STUDIES TOWARDS THE TOTAL SYNTHESIS OF TETRODECAMYCIN

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ABSTRACT

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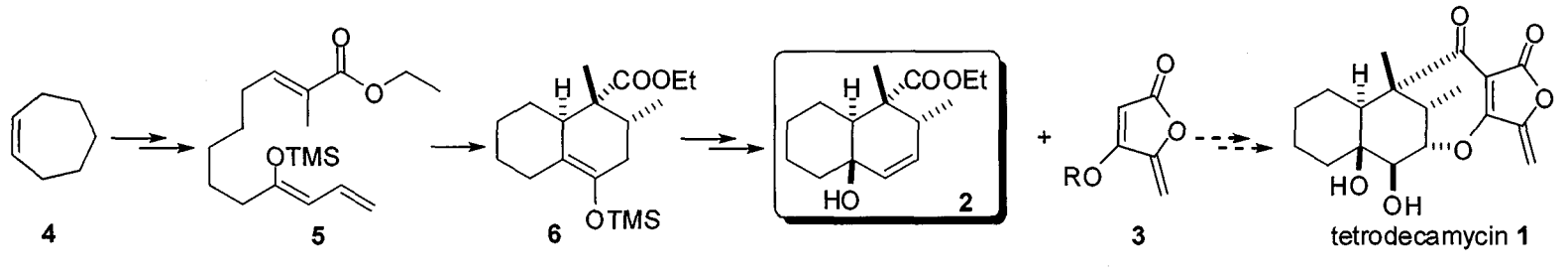
Studies towards the Total Synthesis of Tetrodecamycin

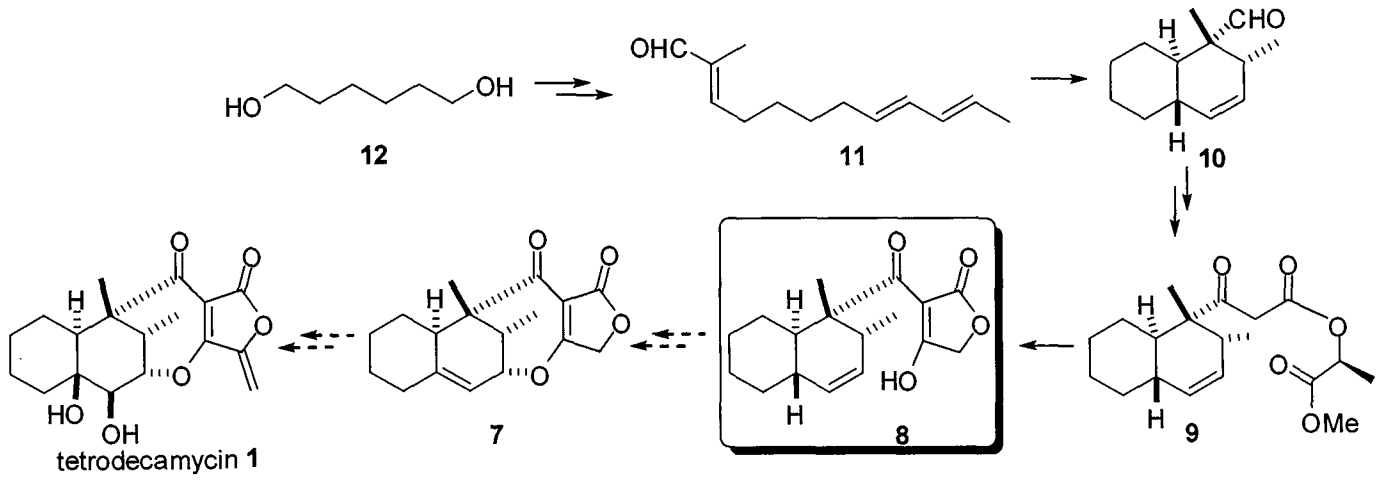
Tetrodecamycin (**1**) is a novel α-(γ-hydroxyacyl) tetronic acid based polyketide antibiotic isolated from the culture broth of *Streptomyces nashvillensis* MJ885-mF8 by Takeuchi *et al.* in 1994. Compound **1** shows potent inhibitory activity against Gram-positive bacteria including *Bacillus anthracis* and methicillin resistant *Staphylococcus aureus* (MRSA).

It was proposed that an Aldol reaction of *trans*-decalin core **2** and tetronic acid derivative **3** followed by a face selective epoxidation and a subsequent epoxide-opening reaction would deliver the 6,6,7,5-skeleton of tetrodecamycin (**1**). To investigate this proposal, the silyl enol ether **5** was prepared from cycloheptene **4** in 7 steps. An unusual domino silyl enol ether reaction sequence was observed when the silyl enol ether **5** was submitted to a Diels-Alder reaction. It afforded cycloadduct **6**, which was converted to the key intermediate **2** after another 3 steps (Scheme 1).



Scheme 1

Concurrently, double functionalisation of simple cyclic silyl enol ethers was investigated. Because of some difficulties in reproducing good overall yields to the cycloadduct **6**, a second synthetic route was proposed. It was envisaged that a palladium-catalysed oxidative cyclisation or an organoselenium-mediated cyclisation reaction of compound **8** would construct the 6,6,7,5-skeleton **7**, which would be converted to tetrodecamycin (**1**) *via* dihydroxylation followed by an introduction of the *exo*-methylene group. The intramolecular Diels-Alder reaction of trienal **11** afforded *trans*-decalin **10**, which was converted to β-keto ester **9** in 2 steps. A Dieckmann-type cyclisation of **9** afforded compound **8** in good yield. However, so far transformation to compound **7** has not been achieved (Scheme 2).



Scheme 2

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ABBREVIATIONS

$[\alpha]_D^{25}$	specific rotation measured at temperature indicated
°C	degrees Celsius
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
APCI	atmospheric pressure chemical ionisation
Ar	aryl
aq.	aqueous
BHT	butylated hydroxy toluene (2,6-di-tert-butyl-4-methylphenol)
Bn	benzyl
Br	bromo
br	broad (spectral)
BTEAC	benzyltriethylammonium chloride
*n*Bu	*n*-butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
cat.	catalytic
Celite	high grade diatomaceous earth
CI	chemical ionisation
concd.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulphonic acid

d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
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
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*'-dimethyl-*N*,*N*'-propyleneurea
DMS	dimethyl sulphide
DMSO	dimethyl sulphoxide
e	electron
EI	electron impact
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq	equivalents
ES	electrospray

Et	ethyl
et al.	*et alia*
g	gram(s)
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
h	hour(s)
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide
Im	imidazole
IR	infrared
KHMDS	potassium hexamethyldisilazide
J	coupling constant (NMR)
KHMDS	potassium (bistrimethylsilyl)amide
L	litre(s)
LDA	lithium diisopropylamide
LHMDS	lithium (bistrimethylsilyl)amide

lit.	literature value
L-selectride	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital
m	medium (IR spectroscopy) or multiplet (NMR spectroscopy)
m-	meta-
M	molar concentration (mol dm^{-3})
MH^+	*protonated* molecular ion
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
MMPP	magnesium monoperoxyphthalate
mp	melting point
MS	mass spectrometry
Ms	methanesulfonyl (mesyl)
m/z	mass-to-charge ratio
n-	normal-
naph	naphthalene
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
[O]	oxidation
o-	ortho-
Oxone	$2KHSO_5.KHSO_4.K_2SO_4$
p-	para-
P	protecting group
Ph	phenyl
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium para-toluenesulphonate
Pr	propyl
Py	pyridine
q	quartet
quat.	quaternary
qui	quintet
R	alkyl group
rt	room temperature
s	sharp (IR spectroscopy) or singlet (NMR spectroscopy)
sat.	saturated
sep	septet
str	strong (IR spectroscopy) or singlet (NMR spectroscopy)
sxt	sextet

t	triplet
t-	tertiary-
tert-	tertiary-
TBAF	tetra *n*-butylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulphonyl (triflyl)
TFA	trifluoroacetic acid or trifluoroacetyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl triflate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl triflate
TPAP	tetra-*N*-propylammonium perruthenate
Tr	trityl
TsOH	*p*-toluenesulphonic acid
UV	ultraviolet
μL	microlitres
v/v	volume per volume
w/v	weight per volume
w/w	weight per weight

CHAPTER 1

INTRODUCTION

CHAPTER 1 INTRODUCTION

1.1 Isolation and structure of Tetrodecamycin

Tetrodecamycin (**1**) and dihydrotetrodecamycin (**2**) are both novel natural products isolated from the fermentation broth of *Streptomyces nashvillensis* MJ885-mF8 by Tsuchida and co-workers in a screening program for novel antimicrobial antibiotics against *Pasteurella piscicida* in 1994. Subsequently in 1995, the structure of **1** was determined by analysis of the NMR data of **1** and its reduced acetyl derivative **3**. The structure of **2** was elucidated by comparison with the spectral data of **1**, which itself was confirmed by its chemical conversion to **2** *via* catalytic reduction. The relative configurations of **2** was finally established by X-ray crystallography, and the absolute configurations of tetrodecamycin (**1**) and dihydrotetrodecamycin (**2**) were eventually determined by using a modified Mosher's method (by the same laboratory).[1]

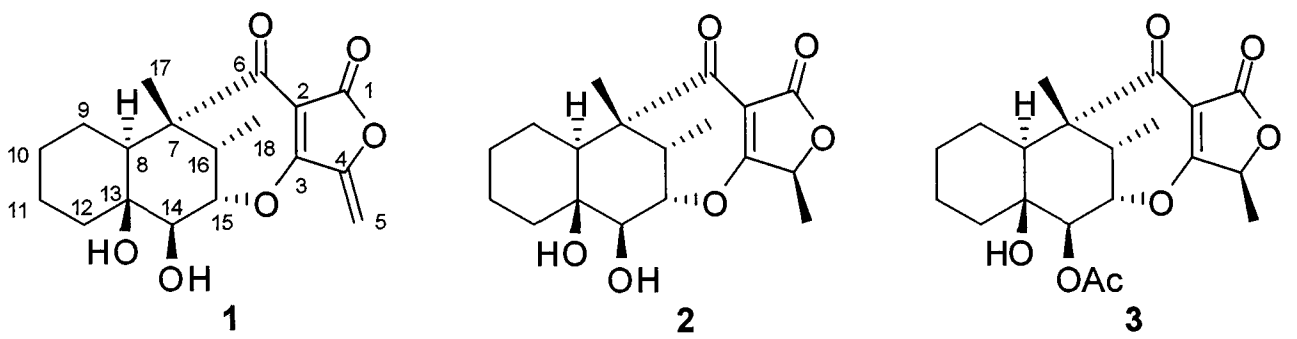


Figure 1

The structure of tetrodecamycin is distinguished by a 6-6-7-5-membered tetracyclic core, one fully and diversely substituted cyclohexane ring in the middle, two quaternary carbons located at C-7 and C-13 with a 2-acyl-4-ylidene tetronic acid derivative portion (Figure 1).[1,2]

1.2 Biological activity

Pasteurella piscicida is a kind of Gram positive bacteria that is known to be the causative agent

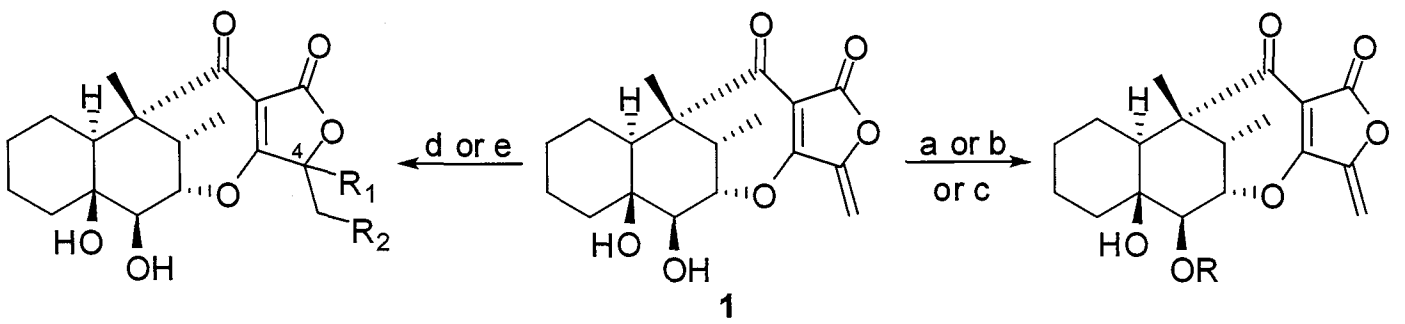
of pseudotuberculosis in cultured yellowtail fish, *Seriolaquinqueradiata*.[3] Pseudotuberculosis presents itself in the hatcheries as a hyperacute or acute septicaemia. Internally granulomatous-like deposits, which comprise of many grayish-white bacterial colonies, develop in the kidney and spleen of the infected fish. The infected fishes have inflamed gills with excessive mucous secretions and areas of necrotic tissue next to congested areas. The liver is most often congested; the spleen is grossly enlarged (splenomegaly) and the kidney pale and oedematous. The intestine carries moderate quantity of transparent fluid. The swim bladder is not distended, thus, the majority of dead and moribund fish are found sunk to the bottom of the tank or cage. This disease has become of considerable economic importance, causing significant losses in farmed yellowtail in Japan. Although various chemotherapeutic agents such as ampicillin, amoxicillin, florfenicol, chloramphenicol, bicozamycin, pyridonecarboxylic acids and tetracycline derivatives have been developed and put into use, the extensive application of these antibiotics has led to an increase in drug resistant strains among fish pathogens. Tetrodecamycin (**1**) shows potent inhibitory activity against 12 strains of *Pasteurella piscicida* without any toxicity, as well as other Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus anthracis*.[4] Therefore, tetrodecamycin (**1**) is potentially a useful therapeutic agent.

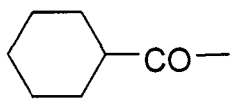
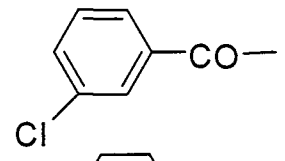
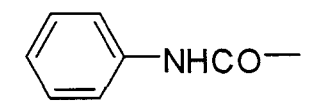
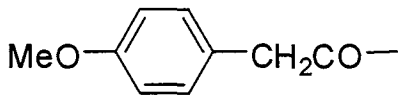
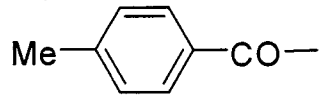
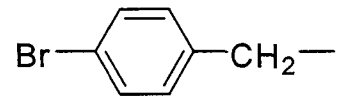
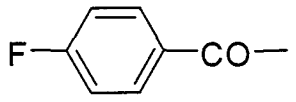
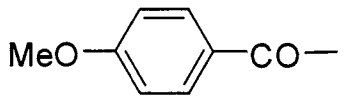
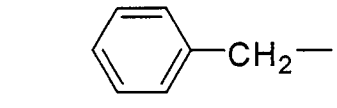
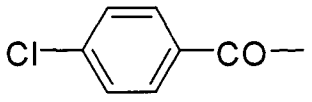
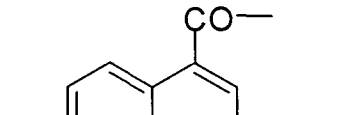
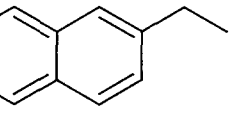
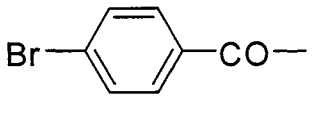
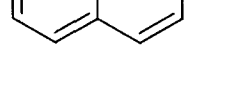
1.3 Related compounds

Tetrodecamycin (**1**) is a kind of 1,2-diakyldecalin polyketide. The plausible biosynthesis and the syntheses of this group of natural products will be discussed later in the Diels-Alder reactions review section (**Chapter 1.5**). Here only the derivatives and clerodane diterpenoids that contain the most similar decalin core will be mentioned.

1.3.1 Derivatives of tetrodecamycin

In the purpose of obtaining a more potent derivative, Tsuchida and co-workers synthesised and evaluated the antibacterial activities of some tetrodecamycin derivatives. The structure-activity relationships were investigated by introduction of substituents or modification at selected sites of the molecule to obtain 14-*O*-acyl-, 14-*O*-carbamoyl-, 14-*O*-alkyl-, 5-*S*-alkyl-4-hydro-, and 4,5-dibromo-tetrodecamycins (Scheme 1).[5]



Compounds:	Compounds: R=
1) R_1=H, R_2=$S(CH_2)_2NHAc$	Ac, Ph-CH=CH-CO-,
2) R_1=H, R_2=$S(CH_2)_2OH$	
3) 4(*S*): R_1=Br, R_2=Br	Ph-CO-, 
4) 4(*R*): R_1=Br, R_2=Br	
	
	
	
	
	
	
	
	
	
	
	

Scheme 1

a) R'COCl, Et_3N, DMAP/DCM; b) R'CNO, Et_3N/DCM; c) 1) $^nBu_2SnO$/toluene, 120°C; 2) RBr, $^nBu_4NI$/toluene, 120°C; d) HS-R/THF; e) 4-(dimethylamino)pyridiniumbromide perbromide/THF

These results showed that although the antibacterial activity against *P. piscicida* was reduced by the introduction of various functional groups to 14-hydroxyl group of tetrodecamycin (**1**), the 14-*O*-subsitituted tetrodecamycin showed higher antibacterial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). The activity order of

the three types of substituents was acyl group> ether group> carbamoyl group. In the 14-*O*-acyl-tetrodecamycins, aryl-acyl derivatives were more potent than alkyl-acyl ones, while the derivative with 2-naphthoyl as the subsitituent was approximately 10-fold more active than tetrodecamycin (**1**).

On the contrary, the modified derivatives at *exo*-methylene moiety of **1** showed weak antibacterial activity, while dihydrotetrodecamycin (**2**) is virtually inactive against Gram-positive bacteria. The results revealed that the *exo*-methylene moiety was crucial in tetrodecamycin (**1**) and derivatives for the biological activity.[5]

1.3.2 Clerodane diterpenoids[6-20]

One of the key features of tetrodecamycin (**1**) is the fully and diversely substituted cyclohexane ring of the 1,2-dialkyldecalin core. Another group of compounds with this system are the clerodane diterpenoids.[7-9] The premnoids **4-6**, isolated from a chloroform-soluble fraction of *Premna tomentosa*, have decalin cores similar to that of tetrodecamycin (**1**).

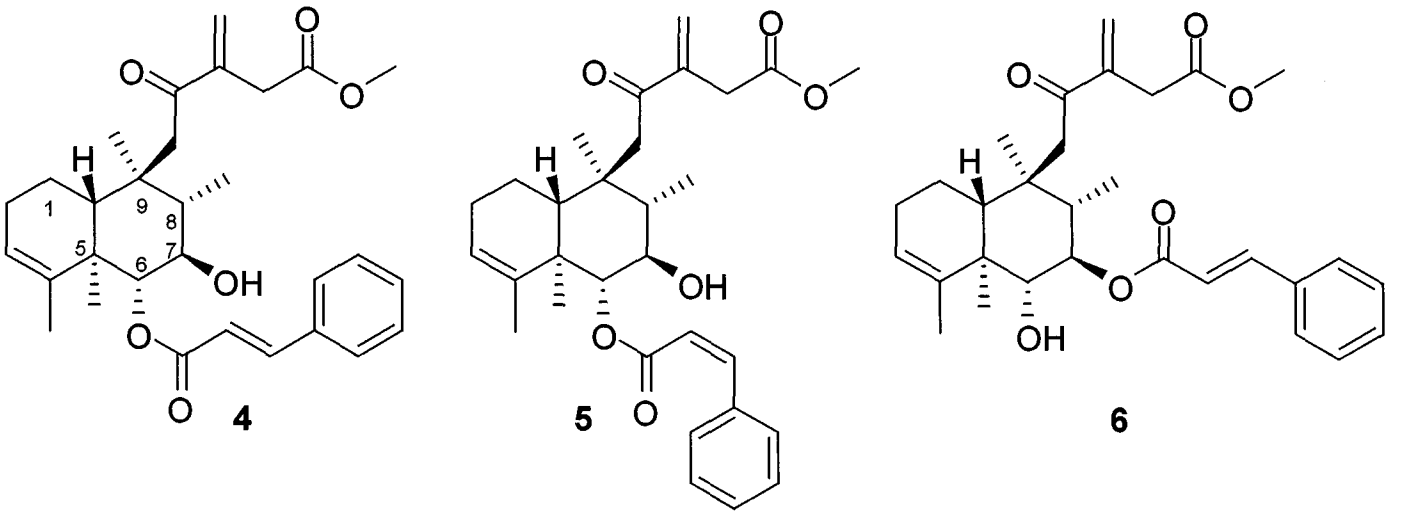


Figure 2

In compounds **4**, **5** and **6** there are two quaternary carbons at C-5 and C-9. Two methyl groups at C-8 and C-9 are found to be *cis* to each other. The hydroxyl groups in compounds **4** and **5** or ether group in compound **6** at C-7 are located *anti* to those at C-6. The differences between compounds **4**, **5** and **6** with tetrodecamycin (**1**) come from the methyl group at C-5 instead a

hydroxyl group as in tetrodecamycin. In addition, the stereocenters at C-5, C-6, C-7 and C-10 in compounds **4**, **5**, and **6** are opposite to that of tetrodecamycin (**1**).[7]

1.4 Previous approaches to the synthesis of tetrodecamycin

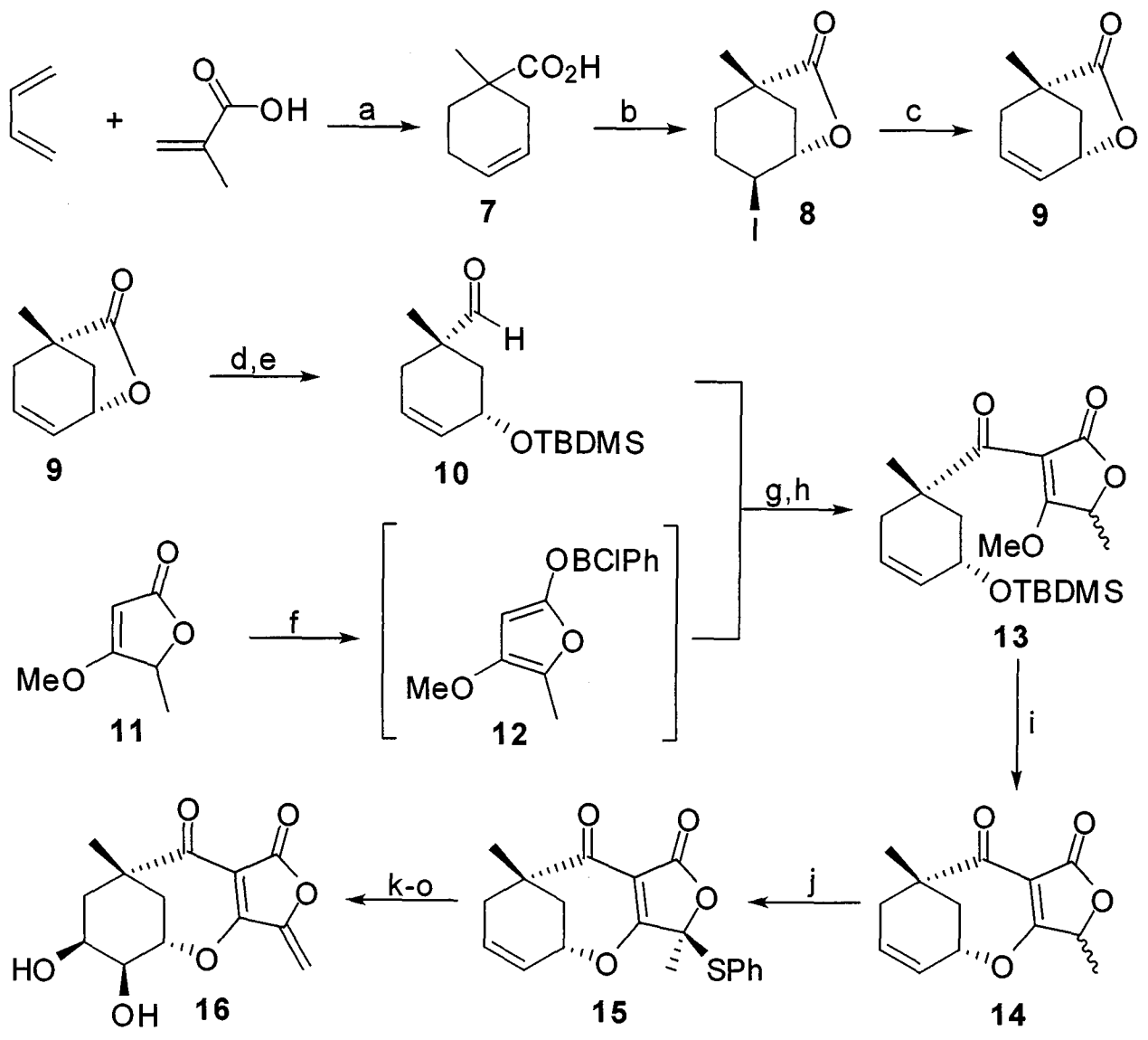
The unique structure of tetrodecamycin and its interesting biological properties have attracted the attention of the synthetic organic community, and the first model studies on the tricyclic core structure were published in 2000 by Paintner and co-workers.[21] So far, only two synthetic studies[4,22,23] and one total synthesis[2] of the titled compound have been published.

1.4.1 Paintner's approaches

1.4.1.1 Paintner's model study

Paintner performed a significant model study dealing with the tetronic part of the molecule and produced a tricyclic core intermediate **16**. The intermolecular Diels-Alder reaction of the commercially available butadiene and methacrylic acid was carried out by steam distillation with the addition of pyrogallol to give the 1-methyl-3-cyclohexenoic acid **7** in high yield.[24] According to Stork's method[25] the lactone **9** was produced by converting the acid **7** to iodolactone **8** followed by elimination of hydrogen iodide. After reduction with DIBAL in dichloromethane at -90°C and selective silylation of the ring opened hydroxyl aldehyde, the lactone **9** was converted to the aldehyde **10**. A boronated 4-methoxy-2-furanolate intermediate **12** was used to introduce the tetronate moiety through a regioselective aldol reaction with the aldehyde **10** followed by an oxidation of the intermediate alcohol to give the cyclisation precursor **13**. The 3-acyl tetronate **13** was treated with catalytic amounts of concentrated H_2SO_4 in dichloromethane at room temperature to afford the cyclised product **14** in high yield. A phenylsulfanyl group was introduced at the γ-position of compound **14** to give sulfide **15**. After

dihydroxylation, monoprotection, oxidative elimination and deprotection, the tetrodecamycin partial structure **16** was obtained in good yield.[4,21,26]



Scheme 2

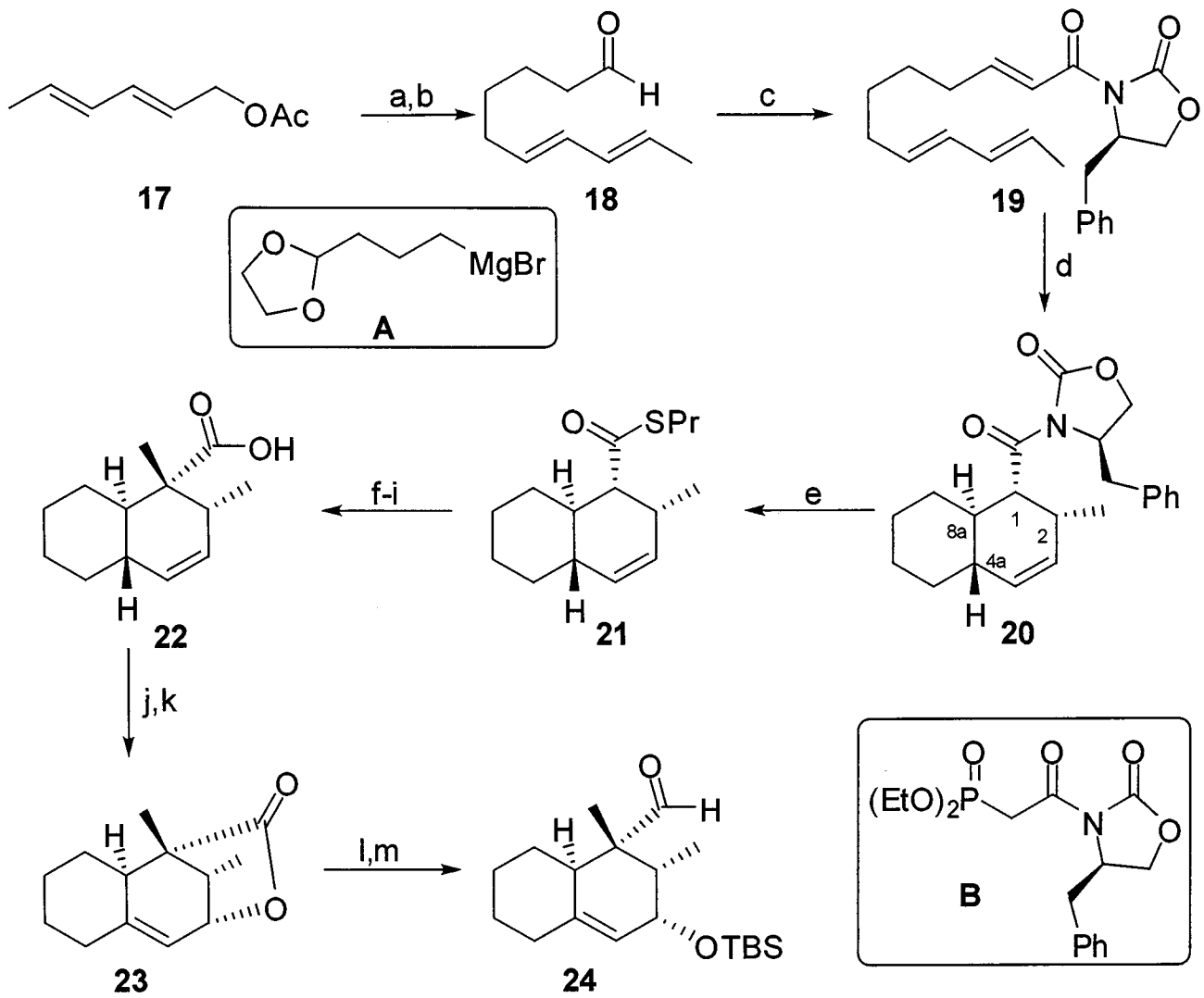
a) pyrogallol, toluene, 150°C (85%); b) I_2, KI, aqueous $NaHCO_3$ (97%); c) diazabicyclononene (DBN, 1.2 eq), benzene, reflux, 7 h (94%); d) DIBAL, DCM, -90°C (87%); e) TBSOTf, lutidine, DCM, -78°C (94%); f) $PhBCl_2$, *i*-Pr_2NEt, DCM, -78°C; g) -78°C to rt (86%); h) IBX, DMSO, rt (91%); i) concd. H_2SO_4 (cat.), DCM, rt (89%); j) 1) LHMDS, THF, -78°C; 2) *N*-phenylmercaptophthalimide, -78°C to rt (87%); k) OsO_4, pyridine, CCl_4, rt; then aq. $NaHSO_3$ (87%); l) TBSOTf, lutidine, DCM, -78°C (92%); m) *m*CPBA, DCM, -20°C; n) $BaCO_3$, benzene, 80°C (57%); o) HF, MeCN, 0°C (100%)

Paintner's model study chose the mono cyclohexane ring instead of the bicyclic system to investigate the construction of the seven-membered ring, and their later work was centred on the synthesis of the decalin core system.

1.4.1.2 Paintner's route to the decalin core

Starting from (2*E*,4*E*)-2,4-hexadien-1-yl acetate **17**, (6*E*,8*E*)-deca-6,8-dienal **18** was obtained by Li_2CuCl_4-catalysed cross coupling with the Grignard **A** and hydrolysis of the resultant acetal.

Modified Horner-Wadsworth-Emmons reaction of the aldehyde **18** with the chiral phosphonate **B** selectively led to the triene **19**, the precursor of the cycloaddition. The asymmetric intramolecular Diels-Alder (IMDA) reaction of trienimide **19** was controlled by the Evans' chiral 4-benzyl-2-oxazolidinone auxiliary component to simultaneously generate the four stereogenic centres at C-1, C-2, C-4a and C-8a of the resulting octahydronaphthalene ring skeleton of **20**. The direct removal of the chiral auxiliary from compound **20** by hydrolysis with lithium hydroperoxide failed due to competing endocyclic cleavage of the *N*-acyloxazolidinone, so the cycloadduct **20** was converted into the thioester **21** by Damon's lithio mercaptide method. After stereoselective methylation and hydrolysis, the stereospecific transformation of the γ,δ-unsaturated acid **22** into lactone **23** was achieved by phenylselenolactonisation and subsequent oxidative removal of the phenylselenanyl substituent to establish the crucial *endo*-cyclic double bond. The building block **24** was produced from compound **23** after reduction of the lactone to lactol and treatment with TBSOTf. With the intermediate **24** in hand, it was proposed to apply the method of the model system to achieve the target molecule (**1**). However, they have not completed the total synthesis of tetrodecamycin (**1**) so far.



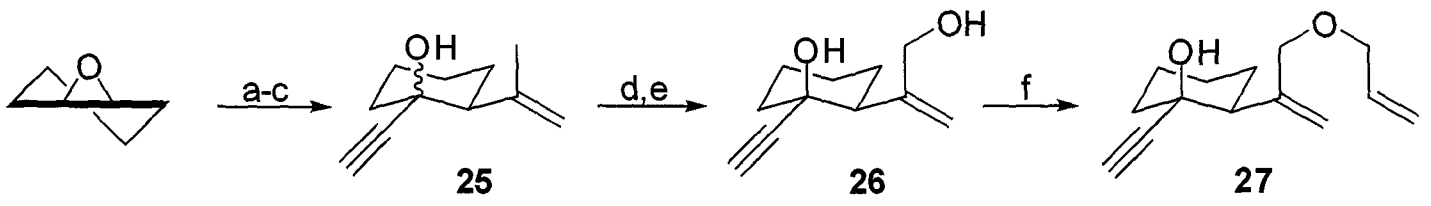
Scheme 3

a) **A**, Li_2CuCl_4 (cat.), THF, -20°C (69%); b) AcOH, H_2O, THF, 80°C (88%); c, , LiCl, *i*-Pr_2NEt, CH_3CN, rt (91%); d) Me_2AlCl (1.4 eq), DCM, -30°C (92%); e) PrSLi, PrSH, THF, 0°C (96%); f) 2M aq. NaOH, MeOH, 120°C; g) trimethyloxonium tetrafluoroborate, *i*-Pr_2NEt, DCM, rt (90%); h) 1) LDA, THF, -78°C to rt; 2) CH_3I, -90°C to rt (84%); i) 3M aq. NaOH, MeOH, 125°C (91%); j) PhSeCl, DCM, -78°C to rt; k) MMPP/SiO_2, DCM, rt (90%); l) DIBAL, DCM, -78°C (74%); m) TBSOTf, *i*-Pr_2NEt, DCM, 0°C (65%)

1.4.2 Barriault's route to the decalin core

Barriault and co-workers divided the molecule into two parts, one compact *trans*-decalin core possessing six contiguous stereocenters and a tetronic acid derivative portion.[23] The key step in the Barriault synthesis of the decalin core was a cascade oxy-Cope/ene/Claisen rearrangement of the allyl ether **27**. The synthesis commenced with epoxide opening of cyclohexene oxide with isopropenylmagnesium bromide followed by Swern oxidation and alkylation with ethynylmagnesium bromide to provide **25** as a 1.5:1 ratio of inseparable stereomers. The allylic oxidation of **25** was accomplished with SeO_2 and *tert*-butyl hydroperoxide at room temperature. After purification the desired diol **26** was obtained in 34% yield. Treatment of the diol **26** with allyl bromide and sodium hydride in the presence of sodium iodide gave the corresponding allyl

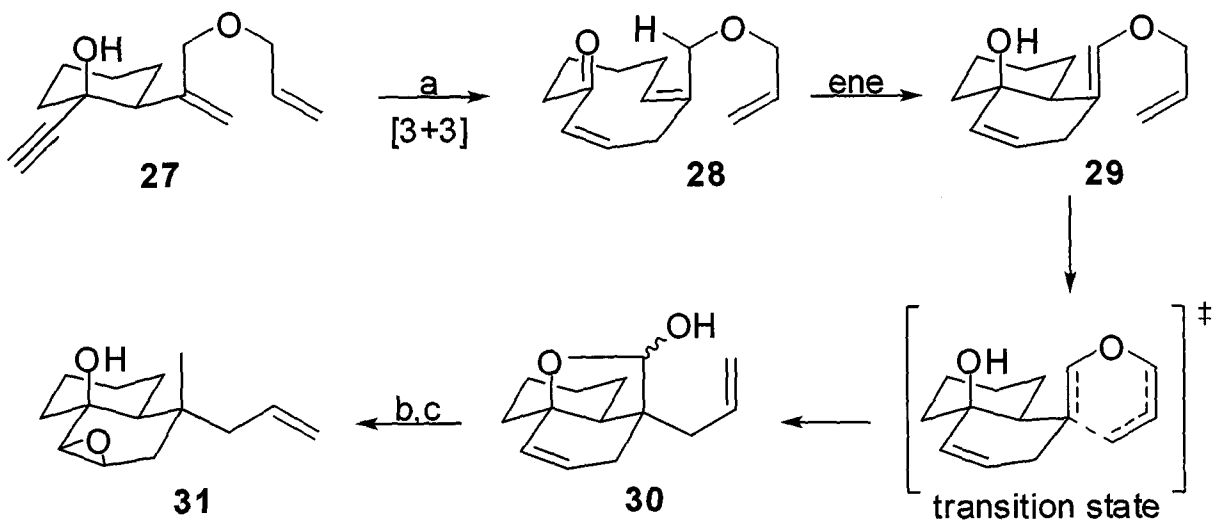
ether **27** in 77% yield (Scheme 4).



Scheme 4

a) isopropenylmagnesium bromide, CuBr, DMS; b) Swern Oxidation (77%); c) ethynylmagnesium bromide, THF; d) SeO_2, TBHP, AcOH (cat.), DCM; e) Silica gel purification (34%); f) allylbromide, NaH, NaI, THF/DMF (9:1), (77%);

The allyl ether **27** was exposed to microwave irradiation for 45 min in degassed toluene and triethylamine to give the desired enone **28**, which derived from a [3,3]-Cope rearrangement and tautomerisation of enol ether. This was followed by an ene reaction and a Claisen reaction in the same pot to give the desired *trans*-decalin **30** in 87% yield. The Wolff-Kishner reduction of the lactol **30** followed by a hydroxyl directed epoxidation furnished the epoxide **31** (Scheme 5).

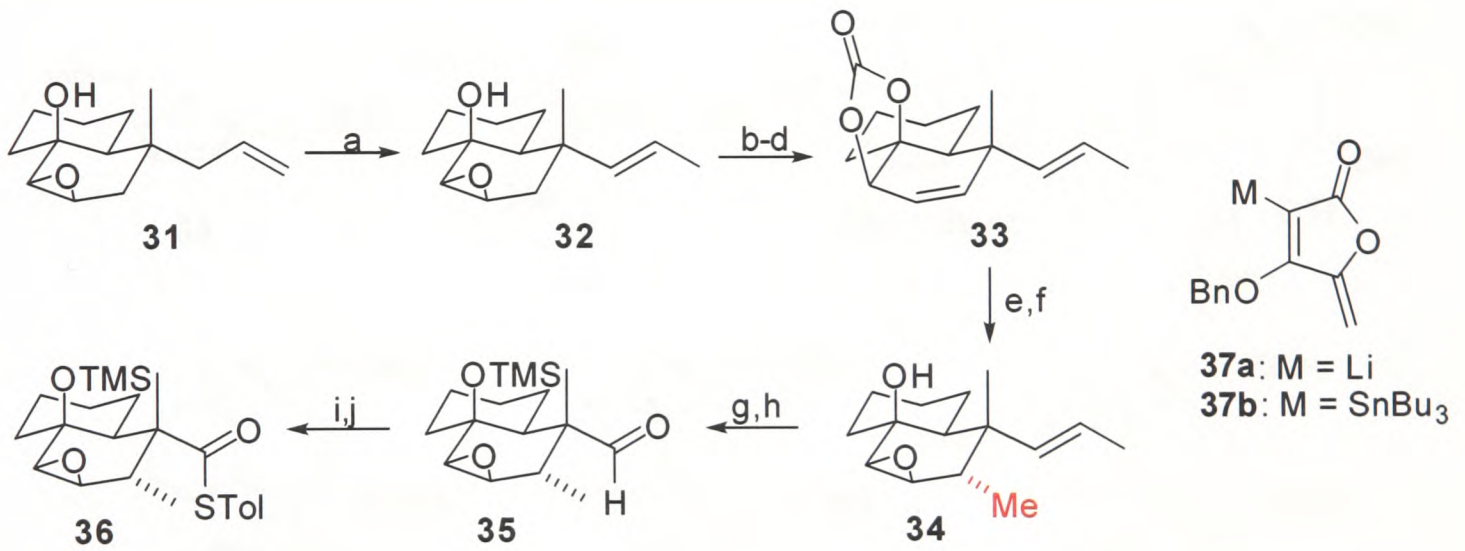


Scheme 5

a) microwaves, toluene, Et_3N, 220°C, 45 min (87%); b) $N_2H_4 \cdot H_2O$; then KOH (82%); c) $VO(acac)_2$, TBHP, PhMe (91%);

The exposure of **31** to a catalytic amount of $RuCl_2(PPh_3)_2$ and excess Hunig's base at 150°C in toluene overnight led to the migration of the terminal double bond to give the internal olefin **32** in high yield. The epoxide **32** was converted to the corresponding selenide by epoxide opening with potassium phenylselenide. The selenide thus formed was treated with triphosgene followed by oxidative elimination to give the internal olefin **33** in quantitative yield. An S_N2' addition of

methyl cuprate and allylic epoxidation of the crude gave the desired olefin **34** in 61% yield. Barriault *et al.* also attempted to introduce the methyl (the red one in Scheme 6) onto the epoxide **31** before the migration of the terminal double bond. However, the internal migration of the double bond suffered from poor yields. The tertiary alcohol was protected by TMS-imidazole and subsequently ozonolysed to the aldehyde **35**, which, in their synthetic plan, would be connected together with **37a** *via* aldol condensation to give the target molecule. Alternatively, oxidation of the aldehyde **35** afforded the corresponding carboxylic acid, which was transformed into the thioester **36**. Barriault *et al.* further planned to perform a palladium-catalysed cross coupling reaction[27] of the thioester **36** with stannyl tetronate **37b** (Scheme 6). The final steps of the retrosynthesis have not been disclosed yet.



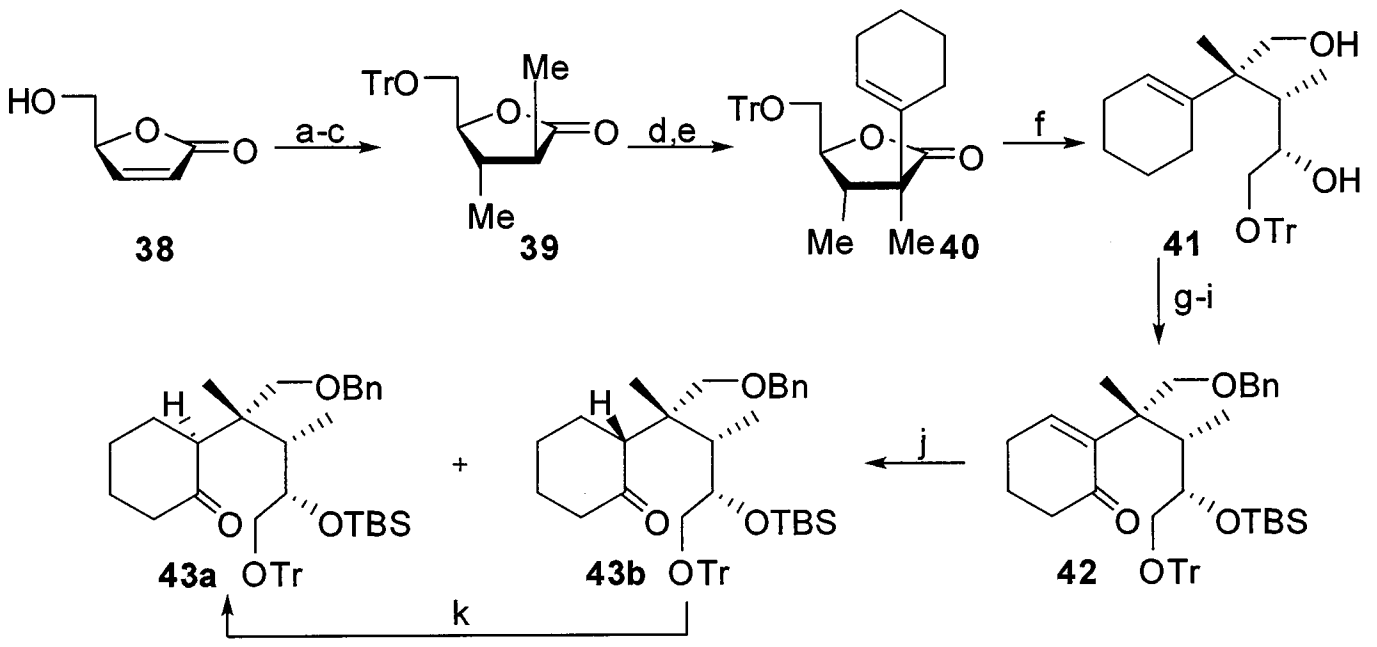
Scheme 6

a) $RuCl_2(PPh_3)_2$ DIPEA, PhMe (83%); b) KSePh, LiBr, THF, rt (86%); c) $CO(OCCl_3)_2$, C_5H_5N, DCM; d) H_2O_2, C_5H_5N, DCM/MeOH (99%); e) MeMgBr, CuCN, THF; f) $VO(Acac)_2$, TBHP, PhMe (61%); g) TMS-Imidazole, LHMDS (62%); h) O_3, then DMS, DCM/C_5H_5N (95:5), (71%); i) $NaClO_2$, NaH_2PO_4, cyclopentene, *t*-BuOH/H_2O (2:1), (85%); j) thiocresol, DCC, DMAP, PhMe (46%)

1.4.3 Tatsuta's asymmetric total synthesis

Tatsuta followed a synthetic route that comprised of a number of interesting ideas to build the various key fragments of tetrodecamycin.[2] Different from the former two ideas, Tatsuta chose to form the seven-membered ring before the tetronic acid part. The synthesis was initiated with the

stereoselective introduction of two methyl groups onto the butenolide, which was prepared by tritylation of the commercially available (*S*)-(-)-5-(hydroxymethyl)-2(5*H*)-furanone **38**. Conjugate addition of MeCu to the protected butenolide followed by treatment with LDA and MeI provided the dimethylated lactone **39** in 67% yield. Treatment of the lactone **39** with LDA and cyclohexanone followed by dehydration of the tertiary alcohol gave the quaternary product **40** stereoselectively. Hydride reduction of **40** to the diol **41** followed by protection and regioselective oxidation with SeO_2 afforded the α,β-unsaturated ketone **42**. Ketone **42** was treated with $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ to give the 1,4-reduction products **43a** and **43b** in 77% and 15% yields respectively. The undesired product **43b** could be recycled by epimerisation to the desired **43a** in alkaline MeOH (Scheme 7).

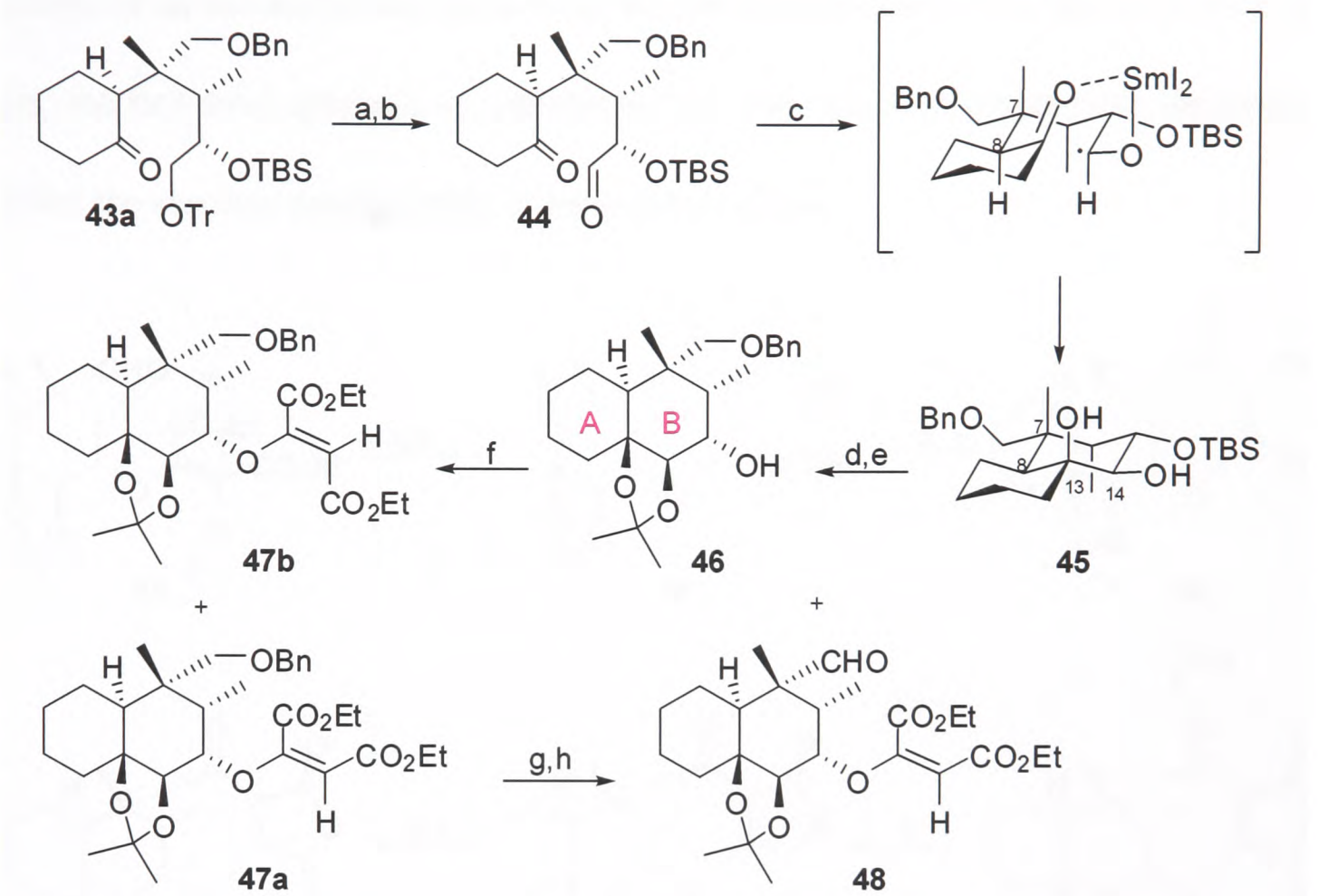


Scheme 7

a) TrCl, NH_4NO_3/DMF, rt, 16h; b) MeMgBr, CuBr·SMe_2, TMSCl, HMPA/THF, -78°C to -50°C, 20 min; c)MeI, LDA/THF, -78°C, 20 min (81%); d) cyclohexanone, LDA/THF, -78°C, 10 min; e) $SOCl_2$/Py, 0°C, 1 h (91%); f) $LiBH_4$/THF, 65°C, 38h; g) BnBr, K_2CO_3, 18-crown-6-ether/MeCN, 50°C, 8 h; h) TBSCl, DBU/MeCN, 65°C, 20 h (88%); i) SeO_2/aq dioxane, 90°C, 17 h (86%); j) $NaBH_4$, $NiCl_2 \cdot 6H_2O$/MeOH-DCM, 0°C, 10 min (**43a**: 77%, **43b**: 15%); k) KOH/MeOH, 60°C, 2 h (60%)

Ketone **43a** was de-*O*-tritylated and subsequently oxidised to afford the keto-aldehyde **44**. The fully substituted B ring was formed by a SmI_2-mediated stereoselective cyclisation of **44**. The *cis*-diol **45** was obtained as a single product, probably resulting from the most stable transition

state of the chelation-controlled reaction.[28] After acetonation of the diol and desilylation, the Michael addition of acetonide **46** to diethyl acetylenedicarboxylate gave the desired (*E*)-olefin **47a** in 75% yield together with 15% (*Z*)-olefin **47b**. The olefin **47a** was reductively de-*O*-benzylated to alcohol, which was oxidised to aldehyde **48** (Scheme 8).

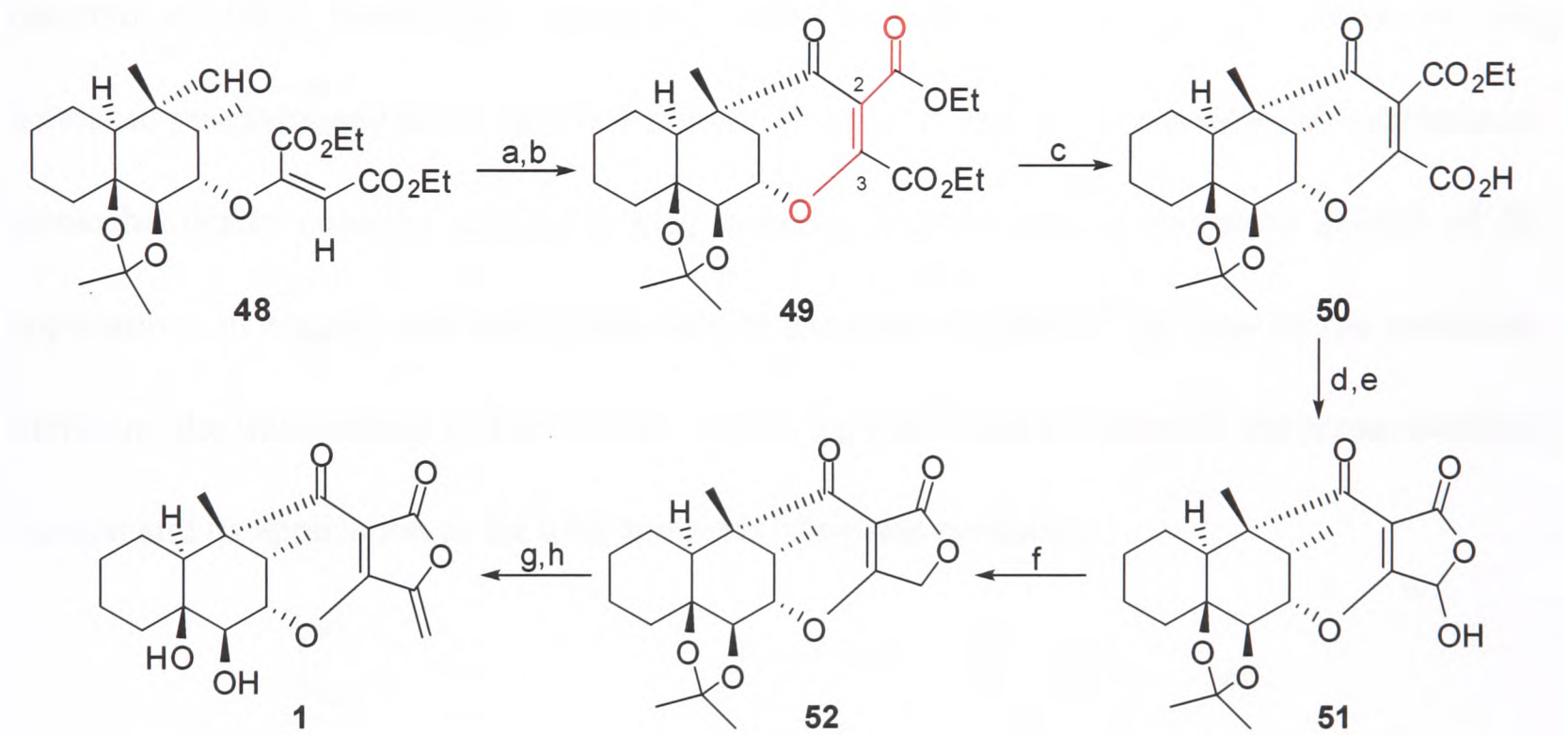


Scheme 8

a) Et_2AlCl/DCM, -78°C to 0°C, 0.5 h; b) PCC, Al_2O_3/DCM, rt, 6 h; c) SmI_2, ^tBuOH/THF, -78°C, 0.5 h (73%); d) 2-methoxypropene, PPTS/DCM, rt, 8 h; e) TBAF/THF, 50°C, 15 h (71%); f) diethyl acetylene-dicarboxylate, KH/$ClCH_2CH_2Cl$, 75°C, 6 h (**47a**:75%, **47b**: 15%); g) H_2, Pd-C/EtOH, rt, 2 h; h) PCC, Al_2O_3/DCM, rt, 6 h (88%)

The aldehyde **48** was then submitted to a Baylis-Hillman-type reaction. Treatment of **48** with NaHMDS constructed smoothly the seven-membered ring to afford a 5:1 diastereometric mixture of alcohols, which was oxidised to a single product **49** as expected. In the diester **49**, the C-2 ester was anticipated to be less reactive than the C-3 ester for saponification because of the conjugation to the ring oxygen. Therefore, compound **49** was selectively hydrolysed to the mono-acid **50**. The acid **50** was transformed to a thioester, which was reduced by Et_3SiH to an

aldehyde with concomitant cyclisation to a diastereomeric mixture of acetal **51**. Deoxygenation of the acetal **51** was effected in one operation by bromination, subsequent debromination with PPh_3 and protonation to furnish the lactone **52**. Deacetonation of lactone **52** afforded a diol, which, upon treatment with Eschenmoser's reagent under basic conditions, underwent introduction of an *exo*-methylene goup to give (-)-tetrodecamycin (**1**) (Scheme 9). In a total of 26 steps, the first total synthesis of tetrodecamycin was achieved, which also simultaneously established the absolute configuration of the natural product.



Scheme 9

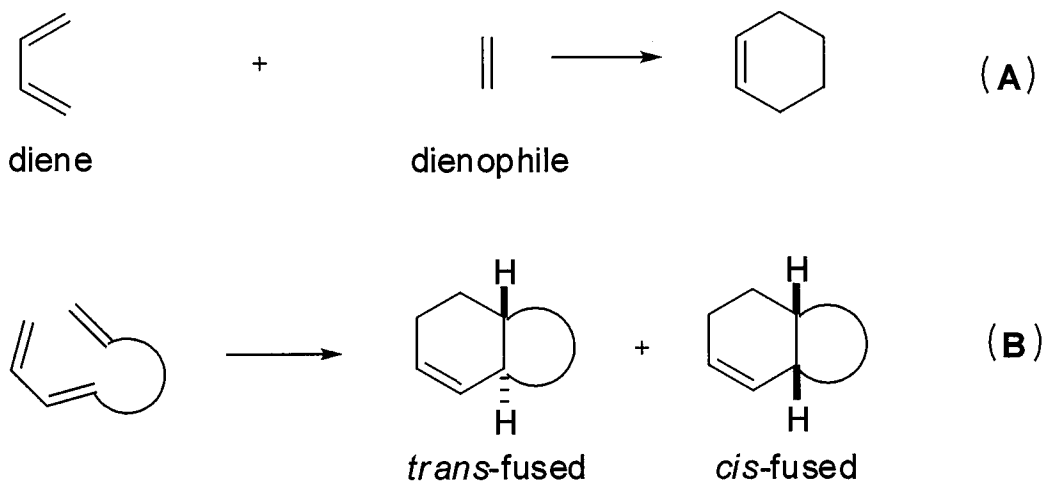
a) NaHMDS/THF, -78°C, 10 min; b) IBX/PhMe-DMSO, rt, 3 h (81%); c) Na_2CO_3/aq. THF, rt, 15 h (91%); d) EtSH, WSCI·HCl, Py/DCM, rt, 1 h (74%); e) Et_3SiH, Lindlar cat./acetone, rt, 0.5 h (80%); f) CBr_4, PPh_3/DCM, rt, 0.5 h (75%); g) 70% aq TFA, 50°C, 10 h (85%); h) $CH_2=N^+Me_2I^-$, i-Pr_2NEt/1,4-dioxane, rt, 12 h; then MeI, rt, 11 h (63%)

1.5 Diels-Alder Reactions in total syntheses

1.5.1 Diels-Alder Reaction

The Diels-Alder reaction is a [4+2] cycloaddition of a diene and a dienophile discovered in 1928.[29] It is particularly valuable in that it forms two new σ-bonds at the expense of one π bond to afford a cyclohexenyl system, and simultaneously, in this single concerted step it defines up to

four contiguous stereocentres, from a 4π electron system (diene - a conjugated alkenyl system for homonuclear Diels-Alder reactions) and a 2π electron system (dienophile - a single olefin for homonuclear Diels-Alder reactions) to increase molecular complexity and often achieve high regio- and stereo-selectivity.[30,31] There are two major classes of the Diels-Alder reaction, intermolecular and intramolecular (Scheme 10). The intermolecular version requires bimolecular additions of 1,3-dienes to alkenes and alkynes. The intramolecular reaction (IMDA), in which the diene and dienophile are tethered by a connecting chain in one molecule, was firstly reported in 1953, twenty-five years later than the intermolecular one.[32-36] However, the increased reactivity and the heightened regioselectivity, as well as the potential for synthesis of stereochemically complex polycyclic ring systems, account for the enormous growth of its applications in organic and particularly natural products synthesis.[30] In view of the extensive literature, the introduction of Diels-Alder reaction in this thesis is limited to the intramolecular version and its application in the total synthesis of natural products.



Scheme 10

1.5.2 Simple effects on diastereoselectivity

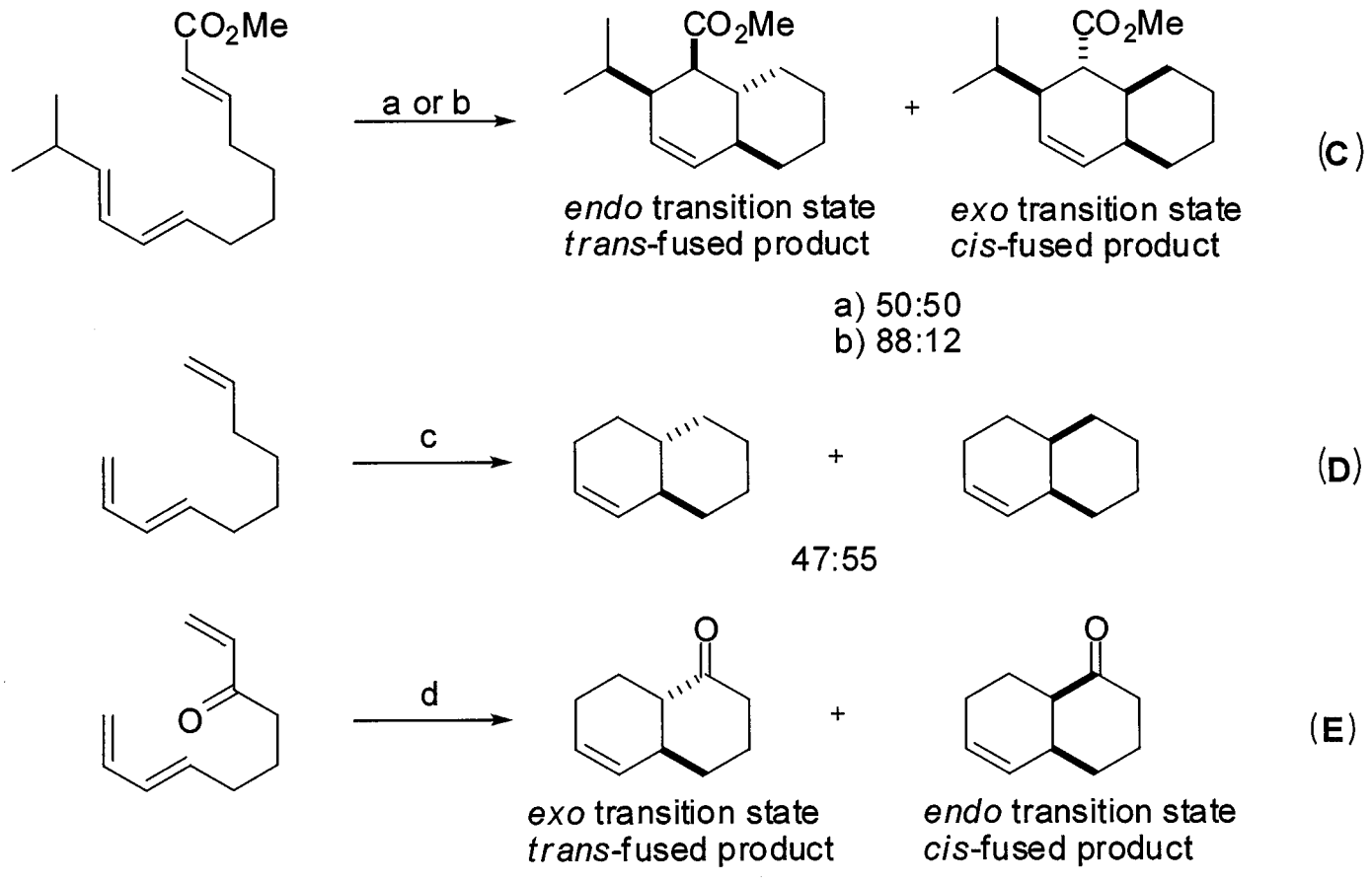
Theoretically, the Diels-Alder reaction could afford a number of isomeric products in equal abundance, but in reality, it is often observed that one isomer predominates depending on conditions under which the reaction is conducted and on the structural properties of the

Diels-Alder reactants.[37] Here two simple effects on this problem will be introduced.

1.5.2.1 Effect of the dienophile

It has been recognised for many years that the presence of a dienophile activating group has a significant effect on the stereoselectivity of IMDA reactions. The IMDA reactions are feasible only if the connecting chains contain three or more atoms, and here in this thesis the deca-trienes are used as the precursors, so this part will be focused on the effect of the dienophile to the (*E*,*E*,*E*)-deca-trienes.

An electron-withdrawing group conjugating to the alkene will lower the alkene LUMO energy and in effect narrow its energy gap with HOMO of the diene. This will increase the rate of the Diels-Alder reaction. There are two possible positions of the activating groups: internal (Equation E in Scheme 11) and terminal (Equation C in Scheme 11).



Scheme 11

a) 160-180°C (69-71%); b) $AlEtCl_2$, 23°C; c) 190°C; d) 15°C

The activating group also has an effect on stereoselectivity when compared to the unsubsitituted

triene (Scheme 11). This result was attributed to the Alder *endo* stabilisation, which is rationalised as the result of the secondary orbital interactions between the dienophile substituent and the π electrons of the diene[38]. For (*E,E,E*)-decatrienes, the dienophile activating group occupies an *endo* position in the transition state to give the *trans*-fused cycloadduct for the terminal activating groups while the *cis*-fused cycloadduct for the internal ones (Figure 3). Apparently, equation C and E in Scheme 11 indicated that the Alder *endo* effect on stereoselectivity is more significant in the decatrienone IMDA comparing with the terminal substituted triene. However, further increases in selectivity occur when Lewis acid catalysis was employed (Equation C condition b).

endo transition state
trans-fused product

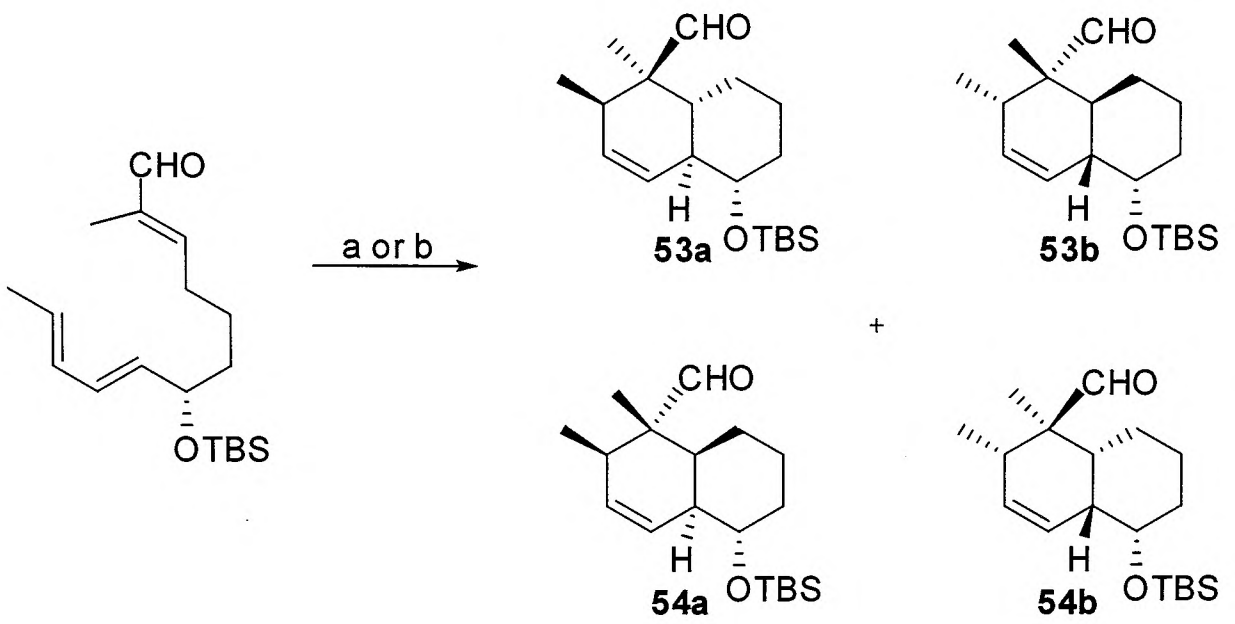
endo transition state
cis-fused product

Figure 3

1.5.2.2 Effect of catalysts: Lewis acids, enzyme and other catalysts[39,40]

1.5.2.2.1 Lewis acid and other catalysts

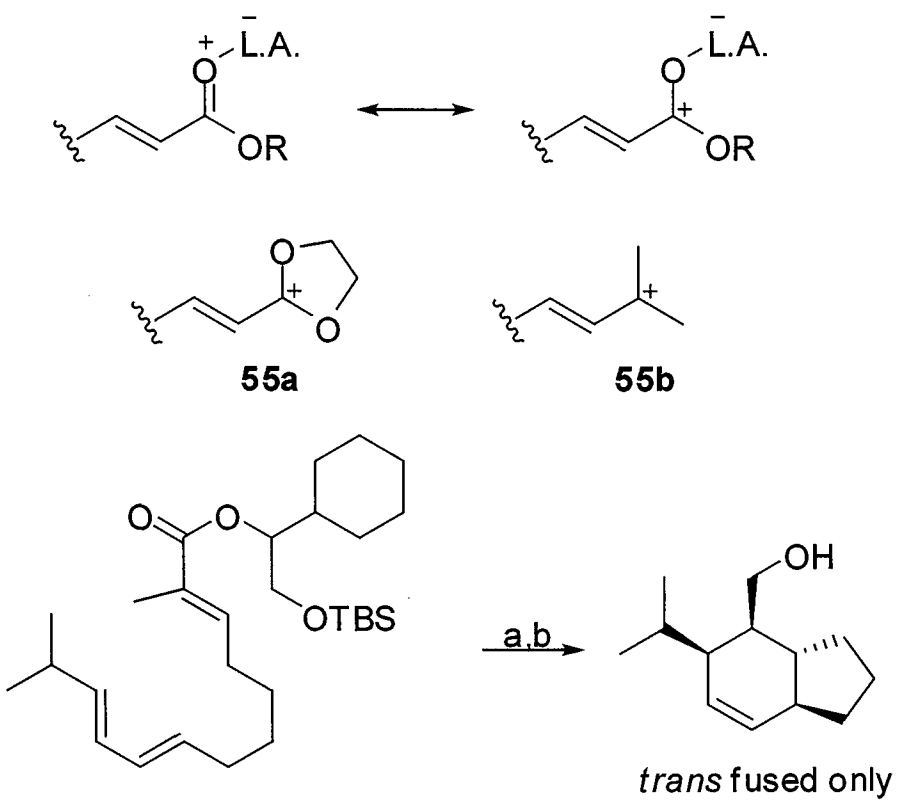
The use of Lewis acid catalysis is a powerful method for increasing the rates and diastereoselectivity of many IMDA reactions. An example is shown in Scheme 12. With Lewis acid, the reaction can occur under mild conditions and give a higher ratio of *trans* and *cis* products.[41]



Scheme 12

Conditions	*53a*	*53b*	*54a*	*54b*	*trans:cis*
a) Me_2AlCl, DCM, -78 to -15°C	15	75	10	0	90:10
b) BHT, toluene, 150-160°C	27	27	33	13	54:46

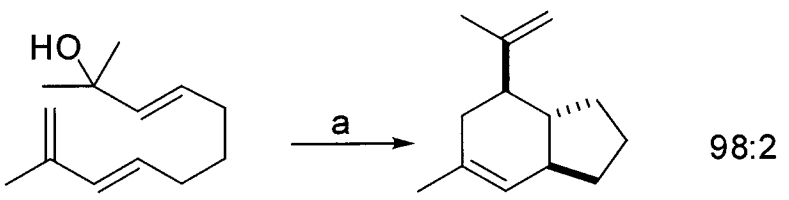
The reactive species in the Lewis acid catalysed IMDA reactions of α,β-unsaturated ester dienophiles is formally a Lewis acid stablised dioxolenium ion such as **55a** and **55b**, which is a powerful electron-withdrawing group, and thus further lowers the energy level of the dienophile LUMO and increases the rate of the Diels-Alder reaction (Scheme 13).[42] At the end of 1980s, Gassman's studies shows that α,β-unsaturated dioxolenium ions, generated by treatment of triethyl orthoacrylate with trimethylsilyl triflate in dichloromethane at -78°C, are excellent dienophiles for intermolecular Diels-Alder reactions.[43] Similarly, acetals of α,β-unsaturated aldehydes are precursors to alkoxy-substituted allyl cations that are also excellent ionic Diels-Alder dienophiles.[44]



Scheme 13

a) HF (2 eq), MeCN, DCM, rt, 72 h; b) $LiAlH_4$ (78%)

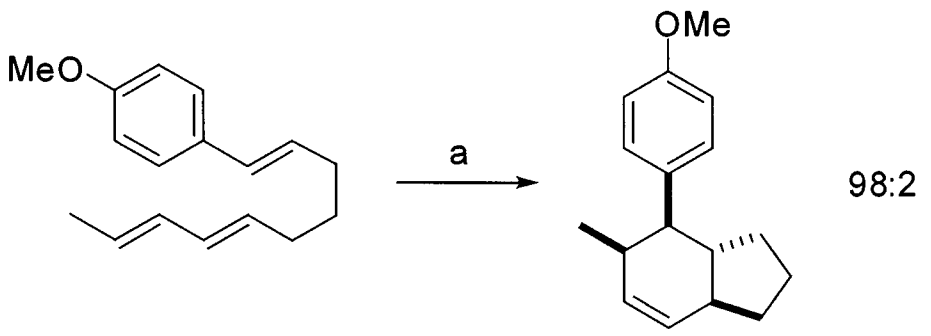
Protic acids can catalyse the formation of allyl cation dienophiles from the allylic alcohols and allylic ethers at low temperatures. These reaction species can undergo [4+2] cation cycloadditions in high yield with high stereoselectivity (Scheme 14).[45,46]



Scheme 14

a) CF_3SO_3H (5%), -23°C, DCM (77%)

Besides, cation radical Diels-Alder reactions catalysed by $Ar_3N^{\cdot+}\cdot Cl_6Sb^-$ occur when the reactions are carried out in the presence of 2,6-di-*t*-butylpyridine (in excess, based on aminium cation salt) to scavenge protic acids generated either from loss of protons from initially generated cation radicals or from dimerisation of cation radical intermediates.[45] This type of Diels-Alder reactions have been observed to be routinely capable of extraordinarily high *endo* stereoselection.[47,48]



Scheme 15

a) $Ar_3N^{\cdot+}\cdot Cl_6Sb^-$ (0.5 eq), 2,6-di-*t*-butylpyridine, DCM, 0°C, 10 min (83%)

1.5.2.2.2 Enzyme

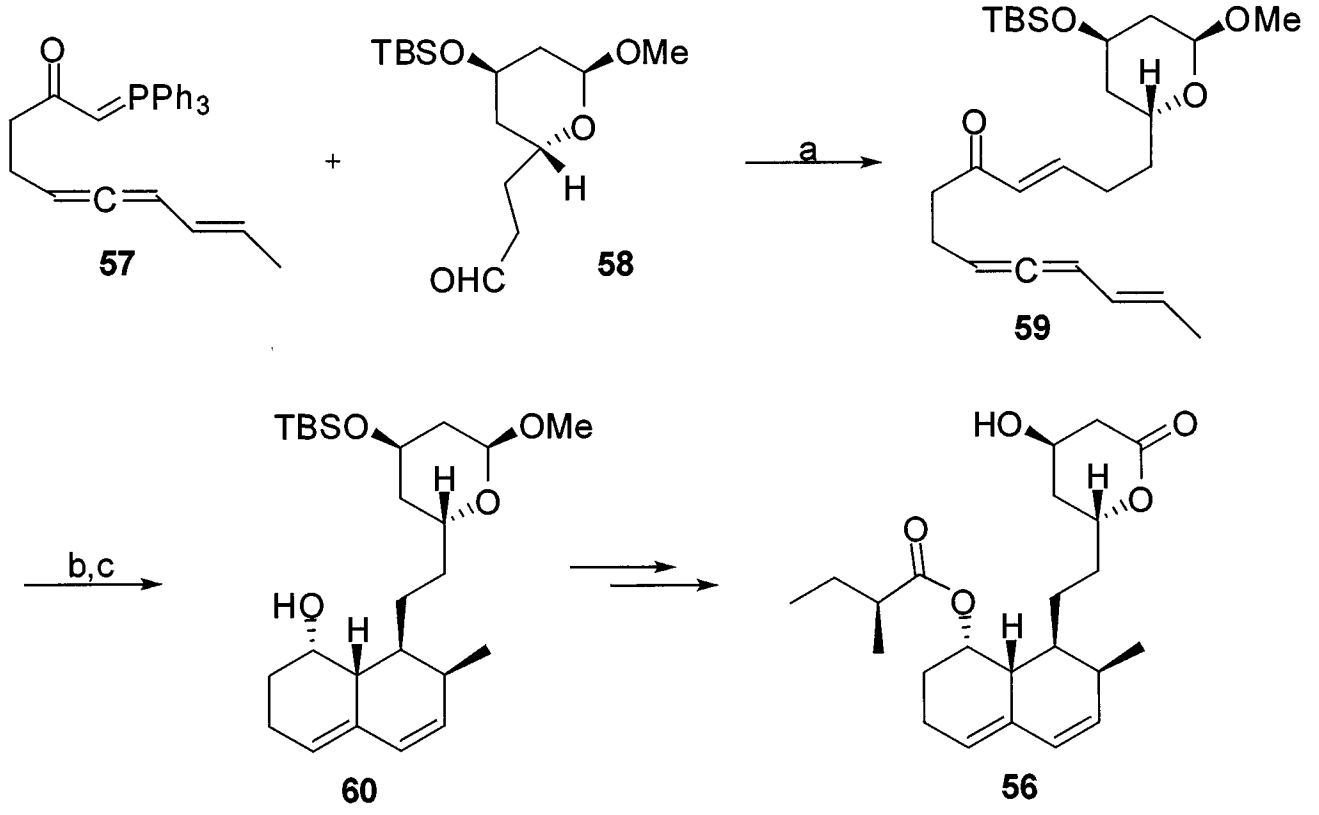
Nature's repertoire of biosynthetic transformations has recently been recognised to include the Diels-Alder cycloaddition reaction. Evidence exists that enzymes can mediate the Diels-Alder reaction in secondary metabolic biosynthetic pathways.[49] Enzymes catalysing the Diels-Alder reaction are named "Diels-Alderase".[50,51] An intriguing aspect of many biosynthetic proposals involves the possibility of enzymatic catalysis of the cycloaddition to accommodate the stereochemistry extant in the respective natural products.[49] The general strategy of enzyme catalysis of the Diels-Alder reaction is entropy trapping with activation of the substrate by hydrogen bonding.

1.5.3 The application of IMDA reactions in total syntheses of natural products

A significant number of total syntheses of various natural products, such as polyketides, alkaloids, terpenoids, steroids and so on, have been achieved by using IMDA reactions as key steps in the construction of their basic frameworks. A number of polyketides formed *via* a putative Diels-Alder reactions belong to the 1,2-dialkyldecalin class of polyketides, which is related to tetrodecamycin (**1**).[51] 1,2-Dialkyldecalin polyketides could be synthesised *via* intramolecular Diels-Alder reactions of a linear polyolefin chain, and have a decalin moiety with two neighbouring alkyl groups at the same ring.[52] Herein are some examples of the total synthesis of 1,2-dialkyldecalin polyketides *via* IMDA reactions.

1.5.3.1 Total synthesis of compactin

Compactin (**56**), isolated from cultures of *Penicillium brevicompactum* in 1976, is a potent inhibitor of sterol biosynthesis, both *in vitro* and *in vivo*.[53,54] In 1986, Keck and his co-worker published a highly convergent route to (+)-compactin (**56**).[55] The cycloaddition precursor **59** was produced *via* a Wittig reaction of the phosphorane **57** with the aldehyde **58**. The vinylallene **59** was heated in toluene with BHT (butylated hydroxytoluene) in a sealed tube at 140°C for 1.25 h to give a mixture of diastereomers, which were directly submitted to the reduction with L-selectride to give **60** in a total yield of 84%. BHT is a free radical inhibitor, which is used as an additive for high temperature reaction. The ratio between the *trans*-fused product **60** and the *cis*-fused product was 2.3: 1 (Scheme 16).



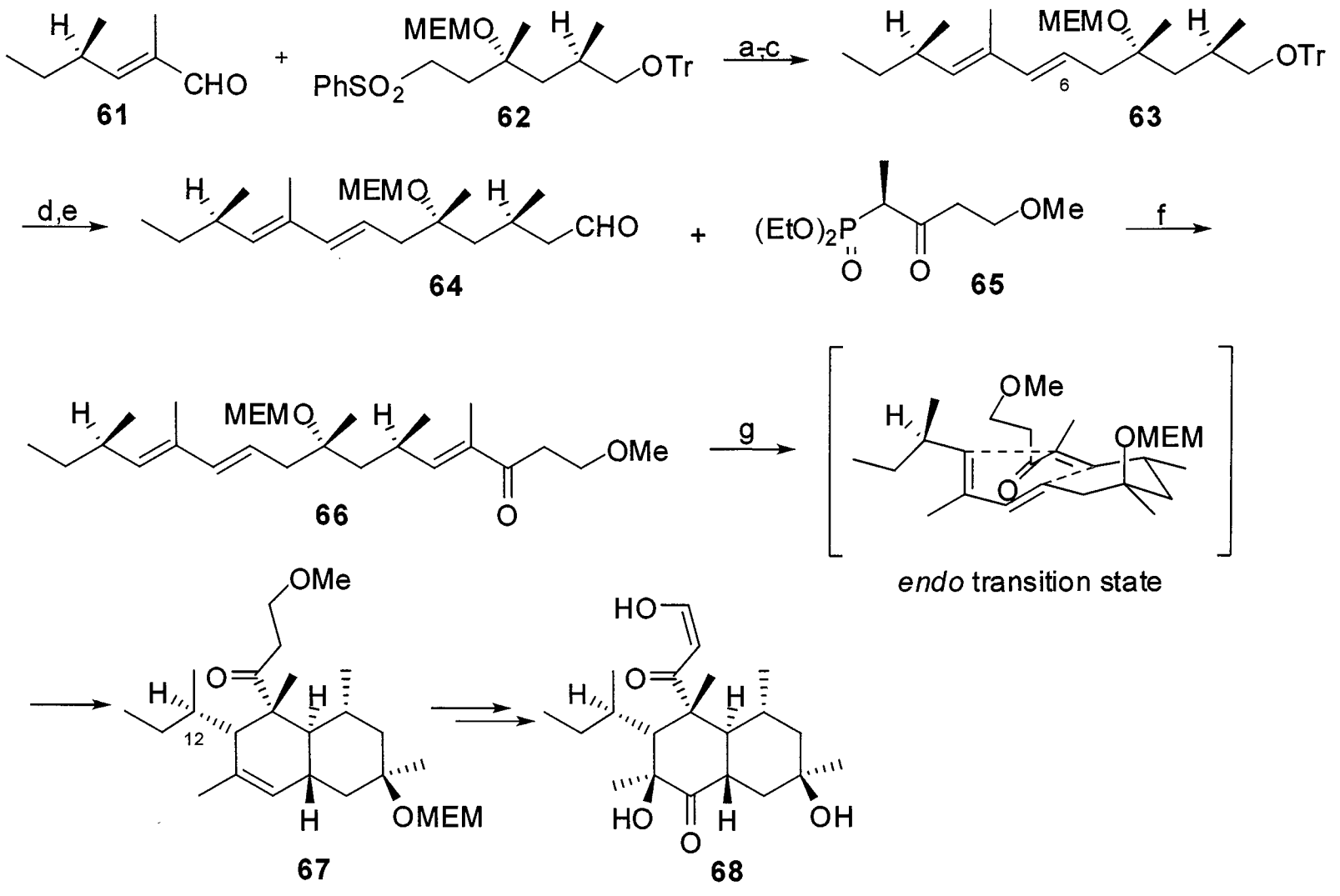
Scheme 16

a) $CHCl_3$, rt (74%); b) BHT (cat.), toluene, Dumas tube, 140°C, 1.25 h; c) L-Selectride, THF, 0°C, 30 min (84% two isomers)

1.5.3.2 Total synthesis of (-)-Betaenone C[56]

(-)-Betaenone C (**68**) was isolated from the culture filtrate of *Phoma Betae* Fr., causal fungus of leaf spot disease on sugar beet. (-)-Betaenone C (**66**) showed higher phytotoxic activity than

other betaenones to the host plant and completely inhibited the *in vivo* RNA and protein synthesis of starfish gastrula. The total synthesis of this compound adopted an IMDA as a key step was reported in 1989 by Ichihara and co-workers.[56] The condensation of aldehyde **61** with sulphone **62** afforded an adduct, which was treated with acetic anhydride and then sodium amalgam (5%) to give diene **63**. By removal of the protective trityl group and Swern oxidation with oxalyl chloride, diene **63** was converted to aldehyde **64**. The Wittig-Horner reaction of the aldehyde **64** with the phosphonate **65** afforded the trienone **66**. The intramolecular Diels-Alder reaction of the trienones **66** was carried out in a sealed tube heating at 115˚C for 36 h to yield cycloadducts **67** in 41% yield. Only 20% 12-epimer was separated after chromatographic purification, but no other diastereoisomers were detected. The *endo* Diels-Alder reaction transition state is even more favourable because of the absence of severe non-bonded atom interaction.[57] After dihydroxylation, oxidation and further furnishing of the upper part of the molecule, (-)-betaenone C (**68**) was synthesised (Scheme 17).



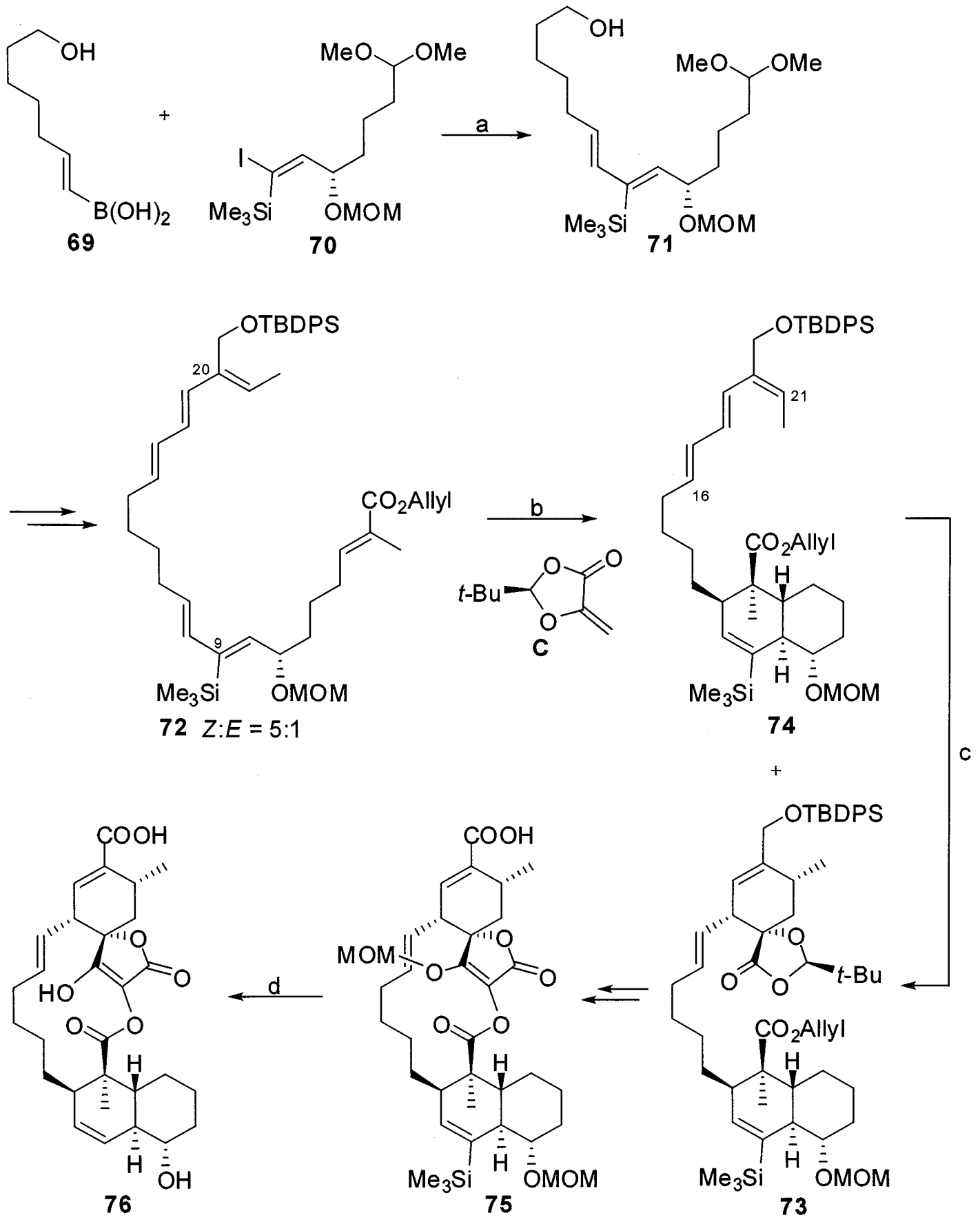
Scheme 17

a) ^{n}BuLi, -75°C; b) Ac_2O; c) Na(Hg) (59% over three steps); d) SiO_2, benzene, rt, 36 h; e) $(COCl)_2$, DMSO, -55°C, 20 min (79%); f) ^{n}BuLi, -3-4°C, 40 h (47% over three steps); g) toluene, 115°C, 36 h (41%)

1.5.3.3 Total synthesis of (-)-Chlorothricolide[52,58-60]

(-)-Chlorothricolide (**76**) is the aglycon of chlorothricin, which was isolated from *Streptomyces antibioticus*.[61,62] It is an inhibitor of pyruvate carboxylase and is also active against Gram-positive bacteria. In 1998, Roush and Sciotti reported their enantioselective total synthesis of (-)-chlorothricolide (**76**) *via* a simultaneous inter- and intramolecular Diels-Alder reactions of a 21-carbon linear substrate **72** (Scheme 18). Precursor **72** was synthesised by a Suzuki cross coupling of the α-iodovinylsilane **70** with vinylboronic acid **69** under Kishi's modified conditions to afford a silicon-containing conjugate diene structure **71**. Compound **71** was further elaborated to the IMDA precursor **72** through sequential Horner-Wadsworth- Emmons olefination. The tandem intermolecular and intramolecular Diels-Alder reactions were performed by heating a mixture of **72** and (*R*)-**C** in toluene at 120°C for 20 h. This afforded the

expected doubly cyclised product **73** (40-45%) together with other cycloadduct isomers (19%) and the IMDA adduct (*E,E,E*)-**74** (25-30%) with an isomerised C20-C21 trisubstituted double bond. Notably, the intermolecular [4+2] cycloaddition of **72** occurred with strict regioselectivity regarding the upper conjugate triene part. It had already been noticed that the C20-C21 trisubstituted double bond of the olefin **74** readily isomerised under the Diels-Alder reaction conditions, so the isomerised product **74** was independently subjected to the intermolecular Diels-Alder reaction with **A** in Cl_2C=CHCl at 125˚C for 28-36 h in a sealed tube to provide additional **73** in a total of 55-59% yield after one recycle (Scheme 18). The intermolecular Diels-Alder reaction shows high diastereofacial and *exo*-selectivity of the chiral dienophile **C**, so that it enables the introduction of the desired relative and absolute stereochemistry for the three stereocenters in the top half fragment. Also, the stereoselectivity of the intramolecular Diels-Alder reaction was controlled by the steric hindrance of the C9-trimethylsilyl group in **72**.

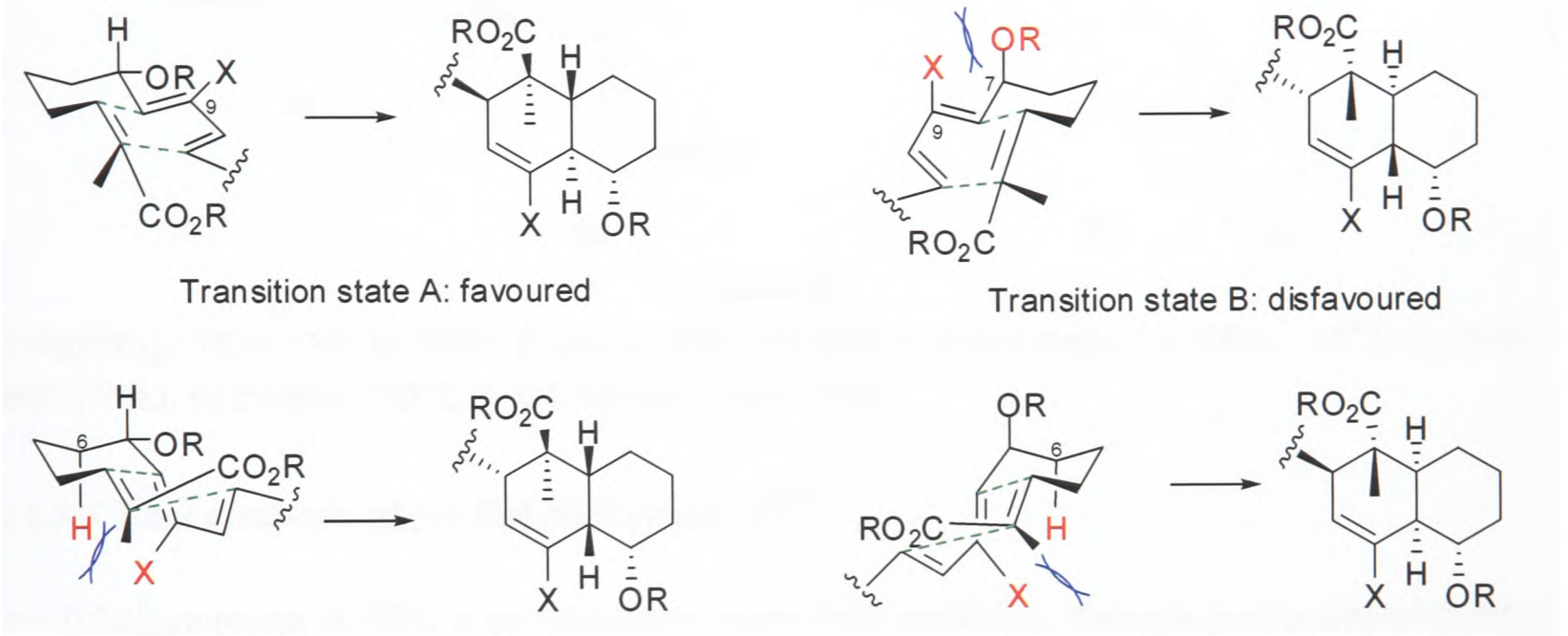


Scheme 18

a) $Pd(PPh_3)_4$, TlOH, THF-H_2O; b) BHT, toluene (1.0 M), 120°C, 20 h (55-59% of **73** after one recycle of **74**); c) **C**, $Cl_2C{=}CHCl$, 125°C, 28-36 h; d) EtSH, $BF_3{\cdot}Et_2O$ (91%)

The IMDA reactions of a series of C7-alkoxy-substituted (2*E*,8*Z*,10*E*)-undecatrienoates containing C9-bromo or C9-trimethylsilyl substituents were previously studied by Roush.[63] *Cis*-fused transition states C and D were expected to suffer from serious interaction between the axial H6 and the C9-X substituent, while transition state B would be destabilised by a 1,3-eclipsing interaction between C7-OR and C9-X. On the basis of this analysis, only the

trans-fused transition state A suffers from no serious interaction involving the C-9 steric directing group (Scheme 19). Therefore, the IMDA reaction of **72** led to the bottom half octahydronaphthalene unit of **76** with the desired stereoinduction. Elaboration of **73** to **75** was accomplished by a conventional reaction sequence, including the construction of the spiro-tetronate subunit and macrolactonization of the seco acid. Finally, removal of the MOM ethers and cleavage of the trimethylsilyl substituent were carried out simultaneously by treatment of **75** with EtSH and $BF_3 \cdot Et_2O$ to provide (-)-chlorothricolide (**76**) (Scheme 18).

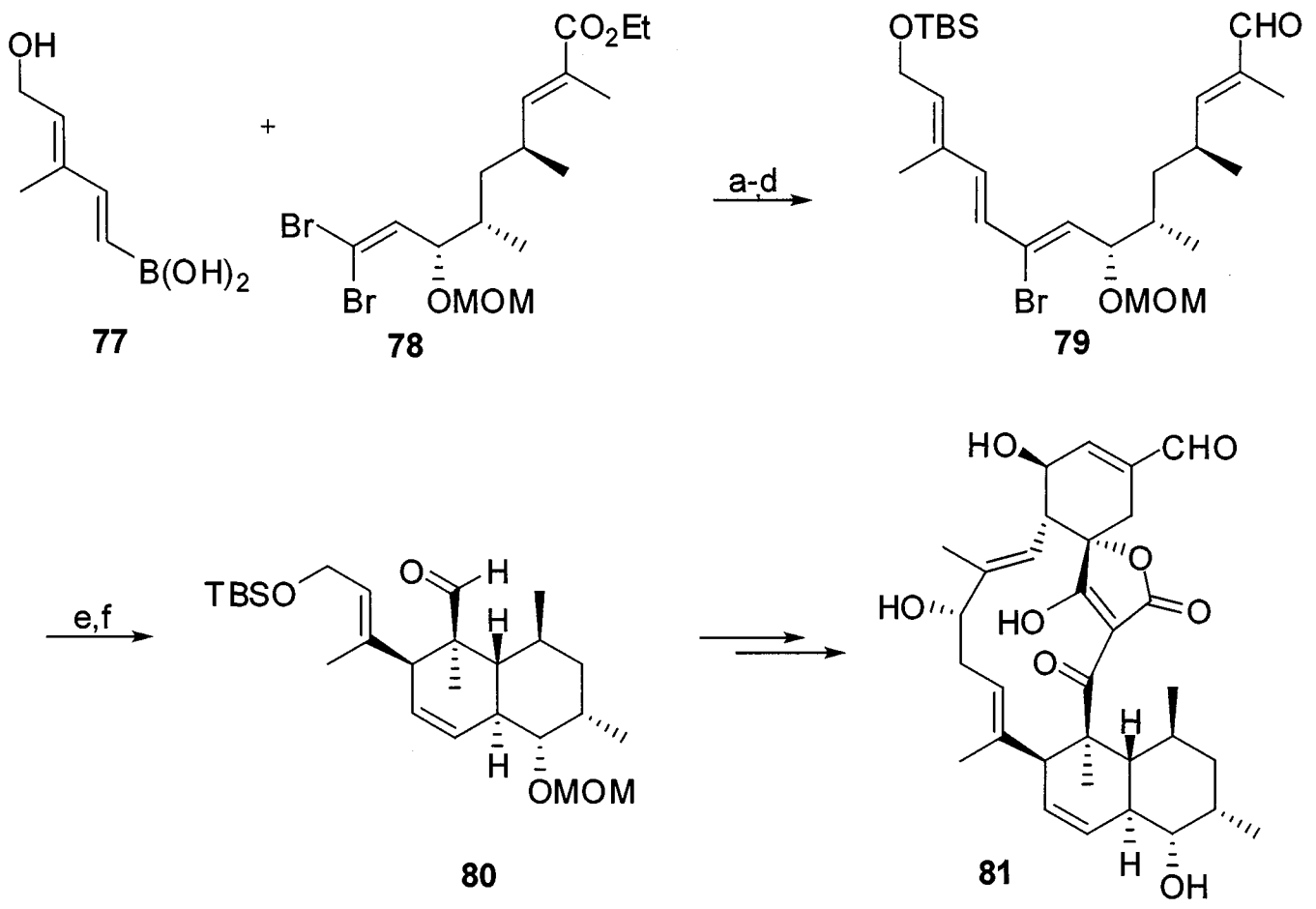


Scheme 19

1.5.3.4 Total synthesis of (+)-Tetronolide

Roush *et al.* also applied the steric-directing group effect on the IMDA reaction to synthesise the bottom half fragment of (+)-tetronolide (**81**),[64,65] the aglycon of the tetrocarcins.[52] The α,α'-dibromoolefin **78** underwent cross coupling with vinylboronic acid **77** under Kishi's modified Suzuki cross-coupling conditions to provide the C9-bromo-substituted tetraenoate, which was then converted into the unsaturated tetraenal **79**. A toluene solution of **79** was heated at 130°C to afford the desired cycloadduct as a single diastereomer. Subsequent removal of the C9-bromo steric directing group provided the bottom half fragment **80** of the targeted tetronolide **81** in 74% yield (Scheme 20). The compound **80** served as a key intermediate in

Yoshii's total synthesis of (+)-**81**.[66]



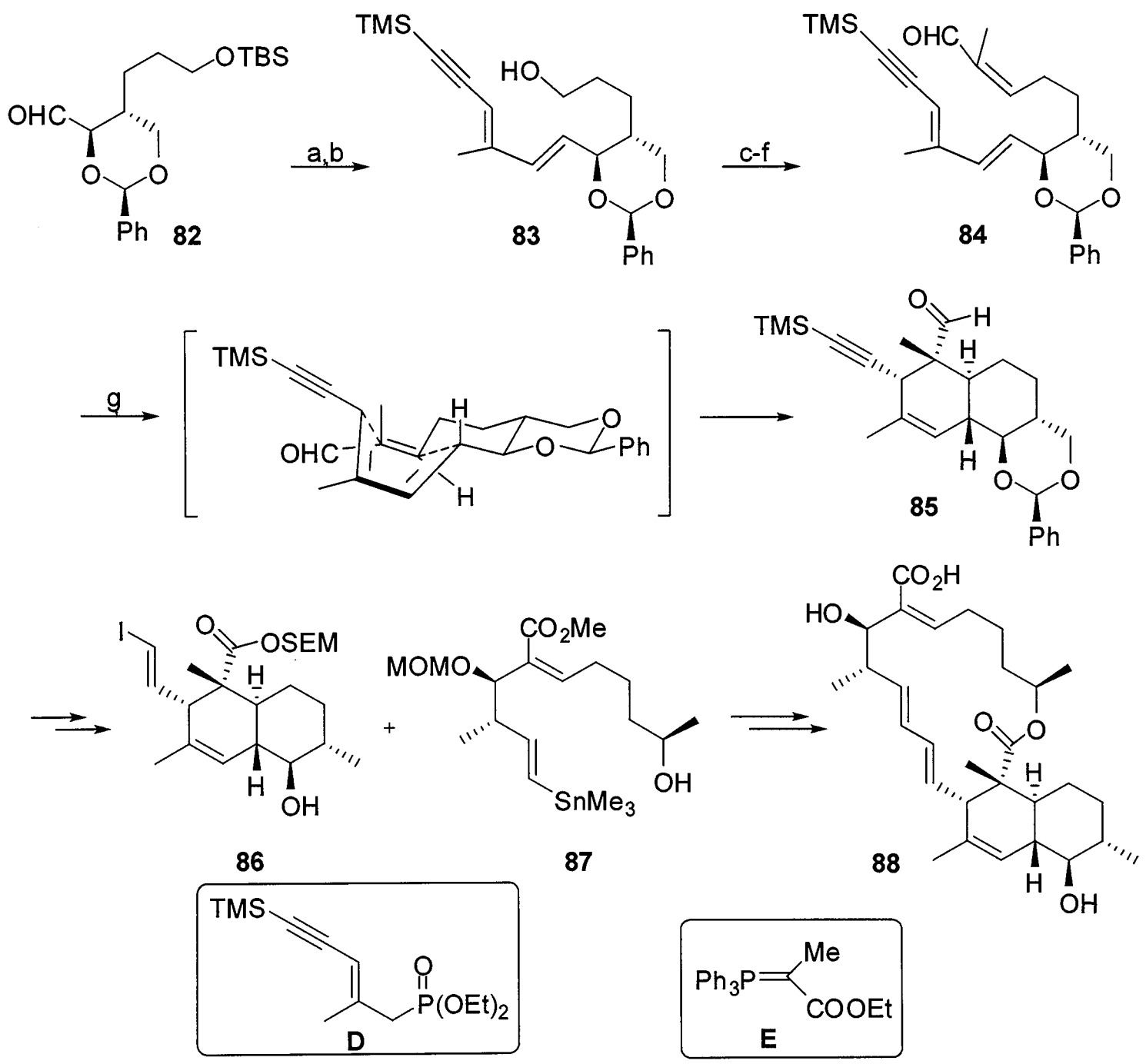
Scheme 20

a) $Pd(PPh_3)_4$, TlOH, THF; b) TBSCl, imidazole, DMF (61-85% over two steps); c) DIBAL, -78°C; d) TPAP, NMO (74%); e) toluene, 130°C; f) 5% Na(Hg), MeOH (74%)

1.5.3.5 Total synthesis of (+)-Tubelactomicin A[67,68]

(+)-Tubelactomicin A (**88**), a 16-membered macrolide antibiotic, showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[52] Tadano and co-workers have used an IMDA reaction for the stereoselective synthesis of the lower-half segment **86** and completed the total synthesis of natural (+)-**88**. An *E*-selective Horner-Emmons olefination of an aldehyde **82** with the phosphonate **D** provided the (*E*,*E*)-conjugated dienyne **83** after acidic deprotection of the TBS group. Installation of the dienophile part into **83** was achieved through a Wittig olefination of the aldehyde prepared from **83** by Dess-Martin oxidation, followed by a two-step reduction/oxidation protocol. Eventually, a β-substituted (*E*)-methacrolein derivative **84**, possessing a 10-carbon tether incorporating an (*E*,*E*)-dienyne terminal, was obtained. The thermal IMDA reaction of unsaturated aldehyde **84** in toluene with BHT at 80°C for 24 h proceeded with stereoselectively to provide the desired *trans*-fused cycloadduct **85** with an 8:1

endo:*exo* ratio in a combined yield of 93%. The chairlike transition states were conformationally locked by the presence of the *trans*-oriented benzylidene acetal, and no severe nonbonded interaction occurred in the *endo*-transition state. Therefore, the IMDA reaction proceeded through an *endo*-transition state leading to the predominant formation of the desired **85**, which was converted into the lower-half segment **86** in several steps. On the other hand, the upper-half segment **87** was synthesised from methyl (*R*)-lactate. The two segments were connected by sequential Stille coupling and macrolactonsation to provide (+)-**88** (Scheme 21).

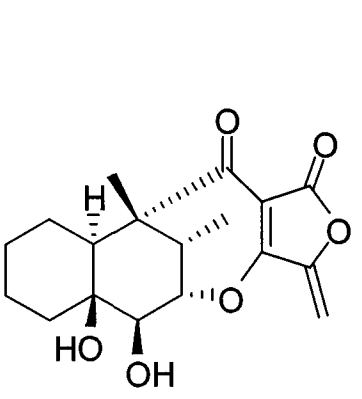


Scheme 21

a) **D**, LHMDS, HMPA, THF, -78-15°C; b) AcOH/THF/H_2O 3:2:1 (70% over two steps); c) Dess-Martin periodinane, DCM (99%); d) **E**, benzene, reflux (91%); e) DIBAL, DCM, -78°C (95%); f) Dess-Martin periodinane, DCM (96%); g) BHT, toluene, 80°C (93%)

1.6 Tetronic acid compounds

One of the key parts of tetrodecamycin (**1**) is the tetronic acid derivative part, which is quite important to the biological activity of tetrodecamycin (Figure 4).[4] Tetronic acids, 4-hydroxy-2(5*H*)-furanones, comprise a subclass of *β*-hydroxybutenolides with the generic structure **89a** or **89b**. The best known members of this family are vitamin C (ascorbic acid) and penicillic acid (Figure 4). A large number of tetronic acids and derivatives are widespread in nature, and exhibit a wide array of biological properties, such as antibiotic, antitumor, anticoagulant, antiepileptic, antifungal, insecticidal, analgesic and anti-inflammatory activity.[69] In some tetronic acid natural products, the tetronic core constitutes the main structural feature of the molecule, while in others, tetronic acid is fused to more complex structural motifs such as alkaloids, macrolides, terpenes and tannins. In this part, the synthesis and the reactivity of the tetronic acids, as well as the application in total synthesis will be introduced. Tetrodecamycin (**1**) itself is a 3-acyl-4-*O*-alkyl-5-alkenyl tetronic acid derivative, so the introduction will be focused on the 3-alkylation, 4-*O*-alkylation and 5-alkylation and alkenylation of tetronic acids.



