) δ 20.5 (C-3), 23.7 (C-4'), 37.9 (C-2'), 62.9 (C-1'), 64.8 (C-3'), 66.8 (C-2), 176.0 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3386 (br), 2975 (w), 1732 (s), 1275 (m), 1210 (m), 1130 (s), 1049 (m); HRMS (ESI⁺) m/z calcd. for $\text{C}_7\text{H}_{14}\text{NaO}_4^+$ $[\text{MNa}]^+$ 185.0784, found 185.0787.

(3*R*)-Hydroxybutyl (4*R*)-hydroxypentanoate (3.66)



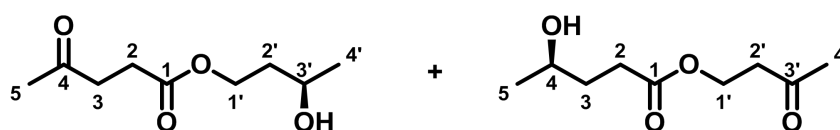
The *title compound* was synthesised by applying general procedure C on diketone **3.46** (129 mg, 0.693 mmol). The product (**3.66**) was obtained as a colourless oil (126 mg, 96%). [*d.r.* > 99:1 (^1H NMR); *e.e.* > 99% (Mosher's analysis), see appendix D] together with other reduction products **3.67** (4 mg, 3%). [*d.r.* > not applicable; *e.e.* > 99% (see Mosher's analysis of diol **3.66**), appendix D] and **3.68** (4 mg, 3%) [*d.r.* not applicable; *e.e.* > 99% (see Mosher's analysis of diol **3.66**), appendix D]^{ai}. R_f (petrol/ethyl acetate; 20:80) = 0.33; $[\alpha]_{\text{D}}^{24}$ -25.2 (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.22 (3 H, d, $J_{4',3'}$ or $_{5,4}$ = 6.0 Hz, H-4' or H-5), 1.24 (3 H, d, $J_{5,4}$ or $_{4',3'}$ = 6.0 Hz, H-5 or H-4'), 1.68–1.86 (5 H, m, H-2', H-3, 1 $\times$ OH), 2.09 (1 H, d, $J_{\text{OH}, 3'}$ or $J_{\text{OH}, 4}$ = 4.0 Hz, 1 $\times$ OH), 2.46 (2 H, t, $J_{2, 3}$ = 7.5 Hz, H-2), 3.81–3.95 (2 H, m, H-4, H-3'), 4.15 (1 H, dt, $J_{1', 1'}$ = 11.5 Hz, $J_{1', 2'}$ = 5.5 Hz, 1 $\times$ H-1'), 4.36 (1 H, ddd, $J_{1', 1'}$ = 11.5 Hz, $J_{1', 2'}$ = 8.5 Hz, $J_{1', 2'}$ = 5.0 Hz, 1 $\times$ H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 23.6 (C-4', C-5), 30.9 (C-2), 33.9 (C-3), 38.0 (C-2'), 61.9 (C-1'), 65.0 (C-3'), 67.5 (C-4), 174.5 (C-1); IR (thin

^{ai} Yield of all reduction products is 102%, probably due to accuracy limit of balance; **3.67** and **3.68** were obtained as an inseparable mixture.

film) $\nu_{\max}/\text{cm}^{-1}$ 3372 (br), 2699 (s), 2931 (s), 1711 (s), 1270 (s), 1175 (s), 1132 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_9\text{H}_{18}\text{NaO}_4^+$ [MNa]⁺ 213.1097, found 213.1106. **Data for 3.67, 3.68:** see page 328.

(3*R*)-Hydroxybutyl 4-oxopentanoate (3.67) &

3-Oxobutyl (4*R*)-hydroxypentanoate (3.68)

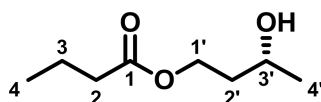


The *title compound* was synthesised by applying general procedure C on diketone **3.46** (129 mg, 0.693 mmol). The product (**3.67**) was obtained as a colourless oil (4 mg, 3%) [*d.r.* not applicable; *e.e.* > 99% (see Mosher's analysis of diol **3.66**), appendix D] together with the other reduction products **3.66** (126 mg, 96%) [*d.r.* > 99:1 (¹H NMR); *e.e.* > 99% (Mosher's analysis), see appendix D] and **3.68** (4 mg, 3%) [*d.r.* not applicable; *e.e.* > 99% (see Mosher's analysis of diol **3.66**), appendix D]^{aj}. **Data for 3.67:** R_f (petrol/ethyl acetate; 20:80) = 0.43; ¹H NMR (500 MHz, CDCl₃) δ 1.23 (3 H, d, $J_{4',3'} = 6.0$ Hz, H-4'), 1.67–1.83 (2 H, m, H-2'), 2.20 (3 H, s, H-5), 2.58 (2 H, t, $J_{2,3} = 6.5$ Hz, H-2), 2.75–2.79 (2 H, m, H-3), 3.86–3.93 (1 H, m, H-3'), 4.12–4.16 (1 H, m, 1 $\times$ H-1'), 4.33–4.39 (1 H, m, 1 $\times$ H-1'); ¹³C NMR (125 MHz, CDCl₃) δ 23.5 (C-4'), 27.9 (C-2), 29.8 (C-5), 37.9 (C-3), 38.0 (C-2'), 61.9 (C-1'), 64.8 (C-3'), 173.2 (C-1), 206.7 (C-4); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3410 (br), 2966 (w), 2928 (w), 1714 (s), 1162 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_9\text{H}_{16}\text{NaO}_4^+$ [MNa]⁺ 211.0941, found 211.0948. **Data**

^{aj} Yield of all reduction products is 102%, probably due to accuracy limit of balance; **3.67** and **3.68** were obtained as an inseparable mixture.

for 3.68: R_f (petrol/ethyl acetate; 20:80) = 0.43; ^1H NMR (500 MHz, CDCl_3) δ 1.21 (3 H, d, $J_{5,4} = 6.0$ Hz, H-5), 1.67–1.83 (2 H, m, H-3), 2.20 (3 H, s, H-4'), 2.43 (2 H, t, $J_{2,3} = 7.5$ Hz, H-2), 2.75–2.79 (2 H, m, H-2'), 3.80–3.86 (1 H, m, H-4), 4.33–4.39 (2 H, m, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 23.5 (C-5), 30.2 (C-4'), 30.6 (C-2), 33.8 (C-3), 42.2 (C-2'), 59.3 (C-1'), 67.3 (C-4), 173.9 (C-1), 205.7 (C-3'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3410 (br), 2966 (w), 2928 (w), 1714 (s), 1162 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_9\text{H}_{16}\text{NaO}_4 + [\text{MNa}]^+$ 211.0941, found 211.0948. **Data for 3.66:** see page 327.

(3R)-Hydroxybutyl butyrate (3.69)



The *title compound* was synthesised by applying general procedure C on diketone **3.47** (141 mg, 0.892 mmol). The product (**3.69**) was obtained as a colourless oil (118 mg, 83%). [d_r : not applicable; $e.e.$ > 99% (Mosher's analysis), see appendix D]. R_f (petrol/ethyl acetate; 20:80) = 0.72; $[\alpha]_{\text{D}}^{25} -14.2$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.96 (3 H, t, $J_{4,3} = 7.5$ Hz, H-4), 1.24 (3 H, d, $J_{4',3'} = 6.5$ Hz, H-4'), 1.66 (2 H, sext, $J_{3,4} = J_{3,2} = 7.5$ Hz, H-3), 1.70–1.84 (2 H, m, H-2'), 2.02 (1 H, br.s, C(3')OH), 2.30 (2 H, t, $J_{2,3} = 7.5$ Hz, H-2), 3.85–3.92 (1 H, m, H-3'), 4.13 (1 H, dt, $J_{1',1'} = 11.5$ Hz, $J_{1',2'} = 5.5$ Hz, 1 $\times$ H-1'), 4.37 (1 H, ddd, $J_{1',1'} = 11.5$ Hz, $J_{1',2'} = 8.5$ Hz, $J_{1',2'} = 5.0$ Hz, 1 $\times$ H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 13.7 (C-4), 18.5 (C-3), 23.5 (C-4'), 36.2 (C-2), 38.2 (C-2'), 61.6 (C-3'), 65.0 (C-1'), 174.1 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3416 (br), 2966 (s), 1712 (s), 1183 (s), 1139 (m), 1097 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_8\text{H}_{16}\text{NaO}_3 + [\text{MNa}]^+$ 183.0992, found 183.0993.

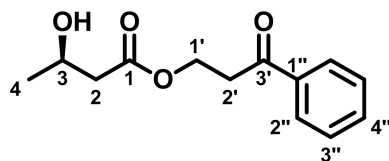
(3R)-Hydroxybutyl 3-oxo-3-phenylpropanoate (3.70) & (3R,Z)-3-hydroxybutyl 3-hydroxy-3-phenylacrylate (3.70 enol form)



The *title compounds* were synthesised by applying general procedure C on diketone **3.48** (234 mg, 1.00 mmol). The products (**3.70**) were obtained as a mixture of **keto** and **enol** forms (**keto:enol** = 5:1) as a colourless oil (193 mg, 82%). [*d.r.* not applicable; *e.e.* > 99% (Mosher's analysis), see appendix D]. *R_f* (petrol/ethyl acetate; 20:80) = 0.69; IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3413 (br), 2965 (w), 1733 (m), 1685 (s), 1626 (m), 1598 (m), 1451 (m), 1273 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₃H₁₆NaO₄⁺ [MNa]⁺ 259.0941, found 259.0947. **NMR data for keto form:** ¹H NMR (500 MHz, CDCl₃) δ 1.20 (3 H, d, *J*_{4',3'} = 6.5 Hz, H-4'), 1.68–1.84 (2 H, m, H-2'), 1.97 (1 H, br.s, C(3')OH), 3.84–3.90 (1 H, m, H-3'), 4.03 (2 H, s, H-2), 4.22–4.28 (1 H, m, 1 $\times$ H-1'), 4.41–4.46 (1 H, m, 1 $\times$ H-1'), 7.50 (2 H, t, *J*_{3'',2''} = *J*_{3'',4''} = 8.0 Hz, 2 $\times$ H-3''), 7.62 (1 H, t, *J*_{4'',3''} = 8.0 Hz, H-4''), 7.95 (2 H, d, *J*_{2'',3''} = 8.0 Hz, 2 $\times$ H-2''); ¹³C NMR (125 MHz, CDCl₃) δ 23.5 (C-4'), 37.8 (C-2'), 45.9 (C-2), 62.6 (C-1'), 64.8 (C-3'), 128.5 (C-2''), 128.8 (C-3''), 133.9 (C-4''), 135.9 (C-1''), 167.8 (C-1), 192.6 (C-3); **NMR data for enol form:** ¹H NMR (500 MHz, CDCl₃) δ 1.26 (3 H, d, *J*_{4',3'} = 6.0 Hz, H-4'), 1.78–1.91 (2 H, m, H-2'), 2.05 (1 H, br.s, 1 $\times$ OH), 3.92–3.98 (1 H, m, H-3'), 4.03 (1 H, s, H-2), 4.26–4.29 (1 H, m, 1 $\times$ H-1'), 4.49–4.54 (1 H, m, 1 $\times$ H-1'), 4.87 (1 H, br.s, 1 $\times$ OH), 7.43 (2 H, t, *J*_{3'',2''} = *J*_{3'',4''} = 7.5 Hz, 2 $\times$ H-3''), 7.48 (1 H, t, *J*_{4'',3''} = 7.5 Hz, H-4''), 7.79 (2 H, d, *J*_{2'',3''} =

7.5 Hz, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ 23.5 (C-4'), 38.1 (C-2'), 61.5 (C-1'), 64.8 (C-3'), 87.1 (C-2), 126.1 (C-2''), 128.6 (C-3''), 131.4 (C-1''), 133.3 (C-4''), 171.9 (C-1), 173.4 (C-3).

(3*R*)-3-Oxo-3-phenylpropyl 3-hydroxybutanoate (3.71)

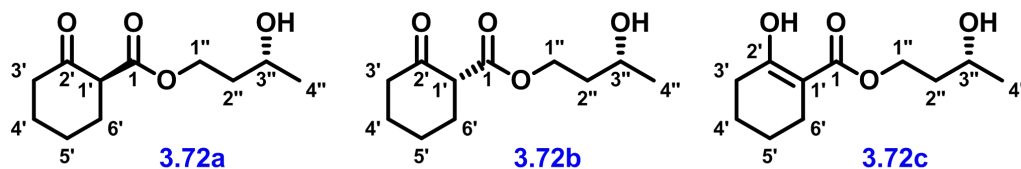


The *title compound* was synthesised by applying general procedure C on diketone **3.49** (100 mg, 0.427 mmol). The product (**3.71**) was obtained as a colourless oil (54 mg, 54%). [*d.r.* not applicable; *e.e.* > 99% (Mosher's analysis), see appendix D]. R_f (petrol/ethyl acetate; 20:80) = 0.50; $[\alpha]_D^{24} -18.6$ (*c* 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.22 (3 H, d, $J_{4,3} = 6.5$ Hz, H-4), 2.41 (1 H, dd, $J_{2,2} = 16.5$ Hz, $J_{2,3} = 9.0$ Hz, $1 \times \text{H-2}$), 2.49 (1 H, dd, $J_{2,2} = 16.5$ Hz, $J_{2,3} = 3.5$ Hz, $1 \times \text{H-2}$), 2.96 (1 H, d, $J_{\text{OH},3} = 4.0$ Hz, C(3)OH), 3.34 (2 H, t, $J_{2',1'} = 6.0$ Hz, H-2'), 4.16–4.23 (1 H, m, H-3), 4.54–4.62 (2 H, m, H-1'), 7.49 (2 H, t, $J_{3'',2''} = J_{3'',4''} = 8.0$ Hz, $2 \times \text{H-3''}$), 7.60 (1 H, t, $J_{4'',3''} = 8.0$ Hz, H-4''), 7.97 (2 H, d, $J_{2'',3''} = 8.0$ Hz, $2 \times \text{H-2''}$); ^{13}C NMR (125 MHz, CDCl_3) δ 22.4 (C-4), 37.2 (C-2'), 42.8 (C-2), 59.8 (C-1'), 64.2 (C-3), 128.1 (C-2''), 128.7 (C-3''), 133.5 (C-4''), 136.5 (C-1''), 172.7 (C-1), 196.9 (C-3'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3505 (br), 2975 (w), 1732 (m), 1685 (s), 1450 (w), 1291 (w), 1176 (s); HRMS (ESI⁺) *m/z* calcd. for $\text{C}_{13}\text{H}_{16}\text{NaO}_4^+ [\text{MNa}]^+$ 259.0941, found 259.0942.

(3*R*)-Hydroxybutyl (1*S*)-2-oxocyclohexanecarboxylate (**3.72a**),

(3*R*)-hydroxybutyl (1*R*)-2-oxocyclohexanecarboxylate (**3.72b**),

& (3*R*)-hydroxybutyl 2-hydroxycyclohex-1-enecarboxylate (**3.72c**)



The *title compounds* were synthesised by applying general procedure C on diketone **3.50** (95 mg, 0.448 mmol). The products (**3.72a**, **3.72b**, **3.72c**) were obtained as an inseparable mixture of three isomers (**3.72a**:**3.72b**:**3.72c** = 1:1:3.5) as a colourless oil (82 mg, 85%; *d.r.* and *e.e.* see table below) together with doubly reduced product **3.73** (3 mg, 3%; *d.r.* and *e.e.* not determined^{ak}) as a colourless oil.

Compound	3.72a/3.72b	3.72c
<i>d.r.</i>	1:1 (¹ H NMR)	not applicable
<i>e.e.</i>	not determined ^{al}	not determined ^{am}

Data for 3.72a, 3.72b, 3.72c: R_f (petrol/ethyl acetate; 50:50) = 0.54; ¹H NMR (500 MHz, CDCl₃) δ 1.22–1.27 (3 H, m, H-4'', **3.72a**, **3.72b**, **3.72c**), 1.54–2.56 (10 H, m, H-3', H-4', H-5', H-6', H-2'', **3.72a**, **3.72b**, **3.72c**), 3.39 (0.36 H, dd, $J_{1',6'} = 10.0$ Hz, $J_{1',6'} = 6.5$ Hz, H-1', **3.72a**, **3.72b**), 3.87–4.00 (1 H, m, H-3'', **3.72a**, **3.72b**, **3.72c**), 4.14–4.53 (2 H, m, H-1'', **3.72a**,

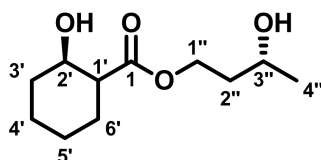
^{ak} The amount of **3.73** (3mg) was not sufficient for *d.r.* and *e.e.* determinations.

^{al} Not able to determine *e.e.* for **3.72a**, **3.72b**, and **3.72c** because they are inseparable.

^{am} Not able to determine *e.e.* for **3.72a**, **3.72b**, and **3.72c** because they are inseparable.

3.72b, 3.72c); ^{13}C NMR (125 MHz, CDCl_3) δ 21.8 (C-4', **3.72a, 3.72b, 3.72c**), 22.3 (C-5', **3.72a, 3.72b, 3.72c** and C-6', **3.72c**), 23.4 (C-4'', **3.72a, 3.72b, 3.72c**), 27.1 (C-6', **3.72a** or **3.72b**), 29.1 (C-3', **3.72c**), 29.9 (C-6', **3.72b** or **3.72a**), 37.9 (C-2'', **3.72a, 3.72b**), 38.1 (C-2'', **3.72c**), 41.6 (C-3', **3.72a** or **3.72b**), 41.7 (C-3', **3.72b** or **3.72a**), 57.3 (C-1', **3.72a** and **3.72b**), 61.4 (C-1'', **3.72c**), 62.4 (C-1'', **3.72a** or **3.72b**), 62.5 (C-1'', **3.72b** or **3.72a**), 64.7 (C-3'', **3.72a** or **3.72b**), 64.9 (C-3'', **3.72c**), 65.0 (C-3'', **3.72b** or **3.72a**), 97.5 (C-1', **3.72c**), 170.2 (C-1, **3.72a, 3.72b**), 172.7 (C-1, **3.72c**), 172.8 (C-2', **3.72c**), 206.4 (C-2', **3.72a** or **3.72b**), 206.5 (C-2', **3.72b** or **3.72a**); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3417 (br), 2937 (m), 1710 (m), 1651 (s), 1402 (w), 1298 (s), 1260 (s), 1218 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{11}\text{H}_{18}\text{NaO}_4^+$ [MNa]⁺ 237.1097, found 237.1102. **Data for 3.73:** see page 333.

(3R)-Hydroxybutyl (2R)-hydroxycyclohexanecarboxylate (3.73)

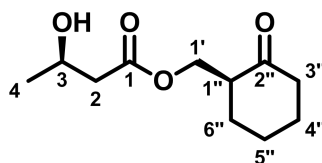


The *title compound* was synthesised by applying general procedure C on diketone **3.50** (95 mg, 0.448 mmol). The product (**3.73**) was obtained as a colourless oil (3 mg, 3%; *d.r.* and *e.e.* not determined^{an}) together with other reduction products **3.72a** (15 mg, 16%), **3.72b** (15 mg, 16%), and **3.72c** (53 mg, 56%). **Data for 3.73:** R_f (petrol/ethyl acetate; 20:80) = 0.31; ^1H NMR (500 MHz, CDCl_3) δ 1.24 (3 H, d, $J_{4'',3''} = 6.5$ Hz, H-4''), 1.41–1.94 (10 H, m, H-3', H-4', H-5', H-6', H-2''), 2.46–2.52 (1 H, m, H-1'), 3.87–3.97 (1 H, m, H-3''), 4.16–4.24 (2 H,

^{an} The amount of **3.73** (3mg) was not sufficient for *d.r.* and *e.e.* determinations.

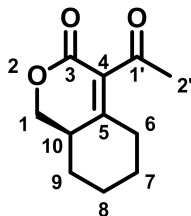
m, $1 \times \text{H-1''}$, H-2'), 4.35–4.41 (1 H, m, $1 \times \text{H-1''}$); ^{13}C NMR (125 MHz, CDCl_3) δ 20.0 (C-4'), 23.6 (C-4''), 23.8 (C-5'), 24.8 (C-6'), 31.8 (C-3'), 37.8 (C-2''), 46.8 (C-1'), 61.9 (C-1''), 65.2 (C-3''), 66.7 (C-2'), 175.9 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3416 (br), 2933 (s), 1710 (s), 1298 (m), 1259 (m), 1176 (s); HRMS (ESI^+) m/z calcd. for $\text{C}_{11}\text{H}_{20}\text{NaO}_4^+ [\text{MNa}]^+$ 239.1254, found 239.1256. **Data for 3.72a, 3.72b, 3.72c:** see page 332.

