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Permanganate Mediated Oxidative Cyclisation and its Application to the Synthesis of Natural Products

by

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Abstract

Cis-2,5-disubstituted tetrahydrofurans (THFs) are present in a large number of biologically active molecules, including many polyether antibiotics and acetogenins. In view of the importance of THF-containing structures, their efficient stereocontrolled synthesis remains an important objective.

Permanganate mediated oxidative cyclisation of 1,5,9-trienoates and subsequent oxidative cleavage provided the corresponding perhydro-2,2-bifuranyl systems with control of relative stereochemistry at four new stereocentres. Optically pure THF-lactones were obtained through the use of the Oppolzer sultam chiral auxiliary. The requisite starting trienes were prepared stereoselectively in just three steps from geranyl and neryl chlorides, providing a short and versatile route to polyether fragments.

Permanganate promoted oxidative oxidation was applied toward the synthesis of a natural product, intricatetraol. The construction of a non adjacent *bis*-THF diol core was investigated *via* tandem oxidative cyclisation of a tetraene precursor. The tetraene precursor was selectively prepared by coupling two moieties synthesised from neryl acetate. An alternative approach to the synthesis of intricatetraol was also investigated where the *bis*-THF core was formed *via* the coupling of two THF rings. The revised approach relied on a metathesis reaction to couple the two THF-containing fragments. Selective oxidative cyclisation of readily available 1,5,9-trieneoates provided the desired mono-THFs that would provide the non adjacent *bis*-THF segment *via* metathesis.

The oxidation of readily available 1,5-dienoates and 1,5,9-trienoates containing a terminal double bond afforded *cis*-THF-containing products that were easily converted to the corresponding *trans*-THF adducts. This new methodology was applied toward the synthesis of eurylene, a natural product.

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And finally, I would like to thank my parents for the moral support, trust and love. They have always been there for me throughout these three years.

Abbreviations

δ	chemical shift
AIBN	2,2′-azobisisobutyronitrile
app.	apparent
aq.	aqueous
arom	aromatic
br	board
CAN	ammonium cerium(IV) nitrate
CH_2Cl_2	dichloromethane
CI	chemical ionisation
CSA	10-camphorsulfonic acid
d	doublet(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereoisomeric excess
DIBALH	di-iso-butylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethyl-*N*,*N*′-propylene urea
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
ee	enantiomeric excess
EI	electron impact ionisation
eq.	equivalent(s)
Et_2O	diethyl ether
EtOAc	ethyl acetate
FT	Fourier transformation
GC	gas chromatography

h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IDCP	iodonium dicollidine perchlorate
i-Pr	*iso*-propyl
IR	infrared
IUPAC	International union of pure and applied chemistry
J	coupling constant
KHMDS	potassium hexamethyldisilazide
$LiAlH_4$	lithium aluminum hydride
LiHMDS	lithium hexamethyldisilazanide
m	multiplet(s)
m/z	mass to charge ratio
m-CPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile
MEM	methoxyethoxymethy
min	minute(s)
mmol	millimole(s)
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonnance
NOE	nuclear Overhauser effect
PDC	pyridinium dichromate
Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PS	polystyrene
p-TSA	*p*-toluenesulfonic acid
q	quartet(s)
qu	quintet

r.t.	room temperature
s	singlet
SiO_2	silica gel
sol.	solution
t	triplet(s)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammunium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
UV	ultraviolet

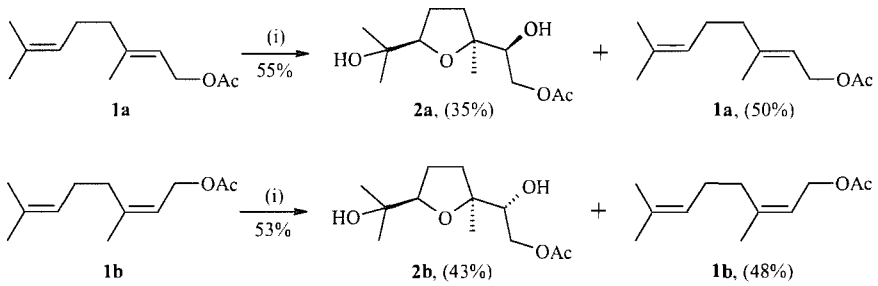
Chapter 1: Synthetic routes to 2,5-disubstituted tetrahydrofurans