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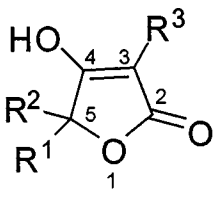
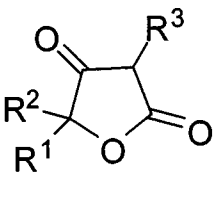
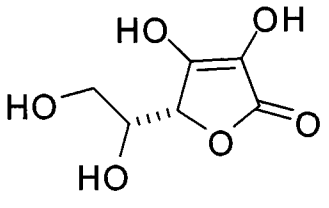


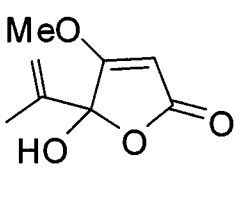
89a



89b



Ascorbic acid



Penicillic acid

Figure 4

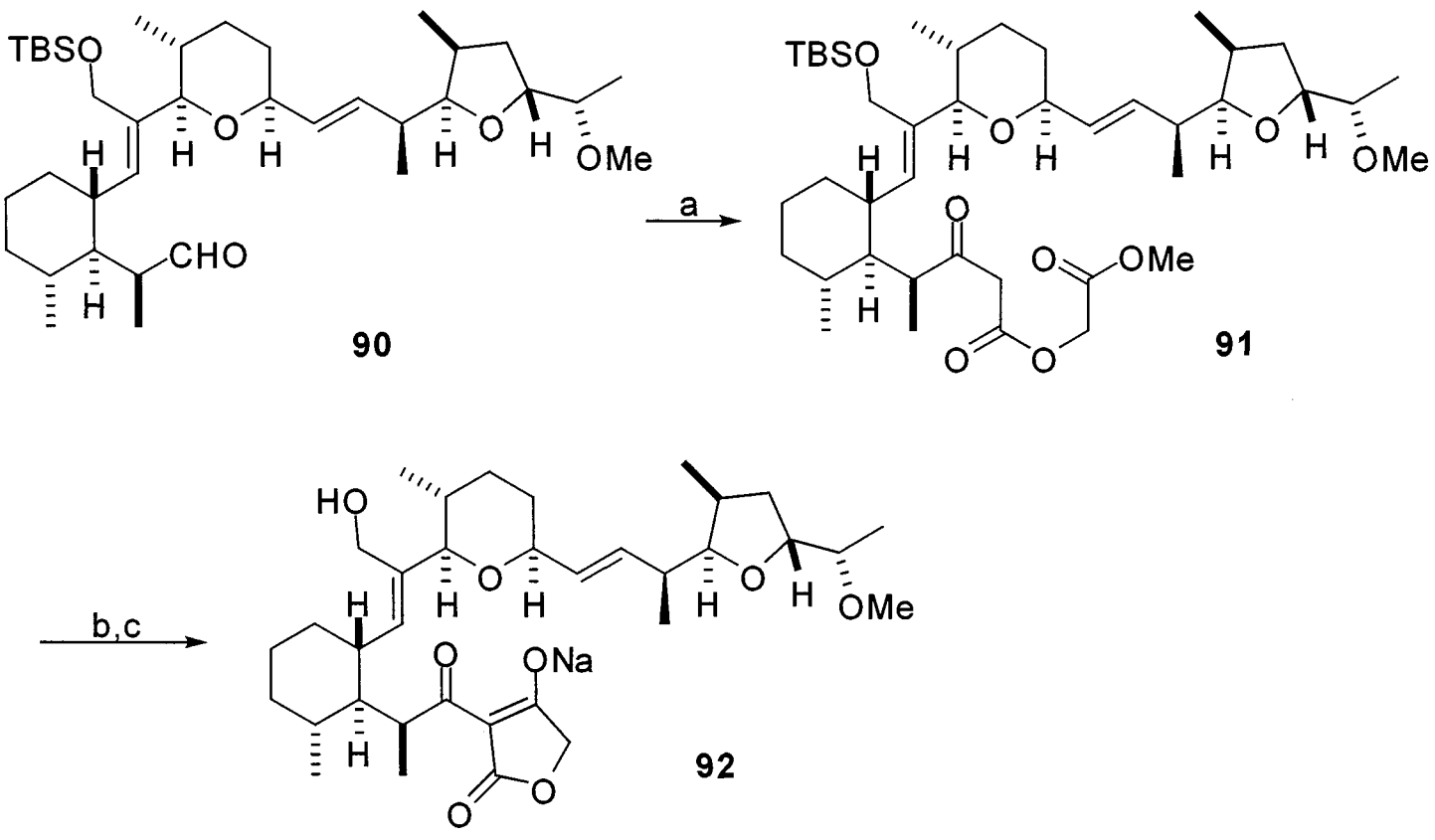
1.6.1 Synthesis of tetronic acids

1.6.1.1 Dieckmann-type Cyclisation

3,5-Disubstituted tetronic acids present medicinal interest as potential antibiotic, antiviral and antineoplastic agents. Among them, the 3-acyl derivatives comprise a structural motif present in a great number of active natural products. The base-promoted Dieckmann-type cyclisation is the most powerful way to produce the 3-acyl derivatives. It has been a preferred synthetic method to construct the 3-acyl-5-substituted tetronic acid core in natural products, such as tetronasin,[70] abyssomicin C,[71] quartromicins,[72-77] tetronolide,[78] kijanolide,[79] chlorothricolide,[60,80] chlorothricin,[81] and so on. Herein the synthesis of tetronasin, tetronolide and abyssomicin C are used as examples for illustration.

1.6.1.1.1 Tetronasin[70]

A zirconium-catalysed C-H insertion reaction of the methyl (diazoacetoxy)acetate unit to aldehyde **90** afforded the required β-keto ester intermediate **91**. The intermediate **91** was submitted to a tetrabutylammonium fluoride-promoted intramolecular Dieckmann-type cyclisation at room temperature to afford the sodium salt form of tetronasin **92** (Scheme 22).

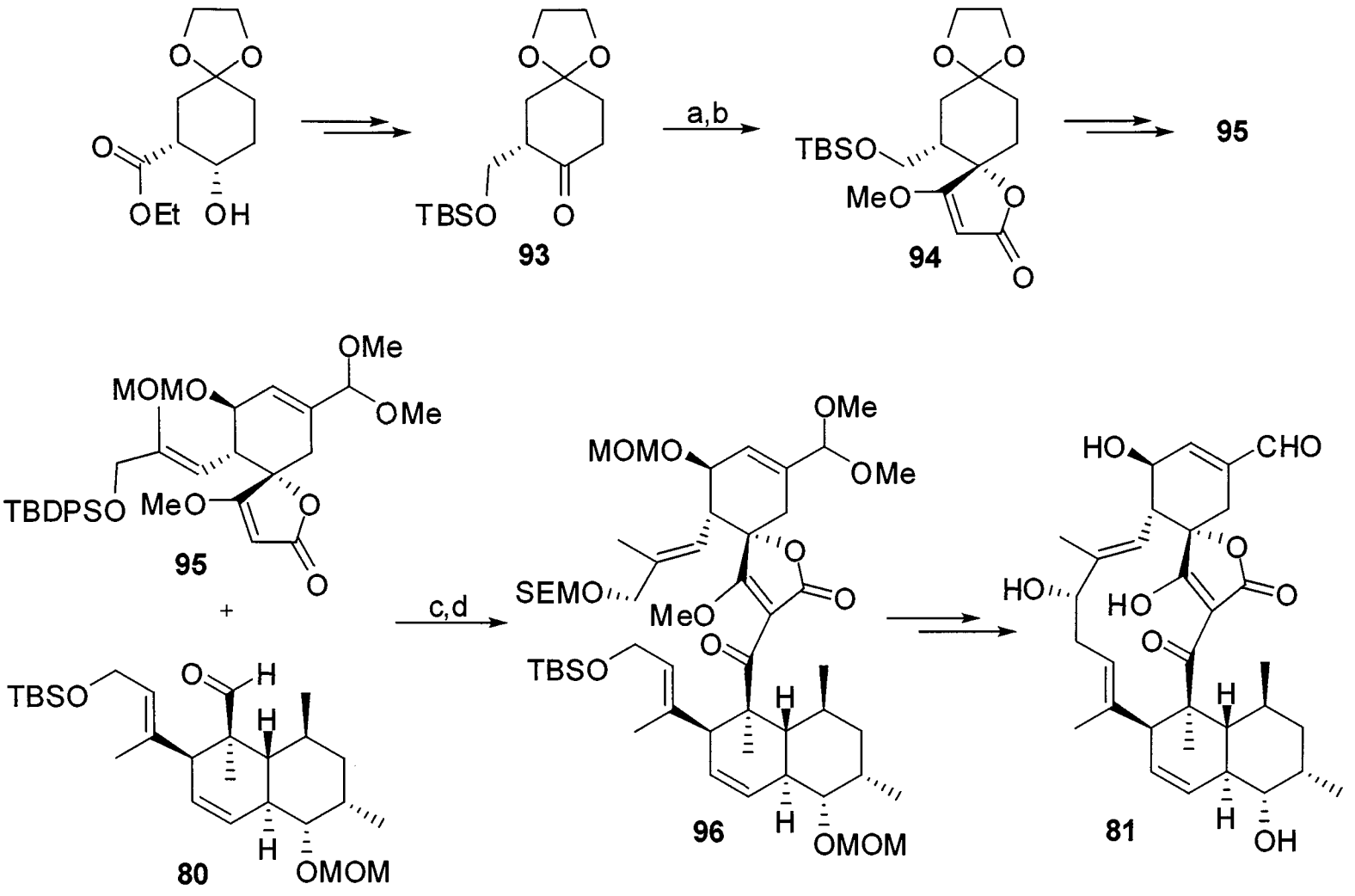


Scheme 22

a) $ZrCl_4$, DCM, $N_2CHCO_2CH_2CO_2Me$ (80%); b) TBAF, THF, rt; c) HF, MeCN, $NaHCO_3$ (92%)

1.6.1.1.2 Tetronolide[82,83]

In this synthesis, there are a formation of tetronic derivative part and a 3-acylation of the tetronic acid derivative. The formation of tetronic derivative **94** was achieved by a condensation of the chiral α-silyloxymethyl ketone **93** with the β-dichlorocerium derivative of methyl *trans*-β-methoxyacrylate. The tetronic derivative **94** allowed the access to the optically pure top-half fragment **95**. The 3-acylation of the tetronic acid part was accomplished by an aldol-type reaction between the spirotetronic top-half and an aldehyde moiety situated on the bottom-half fragment **80**, and further oxidation to give the 3-acyl-5-dialkyl tetronic acid derivative **96**, which was converted to (+)-tetronolide **81** in another thirteen steps (Scheme 23). The coupling between the aldehyde **80** and the lithiated tetronate derivative **95** afforded the desired product **96** in satisfactory yield. This procedure only works well in the absence of free proton at the C-5 position. This reaction will be included in **Chapter 1.6.2**.

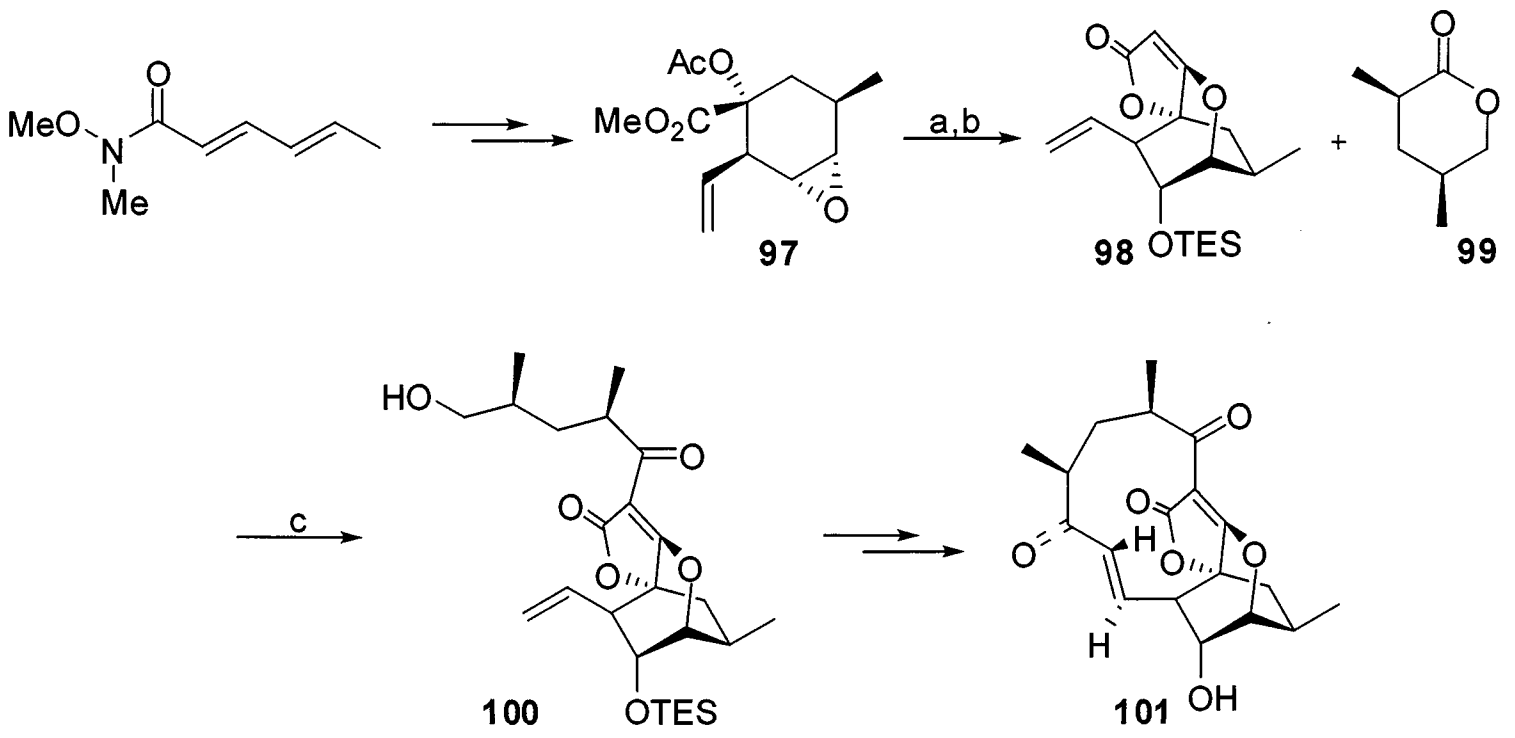


Scheme 23

a) LDA, $CeCl_3$, -90°C, *trans*-β-methoxyacrylate; b) TBAF, THF, rt; c) ^tBuLi, -80°C; d) TPAP, NMO (54% over two steps)

1.6.1.1.3 Abyssomicin C[71]

In the last two syntheses, the Dieckmann-type reactions were both promoted by TBAF, while in the synthesis of Abyssomicin C, LHMDS was using as base to perform this reaction. The acetate **97** was deprotonated with LHMDS in THF at -78°C, followed by warming to ambient temperature, which allowed the cyclisation to occur. Thereafter, the addition of saturated aqueous NH_4Cl and heating at reflux for two hours allowed the regioselective epoxide opening to give 4-*O*-alkyl tetronate derivative **98** in high yield after standard silylation. The 3-acylation of the tetronate derivative **98** was achieved by lithiation and coupling with the enantiomerically enriched lactone **99** (Scheme 24).

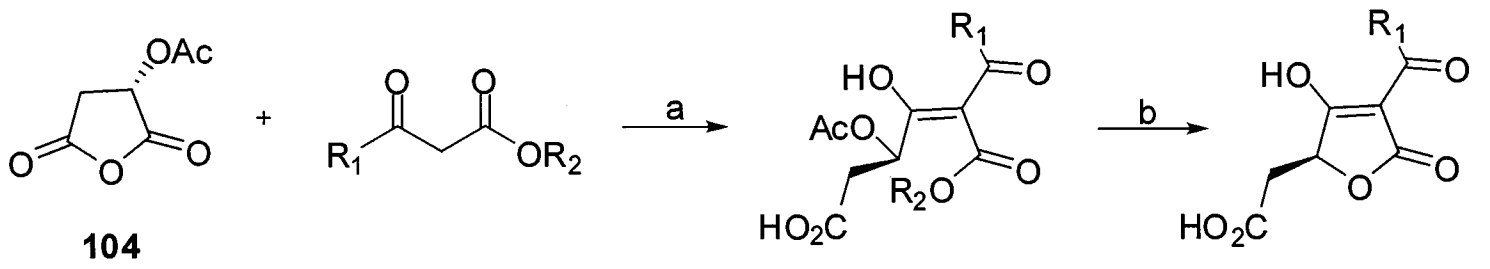


Scheme 24

a) LHMDS, THF, -78°C to rt; then sat. aq. NH_4Cl, reflux, 2 h; b) TESCl, imidazole, DMAP, DMF, rt, 2 h (97% over two steps); c) ^{t}BuLi, THF, -78°C, 10 min

1.6.1.2 Cyclisation of γ-oxygenated or γ-halogenated β-ketoester

Suitable β-ketoester derivatives bearing a γ-halogen atom or a γ-oxygenated function have been widely used as tetronic acid precursors to synthesise optically active 3,5-disubstituted tetronate derivatives.[69] The following example shows the application of this method to synthesise the (*S*)-carlosic acid **102** and (*S*)-viridicatic acid **103** (Scheme 25).[84-86]



102: R_1=*n*-Pr, R_2=Me, 72%
103: R_1=*n*-C_5H_{11}, R_2=Me, 62%

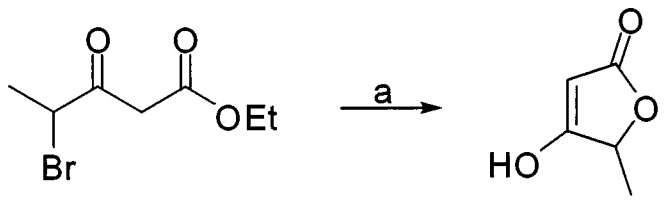
Scheme 25

a) NaH, THF; b) NaOH, H_2O, MeOH

The *O*-protected hydroxysuccinic anhydrides **104** derived from (*S*)-malic acid anhydride could react regioselectively at the C-2 site with anions of β-ketoesters generated with sodium hydride to afford optically pure γ-acetoxy-β-hydroxy-β-ketoesters, which are good precursors to synthesise tetronic acid derivative. Base-promoted cyclisation of these precursors produced the

chiral 5-alkyl-3-acyl tetronic acids, (*S*)-carlosic acid **102** and (*S*)-viridicatic acid **103** (Scheme 25).

Tetronic acid could also be prepared in satisfactory yields from the γ-bromo-β-keto esters by treating with 2.5 N KOH as cyclising agent followed by working up with 4 N HCl (Scheme 26).[87]

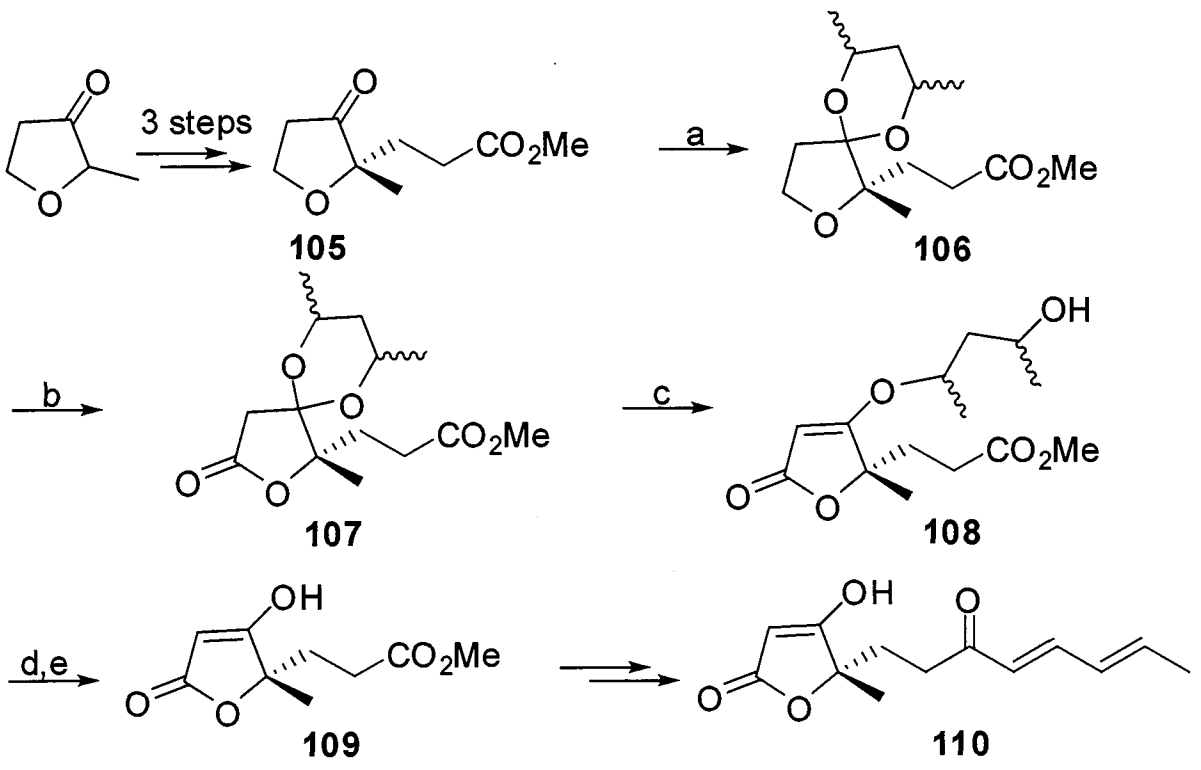


Scheme 26

a) 2.5 N KOH, 0°C, 4 h; then 4 N HCl

1.6.1.3 Synthesis from other heterocycles

Other heterocycles could be used for the enantioselective construction of tetronic acid derivatives bearing a stereogenic center at C-5. The total synthesis of (-)-Vertinolide **110** relied on the straightforward preparation of highly optically pure 2,2-dialkyl-4,5-dihydro-3-furanone **105** (Scheme 27).[88]



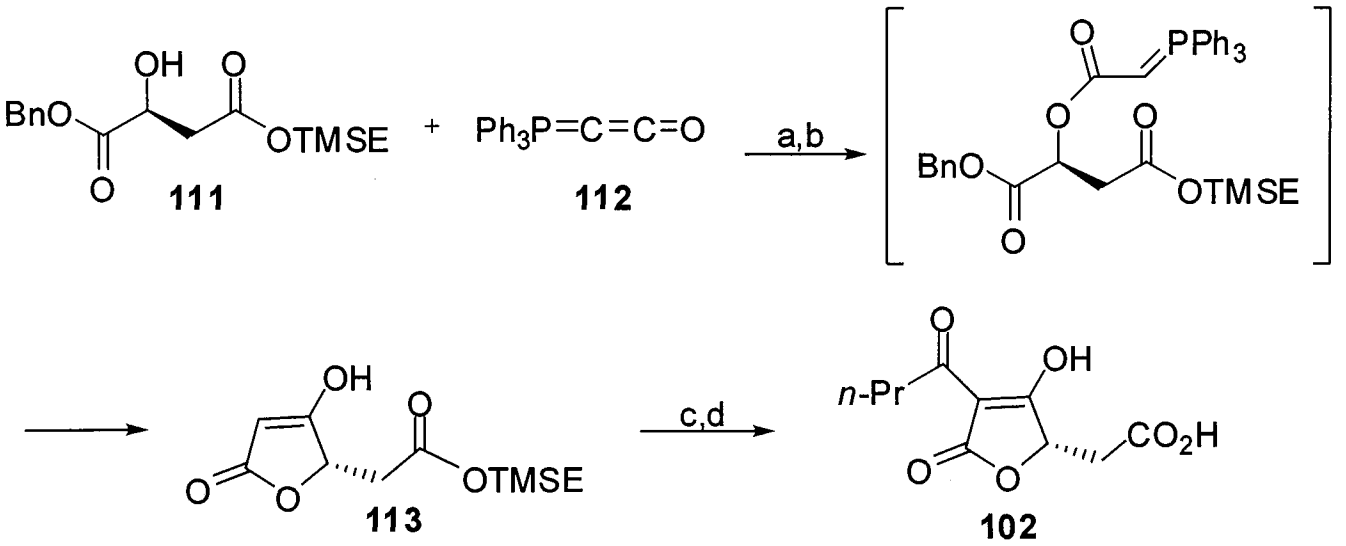
Scheme 27

a) 2,4-pentanediol, TsOH, benzene, reflux, 1 h (75%); b) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $H_2O/CCl_4/CH_3CN$, 24 h (84%); c) NaOMe; d) CrO_3/H^+; e) NaOMe, MeOH, 1 h (65% over three steps)

Ketalisation of the keto ester **105** with pentan-2,4-diol yielded ketal **106**, which was exposed to the Sharpless oxidation conditions to give butyrolactone **107**. After base induced elimination, the ketal ring was opened to give the *O*-alkyl tetronate derivative **108**. Jones oxidation of the alcohol function of butenolide **108** led to ketone, which was then treated with sodium methoxide to afford, after acidic work-up, the desired tetronic acid **109** in 65% yield overall. The tetronic acid derivative **109** was converted into (-)-**110** in several steps (Scheme 27).

1.6.1.4 Wittig reaction with triphenylphosphoranylidene ketene

The α-hydroxyesters and triphenylphosphoranylidene ketene **112** could be used to construct tetronic structures. In 2005, Schobert and Jagusch employed this methodology to complete an efficient synthesis of (*S*)-carlosic acid **102** (Scheme 28).[89]



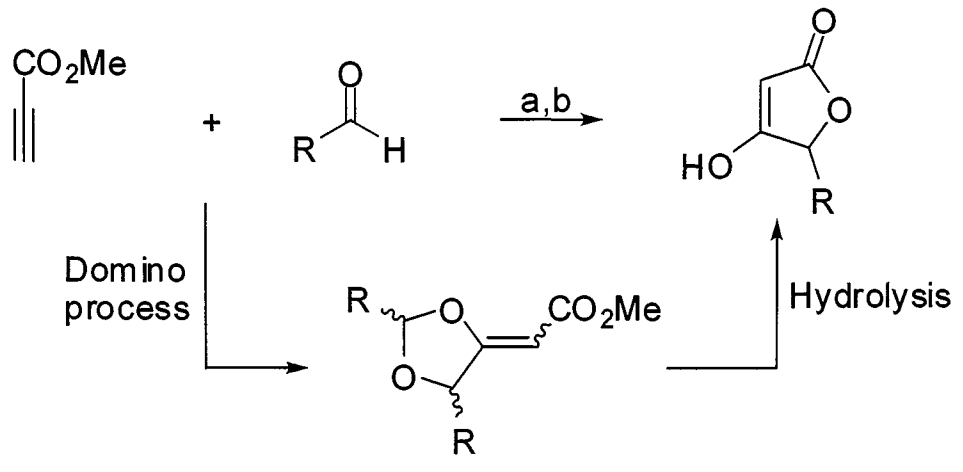
Scheme 28

a) PhH, reflux, 16 h; b) H_2, Pd/C 5% (84% over two steps); c) C_3H_7COOH, DCC, DMAP, Et_3N, rt, 16 h; d) TBAF·$3H_2O$ (82% over two steps)

1.6.1.5 One-pot Synthesis

5-Substituted tetronic acid derivatives could be prepared from simple commercially available starting materials, aldehydes and terminal conjugated alkyne. The entire process embodies two consecutive chemical events: a catalytic domino reaction to build a 1,3-dioxolane scaffolds and a two-step acid-catalysed *trans*-acetalisation-lactonisation reaction to furnish the tetronic acid

derivatives (Scheme 29).[90]



Scheme 29

a) Et3N, -78°C, 2 h; HCl (concd.), 60°C, 24 h (69% when R=Me)

1.6.2 Reactivity of tetronic acids

Tetronic acids can be modified according to the scheme outlined in Figure 5. The 3-acylation and 4-*O*-alkylation are related to the total synthesis of tetrodecamycin.[91]

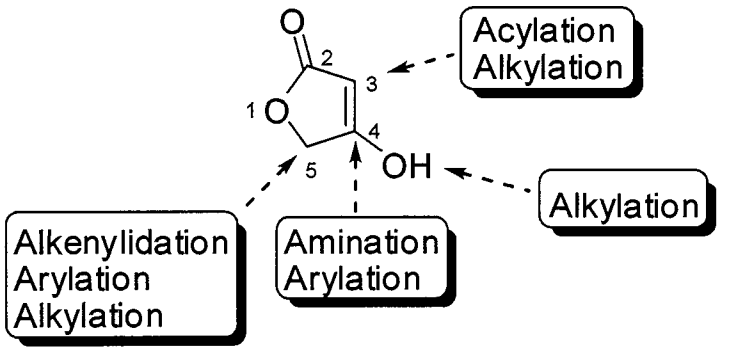
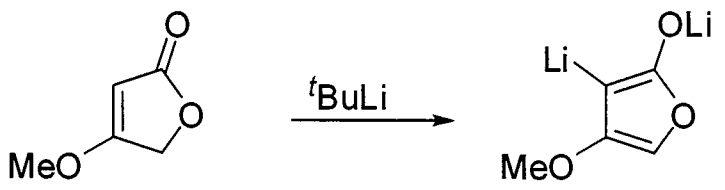


Figure 5

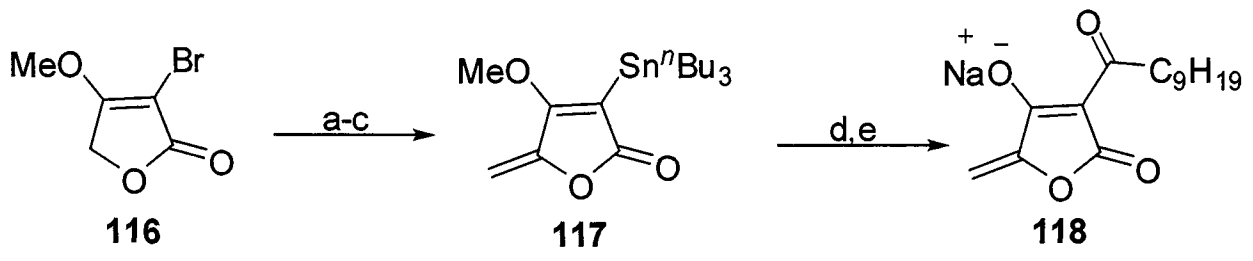
1.6.2.1 3-Acylation

The direct acylation at the C-3 position can be achieved by coupling of an acid chloride and a 3-metallated tetronate derivative.[92-94] It has been shown that this process works well for the 5-substituted tetronates, but it fails when this C-5 position is vacant due to the preferential C-5 deprotonation when unsubstituted tetronates are treated with strong bases.[93,95] On the other hand, the regioselective acylation of a 3,5-tetronate dianion is not a useful reaction because it affords mixtures of mono and diacylated compounds (Scheme 30).[96]



Scheme 30

A palladium-catalysed acylation of a 3-tri-(*n*-butylstannyl) tetronate derivative can help to solve the problems associated with substituents on the tetronate molecule. In addition, the stability of the C-Sn bond permits functionalisation of the tetronate ring system. This protocol has been exploited in the total synthesis of carolini acid and the agglomerin A (**118**) (Scheme 31).[97]



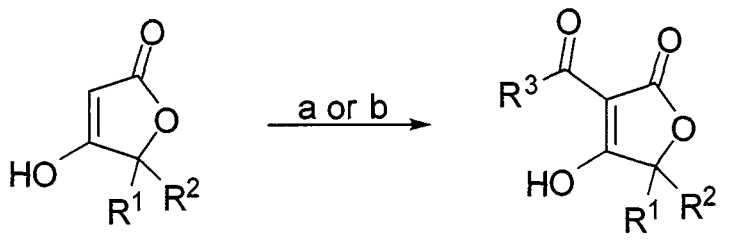
Scheme 31

a) $Na^+[naph]^-$, *n*-Bu_3SnCl, -78°C; b) LDA, THF, $Me_2NCH_2{}^+I^-$, -78°C; c) MeI, then NaOH (47%); d) $C_9H_{19}COCl$, *trans*-Bn(Cl)Pd(PPh_3)$_2$, $ClCH_2CH_2Cl$, 60°C; e) NaOH, MeOH (28%)

The coupling reaction between the 3-lithiated tetronic derivatives with aldehydes, acid chlorides or lactones has been widely used in the total synthesis of the 3-acyl-5-disubstituted natural products, such as tetronolide (Scheme 23), Abyssomycin C (Scheme 24), and so on.

Boron enolates have also proved to be very good options to achieve C-3 acylation. Paintner had employed this method to build the tricyclic core of tetrodecamycin (Scheme 2, **Chapter 1.4.1**).

The 3-acylation of 3-unsubstituted tetronic acids can also be achieved with carboxylic acid in combination with DCC or using an acid anhydride in the presence of triethylamine and DMAP (Scheme 32).[98] This method gives good to excellent yields only when the acyl group bears α-protons.

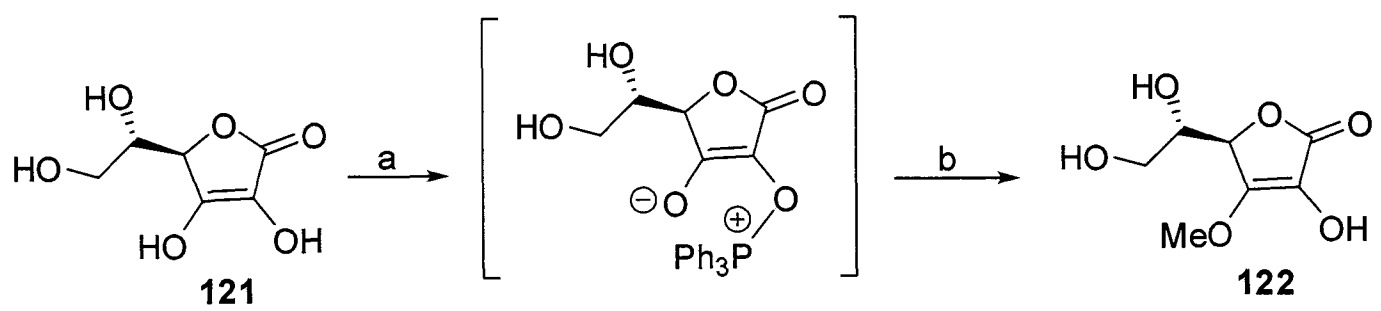


Scheme 32

a) **119a**: R^1=H, R^2=H, R^3=cyclo-C_3H_5, cyclo-C_3H_5COOH, Et_3N, DMAP, DCC, DCM, rt (91%); b) **119b**: R^1=H, R^2=Me, R^3=$C_6H_5CH_2$, $C_6H_5CH_2COOH$, Et_3N, DMAP, DCM, rt (80%)

1.6.2.2 4-O-alkylation

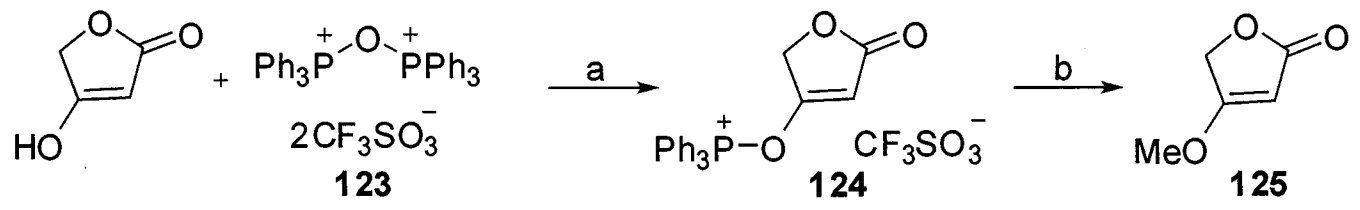
In 1990, Bajwa and Anderson reported a versatile and high-yielding method of the 4-*O*-alkylation.[99] This method involved the alkylation of tetronic acids with primary or secondary alcohols under Mitsunobu conditions. Recently this method was adapted to the regio- and chemoselective alkylation of *L*-ascorbic acid and derivatives thereof (Scheme 33).[100]



Scheme 33

a) DEAD, Ph_3P, THF/DMF, -78°C; b) MeOH (77%)

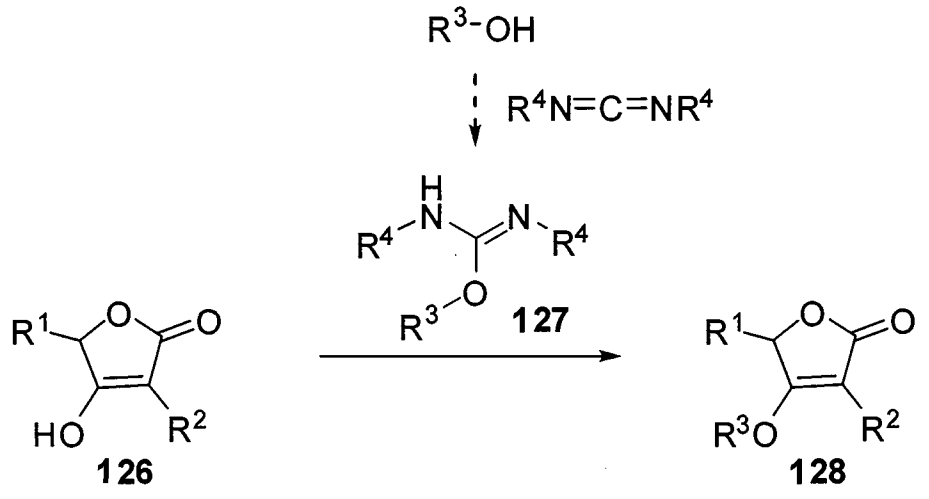
Another highly efficient and versatile method for the regioselective 4-*O*-alkylation of tetronic acids involves (5-oxo-2,5-dihydrofuran-3-yloxy) phosphonium trifluoromethanesulfonate **124** as a key intermediate (Scheme 34). This activated tetronate derivative **124**, generated *in situ* on reaction of tetronic acids with triphenylphosphonium anhydride trifluoromethanesulfonate **123** (Hendrickson's reagent), can react with stoichiometric amounts of primary and secondary alcohols to give the 4-alkoxy-5*H*-furan-2ones (Scheme 34).[101]



Scheme 34

a) *i*-Pr_2NEt, DCM, 0°C; b) MeOH, *i*-Pr_2NEt, 0°C to rt (82%)

The reaction of various types of substituted tetronic acids **126** with stoichiometric amounts of isoureas **127** of the respective primary or secondary alcohols could afford the specific 4-*O*-alkylation products **128** (Scheme 35).[102]

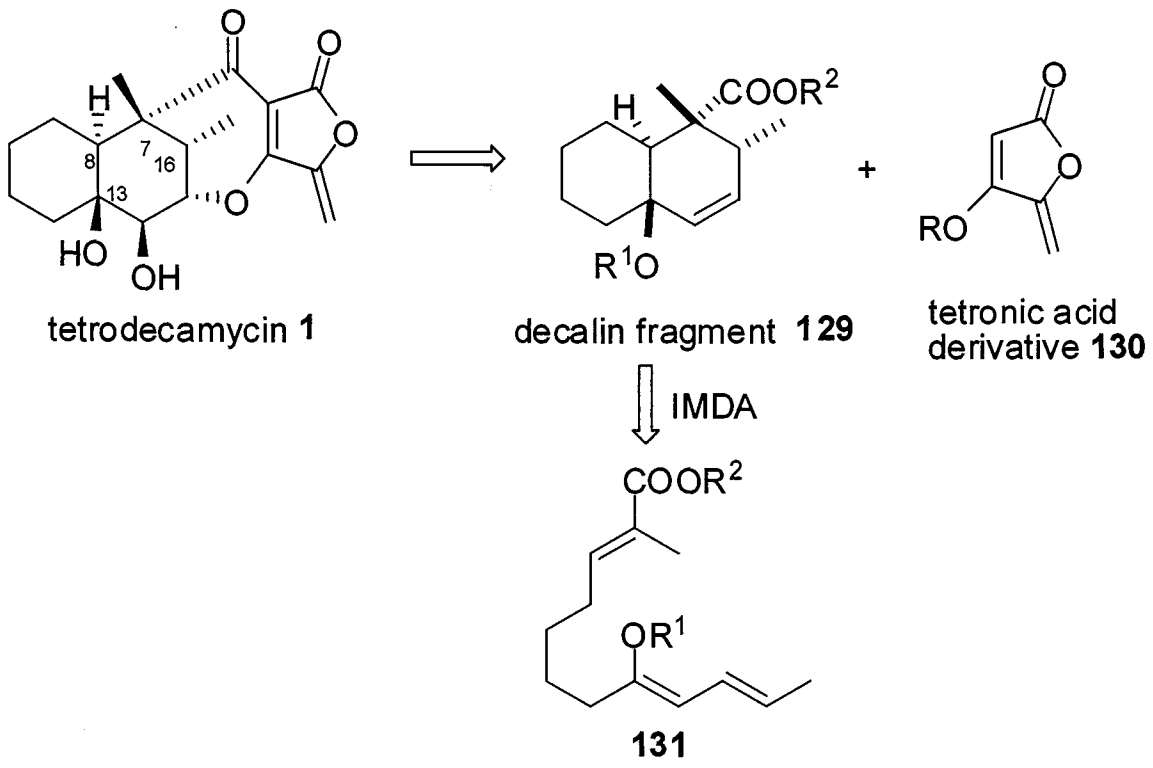


Scheme 35

1.7 Aim of project

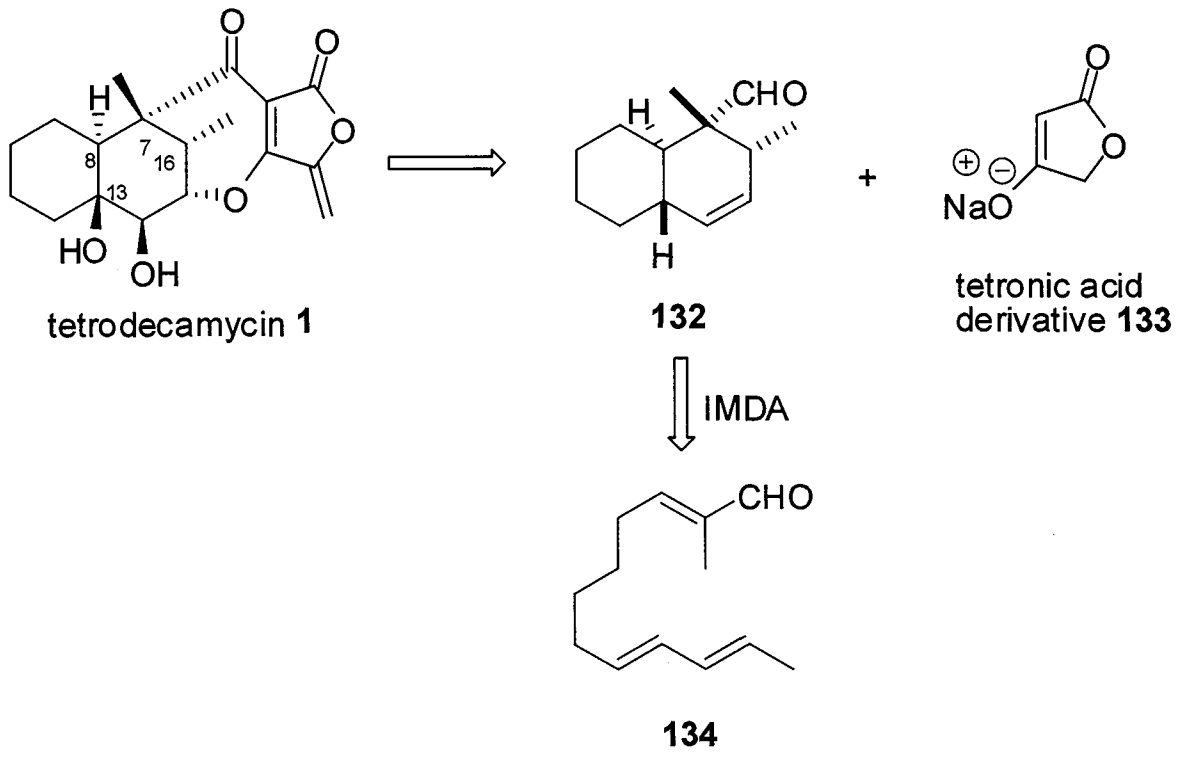
So far only one 26-step total synthesis of tetrodecamycin (**1**) has been reported. The aim of the project is to investigate a novel practical and efficient synthetic route to tetrodecamycin (**1**) *via* a key intramolecular Diels-Alder reaction.

The first part of the proposed total synthesis was based on the intramolecular Diels-Alder reaction of an enol ether **131** to build the key intermediate **129** with four chiral centres, C-7, C-8, C-13 and C-16, created in one step (Scheme 36). In this route, the tertiary hydroxyl group would be generated in the Diels-Alder reaction. This part of work will be illustrated in **Chapter 2**.



Scheme 36

Since the intramolecular Diels-Alder reaction in the initial protocol was difficult to repeat on large scale, a simplified protocol was proposed. It would be focused on the intramolecular Diels-Alder reaction of the aldehyde **134** to achieve the decalin fragment **132** with three stereocenters, C-7, C-8 and C-16, created (Scheme 37). The two hydroxyl groups would be introduced at a later stage in this protocol *via* dihydroxylation. This part of work will be illustrated in **Chapter 3**.



Scheme 37

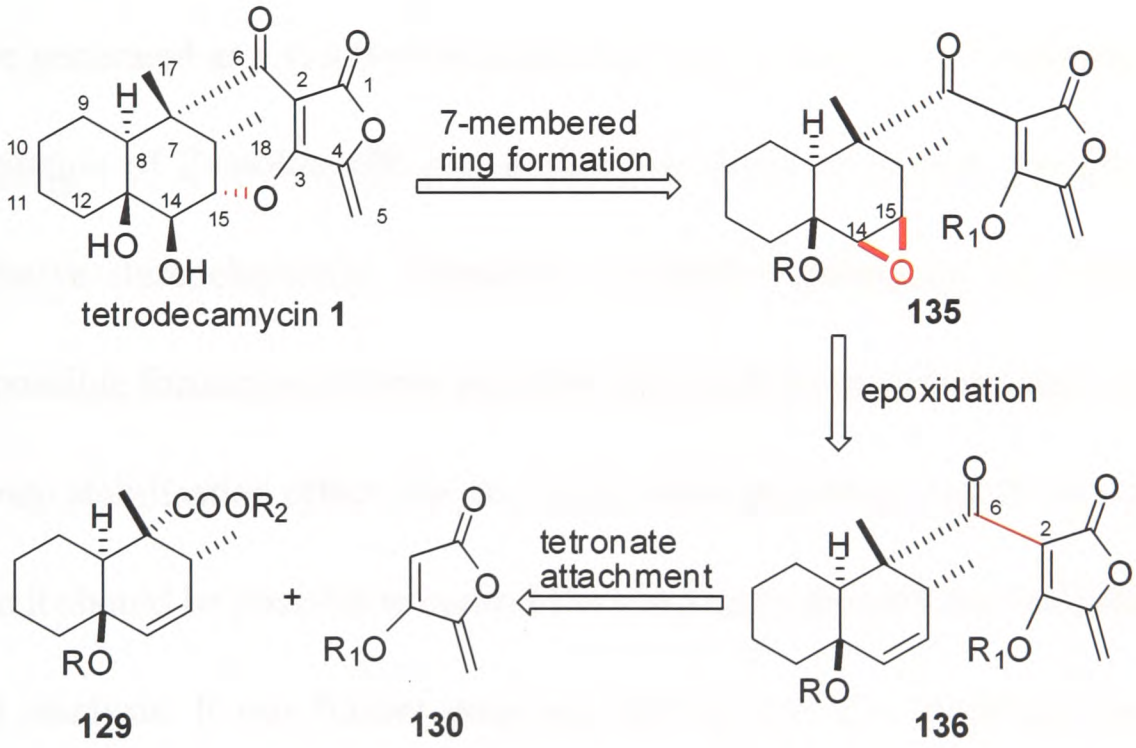
CHAPTER 2

RESULTS AND DISCUSSION (PART A)

CHAPTER 2 RESULTS AND DISCUSSION - PART A

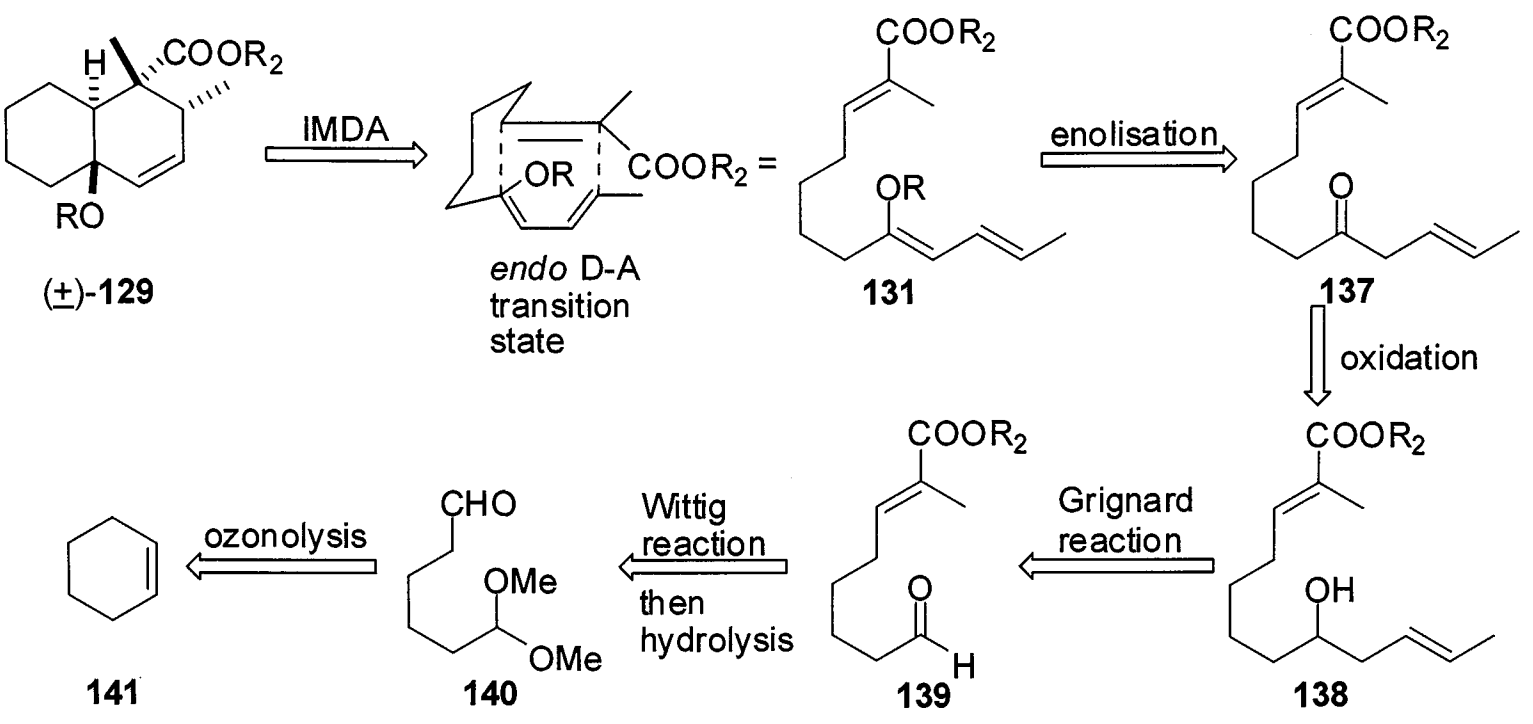
2.1 Retrosynthetic analysis

The initial synthetic approach to tetrodecamycin (**1**) was based on the key epoxide **135**, which was envisioned to arise from the olefin **136** *via* a face selective epoxidation reaction. The disconnection of C2-C6 acyl bond of **136** revealed the *trans*-decalin core **129** possessing four contiguous stereocenters including two quaternary carbon center at C7 and C13 and a tetronic acid derivative portion **130** (Scheme 38).



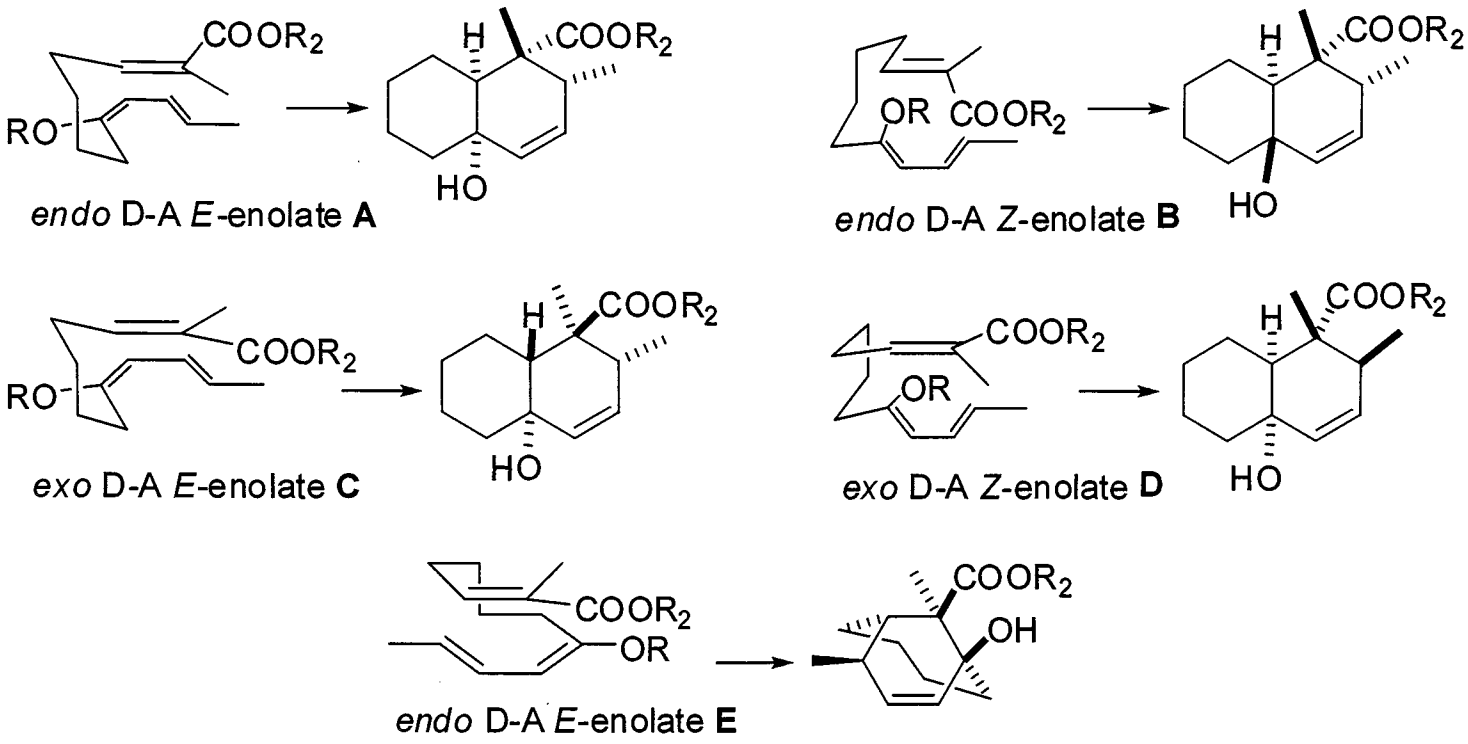
Scheme 38

The *trans*-decalin subunit of **129** could be constructed *via* an intramolecular Diels-Alder reaction of the *cis*-enol ether **131**. A simple model showed that the intramolecular Diels-Alder cycloaddition of the *cis*-enol ether proceeding *via* an *endo* transition state would result in a *trans*-decalin structure **129**, possessing the relative stereochemistry required for the total synthesis of tetrodecamycin (**1**) (Scheme 39).



Scheme 39

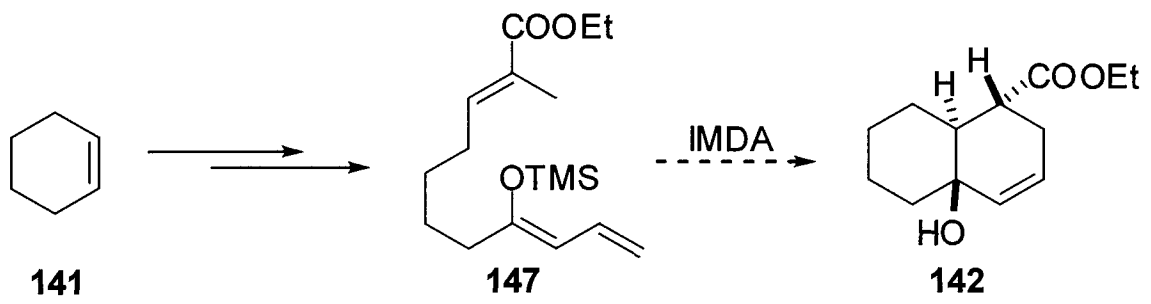
It was possible that four diastereomeric isomers of the decalin **129** arising from four transition states would be generated as a result of non-selective enolisation of **137** (Scheme 40). The *endo* Diels-Alder reaction of *Z*-enolate (B) was required to form the desired decalin part **129** with anticipated relative stereochemistry. Therefore, a selective generation of *Z*-enol ether would eliminate the possible formation of three possible adducts from transition states A, C and E. Due to the Alder *endo* stabilisation effect, the *exo* Diels-Alder transition state D was not favoured in the reaction, so it should be possible to control the reaction to proceed *via endo* transition state B by Lewis acid catalysts. It was further proposed that the use of a chiral auxiliary in the ester fragment would result in a diastereoselective cycloaddition and formation of **129** as a single enantiomer after the cleavage of the ester and re-esterification. Thus it was of great interest to establish the outcome of the proposed reaction and possibility of selective direct formation of **129**.



Scheme 40

2.2 Model study

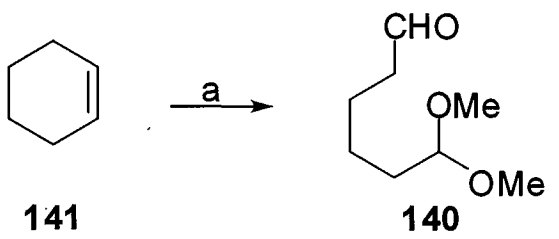
Since no cycloadditions of silyl enol ethers of type **131** have been previously reported in literature, silyl enol ether **147** was synthesised to investigate the intramolecular Diels-Alder reaction in a model study (Scheme 41).



Scheme 41

2.2.1 Ozonolysis

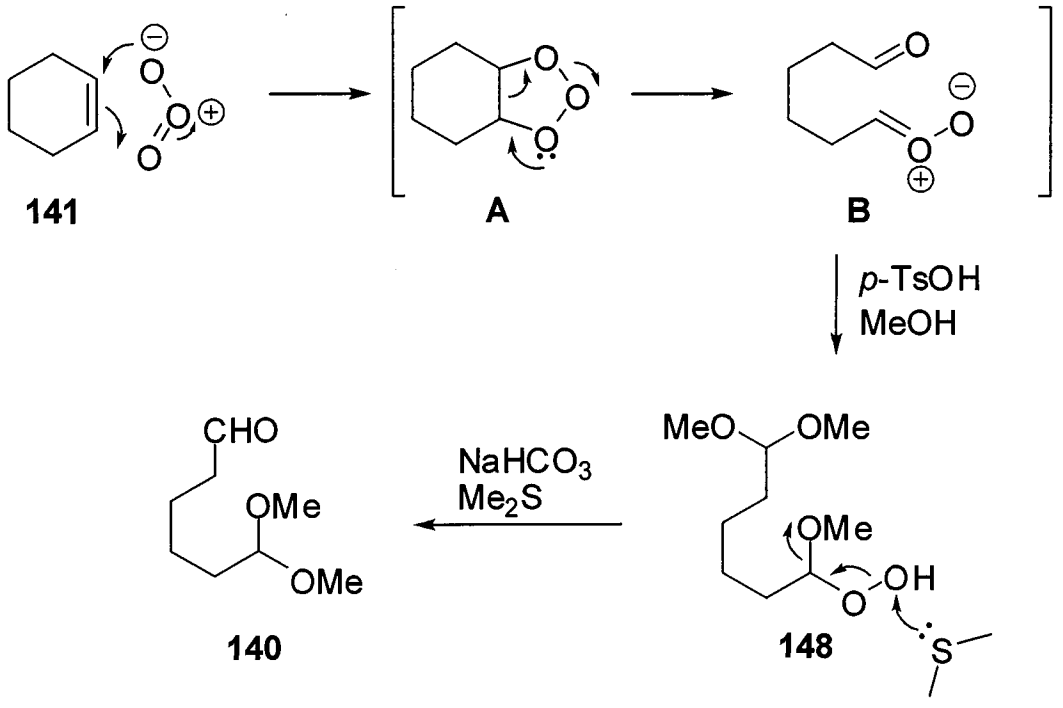
Ozonolysis of commercially available cyclohexene **141** provided mono-aldehyde **140** in good yield (Scheme 42).[103] The acetal-aldehyde **140** was used directly in the following reaction without any purication.



Scheme 42

a) O_3, DCM, MeOH, -78°C; *p*-TsOH; $NaHCO_3$, Me_2S

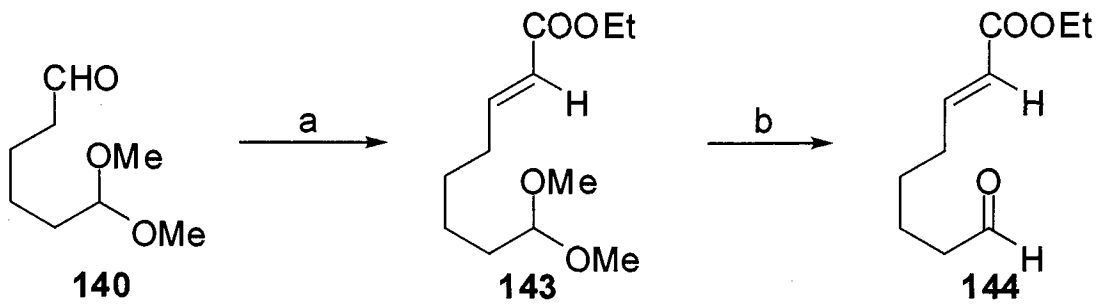
The ozonolytic cleavage of cycloalkenes in the presence of an alcohol afforded intermediate **B** as depicted in Scheme 43 with an aldehyde and an α-alkoxy hydroperoxide at the terminal. The addition of *p*-toluenesulphonic acid to the ozonolysis reaction medium led to the formation of an acetal-alkoxy hydroperoxide **148**. The reaction was left at room temperature for 1.5 h to ensure the completion of the acetal formation. Thereafter, the solution was neutralised to prevent bisacetal formation on the subsequent reduction. Reduction of the hydroperoxide **148** with dimethyl sulphide afforded the acetal-aldehyde **140** (Scheme 43).[104]



Scheme 43

2.2.2 Wittig reaction and hydrolysis

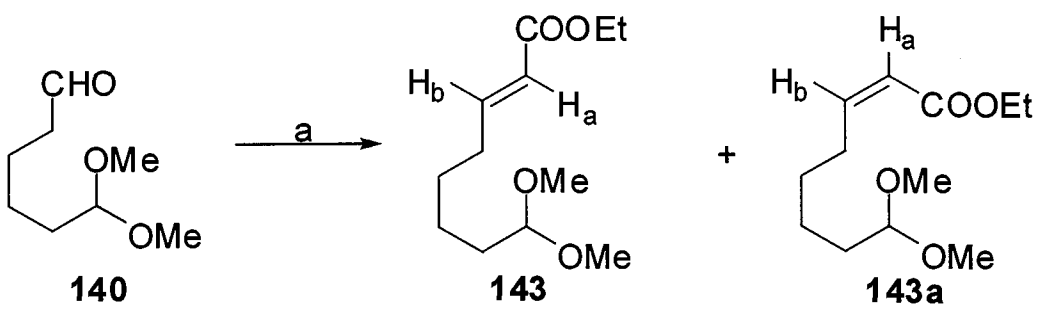
The crude acetal-aldehyde **140** was treated with (carbethoxymethylene)triphenylphosphorane in DCM under reflux overnight to generate the desired conjugated ester **143**.[105] Hydrolysis of **143** afforded the aldehyde **144** in high yield (Scheme 44).[106]



Scheme 44

a) (carbethoxymethylene)triphenylphosphorane, DCM, reflux, overnight (84% from **141**); b) 1N HCl, H_2O, Et_2O, rt (81%)

For the Wittig olefination, two reaction conditions were evaluated. Firstly, the solution of the aldehyde **140** and the ylid reagent, (carbethoxymethylene)triphenylphosphorane, in methanol was stirred at 0 °C for 5 h and afterwards warmed to room temperature and stirred overnight.[107] After work-up and chromatography, both *cis*- and *trans*-olefins **143** and **143a** were obtained in a 1:2 ratio (Scheme 45). The configuration of the double bond was determined based on the NMR spectra analysis. The *trans*-olefin **143** showed chemical shift of H_b δ_{Hb} 6.96 ppm with coupling constant of $^3J_{Hb\text{-}Ha}$ 15.5 Hz, while the *cis*-olefin **143a** gave chemical shift of H_b δ_{Hb} 6.22 ppm with coupling constant of $^3J_{Hb\text{-}Ha}$ 11.5 Hz. To minimize the formation of the kinetic product (*Z*)-olefin, higher temperature was adopted in this reaction. The solution of the aldehyde **140** in DCM was left under reflux overnight, and the pure thermodynamic product (*E*)-olefin was generated in 81% yield.[105]

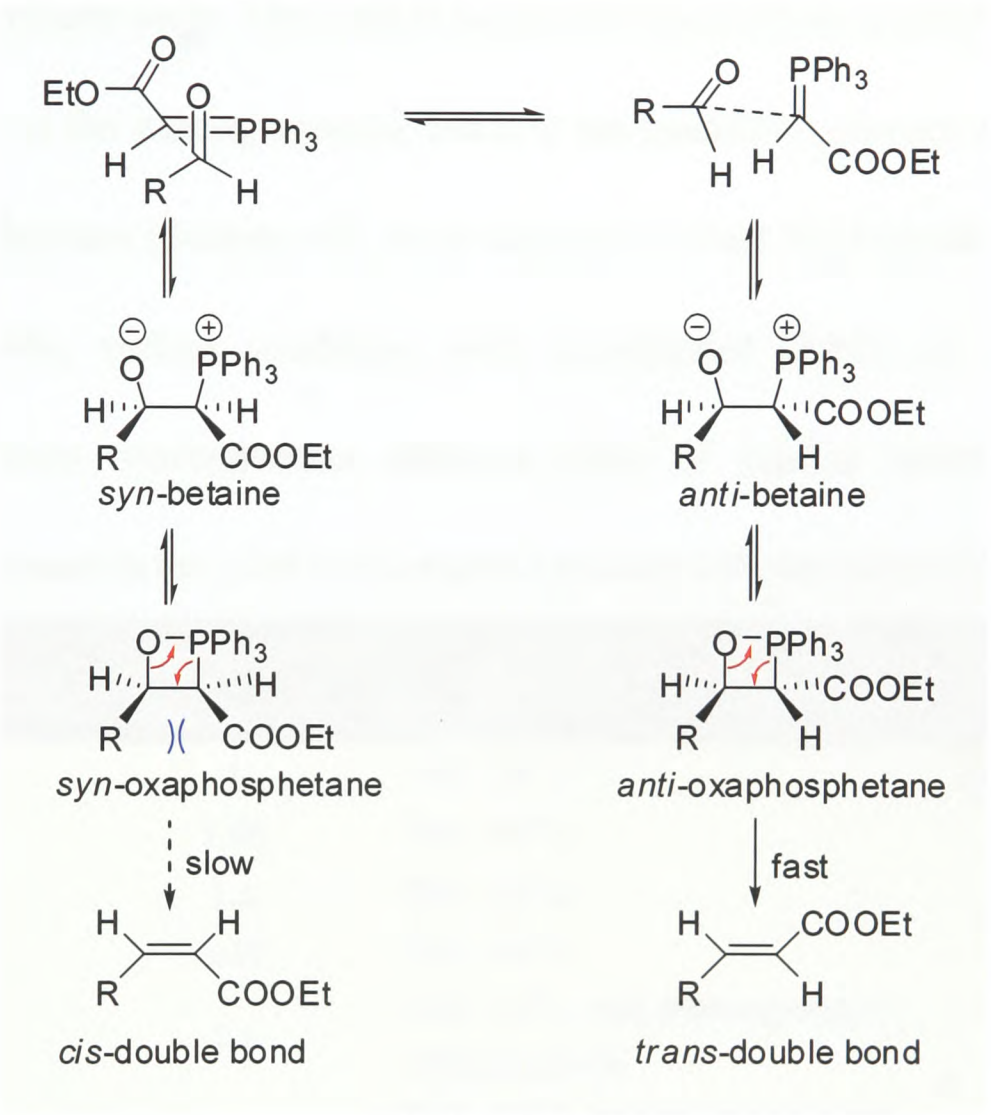


Scheme 45

a) (carbethoxymethylene)triphenylphosphorane, MeOH, 0°C-rt, overnight (81%)

Although the exact mechanism of Wittig reaction is still under investigation,[108] a commonly

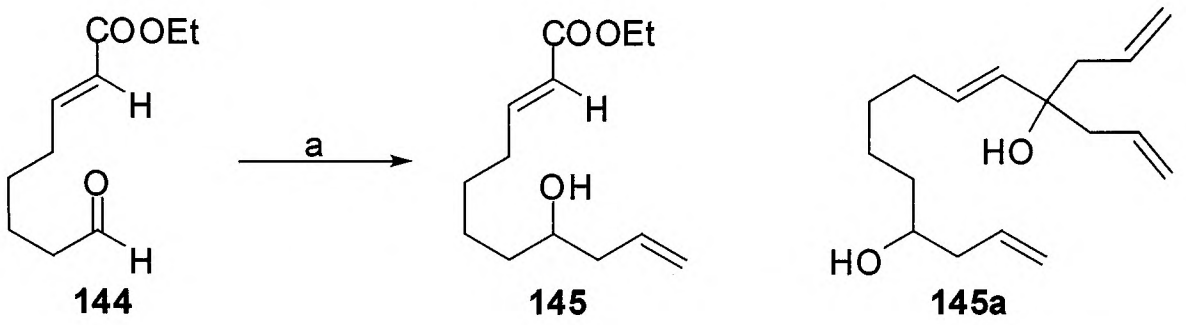
proposed mechanism is outlined in Scheme 46. Stereoselectivity in this reaction is thought to arise from reversible formation of the *syn*- and *anti*-betaine intermediates. The thermodynamically favourable *anti*-betaine forms an *anti*-oxaphosphatane, which collapses to a *trans*-double bond in a fast rate. However, in contrast, the collapse of *cis*-oxaphosphatane is slow due to inihibiting steric interactions. The net result of this drives the equilibrium over to the (*E*)-olefin product.[109]



Scheme 46

2.2.3 Grignard reaction

With the aldehyde **144** in hand, the preparation of alcohol **145** was attempted *via* a Grignard addition to **144** with allyl magnesium chloride (Scheme 47).[110,111]



144 **145** **145a**

Scheme 47

a) allylmagnesium chloride, THF, -78°C (32%)

However, the simple and well-documented Grignard reaction turned out to be the major obstacle on the described synthetic route. The yield of the desired homoallylic alcohol **145** was low, and a significant amount of the starting material **144** and the triaddition product **145a** were found in the crude product mixture (Scheme 47). In an attempt to avoid the formation of the undesired tertiary alcohol **145a**, various conditions were investigated (Table 1), including different temperatures, different concentrations, different ratios of starting materials. However, no significant improvement in the yield of the desired product **145** was achieved.

No.	*Aldehyde (eq)*	*Grignard reagent (eq)*	*Reaction Conditions*	*Yields of 145 (%)*
1	1	1	THF, -78°C	22 (13% of **145a**)
2	1	1.05	THF, -42°C	13
3	1	1.1	THF, -20°C	--------
4	1	1.15	THF, -78°C	7
5	1	1.1	THF, -78°C, add allylmagnesium chloride slowly	22
6	1	1.1	THF, -78°C, add allylmagnesium chloride quickly	22
7	1	1.3	THF, -78°C	22
8	1	1.5	$CeCl_3$ (1.5 eq), THF, -78°C	No reaction
9	1	1.5	$CeCl_3$ (1.5 eq), THF, -78-0°C	5
10	1	1.5	$CeCl_3$ (1.5 eq), THF, -40-0°C	5
11	1 (100mg)	1.1	THF (50 mL), –78-0°C	32
12	1 (500mg)	1.2	THF (150 mL), –78-0°C	26
13	1 (500mg)	0.5	THF (150 mL), –78-0°C	--------
14	1 (600mg)	1.1	THF (250 mL), 0°C	31

Table 1

In 1992, Reetz reported that the Ce/Mg-ate complexes were highly selective to react with

aldehyde in simple competition reactions involving 1:1 mixtures of benzaldehyde and acetophenone.[112] Besides, with the addition of cerium chloride, the yields of the alcohols could also be improved, because the strong basicity of Grignard reagents is weakened by mixing with cerium chloride, which would contribute to suppression of side reactions, especially enolisation, reduction, condensation, conjugation addition and pinacol coupling.[113] Based on this procedure, $CeCl_3$ was added to the reaction in an attempt to improve the selectivity of the Grignard addition. Surprisingly, $CeCl_3$ appeared to have a detrimental effect on the reaction (Entry 8, 9 and 10 in Table 1). Cerium chloride has strong oxophilicity, which conduces to activate not only the aldehyde but also other carbonyl components by coordination. Besides, the anhydrous $CeCl_3$ (99.99+%) was bought from the Aldrich-Sigma company, and Karl Fischer titration was not performed on the commercial $CeCl_3$, so it was possible that some water was present in the commercial $CeCl_3$, and would have a significant effect on the outcome of this reaction.[114]

One of the reasons for low selectivity of the addition might be due to an interaction between the alkoxide magnesium and the oxygen of the ester group in the product of the first Grignard addition (Figure 6), which would increase the electrophilicity of the ester carbonyl. The effect of the intramolecular Lewis acid activation is probably also the explanation of why even higher dilution (Entries 11 and 14 in Table 1) did not increase the yield of alcohol **145**.

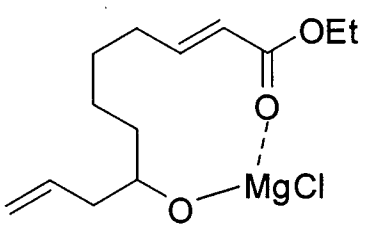
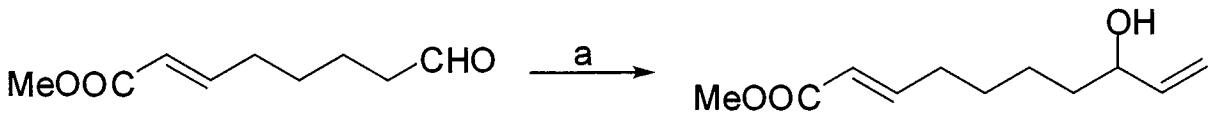


Figure 6

Later it was found that Corey and co-workers achieved a much higher yield in a similar Grignard addition. Under identical conditions to those that were utilised on the aldehyde **144**, vinylmagnesium bromide was reported to have selectively added to the aldehyde in 85% yield

(Scheme 48).[115] The only possible explanation lies in lower Lewis acidity of magnesium in case of the bromo reagent, lower reactivity of vinylmagnesium bromide and the lower activation of the carboxylate towards the addition reaction in case of this Grignard reagent.

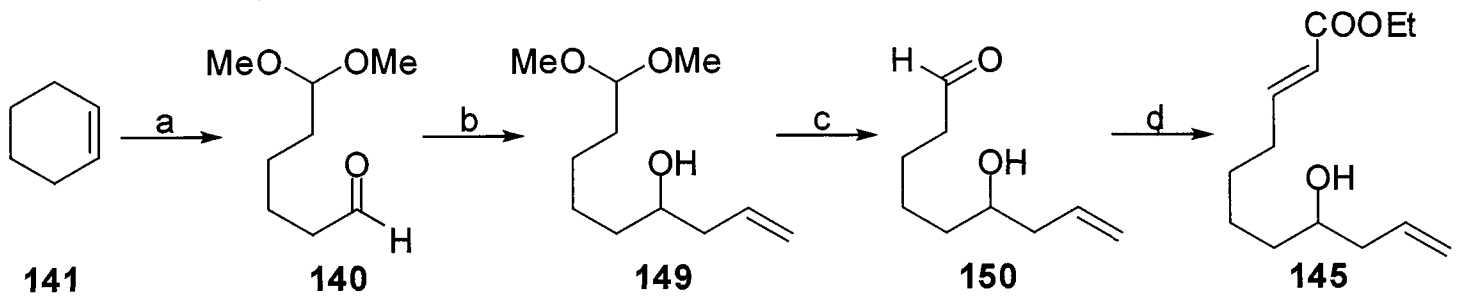


Scheme 48

a) vinylmagnesium bromide, THF, -78°C, 1 h (85%)

2.2.4 Revised route to (*E*)-ethyl 8-hydroxyundeca-2,10-dienoate

To eliminate the possibility of the multiple addition of the Grignard reagent so as to synthesise the desired dienoate **145** in a satisfactory yield, a modified synthetic route was investigated (Scheme 49). In the new approach, the Grignard reaction was conducted directly after the ozonolysis to afford the acetal-alcohol **149**. Hydrolysis of the acetal **149** produced the aldehyde **150** cleanly, which, without purification, was converted to dienoate **145** directly in a good yield. In this synthetic pathway, only one carbonyl group existed at the point of the allyl magnesium chloride addition, thus the problem of regioselectivity of the Grignard addition was avoided. Besides, the modified synthesis did not require extensive column chromatography as the reactions proceeded cleanly, leading to a significant improvement in the overall yield.



Scheme 49

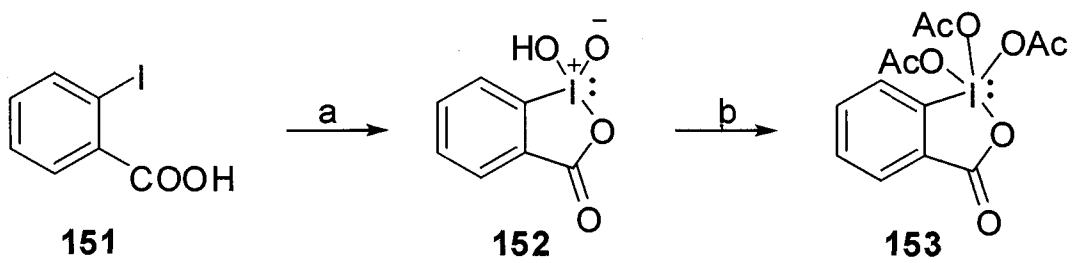
a) O_3, DCM, MeOH, -78°C; *p*-TsOH; $NaHCO_3$; Me_2S; b) allylmagnesium chloride, THF, -78°C; c) 1N HCl, H_2O, Et_2O, rt; d) DCM, (carbethoxymethylene)triphenylphosphorane, reflux (59% from **141**)

2.2.5 Dess-Martin Oxidation

The Dess-Martin periodinane (DMP),[116,117] 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)- one **153**, has become the reagent of choice for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively. The mild reaction conditions (at room temperature and either slightly acidic or virtually neutral pH) are especially suitable for substrates containing sensitive functional group.[118]

2.2.5.1 Preparation of Dess-Martin periodinane and the oxidation mechanism

The Dess-Martin periodinane **153** can be prepared from the commercially available 2-iodobenzoic acid. Oxidation of 2-iodobenzoic acid with potassium bromate in dilute H_2SO_4 affords the cyclic tautomer of 2-iodoxybenzoic acid **152**,[116] which is subsequently converted to the periodinane **153** by treating with acetic anhydride in the presence of catalytic amount of *p*-toluenesulphonic acid following the Ireland's modified procedure (Scheme 50).[118]

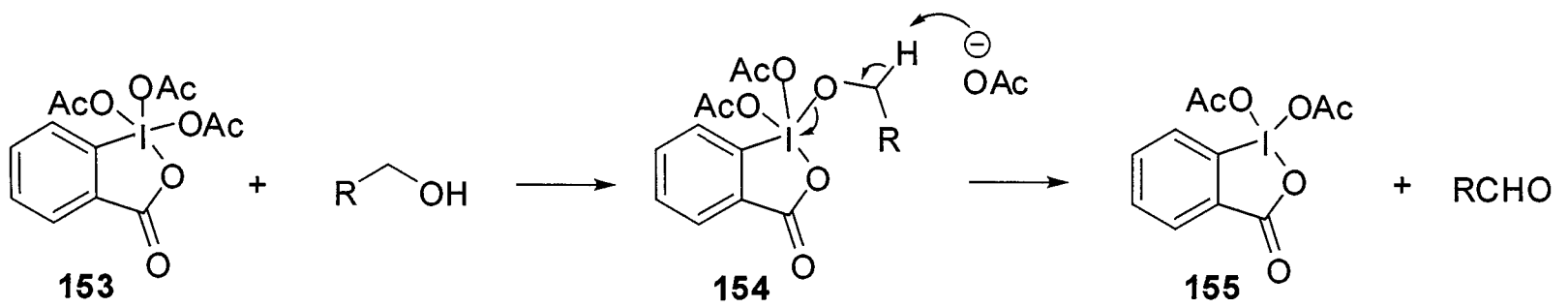


151 **152** **153**

Scheme 50

a) [Dess-Martin] $KBrO_3$, H_2SO_4, 3.5 h, 65°C (93%); b) [Ireland] Ac_2O, 0.5% *p*-TsOH, 2 h, 80°C (91%)

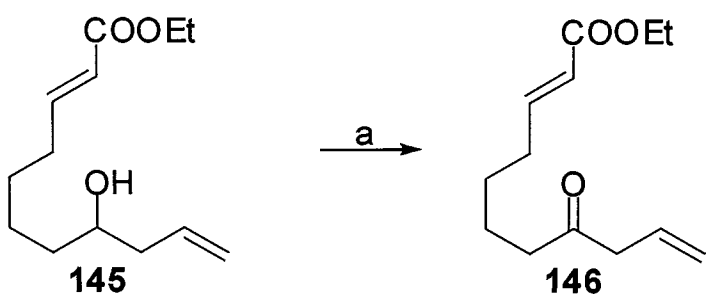
The mechanism of the Dess-Martin oxidation involves exchange of one of the acetates for the alcohol to form the intermediate **154**, followed by an acetate mediated proton removal to give the aldehyde (Scheme 51).[119]



Scheme 51

2.2.5.2 Dess-Martin oxidation

The alcohol **145** was submitted to oxidation by treating with Dess-Martin periodinane **153** in dichloromethane at room temperature for two hours and afforded the ketone **146** in high yield (Scheme 52).[120]

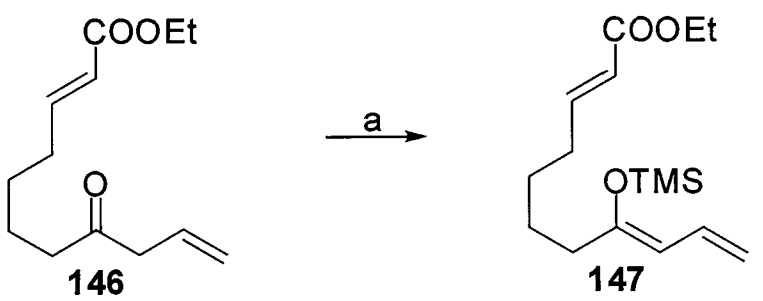


Scheme 52

a) Dess-Martin periodinane **153**, DCM, 2 h, rt (81%)

2.2.6 Enol ether formation

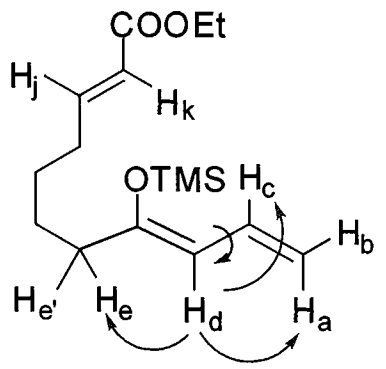
After the Dess-Martin oxidation, the ketone was treated with LHMDS, HMPA and TMSCl at –78 °C to give the pure *cis*- silyl enol ether **147** (Scheme 53).[121]



Scheme 53

a) LHMDS, HMPA, THF, -78°C; TMSCl, -78°C (74%)

The configuration of the silyl enol ether **147** was confirmed by n.O.e analysis (Figure 7).

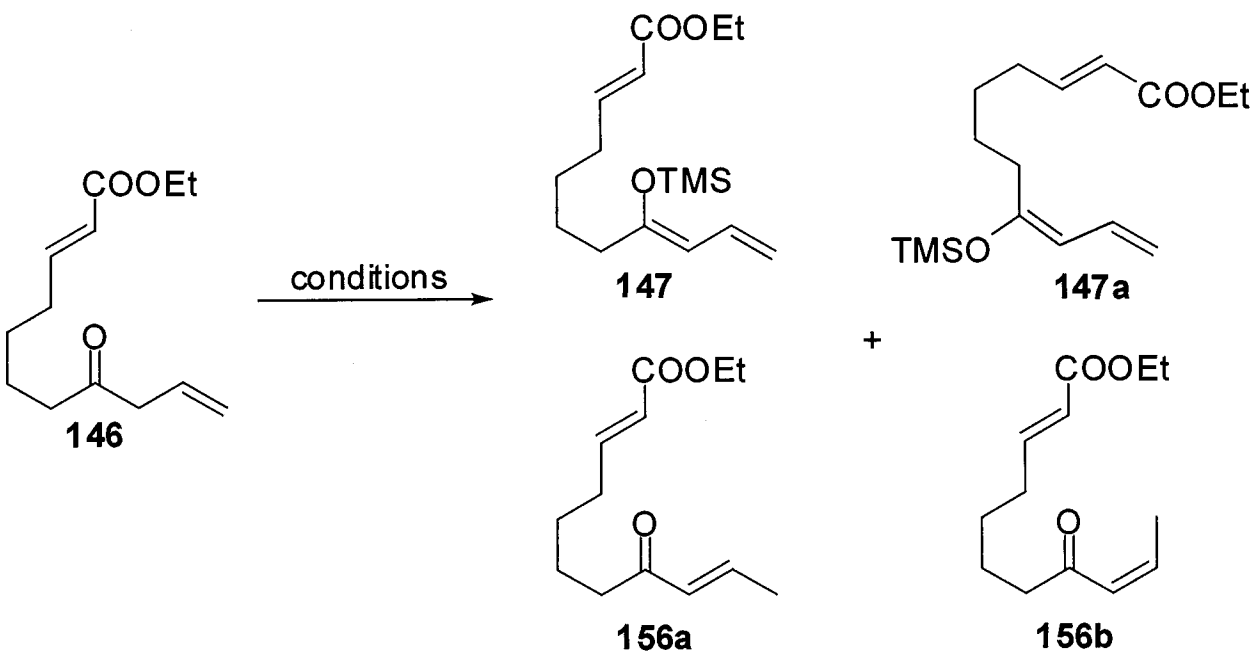


147

Figure 7

When H_d of the *cis*-silyl enol ether **147** was irradiated, the through-space interaction between H_d and H_a as well as H_d and H_e could be detected. Because of the free rotation of the C-C single bond, the interaction between H_d and H_c could also be detected.

It should be noted that a number of reaction conditions were investigated in order to achieve such high *cis*-selectivity (Table 2). The most common conditions,[122] employing triethylamine in presence of TMSCl, resulted in the formation of the enones **156a** and **156b** as major products (Entry 1). The use of lithium diisopropylamide (LDA), one of the most popular kinetic enolate-forming reagents, afforded a 1 to 1 mixture of *cis*- and *trans*- silyl enol ether (Entry 2).[123] Substitution of lithium diisopropylamide (LDA) for lithium hexamethyldisilazide (LHMDS) improved the ratio of the *cis* and *trans* products slightly (Entry 3). Inclusion of HMPA, on the contrary, led to selective formation of the desired *cis*-silyl enol ether (Entry 4).[124]



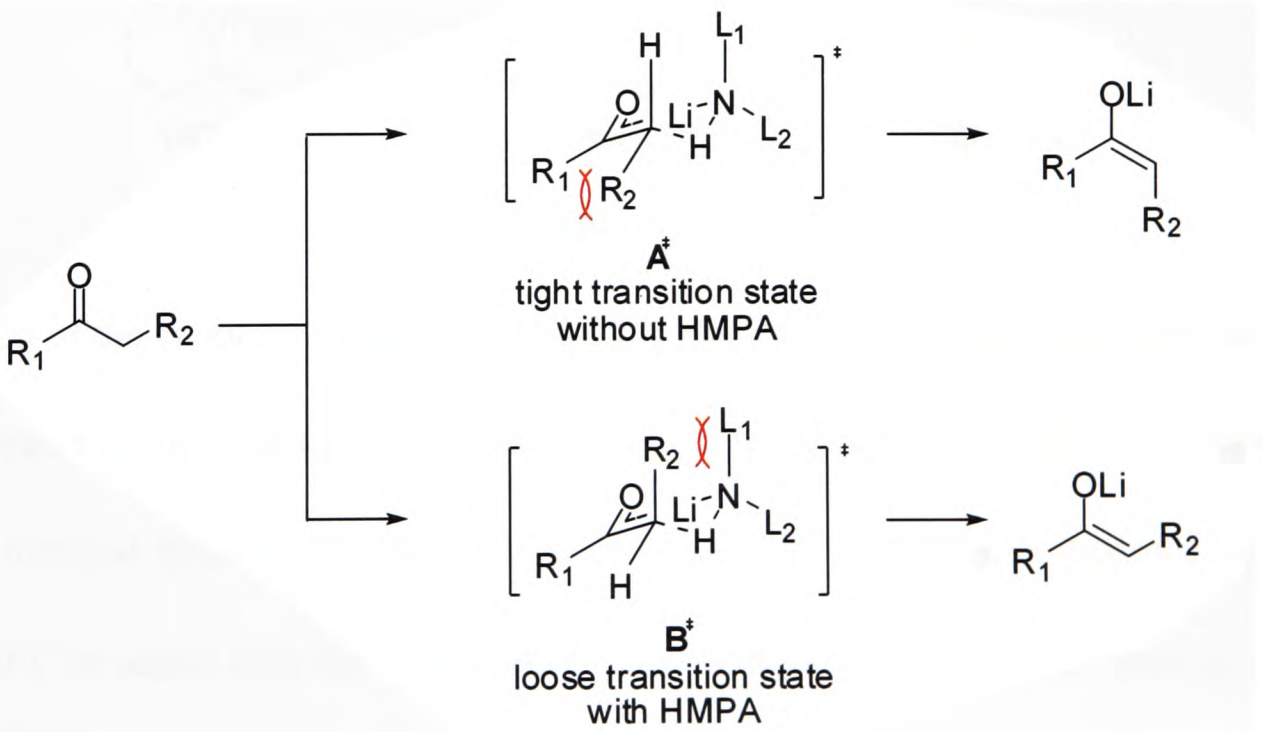
Scheme 54

No.	*Conditions*	*Yields*	*cis: trans*
1	Et_3N (1.2 eq), TMSCl (1.2 eq), toluene, rt; then reflux[125]	**147** and **147a**: 3% **156a**: 67%, **156b**: 21%	1:1
2	LDA (1 eq), THF, -78°C, 2 h; then TMSCl (1.2 eq), –78°C, 1 h[126,127]	**147** and **147a**: 42%	1:1
3	LHMDS (1.2 eq), THF, -78°C, 15 min; then TMSCl (1.2 eq), 1 h[124]	**147** and **147a**: 49%	1.2:1
4	LHMDS (1.2 eq), HMPA (1.1 eq), THF, -78°C, 15 min; then TMSCl (1.2 eq), -78°C, 1 h[121]	**147**: 74%	Only *cis*-product

Table 2

a) In all conditions, 1 eq of ketone **146** was used; b) the ratios of *cis* and *trans*-isomers were determined by 1H NMR spectra.

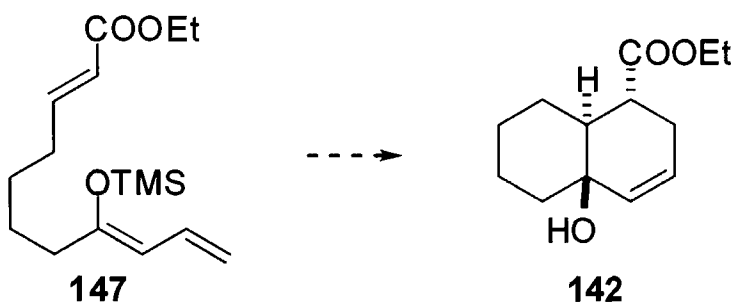
These observations could be rationalised by employing the Ireland's enolisation transition state model (Scheme 55).[124,128] The use of HMPA can both increase the reactivity of the amide base and enhance solvation of the lithium cation, thus making the lithium-carbonyl oxygen interaction much weaker, and resulting in a rather more 'loose' transition state $\mathbf{B}^{\neq}$. The diaxial interaction in transition state $\mathbf{B}^{\neq}$ becomes less pronounced than the steric hindrance in transition state $\mathbf{A}^{\neq}$ leading to higher *cis* selectivity.



Scheme 55

2.2.7 Diels-Alder reaction

With the *cis*-enol ether **147** in hand, its intramolecular Diels-Alder cycloaddition was next investigated (Scheme 56).



Scheme 56

Since the silyl enol ether **147** was presumed to be highly acid sensitive, thermal conditions were first examined. The silyl enol ether **147** was heated under reflux in toluene for a couple of days,[129] which only afforded the starting material **147** (24%) as well as *trans*- and *cis*-ketones **156a** (15%) and **156b** (15%), without any traces of the desired cycloaddition product **142** (Figure 8).

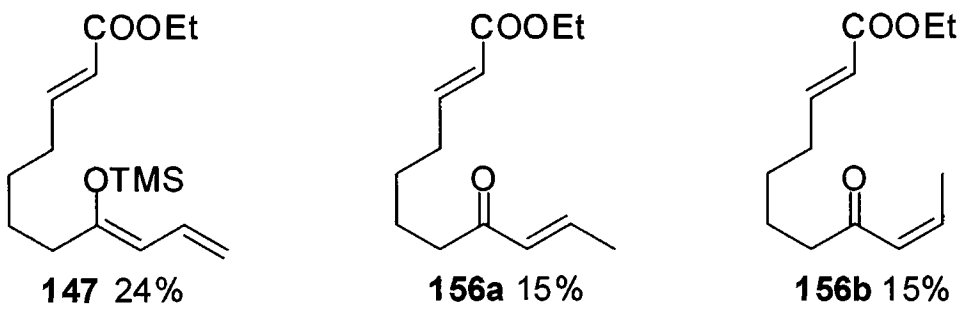
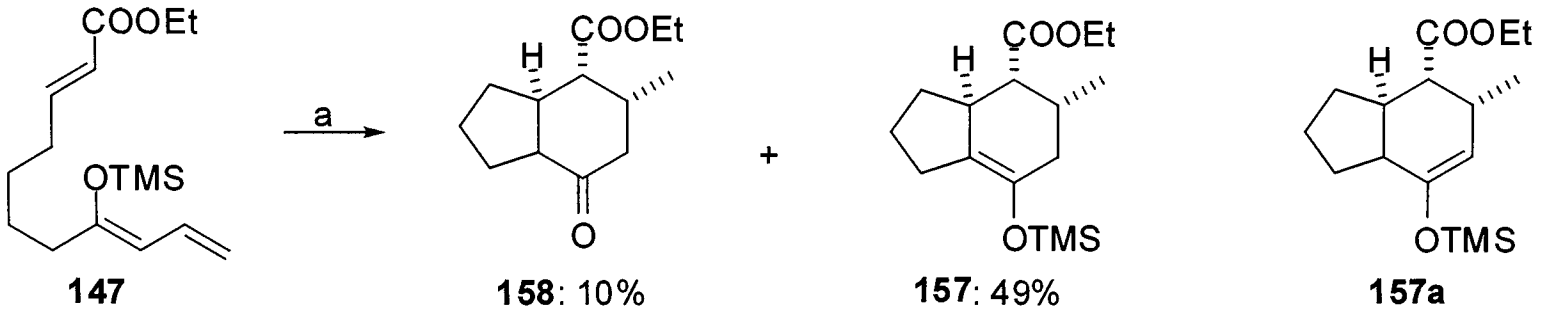


Figure 8

The formation of the enone products **156a** and **156b** should be attributed to the presence of trace amount of water in the reaction. In order to avoid the undesirable hydrolysis, toluene was additionally distilled from CaH_2. The solution of silyl enol ether **147** in anhydrous toluene was heated at 150°C in sealed tube for one week,[130] and disappointingly, only the starting enol ether **147** was observed by TLC. In an attempt to initiate the desired Diels-Alder reaction, the reaction temperature was increased to 180°C. The mixture was kept at this temperature for 5 days. Two new compounds were isolated, both surprisingly lacking the vinylic protons. Later the structures

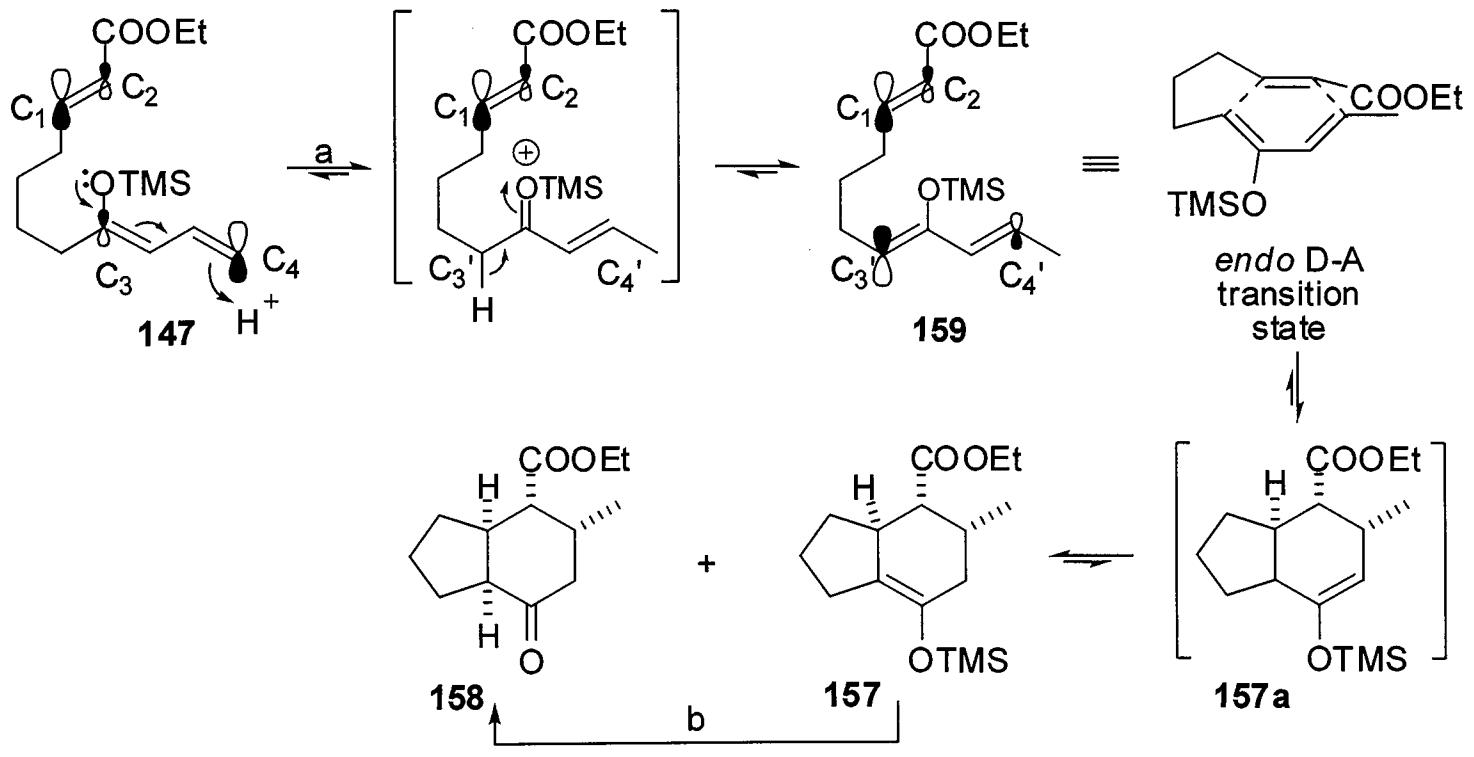
were assigned as the silyl enol ether **157** and the enone **158** (Scheme 57).



Scheme 57

a) anhydrous toluene, 180°C, sealed tube, 5 days (**157**: 49%, **158**: 10%)

It is presumed that the silyl enol ether **147** underwent an acid (probably, acidic Si-OH components on the glass surface of the sealed tube) catalysed tautomerisation leading to an isomeric silyl enol ether **159**, which underwent an *endo*-Diels-Alder cycoaddition producing the bicyclo[3.4.0]nonane adduct **157a**. At high temperature, tri-substituted double bond of **157a** rearranged to a more thermodynamically stable tetra-substituted double bond of **157**. This process was probably also acid catalysed. Part of the silyl enol ether **157** was hydrolysed to the ketone **158** under these reaction conditions (Scheme 58).



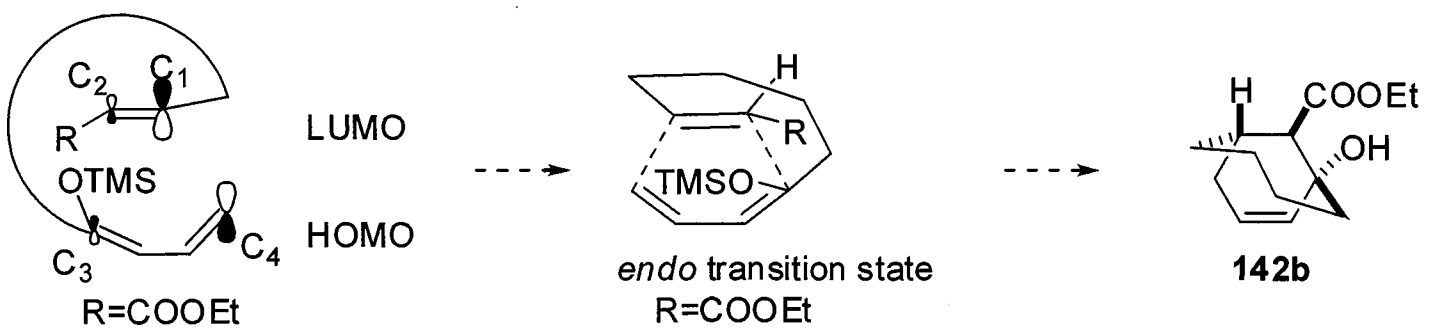
Scheme 58

a) toluene, 180°C, 5 days (**157**: 49%, **158**: 10%); b) 1N HCl, H_2O, Et_2O, rt (100%)

The lack of reactivity of the silyl enol ether **147** to undergo the desired cycloaddition could be explained by the Frontier Orbital theory. The electron-withdrawing group, -COOEt, lowered the

energy of the LUMO of the dienophile, while the electron-releasing group, -OTMS, raised the HOMO of the diene, which contributed to minimise the energy gap between the two orbitals.[131] The lowered energy gap should have accelerated the reaction, but from the orbital theory it was found that the corresponding dienophile LUMO and the diene HOMO orbital coefficients were unsymmetrical. The highest HOMO coefficient in the triene **147** was at C_4, while the highest LUMO coefficient of the dienophile component was at C_1. This disfavoured the desired overlap of the orbitals and formation of the C_1-C_3 carbon-carbon bond in the compound **147**. On the contrary, in the rearranged compound **159** the highest HOMO was at the C_3' (Scheme 58), leading to an efficient orbital overlap and cycloaddition.[132,133]

In fact the polarisation of the molecular orbitals in **147** should facilitate the formation of a different cycloadduct **142b** (Scheme 59). However, the large torsional and angle strain in the transition state disfavoured this pathway.



Scheme 59

Following these observations, it could be postulated that the first isomerisation was the rate-limiting step (Scheme 58) with the subsequent cycloaddition and final silyl enol ether rearrangement proceeding more rapidly.

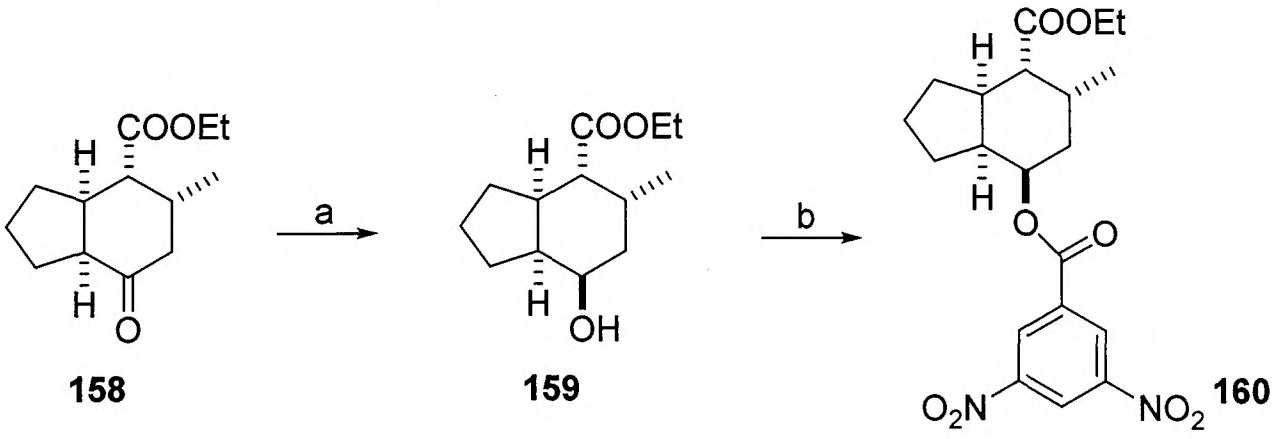
Houk pointed out that a Lewis acid could improve the efficiency of Diels-Alder reaction through coordination to the dienophile, so that the LUMO energy of the dienophile would be lowered to a large extent.[134,135] Therefore, Lewis acid was introduced to catalyse the Diels-Alder cycloaddition. The mixture of the silyl enol ether **147** and catalytic amount of diethylaluminium

chloride[136] in toluene was heated at 170°C in a sealed tube for 4 days. However, only 39% of **157** and 8% of **158** were isolated. When the precursor **147** and TMSOTf in CD_2Cl_2 was heated at 100°C in a sealed NMR tube,[137,138] only formation of the *trans*-enone **156a** was observed in an NMR-scale experiment. Another attempt was made to heat the precursor **147** and zinc bromide in D6-toluene at 150°C for 3 days in a sealed NMR tube.[139] The crude product ^{1}H NMR spectrum showed formation of the enone **156a** and the cyclised ketone **158** (Table 3). This result proved that the rearrangement of the silyl enol ether **147** to **159** could be catalysed by the right choice of an acidic catalyst.

No.	*Conditions*	*Products*
1	150°C, toluene, one week in sealed tube	Starting material
2	180°C, toluene, 5 days in sealed tube	**157**: 49%, **158**: 10%
3	170°C, Et_2AlCl (cat.), toluene, 4 days in sealed tube	**157**: 39%, **158**: 8%
4	100°C, TMSOTf (1 eq), CD_2Cl_2, one week in sealed NMR tube	**156a**
5	150°C, $ZnBr_2$ (one crystal), toluene, 3 days in sealed NMR tube	**158** and **156a**

Table 3

Because of overlapping signals in the ^{1}H NMR spectrum, it was difficult to determine the relative stereochemistry of the bicyclic fragment **157** or **158**, if based only on the correlation of the spectroscopic data. Therefore, the bicyclic ketone **158** was converted into the 3,5-dinitrobenzoate **160**,[140] first by stereoselective reduction[141] with L-selectride to alcohol **159** followed by esterification with 3,5-dinitrobenzoic acid chloride (Scheme 60).



158 **159** **160**

Scheme 60

a) L-selectride, THF, 0°C (37%); b) 3,5-dinitrobenzoyl chloride, pyridine, rt (89%)

The single crystal X-ray diffraction of **160** confirmed the desired stereochemistry of the four relative stereocenters generated in the expected in the intramolecular Diels-Alder reaction (Figure 9).

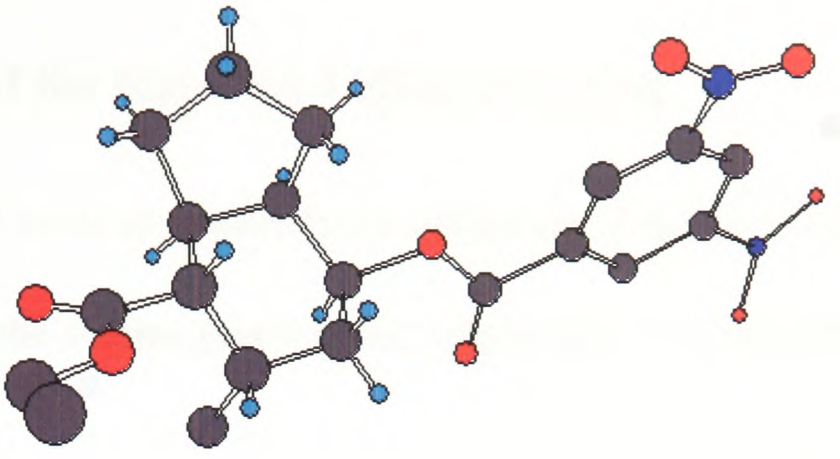


Figure 9

The observed sequence of reactions happening in a single step provided an interesting example of domino silyl enol ether chemistry. The relative configuration of the three contiguous stereocentres matched those of tetrodecamycin (**1**) (Figure 10). Moreover, the cycloaddition installed the α-methyl group at C-16, which avoided further investigation of its installation in a separate step.

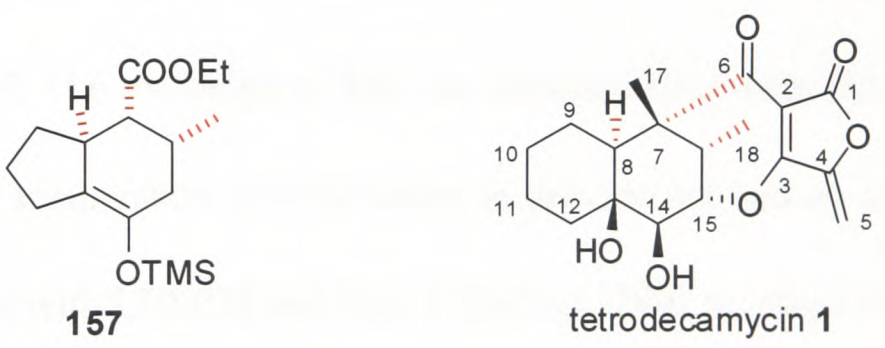


Figure 10

2.2.8 Conclusion to section 2.2

An unusual domino silyl enol ether reaction sequence from **147** was observed (Scheme 58). Silyl enol ether isomeration followed by an intramolecular Diels-Alder cycloaddition and a further silyl enol ether isomeration cascade afforded the bicyclo[3.4.0]nonane adduct **157** from the silyl enol ether **147**. The relative configuration of **147** was confirmed by the X-ray diffraction of the

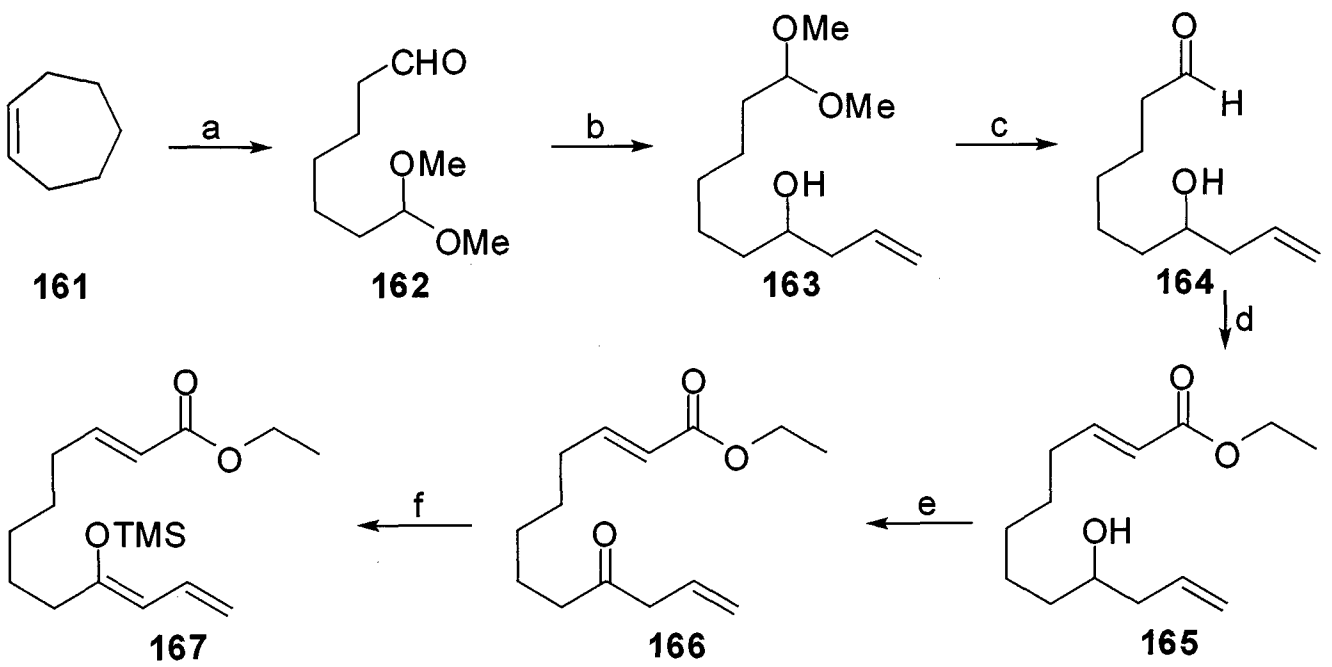
3,5-dinitrobenzoate derivative **160**, which indicated the three correct relative stereocentres of tetrodecamycin (**1**) as well as the installation of the methyl group at C-16 in the cycloaddition (Figure 9).