[(1*S*)-2-Oxocyclohexyl]methyl (3*R*)-hydroxybutanoate (3.74)



The *title compound* was synthesised by applying general procedure C on diketone **3.51** (110 mg, 0.519 mmol). The product (**3.74**) was obtained as a colourless oil (98 mg, 88%). [*d.r.* >99:1 (^1H NMR); *e.e.* > 99% (Mosher's analysis), see appendix D]. R_f (petrol/ethyl acetate; 20:80) = 0.63; $[\alpha]_{\text{D}}^{25} -38.0$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 1.23 (3 H, d, $J_{4,3} = 6.5$ Hz, H-4), 1.42–1.52 (1 H, m, $1 \times \text{H-6''}$), 1.66–1.74 (2 H, m, $1 \times \text{H-4''}$, $1 \times \text{H-5''}$), 1.90–1.97 (1 H, m, $1 \times \text{H-5''}$), 2.07–2.14 (1 H, m, $1 \times \text{H-4''}$), 2.14–2.20 (1 H, m, $1 \times \text{H-6''}$), 2.30–2.53 (4 H, m, H-2, H-3''), 2.65–2.71 (1 H, m, H-1''), 2.98 (1 H, br.s, C(3)OH), 4.10 (1 H, dd, $J_{1',1''} = 11.5$ Hz, $J_{1',1'} = 6.0$ Hz, $1 \times \text{H-1'}$), 4.16–4.23 (1 H, m, H-3), 4.41 (1 H, dd, $J_{1',1''} = 11.5$ Hz, $J_{1',1'} = 6.5$ Hz, $1 \times \text{H-1'}$); ^{13}C NMR (125 MHz, CDCl_3) δ 22.4 (C-4), 24.7 (C-5''), 27.6 (C-4''), 30.8 (C-6''), 42.0 (C-3''), 42.8 (C-2), 49.4 (C-1''), 63.4 (C-1'), 64.2 (C-3), 172.6 (C-1), 210.4 (C-2''); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3444 (br), 2937 (m), 1732 (s), 1710 (s), 1292 (m), 1176 (m), 1084 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{11}\text{H}_{18}\text{NaO}_4^+ [\text{MNa}]^+$ 237.1097, found

237.1091.

(*R*)-4-Acetyl-6,7,8,8a-tetrahydro-1*H*-isochromen-3(5*H*)-one (3.75)

The *title compound* was synthesised by applying general procedure C on diketone **3.51** (110 mg, 0.519 mmol). The product (**3.75**) was obtained as a colourless oil (4 mg, 4%; *d.r.* not applicable, *e.e.* not determined^{ao}) as a side product. R_f (petrol/ethyl acetate; 20:80) = 0.75; ^1H NMR (500 MHz, CDCl_3) δ 1.16–1.27 (1 H, m, 1 $\times$ H-9), 1.36–1.52 (2 H, m, 1 $\times$ H-7, 1 $\times$ H-8), 1.84–1.99 (3 H, m, 1 $\times$ H-7, 1 $\times$ H-8, 1 $\times$ H-9), 2.08–2.15 (1 H, m, 1 $\times$ H-6), 2.43 (3 H, s, H-2'), 2.56–2.63 (1 H, m, H-10), 2.83 (1 H, d, $J_{6,6} = 16.0$ Hz, 1 $\times$ H-6), 4.01 (1 H, t, $J_{1,1} = J_{1,10} = 11.0$ Hz, 1 $\times$ H-1), 4.37 (1 H, dd, $J_{1,1} = 11.0$ Hz, $J_{1,10} = 5.5$ Hz, 1 $\times$ H-1); ^{13}C NMR (125 MHz, CDCl_3) δ 23.8 (C-8), 25.6 (C-7), 28.8 (C-9), 30.0 (C-6), 31.3 (C-2'), 35.7 (C-10), 70.0 (C-1), 128.3 (C-4), 161.6 (C-3), 162.9 (C-5), 200.9 (C-1'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2936 (m), 2862 (m), 1703 (s), 1404 (m), 1309 (m), 1070 (m); HRMS (ESI^+) m/z calcd. for $\text{C}_{11}\text{H}_{14}\text{NaO}_3^+ [\text{MNa}]^+$ 217.0835, found 217.0839.

^{ao} The amount of **3.75** (4mg) was not sufficient for *e.e.* determination.

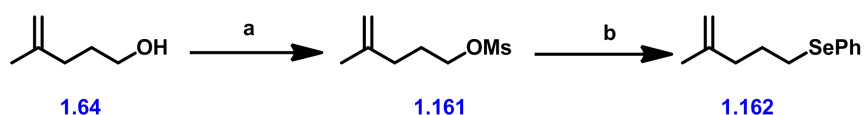
Miscellaneous compounds

In this section, compounds that are not mentioned in the previous chapters are described below. These compounds were made to conduct model studies in order to preserve precious intermediates and validate the viability of the method.

Chapter 1 related compounds

1. Deoxygenation model studies

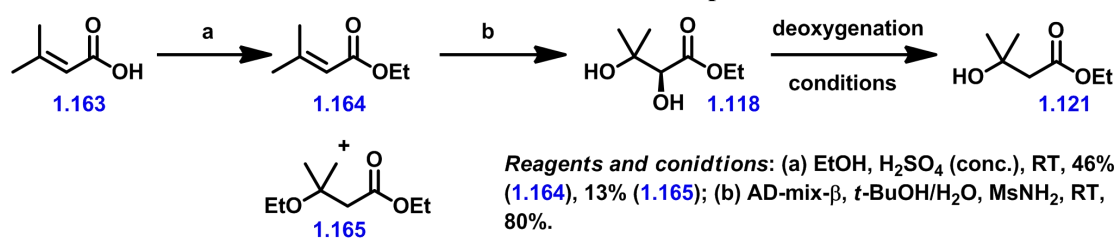
To test the nucleophilic attack towards leaving group (page 43) so as to achieve deoxygenation, NaSePh was prepared by sonication then used *in situ* to displace mesylate **1.161** to generate selenide **1.162** (Scheme 1).



Reagents and conditions: (a) MsCl, py, 0 °C, 84%; (b) NaSePh, THF, RT, 67%.

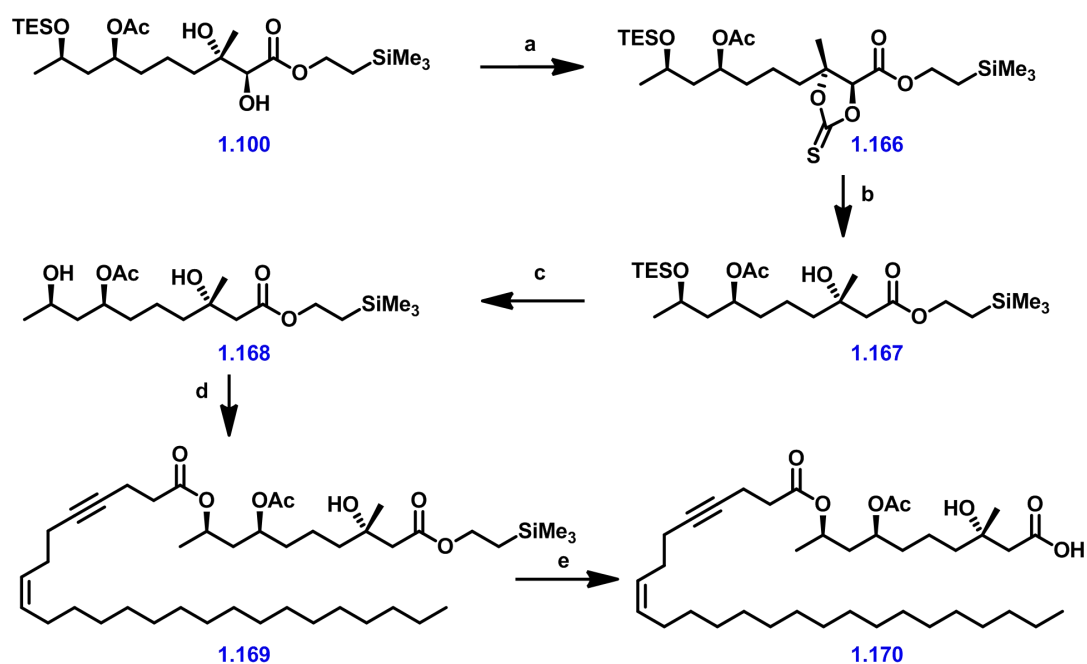
Scheme 1

In order to synthesise diol **1.118** towards cyclic sulfite **1.119** and cyclic sulfate **1.120** (page 45), a SAD reaction was performed on alkene **1.164**, which came from an esterification of unsaturated acid **1.163** (Scheme 2).



Scheme 2

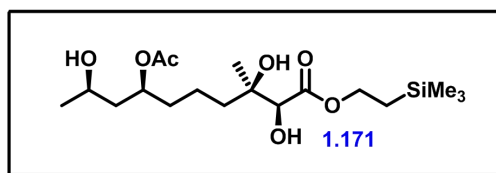
Finally, when Barton-McCombie conditions were found to be feasible for α-deoxygenation (page 46), model diol **1.100** was used to test the deoxygenation conditions. Pleasingly, desired product **1.167** was obtained for further investigations including selective TES deprotection, esterification and TMSE removal (**Scheme 3**).



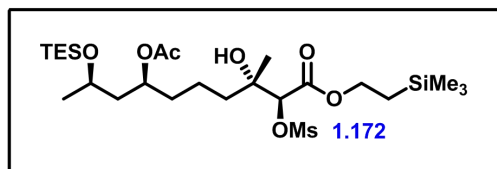
Reagents and conditions: (a) TCDI, DMAP, DCM, reflux, 100%; (b) Bu₃SnH, AIBN, toluene, reflux, 66%; (c) 1% HF, aq. CH₃CN, 20 °C, 57%; (d) **1.57**, *i*-Pr₂NEt, DIC, DMAP, DCM, 20 °C, 51%; (e) TASf, DMF, 20 °C, 57 %.

Scheme 3

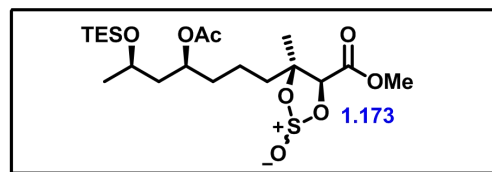
Other compounds involved in deoxygenation attempts are listed in **Scheme 4**.



side product in making cyclic sulfite
from diol **1.88**



Model mesylate synthesised from diol **1.88**



Model cyclic sulfite synthesised
from diol **1.97**

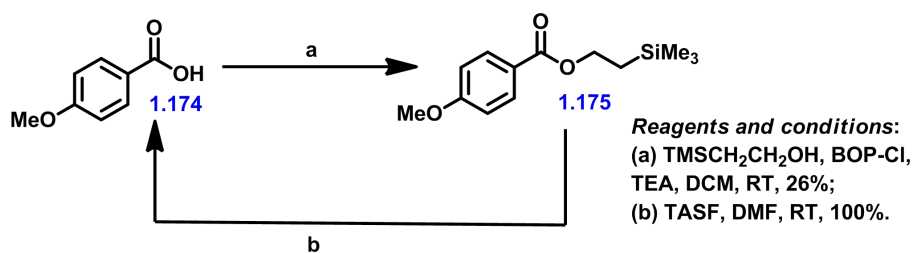
Scheme 4

2. TMSE group deprotection model studies (page 54)

As has been described, TBAF turned out to be unreliable for TMSE group deprotection.

Before TASF was used to remove the silyl group on TMSE ester **1.153**, a model compound

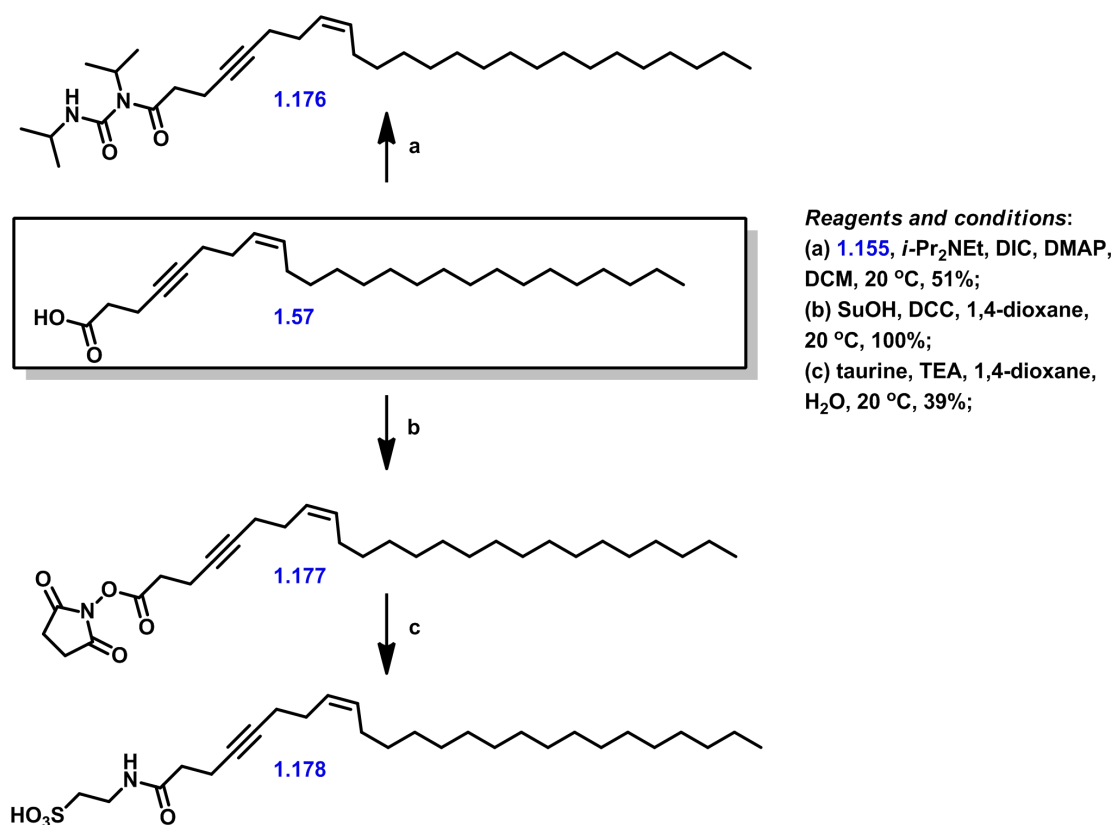
1.175 was prepared to ascertain the viability of the TASF conditions (Scheme 5).



Scheme 5

3. Taurine coupling model (page 54)

Taurine coupling is the last step to complete the taurospongins A synthesis. However, as mentioned before (page 54), Jacobsen's method¹¹ gave undesired results, therefore, Kobayashi's protocol³⁸ was repeated to synthesise amide **1.178** as a model system (Scheme 6).

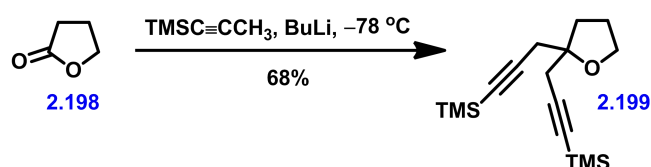


Scheme 6

Chapter 2 related compounds

1. Lactone propargylation model studies (page 105)

In order to test the organometallic addition using Corey's method³⁹, γ -butyrolactone was subjected to propargylation which resulted in over-alkylation. Therefore, TMSCl was included in order to trap the so-formed lactol *in situ* for subsequent propargylation studies (Scheme 7).



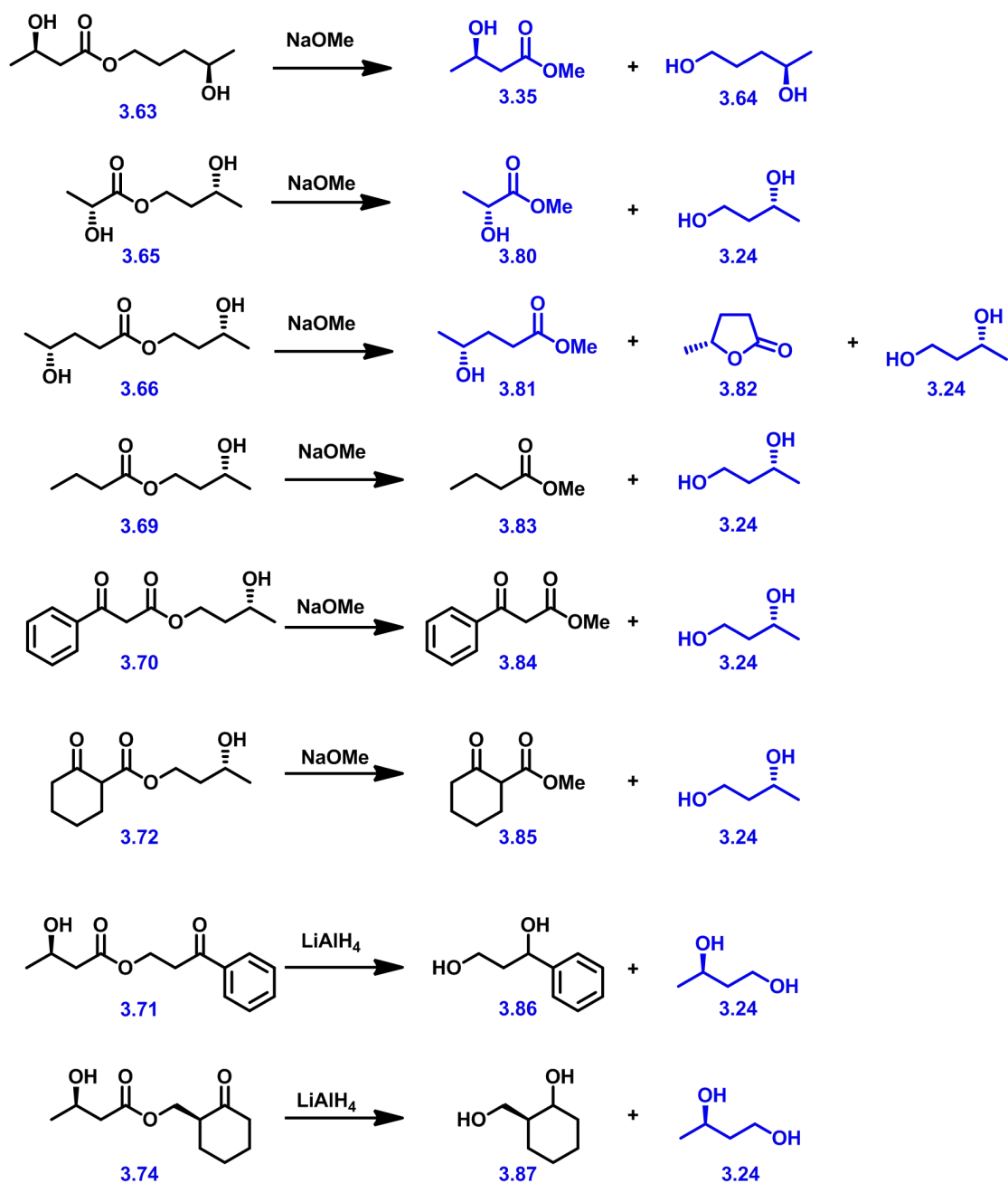
Scheme 7

Chapter 3 related compounds

1. Absolute configuration determination of reduced diketones (page 154–160)

Two different methods (methanolysis and LAH reduction) were employed to provide known molecules from which the absolute configurations could be determined (Scheme 8). The specific rotations of chiral fragments (in blue in Scheme 8) were determined and compared with known data, as summarised in Appendix C; for the achiral fragments^{ap} and diol 3.87, the data are summarised in this section.

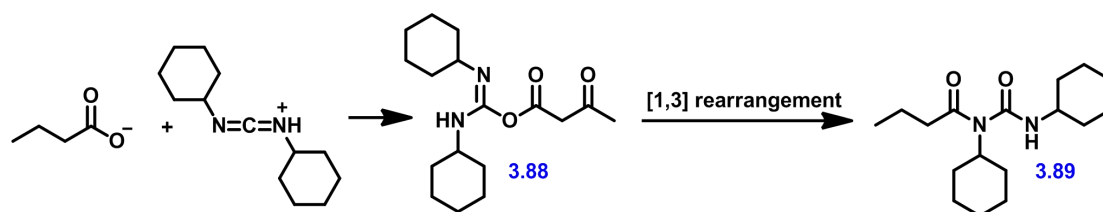
^{ap} For ester 3.83, probably due to its volatility, it could not be isolated after hydrolysis.



Scheme 8

Other miscellaneous compounds (*cf.* page 147)

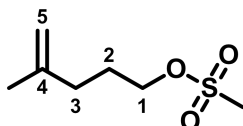
As mentioned earlier, formal [1,3]-rearrangement in the Steglich⁴⁰ reaction would decrease the yield of desired esters **3.45**–**3.47**. As an example, *N*-acyl urea **3.89** was isolated (**Scheme 9**).



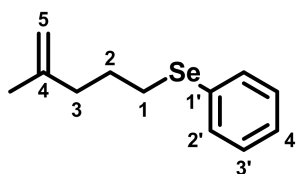
Scheme 9

Experimental Procedures and characterisation data for miscellaneous compounds

Chapter 1 related compounds

4-Methylpent-4-en-1-yl methanesulfonate (**1.161**)⁴¹

To a stirred solution of alcohol **1.64** (100 mg, 1.00 mmol) in freshly distilled pyridine (10 mL) was added methanesulfonyl chloride (120 μ L, 1.55 mmol) at 0 °C. When TLC showed there was no starting material, ether (30 mL) and CuSO₄ solution (sat. aq., 20 mL) were added to dilute the solution. The organic layer was further washed with CuSO₄ solution (sat. aq., 2 $\times$ 15 mL) and organic layer was dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the title compound (**1.161**) as a colourless oil (150 mg, 84%). R_f (petrol/ether; 70:30) = 0.27; ¹H NMR (400 MHz, CDCl₃) δ 1.74 (3 H, s, C(4)CH₃), 1.88–1.95 (2 H, m, H-2), 2.14 (2 H, t, $J_{3,2}$ = 7.0 Hz, H-3), 3.01 (3 H, s, SCH₃), 4.24 (2 H, t, $J_{1,2}$ = 6.5 Hz, H-1), 4.72 (1 H, s, 1 $\times$ H-5), 4.79 (1 H, s, 1 $\times$ H-5); ¹³C NMR (100 MHz, CDCl₃) δ 22.3 (C(4)CH₃), 26.9 (C-2), 33.3 (C-3), 37.3 (SCH₃), 69.5 (C-1), 111.1 (C-5), 143.8 (C-4); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2969 (m), 2942 (m), 1651 (m), 1447 (m), 1353 (s), 1174 (s); HRMS (ESI⁺) m/z calcd. for C₇H₁₄NaO₃S⁺ [MNa]⁺ 201.0556, found 201.0558.