2,5-Disubstituted tetrahydrofurans (THF) are a common part of many biologically active natural products.[1-5] Therefore, numerous synthetic approaches to THF fragments have been developed and published over the years. The following chapter summarises the main synthetic routes used to prepare 2,5-disubstituted tetrahydrofurans directly from alkene precursors.[6]

1-I Oxidative cyclisation of 1,5-dienes

1-I-1 Permanganate mediated oxidative cyclisation

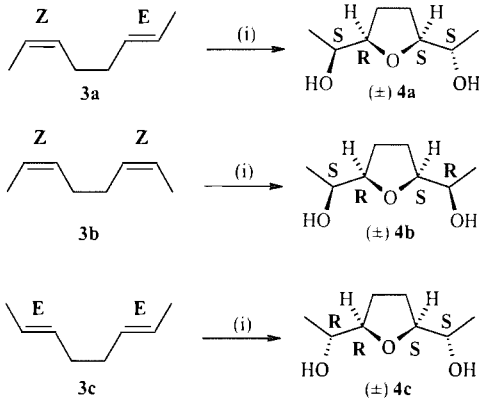
In 1924, Kötz *et al.* attempted oxidation of geranyl acetate with potassium permanganate under slightly basic conditions.[7] Unfortunately, they failed to identify the product and described it as a "oxidodioxygeraniolmonoacetate". Twenty-two years later, Klein *et al.*[8] attempted the same reaction and elucidated the product isolated by Kötz *et al.* as a 2,5-disubstituted THF (Scheme 1.1). This reaction proceeded stereospecifically and yielded only *cis*-isomers.



Conditions and reagents: (i) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, 0°C, 30 min.

Scheme 1.1: First example of $KMnO_4$ mediated oxidative cyclisation.

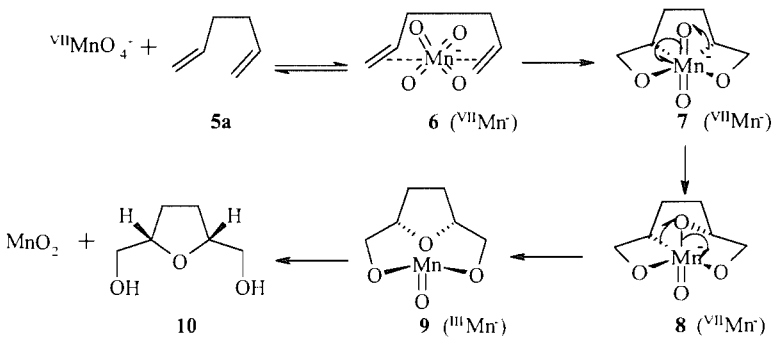
The synthetic potential of this stereoselective reaction is quite important as it opens the possibility of stereocontrolled total synthesis of THF containing natural products. Walba *et al.* investigated the extent of the stereoselectivity of this reaction and the mechanism of action of potassium permanganate on the 1,5-dienes.[9] After oxidative cyclisation of the 1,5-dienes **3a-c**, analysis by gas chromatography showed that the corresponding racemic THFs **4a-c** were obtained with approximately 97% stereoselectivity (Scheme 1.2). This study also showed that the resulting stereochemistry of the THF depends on the geometry of the polyene precursor.



Conditions and reagents: (i) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, –20°C, 30 min.