2.3 Construction of the bicyclo[4.4.0]decaline ring

The results of the model study prompted the investigation of the cycloaddition of a homologue (**167**) of **146** to confirm the domino process and compare the stereochemistry of the cycloadduct with tetrodecamycin (**1**).

2.3.1 Synthesis of the Diels-Alder precursor

The synthesis of *cis*-silyl enol ether **167** commenced with ozonolysis of the cycloheptene **161** to afford the acetal-aldehyde **162**, which was submitted to Grignard addition directly without purification to give an acetal-alcohol **163**. After hydrolysis of **163** with 1N HCl and purification, the aldehyde **164** was produced in 70% yield over three steps. Wittig reaction of the aldehyde **164** with the (carbethoxymethylene)triphenylphosphorane in DCM under reflux selectively led to the *trans*-olefin **165**. The oxidation of **165** was accomplished with Dess-Martin periodinane **153** in DCM at room temperature for two hours to provide the ketone **166** in high yield. The ketone **166** was treated with LHMDS and then TMSCl at -78˚C to afford the desired Diels-Alder precursor (*Z*)-**167** of the Diels-Alder reaction in 75% yield (Scheme 61).



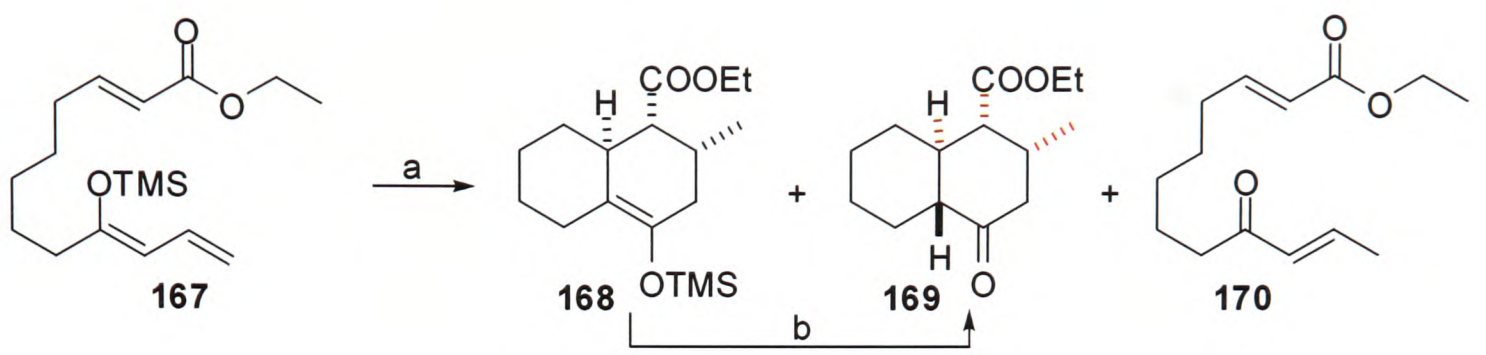
Scheme 61

a) O_3, DCM, MeOH, -78°C; *p*-TsOH; $NaHCO_3$; Me_2S; b) allylmagnesium chloride, THF, -78°C; c) 1N HCl, H_2O, Et_2O, rt (70% from **161**); d) DCM, (carbethoxymethylene)triphenylphosphorane, reflux (79%); e) Dess-Martin periodinane **153**, DCM, 2 h, rt (78%); f) LHMDS, HMPA, THF, -78°C; TMSCl, -78°C (75%)

2.3.2 The Diels-Alder reaction

With the *cis*-silyl enol ether **167** in hand, the intramolecular Diels-Alder reaction was next investigated (Scheme 62). The solution of the precursor (*Z*)-**167** in toluene was heated at 170°C for two days. Only the starting material was detected by TLC. Therefore, a catalytic amount of diethylaluminium chloride was added to the solution, and the mixture was left stirring at 170°C. After another 6 days, both crude ^{1}H NMR spectrum and TLC indicated the formation of the cycloadducts **168** and **169** together with enone **170**. The crude product was submitted to hydrolysis directly. After purification a 28% yield of the ketone **169** and a 10% yield of the enone **170** were obtained. The other acid catalyst examined was freshly recrystallised camphorsulphonic acid (CSA).[138] Under similar conditions, the reaction catalysed by CSA followed by hydrolysis afforded 63% yield of the cycloadduct **169** together with only 6% yield of the enone **170**. In this reaction, a trace amount of compound, which was apparently isomeric to **169**, was also obtained. The ratio between **169** and the alleged isomer was 4:1 based on the integration of the ^{1}H NMR spectrum. However, overlapping of resonance signals occurred in the

^{1}H NMR spectrum of the minor isomer in deuterated chloroform. Therefore, the NMR experiment was run in deuterated toluene or benzene, but none of them could give good signal resolution. As a result, the stereochemistry of the minor isomer was not able to be established.

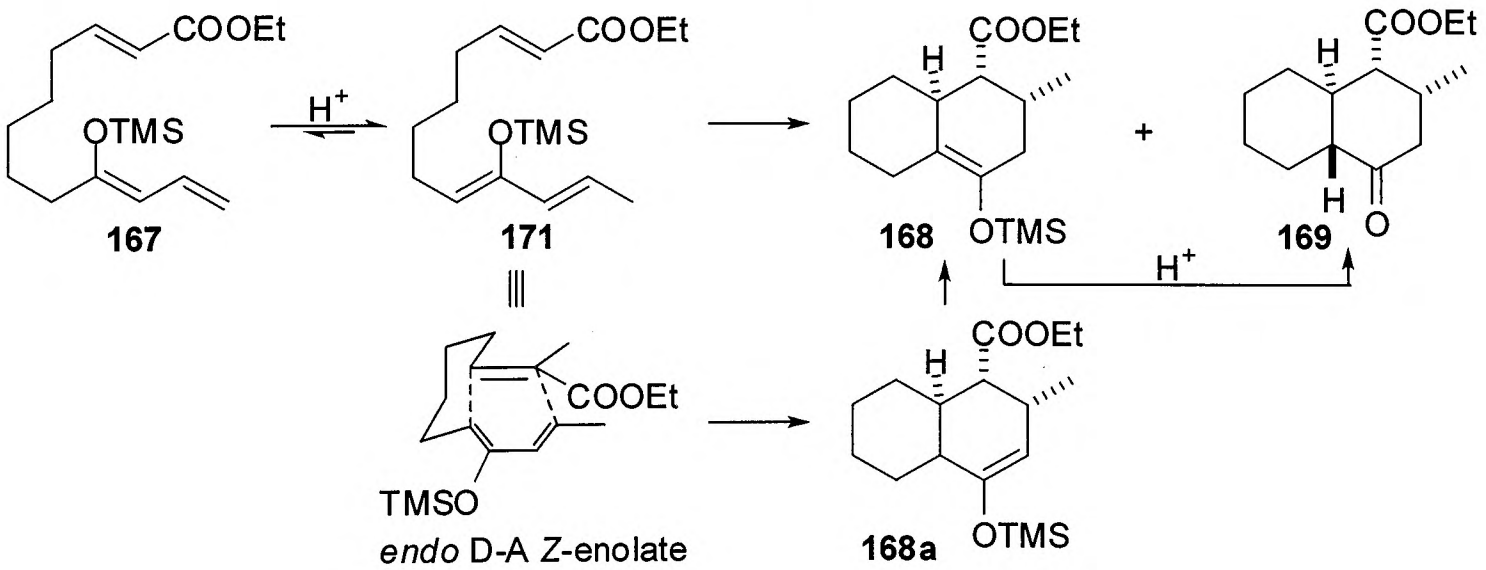


Scheme 62

Method 1: a) Et_2AlCl (cat.), toluene, 170°C, 6 days; b) 1N HCl (**169**: 28%, **170**: 10%)

Method 2: a) CSA (cat.), toluene, 180°C, 4 days; b) 1N HCl (**169**: 63%, **170**: 6%)

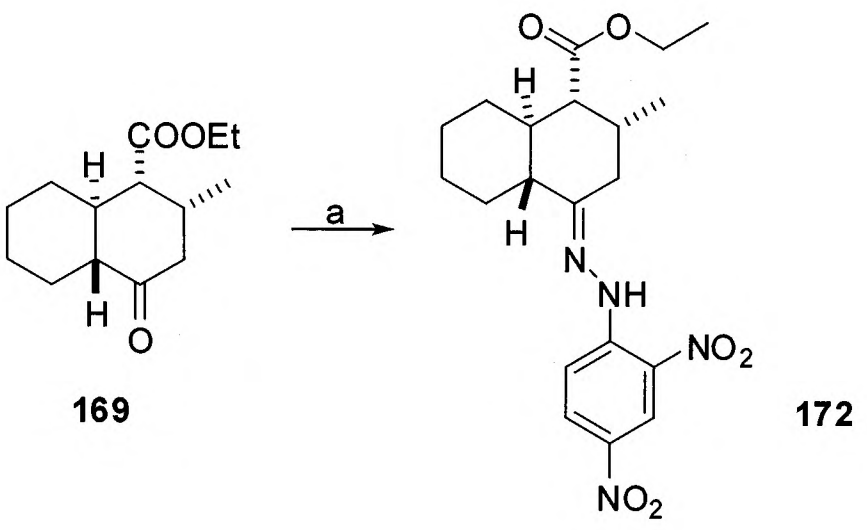
The *cis*-silyl enol ether **167** underwent acid catalysed tautomerisation into the *Z,E*-silyl enol ether **171**, which was set for *endo*-cycloaddition producing the bicyclo[4.4.0]decalin framework of **168a**. The cycloadduct **168a** underwent another acid catalysed rearrangement to give the more stable tetrasubsituted double bond in silyl enol ether **168**, which upon acidification provided the kinetic *trans*-decalin **169** in a satisfactory yield (Scheme 63).



Scheme 63

Because of the overlapping signals on the ^{1}H NMR spectrum, it was difficult to determine the relative stereochemistry of **168** and **169** by NMR spectra analysis. Therefore, to confirm the

structure, the cycloadduct **169** was converted into a crystalline derivative, a hydrazone **172** (Scheme 64).[142]



169 **172**

Scheme 64

a) 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH, rt, 5 min (75%)

As expected, the X-ray crystallography of the hydrazone **172** (Figure 11) established that the cycloadduct **169** possessed the same relative stereochemistry as that in tetrodecamycin (**1**).

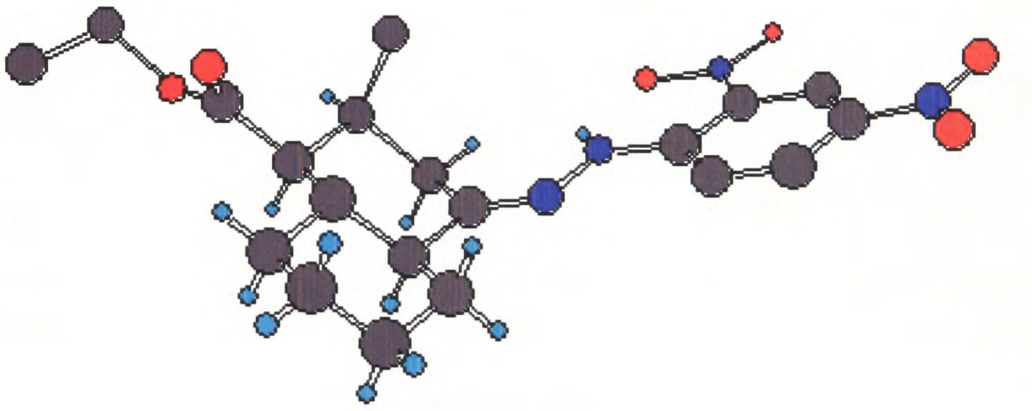


Figure 11

2.3.3 Conclusion of section 2.3

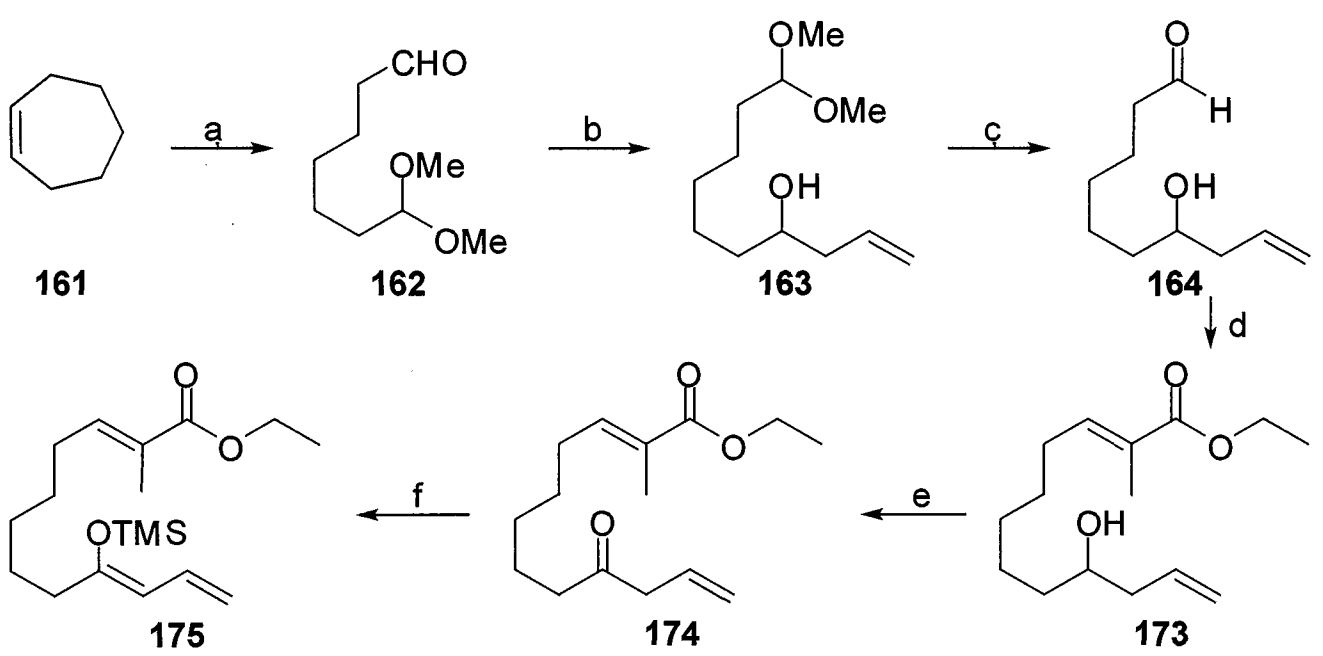
Starting from cycloheptene, the precursor (*Z*)-**167** was obtained (Scheme 61). The intramolecular Diels-Alder reaction of (*Z*)-**167** catalysed by camphor-10-sulphonic acid and the subsequent acidification provided the cycloadduct **169** in good yield (Scheme 62). The relative stereochemistry of **169** was established by the X-ray crystallography of its hydrazone derivative **172** (Figure 11), which showed the same relative stereochemistry to that of tetrodecamycin (**1**).

These results encouraged the investigation of the synthesis of the key intermediate **134** *via* this synthetic route.

2.4 Synthesis of the key intermediate (186)

2.4.1 Synthesis of the Diels-Alder precursor (175)

Following the standard sequence described earlier, the Diels-Alder precursor (*Z*)-**175**, possessing an extra methyl substituent at the double bond, was synthesised *via* ozonolysis, Grignard addition, hydrolysis, Wittig reaction with (carbethoxyethylidene)triphenyl-phosphorane, Dess-Martin oxidation and stereoselective enolisation (Scheme 65).



Scheme 65

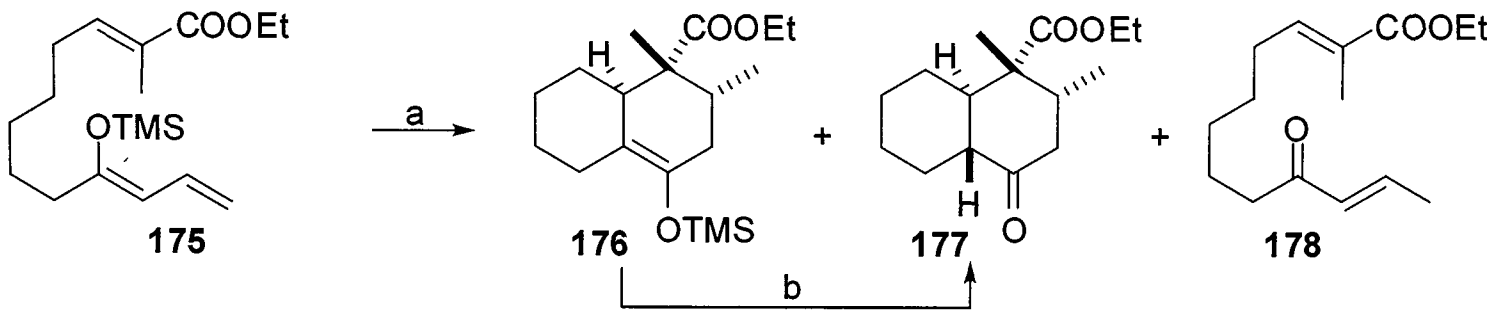
a) O_3, DCM, MeOH, -78°C; *p*-TsOH; $NaHCO_3$; Me_2S; b) allylmagnesium chloride, THF, -78°C; c) 1N HCl, H_2O, Et_2O, rt (70% from **161**); d) DCM, (carbethoxyethylidene)triphenylphosphorane, reflux (79%); e) Dess-Martin periodinane **153**, DCM, 2 h, rt (88%); f) LHMDS, HMPA, THF, -78°C; TMSCl, -78°C (79%)

2.4.2 Synthesis of the key intermediate (186)

2.4.2.1 Investigation on the IMDA reaction of the TMS enol ether

Following the previously established conditions the *cis*-TMS enol ether **175** was submitted to the Diels-Alder cycloaddition. The best yield of cycloadduct **176** was obtained when the reaction was catalysed by freshly recrystallised camphor-10-sulphonic acid (4 mol%) on a 100

mg scale (Scheme 66).



Scheme 66

a) CSA (cat.), toluene, 180°C, 4 days (**176**: 68%, **177**: 6%); b) 1N HCl, Et_2O, rt (71%)

Numerous attempts to optimize the reaction conditions for selective conversion of the *cis*-silyl enol ether **175** to the cycloadduct **176** were carried out. It was discovered that when the reaction was performed on a small scale (100 mg of starting material (*Z*)-**175**) and catalysed by small amount of catalysts (Et_2AlCl or CSA), the Diels-Alder reaction afforded cycloadduct **176** in satisfactory yields. Unfortunately, it was found that a scaled-up reaction was problematic. The results of multiple attempts to optimise reaction conditions are summarised in Table 4.

When the cycloaddition was carried out on a 100 mg scale at 170°C with 2 mol% of Et_2AlCl in toluene for 5 days, the desired product **176** was obtained in a 60% yield together with 13% of the ketone **177** (Entry 1, Table 4). In the next attempt, the catalyst loading was increased to 5 mol%, and after 4 days at 170°C only the ketone **177** was isolated (Entry 2, Table 4). Subsequently, a 500 mg scaled reaction of the starting material (*Z*)-**175** with 2 mol% of Et_2AlCl was heated at 170°C for 5 days. At this point, the crude ^1H NMR spectrum showed the presence of a considerable amount of the starting *cis*-enol ether **175**. Therefore, another 2 mol% of Et_2AlCl was added and the stirring was continued at 170°C for 3 more days, when only the ketone **177** was observed in the crude ^1H NMR spectrum (Entry 3, Table 4). However, another 650 mg scaled reaction of the starting material (*Z*)-**175** even with 6 mol% of the Lewis acid did not lead to the full conversion at 180°C for 9 days (Entry 5, Table 4). When CSA was chosen to catalyse

the cycloaddition,[138] similar results were obtained. *cis*-Silyl enol ether **175** (90 mg) was heated at 180°C with 2 mol% of CSA for 2 days. ^{1}H NMR spectrum analysis of the reaction mixture indicated the presence of a significant amount of starting material (*Z*)-**175**. After addition of another 2 mol% of CSA and 2 more days of heating at 180°C, the reaction gave 68% of the desired cycloadduct **176** (Entry 7, Table 4). However, when performed on a 500 mg scale with 2 mol% of CSA, the reaction yielded only the starting material (*Z*)-**175** and enone **178** (Entry 8, Table 4). No improvement was observed when ethereal HCl or $MeAlCl_2$ were used for catalysis (Entry 6 and 10, Table 4).

These observations could be accounted by the instability of the TMS-enol ether **175** under acidic conditions. Trace amounts of moisture could lead to significant formation of the hydrolysis products **177** and **178**.

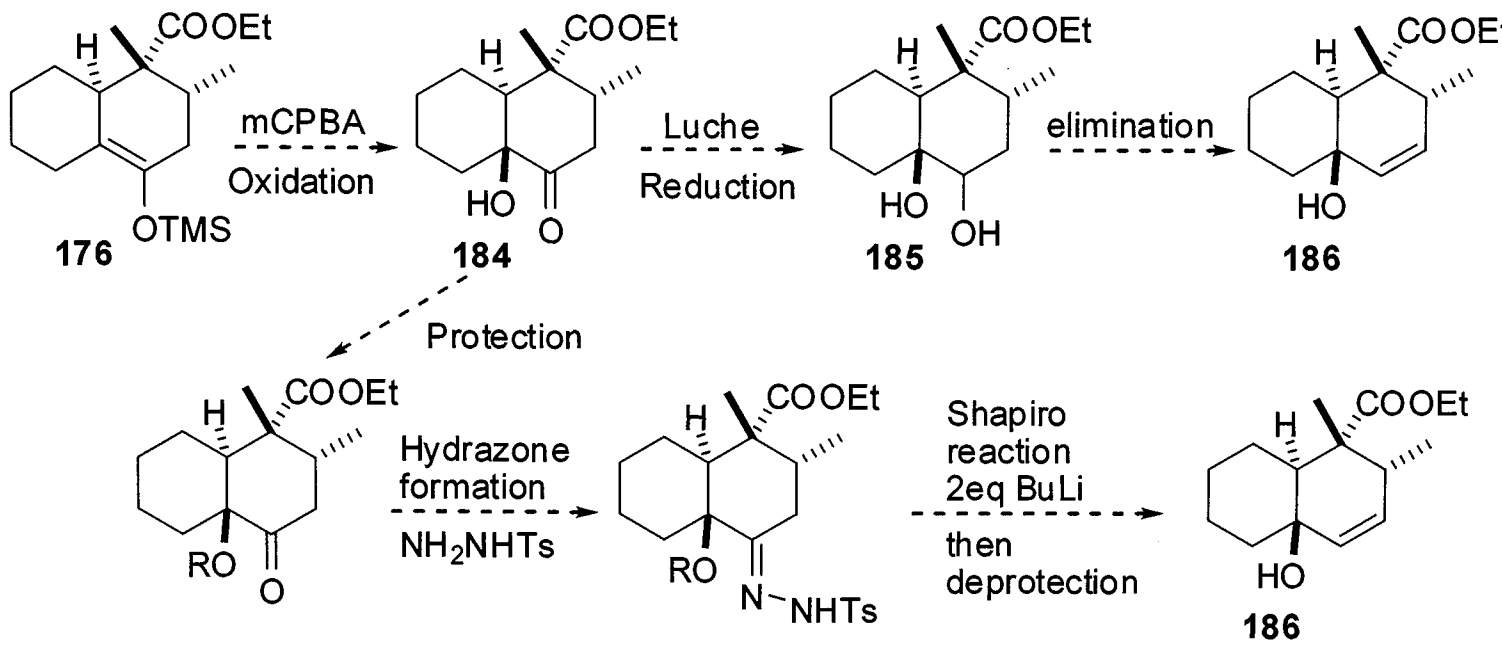
No	Catalyst (mol%)	Starting 175 (mg)	Condition	Result
1	Et_2AlCl (2)	103	170°C, 5 days	**176**: 60%, **177**: 13%
2	Et_2AlCl (5)	173	170°C, 4 days	Only **177**: 63%
3	Et_2AlCl (4)	512	2 mol% Et_2AlCl, 170°C, 4 days; then another 2 mol% Et_2AlCl, 170°C, 3 days	Presence of significant amount of **175** after 4 days; after 7 days only **177**: 51%
4	Et_2AlCl (3)	500	180°C, 5 days	**176**: 51%, **177**: 19%, **178**: 8%
5	Et_2AlCl (6)	648	2 mol% Et_2AlCl, 180°C, 3 days; another 2 mol% Et_2AlCl, 180°C, 3 days; another 2 mol% Et_2AlCl, 180°C, 3 days	Presence of significant amount of **175** even after 9 days. Recovered **175**: 40%
6	$MeAlCl_2$ (2)	50	180°C, 3 days	Crude ^1H NMR spectrum only showed **177** and **178**
7	CSA (4)	90	2 mol% CSA, 180°C, 2 days; then another 2 mol% CSA, 2 days	**176**: 68%, **177**: 5%, **178**: 7%
8	CSA (2)	500	180°C, 3 days	Recovered **175**: 27%, **178**: 35%
9	CSA (1.5)	167	180°C, 5 days	**176**: 29%, **177**: 16%, **178**: 15%
10	HCl (10)	50	180°C, 5 days	Recovered **175**: 25%, **177**: 18%, **178**: 31%

Table 4

1. All the reactions were performed in toluene in sealed tube; 2. The reactions were traced with ^1H NMR spectrum and TLC; 3. Et_2AlCl, $MeAlCl_2$ and HCl are 1.0 M solution in anhydrous Et_2O; 4. CSA was freshly recrystallised.

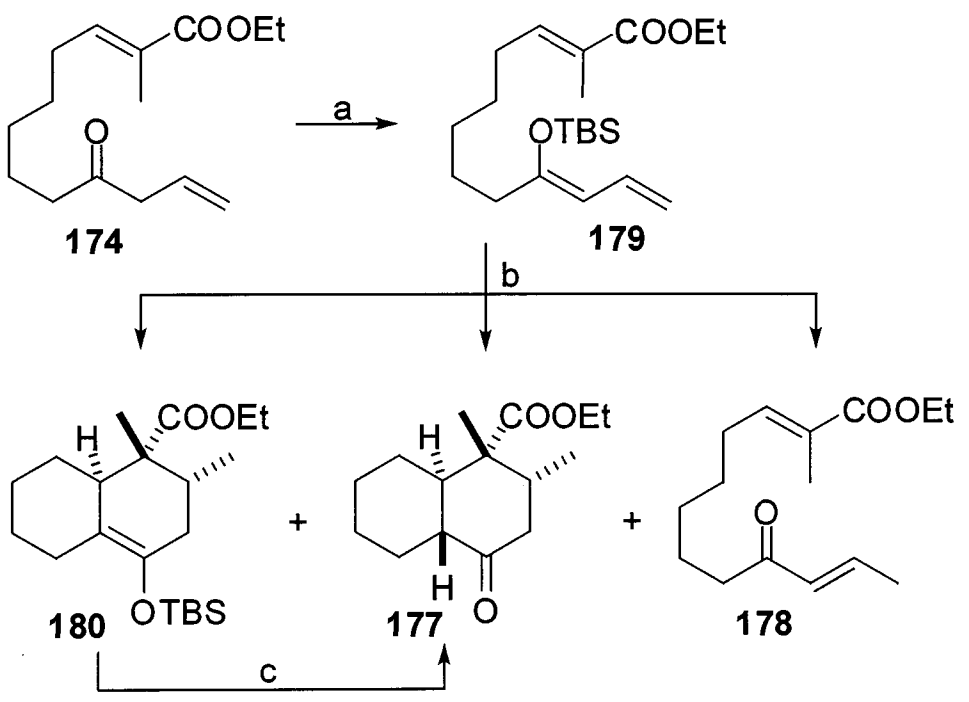
2.4.2.2 Investigation on the IMDA reaction of the TBS enol ether (179)

In the advanced synthetic plan outlined in Scheme 67, oxidation of the silyl enol ether **176** would form an α-hydroxy ketone **184**, setting the tertiary hydroxyl at the ring junction. With the α-hydroxy ketone **184** in hand, the key intermediate **186** could be produced *via* Lüche reduction[143] and subsequent oxidative elimination,[144] or alternatively *via* tosylhydrazone formation followed by Shapiro reaction.[145] However, the reproduction of the TMS enol ether **176** turned out to be difficult because of its instability; hence the cycloaddition of TBS enol ether (*Z*)-**179**, which was expected to be more stable than the TMS enol ether, was explored.



Scheme 67

The TBS enol ether (*Z*)-**179** was synthesised under the standard conditions (LHMDS, HMPA, THF, TBSOTf, -78°C) in high yield. With the precursor (*Z*)-**179** in hand, the Diels-Alder reaction was carried out in toluene catalysed by 4 mol% of freshly recrystallised camphor-10-sulphonic acid at 180°C for 4 days to produce the desired cycloadduct **180** in 69% yield together with a small amount of ketone **177** and trace of enone **178** (Scheme 68).

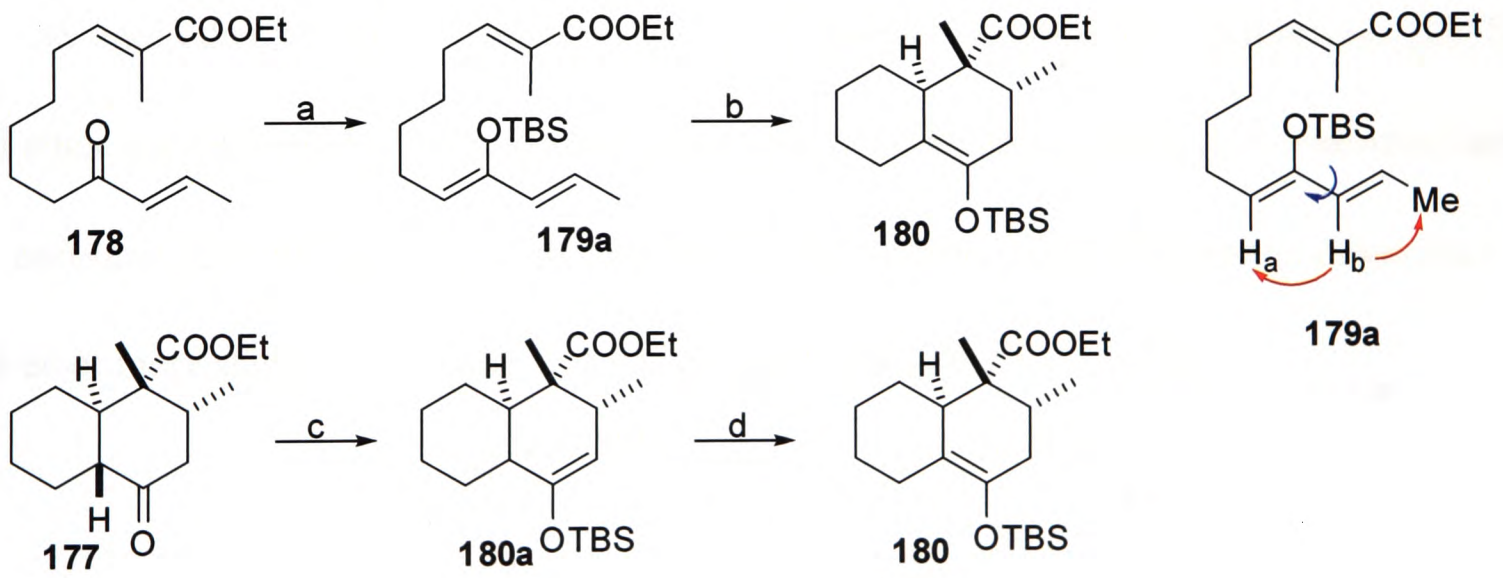


Scheme 68

a) LHMDS, HMPA, THF, -78°C; then TBSOTf, -78°C (91%); b) CSA (cat.), toluene, 180°C, 4 days (**180**: 69%, **177**: 7%, **178**: trace); c) 1N HCl, Et_2O, rt (quant.)

Another two methods were explored for the conversion of the by-products **177** and **178** into the cyclised silyl enol ether **180** (Scheme 69). The enone **178** was enolised to the TBS enol ether

(*Z*)-**179a** following Corey's procedure,[115] and its structure was confirmed by n.O.e NMR spectra analysis shown in Scheme 69. The irradiation of H_b enhanced the signals of both H_a and Me. The *Z,E*-silyl enol ether was postulated to be an intermediate in the previously described Diels-Alder cycloadditions. The TBS enol ether (*Z*)-**179a** was converted to the rearranged cycloadduct **180** when heated at 180°C in presence of a catalytic amount of Et_2AlCl in toluene for 4 h. The Diels-Alder reaction of (*Z*)-**179a** proceeded quickly due to the minimised energy gap between the dienophile LUMO and the diene HOMO orbitals and the efficient orbital overlap. Meanwhile, the cyclised ketone **177** was converted to the kinetic product, the TBS enol ether **180a**, under Corey's conditions as well. The ^1H NMR spectrum of the crude product **180a** indicated the existence of a vinylic proton of the enol ether double bond. The crude silyl enol ether **180a** was treated with catalysed amount of CSA in toluene. The mixture was heated at 180°C for 7 h to afford the desired thermodynamic product, the TBS enol ether **180** in high yield. The independent synthesis and inter-conversion of the previously proposed intermediates provided extra evidence in favour of the proposed mechanism of the domino process.

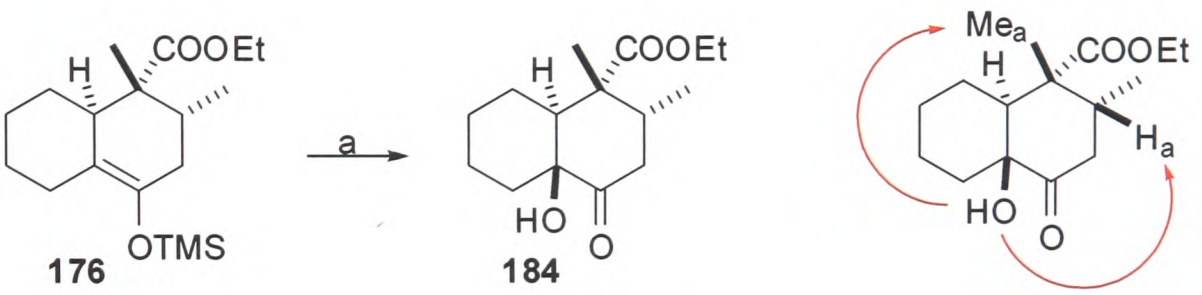


Scheme 69

a) KHMDS, THF, -78°C; then TBSOTf, -78°C (86%); b) Et_2AlCl (cat.), toluene, 180°C, 4 h (76%); c) KHMDS, THF, -78°C; then TBSOTf, -78°C; d) CSA (cat.), toluene, 180°C, 7 h (80% over two steps)

2.4.2.3 mCPBA oxidation

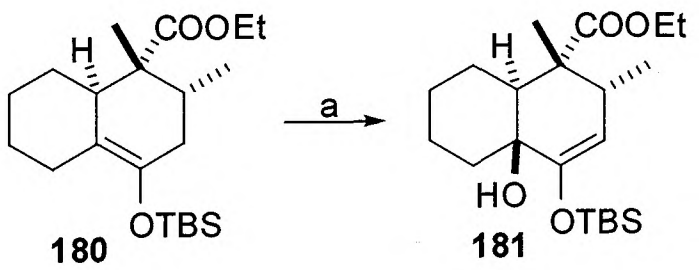
With substantial amount of the cyclised silyl enol ethers **176** and **180** in hand, the *m*-chloroperbenzoic acid (*m*CPBA) oxidation to form the α-hydroxy ketone **184** was investigated.[146] On treatment with *m*CPBA at -78˚C in dichloromethane the TMS enol ether **176** was converted to, after aqueous work-up, the expected hydroxy-ketone **184** as a 9:1 mixture of epimers, favouring the desired *tran*-decalin product **184**, which was confirmed by an n.O.e experiment. The enhancements of H_a and $(Me)_a$ were observed upon irradiation of the hydroxyl proton in deuterated benzene (Scheme 70).



Scheme 70

a) *m*CPBA, DCM, -78°C-rt (42%, (9:1 diastereomeric ratio))

When the TBS enol ether **180** was treated with *m*CPBA under the same conditions, surprisingly, the TBS enol ether **181** was obtained as the major product (Scheme 71). In this case, the TBS enol ether was retained by isomerisation rather than conversion to ketone as it was observed in the reaction with TMS enol ether **176**. This is because the more bulky TBS group makes the silyl enol ether more stable under acidic conditions compared to the TMS group.

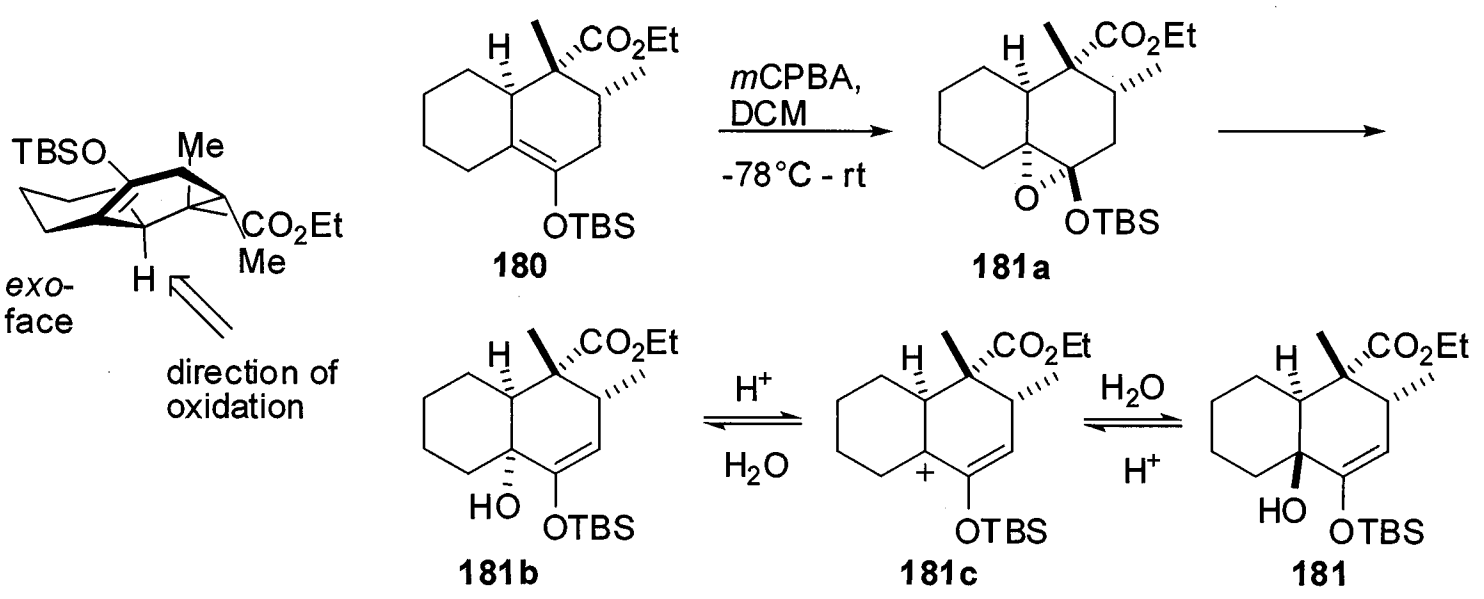


Scheme 71

a) *m*CPBA, DCM, -78°C to rt (52%)

Simple molecular modelling of the enol ether **180** predicted that epoxidation would occur on the

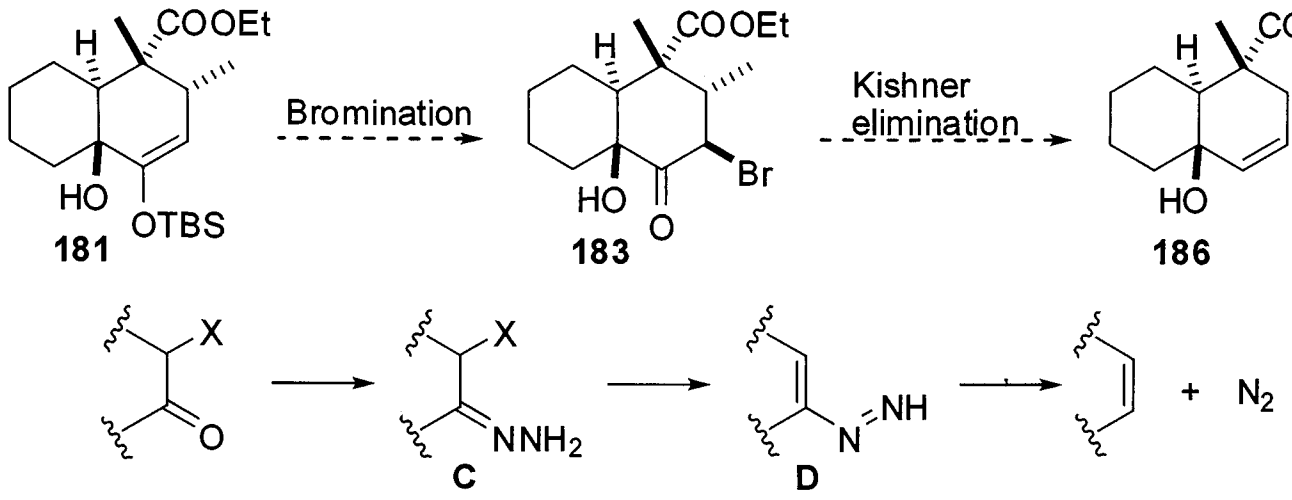
'*exo*'-face (the same side to hydrogen at the ring junction) of the molecule to produce a *cis*-decalin product **181a** (Scheme 72). It was thus postulated the initial formation of a *cis*-decalin structure **181b**, which is equilibrated into a more stable *trans*-decalin product **181** under non buffered acidic conditions *via* an intermediate tertiary allylic cation **181c**. Further evidence in favour of the intermediate carbocation **181c** and its possible equilibration was obtained in the attempted α,α'-functionalisation of silyl enol ether derivatives of simple cyclic ketones (**Chapter 2.6**).



Scheme 72

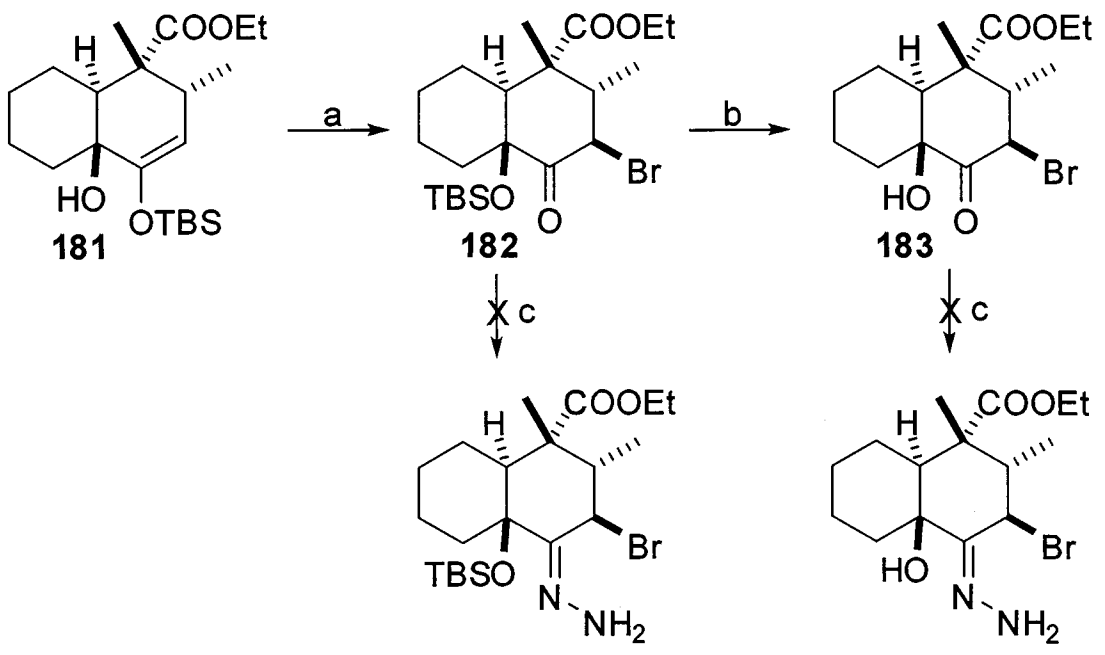
2.4.2.4 Synthesis of the key intermediate (186)

Based on the availability of the oxidation product **181** produced from the silyl enol ether **180**, a new synthetic plan was brought forward. It was proposed that the key intermediate **186** could be produced by bromination[147] of **181** followed by Kishner eliminative reduction,[148] which involves the formation of hydrazone **C**, internal elimination of the α-substituent, and collapse of alkenyldiimide **D** to olefin and nitrogen (Scheme 73).



Scheme 73

Treatment of the hydroxy-silyl enol ether **181** with *N*-bromosuccinimide (NBS) led to clean formation of the bromide **182** as a single diastereoisomer. Examples of 1,2- and 1,3-TBS migration usually under basic conditions are well known.[149] Numerous attempts to access the allylic alcohol **186** *via* Kishner elimination of the α-bromo ketone **182** and its deprotected version **183** met with failure. Both anhydrous hydrazine or hydrazine hydrate, without or with different amount of potassium acetate[148] and higher temperature were examined for this reaction, but only the starting materials **182** or **183** were recovered together with some decomposition products. The acid catalysed elimination with glacial acetic acid[150] also failed to provide access to **186** (Scheme 74).



Scheme 74

a) NBS, DCM, 0°C (95%); b) H_2SiF_6, MeCN, rt (80%); c) hydrazine anhydrous or hydrazine hydrate, KOAc or cat. AcOH, 1,2-dimethoxyethane, rt to reflux, no reaction

The stereochemistry of compound **183** was established by the n.O.e analysis and X-ray crystallography. The n.O.e spectrum showed a direct enhancement of H_a by H_b in deuterated benzene. The X-ray analysis of the single crystal of the alcohol **183** (Figure 12) indicated that the more substituted six-membered ring adopts an unusual boat conformation in a *trans*-fused decalin system. This allows the bulky halogen to adopt a pseudo-equatorial position contributing no doubt to the difficulty observed in attempted hydrazone formation reaction. The X-ray of **183** provided final confirmation of the *trans*-decalin structure of the mCPBA oxidation products, as required for the synthesis of tetrodecamycin (**1**).

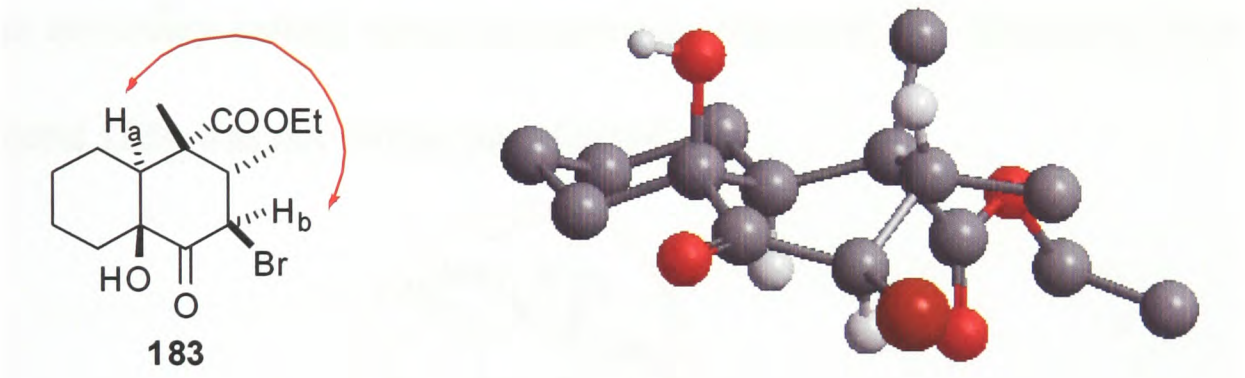
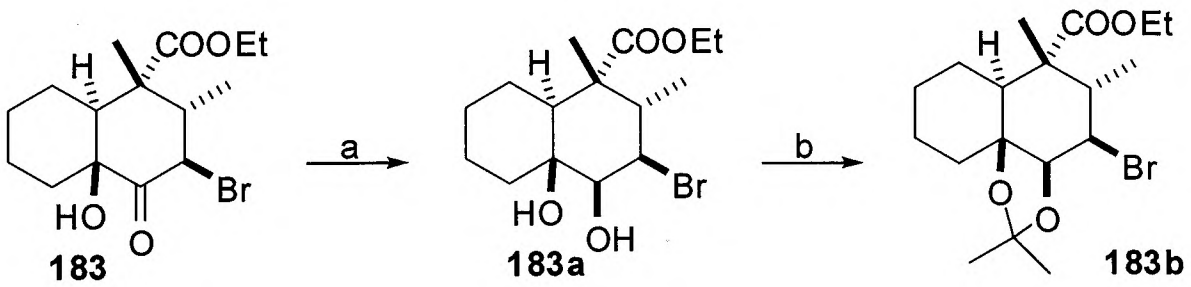


Figure 12

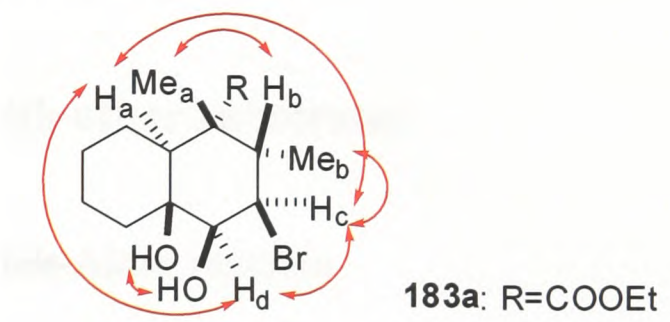
At this point, it was decided to reduce the ketone of the α,α'-hydroxy bromo ketone **183** to give the *syn*-diol **183a**. L-selectride came as the first choice, but only a complex mixture of products was obtained. When Lüche reduction[143] was applied to this reaction, the diol **183a** was obtained as a single diastereoisomer, which subsequently reacted with 2,2-dimethoxypropane[151] to form the acetal **183b** (Scheme 75).



Scheme 75

a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 30 min (73%); b) 2,2-dimethoxypropane, CSA (cat.), acetone, rt, 2 h (98%)

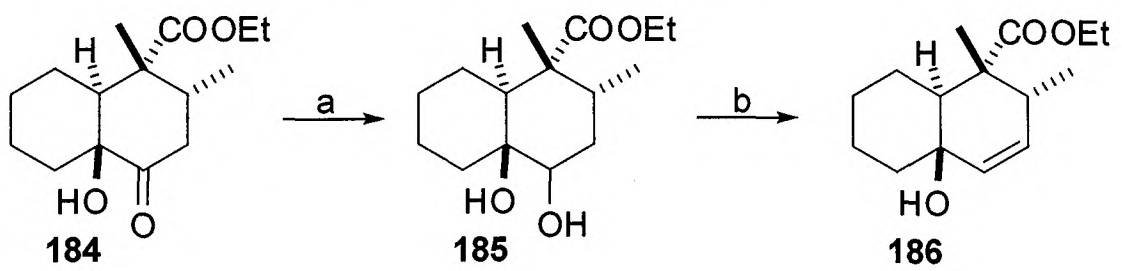
The relative stereochemistry of the diol **183a** and the acetal **183b** was confirmed by the NOESY analysis (Figure 13). It showed the direct enhancement of H_a by H_c and H_d, which was accompanied by enhancement of H_c by H_d. The enhancement of H_c by $(Me)_b$, H_b by $(Me)_a$, as well as the enhancement of one OH by another allowed to establishing that the two hydroxyl groups, the bromine, H_b and $(Me)_a$ were on the same side of the molecule (Figure 13). After protection of the two hydroxyl groups with 2,2-dimethoxypropane, the acetal **183b** was obtained. However, it was assumed that direct substitution of the bromine will be problematic due to its locked equatorial position. In a highly functionalised molecule, substitution reaction of a bromine at secondary carbon atoms is sometimes impossible.[152] Therefore, the converstion of the compound **183b** was not further investigated.



183a: R=COOEt

Figure 13

At this stage, it was decided to reinvestigate the original route from the hydroxy-ketone **184** to the desired intermediate **186**. Lüche reduction[143] of the ketone **184** produced the diol **185** as a single diastereoisomer. The stereochemistry of the secondary hydroxyl was not established, since in the next step it was converted into a selenide followed by an *in situ* oxidative elimination[144,153] to afford the key intermediate allylic alcohol **186** (Scheme 76).



Scheme 76

a) $NaBH_4$, $CeCl_3$, MeOH (79%); b) *o*-$NO_2C_6H_4SeCN$, Bu_3P, $CHCl_3$; then H_2O_2, py, -40°C to rt (59%)

2.4.3 Conclusion of section 2.4

In this part, the intramolecular Diels-Alder reactions of the TMS enol ether (*Z*)-**175**, TBS enol ethers (*Z*)-**179** and (*Z*)-**179a** were investigated to afford the bicyclic silyl enol ethers, **176** and **180** correspondingly. The TMS enol ether **176** was transformed to the key intermediate **186** in the proposed total synthesis of tetrodecamycin (**1**). The TBS enol ether **180** was converted into the protected diol **183b** in a high yield, which possessed the same relative stereochemistry to that of tetrodecamycin (**1**). The mechanism of the domino silyl enol ether reaction sequence was probed. Besides, the success in sequential oxidation and bromination of the bicyclic enol ether **180** prompted further investigation on the application of the sequence to simple monocyclic silyl enol ethers of cyclic ketones, which is illustrated in **Chapter 2.6**.

2.5 Cycloadditions with other substrates

2.5.1 Intramolecular Diels-Alder reaction

According to the original synthetic plan (Scheme 39), the tertiary hydroxyl group at the ring junction of the *trans*-decalin fragment of tetrodecamycin **186** would be derived directly from the Diels-Alder reaction. In order to follow the original synthetic plan, it was decided to change the ester group on the dienophile part of the triene to another functional group, which would modify the orbital coefficients at C_1 and C_2 to be more compatible to those at C_3 and C_4, so that good overlap of both orbitals C_1 - C_4, and C_2 - C_3 would be possible (Figure 14).

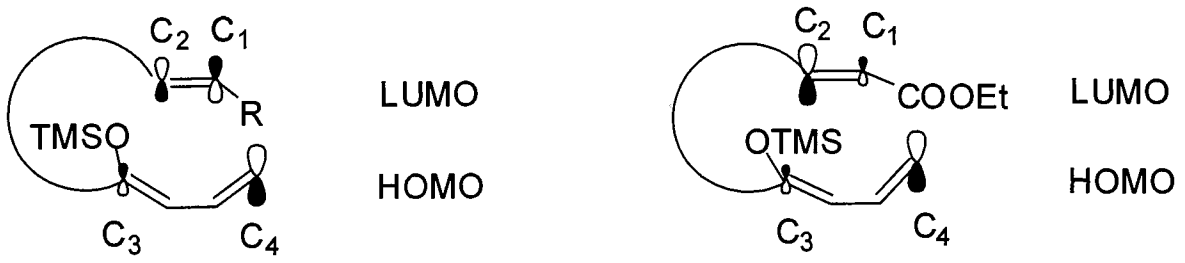
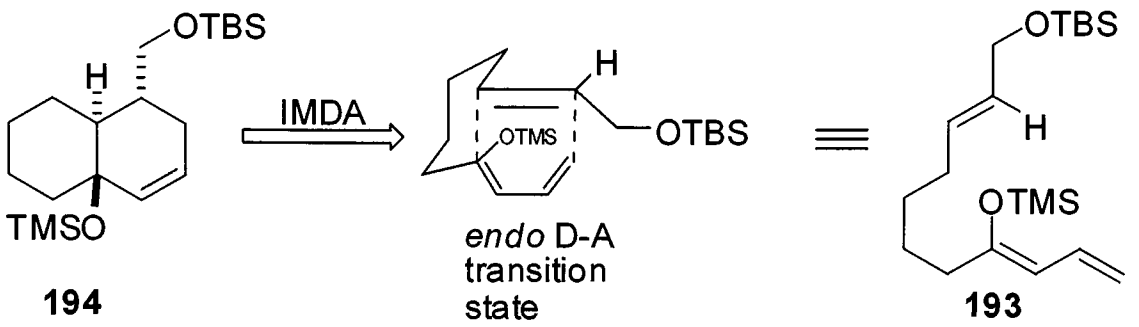


Figure 14

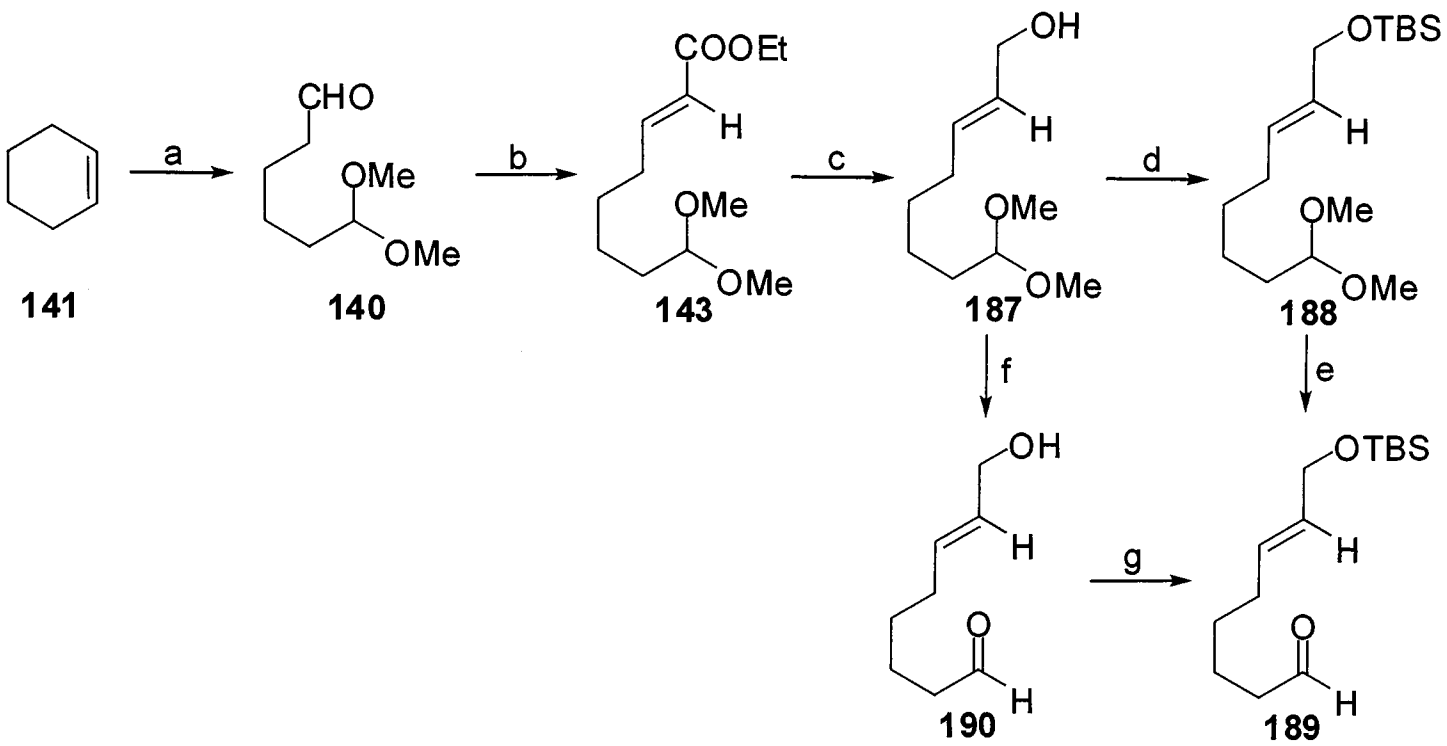
Attention was thus drawn to the CH_2OTBS (Scheme 77). Although the CH_2OTBS has little

effect on the lowering the energy of the LUMO orbital of the dienophile, the orbital coefficients at C_1 and C_2 are similar, preventing the unwanted polarisation of the LUMO observed in the silyl enol ether (Figure 14). The moderate cofficients could result in better overlapping of the molecular orbitals at C_1 with C_4 and C_2 with C_3.



Scheme 77

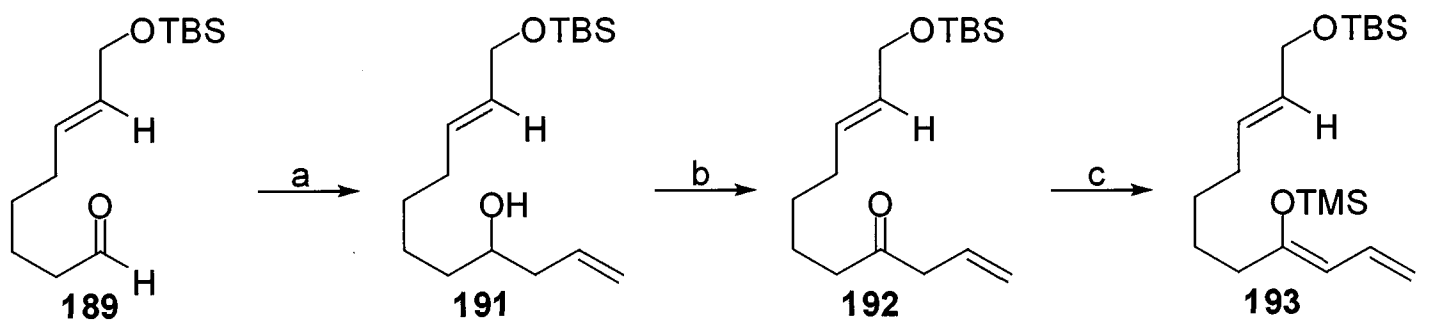
The synthesis of the triene **193** is outlined below. The ester **143** was produced by ozonolysis of cyclohexene and a Wittig reaction followed by reduction to an allylic alcohol **187** with DIBAL-H.[154] After protection with a TBS group,[155] the acetal **188** was hydrolysed to an aldehyde **189** with camphor-10-sulphonic acid in dichloromethane. Other methods attempted for hydrolysis included 1N HCl in diethyl ether and water, 5% HCl in diethyl ether and water as well as acetic acid, but the TBS group was also cleaved under these conditions. Finally, the use of CSA led to a selective hydrolysis of the acetal (Scheme 78). However, both the silylation and hydrolysis gave the desired products in low yields. Therefore, the sequence was changed to perform the hydrolysis first to give the aldehyde **190**, which without purification was submitted to the silylation with TBSCl and imidazole in *N*,*N*-dimethylformamide. This procedure provided the aldehyde **189** in a satisfactory yield (Scheme 78).



Scheme 78

a) O_3, DCM, MeOH, -78°C; *p*-TsOH; $NaHCO_3$; Me_2S; b) (carbethoxymethylene)triphenylphosphorane, DCM, reflux (82% from **141**); (c) DIBAL-H (2.2 eq), DCM, -78°C, 1 h (82%); (d) TBSCl, imidazole, DMF, 0°C to rt (59%); (e) CSA, DCM, 40°C, 24 h (54%); f) 5% HCl, H_2O, Et_2O, rt; g) TBSCl, imidazole, DMF, DMF, 0°C to rt (58% from **187**)

Aldehyde **189** was then treated with allyl magnesium chloride, followed by reaction with Dess-Martin periodinane, and subsequently LHMDS, HMPA and TMSCl to afford the desired *cis*-silyl enol ether **193** in good yield (Scheme 79).

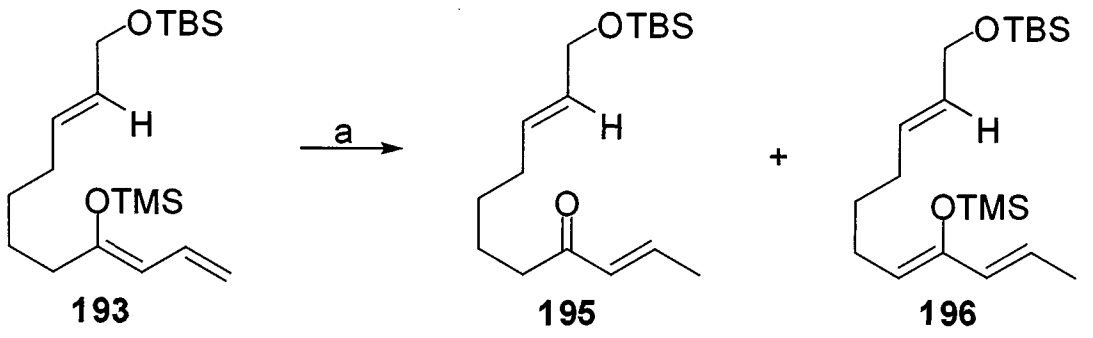


Scheme 79

a) allylmagnesium chloride, THF, -78°C (67%); (b) Dess-Martin periodinane, DCM, rt (85%); (c) LHMDS, HMPA, -78°C; TMSCl, -78°C (76%)

The *cis*-silyl enol ether **193** was first heated in toluene at 100°C for 1 day, but only starting material was detected in the crude ^1H NMR spectrum. Further increase in the reaction temperature (150-180°C) did not result in any improvement. However, upon heating at 200°C for 3 days, enone **195** and the rearranged *cis*-silyl enol ether **196** were formed. The formation of the *cis*-silyl enol ether **196** provided evidences to the possibility of the tautomerisation of silyl

enol ethers in the previously described domino process (**Chapter 2.2.7**). However, no cycloaddition product **194** was observed. The larger energy gap between the LUMO of the dienophile and the HOMO of the diene of the silyl enol ether **196**, compared to that in **159**, presumably played an important role in the difficulty of this cycloaddition (Scheme 80).



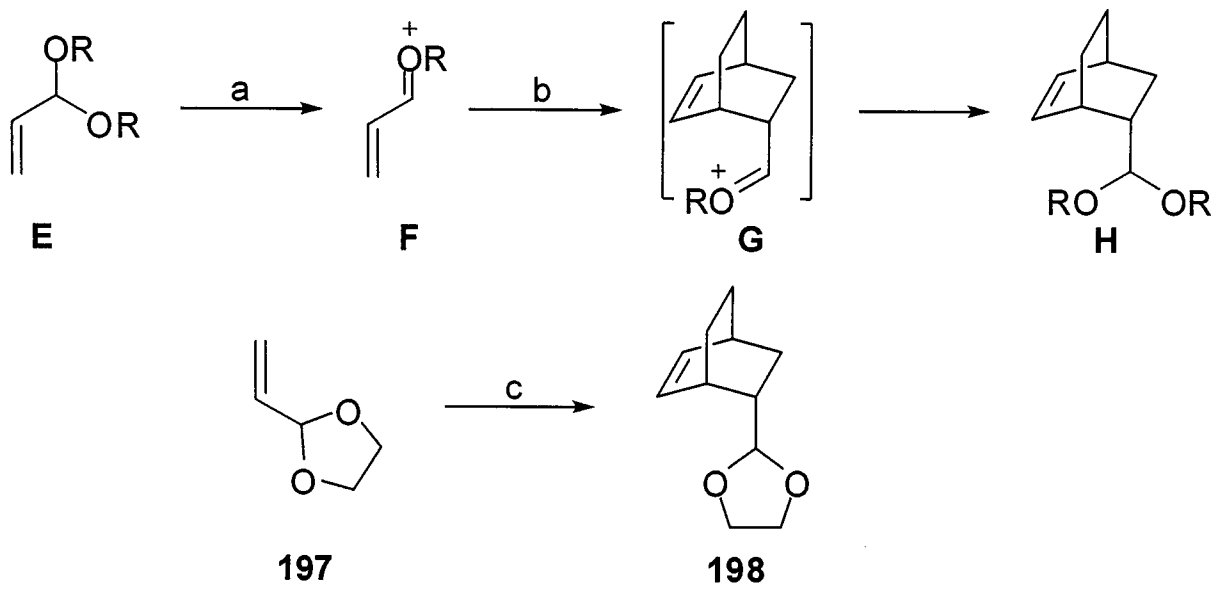
193 **195** **196**

Scheme 80

a) toluene, 200°C, sealed tube, 3 days (**195**: 41%, **196**: 20%)

2.5.2 Gassman conditions

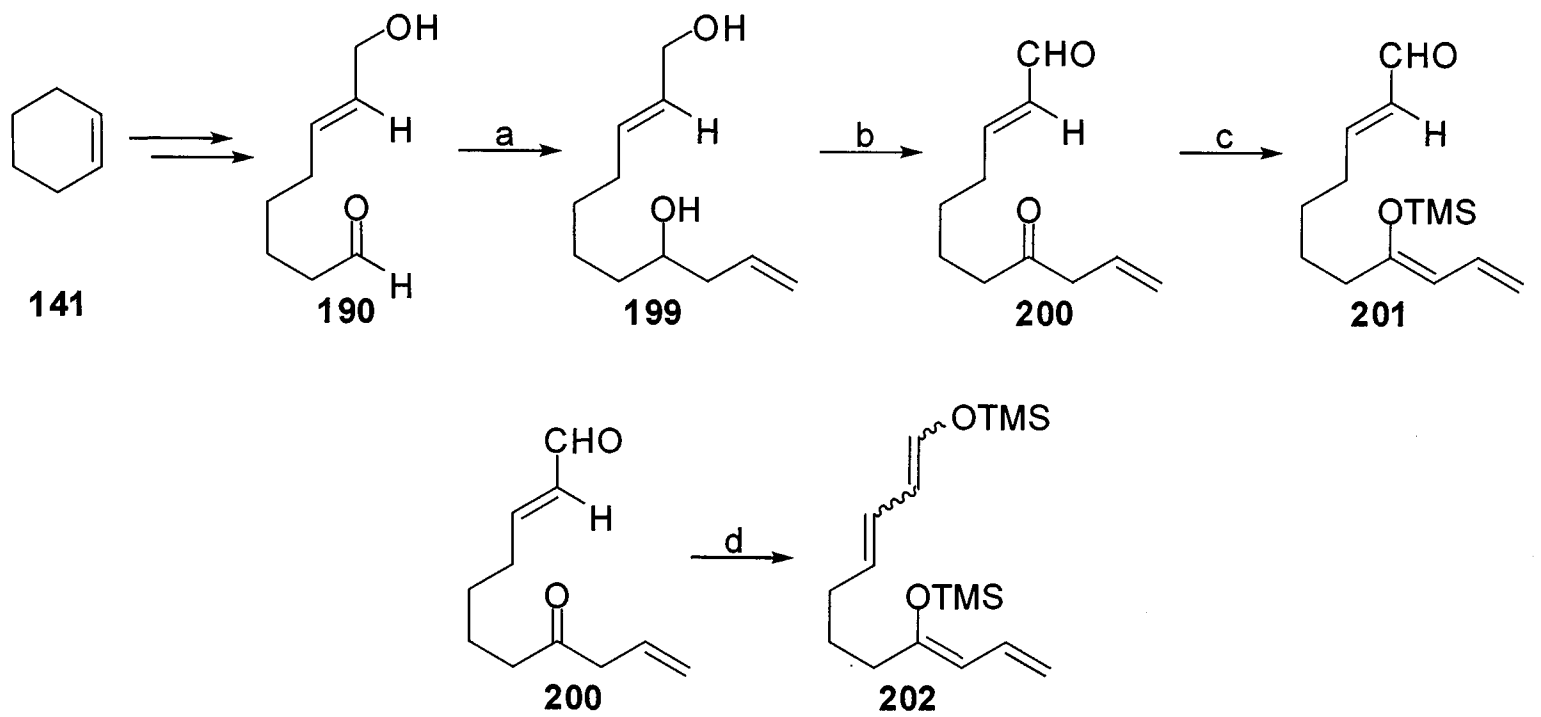
In 1986, Gassman developed a new method of activation of dienophiles in a Diels-Alder reaction, involving the use of acrolein acetals **E**, which, in the presence of Lewis or protic acids, formed oxonium ions **F** containing an allylic cation resonance structure. The cations **G** were highly reactive dienophiles and underwent cycloadditions with dienes at temperatures as low as –78°C to afford **H**. Cyclic acetals, such as **197**, afforded better yields than acyclic acetals. That could be explained by the ease of the diffusion of the alcohol away from the oxonium ion (Scheme 81).[44,46,156] It was envisaged that the application of this method would enhance the desired Diels-Alder reaction.



Scheme 81

a) TfOH (cat.), DCM -78°C to -20°C; b) cyclohexadiene; c) cyclohexadiene, TfOH (cat.), DCM, -78°C to -20°C (94%)

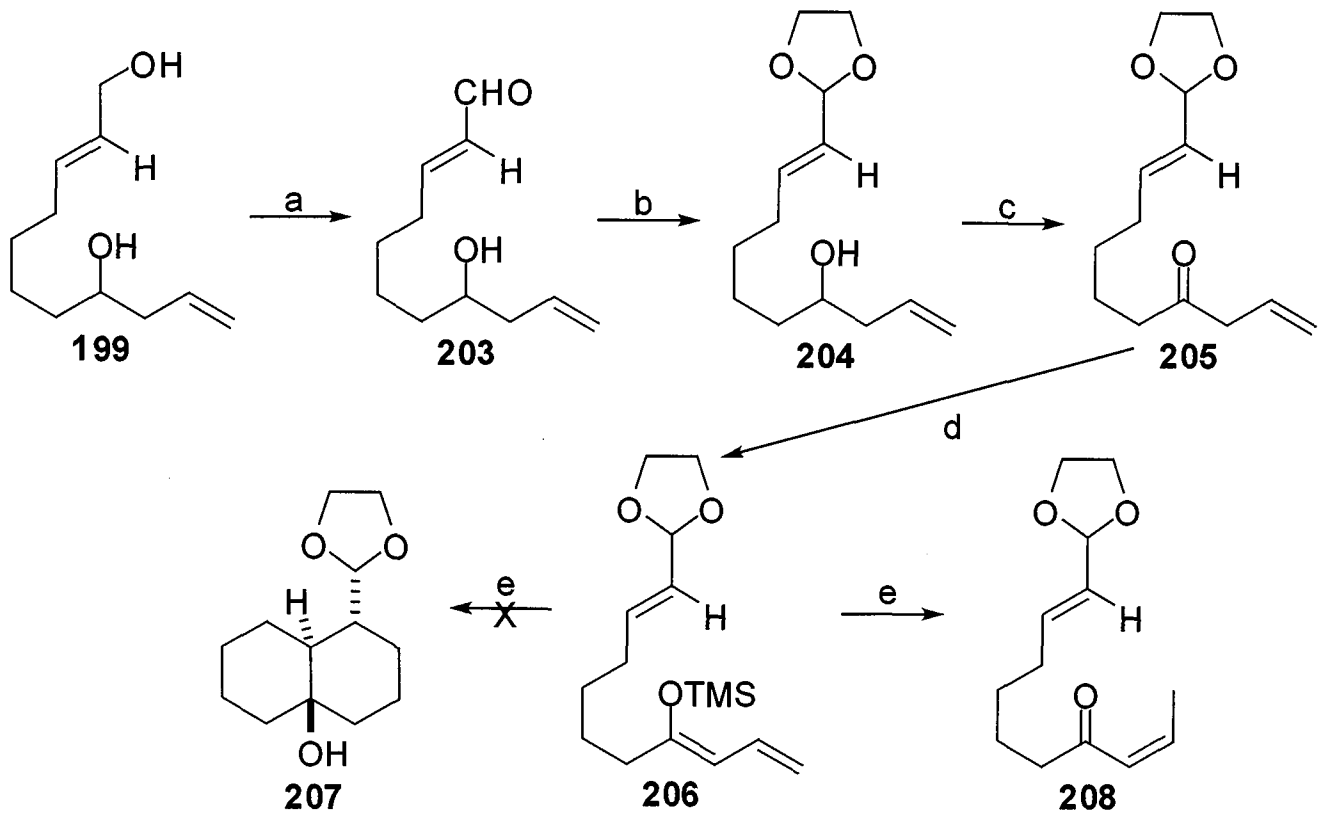
The next approach was focused on preparing the Gassman Diels-Alder reaction precursor **201**, which would be treated with 1,2-bis(trimethylsilyloxy) ethane, TMSOTf in dichloromethane at –78°C to form the cyclic acetal, which would undergo a cycloaddition *in situ*.[157] The synthesis of silyl enol ether **201** was outlined in the following synthetic scheme (Scheme 82). The aldehyde **190** was treated with the 2.3 eq. of Grignard reagent to produce the diol **199** in good yield, which after oxidation afforded the aldehyde **200**. The silyl enol ether **201** was obtained by treatment of the aldehyde **200** with LHMDS, HMPA and TMSCl at -78°C together with a significant amount of the starting materials **200**. However, attempts to perform an aqueous work up of the enolisation led to recovery of the standing ketone **200**. Besides, attempts to purify the silyl enol ether **201** without working-up by means of column chromatography led to recovery of the hydrolysed starting material **200** as well. Therefore, the reaction conditions were modified so as to obtain the crude silyl enol ether **201** with acceptable purity for the next step. First, the effect of base quantity was investigated. Not surprisingly, this led to ^{1}H NMR detection of the *bis*-enol ether **202**, as identified from the crude NMR spectra, suggesting that the α,β-unsaturated aldehyde underwent facile enolisation in presence of an excess of base. The stereochemistry of the *bis*-enol ether **202** was not established, since it decomposed during purification (Scheme 82).



Scheme 82

a) allylmagnesium chloride (2.3 eq), THF, -78°C (76% from **187**); b) Dess-Martin periodinane, DCM, r.t (48%); c) LHMDS (1.2 eq), HMPA, -78°C; TMSCl (1.2 eq), -78°C; d) LHMDS (2.0 eq), HMPA, -78°C; TMSCl (1.2 eq), -78°C

Since silyl enol ether **201** had proven to be too labile, focus was turned to acetal **206** (Scheme 83), which would be submitted to the Gassman conditions.[157] The synthesis of compound **206** commenced with the selective oxidation of the allylic hydroxyl group of the diol **199** to aldehyde **203** with MnO_2 in chloroform.[158] Aldehyde **203** under reflux in a Dean-Stark apparatus in benzene with ethylene glycol and *p*-toluenesulphonic acid (*p*-TsOH) produced the cyclic acetal **204**. After Dess-Martin oxidation and enolisation, the desired silyl enol ether **206** was afforded, which was proved to be sufficiently stable to be purified by flash column chromatography. However, after treatment with trimethylsilyltrifluoromethanesulphonate (TMSOTf) at -78°C, the only product was *cis*-enone **208** (Scheme 83). The configuration of **208** was confirmed by an NMR experiment.



Scheme 83

a) MnO_2, $CHCl_3$, rt (67%); (b) ethylene glycol, *p*-TsOH, benzene, reflux with an attached Dean-Stark trap (53%); (c) Dess-Martin periodinane, DCM, rt (63%); (d) LHMDS, HMPA, THF, -78°C; TMSCl (69%); e) TMSOTf (cat.), -78-0°C; $NaHCO_3$ (sat.), 0°C-rt (**208**: 19%);

2.5.3 Conclusion of Section 2.5

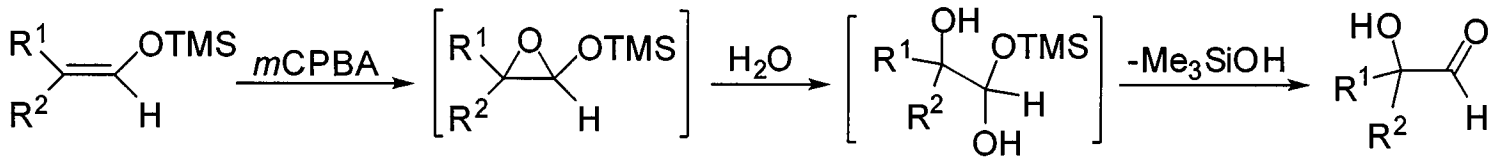
In conclusion, two silyl enol ethers **193** and **206** were synthesised, with which the thermal and Gassman Diels-Alder reactions were performed. However, no formation of desired Diels-Alder adducts were observed. For the thermal Diels-Alder reaction, the obstacle might lie in the bigger energy gap between the HOMO of the diene and the LUMO of the dienophile of the silyl enol ethers **193** and **196** compared with that of the corresponding silyl enol ethers **147** and **159**, due to no activating effect of the substituent on the dienophiles. While under Gassman conditions, the instability of the starting silyl enol ether **206** under the reaction condition led to hydrolysis rather than cycloaddition.

2.6 Double functionalisation of simple cyclic silyl enol ethers

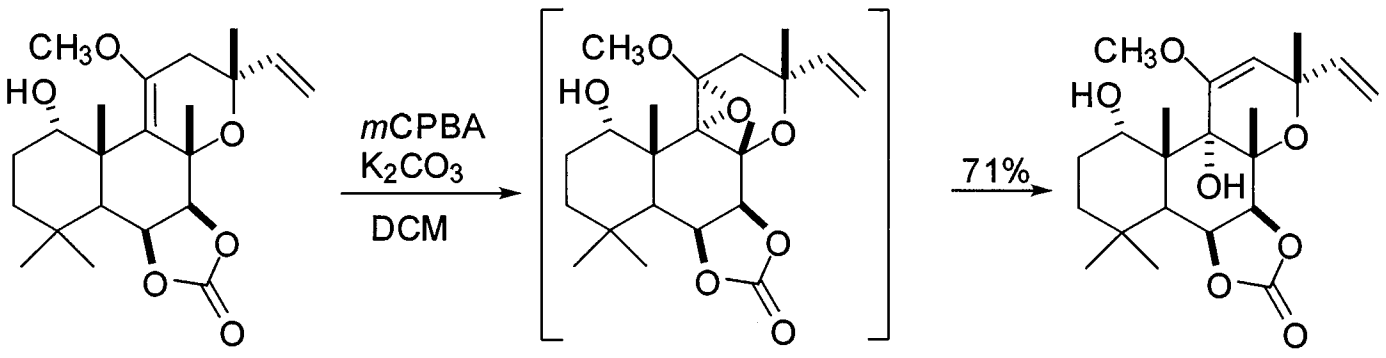
2.6.1 Introduction

In 1975, Hassner reported that the oxidation of silyl enol ethers with peracid as a reliable method

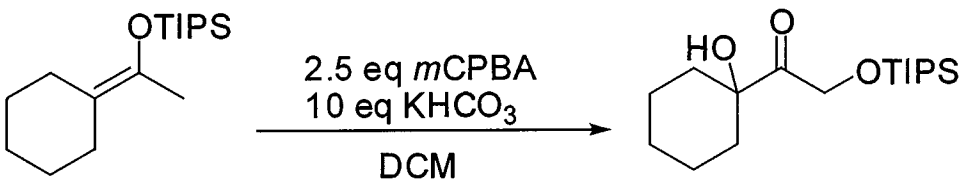
for the preparation of α-hydroxy ketones (Equation A, Scheme 84).[146] In 1987, Hrib observed that when a methyl enol ether was treated with *m*CPBA at -78°C, the reaction occurred to provide, in one pot, an hydroxy enol ether in good yield (Equation B, Scheme 84).[159] This was the first report on the *m*CPBA oxidation of enol ethers to give a hydroxy enol ether. Later in 1989, Kuwajima and coworkers observed that the α,α'-dihydroxylated ketones could be formed by treatment of silyl enol ethers possessing certain structural features with 2.5 eq *m*CPBA in presence of potassium bicarbonate (Equation C, Scheme 84). However, they also pointed out that only the more substituted regioisomer of the silyl enol ether of a methyl *sec*-alkyl ketone could give the desired α,α'-dihydroxylated ketones, other silyl enol ethers would give the normal products, namely α-siloxy and α-hydroxy ketones.[160]



Equation A



Equation B

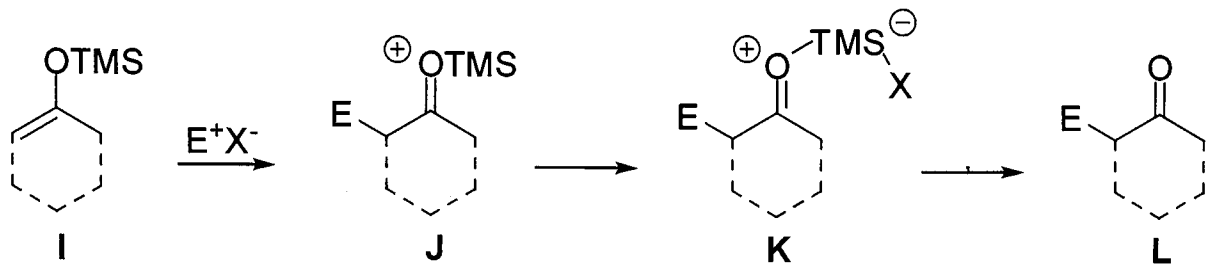


Equation C

Scheme 84

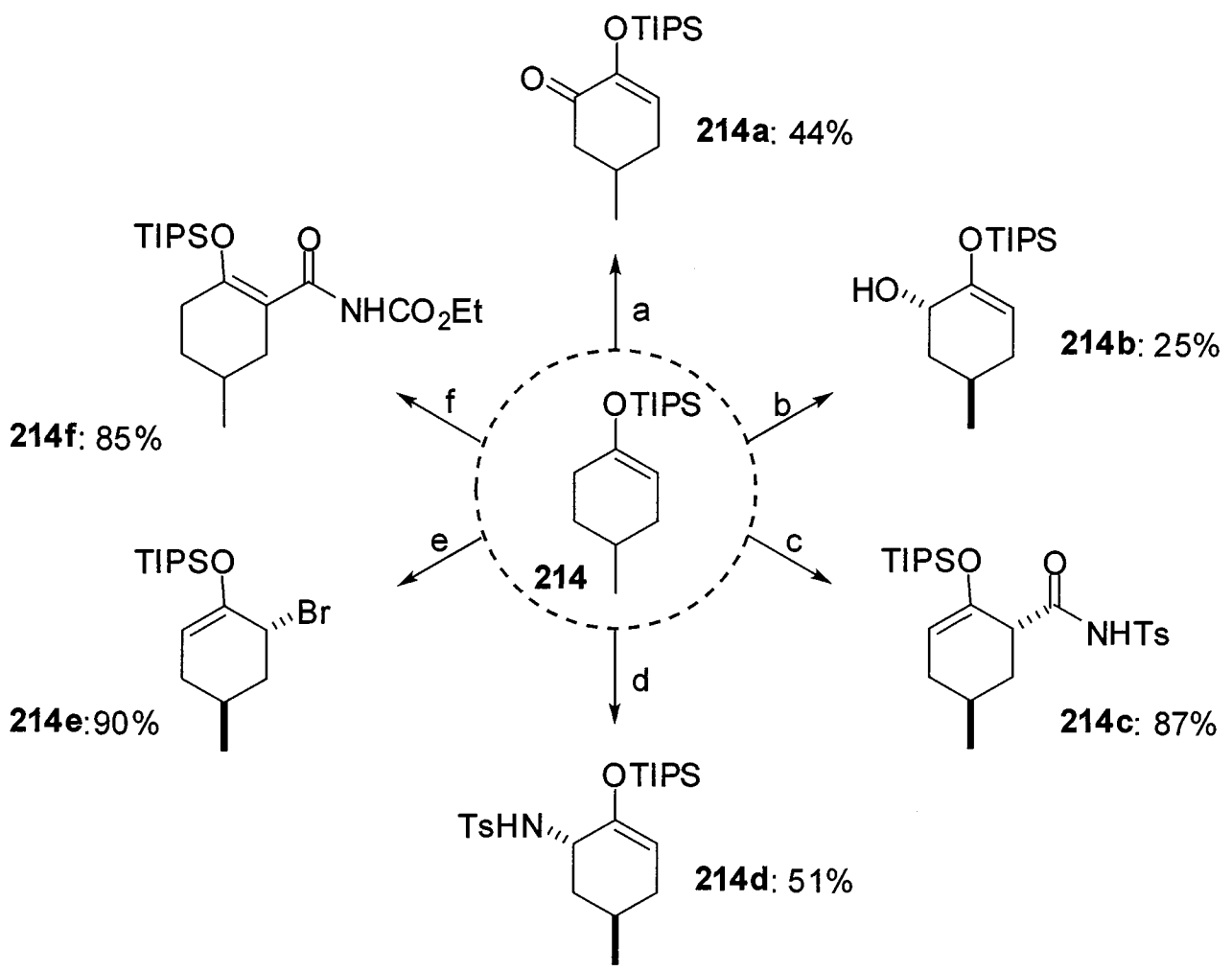
Normally, regiospecifically generated trimethylsilyl enol ethers **I** react with electrophiles to give the so-called kinetic products with concomitant loss of the trimethylsilyl group. The presumed oxonium intermediate **J** is attacked by the counterion to give an "ate" complex **K** (intermediate

or transition state) leading to desilylation to give **L** (Scheme 85).



Scheme 85

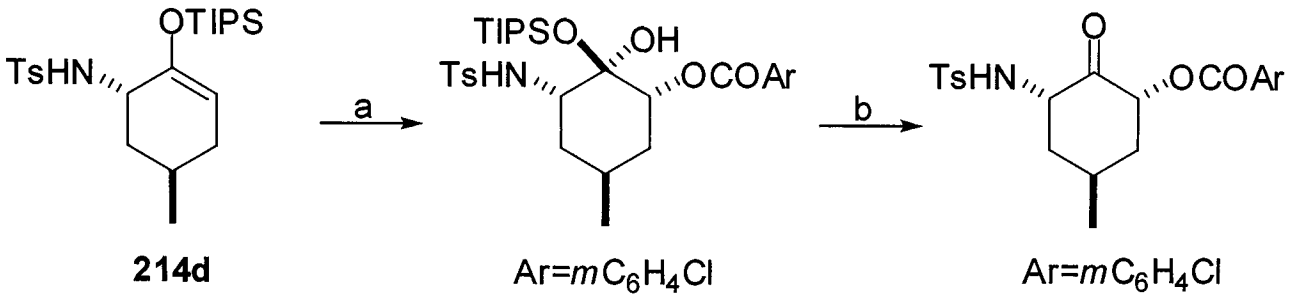
Magnus *et al.* conducted a series of investigations on diverting the oxonium ion intermediate **J** by a proton loss rather than the usual nucleophilic attack on the silicon atom. The TIPS-enol ether **214** was treated with a range of electrophiles to give the products shown in Scheme 86.[161]



Scheme 86

a) SeO_2, DMF, rt; b) SeO_2 (cat.), H_2O_2; c) TsNCO, rt; d) TsNSeNTs, rt; e) NBS, rt; f) $OCNCO_2Et$, 40°C

When the aminated adduct **214d** was treated with *m*CPBA and $NaHCO_3$ at room temperature, a hemiacetal was isolated as a moderately stable compound. Aqueous sodium bicarbonate solution converted the hemiacetal into α-OCOAr-α'-NHTs ketone (Scheme 87).[162-164]

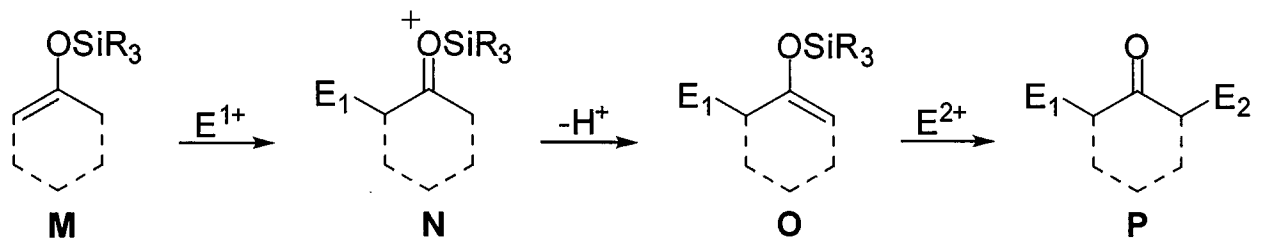


214d Ar=*m*C_6H_4Cl Ar=*m*C_6H_4Cl

Scheme 87

a) *m*CPBA, $NaHCO_3$, rt (75%); b) aq. $NaHCO_3$, rt (93%)

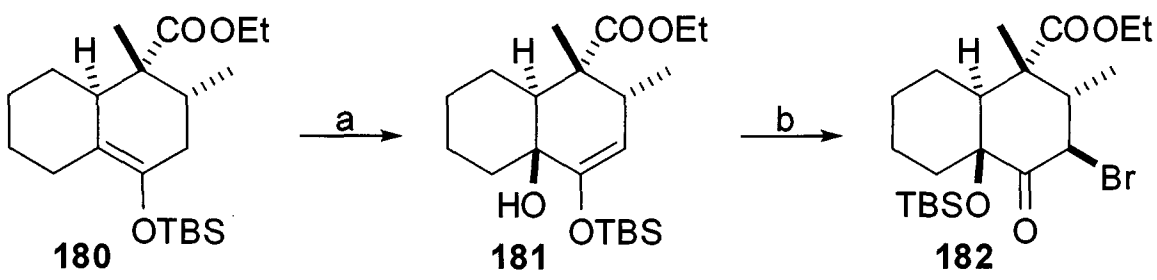
It was noticed that the reactions of silylated enol ethers possessing bulky alkyl substituents on silicon with electrophiles proceeded *via* an enolisation mechanism as shown in Scheme 88.[161-167] For example, the oxonium species **N** generated on electrophilic addition to the silyl enol ether **M** is stabilised not *via* loss of the bulky trialkylsilyl group, but *via* deprotonation of the adjacent α'-position resulting in an ene-type product, silyl enol ether **O**. The proton loss from **N** should be stereospecific (axial) resulting in a new regiospecifically generated silyl enol ether **O**. An extended process, which would involve a direct transformation of the silyl enol ether **O** to product **P** would be of even more interest, as it will lead to an increase in structural complexity of the substrate (Scheme 88).



M **N** **O** **P**

Scheme 88

In the studies on the total synthesis of tetrodecamycin (**1**), the sequential oxidation and bromination of the bicyclic enol ether **180** was performed successfully to afford a α,α'-hydroxy bromo ketone **182** accompanied by a TBS migration (Scheme 89).



180 **181** **182**

Scheme 89

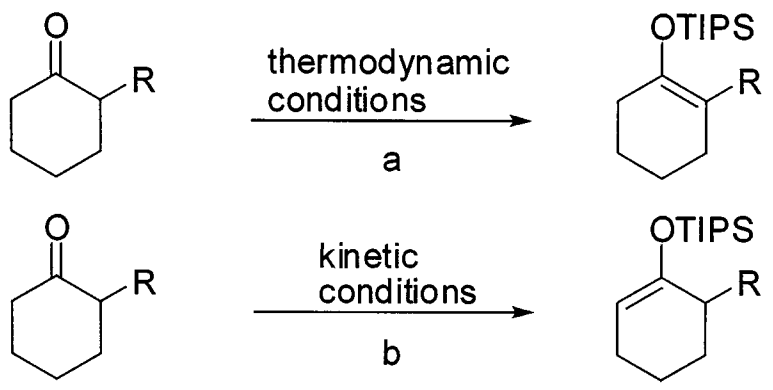
a) *m*CPBA, DCM, -78°C to rt (52%); b) NBS, DCM, 0°C (95%)

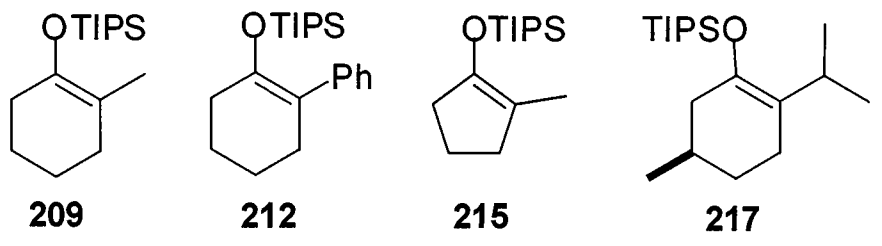
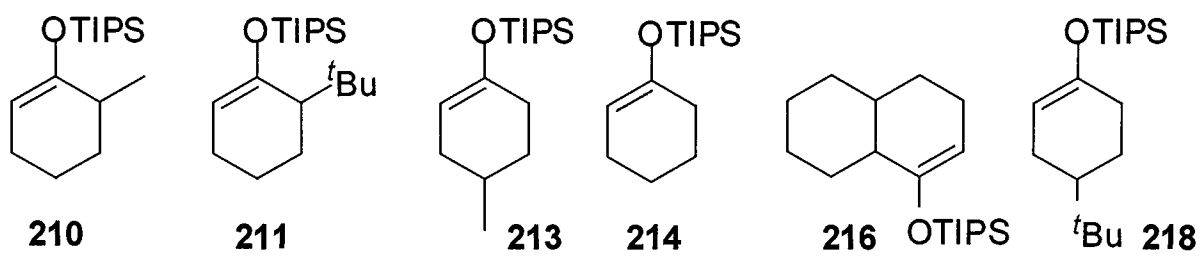
This result encouraged to investigate the application of the same reaction sequence to simple monocyclic silyl enol ethers. Besides, it was also of interest to develop a one-pot procedure leading to α,α'-disubstituted ketones.

2.6.2 Reactions and proposed mechanism

2.6.2.1 Methods and proposed mechanism

The triisopropylsilyl (TIPS) group instead of the *tert*-butyldimethylsilyl (TBS) group was chosen to be used in the cyclic silyl enol ethers system, because of the greater bulk of the TIPS group, which makes it more stable than the TBS group. The TIPS enol ethers were prepared either under kinetic or under thermodynamic conditions (Scheme 90).[162]

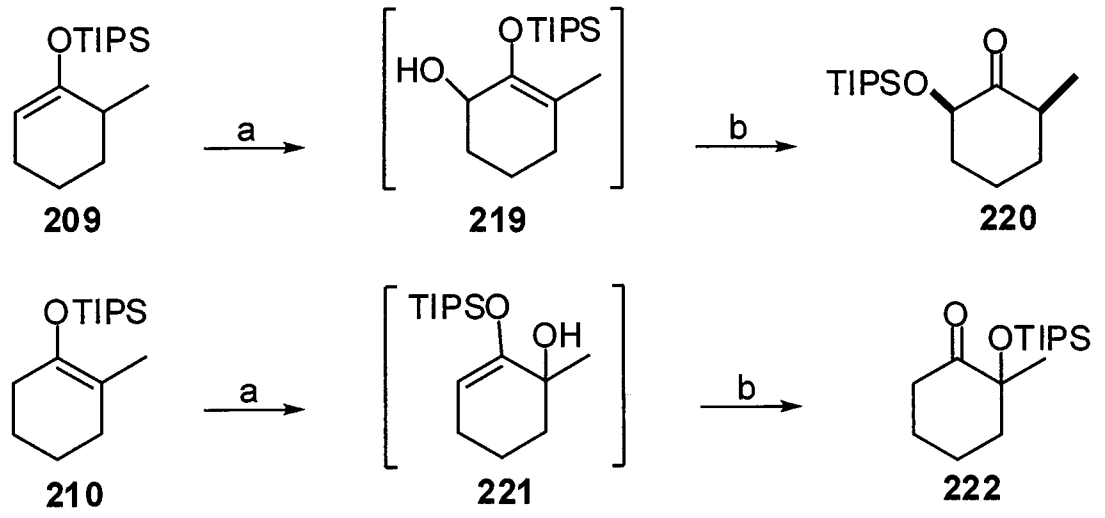


TiPS enol ethers produced under thermodynamic conditions	 **209** **212** **215** **217**
TIPS enol ethers produced under kinetic conditions	 **210** **211** **213** **214** **216** **218**

Scheme 90

a) Thermodynamic conditions: Et_3N, DCM, 0°C; then TIPSOTf; b) Kinetic conditions: KHMDS, THF, -78°C; then TIPSOTf

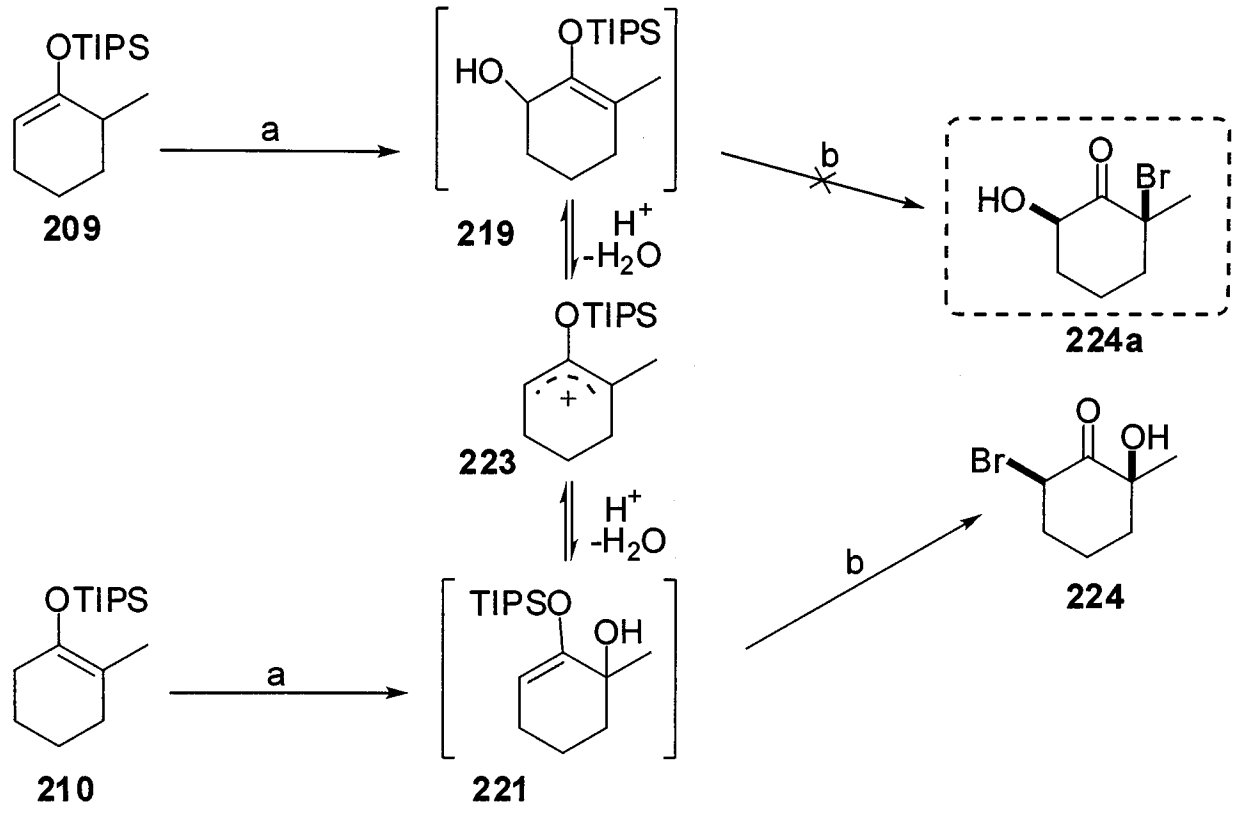
When the 2-methyl cyclohexanone derivatives **209** and **210** were treated with *m*CPBA in DCM at -78°C, presumably two new silyl enol ethers **219** and **221** were formed. Unfortunately, both of the hydroxy enolates **219** and **221** were not stable enough to be isolated, although their formation could be monitored by means of GCMS and NMR spectroscopy. Aqueous work-up of the reactions only resulted in the isolation of silyloxy-ketones **220** and **222** (Scheme 91).



Scheme 91

a) *m*CPBA, DCM, -78°C; b) $NaHCO_3$ (sat.) (**216**: 49%, **218**: 57%)

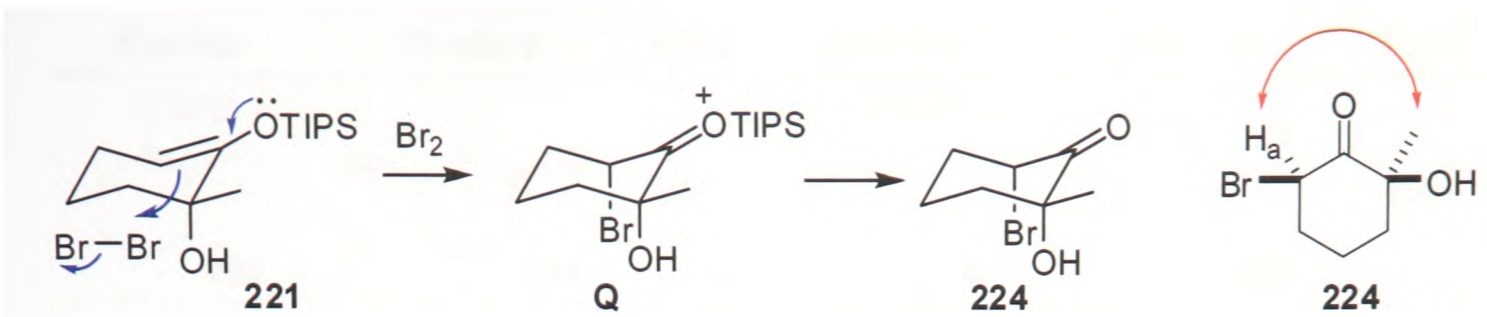
Therefore, on completion of the oxidation, both of the reaction intermediates were trapped with bromine[168] at -78°C followed by slow warming up to room temperature. Only one major product, the bromide **224**, was isolated in both cases (Scheme 92). The formation of the same product from two isomeric silyl enol ethers could be explained by the equilibration of the two enol ethers, **209** and **210**, *via* a carbocation species **223**. The higher reactivity of the trisubstituted enol ether **221** led to dominant formation of the bromination product **224** (Scheme 92).



Scheme 92

a) *m*CPBA, DCM, -78°C; then $NaHCO_3$ (sat.); b) Br_2, -78°C-rt (80% from **209**, 64% from **210**)

The products of the α,α'-derivatisation were obtained as single stereoisomers and the relative stereochemistry was established *via* n.O.e analysis of **224**, which showed enhancement of H_a when the methyl was irradiated. A model accounting for the observed stereochemical outcome of the reactions is presented in Scheme 93. The hydroxyl in the intermediate **221** adopted an axial position due to the stabilising anomeric interaction between the σ^* (C-OH) and the π system.[161-164] Subsequent approach of the bromine from an axial trajectory resulted in a relative *syn* orientation of the newly introduced bromine and hydroxyl substituents.



Scheme 93

2.6.2.2 Synthesis of analogues

Following the successful reaction sequence of oxidation and bromination of the TIPS enol ethers **209** and **210**, a number of similar TIPS enol ethers were converted into the α-hydroxy-α'-bromo derivatives (Table 5). The silyl enol ether derivatives of 2-substituted cyclohexanones **209**, **210**, **211** and **212** and cyclohexanone **214** afforded the desired α-hydroxy-α'-bromo ketones in good yields. The silyl enol ether derivative of the 4-methyl cyclohexanone **213** provided the α-hydroxy-α'-bromo ketone **227** in satisfactory yield. However, when submitted to the same conditions, TIPS enol ethers **215**, **216**, **217** and **218** did not give clean reactions. This was attributed to slower reactions of the hindered double bonds with *m*CPBA at -78˚C. Due to the time constraints of this project no further optimisation of the reaction conditions for these substrates was carried out.

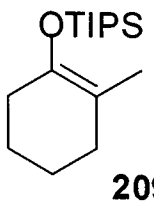
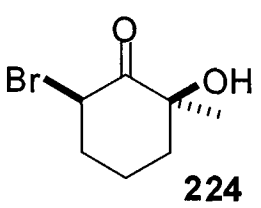
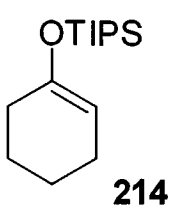
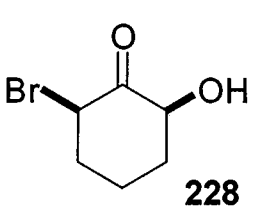
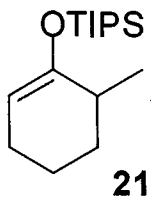
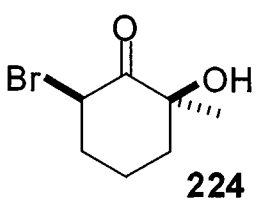
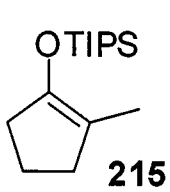
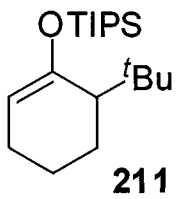
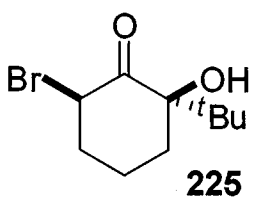
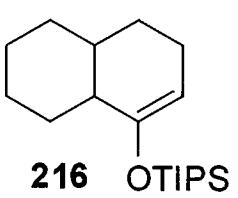
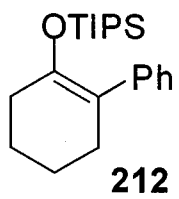
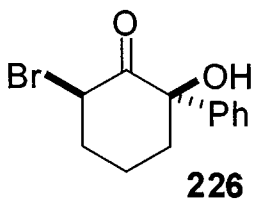
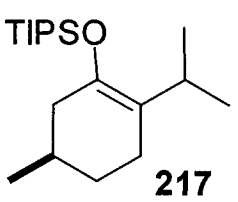
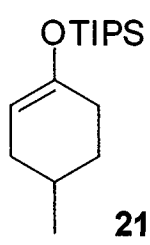
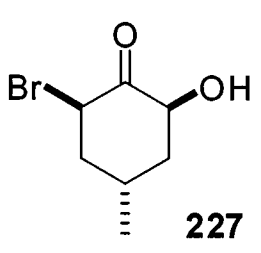
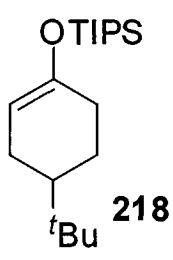
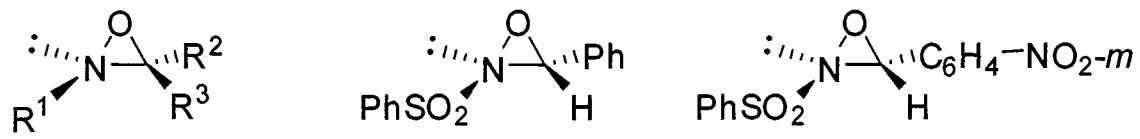
Enolate	*Product*	*Yield*	*Enolate*	*Product*	*Yield*
 **209**	 **224**	64%	 **214**	 **228**	45%
 **210**	 **224**	80%	 **215**	Complex compounds	----
 **211**	 **225**	68%	 **216**	Complex compounds	----
 **212**	 **226**	56%	 **217**	Complex compounds	----
 **213**	 **227**	68%	 **218**	Complex compounds	----

Table 5

2.6.2.3 Reactions with oxaziridine

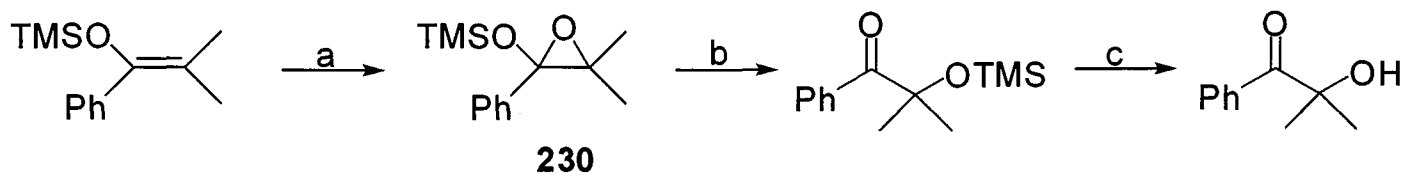
Oxaziridines (Figure 15) are heterocyclic compounds containing oxygen, nitrogen and carbon atoms in a three-membered ring. They were first reported in the mid-fifties by Krimm, Emmons, Horner and Jurgens. Their unusual reactivity was undoubtedly related to the presence of the strained three-membered ring and a relatively weak N-O bond. The active oxygen of the three-membered ring makes ozaziridines excellent reagents for the oxygen-transfer reactions.[169] *N*-H, *N*-alkyl and *N*-acyl oxaziridines can oxidise I^- to I_2 and phosphines to phosphine oxides, but they are poor reagents for epoxidation of alkenes or for oxidation of suphides to sulphoxides. *N*-Sulfonyloxaziridines, such as **229** and **229a**, are the only oxaziridines able to oxidise nucleophilic substrates in a similar way to peracids. Since *N*-sulfonyloxaziridines are neutral, aprotic oxidising reagents, they are among the few reagents available for the direct oxidation of carbanions and enolates.[169]



229 **229a**

Figure 15

In 1987 Davis and coworker reported that the oxidation of silyl enol ethers using 2-sulfonyloxaziridine **229a** followed by hydrolysis could afford the α-hydroxy ketones. The neutral and aprotic nature of the *N*-sulfonyloxaziridine **229a** allowed the isolation of α-siloxy epoxide **230** (Scheme 94). This result prompted the investigation on the oxidation and bromination sequence with *N*-sulfonyloxaziridine **229** instead of *m*CPBA.[170]

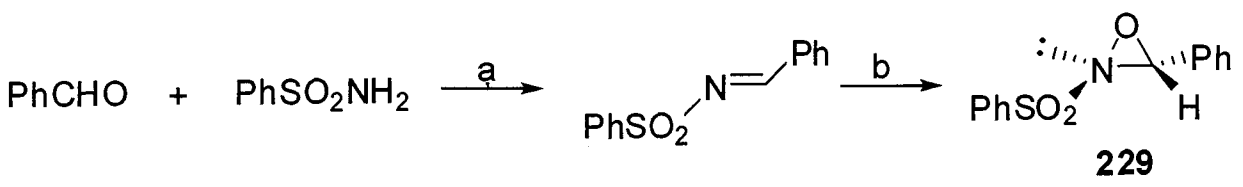


230

Scheme 94

a) **229a**, $CHCl_3$, rt; b) p-TsOH (cat.) (>90%); c) Bu_4NF, THF, rt (79%)

The *N*-sulfonyloxaziridine **229** was prepared following Davis' protocol.[171] The solution of freshly distilled benzaldehyde and benzenesulfonamide in anhydrous toluene was treated with Amberlyst 15 ion exchange resin under reflux for 15 h to give the *N*-benzylidenebenzene--sulfonamide, which was further converted to the desired **229** by oxidation with *m*CPBA in presence of $NaHCO_3$ and benzyltriethylammonium chloride in high yield (Scheme 95).