(4-Methylpent-4-en-1-yl)(phenyl)selenane (1.162)

- **Preparation of NaSePh solution**

Na (30–35% dispersion in paraffin, 77 mg, *ca.* 1.17 mmol) was added into a solution of benzophenone (*ca.* 2 mg) in anhydrous THF (2 mL) under argon. The mixture was then sonicated until a deep blue colour was developed. A solution of diphenyldiselenide (158 mg, 0.507 mmol) in THF (1 mL) was added dropwise to the deep blue solution. After 15 min, the reaction mixture turned pale purple and sonication was continued until all traces of colour disappeared.

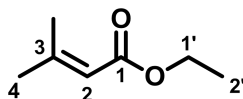
- **Synthesis of phenylselenane 1.162**

To the NaSePh solution prepared as above was added a solution of mesylate **1.161** (150 mg, 0.84 mmol) in anhydrous THF (8 mL) at RT. After 1 h, H₂O (20 mL) and ether (20 mL) were added to dilute the mixture. The aqueous layer was extracted with ether (3 × 20 mL) and the combined organic layers were dried (MgSO₄) then concentrated. Flash chromatography (petrol then petrol/ether, 90:10) furnished the *title compound* (**1.162**) as a yellow liquid (135 mg, 67%). *R_f* (petrol/ether; 80:20) = 0.88; ¹H NMR (400 MHz, CDCl₃) δ 1.70 (3 H, s, C(4)CH₃), 1.85 (2 H, qn, *J*_{2,1} = *J*_{2,3} = 7.5 Hz, H-2), 2.14 (2 H, t, *J*_{3,2} = 7.5 Hz, H-3), 2.91 (2 H,

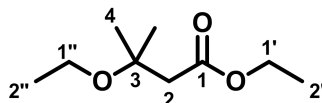
Experimental – Miscellaneous Compounds

t, $J_{1,2} = 7.5$ Hz, H-1), 4.68 (1 H, s, $1 \times$ H-5), 4.74 (1 H, s, $1 \times$ H-5), 7.24–7.29 (3 H, m, arom), 7.48–7.53 (2 H, m, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 22.3 (C(4)CH₃), 27.4 (C-1), 27.9 (C-2), 37.7 (C-3), 110.6 (C-5), 126.7, 128.7, 130.4, 132.5 (arom), 144.7 (C-4); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3072 (m), 2967 (m), 2934 (s), 1649 (m), 1579 (m), 1477 (s), 1374 (m), 1023 (m); HRMS (FI⁺) m/z calcd. for $\text{C}_{12}\text{H}_{16}\text{Se}^+ [\text{M}]^+$ 240.0417, found 240.0413.

Ethyl 3-methylbut-2-enoate (**1.164**)⁴²

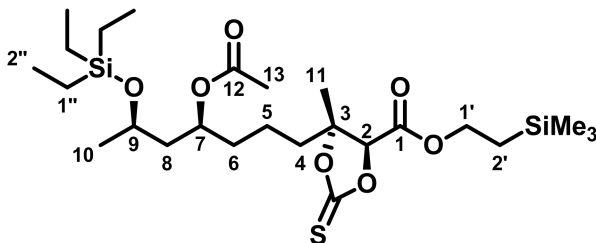


Concentrated H_2SO_4 (1.1 mL) was added to a solution of 3,3-dimethylacrylic acid **1.163** (1.00 g, 10 mmol) in absolute ethanol (12.5 mL). The resulting mixture was heated under reflux for 24 h. H_2O (40 mL) and NaOH solution (5% in H_2O , 2.5 mL) were added and the resulting mixture was extracted with ether (3×30 mL). The combined organic layers were dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 90:10) furnished the title compound (**1.164**) as a colourless oil (600 mg, 46%). R_f (petrol/ether; 70:30) = 0.84; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (3 H, t, $J_{2',1'} = 7.0$ Hz, H-2'), 1.87 (3 H, s, H-4), 2.15 (3 H, s, C(3)CH₃), 4.12 (2 H, q, $J_{1',2'} = 7.0$ Hz, H-1'), 5.65 (1 H, s, H-2); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (C-2'), 20.1 (C-4), 27.3 (C(3)CH₃), 59.4 (C-1'), 116.1 (C-2), 156.4 (C-3), 166.7 (C-1). All the other data are as reported.

Ethyl 3-ethoxy-3-methylbutanoate (1.165)⁴³

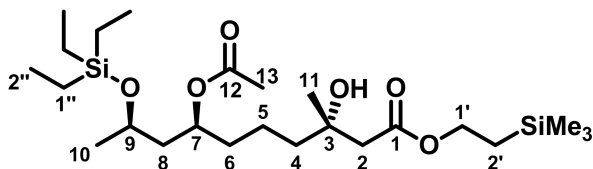
Concentrated H₂SO₄ (1.1 mL) was added to a solution of 3,3-dimethylacrylic acid **1.163** (1.00 g, 10.0 mmol) in absolute ethanol (12.5 mL). The resulting mixture was heated under reflux for 24 h then cooled to RT. H₂O (40 mL) and NaOH solution (5% in H₂O, 2.5 mL) were added and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 90:10) furnished the title compound (**1.165**) as a colourless oil (232 mg, 13%) as a side product. *R_f* (petrol/ether; 70:30) = 0.43; ¹H NMR (400 MHz, CDCl₃) δ 1.16 (3 H, t, *J*_{2'',1''} = 7.0 Hz, H-2''), 1.27 (3 H, t, *J*_{2',1'} = 7.0 Hz, H-2'), 1.31 (6 H, s, H-4, C(3)CH₃), 2.51 (2 H, s, H-2), 3.45 (2 H, q, *J*_{1'',2''} = 7.0 Hz, H-1''), 4.14 (2 H, q, *J*_{1',2'} = 7.0 Hz, H-1'); ¹³C NMR (100 MHz, CDCl₃) δ 14.2 (C-2'), 15.9 (C-2''), 26.0 (C-4 and C(3)CH₃), 45.1 (C-2), 56.9 (C-1''), 60.2 (C-1'), 73.6 (C-3), 171.0 (C-1). All the other data are as reported.

2-Trimethylsilylethyl (2*S*,3*S*,7*S*,9*R*)-7-acetoxy-3-methyl-2,3-thiocarbonyldioxy-9-(triethylsilyloxy)decanoate (1.166)



A stirred solution of diol **1.100** (30 mg, 59.3 μmol), 1,1'-thiocarbonyldiimidazole (16 mg, 89.8 μmol), and DMAP (9.5 mg, 77.8 μmol) in anhydrous DCM (3 mL) was refluxed under argon atmosphere for 5 h. The reaction mixture was then cooled to RT and concentrated. The residue was purified by flash chromatography (petrol/ether, 90:10 then 80:20) to furnish the *title compound* (**1.166**) as a colourless oil (33 mg, 100%). R_f (petrol/ether; 50:50) = 0.74; $[\alpha]_{\text{D}}^{25} -15.8$ (c 0.58, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.07 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.06–1.10 (2 H, m, H-2'), 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.44–1.62 (9 H, m, $1 \times$ H-4, H-5, H-6, $1 \times$ H-8, H-11), 1.74–1.84 (2 H, m, $1 \times$ H-4, $1 \times$ H-8), 2.05 (3 H, s, H-13), 3.79–3.85 (1 H, m, H-9), 4.30–4.39 (2 H, m, H-1'), 4.84 (1 H, s, H-2), 4.89–4.94 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.8 (C-1''), 6.9 (C-2''), 17.5 (C-2'), 19.0 (C-5), 21.2 (C-13), 23.4 (C-10), 24.0 (C-11), 34.5 (C-6), 34.7 (C-4), 44.1 (C-8), 65.3 (C-9), 65.4 (C-1'), 71.1 (C-7), 85.3 (C-2), 91.3 (C-3), 165.1 (C-1), 170.6 (C-12), 189.5 (C=S); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956 (s), 1735 (s), 1458 (m), 1359 (m), 1249 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{25}\text{H}_{48}\text{NaO}_7\text{SSi}_2^+$ $[\text{MNa}]^+$ 571.2551, found 571.2551.

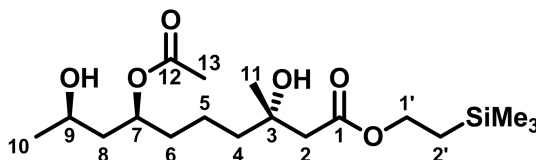
(3*S*,7*S*,9*R*)-2-Trimethylsilylethyl 7-acetoxy-3-hydroxy-3-methyl-9-(triethylsilyloxy)decanoate (1.167)



To a solution of thionocarbonate **1.166** (30 mg, 55 μ mol) in degassed toluene (1.1 mL) under argon atmosphere was added Bu_3SnH (18 μ L, 0.066 mmol) followed by addition of AIBN solution (0.12 M in toluene, 70 μ L, 8.25 μ mol). The resulting mixture was heated under reflux for 3 h and quenched with NH_4Cl solution (sat. aq., 5 mL). The mixture was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried (MgSO_4) and concentrated. Slow flash chromatography (petrol/ether, 90:10 then 80:20) furnished the *title compound* (**1.167**) as a colourless oil (18 mg, 66%). R_f (petrol/ether; 50:50) = 0.73; $[\alpha]_D^{25} +1.20$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ -0.05 (9 H, s, SiCH_3), 0.59 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.96 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.01 (2 H, m, H-2'), 1.17 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.22 (3 H, s, H-11), 1.37 – 1.63 (7 H, m, H-4, H-5, H-6, $1 \times$ H-8), 1.82 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, $1 \times$ H-8), 2.03 (3 H, s, H-13), 2.40 (1 H, d, $J_{2,2} = 15.5$ Hz, $1 \times$ H-2), 2.47 (1 H, d, $J_{2,2} = 15.5$ Hz, $1 \times$ H-2), 3.59 (1 H, br.s, OH), 3.82 (1 H, m, H-9), 4.21 (2 H, m, H-1'), 4.95 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 4.9 (C-1''), 6.8 (C-2''), 17.3 (C-2'), 19.5 (C-5), 21.2 (C-13), 23.5 (C-10), 26.6 (C-11), 35.0 (C-6), 41.7 (C-4), 44.3 (C-8), 44.9 (C-2), 63.0 (C-1'), 65.4 (C-9), 70.8 (C-3), 71.6 (C-7), 170.6 (C-12), 173.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3519 (br), 2956 (s), 1737 (s), 1720 (s), 1460 (w), 1376 (m), 1249 (s); HRMS (ESI $^+$) m/z calcd. for

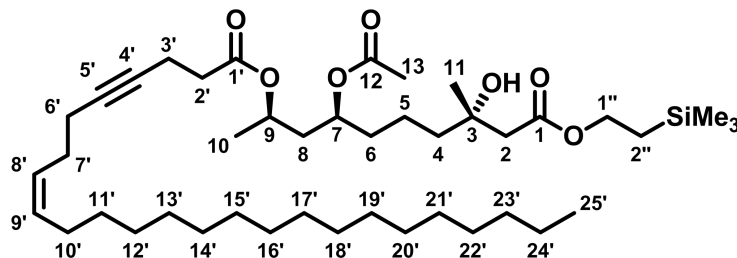
$\text{C}_{24}\text{H}_{50}\text{NaO}_6\text{Si}_2^+ [\text{MNa}]^+$ 513.3038, found 513.3043.

(3*S*,7*S*,9*R*)-2-Trimethylsilylethyl 7-acetoxy-3,9-dihydroxy-3-methyldecanoate (1.168)



To a stirred solution of silyl ether **1.167** (15.5 mg, 31.6 μmol) in MeCN (0.7 mL) was added hydrofluoric acid solution (1% in H_2O , 66 μL , 31.6 μmol). The reaction mixture was stirred for 60 min before being quenched with NaHCO_3 solution (sat. aq., 5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with NH_4Cl solution (sat. aq., 5 mL), dried (MgSO_4) and concentrated. The residue (**1.168**) was subjected to next step without further purification (13 mg, 100%). R_f (petrol/ether; 30:70) = 0.25; $[\alpha]_{\text{D}}^{25} -0.80$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.05 (9 H, s, SiCH_3), 1.01 (2 H, m, H-2'), 1.20 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.22 (3 H, s, H-11), 1.35–1.67 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.79 (1 H, m, 1 $\times$ H-8), 2.05 (3 H, s, H-13), 2.39 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 2.47 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 3.60 (1 H, s, 1 $\times$ OH), 3.87 (1 H, m, H-9), 4.21 (2 H, m, H-1'), 4.99 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 17.3 (C-2'), 19.5 (C-5), 21.3 (C-13), 23.8 (C-10), 26.7 (C-11), 34.9 (C-6), 41.6 (C-4), 43.6 (C-8), 44.9 (C-2), 63.0 (C-1'), 65.8 (C-7), 70.8 (C-3), 72.5 (C-9), 171.0 (C-12), 173.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3446 (br), 2957 (s), 2874 (s), 1733 (s), 1460 (w), 1376 (m), 1250 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{18}\text{H}_{36}\text{O}_6\text{SiNa}^+ [\text{MNa}]^+$ 399.2173, found 399.2175.

2-Trimethylsilylethyl (3*S*,7*S*,9*R*)-7-acetoxy-3-hydroxy-3-methyl-9-[(*Z*)-pentacos-8'-en-4'-ynoxy]decanoate (1.169)

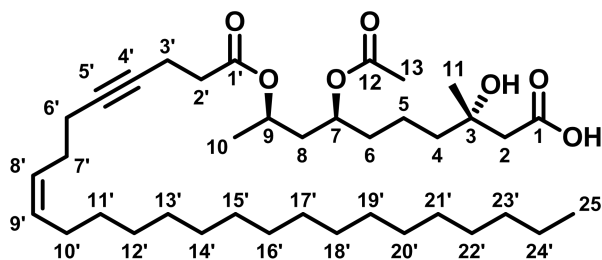


To a solution of alcohol **1.168** (12 mg, 31.6 μmol) and acid **1.57** (15 mg, 41 μmol) in DCM (2 mL) was added successively *N,N*-diisopropylethylamine (22 μL , 0.126 mmol), DMAP (2 mg, 15.8 μmol) and *N,N'*-diisopropylcarbodiimide (19.6 μL , 0.126 mmol). The resulting mixture was stirred for 15 h at RT then poured into a mixture of NH_4Cl solution (sat. aq., 5 mL) and ether (10 mL). The layers were separated and the organic layer was washed with hydrochloric acid (1.2 M in H_2O , 5 mL), NaHCO_3 solution (sat. aq., 5 mL), and brine (5 mL). The organic layer was dried (MgSO_4), and concentrated. The residue was purified by flash chromatography (petrol/ether, 85:15) to furnish the *title compound* (**1.169**) as a colourless oil (12 mg, 51%). R_f (petrol/ether; 30:70) = 0.76; $[\alpha]_{\text{D}}^{25} -1.00$ (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.05 (9 H, s, SiCH_3), 0.88 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 0.99–1.02 (2 H, m, H-2''), 1.22 (3 H, s, H-11), 1.24 (3 H, d, $J_{10,9} = 6.5$ Hz, H-10), 1.25 (28 H, br.s, H-11'–H-24'), 1.38–1.58 (6 H, m, H-4, H-5, H-6), 1.68 (1 H, ddd, $J_{8,8} = 14.5$ Hz, $J_{8,7 \text{ or } 8,9} = 6.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 1.94 (1 H, ddd, $J_{8,8} = 14.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.0$ Hz, $J_{8,9 \text{ or } 8,7} = 6.5$ Hz, 1 $\times$ H-8), 2.01–2.03 (2 H, m, H-10') 2.04 (3 H, s, H-13), 2.13–2.22 (4 H, m, H-6', H-7'), 2.39 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 2.46 (4 H, app.s, H-2', H-3'), 2.47 (1 H, d, $J_{2,2} = 15.5$ Hz, 1 $\times$ H-2), 3.59 (1 H, s, OH), 4.19–4.23 (2 H, m, H-1''), 4.91–4.98 (2 H, m, H-7, H-9), 5.35–5.46

Experimental – Miscellaneous Compounds

(2 H, m, H-8', H-9'); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 14.1 (C-25'), 14.8 (C-3'), 17.3 (C-2''), 19.1 (C-6'), 19.4 (C-5), 20.0 (C-10), 21.2 (C-13), 22.7 (C-24'), 26.6 (C-11), 26.8 (C-7'), 27.3 (C-10'), 29.3–31.9 (C-11'–C-23'), 34.3 (C-2'), 34.6 (C-6), 40.1 (C-8), 41.6 (C-4), 44.9 (C-2), 63.0 (C-1''), 68.2 (C-9), 70.7 (C-7), 70.9 (C-3), 78.2 (C-4'), 80.7 (C-5'), 127.8 (C-8'), 131.2 (C-9'), 170.6 (C-12), 171.5 (C-1'), 173.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3520 (br), 2925 (s), 2854 (s), 1737 (s), 1460 (w), 1374 (w), 1250 (m); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{43}\text{H}_{78}\text{O}_7\text{SiNa}^+ [\text{MNa}]^+$ 757.5409, found 757.5411.

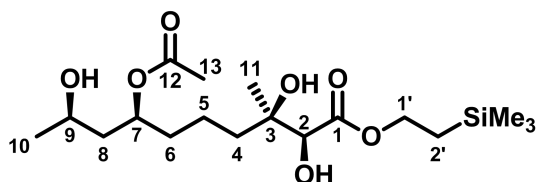
(3*S*,7*S*,9*R*)-7-Acetoxy-3-hydroxy-3-methyl-9-[(*Z*)-pentacos-8-en-4-ynoyloxy]decanoic acid (**1.170**)



To a solution of ester **1.169** (9 mg, 12.3 μmol) in DMF (0.3 mL) was added a solution of tris(dimethylamino)sulfonium difluorotrimethylsilicate (0.145 M in DMF, 170 μL , 24.7 μmol) at RT. The resulting mixture was stirred for 60 min. Ethyl acetate (10 mL) was added to dilute the mixture and it was washed with hydrochloric acid (1.2 M in H_2O , 2.5 mL), dried (MgSO_4), and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20 then ethyl acetate) furnished the *title compound* (**1.170**) as a colourless oil (5 mg, 57%). R_f (DCM/MeOH; 95:5) = 0.32; $[\alpha]_{\text{D}}^{25}$ -1.20 (c 0.50, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.88 (3 H, t, $J_{25',24'} = 7.0$ Hz, H-25'), 1.24–1.62 (40 H, m, H-11, H-4, H-5, H-6, H-10,

H-11'–H-24'), 1.66–1.71 (1 H, m, 1 × H-8), 1.93–1.99 (1 H, m, 1 × H-8), 2.00–2.06 (5 H, m, H-10', H-13) 2.14–2.23 (4 H, m, H-6', H-7'), 2.47–2.51 (5 H, m, H-2', H-3', 1 × H-2), 2.57 (1 H, d, $J_{2,2} = 16.0$ Hz, 1 × H-2), 4.93–5.01 (2 H, m, H-7, H-9), 5.36–5.47 (2 H, m, H-8', H-9'); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-25'), 14.8 (C-3'), 19.1 (C-6'), 19.3 (C-5), 20.0 (C-10), 21.2 (C-13), 22.7 (C-24'), 26.6 (C-11), 26.8 (C-7'), 27.3 (C-10'), 29.3–31.9 (C-11'–C-23'), 34.3 (C-2'), 34.4 (C-6), 40.2 (C-8), 41.4 (C-4), 44.6 (C-2), 68.2 (C-9), 70.7 (C-7), 71.1 (C-3), 78.2 (C-4'), 80.7 (C-5'), 127.8 (C-8'), 131.3 (C-9'), 170.9 (C-12), 171.7 (C-1'), 174.2 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3418 (br), 2923 (s), 2853 (s), 1737 (s), 1463 (m), 1375 (m), 1243 (s); HRMS (ESI[−]) m/z calcd. for $\text{C}_{38}\text{H}_{65}\text{O}_7$ [M–H][−] 633.4736, found 633.4739.

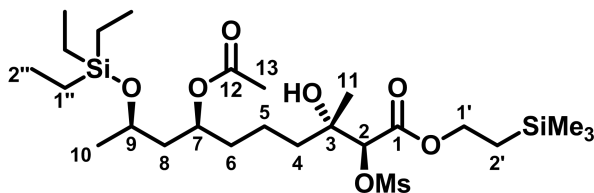
(2*S*,3*R*,7*S*,9*R*)-2-Trimethylsilylethyl 7-acetoxy-2,3,9-trihydroxy-3-methyldecanoate
(1.171)



To a stirred solution of diol **1.88** (10 mg, 19.7 μmol) in freshly distilled pyridine (0.5 mL) was added thionyl chloride (1.6 μL , 21.4 μmol) at -30 °C. The mixture was stirred for 14 h, then diluted with ether (20 mL), washed with CuSO_4 solution (sat. aq., 3×10 mL), dried (MgSO_4), and concentrated. Flash chromatography (ether) furnished the *title compound* (**1.171**) as a colourless oil (5 mg, 68%) as a side product. R_f (ether) = 0.33; $[\alpha]_{\text{D}}^{26} +4.05$ (c 0.37, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.07 (9 H, s, SiCH_3), 1.05–1.09 (2 H, m, H-2'), 1.16 (3 H, s, H-11), 1.21 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.37–1.69 (7 H, m, H-4, H-5, H-6, 1 ×

H-8), 1.80 (1 H, dt, $J_{8,8} = 15.0$ Hz, $J_{8,7} = J_{8,9} = 7.5$ Hz, 1 $\times$ H-8), 2.06 (3 H, s, H-13), 2.54 (1 H, br.s, 1 $\times$ OH), 3.15 (1 H, d, $J_{OH,2} = 6.5$ Hz, C(2)OH), 3.85–3.91 (1 H, m, H-9), 3.97 (1 H, d, $J_{2,OH} = 6.5$ Hz, H-2), 4.30–4.34 (2 H, m, H-1'), 4.99–5.04 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ -1.6 (SiCH_3), 17.6 (C-2'), 19.1 (C-5), 21.3 (C-13), 22.4 (C-11), 23.8 (C-10), 34.9 (C-6), 37.8 (C-4), 43.7 (C-8), 64.6 (C-1'), 65.8 (C-9), 72.4 (C-7), 73.8 (C-3), 76.0 (C-2), 171.1 (C-12), 173.3 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3445 (br), 2958 (s), 1732 (s), 1460 (m), 1376 (m), 1252 (s); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{18}\text{H}_{36}\text{NaO}_7\text{Si}^+$ $[\text{MNa}]^+$ 415.2123, found 415.2117.