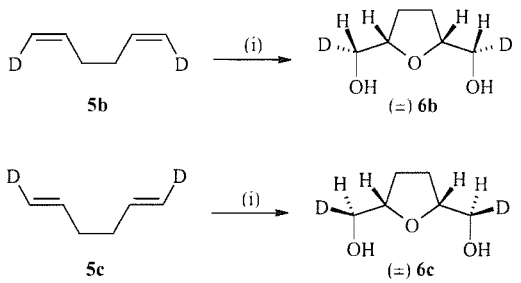
Scheme 1.2: $KMnO_4$ oxidation of dienes.

Walba *et al.* applied Sharpless[10] proposals concerning the mechanism of oxidations of olefins by oxo transition metal species to the permanganate mediate oxidative cyclisation (Scheme 1.3). It is thought that after the formation of *bis*-π-complex **6** between diene **5a** and MnO_4^-, an octahedral Mn (VII) intermediate **7** is produced *via* two Sharpless-type [2+2] additions. Alkyl migration from the Mn to one of the oxygen atoms with retention affords **8** and after a reductive elimination, Mn (III) diester **9** undergoes oxidation and hydrolysis to yield MnO_2 and the desired *cis*-THF **10** with the correct relative stereochemistry.



Scheme 1.3: Walba's mechanism for the $KMnO_4$ oxidative cyclisation

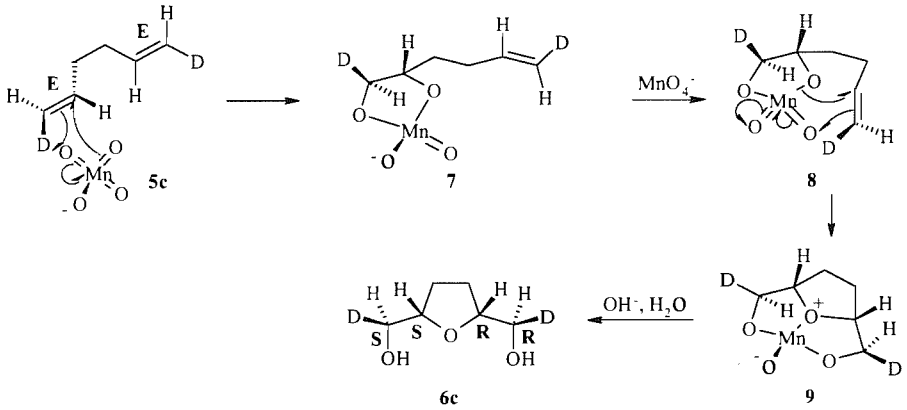
At the same time, Baldwin *et al.* investigated this reaction and its mechanism.[11] Deuterated dienes **5b,c** were oxidised with permanganate and yielded the corresponding racemic THFs **6b,c** (Scheme 1.4). NMR analysis confirmed the *cis* stereoselectivity of the reaction.



Conditions and reagents: (i) $KMnO_4$, acetone/water (5:1), pH = 7.5, CO_2 bubbling, –20°C, 30 min.

Scheme 1.4: $KMnO_4$ oxidation of dienes.