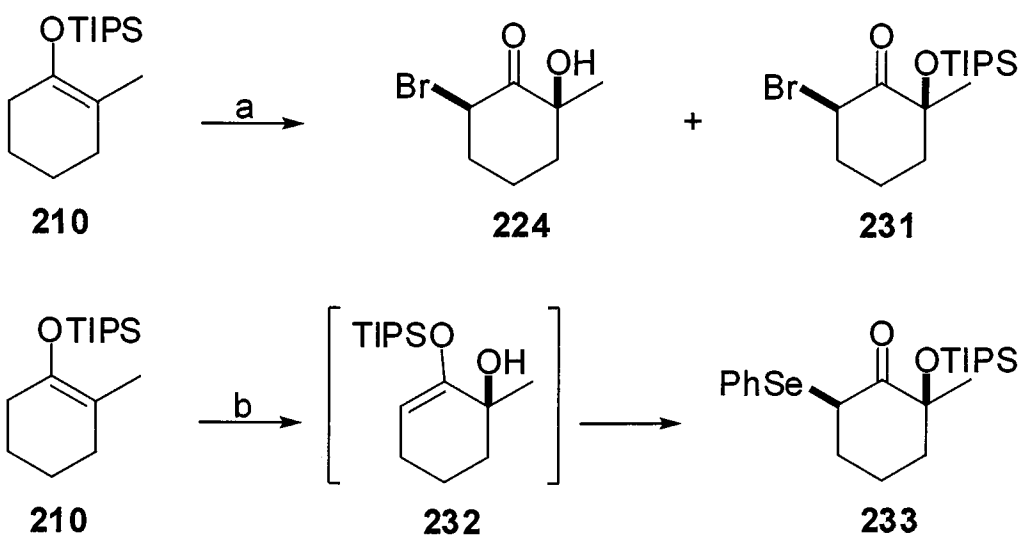
229

Scheme 95

a) 5 Å molecular sieves, Amberlyst 15, toluene, reflux, 15 h (87%); b) *m*CPBA, benzyltriethylammonium chloride (BTEAC), $NaHCO_3$, $CHCl_3$, 0°C (88%)

With the oxaziridine **229** in hand, oxidation was performed with silyl enol ether **210** followed by bromination (Scheme 96). After column chromatography, the α-hydroxy-α'-bromo ketone **224**

was isolated in 34% yield together with 25% of the TIPS protected compound **231** (Scheme 96). It was also attempted to trap the reaction intermediate of the silyl enol ether **210** and *N*-sulfonyloxaziridine **229** with phenylselenyl bromide. The TIPS protected α-hydroxy-α'-seleno ketone **233** was afforded in 38% yield.



Scheme 96

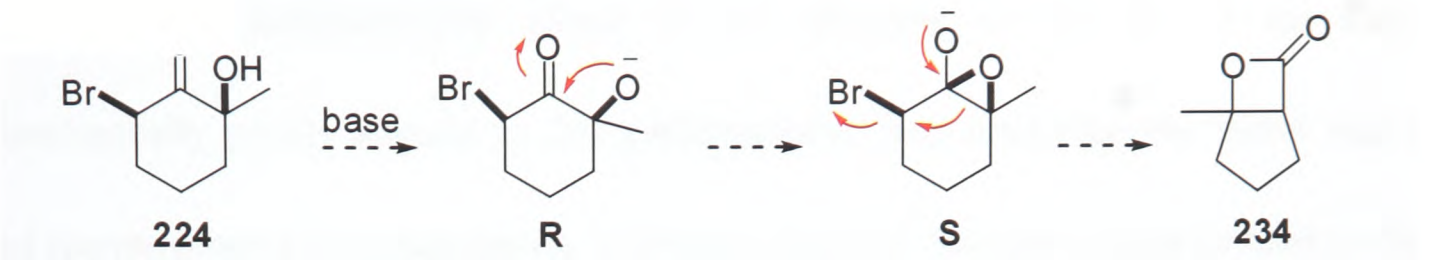
a) **229**, DCM, rt; then Br_2, -78°C (**224**: 34%, **231**: 25%); b) **229**, DCM, rt; then PhSeBr, -78°C (38%)

Attempts were made to optimise the reaction conditions in order to improve the yields, but no significant improvement was achieved. The best yield of the oxidation and bromination sequence with oxaziridine **229** was achieved when the reaction was performed in chloroform (45% of **224** and 22% of **231**). This indicated that the intermediate hydroxy-ketone rearrangement (like in Scheme 92) requires protic catalysis (present in low concentration in chloroform), which is more efficient in case of the *m*CPBA. In the oxaziridine reaction, it is presumably the bromine that carries a small amount of HBr which can catalyse the reaction to certain extent. Due to the unsatisfactory yields, oxidation with oxaziridines was not further investigated.

2.6.2.4 Further investigation

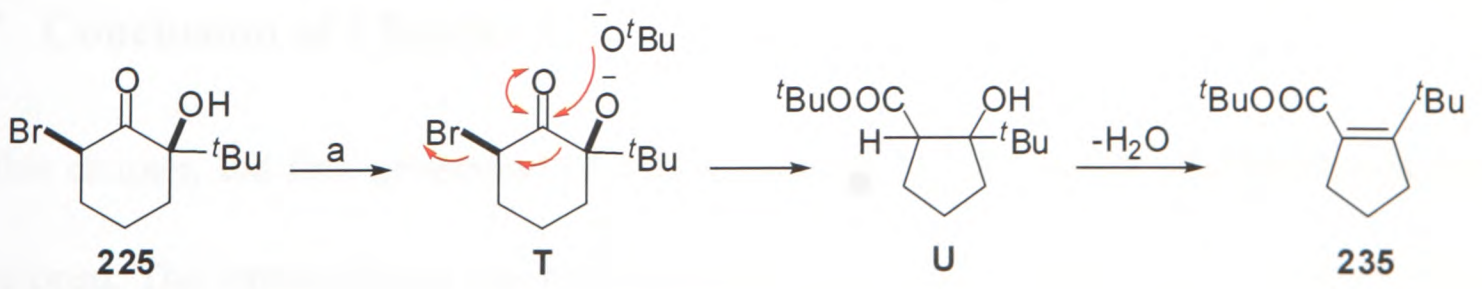
With the α-hydroxy-α'-bromo ketone **224** in hand, it was of great interest to induce a Favorskii-type rearrangement (Scheme 97). The α-hydroxy-α'-bromo ketone **224** would be treated with

strong base to deprotonate the hydroxyl group. The naked oxygen anion of **R** then might initiate a nucleophilic attack on the carbonyl to form an epoxide **S** leading to a carbon-carbon migration with elimination of the bromine to give the interesting β-lactone **234**.



Scheme 97

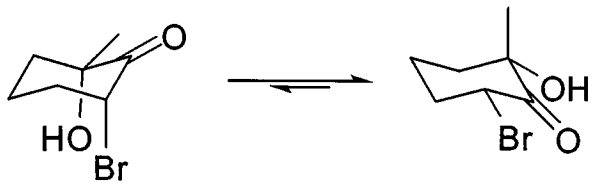
With this idea in mind, freshly purified dry potassium *tert*-butoxide was chosen as a base to react with the α-hydroxy-α'-bromo ketone **224**. The GCT analysis of the crude reaction mixture indicated presence of a product with correct molecular mass, but none of the desired lactone was isolated after the work-up. It was presumed that the β-lactone **234** would be volatile and thus hard to isolate. Thus α-hydroxy-α'-bromo ketone **225** was chosen as a substrate in the hope that the tertiary butyl substituent would reduce the volatility of the product. Quite unexpectedly, the product of the reaction was not a β-lactone, but a cyclopentene **235** (Scheme 98). The mechanistic explanation of **235** formation involves addition of the *tert*-butoxide to the carbonyl group, followed by a carbon-carbon bond migration with bromide displacement to produce **U**. Finally, elimination of water leads to the α,β-unsaturated double bond in **235**. The reaction was repeated with various quantity of sodium hydride or sodium methoxide as bases, but unfortunately no desired product was formed.



Scheme 98

a) KO^{t}Bu, THF, rt (47%)

The failure to perform the Favorskii-type reaction on the cyclic α-hydroxy-α'-bromo ketone **225** was attributed to their conformation. It is presumed that the cyclohexane ring adopts a more stable conformation in which the bulky bromine and hydroxyl adopt equatorial positions (Scheme 99). The intramolecular attack of the alkoxide on the π* of the ketone is stereoelectionically poorly aligned in this conformation, thus hindering the initial step of the proposed rearrangement from happening. Likewise, the axial bromine would be hard to displace even if the intermediate **S**, as shown in Scheme 97, could be formed.



Scheme 99

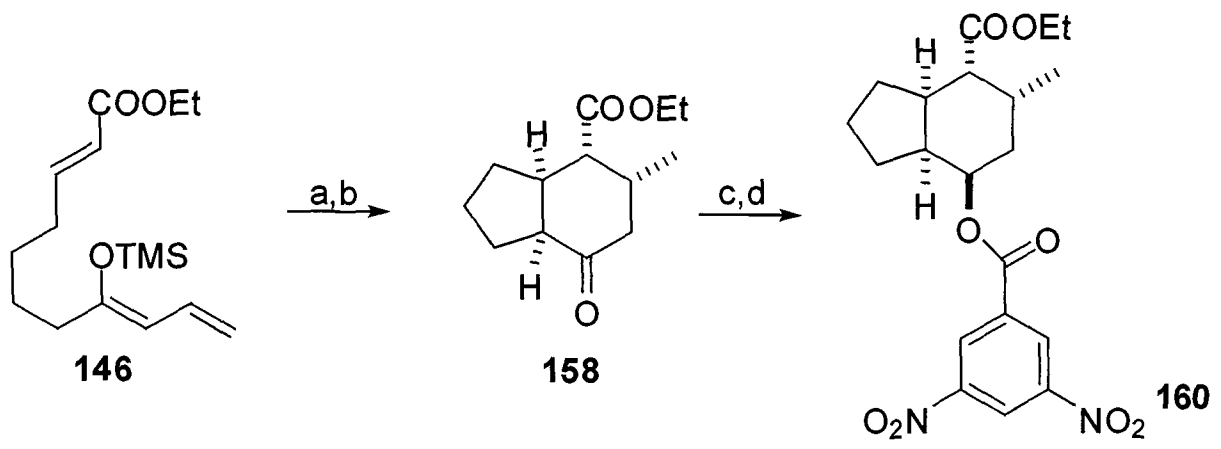
2.6.3 Conclusion of section 2.6

In this chapter, a new procedure for a one-pot α-hydroxylation α'-bromination of silyl enol ethers of cyclic ketones with *m*-chloroperbenzoic acid and bromine was investigated. This provided a new method of double functionalisation of simple cyclic silyl enol ethers. The oxidation with *N*-sulfonyloxaziridine was also investigated, yet the yield was found to be lower in this case. This indicated that acidic conditions were necessary for the new procedure. This sequence of consecutive silyl enol ether reactions provided a second example of a domino-type process, which had not previously been described in the chemical literature.

2.7 Conclusion of Chapter 2

In this chapter, the first generation of a new synthetic route towards tetrodecamycin (**1**) was developed. The retrosynthesis was based on an intramolecular Diels-Alder reaction (IMDA) of *cis*-silyl enol ether **147**. Delightfully, a new domino silyl enol ether process was discovered to

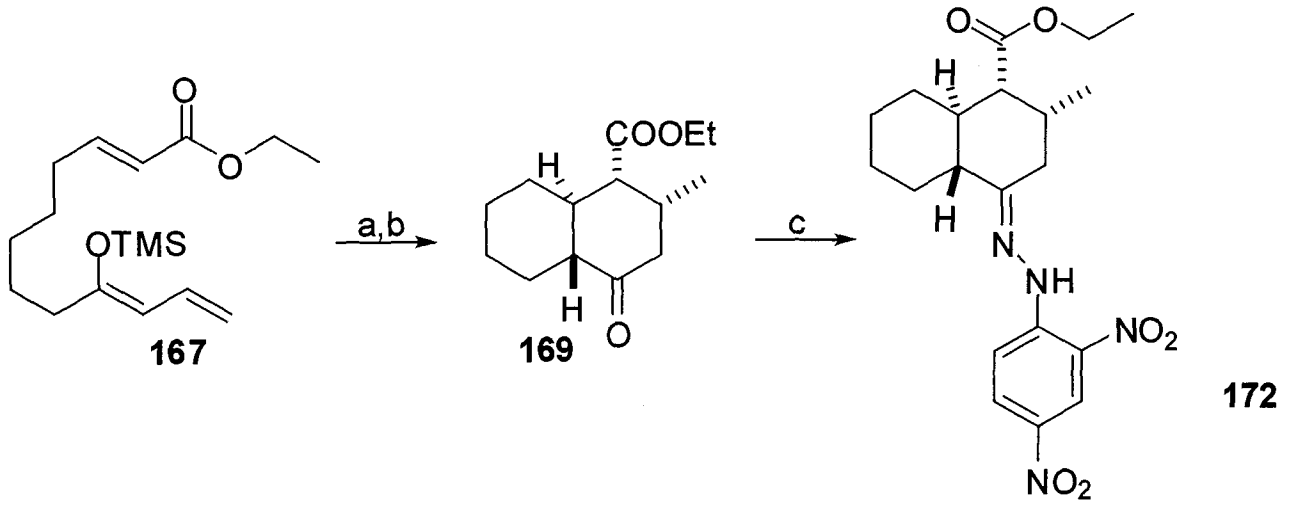
afford a cyclised silyl enol ether **157**, the relative stereochemistry of which was confirmed by the X-ray crystallography of its 3,5-dinitrobenzate derivative **160** (Scheme 100).



Scheme 100

a) anhydrous toluene, 180°C, sealed tube, 5 days (49%); b) 1N HCl, H_2O, Et_2O, rt (100%); c) L-selectride, THF, 0°C (37%); 3,5-dinitrobenzoyl chloride, pyridine, rt (89%)

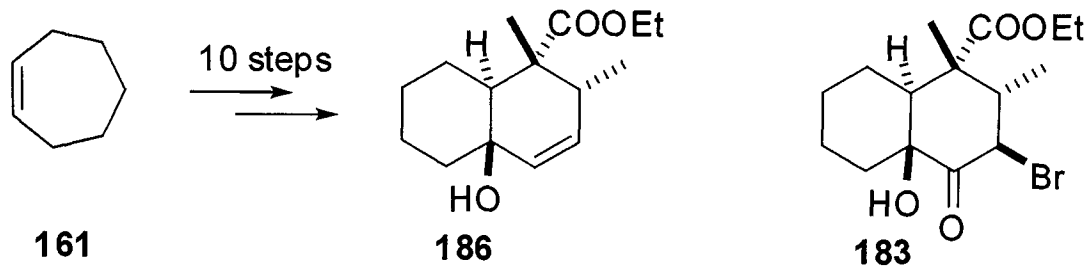
Based on this result, the [4.4.0]decalin framework **168** was constructed from *cis*-silyl enol ether **167**, and its relative stereostructure was confirmed by the X-ray crystallography of its hydrazone derivative **172** (Scheme 101).



Scheme 101

a) CSA (cat.), toluene, 180°C, 4 days; b) 1N HCl (**169**: 63%, **170**: 6%); c) 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH, rt, 5 min (75%)

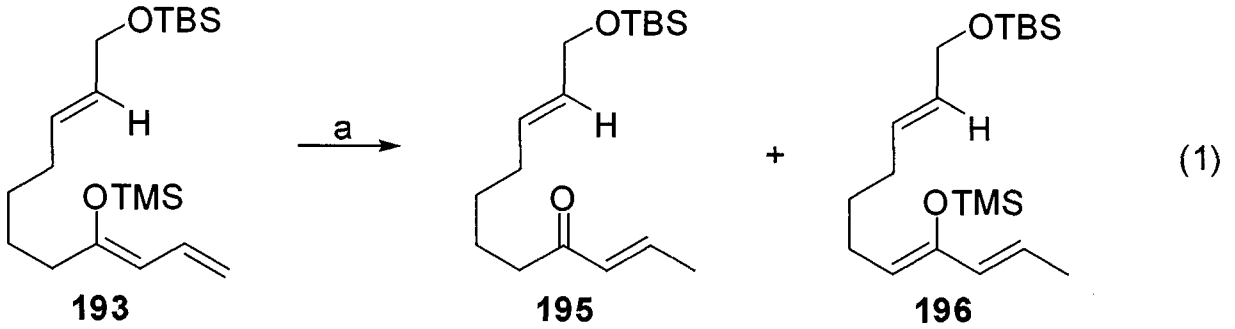
These two results encouraged the completion of the synthesis of the key intermediate **186** following a similar route from the commercially available cycloheptene **161**. The relative stereochemistry of **186** was established by means of NMR spectroscopy and was confirmed by the X-ray crystallography of the hydroxy-bromo ketone **183** (Scheme 102).



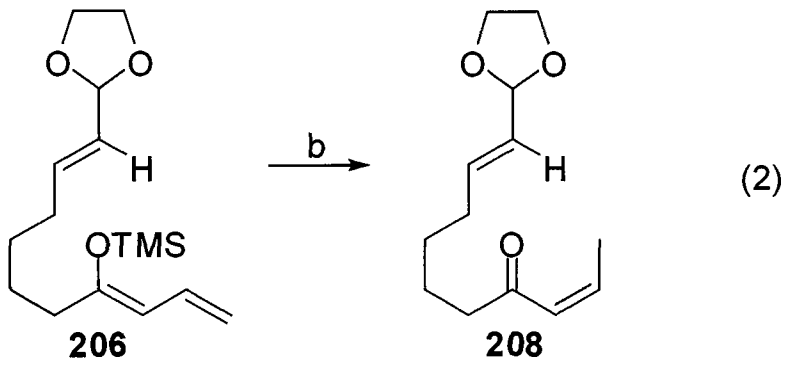
161 **186** **183**

Scheme 102

Meanwhile, efforts to push the IMDA reaction in the anticipated way were also investigated by change of the ester group to CH_2OTBS on the dienophile part (Equation (1), Scheme 103). Unfortunately, no cycloadduct was observed probably because of the bigger energy gap between the LUMO of the dienophile and the HUMO of the diene. Gassmann conditions were also investigated, but only led to the hydrolysed enone **208** (Equation (2), Scheme 103).



193 **195** **196** (1)

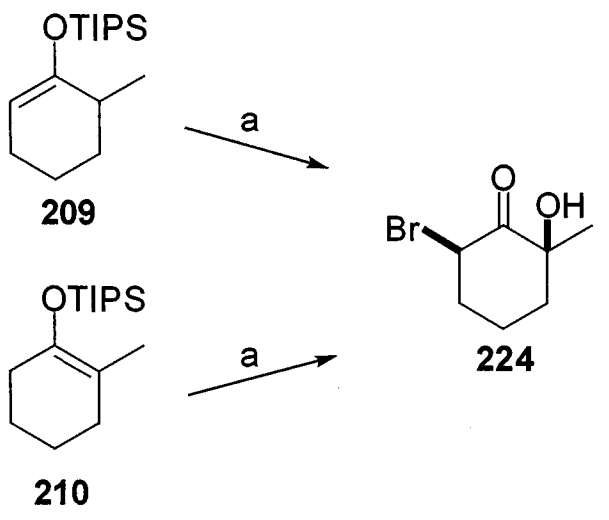


206 **208** (2)

Scheme 103

a) toluene, 200°C, sealed tube, 3 days (**195**: 41%, **196**: 20%); b) TMSOTf (cat.), -78-0°C; $NaHCO_3$ (sat.), 0°C-rt (**208**: 19%);

During the research on the total synthesis, the success in sequential oxidation and bromination of the bicyclic enol ether **180** prompted the investigation on this type of reaction on simple cyclic enol ethers, which provided a new method of double functionalisation of simple silyl enol ethers. The result that both silyl enol ether **209** and **210** produced the same α-hydroxy-α'-bromo ketone **224** supported our proposed mechanism for this type of reactions (Scheme 104).



Scheme 104

a) *m*CPBA, DCM, -78°C; then $NaHCO_3$ (sat.); b) Br_2, -78°C-rt (80% from **209**, 64% from **210**)

Six analogues of **224** were produced in satisfactory yields. *N*-Sulfonyloxaziridine was chosen as an alternative oxidant instead of *m*CPBA, yet the overall yield was not as good as expected. Subsequent postulated Favorskii-type reaction did not proceed as expected.

Since the Diels-Alder reaction of the TMS enol ether **175** was difficult to repeat on a larger scale, and the cycloadduct **176** was required for the synthesis of the key intermediate **186**, this synthetic route was abandoned. Besides, later research will point out the difficulties lying in the coupling of **186** to tetronic acid derivative. As a result, a second generation of the retrosynthetic route was proposed.

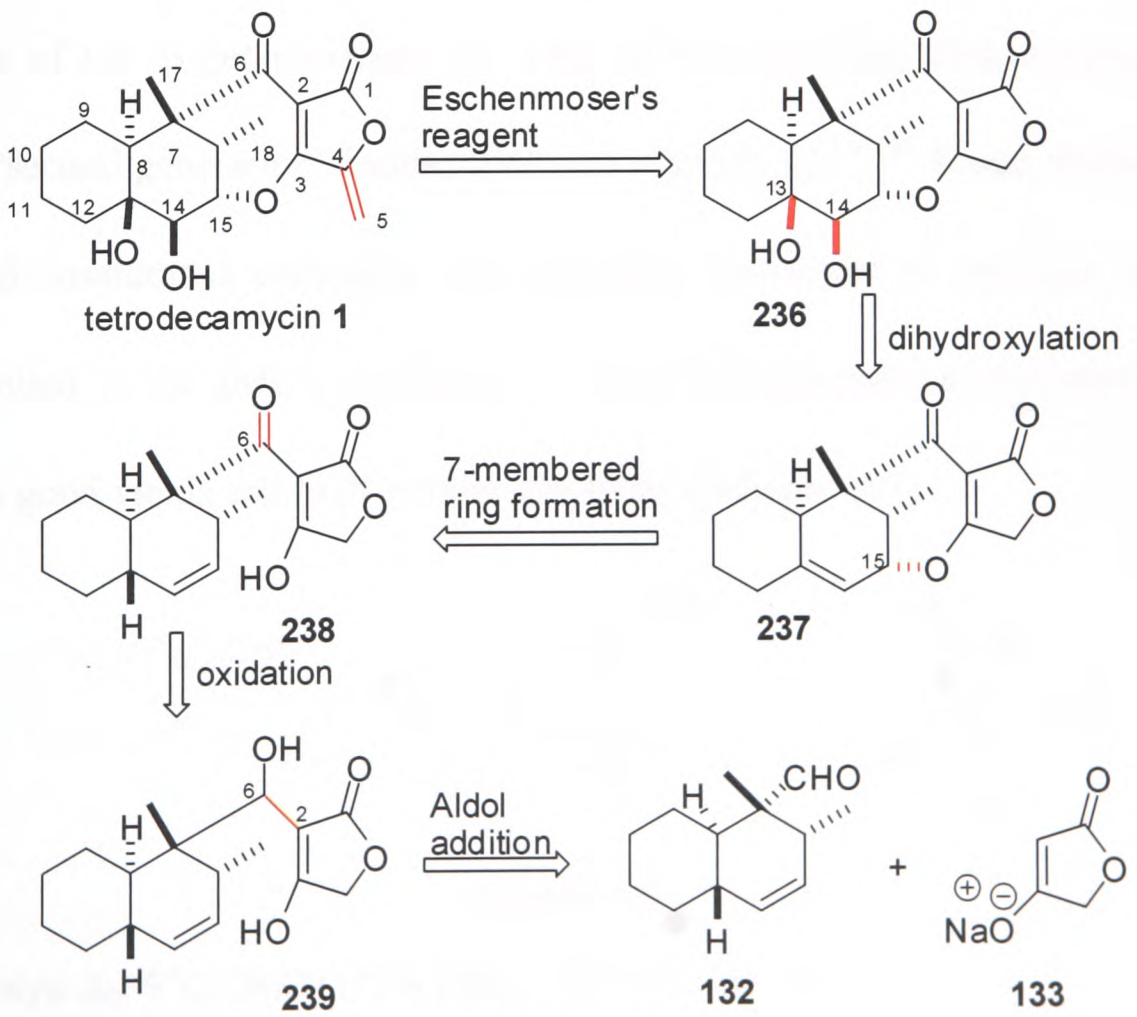
CHAPTER 3

RESULTS AND DISCUSSION (PART B)

CHAPTER 3 RESULTS AND DISCUSSION - PART B

3.1 Retrosynthetic analysis

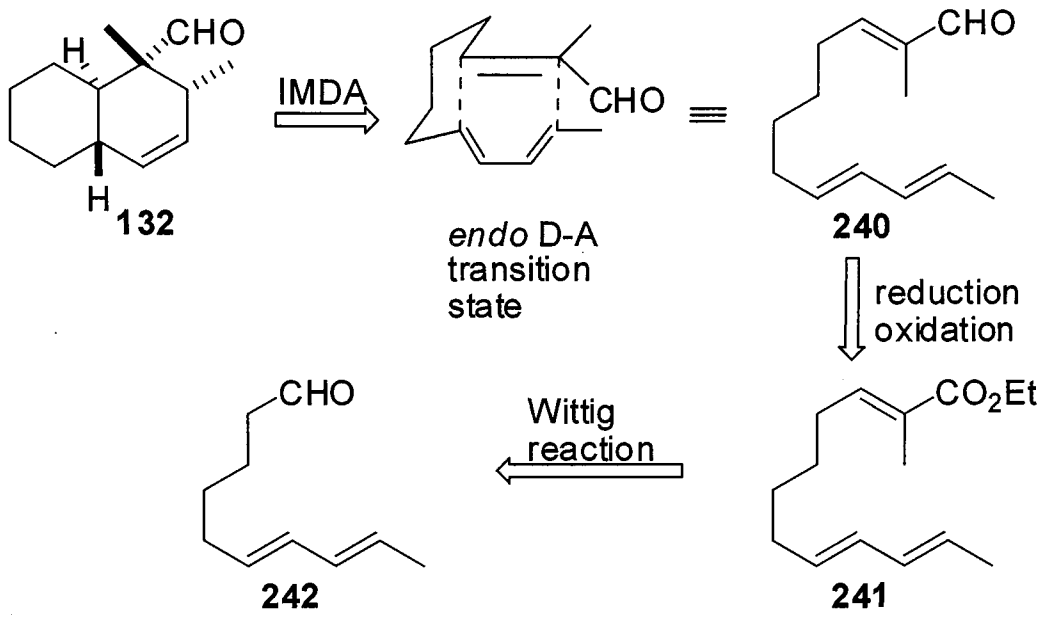
The second generation of retrosynthesis analysis is outlined below (Scheme 105). The key step was the construction of the 7-membered ring from **238** to build the 6-6-7-5-membered ring skeleton of the target molecule **237**. It was envisaged that compound **237** could be converted to tetrodecamycin (**1**) *via* dihydroxylation at C-13 and C-14 double bond followed by the introduction of the *exo*-methylene group at C-4 using Eschenmoser's method[172] as the final step. It was possible that the construction of the 7-membered ring from compound **238** could be achieved *via* a palladium-catalysed oxidative cyclisation[173,174] or an organoselenium-induced cyclisation reaction.[175-177] It was envisaged that olefin **238** could be synthesised by an aldol addition of enolate **133** to *trans*-decalin core **132** followed by an IBX oxidation.



Scheme 105

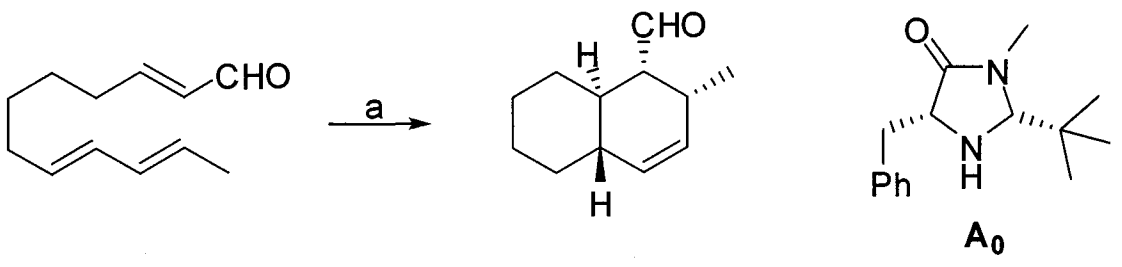
The *trans*-decalin subunit **132** could be constructed *via* an *endo* intramolecular Diels-Alder

reaction (IMDA) of the *trans*-trienal **240**. In this step, three stereogenic centres required for the total synthesis of tetrodecamycin (**1**) were expected to be generated simultaneously. Two carbon homologation of the aldehyde **242**[178] followed by reduction and oxidation was envisaged to be a practical way to afford the desired Diels-Alder precursor **240**.



Scheme 106

If this preliminary approach turned out as anticipated, it might be possible to introduce chirality *via* the use of chiral catalysis in the intramolecular Diels-Alder reactions for the asymmetric total synthesis of the target molecule (**1**). One of the appealing organocatalysts would be MacMillan's "second generation" imidazolidinone catalyst $\mathbf{A_0}$.[179,180] It was shown to lower the LUMO of α,β-unsaturated carbonyls *via* reversible formation of iminium ion.[181] It was previously applied to the IMDA reaction of (2*E*,8*E*,10*E*)-dodeca-2,8,10-trienal to afford the cycloadduct in good yields and high enantioselectivity (Scheme 107).



Scheme 107

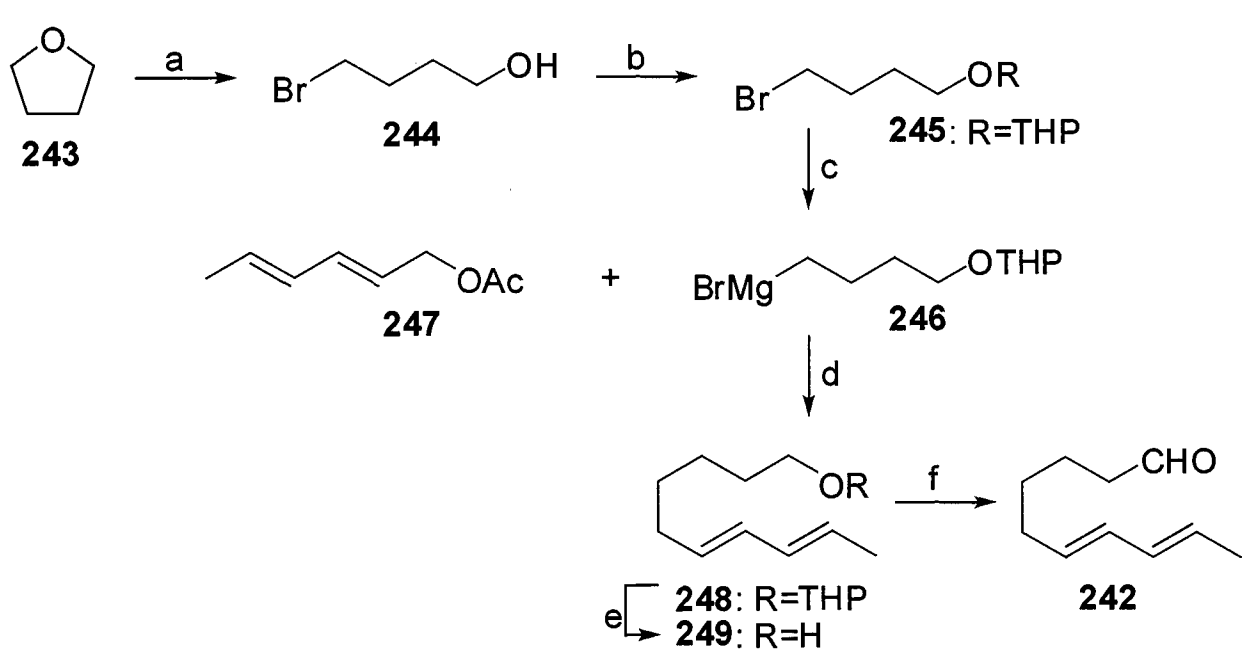
a) 20 mol% catalyst $\mathbf{A_0}$, 5°C, CH_3CN (71% yield, > 20:1 dr, 90% ee)

3.2 Synthesis of the intramolecular Diels-Alder reaction precursor

3.2.1 Synthesis of the *trans*-alkenal (242)

3.2.1.1 Reported synthesis of trans-alkenal (242)

The synthesis of (6*E*,8*E*)-deca-6,8-dienal **242** was previously reported by several research groups. The tested method relied on a Li_2CuCl_4-catalysed cross coupling between the Grignard reagent **246**, prepared from the protected 4-bromobutanol **244**, and commercially available (2*E*,4*E*)-2,4-hexadien-1-yl acetate **247** (Scheme 108).[178] Paintner *et al.* introduced a similar method to their synthesis of the aldehyde **242** (Scheme 3, **Chapter 1**).[22] However, this route was inefficient, both in terms of the preparation of Grignard reagent (strict anhydrous conditions under the protection of argon was required), and the low yields (25% after acid hydrolysis) of Li_2CuCl_4-catalysed cross coupling reactions.



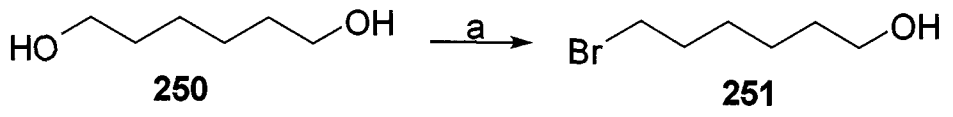
Scheme 108

a) THF, HBr (48% aq.), reflux (27%); b) dihydropyran, PPTS, DCM, rt, 4 h (97%), c) Mg turnings, THF, rt; d) Li_2CuCl_4 (cat.), THF, -10°C; e) *p*-TsOH, MeOH (25%); f) $(COCl)_2$, DMSO, Et_3N (92%)

Therefore, a new route was designed to simplify the synthesis of (6*E*,8*E*)-deca-6,8-dienal **242** based on a Schlösser modification of the Wittig reaction.

3.2.1.2 Synthesis of the ylide reagent

Treatment of commercially available 1,6-hexanediol **250** with hydrogen bromide (48% aq.) in toluene under reflux afforded monobrominated alcohol **251** in high yield (Scheme 109).[182]

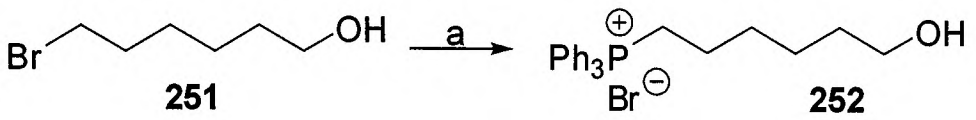


250 **251**

Scheme 109

a) HBr (48% aq.), toluene, reflux (94%)

The preparation of 6-hydroxy-triphenylphosphonium bromide **252** from 6-bromohexanol **251** and triphenylphosphine was investigated under variation of solvents and concentrations (Scheme 110, Table 6). A mixture of **251** and triphenylphosphine were left under reflux in ethanol for 2 days, but only the starting material **251** was recovered (Entry 1). The reaction took four days to complete when it was left under reflux in toluene (Entry 2).[183] The solvent was then changed to acetonitrile,[184] but the reaction was found to be extremely slow (Entry 3). The neat reaction carried out at 100°C overnight afforded an acceptable yield (Entry 4). It was suggested that a high concentration of the reactants could undergo a faster reaction and avoid the unexpected side-reactions occurring in the neat reaction. Therefore, the reaction was carried out in an almost saturated solution of 6-bromohexanol **251** and triphenylphosphine in acetonitrile under reflux overnight. The phosphonium salt **252** was obtained in 99% yield.



251 **252**

Scheme 110

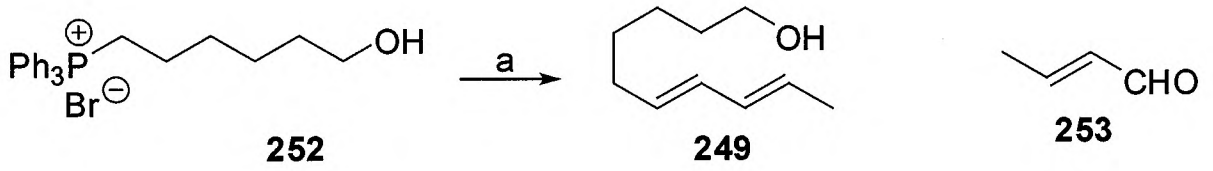
No.	*Condition (a)*	*Yield*
1	EtOH, reflux, 2 days	No reaction
2	Toluene, reflux, 4 days	83%
3	CH_3CN, reflux, 6 days	A big amount of **251** is left
4	Neat, 100°C, overnight	75%
5	CH_3CN, high concentration (sat.), reflux, 24 h	99%

Table 6

3.2.1.3 Schlösser modification of Wittig reaction

The Schlösser modification of Wittig reaction has high selectivity in producing *trans*-olefins.[185]

The multistep one-pot betaine-ylide modification of Wittig reaction was conducted under different conditions (Scheme 111, Table 7).



252 **249** **253**

Scheme 111

No	*Condition (a)*	*Yield*	*trans:cis*
1	MeLi·LiBr[a] (2 eq), THF, -78°C; rt, 30 min; **253**, -78°C; MeLi·LiBr (1.2 eq), -30°C; rt, 30 min; HCl[c] (1.1 eq), -78°C, 30 min; KO^{t}Bu (1.24 eq) -78°C-rt[186]	53%	25:1
2	MeLi·LiBr (2 eq), THF, -78°C; rt, 30 min; **253**, -78°C; MeLi·LiBr (1.2 eq), -78°C; rt, 30 min; TFA (1.1 eq), -78°C, 30 min; KO^{t}Bu (1.24 eq) -78°C-rt[185]	62%	90:10
3	MeLi·LiBr (2 eq), LiCl[b] (3 eq), THF, -78°C; rt, 30 min; **253**, -78°C; MeLi·LiBr (1.2 eq), -78°C; rt, 30 min; TFA (1.1 eq), -78°C, 30 min; KO^{t}Bu (1.24 eq) -78°C-rt	71%	95:5

Table 7

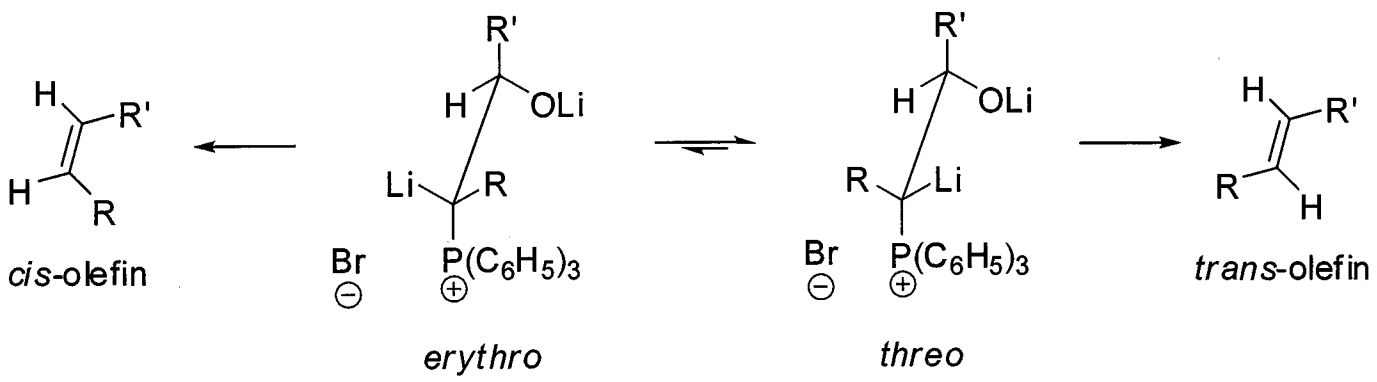
a) MeLi·LiBr was a 1.5 M solution in Et_2O. b) Lithium chloride was dried at 150°C in vacuo over night. c) HCl was as a 1.0 M solution in Et_2O.

The reaction was sensitive to three major factors: solvent, temperature and concentration of the

soluble lithium salt.

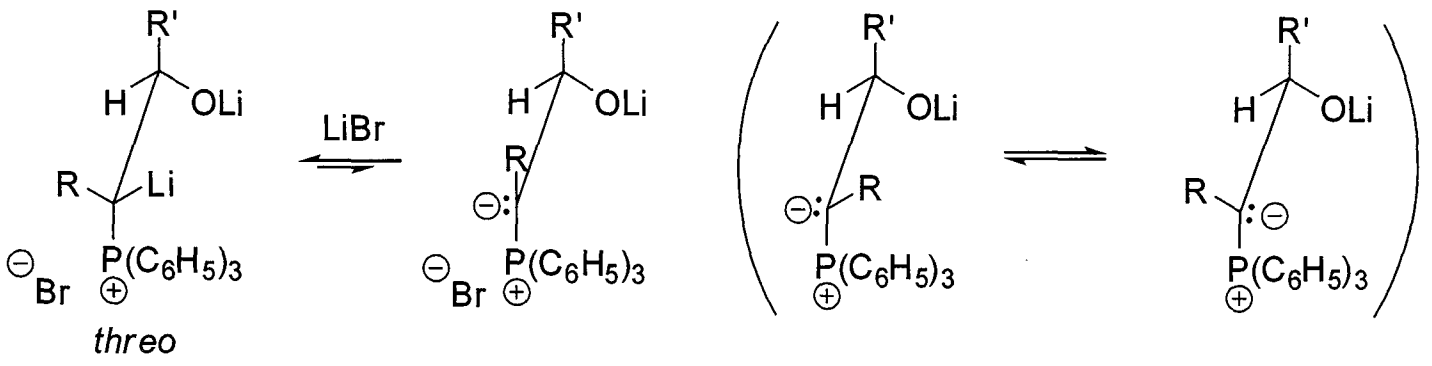
The commercially available MeLi·LiBr came as a solution in diethyl ether. However, the phosphonium salt **252** carrying free hydroxyl on the long hydrocarbon chain led to poor solubility of the corresponding betaine/lithium bromide adduct in diethyl ether, which caused the subsequent betaine-ylide formation to proceed incompletely. To overcome this problem, the amount of tetrahydrofuran serving as a co-solvent was increased after some experimentation. It was found that having the ratio of tetrahydrofuran/diethyl ether at 1:1 was ideal for substrate **252**.[186]

Besides, temperature had an important effect on the stereoselectivity. The additions of reagents were performed at -78°C, and subsequently it was allowed to warm slowly to room temperature and left stirring at room temperature for another 30 min (Entry 1 and 2, Table 7). This effected the equilibrium of the betaine ylide to its *threo* form (Scheme 112), which was thermodynamically stable, thus afforded the *trans*-diene.[185]



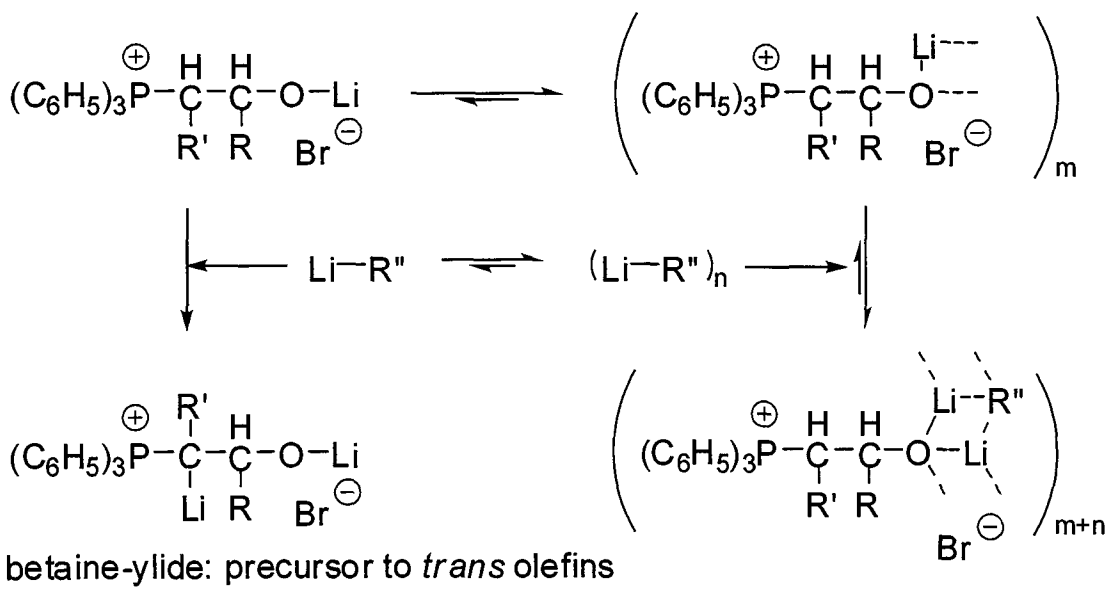
Scheme 112

Schlösser *et al.* reported that PhLi·LiBr complex was the best organolithium reagent in this reaction leading to high *trans*-selectivity.[186] An over-stoichiomeric amount of LiBr was crucial for achieving stereocontrol. Its role was probably to suppress the dissociation of the α-lithiated betaine ylide to an α-metal-free betaine ylide, which had no stereoselectivity between *threo* form and *erthro* form of betaine ylide (Scheme 113).[187,188]



Scheme 113

Besides, Schlösser *et al.* reported that the *trans*-selectivity depended on betaine ylide generation as a prerequisite. Lithium alcoholates were known to form mixed aggregate with organolithium. If the α-deprotonation of the betaine precursor could not be cleanly achieved, heteroaggregation of betaine/lithium bromide adducts sequestering alkyllithium would afford mixed superclusters. They were so stable that the sequestered alkyllithium component lost some of its inherent reactivity, being no longer able to bring about complete betaine ylide formation (Scheme 114).[185] Phenyllithium was well-known as having low propensity to aggregate, so that it was the optimal organolithium reagent for this reaction.[186]

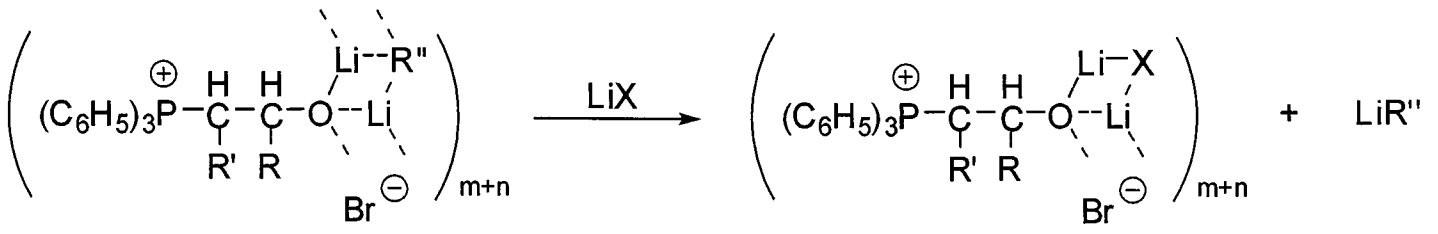


Scheme 114

However, PhLi·LiBr complex is inconvenient to use, because of its hazardous preparation and limited shelf life,[189] so the use of commercially available MeLi·LiBr complex instead of PhLi·LiBr complex for the *trans*-selective Wittig reaction was investigated.

Considering the negative effect of the formation of superclusters, it was proposed that a high

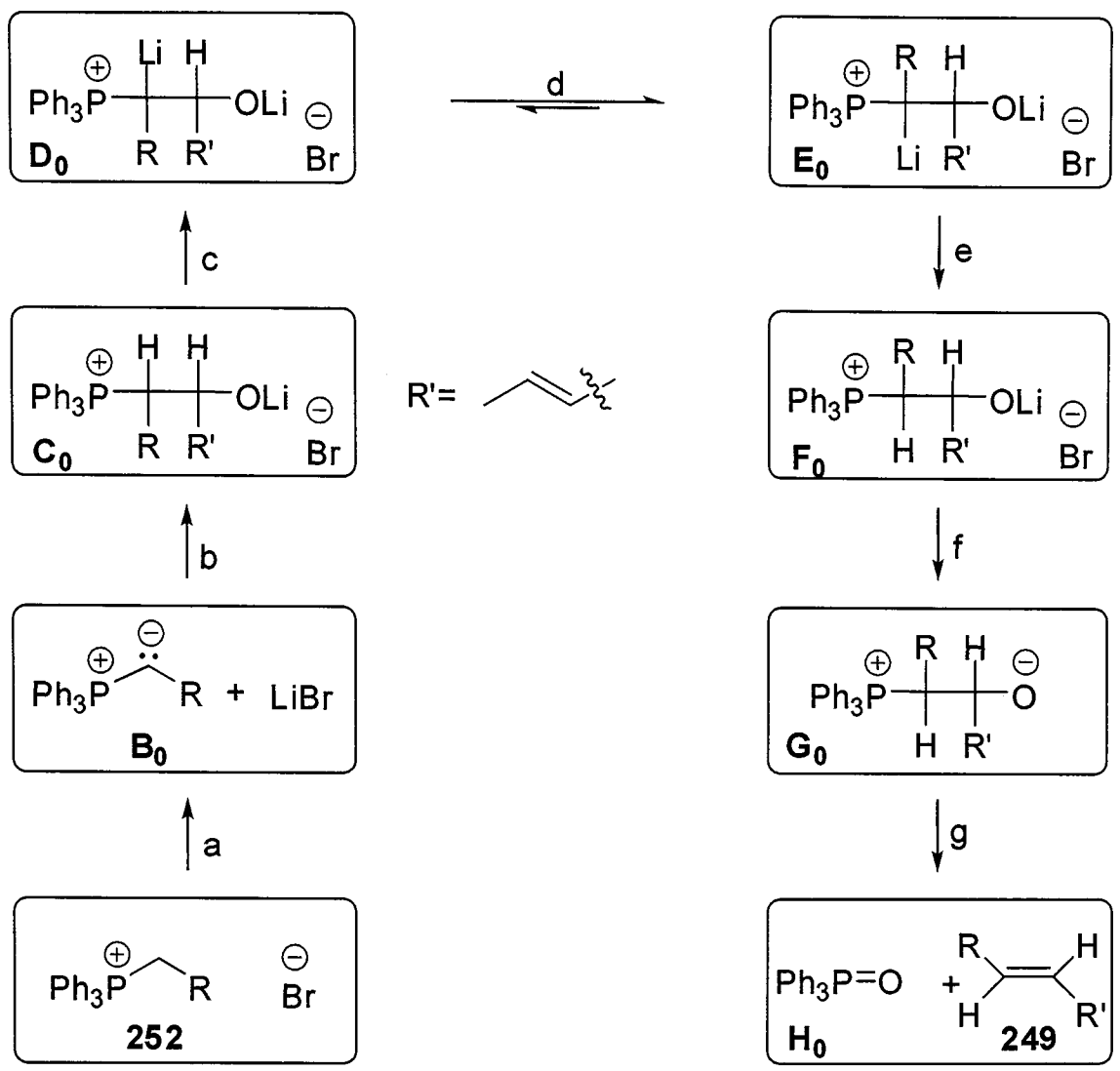
concentration of a soluble lithium salt would conduce to break the superclusters to release the organolithium reagent. The origin of this effect was interpreted as a deaggregation of the cross-linked aggregates between the polylithiated species to form mixed aggregates with the added salt. (Scheme 115).[190,191]



Scheme 115

With this concept in mind, the investigation on the combination of MeLi·LiBr, as the organolithium reagent, together with an excess amount of freshly dried lithium chloride, as a lithium ion source, was conducted (Entry 3, Table 7). Compared with Entry 2, Entry 3 showed that the *trans/cis*- selectivity was improved from 90:10 to 95:5 by addition of 3 eq of freshly dried LiCl, which was comparable to Schlösser's result (98:2 with PhLi·LiBr). Moreover, without the addition of LiCl, the yields and *trans*/*cis* ratio of this reaction were not consistent. Besides, a practical improvement was made by using the much cheaper trifluoroacetic acid to protonate the α-position of betaine ylide instead of hydrogen chloride (1M in diethyl ether), which was used in the original Schlösser's procedure.

The mechanism of the one-pot multistep protocol for *trans*-selective olefin formation is outlined in detail in Scheme 116.[185]



Scheme 116

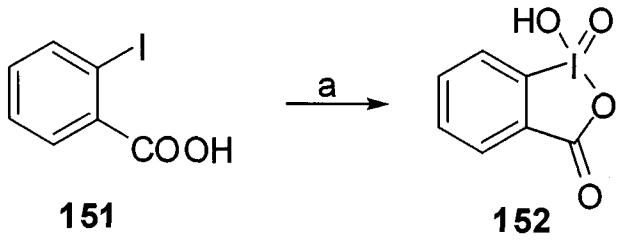
a) MeLi·LiBr, LiCl THF/Et_2O, -78°C; then 30 min, rt; b) crotonylaldehyde **253**, -78°C; c) MeLi·LiBr, -78°C; d) rt, 30 min; e) TFA, -78°C; f) KO^{t}Bu; g) 1 h, rt

The phosphonium salt **252** was deprotonated upon treatment of 2 eq MeLi·LiBr to give $\mathbf{B_0}$, which reacted with crotonylaldehyde **253** to afford the phosphorus betaine $\mathbf{C_0}$. α-Lithiation of the betaine $\mathbf{C_0}$ with another 1 eq MeLi·LiBr gave the betaine-ylide $\mathbf{D_0}$ as a key intermediate in the *trans*-selective reaction. When left at room temperature for 30 min, an equilibrium was established to favour the *threo*-configuration, which was thermodynamically more stable than the *erythro* one $\mathbf{E_0}$. Protonation of the α-position in $\mathbf{E_0}$ by acidification provided $\mathbf{F_0}$, and finally it was converted to the desired *trans*-olefin **249** and triphenylphosphine oxide $\mathbf{H_0}$ as the byproduct by treating with potassium *tert*-butoxide.

3.2.1.4 IBX oxidation

2-Iodoxybenzoic acid (IBX) **152** was reported to be a versatile and convenient oxidant that is compatible with a wide range of functional groups and substrates.[192] Frigerio *et al.* have shown

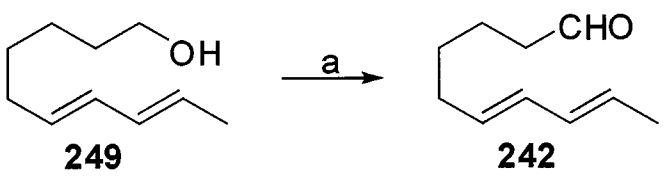
that it could be easily prepared in greater than 95% purity by oxidising 2-iodobenzoic acid **151** with Oxone® (monopersulphate compound) in deionised water to give a crystalline solid, which is completely stable to moisture (Scheme 117).[193]



Scheme 117

a) Oxone®, H_2O, 2 h, 70°C (79-81%)

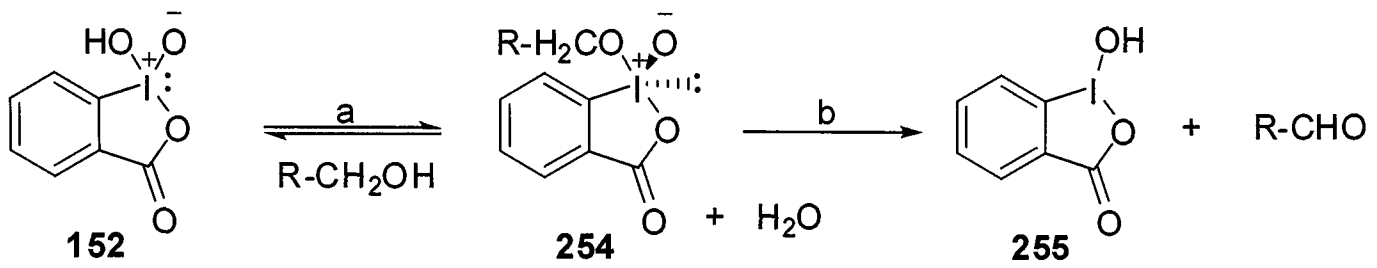
The only drawback of this reagent is the solubility – IBX is virtually insoluble in most common organic solvents apart from DMSO.[194] DMSO is therefore required as a co-solvent with THF in IBX oxidation, which may cause problems during the workup of large-scale reactions. Despite this minor difficulty, the oxidation of alcohol **249** to aldehyde **242** proceeded cleanly in 87% yield (Scheme 118).



Scheme 118

a) IBX **152**, DMSO, THF, rt, 2 h (87%)

It has been proposed that the mechanism of IBX oxidation includes a pre-equilibrium step in which the alcohol undergoes ligand exchange with a hydroxyl group, giving an axial alkoxy substituent **254**.[119] This species then disproportionates in the rate-determining step to form the aldehyde and **255** (Scheme 119).

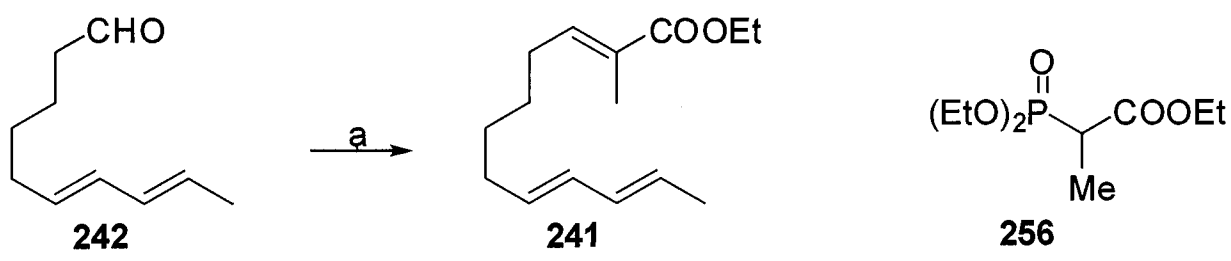


Scheme 119

a) Fast pre-equilibrium; b) Rate determining disproportionation

3.2.2 Synthesis of the intramolecular Diels-Alder precursors

With the *trans*-alkenal **242** in hand, the first intramolecular Diels-Alder reaction precursor **241** could be prepared *via* a Horner-Wadsworth-Emmons reaction. Treatment of **242** with triethyl 2-phosphonopropionate **256** in presence of lithium chloride and 1,8-diazabicyclo[5.4.0]undec--7-ene (DBU) in acetonitrile at room temperature afforded the *trans*-olefin **241** in high yield (Scheme 120).[195]

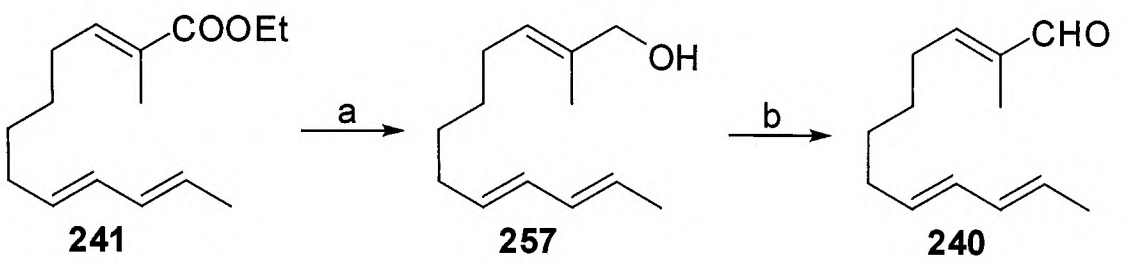


242 **241** **256**

Scheme 120

a) **256**, LiCl, DBU, CH_3CN, rt, overnight (93%)

Besides trienoate **241**, trienal **240** was also synthesised to investigate the intramolecular Diels-Alder reaction (Scheme 121). The attempt on the partial reduction of the trienoate **241** to trienal **240** by 1 eq of DIBAL only gave allylic alcohol **257** as well as the starting material **241** due to the higher reactivity and instability of the trienal **240**. Therefore, 2.5 eq of DIBAL was added into the reaction to afford allylic alcohol **257** in high yield.[196-198]



Scheme 121

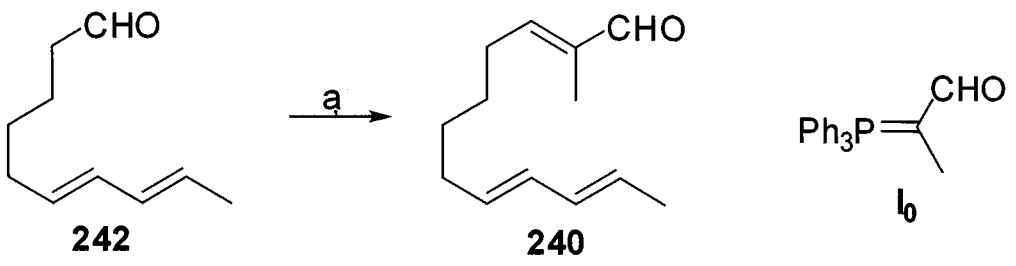
a) DIBAL, Et_2O, -78-0°C (95%); b) TPAP (cat.), NMO, 4 Å molecular seives, DCM, rt (89%)

The subsequent oxidation of the allylic alcohol **257** to the trienal **240** was investigated in different conditions (Table 8). The IBX oxidation of allylic alcohol **257** only produced the trienal **240** in 29% yield together with some inseparable compounds (Entry 1). The oxidation with activated manganese(IV) oxide, which is the most common method to oxidise allylic alcohols to aldehydes,[158,199] was also investigated. However, the reaction was found to be sluggish, and TLC analysis showed that most of the starting material **257** remained even after 5 days (Entry 2). The oxidation with SO_3·pyridine[200] only afforded 44% of product (Entry 3). Delightfully, oxidation of the allylic alcohol **257** by catalytic amount of tetrapropylammonium perruthenate (TPAP) together with *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant afforded the trienal **240** in high yield (Entry 4).[179,201]

No.	*Condition*	*Yield of 240*
1	IBX, DMSO, THF, rt, 2 h	29%
2	MnO_2, DCM, rt, 5 days	**257** (major), **240** (minor)
3	SO_3·pyridine, Et_3N, DMSO, DCM, rt, 2 h	44%
4	TPAP (cat.), NMO, 4 Å MS, DCM, rt, 1 h	89%

Table 8

To reduce the reaction steps, two carbon homologation using commercially available (α-formylethylidene)triphenylphosphorane $\mathbf{I_0}$ was investigated. The mixture of the aldehyde **241** and phosphorane $\mathbf{I_0}$ was left under reflux for 4 days in benzene to afford the desired aldehyde **240** in one step with satisfactory yield (Scheme 122).[202]



242 **240**

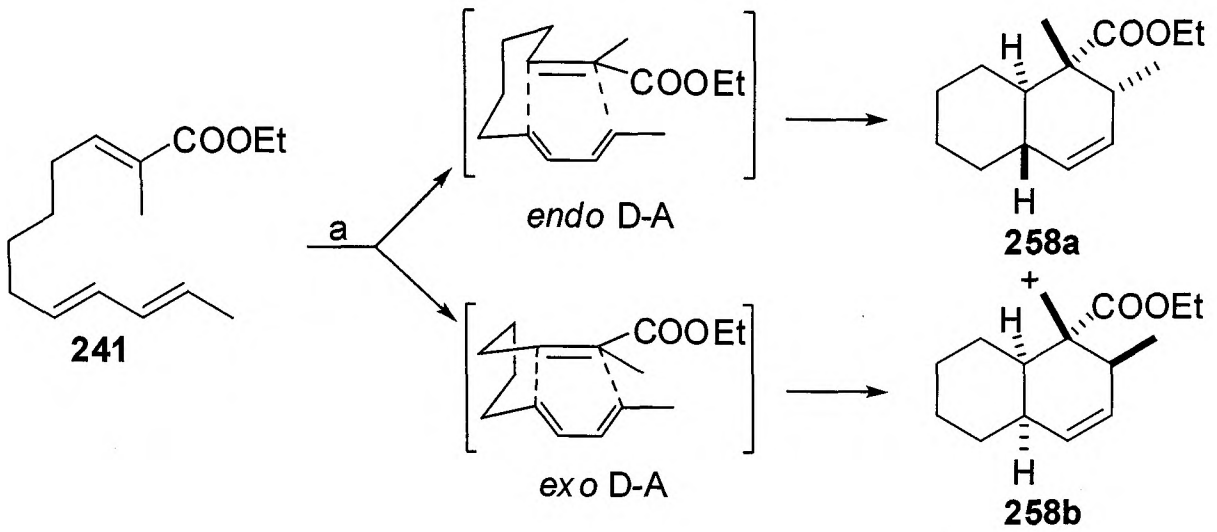
Scheme 122

a) $\mathbf{I_0}$, benzene, reflux, 4 days (87%)

3.2.3 Intramolecular Diels-Alder reaction

3.2.3.1 IMDA reaction of the trienoate 241

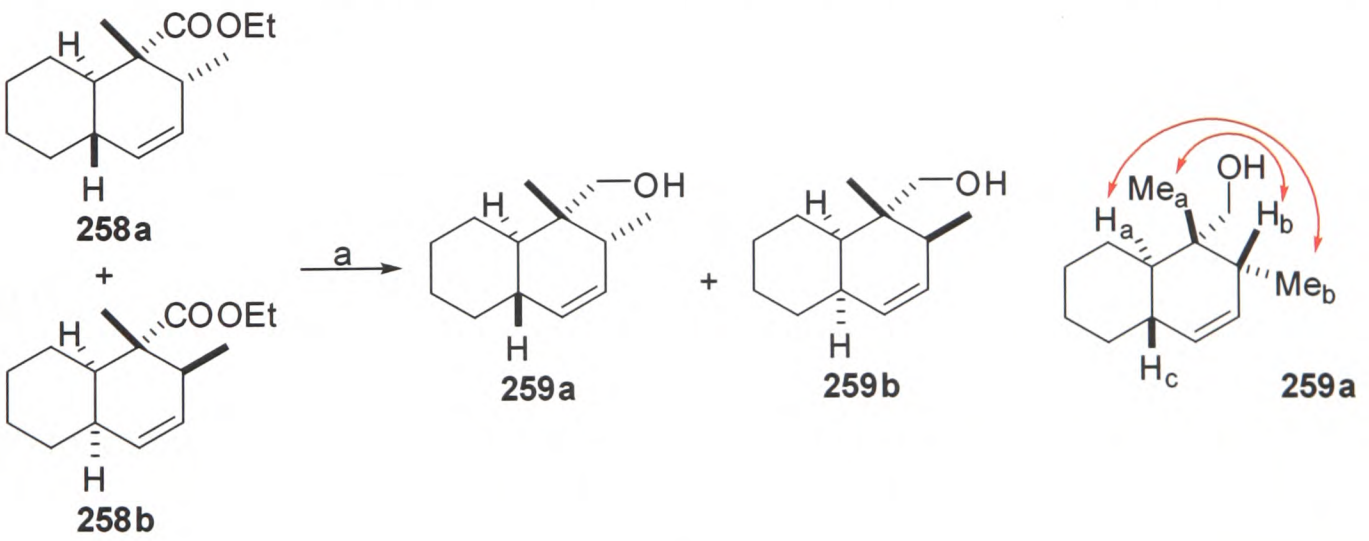
At first, the intramolecular Diels-Alder reaction of trienoate **241** was investigated. A solution of trienoate **241** in toluene with catalytic amount of BHT was heated at 180°C in sealed tube for three days (Scheme 123).[203] This reaction afforded an inseparable mixture of two diastereoisomers, **258a** and **258b**, in a 2.5:1 ratio based on NMR analysis of the reduction products. Microwave conditions, which were known to accelerate the cycloaddition, were applied to the IMDA reactions. A solution of trienoate **241** and BHT in toluene was heated to 150°C in microwave reactor for 3 h. TLC analysis showed that a large amount of starting material **241** was left. The reaction medium was then changed to 1,2-dichloroethane, a better solvent for microwave reactions due to its strong ability to absorb microwave energy. However, it did not lead to full conversion of **241** after 3 h either. Besides, Lewis acids, such as Et_2AlCl and $MeAlCl_2$, were also tested in the IMDA reaction,[105,204] but no reaction was observed at room temperature.



Scheme 123

a) BHT, toluene, 180°C, 3 days (totally 85%, *endo*:*exo* 2.5:1)

In order to establish the relative configurations of the cycloadducts, the mixture of **258a** and **258b** was submitted to DIBAL reduction affording two corresponding alcohols **259a** and **259b**, which were separable by chromatography on silica gel. The relative stereochemistry of the major isomer **259a** was confirmed by NOESY analysis. The enhancement between H_b and $(Me)_a$, and that between H_a and $(Me)_b$ indicated that the major stereoisomer of the IMDA reaction was formed *via* the *endo*-transition state to give the desired *trans*-decalin **258a** (Scheme 124).



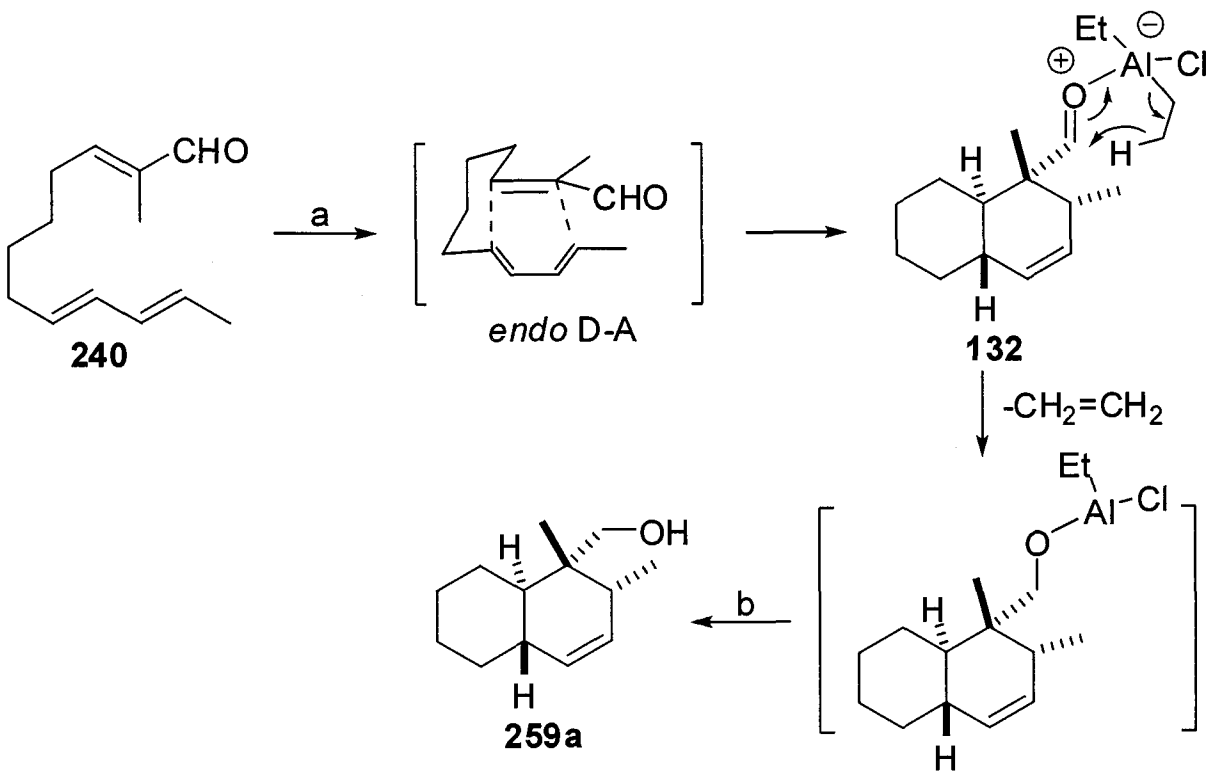
Scheme 124

a) DIBAL, Et_2O, -78-0°C (**259a**: 53%, **259b**: 23%)

3.2.3.2 IMDA reaction of the trienal (240)

The investigation on the cycloaddition of trienal **240** was focused on the Lewis acid catalysed intramolecular Diels-Alder reaction (Scheme 126, Table 9). The first attempt was to treat the

trienal **240** with Et_2AlCl (1.3 eq) in dichloromethane at 0°C following the method reported by Kobayashi *et al.*.[199] Unfortunately, only a complex mixture was produced. It was claimed by Kobayashi *et al.* that under these conditions, the intramolecular Diels-Alder reaction was highly *endo*-selective to give *trans*-fused decalin core; however, the major product was not the desired cycloadduct **132** but the reduced alcohol **259a**. Apparently, the initially formed aldehyde **132** underwent an Et_2AlCl-mediated Meerwein-Ponndorf-Verley-type reduction directly in the same pot to afford the alcohol **259a** (Scheme 125).

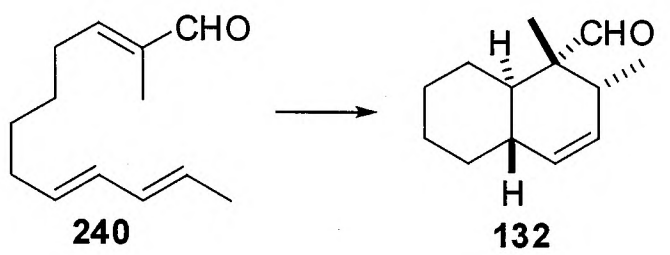


Scheme 125

a) Et_2AlCl (1.3 eq), DCM, 0°C; b) H_2O (54%)

In order to minimize the afforementioned reduction, variation of temperature (-78-0°C), variation of the amount of Et_2AlCl and variation of solvents (DCM, toluene) were investigated independently in the cycloaddition reaction, but only **240** and an inseparable complex mixture was obtained (Entry 1,2 and 3, Table 9). Finally, zinc chloride was used instead of Et_2AlCl in the IMDA reaction, for it was reported to perform well in catalysing cycloaddition of allyl aldehyde without reduction.[205] Upon exposure of **240** to the action of commercially available $ZnCl_2$ (1.0 M in THF, 1.2 eq) in DCM at room temperature for 3 days, the desired cycloadduct **132** was

produced in 25% yield together with 53% of starting aldehyde **240** (Entry 4). The yield of the desired cycloadduct **132** was improved to 66% when the commercially available $ZnCl_2$ in Et_2O instead of that in THF was used (Entry 5), probably due to the weaker coordination ability of Et_2O to $ZnCl_2$ compared with that of THF. The coordination of stray σ-donor ligand would decrease the Lewis acidity of $ZnCl_2$. The relative stereochemistry of **132** was confirmed by comparing NMR data with the reported ones by Kobayashi and co-workers.[199]



Scheme 126

No.	*Condition*	*Result*
1	Et_2AlCl (1.3 eq), DCM, 0°C, 3 h	complex mixture
2	Et_2AlCl (1.02 eq), DCM, -78°C, 6 h	**240** (major)
3	Et_2AlCl (0.95 eq), toluene, -78°C-rt, overnight	**240** and complex mixture
4	$ZnCl_2$ (1.0 M in THF, 1.2 eq), DCM, rt, 3 days	**132**: 25%, **240**: 53%
5	$ZnCl_2$ (1.0 M in Et_2O, 1.2 eq), DCM, rt, 4 days	**240**: 66%

Table 9

3.2.4 Conclusion of section 3.2

In this section, the synthesis of *trans*-alkenal **242** was successfully simplified by introducing Schlösser's multistep one-pot betaine-ylide modification of Wittig reaction from the reported six or more steps to four steps in high *trans*-selectivity and yield. The addition of 3 eq freshly dried lithium chloride in this reaction simplified the classical procedure and avoided the use of heavier reagent PhLi·LiBr complex, which had to be prepared freshly and had limited shelf life.

Two intramolecular Diels-Alder reaction precursors, trienoate **241** and trienal **240** were prepared in high yield. It was found that the thermal conditions of IMDA cycloaddition of trienoate **241** gave inseparable *endo* and *exo* cycloadducts **258a** and **258b** in a ratio of 2.5:1. The relative

stereochemistry of **258a** was confirmed by the n.O.e analysis of its corresponding alcohol **259a**. However, the Lewis acid catalysed IMDA reaction failed on the substrate **241**.

The IMDA reaction of the enal **240** with Et_2AlCl, in contrast to a literature report, yielded an inseparable complex. When $ZnCl_2$ (1.0 M in Et_2O) was introduced as Lewis acid, the desired cyclic aldehyde **132** was obtained in a satisfactory yield. Aldehydes **240** and **132** were quite unstable. Aldehyde **240** was easily polymerised in air, and aldehyde **132** was easily oxidised to acids, so that they had to be submitted to the next step as soon as possible, or stored under argon at low temperature (-78˚C) for a short time.

3.3 Model study to install the tetronic acid derivative protion

According to the numbering on the tetronic acid, tetrodecamycin (**1**) is a 3-acylated--4-*O*-alkylated-5-alkenylidated tetronic acid derivative compound, in which the decalin portion and the tetronic acid derivative were coupled *via* 3-acylation and 4-*O*-alkylation (Figure 16). In this chapter, the installation of the tetronic acid derivative onto the decalin part will be discussed.

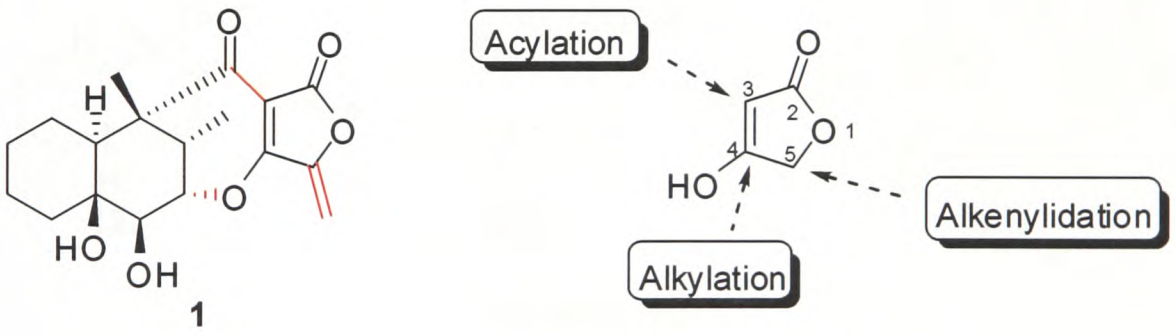


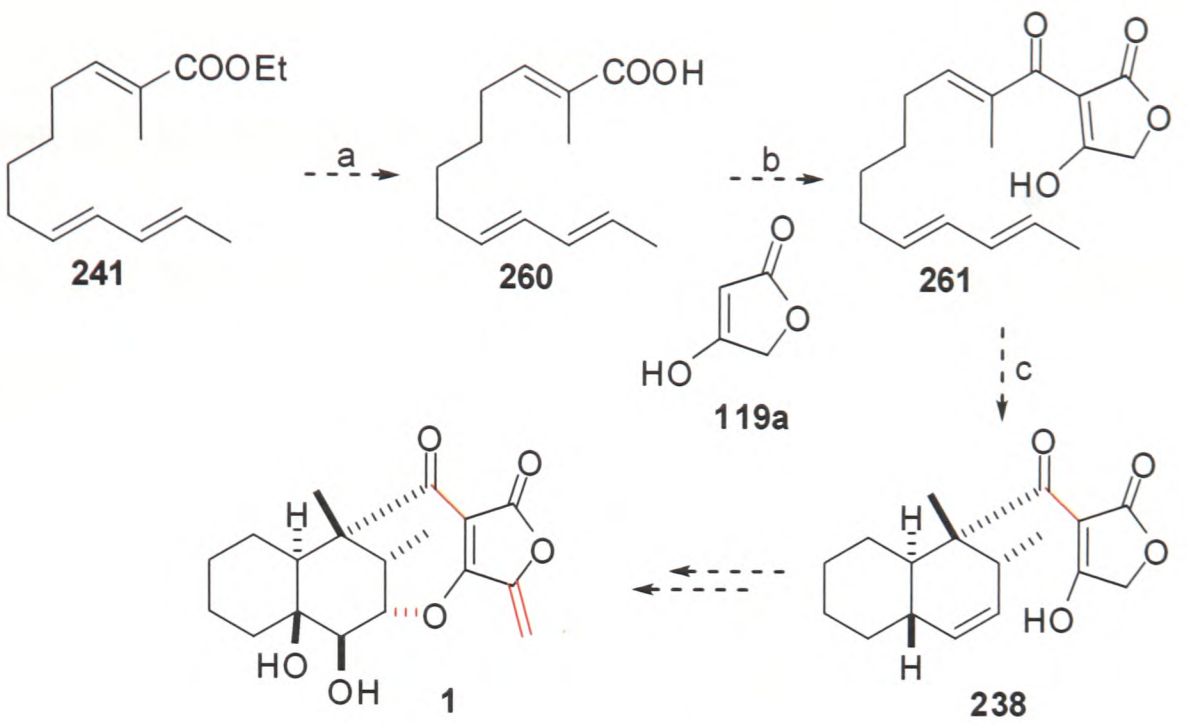
Figure 16

3.3.1 Installation of the tetronic acid derivative *via* 3-acylation

3.3.1.1 Synthetic Plan

It was anticipated that hydrolysis of ester **241** would give the carboxylic acid **260**,[206] which was expected to afford the IMDA reaction precursor **261** *via* a DCC-DMAP coupling with the tetronic acid **119a**.[207] The triene **261** would be cyclised to the decalin framework **238** (Scheme

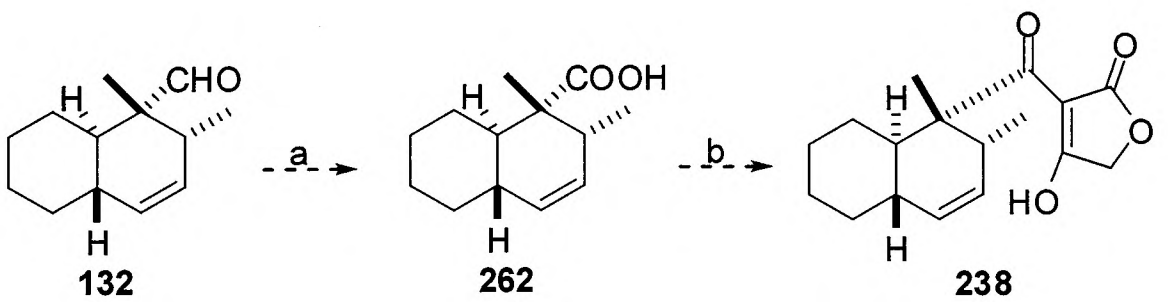
127), which would be further converted to the target molecule (**1**) following the initial plan (Scheme 105).



Scheme 127

a) hydrolysis; b) 3-acylation with tetronic acid **119a**; c) IMDA reaction

An alternative route to produce compound **238** would be *via* the coupling reaction between the acid **262** and tetronic acid **119a** (Scheme 128).

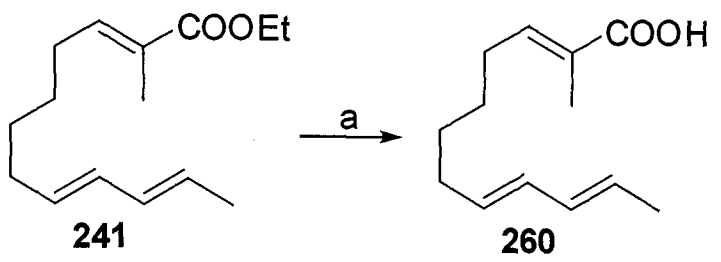


Scheme 128

a) oxidation; b) 3-acylation with tetronic acid **119a**

3.3.1.2 Synthesis of carboxylic acids (260) and (262)

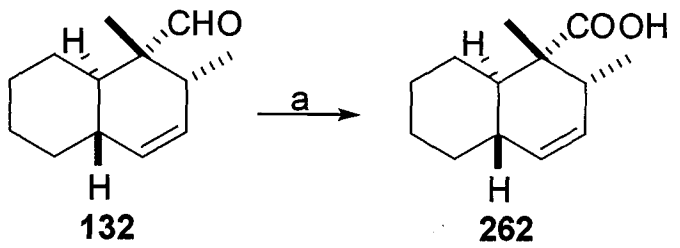
The trienoate **241** was converted to the corresponding trienoic acid **260** by hydrolysis in high yield (Scheme 129).[206]



Scheme 129

a) LiOH, H_2O/THF, rt, 2 day; then 1N HCl (90%);

The carboxylic acid **262** was obtained by sodium chlorite oxidation of the aldehyde **132** (Scheme 130).[208]

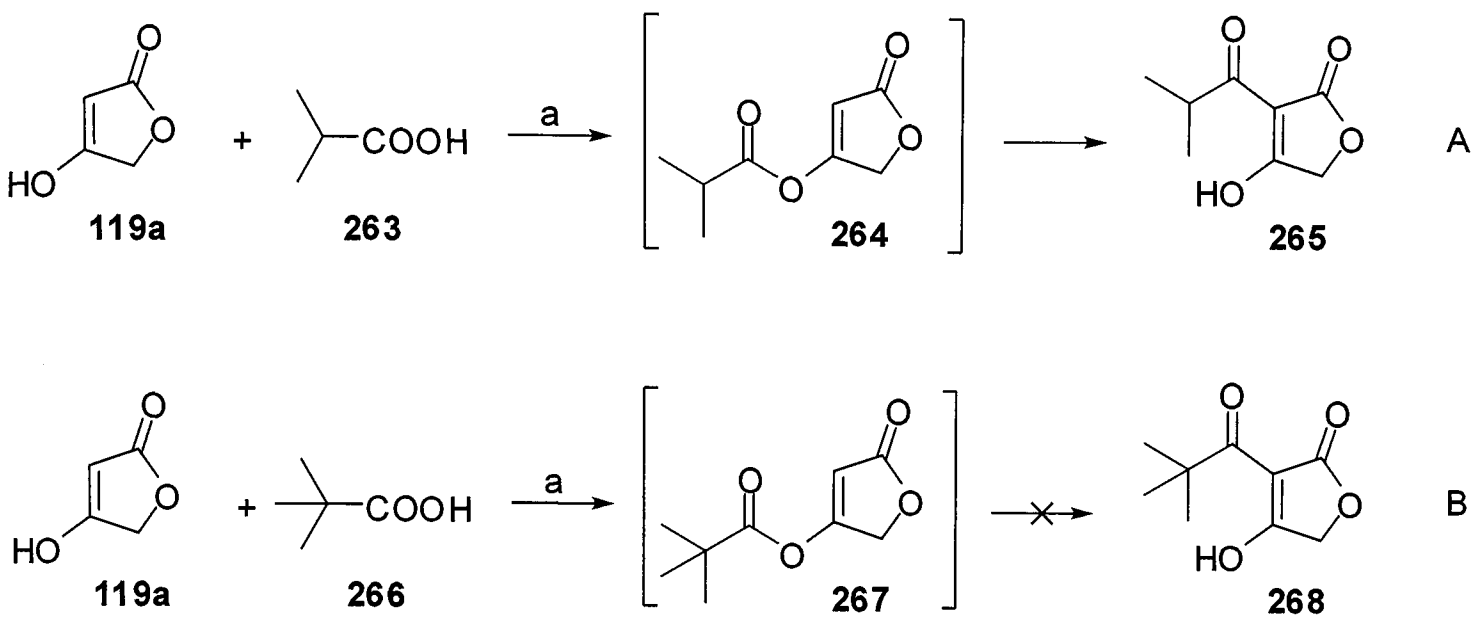


Scheme 130

a) $NaClO_2$, ^tBuOH, 2-methylbut-2-ene, KH_2PO_4, H_2O, rt (67%)

3.3.1.3 Model study on 3-acylation of tetronic acid

Yoshii *et al.* reported that the 3-acylation of 3-unsubstituted tetronic acids was achieved *via* a DCC-coupling reaction with carboxylic acid. In this one-pot procedure, the kinetic *O*-acylation product **264** was involved as an intermediate by DCC-coupling reaction, which underwent a DMAP-mediated rearrangement to produce **265** (Equation A, Scheme 131). However, they observed that benzoylation and trimethylacetylation could not be achieved, because the reactions were interrupted at the stage of *O*-acylates probable due to steric hindrance in the *C*-acylation (Equation B, Scheme 131). This method was only suitable for the acyl group bearing α-hydrogen.[207]

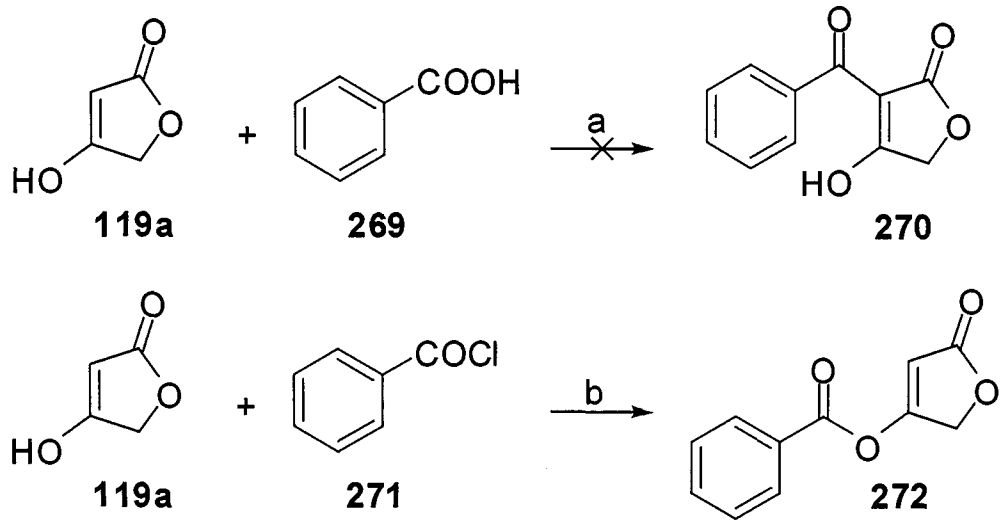


Scheme 131

a) DCC, DMAP, NEt_3, DCM, 0°C-rt (**265**: 55%)

Based on their results, it was suggested that a more powerful nucleophilic catalyst than DMAP might be able to catalyse the rearrangement of compounds with acyl group bearing no α-hydrogen to give the desired 3-acylated product, since both carboxylic acids **260** and **262** had no α-hydrogen. Therefore, 4-pyrrolidinopyridine was used instead of DMAP. The model study was performed on benzoic acid **269** bearing no α-hydrogen. Tetronic acid **119a** and benzoic acid **269** were exposed to DCC, 4-pyrrolidinopyridine and triethylamine in dichloromethane. This reaction was left at 0°C for 15 min, but no reaction was observed by TLC analysis. Thus, it was warmed to room temperature for several hours, but only a complex mixture was obtained. It was speculated that it was probably that DCC-mediated reaction might be problematic. Thereafter, a more reactive reagent, benzoyl chloride **271** was used instead of benzoic acid **269** to avoid the utility of DCC. However, this reaction stopped at the stage of the 4-*O*-benzoate compound **272** without further rearrangement to the desired **270** (Scheme 132). The resulted benzoate **272** was left under reflux in toluene together with catalytic amount of 4-pyrrolidinopyridine for two days in an attempt to initiate the rearrangement, but only starting material **272** was recovered. After an addition of 1 eq triethylamine, the mixture was left under reflux for another day, only leading

to decomposition of the starting material.



Scheme 132

a) DCC, 4-pyrrolidinopyridine (cat.), Et_2N, DCM, 0°C-rt; b) 4-pyrrolidinopyridine (cat.), Et_2N, DCM, 0°C-rt (81%)

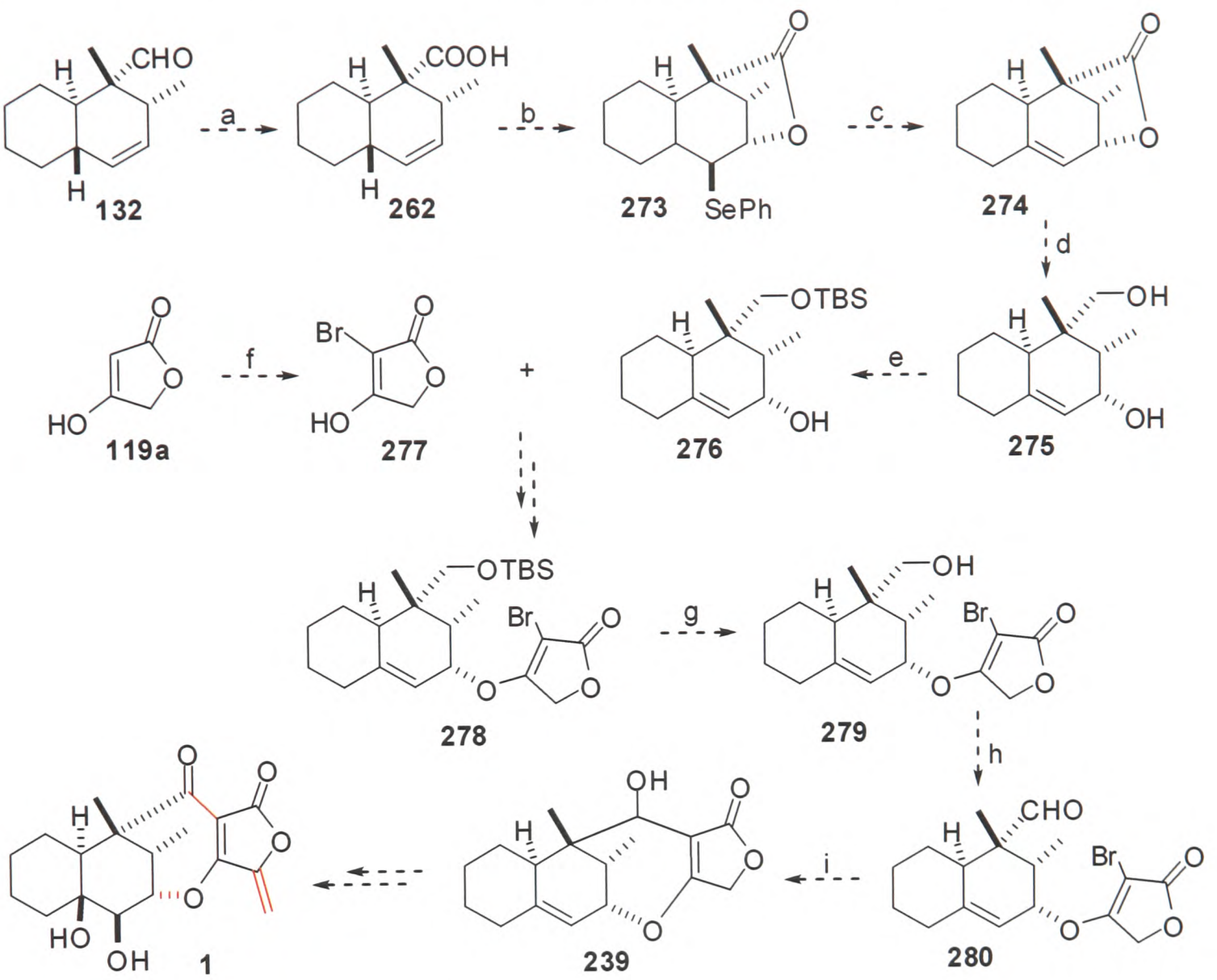
3.3.2 Installation of the tetronic acid derivative *via* 4-*O*-alkylation

Having concluded that the studies on the 3-acylation of tetronic acid was not a viable route, focus was returned to install the tetronic acid derivative part onto the decalin portion *via* 4-*O*-alkylation first.

3.3.2.1 Synthetic plan

This route was based on the 4-*O*-alkylation of tetronic acid derivative **277** with the allylic alcohol **276**. It was envisaged that the allylic alcohol **276** would be achieved by a reductive opening of the lactone **274** followed by a protection of the primary hydroxyl group. The lactone **274** could be easily produced from the aldehyde **132** *via* oxidation,[208] phenylselenolactonisation[22,209] and subsequent oxidative removal[210] of the phenylselenanyl substituent to establish the double bond. Meanwhile, bromination of the tetronic acid **119a** would provide the tetronic acid derivative **277**. It was proposed that the 4-*O*-alkylation of tetronic acid derivative **277** with the alcohol **276** would result in compound **278**, which was transformed to the aldehyde **280** *via* desilylation and oxidation. A Nozaki-Hiyama-Kishi

reaction of compound **280** would afford the 6-6-7-5- tetracyclic ring framework **239** (Scheme 133), which would be furnished to the target molecule (**1**) following Scheme 105.

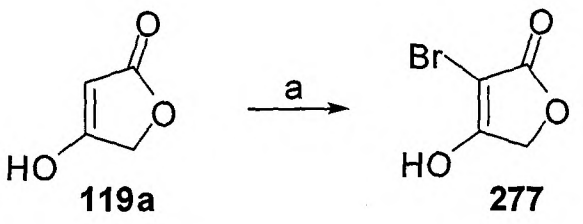


Scheme 133

a) $NaClO_2$; b) PhSeCl; c) H_2O_2; d) $LiAlH_4$; e) TBS, imidazole; f) NBS; g) TBAF; h) IBX; i) $CrCl_2$, $NiCl_2$

3.3.2.2 Model study on 4-O-alkylation of tetronic acid derivative

The bromide **277** was obtained in quantitative yield by the bromination of tetronic acid **119a** with NBS in ethanol (Scheme 134).[211]

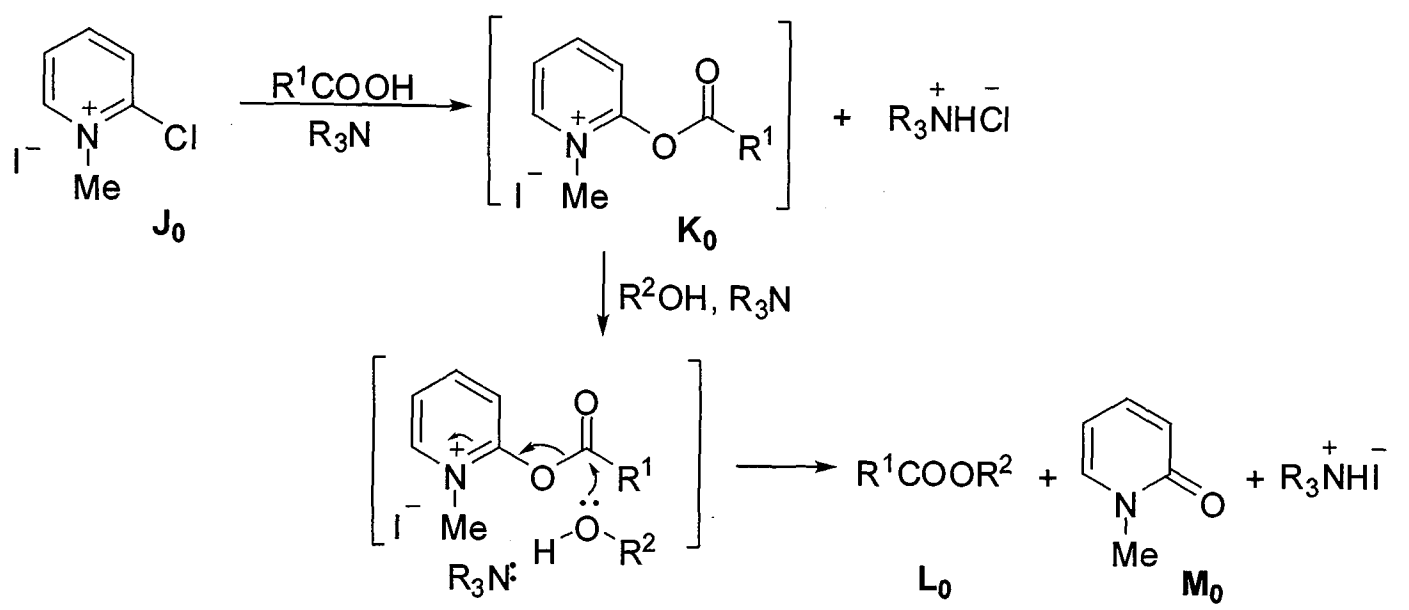


Scheme 134

a) NBS, EtOH, rt (quant.)

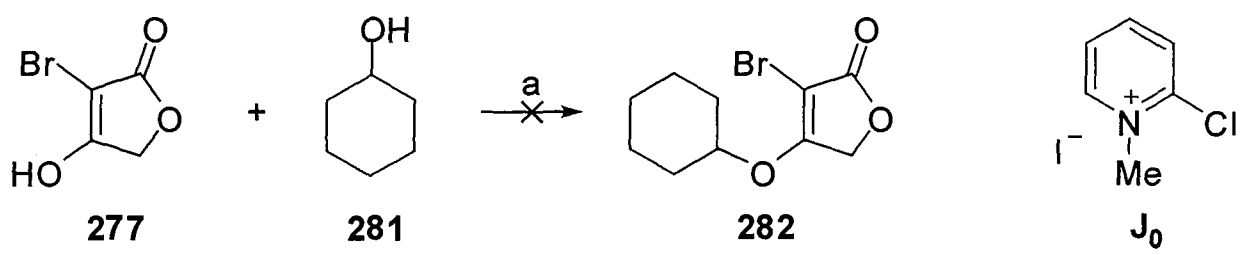
Saigo *et al.* reported that 2-chloro- and 2-bromopyridinium salts are efficient for the preparation

of carboxylic esters from equimolar amounts of free carboxylic acids and alcohols.[212] A nucleophilic attack of the carboxylate ion on 2-chloro-1-methylpyridinium iodide **J_0** produces 2-acyloxy-1-methylpyridinium iodide **K_0**, an active acylating intermediate, since the halogen atom at 2-position of **J_0** is facile to be displaced by the attack of nucleophiles. The intermediate **K_0** is converted into stable molecules, *i.e.*, carboxylic esters **L_0**, 1-methyl-2-pyridone **M_0** and ammonium salt, by another nucleophilic attack of an alcohol onto the carbonyl carbon of **K_0** in the presence of a hydrogen iodide captor, *e.g.*, tertiary amine (Scheme 135).



Scheme 135

With this concept in mind, tetronic acid **277** and cyclohexanol **281** was treated with 2-chloro-1-methylpyridinium iodide **J_0** and triethylamine under reflux in DCM. However, this only resulted in the formation of a complex mixture and the alcohol **281** was recovered unchanged (Scheme 136).

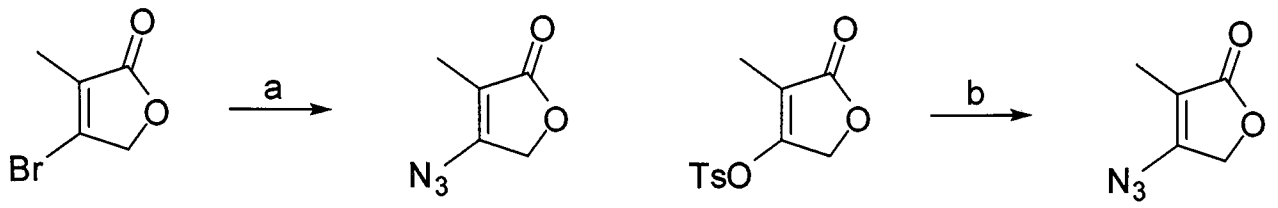


Scheme 136

a) **J_0** (1.2 eq), Et_3N (2.4 eq), DCM, rt to reflux

It was reported that the reaction of the 4-bromotetronic compounds with sodium azide could

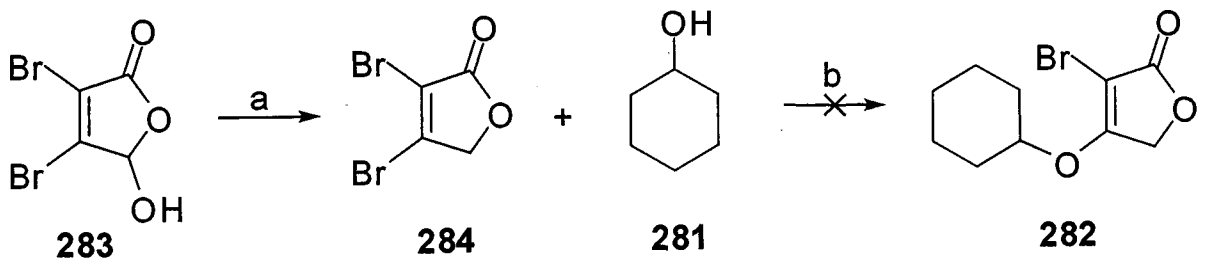
afford the corresponding 4-azidotetronic derivatives bearing different substituent groups at the carbon atom in position 3 in good yield. However, the reaction of tetronic acid tosylates with sodium azide could only afford the 4-azidotetronic derivatives in about 20% (*e.g.* Scheme 137). This is due to the good leaving ability of the conjugated base of tetronic acid, which acts in competition with tosylate in the reaction with sodium azide.[213,214]



Scheme 137

a) NaN_3, MeOH, rt (70%); b) NaN_3, MeOH, rt (20%)

Therefore, the hydroxyl group of tetronic acid was transformed to a halo-derivative. 3,4-Dibromo-2(5*H*)- furanone **284** was prepared from the commercially available mucobromic acid by treating with sodium borohydride at 0°C. The crude product was recrystallised from hexane and diethyl ether to give dibromide **284** in good yield.[215] The coupling reaction of the dibromide **284** and cyclohexanol **281** was performed with different bases, such as triethylamine, sodium hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), as well as DMAP together with pyridine (Scheme 138). However, all of these trial reactions produced black complex mixtures, probably due to the instability of the dibromide **284** under basic conditions.

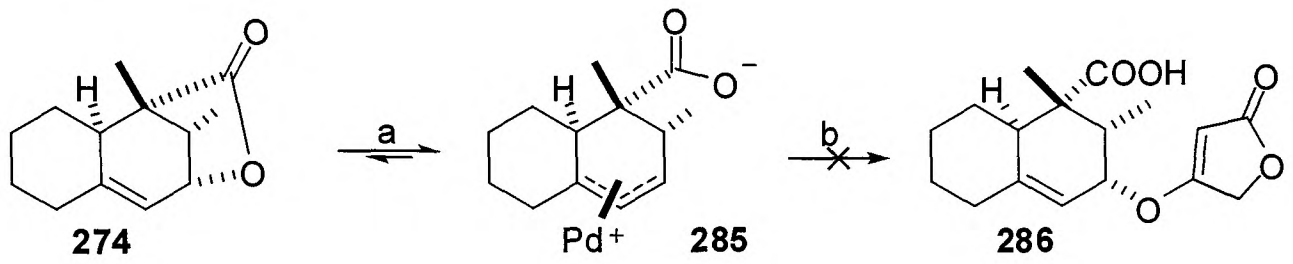


Scheme 138

a) $NaBH_4$, MeOH, 0°C; then conc. H_2SO_4 (75%); b) Et_3N, NaH, DBU, or pyridine and DMAP, 0°C

It is well-known that palladium can catalyse a variety of heteroatom nucleophiles to react with olefins. Therefore, lactone **274** was treated with catalytic amount of $Pd(PPh_3)_4$ in the hope to

form a palladium-complex **285**, which would be attacked by the deprotonated tetronic acid **119a** (Scheme 139). Unfortunately, the attempted reaction failed and only starting material **274** was recovered, probably due to its twisted structure. The model of the stereochemistry of **274** showed steric hindrance on both sides of the ring, which might hinder the palladium(0) to coordinate (Figure 17).



274 **285** **286**

Scheme 139

a) $Pd(PPh_3)_4$ (cat.); b) tetronic acid **119a** (3 eq.), Et_3N (3 eq.)

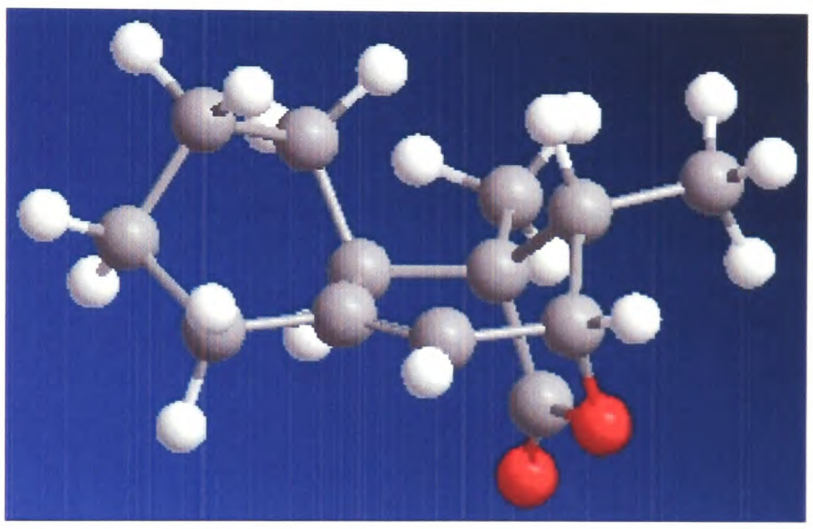


Figure 17: Modeling structure of **274**

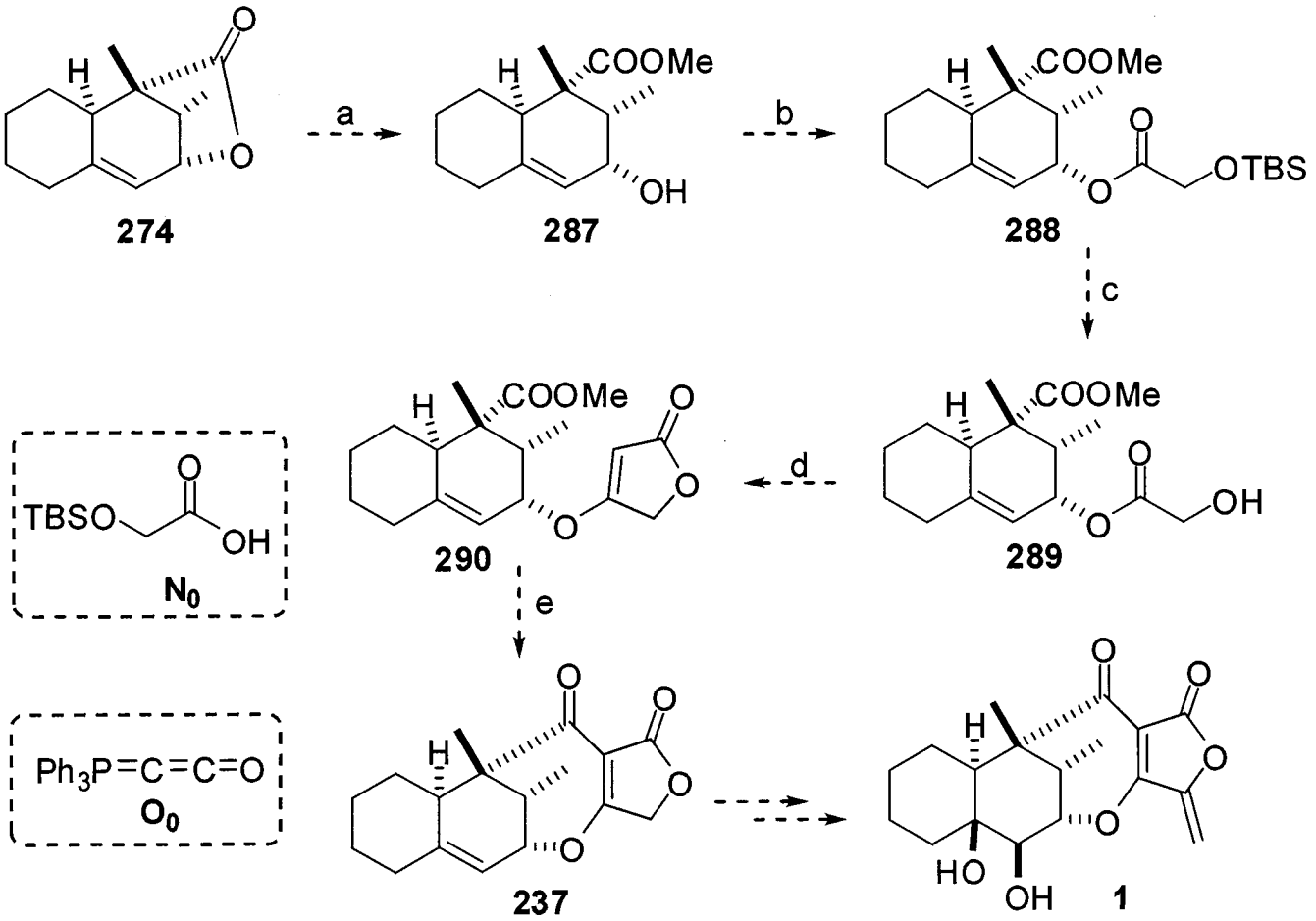
3.3.3 Conclusion of section 3.3

In a conclusion, the model studies on 3-acylation and 4-*O*-alkylation of tetronic acid met with frustration. Focus was turned to the construction of tetronic acid derivative part on the decalin portion *via* Wittig reaction or Dieckmann-type cyclisation directly instead of the coupling reactions between the acid **262** or alcohol **276** and tetronic acid derivative.