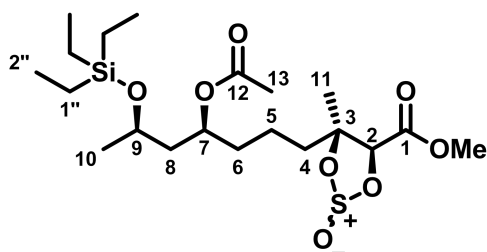
(2*S*,3*S*,7*S*,9*R*)-2-Trimethylsilylethyl 7-acetoxy-3-hydroxy-3-methyl-2-(methylsulfonyloxy)-9-(triethylsilyloxy)decanoate (1.172)



To a stirred solution of diol **1.100** (20 mg, 39.5 μmol) in freshly distilled pyridine (0.5 mL) was added methanesulfonyl chloride (3.67 μL , 47.3 μmol) at 0 $^{\circ}\text{C}$. When TLC showed there was no starting material left in the reaction mixture, ether (20 mL) was added to dilute the solution. The mixture was then washed with CuSO_4 solution (sat. aq., 2 $\times$ 10 mL), and the aqueous layer was extracted with ether (2 $\times$ 10 mL). The combined organic layers were dried (MgSO_4) then concentrated to furnish the *title compound* (**1.172**) for further steps without any purification (21 mg, 91%). R_f (petrol/ether; 50:50) = 0.17; $[\alpha]_{\text{D}}^{25}$ -10.0 (c 1.00, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.08 (s, 9 H, SiCH_3), 0.60 (6 H, q, $J_{1'',2''} = 8.0$ Hz,

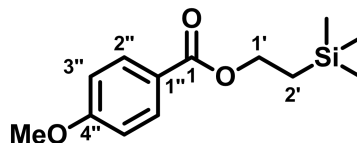
H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.06–1.10 (2 H, m, H-2') 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.27 (3 H, s, H-11), 1.42–1.70 (7 H, m, H-4, H-5, H-6, 1 × H-8), 1.83 (1 H, ddd, $J_{8,8} = 14.0$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 × H-8), 2.05 (3 H, s, H-13), 2.65 (1 H, br.s, OH), 3.16 (3 H, s, SCH₃), 3.80–3.86 (1 H, m, H-9), 4.31–4.35 (2 H, m, H-1'), 4.84 (1 H, s, H-2), 4.94–4.99 (1 H, m, H-7); ¹³C NMR (125 MHz, CDCl₃) δ −1.6 (SiCH₃), 4.9 (C-1''), 6.8 (C-2''), 17.5 (C-2'), 18.3 (C-5), 21.2 (C-13), 23.0 (C-11), 23.5 (C-10), 34.8 (C-6), 37.4 (C-4), 39.1 (SCH₃), 44.4 (C-8), 65.0 (C-1'), 65.4 (C-9), 71.3 (C-7), 73.1 (C-3), 82.0 (C-2), 168.1 (C-1), 170.9 (C-12); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3516 (br), 2959 (s), 2878 (s), 1737 (s), 1366 (s), 1259 (s), 1178 (s); HRMS (ESI⁺) m/z calcd. for C₂₅H₅₂NaO₉SSi₂⁺ [MNa]⁺ 607.2763, found 607.2752.

(4*S*,5*R*)-Methyl 5-[(4*S*,6*R*)-4-acetoxy-6-(triethylsilyloxy)heptyl]-5-methyl-1,3,2-dioxathiolane-4-carboxylate 2-oxide (1.173)

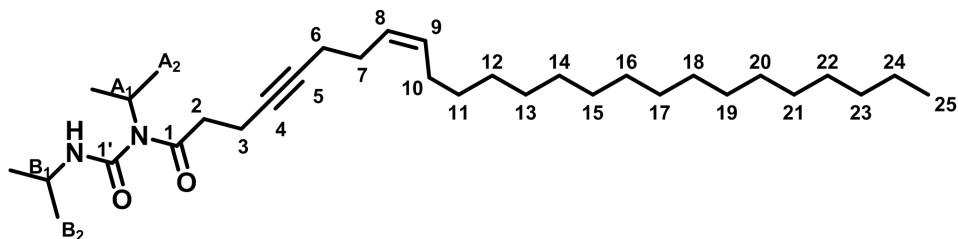


To a stirred solution of diol **1.97** (9 mg, 19.3 μmol) and triethylamine (7.6 μL , 53.5 μmol) in DCM (2 mL) was added thionyl chloride (1.6 μL , 21.4 μmol) at −30 °C. Stirring was continued for another 45 min before H₂O (2 mL) and DCM (5 mL) were added. The mixture was washed with NaHCO₃ solution (sat. aq., 5 mL) and H₂O (5 mL), and the organic layer was dried (MgSO₄) and concentrated. Flash chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.173**), as a mixture of two diastereomers **A** and **B** (10 mg, 100%, **A**:**B** =

2:1) as a colourless oil. R_f (petrol/ether; 50:50) = 0.68; IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2957 (s), 2877 (s), 1771 (s), 1736 (s), 1459 (m), 1439 (m), 1375 (m), 1239 (s), 1051 (s), 1018 (s); HRMS (ESI⁺) m/z calcd. for $\text{C}_{20}\text{H}_{38}\text{NaO}_8\text{SSi}^+ [\text{MNa}]^+$ 489.1949, found 489.1948. **NMR data for diastereomer A:** ^1H NMR (500 MHz, CDCl_3) δ 0.60 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.27 (3 H, s, H-11), 1.42–1.67 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.84 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 2.05 (3 H, s, H-13), 3.82–3.87 (4 H, m, OCH_3 , H-9), 4.96–5.01 (1 H, m, H-7), 5.08 (1 H, s, H-2); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1''), 6.8 (C-2''), 19.6 (C-5), 21.0 (C-11), 21.2 (C-13), 23.5 (C-10), 34.4 (C-6), 39.3 (C-4), 44.4 (C-8), 52.9 (OCH_3), 65.4 (C-9), 71.1 (C-7), 81.7 (C-2), 93.2 (C-3), 166.4 (C-1), 170.7 (C-12); **NMR data for diastereomer B:** ^1H NMR (500 MHz, CDCl_3) δ 0.60 (6 H, q, $J_{1'',2''} = 8.0$ Hz, H-1''), 0.97 (9 H, t, $J_{2'',1''} = 8.0$ Hz, H-2''), 1.18 (3 H, d, $J_{10,9} = 6.0$ Hz, H-10), 1.26 (3 H, s, H-11), 1.42–1.67 (7 H, m, H-4, H-5, H-6, 1 $\times$ H-8), 1.84 (1 H, ddd, $J_{8,8} = 13.5$ Hz, $J_{8,7 \text{ or } 8,9} = 8.5$ Hz, $J_{8,9 \text{ or } 8,7} = 5.0$ Hz, 1 $\times$ H-8), 2.05 (3 H, s, H-13), 3.82–3.87 (4 H, m, OCH_3 , H-9), 4.67 (1 H, s, H-2), 4.96–5.01 (1 H, m, H-7); ^{13}C NMR (125 MHz, CDCl_3) δ 4.9 (C-1''), 6.8 (C-2''), 19.2 (C-5), 21.0 (C-11), 21.2 (C-13), 22.9 (C-10), 34.4 (C-6), 39.6 (C-4), 44.3 (C-8), 53.0 (OCH_3), 65.4 (C-9), 71.1 (C-7), 85.4 (C-2), 92.1 (C-3), 167.0 (C-1), 170.7 (C-12).

2-(Trimethylsilyl)ethyl 4-methoxybenzoate (1.175)

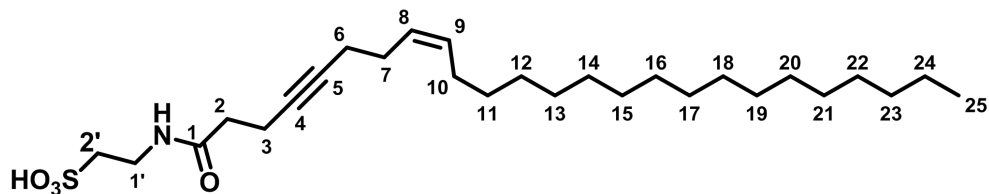
BOP-Cl (206 mg, 1.05 mmol) was added to a solution of *p*-anisic acid **1.174** (160 mg, 1.05 mmol), 2-(trimethylsilyl)ethanol (166 μ L, 1.16 mmol) and triethylamine (292 μ L, 2.10 mmol) in anhydrous DCM (2.6 mL). The initial suspension turned into a clear solution within minutes, and the mixture was stirred at RT for 14 h. Na₂CO₃ solution (5% in H₂O, 10 mL) and DCM (20 mL) were added to dilute the mixture, and the organic layer was washed with H₂O (10 mL), brine (10 mL), then dried (MgSO₄) and concentrated. Flash Chromatography (petrol/ether, 70:30) furnished the *title compound* (**1.175**) as a colourless oil (68 mg, 26%). *R_f* (petrol/ether; 70:30) = 0.79; ¹H NMR (500 MHz, CDCl₃) δ 0.08 (9 H, s, SiCH₃), 1.09–1.15 (2 H, m, H-2'), 3.86 (3 H, s, OCH₃), 4.36–4.42 (2 H, m, H-1'), 6.91 (2 H, d, *J*_{3'',2''} = 8.5 Hz, 2 $\times$ H-3''), 7.99 (2 H, d, *J*_{2'',3''} = 8.5 Hz, 2 $\times$ H-2''); ¹³C NMR (125 MHz, CDCl₃) δ -1.43 (SiCH₃), 17.4 (C-2'), 55.4 (OCH₃), 62.9 (C-1'), 113.5 (C-3''), 123.1 (C-1''), 131.5 (C-2''), 163.2 (C-4''), 166.5 (C-1); IR (thin film) ν_{max} /cm⁻¹ 2955 (m), 1711 (s), 1607 (s), 1512 (m), 1275 (s), 1256 (s); HRMS (ESI⁺) *m/z* calcd. for C₁₃H₂₀NaO₃Si⁺ [MNa]⁺ 275.1074, found 275.1071.

(Z)-N-Isopropyl-N-(isopropylcarbamoyl)pentacos-8-en-4-ynamide (1.176)

To a solution of alcohol **1.155** (24 mg, 63.8 μmol) and acid **1.57** (30 mg, 63.8 μmol) in DCM (2 mL) was added successively *N,N*-diisopropylethylamine (44 μL , 0.252 mmol), DMAP (4 mg, 32.7 μmol) and *N,N'*-diisopropylcarbodiimide (40 μL , 0.258 mmol). The resulting mixture was stirred for 15 h at RT then poured into a mixture of NH_4Cl solution (sat. aq., 5 mL) and ether (10 mL). The organic layer was washed with hydrochloric acid (1.2 M in H_2O , 5 mL), NaHCO_3 solution (sat. aq., 5 mL), brine (5 mL), then dried (MgSO_4) and concentrated. Flash chromatography (petrol/ether, 85:15) furnished the *title compound* (**1.176**) as a colourless oil (12 mg, 37%) as a side product. R_f (petrol/ether; 30:70) = 0.66; ^1H NMR (500 MHz, CDCl_3) δ 0.87 (3 H, t, $J_{25,24} = 7.0$ Hz, H-25), 1.20 (6 H, d, $J_{\text{B}_2, \text{B}_1} = 6.5$ Hz, $2 \times \text{H-B}_2$), 1.25 (28 H, br.s, H-11–H-24), 1.41 (6 H, d, $J_{\text{A}_2, \text{A}_1} = 7.0$ Hz, $2 \times \text{H-A}_2$), 2.01 (2 H, q, $J_{10,9} = J_{10,11} = 7.0$ Hz, H-10), 2.13–2.24 (4 H, m, H-6, H-7), 2.51 (2 H, t, $J_{3,2} = 7.5$ Hz, H-3), 2.65 (2 H, t, $J_{2,3} = 7.5$ Hz, H-2), 3.94–4.02 (1 H, m, H-B₁), 4.27–4.37 (1 H, m, H-A₁), 5.34–5.45 (2 H, m, H-8, H-9), 7.61 (1 H, br.s, NH); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (C-25), 15.1 (C-3), 19.2 (C-6), 20.9 (C-A₂), 22.6 (C-B₂), 22.7 (C-24), 26.8 (C-7), 27.3 (C-10), 29.3–31.9 (C-11–C-23), 35.5 (C-2), 42.6 (C-B₁), 48.3 (C-A₁), 78.7 (C-4), 81.0 (C-5), 127.7 (C-8), 131.4 (C-9), 153.7 (C-1), 173.0 (C-1'); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2924 (s), 2854 (s), 1709 (s), 1645 (s), 1524 (m), 1458 (m), 1387 (m), 1367 (m), 1255 (m); HRMS

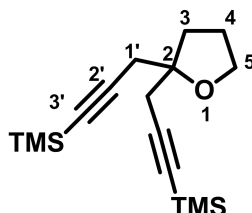
Chemical structure of compound 1, showing a 2,5-dioxolane-4-one ring system connected to a long chain with a triple bond and a double bond. The chain is numbered 1 to 25, and the ring carbons are numbered 2' to 5'.

- 358 -

(Z)-2-(Pentacos-8-en-4-ynamido)ethanesulfonic acid (1.178)

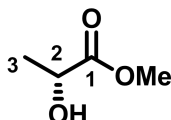
A solution prepared by dissolving taurine (13 mg, 0.104 mmol) and triethylamine (30 μ L, 0.215 mmol) in 1,4-dioxane (0.5 mL) and H₂O (0.4 mL) was added to *N*-hydroxysuccinic ester **1.177** (15 mg, 31.6 μ mol). The reaction mixture was stirred at RT for 24 h. Toluene (2 mL) was added and the reaction mixture was concentrated to remove H₂O azeotropically (repeated twice). The residue was first purified by ion-exchange column (Amberlite® IR-120 Na⁺ form, DCM/MeOH, 80:20) followed by flash chromatography (DCM/MeOH, 80:20) to furnish the *title compound* (**1.178**) as a waxy solid (6 mg, 39%). R_f (CH₃Cl/MeOH; 80:20) = 0.42; ¹H NMR (500 MHz, CD₃OD) δ 0.90 (3 H, t, $J_{25,24}$ = 7.0 Hz, H-25), 1.21–1.42 (28 H, br.s, H-11–H-24), 2.04 (2 H, q, $J_{10,9}$ = $J_{10,11}$ = 6.0 Hz, H-10), 2.11–2.22 (4 H, m, H-6, H-7), 2.34 (2 H, t, $J_{2,3}$ = 7.0 Hz, H-2), 2.42 (2 H, t, $J_{3,2}$ = 7.0 Hz, H-3), 2.97 (2 H, t, $J_{1',2'}$ = 7.0 Hz, H-1'), 3.60 (2 H, t, $J_{2',1'}$ = 7.0 Hz, H-2'), 5.37–5.47 (2 H, m, H-8, H-9); ¹³C NMR (125 MHz, CDCl₃) δ 14.5 (C-25), 16.2 (C-3), 19.9 (C-6), 23.8 (C-24), 28.0 (C-7), 28.3 (C-10), 30.4–33.9 (C-11–C-23), 36.9 (C-2'), 36.9 (C-2), 51.6 (C-1'), 79.4 (C-4), 81.6 (C-5), 129.3 (C-8), 132.0 (C-9), 174.3 (C-1); IR (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3384 (br), 2916 (s), 2849 (s), 1634 (m), 1446 (m), 1206 (m); HRMS (ESI[−]) m/z calcd. for C₂₇H₄₈NO₄S[−] [M−H][−] 482.3310, found 482.3308.

Chapter 2 related compounds

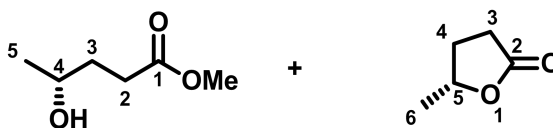
2,2-Bis[(3-trimethylsilyl)prop-2-yn-1-yl]tetrahydrofuran (2.199)

BuLi (1.6 M in hexanes, 0.9 mL, 1.44 mmol) was added to a solution of 1-(trimethylsilyl)propyne (206 μ L, 1.39 mmol) in anhydrous THF (3 mL) at -78 $^{\circ}$ C. After 1 h, a solution of dihydrofuran-2(3*H*)-one (89.3 μ L, 1.16 mmol) in anhydrous THF (7 mL) was added to the first solution, and the resulting mixture was stirred at -78 $^{\circ}$ C for 1 h. NH_4Cl solution (sat. aq., 10 mL) was used to quench the reaction and ether (15 mL) was added to dilute the mixture. The aqueous layer was extracted with ether (3×15 mL), and the combined organic layers were washed with brine (20 mL), dried (MgSO_4) and concentrated. Flash chromatography furnished the *title compound* (**2.199**) as a colourless oil (156 mg, 68%). R_f (petrol/ether; 90:10) = 0.95; ^1H NMR (500 MHz, CDCl_3) δ 0.17 (18 H, s, SiCH_3), 1.69–1.76 (2 H, m, H-4), 1.76–1.81 (2 H, m, H-3), 2.54 (2 H, d, $J_{1',1'} = 17.0$ Hz, $2 \times \text{H-1'}$), 2.59 (2 H, d, $J_{1',1'} = 17.0$ Hz, $2 \times \text{H-1'}$), 3.69 (2 H, t, $J_{5,4} = 5.5$ Hz, H-5); ^{13}C NMR (125 MHz, CDCl_3) δ 0.00 (SiCH_3), 26.8 (C-4), 31.1 (C-1'), 34.9 (C-3), 63.2 (C-5), 72.6 (C-2), 88.4 (C-3'), 104.2 (C-2'); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3383 (br), 2959 (s), 2177 (s), 1250 (s), 1038 (m); HRMS (FI^+) m/z calcd. for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{Si}_2^+ [\text{MH}_3\text{O}]^+$ 311.1853, found 311.1837.

Chapter 3 related compounds

Methyl (2*R*)-hydroxypropanoate (**3.80**)⁴⁴

The title compound was synthesised by applying the general procedure E (*cf.* page 301) to ester **3.65** (14 mg, 86.4 μ mol). Flash chromatography (petrol/ethyl acetate, 70:30) furnished the title compound (**3.80**) as a colourless oil (3 mg, 33%). R_f (petrol/ethyl acetate; 50:50) = 0.40; $[\alpha]_D^{25} -4.0$ (*c* 0.25, CH_2Cl_2), *lit*⁴⁵ $[\alpha]_D^{21} -8.4$ (neat); ^1H NMR (200 MHz, CDCl_3) δ 1.36 (3 H, d, $J_{3,2} = 7.0$ Hz, H-3), 3.16 (br.s, 1 H, OH), 3.72 (3 H, s, OCH_3), 4.24 (1 H, q, $J_{2,3} = 7.0$ Hz, H-2). All the other data were as reported.

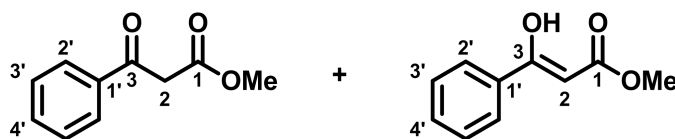
Methyl (4*R*)-hydroxypentanoate (**3.81**)⁴⁶ & (5*R*)-Methyldihydrofuran-2(3*H*)-one (**3.82**)⁴⁷

The title compounds was synthesised by applying the general procedure E (*cf.* page 301) to ester **3.66** (33 mg, 0.174 mmol). Flash chromatography (petrol/ethyl acetate, 70:30) furnished the products **3.81** (4 mg, 15%) and **3.82** (13 mg, 75%), both as colourless oils.

Data for 3.81: R_f (petrol/ethyl acetate; 50:50) = 0.39; $[\alpha]_D^{24} -18.2$ (*c* 0.22, CHCl_3), *lit*⁴⁸ $[\alpha]_D$

–15.3 (*c* 19.6, CH₂Cl₂)^{aq}; ¹H NMR (400 MHz, CDCl₃) δ 1.21 (3 H, d, *J*_{5,4} = 6.0 Hz, H-5), 1.64–1.84 (2 H, m, H-3), 2.45 (2 H, t, *J*_{2,3} = 7.0 Hz, H-2), 3.68 (3 H, s, OCH₃), 3.76–3.90 (1 H, m, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 23.4 (C-5), 30.4 (C-2), 33.7 (C-3), 51.6 (OCH₃), 67.1 (C-4), 174.6 (C-1). All the other data were as reported. **Data for 3.82:** *R_f* (petrol/ethyl acetate; 50:50) = 0.27; [α]_D²⁴ +22.7 (*c* 0.78, CHCl₃), lit⁴⁹ [α]_D²⁰ +30.0 (*c* 18.0, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 1.42 (3 H, d, *J*_{6,5} = 6.0 Hz, H-6), 1.73–2.64 (4 H, m, H-3, H-4), 4.62 (1 H, tq, *J*_{5,4} = 8.0 Hz, *J*_{5,6} = 6.0 Hz, H-5). All the other data were as reported.