3.4 Attempted construction of the tetronic acid portion *via* Wittig reaction

3.4.1 Synthetic plan

The envisaged route was to start from the ring-opening of the lactone **274** to prepare the allylic alcohol **287**. The DCC-DMAP coupling of the allylic alcohol **287** with the acetic acid $\mathbf{N_0}$[216] followed by desilylation would afford the precursor **289** to construct the 5-membered ring. Wittig reaction of **289** with triphenylphosphoranylidene ketene $\mathbf{O_0}$ would produce the *O*-alkyl tetronic acid derivative **290**.[89] Deprotonation of the tetronic acid derivative part with base would hopefully lead to Claisen condensation product **237** to install the 7-membered ring (Scheme 140). Afterwards, tetrodecamycin (**1**) would be synthesised following the synthetic route outlined in Scheme 105.



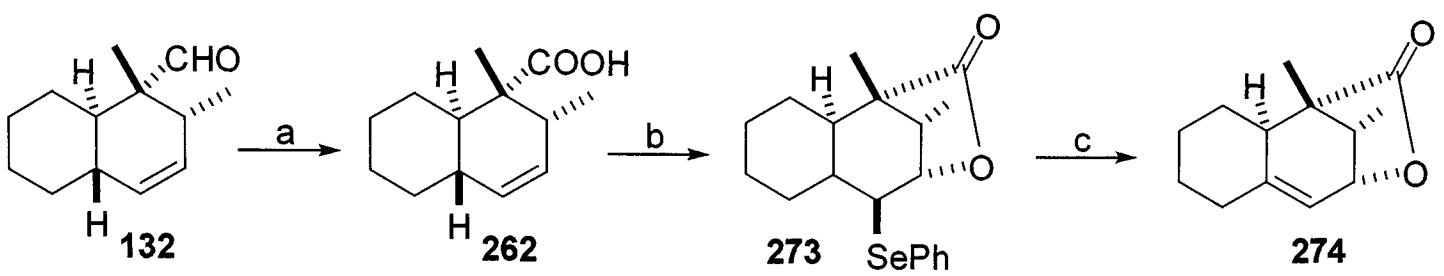
Scheme 140

a) DBU, MeOH; b) $\mathbf{N_0}$, DCC, DMAP; c) AcOH, THF, H_2O; d) $\mathbf{O_0}$; e) LDA

3.4.2 Synthesis of the lactone (274)

Aldehyde **132** was oxidised to γ,δ-unsaturated carboxylic acid **262** with sodium chlorite in

presence of a buffer and 2-methylbut-2-ene.[208] The transformation of carboxylic acid **262** into lactone **274** was achieved by phenylselenolactonisation with phenylselenyl chloride[22,209] and subsequent oxidative removal[210] of the phenylselenanyl substituent to establish the double bond (Scheme 141).

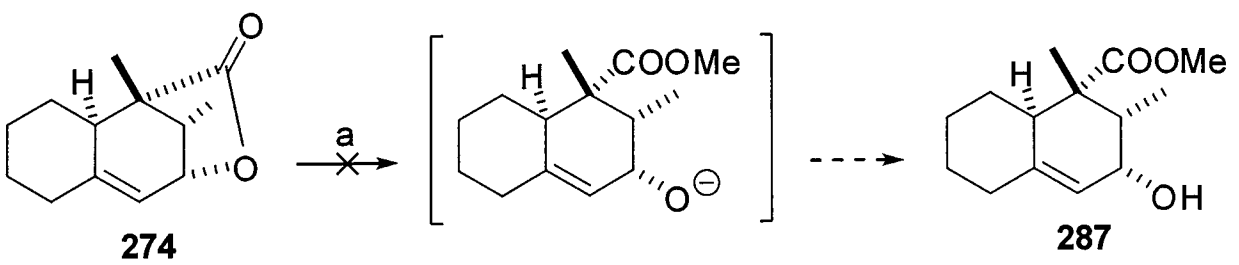


Scheme 141

a) $NaClO_2$, ^tBuOH, 2-methylbut-2-ene, KH_2PO_4, H_2O, rt (67%); b) PhSeCl, Et_3N, DCM, -78°C-rt (73%); c) H_2O_2, pyridine, THF, 0°C (90%)

3.4.3 Attempted ring-opening reactions of lactones

The lactone **274** was treated with DBU in excess amount of methanol and left stirring at room temperature for 2 days. However, no evidence of the formation of the allylic alcohol **287** was observed. Even after being kept at 50°C for 2 days, only starting lactone **274** was recovered (Scheme 142). The difficulty of opening the lactone **274** was probably because of a large steric hindrance induced by the tetra-substituted carbon next to the carbonyl group. Therefore, this idea was aborted.



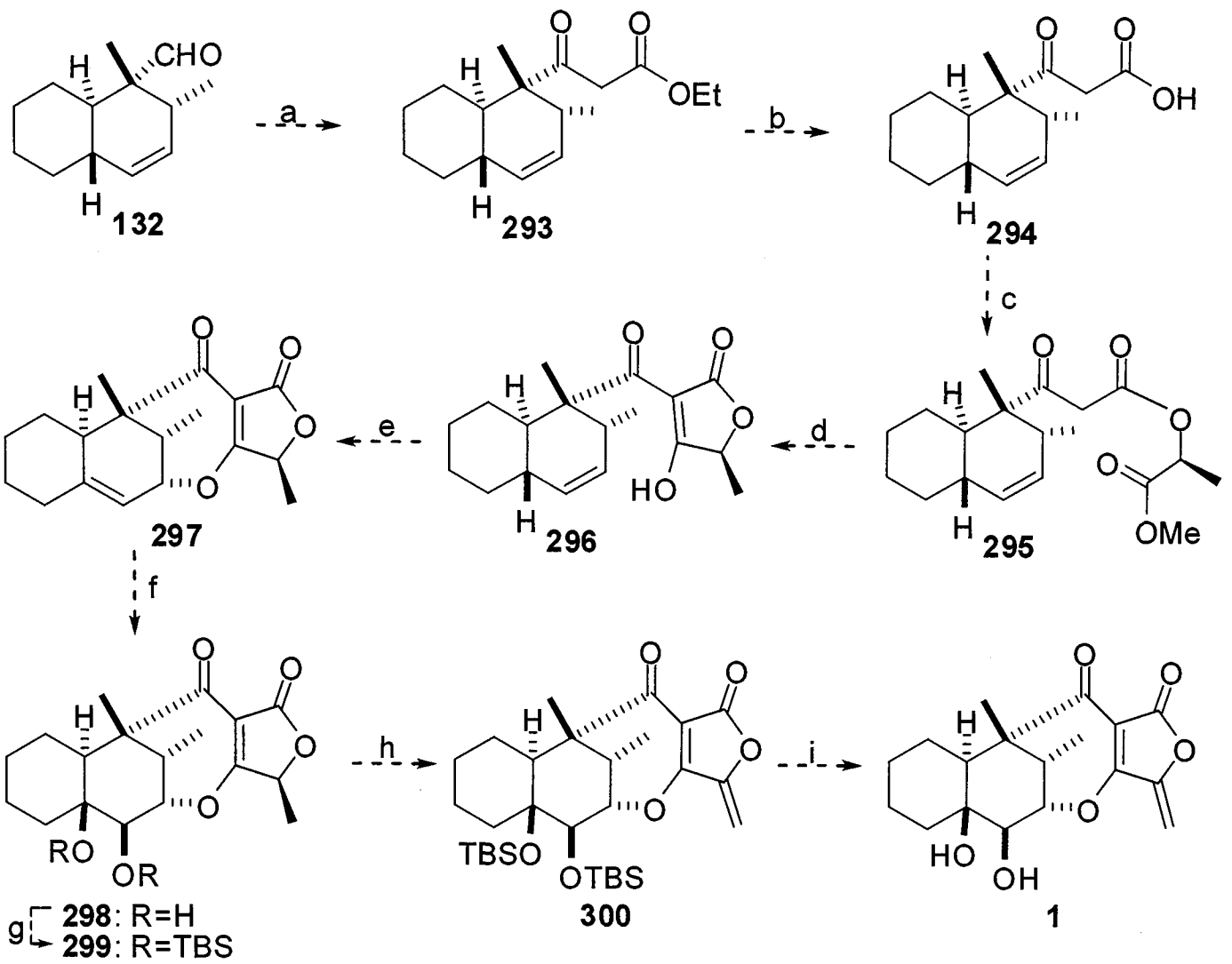
Scheme 142

a) DBU, MeOH, rt-50°C

3.5 Construction of the tetronic acid portion *via* Dieckmann-type cyclisation

3.5.1 Synthetic plan

The failure in the ring-opening reaction of lactone **274** encumbered the formation of tetronic acid derivative part *via* Wittig reaction with triphenylphosphoranylidene ketene. The attention was drawn to the Dieckmann conditions to construct the tetronic acid derivative portion (Scheme 143). It was envisaged that niobium(V) chloride[217] or tin(II) chloride[218] catalysed C-H insertion of **132** with ethyl diazoacetate would afford the β-keto ester **293**. Subsequently, the β-keto ester **293** would be converted into the Dieckmann-type reaction precursor **295** *via* a hydrolysis followed by a DCC-DMAP coupling[219] or Mitsunobu reaction.[220] The precursor **295** could then be exposed to a base, such as TBAF, to install the tetronic acid derivative part.[221,222] The Pd-catalysed oxidative cycloaddition to form the 7-membered ring would be a big challenge in this approach.[173,174,223] When the 6-6-7-5-membered tetracyclic core **297** was constructed, dihydroxylation with OsO_4 followed by TBS protection would give **299**. Compound **299** was then converted to a sulfide by treating with LDA and *N*-phenylmercaptophthalimide. The sulfide would be oxidised to corresponding sulfoxide by *m*CPBA, which on pyrolysis with $BaCO_3$ in benzene would provide the desired *exo*-methylene derivative **300**.[4] After deprotection, tetrodecamycin (**1**) would be synthesised (Scheme 143).



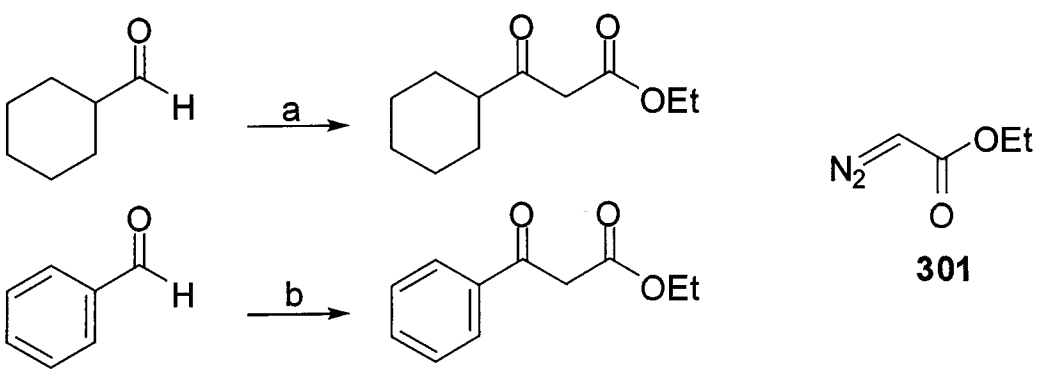
Scheme 143

a) β-keto ester formation; b) hydrolysis; c) DCC-DMAP coupling or Mitsunobu reaction; d) Dieckmann-type cylclisation; e) Pd-catalysed oxidative cycloaddition; f) dihydroxylation; g) TBS-protection; h) *exo*-methylene formation; i) deprotection

3.5.2 Synthesis of β-keto ester

3.5.2.1 Attempts on the direct conversion of aldehydes into β-keto esters

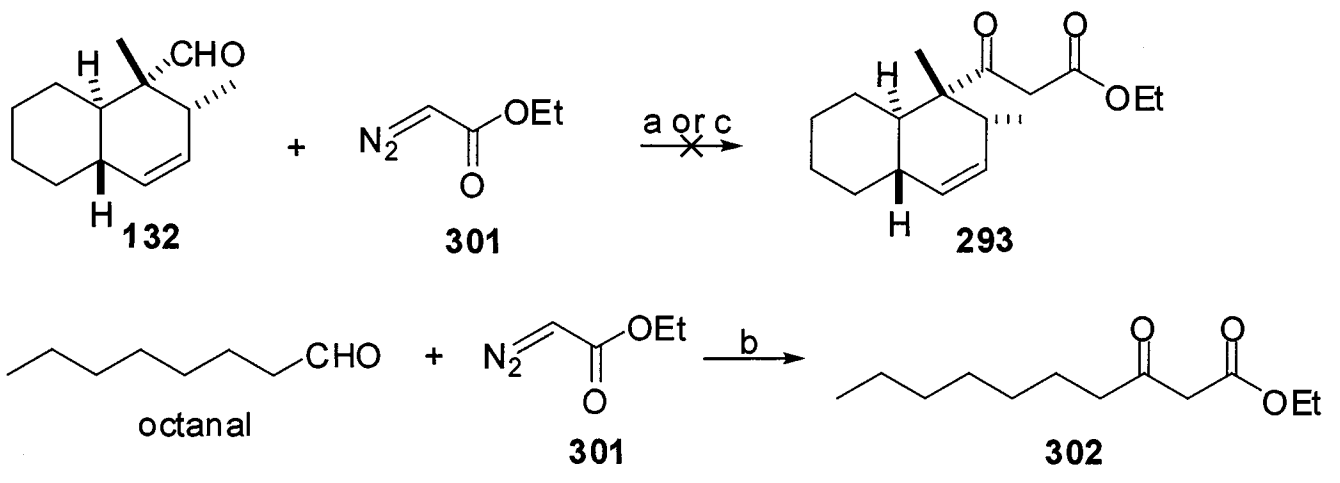
It was reported that reactions of aldehydes with ethyl diazoacetate **301** in the presence of 5 mol% of niobium(V) chloride in dichloromethane could produce the corresponding β-keto esters in good yields (Scheme 144).[217]



Scheme 144

a) **301**, 5 mol% $NbCl_5$, DCM, rt, 3.5 h (85%); b) **301**, 5 mol% $NbCl_5$, DCM, rt, 3.0 h (85%)

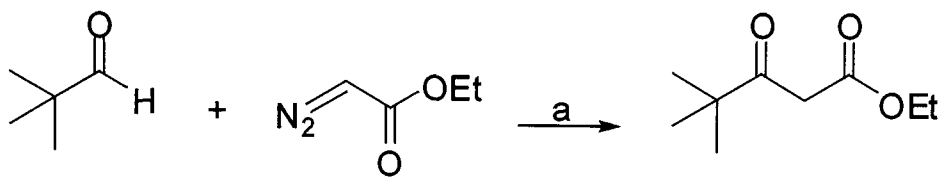
This method was applied to synthesise the desired β-keto ester **293**. However, after the reaction being left at room temperature overnight, TLC only showed starting aldehyde **132**. The mixture was then left under reflux for a whole day, but no reaction was detected, even after another addition of 5 mol% of $NbCl_5$ (Condition a, Scheme 145). The reaction was executed on octanal under the same conditions, which gave the expected β-keto ester **302** in good yield (Scheme 145). This indicated that this reaction condition was not suitable for tertiary aldehydes probably due to the steric hindrance.



Scheme 145

a) 5 mol% $NbCl_5$, DCM, rt, overnight; then reflux, overnight; another 5 mol% $NbCl_5$, reflux, overnight; b) 5 mol% $NbCl_5$, DCM, rt, 4 h (81%); c) 10 mol% $SnCl_2$, DCM, rt; then reflux; another 10 mol% $SnCl_2$, overnight

Literature searching showed that tin(II) chloride could also catalyse the conversion of aldehydes into β-keto esters with ethyl diazoacetate **301**. Moreover, it is applicable to tertiary aldehydes, but requires larger amount of catalyst (Scheme 146). That is because the reaction with tertiary aldehydes takes a long time, and in slow reactions, the catalyst is consumed by the enol form of the β-keto ester at a rate which is competitive with keto ester formation. This produces a complex of metalated enol, which no longer catalysed the reaction.[224]



301

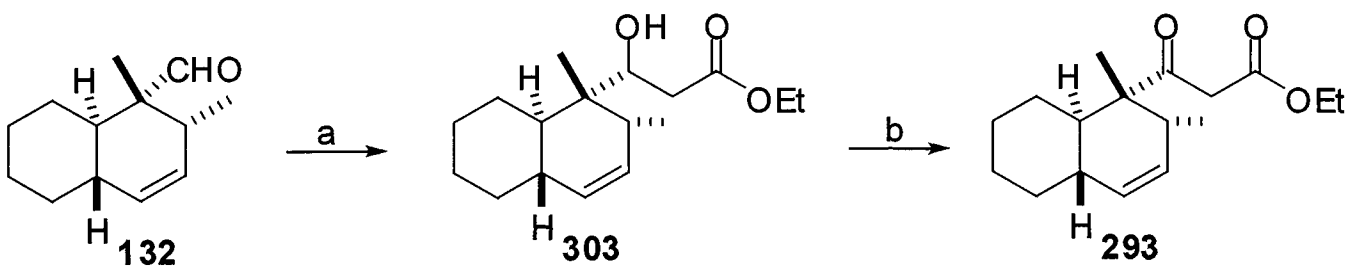
Scheme 146

a) 10 mol% $SnCl_2$, DCM, rt; an additional amount of $SnCl_2$ was added when the nitrogen evolution stopped; this procedure was repeated until there was no longer nitrogen evolution observed.

However, when this condition was applied to substrate **132**, no reaction could be observed even under reflux. Only aldehyde **132** was recovered probably due to the too hindered position of the carbonyl group (Condition c, Scheme 145).

3.5.2.2 Aldol reaction

The frustration in the efficient preparation of β-keto ester **293** from aldehyde **132** indicated that the investigation of the aldol reaction of **132** with ethyl acetate followed by an oxidation to form β-keto ester **293** had to be pursued. Ethyl acetate was lithiated with LDA at -78°C and subsequently treated with aldehyde **132** to give β-hydroxy ester **303** in good yield.[225] IBX oxidation of **303** afforded the desired β-keto ester **293** in satisfactory yield (Scheme 147). The relative stereochemistry of the hydroxyl group in compound **303** was not determined because of subsequent oxidation to form a carbonyl group.



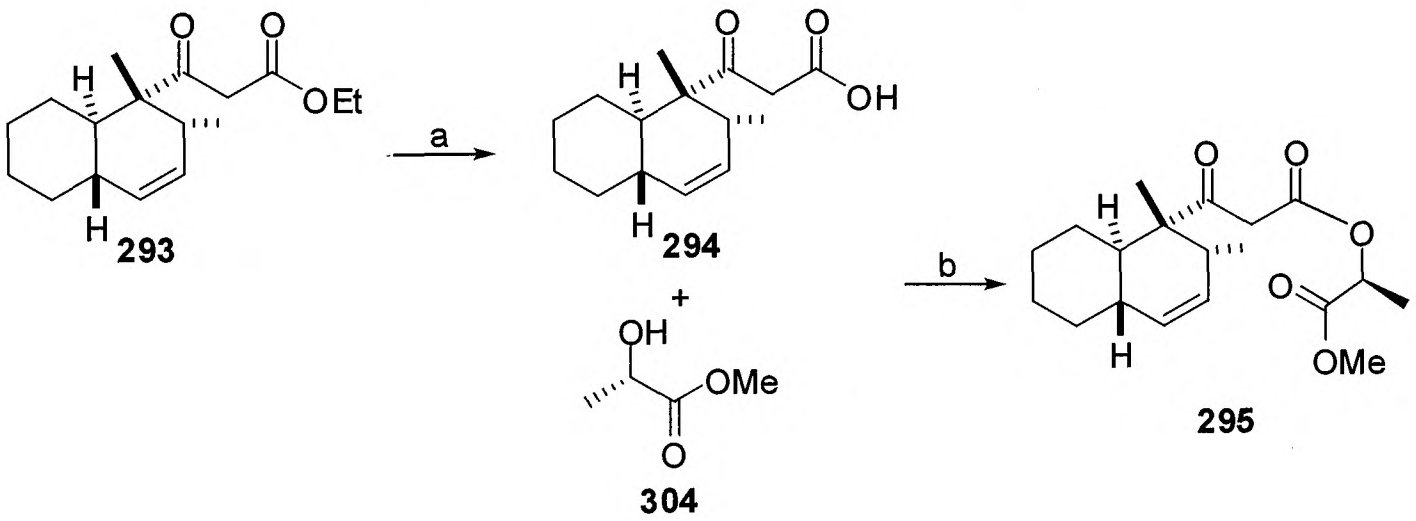
Scheme 147

a) ^{n}BuLi, $^{i}Pr_2NH$, THF, -78°C, 30 min; EtOAc, -78°C, 30 min; **132**, -78°C, 30 min; NH_4Cl (sat.) (85%); b) IBX, DMSO-THF, rt (75%)

3.5.3 Dieckmann-type cyclisation

3.5.3.1 Synthesis of Dieckmann-type cyclisation precursor

Hydrolysis of β-keto ester **293** afforded β-keto carboxylic acid **294** in quantitative yield (Scheme 148). The DCC-DMAP coupling of 1 eq of β-keto acid **294** and 1 eq of methyl (*S*)-(-)-lactate **304** only afforded 39% of **295** following the literature procedure (Entry 1, Table 10).[219] It was because the O→N acyl migration of the *O*-acylisourea intermediate that was formed in the coupling reaction led to urea, which was unable to undergo further reaction. Therefore, a Mitsunobu reaction was investigated.[220] Treatment of the β-keto acid **294** with methyl lactate **304** in the presence of DIAD and PPh_3 afforded the desired compound **295** in 59% yield (Entry 2, Table 10). Meanwhile, when the DCC-DMAP coupling reaction was performed with 2 eq methyl lactate **304**, the yield of **295** was improved to 80% (Entry 3, Table 10). The excess amount of methyl lactate **304** attributed to accelerate the rate to form the desired product **295**.



Scheme 148

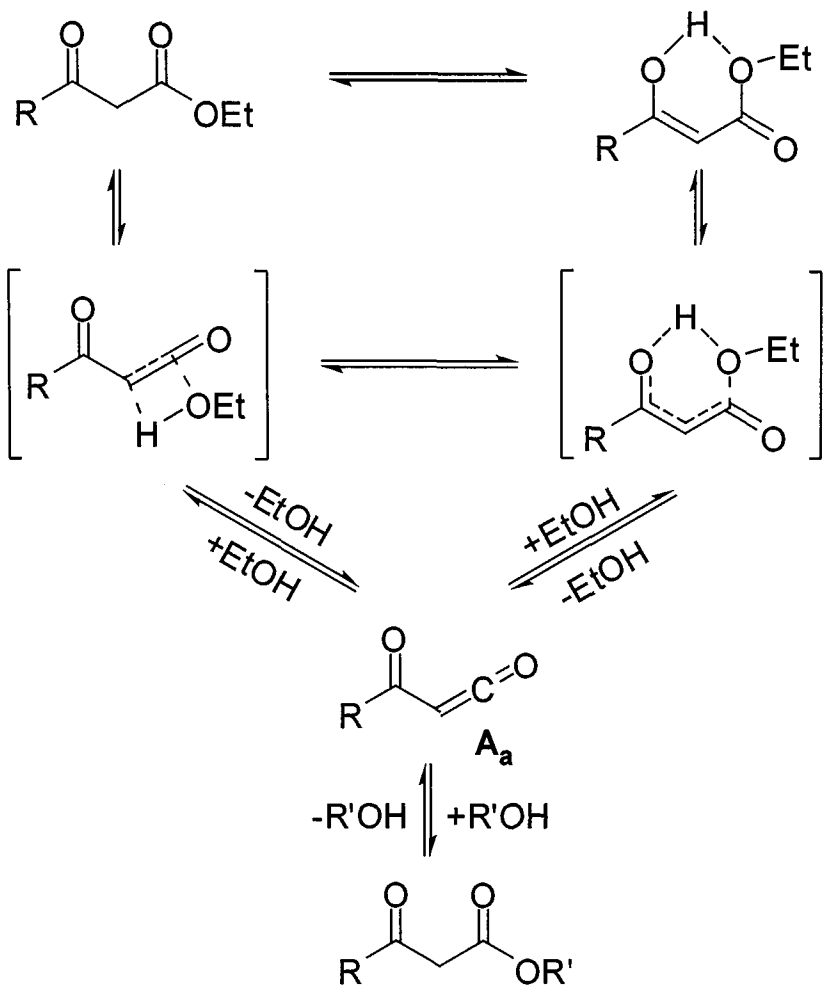
a) LiOH, MeOH, 40°C, overnight (96%)

No.	*294*	*304*	*Condition (b)*	*Yield*
1	1 eq	1 eq	DCC (2 eq), DMAP (0.3 eq), DCM, rt, 5 h[219]	39%
2	1 eq	1 eq	DIAD (1 eq), PPh_3 (1 eq), THF, rt, 2 h[220]	59%
3	1 eq	2 eq	DCC (1.1 eq), DMAP (0.3 eq), DCM, rt, 5 h	80%

Table 10

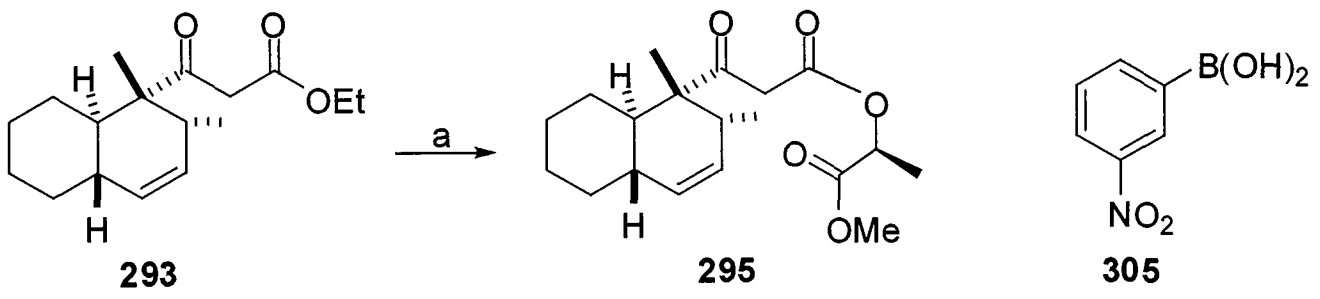
In 2006, Tale *et al.* reported that 3-nitrobenzeneboronic acid **305** is an efficient and specific

catalyst for transesterification of β-keto esters.[226] This was rationalised by the conversion of β-keto esters to an acylketene intermediate $\mathbf{A_a}$ (Scheme 149), which is not possible in other esters.[227]



Scheme 149

This procedure was applied to the synthesis of **295** to simplify the route. Delightfully, it proceeded smoothly to give the desired **295** in one step in high yield (Scheme 150).



293 **295** **305**

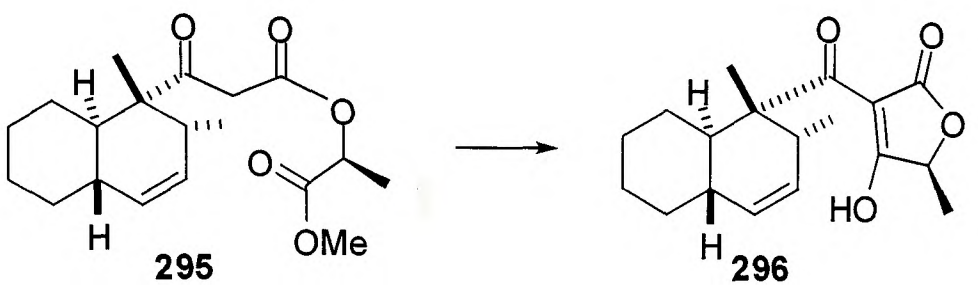
Scheme 150

a) **304**, 2.5 mol% **305**, toluene, reflux, overnight (82%)

3.5.3.2 Dieckmann-type cyclisation

With the acetoacetate **295** in hand, different bases were examined for Dieckmann-type cyclisation reaction (Scheme 151). First, the ketoacetate **295** was treated with an excess amount

of TBAF in THF at room temperature. The TLC analysis indicated a new product was formed, but the reaction proceeded very slowly. Therefore, the mixture was warmed to 40°C for five days until the ketoacetate **295** was all consumed. The crude product was purified by chromatography on silica gel eluting with ethyl acetate to afford the desired product **296** in 78% yield (Entry 1, Table 11).[221,222] Pure **296** had good solubility in methanol and DMSO, but poor solubility in acetonitrile, acetone, chloroform, dichloromethane and toluene. Meanwhile, cesium fluoride was also tested for the cyclisation reaction in different solvents (Entry 2 and 3, Table 11). These reactions were carried out in DMF and DMSO respectively at 50°C until all **295** was consumed. Both reactions took 4 days, and DMSO turned to be a better reaction solvent than DMF (60% in DMF and 71% in DMSO). Subsequently, potassium *tert*-butoxide was employed as a base following Bloomer and Kappler's method (Entry 4,5 and 6, Table 11). It was reported that the use of a *tert*-butoxide salt in *tert*-butanol under reflux would improve the yield of reactions with secondary 2-hydroxy ester derivatives.[228] However, when potassium *tert*-butoxide was added to the reaction mixture at 0°C, no reaction was observed. The mixture was then warmed to room temperature and subsequently put under reflux, but again no desired product **296** was formed. Instead, the acetoacetate **295** was hydrolysed to the corresponding acid probably due to trace amount of moisture in this reaction. In order to reduce exposure to moisture, a 1.0 M solution of lithium *tert*-butoxide in hexane was used instead of potassium *tert*-butoxide. After neutralisation with hydrochloric acid (aq. 1 N), the starting material **295** was also found to be hydrolysed (Entry 7, Table 11).



Scheme 151

No.	*Condition*	*Yield of 296*
1	TBAF (3 eq), THF, 40°C, 5 days	78%
2	CsF (4 eq), DMF, 50°C, 4 days	60%
3	CsF (4 eq), DMSO, 50°C, 4 days	71%
4	KO^{t}Bu (1.5 eq), THF, 0°C-reflux, 2 days	**295**
5	KO^{t}Bu (10 eq), ^{t}BuOH[a], 0°C-reflux, 1 days	Complex
6	KO^{t}Bu (2.5 eq), ^{t}BuOH[a], 0°C-reflux, 2 days	hydrolysed
7	LiO^{t}Bu[b] (10 eq), THF, 0°C-reflux, 2 days	hydrolysed

Table 11

a) ^{t}BuOH was freshly distilled from CaH_2. b) LiO^{t}Bu was a 1.0 M solution in hexane.

3.5.4 Conclusion of section 3.5

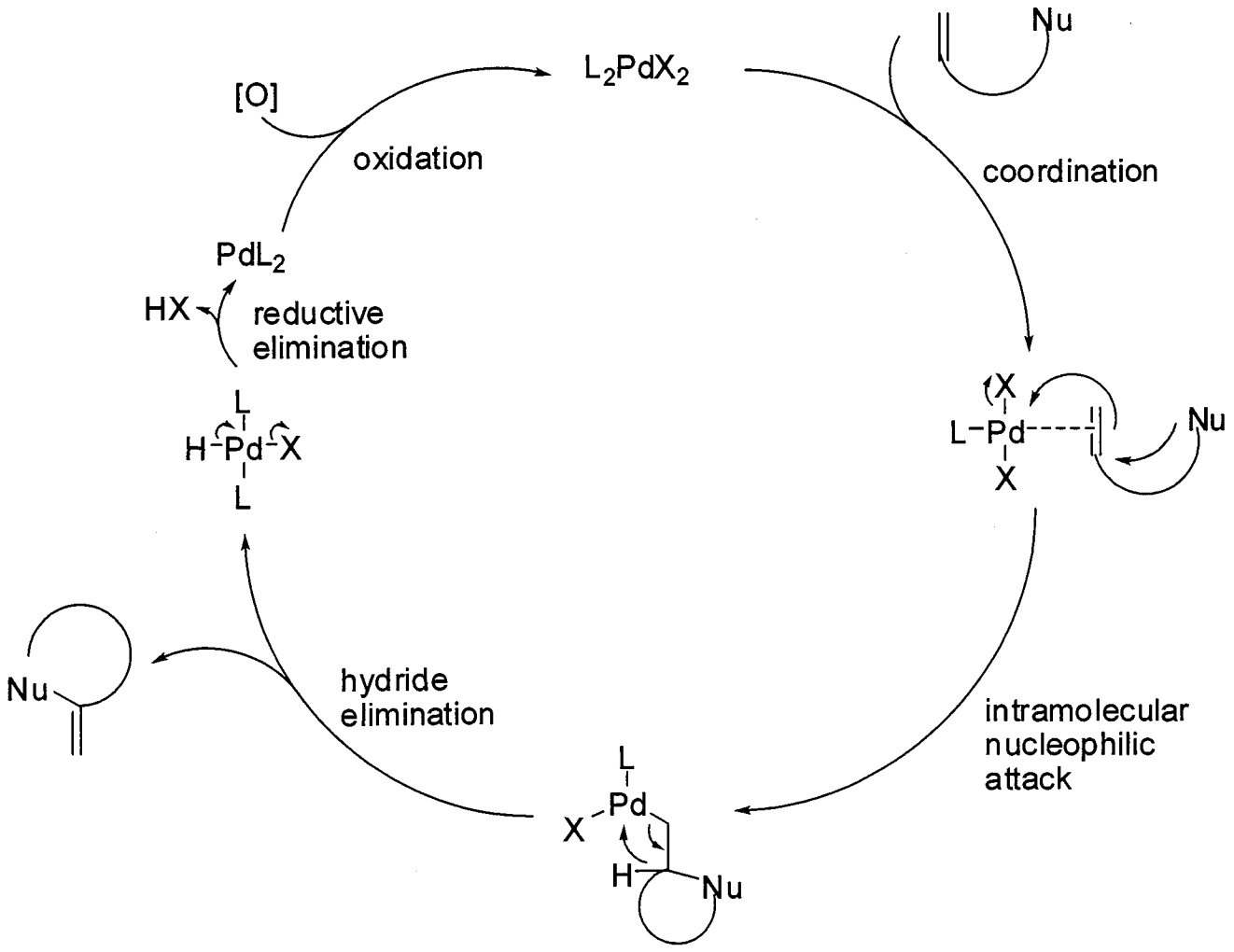
Although direct conversion of aldehyde **132** to β-keto ester **293** catalysed by $NbCl_5$ or $SnCl_2$ failed due to the large steric hindrance, β-keto ester **293** was produced *via* an aldol reaction followed by an IBX oxidation. Thereafter, the transesterification of **293** catalysed by 3-nitrobenzeneboronic acid **305** afforded the Dieckmann-type reaction precursor **295** efficiently in high yield. The Dieckmann-type cyclisation reaction of the acetoacetate **295** proceeded smoothly under treatment with TBAF or CsF. The expected product **296** was achieved in satisfactory yield, which allowed the investigation of 7-membered ring closure reactions.

3.6 Attempts to close the 7-membered ring

3.6.1 Palladium(II)-catalysed cyclisation reaction

3.6.1.1 Introduction

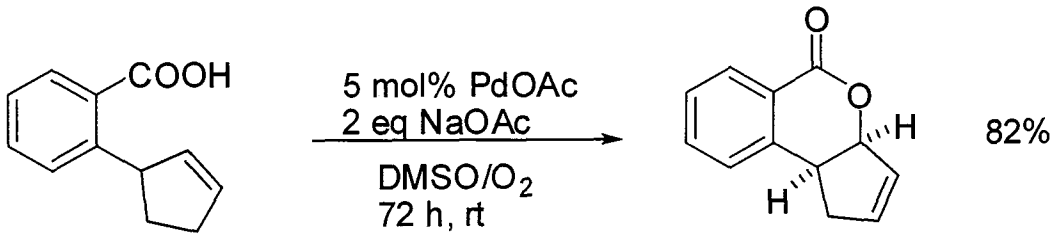
The reactivity of an alkene can be changed dramatically by coordination with palladium(II) to form a π-complex, as the electron density is drawn towards the metal and away from the π-orbitals of the alkene. This leads to activation towards attack by nucleophiles. If the nucleophilic group is an intramolecular one, cyclisation will work. The resulting Pd(II) σ-alkyl species decomposes by β-hydride elimination to reveal the substituted alkene. Reductive elimination of a proton and the leaving group X leads to Pd(0), which will be oxidised to Pd(II) by additive oxidants (Scheme 152).[229]



Scheme 152

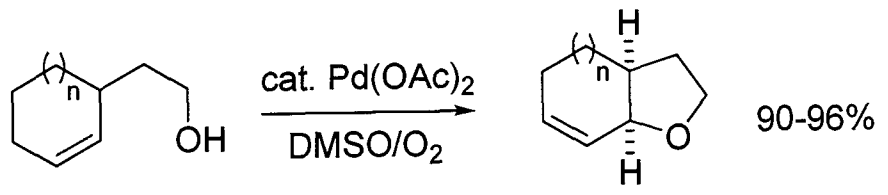
Larock and Hightower[230] reported that unsaturated lactones could be synthesised from alkenoic acids *via* a palladium(II)-catalysed cyclisation (Scheme 153). In this type of reaction oxygen

alone was remarkably efficient in reoxidising palladium, so $Cu(OAc)_2$, a common co-oxidant, could be omitted. The addition of 2 eq NaOAc was necessary to neutralise the resulting acid and keep basic reaction media in order to prevent side reactions and to maintain catalyst activity. They found that disubstituted alkene was more reactive than trisubstituted or monosubstituted ones due to its fine balance between the effects of electron density and steric hindrance. Lactones bearing 5- or 6-membered rings are all formed readily, while attempts to close 4-, 7- and 12-membered rings have thus far been unsuccessful.[223]



Scheme 153

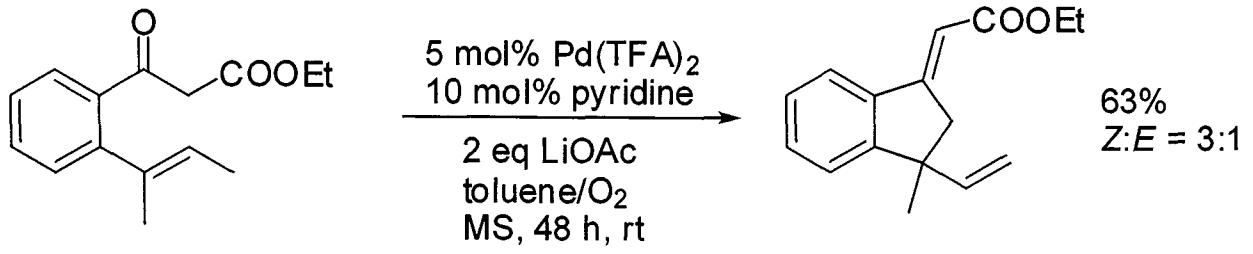
Andersson and co-workers developed a palladium(II)-catalysed intramolecular allylic oxidation using oxygen nucleophiles and molecular oxygen as reoxidant (Scheme 154). They also pointed out that using 1,4-benzoquinone as reoxidant resulted in a fast consumption of the starting material but led to an inseparable mixture of products. DMSO was an excellent solvent for Pd(II)-catalysed reactions and allows for the direct reoxidation of the palladium by molecular oxygen, while other solvents such as DMF or EtOH did not result in any reaction at all.[173]



Scheme 154

Later in 2005, Stoltz and co-workers reported that oxidative cyclisations of a variety of heteroatom nucleophiles onto unactivated olefins are catalysed by palladium(II) and pyridine using molecular oxygen as the sole stoichiometric oxidant in toluene (Scheme 155). Pyridine is added as a competent ligand to coordinate with palladium in order to minimize the precipitation

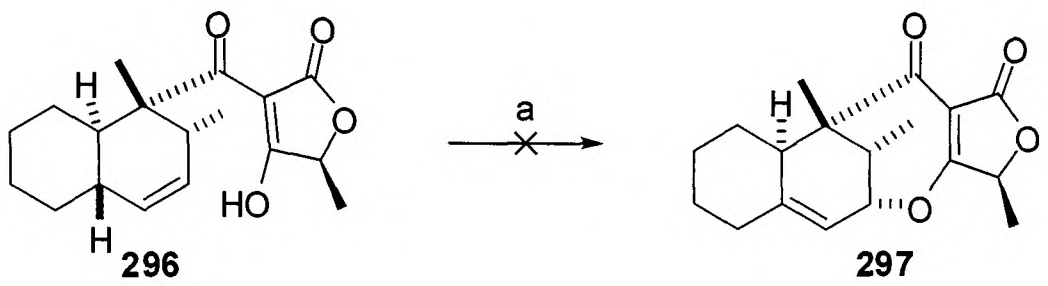
of Pd black. Toluene was used as solvent instead of DMSO, because DMSO is a highly donating solvent that could interfere with the coordination of pyridine to palladium. The reaction was accelerated by an addition of a proper exogenous base.[174]



Scheme 155

3.6.1.2 Attempted cyclisation of 7-membered ring

This Pd(II)-catalysed oxidative cyclisation was applied to compound **296** (Scheme 156). Firstly, 5 mol% $Pd(OAc)_2$ was employed in this reaction together with 0.2 eq pyridine, 2 eq NaOAc and 3Å molecular sieves in DMSO under oxygen. The reaction was left at 80°C for 1 day, and no desired product was formed but instead, precipitation of Pd black was observed. Therefore, another 5 mol% of $Pd(OAc)_2$ was added, and the reaction was left at 80°C for another two days. Unfortunately, no product was formed (Entry 1, Table 12). It was reported that a more electron-deficient Pd source would be more selective in the cyclisation, but the use of palladium triflate ($Pd(OTf)_2$) only resulted in degradation of the catalyst (formation of Pd black).[174] Palladium trifluoroacetate ($Pd(TFA)_2$) was reported to be the best choice as Pd source.[174] However, no reaction was observed when palladium trifluoroacetate ($Pd(TFA)_2$) was utilised instead of $Pd(OAc)_2$ (Entry 2, Table 12). Probably, the solvent, DMSO, affected the coordination between Pd and pyridine resulting precipitation of Pd black. Therefore, toluene was used instead of DMSO. Although **296** had poor solubility in toluene, it was hoped that the consumption of the soluble starting material **296** in the reaction would lead more **296** to dissolve and undergo cycloaddition. However, even after a few days, only starting material **296** was recovered. This might be due to the poor solubility of **296** (Entry 3, Table 12).



Scheme 156

No.	Condition (a)	result
1	$Pd(OAc)_2$ (5 mol%), py (0.2 eq), NaOAc (2 eq), 3Å MS, DMSO/O_2, rt to 80°C; then another addition of $Pd(OAc)_2$ (5 mol%), 80°C	-----
2	$Pd(TFA)_2$ (5 mol%), py (0.2 eq), NaOAc (2 eq), 3Å MS, DMSO/O_2, rt to 80°C; then another addition of $Pd(TFA)_2$ (5 mol%), 80°C	-----
3	$Pd(TFA)_2$ (5 mol%), py (0.2 eq), NaOAc (2 eq), 3Å MS, toluene/O_2, rt to 80°C; then another addition of $Pd(TFA)_2$ (5 mol%), 80°C	-----

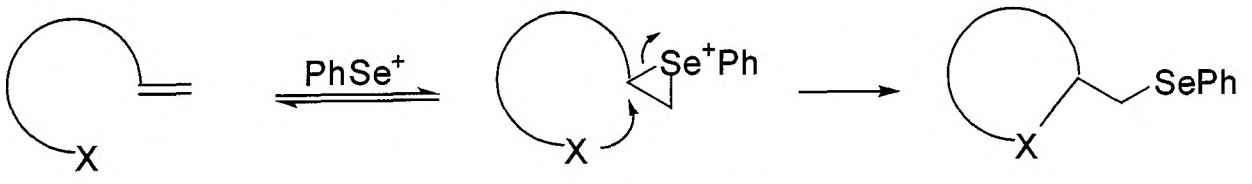
Table 12

The frustration of the cycloaddition of **296** was probably due to the steric hindrance of the disubstituted double bond and the disfavour in the formation of 7-membered ring *via* Pd(II)-catalysed oxidative cyclisation.[174]

3.6.2 Organoselenium-mediated cyclisation reaction

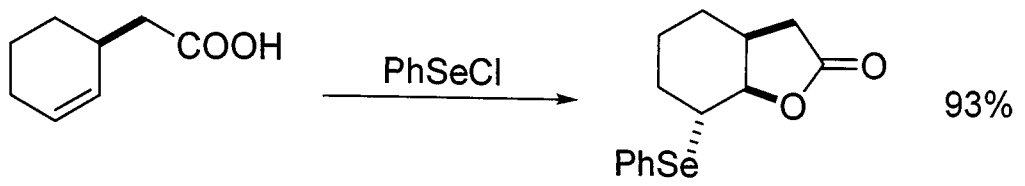
3.6.2.1 Introduction

Electrophilic selenium reagents are reported to be very effective in promoting cyclisation of unsaturated molecules containing potentially nucleophilic substituents (Scheme 157).[231]



Scheme 157

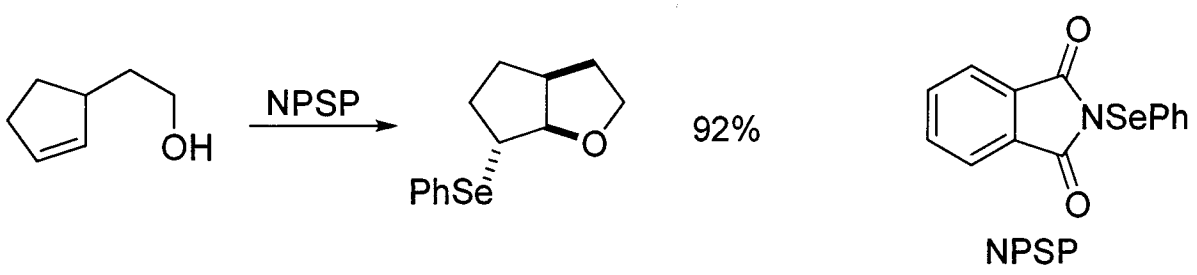
Unsaturated carboxylic acids can be converted to selenolactones *via* selenolactonisation (Scheme 158). It appears that the formation of five-membered lactones are preferred over four- and six-membered lactones, while four- and six-membered lactones are preferred over seven- and eight-membered ones, respectively.[232]



Scheme 158

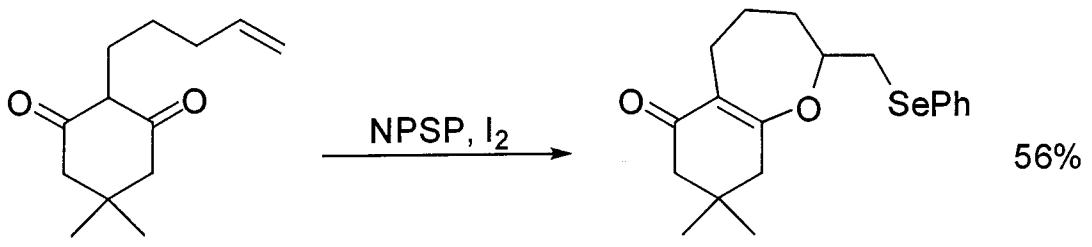
N-Phenylseleneophthalimide (NPSP) is an excellent reagent for this process and permits the formation of large-ring lactones. The advantage of this reagent lies in the low nucleophilicity of the phthalimide anion, which does not compete with the remote internal nucleophile.[176]

Unsaturated hydroxy and thio compounds that were subjected to phenylselenoetherification process could afford a series of phenyl selenoethers and phenyl selenothioethers. These compounds could be transformed to a variety of heterocyclic systems by reductive or oxidative removal of the selenium group (Scheme 159).[233] Similarly, this process also leads preferentially to the formation of five-membered rings rather than four- or six-membered rings. A six-membered ring is formed in preference to a seven-membered ring.[233]



Scheme 159

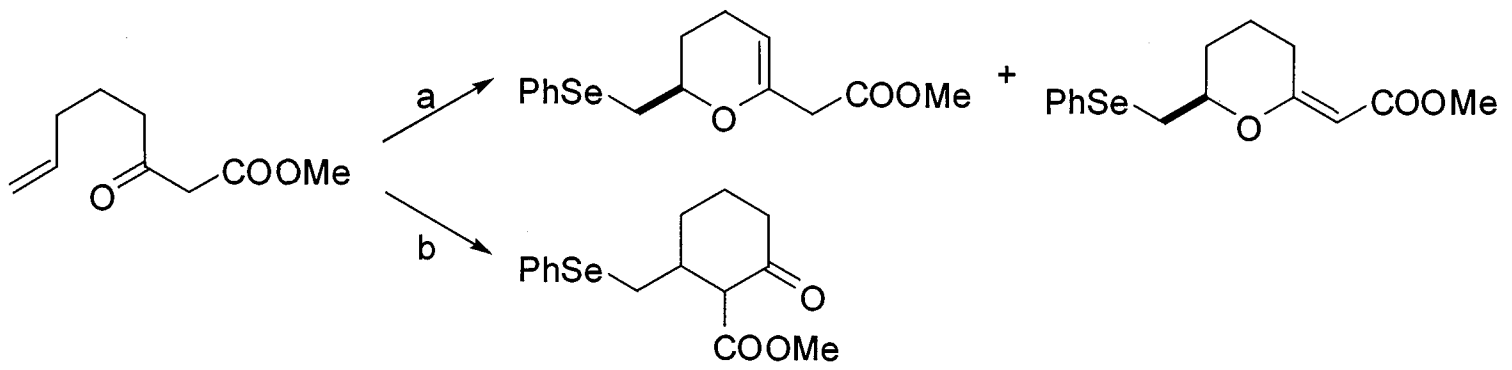
Ley *et al.* reported that NPSP can be used as an effective cyclising reagent for certain alkenyl-substituted β-dicarbonyl compounds *via* the oxygen atom of the enolic form of the dicarbonyl system with a presumed intermediate seleniranium ion (Scheme 160).[234]



Scheme 160

Later Ley and co-workers found that NPSP together with a Lewis acid catalyst, $SnCl_4$, was a

good reagent combination for this type of reaction.[175,235] However, different amounts of $SnCl_4$ led to different products. The reaction with trace amount of $SnCl_4$ (0.01 eq) afforded heterocyclic rings; while the reaction with a greater quantity of $SnCl_4$ (1 eq) resulted in the rapid formation of the carbocyclic product (Scheme 161).[235]



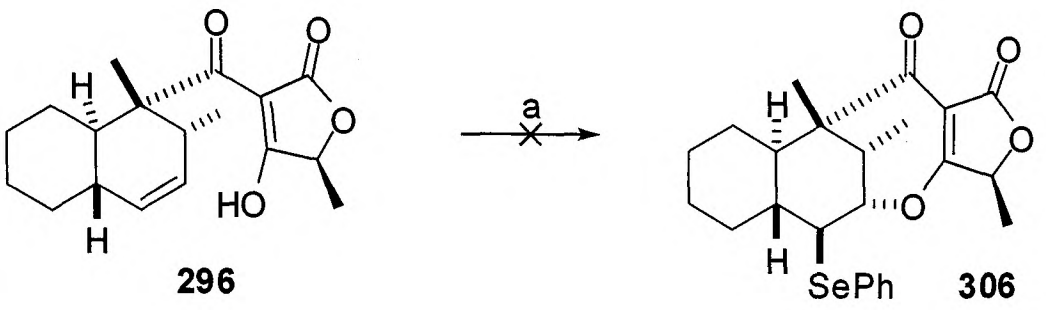
Scheme 161

a) NPSP-$SnCl_4$ (1.1:0.01), rt, DCM, 2 h (combined yield: 84%); b) NPSP-$SnCl_4$ (1.1:1.0), rt, DCM, 30 min (83%)

Other phenylselenating reagents, such as $PhSeSbF_6$, $PhSePF_6$, PhSeBr and PhSeCl can also react with alkenyl-substituted β-ketoesters to afford cyclised products.[177,236]

3.6.2.2 Attempted cyclisation of 7-membered ring

The investigation on the organoselenium-mediated cyclisation reaction of compound **296** was explored under different conditions (Scheme 162, Table 13). Compound **296** was firstly treated with NPSP and 0.01 eq $SnCl_4$ in chloroform because of the low solubility of **296** in dichloromethane and tetrahedrofuran. The mixture was left at room temperature for 3 days, but no product was observed even after another 0.09 eq $SnCl_4$ was added (Entry 1, Table 13). The addition of 1 eq of $SnCl_4$ or a crystal of iodine did not lead to the cyclised product (Entry 2 and 3, Table 13). Finally, the cyclisation reaction was carried out with PhSeCl and triethylamine, and it was left stirring at room temperature for one week. However, only starting material **296** was recovered (Entry 4, Table 13).



Scheme 162

No.	Condition (a)	result
1	NPSP (1.1 eq), $SnCl_4$ (0.01 eq), $CHCl_3$, rt, 3 days; then another $SnCl_4$ (0.09 eq) was added, rt, 3 days	-----
2	NPSP (1.1 eq), $SnCl_4$ (0.5 eq), $CHCl_3$, rt, 3 days; then another $SnCl_4$ (0.5 eq) was added, rt, 3 days	-----
3	NPSP (1.1 eq), I_2 (a crystal), DCM, rt, 3 days; then another $SnCl_4$ (0.5 eq) was added, rt, 3 days	-----
4	PhSeCl (1.1 eq), Et_3N (1.1 eq), DCM, rt, 7 days	-----

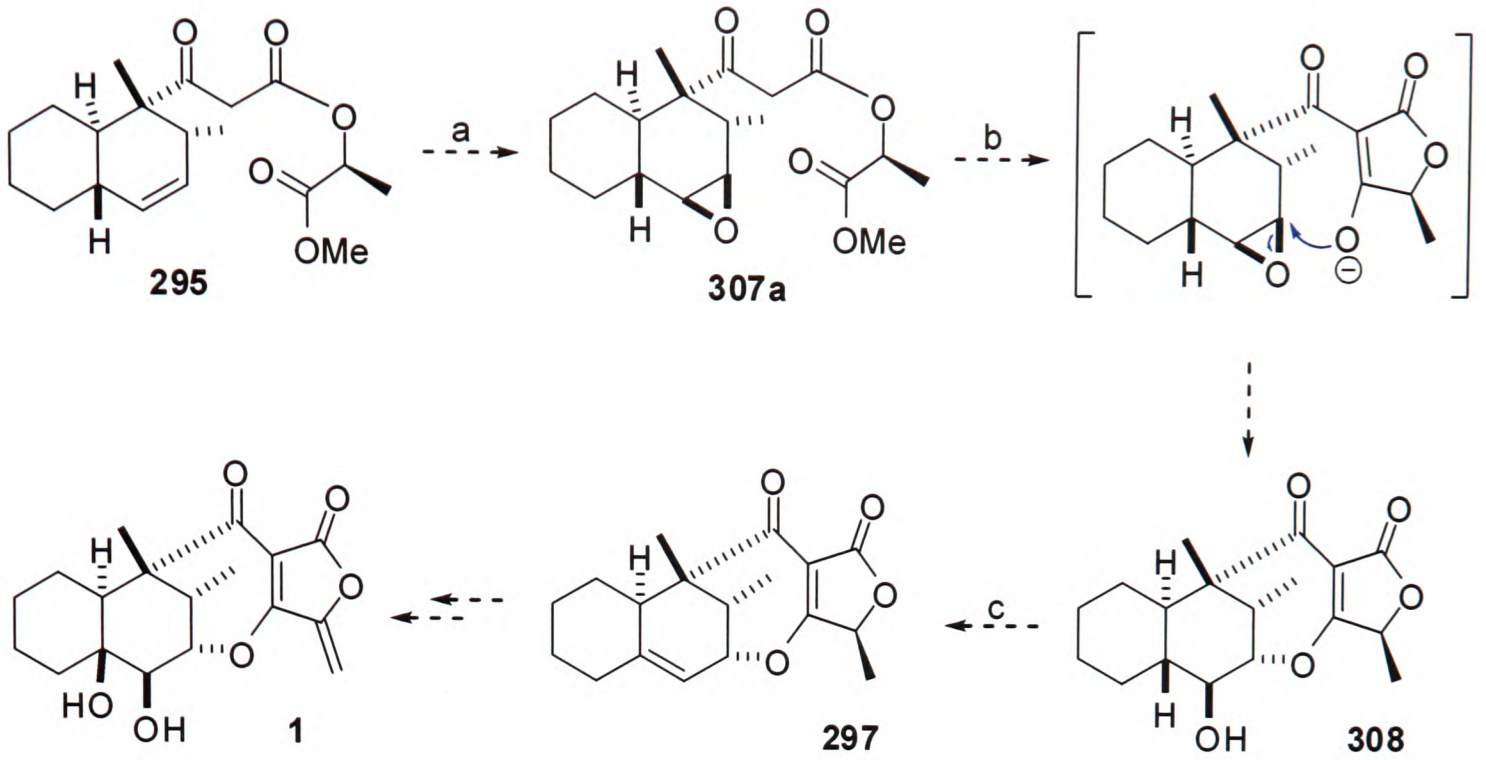
Table 13

It was speculated that the poor solubility of **296** in chloroform and dichloromethane was the main obstacle. Therefore, the attention was drawn to the investigation on a one-pot cyclisation.

3.6.3 Investigations on one-pot cyclisation

3.6.3.1 Attempted one-pot cyclisation of the epoxide

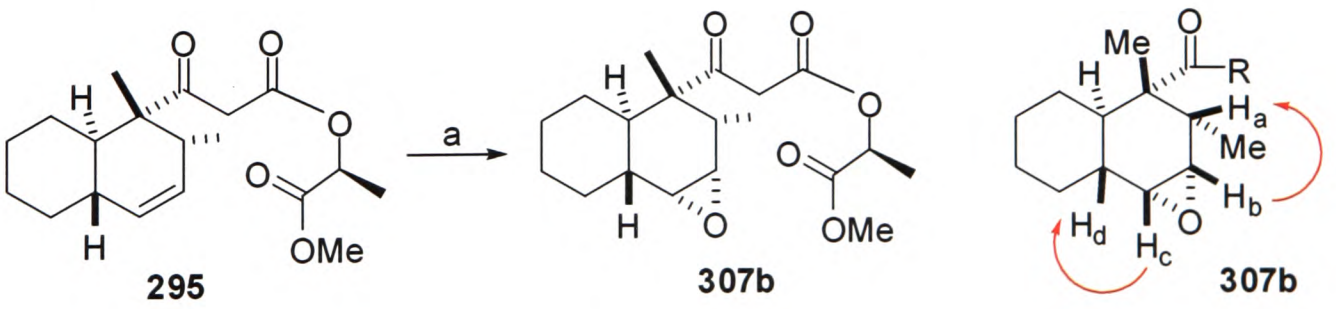
It was proposed that the epoxidation of **295** would afford the epoxide **307a** with the oxygen attacking from the top face of the decalin ring because of less steric hindrance. It was hoped that the epoxide **307a** would undergo a cyclisation under Dieckmann conditions to form a nucleophilic oxygen anion. The nucleophilic oxygen anion would subsequently attack the epoxide in an S_N2 manner to give the 6-6-7-5-membered skeleton **308** in one pot. Dehydration of **308** with Burgess reagent, (methoxycarbonylsulfamoyl)triethylammonium hydroxide, would afford olefin **297**, which would be elaborated to the target molecule (**1**) (Scheme 163).



Scheme 163

a) *m*CPBA; b) TBAF or CsF; c) $Et_3NSO_2NCOOMe$

Epoxidation of acetoacetate **295** with mCPBA provided the epoxide **307b** in good yield (Scheme 164). Unexpectedly, the enhancements of H_a by H_b and H_d by H_c on the n.O.e spectra were observed, which indicated that *m*CPBA attacked from lower face of the ring to afford the diastereoisomer **307b**. It was probably the hydrogen bond between *m*CPBA and the carbonyl groups in **295** that led to the formation of **307b** other than **307a**. This diastereoisomer was unable to undergo an S_N2 reaction. Treatment of the epoxide **307b** with TBAF only produced a complex mixture.



Scheme 164

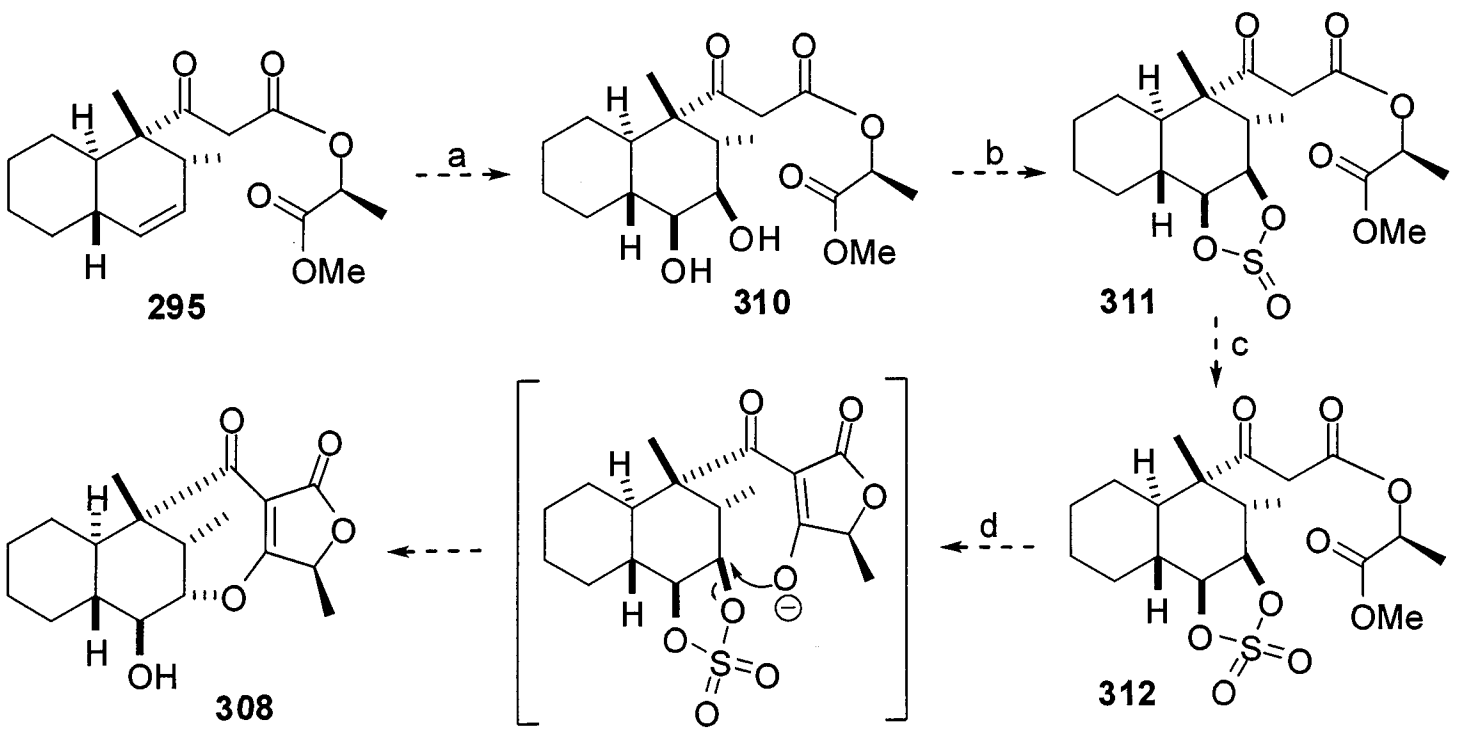
a) *m*CPBA, DCM, -78°C-rt, overnight (57%)

3.6.3.2 Attempted one-pot cyclisation of the cyclic sulphate and cyclic sulphite

The cyclic sulphate has been widely used as an important intermediate in organic synthesis. The

high reactivity of cyclic sulphates has been attributed to the ring strain. The origin of the ring strain is probably caused by the angle strain, partial double bond character between the ring oxygen and sulfur due to the 2p(O)-3d(S) orbital interaction, and the 1,3-nonbonding interactions between the ring oxygen and the exocyclic oxygen. In addition to the ring strain, the good leaving ability of the $ROSO_3^-$ moiety makes the 5-membered cyclic sulphate highly reactive towards various nucleophiles, like alcohols, azides or amines, thiols, halides and C-nucleophiles as well.[237]

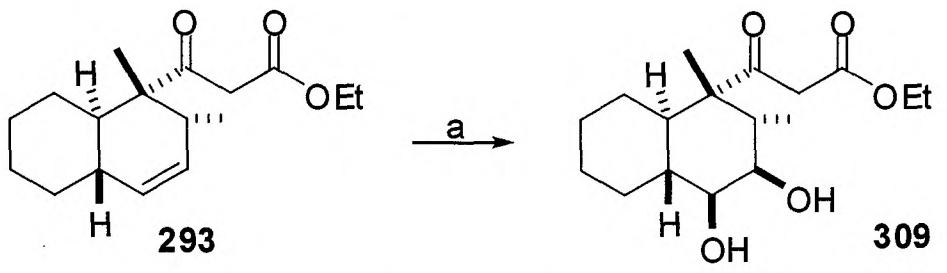
The formation of the undesired isomer **307b** turned focus onto the one-pot cyclisation of the cyclic sulphate **312**. Hopefully, without the effect of hydrogen bond, dihydroxylation of **295** with osmium tetroxide would afford the diol **310** by attacking from the less hindered top face. The diol **310** would be converted to the cyclic sulphite **311** upon treatment with thionyl chloride. The subsequent oxidation of **311** would afford cyclic sulphate **312**, which would possess the necessary configuration to undergo an S_N2 substitution forming the 6-6-7-5-membered skeleton **308** in one pot (Scheme 165).



Scheme 165

a) OsO_4; b) $SOCl_2$; c) $NaIO_4$, $RuCl_3$; d) TBAF or CsF

Dihydroxylation reaction was performed on the β-keto ester **293** as a model reaction, since it was more easily available. The OsO_4-NMO dihydroxylation of the β-keto ester **293** afforded the diol **309** in high yield (Scheme 166).[238] The n.O.e analysis established the expected stereochemistry of the diol **309**. The direct enhancements between H_a and Me_b, H_a and H_d, H_c and $(Me)_b$, H_c and H_d, H_d and $(Me)_b$ were observed, which indicated that H_a, H_c, H_d and $(Me)_b$ were on the same side, while the enhancement of $(Me)_a$ by H_b confirmed that they were on the other side of the ring (Figure 18).



Scheme 166

a) OsO_4 (cat.), NMO, $^tBuOH/H_2O$, rt, 4 h (92%)

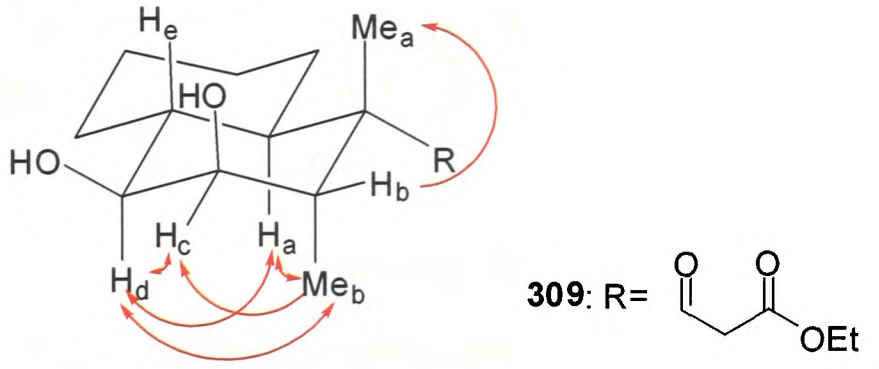
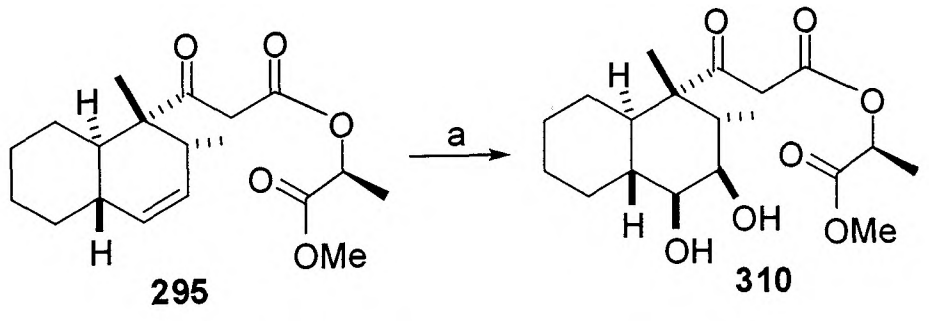


Figure 18

This dihydroxylation protocol was applied to the acetoacetate **295** to afford the diol **310** in high yield (Scheme 167), the stereochemistry of which was confirmed by n.O.e analysis as well (Figure 19).



Scheme 167

a) OsO_4 (cat.), NMO, $^tBuOH/H_2O$, rt, overnight (76%)

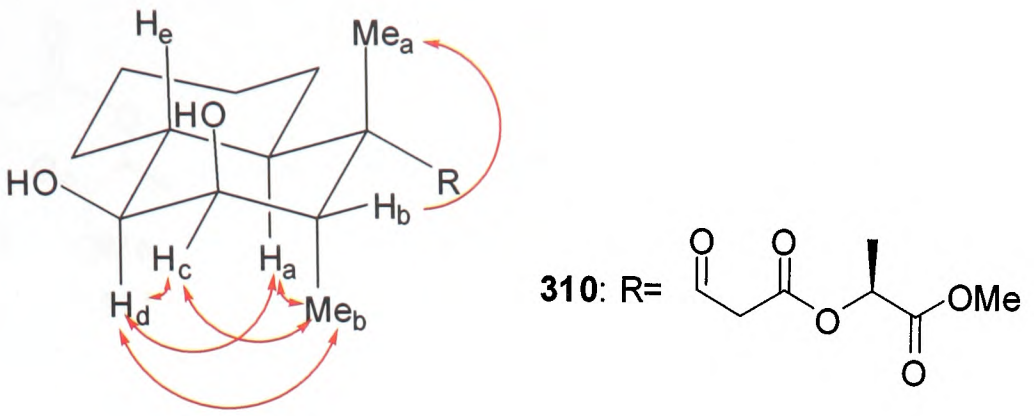
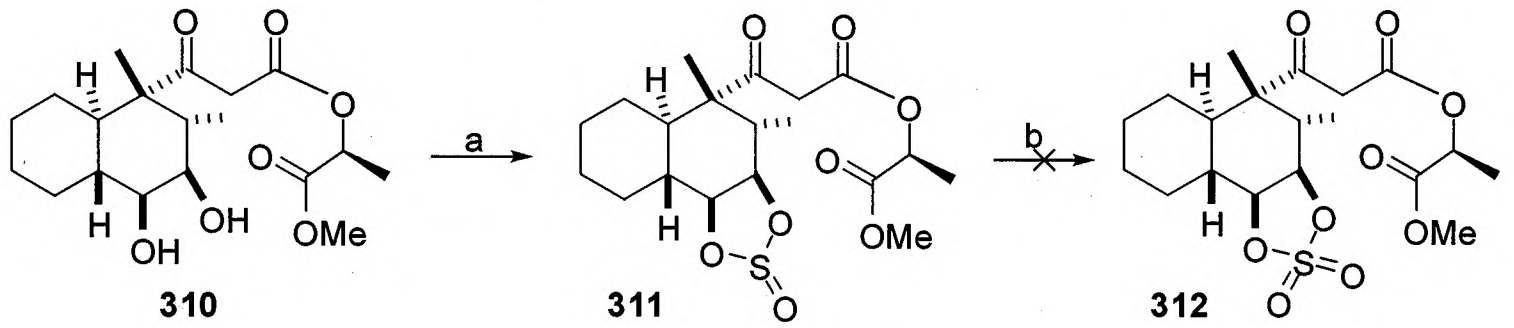


Figure 19

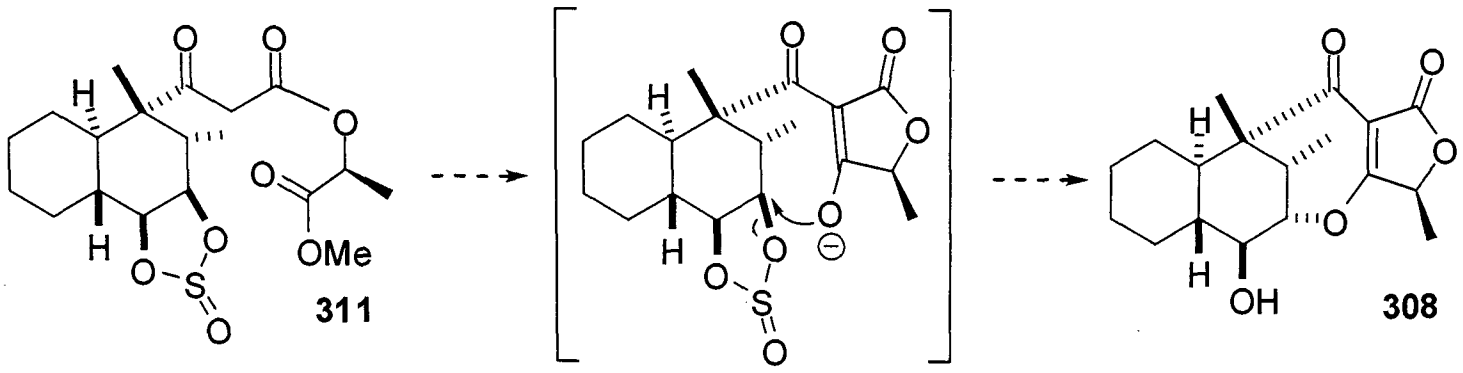
The synthesis of cyclic sulphite and cyclic sulphate was using the general procedure reported by Sharpless *et al.*[239] The formation of diol cyclic sulphite **311** proceeded smoothly by treatment of diol **310** with thionyl chloride in presence of pyridine at room temperature.[240,241] However, attempted catalytic oxidation of cyclic sulphite **311** using a ruthenium catalyst failed to deliver the cyclic sulphate **312** (Scheme 168). Instead, a complex mixture was afforded.



Scheme 168

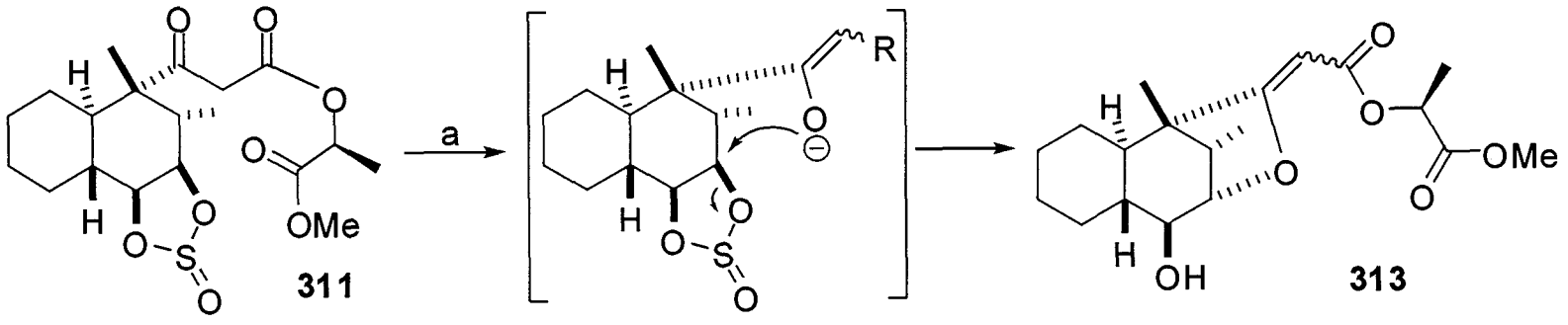
a) $SOCl_2$, pyridine, DCM, 0°C, 12 h (95%); b) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$ (2:3:3, v/v/v), rt

Since cyclic sulphites also have high reactivities towards nucleophiles,[237] compound **311** was submitted to the Dieckmann conditions. It was hoped that the tetronic acid derivative portion would be formed rapidly, and the resulting oxygen anion would undergo a nucleophilic attack to open the cyclic sulphite so as to afford the desired product **308** (Scheme 169).



Scheme 169

However, upon treatment with TBAF, the reaction did not undergo Dieckmann-type cyclisation as expected. Instead, the oxygen anoin of the enolised carbonyl group attacked the cyclic sulphite directedly to form substituted tetrahydrofuran ring **313** (Scheme 170). The NMR spectra indicated it to be a homogeneous substance. However, the geometry of the C=C double bond was not determined. This indicated the formation of 5-membered ring was faster than the Dieckmann-type cyclisation.

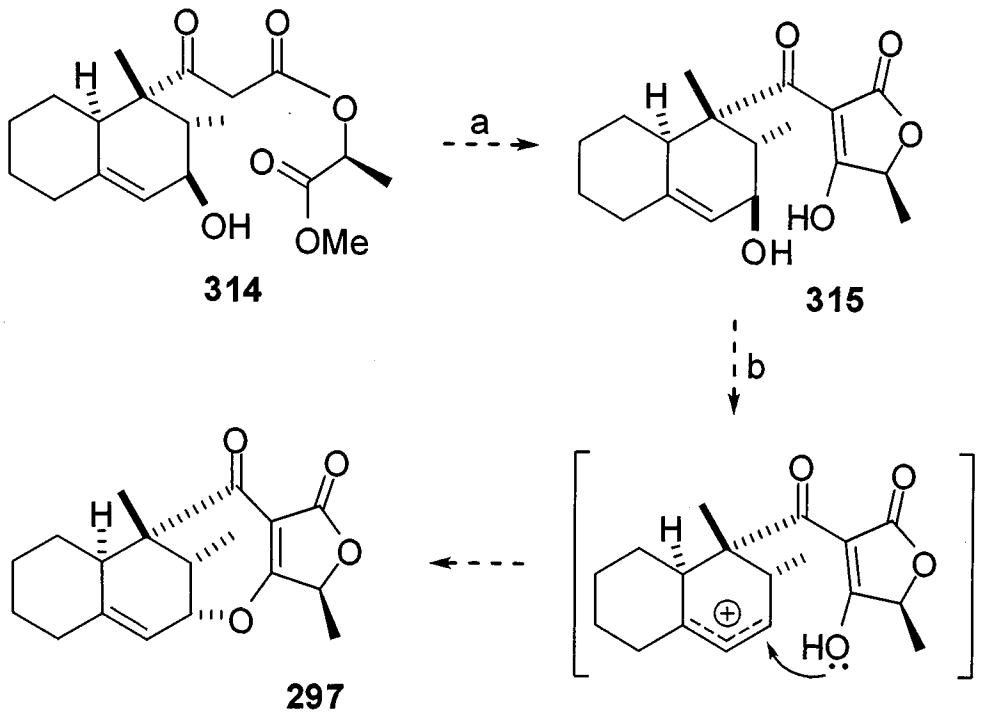


Scheme 170

a) TBAF, THF, rt, 3 days (62%)

3.6.3.3 Attempted cyclisation of the allylic alcohol

It was proposed that when the allylic alcohol **314** was exposed to TBAF, a Dieckmann-type cyclisation would proceed to form **315**. Treatment compound **315** with strong acid directly without work-up or purification would hopefully lead to a nucleophilic attack of the allylic cation by oxygen on the tetronic acid part to give the desired **297** (Scheme 171).

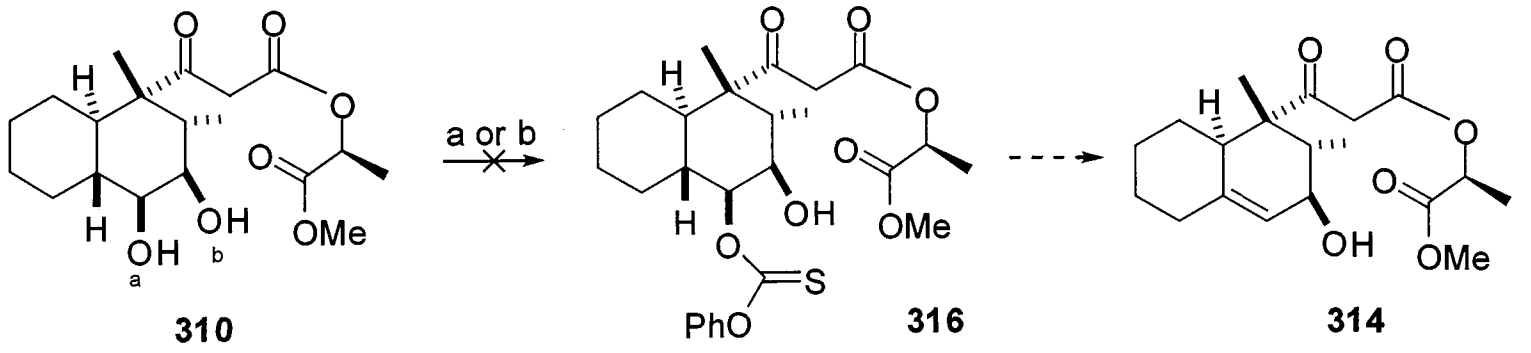


Scheme 171

a) TBAF; b) strong H^+

Gerlach *et al.* reported that olefins can be synthesised from sterically hindered alcohols *via* pyrolysis of thiocarbonate *O*-esters. Treatment of alcohol with phenyl chlorothioformate in pyridine at room temperature gives the corresponding thiocarbonate *O*-esters, which decomposes smoothly at temperature ≥ 135°C into olefin.[242]

It was postulated that the $(OH)_a$ of diol **310** adopted a pseudo-equatorial position, while $(OH)_b$ adopted a pseudo-axial position, which made the $(OH)_a$ less hindered. Therefore, the phenyl cholorothioformate would react with $(OH)_a$ to give thiocarbonate *O*-ester **316**, which would hopefully be converted into the allylic alcohol **314** under high temperature (Scheme 172).

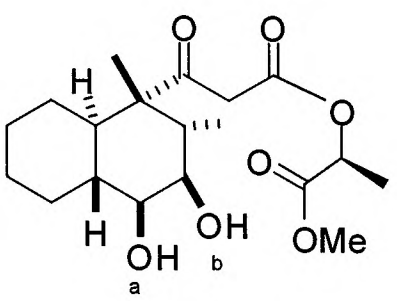


Scheme 172

a) PhOCSCl, pyridine; b) PhOCSCl, pyridine, 4-pyrrolidinylpyridine, rt-50°C

Surprisingly, treatment of the diol **310** with phenyl chlorothioformate did not lead to the

formation of the thiocarbonate *O*-ester **316** even after 4-pyrrolidinylpyridine was added and the mixture was warmed to 50°C. The steric hindrance was possibly the major problem that caused the failure. This effect could be seen from the modelling structure of **310** (Figure 20: Modelling structure of **310**).



310

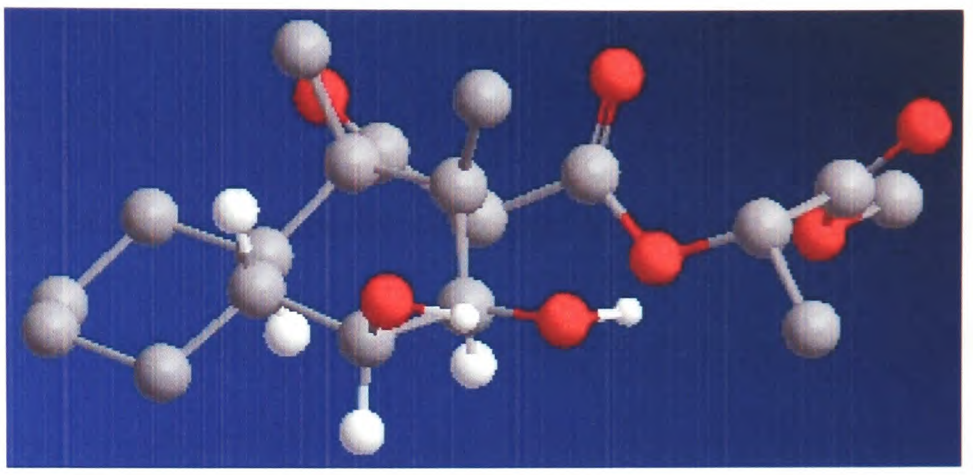


Figure 20: Modelling structure of **310**

3.6.4 Conclusion of section 3.6

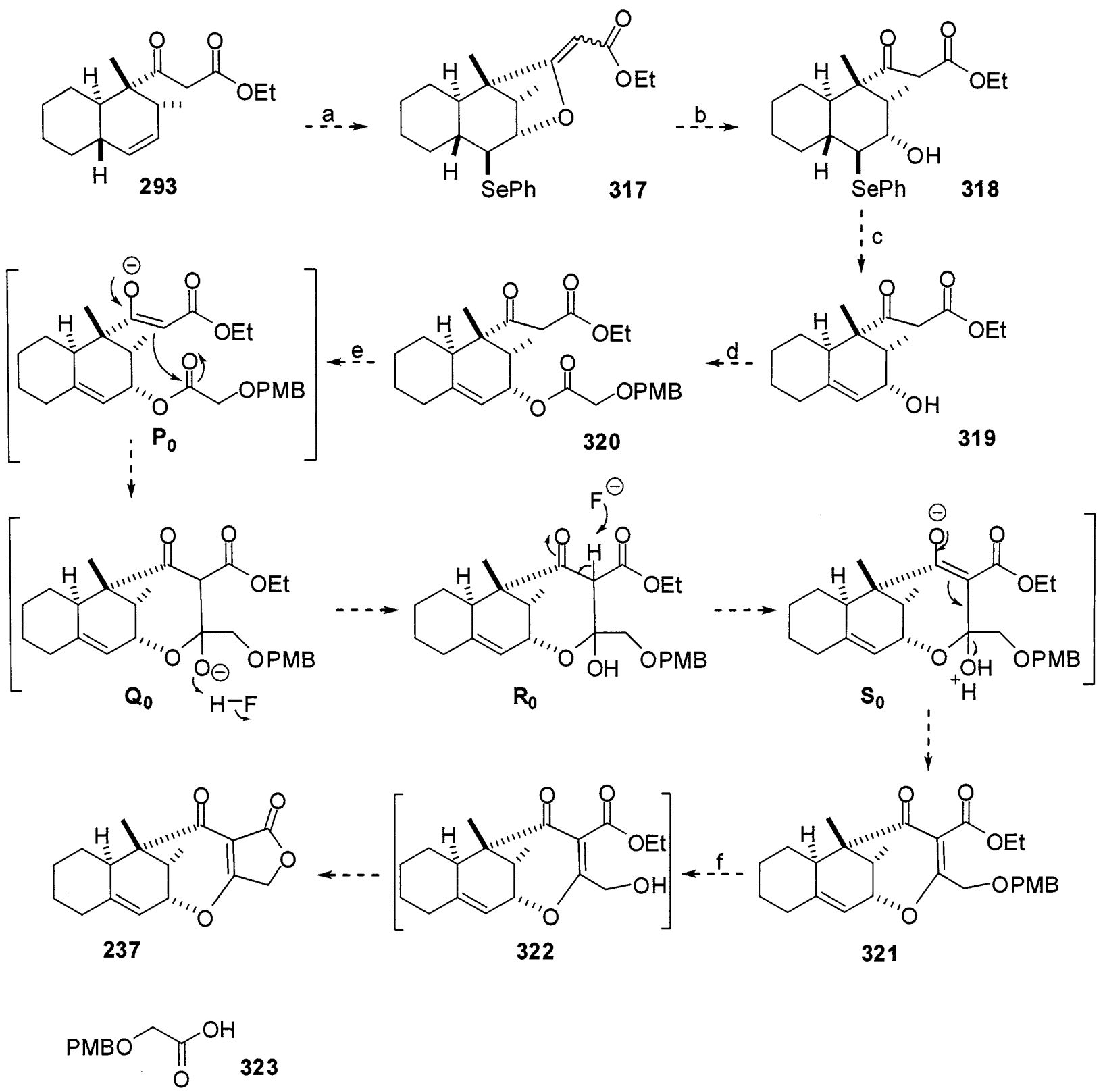
Both palladium-catalysed cyclisation and organoselenide-mediated cyclisation were investigated on the tetronic acid derivative **296**. However, due to the poor solubility of **296** in most organic solvents, the large steric hindrance and the disfavouring formation of 7-membered ring in both cases, these protocols were aborted.

The poor solubility of **296** led to the exploration of the one-pot cyclisation reaction to form the 5- and 7-membered ring. The initial plan to investigate this reaction on epoxide **307a** was abandoned because the *m*CPBA epoxidation led to the formation of an unexpected isomer **307b**, which was unable to undergo an S_N2 reaction (Scheme 164). The dihydroxylation of **295** provided the desired diol **310**, which was converted to cyclic sulphite **311** in good yield. Although the attempts to produce the cyclic sulphate **312** met with failure, the cyclic sulphite **311** also had high reactivity with nucleophiles and could be used to this reaction. However, the cyclic sulphite **311** underwent an undesired cyclisation reaction and afforded a tetrahydrofuran

ring **313**, which established that the formation of 5-membered ring was faster than the Dieckmann cyclisation (Scheme 170). The investigation on the ring closure reaction of the allylic alcohol **314** was aborted because of the failure in synthesising **314** *via* Gerlach's method.

3.7 Other attempts to complete the total synthesis

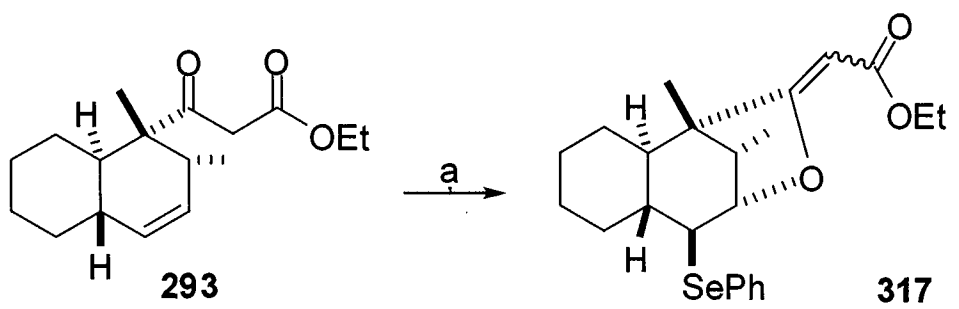
The difficulties in the formation of 7-membered ring at the last stage encouraged the pursuit of a new synthetic route (Scheme 173). In this approach, the 7-membered ring would be constructed before the 5-memebered tetronic acid derivative part. Organoselenium-mediated cyclisation of β-keto ester **293** would produce the selenide **317**. Ring-opening reaction of **317** followed by a oxidative elimination and DCC-DMAP coupling with 2-(4-methoxybenzyloxy)- acetic acid **323** would afford the ring-closure precursor **320**. It was proposed that upon treatment with TBAF, a nucleophilic attack to form the 7-membered ring followed by dehydration would provide the 6-6-7-membered skeleton **321**. Compound **321** was then treated with DDQ to deprotect the PMB group and in the mean time install the 5-membered ring to give **237** (Scheme 173). This route avoided the undesirable low solubility of **296** when the tetronic acid part was installed.



Scheme 173

a) NPSP; b) TFA, H_2O; c) H_2O_2, pyridine, THF; d) **323**, DCC, DMAP; e) TBAF; f) DDQ, buffer

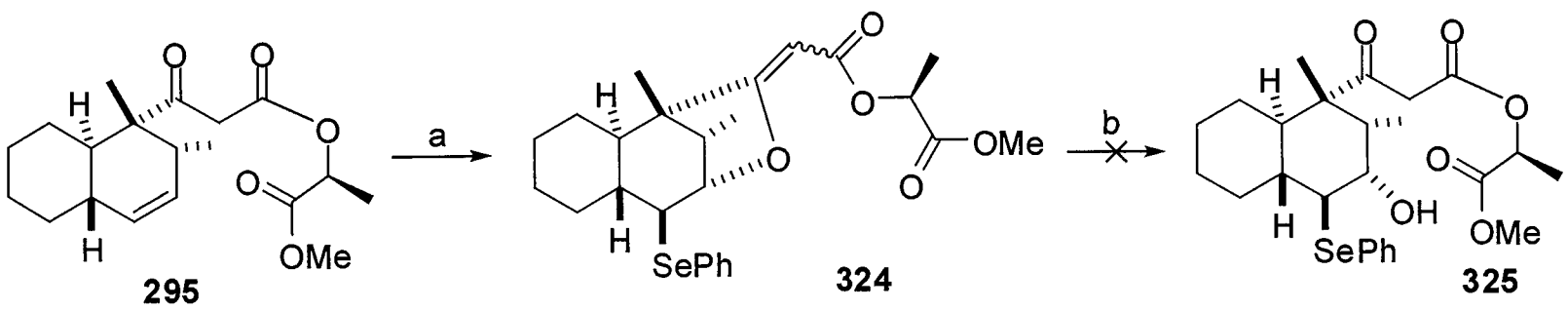
The selenide **317** was achieved from β-keto ester **293** following Ley's method (Scheme 174).[235] The NMR spectra showed **317** to be a homogeneous compound, but the geometry of the C=C double bond was not confirmed.



Scheme 174

a) NPSP, $SnCl_4$ (0.01 eq), DCM, rt, 4 h (53%);

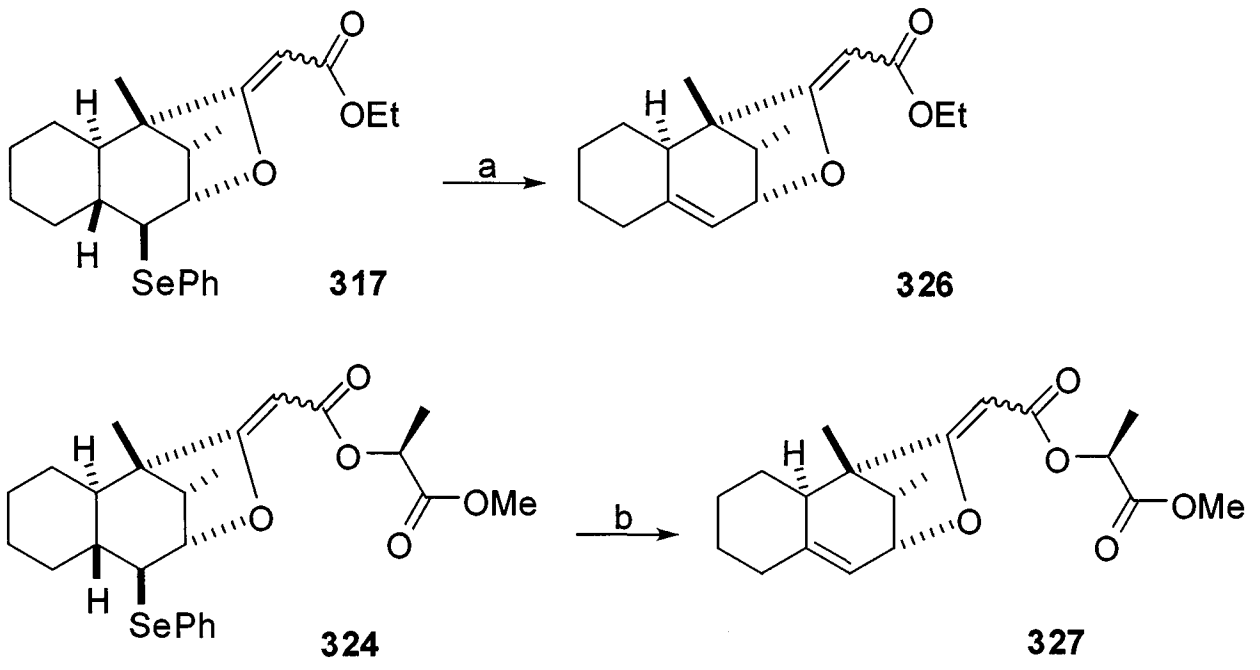
The ring-opening reaction was investigated on the selenide **324**, which was obtained by organoselenium-mediated cyclisation of ketoacetate **295**, since it was available at that time. Selenide **324** was produced as a single isomer, but the geometry of the C=C double bond was not confirmed. In the beginning, the solution of selenide **324** in dichloromethane was treated with 0.1 eq of trifluoroacetic acid (TFA) and a drop of water at room temperature. After being left overnight, no reaction was observed from the TLC analysis. Therefore, the amount of TFA was increased to 0.2 eq, subsequently 1 eq and then 2 eq, TLC only showed the existence of the starting material **324**. However, addition of a larger excess amount of TFA led to decomposed products (Scheme 175).



Scheme 175

a) NPSP, $SnCl_4$ (0.01 eq), DCM, rt, 4 h (80%); b) TFA, H_2O (one drop), DCM, rt

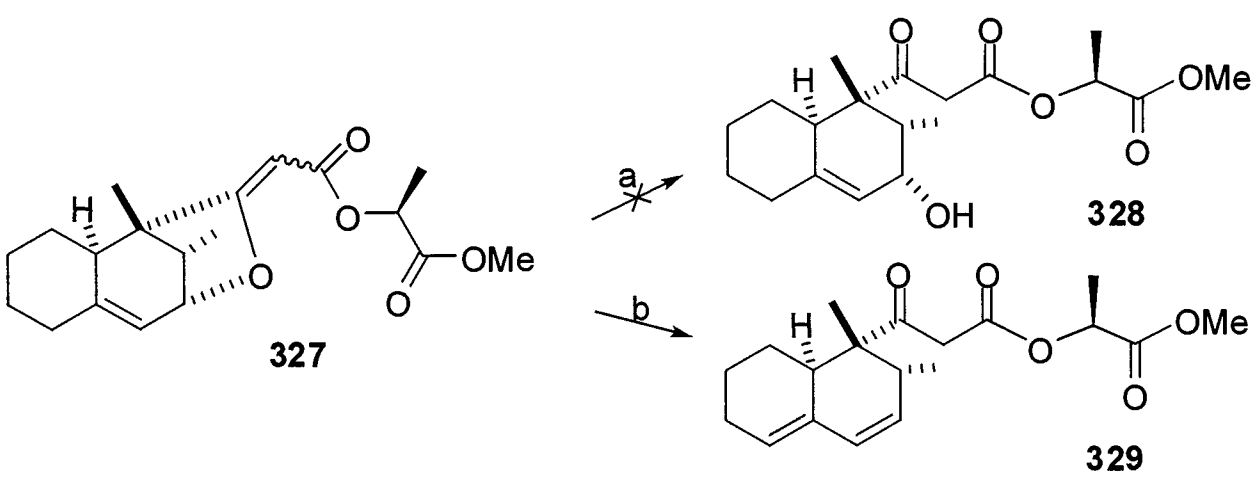
At this point, the attention was drawn to the oxidative elimination of selenides **317** and **324** to olefins **326** and **327** respectively (Scheme 176).[210]



Scheme 176

a) H_2O_2, pyridine, THF, rt, 1 h (41%); b) H_2O_2, pyridine, THF, rt , 1 h (85%)

The ring-opening experiments were carried out with olefin **327** with TFA and one drop of water. Surprisingly, the addition of 0.1 eq, 0.2 eq, 1 eq or even 2 eq of TFA did not initiate any reaction, while the addition of an excess amount of TFA resulted in 18% of dehydrated ring-opend product **329**, 22% of starting material **324** together with some complex compounds (Scheme 177).



Scheme 177

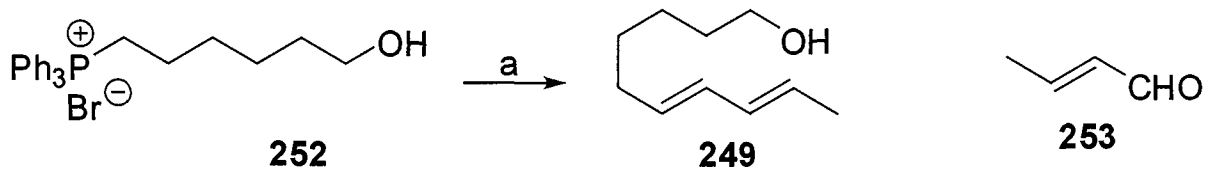
a) TFA (0.1-2.0 eq), DCM, rt; b) TFA (excess), H_2O (one drop), DCM, rt, 2 days (**327**: 22%, **329**: 18%)

The difficulties in the ring-opening reaction of **317** and **326** set a big obstacle in this new route.

3.8 Conclusion of Chapter 3

The synthesis of *trans*-alkenal **242** was successfully simplified *via* Schlösser's modification of

Wittig reaction. The combination of MeLi·LiBr complex and an excess amount of freshly dried lithium chloride could provide high *trans*/*cis* ratio (95:5) and satisfactory yield, so that it was unnecessary to use PhLi·LiBr complex in this reaction (Scheme 178).

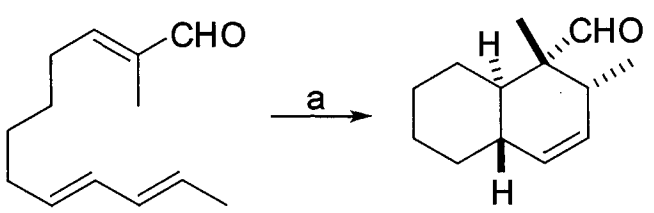


252 **249** **253**

Scheme 178

a) MeLi·LiBr (2 eq), LiCl (3 eq), THF, -78°C; rt, 30 min; **253**, -78°C; MeLi·LiBr (1.2 eq), -78°C; rt, 30 min; TFA (1.1 eq), -78°C, 30 min; KO^{t}Bu (1.24 eq) -78°C-rt (71%)

The intramolecular Diels-Alder reaction of trienal **240** was carried out with $ZnCl_2$ (1.0 M in Et_2O) other than Et_2AlCl so as to avoid the alleged Meerwein-Ponndorf-Verley-type reduction of the initially formed aldehyde **132** to alcohol **259a** (Scheme 179).

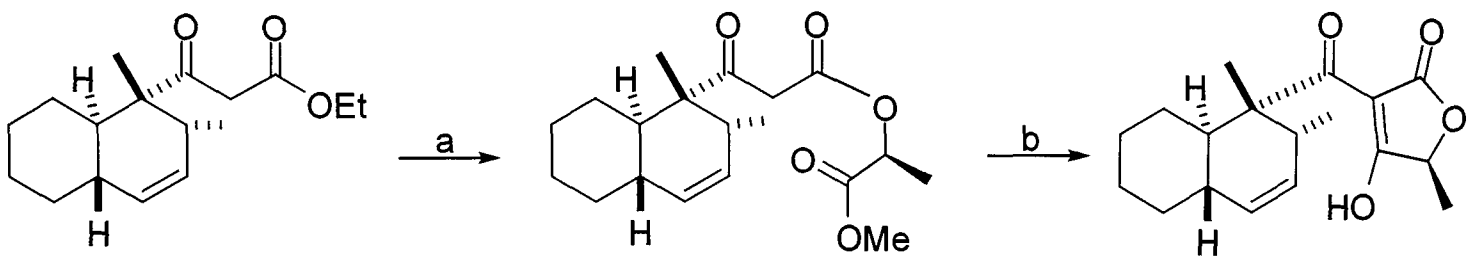


240 **132**

Scheme 179

a) $ZnCl_2$ (1.0 M in Et_2O, 1.2 eq.), DCM, rt, 4 days (66%)

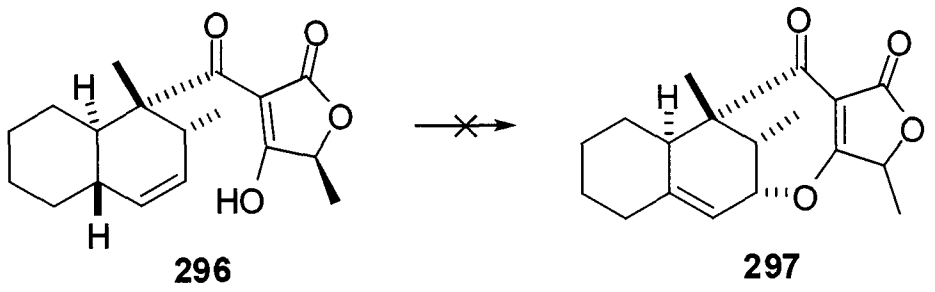
The model studies on 3-acylation and 4-*O*-alkylation of tetronic acid met with failure, but this prompted the investigation on the formation of tetronic acid derivative part *via* Dieckmann-type cyclisation. The β-keto ester **293** was converted into the Dieckmann-type reaction precursor **295** efficiently by employing 3-nitrobenzeneboronic acid **305** as catalyst. The acetoacetate **295** underwent Dieckmann-type cyclisation smoothly upon treatment with TBAF or CsF to afford the expected product **296** in satisfactory yield, which allowed the investigation of 7-membered ring closure reactions (Scheme 180).



Scheme 180

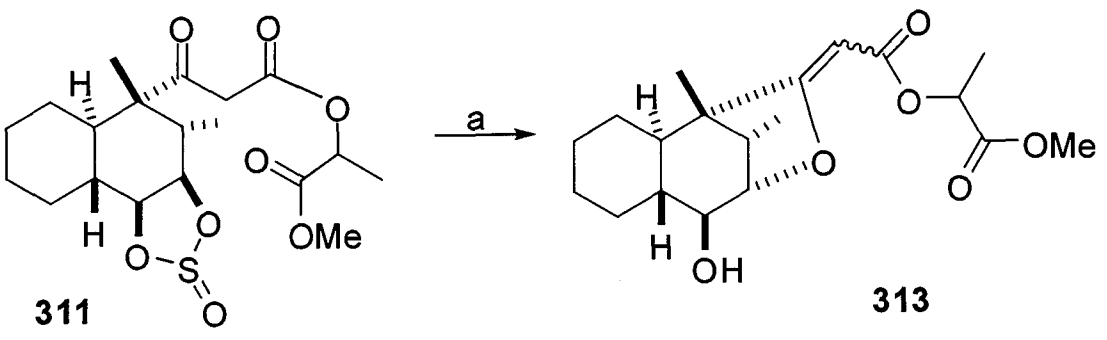
a) methyl (*S*)-(-)-lactate **304**, 3-nitrobenzeneboronic acid **305** (2.5 mol%), toluene, reflux, overnight (82%); b) TBAF, THF, 40°C, 5 days (78%)

Unfortunately, due to the poor solubility of **296** in most organic solvents, the steric hindrance and the disfavoured formation of 7-membered ring, both palladium-catalysed cyclisation and organoselenide-mediated cyclisation were unsuccessful (Scheme 181).



Scheme 181

Thereafter, focus was turned on the formation of the 5- and 7-membered rings in a one pot reaction of cyclic sulphite **311**. The exploration the cyclic sulphite **311** to an excess amount of TBAF afforded an undesirable cyclisation product, a tetrahydrofuran derivative **313**, other than the expected Dieckmann-type cyclisation product **308** probably due to the favourable formation of the 5-membered ring (Scheme 182).



Scheme 182

a) TBAF, THF, 40°C, 5 days (62%)

The attempts to construct the 7-membered ring followed by the 5-membered tetronic acid part

were met with frustration at the stage of the ring-opening reaction of **317** and **326** (Figure 21).

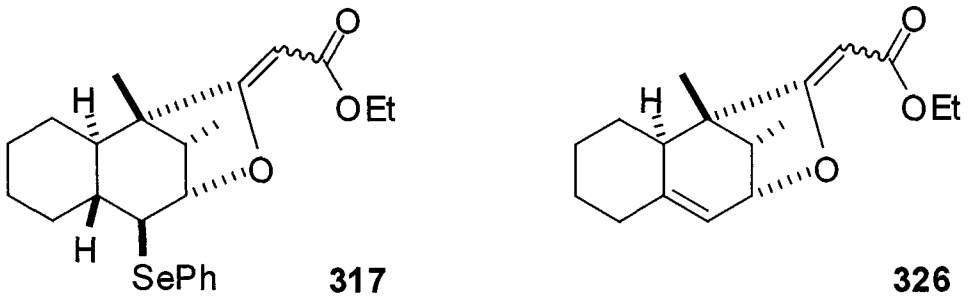


Figure 21

In a conclusion, different methods to construct of the 6-6-7-5-membered skeleton of tetrodecamycin (**1**) have been investigated. However, the construction of the 7-membered ring turned to be a big problem in the protocols. Because of time limitation, no further investigation was carried out.

CHAPTER 4

EXPERIMENTAL

CHAPTER 4 EXPERIMENTAL SECTION

4.1 General Procedure

Proton magnetic resonance spectra were recorded on Varian Gemini 200 (200 MHz), Bruker DQX 400 (400 MHz), Bruker DPX 400 (400 MHz), Bruker AVC 500 (500 MHz) and Bruker DRX500 (500 MHz) instruments, spectrometers at ambient temperature. Proton assignments are supported by ^{1}H-^{1}H correlations (COSY) and ^{1}H-^{13}C correlations (HMQC) where necessary or by comparing similar compounds. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sxt, sextet; sep, septet; m, mutiple. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate, assignment). Coupling constants (*J*) are reported to the nearest 0 or 0.5 Hz. The numbering of compounds is not related to nomination. The superscript star (*) marked on the right side of the chemical shifts indicated the chemical shifts of the minor diastereoisomer.

Carbon magnetic resonance spectra were recorded on Varian Gemini 200 (50.3 MHz), Bruker DQX 400 (100.6 MHz), Bruker AVC 500 (125.8 MHz) and Bruker DRX500 (125.8 MHz), spectrometers at ambient temperature. Chemical shifts (δ_C) are reported in parts per million (ppm) and are referenced to the appropriate residual solvent peak. Carbon spectra assignments are supported by DEPT or APT analysis and ^{13}C-^{1}H correlations (HMQC) where necessary or by comparing similar compounds. The numbering of compounds is not related to nomination.

Infrared spectra of oil compounds were recorded as a thin film between NaCl plates on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer or Bruker Tensor 27 with internal referencing. Infrared spectra of solid compounds were recorded as a KBr disk on a Perkin-Elmer

Paragon 1000 Fourier Transform spectrometer or Bruker Tensor 27 with internal referencing. Absorption maxima (ν_{max}) of the major peaks are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; str, strong; br, broad; s, sharp. Only selected peaks are reported.

High solution mass spectra were recorded on Agilent 6890 series GC system (Micromass GCT) or by Mr. Robin Procter at Chemistry Research Laboratory, University of Oxford, on a Micromass ZAB 1F (Probe EI^+). Only molecular ions, (MH^+), (MNH_4^+) or (MNa^+) being reported. The quoted masses are accurate to ±5 ppm.

Melting points were measured using a Cambridge Instruments Gallen^{TM} III hot stage melting point apparatus and are uncorrected.

Specific rotations (α) were recorded on a Perkin-Elmer 241 polarimeter. They were recorded as an average of ten readings in a cell of path length (l) 1 dm, at the sodium D-line (589 nm), at the stated temperature (°C) and concentration (c) measured in units of g/100 mL. Specific rotations were converted to optical rotations $[\alpha]_D^t$ *via* the equation:

$$[\alpha]_D^t = 100\alpha / (l \times c)$$

Flash column chromatography was performed on silica gel (0.125-0.25 mm, 60-120 mesh). Thin layer chromatography was carried out on aluminum plates pre-coated with silica (Merck silica gel 60 F_{254} 1.05554), which were visualized by quenching of UV fluorescence (λ_{max}=254 mm), and/or by staining with 1% w/v potassium permanganate in aqueous alkaline solution or phosphomolybdic acid solution in EtOH followed by heating, as appropriate.

All solvents were dried and reagents were purified according to the procedures described by Perrin,[243] or used as supplied from commercial sources as appropriate. Anhydrous tetrahydronfuran (THF) and anhydrous diethyl ether were distilled from sodium/benzophenone

ketyl under nitrogen. Anhydrous dichloromethane (DCM) was distilled from calcium hydride under nitrogen. Diethylamine, triethylamine, dimethyl formamide (DMF), toluene, chloroform and dimethyl sulfoxide (DMSO) were distilled from calcium hydride under argon or reduced pressure and stored over 4Å molecular sieves under argon.

Commercial solutions of *n*-BuLi and MeLi·LiBr were titrated against 1,3-diphenylacetone-*p*-toluenesulphonylhydrazone in anhydrous THF prior to use.[244]

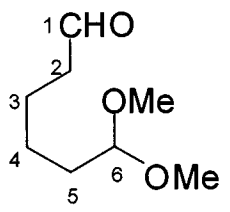
Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotary Evaporator fitted with a water condensor as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 1 mmHg.

All experiments were carried out under N_2 or inert atmosphere unless otherwise stated. All operations involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringes and oven-dried glassware. All chemicals were handled in accordance with the safety instructions identified in "good Laboratory Practice" August 1998.

4.2 Experimental procedures for Chapter 2

4.2.1 Experimental for the model study

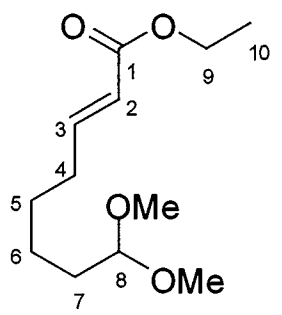
6,6-Dimethoxyhexanal (140)[103]



Prepared by application of literature method[103] on cyclohexene **141** (6.16 g, 75.0 mmol), ozone, *p*-TsOH (1.29 g, 7.50 mmol), anhydrous sodium bicarbonate (2.52 g, 30.0 mmol) and dimethyl sulfide (12 mL, 150.0 mmol) in DCM (250 mL) and methanol (50 mL) to give colourless oil product **140**, which could be used in the next step directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40

(2H, m, H-4), 1.59-1.69 (4H, m, H-3 and H-5), 2.45 (2H, dt, J = 7.5 and 1.5 Hz, H-2), 3.32 (6H, s, CH_3), 4.36 (1H, t, J = 6.0 Hz, H-6), 9.77 (1H, t, J = 1.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 21.8 (C-4), 24.1 (C-5), 32.2 (C-3), 43.7 (C-2), 52.6 (CH_3), 104.2 (C-6), 202.4 (C-1); m/z (GCMS) Calculated for $C_8H_{17}O_3$ (MH^+): 161.1178 Found 161.1186; ν_{max}/cm^{-1} (thin film) 2948 (str, C-H stretch), 2832 (m, s, C-H), 2723 (w, s, C-H of CHO), 1725 (str, C=O), 1462 (m, C-H deformation)

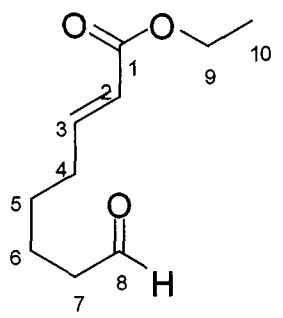
(*E*)-8,8-Dimethoxy-oct-2-enoic acid ethyl ester (143)



To a solution of 6,6-dimethoxyhexanal **140** (13.2 g, 82.5 mmol, crude product) in dichloromethane (200 mL) was added (carbethoxymethylene)triphenylphosphorane (28.7 g, 82.5 mmol). The mixture was under reflux for 24 h. The solvent was removed in vacuo, and the residue was extracted with three 100 mL portions of diethyl ether/hexane (1:1). The combined extracts were concentrated and chromatographed over silica gel, eluted with ethyl acetate/petrol 1:9 to give **143** as a colourless oil (14.9 g, 84% from **141**). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J = 7.0 Hz, H-10), 1.36-1.40 (2H, m, H-6), 1.49 (2H, qui, J = 7.0 Hz, H-5), 1.58-1.62 (2H, m, H-7), 2.22 (2H, q, J = 7.0 Hz, H-4), 3.32 (6H, s, $CH(OCH_3)_2$), 4.19 (2H, q, J = 7.0 Hz, H-9), 4.36 (1H, t, J = 6.0 Hz, H-8), 5.82 (1H, d, J = 16.0 Hz, H-2), 6.95 (1H, dt, J = 16.0 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-10), 24.1 (C-6), 27.8 (C-5), 32.1 (C-4), 32.2 (C-7), 52.7 ($CH(OCH_3)_2$), 60.1 (C-9), 104.3 (C-8), 121.4 (C-2), 148.9 (C-3), 166.7 (C-1); m/z (GCMS) Calculated for $C_{11}H_{19}O_3$ ($M\text{-}OMe^+$): 199.1334 Found 199.1332; ν_{max}/cm^{-1} (thin film) 2944 (str, C-H stretch), 2831 (m, s, C-H), 1721 (str, C=O), 1655 (str, s, C=C), 1464 (m, C-H

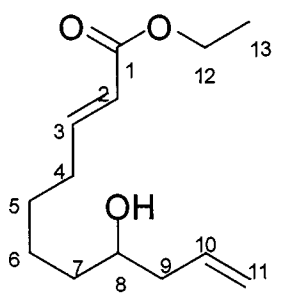
deformation), 1186 (m, s, C-O)

(*E*)-8-Oxo-oct-2-enoic acid ethyl ester (144)[245]



To a solution of (*E*)-8, 8-dimethoxy-oct-2-enoic acid ethyl ester **143** (14.9 g, 64.5 mmol) in acetone (300 mL) a solution of hydrochloric acid (aq., 1N, 6 mL) in water (30 mL) was added and the resulting mixture was stirred at room temperature. After 24 h sodium bicarbonate solution (sat., 150 mL) was added, and the content of the flask was partitioned between water (150 mL) and ethyl acetate (200 mL). The organic phase was separated and the aqueous phase was washed with ethyl acetate (3x200 mL). The combined organic layers were dried over magnesium sulphate and concentrated. The crude residue was chromatographed over silica gel (ethyl acetate/petrol 1:9) to give the title compound **144** as a light yellow oil (9.68 g, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.26 (3H, t, J = 7.0 Hz, H-10), 1.40-1.55 (2H, m, H-6), 1.55-1.72 (2H, m, H-5), 2.21 (2H, q, J = 7.0 Hz, H-4), 2.44 (2H, dt, J = 7.0 and 1.5 Hz, H-7), 4.18 (2H, q, J = 7.0 Hz, H-9), 5.79 (1H, d, J = 16.0 Hz, H-2), 6.91 (1H, dt, J = 16.0 and 7.0 Hz, H-3), 9.75 (1H, t, J = 1.5 Hz, H-8); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 14.7 (C-10), 21.9 (C-6), 27.9 (C-5), 32.3 (C-4), 44.0 (C-7), 60.6 (C-9), 122.2 (C-2), 148.7 (C-3), 167.0 (C-1), 203.3 (C-8); m/z (GCMS) Calculated for $C_{10}H_{17}O_3$ (MH^+): 185.1178 Found 185.1175; ν_{max}/cm^{-1} (thin film) 2937 (str, s, C-H stretch), 2863 (m, s, C-H), 2723 (w, s, CH of CHO), 1716 (str, s, C=O), 1654 (str, s, C=C), 1368 (m, s), 1268 (m), 1187 (m, C-O)

(*E*)-8-Hydroxy-undeca-2,10-dienoic acid ethyl ester (145)



Method 1:

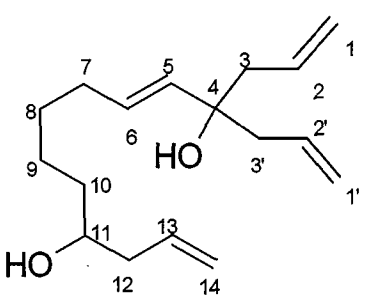
To a -78˚C solution of (*E*)-8-oxo-oct-2-enoic acid ethyl ester **144** (0.50 g, 2.72 mmol) in tetrahydrofuran (150 mL) was added dropwise allyl magnesium chloride (2M, 1.63 mL). After stirring at –78˚C for 30 min, the mixture was warmed to 0˚C. After 4 h the reaction was quenched by adding saturated ammonium chloride solution (5 mL) and the mixture was allowed to warm to room temperature. Then water (200 mL) and ethyl acetate (200 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with ethyl acetate (2x200 mL). The combined organic layers were dried over magnesium sulphate and concentrated. Purification of the crude product was achieved by silica gel chromatography (ethyl acetate/petrol 1:6) to give 0.20 g (32%) of the title compound **145** as a colourless oil.

Method 2:

To a solution of 6-hydroxy-non-8-enal **150** (5.04 g, 32.3 mmol) in dichloromethane (300 mL) was added (carbethoxymethylene)triphenylphosphorane (12.38 g, 35.5 mmol). The mixture was under reflux for 24 h. The solvent was removed in vacuo, and the residue was extracted with three 100 mL portions of diethyl ether/hexane (1:1). The combined extracts were concentrated and chromatographed over silica gel, eluted with ethyl acetate/petrol 1:9 to give 6.13 g **145** (54% from **141**) of the product as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J = 7.0 Hz, H-13), 1.36-1.52 (6H, m, H-5, H-6 and H-7), 2.14 (1H, m, 1xH-9), 2.22 (2H, q, J = 7.0 Hz, H-4), 2.28-2.31 (1H, m, 1xH-9), 3.65 (1H, m, H-8), 4.19 (2H, q, J = 7.0, H-12), 5.14-5.17

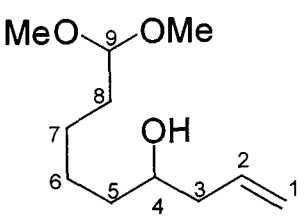
(2H, m, H-11), 5.78-5.88 (2H, m, H-2 and H-10), 6.96 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-13), 25.2 (C-6), 28.0 (C-5), 32.1 (C-4), 36.5 (C-7), 42.0 (C-9), 60.1 (C-12), 70.4 (C-8), 118.3 (C-11), 121.4 (C-2), 134.7 (C-10), 149.1 (C-3), 166.7 (C-1); m/z (GCMS) Calculated for $C_{13}H_{23}O_3$ (MH^+): 227.1647 Found 227.1653; ν_{max}/cm^{-1} (thin film) 3433 (str, br, O-H), 3076 (w, s, C-H of CH=CH), 2934 (str, C-H stretch), 2860 (m), 1720 (str, C=O), 1654 (m, s, C=C), 1445 (w, C-H deformation), 1369 (m, s), 1271 (m), 1187 (m, C-O)

(*E*)-4-Allyl-tetradeca-1,5,13-triene-4,11-diol (145a)



This side product was isolated from the crude product mixture via column chromatography during the preparation of compound **145** via method 1. Yield: 67.0 mg (9%, colourless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.24-1.33 (2H, m, H-9), 1.38-1.43 (2H, m, H-8), 1.46-1.51 (2H, m, H-10), 2.05-2.10 (2H, m, H-7), 2.24-2.35 (6H, m, H-3, H-3' and H-12), 3.62-3.68 (1H, m, H-11), 5.09-5.18 (6H, m, H-1, H-1' and H-14), 5.48 (1H, d, J = 15.5 Hz, H-5), 5.62 (1H, dt, J = 15.5 and 6.5 Hz, H-6), 5.76-5.89 (3H, m, H-2, H-2' and H-13)

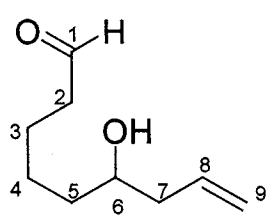
9,9-Dimethoxy-non-1-en-4-ol (149)[246]



To a solution of 6, 6–dimethoxyhexanal **140** (5.0 g, 31.3 mmol) in THF (300 mL) at -78°C was added allyl magnesium chloride (2M, 18.0 mL) dropwise. After stirring at -78°C for 3 h the solution was warmed to room temperature, ammonium chloride (sat., 100 mL) was added and the resulting mixture was extracted with ethyl acetate (3x100 mL). The combined organic layers

were dried over magnesium sulphate and concentrated in vacuo to give a light yellow oil. The crude product **149** was pure enough for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.35-1.39 (2H, m, H-7), 1.45-1.49 (2H, m, H-6), 1.58-1.69 (4H, m, H-5 and H-8), 2.04 (1H, s, OH), 2.15-2.18 (1H, m, 1xH-3), 2.26-2.29 (1H, m, 1xH-3), 3.31 (6H, s, CH_3), 3.64-3.68 (1H, m, H-4), 4.33-4.38 (1H, m, H-9), 5.11-5.14 (2H, m, H-1), 5.79-5.83 (1H, m, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.4 (C-7), 25.8 (C-6), 32.7 (C-8), 36.9 (C-5), 41.7 (C-3), 52.8 (CH_3), 70.8 (C-4), 104.8 (C-9), 117.9 (C-1), 134.5 (C-2); m/z (GCMS) Calculated for $C_{10}H_{19}O_2$ ($M\text{-}OMe^+$) 171.1385 Found 171.1384; ν_{max}/cm^{-1} (thin film) 3424 (str, br, O-H), 2939 (str, C-H stretch), 1641 (w, s, C=C), 1129 (str, s, C-O)

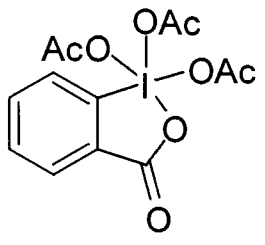
6-Hydroxy-non-8-enal (150)[247]



A mixture of 9,9-dimethoxy-non-1-en-4-ol **149** (5.34 g, 26.5 mmol) in acetone (100 mL) and aqueous hydrochloric acid (1N, 2 mL) in water (10 mL) was stirred at room temperature for 20 h. After such time sodium bicarbonate (sat., 150 mL) was added slowly to the mixture followed by ethyl acetate (200 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3x150 mL). The combined organic layers were dried over magnesium sulphate and concentrated in vacuo to give crude product **150** as a light oil, which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40-1.45 (2H, m, H-4), 1.47-1.51 (2H, m, H-5), 1.62-1.67 (2H, m, H-3), 2.12-2.17 (1H, m, 1xH-7), 2.27-2.31 (1H, m, 1xH-7), 2.47 (2H, td, J = 7.0 and 1.5 Hz, H-2), 3.63-3.68 (1H, m, H-6), 5.04- 5.16 (2H, m, H-9), 5.77-5.88 (1H, m, H-8), 9.78 (1H, d, J = 1.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 22.1 (C-3), 25.3 (C-4), 36.5 (C-5), 42.0 (C-7), 43.8 (C-2), 70.4 (C-6), 118.2 (C-9), 134.6 (C-8), 202.7

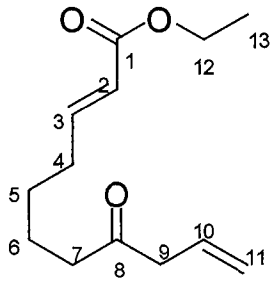
(C-1); m/z (GCMS) Calculated for $C_9H_{17}O_2$ (MH^+) 157.1229 Found 157.1234; ν_{max}/cm^{-1} (thin film) 3418 (str, br, O-H), 3076 (w, s, C-H of CH=CH), 2934 (str, C-H stretch), 1723 (str, s, C=O), 1641 (w, s, C=C), 1441 (m, C-H deformation)

Dess-Martin periodinane: l,l,l-triacetoxy-1,l-dihydro-1,2-benziodoxol-3(l*H*)-one(153)[116,118]



The Dess-Martin periodinane was prepared following Ireland's modified method. Mp 132-134°C lit. Mp 133-134°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.01 (6H, s, CH_3CO), 2.46 (3H, s, CH_3CO), 7.88-7.92 (1H, m, H-Ph), 8.29 (1H, d, J = 8.5 Hz, H-Ph), 8.31 (1H, d, J = 8.5 Hz, H-Ph), 8.69-8.71 (1H, m, H-Ph)

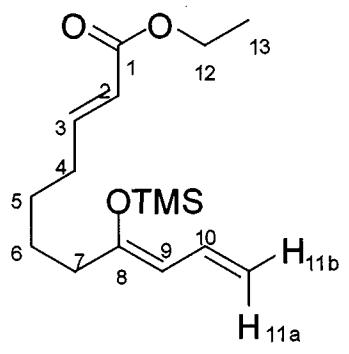
(2*E*)-8-Oxo-undeca-2,10-dienoic acid ethyl ester (146)



Dess-Martin reagent **153** (2.56 g, 5.49 mmol) was added in one portion to a solution of (*E*)-8-hydroxy-undeca-2,10-dienoic acid ethyl ester **145** (0.62 g, 2.74 mmol) in anhydrous DCM (20 mL). After 2 h, the mixture was diluted with DCM (20 mL) and sequently washed with $Na_2S_2O_3$ (aq., sat., 20 mL), and $NaHCO_3$ (aq. 5%, 20 mL). The combined aqueous layers were extracted once with DCM (3x30 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc/petrol 1:7) to yield the 8-oxo-undeca-2,9-dienoic acid ethyl ester **146** as a colourless oil (0.50 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J = 7.0 Hz, H-13), 1.46 (2H, qui, J = 7.0 Hz, H-5), 1.62 (2H, qui, J = 7.0 Hz, H-6), 2.21 (2H, q, J = 7.0 Hz, H-4), 2.46 (2H, t, J = 7.0 Hz, H-7), 3.17 (2H,

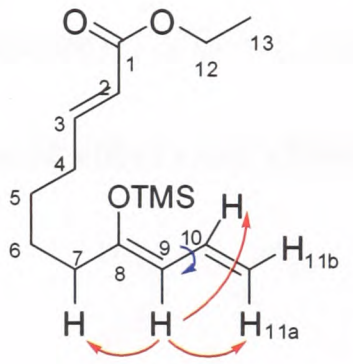
d, J = 7.0 Hz, H-9), 4.19 (2H, q, J = 7.0 Hz, H-12), 5.14 (1H, dd, J = 17.0 and 1.5 Hz, 1xH-11), 5.19 (1H, dd, J = 10.5 and 1.5 Hz, 1xH-11), 5.82 (1H, d, J = 15.5 Hz, H-2), 5.90-5.94 (1H, m, H-10), 6.94 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-13), 23.0 (C-6), 27.5 (C-5), 31.9 (C-4), 41.9 (C-7), 47.8 (C-9), 60.2 (C-12), 118.9 (C-11), 121.6 (C-2), 130.5 (C-10), 148.6 (C-3), 166.6 (C-1), 208.4 (C-8); m/z (GCMS) Calculated for $C_{13}H_{21}O_3$ (MH^+): 225.1491 Found 225.1488; ν_{max}/cm^{-1} (thin film) 2938 (str, C-H stretch, 1717 (str, C=O), 1654 (m, s, C=C), 1368 (m, s), 1268 (m), 1183 (m, C-O)

(*2E*,*8Z*)-8-Trimethylsilanyloxy-undeca-2,8,10- trienoic acid ethyl ester (147)

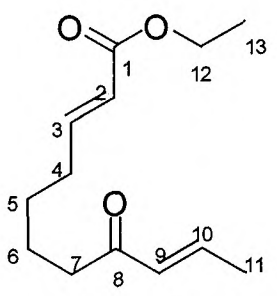


To a solution of 8-oxo-undeca-2,9-dienoic acid ethyl ester **146** (500.0 mg, 2.23 mmol) in anhydrous THF (15 mL) was added HMPA (440.0 mg, 2.48 mmol). The mixture was cooled to -78°C and then was added LHMDS (1M sol. in THF, 2.68 mL, 2.68 mmol). After 15 min, the enolate was quenched with freshly distilled TMSCl over CaH_2 (290.0 mg, 2.68 mmol). After being stirred for 1 hr, the reaction mixture was allowed to warm to room temperature and poured into pentane (20 mL) in a small separatory funnel. The mixture was washed with $NaHCO_3$ (aq. sat., 2x10 mL) and brine (10 mL) and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (EtOAc/petrol 1:6) to yield 490.0 mg enolate **147** as a colousless oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.21 (9H, s, $Si(CH_3)_3$), 1.29 (3H, t, J = 7.0 Hz, H-13), 1.44-1.54 (4H, m, H-5 and H-6), 2.07 (2H, t, J = 7.5 Hz, H-7), 2.22 (2H, q, J = 7.0 Hz, H-4), 4.19 (2H, q, J = 7.0 Hz, H-12), 4.83 (1H, dd, J = 10.5 and 1.5 Hz, H-11b), 5.05 (1H, dd, J = 17.0 and 1.5 Hz, H-11a), 5.29 (1H, d, J = 10.5 Hz, H-9),

5.83 (1H, d, J = 15.5 Hz, H-2), 6.54 (1H, dt, J = 17.0 and 10.5 Hz, H-10), 6.95 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 0.6 ($Si(CH_3)_3$), 14.3 (C-13), 26.3 (C-6), 27.4 (C-5), 32.0 (C-4), 36.3 (C-7), 60.1 (C-12), 110.6 (C-9), 111.9 (C-11), 121.5 (C-2), 131.5 (C-10), 148.9 (C-3), 152.8 (C-8), 166.7 (C-1); m/z (GCMS) Calculated for $C_{16}H_{29}O_3Si$ (MH^+): 297.1886 Found 297.1901; ν_{max}/cm^{-1} (thin film) 3085 (w, s, C-H of CH=CH), 2939 (str, C-H stretch), 1722 (str, s, C=O), 1650 (str, s, C=C), 1420 (m, s, C-H deformation), 1368 (w), 1254 (m, s, TMS), 1144 (m, C-O); n.O.e experiments: irradiation at 5.29 (H-9) saw reciprocal signal enhancement at 2.07 (H-7), 5.05 (H-11a) and 6.54 (H-10)



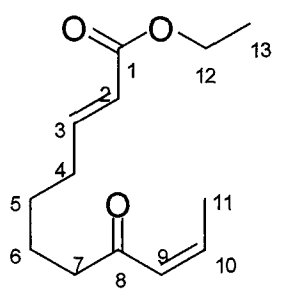
(*2E*,*9E*)-8-Oxo-undeca-2,9-dienoic acid ethyl ester (156a)



The side product **156a** was isolated from the reaction of producing silyl enol ether **147**. It is also a side product of the Diels-Alder reaction. To the solution of ketone **146** (200.0 mg, 0.89 mmol) in toluene (20 mL) was added triethyl amine (150 µL, 1.07 mmol) and TMSCl (140 µL, 1.07 mmol). After stirring at room temperature for 24 h the solvent was removed in vacuo. The crude NMR showed only starting materials. Toluene (20 mL) was added to the residue and the mixture was under reflux for 5 h. After that the solution was cooled to room temperature, toluene was removed in vacuo. The residue was chromatographed over the silica gel (EtOAc/petrol 1:6) to give **156a** (134.0 mg, 67%, colourless oil), **156b** (42.0 mg, 21%, colourless oil) and **147** (7.0 mg,

3%, colourless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J = 7.0 Hz, H-13), 1.48 (2H, qui, J = 7.0 Hz, H-5), 1.63 (2H, qui, J = 7.0 Hz, H-6), 1.91 (1H, d, J = 7.0 Hz, H-11), 2.23 (2H, q, J = 7.0 Hz, H-4), 2.56 (2H, t, J = 7.0 Hz, H-7), 4.19 (2H, q, J = 7.0 Hz, H-12), 5.81 (1H, d, J = 15.5 Hz, H-2), 6.11 (1H, d, J = 15.5 Hz, H-9); 6.85 (1H, dq, J = 15.5 and 7.0 Hz, H-10), 6.95 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.4 (C-13), 18.3 (C-11), 23.8 (C-6), 27.6 (C-5), 32.1 (C-4), 39.6 (C-7), 60.2 (C-12), 121.4 (C-2), 131.9 (C-9), 142.4 (C-10), 148.8 (C-3), 166.8 (C-1), 200.2 (C-8); m/z (GCMS) Calculated for $C_{13}H_{21}O_3$ (MH^+): 225.1491 Found 225.1481; ν_{max}/cm^{-1} (thin film) 2937 (str, C-H stretch), 2862 (m, s, C-H), 1717 (str, C=O), 1654 (m, C=C), 1444 (m, C-H deformation), 1376 (w), 1268 (m), 1185 (m, C-O)

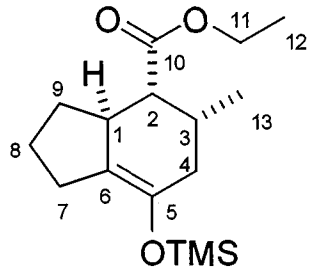
(*2E,9Z*)-8-Oxo-undeca-2,9-dienoic acid ethyl ester (156b)



The side product **156b** was isolated from the reaction of producing silyl enol ether **147**. It is also a side product of the Diels-Alder reaction. It was a colourless oil (42.0 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.27 (3H, t, J = 7.0 Hz, H-13), 1.46 (2H, J = 7.0 Hz, H-5), 1.62 (2H, J = 7.0 Hz, H-6), 2.09 (3H, d, J = 6.5 Hz, H-11), 2.20 (2H, q, J = 7.0 Hz, H-4), 2.45 (2H, t, J = 7.0 Hz, H-7), 4.17 (2H, q, J = 7.0 Hz, H-12), 5.82 (1H, d, J = 15.5 Hz, H-2), 6.10-6.23 (2H, m, H-9 and H-10), 6.93 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-13), 15.9 (C-11), 23.3 (C-6), 27.5 (C-5), 32.0 (C-4), 43.8 (C-7), 60.1 (C-12), 121.5 (C-2), 127.469 (C-9), 143.0 (C-10), 148.7 (C-3), 166.6 (C-1), 201.4 (C-8); m/z (GCMS) Calculated for $C_{13}H_{21}O_3$ (MH^+): 225.1491 Found 225.1497; ν_{max}/cm^{-1} (thin film) 2937 (str, s, C-H), 2864 (m, s, C-H), 1716 (str, C=O), 1693 (s), 1654 (w, C=C), 1621 (m), 1440 (m, C-H deformation), 1368 (w),

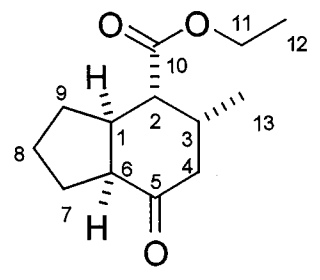
1268 (m), 1183 (m, C-O)

(3a*S,4*R**,5*R**)-5-Methyl-7-trimethylsilanyloxy-2,3,3a,4,5,6-hexahydro-1*H*-indene-4-carboxylic acid ethyl ester (157)**



A solution of silyl enol ether **147** (280.0 mg, 0.94 mmol) in anhydrous toluene (10 mL) was heated to 180°C in a sealed tube. After 5 days it was concentrated and chromatographed over silica gel (Et_2O/petrol 1:4, then EtOAc/petrol 1:3 and EtOAc/petrol 1:1) to give product **157** as a colourless oil (137.2 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.17 (9H, s, TMS), 0.96 (3H, d, J = 7.5 Hz, H-13), 0.97-1.01 (1H, m, 1xH-9), 1.27 (3H, t, J = 7.0 Hz, H-12), 1.55-1.62 (1H, m, 1xH-8), 1.68-1.82 (2H, m, 1xH-4 and 1xH-8), 2.07-2.12 (1H, m, 1xH-9), 2.14-2.17 (1H, m, H-1), 2.17-2.22 (1H, m, 1xH-7), 2.27-2.36 (1H, m, 1xH-7), 2.40-2.48 (2H, m, H-3 and 1xH-4), 2.54-2.62 (1H, m, H-2), 4.13-4.21 (2H, m, H-11); ^{13}C NMR (125.7MHz, $CDCl_3$) 0.6 (TMS), 14.2 (C-12), 15.4 (C-13), 23.4 (C-8), 26.1 (C-7), 31.1 (C-3), 33.2 (C-9), 37.3 (C-1), 37.6 (C-4), 49.6 (C-2), 59.9 (C-11), 119.7 (C-6), 139.1 (C-5), 174.6 (C-10); m/z (GCMS) Calculated for $C_{16}H_{29}O_3Si$ (MH^+) 297.1886 Found 297.1881; ν_{max}/cm^{-1} (thin film) 2959 (str, s, C-H stretch), 1734 (str, s, C=O), 1449 (m, C-H deformation), 1252 (str, s, TMS), 1180 (str, C-O)

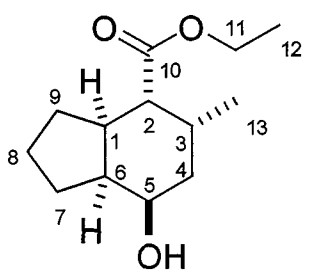
(3a*R,4*R**,5*R**,7a*S**)-5-Methyl-7-oxo-octahydro-indene-4-carboxylic acid ethyl ester (158)**



This product was formed in the preparation of **157** and could be isolated by column chromatography to give **158** as a colourless oil (22.0 mg, 10%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H

1.01 (3H, d, J = 6.5 Hz, H-13), 1.29 (3H, t, J = 7.0 Hz, H-12), 1.32-1.38 (1H, m, 1xH-9), 1.51-1.60 (1H, m, 1xH-8), 1.68-1.78 (2H, m, 1xH-7 and 1xH-8), 1.80-1.87 (1H, m, 1xH-9), 2.03-2.10 (1H, m, 1xH-7), 2.40-2.49 (3H, m, H-3 and H-4), 2.65-2.73 (2H, m, H-1 and H-2), 2,82 (1H, apparent dd, J = 14.5 and 7.5 Hz, H-6), 4.13-4.24 (2H, m, H-11); ^{13}C NMR (125.7MHz, $CDCl_3$) δ_C 14.7 (C-12), 17.9 (C-13), 23.4 (C-8), 27.4 (C-7), 31.5 (C-9), 32.3 (C-3), 42.3 (C-1), 45.2 (C-4), 48.0 (C-2), 51.2 (C-6), 60.8 (C-11), 174.5 (C-10), 213.2 (C-5); m/z (GCMS) Calculated for $C_{13}H_{21}O_3$ (MH^+): 225.1491 Found 225.1488; ν_{max}/cm^{-1} (thin film) 2962 (str, s, C-H), 1728 (str, C=O), 1448 (m, s, C-H deformation), 1179 (str, C-O)

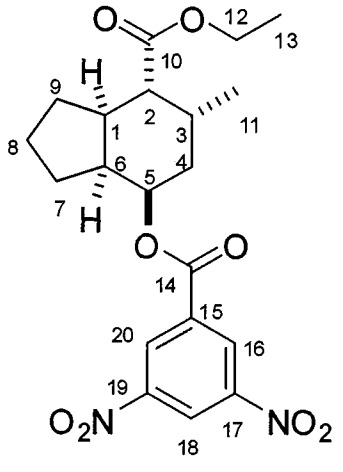
(3a*R,4*R**,5*R**,7*R**,7a*S**)-7-Hydroxy-5-methyloctahydro-1*H*-indene-4-carboxylic ethyl ester (159)**



To a stirred ketone **158** (110 mg, 0.49 mmol) in anhydrous THF (10 mL) at 0°C was added a solution of L-Selectride (1M in THF, 0.74 mL, 0.74 mmol) under nitrogen.[141] After the reaction mixture had been stirred for 30 min, diethyl ether (20 mL) and water (10 mL) were added. The aqueous layer was thoroughly extracted with diethyl ether (3x20 mL) and the combined extracts were washed successively with hydrochloric acid (aq. 10%, 20 mL), sodium hydrogen carbonate (aq. sat., 20 mL), and brine (20 mL). The ethereal solution was then dried with magnesium sulphate, and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with ethyl acetate/petrol (1:7) afforded the alcohol **159** (39.6 mg, 37%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (3H, d, J = 7.0 Hz, H-13), 1.25 (3H, t, J = 7.0 Hz, H-12), 1.41-1.48 (1H, m, 1xH-8), 1.54-1.76 (6H, m, H-4, H-7, 1xH-8 and 1xH-9), 1.76-1.85 (1H, m, 1xH-9), 2.26-2.41 (3H, m, H-1, H-3 and H-6), 2.43-2.50 (1H, m, H-2), 4.08-4.26 (3H, m, H-5

and H-11); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-13), 14.7 (C-12), 21.1 (C-7), 22.3 (C-8), 31.1 (C-4), 31.2 (C-6), 35.4 (C-9), 36.8 (C-3), 45.0 (C-1), 46.2 (C-2), 60.1 (C-11), 66.6 (C-5), 174.7 (C-10); m/z (GCMS) Calculated for $C_{13}H_{22}O_3$ (MH^+) 227.1647, Found 227.1659; ν_{max}/cm^{-1} (thin film) 3418 (br, str, OH), 2959 (str, C-H stretch), 2873 (m), 1715 (m, C=O), 1462 (m, C-H deformation), 1384 (str)

(3a*R,4*R**,5*R**,7*R**,7a*S**)-7-(3,5-Dinitrobenzoyloxy)-5-methyloctahydro-1*H*-indene-4-carboxylic ethyl ester (160)**

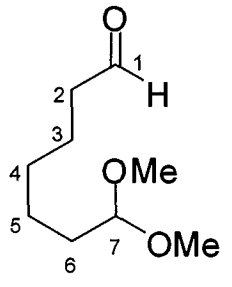


The alcohol **159** (39.6 mg, 0.18 mmol) was stirred in pyridine (5 mL) for 30 min and then treated with 3,5-dinitrobenzoyl chloride (60.4 mg, 0.26 mmol).[140] The reaction was stirred at room temperature for a whole night. Water (5 mL) was then added and extracted with diethyl ether (3x15 mL). The combined organic fractions were washed with $CuSO_4$ (aq. sat., 15 mL), water, $NaHCO_3$ (aq. sat., 15 mL) and water (15 mL) then dried with $MgSO_4$ and concentrated in vacuo to the crude product which was purified on silica gel (DCM/petrol 2:1) to get light yellow solid (61.3 mg, 83%). Mp 102.0-104.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.02 (3H, d, J = 7.0 Hz□ H-11), 1.29 (3H, t, J = 7.0 Hz, H-13), 1.54-1.59 (1H, m, 1xH-8), 1.65-1.80 (4H, m, 1xH-7, 1xH-8 and H-9), 1.84-1.92 (2H, m, 1xH-4 and 1xH-7), 1.96-2.04 (1H, m, 1xH-4), 2.46-2.50 (2H, m, H-1 and H-3), 2.54-2.63 (2H, m, H-2 and H-6), 4.11-4.24 (2H, m, H-12), 5.60-5.65 (1H, m, H-5), 9.12 (2H, d, J = 2.0 Hz, H-16 and H-20), 9.23 (1H, t, J = 2.0 Hz, H-18); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-13), 14.9 (C-11), 21.3 (C-8), 23.8 (C-7), 30.2 (C-9), 31.0 (C-4), 32.0

(C-1), 37.3 (C-2), 41.4 (C-6), 46.1 (C-3), 60.3 (C-12), 74.2 (C-5), 122.2 (C-18), 129.3 (C-16 and C-20), 134.4 (C-15), 148.7 (C-17 and C-19), 162.0 (C-14), 174.1 (C-10); m/z (ESIMS) Calculated for $C_{20}H_{25}N_2O_8$ (MH^+) 421.1605, Found 421.1606; ν_{max}/cm^{-1} (KBr disc) 3100 (w, aromatic C-H), 2964 (str, C-H stretch), 2883 (m, C-H stretch), 1730 (str, C=O), 1629 (w, aromatic C=C), 1550 (str, NO_2), 1462 (w, C-H deformation), 1347 (str, NO_2), 1330 (w), 1286 (m, C-O), 1175 (m)

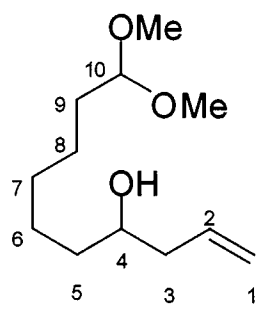
4.2.2 Experimental for the construction of the bicyclo[4.4.0]decaline ring

7,7-Dimethoxyheptanal (162)[248]



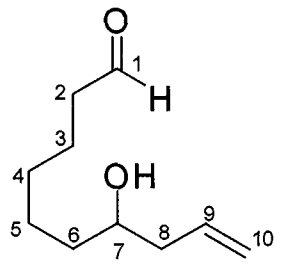
Compound **162** was synthesised following the literature procedure[103] from cycloheptane **161** (12.7 g, 130.0 mmol), ozone, *p*-TsOH (2.50 g, 13.0 mmol), anhydrous sodium bicarbonate (4.46 g, 52.0 mmol) and dimethyl sulfide (16.5 g, 260.0 mmol) in DCM (450 mL) and methanol (90 mL). The crude product **162** (24.1 g) was a colourless oil and was used for the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32-1.41 (4H, m, H-4 and H-5), 1.58-1.68 (4H, m, H-3 and H-6), 2.44 (2H, dt, J = 7.5 and 1.5 Hz, H-2), 3.32 (6H, s, CH_3), 4.36 (1H, t, J = 6.0 Hz, H-7), 9.77 (1H, t, J = 1.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 22.0 (C-5), 24.3 (C-3), 29.0 (C-4), 32.3 (C-6), 43.8 (C-2), 52.7 (CH_3), 104.4 (C-7), 202.7 (C-1); m/z (GCMS) calculated for $C_8H_{15}O_2$ $(M\text{-}OMe)^+$ 143.1072 found 143.1064, (MNH_4^+) 190.1443 found 190.1439; ν_{max}/cm^{-1} (thin film) 2942 (br, str, C-H), 2721 (w, C-H stretch), 1725 (str, C=O), 1463 (m, C-H deformation), 1387 (m, C-O), 1309 (w), 1129 (s), 951 (m)

10,10-Dimethoxydec-1-en-4-ol (163)



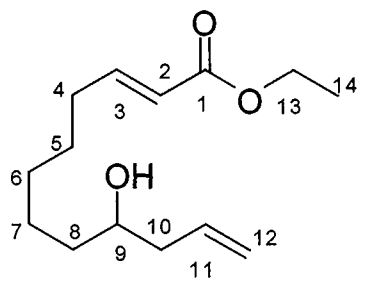
To a solution of 7,7-dimethoxyheptanal **162** (11.5 g, 66.3 mmol) in THF (500 mL) at -78˚C was added dropwise allyl magnesium chloride (2M in THF, 39.8 mL, 79.5 mmol). After stirring at -78˚C for 3 h the solution was warmed to room temperature, ammonium chloride (aq. sat., 200 mL) was added and the resulting mixture was extracted with ethyl acetate (3x250 mL). The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. The light yellow oil alcohol **163** (12.5 g) was obtained, which can be used directly in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.34-1.39 (4H, m, H-7 and H-8), 1.43-1.50 (4H, m, H-5 and H-6), 1.57-1.63 (2H, m, H-9), 2.09-2.17 (1H, m, H-3), 2.28-2.33 (1H, m, H-3), 3.32 (6H, s, CH_3), 3.62-3.68 (1H, m, H-4), 4.36 (1H, t, J = 6.0 Hz, H-10), 5.13-5.16 (2H, m, H-1), 5.78-5.89 (1H, m, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.5 (C-8), 25.6 (C-6), 29.4 (C-7), 32.4 (C-9), 36.7 (C-5), 41.9 (C-3), 52.6 (CH_3), 70.6 (C-4), 104.5 (C-10), 118.1 (C-1), 134.8 (C-2); m/z (GCMS) calculated for $C_{11}H_{21}O_2$ ($M\text{-}OMe^+$) 185.1542 found 185.1541, $C_{12}H_{25}O_3$ (MH^+) 217.1804 found 217.1831, $C_{12}H_{28}NO_3$ (MNH_4^+) 234.2069 found 234.2044; ν_{max}/cm^{-1} (thin film) 3246 (br, str, OH), 3075 (w, C=C-H stretch), 2934 (br, str, C-H stretch), 2859 (m, C-H stretch), 1641 (w, C=C), 1463 (w, C-H deformation), 1386 (w, C-O), 1129 (m), 1054 (m)

7-Hydroxydec-9-enal (164)



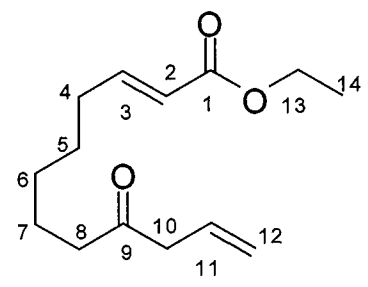
The mixture of acetal **163** (13.1 g, 60.7 mmol) in acetone (500 mL), hydrochloric acid (aq. 1N, 15 mL) and H_2O (500 mL) was stirred at room temperature for 20 hr. After that sodium bicarbonate (sat. solution, 300 mL) was added to the flask, and then partitioned between water (300 mL) and ethyl acetate (300 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3x300 mL). The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. The crude product was purified through silica gel (EtOAc/petrol 1:4) to give 7.25 g (70% from **161**) **164** as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.34-1.41 (2H, m, H-4), 1.45-1.50 (2H, m, H-5), 1.62-1.69 (4H, m, H-3 and H-6), 2.11-2.18 (1H, m, 1xH-8), 2.27-2.33 (1H, m, 1xH-8), 2.44 (2H, dt, J = 7.5 and 2.0 Hz, H-2), 3.62-3.68 (1H, m, H-7), 5.11-5.17 (2H, m, H-10), 5.78-5.88 (1H, m, H-9), 9.77 (1H, t, J = 2.0 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 22.0 (C-3), 25.4 (C-5), 29.1 (C-4), 36.5 (C-6), 42.0 (C-8), 43.8 (C-2), 70.5 (C-7), 118.2 (C-10), 134.7 (C-9), 202.7 (C-1); m/z (GCMS) calculated for $C_{10}H_{19}O_2$ (MH^+) 171.1385 found 171.1389 , $C_{10}H_{22}NO_2$ (MNH_4^+) 188.1651 found 188.1653; ν_{max}/cm^{-1} (thin film) 3426 (br, str, O-H), 3076 (w, C=C-H stretch), 2934 (br, str, C-H stretch), 2860 (m, C-H stretch), 1724 (s, str, C=O), 1641 (w, C=C), 1393 (m), 1243 (w), 988 (m), 915 (m)

Ethyl (2*E*)-9-hydroxydodeca-2,11-dienoate (165)



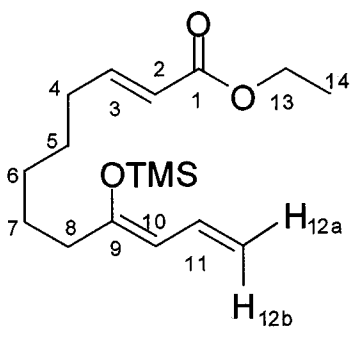
To a solution of aldehyde **164** (1.50 g, 8.91 mmol) in dichloromethane (50 mL) was added (carbethoxymethylene)triphenylphosphorane (3.73 g, 10.69 mmol). The mixture was left under reflux for 24 h. The solvent was removed in vacuo, and the residue was extracted with diethyl ether/hexane (1:1, 3x50 mL). The combined extracts were concentrated and chromatographed over silica gel, eluted with ethyl acetate/petrol 1:9 to give 1.68 g (79%) of product **165** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, J = 7.0 Hz, H-14), 1.32-1.37 (2H, m, H-8), 1.45-1.50 (4H, m, H-5 and H-6), 1.58-1.62 (2H, m, H-7), 2.10-2.34 (3H, m, H-4 and 1xH-10), 2.29-2.33 (1H, m, 1xH-10), 3.63-3.67 (1H, m, H-9), 4.19 (2H, q, J = 7.0 Hz, H-13), 5.14-5.17 (2H, m, H-12), 5.78-5.88 (2H, m, H-2 and H-11), 6.96 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-14), 25.4 (C-7), 27.9 (C-5), 29.1 (C-6), 32.1 (C-4), 36.6 (C-8), 42.0 (C-10), 60.1 (C-13), 70.5 (C-9), 118.2 (C-12), 121.3 (C-2), 134.8 (C-11), 149.3 (C-3), 166.8 (C-1); m/z (GCMS) calculated for $C_{14}H_{25}O_3$ (MH^+) 241.1804 found 241.1798; ν_{max}/cm^{-1} (thin film) 3592 (br, str, O-H), 2925 (str, C-H stretch), 2854 (m, C-H), 1732 (str, C=O), 1650 (m, C=C), 1448 (w, C-H deformations), 1373 (w), 1297 (m), 1172 (m), 1138 (m)

Ethyl (2*E*)-9-oxododeca-2,11-dienoate (166)



Dess-Martin reagent (6.52 g, 14.00 mmol) was added in one portion to a solution of ethyl (2*E*)-9-hydroxydodeca-2,11-dienoate **165** (1.68 g, 7.00 mmol) in anhydrous DCM (50 mL). After 2 h, the mixture was diluted with DCM (20 mL) and sequently washed with $Na_2S_2O_3$ (aq. sat., 40 mL), and $NaHCO_3$ (aq. 5%, 40 mL). The combined aqueous layers were extracted with DCM (3x50 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc/petrol 1:6) to yield the product **166** as light yellow oil (1.30 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δH 1.27-1.35 (2H, m, H-6), 1.29 (3H, t, J = 7.0 Hz, H-14), 1.47 (2H, qui, J = 7.0 Hz, H-5), 1.59 (2H, qui, J = 7.0 Hz, H-7), 2.20 (2H, q, J = 7.0 Hz, H-4), 2.45 (2H, t, J = 7.5 Hz, H-8), 3.17 (2H, d, J = 7.0 Hz, H-10), 4.19 (2H, q, J = 7.0 Hz, H-13), 5.14-5.20 (2H, m, H-12), 5.81 (1H, d, J = 15.5 Hz, H-2), 5.90-5.94 (1H, m, H-11), 6.95 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δC 14.3 (C-14), 23.3 (C-6), 27.8 (C-7), 28.6 (C-5), 31.9 (C-4), 42.1 (C-8), 47.8 (C-10), 60.1 (C-13), 118.8 (C-12), 121.4 (C-2), 130.6 (C-11), 149.0 (C-3), 166.7 (C-1), 208.6 (C-9); m/z (GCMS) calculated for $C_{14}H_{23}O_3$ (MH^+) 239.1647 found 239.1652; ν_{max}/cm^{-1} (thin film) 3075 (w, C=C-H), 2936 (str, C-H stretch), 2859 (m, C-H), 1717 (str, s, C=O), 1654 (m, C=C), 1446 (w, C-H deformations), 1369 (w), 1268 (m), 1183 (m), 1043 (w)

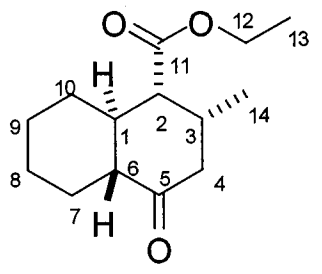
Ethyl (2*E*,9*Z*)-9- (trimethylsilyloxy) dodeca-2,9,11-trienoate (167)



To a solution of ethyl (2*E*)-9-oxododeca-2,11-dienoate **166** (1.22 g, 5.14 mmol) in anhydrous THF (50 mL) was added HMPA (0.99 mL, 5.65 mmol). The mixture was cooled to -78°C and then was added LHMDS (1M in THF, 6.17 mL, 6.17 mmol). After 15 min, the enol ether was

quenched with freshly distilled TMSCl over CaH_2 (0.78 mL, 6.17 mmol). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and poured into pentane (50 mL) in a separation funnel. The mixture was washed with $NaHCO_3$ (aq. sat., 2x50 mL) and brine (50 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:100) to yield 1.19 g enolate **167** as colorless oil (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.22 (9H, s, H-TMS), 1.30 (3H, t, J = 7.0 Hz, H-14), 1.25-1.38 (2H, m, H-6), 1.44-1.54 (4H, m, H-5 and H-7), 2.06 (2H, t, J = 7.0 Hz, H-8), 2.18-2.24 (2H, m, H-4), 4.19 (2H, q, J = 7.0 Hz, H-13), 4.82 (1H, dd, J = 10.5 and 2.0 Hz, H-12a), 5.00 (1H, dd, J = 17.0 and 2.0 Hz, H-12b), 5.29 (1H, d, J = 10.5 Hz, H-10), 5.82 (1H, d, J = 15.5, H-2), 6.55 (1H, dt, J = 17.0 and 10.5 Hz, H-11), 6.96 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 0.6 (C-TMS), 14.3 (C-14), 26.6 (C-7), 27.8 (C-5), 28.6 (C-6), 32.1 (C-4), 36.5 (C-8), 60.1 (C-13), 110.4 (C-10), 111.7 (C-12), 121.3 (C-2), 131.6 (C-11), 149.2 (C-3), 153.2 (C-9), 178.4 (C-1); m/z (GCMS) calculated for $C_{17}H_{31}O_3Si$ (MH^+) 311.2042 found 311.2032; ν_{max}/cm^{-1} (thin film) 2935 (str, C-H stretch), 2860 (w, C-H), 1721 (str, s, C=O), 1650 (m, C=C), 1419 (w, C-H deformation), 1367 (w), 1254 (m), 1181 (m), 1044 (m), 847 (str)

(1*R,2*R**,4a*R**,8a*R**)-2-methyl-4-oxodecahydronaphthalene-1-carboxylic acid ethyl ester (169)**



A solution of ethyl (2*E*,9*Z*)-9- (trimethylsilyloxy) dodeca-2,9,11-trienoate **167** (135.0 mg, 0.43 mmol) in anhydrous toluene (2 mL) was added a few drops of CSA. The mixture was heated to 180°C in a sealed tube. After 4 days it was concentrated and dissolved in ethyl acetate (4 mL). Then hydrochloric acid (aq. 1N, 4 mL) was added into the mixture. After 24 h sodium

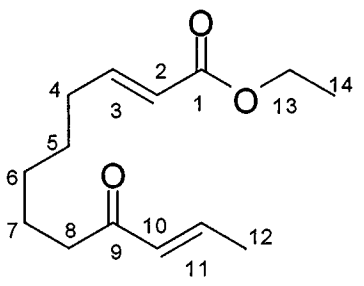
bicarbonate (aq. sat., 5 mL) was added, and the content of the flask was partitioned between water (10 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was washed with ethyl acetate (3x20 mL). The combined organic layers were dried over magnesium sulphate and concentrated. The crude residue was chromatographed over silica gel (DCM/petrol 1:2) to give the major cycloaddition product **169** as colorless oil (65.3 mg, 63%), minor cycloaddition product as a colorless oil (4.0 mg, 4%), and the *trans*-enone **170** as a colorless oil (6.7 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (3H, d, J = 7.0 Hz, H-14), 0.98-1.08 (2H, m, 1xH-8 and 1xH-7), 1.17-1.33 (3H, m, 1xH-9, 1xH-8 and 1xH-10), 1.28 (3H, t, J = 7.0 Hz, H-13), 1.70-1.74 (1H, m, 1xH-10), 1.80-1.82 (1H, m, 1xH-9), 1.90-2.01 (3H, m, H-1, H-6 and 1xH-7), 2.26 (1H, apparent d, J = 10.0 Hz, 1xH-4), 2.60-2.68 (2H, m, H-3 and 1xH-4), 2.73 (1H, dd, J = 11.0 and 3.5 Hz, H-2), 4.15-4.20 (2H, m, H-12); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-13), 16.3 (C-14), 24.7 (C-9), 25.9 (C-8), 26.5 (C-10), 30.1 (C-7), 30.8 (C-3), 37.1 (C-1), 45.7 (C-4), 50.2 (C-2), 51.9 (C-6), 60.3 (C-12), 175.7 (C-11), 212.2 (C-5); m/z (GCMS) calculated for $C_{14}H_{23}O_3$ (MH^+) 239.1647 found 239.1652; ν_{max}/cm^{-1} (thin film) 2934 (str, C-H), 2840 (m, C-H), 1712 (m, C=O), 1449 (w, C-H deformations), 1382 (w), 1292 (w), 1230 (w), 1175 (str, C-O), 1030 (m)

minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89-0.91 (1H, m, 1xH-9), 1.04 (3H, d, J = 6.5 Hz, H-14), 1.16-1.35 (3H, m, 1xH-7, 1xH-9 and 1xH-10), 1.31 (3H, t, J = 7.0 Hz, H-13), 1.44-1.52 (2H, m, 1xH-8 and 1xH-10), 1.70-1.84 (1H, m, 1xH-8), 2.18-2.22 (1H, m, H-1), 2.25-2.29 (1H, m, 1xH-4), 2.31-2.40 (2H, m, H-3 and 1xH-7), 2.58-2.62 (1H, m, H-6), 2.69-2.72 (1H, m, 1xH-4), 2.95-3.01 (1H, m, H-2), 4.17-4.22 (2H, m, H-12); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-13), 15.3 (C-14), 24.9 (C-9), 25.3 (C-8), 25.5 (C-10), 32.3 (C-7), 33.9 (C-3), 40.1 (C-1), 47.9 (C-4),

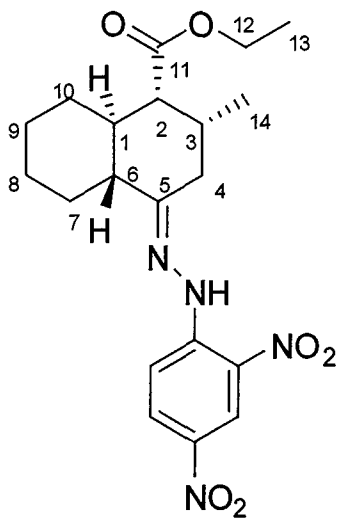
52.0 (C-2), 53.3 (C-6), 60.4 (C-12), 175.5 (C-11), 210.7 (C-5); m/z (GCMS) calculated for $C_{14}H_{23}O_3$ (MH^+) 239.1647 found 239.1647; ν_{max}/cm^{-1} (thin film) 2963 (str, C-H), 2867 (m, C-H), 1734 (m, C=O), 1261 (str, C-O), 1030 (str), 802(str)

Ethyl (2*E*,10*E*)-9-oxododeca-2,10-dienoate (170)



The *trans*-enone **170** was a side product in the formation of **169** in Diels-Alder reaction. It was a colourless oil (6.7 mg, 6%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, t, J = 7.0 Hz, H-14), 1.25-1.37 (2H, m, H-6), 1.45-1.50 (2H, qui, J = 7.5 Hz, H-5), 1.57-1.63 (2H, qui, J = 7.5 Hz, H-7), 1.90 (3H, dd, J = 7.0 and 2.0 Hz, H-12), 2.17-2.22 (2H, q, J = 7.5 Hz, H-4), 2.52 (2H, t, J = 7.5 Hz, H-8), 4.18 (2H, q, J = 7.0 Hz, H-13), 5.80 (1H, dt, J = 15.5 and 1.5 Hz, H-2), 6.12 (1H, d, J = 16.0 Hz, H-10), 6.82-6.86 (1H, m, H-11), 6.94 (1H, dt, J = 15.5 and 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-14), 18.2 (C-12), 23.9 (C-7), 27.8 (C-5), 28.7 (C-6), 32.0 (C-4), 39.7 (C-8), 60.1 (C-13), 121.4 (C-2), 131.9 (C-10), 142.5 (C-11), 149.1 (C-3), 166.7 (C-1), 200.4 (C-9); m/z (GCMS) calculated for $C_{14}H_{23}O_3$ (MH^+) 239.1647 found 239.1649;ν_{max}/cm^{-1} (thin film) 2935 (str, C-H), 2859 (w, C-H), 1714 (str, s, C=O), 1680 (w, C=O), 1635 (w, C=C), 1443 (w, C-H deformations), 1370 (w), 1269 (m), 1087 (w)

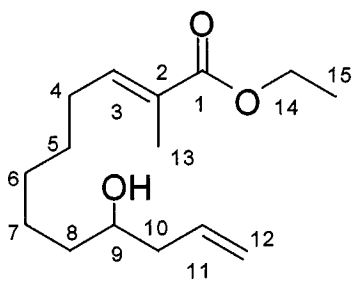
(1*R,2*R**,4a*R**,8a*R**)-2-Methyl-4--[(3,5-dinitrophenyl)hydrazono]decahydro-naphthalene -1-carboxylic acid ethyl ester (172)**



The ketone **169** (65.3 mg, 0.27 mmol, 1 eq) was solved in 0.73 mL EtOH (10% solution). To dinitrophenylhydrazine (30% H_2O, 311.1 mg, 1.10 mmol, 4 eq) was added conc. H_2SO_4 (1.5 mL), H_2O (2.3 mL) and then EtOH (7.8 mL). The two solutions were combined and shaken for 5 min and the product **172** crystallized out as an orange solid (89.6 mg, 75%).[142] Mp 119-120°C; ^{1}H NMR (400 MHz, C_6D_6) δ_H 0.87-0.98 (1H, m, 1xH-10), 0.90 (3H, d, J = 7.5 Hz, H-14), 1.08 (3H, t, J = 7.0 Hz, H-13), 1.15-1.34 (2H, m, 1xH-7 and 1xH-9), 1.47-1.64 (2H, m, H-6 and 1xH-8), 1.68-1.73 (2H, m, 1xH-4 and 1xH-9), 1.85-1.95 (2H, m, H-1 and 1xH-7), 2.05-2.15 (2H, m, 1xH-8 and 1xH-10), 2.18-2.23 (1H, m, H-3), 2.35 (1H, dd, J = 10.5 and 4.5 Hz, H-2), 2.47 (1H, dd, J = 14.5 and 4.5 Hz, 1xH-4), 4.02-4.08 (2H, m, H-12), 7.62 (1H, apparent d, J = 9.5 Hz, H-Ar), 8.34 (1H, apparent d, J = 9.5 Hz, H-Ar), 8.95 (1H, apparent s, H-Ar), 11.03 (1H, s, NH); ^{13}C NMR (100.6 MHz, C_6D_6) δ_C 14.5 (C-13), 15.4 (C-14), 26.1 (C-7), 26.2 (C-9), 27.5 (C-8), 32.8 (C-3), 33.0 (C-10), 33.8 (C-4), 41.3 (C-1), 47.8 (C-6), 52.4 (C-2), 60.4 (C-12), 115.9 (C-Ar), 123.6 (C-Ar), 129.3 (C-Ar), 129.7 (C-Ar), 145.5 (C-Ar), 159.4 (C-Ar), 172.9 (C-5), 173.9 (C-11); m/z (ESIMS) calculated for $C_{20}H_{27}N_4O_6$ (MH^+) 419.1931 found 419.1930; ν_{max}/cm^{-1} (KBr) 3440 (str, wide, N-H), 3319 (m), 2963 (str), 2854 (w), 1730 (m, C=O), 1620 (str), 1508 (w), 1338 (m), 1308 (m, C-O), 1280 (w), 1161 (m)

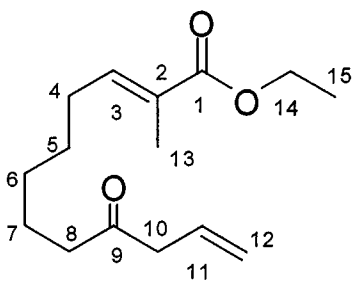
4.2.3 Experimental for synthesis of the key intermediate

(*E*)-Ethyl-9-hydroxy-2-methyldodeca-2,11-dienoate (173)



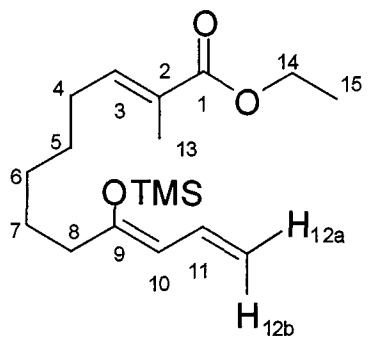
To a solution of 7-hydroxydec-9-enal **164** (7.25 g, 18.55 mmol) in dichloromethane (500 mL) was added (carbethoxyethylidene)triphenylphosphorane (18.55 g, 51.24 mmol). The mixture was left under reflux for 24 hr. The solvent was removed in vacuo, and the residue was extracted with diethyl ether/hexane (1:1, 3x300 mL). The combined extracts were concentrated and chromatographed over silica gel, eluted with ethyl acetate-petrol 1:9 to give 8.56 g (79%) of the alcohol **173** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, t, J = 7.0 Hz, H-15), 1.33-1.40 (2H, m, H-6), 1.40-1.53 (6H, m, H-5, H-7 and H-8), 1.83 (3H, s, H-13), 2.11-2.21 (3H, m, H-4 and 1xH-10), 2.28-2.34 (1H, m, 1xH-10), 3.62-3.68 (1H, m, H-9), 4.19 (2H, q, J = 7.0 Hz, H-14), 5.13-5.17 (2H,m, H-12), 5.78-5.89 (1H, m, H-11), 6.76 (1H, t, J = 7.5 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (C-13), 14.3 (C-15), 25.5 (C-7), 28.5 (C-5), 28.6 (C-4), 29.4 (C-6), 36.7 (C-8), 42.0 (C-10), 60.4 (C-14), 70.6 (C-9), 118.2 (C-12), 127.8 (C-2), 134.8 (C-11), 142.2 (C-3), 168.3 (C-1); m/z (GCMS) calculated for $C_{15}H_{27}O_3$ (MH^+) 255.1960 found 255.1954; ν_{max}/cm^{-1} (thin film) 3444 (br, str, O-H), 3080 (w, C=C-H stretch), 2932 (br, str, C-H stretch), 2858 (m, C-H stretch), 1710 (s, C=O), 1646 (w, C=C), 1444 (w, C-H deformation), 1368 (w), 1271 (m, C-O), 1098 (m)

(*E*)-Ethyl-2-methyl-9-oxododeca-2,11-dienoate (174)



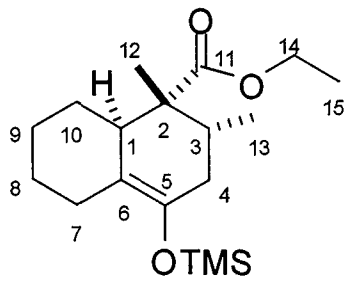
Dess-Martin reagent (31.40 g, 67.00 mmol) was added in one portion to a solution of alcohol **173** (8.56 g, 38.00 mmol) in anhydrous DCM (400 mL). After 2 hr, the mixture was diluted with DCM (200 mL) and sequently washed with $Na_2S_2O_3$ (aq. sat., 200 mL), and $NaHCO_3$ (aq. 5%, 200 mL). The combined aqueous layers were extracted once with DCM (500 Ml) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc/petrol 1:6) to yield the ketone **174** as light yellow oil (7.49 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28-1.36 (2H, m, H-6), 1.30 (3H, t, J = 7.0 Hz, H-15), 1.46 (2H, qui, J = 7.5 Hz, H-5), 1.56-1.63 (2H, qui, J = 7.5 Hz, H-7), 1.83 (3H, s, H-13), 2.17 (2H, q, J = 7.5 Hz, H-4), 2.45 (2H, t, J = 7.5 Hz, H-8), 3.17 (2H, d, J = 7.0 Hz, H-10), 4.19 (2H, q, J = 7.0 Hz, H-14), 5.12-5.21 (2H, m, H-12), 5.87-5.98 (1H, m, H-11), 6.74 (1H, d, J = 7.5 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (C-13), 14.3 (C-15), 23.4 (C-7), 28.3 (C-4), 28.4 (C-5), 28.9 (C-6), 42.2 (C-8), 47.8 (C-10), 60.4 (C-14), 118.8 (C-12), 127.9 (C-2), 130.6 (C-11), 141.9 (C-3), 168.2 (C-1), 208.7 (C-9); m/z (GCMS) calculated for $C_{15}H_{25}O_3$ (MH^+) 253.1804 found 253.1792; ν_{max}/cm^{-1} (thin film) 2935 (m, C-H stretch), 2860 (w, C-H stretch), 1712 (str, C=O), 1648 (w, C=C), 1367 (w), 1272 (m, C-O), 1097 (w)

(2*E*,9*Z*)-Ethyl-2-methyl-9-(trimethylsilyloxy)dodeca-2,9,11-trienoate (175)



To a solution of ketone **174** (2.52 g, 10.00 mmol) in anhydrous THF (100 mL) was added HMPA (1.97 g, 11.00 mmol). The mixture was cooled to -78°C and then was added LHMDS (1M in THF, 12.0 mL, 12.00 mmol). After 15 min, the enol ether was quenched with freshly distilled TMSCl over CaH_2 (1.30 g, 12.00 mol). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and poured into pentane (100 mL) in a separation funnel. The mixture was washed with $NaHCO_3$ (aq. sat., 2x100 mL) and brine (100 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:100) to yield 2.46 g TMS enol ether **175** as colorless oil (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.22 (9H, s, H-TMS), 1.30 (3H, t, J = 7.0 Hz, H-15), 1.31-1.38 (2H, m, H-6), 1.42-1.55 (4H, m, H-5 and H-7), 1.83 (3H, s, H-13), 2.06 (2H, t, J = 7.5 Hz, H-8), 2.17 (2H, q, J = 7.0 Hz, H-4), 4.19 (2H, q, J = 7.0 Hz, H-14), 4.81 (1H, dd, J = 10.5 and 2.0 Hz, H-12a), 5.00 (1H, dd, J = 17.0 and 2.0 Hz, H-12b), 5.30 (1H, d, J = 10.5 Hz, H-10), 6.55 (1H, dt, J = 17.0 and 10.5 Hz, H-11), 6.75 (1H, t, J = 7.5 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 0.6 (C-TMS), 12.3 (C-13), 14.3 (C-15), 26.7 (C-7), 28.4 (C-4), 28.6 (C-5), 28.9 (C-6), 36.5 (C-8), 60.4 (C-14), 110.4 (C-10), 111.7 (C-12), 127.8 (C-2), 131.6 (C-11), 142.1 (C-3), 153.3 (C-9), 168.2 (C-1); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 325.2199 found 325.2200; ν_{max}/cm^{-1} (thin film) 2934 (str, C-H stretch), 2860 (w, C-H stretch), 1710 (str, C=O), 1649 (w, C=C), 1369 (w), 1264(m, $SiMe_3$), 1175 (m, C-O)

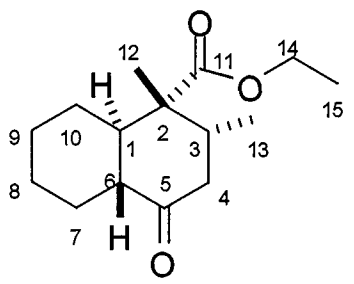
(1*R,2*R**,8a*R**)-1,2-Dimethyl-4-(trimethylsilyloxy)-1,2,3,5,6,7,8,8a-octahydronaphthalene -1-carboxylic acid (176)**



A solution of TMS enol ether **175** (90.00 mg, 0.28 mmol) in anhydrous toluene (10 mL) was added camphor-10-sulphonic acid (4 mol%). The mixture was heated to 180˚C in a sealed tube. After 4 days it was concentrated and chromatographed over silica gel (eluting with gradient solvent from Et_2O/petrol (1:100) to Et_2O/petrol (1: 10)) to give the cycloadduct **176** as light yellow oil (61.2 mg, 68%), the ketone **177** as yellow oil (5 mg, 6%), and trace amount of enone **178**. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.17 (9H, s, H-TMS), 0.87 (3H, d, J = 7.0 Hz, H-13), 1.06 (1H, apparent dd, J = 12.5 and 3.0 Hz, 1xH-10), 1.13 (3H, s, H-12), 1.21-1.29 (4H, m, 1xH-8 and H-15), 1.38 (1H, apparent dd, J = 10.0 and 3.0 Hz, 1xH-9), 1.55-1.60 (1H, m, 1xH-7), 1.69-1.79 (4H, m, 1xH-4, 1xH-8, 1xH-9 and 1xH-10), 1.92-1.98 (1H, m, H-3), 2.40-2.48 (1H, m, 1xH-4), 2.60 (1H, apparent d, J = 12.0 Hz, H-1), 2.84 (1H, apparent d, J = 14.5 Hz, H-7), 4.11-4.17 (2H, m, H-14); ^{13}C NMR (100.6 MHz, $CDCl_3$) δC 0.6 (C-TMS), 14.3 (C-13), 16.2 (C-15), 20.1 (C-12), 26.0 (C-9), 26.3 (C-8), 26.5 (C-10), 28.4 (C-7), 31.0 (C-4), 34.1 (C-3), 36.2 (C-1), 47.1 (C-2), 60.0 (C-14), 115.9 (C-6), 137.9 (C-5), 176.9 (C-11); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 325.2199 found 325.2193; ν_{max}/cm^{-1} (thin film) 2929 (str, C-H stretch), 2855 (w, C-H stretch), 1728 (str, C=O), 1447 (w, C-H deformation), 1363 (w), 1253 (m, $SiMe_3$), 1183 (m, C-O), 1113 (w)

(1*R,2*R**,4a*S**,8a*R**)-Ethyl-1,2-dimethyl-4-oxo-decahydronaphthalene-1-carboxylate**

(177)

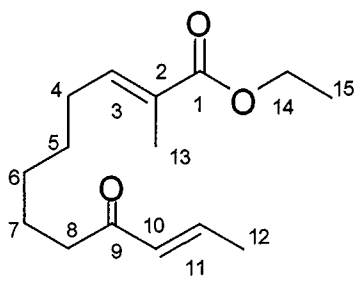


The ketone **177** was a side product in the formation of **176** in the Diels-Alder reaction. It was a colourless oil (5 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.85 (3H, d, J = 7.0 Hz, H-13), 1.11-1.30 (7H, m, 1xH-7, 1xH-8, 1xH-9, 1xH-10 and H-15), 1.44 (3H, s, H-12), 1.71-1.82 (3H, m, 1xH-7, 1xH-8 and 1xH-9), 2.02-2.08 (2H, m, H-3 and 1xH-10), 2.12-2.20 (2H, m, H-4 and H-6), 2.22-2.30 (1H, m, H-1), 2.74 (1H, dd, J = 13.5 and 5.5 Hz, H-4), 4.14-4.20 (2H, q, J = 7.0 Hz, H-14); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-15), 16.8 (C-13), 18.4 (C-12), 25.6 (C-9), 25.7 (C-8), 26.0 (C-10), 28.6 (C-7), 41.2 (C-3), 43.0 (C-4), 44.1 (C-1), 48.3 (C-6), 49.2 (C-2), 60.4 (C-14), 175.5 (C-11), 211.5 (C-5); m/z (GCMS) calculated for $C_{15}H_{24}O_3$ (MH^+) 253.1804 found 253.1803; ν_{max}/cm^{-1} (thin film) 2932 (str, C-H stretch), 2857 (m, C-H stretch), 1713 (str, C=O), 1447 (m, C-H deformation), 1388 (w), 1367 (w), 1270 (m), 1213 (m, C-O), 1134 (m), 1106 (w), 1053 (w)

Trace of another isomer of the ketone **177** was also isolated out as a colourless oil in trial reactions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88-0.97 (1H, m, 1xH-9), 1.09 (3H, d, J = 7.0 Hz, H-13), 1.12-1.23 (2H, m, 1xH-8 and 1xH-10), 1.25 (3H, s, H-12), 1.28 (3H, t, J = 7.0 Hz, H-15), 1.42-1.50 (2H, m, H-7), 1.70-1.82 (2H, m, 1xH-8 and 1xH-9), 1.94-2.04 (1H, m, H-3), 2.20-2.28 (3H, m, 1xH-4, H-6 and 1xH-10), 2.59 (1H, m, H-1), 2.79-2.86 (1H, m, 1xH-4), 4.20 (2H, q, J = 7.0 Hz, H-14); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-15), 16.4 (C-13), 21.9 (C-12), 22.0 (C-9), 24.2 (C-8), 25.2 (C-10), 26.6 (C-7), 35.7 (C-3), 46.6 (C-4), 47.5 (C-1), 48.1 (C-6), 48.8

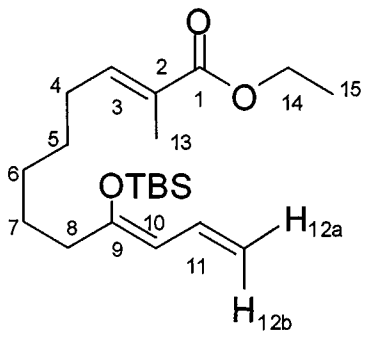
(C-2), 60.3 (C-14), 176.0 (C-11), 212.1 (C-15); m/z (GCMS) calculated for $C_{15}H_{24}O_3$ (MH^+) 253.1804 found 253.1792; ν_{max}/cm^{-1} (thin film) 2938 (str, C-H stretch), 2860 (m, C-H stretch), 1712 (str, C=O), 1448 (m, C-H deformation), 1381 (w), 1340 (w), 1247 (m), 1226 (m, C-O), 1145 (m), 1081 (w), 1027 (w)

(2*E*,10*E*)-Ethyl 2-methyl-9-oxododeca-2,10-dienoate (178)



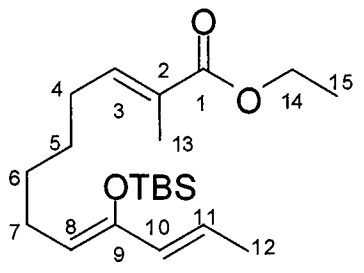
The ketone **178** was a side product in the formation of **176** in the Diels-Alder reaction. It was a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, t, J =7.0 Hz, H-15), 1.32-1.38 (2H, m, H-6), 1.46 (2H, qui, J = 7.5 Hz, H-5), 1.62 (2H, qui, J = 7.5 Hz, H-7), 1.82 (3H, s, H-13), 1.90 (3H, d, J = 7.0 Hz, H-12), 2.17 (2H, q, J = 7.5 Hz, H-4), 2.53 (2H, t, J = 7.5 Hz, H-8), 4.18 (2H, q, J = 7.0 Hz, H-14), 6.11 (1H, d, J = 15.5 Hz, H-10), 6.74 (1H, t, J = 7.5 Hz, H-3), 6.85 (1H, dq, J =15.5 and 7.0 Hz, H-11); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (C-13), 14.3 (C-15), 18.2 (C-12), 24.0 (C-7), 28.4 (C-5), 28.5 (C-6), 29.0 (C-4), 39.8 (C-8), 60.4 (C-14), 127.8 (C-2), 131.9 (C-10), 142.0 (C-11), 142.4 (C-3), 168.3 (C-1), 200.5 (C-9); m/z (GCMS) calculated for $C_{15}H_{24}O_3$ (MH^+) 253.1804 found 253.1805; ν_{max}/cm^{-1} (thin film) 2935 (m□ C-H stretch), 2859 (w, C-H stretch), 1709 (s, C=O), 1673 (w, C=O), 1634 (w, C=C), 1445 (w, C-H deformation), 1367 (w), 1270 (m, C-O), 1097 (w)

(2*E*,9*Z*)-Ethyl-9-(*tert*-butyldimethylsilyloxy)-2-methyldodeca-2,9,11-trienoate (179)

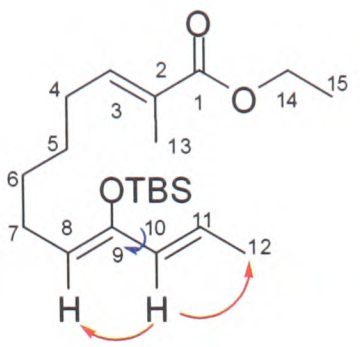


To a solution of ketone **174** (126 mg, 0.50 mmol) in anhydrous THF (10 mL) was added hexamethylphosphoramide (HMPA) (99 mg, 96 μL, 0.55 mmol). The mixture was cooled to -78°C and then was added LHMDS (1M sol. in THF, 0.65 mL, 0.65 mmol). After 15 min, the enolate was quenched with TBOTf (172 mg, 0.065 mmol). After being stirred for 1 hr, the reaction mixture was allowed to warm to room temperature and poured into pentane (20 mL) in a separation funnel. The mixture was washed with $NaHCO_3$ (aq. sat., 2x10 mL) and brine (10 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:100) to yield 167 mg TBS enol ether **179** as colourless oil (91%). ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.15 (6H, s, $Si(C\underline{H}_3)_2$), 0.97 (9H, s, $C(C\underline{H}_3)_3$), 1.30 (3H, t, J = 7.0 Hz, H-15), 1.32-1.38 (2H, m, H-6), 1.42-1.55 (4H, m, H-5 and H-7), 1.83 (3H, s, H-13), 2.06 (2H, t, J = 7.5 Hz, H-8), 2.18 (2H, q, J = 7.5 Hz, H-4), 4.20 (2H, q, J = 7.0 Hz, H-14), 4.81 (1H, dd, J = 10.5 and 1.5 Hz, H-12b), 4.98 (1H, dd, J = 17.0 and 1.5 Hz, H-12a), 5.26 (1H, d, J = 10.5 Hz, H-10), 6.61 (1H, dt, J = 17.0 and 10.5 Hz, H-11), 6.76 (1H, t, J = 7.5 Hz, H-3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C -3.8 ($Si(\underline{C}H_3)_2$), 12.3 (C-13), 14.4 (C-15), 18.3 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 26.9 (C-7), 28.4 (C-4), 28.6 (C-5), 29.0 (C-6), 36.6 (C-8), 60.5 (C-14), 110.0 (C-10), 111.6 (C-12), 127.9 (C-2), 131.8 (C-11), 142.2 (C-3), 153.4 (C-9), 168.4 (C-1); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 367.2668 found 367.2661; ν_{max}/cm^{-1} (thin film) 2933 (Str, C-H stretch), 2859 (w, C-H stretch), 1710 (str, C=O), 1649 (w, C=C), 1463 (w, C-H deformation), 1389 (w), 1368 (w), 1257(m, Si-Me), 1097 (w, C-O)

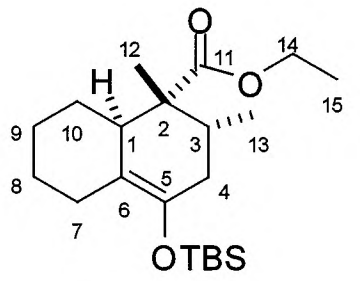
(2*E*,8*E*,10*E*)-Ethyl 9-(*tert*-butyldimethylsilyloxy)-2-methyldodeca-2,8,10-trienoate (179a)



To a solution of enone **178** (0.25 g, 1.00 mmol) and *tert*-butyldimethylsilyl triflate (0.40 g, 1.50 mmol) in anhydrous THF (20 mL) was added potassium hexamethyldisilazide (0.5 M in toluene, 3 mL, 1.50 mmol) dropwise at -78°C under nitrogen. The resulting solution was stirred at -78°C for 30 min and at room temperature for 1h. The solution was quenched with $NaHCO_3$ (aq. sat., 20 mL) and extracted with Et_2O (3x20 mL). The combined organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (ether/petrol = 1:100) to give the product **179a** as a colourless oil (0.32 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.10 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.99 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.29 (3H, t, J = 7.0 Hz, <u>H</u>-15), 1.34-1.41 (2H, m, <u>H</u>-6), 1.42-1.50 (2H, m, <u>H</u>-5), 1.73 (3H, d, J = 6.0 Hz, <u>H</u>-12), 1.82 (3H, s, <u>H</u>-13), 2.09 (2H, q, J = 7.0 Hz, <u>H</u>-7), 2.16 (2H, qui, J = 7.5 Hz, <u>H</u>-4), 4.19 (2H, q, J = 7.0 Hz, <u>H</u>-14), 4.63 (1H, t, J = 7.0 Hz, <u>H</u>-8), 5.71-5.79 (1H, m, <u>H</u>-11), 5.84 (1H, d, J = 15.5 Hz, <u>H</u>-10), 6.75 (1H, t, J = 7.5 Hz, <u>H</u>-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -3.7 (Si(<u>C</u>H$_3$)$_2$), 12.3 (<u>C</u>-13), 14.2 (<u>C</u>-15), 17.6 (<u>C</u>-12), 18.4 (<u>C</u>(CH$_3$)$_3$), 25.8 (<u>C</u>-4), 26.0 (C(<u>C</u>H$_3$)$_3$), 28.4 (<u>C</u>-5), 28.5 (<u>C</u>-6), 29.4 (<u>C</u>-7), 60.3 (<u>C</u>-14), 112.5 (<u>C</u>-8), 123.9 (<u>C</u>-10), 126.1 (<u>C</u>-2), 127.8 (<u>C</u>-11), 148.2 (<u>C</u>-3), 142.3 (<u>C</u>-9), 168.3 (<u>C</u>-1); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 367.2668 found 367.2651; ν_{max}/cm^{-1} (thin film) 2943 (Str, C-H stretch), 2860 (w, C-H stretch), 1714 (str, C=O), 1652 (w, C=C), 1465 (w, C-H deformation), 1389 (w), 1365 (w), 1250(m, Si-Me), 1090 (w, C-O); n.O.e experiments: irradiation at 5.84 (<u>H</u>-10) saw reciprocal signal enhancement at 1.73 (<u>H</u>-12) and 4.63 (<u>H</u>-8)



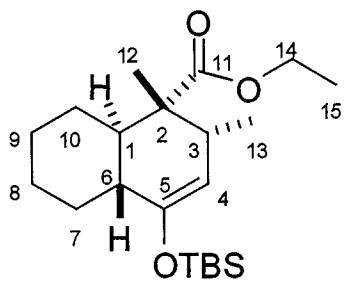
(1*R,2*R**,8a*R**)-4-(*tert*-Butyldimethylsilyloxy)-1,2-dimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalene-1-carboxylic acid ethyl ester (180)**



A solution of TBS enol ether **179** (500.0 mg, 1.36 mmol) in anhydrous toluene (10 mL) was added camphor-10-sulphonic acid (4 mol%). The mixture was heated to 180˚C in a sealed tube. After 4 days it was concentrated and chromatographed over silica gel (eluting with gradient solvent from Et_2O/petrol (1:100) to Et_2O/petrol (1: 10)) to give the cycloadduct **180** as light yellow oil (345.1 mg, 69%), the ketone **177** as yellow oil (25.0 mg, 7%), and trace amount of enone **178**. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.13 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.16 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.93 (3H, d, J = 7.0 Hz, $\underline{H}$-13), 1.00 (9H, s, C(C$\underline{H}_3$)$_3$), 1.06-1.14 (2H, m, 1x$\underline{H}$-8 and 1x$\underline{H}$-10), 1.18 (3H, s, $\underline{H}$-12), 1.30 (3H, t, J = 7.0 Hz, $\underline{H}$-15), 1.39-1.47 (1H, m, 1x$\underline{H}$-8), 1.59-1.64 (1H, m, 1x$\underline{H}$-7), 1.75-1.88 (4H, m, 1x$\underline{H}$-4, $\underline{H}$-9 and 1x$\underline{H}$-10), 2.00-2.02 (1H, m, $\underline{H}$-3), 2.46 (1H, dd, J = 17.0 and 2.5 Hz, $\underline{H}$-4), 2.64 (1H, apparent d, J = 12.0 Hz, $\underline{H}$-1), 2.95 (1H, apparent d, J = 14.0 Hz, 1x$\underline{H}$-7), 4.14-4.21 (2H, m, $\underline{H}$-14); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C -3.9 (Si($\underline{C}H_3$)$_2$), 14.3 ($\underline{C}$-13), 16.3 ($\underline{C}$-15), 18.3 ($\underline{C}$(CH$_3$)$_3$), 20.2 ($\underline{C}$-12), 26.0 (C($\underline{C}$H$_3$)$_3$), 26.1 ($\underline{C}$-7), 26.4 ($\underline{C}$-9), 26.5 ($\underline{C}$-8), 28.5 ($\underline{C}$-10), 34.4 ($\underline{C}$-4), 36.3 ($\underline{C}$-3), 38.5 ($\underline{C}$-1), 47.2 ($\underline{C}$-2), 60.1 ($\underline{C}$-14), 115.6 ($\underline{C}$-6), 138.2 ($\underline{C}$-5), 177.0 ($\underline{C}$-11); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 367.2668 found 367.2668; ν_{max}/cm^{-1} (thin film) 2931 (str, C-H stretch), 2857 (m, C-H stretch), 1728 (str, C=O),

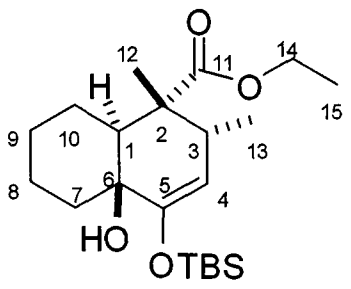
1674 (w, C=C), 1650 (w), 1463 (w, C-H deformation), 1363 (w), 1257 (m, SiMe), 1179 (m, C-O), 1114 (w)

(1*R,2*R**,4a*R**,8a*R**)-4-(*tert*-Butyldimethylsilyloxy)-1,2-dimethyl-1,2,4a,5,6,7,8,8a-octa-hydro-naphthalene-1-carboxylic acid ethyl ester (180a)**



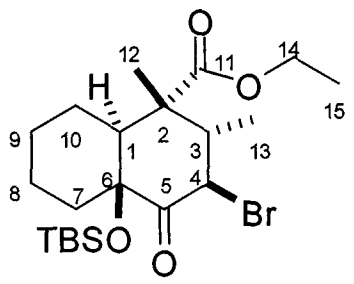
To a solution of ketone **177** (138 mg, 0.55 mmol) and *tert*-butyldimethylsilyl triflate (0.22 g, 0.82 mmol) in anhydrous THF (15 mL) was added potassium hexamethyldisilazide (0.5 M in toluene, 1.64 mL, 0.82 mmol) dropwise at -78°C under nitrogen. The resulting solution was stirred at -78°C for 30 min and at room temperature for 1h. The solution was quenched with $NaHCO_3$ (aq. sat., 10 mL) and extracted with Et_2O (3x15 mL). The combined organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (ether/petrol 1:100) to give the product **180a** as a colourless oil, which was used in the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.13 (3H, s, $Si(C\underline{H}_3)_2$), 0.14 (3H, s, $Si(C\underline{H}_3)_2$), 0.93 (9H, s, $C(C\underline{H}_3)_3$), 0.94 (3H, d, J = 7.0 Hz, $\underline{H}$-13), 1.17 (3H, s, $\underline{H}$-12), 1.27 (3H, t, J = 7.0 Hz, $\underline{H}$-15), 1.68-1.90 (6H, m, 1x$\underline{H}$-7, $\underline{H}$-8, $\underline{H}$-9 and 1x$\underline{H}$-10), 2.02-2.36 (5H, m, $\underline{H}$-1, $\underline{H}$-3, $\underline{H}$-6, 1x$\underline{H}$-7 and 1x$\underline{H}$-10), 4.06-4.25 (2H, m, $\underline{H}$-14), 4.41 (1H, d, J = 5.5 Hz, $\underline{H}$-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C -3.9 ($Si(\underline{C}H_3)_2$), 14.2 ($\underline{C}$-13), 16.2 ($\underline{C}$-15), 18.2 ($\underline{C}(CH_3)_3$), 20.6 ($\underline{C}$-12), 25.9 ($C(\underline{C}H_3)_3$), 26.0 (C-7), 26.3 ($\underline{C}$-8), 26.4 ($\underline{C}$-9), 28.5 ($\underline{C}$-10), 34.3 ($\underline{C}$-1), 36.2 ($\underline{C}$-3), 38.4 ($\underline{C}$-6), 47.1 ($\underline{C}$-2), 60.1 ($\underline{C}$-14), 115.5 ($\underline{C}$-4), 138.2 ($\underline{C}$-5), 176.9 ($\underline{C}$-11); m/z (GCMS) calculated for $C_{18}H_{32}O_3Si$ (MH^+) 367.2668 found 367.2668; ν_{max}/cm^{-1} (thin film) 2931 (str, C-H stretch), 2859 (m, C-H stretch), 1728 (str, C=O), 1257 (m, SiMe), 1179 (m, C-O)

(1*S,2*S**,4a*R**,8a*R**)-4-(*tert*-Butyldimethylsilyloxy)-4a-hydroxy-1,2-dimethyl-1,2,3,5,6,7,8, 8a-octahydronaphthalene-1-carboxylic acid (181)**



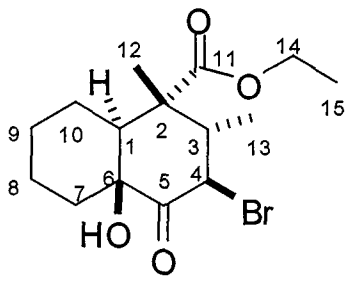
A solution of TBS-enol ether **180** (402.2 mg, 1.10 mmol) in anhydrous DCM (10 mL) was cooled to -78°C, and added a solution of m-CPBA (210.5 mg, 1.22 mmol) in DCM (10 mL). The mixture was warmed to room temperature gradually, and then washed with $NaHCO_3$ (aq. sat., 10 mL), extracted with DCM (3x30 mL). The crude product was purified through silica gel (Et_2O/petrol 1:25) to give colourless oil product **181** (187.0 mg, 52%). ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.19 (6H, s, $Si(C\underline{H}_3)_2$), 0.88 (3H, d, J = 7.0 Hz, <u>H</u>-13), 0.91-0.94 (1H, m, 1x<u>H</u>-10), 0.95 (9H, s, $C(C\underline{H}_3)_3$), 1.20-1.32 (1H, m, 1x<u>H</u>-7), 1.27 (3H, t, J = 7.0 Hz, <u>H</u>-15), 1.35 (3H, s, <u>H</u>-12), 1.38-1.43 (1H, m, O<u>H</u>), 1.50-1.53 (1H, m. 1x<u>H</u>-8), 1.59-1.82 (4H, m, 1x<u>H</u>-8, <u>H</u>-9 and 1xH-10), 2.00-2.03 (1H, m, 1x<u>H</u>-7), 2.08-2.11 (1H, m, <u>H</u>-1), 2.19-2.25 (1H, m, <u>H</u>-3), 4.09-4.18 (2H, m, <u>H</u>-14), 4.71 (1H, d, J = 5.5 Hz, <u>H</u>-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C -4.6 ($Si\underline{C}H_3$), -4.2 ($Si\underline{C}H_3$), 14.2 (<u>C</u>-15), 18.3 ($C(\underline{C}H_3)_3$), 18.9 (<u>C</u>-13), 19.1 (<u>C</u>-12), 21.5 (<u>C</u>-9), 22.5 (<u>C</u>-8), 25.8 ($\underline{C}(CH_3)_3$), 26.5 (<u>C</u>-10), 36.4 (<u>C</u>-7), 42.7 (<u>C</u>-3), 47.8 (<u>C</u>-2), 60.0 (<u>C</u>-14), 70.9 (<u>C</u>-6), 107.5 (<u>C</u>-4), 151.1 (<u>C</u>-5), 176.3 (<u>C</u>-11); m/z (GCMS) calculated for $C_{21}H_{39}O_4Si$ (MH^+) 383.2618 found 383.2622; ν_{max}/cm^{-1} (thin film) 3555 (w, br, O-H), 2933 (str, C-H stretch), 2858 (m, C-H stretch), 1726 (str, C=O), 1670 (m, C=C), 1463 (m, C-H deformation), 1379 (w), 1203 (str, SiMe), 1129 (m, C-O)

(1*S,2*S**,3*R**,4a*S**,8a*S**)-3-Bromo-4a-(*tert*-butyldimethylsilyloxy)-1,2-dimethyl-4-oxo-deca-hydronaphthalene-1-carboxylic acid ethyl ester (182)**

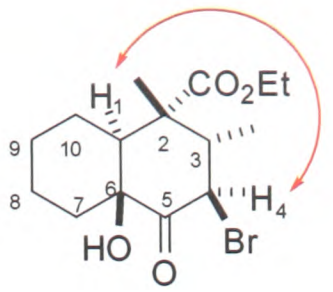


A solution of silyl enol ether **181** (83.5 mg, 0.24 mmol) in anhydrous THF (10 mL) was cooled to -78°C. *N*-Bromosuccinimide (46.7 mg, 0.26 mmol) in THF (10 mL) was added and the solution was stirred at -78°C for 4 h. The reaction mixture was poured into a separation funnel containing ether (15 mL). The mixture was washed with $NaHCO_3$ (aq. sat., 2x10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (ether/petrol 1:100) to give 95.5 mg of **182** as a faintly yellow oil (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.21 (3H, s, $Si(C\underline{H}_3)_2$), 0.31 (3H, s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $C(C\underline{H}_3)_3$), 0.98 (3H, d, J = 7.0 Hz, <u>H</u>-13), 1.25 (3H, t, J = 7.0 Hz, <u>H</u>-15), 1.40 (3H, s, <u>H</u>-12), 1.46-1.63 (4H, m, 1x<u>H</u>-7, 1x<u>H</u>-8, 1x<u>H</u>-9 and 1x<u>H</u>-10), 1.81-1.89 (4H, m, 1x<u>H</u>-7, 1x<u>H</u>-8, 1x<u>H</u>-9 and 1x<u>H</u>-10), 2.31 (1H, dd, J = 11.5 and 3.0 Hz, <u>H</u>-1), 2.45 (1H, qd, J = 7.0 and 2.5 Hz, <u>H</u>-3), 4.13 (2H, q, J = 7.0 Hz, <u>H</u>-14), 4.27 (1H, d, J = 2.5 Hz, <u>H</u>-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -2.5 ($Si\underline{C}H_3$), -3.0 ($Si\underline{C}H_3$), 14.1 (<u>C</u>-15), 18.1 (<u>C</u>-13), 20.4 (<u>C</u>-12), 24.0 (<u>C</u>-9), 25.8 ($C(\underline{C}H_3)_3$), 26.0 ($\underline{C}(CH_3)_3$), 26.2 (<u>C</u>-8), 26.3 (<u>C</u>-10), 30.2 (<u>C</u>-7), 37.7 (<u>C</u>-1), 43.1 (<u>C</u>-3), 47.6 (<u>C</u>-2), 57.4 (<u>C</u>-4), 60.6 (<u>C</u>-14), 74.3 (<u>C</u>-6), 175.8 (<u>C</u>-11), 203.8 (<u>C</u>-5); m/z (GCMS) calculated for $C_{21}H_{38}{}^{79}BrO_4Si$ (MH^+) 461.1723 found 461.1714; ν_{max}/cm^{-1} (thin film) 2933 (str, C-H stretch), 2858 (w, C-H stretch), 1728 (str, C=O), 1464 (w, C-H deformation), 1353(w), 1259 (m, SiMe), 1228 (w, C-O), 1171 (m), 1125 (m, C-O)

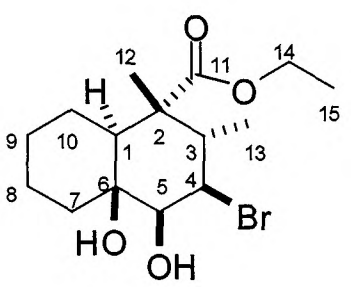
(1*S,2*S**,3*R**,4a*S**,8a*S**)-3-Bromo-4a-hydroxy-1,2-dimethyl-4-oxo-decahydronaphthalene -1-carboxylic acid ethyl ester (183)**



The ketone **182** (63.5 mg, 0.14mmol) was dissolved in acetonitrile (1.5 mL) containing an fluorosilicic acid solution (aq. 25 wt%, 0.15 mL). The mixture was stirred at room temperature for about 1.5 h. After such time, chloroform (10 mL) and water (5 mL) was added. The organic layer was separated out and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (ether/petrol 1:6) to give α-bromo-α'-hydroxyl ketone **183** as a white solid (38.4 mg, 80%). Mp 149.0-150.0°C; ^{1}H NMR (500 MHz, C_6D_6) δ_H 0.97 (3H, t, J = 7.0 Hz, H-15), 1.00 - 1.13 (2H, m, 1xH-7 and 1xH-8), 1.27 (3H, d, J = 7.0 Hz, H-13), 1.30-1.35 (2H, m, 1xH-9 and 1xH-10), 1.40-1.49 (2H, m, 1xH-8 and 1xH-9), 1.43 (3H, s, H-12), 1.58-1.60 (1H, br, OH), 1.71 (1H, dq, J = 13.0 and 3.5 Hz, 1xH-10), 1.77-1.79 (1H, m, 1xH-7), 2.33 (1H, dq, J = 13.5 and 6.5 Hz, H-3), 2.43 (1H, dd, J = 13.0 and 3.5 Hz, H-1), 3.92-4.03 (2H, m, H-14), 5.44 (1H, d, J = 13.5 Hz, H-4); ^{13}C NMR (125.8 MHz, C_6D_6) δ_C 14.2 (C-15), 17.0 (C-13), 20.0 (C-12), 20.6 (C-9), 23.8 (C-10), 26.1 (C-8), 35.4 (C-7), 43.0 (C-3), 44.1 (C-1), 51.4 (C-2), 60.0 (C-4), 60.7 (C-14), 75.2 (C-6), 175.7 (C-11), 203.7 (C-5); m/z (GCMS) calculated for $C_{15}H_{24}{}^{79}BrO_4$ (MH^+) 347.0858 found 347.0856; ν_{max}/cm^{-1} (KBr disc) 3449 (str, br, O-H), 2938 (str, C-H stretch), 2856 (w, C-H stretch), 1727 (str, C=O), 1702(str, C=O), 1466 (w, C-H deformation), 1402 (w), 1303 (w), 1242 (m, C-O), 1222 (w, C-O), 1157 (m); n.O.e experiments: irradiation at 2.43 (H-1) saw reciprocal signal enhancement at 5.44 (H-4); irradiation at 5.44 (H-4) saw reciprocal signal enhancement at 2.43 (H-1)

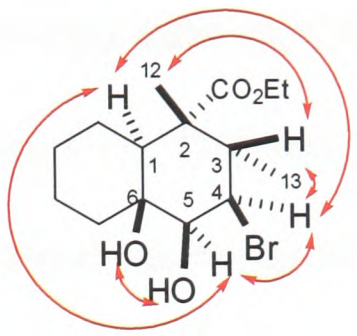


(1*S,2*S**,3*R**,4*S**,4a*S**,8a*S**)-3-Bromo-4,4a-dihydroxy-1,2-dimethyldecahydronaphthalene-1-carboxylic acid ethyl ester (183a)**

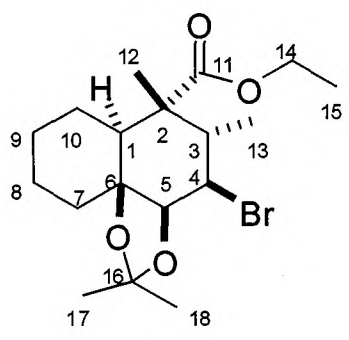


α-Bromo-α'-hydroxyl ketone **183** (46.5 mg, 0.13 mmol) was added to a solution of $CeCl_3 \cdot 7H_2O$ (50.1 mg, 0.13 mmol) in MeOH (0.33 mL). $NaBH_4$ (5.1 mg, 0.13 mmol) was added in small portions. The reaction mixture was stirred for 30 min at room temperature then carefully poured into NH_4Cl (aq. sat., 5 mL). After extraction with Et_2O (2x10 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product was purified by flash chromatography (ether/petrol 1:10) to give 34.0 mg of a white solid **183a** (73%).[143] Mp 106.5-107.5°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.06 (3H, d, J = 7.0 Hz, H-13), 1.22-1.37 (3H, m, 1xH-7, 1xH-8 and 1xH-9), 1.33 (3H, t, J = 7.0 Hz, H-15), 1.43 (3H,s, H-12), 1.55-1.83 (4H, m, 1xH-8, 1xH-9 and H-10), 1.96-2.02 (1H, m, 1xH-7), 2.12 (1H, dd, J = 12.5 and 4.0 Hz, H-1), 2.35 (1H, dq, J = 11.0 and 7.0 Hz, H-3), 2.77 (1H, br, OH), 2.83 (1H, br, OH), 3.69 (1H, d, J = 4.5 Hz, H-5), 4.20 (2H, q, J = 7.0 Hz, H-14), 4.93 (1H, dd, J = 11.0 and 4.5 Hz, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.3 (C-15), 17.1 (C-13), 21.2 (C-12), 23.4 (C-9), 24.4 (C-10), 26.1 (C-8), 38.9 (C-3), 41.7 (C-7), 42.4 (C-1), 51.6 (C-2), 60.6 (C-14), 63.2 (C-4), 73.1 (C-6), 73.3 (C-5), 176.3 (C-11); m/z (ESIMS) calculated for $C_{15}H_{25}{}^{79}BrNaO_4$ (MNa^+) 371.0828 found 371.0831; ν_{max}/cm^{-1} (KBr disk) 3268 (w, str, OH), 2918 (str, C-H stretch), 2859 (w, C-H), 1703

(str, s, C=O), 1451 (w, C-H deformation), 1390 (m, C-O), 1219 (str, s, C-O), 1139 (m), 1033 (m), 985 (str); NOESY spectrum showed reciprocal signal enhancements between 1.06 (H-13) and 4.93 (H-4), 1.43 (H-12) and 2.35 (H-3), 2.12 (H-1) and 3.69 (H-5), 2.12 (H-1) and 4.93 (H-4), 3.69 (H-5) and 4.93 (H-4), and 2.77 (OH) and 2.83 (OH)

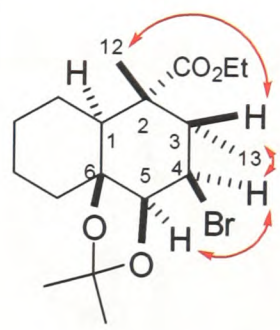


(3a*S*,4*R***,5*S***,6*S***,6a*S***,10^1*S***)-4-Bromo-2,2,5,6-tetramethyloctahydro-3a*H*-naphtho[1-*d*]-[1,3]-dioxole-6-carboxylic acid ethyl ester (183b)**

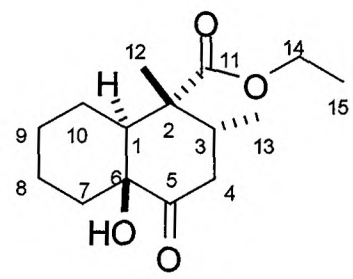


To a solution of the diol **183a** (21.2 mg, 0.06 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 1.5 mL) was added camphor-10-sulphonic acid (a few crystals) and the reaction mixture was stirred at ambient temperature for 2 h. The organic layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 2% Et_2O/petroleum ether as the eluent to yield the acetonide **183b** (23.2 mg, 98%) as a white solid. Mp 113.0-114.0°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.11 (3H, d, J = 7.0 Hz, H-13), 1.25-1.33 (2H, m, 1xH-8 and 1xH-10), 1.32 (3H, s, H-12), 1.33 (3H, t, J = 7.0 Hz, H-15), 1.47-1.53 (1H, m, 1xH-7), 1.54 (3H, s, $C(CH_3)_2$), 1.61 (3H, s, $C(CH_3)_2$), 1.61-1.73 (3H, m, 1xH-8 and H-9), 1.80-1.82 (1H, m, 1xH-10), 2.09-2.13 (2H, m, H-1 and 1xH-7), 2.26 (1H, dq, J = 12.5 and 7.0 Hz, H-3), 4.14-4.27 (2H, m, H-14), 4.36 (1H, d, J = 2.0 Hz, H-5), 4.54 (1H, dd, J

= 12.5 and 2.0 Hz, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.3 (C-15), 16.5 (C-13), 19.4 (C-12), 22.2 (C-9), 25.1 (C-10), 26.1 (C-8), 27.5 ($C(CH_3)_2$), 28.3 ($C(CH_3)_2$), 37.4 (C-3), 40.6 (C-7), 43.9 (C-1), 51.4 (C-2), 56.7 (C-4), 60.6 (C-14), 83.4 (C-6), 85.0 (C-5), 109.2 (C-16), 176.3 (C-11); m/z (GCMS) calculated for $C_{18}H_{30}{}^{79}BrO_4$ (MH^+) 389.1327 found 389.1335; ν_{max}/cm^{-1} (KBr disk) 2925 (m, C-H stretch), 2851 (w, C-H), 1732 (str, s, C=O), 1445 (w, C-H deformation), 1376 (m, C-O), 1249 (m, C-O), 1188 (m), 1132 (m), 1094 (str, s), 1006 (str, s); NOESY spectrum showed reciprocal signal enhancements between 1.11 (H-13) and 4.54 (H-4), 1.32 (H-12) and 2.26 (H-3), and 3.69 (H-5) and 4.93 (H-4)

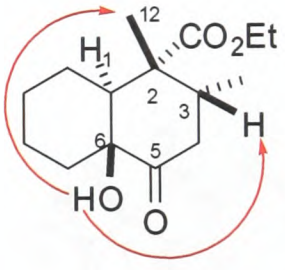


(1*S,2*S**,4a*R**,8a*R**)-4a-Hydroxy-1,2-dimethyl-4-oxo-decahydronaphthalene-1-carboxylic acid ethyl ester (184)**

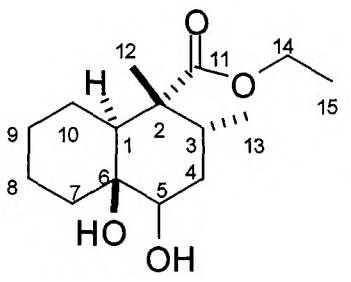


A solution of the TMS enol ether **176** (29 mg, 0.09 mmol) in anhydrous DCM (5 mL) was cooled to -78˚C, and then a solution of mCPBA (18 mg, 0.10 mmol) in DCM (5 mL) was added. The mixture was warmed to room temperature gradually, and then wash with $Na_2S_2O_3$ (aq. sat., 5 mL) and $NaHCO_3$ (aq. sat. 5 mL), extracted with DCM (2x10 mL). The crude product was purified through silica gel (Et_2O/petrol 1:25) to give the product **184** as a colourless oil (11.5 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.93 (3H, d, J = 7.5 Hz, H-13), 1.28-1.33 (1H, m, 1xH-10), 1.32 (3H, t, J = 7.5 Hz, H-15), 1.46-1.54 (2H, m, 1xH-4 and 1xH-8), 1.50 (3H, s,

H-12), 1.59-1.85 (6H, m, 1xH-4, 1xH-8, H-9, and 1xH-10), 1.87 (1H, br, OH), 2.24-2.30 (1H, m, H-3), 2.38-2.41 (1H, m, H-1), 2.42-2.45 (1H, m, 1xH-7), 2.98-3.02 (1H, m, 1xH-7), 4.17-4.23 (2H, m, H-14); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.3 (C-15), 16.7 (C-13), 19.4 (C-12), 21.0 (C-9), 23.6 (C-8), 26.2 (C-10), 33.9 (C-4), 39.3 (C-3), 41.3 (C-7), 44.6 (C-1), 48.8 (C-2), 60.6 (C-14),75.1 (C-6), 176.3 (C-11),212.3 (C-5); m/z (GCMS) calculated for $C_{15}H_{28}NO_4$ (MNH_4^+) 286.2018 found 286.2018, calculated for $C_{15}H_{25}O_4$ (MH^+) 269.1753 found 269.1755 ; ν_{max}/cm^{-1} (thin film) 3485 (str, br, O-H), 2937 (str, C-H stretch), 1715 (str, C=O), 1448 (w, C-H deformation), 1388 (w), 1236 (m, C-O), 1148 (m); n.O.e experiments: irradiation at 1.87 (OH) saw reciprocal signal enhancement at 2.24-2.30 (H-3) and 1.50 (H-12)



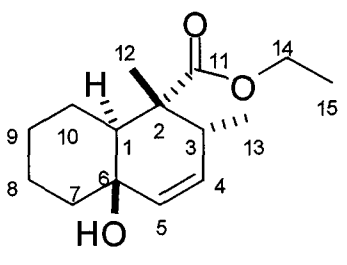
(1*R,2*R**,4a*S**,8a*S**)-4,4a-Dihydroxy-1,2-dimethyldecahydronaphthalene-1-carboxylic acid ethyl ester (185)**



To a stirred solution of the hydroxy ketone **184** (76 mg, 0.29 mmol) and cerium trichloride heptahydrate (103 mg, 0.3 mmol) in methanol (3 mL) was added sodium borohydride (13 mg, 0.3 mmol) and the resulting mixture was stirred for 30 min at room temperature, quenched with NH_4Cl (aq. sat., 3 mL) and extracted with diethyl ether (3x5 mL). Organic extracts were dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (petrol/diethyl ether 1.5:1) gave the diol **185** (60 mg, 79%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.12 (3H, d, J = 7.0 Hz, H-13), 1.30 (3H, t, J = 7.0 Hz, H-15),

1.32-1.40 (2H, m, 1xH-7 and 1xH-10), 1.44 (3H, s, H-12), 1.47-1.67 (6H, m, H-8, H-9, 1xH-10 and OH), 1.68-1.85 (2H, m, 1xH-4 and OH), 1.90-2.02 (2H, m, H-3 and 1xH-7), 2.35-2.39 (1H, m, 1xH-4), 2.44-2.49 (1H, m, 1xH-1), 3.54 (1H, dd, J = 3.5 and 3.0 Hz, H-5), 4.16 (2H, q, J = 7.0 Hz, H-14); ^{13}C NMR (100.6 MHz, $CDCl_3$) 14.2 (C-15), 19.4 (C-13), 19.6 (C-12), 21.6 (C-9), 24.2 (C-10), 26.4 (C-8), 31.5 (C-3), 36.6 (C-4), 36.8 (C-7), 37.0 (C-1), 49.1 (C-2), 60.0 (C-14), 73.5 (C-5), 75.3 (C-6), 176.9 (C-11); m/z (GCMS) calculated for $C_{15}H_{27}O_4$ (MH^+) 271.1909 found 271.1913; ν_{max}/cm^{-1} (thin film) 3509 (br, OH), 2935 (str, C-H stretch), 1721 (str, s, C=O), 1389 (m, C-O), 1258 (m, C-O)

(1*R,2*R**,4a*R**,8a*S**)-4a-hydroxy-1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid ethyl ester (186)**



To a stirred solution of diol **185** (21 mg, 0.08 mmol) and *o*-nitrophenylselenocyanate (20 mg, 0.085 mmol) in anhydrous chloroform (5 mL) was added tri-*n*-butylphosphine (20 μL, 0.085 mmol). The resulting solution was stirred overnight at room temperarure until the TLC showed complete consumption of the starting material. The solution was cooled to -40°C and pyridine (20 μL) was added followed by hydrogen peroxide (aq. 30 wt%, 0.1 mL). The resulting solution was allowed to warm to room temperature over a period of 6 h and sodium bisulphate (aq. sat., 1 mL) was added. The reaction mixture was extracted with ethyl acetate (2x10 mL), and the organic extracts were washed with water (2x5 mL), dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash chromatography (petrol/diethyl ether 4:1) gave the title compound **186** (11.9 mg, 59%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.07 (3H, d, J = 7.0 Hz, H-13), 1.23 (3H, s, H-12), 1.31 (3H, t, J = 7.0 Hz, H-15), 1.34-1.40 (2H, m, 1xH-8 and

1xH-9), 1.44-1.54 (2H, m, 1xH-8 and 1xH-9), 1.60-1.76 (2H, m, 1xH-7 and 1xH-10), 1.77-1.80 (1H, m, OH), 1.83-1.87 (1H, m, 1xH-10), 1.94-2.00 (1H, m, 1xH-7), 2.01-2.11 (2H, m, H-1 and H-3), 4.19 (2H, q, J = 7.0 Hz, H-14), 5.97-5.91 (2H, m, H-4 and H-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) 14.3 (C-15), 16.5 (C-13), 19.9 (C-12), 21.8 (C-9), 24.9 (C-10), 25.1 (C-8), 35.5 (C-3), 37.8 (C-7), 38.7 (C-1), 50.0 (C-2), 60.1 (C-14), 67.4 (C-6), 120.0 (C-4), 139.2 (C-5), 176.3 (C-1); m/z (GCMS) calculate for $C_{15}H_{25}O_3$ (MH^+) 253.1804 found 253.1804; ν_{max}/cm^{-1} (thin film) 3500 (br, OH), 2924 (str, C-H stretch), 1726 (str, C=O)

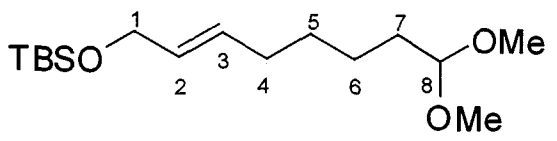
4.2.4 Investigation on the Diels-Alder reaction with other substrates

(*E*)-8,8-Dimethoxy-oxt-2-en-1-ol (187)

To a stirred solution of (*E*)-8, 8-dimethoxy-oct-2-enoic acid ethyl ester **143** (10.91 g, 47.8 mmol) in anhydrous dichloromethane (50 mL) was added diisobutylaluminium hydride (1 M in cyclohexane, 105.2 mL, 105.2 mmol) dropwise at -78°C. After stirring for 2 h at -78°C, sodium sulphate decahydrate (11.24 g, 34.9 mmol) was added and the resulting mixture was allowed to warm to room temperature. The mixture was then filtered and the solid was rinsed with acetone (5x100 mL). After concentration of the filtrate, 7.37g product **187** was formed and was used directly in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31-1.45 (4H, m, H-5 and H-6), 1.59 (2H, q, J = 6.0 Hz, H-7), 2.07 (2H, q, J = 6.5 Hz, H-4), 3.31 (6H, s, $CH(OCH_3)_2$), 4.08 (2H, d, J = 5.5 Hz, H-1), 4.36 (1H, t, J = 6.0 Hz, H-8), 5.65-5.75 (2H, m, H-2 and H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.2 (C-6), 28.8 (C-5), 31.9 (C-4), 32.3 (C-7), 52.5 ($CH(OCH_3)_2$), 63.8 (C-1), 104.6 (C-8), 129.0 (C-2), 132.9 (C-3); m/z (GCMS) Calculated for $C_9H_{17}O_2$ ($M\text{-}OMe^+$) 157.1229 Found 157.1225; ν_{max}/cm^{-1} (thin film) 3418 (str, br, O-H), 2939

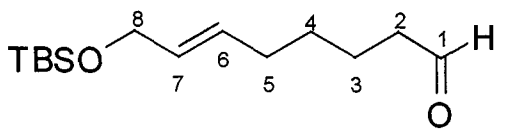
(str, C-H stretch), 1670 (w, s, C=C), 1462 (m, C-H deformation), 1129 (m, C-O)

tert-Butyl-((*E*)-8, 8-dimethoxy-oct-2-enyloxy)-dimethyl silane (188)



To a stirred ice-cooled solution of (*E*)-8,8-dimethoxy-oct-2-en-1-ol **187** (0.29 g, 1.6 mmol) in *N*, *N*-dimethylformamide (5 mL), were added imidazole (0.27 g, 4.0 mmol) and *tert*-butylchloro-dimethylsilane (0.29 g, 1.9 mmol). The resulting solution was allowed to warm to room temperature and stirred at this temperature for 6 h. After that the mixture was poured into NH_4Cl (aq. sat., 10 mL) and the resulting mixture was extracted with diethyl ether (3x20 mL). The combined organic layer was washed with brine (30 mL), dried with sodium sulphate and concentrated to give a residue. After purification by column chromatography (ethyl acetate/petrol 1: 9) the silyl ether **188** (0.28g, 59%) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, Si(C$\underline{H}_3$)$_2$), 0.91 (9H, s, C(C$\underline{H}_3$)$_3$), 1.32-1.45 (4H, m, $\underline{H}$-5 and $\underline{H}$-6), 1.59 (2H, q, J = 6.0 Hz, $\underline{H}$-7), 2.04 (2H, q, J = 6.0 Hz, $\underline{H}$-4), 3.32 (6H, s, CH(OC$\underline{H}_3$)$_2$), 4.12 (2H, d, J = 5.0 Hz, $\underline{H}$-1), 4.36 (1H, t, J = 6.0 Hz, $\underline{H}$-8), 5.51-5.57 (1H, m, $\underline{H}$-2), 5.60-5.68 (1H, m, $\underline{H}$-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.4 (Si($\underline{C}H_3$)$_2$), 18.2 ($\underline{C}$(CH$_3$)$_3$), 24.3 ($\underline{C}$-5), 26.1 (C($\underline{C}$H$_3$)$_3$), 29.2 ($\underline{C}$-6), 32.3 ($\underline{C}$-7), 32.4 ($\underline{C}$-4), 52.6 (CH(O$\underline{C}$H$_3$)$_2$), 64.1 ($\underline{C}$-1), 104.5 ($\underline{C}$-8), 129.3 ($\underline{C}$-2), 131.1 ($\underline{C}$-3); m/z (GCMS) Calculated for $C_{15}H_{31}O_2Si$ (M-OMe$^+$) 271.2093 Found 271.2086; ν_{max}/cm^{-1} (thin film) 2930 (str, C-H stretch), 1463 (m, C-H deformation), 1128 (m, C-O), 969, 837, 776

(*E*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-oct-6-enal (189)



Method 1:

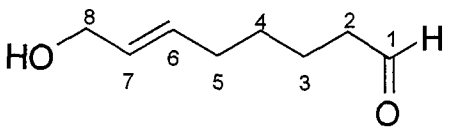
To a solution of the acetal **188** (100 mg, 0.33 mmol) in DCM (5 mL) at 0°C was added camphor-10-sulphonic (15.4 mg, 0.07 mmol). The solution was warmed to 40°C. After stirring at 40°C for 24 h, the solution was washed with $NaHCO_3$ (aq. sat., 10 mL) and then water (10 mL). The aqueous layers were back extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Finally, the residue was chromatographed over silica gel (Et_2O/petrol 1:9) to give 47.3 mg product **189** (54%) as a light yellow oil.