Methyl 3-oxo-3-phenylpropanoate (3.84) & (Z)-methyl 3-hydroxy-3-phenylacrylate (3.84 enol form)⁵⁰

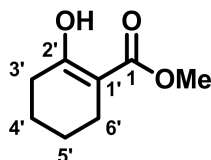


The title compound was synthesised by applying the general procedure E (*cf.* page 301) to ester **3.70** (27 mg, 0.113 mmol). Flash chromatography (petrol/ethyl acetate, 70:30) furnished the products (**3.84**) and its **enol** form (**keto:enol** = 5:1) as a colourless oil (13 mg, 65%). *R_f* (petrol/ethyl acetate; 50:50) = 0.55; **¹H NMR data for keto form** ¹H NMR (200 MHz, CDCl₃) δ 3.73 (3 H, s, OCH₃), 4.01 (2 H, s, H-2), 7.45–7.49 (2 H, m, 2 × H-3'), 7.57–7.60 (1 H, m, H-4'), 7.93 (2 H, d, *J*_{2',3'} = 7.5 Hz, 2 × H-2'); **¹H NMR data for enol form:** ¹H NMR (200 MHz, CDCl₃) δ 3.78 (3 H, s, OCH₃), 5.68 (1 H, s, H-2), 7.38–7.42 (2 H, m, 2 × H-3'), 7.45–7.49 (1 H, m, H-4'), 7.77 (2 H, d, *J*_{2',3'} = 7.5 Hz, 2 × H-2'), 12.52 (1 H, s, OH).

^{aq} Temperature not stated in literature.

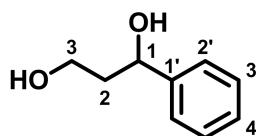
All the other data were as reported.

Methyl 2-hydroxycyclohex-1-enecarboxylate (**3.85**)⁵¹



The title compound was synthesised by applying the general procedure E (*cf.* page 301) to ester **3.72** [a mixture of three isomers (**3.72a**:**3.72b**:**3.72c** = 1:1:3.5), 22 mg, 0.102 mmol]. Flash chromatography (petrol/ethyl acetate, 70:30) furnished the products **3.85** as a colourless oil (10 mg, 64%). R_f (petrol/ethyl acetate; 50:50) = 0.86; ^1H NMR (200 MHz, CDCl_3) δ 1.52–1.76 (4 H, m, H-4', H-5'), 2.11–2.32 (4 H, m, H-3', H-6'), 3.84 (3 H, s, OCH_3)^{ar}. All the other data were as reported.

1-Phenylpropane-1,3-diol (**3.86**)⁵²

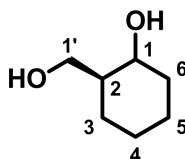


The title compound was synthesised by applying the general procedure F (*cf.* page 301) to ester **3.71** (24 mg, 0.101 mmol). Flash chromatography (petrol/ethyl acetate, 50:50) furnished the products **3.86** as a colourless oil (7 mg, 46%). R_f (petrol/ethyl acetate; 20:80) =

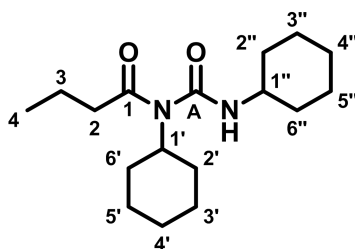
^{ar} OH peak missing.

0.50; ^1H NMR (200 MHz, CDCl_3) δ 1.87–2.03 (2 H, m, H-2), 2.80 (2 H, br.s, $2 \times \text{OH}$), 3.84 (2 H, td, $J_{3,2} = 5.5$ Hz, $J_{3,\text{OH}} = 2.0$ Hz, H-3), 4.94 (1 H, td, $J_{1,2} = 8.0$ Hz, $J_{1,\text{OH}} = 1.5$ Hz, H-1), 7.21–7.40 (5 H, m, $2 \times \text{H-2'}$, $2 \times \text{H-3'}$, H-4'). All the other data were as reported.

(2*S*)-2-(Hydroxymethyl)cyclohexanol (3.87)⁵³



The title compound was synthesised by applying the general procedure F (*cf.* page 301) to ester **3.74** (40 mg, 0.101 mmol). Flash chromatography (petrol/ethyl acetate, 50:50) furnished the product **3.87** as a mixture of two diastereomers **A** and **B** (**A**:**B** = 1:1) as a colourless oil (20 mg, 83%). R_f (petrol/ethyl acetate; 20:80) = 0.30. **^1H NMR data for diastereomer A:** ^1H NMR (200 MHz, CDCl_3) δ 0.89–1.00 (1 H, m, $1 \times \text{H-5}$), 1.28–1.94 (8 H, m, H-2, H-3, H-4, $1 \times \text{H-5}$, H-6), 3.47–3.60 (2 H, m, H-1, $1 \times \text{H-1'}$), 3.81 (1 H, d, $J_{1',2} = 3.0$ Hz, $1 \times \text{H-1'}$); **^1H NMR data for diastereomer B:** ^1H NMR (200 MHz, CDCl_3) δ 1.25–1.33 (1 H, m, $1 \times \text{H-5}$), 1.38–1.78 (8 H, m, H-2, H-3, H-4, $1 \times \text{H-5}$, H-6), 3.67–3.76 (2 H, m, H-1, $1 \times \text{H-1'}$), 4.13 (1 H, app.s, $1 \times \text{H-1'}$). All the other data were as reported.

***N*-Cyclohexyl-*N*-(cyclohexylcarbamoyl)butyramide (3.89)**

The title compound was prepared by applying general procedure B (*cf.* page 147) to butyric acid. The product (**3.89**) was obtained as a colourless oil as a side product (6 mg, 1%). R_f (petrol/ethyl acetate; 20:80) = 0.80; ^1H NMR (500 MHz, CDCl_3) δ 0.97 (3 H, t, $J_{4,3}$ = 7.5 Hz, H-4), 1.13–2.03 (22 H, m, H-3, H-2', H-3', H-4', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''), 2.41 (2 H, t, $J_{2,3}$ = 7.5 Hz, H-2), 3.65–3.74 (1 H, m, H-1''), 3.85–3.94 (1 H, m, H-1'); ^{13}C NMR (125 MHz, CDCl_3) δ 13.8 (C-4), 18.8 (C-3), 24.7 (C-4'), 25.3 (C-4''), 25.5 (C-3'', C-5''), 26.4 (C-3', C-5'), 30.9 (C-2', C-6'), 32.8 (C-2'', C-6''), 37.8 (C-2), 49.6 (C-1''), 56.3 (C-1'), 154.1 (C-A), 174.0 (C-1); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3303 (br), 2931 (s), 1687 (m), 1643 (s), 1530 (m), 1164 (w); HRMS (ESI $^+$) m/z calcd. for $\text{C}_{17}\text{H}_{30}\text{N}_2\text{NaO}_2^+$ [MNa] $^+$ 317.2199, found 317.2193.

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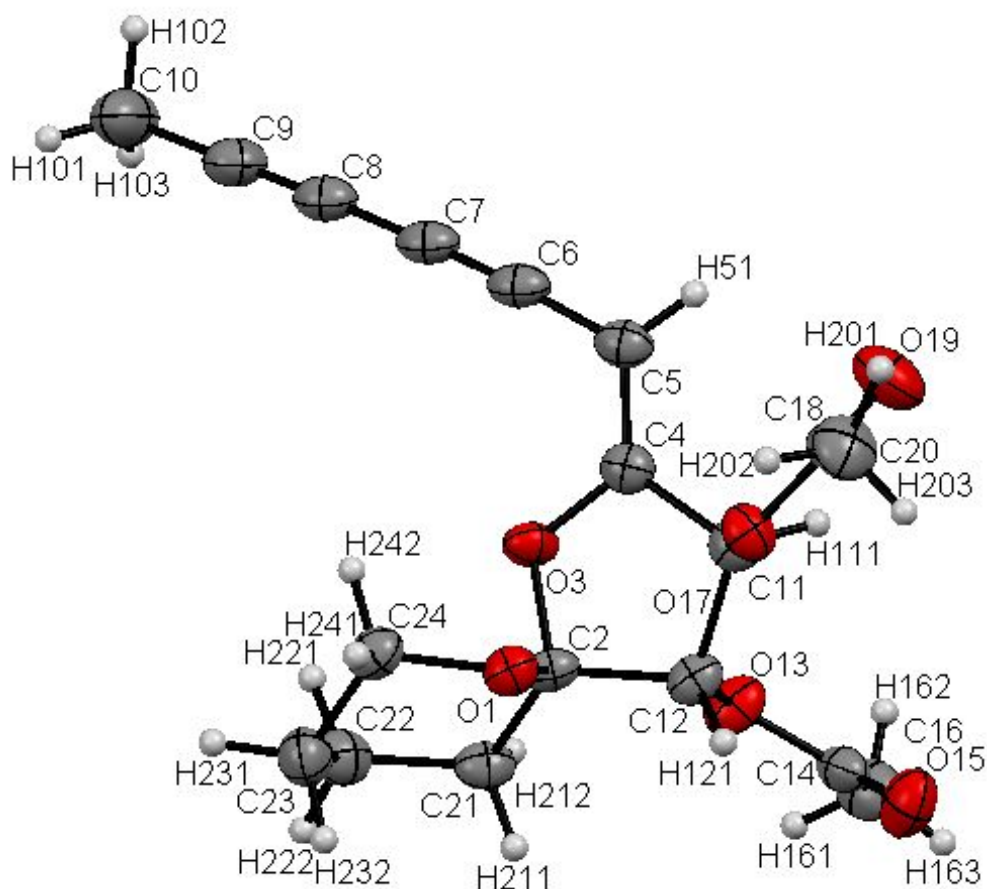
^{as} Some journals do not have volume number, e.g. Synlett, Synthesis, etc.

Tetrahedron **2007**, *63*, 12547.

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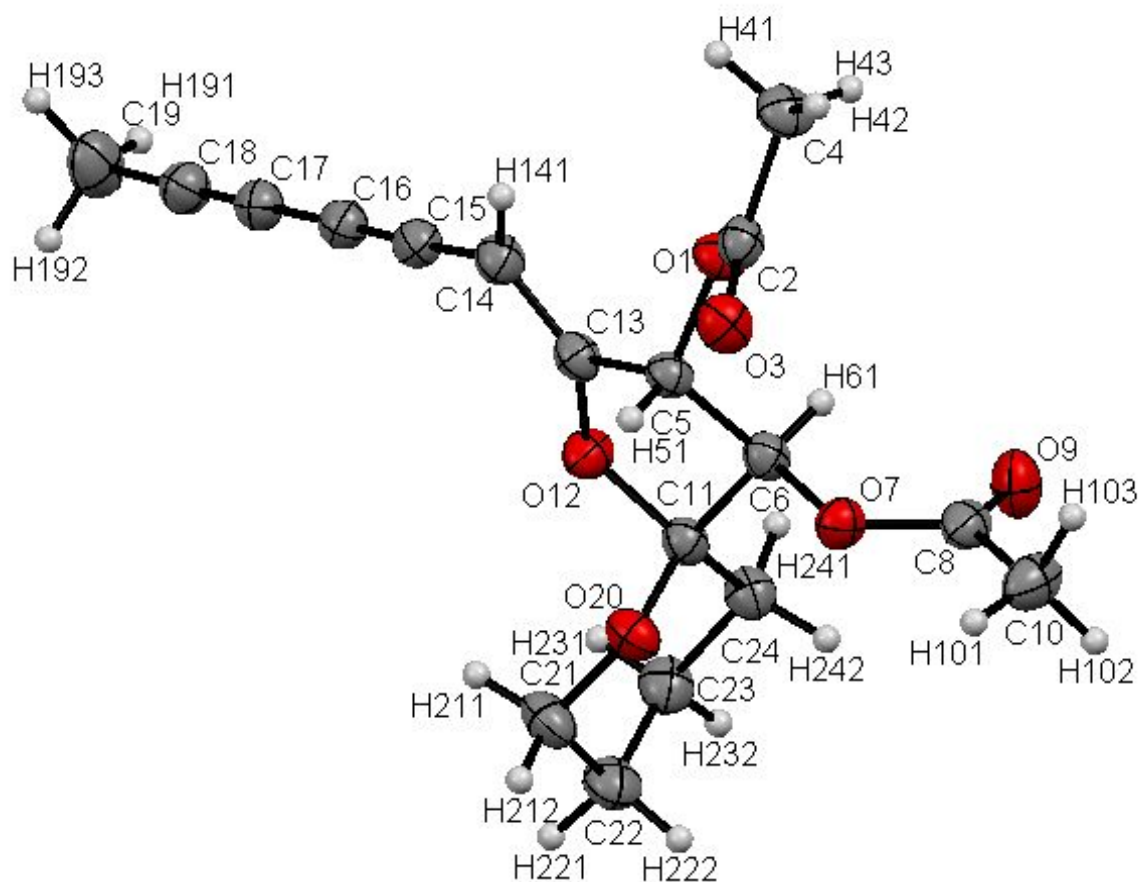
Appendix A: Single crystal X-ray diffraction report for spiroketal 2.91



Chemical Formula	C₁₈H₂₀O₆
Space Group (Hermann-Mauguin)	P -1
<i>a</i> (Å)	8.8737 (2)
<i>b</i> (Å)	9.7374 (2)
<i>c</i> (Å)	11.2420 (3)
α (°)	95.422 (1)
β (°)	112.7103 (12)
γ (°)	99.3154 (13)
Cell Volume (Å³)	871.01 (4)
R (I > 2σ(I))	0.0435 (3478)
wR (I > 2σ(I))	0.1051 (3342)

Full data are located in the cif. file on the attached CD.

Single crystal X-ray diffraction report for spiroketal 2.92

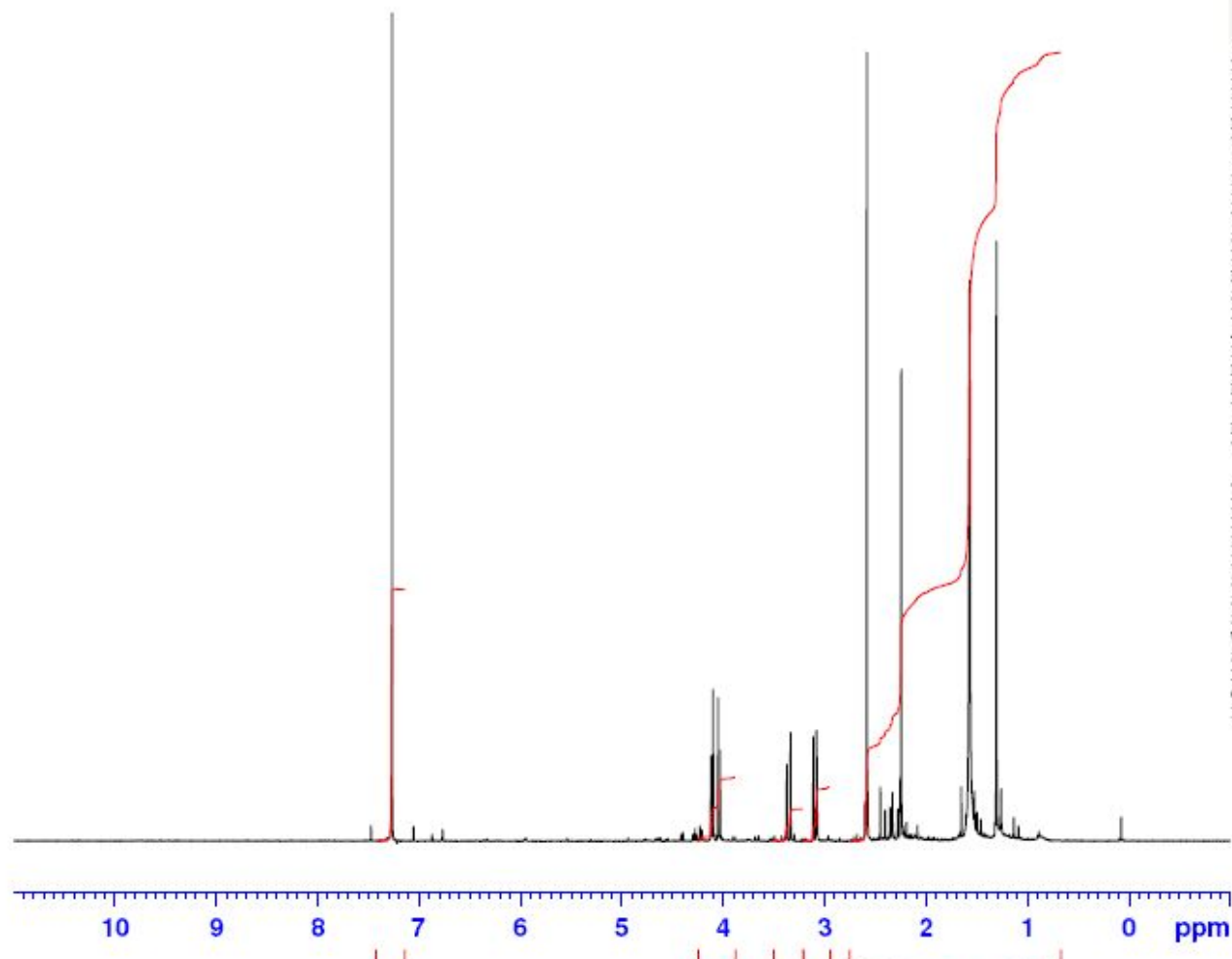


Chemical Formula	C₁₈H₂₀O₆
Space Group (Hermann-Mauguin)	P 2₁/C
<i>a</i> (Å)	9.3035 (2)
<i>b</i> (Å)	9.3322 (3)
<i>c</i> (Å)	19.7057 (6)
α (°)	90
β (°)	100.401 (3)
γ (°)	90
Cell Volume (Å³)	1682.78 (8)
R (I > 2σ(I))	0.0396 (3212)
wR (I > 2σ(I))	0.1175 (3517)

Full data are located in the cif. file on the attached CD.

Instrument AVC500
Group JR
5463 Boshen Wu 17/8/11

¹H NMR-Compound A



NMR@CHEM.OX

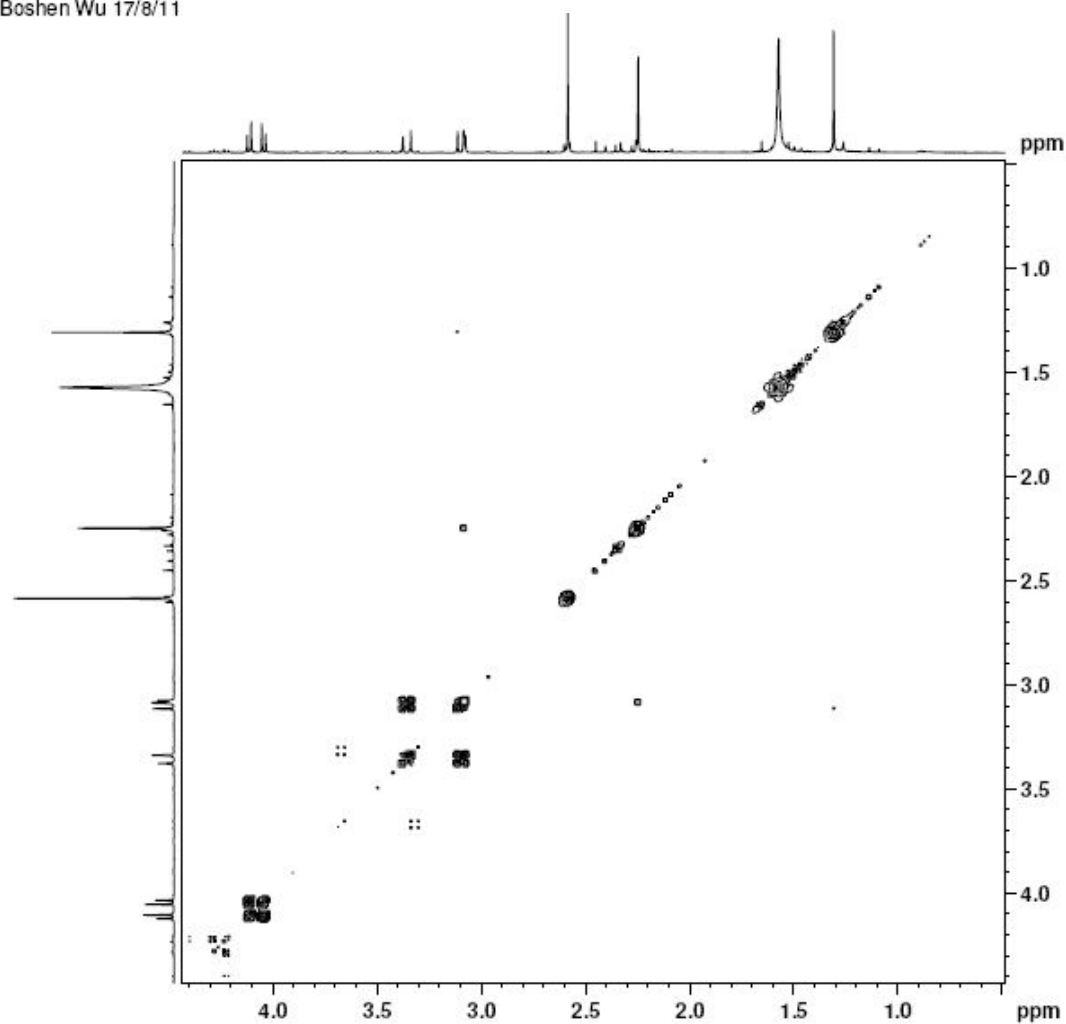
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371