Method 2:

To a stirred ice-cooled solution of the aldehyde **190** (1.36 g, 9.6 mmol) in *N*,*N*-dimethyl-formamide (15 mL), were added imidazole (1.64 g, 24.1 mmol) and *tert*-butylchlorodimethyl-silane (1.74 g, 11.5 mmol). The resulting solution was allowed to warm to room temperature and stirred for 6 h. After that it was poured into NH_4Cl (aq. sat., 20 mL) and the resulting mixture was extracted with diethyl ether (3x50 mL). The combined organic layers were washed with brine (50 mL), dried with sodium sulphate and concentrated. The residue was purified by column chromatography (diethyl ether/petrol 1:6) affording silyl ether **189** as a light yellow oil (1.35g, 58% from **187**). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, Si($C\underline{H}_3$)$_2$), 0.91 (9H, s, C($C\underline{H}_3$)$_3$), 1.43 (2H, qui, J = 7.0 Hz, $\underline{H}$-4), 1.65 (2H, qui, J = 7.0 Hz, $\underline{H}$-3), 2.07 (2H, q, J = 7.0 Hz, $\underline{H}$-5), 2.42 (2H, t, J = 7.0 Hz, $\underline{H}$-2), 4.13 (2H, d, J = 5.0 Hz, $\underline{H}$-8), 5.50-5.59 (1H, m, $\underline{H}$-7), 5.59-5.68 (1H, m, $\underline{H}$-6), 9.77 (1H, s, $\underline{H}$-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.1 (Si($\underline{C}H_3$)$_2$),

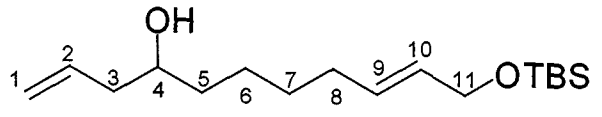
18.4 (C(CH$_3$)$_3$), 21.5 (C-3), 26.0 (C(CH$_3$)$_3$), 28.8 (C-4), 31.9 (C-5), 43.8 (C-2), 63.8 (C-8), 129.9 (C-7), 130.5 (C-6), 202.6 (C-1); m/z (GCMS) Calculated for $C_{14}H_{29}O_2Si$ (MH^+) 257.1937 Found 257.1943; ν_{max}/cm^{-1} (thin film) 2930 (str, C-H stretch), 1728 (str, s, C=O), 1463 (m, C-H deformation), 1255 (str, s, C-O)

(*E*)-8-Hydroxy-oct-6-enal (190)



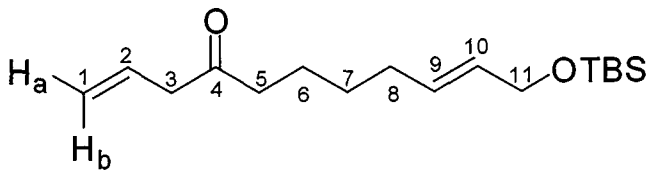
To a stirred solution of (*E*)-8,8-dimethoxy-oxt-2-en-1-ol **187** (2.00 g, 10.6 mol) in anhydrous diethyl ether (25 mL) was added hydrochloric acid (aq. 5%, 25 mL). The two-phase mixture was vigorously stirred at room temperature for 18 h. The organic layer was then separated and the aqueous layer was extracted with diethyl ether (3x30 mL). The combined organic layers were washed with sodium bicarbonate solution (aq. 10%, 20 mL), dried with magnesium sulphate and concentrated to provide crude compound **190** (1.37 g), which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.47 (2H, qui, J = 7.5 Hz, H-4), 1.69 (2H, qui, J = 7.5 Hz, H-3), 2.10-2.14 (2H, m, H-5), 2.49 (2H, t, J = 7.5 Hz, H-2), 4.13 (2H, d, J = 3.0 Hz, H-8), 5.69-5.72 (2H, m, H-6 and H-7), 9.81 (1H, s, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 21.9 (C-3), 28.8 (C-4), 32.3 (C-5), 44.2 (C-2), 64.1 (C-8), 129.8 (C-7), 133.0 (C-6), 203.1 (C-1); m/z (GCMS) Calculated for $C_8H_{18}NO_2$ (MNH_4^+) 160.1338 Found 160.1331; ν_{max}/cm^{-1} (thin film) 3363 (str, br, O-H), 2931 (str, C-H stretch), 2857 (w, C-H), 1641 (w, s, C=C), 1435 (str, C-H deformation)

(*E*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-undeca-1, 9-dien-4-ol (191)



To a –78°C solution of aldehyde **189** (0.61 g, 2.4 mmol) in THF (100 mL) was added a solution of allyl magnesium chloride (2 M in THF, 1.53 mL, 3.6 mmol) dropwise. After stirring at -78°C for 3 h, it was allowed to warm to room temperature, washed with ammonium chloride (aq. sat., 10 mL) and water (2x50 mL). The combined aqueous layers were extracted with ethyl acetate (3x50 mL). After that the organic layers were combined, dried over magnesium sulphate and concentrated. The crude product was then purified by column choromatography (diethyl ether/petrol 1:6) affording pure product **191** 0.49g (67%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.91 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.34-1.50 (6H, m, <u>H</u>-5, <u>H</u>-6 and <u>H</u>-7), 2.03 (2H, q, J = 7.0 Hz, <u>H</u>-8), 2.09-2.18 (1H, m, 1x<u>H</u>-3), 2.27-2.34 (1H, m, 1x<u>H</u>-3), 3.63-3.69 (2H, m, <u>H</u>-4), 4.12 (2H, d, J = 5.5 Hz, <u>H</u>-11), 5.13 (2H, d, J = 8.0 Hz, <u>H</u>-1), 5.54 (1H, dt, J = 15.0 and 5.5 Hz, <u>H</u>-10), 5.64 (1H, dt, J = 15.0 and 7.0 Hz, <u>H</u>-9), 5.78-5.88 (1H, m, <u>H</u>-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.1 (Si(<u>C</u>H$_3$)$_2$), 18.4 (<u>C</u>(CH$_3$)$_3$), 25.2 (<u>C</u>-6), 26.0 (C(<u>C</u>H$_3$)$_3$), 29.1 (<u>C</u>-7), 32.1 (<u>C</u>-8), 36.6 (<u>C</u>-5), 41.9 (<u>C</u>-3), 64.0 (<u>C</u>-11), 70.6 (<u>C</u>-4), 118.1 (<u>C</u>-1), 129.3 (<u>C</u>-10), 131.2 (<u>C</u>-9), 134.8 (<u>C</u>-2); m/z (GCMS) Calculated for $C_{17}H_{35}O_2Si$ (MH^+) 299.2406 Found 299.2419; ν_{max}/cm^{-1} (thin film) 3384 (str, br, O-H), 2930 (str, C-H stretch), 1645 (C=C), 1463 (w, C-H deformation), 1235 (m, s, C-O)

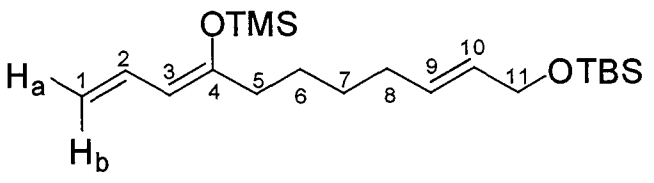
(*E*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-undeca-1, 9-dien-4-one (192)



Dess-Martin reagent (3.41 g, 7.3 mmol) was added in one portion to a solution of the alcohol

191 (1.09 g, 3.6 mmol) in anhydrous DCM (50 mL). After 2 h, the mixture was diluted with DCM (50 mL) and sequently washed with $Na_2S_2O_3$ (aq. sat., 50 mL) and $NaHCO_3$ (aq. 5%, 50 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (Et_2O/petrol 1: 7) to yield the ketone **192** (0.89 g, 85%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $C(C\underline{H}_3)_3$), 1.38 (2H, qui, J = 7.0 Hz, H-7), 1.59 (2H, qui, J = 7.0 Hz, H-6), 2.03 (2H, q, J = 7.0 Hz, H-8), 2.45 (2H, t, J = 7.0 Hz, H-5), 3.17 (2H, d, J = 7.0 Hz, H-3), 4.11 (2H, d, J = 5.0 Hz, H-11), 5.14 (1H, d, J = 17.0 Hz, H-1b), 5.14 (1H, d, J = 10.0 Hz, H-1a), 5.53 (1H, dt, J = 15.0 and 5.0 Hz, H-10), 5.62 (1H, dt, J = 15.0 and 7.0 Hz, H-9), 5.87-5.98 (1H, m, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.1 ($Si(\underline{C}H_3)_2$), 18.4 ($\underline{C}(CH_3)_3$), 23.2 (C-6), 26.0 ($C(\underline{C}H_3)_3$), 28.7 (C-7), 31.9 (C-8), 42.1 (C-5), 47.7 (C-3), 43.958 (C-11), 118.7 (C-1), 129.7 (C-10), 130.7 (C-2 and C-9), 208.7 (C-4); m/z (GCMS) Calculated for $C_{17}H_{33}O_2Si$ (MH^+) 297.2250 Found 297.2261; ν_{max}/cm^{-1} 2930 (str, C-H stretch), 1718 (str, s, C=O), 1638 (w, s, C=C), 1463 (m, s, C-H deformation)

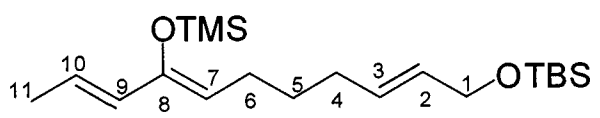
(3*Z*,9*E*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-4-trimethylsilanyloxy-undeca-1,3,9-triene (193)



To a solution of ketone **192** (100 mg, 0.34 mmol) in anhydrous THF (5 mL) was added HMPA (67.2 mg, 65.2 µL, 0.37 mmol). The mixture was cooled to -78°C and then LHMDS (0.41 mL, 0.41 mmol) was added. After 15 min, the silyl enol ether was quenched with TMSCl (44 mg, 0.41 mmol). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and poured into pentane (10 mL) in a small separating funnel. The mixture was washed with $NaHCO_3$ solution (aq. sat., 2x10 mL) and brine (20 mL). The organic layer was

dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:6) to yield 93 mg TMS enol ether **193** (76%) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.22 (9H, s, $Si(C\underline{H}_3)_3$), 0.91 (9H, s, $C(C\underline{H})_3$), 1.40 (2H, qui, J = 7.0 Hz, H-7), 1.50 (2H, qui, J = 7.0 Hz, H-6), 2.05 (4H, q, J = 7.0 Hz, H-5 and H-8), 4.12 (2H, d, J = 5.0 Hz, H-11), 4.81 (1H, dd, J = 10.5 and 2.0 Hz, H-1a), 4.99 (1H, dd, J = 17.0 and 2.0 Hz, H-1b), 5.28 (1H, d, J = 10.5 Hz, H-3), 5.54 (1H, dt, J = 15.0 and 5.0 Hz, H-10), 5.64 (1H, dt, J = 15.0 and 7.0 Hz, H-9), 6.55 (1H, dt, J = 17.0 and 10.5 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.1 ($Si(\underline{C}H_3)_2$), 0.6 ($Si(\underline{C}H_3)_3$), 14.1 ($\underline{C}(CH_3)_3$), 26.0 ($C(\underline{C}H_3)_3$), 26.4 (C-6), 28.7 (C-7), 32.0 (C-8), 36.5 (C-5), 64.0 (C-11), 110.3 (C-3), 111.6 (C-1), 129.4 (C-10), 131.1 (C-9), 131.7 (C-2), 153.3 (C-4); m/z (GCMS) Calculated for $C_{20}H_{41}O_2Si_2$ (MH^+) 369.2645 Found 369.2652; ν_{max}/cm^{-1} 3085 (w, s, C-H of CH=CH), 2930 (str, C-H stretch), 2857 (w, s, C-H), 1649 (str, s, C=C), 1463 (m, C-H deformation), 1250 (str, s, C-O)

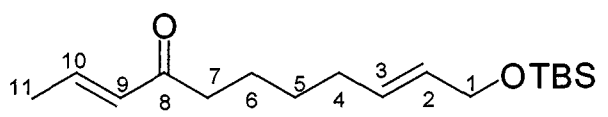
11-(*tert*-Butyl-dimethyl-silanyloxy)-4-trimethylsilanyloxy-undeca-2,4,9-triene (196)



A solution of TMS-enol ether **193** (0.30 g, 0.84 mmol) in distilled toluene (10 mL) was heated up to 200°C for 3 days. Then the solvent was removed. The residue was chromatographed over silica gel, eluting with Et_2O/petrol 1:8 to give two by-products, silyl enol ether **196** (0.06 g, 20%) and enone **195** (0.10 g, 41%), both as colourless oil. ^1H NMR (400 Hz, $CDCl_3$) δ_H 0.05 (6H, s, $Si(C\underline{H}_3)_2$), 0.19 (9H, s, $Si(C\underline{H}_3)_3$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 1.45-1.32 (2H, m, H-5), 1.75 (3H, d, J = 6.5 Hz, H-11), 2.01-2.11 (4H, m, H-4 and H-6), 4.12 (2H, d, J = 5.0 Hz, H-1), 4.69 (1H, t, J = 5.0 Hz, H-7), 5.49-5.55 (1H, m, H-2), 5.63-5.67 (1H, m, H-3), 5.73-5.80 (1H, m, H-10), 5.85-5.94 (1H, m, H-9); ^{13}C NMR (100.6 Hz, $CDCl_3$) δ_C -5.0 ($Si(\underline{C}H_3)_2$), 1.0 ($Si(\underline{C}H_3)_3$), 17.6

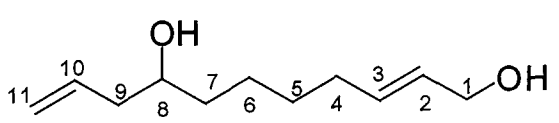
(C(CH$_3$)$_3$), 18.4 (C-11), 25.5 (SiC(CH$_3$)$_3$), 25.9 (C-6), 29.2 (C-5), 31.9 (C-4), 64.0 (C-1), 113.0 (C-7), 123.5 (C-10), 129.3 (C-9), 129.9 (C-2), 131.1 (C-3), 155.8 (C-8); m/z (GCMS) Calculated for $C_{20}H_{41}O_2Si_2$ (MH^+) 369.2645 Found 369.2642; ν_{max}/cm^{-1} 3080 (w, s, C-H of CH=CH), 2930 (str, C-H stretch), 1652 (str, s, C=C), 1463 (m, C-H deformation), 1248 (m, C-O)

(2*Z*,9*E*)-11-(*tert*-Butyldimethylsilanyloxy)undeca-2,9-dien-4-one (195)



This compound **195** (0.10 g, 41%) was isolated from the crude reaction mixture described before. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (6H, s, Si(CH$_3$)$_2$), 0.90 (9H, s, C(CH$_3$)$_3$), 1.40 (2H, qui, J = 7.0 Hz, H-5), 1.62 (2H, qui, J = 7.0 Hz, H-6), 1.90 (3H, d, J = 7.0 Hz, H-11), 2.05 (2H, q, J = 7.0 Hz, H-4), 2.52 (2H, t, J = 7.0 Hz, H-7), 4.12 (2H, d, J = 5.0 Hz, H-1), 5.55 (1H, dt, J = 15.0 and 5.0 Hz, H-2), 5.61 (1H, dt, J = 15.0 and 7.0 Hz, H-3), 6.12 (1H, d, J = 15.5 Hz, H-9), 6.85 (1H, dq, J = 15.5 and 7.0 Hz, H-10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.1 (Si(CH$_3$)$_2$), 15.3 (C(CH$_3$)$_3$), 18.4 (C-11), 23.8 (C-6), 26.0 (SiC(CH$_3$)$_3$), 28.8 (C-5), 31.9 (C-4), 39.8 (C-7), 64.0 (C-1), 129.5 (C-2), 130.8 (C-9), 131.9 (C-3), 142.4 (C-10), 200.6 (C-8); m/z (GCMS) Calculated for $C_{17}H_{33}O_2Si$ (MH^+) 297.2250 Found 297.2247; ν_{max}/cm^{-1} 2928 (str, C-H stretch), 1720 (str, s, C=O), 1628 (w, s, C=C), 1463 (m, s, C-H deformation)

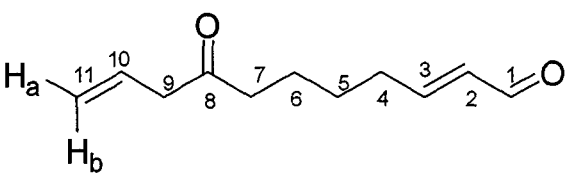
(*E*)-Undeca-2,10-diene-1,8-diol (199)



To a -78°C solution of the aldehyde **190** (0.10 g, 0.70 mmol) in THF (10 mL) was added dropwise allyl magnesium chloride (2M in THF, 1.5 mL). After stirring at -78°C for 1.5 h, the mixture was allowed to warm to 0°C. After 3 h NH_4Cl (aq. sat., 10 mL) was added and the

mixture was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL). The aqueous layer was separated and subsequently extracted with ethyl acetate (3x10 mL). The combined organic layers were dried over magnesium sulphate and concentrated. The crude product was chromatographed over silica gel (ethyl acetate/petrol 1:3) to give 0.12g **199** (76% from **187**) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32-1.47 (6H, m, H-5, H-6 and H-7), 2.07 (2H, q, J = 6.0 Hz, H-4), 2.11-2.18 (1H, m, 1xH-9), 2.28-2.34 (1H, m, 1xH-9), 3.62-3.68 (1H, m, H-8), 4.09 (2H, d, J = 5.0 Hz, H-1), 5.16 (2H, d, J = 13.5 Hz, H-11), 5.61-5.73 (2H, m, H-2 and H-3), 5.78-5.88 (1H, m, H-10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 25.3 (C-6), 29.1 (C-5), 31.9 (C-4), 36.5 (C-7), 42.0 (C-9), 63.7 (C-1), 70.7 (C-8), 118.2 (C-11), 129.0 (C-2), 133.2 (C-3), 134.6 (C-10); m/z (GCMS) Calculated for $C_{11}H_{24}NO_2$ (MNH^+) 202.1807 Found 202.1823; ν_{max}/cm^{-1} (thin film) 3346 (str, br, O-H), 2931 (str, C-H stretch), 2857 (w, s, C-H), 1641 (w, s, C=C), 1435 (str, C-H deformation)

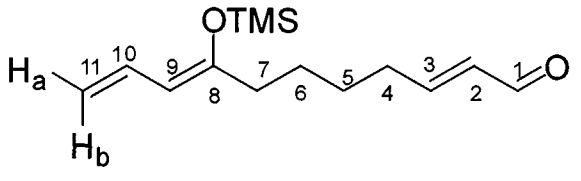
(*E*)-8-Oxo-undeca-2,10-dienal (200)



Dess-Martin reagent (1.06 g, 2.21 mmol) was added in one portion to a solution of the diol **199** (0.10 g, 0.55 mmol) in anhydrous DCM (10 mL). After 2 h, the mixture was diluted with DCM (10 mL) and sequently washed with $Na_2S_2O_3$ solution (aq. sat., 10 mL), and $NaHCO_3$ solution (aq. 5%, 10 mL). The combined aqueous layers were extracted with DCM (2x20 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (Et_2O/petrol 1: 4) to yield the aldehyde-ketone **200** (0.05 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.52 (2H, qui, J = 7.0 Hz, H-5), 1.63 (2H, qui, J = 7.0 Hz, H-6), 2.36 (2H, q, J = 7.0 Hz, H-4), 2.49 (2H, t, J = 7.0 Hz, H-7), 3.18 (2H, d, J = 7.0 Hz, H-9),

5.15 (1H, dd, J = 17.0 and 1.5 Hz, H-11b), 5.19 (1H, dd, J = 10.0 and 1.5 Hz, H-11a), 5.87-5.97 (1H, m, H-10), 6.12 (1H, dd, J = 17.0 and 8.0 Hz, H-2), 6.84 (1H, dt, J = 15.5 and 7.0 Hz, H-3), 9.51 (1H, d, J = 8.0 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 23.3 (C-6), 27.6 (C-5), 33.0 (C-4), 42.0 (C-7), 48.0 (C-9), 119.4 (C-11), 130.9 (C-2), 133.4 (C-10), 158.5 (C-3), 194.4 (C-1), 208.7 (C-8); m/z (GCMS) Calculated for $C_{11}H_{17}O_2$ (MH^+) 181.1229 Found 181.1234 ; ν_{max}/cm^{-1} (thin film) 2939 (str, C-H stretch), 1690 (str, C=O), 1650 (w, C=C), 1408 (m, C-H deformation), 1133 (m)

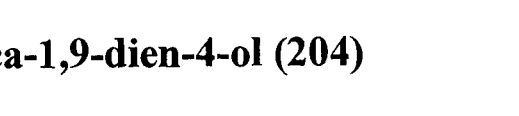
(2*E*,8*Z*)-8-Trimethylsilanyloxy-undeca-2,8,10-trienal (201)



To a solution of aldehyde-ketone **200** (0.22 g, 1.24 mmol) in anhydrous THF (15 mL) was added HMPA (0.24 g, 1.37 mmol). The mixture was cooled to -78°C and then was added LHMDS (1.49 mL, 1.49 mmol). After 15 min, the mixture was quenched with freshly distilled TMSCl (0.16 g, 1.49 mmol). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and poured into pentane (10mL) in a small separatory funnel. The mixture was washed with $NaHCO_3$ solution (aq. sat., 2x15mL) and brine (15 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:6) to yield 0.04 g silyl enol ether **201** (11%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.22 (9H, s, Si(C$\underline{H}_3$)$_3$), 1.48-1.62 (4H, m, H-5 and H-6), 2.05-2.15 (2H, m, H-7), 2.30-2.42 (2H, m, H-4), 4.81 (1H, d, J = 10.5 Hz, H-11a), 4.97 (1H, d, J = 17.0 Hz, H-11b), 5.27 (1H, d, J = 10.5 Hz, H-9), 6.11 (1H, dd, J = 15.5 and 7.5 Hz, H-2), 6.53 (1H, dt, J = 17.0 and 10.5 Hz, H-10), 6.85 (1H, dt, J = 15.5 and 7.5 Hz, H-3), 9.49 (1H, d, J = 7.5 Hz, H-1) ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 0.6 (Si(C$\underline{H}_3$)$_3$), 23.8 (C-6), 27.4 (C-5), 32.5 (C-4), 36.5 (C-7), 110.5 (C-9),

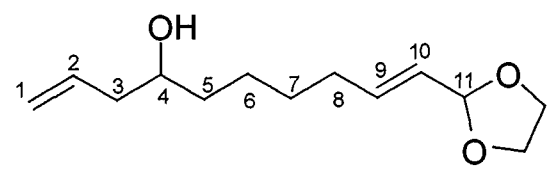
112.0 (C-11), 130.0 (C-2), 131.4 (C-10), 158.4 (C-3), 193.9 (C-8), 204.9 (C-1); Calculated for $C_{14}H_{23}O_2Si$ (MH^+) 251.1462 Found 251.1473; ν_{max}/cm^{-1} (thin film) 2939 (str, C-H stretch), 1688 (str, C=O), 1645 (w, C=C), 1417 (m, C-H deformation), 1133 (m)

(*E*)-8-Hydroxy-undeca-2,10-dienal (203)



To a solution of diol **199** (0.10 g, 0.54 mmol) in chloroform (6 mL) was added MnO_2 (1.38 g, 16.30 mmol). After stirring at room temperature for 5 days, the mixture was filtered through celite, and washed with chloroform (3x10 mL). The collected solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:1) to give 0.66 g (67%) product **203** as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.36-1.58 (6H, m, H-5, H-6 and H-7), 2.11-2.18 (1H, m, 1xH-9), 2.28-2.40 (3H, m, H-4 and 1xH-9), 3.62-3.69 (1H, m, H-8), 5.12-5.17 (2H, m, H-11), 5.77-5.88 (1H, m, H-10), 6.14 (1H, dd, J = 15.5 and 8.0 Hz, H-2), 6.86 (1H, dt, J = 15.5 and 7.0 Hz, H-3), 9.50 (1H, d, J = 8.0 Hz, H-1) ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 25.2 (C-6), 27.8 (C-5), 32.6 (C-4), 36.4 (C-7), 42.0 (C-9), 70.3 (C-8), 118.3 (C-11), 133.1 (C-2), 134.6 (C-10), 158.6 (C-3), 194.1 (C-1); m/z (GCMS) Calculated for $C_{11}H_{19}O_2$ (MH^+) 183.1385 Found 183.1381; ν_{max}/cm^{-1} (thin film) 3425 (str, br, O-H), 2934 (str, C-H stretch), 2860 (w, s, C-H), 1690 (str, s, C=O), 1639 (w, s, C=C), 1435 (m, C-H deformation), 1135 (m, C-O)

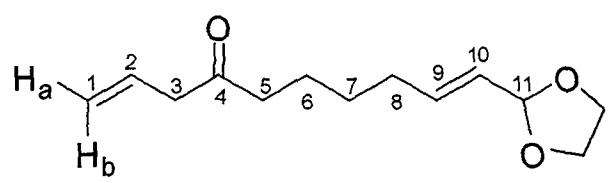
(*E*)-10-(1,3-Dioxolan-2-yl)-deca-1,9-dien-4-ol (204)



A solution of aldehyde **203** (0.18 g, 0.98 mmol), ethylene glycol (0.43 g, 0.70 mmol), and *p*-toluenesulphonic acid (0.006 g, 0.033 mmol) in benzene (10 mL) was left under reflux with an

attached Dean-Stark trap for 22 h. After such time, the reaction solution was allowed to cool to room temperature and K_2CO_3 (1.00 g, 7.24 mmol) was added. After stirring 10 min, the contents were washed with K_2CO_3 solution (aq. 10%, 10 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried over $MgSO_4$, evaporated and chromatographed over silica gel (EtOAc/petrol 1:6) to give a colourless oil **204** (0.11 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39-1.57 (6H, m, H-5, H-6 and H-7), 2.09-2.18 (1H, m, 1xH-3), 2.27-2.33 (1H, m, 1xH-3), 2.37-2.46 (2H, m, H-8), 3.62-3.68 (1H, m, H-4), 3.84-3.89 (2H, m, $CH(OCH_2)_2$), 3.97-4.01 (2H, m, $CH(OCH_2)_2$), 4.85-4.90 (1H, m, H-11), 5.12 (2H, d, J = 14.0 Hz, H-1), 5.48 (1H, dt, J = 15.5 and 7.0 Hz, H-10), 5.56 (1H, dt, J = 15.5 and 6.5 Hz, H-9), 5.78-5.88 (1H, m, H-2); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 25.3 (C-6), 32.5 (C-7), 36.2 (C-5), 37.5 (C-8), 41.9 (C-3), 64.9 ($CH(OCH_2)_2$), 70.5 (C-4), 104.1 (C-11), 118.1 (C-1), 123.7 (C-10), 133.9 (C-9), 134.8 (C-2); m/z (GCMS) Calculated for $C_{13}H_{23}O_3$ (MH^+) 227.1647 Found 227.1650; ν_{max}/cm^{-1} (thin film) 3452 (str, br, O-H), 2933 (str, C-H), 1641 (w, s, C=C), 1138 (str, C-O), 1038 (m)

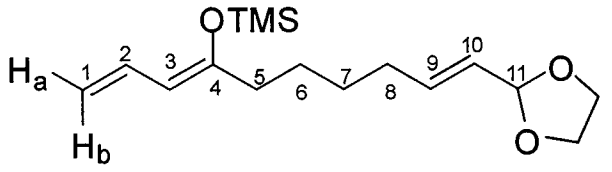
(*E*)-10-(1,3-Dioxolan-2-yl)-deca-1,9-dien-4-one (205)



Dess-Martin reagent (0.62 g, 1.33 mmol) was added in one portion to a solution of alcohol **204** (0.15 g, 0.66 mmol) in anhydrous DCM (12 mL). After 2 h, the mixture was diluted with DCM (15 mL) and sequently washed with $Na_2S_2O_3$ solution (aq. sat., 15 mL), and $NaHCO_3$ solution (aq. 5%, 15mL). The combined aqueous layers were extracted with DCM (2x20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel (Et_2O/petrol 1: 4) to yield the ketone **205** (0.09 g, 63%) as a

light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.66 (2H, qui, J = 7.5 Hz, H-6), 2.01-2.11 (2H, m, H-7), 2.38 (2H, q, J = 5.5 Hz, H-8), 2.44 (2H, t, J = 7.5 Hz, H-5), 3.17 (2H, d, J = 7.0 Hz, H-3), 3.84-3.88 (2H, m, $CH(OCH_2)_2$), 3.97-4.00 (2H, m, $CH(OCH_2)_2$), 4.85-4.90 (1H, m, H-11), 5.13 (1H, dd, J = 17.0 and 1.5 Hz, H-1b), 5.18 (1H, dd, J = 10.0 and 1.5 Hz, H-1a), 5.41-5.56 (2H, m, H-9 and H-10), 5.87-5.97 (1H, m, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 23.1 (C-6), 31.9 (C-7), 37.4 (C-8), 41.5 (C-5), 47.8 (C-3), 64.9 ($CH(OCH_2)_2$), 104.0 (C-11), 118.7 (C-1), 124.4 (C-10), 130.7 (C-9), 133.1 (C-2), 208.8 (C=O); m/z (GCMS) Calculated for $C_{11}H_{21}O_3$ (MH^+) 225.1491 Found 225.1481; ν_{max}/cm^{-1} (thin film) 3079 (w, s, C-H of CH=CH), 2888 (str, C-H stretch), 1715 (str, s, C=O), 1639 (m, s, C=C), 1403 (m, C-H deformation), 1138 (str, C-O), 1039 (m)

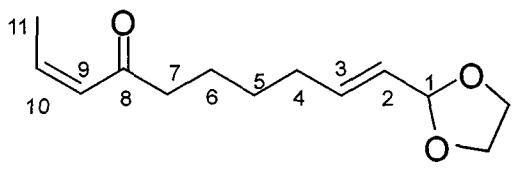
[(*E*)-7-(1,3-Dioxolan-2-yl)-1-prop-2-en-(*Z*)-ylidene-hept-6-enyloxy]trimethylsilane (206)



To a solution of ketone **205** (0.11 g, 0.49 mmol) in anhydrous THF (10 mL) was added HMPA (0.10 g, 0.10 µL, 0.54 mmol). The mixture was cooled to –78°C and then was added LHMDS (0.58 mL, 0.58 mmol). After 15min, the mixture was quenched with freshly distilled TMSCl over CaH_2 (0.064 g, 0.58 mmol). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and poured into pentane (10 mL) in a small separating funnel. The mixture was washed with $NaHCO_3$ (aq. sat., 2x10 mL) and brine (10 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petrol 1:8) to yield 0.10 g TMS enol ether **206** (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.21 (9H, s, $Si(CH_3)_3$), 1.57 (2H, qui, J = 7.5 Hz, H-6), 2.02-2.10 (4H, m, H-5 and H-7), 2.37-2.45 (2H, m, H-8), 3.85-3.88 (2H, m, $CH(OCH_2)_2$), 3.97-3.41 (2H, m, $CH(OCH_2)_2$),

4.80 (1H, dd, J = 10.5 and 1.5 Hz, H-1a), 4.87 (1H, m, H-11), 4.97 (1H, dd, J = 17.0 and 1.5 Hz, H-1b), 5.27 (2H, d, J = 10.5 Hz, H-3), 5.41-5.49 (1H, m, H-10), 5.52-5.60 (1H, m, H-9), 6.54 (1H, dt, J = 17.0 and 10.5 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 0.6 ($Si(CH_3)_3$), 26.4 (C-6), 32.0 (C-7), 36.0 (C-8), 37.5 (C-5), 64.9 ($CH(OCH_2)_2$), 104.1 (C-11), 110.4 (C-3), 111.7 (C-1), 124.0 (C-10), 131.6 (C-2), 134.5 (C-9), 156.6 (C-4); m/z (GCMS) Calculated for $C_{16}H_{29}O_3Si$ (MH^+) 297.1886 Found 297.1887; ν_{max}/cm^{-1} (thin film) 2956 (str C-H stretch), 1649 (str, s, C=C), 1419 (m, C-H deformation), 1332 (m, C-O), 1253 (m), 1204 (w), 1137 (str, C-O), 845 (m)

(2*Z*,9*E*)-10-(1,3-Dioxolan-2-yl)-deca-2,9-dien-4-one (208)



To a stirred solution of the TMS enol ether **206** (0.10 g, 0.34 mmol) in anhydrous DCM (8 mL) at –78°C under an atmosphere of argon was added trimethylsilyl trifluoromethanesulphonate (0.02 g, 0.085 mmol). The solution was quickly became bright yellow. The temperature was increased to 0°C and the colour of the solution darkened as the reaction processed. The mixture was stirred at this temperature for 4 h and then quenched with $NaHCO_3$ solution (aq. sat., 10 mL). The reaction was warmed to room temperature, diluted with DCM (10 mL) and poured into $NaHCO_3$ solution (aq. sat., 10 mL). The layers were separated and the aqueous layer was back extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc/petrol 1:8) to give 0.015 g **208** as colourless oil (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.70 (2H, qui, J = 7.5 Hz, H-6), 1.90 (3H, dd, J = 7.0 and 1.5 Hz, H-11), 2.03-2.13 (2H, m, H-5), 2.37-2.44 (2H, m, H-4), 2.52 (2H, t, J = 7.5 Hz, H-7), 3.84-3.88 (2H, m, $CH(OCH_2)_2$), 3.97-3.01 (2H, m,

$CH(OC\underline{H}_2)_2$), 4.85-4.90 (1H, m, H-1), 5.41-5.49 (1H, m, H-2), 5.51-5.58 (1H, m, H-3), 6.10 (1H, dq, J = 15.5 and 1.5 Hz, H-9), 6.84 (1H, dq, J = 15.5 and 7.0 Hz, H-10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.1 (C-11), 23.7 (C-6), 32.1 (C-5), 37.5 (C-4), 39.2 (C-7), 64.9 ($CH(O\underline{C}H_2)_2$), 104.1 (C-1), 124.3 (C-2), 132.0 (C-9), 133.3 (C-3), 142.4 (C-10), 206.0 (C-8); m/z (GCMS) Calculated for $C_{13}H_{21}O_3$ (MH^+) 225.1491 Found 225.1500; ν_{max}/cm^{-1} (thin film) 2939 (str, C-H), 1672 (str, s, C=O), 1633 (str, s, C=C), 1443 (str, s, C-H deformation), 1135 (str, C-O), 1039 (m), 971 (m)

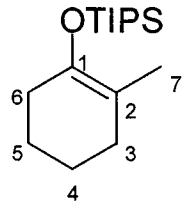
4.2.5 Experimental for double functionalisation of simple cyclic enolates

General procedure for the synthesis of TIPS enol ethers from ketones under kinetic conditions: Under an argon atmosphere, potassium hexamethyldisilazide (1.1 eq) was added dropwise, over 10 min, to a solution, cooled to –78°C, of cyclohexanone (1.0 eq) in anhydrous THF (25 mL). After stirring for 15 min at -78°C, triisopropylsilyl trifluoromethanesulfonate (1.1 eq) was added. The reaction mixture was stirred for 30 min at -78°C and then slowly warmed to room temperature. A solution of NH_4Cl (aq. sat., 30 mL) was added and the phases were separated. The organic phase was washed with NH_4Cl (aq. sat., 2x20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated to give the crude product, which was used directly for the next step.[162]

General procedure for the synthesis of TIPS enol ethers from ketones under thermodynamic conditions: In an oven-dried flask, triethylamine (2.0 eq) was added at 0°C to a solution of cyclohexanone (1.0 eq) in dichloromethane (50 mL). The solution was placed under an argon atmosphere and was stirred for 2 min. Triisopropylsilyl trifluoromethane-sulfonate (1.02 eq) was added dropwise. After 30 min, a solution of NH_4Cl (aq. sat., 40 mL) was added and the phases were separated. The organic phase was washed with NH_4Cl (aq. sat., 30

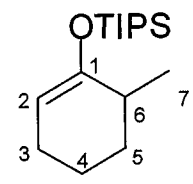
mL) and brine (30 mL), dried over $MgSO_4$ and concentrated to give the crude product, which was used directly for the next step.[162]

Triisopropyl(2-methylcyclohex-1-enyloxy)silane (209)[162]



Following the general procedure for the synthesis of TIPS enol ethers from ketones under thermodynamic conditions, the reaction of 2-methylcyclohexanone (1.04 mL, 10.0 mmol), triethylamine (2.79 mL, 20.0 mmol) and triisopropylsilyl trifluoromethanesulfonate (2.75 mL, 10.2 mmol) in DCM (80 mL) afforded the crude product (2.35 g) as a light yellow oil, which was used for next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.06-1.13 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.52-1.57 (2H, m, <u>H</u>-4), 1.62 (3H, s, <u>H</u>-7), 1.63-1.69 (2H, m, <u>H</u>-5), 1.95 (2H, t, J = 6.0 Hz, <u>H</u>-3), 2.07-2.12 (2H, m, <u>H</u>-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 16.5 (<u>C</u>-7), 18.1 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 22.9 (<u>C</u>-4), 23.9 (<u>C</u>-5), 30.4 (<u>C</u>-3 and <u>C</u>-6), 110.8 (<u>C</u>-2), 143.3 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{16}H_{33}OSi$ (MH^+): 269.2301 Found 269.2297; ν_{max}/cm^{-1} (thin film) 2931 (str, C-H stretch), 2867 (str), 1686 (m, s, C=C), 1464 (m, C-H deformation), 1191 (str)

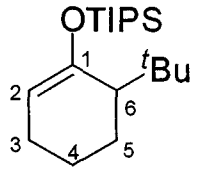
Triisopropyl(6-methylcyclohex-1-enyloxy)silane (210)[162]



Following the general procedure of kinetic conditions the TIPS enol ethers **210** (1.98 g) was produced as a colourless oil from 2-methylcyclohexanone (0.52 mL, 5.0 mmol), KHMDS (11.0 mL, 5.5 mmol, 0.5 M in toluene) and TIPSOTf (1.50 mL, 5.5 mmol) in anhydrous THF (15 mL).

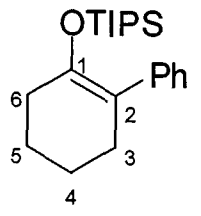
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.00-1.10 (24H, m, H-7 and Si(CH(CH_3)$_2$)$_3$), 1.34-1.43 (1H, m, 1xH-5), 1.44-1.49 (1H, m, 1xH-4), 1.57-1.61 (1H, m, 1xH-4), 1.74-1.81 (1H, m, 1xH-5), 1.97-2.00 (2H, m, H-3), 2.17-2.22 (1H, m, H-6), 4,76 (1H, t, J = 4.0 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.7 (Si(CH(CH$_3$)$_2$)$_3$), 18.1 (Si(CH(CH_3)$_2$)$_3$), 18.9 (C-7), 20.2 (C-5), 24.4 (C-4), 31.7 (C-3), 33.8 (C-6), 101.9 (C-2), 154.5 (C-1); m/z (GCMS) Calculated for $C_{16}H_{33}OSi$ (MH^+): 269.2301 Found 269.2299; ν_{max}/cm^{-1} (thin film) 2943 (str, C-H stretch), 2867 (str), 1660 (str, s, C=C), 1463 (m, C-H deformation), 1376 (w, C-O), 1336 (w), 1259 (m), 1193 (str), 997 (m), 884 (str)

(6-*tert*-Butylcyclohex-1-enyloxy)triisopropylsilane (211)



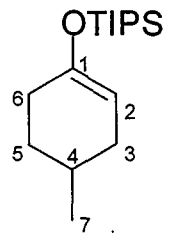
Following the general procedure the TIPS enol ethers **211** (crude 0.93 g) was produced as a colourless oil from 2-*tert*butylcyclohexanone (0.51 g, 4.55 mmol), triethylamine (1.27 mL, 9.10 mmol) and TIPSOTf (1.25 mL, 4.64 mmol) under thermodynamic conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.00 (9H, s, C(CH_3)$_3$), 1.06-1.11 (18H, m, Si(CH(CH_3)$_2$)$_3$), 1.14-1.23 (3H, m, Si(CH(CH$_3$)$_2$)$_3$), 1.30-1.38 (1H, m, 1xH-4), 1.46-1.55 (1H, m, 1xH-5), 1.57-1.75 (2H, m, 1xH-4 and 1xH-5), 1.93-2.02 (3H, m, H-3 and H-6), 4.85 (1H, t, J = 4.0 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.1 (Si(CH(CH$_3$)$_2$)$_3$), 18.2 (Si(CH(CH_3)$_2$)$_3$), 21.8 (C-5), 24.3 (C-4), 27.0 (C-3), 29.4 (C(CH_3)$_3$), 33.8 (C(CH$_3$)$_3$), 47.8 (C-6), 104.4 (C-2), 153.6 (C-1); m/z (GCMS) Calculated for $C_{19}H_{39}OSi$ (MH^+): 311.2770 Found 311.2760; ν_{max}/cm^{-1} (thin film) 2944 (str, C-H stretch), 2867 (str), 1652 (m, s, C=C), 1464 (m, C-H deformation), 1365 (m, C-O), 1173 (str), 907 (w), 883 (str)

Triisopropyl(2-phenylcyclohex-1-enyloxy)silane (212)[249]



Following the general procedure under thermodynamic conditions the TIPS enol ethers **212** (crude 400.2 mg) was produced as a colourless oil from 2-phenylcyclohexanone (0.19 g, 1.06 mmol), triethylamine (0.30 mL, 0.23 mmol) and TIPSOTf (0.29 mL, 1.08 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.94-0.97 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.67-1.72 (2H, m, <u>H</u>-4), 1.74-1.80 (2H, m, <u>H</u>-5), 2.24-2.28 (2H, m, <u>H</u>-3), 2.34-2.38 (2H, m, <u>H</u>-6), 7.12-7.16 (1H, m, <u>H</u>-Ph), 7.25-7.29 (2H, m, <u>H</u>-Ph), 7.32-7.37 (2H, m, <u>H</u>-Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 23.2 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 23.7 (<u>C</u>-4), 30.0 (<u>C</u>-5), 31.1 (<u>C</u>-3 and <u>C</u>-6), 115.3 (<u>C</u>-2), 125.4 (<u>C</u>-Ph), 127.5 (<u>C</u>-Ph), 128.8 (<u>C</u>-Ph), 141.7 (ipso <u>C</u>-Ph), 145.7 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{21}H_{35}OSi$ (MH^+): 331.2457 Found 331.2454; ν_{max}/cm^{-1} (thin film) 3027 (w, C=C), 2942 (str, C-H stretch), 2866 (str, s), 1662 (m, s, C=C), 1493 (w), 1464(m, C-H deformation), 1365 (w, C-O), 1338 (w), 1254 (m), 1185 (str)

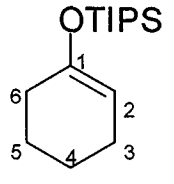
Triisopropyl(4-methylcyclohex-1-enyloxy silane (213)[162]



Following the general procedure the TIPS enol ethers **213** (crude 1.24 g) was produced as a colourless oil from 4-methylcyclohexanone (0.51 g, 4.55 mmol), triethylamine (1.27 mL, 9.10 mmol) and TIPSOTf (1.25 mL, 4.64 mmol) under thermodynamic conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.95 (3H, d, J = 6.0 Hz, <u>H</u>-7), 1.02-1.09 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.58-1.65 (2H, m, <u>H</u>-5), 1.84-1.96 (3H, m, 1x<u>H</u>-3, <u>H</u>-4 and 1x<u>H</u>-6), 2.12-2.20 (2H, m, 1x<u>H</u>-3 and 1x<u>H</u>-6),

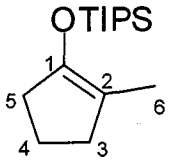
4.83-4.85 (1H, m, H-2); ^{13}C NMR (100.6MHz, $CDCl_3$) δ_C 12.3 (Si(CH$(CH_3)_2)_3$), 17.7 (Si(CH$(CH_3)_2)_3$), 21.0 (C-7), 28.4 (C-5), 29.7 (C-6), 31.2 (C-4), 32.4 (C-3), 103.0 (C-2), 150.4 (C-1); m/z (GCMS) Calculated for $C_{16}H_{33}OSi$ (MH^+): 269.2301 Found 269.2309; ν_{max}/cm^{-1} (thin film) 2946 (str, C-H stretch), 2868 (str), 1670 (m, C=C), 1463 (m, C-H deformation), 1370 (m, C-O), 1288 (w), 1223 (w), 1195 (str), 883 (str)

Cyclohexenyloxytriisopropylsilane (214)[162]



Following the general thermodynamic conditions the cyclohexanone (1.00 g, 10.20 mmol) was treated with triethylamine (26.6 mL, 20.41 mmol) and TIPSOTf (2.8 mL, 10.41 mmol) the TIPS enol ether **214** (2.19 g crude product) as alight yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.06-1.10 (21H, m, Si(CH$(CH_3)_2)_3$), 1.48-1.54 (2H, m, H-4), 1.64-1.70 (2H, m, H-5), 1.99-2.03 (2H, m, H-3), 2.05-2.08 (2H, m, H-6), 4.89 (1H, t, J = 4.0 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.6 (Si(CH$(CH_3)_2)_3$), 18.0 (Si(CH$(CH_3)_2)_3$), 22.4 (C-4), 23.3 (C-5), 23.9 (C-3), 29.9 (C-6), 103.6 (C-2), 150.6 (C-1); m/z (GCMS) Calculated for $C_{15}H_{31}OSi$ (MH^+): 255.2144 Found 255.2148; ν_{max}/cm^{-1} (thin film) 2941 (str, C-H stretch), 2866 (str), 1669 (str, s, C=C), 1464 (m, C-H deformation), 1367 (m, C-O), 1338 (w), 1266 (m) 1196 (str), 998 (m), 886 (str)

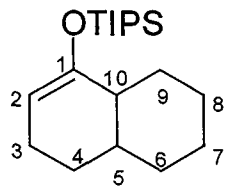
Triisopropyl(2-methylcyclopent-1-enyloxy)silane (215)



Following the general procedure the TIPS enol ethers **215** (crude 293 mg) was produced as a colourless oil from 2-methylcyclopentanone (91.7 mg, 0.93 mmol), triethylamine (2.43 mL, 1.86 mmol) and TIPSOTf (255 μL, 0.95 mmol) under thermodynamic conditions. ^1H NMR (400

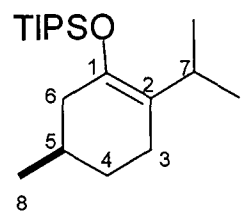
MHz, $CDCl_3$) δ_H 1.06-1.22 (21H, m, Si(C<u>H</u>($C\underline{H}_3$)$_2$)$_3$), 1.58(3H, s, <u>H</u>-6), 1.73-1.83 (2H, m, <u>H</u>-4), 2.13-2.21 (2H, m, <u>H</u>-3), 2.29-2.37 (2H, m, <u>H</u>-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (Si(<u>C</u>H(CH_3)$_2$)$_3$), 12.8 (<u>C</u>-6), 17.7 (Si(CH(<u>C</u>H_3)$_2$)$_3$), 19.8 (<u>C</u>-4), 33.9 (<u>C</u>-3), 46.2 (<u>C</u>-5), 104.6 (<u>C</u>-2), 168.9 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{15}H_{31}OSi$ (MH^+): 255.2144 Found 255.2139; ν_{max}/cm^{-1} (thin film) 2944 (str, C-H stretch), 2867 (s), 1690 (w, C=C), 1465 (m, C-H deformation), 1383 (w, C-O), 1333 (w), 1249 (m), 883 (m)

Triisopropyl((4a*S*,8a*R*)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yloxy)silane (216)



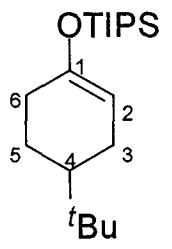
Following the general procedure the TIPS enol ethers **216** (crude 0.51 g) was produced as a colourless oil from *trans*-decalone (0.15 g, 1.00 mmol), KHMDS (2.20 mL, 1.10 mmol, 0.5 M in toluene) and TIPSOTf (295 μL, 1.10 mmol) under kinetic conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.91-0.99 (1H, m, 1x<u>H</u>-9), 1.00-1.03 (1H, m, 1x<u>H</u>-6), 1.06-1.12 (21H, m, Si(C<u>H</u>($C\underline{H}_3$)$_2$)$_3$), 1.13-1.32 (4H, m, 1x<u>H</u>-4, 1x<u>H</u>-7, 1x<u>H</u>-8and 1x<u>H</u>-9), 1.51-1.55 (1H, m, 1x<u>H</u>-4), 1.72-1.82 (4H, m, <u>H</u>-5, 1x<u>H</u>-6, 1x<u>H</u>-7 and 1x<u>H</u>-8), 1.95-2.01 (1H, m, 1x<u>H</u>-3), 2.05-2.10 (1H, m, 1x<u>H</u>-3), 2.22-2.23 (1H, m, <u>H</u>-10), 4.72-4.73 (1H, m, <u>H</u>-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.8 (Si(<u>C</u>H(CH_3)$_2$)$_3$), 18.1 (Si(CH(<u>C</u>H_3)$_2$)$_3$), 24.0 (<u>C</u>-3), 26.6 (<u>C</u>-9), 26.9 (<u>C</u>-7), 28.6 (<u>C</u>-8), 30.1 (<u>C</u>-4), 33.7 (<u>C</u>-6), 41.6 (<u>C</u>-5), 45.9 (<u>C</u>-10), 101.3 (<u>C</u>-2), 152.8 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{19}H_{37}OSi$ (MH^+): 309.2614 Found 309.2610; ν_{max}/cm^{-1} (thin film) 2923 (str, C-H stretch), 2866 (str), 1657 (str, s, C=C), 1464 (m, C-H deformation), 1349 (w, C-O), 1250 (m), 1204 (str)

(*R*)-Triisopropyl(2-isopropyl-5-methylcyclohex-1-enyloxy)silane (217)



Following the general procedure the TIPS enol ethers **217** (crude 0.95 g) was produced as a colourless oil from 1-menthone (0.47 g, 3.02 mmol), triethylamine (0.84 mL, 6.04 mmol) and TIPSOTf (0.85 mL, 3.05 mmol) under thermodynamic conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.90 (3H, d, J = 6.5 Hz, $CH(C\underline{H}_3)_2$), 0.91 (3H, d, J = 6.5 Hz, $CH(C\underline{H}_3)_2$), 1.06-1.11 (21H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$), 1.13-1.18 (1H, m, 1x$\underline{H}$-4), 1.63-1.82 (3H, m, 1x$\underline{H}$-3, 1x$\underline{H}$-4 and $\underline{H}$-5), 1.88-1.99 (2H, m, 1x$\underline{H}$-3 and 1x$\underline{H}$-6), 2.09 (1H, dd, J = 16.0 and 6.0 Hz, 1x$\underline{H}$-6), 3.18 (1H, sep, J = 6.5 Hz, $\underline{H}$-7); ^{13}C NMR (100.6MHz, $CDCl_3$) δ_C 13.4 ($Si(\underline{C}H(CH_3)_2)_3$), 18.2 ($Si(CH(\underline{C}H_3)_2)_3$), 20.2 ($CH(\underline{C}H_3)_2$), 20.4 ($CH(\underline{C}H_3)_2$), 21.6 ($\underline{C}$-8), 21.7 ($\underline{C}$-3), 28.5 ($\underline{C}$-7), 29.7 ($\underline{C}$-4), 31.1 ($\underline{C}$-5), 39.0 ($\underline{C}$-6), 118.7 ($\underline{C}$-2), 141.1 ($\underline{C}$-1); m/z (GCMS) Calculated for $C_{19}H_{39}OSi$ (MH^+): 311.2770 Found 311.2770; ν_{max}/cm^{-1} (thin film) 2946 (str, C-H stretch), 2860 (str), 1655 (m, C=C), 1463 (m, C-H deformation), 1370 (m, C-O), 1275 (w, C-O)

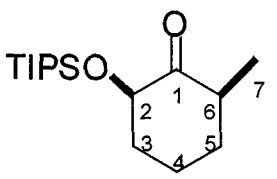
(4-*tert*-Butylcyclohex-1-enyloxy)triisopropylsilane (218)



Following the general procedure the TIPS enol ethers **218** (crude 1.17 g) was produced as a colourless oil from 4-*tert*butylcyclohexanone (0.56 g, 3.66 mmol), triethylamine (1.02 mL, 7.32 mmol) and TIPSOTf (1.18 mL, 4.39 mmol) under thermodynamic conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (9H, s, $C(C\underline{H}_3)_3$), 1.06-1.18 (21H, m, $Si(C\underline{H}(C\underline{H}_3)_2)_3$), 1.20-1.31 (2H, m, $\underline{H}$-5), 1.77-1.84 (2H, m, 1x$\underline{H}$-3 and 1x$\underline{H}$-6), 1.98-2.19 (3H, m, 1x$\underline{H}$-3, $\underline{H}$-4 and 1x$\underline{H}$-6), 4.85-4.88 (1H, m, $\underline{H}$-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.6 ($Si(\underline{C}H(CH_3)_2)_3$), 18.0 ($Si(CH(\underline{C}H_3)_2)_3$), 24.5 ($\underline{C}$-5), 25.1 ($C(\underline{C}H_3)_3$), 27.4 ($\underline{C}$-6), 31.0 ($\underline{C}$-3), 32.1 ($\underline{C}(CH_3)_3$), 44.0 ($\underline{C}$-4), 103.3 ($\underline{C}$-2), 150.6 ($\underline{C}$-1); m/z (GCMS) Calculated for $C_{19}H_{39}OSi$ (MH^+): 311.2770 Found 311.2768; ν_{max}/cm^{-1} (thin film) 2945 (str, C-H stretch), 2867 (str, C-H), 1674 (m, s, C=C), 1466

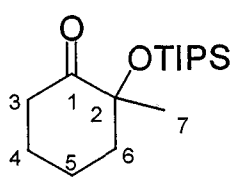
(m, C-H deformation), 1365 (m, C-O), 1255 (w), 1198 (str), 883 (str), 865 (m)

(2*S,6*R**)-2-Methyl-6-(triisopropylsilyloxy)cyclohexanone (220)**



The solution of the TIPS-enol ether **209** (100 mg, 0.37 mmol) in DCM (5 mL) was cooled to –78°C. *m*CPBA (70.3 mg, 0.41 mmol) was solved in anhydrous DCM (5 mL) and added into the former solution drop by drop. After 2 h the solution was warmed to room temperature slowly overnight. The mixture was quenched with $Na_2S_2O_5$ (aq. sat., 10 mL) and $NaCO_3$ (aq. sat., 10 mL), and extracted with DCM (3x10 mL). The combined organic layer was dried over $MgSO_4$. Remove the solvent under reduced pressure and then run chromatography over silica gel (Et_2O/petrol 1:50) to give the ketone **220** as a colourless oil (51.9 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05-1.22 (24H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$ and <u>H</u>-7), 1.28-1.37 (1H, m, 1x<u>H</u>-5), 1.67-1.75 (2H, m, 1x<u>H</u>-3 and 1x<u>H</u>-4), 1.83-1.89 (1H, m, 1x<u>H</u>-4), 2.00-2.07 (1H, m, 1x<u>H</u>-5), 2.29-2.41 (2H, m, 1x<u>H</u>-3 and <u>H</u>-6), 4.30 (1H, m, <u>H</u>-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 14.2 (<u>C</u>-7), 17.9 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 23.5 (<u>C</u>-4), 36.5 (<u>C</u>-5), 38.4 (<u>C</u>-3), 44.2 (<u>C</u>-6), 77.2 (<u>C</u>-2), 210.6 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{16}H_{33}O_2Si$ (MH^+): 285.2250 Found 285.2252; ν_{max}/cm^{-1} (thin film) 2945 (str, C-H stretch), 2857 (m, C-H), 1718 (str, C=O), 1459 (m, C-H deformation), 1370 (w, C-O), 1245 (w), 1190 (m), 1170 (m), 1045 (m)

2-Methyl-2-(triisopropylsilyloxy)cyclohexanone (222)



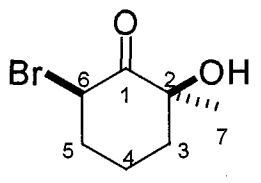
Following the same procedure to produce ketone **220**, ketone **222** was obtained from TIPS-enol ether **210** (268 mg, 1.00 mmol) and mCPBA (190 mg, 1.10 mmol) as a colourless oil (163.8 mg,

57%). ^{1}H NMR (400 MHz, CDCl3) δ_H 1.02-1.07 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.33 (3H, s, <u>H</u>-7), 1.53-1.70 (3H, m, 1x<u>H</u>-3, 1x<u>H</u>-4 and 1x<u>H</u>-5), 1.93-2.06 (3H, m, 1x<u>H</u>-3, 1x<u>H</u>-4 and 1x<u>H</u>-5), 2.22-2.28 (1H, m, 1x<u>H</u>-6), 2.85-2.92 (1H, m, 1x<u>H</u>-6); ^{13}C NMR (100.6 MHz, CDCl3) δ_C 13.5 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 18.3 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 21.3 (<u>C</u>-4), 24.1 (<u>C</u>-7), 27.9 (<u>C</u>-3), 38.3 (<u>C</u>-6), 43.3 (<u>C</u>-5), 78.1 (<u>C</u>-2), 211.7 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{16}H_{33}O_2Si$ (MH^+): 285.2250 Found 285.2249; νmax/cm-1 (thin film) 2943 (str, C-H stretch), 2866 (str, C-H), 1723 (str, s, C=O), 1464 (m, C-H deformation), 1376 (w, C-O), 1241 (w), 1193 (m), 1170 (m) 1055 (str)

General procedure for oxidation and bromination:

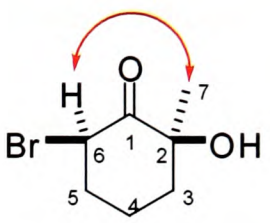
The solution of the TIPS-enol ether (1 eq) in DCM was cooled to –78°C. *m*CPBA (1.1 eq) was solved in DCM and added into the former solution drop by drop. After 2 h, bromine (1.1 eq) in DCM solution was dropped into the flask. The mixture was stirred at -78°C for another 2 h, and then was warmed to room temperature. Remove the solvent under reduced pressure and then chromatograph over silica gel (Et_2O/petrol 1:50).

(2*S,6*R**)-6-Bromo-2-hydroxy-2-methylcyclohexanone (224)**

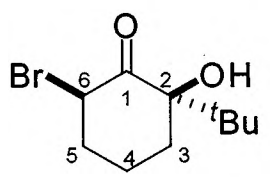


Following the general oxidation and bromination method, the bromide **224** (82.7 mg, 80% over 2 steps) was produced from the TIPS-enol ether **209** (134.0 mg, 0.50 mmol) as a coulorless oil. Also, **224** (132.3 mg, 64% over 2 steps) could be produce from the TIPS-enol ether **210** (268.0 mg, 1.00 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.81-1.89 (2H, m, 1x<u>H</u>-4 and 1x<u>H</u>-3), 1.92 (3H, s, <u>H</u>-7), 2.03-2.12 (1H, m, 1x<u>H</u>-5), 2.18-2.29 (1H, m, 1x<u>H</u>-4), 2.36-2.45 (1H, m, 1x<u>H</u>-3), 2.62-2.69 (1H, m, 1x<u>H</u>-5), 5.59 (1H, dd, *J*=13.5 and 6.5 Hz, <u>H</u>-6); ^{13}C NMR (100.6 MHz, $CDCl_3$)

δ_C 23.6 (C-4), 28.8 (C-7), 39.4 (C-5), 43.3 (C-3), 52.2 (C-6), 64.9 (C-2), 196.2 (C-1); m/z (GCMS) Calculated for $C_7H_{12}{}^{79}BrO_2$ (MH^+): 207.0021 Found 207.0015; ν_{max}/cm^{-1} (thin film) 3443 (w, OH), 2994 (str, C-H stretch), 2867 (str, C-H), 1731 (str, s, C=O), 1447 (m, C-H deformation), 1379 (w, C-O), 1303 (w), 1258 (w), 1176 (m); n.O.e experiments: irradiation at 1.92 (H-7) saw reciprocal signal enhancement at 5.59 (H-6); irradiation at 5.59 (H-6) saw reciprocal signal enhancement at 1.92 (H-7)

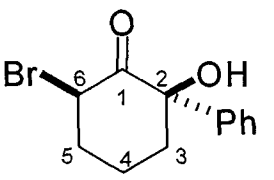


(2*R,6*R**)-6-Bromo-2-*tert*-butyl-2-hydroxycyclohexanone (225)**



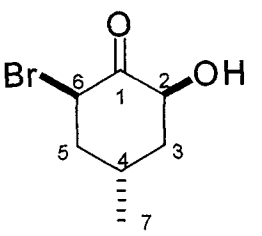
Following the general oxidation and bromination method, the bromide **225** (2.23 g, 68% over 2 steps) was produced from the TIPS-enol ether **211** (4.11 g, 13.27 mmol) as a coulorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.24 (9H, s, $C(CH_3)_3$), 1.85-1.92 (1H, m, H, 1xH-4), 1.98-2.12 (2H, m, 1xH-3 and 1xH-5), 2.20-2.32 (1H, m, 1xH-4), 2.42-2.48 (1H, m, 1xH-3), 2.58-2.65 (1H, m, 1xH-5), 5.72 (1H, dd, J = 13.5 and 6.0 Hz, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 23.7 (C-4), 30.3 ($C(CH_3)_3$), 36.6 (C-3), 38.9 (C-5), 39.7 ($C(CH_3)_3$), 54.6 (C-6), 81.7 (C-2), 194.6 (C-1); m/z (GCMS) Calculated for $C_{10}H_{18}{}^{79}BrO_2$ (MH^+): 249.0490 Found 249.0494; ν_{max}/cm^{-1} (thin film) 3434 (w, OH), 2963 (str, C-H stretch), 2870 (m), 1728 (str, C=O), 1448 (m, C-H deformation), 1367 (m, C-O), 1300 (w), 1227 (w), 1178 (w), 1089 (m)

(2*R,6*R**)-6-Bromo-2-hydroxy-2-phenylcyclohexanone (226)**



Following the general oxidation and bromination method, the bromide **226** (2.88 g, 56% over 2 steps) was produced from the TIPS-enol ether **212** (6.59 g, 19.94 mmol) as a coulorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.03-2.10 (1H, m, 1xH-4), 2.18-2.25 (1H, m, 1xH-5), 2.37-2.48 (1H, m, 1xH-4 and 1xH-3), 2.53-2.61 (1H, m, 1xH-3), 2.71-2.78 (1H, m, 1xH-5), 5.80 (1H, dd, *J* = 13.0 and 6.0 Hz, H-6), 7.34-7.40 (3H, m, H-Ph), 7.49-7.52 (2H, m, H-Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 19.2 (C-4), 38.9 (C-5), 41.1 (C-3), 52.5 (C-6), 56.8 (C-2), 125.5(C-Ph), 128.0 (C-Ph), 128.7 (C-Ph), 138.9 (*ipso* C-Ph), 194.6 (C-1); m/z (GCMS) Calculated for $C_{12}H_{14}{}^{79}BrO_2$ (MH^+): 269.0177 Found 269.0175; ν_{max}/cm^{-1} (thin film) 3445 (w, OH), 2943 (str, C-H stretch), 2866 (str), 1725 (str, C=O), 1464 (m, C-H deformation), 1377 (w, C-O), 1242 (w), 1170 (m), 1055 (m)

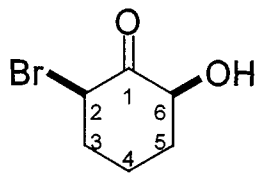
(2*R,4*S**,6*S**)-2-Bromo-6-hydroxy-4-methylcyclohexanone (227)**



Following the general oxidation and bromination method, the bromide **227** (65.7 mg, 56% over 2 steps) was produced from the TIPS-enol ether **213** (153.0 mg, 0.57 mmol) as a coulorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.08 (3H, d, *J* = 6.5 Hz, H-7), 1.82-1.98 (2H, m, 1xH-3 and 1xH-5), 2.31 (1H, m, 1xH-3), 2.54-2.64 (2H, m, H-4 and 1xH-5), 4.55 (1H, t, *J* = 3.0 Hz, H-2), 5.49 (1H, dd, *J* = 13.5 and 6.0, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 20.1 (C-7), 28.4 (C-4), 42.6 (C-3), 47.0 (C-5), 49.2 (C-6), 50.1 (C-2), 195.8 (C-1); m/z (GCMS) Calculated for $C_7H_{12}{}^{79}BrO_2$ (MH^+): 207.0021 Found 207.0013; ν_{max}/cm^{-1} (thin film) 3440 (w), 2986 (str), 2877

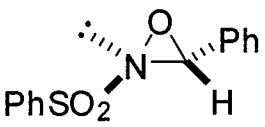
(m), 1729 (str), 1429 (m), 1369 (w), 1303 (w), 1260 (w), 1158 (w), 1070 (m)

(2*R,6*S**)-2-Bromo-6-hydroxycyclohexanone (228)**



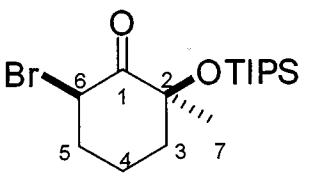
Following the general oxidation and bromination method, the bromide **228** (43.2 mg, 45% over 2 steps) was produced from the TIPS-enol ether **214** (127.0 mg, 0.50 mmol), mCPBA (94.9 mg, 0.55 mmol) and Br_2 (28.2 μL, 0.55 mmol) as a coulorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.98-2.07 (2H, m, H-4), 2.17-2.26 (1H, m, 1xH-3), 2.29-2.38 (1H, m, 1xH-5), 2.40-2.48 (1H, m, 1xH-3), 2.95-3.03 (1H, m, 1xH-5), 4.45 (1H, t, J = 5.5 Hz, H-6), 4.45 (1H, dd, J = 8.0 and 5.0 Hz, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 22.1 (C-4), 37.1 (C-3), 37.9 (C-5), 50.8 (C-2), 53.4 (C-6), 203.5 (C-1); m/z (GCMS) Calculated for $C_6H_{10}{}^{79}BrO_2$ (MH^+): 192.9859 Found 192.9862; ν_{max}/cm^{-1} (thin film) 3445 (w, OH), 2984 (str, C-H stretch), 2867 (str), 1731 (str, s, C=O), 1447 (m, C-H deformation), 1379 (w, C-O), 1303 (w), 1258 (w), 1176 (m), 1073 (m)

(±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine (229)[171]



Reagent **229** was prepared according to the method reported by Davis *et al.*[171] MP: 94-96°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.50 (1H, s, CH), 7.41 (5H, s, H-Ph), 7.60-7.80 (3H, m, H-Ph), 8.05 (2H, d, J = 7.0 Hz, H-Ph)

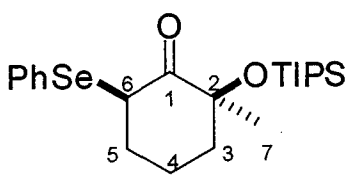
(2*S,6*R**)-6-Bromo-2-methyl-2-(triisopropylsilyloxy)cyclohexanone (231)**



To a solution of the TIPS-enol ether **210** (132.0 mg, 0.49 mmol, 1 eq) in DCM (5 mL) at –78°C

was added a solution of oxaziridine **229** (135 mg, 0.52 mmol, 1.05 eq) in DCM (5 mL) dropwise. After 2 h, a solution of bromine (86.6 mg, 0.54 mmol, 1.1 eq) in DCM (3 mL) was added into the flask. The mixture was stirred at -78°C for another 2 h, and then was warmed to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography over silica gel (Et_2O/petrol 1:200) to give the TIPS protected bromide **231** (44.2 mg, 25%) and the hydroxy bromide **224** (40.0 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.02-1.08 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.44 (3H, s, <u>H</u>-7), 1.58-1.66 (2H, m, 1x<u>H</u>-3 and 1x<u>H</u>-4), 1.96-2.04 (1H, m, 1x<u>H</u>-5), 2.10-2.19 (2H, m, 1x<u>H</u>-4 and 1x<u>H</u>-3), 2.57-2.64 (1H, m, 1x<u>H</u>-5), 5.34 (1H, dd, J = 13.0 and 6.0 Hz, <u>H</u>-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.4 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 18.2 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 21.9 (<u>C</u>-4), 24.2 (<u>C</u>-7), 40.2 (<u>C</u>-5), 42.9 (<u>C</u>-3), 54.5 (<u>C</u>-6), 79.5 (<u>C</u>-2), 202.2 (<u>C</u>-1); m/z (GCMS) Calculated for $C_{16}H_{32}{}^{79}BrO_2Si$ (MH^+): 363.1355 Found 363.1342; ν_{max}/cm^{-1} (thin film) 2945 (str, C-H stretch), 2867 (str), 1740 (str, s, C=O), 1463 (m, C-H deformation), 1377 (w, C-O), 1260 (w), 1178 (str), 1145 (str)

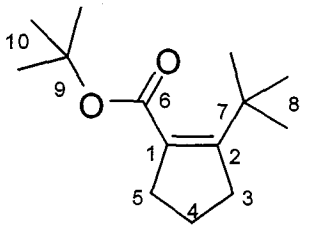
(2*S,6*R**)-2-Methyl-6-(phenylselanyl)-2-(triisopropylsilyloxy)cyclohexanone (233)**



To a solution of the TIPS-enol ether **210** (142.6 mg, 0.53 mmol, 1 eq) in anhydrous DCM (6 mL) at –78°C was added a solution of oxaziridine **229** (145.8 mg, 0.56 mmol, 1.05 eq) in DCM (5 mL) dropwise. After 2 h, a solution of phenylselenyl bromide (138.1 mg, 0.58 mmol, 1.1 eq) in DCM (5 mL) was added into the flask. The mixture was stirred at -78°C for another 2 h, and then was warmed to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography over silica gel (Et_2O/petrol 1:200) to give the TIPS protected selenide **233** (88.2 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.03-1.09 (21H, m,

$Si(C\underline{H}(C\underline{H}_3)_2)_3)$, 1.40 (3H, s, H-7), 1.55-1.62 (2H, m, 1xH-3 and 1xH-4), 1.73-1.84 (1H, m, 1xH-5), 1.95-2.07 (1H, m, 1xH-4), 2.08-2.15 (1H, m, 1xH-3), 2.26-2.33 (1H, m, 1xH-5), 4.81 (1H, dd, J = 13.0 and 6.0 Hz, H-6), 7.25-7.30 (3H, m, H-Ph), 7.55-7.59 (2H, m, H-Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.4 ($Si(\underline{C}H(CH_3)_2)_3$), 18.4 ($Si(CH(\underline{C}H_3)_2)_3$), 21.9 (C-4), 23.9 (C-7), 37.4 (C-5), 43.4 (C-3), 51.0 (C-6), 79.1 (C-2), 127.7 (*ipso* C-Ph), 128.4 (C-Ph), 129.0 (C-Ph), 135.3 (C-Ph), 208.2 (C-1); m/z (GCMS) Calculated for $C_{22}H_{37}O_2Si^{78}Se$ (MH^+): 447.1728 Found 447.1716; ν_{max}/cm^{-1} (thin film) 2942 (str, C-H stretch), 2866 (m), 1720 (str, s, C=O), 1463 (m, C-H deformation), 1376 (w, C-O), 1176 (str), 1140 (m), 1066 (str)

tert-Butyl 2-_tert_-butylcyclopent-1-enecarboxylate (235)

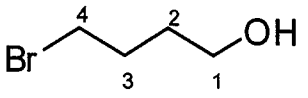


The solution of the α-bromo-α'-hydroxy ketone **225** (23.5 mg, 0.095 mmol) in anhydrous THF (2.0 mL) was cooled to 0°C. Potassium *tert*-butoxide (21.3 mg, 0.19 mmol) was added, and the mixture was warmed to room temperature. After 1 day, it was washed with H_2O (2.0 mL) and extracted with EtOAc (3x10 mL). The solution was dried over $MgSO_4$ and concentrated. After purification on silica gel (DCM/petrol 1:8), the product **235** was obtained as a colourless oil (9.97 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.16 (9H, s, H-8), 1.50 (9H, s, H-10), 1.77 (2H, qui, J = 7.5 Hz, H-4), 2.49 (2H, t, J = 7.5 Hz, H-3), 2.58 (2H, t, J = 7.5 Hz, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 21.8 (C-4), 28.0 (C-10), 29.3 (C-8), 34.1 (C-7), 35.4 (C-3), 37.0 (C-5), 80.4 (C-9), 128.2 (C-1), 153.2 (C-2), 169.5 (C-6); m/z (GCMS) Calculated for $C_{14}H_{25}O_2$ (MH^+): 225.1855 Found 225.1858; ν_{max}/cm^{-1} (thin film) 2943 (str, C-H stretch), 2866 (m), 1725 (s, C=O), 1670 (C=C), 1464 (m, C-H deformation), 1346 (w, C-O)

4.3 Experimental procedures for Chapter 3

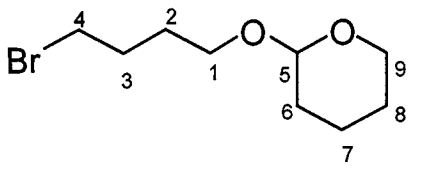
4.3.1 Experimental for Synthesis of the intramolecular Diels-Alder reaction precursor

4-Bromo-1-butanol (244)[250]



To THF (500 mL) was added 48% HBr (335.0 g, 1.98 mol of HBr) dropwise under reflux over a 3.75-h period. The reaction was left under reflux for another 1.25 h, and then cooled down, neutralized with $NaHCO_3$, Partition with water (300 mL), washed with brine (300 mL), and dried over $MgSO_4$. Concentration of the solution yielded 91.00 g **244** (30%) as an orange oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.76 (2H, qui, J = 6.5 Hz, H-2), 1.98 (2H, qui, J = 6.5 Hz, H-3), 3.47 (2H, t, J = 6.5 Hz, H-4), 3.74 (2H, t, J = 6.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 29.1 (C-3), 30.7 (C-2), 33.5 (C-4), 62.1 (C-1); m/z (GCMS) Calculated for $C_4H_{10}{}^{79}BrO$ (MH^+): 152.9915 Found 152.9906; ν_{max}/cm^{-1} (thin film) 3286 (str, br, -OH), 2943 (str, C-H stretch), 2874 (m, C-H stretch), 1439 (m, C-H deformation), 1246 (m, C-O), 1058 (str), 750 (w)

2-(4-Bromobutoxy)tetrahydro-2*H*-pyran (245)[251]



A solution of alcohol **244** (7.19 g, 46.99 mmol) and dihydropyran (5.93 g, 70.49 mmol) in anhydrous DCM (500 mL) containing PPTS (1.18 g, 4.70 mmol) was stirred for 4 h at room temperature. Then the solution was diluted with ether (300 mL) and washed water (300 mL) and brine (300 mL) to remove the catalyst. After evaporation of the solvent, the residue was purified by chromatography (Et_2O/petrol 1:30) to give 10.87 g (97.0%) product **245** as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.50-1.58 (4H, m, 1xH-6, 1xH-7 and H-8), 1.67-1.85 (4H, m,

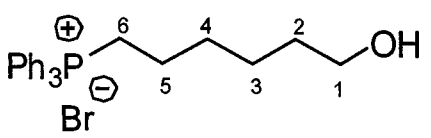
H-2, 1xH-6 and 1xH-7), 1.96-1.99 (2H, m, H-3), 3.42-3.45 (1H, m, 1xH-1), 3.46 (2H, t, J = 7.0 Hz, H-4), 3.49-5.53 (1H, m, 1xH-9), 3.77 (1H, dt, J = 9.5 and 6.5 Hz, 1xH-1), 3.84-3.87 (1H, m, H-9), 4.56-4.60 (1H, m, H-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 19.6 (C-7), 25.4 (C-8), 28.4 (C-2), 29.8 (C-3), 30.7 (C-6), 33.8 (C-4), 62.4 (C-9), 66.4 (C-1), 98.8 (C-5); m/z (GCMS) Calculated for $C_9H_{21}N^{79}BrO_2$ (MNH_4^+): 254.0756 Found 254.0762; ν_{max}/cm^{-1} (thin film) 2942 (str, C-H stretch), 2870 (m, C-H stretch), 1440 (w, C-H deformation), 1352 (w, C-O), 1257 (w, C-O), 1135 (m), 1077 (m), 1034 (str)

6-Bromo-1-hexanol (251)[182]

To a mixture of diol **250** (15.15 g, 0.13 mol, 1 eq) and toluene (350 mL) was added concentrated hydrobromic acid (aq. 48%, 17.26 mL, 0.15 mol, 1.2 eq). The heterogeneous mixture was stirred and heated at reflux for 12 h. TLC analysis indicated that substantial amounts of diol still remained. Thus, a further quantity of hydrobromic acid (4.35 mL, 0.03 mol, 0.3 eq) was added, and the mixture was heated at reflux for a room temperature whole night, at which time TLC analysis showed little diol **250** remaining. The reaction mixture was allowed to cool to room temperature, and the phases were separated. The organic layer was diluted with ether and washed with 1M NaOH and brine. Drying over Na_2SO_4 and concentration of the organic layer gave a yellow oil which was puried by column chromatography (Et_2O/petrol 1:1) to give 21.65 g (94%) product **251** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.36-1.52 (4H, m, H-3 and H-4), 1.57-1.71 (2H, m, H-2), 1.86-1.90 (2H, m, H-5), 3.42 (2H, t, J = 7.0 Hz, H-6), 3.66 (2H, t, J = 6.5 Hz, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.9 (C-3), 27.9 (C-4), 32.5 (C-2), 32.7 (C-5), 33.9 (C-6), 62.8 (C-1); m/z (GCMS) Calculated for $C_{16}H_{17}BrON$ (MNH_4^+): 198.0493 (79Br), 200.0473 (81Br) Found 198.0491 (79Br), 200.0493 (81Br); ν_{max}/cm^{-1} (thin

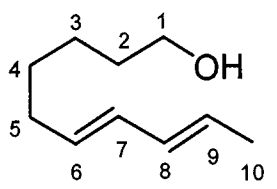
film) 3333 (str, br, -OH), 2935 (str, C-H stretch), 2860 (str, C-H stretch), 1460 (m, C-H deformation), 1259 (m, C-O), 1054 (str), 728 (w), 644 (w)

(6-Hydroxyhexyl)triphenylphosphonium bromide (252)[184]



A mixture of 6-bromohexan-1-ol **251** (10.13 g, 5.63 mmol) and triphenylphosphine (16.23 g, 6.19 mmol) in anhydrous acetonitrile (30 mL) was heated at reflux for 24 h, and a white precipitate appeared. The reaction mixture was cooled to room temperature and acetonitril was decanted. The phosphonium salt obtained was solved in chloroform (80 mL) and precipitated out by treating with Et_2O (200 mL). The mixture was stirred at room temperature overnight. The yield of **252** was 99% (24.71 g, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43-1.55 (4H, m, H-2 and H-3), 1.59-1.72 (4H, m, H-4 and H-5), 2.99 (1H, m, OH), 3.57-3.64 (2H, m, H-1), 3.67-3.75 (2H, m, H-6), 7.68-7.72 (9H, m, Ph-H), 7.76-7.84 (6H, m, Ph-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 22.3 (C-5), 22.7 (C-6), 24.8 (C-3), 29.5 (C-4), 31.9 (C-2), 61.5 (C-1), 130.5 (Ph-C), 130.7 (Ph-C), 133.6 (Ph-C), 135.0 (Ph-C); m/z (ESIMS) Calculated for $C_{24}H_{28}OP$ ($M\text{-}Br^+$): 363.1878 Found 363.1889; ν_{max}/cm^{-1} (thin film) 3302 (str, br, -OH), 2922 (str, C-H stretch), 2860 (str, C-H stretch), 1587 (w), 1485 (w), 1437 (str, C-H deformation), 1331 (w), 1114 (str, C-O), 1077 (m), 996 (m), 887 (w, aromatic C-H), 769 (m, aromatic C-H), 749 (str, aromatic C-H)

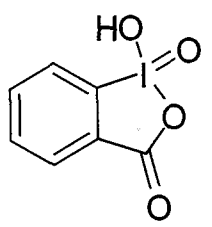
(6*E*,8*E*)-Deca-6,8-dien-1-ol (249)[252]



A solution of methyllithium/lithium bromide complex (1.24 M in Et_2O, 2 3.44 mL, 29.07 mmol)

was added dropwise to a slurry of 6-hydroxybutyl-triphenylphosphonium bromide **252** (6.43 g, 14.54 mmol) in anhydrous THF (50 mL) at -78˚C. After 30 min of vigorous stirring at room temperature, the clear red solution was cooled to -78˚C and treated with crotonaldehyde (1.02 g, 14.54 mmol). The reaction was left at -78˚C for 30 min, then methyllithium/lithium bromide complex (1.24 M in Et_2O, 12.90 mL, 15.99 mmol) was added dropwise to the orange-coloured precipitate. The resulting dark red betaine-ylid solution was kept at room temperature for 30 min and at -78˚C 30 min for another 30 min before the addition of CF_3COOH (1.19 mL, 15.99 mmol). After the addition of potassium *tert*-butoxide (2.02 g, 18.03 mmol) and stirring for 1 h at room temperature, the mixture was poured into water (40 mL) and extracted with diethyl ether (3x60 mL). After drying and evaporating the organic layers, the residue was purified by silica gel chromatography (Et_2O/petrol 1:4) to give the alcohol **249** (1.59 g, 71%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32-1.46 (5H, m, H-3, H-4 and OH), 1.57 (2H, q, J = 7.0 Hz, H-2), 1.73 (3H, d, J = 6.5 Hz, H-10), 2.07 (2H, q, J = 7.0 Hz, H-5), 3.64 (2H, t, J = 7.0 Hz, H-1), 5.51-5.62 (2H, m, H-6 and H-9), 5.96-6.02 (2H, m, H-7 and H-8); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 18.0 (C-10), 25.3 (C-3), 29.2 (C-4), 32.5 (C-5), 32.6 (C-2), 62.3 (C-1), 126.9 (C-7), 130.4 (C-6), 131.6 (C-9), 131.8 (C-8); m/z (GCMS) Calculated for $C_{10}H_{22}ON$ (MNH_4^+): 172.1701 Found 172.1696; ν_{max}/cm^{-1} (thin film) 3332 (str, wide, -OH), 3016 (m), 2930 (str, C-H), 2860 (m, C-H), 1437 (m, C-H deformation), 1377 (w), 1054 (m, C-O), 986 (m)

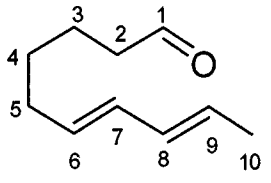
IBX, 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-Oxide (153)[192]



IBX was prepared according to the modified method reported by Santagostino *et al.*[193] Mp 231-233˚C, lit. mp 233˚C; ^{1}H NMR (200 MHz, D6-DMSO) δ_H 7.84 (1H, t, J = 7.5), 7.90-8.06

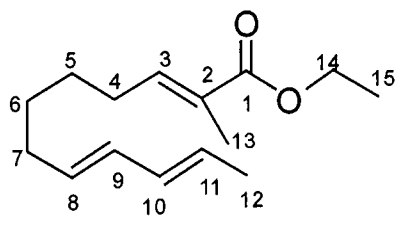
(2H, m), 8.14 (1H, d, J = 8.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 125.0 (CH), 130.1 (CH), 131. (CH), 133.0 (CH), 133.4 (CH), 146.6 (CH), 167.5 (C=O)

(6*E*,8*E*)-Deca-6,8-dienal (242)[178]



To a solution of IBX (4.34 g, 15.50 mmol) in anhydrous DMSO (15 mL) was added alcohol **249** (1.59g, 10.3 mmol) in THF (8 mL) *via* canular. After stirring at room temperature for 2 h, the reaction was quenched by water (20 mL). The resulting suspension was filtered through a course fritted funnel, and extracted with diethyl ether (3x30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by chromatography (DCM/petrol 1:4) provided aldehyde **242** (1.36 g, 87%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (2H, qui, J = 7.5 Hz, H-4), 1.65 (2H, qui, J = 7.5 Hz, H-3), 1.73 (3H, d, J = 6.5 Hz, H-10), 2.09 (2H, q, J = 7.5 Hz, H-5), 2.43 (2H, t, J = 7.5 Hz, H-2), 5.49-5.63 (2H, m, H-6 and H-9), 5.97-6.05 (2H, m, H-7 and H-8), 9.77 (1H, s, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 18.0 (C-10), 21.5 (C-3), 28.8 (C-4), 32.2 (C-5), 43.7 (C-2), 127.2 (C-7), 130.8 (C-6), 131.0 (C-9), 131.5 (C-8), 202.7 (C-1); m/z (GCMS) Calculated for $C_{10}H_{17}O$ (MH^+): 153.1279 Found 153.1279; ν_{max}/cm^{-1} (thin film) 3016 (w, C=C-H), 2932 (str, C-H), 2856 (m, C-H), 1726 (str, C=O), 1439 (w, C-H deformation), 1390 (w), 989 (m)

Ethyl (2*E*,8*E*,10*E*)-2-methyldodeca-2,8,10-trienoate (240)

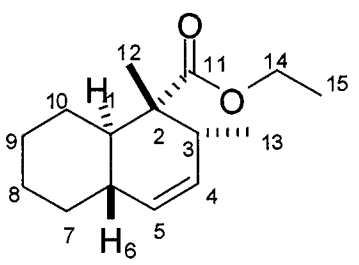


A solution of **242** (1.96 g, 12.9 mmol) in anhydrous CH_3CN (20 mL) was added dropwise over

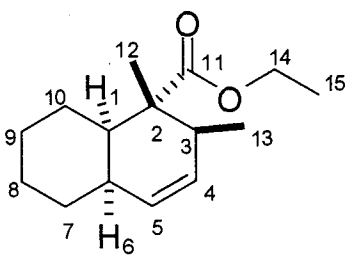
10 min to a solution of triethyl 2-phosphonopropionate (4.82 g, 19.3 mmol), LiCl (0.82 g, 19.3 mmol) and DBU (2.51 mL, 16.8 mmol) in CH_3CN (80 mL). The solution was stirred at room temperature for 16 h. The reaction was quenched with NH_4Cl (aq. sat., 50 mL) and diluted with Et_2O (100 mL). The organic layer was washed with $NaHCO_3$ (aq. sat., 100 mL) and brine (100 mL), and dried over $MgSO_4$. The solvent was removed and the crude oil was purified by column chromatography (DCM/petrol 1:4) to yield the ester **240** (2.79 g, 93%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, t, J = 7.0 Hz, H-15), 1.37-1.50 (4H, m, H-5 and H-6), 1.73 (3H, d, J = 6.5 Hz, H-12), 1.83 (3H, d, J = 1.5 Hz, H-13), 2.07 (2H, q, J = 6.5 Hz, H-7), 2.17 (2H, q, J = 7.5 Hz, H-4), 4.19 (2H, q, J = 7.0 Hz, H-14), 5.50-5.63 (2H, m, H-8 and H-11), 5.96-6.06 (2H, m, H-9 and H-10), 6.75 (1H, tq, J = 7.5 and 1.5 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.3 (C-13), 14.3 (C-15), 18.0 (C-12), 28.1 (C-6), 28.5 (C-5), 29.1 (C-4), 32.3 (C-7), 60.4 (C-14), 127.0 (C-9), 127.8 (C-2), 130.6 (C-8), 131.5 (C-11), 131.6 (C-10), 142.2 (C-3), 168.3 (C-1); m/z (GCMS) Calculated for $C_{10}H_{25}O_2$ (MH^+): 237.1855 Found 237.1856; ν_{max}/cm^{-1} (thin film) 2930 (str, C-H), 2857 (m, C-H), 1711 (str, s, C=O), 1650 (w, C=C), 1446 (w, C-H deformation), 1367 (w), 1254 (m, C-O), 988 (m)

(1*R,2*R**,4a*S**,8a*R**)-Ethyl 1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (258a)**

(1*R,2*S**,4a*R**,8a*R**)-Ethyl 1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (258b)**



endo

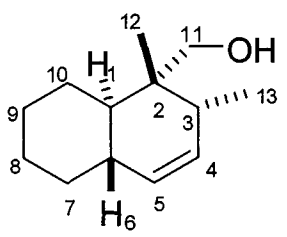


exo

Compound **241** (58.9 mg, 0.25 mmol) was dissolved in anhydrous toluene (2.5 mL) in a sealed

tube and a crystal of BHT was added. The solution was heated to 180°C for 4 days. After cooled to ambient temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM/petrol 1:3) to provide 51.1 mg (85%) of **258a** and **258b** (*endo*/*exo* 2.5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.96 and 0.89* (3H, d, J = 7.5 Hz, H-13), 1.18 and 1.16* (3H, s, H-12), 1.25 and 1.27* (3H, d, J = 7.0 Hz, H-15), 1.21-1.28 (1H, m, 1xH-10), 1.32-1.46 (2H, m, 1xH-7 and 1xH-8), 1.52-1.82 (6H, m, H-1, 1xH-7, 1xH-8, H-9 and 1xH-10), 2.09-2.14 and 2.19-2.24* (1H, m, H-6), 2.82-2.88 and 2.08-2.10* (1H, m, H-3), 4.10-4.17 (2H, m, H-14), 5.41 and 5.35* (1H, apparent d, J = 10.0 Hz, H-4), 5.52-5.56 and 5.48-5.51* (1H, m, H-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-15), 17.4 and 16.8* (C-13), 18.8 (C-12), 25.8 (C-9), 27.0 (C-8), 28.0 (C-7), 33.5 (C-10), 34.7 (C-3), 38.7 (C-1), 40.5 and 39.9* (C-6), 47.9 (C-2), 60.4 and 59.8* (C-14), 129.8 and 129.2* (C-4), 131.8 (C-5), 178.4 and 176.2* (C-11); m/z (GCMS) Calculated for $C_{15}H_{25}O_2$ (MH^+): 237.1849 Found 237.1855; ν_{max}/cm^{-1} (thin film) 3000 (w, C=C-H), 2923 (str, C-H stretch), 2852 (m, C-H), 1724 (str, s, C=O), 1447 (m, C-H deformation), 1377 (w), 1232 (m, C-O), 1128 (m), 1112 (m), 1042 (w)

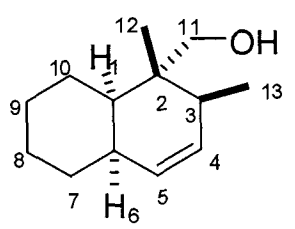
((1*R,2*R**,4a*S**,8a*R**)-Ethyl 1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-methanol (259a)**[199]



To a solution of the mixture **258a** and **258b** (53.0 mg, 0.22 mmol) in anhydrous Et_2O (1.5 mL) cooled to -78°C was added DIBAL-H (1.0 M in Et_2O, 0.67 ml, 0.68 mmol). The solution was allowed to stir for 1 h at -78°C, after which it was warmed to 0°C. After stirring at 0°C for 2 h, the reaction was quenched with a solution of sodium potassium tartrate (aq. sat., 2 mL) and was

stirred at room temperature vigorously for 3 h. The mixture was extracted with Et_2O (3x10 mL), and the combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the resultant crude oil was purified by chromatography (Et_2O/petrol 1: 4) to give the title compounds as a colourless solid. Mp 107.0-108.0°C; *endo*-isomer **259a** (22.9 mg, 53.0%) ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, s, H-12), 1.00 (3H, d, J = 7.0 Hz, H-13), 1.03-1.10 (2H, m, 1xH-7 and 1xH-10), 1.16-1.33 (3H, m, H-1, 1xH-8 and 1xH-9), 1.50-1.53 (1H, m, 1xH-10), 1.71-1.81 (4H, m, H-6, 1xH-7, 1xH-8 and 1xH-9), 1.92-1.97 (1H, m, H-3), 3.49 (1H, d, J = 10.5 Hz, H-11), 3.53 (1H, d, J = 10.5 Hz, H-11), 5.34 (1H, d, J = 10.0 Hz, H-5), 5.52-5.55 (1H, m, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 16.8 (C-13), 17.0 (C-12), 25.5 (C-10), 26.6 (C-9), 26.9 (C-8), 33.4 (C-7), 38.3 (C-2), 38.5 (C-3), 38.5 (C-6), 40.5 (C-1), 68.7 (C-11), 130.0 (C-5), 131.4 (C-4); m/z (GCMS) Calculated for $C_{13}H_{23}O$ (MH^+): 195.1749 Found 195.1746; ν_{max}/cm^{-1} (thin film) 3270 (str, w, OH), 3000 (w, C=C-H), 2920 (str, C-H stretch), 2851 (m, C-H), 1445 (m,C-H deformation), 1347 (w), 1221 (w), 1095 (w), 1047 (m), 1024 (str, C-O)

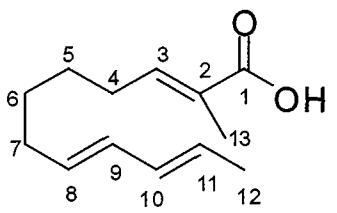
((1*R,2*S**,4a*R**,8a*R**)-Ethyl 1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-methanol (259b)**[199]



exo-Isomer **259b** was obtained as a colourless oil (10.1 mg, 23%) from the reduction. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.01 (3H, s, H-12), 1.02 (3H, d, J = 7.0 Hz, H-13), 1.09-1.26 (2H, m, 1xH-7 and 1xH-10), 1.32-1.62 (6H, m, H-1, H-8, H-9 and 1xH-10), 1.67-1.75 (3H, m, H-3, H-6 and 1xH-7), 2.48 (1H, m, OH), 3.22 (1H, d, J = 10.5 Hz, H-11), 3.54 (1H, d, J = 10.5 Hz, H-11),

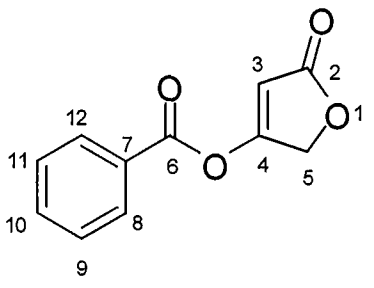
5.34-5.39 (1H, m, H-5), 5.55-5.59 (1H, m, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 17.3 (C-13), 19.4 (C-12), 222.6 (C-9), 23.7 (C-8), 27.2 (C-7), 31.8 (C-10), 32.4 (C-6), 34.7 (C-3), 39.5 (C-2), 39.7 (C-1), 72.1 (C-11), 128.8 (C-4), 132.9 (C-5); m/z (GCMS) Calculated for $C_{13}H_{23}O$ (MH^+): 195.1749 Found 195.1747; ν_{max}/cm^{-1} (thin film) 3270 (str, w, OH), 3000 (w, C=C-H), 2925 (str, C-H stretch), 2856 (m, C-H), 1446 (m,C-H deformation), 1347 (w), 1221 (w), 1095 (w), 1047 (m), 1024 (str, C-O)

(2*E*,8*E*,10*E*)-2-Methyldodeca-2,8,10-trienoic acid (260)



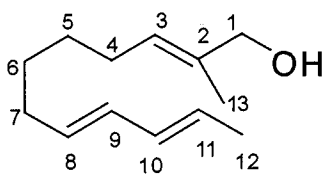
The ester **241** (114.9 mg, 0.49 mmol) was added to a solution of THF (1.5 mL) and H_2O (0.5 mL). The mixture was cooled to 0°C and LiOH (61.4 mg, 1.46 mmol) was added followed by stirring at room temperature for 2 days upon which TLC showed disappearance of the ester. The solution was extracted with EtOAc, dried over $MgSO_4$ and concentrated to give the acid residue **260** as a colourless oil (95.5 mg, 90.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.36-1.51 (4H, m, H-5 and H-6), 1.74 (3H, d, J = 6.5 Hz, H-12), 1.84 (3H, s, H-13), 2.08 (2H, q, J = 6.5 Hz, H-7), 2.21 (2H, q, J = 7.0 Hz, H-4), 5.50-5.63 (2H, m, H-8 and H-11), 5.94-6.06 (2H, m, H-9 and H-10), 6.91 (1H, t, J = 7.0 Hz, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 12.0 (C-13), 18.0 (C-12), 27.9 (C-6), 28.7 (C-5), 29.0 (C-4), 32.3 (C-7), 126.9 (C-9), 127.1 (C-2), 130.6 (C-8), 131.4 (C-11), 131.5 (C-10), 145.2 (C-3), 173.0 (C-1); m/z (ESIMS) Calculated for $C_{13}H_{21}O_2$ (MH^+): 205.1536 Found 205.1541; ν_{max}/cm^{-1} (thin film) 3450 (br, OH), 2932 (m, C-H), 2861 (w, C-H), 1687 (str, s, C=O), 1644 (m, C=C), 1417 (w,C-H deformation), 1375 (w), 1259 (m), 1139 (m), 1085 (m), 971 (m, C=C-H)

5-Oxo-2,5-dihydrofuran-3-yl benzoate (272)



To a stirred solution of tetronic acid **119a** (160.0 mg, 1.60 mmol) in anhydrous DCM (10 mL) at 0°C was added triethylamine (178.1 mg, 245.3μL, 1.76 mmol), 4-pyrrolidinopyridine (78.3 mg, 0.53 mmol) followed by benzoyl chloride **271** (247.2 mg, 204.2 μL, 1.76 mmol). After 10 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 15 h. The mixture was washed with NH_4Cl (aq. sat., 10 mL). The aqueous layer was extracted with DCM (2x20 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (EtOAc/petrol 1:5) to give **272** as a white solid (261.1 g, 81%). Mp105.0-106.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.08 (2H, s, H-5), 6.18 (1H, s, H-3), 7.55 (2H, q, J = 7.5 Hz, H-9 and H-11), 7.72 (1H, q, J = 7.5 Hz, H-10), 8.13 (2H, d, J = 7.5 Hz, H-8 and H-12); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 68.7 (C-5), 101.2 (C-3), 127.0 (C-7), 129.0 (C-9 and 11), 130.6 (C-8 and 12), 135.1 (C-10), 161.6 (C-4), 166.8 (C-6), 169.1 (C-2); m/z (ESIMS) Calculated for $C_{11}H_9O_4$ (MH^+): 205.0495 Found 205.0499; ν_{max}/cm^{-1} (thin film) 3148 (w, C=C-H), 1785 (m, C=O), 1750 (str, s, C=O), 1689 (w, C=C), 1632 (str, C=C), 1598 (C=C), 1452 (m, C-H deformation), 1371 (w), 1234 (str, C-O), 1186 (m),1152 (m)

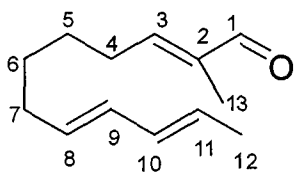
(2*E*,8*E*,10*E*)-2-Methyldodeca-2,8,10-trien-1-ol (257)



To a solution of the ester **241** (2.15 g, 9.11 mmol) in anhydrous Et_2O (40 mL) at -78°C was

added DIBAL-H (27.4 ml, 27.4 mmol, 1.0 M in Et_2O). The solution was allowed to stir for 1 h at -78°C, after which it was warmed to 0°C. After stirring at 0°C for 2 h, the reaction was quenched with a saturated solution of sodium potassium tartrate (40 mL) and was stirred at room temperature vigorously for 3 h. The mixture was extracted with Et_2O (3x40 mL), and the combined organic extracts were washed with brine (40 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the resultant crude oil was purified by chromatography (Et_2O/petrol 1: 4) to give the title compound **257** as a colourless oil in 95% yield (1.66 g). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.33-1.44 (4H, m, H-5 and H-6), 1.67 (3H, s, H-13), 1.73 (3H, d, J = 6.5 Hz, H-12), 2.01-2.09 (4H, m, H-4 and H-7), 4.01 (2H, s, H-1), 5.41 (1H, t, J = 7.5 Hz, H-3), 5.51-5.62 (2H, m, H-8 and H-11), 5.96-6.06 (2H, m, H-9 and H-10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.7 (C-13), 18.0 (C-12), 27.4 (C-4), 29.0 (C-5), 29.1 (C-6), 32.4 (C-7), 69.1 (C-1), 126.4 (C-9), 126.8 (C-3), 130.4 (C-11), 131.6 (C-10), 131.9 (C-8), 134.7 (C-2); m/z (GCMS) Calculated for $C_{13}H_{23}O$ (MH^+): 195.1749 Found 195.1743; ν_{max}/cm^{-1} (thin film) 3332 (str, br, -OH), 3015 (m, C=C-H), 2926 (str, C-H), 2855 (m, C-H), 1693(w, C=C), 1438 (m, C-H deformation), 1377 (w), 1306 (w, C-O), 1218 (w), 1070 (m), 986 (m)

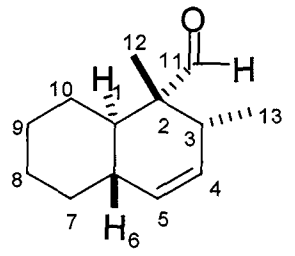
(2*E*,8*E*,10*E*)-2-Methyldodeca-2,8,10-trienal (240)[199]



To a solution of the alcohol **257** (98.9 mg, 5.15 mmol, 1 equiv) was added NMO (93.3 mg, 7.73 mmol, 1.5 equiv) and powdered 4Å molecular sieves (2.58 g, 500 mg/mmol). After stirring for 20 min, Solid TPAP (90.6 mg, 0.26 mmol, 5 mol %) was added in one portion to the mixture. The reaction was worked up after an additional 1 h by loading the black coloured mixture onto a silica column and eluting with DCM. The solution was concentrated and the residue was

purified by silica gel chromatography (Et_2O/petrol 1:25) to afford the title compound **240** as a yellow oil in 89% yield (87.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41-1.56 (4H, m, H-5 and H-6), 1.74 (3H, d, J = 6.5 Hz, H-12), 1.75 (3H, s, H-13), 2.10 (2H, q, J = 7.0 Hz, H-7), 2.36 (2H, q, J = 7.0 Hz, H-4), 5.50-5.64 (2H, m, H-8 and H-11), 5.97-6.06 (2H, m, H-9 and H-10), 6.49 (1H, t, J = 7.5 Hz, H-3), 9.40 (1H, s, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 9.2 (C-13), 18.0 (C-12), 27.8 (C-6), 28.8 (C-5), 29.0 (C-4), 32.2 (C-7), 127.2 (C-9), 130.8 (C-11), 131.2 (C-10), 131.5 (C-8), 139.4 (C-2), 154.8 (C-3), 195.4 (C-1); m/z (GCMS) Calculated for $C_{13}H_{21}O$ (MH^+): 193.1592 Found 193.1588; ν_{max}/cm^{-1} (thin film) 3016 (w, C=C-H), 2928 (str, C-H), 2856 (m, C-H), 1689 (str, C=O), 1645 (w, C=C), 1438 (m, C-H deformation), 238 (w), 988 (m)

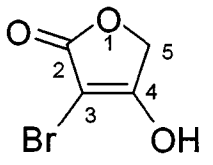
(1*R,2*R**,4a*S**,8a*R**)-1,2-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (132)**[199]



To a solution of **240** (544.3 mg, 2.86 mmol) in anhydrous DCM (12.0 mL) was added $ZnCl_2$ (1.0 M in diethyl ether, 2.98 mL, 2.98 mmol). The mixture was stirred at room temperature for 4 days, diluted by NH_4Cl (aq. sat., 10 mL), and extracted with DCM (2x20 mL). Combined organic layers were dried over sodium sulphate, concentrated, and chromatographed on silica (DCM/petrol 1:3) to give **132** as a yellowish oil (360.4 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.03 (3H, s, H-12), 1.06 (3H, d, J = 7.0 Hz, H-13), 1.11-1.21 (2H, m, 1xH-7 and 1xH-10), 1.30-1.50 (3H, m, 1xH-7, 1xH-8 and 1xH-9), 1.71-1.86 (5H, m, H-1, H-6, 1xH-8, 1xH-9 and 1xH-10), 2.02-2.05 (1H, m, H-3), 5.40-5.43 (1H, m, 1xH-5), 5.47-5.52 (1H, m, H-4), 9.62 (1H, s, H-11); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.4 (C-12), 17.3 (C-13), 26.9 (C-9), 26.9 (C-8), 27.2

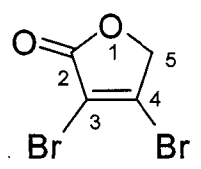
(C-7), 32.5 (C-10), 37.8 (C-6), 38.7 (C-1), 39.7 (C-3), 49.7 (C-2), 130.0 (C-4), 130.2 (C-5), 209.2 (C-11); m/z (GCMS) Calculated for $C_{13}H_{24}NO$ (MNH_4^+): 210.1858 Found 210.1858; ν_{max}/cm^{-1} (thin film) 3012 (w, C=C-H), 2925 (str, C-H stretch), 2855 (m, C-H stretch), 1725 (str, s, C=O), 1654 (w, C=C), 1448 (m, C-H deformation), 1374 (w), 1041 (w)

2-Bromo-4-hydroxyfuran-2(5*H*)-one (277)[211]



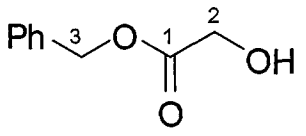
Prepared by application of literature method[211] on tetronic acid (500 mg, 5 mmol) and *N*-bromosuccinimide (885 mg, 5 mmol) to give **277** (889 mg, quantitative) as light yello solid. Mp 181-183°C; ^{1}H NMR (200 MHz, D6-DMSO) δ_H 4.78 (2H, s, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 66.3 (C-5), 93.8 (C-3), 173.1 (C-2), 175.2 (C-4); m/z (ESIMS) Calculated for $C_4H_4{}^{79}BrO_3$ (MH^+): 178.9338 Found 178.9330; ν_{max}/cm^{-1} (thin film) 2921 (str, C-H stretch), 2610 (str, br, OH), 1716 (str, s, C=O), 1589 (str, br, C=C), 1396 (w), 1360 (m, C-O), 1056 (str)

3,4-Dibromo-2(5*H*)-furanone (284)[215]



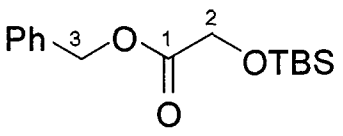
Prepared by application of literature method[215] on mucobromic acid (500 mg, 1.94 mmol), $NaBH_4$ (1.10 g, 29.1 mmol) and sulphuric acid (conc., 0.19 g, 1.94 mmol) to give **284** (352.3 mg, 75%) as white needles. Mp 88-90°C, lit. mp 90-91°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 4.89 (2H, s, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 74.5 (C-5), 114.7 (C-3), 143.9 (C-2), 167.0 (C-4); m/z (ESIMS) Calculated for $C_4H_3{}^{79}Br_2O_2$ (MH^+): 240.8494 Found 240.8480; ν_{max}/cm^{-1} (thin film) 1749 (str, s, C=O), 1605 (str, C=C), 1429 (w, C-H defromation), 1338 (m, C-O), 1215 (m), 1021 (str)

Benzyl 2-hydroxyacetate[216]



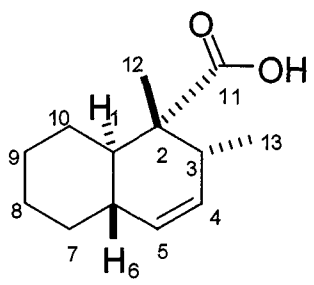
Prepared by the literature method[216] on glycolic acid (1.00 g, 13.2 mmol), benzyl bromide (1.74 mL, 14.5 mmol) and triethylamine (2.13 mL, 14.5 mmol) to afford 1.98 g (93%) of crude benzyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.21 (2H, s, H-2), 5.25 (2H, s, H-3), 7.38 (5H, s, H-Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 60.7 (C-2), 67.3 (C-3), 128.5 (C-Ph), 128.7 (C-Ph), 128.7 (C-Ph), 135.0 (C-Ph), 173.2 (C-1); m/z (GCMS) Calculated for $C_9H_{14}NO_3$ (MNH_4^+): 184.0974 Found 184.0979; ν_{max}/cm^{-1} (thin film) 3439 (str, br, O-H), 3035 (w, aromatic C-H), 2956 (w, C-H stretch), 1746 (str, s, C=O), 1587 (w, C=C), 1456 (w, C-H defromation), 1364 (w, C-O), 1215 (str, TBS), 1097(str)

Benzyl 2-(*tert*-butyldimethylsilyloxy)acetate[216]



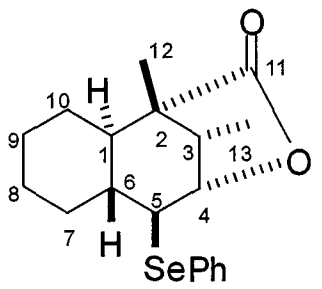
Prepared by the literature method[216] on crude benzyl ester (1.98 g, 12.3 mmol), imidazole (1.84 g, 27.1 mmol) and *tert*-butyldimethylchlorosilane (2.15 g, 14.7 mmol) to afford the silyl ether (3.11 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.10 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $C(CH_3)_3$), 4.30 (2H, s, H-2), 5.19 (2H, s, H-3), 7.37 (5H, s, H-Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C -5.5 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 61.8 (C-2), 66.5 (C-3), 128.4 (C-Ph), 128.4 (C-Ph), 128.6 (C-Ph), 135.6 (C-Ph), 171.6 (C-1); m/z (GCMS) Calculated for $C_{15}H_{25}O_3Si$ (MH^+): 281.1573 Found 281.1564; ν_{max}/cm^{-1} (thin film) 2930 (str, C-H stretch), 2858 (m, C-H stretch), 1764 (str, s, C=O), 1463 (w, C-H defromation), 1363 (w, C-O), 1256 (m, TBS), 1144 (str), 839 (str, aromatic C-H), 780 (m, aromatic C-H), 740 (w, aromatic C-H)

(1*S,2*R**,4a*S**,8a*R**)-1,2-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid (262)**[22]



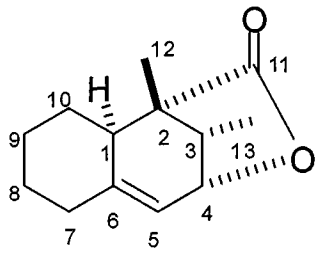
To a solution of the aldehyde **132** (106.4 mg, 0.55 mmol) in *tert*-butanol (6.4 mL) was added 2-methyl-2-butene (3.7 Ml, 34.9 mmol) followed by a solution of sodium chlorite (388.4 mg, 3.44 mmol) and potassium dihydrogen phosphate (468.2 mg, 3.44 mmol) in water (6.4 mL). The mixture was stirred at 25°C for 3 h. The solution was then diluted with water (10 mL) and extracted with diethyl ether (3x15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. Column chromatography on silica gel using diethyl ether/petrol ether (1:6) afforded the desired acid **262** (77.6 mg) as a white solid in 67 % yield. Mp 95.0-96.0°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.98 (3H, d, J = 7.0 Hz, H-13), 1.01-1.09 (1H, m, 1xH-10), 1.09-1.17 (1H, m, 1xH-7), 1.19 (3H, s, H-12), 1.26-1.44 (2H, m, 1xH-8 and 1xH-9), 1.58-1.62 (1H, m, H-1), 1.67-1.72 (1H, m, H-6), 1.76-1.83 (4H, m, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 2.09-2.14 (1H, m, H-3), 5.36-5.38 (1H, m, H-5), 5.49-5.52 (1H, m, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 17.2 (C-12), 18.8 (C-13), 26.9 (C-9), 26.9 (C-8), 27.9 (C-10), 33.4 (C-7), 38.6 (C-6), 39.6 (C-1), 40.3 (C-3), 48.0 (C-2), 129.4 (C-4), 129.8 (C-5), 182.4 (C-11); m/z (GCMS) Calculated for $C_{13}H_{21}O_2$ (MH^+): 209.1542 Found 209.1538; ν_{max}/cm^{-1} (thin film) 3420 (br, OH), 2941 (str, C-H stretch), 2855 (m, C-H stretch), 1687 (str, s, C=O), 1660 (w, C=C), 1448 (w, C-H deformation), 1374 (w), 1281 (m), 1032 (m)

(1*S,2*R**,7*R**,8*S**,9*S**,12*S**)-1,12-Dimethyl-7-(phenylselanyl)-10-oxatricyclo[7.2.1.$0^{2,7}$]-dodecan-11-one (273)**[22]



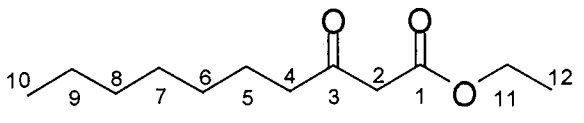
Triethylamine (113.0 μL, 0.81 mmol) was added to a solution of acid **262** (168.4 mg, 0.81 mmol) in anhydrous dichloromethane (8.0 mL) at 25°C, and the mixture was stirred for 30 min, cooled to -78°C, and treated slowly with PhSeCl (174.2 mg, 0.89 mmol) in DCM (2.0 mL) under nitrogen. After stirring at room temperature for 10 h, the solution was concentrated. The residue was purified by column chromatography (Et_2O/petrol 1:15) to give the desired product **273** as a light yellow oil (214.5 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.94 (3H, d, J = 7.0 Hz, H-13), 0.97-1.06 (1H, m, 1xH-10), 1.00 (3H, s, H-12), 1.17-1.39 (4H, m, H-6, 1xH-7, 1xH-8 and 1xH-9), 1.56 (1H, dt, J = 11.0 and 2.5 Hz, H-1), 1.78-1.92 (3H, m, 1xH-8, 1xH-9 and 1xH-10), 2.29-2.36 (2H, m, H-3 and 1xH-7), 3.12 (1H, apparent d, J = 11.0 Hz, H-5), 4.43 (1H, apparent s, H-4), 7.31-7.33 (3H, m, H-Ph), 7.53-7.55 (2H, m, H-Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 12.4 (C-12), 14.2 (C-13), 26.3 (C-9), 27.2 (C-8), 29.6 (C-10), 32.7 (C-7), 35.5 (C-3), 42.9 (C-6), 45.8 (C-2), 46.0 (C-1), 46.8 (C-5), 86.7 (C-4), 127.8 (Ph-C), 128.0 (Ph-C), 129.4 (Ph-C), 134.3 (Ph-C), 182.6 (C-11); m/z (GCMS) Calculated for $C_{19}H_{25}O_2{}^{78}Se$ (MH^+): 365.1020 Found 365.1021; ν_{max}/cm^{-1} (thin film) 2928 (str, C-H stretch), 2855 (m, C-H stretch), 1779 (str, s, C=O), 1579 (w, C=C), 1439 (w, C-H deformation), 1347 (w, C-O), 1195 (w), 1123 (m), 1073 (w), 950 (m, aromatic C-H), 851 (w, aromatic C-H), 740 (m, aromatic C-H)

(1*S,2*R**,9*S**,12*S**)-1,12-Dimethyl-10-oxatricyclo[7.2.1.0^{2,7}]dodec-7-en-11-one (274)**[22]



The selenolactone **273** (244.5 mg, 0.67 mmol) in THF (7 mL) was treated with H_2O_2 (aq. 35% w/w, 357.0 µL, 4.04 mmol) and one drop of pyridine initially at 0°C for 1 h, and subsequently at room temperature for another 2 h under nitrogen. The solution was diluted with H_2O (10 mL) and extracted with dichloromethane (3x20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (Et_2O:petrol1:10) to give colourless oil **274** (124.9 mg, 90.0%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.05 (3H, d, J = 7.0 Hz, H-13), 1.09-1.27 (2H, m, 1xH-8 and 1xH-10), 1.12 (3H, s, H-12), 1.34-1.43 (1H, m, 1xH-9), 1.80-1.98 (4H, m, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 2.13 (1H, dd, J = 12.5 and 4.0 Hz, H-1), 2.20-2.24 (1H, m, 1xH-7), 2.36 (1H, apparent q, J = 7.0 Hz, H-3), 4.24 (1H, apparent d, J = 5.5 Hz, H-4), 5.91 (1H, d, J = 5.5 Hz, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 13.8 (C-12), 15.3 (C-13), 25.9 (C-9), 27.9 (C-8), 28.2 (C-10), 34.7 (C-7), 40.9 (C-3), 46.5 (C-1), 48.6 (C-2), 78.2 (C-4), 121.1 (C-5), 147.1 (C-6), 182.0 (C-11); m/z (GCMS) Calculated for $C_{13}H_{19}O_2$ (MH^+): 207.1385 Found 207.1382; ν_{max}/cm^{-1} (thin film) 2933 (str, C-H stretch), 2856 (m, C-H stretch), 1767 (str, s, C=O), 1446 (w, C-H defromation), 1336 (w, C-O), 1206 (m), 1119 (w), 1073 (w), 941 (m), 927 (m)

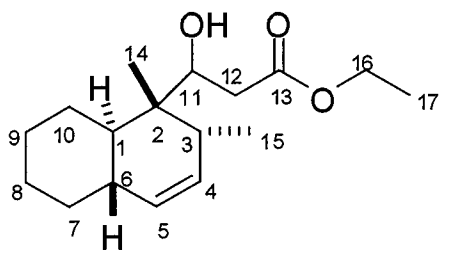
Ethyl 3-oxodecanoate (302)[253]



A mixture of octanal (250.1 mg, 1.95 mmol), ethyl diazoacetate (267.4 mg, 2.34 mmol) and $NbCl_5$ (26.4 mg, 0.10 mmol) in DCM (20 mL) was stirred for 4 h at room temperature. After

completion of the reaction, as indicated by TLC, the reaction mixture was washed with brine (20 mL), and extracted with DCM (3x20 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified on silica gel (EtOAc/petrol 1:9) to afford **302** as a colourless oil (337.5 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (3H, t, J = 7.0 Hz, H-12), 0.85-1.32 (11H, m, H-6, H-7, H-8, H-9 and H-10), 1.59 (1H, qui, J = 7.0 Hz, H-5), 2.53 (2H, t, J = 7.0 Hz, H-4), 3.43 (2H, s, H-2), 4.19 (2H, q, J = 7.0 Hz, H-11), 5.30 (1H, d, J = 10.0 Hz, H-5), 5.48-5.52 (1H, m, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.0 (C-10), 14.2 (C-12), 22.5 (C-9), 25.4 (C-5), 28.9 (C-6), 30.1 (C-7), 31.7 (C-8), 42.0 (C-4), 42.3 (C-3), 59.9 (C-2), 61.3 (C-11), 167.5.0 (C-1), 203.1 (C-3); m/z (GCMS) Calculated for $C_{12}H_{23}O_3$ (MH^+): 215.1642 Found 215.1640; ν_{max}/cm^{-1} (thin film) 2928 (str, C-H stretch), 2858 (m), 1740 (str, C=O), 1650 (w, C=C), 1447 (m, C-H deformation), 1310 (m, C-O), 1255 (m), 1156 (m), 1027 (m)

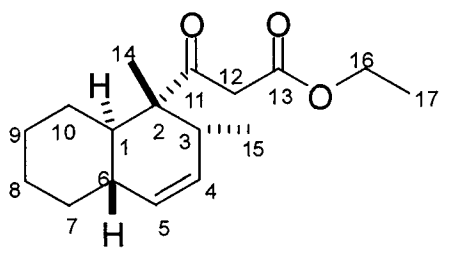
Ethyl 3-((1*R,2*R**,4a*S**,8a*R**)-1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-hydroxyl propanoate (303)**



n-BuLi (1.31 M in hexane, 4.24 mL, 5.56 mmol) was added to a stirred solution of diisopropylamine (613.5 mg, 852.1 µL, 6.06 mmol) in anhydrous THF (40 mL) at -78°C and the solution was stirred for 30 min. A solution of ethyl acetate (544.0 µL, 5.56 mmol) in THF (10.0 mL) was added slowly and the solution was stirred for another 30 min. A solution of aldehyde **132** (970.2 mg, 5.05 mmol) in THF (10.0 mL) was added dropwise and the mixture was stirred for 30 min. NH_4Cl (aq. sat., 40 mL) was added, and the resulting solution was extracted with ether (3x40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The

residue was purified by flash column chromatography on silica gel (Et_2O/petrol 1:9) to give the ester **303** as a colourless oil (1.19 g, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.79 (3H, s, H-14), 0.98-1.09 (1H, m, 1xH-10), 1.08-1.19 (1H, m, 1xH-7), 1.12 (3H, d, J = 7.0 Hz, H-15), 1.29 (3H, t, J = 7.0 Hz, H-17), 1.24-1.39 (2H, m, 1xH-8 and 1xH-9), 1.57-1.61 (1H, m, H-1), 1.71-1.89 (6H, m, H-3, H-6, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 2.56-2.68 (2H, m, H-12), 4.04 (1H, dd, J = 10.0 and 3.0 Hz, H-11), 4.19 (2H, q, J = 7.0 Hz, H-16), 5.30 (1H, d, J = 10.0 Hz, H-5), 5.48-5.52 (1H, m, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 14.2 (C-17), 18.3 (C-15), 18.8 (C-14), 25.9 (C-9), 26.8 (C-8), 27.0 (C-10), 33.6 (C-7), 36.3 (C-12), 38.6 (C-3), 39.1 (C-1), 39.8 (C-6), 40.3 (C-2), 60.8 (C-16), 72.6 (C-11), 129.4 (C-5), 132.0 (C-4), 174.1 (C-13); m/z (GCMS) Calculated for $C_{17}H_{29}O_3$ (MH^+): 281.2117 Found 281.2112; ν_{max}/cm^{-1} (thin film) 3527 (str, wide, -OH), 2923 (str, C-H stretch), 2853 (m, C-H stretch), 1716 (str, C=O), 1657 (w, C=C), 1447 (m, C-H deformation), 1375 (m), 1310 (m, C-O), 1184 (m), 1027 (m)

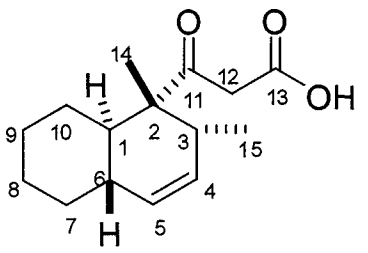
Ethyl 3-((1*R,2*R**,4a*S**,8a*R**)-1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxopropanoate (293)**



To a solution of IBX (242.0 mg, 0.86 mol) in DMSO (10 mL) at room temperature was added the solution of alcohol **303** (120.8 mg, 0.43 mol) in THF (5 mL) dropwise *via* a canular. After stirring at room temperature for 2 h, the reaction was quenched by the addition of H_2O (15 mL). The resulting suspension was filtered through a course fritted funnel, and extracted with diethyl ether (3x30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography (Et_2O/petrol 1:15) provided aldehyde **293** (88.5

mg, 75%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.85 (3H, d, J = 7.0 Hz, H-15), 0.86-0.92 (1H, m, 1xH-10), 1.13-1.20 (1H, m, 1xH-7), 1.13-1.23 (1H, m, 1xH-9), 1.20 (3H, s, H-14), 1.28 (3H, t, J = 7.0 Hz, H-17), 1.25-1.43 (2H, m, 1xH-8 and 1xH-9), 1.65-1.81 (6H, m, H-1, H-6, 1xH-7, 1xH-8 and 1xH-10), 2.05-2.12 (1H, m, H-3), 3.48 (2H, s, H-12), 4.16-4.25 (2H, m, H-16), 5.37 (1H, d, J = 10.0 Hz, H-5), 5.51 (1H, dd, J = 10.0 and 5.0 Hz, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.1 (C-17), 17.3 (C-14), 18.5 (C-15), 26.9 (C-9), 27.0 (C-8), 27.4 (C-10), 33.5 (C-7), 38.9 (C-1), 39.0 (C-6), 39.6 (C-3), 46.5 (C-12), 53.0 (C-2), 61.2 (C-16), 129.2 (C-4), 130.0 (C-5), 167.9 (C-13), 206.4 (C-11); m/z (ESIMS) Calculated for $C_{17}H_{26}NaO_3$ (MNa^+): 301.1774 Found 301.1775; ν_{max}/cm^{-1} (thin film) 2924 (str, C-H stretch), 2854 (m, C-H stretch), 1747 (str, s, C=O), 1706 (str, s, C=O), 1643 (w, C=C), 1614 (m, C=C), 1448 (m, C-H deformation), 1379 (w), 1308 (m, C-O), 1224 (m, C-O), 1152 (w), 1035 (w), 1015 (w)

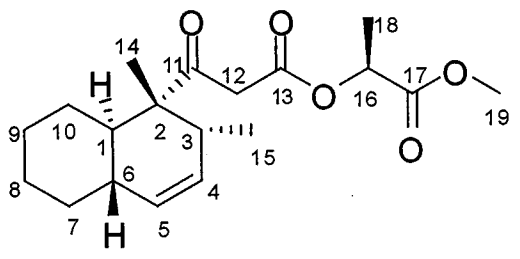
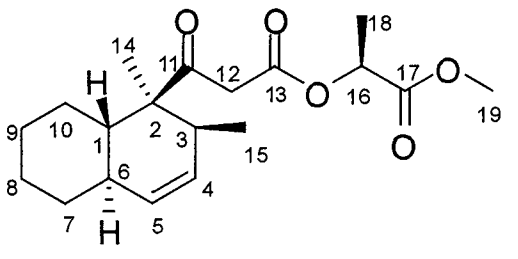
3-((1*R,2*R**,4a*S**,8a*R**)-1,2-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxopropanoic acid (294)**



To a solution of β-keto ester **293** (300.1 mg, 1.08 mmol) in THF (4.0 mL) and H_2O (1.1 mL) at to 0°C was added LiOH (407.9 mg, 9.71 mmol). The mixture was stirred at room temperature for 2 days upon which TLC showed disappearance of the ester. The solution was neutralised with hydrochloric acid (aq. 1N, 10 mL) and extracted with EtOAc (3x20 mL), dried over $MgSO_4$ and concentrated to give the acid residue **294** as a colourless oil (216.4 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.83 (3H, d, J = 7.0 Hz, H-15), 0.85-0.92 (1H, m, 1xH-10), 1.13-1.45 (4H, m, 1xH-7, 1xH-8 and H-9), 1.22 (3H, s, H-14), 1.65-1.83 (5H, m, H-1, H-6, 1xH-7, 1xH-8 and 1xH-10), 2.09-2.12 (1H, m, H-3), 3.51 (1H, d, J = 18.0 Hz, H-12), 3.60 (1H, d, J = 18.0 Hz,

H-12), 5.39 (1H, d, J = 10.0 Hz, H-5), 5.51 (1H, dd, J = 10.0 and 5.0 Hz, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 17.1 (C-14), 18.6 (C-15), 26.9 (C-9), 26.9 (C-8), 27.5 (C-10), 33.4 (C-7), 38.8 (C-1), 38.9 (C-6), 39.6 (C-3), 44.3 (C-12), 53.3 (C-2), 128.8 (C-4), 130.1 (C-5), 186.2 (C-13), 212.4 (C-11); m/z (ESIMS) Calculated for $C_{15}H_{21}O_3$ (M-H): 249.1485 Found 249.1483; ν_{max}/cm^{-1} (thin film) 3010 (w, C=C-H), 2969 (br, OH), 2921 (str, C-H stretch), 2852 (m, C-H stretch), 1703 (str, s, C=O), 1658 (w, C=C), 1447 (m, C-H deformation), 1352 (m), 1125 (w)

(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1*R,2*R**,4a*S**,8a*R**)-1,2-dimethyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl)-3-oxopropanoate (295)**

Method 1:

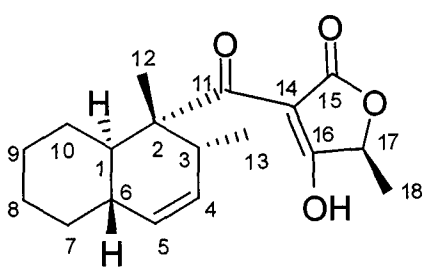
To a solution of methyl (*S*)-(-)-lactate **304** (697.1 mg, 6.70 mmol), β-keto acid **294** (836.9 mg, 3.35 mmol) and DMAP (135.0 mg, 1.10 mmol) in anhydrous DCM (30 mL) under N_2 was added DCC (759.3 mg, 3.68 mmol). The reaction was stirred for 12 h before the precipitate formed was removed by filtration, and the filtrate was concentrated in vacuo. Purification of the crude product by silica gel chromatography (Et_2O/petrol 1:10) yielded the desired β-keto ester **295** (726.3 mg, 65%) as a colourless oil.

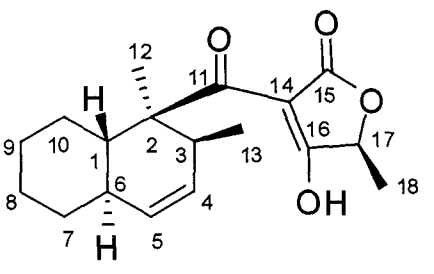
Method 2:

The β-keto ester **294** (2.67 g, 9.61 mmol), methyl (*S*)-(-)-lactate **304** (1.00 g, 9.61 mmol), and 3-nitrobenzeneboronic acid (41.11 mg, 2.5 mmol%) in toluene (100 mL) was heated at reflux for 1 day with the removal of toluene-ethanol azeotrope by distillation. The process of the reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated and the

residue was chromatographed on silica gel (Et_2O/petrol 1:10) to afford the pure product **295** (2.58 g, 82%) as a colourless oil. $[\alpha]_D^{20.4}$ = -10.0 (3.5 mg/mL, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.85 (3H, d, J = 7.0 Hz, H-15), 0.87-0.91 (1H, m, 1xH-10), 1.10-1.18 (1H, m, 1xH-7), 1.21 and 1.20* (3H, s, H-14), 1.26-1.41 (2H, m, 1xH-8 and 1xH-9), 1.52 and 1.49* (3H, d, J = 7.0 Hz, H-18), 1.65-1.81 (6H, m, H-1, H-6, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 2.08-2.12 (1H, m, H-3), 3.52-3.64 (2H, m, H-12), 3.76 (3H, s, H-19), 5.19 (1H, q, J = 7.0 Hz, H-16), 5.37 (1H, apparent d, J = 10.0 Hz, H-5), 5.50-5.53 (1H, m, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 16.9 and 17.0* (C-18), 17.2 and 17.3* (C-14), 18.5 (C-15), 26.9 (C-9), 27.0 (C-8), 27.4 (C-10), 33.5 (C-7), 38.9 (C-1), 39.0 (C-6), 39.5 (C-3), 46.0 and 46.1* (C-12), 52.4 (C-19), 53.1 (C-2), 69.1 and 69.2* (C-16), 129.1 (C-4), 130.0 (C-5), 167.1 (C-17), 170.9 (C-13), 205.9 and 205.7* (C-11); m/z (ESIMS) Calculated for $C_{19}H_{28}NaO_5$ (MNa^+): 359.1829 Found 359.1831; ν_{max}/cm^{-1} (thin film) 2924 (str, C-H stretch), 2853 (m, C-H stretch), 1751 (str, s, C=O), 1707 (m, s, C=O), 1656 (w, C=O), 1609 (w, C=C), 1450 (m, C-H deformation), 1380 (w), 1301 (m, C-O), 1215 (m, C-O), 1133 (w), 1100 (w)

(*S*)-3-((1*R,2*R**,4a*S**,8a*R**)-1,2-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-4-hydroxyl-5-methylfuran-2(5*H*)-one (296)**

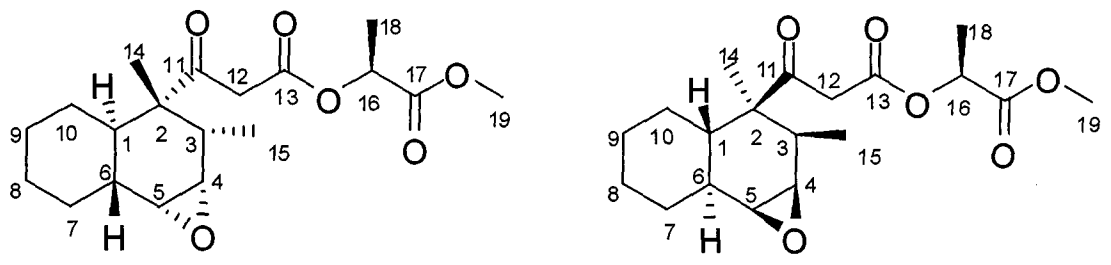




Tetrabutylammonium fluoride (1M in THF, 1.22 mL, 1.22 mmol) was added to the β-keto ester **295** (136.3 mg, 0.41 mmol), and the solution was stirred for 5 days. The reaction mixture was partition between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was acidified with HCl (1N, 1.5 mL), and extracted with ethyl acetate (3x20 mL). The combined organic layer was

washed with brine (40 mL), and dried over $MgSO_4$. After concentration, the residue was purified on silica gel (EtOAc) to afford the pure product **296** (163.2 mg, 78%) as a white solid. Decomp. >250°C; $[\alpha]_D^{20.4}$ = -33.2 (3.7 mg/mL, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ_H 0.80 (3H, d, J = 7.0 Hz, H-13), 0.80-0.92 (1H, m, 1xH-7), 1.10-1.16 (1H, m, 1xH-10), 1.31-1.40 (2H,m, 1xH-8 and 1xH-9), 1.38 (3H, s, H-12), 1.39 (3H, d, J = 6.5 Hz, H-18), 1.67-1.81 (5H, m, H-1, H-6, 1xH-8, 1xH-9 and 1xH-10), 1.87-1.93 (1H, m, 1xH-7), 3.30 (1H, m, H-3), 3.38 (1H, q, J = 6.5 Hz, H-17), 5.30 (1H, apparent d, J = 9.5 Hz, H-5), 5.52 (1H, dd, J = 9.5 and 5.0 Hz, H-4); ^{13}C NMR (125.8 MHz, CD_3OD) δ_C 15.1 (C-12), 18.0 (C-18), 19.8 (C-13), 28.4 (C-8), 28.7 (C-9), 29.8 (C-10), 35.6 (C-7), 35.8 (C-3), 40.6 (C-6), 41.4 (C-1), 52.3 (C-2), 77.9 (C-17), 98.8 (C-14), 130.2 (C-5), 131.7 (C-4), 178.6 (C-15), 198.4 (C-16), 205.0 (C-11); m/z (ESIMS) Calculated for $C_{18}H_{23}O_4$ (M-H): 303.1591 Found 303.1591; ν_{max}/cm^{-1} (thin film) 2918 (m, C-H stretch), 2849 (w), 1705 (m, C=O), 1614 (str, C=C), 1418 (m, C-H deformation), 1371 (w), 1092 (w), 1058 (w)

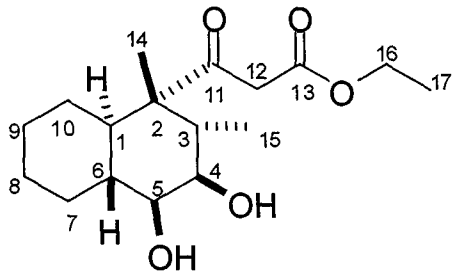
(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1a*S,2*S**,3*S**,3a*R**,7a*R**,7b*R**)-2,3-dimethyldeca-hydronaphtho-[1,2-*b*]oxiren-3-yl)-3-oxopropanoate (307b)**



To a solution of β-keto ester **295** (197.7 mg, 0.59 mmol) was dissolved in anhydrous DCM (10 mL) at 0°C was added mCPBA (144.3 mg, 0.59 mmol) in one portion. The mixture was left at room temperature overnight. The reaction was diluted with DCM (20 mL) and was washed with $Na_2S_2O_3$ solution (aq. sat., 20 mL) and brine (20 mL) successively. The organic layer was dried over $MgSO_4$, concentrated and flash chromatographed to give the epoxide **307b** (113.5 mg, 54.8%) as a colourless oil. $[\alpha]_D^{20.4}$ = -22.6 (5.8 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ_H 0.82-0.89 (1H, m, 1xH-10), 0.95 (3H, d, J = 7.5 Hz, H-15), 1.21 (3H, s, H-14), 1.25-1.43 (3H, m,

1xH-7, 1xH-9 and 1xH-10), 1.49 (3H, d, J = 7.0 Hz, H-18), 1.56-1.70 (4H, m, H-1, H-6, 1xH-8 and 1xH-9), 1.78-1.88 (2H, m, 1xH-7 and 1xH-8), 1.98-2.02 (1H, m, H-3), 3.04-3.08 (1H,m, H-5), 3.16-3.19 (1H, m, H-4), 3.15-3.58 (2H, m, H-12), 3.75 (3H, s, H-19), 5.16 (1H, q, J = 7.0 Hz, H-16); ^{13}C NMR (125.8 MHz, C_6D_6) δ_C 13.4 (C-15), 16.9 and 17.0* (C-18), 18.3 (C-14), 26.5 (C-8), 26.7 (C-9), 27.2 (C-10), 30.2 (C-7), 34.9 (C-1), 36.6 (C-3), 37.3 (C-6), 46.6 (C-12), 52.4 (C-19), 52.5 (C-2), 54.7 (C-4), 57.1 (C-5), 69.1 and 69.2* (C-16), 166.8 (C-17), 170.9 (C-13), 204.7 and 204.8 (C-11); m/z (ESIMS) Calculated for $C_{19}H_{28}NaO_6$ (MNa^+): 375.1778 Found 375.1777; ν_{max}/cm^{-1} (thin film) 2927 (m, C-H stretch), 2855 (w, C-H), 1745 (str, s, C=O), 1704 (m, C=O), 1610 (w), 1449 (str, C-H defromation), 1208 (m, C-O), 1096 (m,C-O)

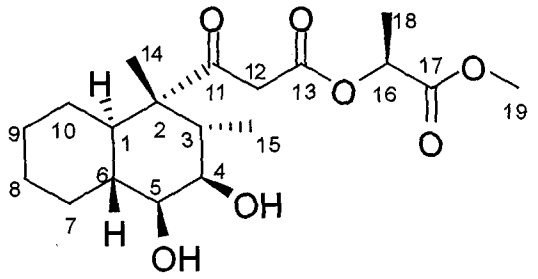
Ethyl 3-((1*R,2*S**,3*R**,4*S**,4a*R**,8a*R**)-3,4-dihydroxy-1,2-dimethyldecahydronaphthalen-1-yl)-3-oxo-propanoate (309)**

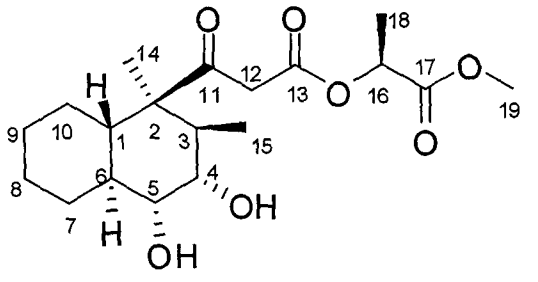


To a solution of the olefin **293** (53.5 mg, 0.19 mmol) in *t*-butanol (2.0 mL) was added *N*-methylmorpholine-*N*-oxide·2H_2O (24.7 mg, 0.20 mmol), H_2O (0.20 mL) and a crystal of osmium tetroxide. The reaction was stirring overnight at room temperature. The process of the reaction was monitored by TLC. After completion of the reaction, a solution of $Na_2S_2O_3$ (aq. sat., 5 mL) was added. The solution was extracted with ethyl acetate (3x10 mL). The combined organic layer was washed with brine, dried over MgSO4 and concentrated. The residue was purified on silica gel (EtOAc/petrol 1:2) to afford the diol **309** (54.2 mg, 90 %) as a colourless oil. ^{1}H NMR (500 MHz, CDCl3) δ_H 0.82 (3H, d, J = 7.5 Hz, H-15), 0.89-0.97 (1H, m, 1xH-10), 0.97-1.05 (1H, m, 1xH-7), 1.17-1.35 (2H, m, 1xH-8 and 1xH-9), 1.27 (3H, t, J = 7.5 Hz, H-17),

1.41 (3H, s, H-14), 1.52-1.62 (2H, m, H-6 and 1xH-10), 1.68-1.71 (1H, m, 1xH-9), 1.77-1.80 (1H, m, 1xH-8), 1.92 (1H, dt, J = 11.5 and 2.5 Hz, H-1), 2.13-2.24 (2H, m, H-3 and 1xH-7), 3.38 (1H, dd, J = 10.5 and 2.5 Hz, H-5), 3.45 (2H, s, H-12), 3.85 (1H, dd, J = 2.5 Hz, H-4), 4.16-4.23 (2H, m, H-16); ^{13}C NMR (125.8 MHz, CDCl3) δ_C 14.1 (C-17), 14.8 (C-15), 19.7 (C-14), 26.0 (C-8), 26.3 (C-9), 28.0 (C-10), 30.4 (C-7), 37.9 (C-6), 38.6 (C-1), 42.1 (C-3), 45.1 (C-12), 52.7 (C-2), 61.2 (C-16), 72.4 (C-5), 76.4 (C-4), 167.9 (C-13), 205.8 (C-11); m/z (GCMS) Calculated for $C_{17}H_{28}NaO_5$ (MNa^+): 335.1829 Found 335.1823; ν_{max}/cm^{-1} (thin film) 3441 (str, br, O-H), 2926 (str, C-H stretch), 2855 (m, C-H stretch), 1742 (str, C=O), 1704 (str, C=O), 1449 (w, C-H defromation), 1309 (str, C-O), 1368 (m, C-O), 1014 (m)

(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1*S,2*S**,4a*R**,8a*R**)-3,4-dihydroxy-1,2-dimethyl-decahydronaphthalen-1-yl)-3-oxopropanoate (310)**



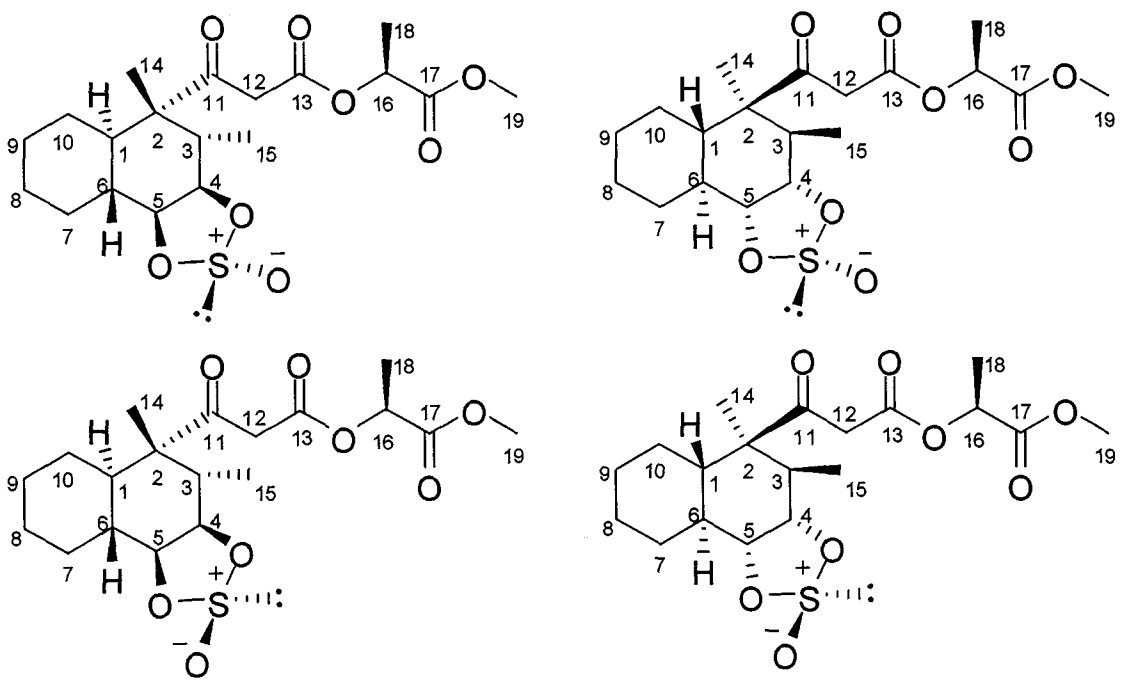


To a solution of the olefin **295** (108.2 mg, 0.32 mmol) in *t*-butanol (3.0 mL) was added *N*-methylmorpholine-*N*-oxide·2H_2O (41.3 mg, 0.34 mmol), H_2O (0.3 mL) and a crystal of osmium tetroxide. The reaction was stirring overnight at room temperature. The process of the reaction was monitored by TLC. After completion of the reaction, a solution of $Na_2S_2O_3$ (sat., 10 mL) was added. The solution was extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (EtOAc/petrol 1:1.5) to afford the diol **310** (69.7 mg, 76.3 %) as a colourless oil. $[\alpha]_D^{20.4}$ = -15.9 (6.4 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.83 (3H, d, J = 7.5 Hz, H-15), 0. 90-1.05 (2H, m, 1xH-7 and 1xH-10), 1.17-1.36 (2H, m, 1xH-8 and 1xH-9),

1.42 (3H, s, H-14), 1.51 and 1.49* (3H, d, J = 7.0 Hz, H-18), 1.49-1.62 (2H, m, H-6 and 1xH-10), 1.68-1.71 (1H, m, 1xH-9), 1.77-1.80 (1H, m, 1xH-8), 1.90-1.94 (1H, m, H-1), 2.05 (2H, m, OH), 2.11-2.18 (1H, m, 1xH-7), 2.20-2.25 (1H, m, H-3), 3.38 (1H, dd, J = 10.0 and 2.5 Hz, H-5), 3.50-3.60 (2H, m, H-12), 3.75 and 3.76* (3H, s, H-19), 3.85 (1H, m, H-4), 5.17 (1H, q, J = 7.0 Hz, H-16); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.8 (C-15), 16.9 and 17.0* (C-18), 19.7 (C-14), 26.0 (C-8), 26.3 (C-9), 28.0 (C-10), 30.0 (C-7), 37.9 (C-6), 38.6 (C-1), 42.1 (C-3), 44.6 and 44.7* (C-12), 52.4 (C-19), 52.8 (C-2), 69.1 and 69.2* (C-16), 72.4 (C-5), 76.4 (C-4), 167.0 and 167.1* (C-17), 170.9 (C-13), 205.1 and 205.2* (C-11); m/z (ESIMS) Calculated for $C_{19}H_{30}NaO_7$ (MNa^+): 393.1884 Found 393.1883; ν_{max}/cm^{-1} (thin film) 3516 (str, br, O-H), 2928 (str, C-H stretch), 2855 (m, C-H stretch), 1748 (str, C=O), 1706 (str, C=O), 1450 (w, C-H defromation), 1310 (m, C-O), 1268 (m, C-O), 1217 (m, C-O), 1096 (m)

(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1a*R,2*S**,3*S**,3a*R**,7a*R**,7b*S**, R_S)-2,3-dimethyl-decahydronaphtho[1,2-*b*]dioxathiolo-3-yl)-3-oxopropanoate (311)**

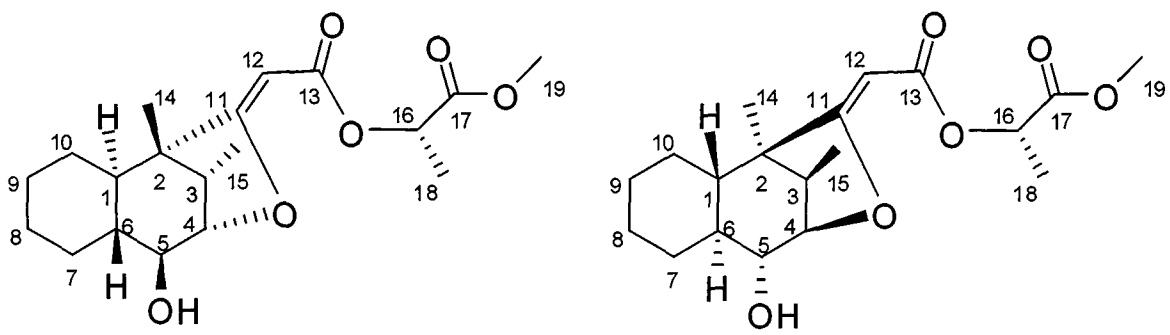
(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1a*R,2*S**,3*S**,3a*R**,7a*R**,7b*S**, S_S)-2,3-dimethyl-decahydronaphtho[1,2-*b*]dioxathiolo-3-yl)-3-oxopropanoate (311)**



Anhydrous pyridine (53.7 μL, 0.66 mmol) was added at room temperature to a solution of diol **310** (106.3 g, 0.29 mmol) in anhydrous DCM (4.0 mL). The mixture was then cooled to 0°C and

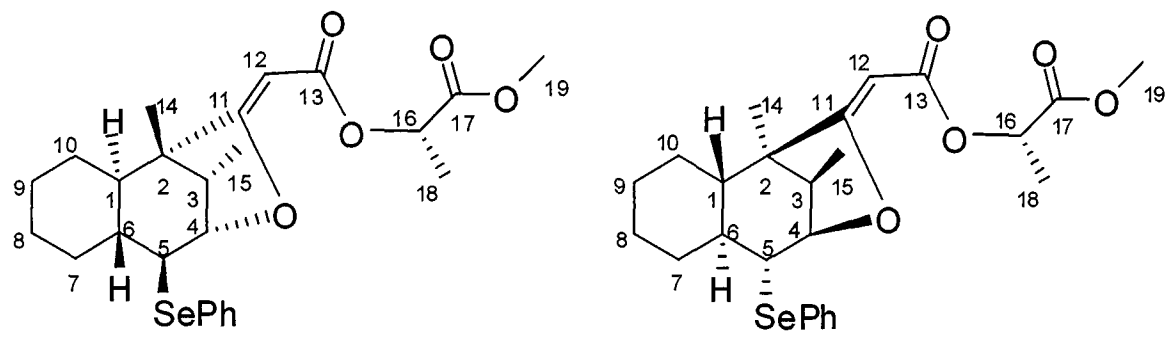
a solution of $SOCl_2$ (35.0 μL, 0.38 mmol) in DCM (2.0 mL) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 12 h, and was then hydrolyzed with water (5.0 mL). The organic layer was decanted and the aqueous layer was extracted with DCM (3x15 mL). The combined extracts were then washed with brine (20 mL), dried with $MgSO_4$, and the solvents were evaporated under vacuum. The residue was purified by chromatography on silica gel (EtOAc/petrol 1:6) to afford **311** as a colourless oil (112.7 mg, 94.6%). $[\alpha]_D^{22.4}$ = -25.3 (2.7 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.00-1.04 (1H, m, 1xH-9), 1.02 (3H, d, J = 7.0 Hz, H-15), 1.12-1.19 (2H, m, 1xH-8 and 1xH-10), 1.24-1.32 (1H, m, H-7), 1.34 (3H, s, H-14), 1.54 and 1.53* (3H, d, J = 7.0 Hz, H-18), 1.57-1.65 (1H, m, 1xH-9), 1.72-1.89 (3H, m, H-1, H-6 and 1xH-8), 2.18-2.25 (2H, m, H-3 and 1xH-10), 2.29-2.40 (1H, m, 1xH-7), 3.54-3.62 (2H, m, H-12), 3.77 and 3.79* (3H, s, H-19), 4.48-4.51 (1H, m, H-5), 4.89 (1H, dd, J = 5.0 and 5.0 Hz, H-4), 5.15-5.20 (1H, m, H-16); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 14.8 (C-15), 16.9 and 17.0* (C-18), 18.8 (C-14), 25.9 (C-8), 27.8 (C-9), 31.2 (C-10), 33.0 (C-7), 38.3 (C-3), 38.7 (C-1), 39.2 (C-6), 46.0 (C-12), 52.5 and 52.6* (C-19), 53.4 (C-2), 68.4 and 69.3* (C-16), 81.2 (C-4), 84.0 (C-5), 170.7 (C-13), 171.8 (C-17), 205.6 (C-11); m/z (ESIMS) Calculated for $C_{19}H_{28}NaO_8S$ (MNa^+): 439.1397 Found 439.1397; ν_{max}/cm^{-1} (thin film) 2933 (str, C-H stretch), 2857 (m, C-H), 1752 (str, C=O), 1708 (m, C=O), 1613 (m), 1451 (m, C-H defromation), 1410 (m), 1306 (m, S=O), 1208 (str, C-O), 1099 (m, S=O), 950 (m)

(*S*)-1-Methoxy-1-oxopropan-2-yl ethyl 2-((1*S,2*R**,7*R**,8*S**,9*S**,12*S**)-1,12-dihydroxy-8-hydroxy-10-oxatricyclo[7.2.1.$0^{2,7}$]dodecan-11-ylidene)acetate (313)**



Tetrabutylammonium fluoride (1.0 M in THF, 0.68 mL, 0.68 mmol) was added to the β-keto ester **311** (94.7 mg, 0.23 mmol) in THF (0.3 mL), and the solution was stirred for 1 day. The reaction mixture was Partition between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was acidified with hydrochloric acid (1N, 0.7 mL), left at room temperature for 2 h, and then extracted with ether (2x10 mL). The combined organic layer was washed with brine (10 mL), and dried over $MgSO_4$. After concentration, the residue was purified on silica gel (EtOAc/petrol 1:12) to afford the pure product **313** (50.0 mg, 62%) as a light yellow oil. $[\alpha]_D^{22.4}$ = -20.7 (3.0 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, d, *J* = 7.0 Hz, H-15), 0.96-1.06 (2H, m, 1xH-7 and 1xH-10), 1.02 (3H, s, H-14), 1.13-1.36 (4H, m, H-1, H-6, 1xH-8 and 1xH-9), 1.46 (3H, d, *J* = 7.0 Hz, H-18), 1.70-1.86 (3H, m, 1xH-8, 1xH-9 and 1xH-10), 2.02-2.04 (1H, m, 1xH-7), 2.38-2.42 (1H, m, H-3), 2.74 (1H, m, OH), 3.49 (1H, t, *J* = 9.0 Hz, H-5), 3.73 (3H, s, H-19), 4.27-4.48 (1H, m, H-4), 4.81 (1H, s, H-12), 5.07-5.13 (1H, m, H-16); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 13.6 (C-15), 13.9 (C-14), 17.2 (C-18), 26.0 (C-8), 27.4 (C-9), 29.7 (C-10), 30.9 (C-7), 35.3 (C-3), 44.5 (C-6), 46.3 (C-1), 48.8 (C-2), 52.2 (C-19), 67.4 (C-16), 73.5 (C-5), 83.9 (C-4), 91.1 (C-12), 165.4 (C-11), 172.1 (C-17), 182.9 (C-13); m/z (GCMS) Calculated for $C_{19}H_{29}O_6$ (MH^+): 353.1959 Found 353.1960; ν_{max}/cm^{-1} (thin film) 3473 (br, O-H), 2925 (m, C-H stretch), 2855 (w, C-H), 1754 (m, C=O), 1701 (m, C=O), 1639 (str,s, C=C), 1446 (w, C-H defromation), 1377 (w, C-O), 1261 (m, C-O), 1195 (m),1098 (m), 973 (str, C=C-H)

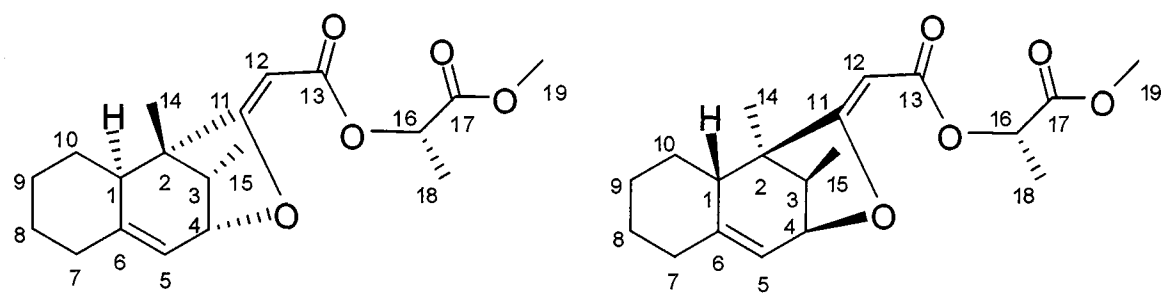
(*S*)-1-Methoxy-1-oxopropan-2-yl ethyl 2-((1*S,2*R**,7*R**,8*S**,9*S**,12*S**)-1,12-dihydroxy-8-(phenylselanyl) -10-oxatricyclo[7.2.1.$0^{2,7}$]dodecan-11-ylidene)acetate (324)**



N-(Phenylseleno)phthalimide (423.6 mg, 1.32 mmol) in anhydrous dichloromethane (10.0 ml) was added dropwise to a stirred solution of β-keto ester **295** (402.5 mg, 1.20 mmol) in anhydrous dichloromethane (5.0 ml) at room temperature under argon. Then tin(IV) chloride (0.1 M in DCM, 240 µl, 2.4% mmol) was added dropwise to the mixture. After 4 h, the reaction mixture was concentrated in vacuo to afforded a residue, which was purified by column chromatography (ethyl acetate/petrol, 1:12) to give **324** (494.4 mg, 80%) as a light yellow oil.[235,254] $[\alpha]_D^{20.4}$ = -22.5 (10.5 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.84 (3H, d, *J* = 7.0 Hz, H-15), 0.95-1.04 (1H, m, 1xH-10), 1.00 (3H, s, H-14), 1.11-1.27 (4H, m, H-6, 1xH-7, 1xH-8 and 1xH-9), 1.42-1.52 (1H, m, H-1), 1.47 (3H, d, *J* = 7.0 Hz, H-18), 1.75-1.86 (3H, m, 1xH-8, 1xH-9 and 1xH-10), 2.14 (1H, apparent q, *J* = 7.0 Hz, H-3), 2.30-2.32 (1H, m, 1xH-7), 3.11 (1H, apparent d, *J* = 10.0 Hz, H-5), 3.72 (3H, s, H-19), 4.62 (1H, s, H-12), 4.80 (1H, apparent s, H-4), 5.10 (1H, d, *J* = 7.0 Hz, H-16), 7.28-7.32 (3H, m, H-Ph), 7.55-7.58 (2H, m, H-Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 13.7 (C-14), 13.9 (C-15), 17.2 (C-18), 26.3 (C-9), 27.5 (C-8), 29.7 (C-10), 32.7 (C-7), 36.2 (C-3), 42.4 (C-6), 47.7 (C-5), 48.8 (C-2), 49.6 (C-1), 52.2 (C-19), 67.5 (C-16), 83.7 (C-4), 91.8 (C-12), 127.4 (Ph-C), 128.2 (Ph-C), 129.3 (Ph-C), 135.3 (Ph-C), 165.3 (C-11), 172.0 (C-17), 182.7 (C-13); m/z (ESIMS) Calculated for $C_{25}H_{33}O_5{}^{78}Se$ (MH^+): 493.1489 Found 493.1488; ν_{max}/cm^{-1} (thin film) 2928 (m, C-H stretch), 2853 (w), 1757 (m, C=O), 1719 (str, s, C=O), 1643 (str, s, C=C), 1446 (w, C-H defromation), 1375 (w, C-O),

1276 (m, C-O), 1195 (str), 1157 (str), 1097 (m),962 (str, C=C-H)

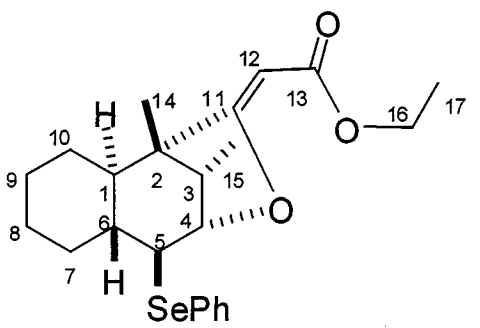
(*S*)-1-Methoxy-1-oxopropan-2-yl ethyl 2-((1*S,2*R**,9*S**,12*S**)-1,12-dihydroxy-10-oxatricyclo-[7.2.1.0^{2,7}]dodec-7-en-11-ylidene)acetate (327)**



A solution of **324** (181.1 mg, 0.37 mmol) in THF (5.0 mL) was cooled in an ice bath. Then pyridine (1 drop) and H_2O_2 (aq. 35% w/w, 195.1 μL, 2.21 mmol) were added. The reaction was stirred for 1 h and was then quenched by adding water (5.0 mL). The reaction mixture was extracted with dichloromethane (3x20 mL), and the organic phase was dried with magnesium sulphate and evaporated under vacuum.[210] The residue obtained was purified by flash chromatography eluting with ethyl acetate/petrol 1:5, to obtain compound **327** as a colourless oil (104.3 mg, 84.8%). $[\alpha]_D^{20.4}$ = -24.0 (4.2 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.95 (3H, d, *J* = 7.0 Hz, H-15), 1.17 (3H, s, H-14), 1.13-1.23 (2H, m, 1xH-8 and 1xH-10), 1.31-1.40 (1H, m, 1xH-9), 1.47 (3H, d, *J* = 7.5 Hz, H-18), 1.78-1.92 (4H, m, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 1.99-2.06 (1H, m, H-1), 2.14-2.16 (1H, m, 1xH-7), 2.21 (1H, q, *J* = 7.0 Hz, H-3), 3.73 (3H, s, H-19), 4.42 (1H, apparent d, *J* = 5.5 Hz, H-4), 4.93 (1H, s, H-12), 5.08-5.15 (1H, m, H-16), 5.82 (1H, d, *J* = 5.5 Hz, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 13.5 (C-15), 17.3 (C-18), 17.4 (C-14), 26.1 (C-9), 28.0 (C-8), 29.2 (C-10), 35.0 (C-7), 40.7 (C-3), 50.9 (C-1), 51.4 (C-2), 52.2 (C-19), 67.4 (C-16), 82.8 (C-4), 86.7 (C-12), 121.2 (C-5), 146.4 (C-6), 165.3 (C-11), 172.3 (C-17), 182.0 (C-13); m/z (ESIMS) Calculated for $C_{19}H_{26}O_5Na$ (MNa^+): 357.1672 Found 357.1673; ν_{max}/cm^{-1} (thin film) 2933 (m, C-H stretch), 2856 (m), 1757 (m, C=O), 1716 (str, C=O), 1636 (str, C=C), 1445 (w, C-H defromation), 1374 (w, C-O), 1277 (m, C-O), 1147 (str),

1097 (str), 951 (str)

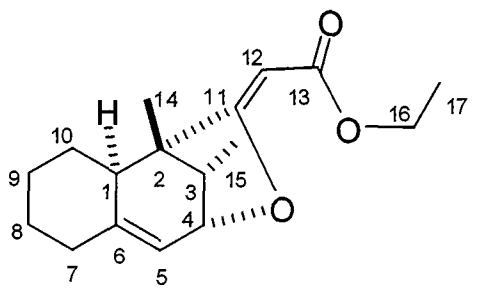
Ethyl 2-((1*S,2*R**,7*R**,8*S**,9*S**,12*S**)-1,12-dihydroxy-8-(phenylselanyl)-10-oxatricyclo-[7.2.1.$0^{2,7}$]dodecan-11-ylidene)acetate (317)**



N-(Phenylseleno)phtalimide (67.7 mg, 0.21 mmol) in anhydrous DCM (2.0 ml) was added dropwise to a stirred solution of β-keto ester **293** (53.2 mg, 0.19 mmol) in anhydrous DCM (2.0 ml) at room temperature under argon. Then tin(IV) chloride (0.01 M solution in DCM, 191.4 µl, 0.19% mmol) was added dropwise to the mixture. After 4 h, the reaction mixture was concentrated in vacuo to afforded a residue, which was purified by column chromatography (ethyl acetate/petrol, 1:10) to give **317** (43.2 mg, 53%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.84 (3H, d, J = 7.0 Hz, H-15), 0.91-1.05 (1H, m, 1xH-10), 0.98 (3H, s, H-14), 1.13-1.28 (4H, m, H-6, 1xH-7, 1xH-8 and 1xH-9), 1.25 (3H, d, J = 7.0 Hz, H-17), 1.43-1.48 (1H, m, H-1), 1.74-1.87 (3H, m, 1xH-8, 1xH-9 and 1xH-10), 2.09-2.14 (1H, m, H-3), 2.30-2.32 (1H, m, 1xH-7), 3.12 (1H, apparent d, J = 9.5 Hz, H-5), 4.12 (2H, d, J = 7.0 Hz, H-16), 4.61 (1H, s, H-12), 4.68 (1H, apparent s, H-4), 7.27-7.34 (3H, m, Ph-H), 7.56-7.58 (2H, m, Ph-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.8 (C-15), 13.9 (C-14), 14.4 (C-17), 26.3 (C-8), 27.5 (C-9), 29.7 (C-10), 32.7 (C-7), 36.2 (C-3), 42.3 (C-6), 47.7 (C-5), 48.5 (C-2), 49.6 (C-1), 59.2 (C-16), 84.8 (C-4), 91.5 (C-12), 127.5 (Ph-C), 128.2 (Ph-C), 129.3 (Ph-C), 135.3 (Ph-C), 166.3 (C-11), 181.0 (C-13); m/z (GCMS) Calculated for $C_{23}H_{30}O_3Na^{78}Se$ (MNa^+): 457.1252 Found 457.1253; ν_{max}/cm^{-1} (thin film) 2928 (m, C-H stretch), 2853 (w, C-H stretch), 1716 (m, C=O), 1644 (m, C=C), 1438 (w, C-H defromation), 1375 (w, C-O), 1276 (w, C-O), 1195 (m), 1157 (str, s), 1097

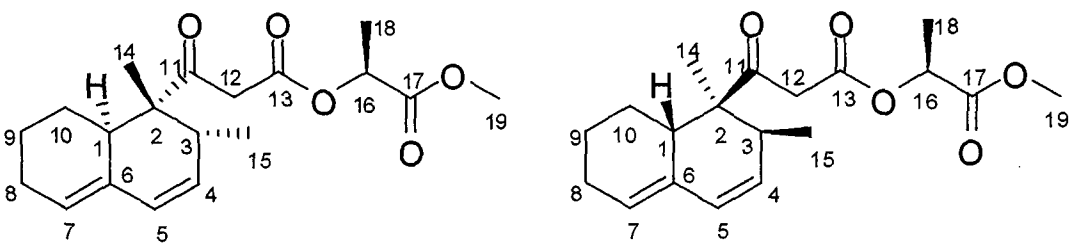
(str), 967 (str, s)

Ethyl 2-((1*S,2*R**,7*R**,8*S**,9*S**,12*S**)-1,12-dihydroxy-10-oxatricyclo[7.2.1.$0^{2,7}$]dodec-7-en-11-ylidene)acetate (326)**



A solution of **317** (38.1 mg, 0.09 mmol) in THF (1 mL) was cooled in an ice bath. Then pyridine (1 drop) and H_2O_2 (aq. 35 % w/w, 47.0 μL, 0.53 mmol) were added. The reaction was stirred for 1 h and was then quenched by adding water (2 mL). The reaction mixture was extracted with dichloromethane (2x10 mL), and the organic phase was dried with magnesium sulphate and evaporated under vacuum. The residue obtained was purified by flash chromatography eluting with ethyl acetate/petrol 1:8, to obtain compound **326** as a light yellow oil (12.0 mg, 41%).^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.96 (3H, d, J = 7.0 Hz, H-15), 1.13 (3H, s, H-14), 1.14-1.21 (2H, m, 1xH-8 and 1xH-10), 1.26 (3H, t, J = 7.0 Hz, H-17), 1.31-1.42 (1H, m, 1xH-9), 1.78-1.90 (4H, m, 1xH-7, 1xH-8, 1xH-9 and 1xH-10), 2.01 (1H, dd, J = 12.0 and 4.0 Hz, H-1), 2.11-2.23 (2H, m, H-3 and 1xH-7), 4.14 (2H, q, J = 7.0 Hz, H-16), 4.41 (1H, apparent d, J = 6.0 Hz, H-4), 4.83 (1H, s, H-14), 5.84 (1H, d, J = 6.0 Hz, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 13.6 (C-17), 14.5 (C-15), 17.6 (C-14), 26.1 (C-9), 28.0 (C-8), 29.3 (C-10), 35.0 (C-7), 40.6 (C-3), 51.1 (C-2), 51.4 (C-1), 59.1 (C-16), 82.3 (C-4), 87.9 (C-12), 121.4 (C-5), 146.3 (C-6), 164.3 (C-11), 180.6 (C-13); m/z (GCMS) Calculated for $C_{17}H_{25}O_3$ (MH^+): 277.1804 Found 277.1806; ν_{max}/cm^{-1} (thin film) 2928 (m, C-H stretch), 2854 (w, C-H stretch), 1713 (m, C=O), 1688 (m, C=C), 1639 (str, C=C), 1445 (w, C-H defromation), 1372 (w, C-O), 1277 (m, C-O), 1187 (m), 1149 (str, s), 951 (str, s)

(*S*)-1-Methoxy-1-oxopropan-2-yl 3-((1*R,2*R**,8a*R**)-1,2-dimethyl-1,2,6,7,8,8a-hexahydro-naphthalene-1-yl)-3-oxopropanoate (329)**



A solution of **327** (55.0 mg, 0.16 mmol) in DCM (1.0 mL) was added TFA (50.0 μL) and H_2O (1 drop). After being stirred at room temperature overnight, the homogenous mixture was diluted and neutralized by $NaHCO_3$ (aq. sat., 5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (ethyl acetate/petrol 1:12) to give **327** (10.0 mg, 18%) as a colourless oil. $[\alpha]_D^{20.4}$ = -15.7 (3.7 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, d, *J* = 7.0 Hz, H-15), 1.01-1.08 (1H, m, 1xH-10), 1.12 (3H, s, H-14), 1.50 (3H, d, *J* = 7.0 Hz, H-18), 1.57-1.62 (1H, m, 1xH-9), 1.79-1.86 (2H, m, 1xH-9 and 1xH-10), 2.11-2.15 (2H, m, H-8), 2.23-2.29 (1H, m, H-3), 2.86-2.89 (1H, m, H-1), 3.53-3.66 (2H, m, H-12), 3.76 (3H, s, H-19), 5.19 (1H, d, *J* = 7.0 Hz, H-16), 5.55 (1H, dd, *J* = 9.5 and 5.5 Hz, H-4), 5.67 (1H, m, H-7), 5.93 (1H, d, *J* = 9.5 Hz, H-5); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ_C 16.9 (C-18), 17.6 (C-15), 18.2 (C-14), 22.7 (C-9), 23.6 (C-10), 25.9 (C-8), 34.3 (C-1), 39.9 (C-3), 45.2 (C-12), 52.4 (C-19), 53.2 (C-2), 69.1 (C-16), 127.5 (C-4), 128.3 (C-5), 128.8 (C-7), 134.7 (C-6), 167.1 (C-13), 171.0 (C-17), 205.6 (C-11); m/z (ESIMS) Calculated for $C_{19}H_{26}NaO_5$ (MNa^+): 357.1672 Found 357.1681; ν_{max}/cm^{-1} (thin film) 2932 (m, C-H stretch), 2878 (m, C-H), 1747 (str, s, C=O), 1707 (m, C=O), 1452 (m, C-H deformation), 1380 (w), 1214 (m, C-O), 1098 (w)

CHAPTER 5

REFERENCES

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CHAPTER 6

APPDENDIX

CHAPTER 6 APPENDIX

6.1 X-ray crystallographic structure of benzoate (160)

Single-crystal X-ray diffraction report for C20H24N2O8 (ARC996)

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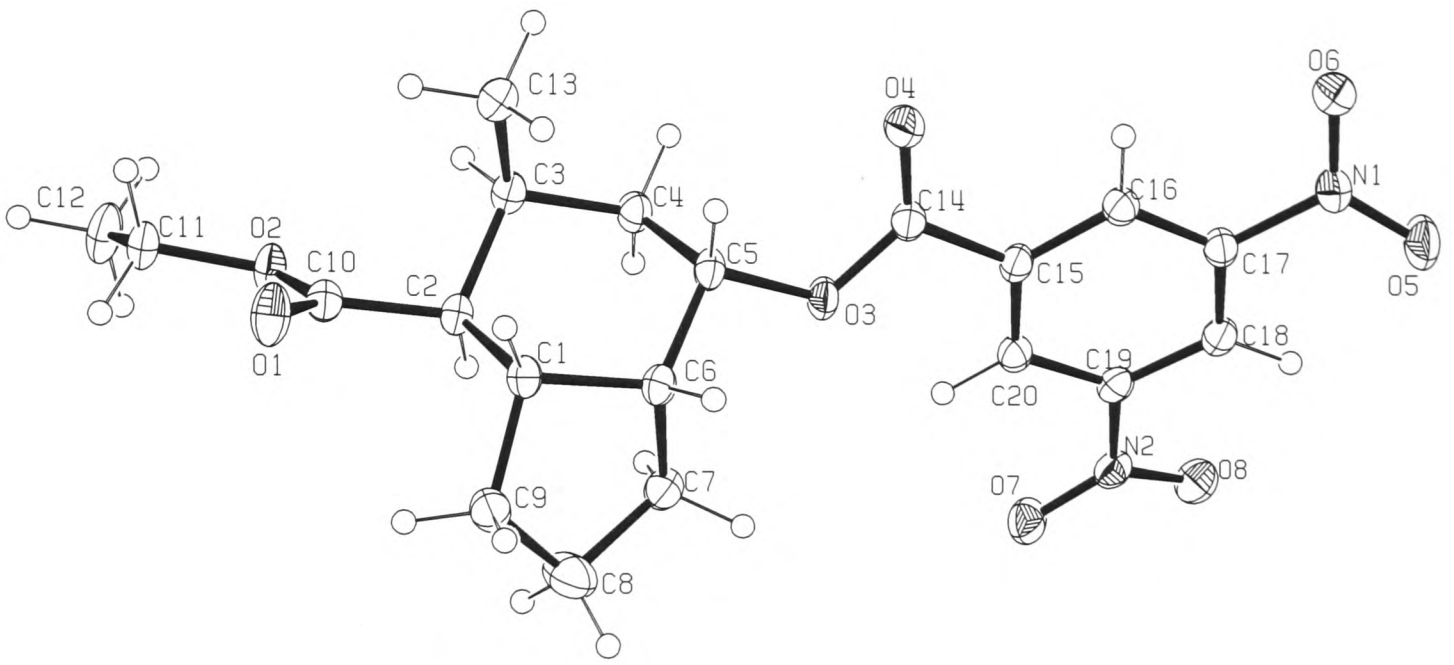

Crystals of **ARC996** were grown by *. A large prismatic crystal was cut to give a fragment having dimensions approximately 0.26 x 0.30 x 0.34 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package1.

Examination of the systematic absences of the intensity data showed the space group to be *P b c a*. The structure was solved using the direct-methods program SIR922, which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite3. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0362, wR = 0.0418.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

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Table 1: Crystal data and refinement details

Crystal identification	ARC996
Chemical formula	C20H24N2O8
Formula weight	420.42
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	*P b c a*
a (Å)	10.0673(2)
b (Å)	12.4039(2)
c (Å)	31.6904(4)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å3)	3957.30(11)
Z	8
Calculated density (Mg/m3)	1.411
Absorption coefficient (mm-1)	0.110
F000	1776
Crystal size (mm)	0.26 x 0.30 x 0.34
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.96, 0.97
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$0 \leq h \leq 13$, $0 \leq k \leq 16$, $0 \leq l \leq 40$
Reflections measured	31817
Unique reflections	5018
Rint	0.041
Observed reflections ($I > 3\sigma(I)$)	2928
Refinement method	Full-matrix least-squares on *F*
Parameters refined	271
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.1042
R	0.0362
wR	0.0418
Residual electron density (min,max) (eÅ-3)	-0.23, 0.24

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C(1)	0.56431(15)	0.32561(12)	0.31455(5)	0.0241
C(2)	0.48445(14)	0.28243(12)	0.27696(5)	0.0231
C(3)	0.46373(16)	0.15903(13)	0.27951(5)	0.0262
C(4)	0.38546(16)	0.13453(13)	0.31989(5)	0.0265
C(5)	0.45954(15)	0.17379(13)	0.35855(5)	0.0251
C(6)	0.49842(16)	0.29250(13)	0.35685(5)	0.0246
C(7)	0.38454(16)	0.37460(14)	0.36194(5)	0.0295
C(8)	0.4392(2)	0.47886(16)	0.34274(7)	0.0477
C(9)	0.56294(17)	0.44960(13)	0.31759(5)	0.0320
C(10)	0.54707(16)	0.31022(13)	0.23480(5)	0.0259
O(1)	0.65749(12)	0.34462(12)	0.22904(4)	0.0393
O(2)	0.46122(11)	0.28980(10)	0.20347(3)	0.0309
C(11)	0.50869(17)	0.30637(14)	0.16069(5)	0.0310
C(12)	0.3917(2)	0.29633(18)	0.13206(5)	0.0438
C(13)	0.59413(17)	0.09534(14)	0.27668(5)	0.0327
O(3)	0.37170(11)	0.16080(9)	0.39553(3)	0.0283
C(14)	0.38424(16)	0.07071(13)	0.41781(5)	0.0269
O(4)	0.45953(13)	-0.00236(10)	0.41036(4)	0.0392
C(15)	0.29373(15)	0.07003(12)	0.45543(4)	0.0249
C(16)	0.32144(16)	-0.00457(12)	0.48717(5)	0.0261
C(17)	0.24411(17)	-0.00301(13)	0.52335(5)	0.0267
C(18)	0.13731(16)	0.06587(13)	0.52859(5)	0.0269
C(19)	0.11017(16)	0.13554(12)	0.49558(5)	0.0248
C(20)	0.18731(16)	0.14125(12)	0.45950(5)	0.0258
N(1)	0.27444(15)	-0.07930(11)	0.55768(4)	0.0331
O(5)	0.22489(15)	-0.06134(12)	0.59231(4)	0.0500
O(6)	0.34851(14)	-0.15496(10)	0.55009(4)	0.0399
N(2)	-0.00844(15)	0.20417(11)	0.49916(4)	0.0293
O(7)	-0.02415(13)	0.27554(11)	0.47277(4)	0.0402
O(8)	-0.08573(13)	0.18538(10)	0.52807(4)	0.0400

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(11)	0.6556	0.2960	0.3100	0.0290
H(21)	0.3962	0.3192	0.2788	0.0277
H(31)	0.4117	0.1345	0.2544	0.0314
H(41)	0.3717	0.0549	0.3222	0.0318
H(42)	0.2973	0.1715	0.3184	0.0318
H(51)	0.5430	0.1303	0.3602	0.0302
H(61)	0.5600	0.2960	0.3816	0.0296
H(71)	0.3623	0.3851	0.3924	0.0354
H(72)	0.3036	0.3501	0.3464	0.0354
H(81)	0.4625	0.5309	0.3657	0.0573
H(82)	0.3713	0.5120	0.3237	0.0573
H(91)	0.6444	0.4758	0.3324	0.0384
H(92)	0.5587	0.4822	0.2888	0.0384
H(111)	0.5488	0.3798	0.1580	0.0372
H(112)	0.5767	0.2506	0.1534	0.0372
H(121)	0.4207	0.3073	0.1022	0.0526
H(122)	0.3240	0.3521	0.1397	0.0526
H(123)	0.3519	0.2229	0.1351	0.0526
H(131)	0.5747	0.0164	0.2785	0.0393
H(132)	0.6538	0.1167	0.3005	0.0393
H(133)	0.6389	0.1114	0.2492	0.0393
H(161)	0.3953	-0.0579	0.4839	0.0313
H(181)	0.0825	0.0654	0.5549	0.0323
H(201)	0.1672	0.1951	0.4369	0.0310

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0221(7)	0.0296(8)	0.0207(7)	0.0026(6)	-0.0009(6)	-0.0014(6)
C(2)	0.0210(7)	0.0295(8)	0.0187(6)	0.0017(6)	0.0011(6)	0.0003(6)
C(3)	0.0263(8)	0.0313(8)	0.0209(7)	-0.0008(6)	0.0015(6)	-0.0044(7)
C(4)	0.0268(8)	0.0289(8)	0.0238(7)	0.0012(6)	0.0032(6)	-0.0034(6)
C(5)	0.0251(8)	0.0319(8)	0.0185(6)	0.0032(6)	0.0047(6)	0.0010(6)
C(6)	0.0256(7)	0.0297(8)	0.0186(7)	0.0007(6)	-0.0024(6)	0.0004(6)
C(7)	0.0299(8)	0.0330(8)	0.0257(7)	-0.0017(6)	0.0012(6)	0.0030(7)
C(8)	0.0479(12)	0.0334(9)	0.0619(13)	0.0073(9)	0.0114(10)	0.0084(9)
C(9)	0.0381(9)	0.0302(8)	0.0278(8)	0.0015(6)	-0.0023(7)	-0.0056(7)
C(10)	0.0245(8)	0.0297(8)	0.0236(7)	0.0025(6)	0.0012(6)	0.0018(6)
O(1)	0.0254(6)	0.0640(9)	0.0284(6)	0.0071(6)	0.0026(5)	-0.0070(6)
O(2)	0.0308(6)	0.0446(7)	0.0173(5)	0.0032(5)	0.0007(4)	-0.0081(5)
C(11)	0.0347(9)	0.0397(9)	0.0185(7)	0.0034(6)	0.0045(6)	-0.0025(7)
C(12)	0.0461(11)	0.0666(13)	0.0188(7)	-0.0020(8)	0.0018(7)	-0.0152(10)
C(13)	0.0359(9)	0.0333(9)	0.0289(8)	-0.0010(7)	0.0061(7)	0.0025(7)
O(3)	0.0319(6)	0.0327(6)	0.0203(5)	0.0051(4)	0.0068(4)	0.0028(5)
C(14)	0.0320(9)	0.0273(8)	0.0215(7)	0.0006(6)	0.0017(6)	-0.0024(7)
O(4)	0.0503(7)	0.0322(6)	0.0352(6)	0.0058(5)	0.0166(6)	0.0081(6)
C(15)	0.0290(8)	0.0268(8)	0.0189(7)	-0.0013(6)	0.0013(6)	-0.0049(6)
C(16)	0.0290(8)	0.0251(7)	0.0241(7)	-0.0001(6)	0.0012(6)	-0.0034(6)
C(17)	0.0320(8)	0.0260(7)	0.0220(7)	0.0021(6)	0.0003(6)	-0.0038(6)
C(18)	0.0298(8)	0.0288(8)	0.0221(7)	-0.0024(6)	0.0030(6)	-0.0048(7)
C(19)	0.0256(8)	0.0260(7)	0.0227(7)	-0.0044(6)	-0.0004(6)	-0.0021(6)
C(20)	0.0309(8)	0.0254(8)	0.0210(7)	-0.0010(6)	-0.0020(6)	-0.0040(6)
N(1)	0.0404(8)	0.0330(8)	0.0259(7)	0.0057(6)	0.0056(6)	0.0000(7)
O(5)	0.0651(9)	0.0563(8)	0.0287(6)	0.0145(6)	0.0178(6)	0.0159(7)
O(6)	0.0520(8)	0.0346(6)	0.0332(6)	0.0029(5)	0.0022(6)	0.0106(6)
N(2)	0.0322(7)	0.0320(7)	0.0239(6)	-0.0051(5)	-0.0021(5)	0.0007(6)
O(7)	0.0467(8)	0.0464(7)	0.0276(6)	0.0038(5)	-0.0033(6)	0.0136(6)
O(8)	0.0380(7)	0.0444(7)	0.0377(6)	-0.0013(6)	0.0126(6)	0.0051(6)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.534(2)	C(11) - C(12)	1.492(3)
C(1) - C(6)	1.551(2)	O(3) - C(14)	1.3278(18)
C(1) - C(9)	1.541(2)	C(14) - O(4)	1.2049(19)
C(2) - C(3)	1.547(2)	C(14) - C(15)	1.501(2)
C(2) - C(10)	1.517(2)	C(15) - C(16)	1.395(2)
C(3) - C(4)	1.533(2)	C(15) - C(20)	1.395(2)
C(3) - C(13)	1.535(2)	C(16) - C(17)	1.386(2)
C(4) - C(5)	1.515(2)	C(17) - C(18)	1.383(2)
C(5) - C(6)	1.525(2)	C(17) - N(1)	1.474(2)
C(5) - O(3)	1.4770(17)	C(18) - C(19)	1.384(2)
C(6) - C(7)	1.542(2)	C(19) - C(20)	1.384(2)
C(7) - C(8)	1.531(3)	C(19) - N(2)	1.471(2)
C(8) - C(9)	1.523(3)	N(1) - O(5)	1.2261(18)
C(10) - O(1)	1.2046(19)	N(1) - O(6)	1.2225(18)
C(10) - O(2)	1.3405(19)	N(2) - O(7)	1.2281(18)
O(2) - C(11)	1.4524(18)	N(2) - O(8)	1.2243(18)

Note – H atoms have been excluded

Table 6: Bond angles (°)

C(2) - C(1) - C(6)	110.77(12)	O(2) - C(11) - C(12)	107.22(13)
C(2) - C(1) - C(9)	113.10(13)	C(5) - O(3) - C(14)	117.18(12)
C(6) - C(1) - C(9)	101.91(12)	O(3) - C(14) - O(4)	126.06(14)
C(1) - C(2) - C(3)	112.06(12)	O(3) - C(14) - C(15)	111.68(13)
C(1) - C(2) - C(10)	112.75(12)	O(4) - C(14) - C(15)	122.24(14)
C(3) - C(2) - C(10)	109.08(12)	C(14) - C(15) - C(16)	117.08(14)
C(2) - C(3) - C(4)	108.00(12)	C(14) - C(15) - C(20)	122.44(14)
C(2) - C(3) - C(13)	113.01(13)	C(16) - C(15) - C(20)	120.48(14)
C(4) - C(3) - C(13)	112.73(13)	C(15) - C(16) - C(17)	118.35(14)
C(3) - C(4) - C(5)	110.99(12)	C(16) - C(17) - C(18)	123.00(14)
C(4) - C(5) - C(6)	114.10(13)	C(16) - C(17) - N(1)	119.03(14)
C(4) - C(5) - O(3)	108.18(12)	C(18) - C(17) - N(1)	117.96(13)
C(6) - C(5) - O(3)	106.68(12)	C(17) - C(18) - C(19)	116.63(14)
C(1) - C(6) - C(5)	113.33(12)	C(18) - C(19) - C(20)	123.06(15)
C(1) - C(6) - C(7)	103.50(12)	C(18) - C(19) - N(2)	117.59(13)
C(5) - C(6) - C(7)	116.32(13)	C(20) - C(19) - N(2)	119.33(14)
C(6) - C(7) - C(8)	104.43(13)	C(15) - C(20) - C(19)	118.36(14)
C(7) - C(8) - C(9)	107.49(14)	C(17) - N(1) - O(5)	117.38(14)
C(1) - C(9) - C(8)	106.13(14)	C(17) - N(1) - O(6)	118.29(13)
C(2) - C(10) - O(1)	126.69(14)	O(5) - N(1) - O(6)	124.32(14)
C(2) - C(10) - O(2)	109.96(13)	C(19) - N(2) - O(7)	117.98(14)
O(1) - C(10) - O(2)	123.35(14)	C(19) - N(2) - O(8)	117.62(13)
C(10) - O(2) - C(11)	116.91(12)	O(7) - N(2) - O(8)	124.39(15)

Note – H atoms have been excluded

6.2 X-ray crystallographic structure of hydrazone (172)

Single-crystal X-ray diffraction report for $C_{20}H_{26}N_4O_6$ (ARC1042)

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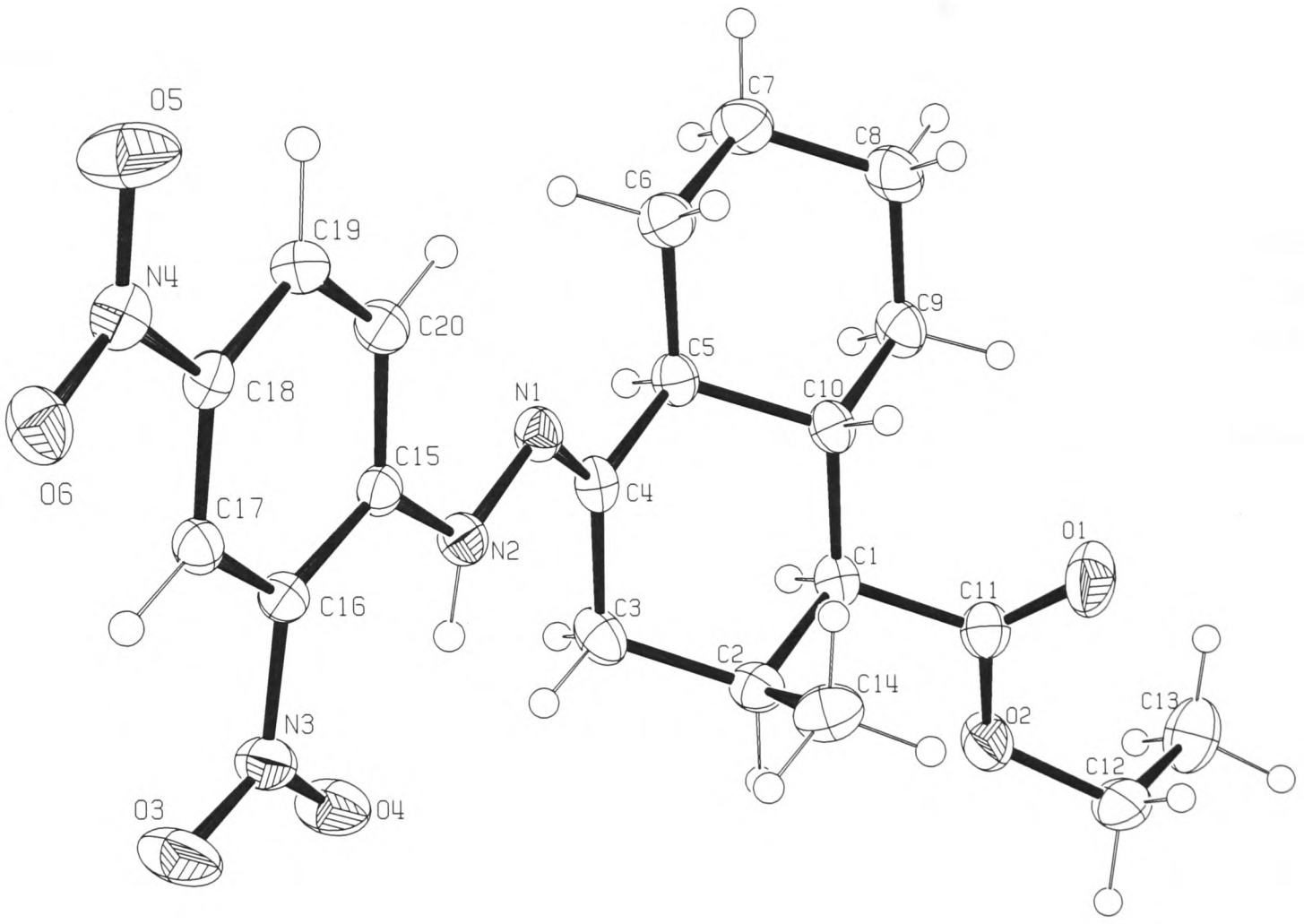


Crystals of **ARC1042** were grown by *. A single crystal having dimensions approximately 0.24 x 0.30 x 0.30 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package1.

Examination of the systematic absences of the intensity data showed the space group to be $P\ 21/c$. The structure was solved using the direct-methods program SIR922, which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite3. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atom was located in a difference Fourier map and its coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0394, wR = 0.0446.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comment:

The NH group interacts with one of the O atoms of the *ortho* nitro substituent (N(2)···O(4) 2.611(2) Å). The N-H···O angle is relatively small (131.9(18)°), suggesting that this may not be a typical hydrogen bond.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC1042
Chemical formula	C20H26N4O6
Formula weight	418.45
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	*P* 21/*c*
a (Å)	12.6942(2)
b (Å)	11.4021(3)
c (Å)	15.3269(7)
α (°)	90
β (°)	113.2169(7)
γ (°)	90
Cell volume (Å3)	2038.77(11)
Z	4
Calculated density (Mg/m3)	1.363
Absorption coefficient (mm-1)	0.102
F000	888
Crystal size (mm)	0.24 x 0.30 x 0.30
Description of crystal	Orange octahedron
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.98
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-16 \leq h \leq 15$, $0 \leq k \leq 14$, $0 \leq l \leq 19$
Reflections measured	21788
Unique reflections	4857
Rint	0.045
Observed reflections ($I > 3\sigma(I)$)	2758
Refinement method	Full-matrix least-squares on *F*
Parameters refined	275
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.1154
R	0.0394
wR	0.0446
Residual electron density (min,max) (eÅ-3)	-0.19, 0.21

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C(1)	-0.15145(14)	0.39292(15)	0.14174(12)	0.0283
C(2)	-0.03938(14)	0.37416(16)	0.12612(12)	0.0320
C(3)	0.03072(14)	0.27626(17)	0.19356(14)	0.0346
C(4)	0.05257(13)	0.30911(15)	0.29424(13)	0.0283
C(5)	-0.05499(13)	0.32463(15)	0.31232(12)	0.0284
C(6)	-0.03393(15)	0.35112(18)	0.41540(14)	0.0355
C(7)	-0.14691(16)	0.36101(19)	0.42880(15)	0.0415
C(8)	-0.22362(16)	0.45358(19)	0.36227(15)	0.0404
C(9)	-0.24435(14)	0.42858(17)	0.25943(14)	0.0356
C(10)	-0.13175(14)	0.41993(15)	0.24484(12)	0.0285
C(11)	-0.22120(15)	0.48748(16)	0.07460(13)	0.0337
O(1)	-0.23425(14)	0.58557(13)	0.09653(11)	0.0544
O(2)	-0.26478(12)	0.44924(13)	-0.01505(9)	0.0469
C(12)	-0.32573(19)	0.5367(2)	-0.08728(15)	0.0519
C(13)	-0.44812(19)	0.5466(2)	-0.09969(18)	0.0554
C(14)	0.03172(16)	0.48576(19)	0.13878(14)	0.0416
N(1)	0.14853(11)	0.32963(13)	0.36333(10)	0.0281
N(2)	0.24611(11)	0.31678(13)	0.34463(11)	0.0276
C(15)	0.34965(13)	0.32641(14)	0.41624(12)	0.0240
C(16)	0.45396(13)	0.30832(14)	0.40344(11)	0.0251
C(17)	0.55995(13)	0.32812(15)	0.47630(12)	0.0261
C(18)	0.56454(13)	0.36377(15)	0.56294(12)	0.0259
C(19)	0.46446(15)	0.37640(16)	0.58065(12)	0.0296
C(20)	0.36005(14)	0.35821(16)	0.50860(13)	0.0291
N(3)	0.45494(12)	0.26966(14)	0.31389(10)	0.0324
O(3)	0.54765(11)	0.25766(15)	0.30699(10)	0.0505
O(4)	0.36270(10)	0.24894(14)	0.24636(9)	0.0430
N(4)	0.67497(12)	0.39186(13)	0.63785(11)	0.0309
O(5)	0.67739(12)	0.42200(16)	0.71532(10)	0.0524
O(6)	0.76136(10)	0.38618(12)	0.61975(10)	0.0372

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.2438(17)	0.2886(19)	0.2887(16)	0.043(6)
H(11)	-0.1949	0.3173	0.1275	0.0327
H(21)	-0.0607	0.3505	0.0585	0.0376
H(31)	0.1055	0.2663	0.1869	0.0406
H(32)	-0.0132	0.2010	0.1769	0.0406
H(51)	-0.0953	0.2472	0.2987	0.0339
H(61)	0.0087	0.4269	0.4344	0.0431
H(62)	0.0130	0.2865	0.4566	0.0431
H(71)	-0.1304	0.3836	0.4960	0.0517
H(72)	-0.1871	0.2835	0.4146	0.0517
H(81)	-0.2989	0.4545	0.3688	0.0508
H(82)	-0.1860	0.5320	0.3804	0.0508
H(91)	-0.2918	0.4933	0.2188	0.0422
H(92)	-0.2867	0.3527	0.2401	0.0422
H(101)	-0.0927	0.4979	0.2601	0.0338
H(121)	-0.2876	0.6146	-0.0674	0.0614
H(122)	-0.3227	0.5131	-0.1491	0.0614
H(131)	-0.4876	0.6067	-0.1493	0.0600
H(132)	-0.4518	0.5705	-0.0382	0.0600
H(133)	-0.4869	0.4690	-0.1199	0.0600
H(141)	0.1026	0.4677	0.1278	0.0502
H(142)	0.0535	0.5164	0.2048	0.0502
H(143)	-0.0144	0.5462	0.0921	0.0502
H(171)	0.6320	0.3165	0.4656	0.0322
H(191)	0.4697	0.3985	0.6454	0.0364
H(201)	0.2891	0.3676	0.5214	0.0361

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0244(8)	0.0248(8)	0.0324(9)	-0.0025(7)	0.0077(7)	-0.0004(7)
C(2)	0.0274(8)	0.0396(10)	0.0270(9)	-0.0044(8)	0.0085(7)	0.0002(7)
C(3)	0.0246(8)	0.0382(10)	0.0386(10)	-0.0079(8)	0.0098(7)	0.0034(7)
C(4)	0.0243(8)	0.0238(8)	0.0358(9)	0.0013(7)	0.0109(7)	0.0027(6)
C(5)	0.0220(8)	0.0292(9)	0.0336(9)	0.0003(7)	0.0104(7)	0.0011(6)
C(6)	0.0274(9)	0.0445(11)	0.0359(10)	0.0021(8)	0.0140(7)	0.0020(8)
C(7)	0.0333(10)	0.0550(13)	0.0408(11)	0.0041(9)	0.0196(8)	0.0025(9)
C(8)	0.0322(9)	0.0484(12)	0.0465(12)	-0.0015(9)	0.0219(9)	0.0042(8)
C(9)	0.0242(8)	0.0406(10)	0.0407(10)	0.0007(9)	0.0113(7)	0.0059(7)
C(10)	0.0231(7)	0.0278(9)	0.0336(9)	-0.0016(7)	0.0101(7)	0.0012(7)
C(11)	0.0304(9)	0.0317(10)	0.0358(10)	0.0000(8)	0.0095(8)	0.0010(7)
O(1)	0.0704(10)	0.0293(8)	0.0465(9)	-0.0011(7)	0.0049(8)	0.0088(7)
O(2)	0.0478(8)	0.0519(9)	0.0308(7)	-0.0024(6)	0.0048(6)	0.0198(7)
C(12)	0.0540(13)	0.0707(16)	0.0288(10)	0.0096(10)	0.0140(9)	0.0254(11)
C(13)	0.0413(11)	0.0524(14)	0.0562(14)	0.0100(11)	0.0018(10)	0.0035(10)
C(14)	0.0366(10)	0.0514(12)	0.0374(11)	0.0001(9)	0.0153(8)	-0.0089(9)
N(1)	0.0218(7)	0.0294(8)	0.0337(8)	0.0032(6)	0.0117(6)	0.0026(6)
N(2)	0.0213(7)	0.0322(8)	0.0296(8)	0.0022(7)	0.0103(6)	0.0024(6)
C(15)	0.0249(8)	0.0215(8)	0.0261(8)	0.0042(7)	0.0105(6)	0.0025(6)
C(16)	0.0242(8)	0.0270(9)	0.0255(8)	0.0020(7)	0.0113(7)	0.0022(6)
C(17)	0.0241(8)	0.0259(8)	0.0304(9)	0.0034(7)	0.0130(7)	0.0031(6)
C(18)	0.0239(8)	0.0260(9)	0.0251(9)	0.0044(7)	0.0068(7)	0.0022(6)
C(19)	0.0329(9)	0.0313(9)	0.0269(9)	0.0012(7)	0.0143(7)	0.0013(7)
C(20)	0.0264(8)	0.0328(10)	0.0310(9)	0.0021(7)	0.0145(7)	0.0023(7)
N(3)	0.0292(7)	0.0409(9)	0.0284(8)	-0.0014(7)	0.0129(6)	0.0012(6)
O(3)	0.0303(7)	0.0869(12)	0.0387(8)	-0.0111(8)	0.0184(6)	0.0036(7)
O(4)	0.0306(6)	0.0669(10)	0.0292(7)	-0.0110(7)	0.0094(5)	-0.0028(6)
N(4)	0.0299(7)	0.0286(8)	0.0307(8)	0.0021(6)	0.0082(6)	-0.0007(6)
O(5)	0.0439(8)	0.0817(11)	0.0301(7)	-0.0106(7)	0.0130(6)	-0.0161(8)
O(6)	0.0234(6)	0.0417(8)	0.0423(8)	-0.0027(6)	0.0084(5)	0.0028(5)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.548(2)	C(12) - C(13)	1.493(3)
C(1) - C(10)	1.531(2)	N(1) - N(2)	1.3848(19)
C(1) - C(11)	1.512(3)	N(2) - C(15)	1.344(2)
C(2) - C(3)	1.543(3)	N(2) - H(1)	0.90(2)
C(2) - C(14)	1.527(3)	C(15) - C(16)	1.428(2)
C(3) - C(4)	1.504(3)	C(15) - C(20)	1.416(2)
C(4) - C(5)	1.507(2)	C(16) - C(17)	1.387(2)
C(4) - N(1)	1.282(2)	C(16) - N(3)	1.446(2)
C(5) - C(6)	1.525(3)	C(17) - C(18)	1.368(2)
C(5) - C(10)	1.551(2)	C(18) - C(19)	1.407(2)
C(6) - C(7)	1.531(2)	C(18) - N(4)	1.455(2)
C(7) - C(8)	1.523(3)	C(19) - C(20)	1.366(2)
C(8) - C(9)	1.519(3)	N(3) - O(3)	1.2300(18)
C(9) - C(10)	1.535(2)	N(3) - O(4)	1.2421(18)
C(11) - O(1)	1.198(2)	N(4) - O(5)	1.225(2)
C(11) - O(2)	1.336(2)	N(4) - O(6)	1.2345(18)
O(2) - C(12)	1.464(3)		

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

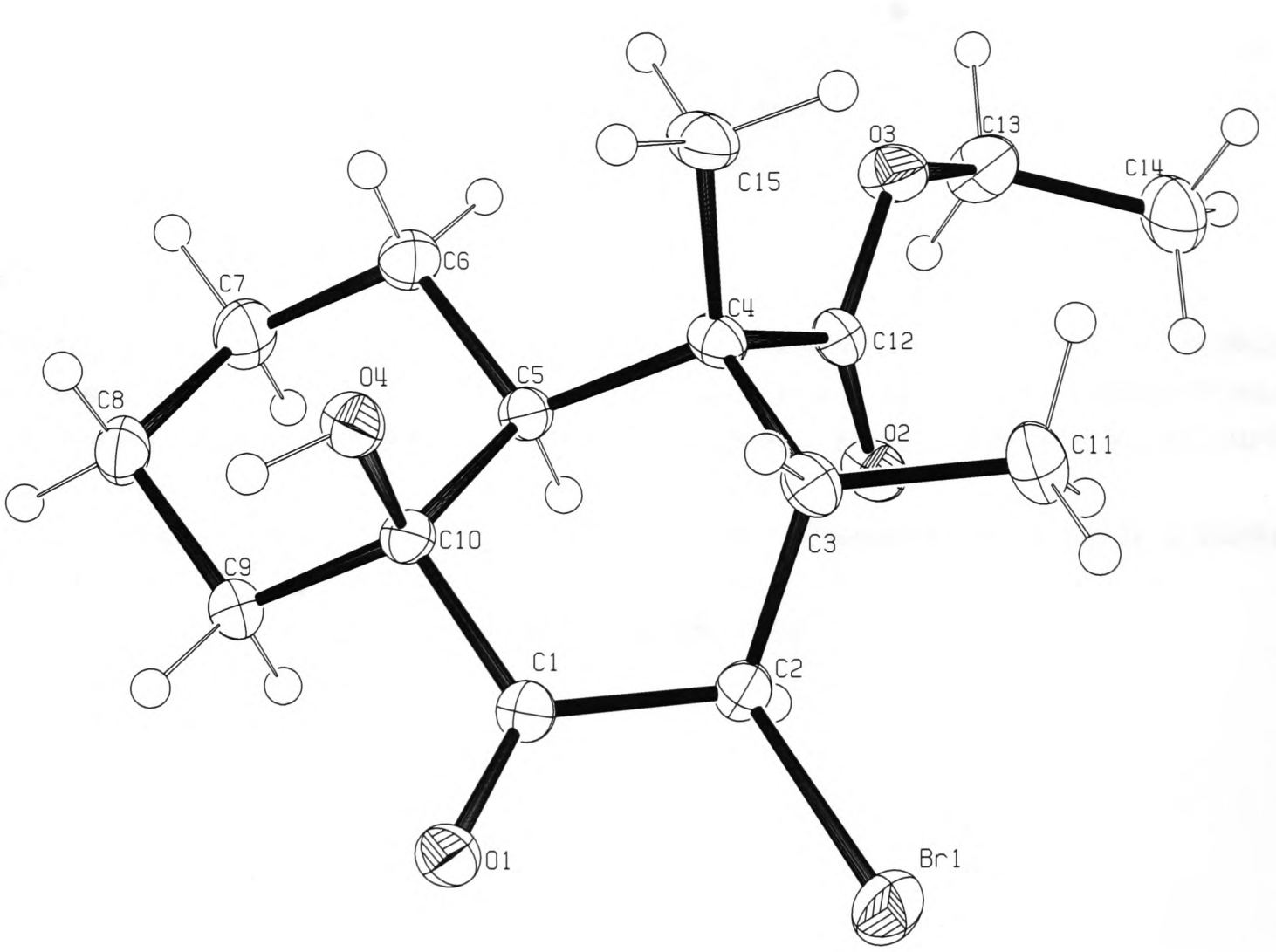
C(2) - C(1) - C(10)	113.67(13)	O(2) - C(12) - C(13)	111.15(19)
C(2) - C(1) - C(11)	108.70(15)	C(4) - N(1) - N(2)	116.49(15)
C(10) - C(1) - C(11)	111.88(14)	N(1) - N(2) - C(15)	119.26(15)
C(1) - C(2) - C(3)	108.59(15)	N(1) - N(2) - H(1)	122.4(13)
C(1) - C(2) - C(14)	113.47(15)	C(15) - N(2) - H(1)	117.3(13)
C(3) - C(2) - C(14)	111.20(15)	N(2) - C(15) - C(16)	122.50(15)
C(2) - C(3) - C(4)	109.37(14)	N(2) - C(15) - C(20)	120.86(15)
C(3) - C(4) - C(5)	113.84(14)	C(16) - C(15) - C(20)	116.63(14)
C(3) - C(4) - N(1)	128.61(15)	C(15) - C(16) - C(17)	121.58(15)
C(5) - C(4) - N(1)	117.49(16)	C(15) - C(16) - N(3)	121.99(14)
C(4) - C(5) - C(6)	114.35(14)	C(17) - C(16) - N(3)	116.43(14)
C(4) - C(5) - C(10)	109.64(14)	C(16) - C(17) - C(18)	119.12(15)
C(6) - C(5) - C(10)	111.08(14)	C(17) - C(18) - C(19)	121.43(15)
C(5) - C(6) - C(7)	111.26(15)	C(17) - C(18) - N(4)	119.38(14)
C(6) - C(7) - C(8)	110.28(16)	C(19) - C(18) - N(4)	119.17(15)
C(7) - C(8) - C(9)	111.61(16)	C(18) - C(19) - C(20)	119.38(16)
C(8) - C(9) - C(10)	111.90(15)	C(15) - C(20) - C(19)	121.70(15)
C(1) - C(10) - C(5)	110.58(14)	C(16) - N(3) - O(3)	118.81(14)
C(1) - C(10) - C(9)	112.39(14)	C(16) - N(3) - O(4)	119.39(13)
C(5) - C(10) - C(9)	108.92(14)	O(3) - N(3) - O(4)	121.80(15)
C(1) - C(11) - O(1)	125.68(18)	C(18) - N(4) - O(5)	118.36(14)
C(1) - C(11) - O(2)	111.17(15)	C(18) - N(4) - O(6)	118.43(15)
O(1) - C(11) - O(2)	123.11(18)	O(5) - N(4) - O(6)	123.20(15)
C(11) - O(2) - C(12)	115.88(16)		

Note – geometrically-positioned H atoms have been excluded

6.3 X-ray crystallographic structure of α-bromo-α'-hydroxy ketone (183)

Single-crystal X-ray diffraction report for $C_{15}H_{23}BrO_4$ (ARC1177)

Andrew R. Cowley
E-mail: andrew.cowley@chem.ox.ac.uk
Tel. (2)85018



Crystals of **ARC1177** were grown by *. A single crystal having dimensions approximately 0.06 x 0.06 x 0.14 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package1.

The structure was solved in the space group $P\ \bar{1}$ using the direct-methods program SIR922, which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite3. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The OH hydrogen atom was located in a difference Fourier map and its coordinates and isotropic thermal parameter subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0289, wR = 0.0328.

Attached is a thermal ellipsoid plot (ORTEP-3[4]) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comment:

The hydroxyl group forms a hydrogen bond to the ketone oxygen atom of a neighbouring molecule (O(4)···O(1)' 2.8233(19) Å, symmetry operator 1-*x*, 1-*y* 1-z), resulting in the formation of a centrosymmetric dimer.

References:

1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.

2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi ,M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.

3 CRYSTALS Issue 12, P. W. Betteridge, J. R. Cooper, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.*, 2003, **36**, 1487

4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC1177
Chemical formula	C15H13BrO4
Formula weight	347.25
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\ \bar{1}$
a (Å)	9.1277(2)
b (Å)	9.4920(2)
c (Å)	10.3893(2)
α (°)	116.9735(10)
β (°)	101.0718(10)
γ (°)	93.4861(9)
Cell volume (Å3)	775.94(3)
Z	2
Calculated density (Mg/m3)	1.486
Absorption coefficient (mm-1)	2.659
F000	360
Crystal size (mm)	0.06 x 0.06 x 0.14
Description of crystal	Colourless prism
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.69, 0.85
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 10$, $0 \leq l \leq 13$
Reflections measured	11368
Unique reflections	3527
Rint	0.028
Observed reflections ($I > 3\sigma(I)$)	2915
Refinement method	Full-matrix least-squares on *F*
Parameters refined	185
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.0692
R	0.0289
wR	0.0328
Residual electron density (min,max) (eÅ-3)	-0.65, 0.31

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C(1)	0.4581(2)	0.2331(2)	0.30555(18)	0.0210
C(2)	0.4274(2)	0.0518(2)	0.23323(19)	0.0220
C(3)	0.5504(2)	-0.0072(2)	0.3107(2)	0.0236
C(4)	0.7074(2)	0.0318(2)	0.28218(19)	0.0218
C(5)	0.71713(19)	0.1838(2)	0.25848(19)	0.0207
C(6)	0.8810(2)	0.2620(2)	0.2893(2)	0.0298
C(7)	0.8877(2)	0.4001(2)	0.2519(3)	0.0343
C(8)	0.7950(2)	0.5243(2)	0.3353(2)	0.0313
C(9)	0.6322(2)	0.4456(2)	0.3031(2)	0.0249
C(10)	0.62499(19)	0.3088(2)	0.34327(18)	0.0203
O(1)	0.36116(15)	0.31524(16)	0.33936(15)	0.0284
Br(1)	0.22181(2)	-0.02048(3)	0.23183(3)	0.0391
C(11)	0.5107(3)	-0.1844(2)	0.2680(3)	0.0337
C(12)	0.7175(2)	-0.1049(2)	0.1328(2)	0.0221
O(2)	0.62365(16)	-0.14550(16)	0.01657(14)	0.0288
O(3)	0.84000(16)	-0.17307(17)	0.13979(16)	0.0315
C(13)	0.8627(2)	-0.2928(3)	-0.0028(2)	0.0370
C(14)	0.7705(3)	-0.4537(3)	-0.0561(3)	0.0429
C(15)	0.8323(2)	0.0483(2)	0.4121(2)	0.0299
O(4)	0.68168(15)	0.36453(16)	0.49997(14)	0.0257

Table 3: Atomic coordinates and isotropic thermal parameters ($Å^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.659(3)	0.454(4)	0.545(3)	0.052(8)
H(21)	0.4326	0.0033	0.1267	0.0254
H(31)	0.5575	0.0524	0.4201	0.0293
H(51)	0.6687	0.1410	0.1501	0.0236
H(61)	0.9311	0.3042	0.3972	0.0347
H(62)	0.9361	0.1792	0.2271	0.0347
H(71)	0.9955	0.4529	0.2808	0.0418
H(72)	0.8462	0.3566	0.1423	0.0418
H(81)	0.8418	0.5750	0.4448	0.0362
H(82)	0.7950	0.6085	0.3026	0.0362
H(91)	0.5757	0.5284	0.3629	0.0291
H(92)	0.5837	0.4015	0.1945	0.0291
H(111)	0.5949	-0.2152	0.3218	0.0434
H(112)	0.4962	-0.2516	0.1580	0.0434
H(113)	0.4151	-0.2020	0.2962	0.0434
H(131)	0.9723	-0.3029	0.0099	0.0374
H(132)	0.8324	-0.2562	-0.0789	0.0374
H(141)	0.7888	-0.5320	-0.1533	0.0484
H(142)	0.8005	-0.4916	0.0191	0.0484
H(143)	0.6606	-0.4449	-0.0697	0.0484
H(151)	0.9335	0.0732	0.3965	0.0344
H(152)	0.8250	-0.0545	0.4172	0.0344
H(153)	0.8201	0.1371	0.5074	0.0344

Table 4: Anisotropic thermal parameters ($Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0244(8)	0.0207(8)	0.0150(8)	0.0054(6)	0.0062(6)	0.0046(6)
C(2)	0.0209(8)	0.0207(8)	0.0218(8)	0.0075(7)	0.0070(6)	0.0023(6)
C(3)	0.0290(9)	0.0220(8)	0.0221(9)	0.0110(7)	0.0091(7)	0.0079(7)
C(4)	0.0241(9)	0.0213(8)	0.0191(8)	0.0082(7)	0.0058(7)	0.0084(6)
C(5)	0.0202(8)	0.0196(8)	0.0193(8)	0.0065(6)	0.0047(6)	0.0046(6)
C(6)	0.0217(9)	0.0279(9)	0.0372(11)	0.0127(8)	0.0087(8)	0.0046(7)
C(7)	0.0287(10)	0.0304(10)	0.0455(12)	0.0170(9)	0.0156(9)	0.0032(8)
C(8)	0.0292(10)	0.0215(8)	0.0397(11)	0.0117(8)	0.0093(8)	0.0012(7)
C(9)	0.0255(9)	0.0199(8)	0.0273(9)	0.0096(7)	0.0059(7)	0.0047(7)
C(10)	0.0206(8)	0.0190(7)	0.0162(8)	0.0049(6)	0.0024(6)	0.0036(6)
O(1)	0.0246(7)	0.0234(6)	0.0300(7)	0.0056(5)	0.0084(5)	0.0081(5)
Br(1)	0.02609(11)	0.03279(12)	0.05663(15)	0.01845(10)	0.01474(9)	0.00149(8)
C(11)	0.0420(11)	0.0252(9)	0.0414(11)	0.0191(9)	0.0172(9)	0.0089(8)
C(12)	0.0254(9)	0.0193(8)	0.0233(9)	0.0102(7)	0.0085(7)	0.0069(6)
O(2)	0.0361(7)	0.0269(7)	0.0193(6)	0.0075(5)	0.0050(5)	0.0106(6)
O(3)	0.0261(7)	0.0279(7)	0.0289(7)	0.0032(6)	0.0063(5)	0.0122(5)
C(13)	0.0278(10)	0.0303(10)	0.0354(11)	-0.0013(8)	0.0126(8)	0.0091(8)
C(14)	0.0527(14)	0.0260(10)	0.0422(13)	0.0094(9)	0.0106(10)	0.0119(9)
C(15)	0.0317(10)	0.0302(9)	0.0242(9)	0.0116(8)	0.0006(7)	0.0109(8)
O(4)	0.0304(7)	0.0216(6)	0.0171(6)	0.0036(5)	0.0025(5)	0.0067(5)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.514(2)	C(5) - C(10)	1.533(2)
C(1) - C(10)	1.540(2)	C(6) - C(7)	1.528(3)
C(1) - O(1)	1.213(2)	C(7) - C(8)	1.527(3)
C(2) - C(3)	1.536(2)	C(8) - C(9)	1.525(3)
C(2) - Br(1)	1.9531(17)	C(9) - C(10)	1.536(2)
C(3) - C(4)	1.574(3)	C(10) - O(4)	1.435(2)
C(3) - C(11)	1.531(3)	C(12) - O(2)	1.217(2)
C(4) - C(5)	1.570(2)	C(12) - O(3)	1.332(2)
C(4) - C(12)	1.531(2)	O(3) - C(13)	1.465(2)
C(4) - C(15)	1.530(2)	C(13) - C(14)	1.499(3)
C(5) - C(6)	1.535(3)	O(4) - H(1)	0.83(3)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(2) - C(1) - C(10)	115.30(14)	C(6) - C(5) - C(10)	110.80(14)
C(2) - C(1) - O(1)	123.21(16)	C(5) - C(6) - C(7)	111.68(16)
C(10) - C(1) - O(1)	121.39(15)	C(6) - C(7) - C(8)	111.11(17)
C(1) - C(2) - C(3)	109.96(14)	C(7) - C(8) - C(9)	110.60(16)
C(1) - C(2) - Br(1)	109.64(12)	C(8) - C(9) - C(10)	111.74(15)
C(3) - C(2) - Br(1)	113.83(12)	C(1) - C(10) - C(5)	111.06(13)
C(2) - C(3) - C(4)	109.83(14)	C(1) - C(10) - C(9)	109.00(14)
C(2) - C(3) - C(11)	113.38(16)	C(5) - C(10) - C(9)	110.05(14)
C(4) - C(3) - C(11)	112.08(15)	C(1) - C(10) - O(4)	105.61(14)
C(3) - C(4) - C(5)	111.71(13)	C(5) - C(10) - O(4)	108.67(13)
C(3) - C(4) - C(12)	107.89(14)	C(9) - C(10) - O(4)	112.39(14)
C(5) - C(4) - C(12)	104.01(14)	C(4) - C(12) - O(2)	122.97(16)
C(3) - C(4) - C(15)	107.93(15)	C(4) - C(12) - O(3)	114.37(15)
C(5) - C(4) - C(15)	113.04(15)	O(2) - C(12) - O(3)	122.63(16)
C(12) - C(4) - C(15)	112.16(14)	C(12) - O(3) - C(13)	116.24(15)
C(4) - C(5) - C(6)	112.65(14)	O(3) - C(13) - C(14)	111.75(19)
C(4) - C(5) - C(10)	114.28(14)	C(10) - O(4) - H(1)	108(2)

Note – geometrically-positioned H atoms have been excluded