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NMR@CHEM.OX

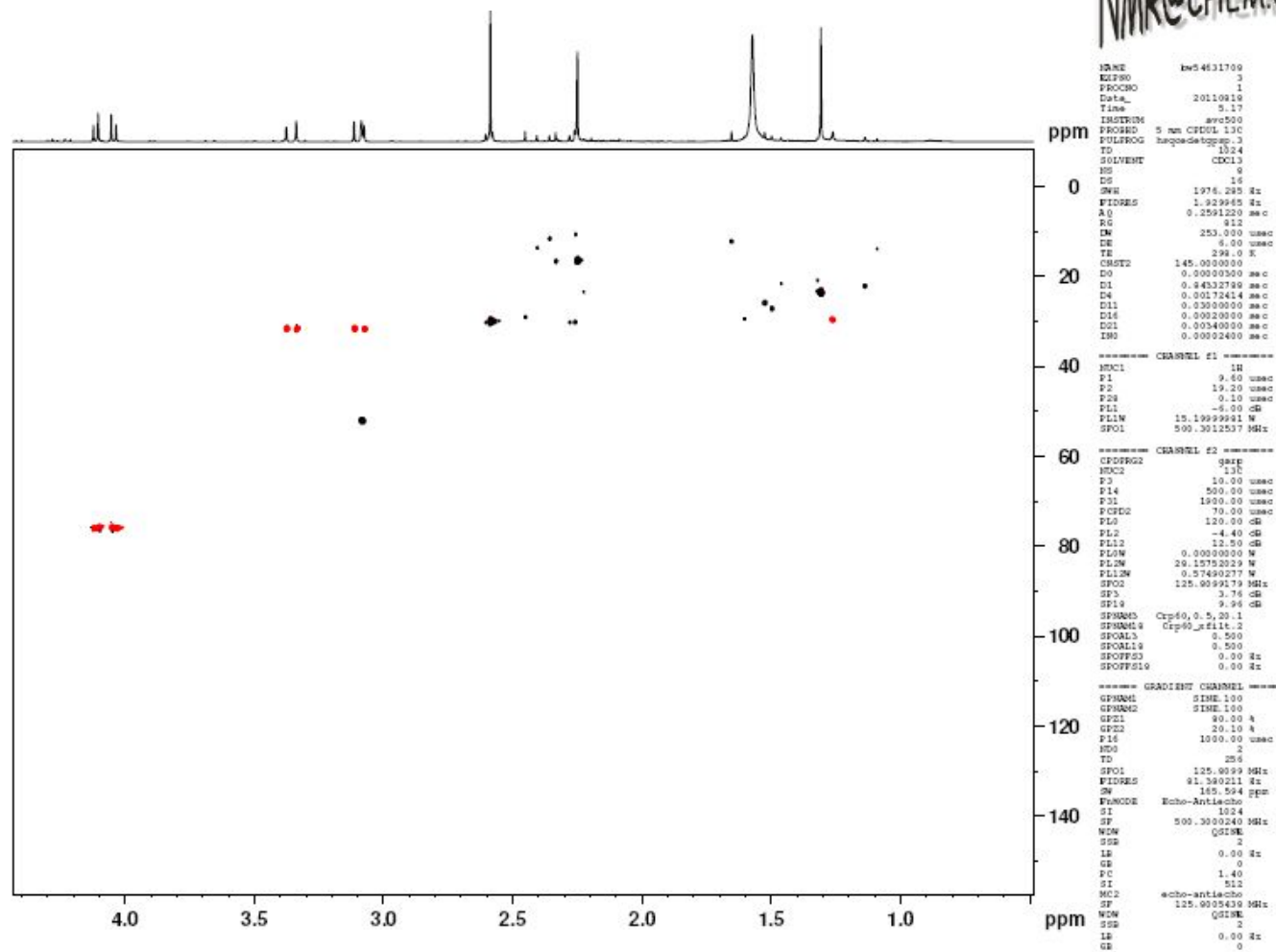
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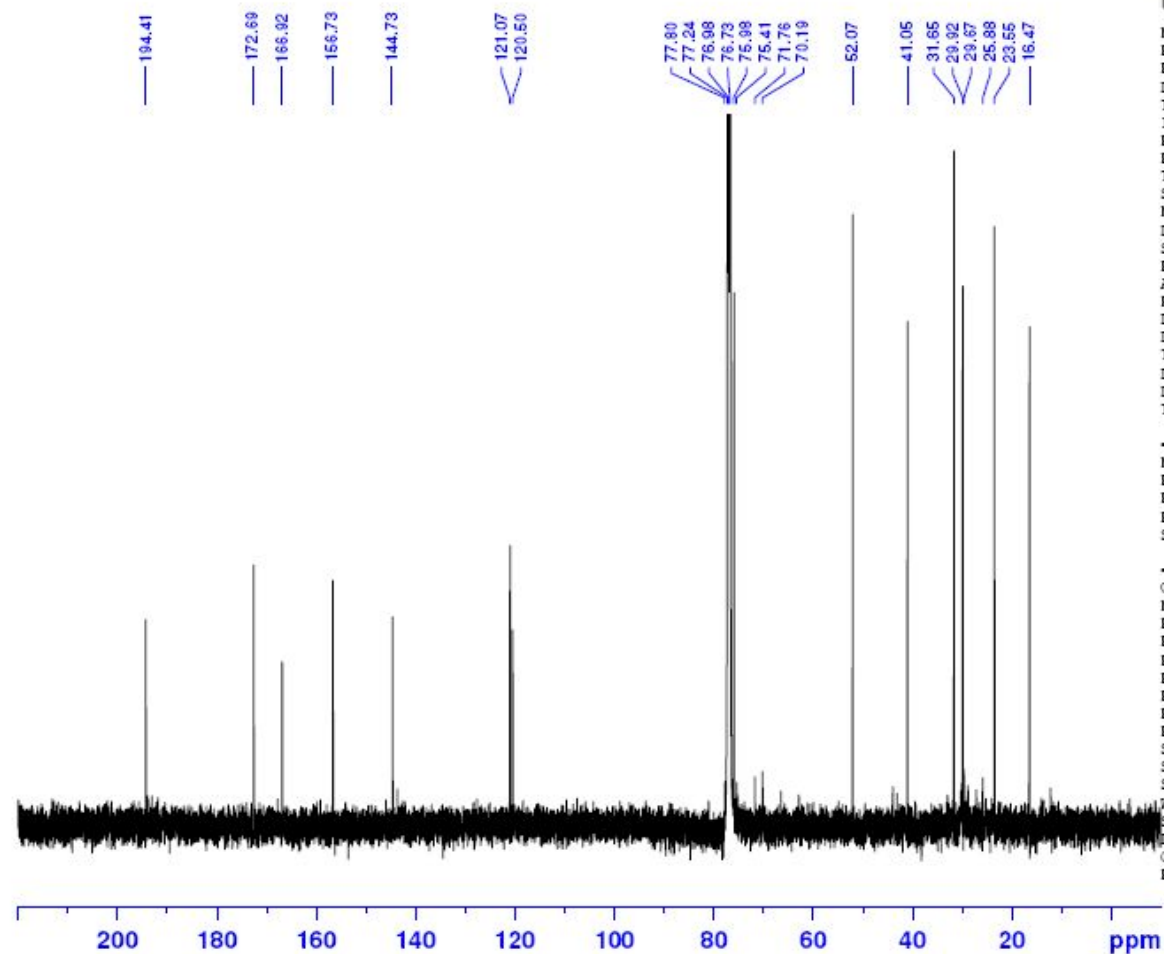
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HSQC-Compound A



373

Instrument AVC500
Group JR
5463 Boshen Wu 17/8/11

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NMR@CHEM.OX

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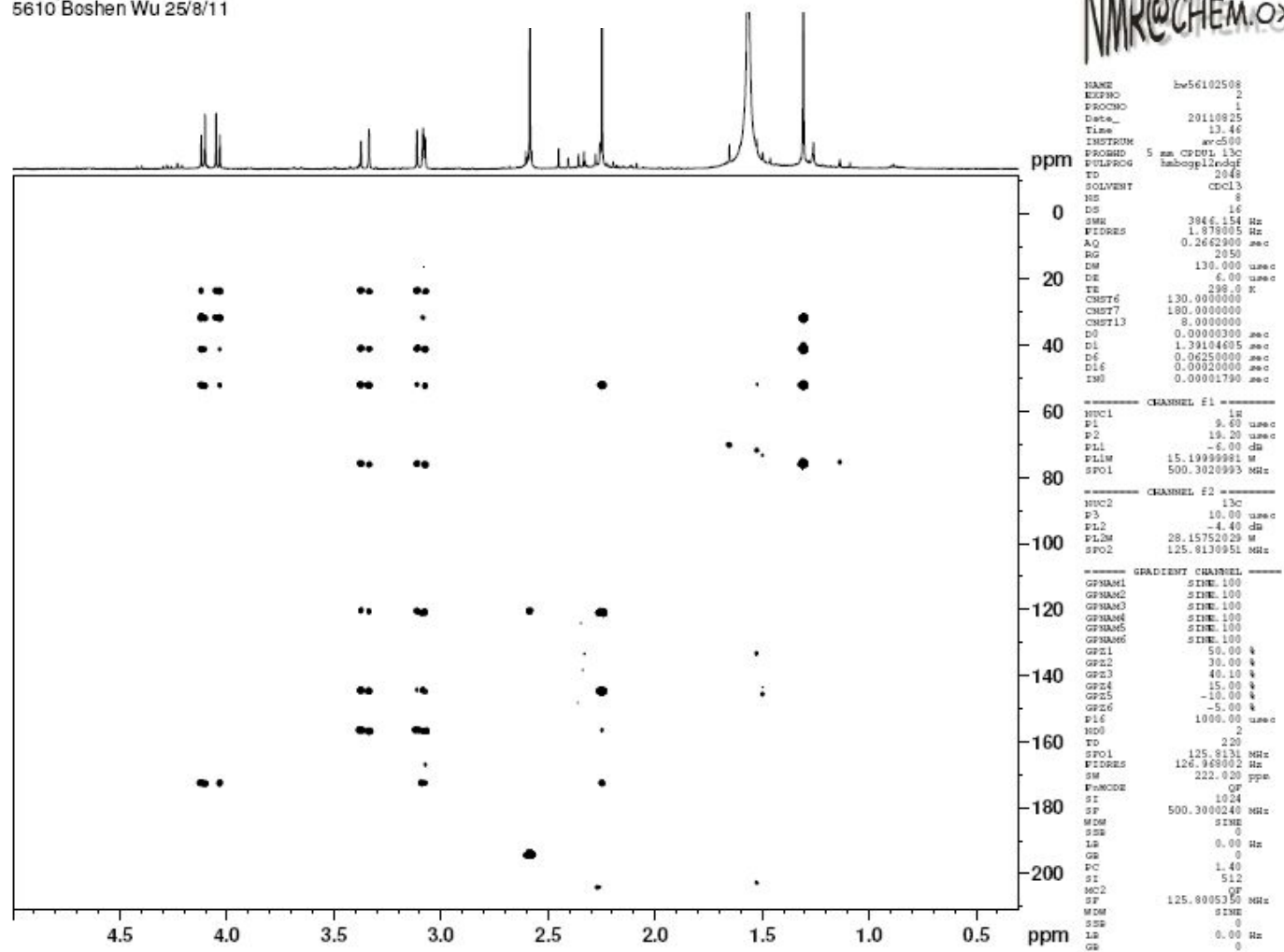
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CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 12.42 dB
PL13 18.42 dB
PL2W 15.19999981 W
PL12W 0.21869738 W
PL13W 0.05493430 W
SFO2 500.3020012 MHz
SI 32768
SF 125.8005438 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

374

Instrument AVC500
Group JR
5610 Boshen Wu 25/8/11

HMBC-Compound A



375

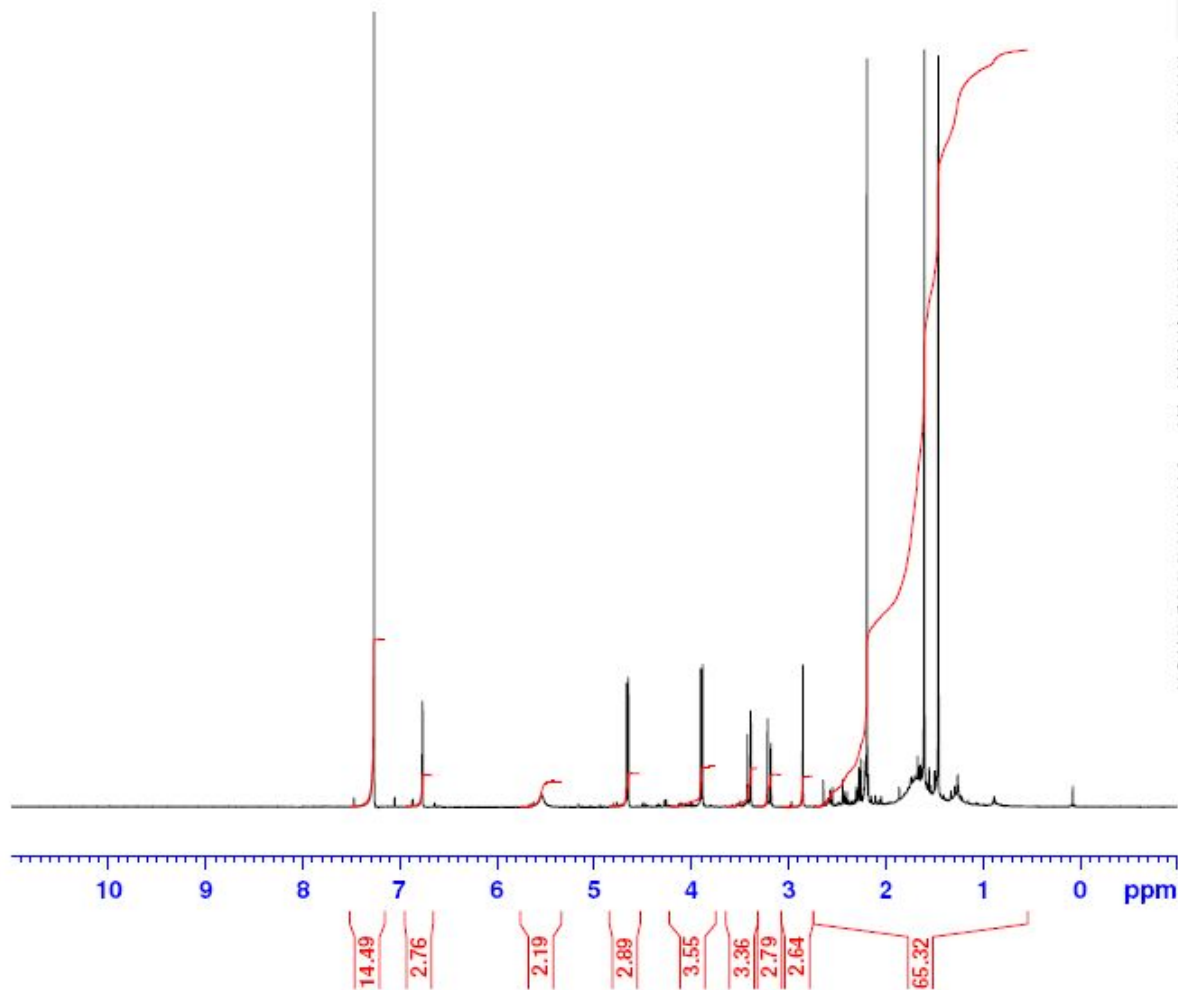
Instrument AVC500
Group JR
5462 Boshen Wu 17/8/11

¹H NMR-Compound B

NMROCHEM.OX

NAME bw54621708
EXPNO 1
PROCNO 1
Date_ 20110818
Time 1.39
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 4
DW 48.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

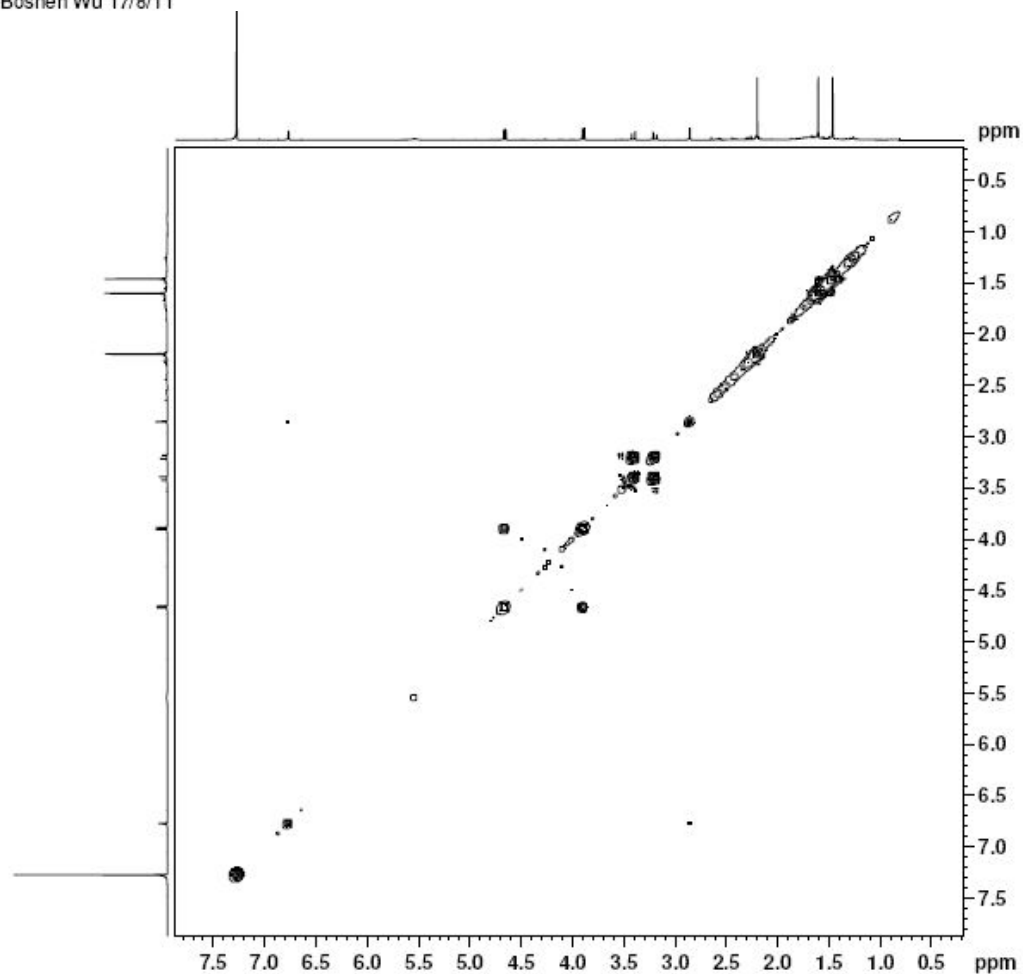
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P1 9.60 usec
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PL1W 15.19999981 W
SFO1 500.3030896 MHz
SI 32768
SF 500.3000240 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



376

Instrument AVC500
Group JR
5462 Boshen Wu 17/8/11

COSY-Compound B



NMR@CHEM.OX

NAME lw54621708
EXPNO 2
PROCNO 1
Date_ 20110818
Time 1.40
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG cosygpgf45
TD 1024
SOLVENT CDCl3
NS 2
DS 4
SWH 3946.154 Hz
FIDRES 3.756010 Hz
AQ 0.1331700 sec
RG 7.12
DW 130.000 usec
DE 6.00 usec
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D0 0.00000300 sec
D1 0.96620780 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00026000 sec

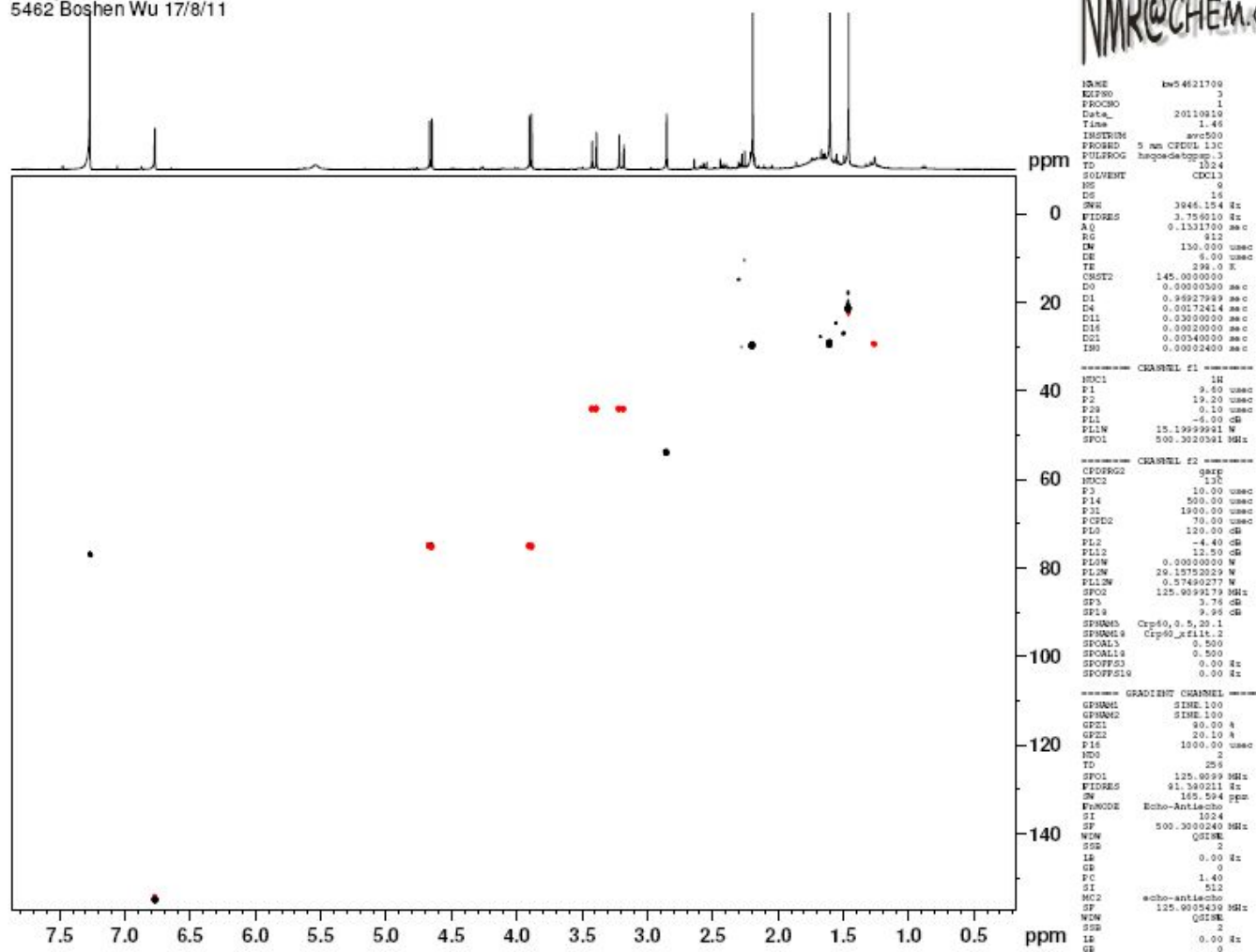
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P1 9.60 usec
PL1 -6.00 dB
PL1W 15.19999981 W
SFO1 500.3020381 MHz

===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GP21 10.00 %
GP22 10.00 %
P16 1000.00 usec
ND0 1
TD 128
SFO1 500.302 MHz
FIDRES 30.048077 Hz
SW 7.688 ppm
FHMCOE QF
SI 1024
SF 500.3000240 MHz
WDW SINE
SSB 0
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377

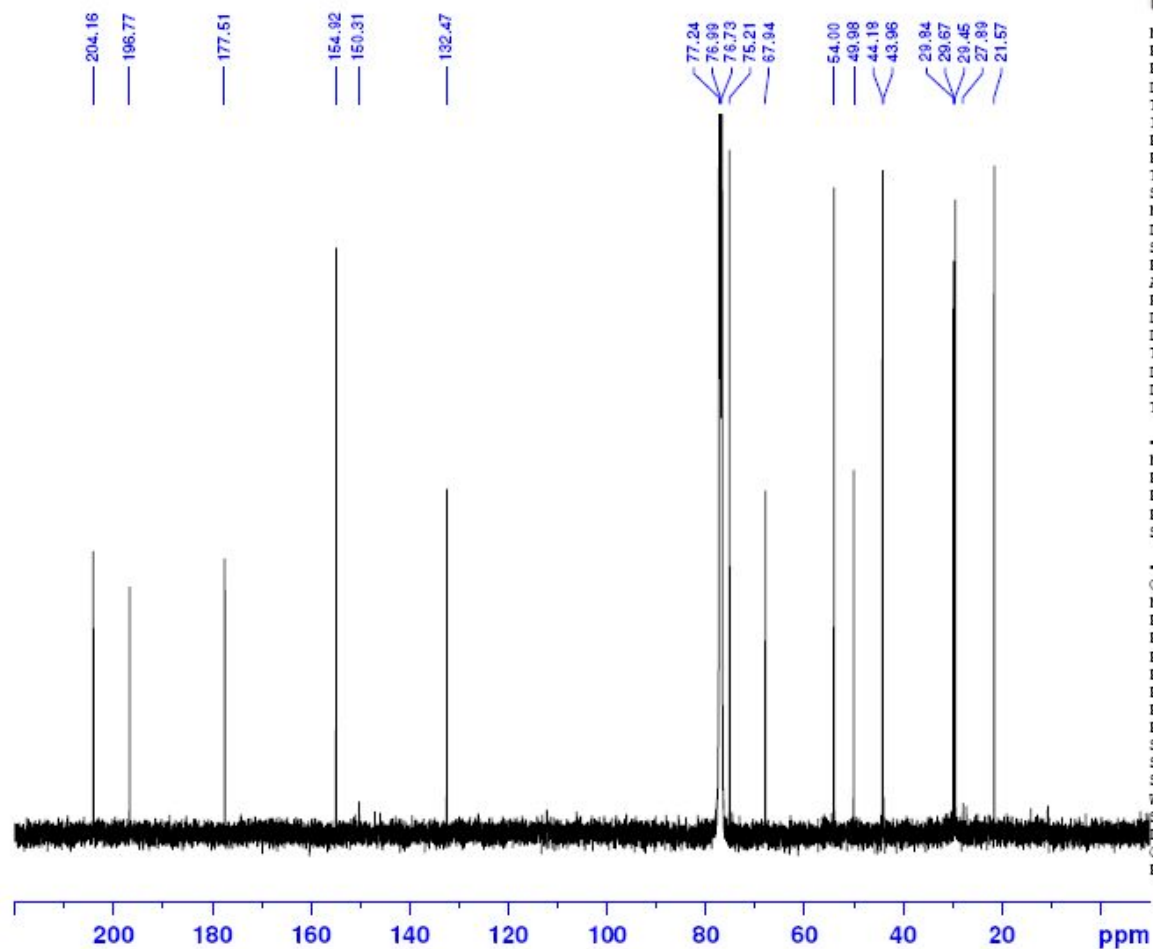
Instrument AVC500
Group JR
5462 Boshen Wu 17/8/11

HSQC-Compound B



378

Instrument AVC500
Group JR
5462 Boshen Wu 17/8/11

 ^{13}C NMR-Compound B

NMR@CHEM.OX

NAME bw54621708
EXPNO 4
PROCNO 1
Date_ 20110818
Time 5.04
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zgpg30
ID 65536
SOLVENT CDCl3
NS 3072
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
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DE 20.00 usec
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D11 0.03000000 sec
TD0 1

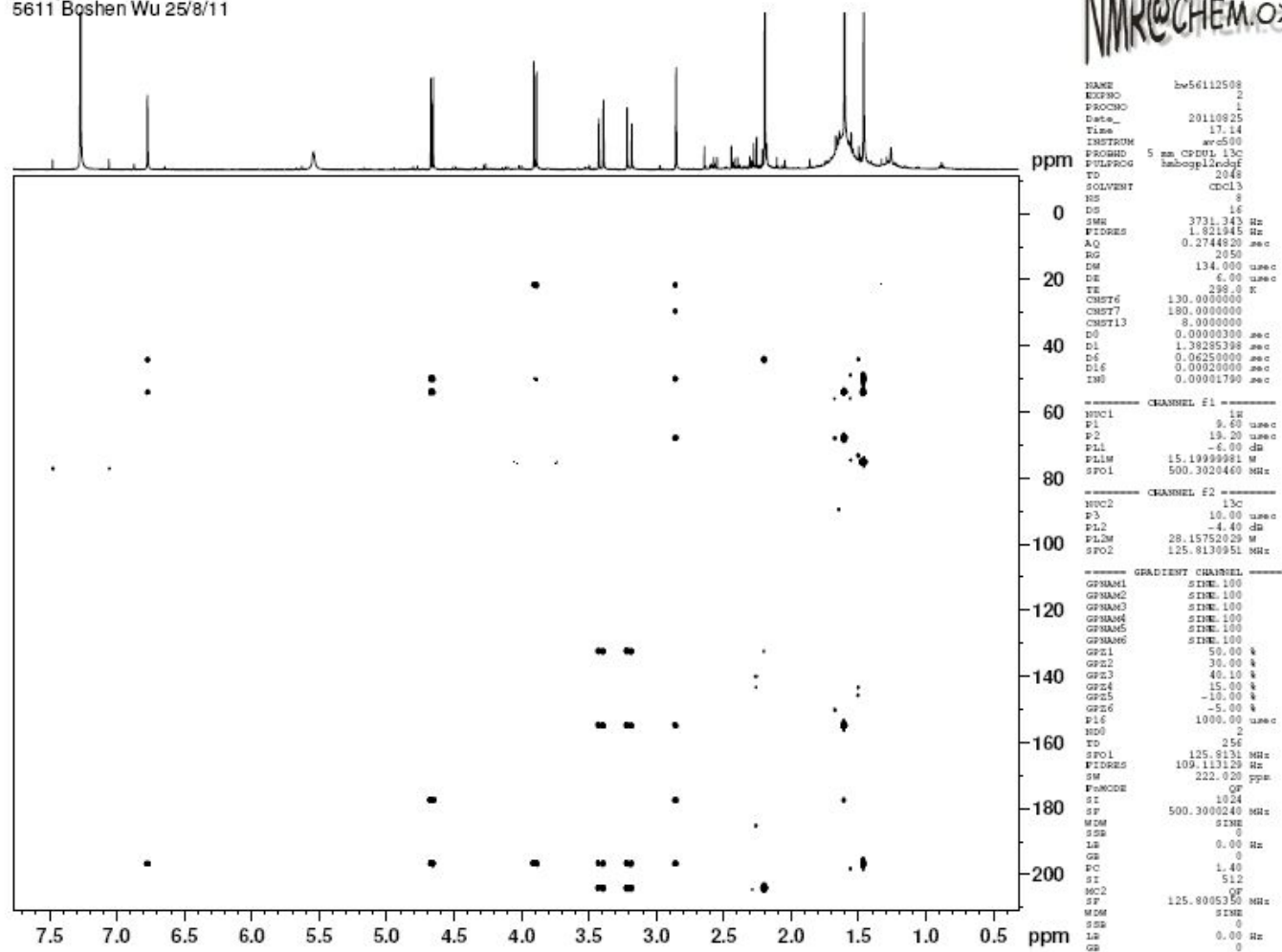
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P1 10.00 usec
PL1 -4.40 dB
PL1W 28.15752029 W
SFO1 125.8131151 MHz

----- CHANNEL f2 -----
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 12.42 dB
PL13 18.42 dB
PL2W 15.19999981 W
PL12W 0.21869738 W
PL13W 0.05493430 W
SFO2 500.3020012 MHz
SI 32768
SF 125.8005438 MHz
WDW ZM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

379

Instrument AVC500
Group JR
5611 Boshen Wu 25/8/11

HMBC-Compound B



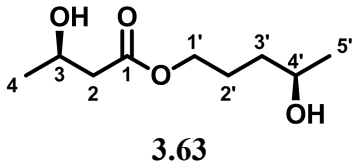
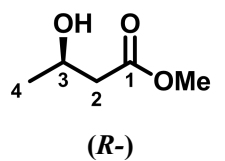
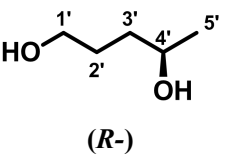
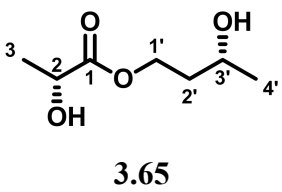
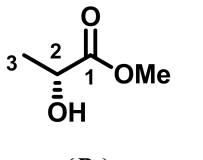
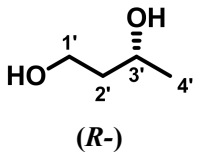
380

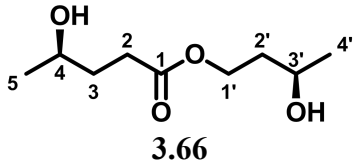
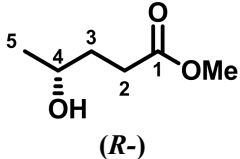
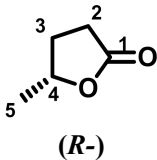
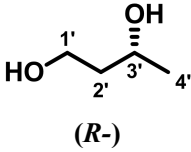
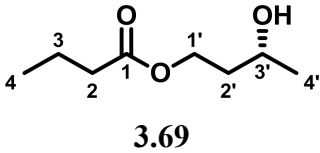
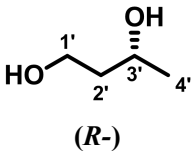
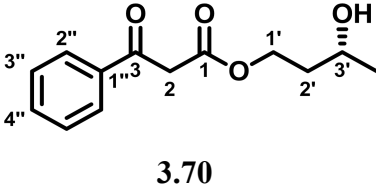
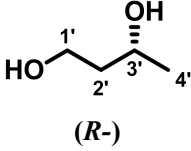
Appendix B: NMR spectrum for unidentified compound A and B

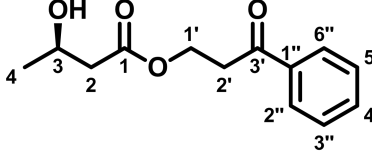
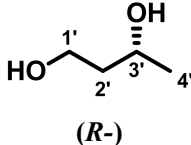
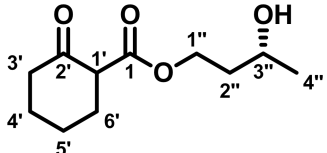
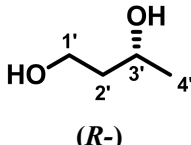
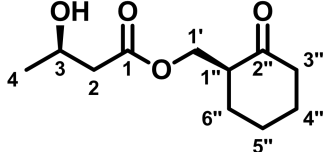
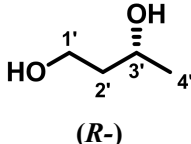
● Data summary

	Compound A	Compound B
Formula	C ₁₄ H ₁₄ NaO ₅	C ₁₃ H ₁₆ NaO ₅
HRMS	calcd. for 285.0733, found 285.0737	calcd. for 275.0890, found 275.0890
R_f	0.83 (petrol/ethyl acetate; 50:50)	0.58 (petrol/ethyl acetate; 50:50)
¹H NMR (CDCl₃)	1.31 (3 H, s), 2.26 (3 H, s), 2.59 (3 H, s), 3.08 (1 H, br.s, OH?), 3.09 (1 H, d, <i>J</i> = 19.0 Hz), 3.36 (1 H, d, <i>J</i> = 19.0 Hz), 4.04 (1 H, d, <i>J</i> = 9.5 Hz), 4.11 (1 H, d, <i>J</i> = 9.5 Hz)	1.46 (3 H, s), 1.60 (3 H, s), 2.19 (3 H, s), 2.85 (1 H, d, <i>J</i> = 1.5 Hz), 3.19 (1 H, d, <i>J</i> = 17.0 Hz), 3.41 (1 H, d, <i>J</i> = 17.0 Hz), 3.90 (1 H, d, <i>J</i> = 9.0 Hz), 4.66 (1 H, d, <i>J</i> = 9.0 Hz), 6.77 (1 H, s)
¹³C NMR (CDCl₃)	16.5, 23.6, 29.9, 31.7, 41.0, 52.1, 76.0, 120.5, 121.1, 144.8, 166.7, 166.9, 172.7, 194.4	21.6, 29.5, 29.8, 44.2, 50.0, 54.0, 67.9, 75.2, 132.5, 154.9, 177.5, 196.8, 204.2
IR (thin film)	1763 (s), 1674 (m), 1590 (m)	1769 (s), 1675 (s), 1163 (s), 1020 (s)

Appendix C: Specific rotation data for enzymatic reduction product fragments

Reduced compound	Method to obtain chiral fragment	Chiral fragment & absolute configuration	Measured $[\alpha]_D$	Reported $[\alpha]_D$ & references
 3.63	Methanolysis	 (<i>R</i>-)	$[\alpha]_D^{24} - 23.0$ (<i>c</i> 1.00, CHCl ₃)	$[\alpha]_D^{22} - 45.1$ (<i>c</i> 1.00, CHCl ₃) ¹ <i>NB</i> : in a more recent article, ² the specific rotation for the (<i>S</i>)-isomer is much smaller $[\alpha]_D^{23} + 25.7$ (<i>c</i> 0.30, CHCl ₃)
	Methanolysis	 (<i>R</i>-)	$[\alpha]_D^{24} - 12.7$ (<i>c</i> 1.00, MeOH)	$[\alpha]_D^{20} - 13.9$ (<i>c</i> 1.02, MeOH) ³
 3.65	Methanolysis	 (<i>R</i>-)	$[\alpha]_D^{24} - 4.0$ (<i>c</i> 0.25, CH ₂ Cl ₂)	$[\alpha]_D^{21} - 8.4$ (neat) ⁴
	Methanolysis	 (<i>R</i>-)	$[\alpha]_D^{24} - 15.6$ (<i>c</i> 0.46, CHCl ₃)	$[\alpha]_D^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB</i> : in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_D^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)

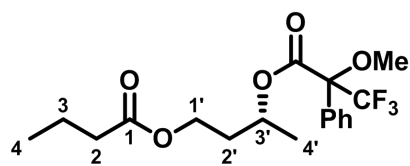
 3.66	Methanolysis	 (<i>R</i>-)	$[\alpha]_{\text{D}}^{24} - 18.2$ (<i>c</i> 0.22, CHCl ₃)	$[\alpha]_{\text{D}} - 15.3$ (<i>c</i> 19.6, CH ₂ Cl ₂) ⁶ <i>NB</i> : solvent is CH ₂ Cl ₂ , not CHCl ₃ ; temperature not stated in the literature
	Methanolysis	 (<i>R</i>-)	$[\alpha]_{\text{D}}^{24} + 22.7$ (<i>c</i> 0.78, CHCl ₃)	$[\alpha]_{\text{D}}^{20} + 30.0$ (<i>c</i> 18.0, CHCl ₃) ⁷
	Methanolysis	 (<i>R</i>-)	$[\alpha]_{\text{D}}^{24} - 18.2$ (<i>c</i> 0.64, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB</i> : in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)
 3.69	Methanolysis	 (<i>R</i>-)	$[\alpha]_{\text{D}}^{24} - 14.0$ (<i>c</i> 1.00, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB</i> : in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)
 3.70	Methanolysis	 (<i>R</i>-)	$[\alpha]_{\text{D}}^{24} - 13.5$ (<i>c</i> 0.55, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB</i> : in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)

 3.71	LAH reduction	 (R-)	$[\alpha]_{\text{D}}^{24} - 17.2$ (<i>c</i> 0.27, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB:</i> in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)
 3.72	Methanolysis	 (R-)	$[\alpha]_{\text{D}}^{24} - 14.1$ (<i>c</i> 0.64, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB:</i> in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)
 3.74	LAH reduction	 (R-)	$[\alpha]_{\text{D}}^{24} - 17.6$ (<i>c</i> 0.18, CHCl ₃)	$[\alpha]_{\text{D}}^{22} - 30.1$ (<i>c</i> 1.66, CHCl ₃) ⁵ <i>NB:</i> in the classical route (<i>cf.</i> page 137) this fragment has a specific rotation of $[\alpha]_{\text{D}}^{25} - 19.0$ (<i>c</i> 1.00, CHCl ₃)

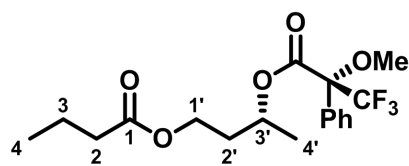
References:

1. Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H., *J. Am. Chem. Soc.* **1995**, *117*, 4279.
2. Denmark, S. E.; Ahmad, M., *J. Org. Chem.* **2007**, *72*, 9630.
3. Carpita, A.; Chini, M.; Rossi, R., *Gazz. Chim. Ital.* **1986**, *116*, 29.
4. Bursi, R.; Devlin, F. J.; Stephens, P. J., *J. Am. Chem. Soc.* **1990**, *112*, 9430.
5. Zarbin, P. H. G.; de Oliveira, A. R. M.; Delay, C. E., *Tetrahedron Lett.* **2003**, *44*, 6849.
6. Gutman, A. L.; Zuobi, K.; Boltansky, A., *Tetrahedron Lett.* **1987**, *28*, 3861.
7. Barbier, P.; Benezra, C., *J. Med. Chem.* **1982**, *25*, 943.

Appendix D: NMR data for Mosher's ester derivatives

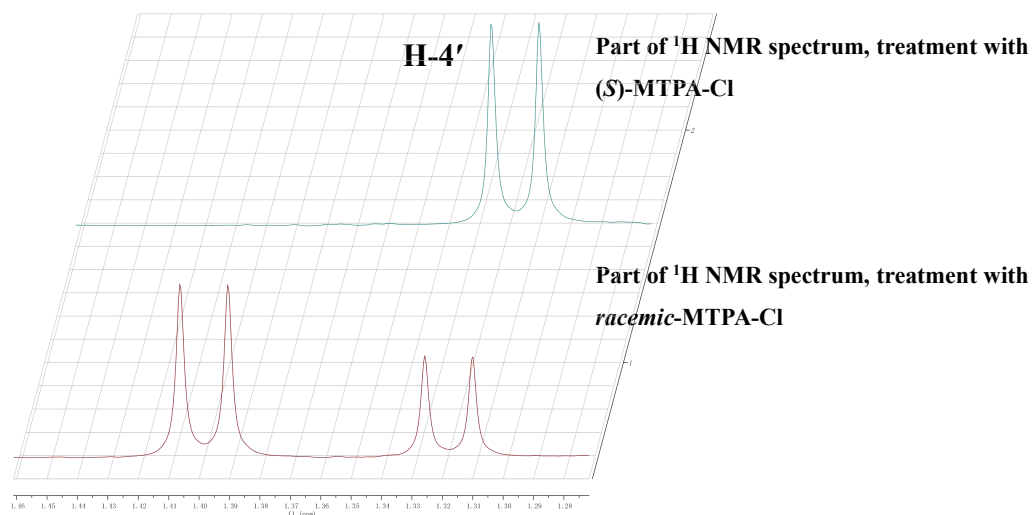


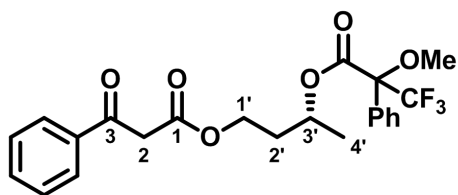
2 diastereomers



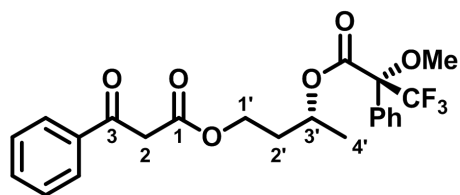
1 diastereomer

	Racemic Mosher's ester	(<i>R</i>)-Mosher's ester
H-2	2.28 (2 H, t, $J_{2,3} = 7.5$ Hz); 2.29 (2 H, t, $J_{2,3} = 7.5$ Hz)	2.29 (2 H, t, $J_{2,3} = 7.5$ Hz)
H-3	1.65 (4 H, sext, $J_{3,2} = J_{3,4} = 7.5$ Hz)	1.65 (2 H, sext, $J_{3,2} = J_{3,4} = 7.5$ Hz)
H-4	0.96 (6 H, t, $J_{4,3} = 7.5$ Hz)	0.96 (3 H, t, $J_{4,3} = 7.5$ Hz)
H-1'	3.86–3.94 (1 H, m); 4.01–4.18 (3 H, m)	4.05–4.18 (2H, m)
H-2'	1.89–2.04 (4 H, m)	1.89–2.04 (2 H, m)
H-3'	5.22–5.29 (2 H, m)	5.22–5.29 (1 H, m)
H-4'	1.32 (3H, d, $J_{4',3'} = 6.0$ Hz); 1.40 (3H, d, $J_{4',3'} = 6.0$ Hz)	1.32 (3H, d, $J_{4',3'} = 6.0$ Hz)
OMe	3.54 (3 H, s); 3.57 (3 H, s)	3.54 (3 H, s)
arom	7.38–7.44 (6 H, m); 7.48–7.54 (4 H, m)	7.38–7.44 (3 H, m); 7.48–7.54 (2 H, m)



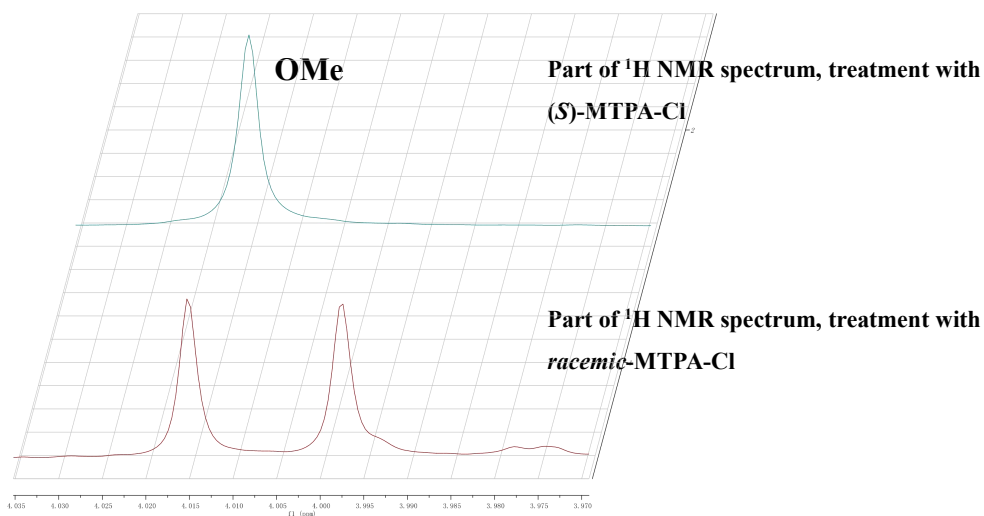


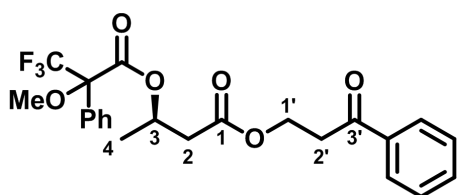
2 diastereomers



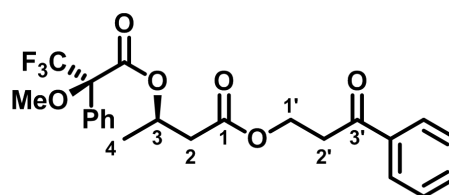
1 diastereomer

	Racemic Mosher's ester	(<i>R</i>)-Mosher's ester
H-2	4.00 (2 H, s); 4.02 (2 H, s)	4.02 (2 H, s)
H-1'	4.12–4.32 (4 H, m)	4.12–4.32 (2 H, m)
H-2'	1.89–2.07 (4 H, m)	1.89–2.07 (2 H, m)
H-3'	5.15–5.23 (2 H, m)	5.15–5.23 (1 H, m)
H-4'	1.28 (3 H, d, $J_{4',3'} = 6.5$ Hz); 1.36 (3 H, d, $J_{4',3'} = 6.5$ Hz,)	1.28 (3 H, d, $J_{4',3'} = 6.5$ Hz)
OMe	3.52 (3 H, s); 3.56 (3 H, s)	3.52 (3 H, s)
arom	7.27–7.97 (20 H, m)	7.27–7.97 (10 H, m)



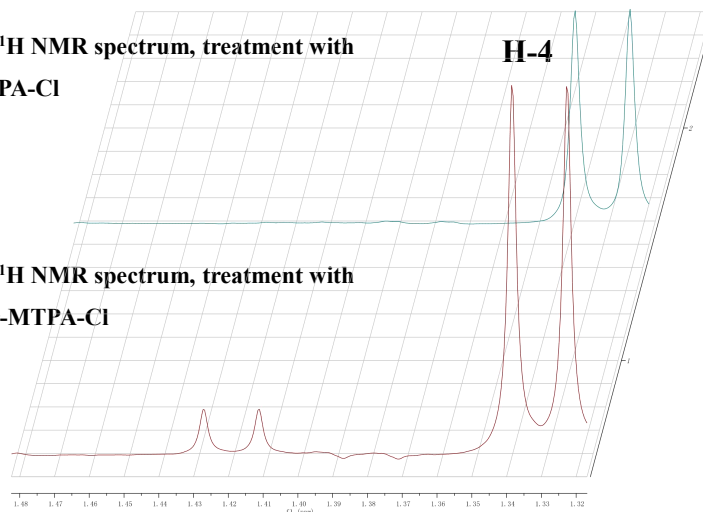


2 diastereomers

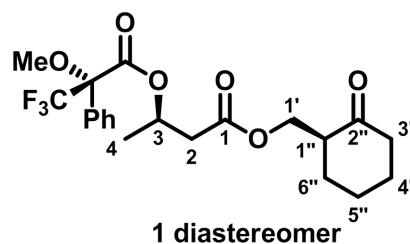
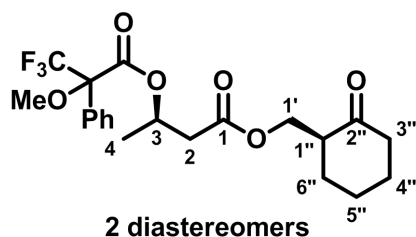


1 diastereomer

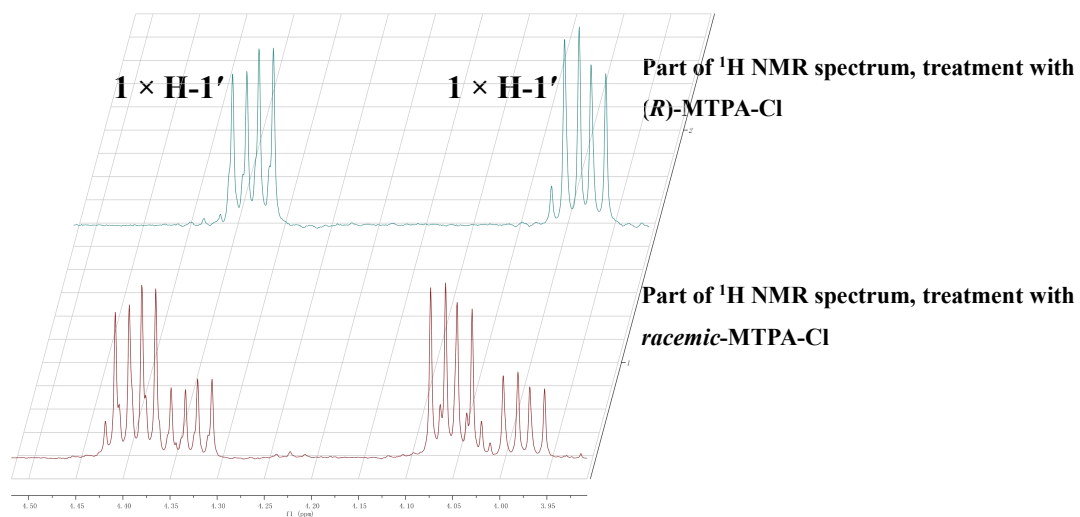
	Racemic Mosher's ester ^{at}	(<i>R</i>)-Mosher's ester
H-2	2.53–2.76 (4 H, m)	2.57 (1 H, dd, $J_{2,2} = 16.0$ Hz, $J_{2,3} = 4.5$ Hz); 2.72 (1 H, dd, $J_{2,2} = 16.0$ Hz, $J_{2,3} = 8.5$ Hz)
H-3	5.50–5.58 (2 H, m)	5.50–5.58 (1 H, m)
H-4	1.33 (3 H, d, $J_{4,3} = 6.5$ Hz); 1.42 (3 H, d, $J_{4,3} = 7.5$ Hz)	1.33 (3 H, d, $J_{4,3} = 6.5$ Hz)
H-1'	4.46 (2 H, t, $J_{1',2'} = 7.0$ Hz); 4.53 (2 H, t, $J_{1',2'} = 6.5$ Hz)	4.53 (2 H, t, $J_{1',2'} = 6.5$ Hz)
H-2'	3.28 (4 H, t, $J_{2',1'} = 6.5$ Hz)	3.28 (2 H, t, $J_{2',1'} = 6.5$ Hz)
OMe	3.42 (3 H, s); 3.53 (3 H, s)	3.53 (3 H, s)
arom	7.36–7.96 (20 H, m)	7.36–7.96 (10 H, m)

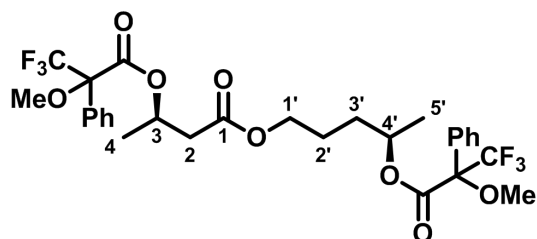
Part of ¹H NMR spectrum, treatment with
(*S*)-MTPA-ClPart of ¹H NMR spectrum, treatment with
racemic-MTPA-Cl

^{at} The racemic MTPA-Cl treatment was done by adding 50% (*S*)-MTPA-Cl followed by 50% (*R*)-MTPA-Cl in the reaction mixture. As shown in the diagram, the integrations of each Mosher's ester derivative does *not* match one another, probably due to the procedure mentioned above.

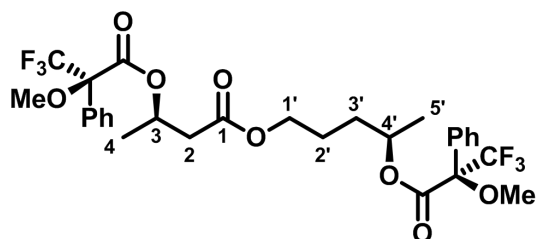


	Racemic Mosher's ester	(S)-Mosher's ester
H-2	2.49–2.73 (6 H, m, overlap with H-1'')	2.49–2.73 (3 H, m, overlap with H-1'')
H-3	5.50–5.60 (2 H, m)	5.50–5.60 (1 H, m)
H-4	1.34 (3 H, d, $J_{4,3} = 6.5$ Hz); 1.42 (3 H, d, $J_{4,3} = 6.5$ Hz)	1.42 (3 H, d, $J_{4,3} = 6.5$ Hz)
H-1'	3.98 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.5$ Hz); 4.05 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.5$ Hz); 4.33 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.0$ Hz); 4.39 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.0$ Hz);	3.98 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.5$ Hz); 4.33 (1 H, dd, $J_{1',1'} = 11.5$ Hz, $J_{1',1''} = 6.0$ Hz)
H-1''	2.49–2.73 (6 H, m, overlap with H-2)	2.49–2.73 (3 H, m, overlap with H-2)
H-3''	2.25–2.45 (4 H, m)	2.25–2.45 (2 H, m)
H-4'', H-5'', H-6''	1.63–2.17 (12 H, m)	1.63–2.17 (6 H, m)
OMe	3.54 (6 H, s)	3.54 (3 H, s)
arom	7.38–7.44 (6 H, m); 7.48–7.55 (4 H, m)	7.38–7.44 (3 H, m); 7.48–7.55 (2 H, m)



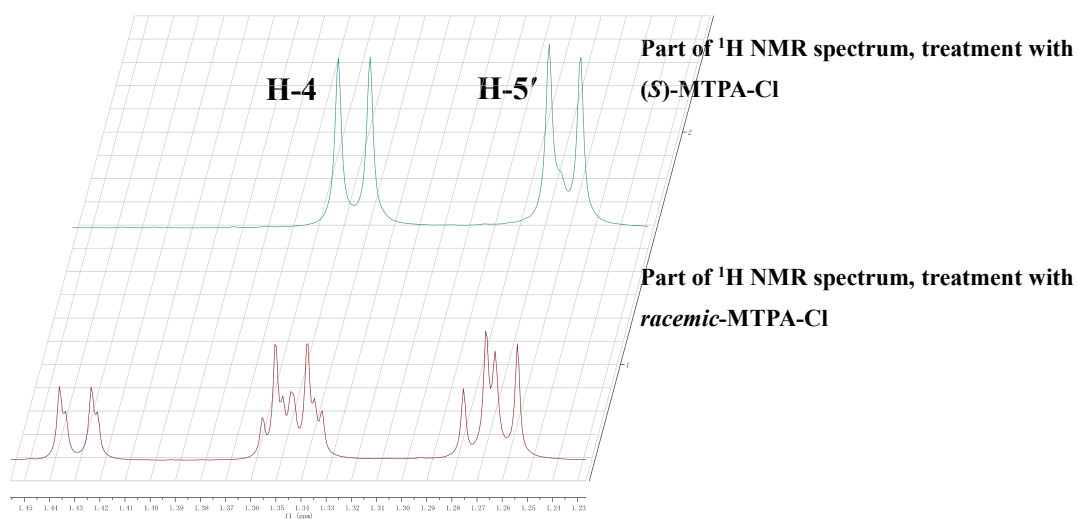


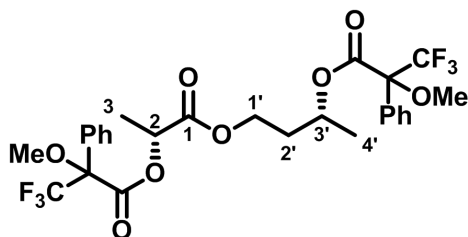
4 diastereomers



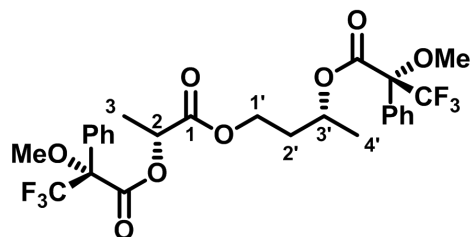
1 diastereomer

	Racemic Mosher's ester	(<i>R</i>)-Mosher's ester
H-2	2.49–2.76 (m)	2.57 (1 H, dd, $J_{2,2} = 16.0$ Hz, $J_{2,3} = 4.5$ Hz); 2.72 (1 H, dd, $J_{2,2} = 16.0$ Hz, $J_{2,3} = 8.5$ Hz)
H-3	5.51–5.59 (m)	5.51–5.59 (1 H, m)
H-4	1.24–1.45 (m, overlap with H-5')	1.34 (3 H, d, $J_{4,3} = 6.0$ Hz)
H-1'	3.73–4.11 (m)	4.02–4.10 (2 H, m)
H-2', H-3'	1.46–1.74 (m)	1.54–1.74 (4 H, m)
H-4'	5.10–5.18 (m)	5.10–5.18 (1 H, m)
H-5'	1.24–1.45 (m, overlap with H-4)	1.26 (3 H, d, $J_{5',4'} = 6.5$ Hz)
OMe	3.50–3.58 (m)	3.52 (3 H, s); 3.54 (3 H, s)
arom	7.36–7.55 (m)	7.36–7.44 (6 H, m) 7.49–7.55 (4 H, m)



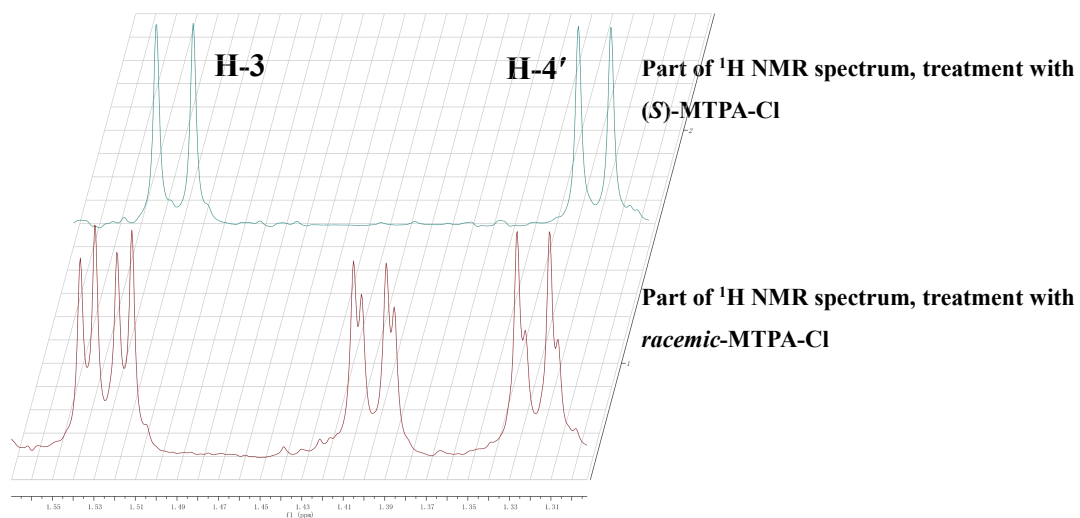


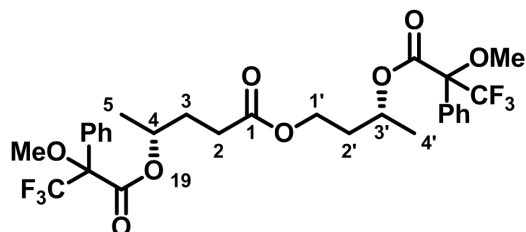
4 diastereomers



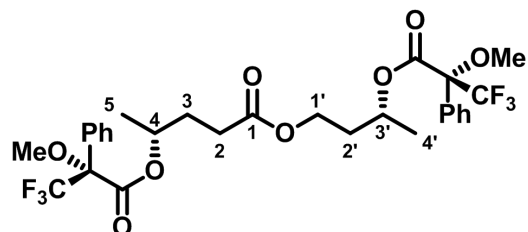
1 diastereomer

	Racemic Mosher's ester	(<i>R</i>)-Mosher's ester
H-2	5.18–5.33 (m, overlap with H-3')	5.18–5.36 (2 H, m, overlap with H-3')
H-3	1.29–1.58 (m, overlap with H-4')	1.52 (3 H, d, $J_{3,2} = 7.0$ Hz)
H-1'	3.94–4.29 (m)	4.17–4.29 (2 H, m)
H-2'	1.84–2.03 (m)	1.95–2.04 (2 H, m)
H-3'	5.18–5.33 (m, overlap with H-2)	5.18–5.36 (2 H, m, overlap with H-2)
H-4'	1.29–1.58 (m, overlap with H-3)	1.32 (3 H, d, $J_{4',3'} = 6.0$ Hz)
OMe	3.53–3.66 (m)	3.53 (3 H, s); 3.66 (3 H, s)
arom	7.38–7.46 (m); 7.47–7.54 (m); 7.60–7.67 (m)	7.38–7.46 (6 H, m); 7.47–7.54 (2 H, m); 7.60–7.67 (2 H, m)





4 diastereomers



1 diastereomer

	Racemic Mosher's ester	(<i>R</i>)-Mosher's ester
H-2	2.16–2.41 (m)	2.32–2.39 (2 H, m)
H-3	1.83–2.03 (m, overlap with H-2')	1.89–2.03 (4 H, m, overlap with H-2')
H-4	5.12–5.31 (m, overlap with H-3')	5.14–5.28 (2 H, m, overlap with H-3')
H-5	1.25–1.41 (m, overlap with H-4')	1.29 (3 H, d, $J_{5,4} = 8.0$ Hz)
H-1'	3.86–4.19 (m)	4.06–4.19 (2 H, m)
H-2'	1.83–2.03 (m, overlap with H-3)	1.89–2.03 (4 H, m, overlap with H-3)
H-3'	5.12–5.31 (m, overlap with H-4)	5.14–5.28 (2 H, m, overlap with H-4)
H-4'	1.25–1.41 (m, overlap with H-5)	1.31 (3 H, d, $J_{4',3'} = 8.5$ Hz)
OMe	3.42–3.57 (m)	3.65 (6 H, app. s)
arom	7.38–7.46 (m); 7.48–7.54 (m)	7.38–7.46 (6 H, m); 7.48–7.54 (4 H, m)