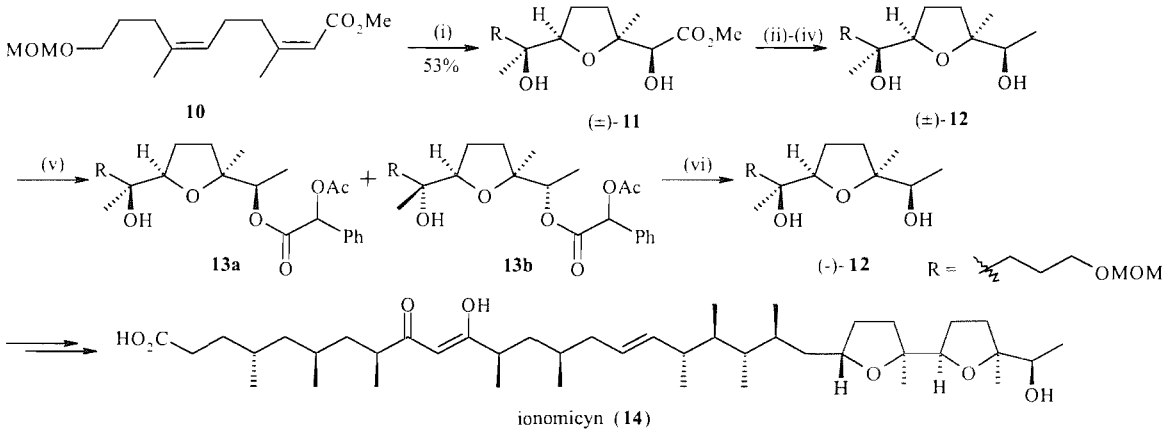
In the reported mechanism, the Mn atom is thought to undergo a [3+2] cycloaddition on the first double bond forming the intermediate Mn^V ester **7**. After rapid oxidation with permanganate, a second [3+2] cycloaddition occurs on the remaining double bond. Basic hydrolysis of the intermediate **9** affords cyclised product **6c** with retention of configuration (scheme 1.5). This mechanism is also supported by evidence for the intermediacy of a cyclic Mn^V ester in the reaction of alkenes with permanganate.[12]



Scheme 1.5: Baldwin's proposed mechanism for the $KMnO_4$ oxidative cyclisation

Wolfe *et al.*[13] have repeated the permanganate oxidative cyclisation on 1,5-hexadiene **5a** in the presence of 92% $H_2{}^{18}O$. Mass spectrometry analysis showed the presence of a labelled oxygen in the THF adduct. It proved that only one of the oxygen atoms was derived from the solvent. This finding is incompatible with the mechanism described by Walba *et al.* in which all three oxygen atoms are derived from a single molecule of permanganate. The fact that a symmetrical substrate is converted into a symmetrical product in an unsymmetrical manner confirms a sequential oxidation of the two double bonds *via* the intermediate Mn^V ester **7** and therefore is in accord with the mechanism proposed by Baldwin *et al.*

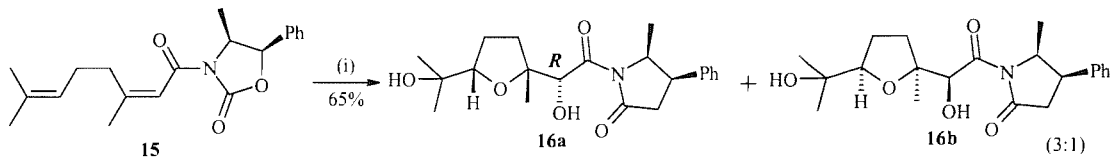
Spino *et al.* have described the synthesis of the THF unit in natural product ionomycin (**14**) using permanganate mediated oxidative cyclisation.[14] Diene **10** was treated with potassium permanganate under Walba's conditions and afforded THF **11** in good yield (scheme 1.6). Sequential reduction of the ester group with $LiAlH_4$, tosylation of the resulting primary alcohol and reduction with $LiAlH_4$ gave racemic THF adduct **12** in good yield. Resolution was achieved using (*S*)-(+)-*O*-acetyl-mandelic acid. After selective condensation at the secondary alcohol with the resoling agent, the resulting diastereoisomers **13a** and **13b** were separated. Basic hydrolysis afforded the optically active diol (–)-**12**.



Reagents and conditions: (i) $KMnO_4$, acetone:H_2O, –25°C; (ii) $LiAlH_4$, THF, 0°C; (iii) TsCl, pyridine, 0°C; (iv) $LiAlH_4$, THF, reflux; (v) (*S*)-(+)-*O*-acetyl mandelic acid, DCC DMAP, CH_2Cl_2, 0°C; (vi) NaOH, H_2O.

Scheme 1.6: Synthesis of optically pure THF fragment **12** *via* $KMnO_4$ oxidative cyclisation

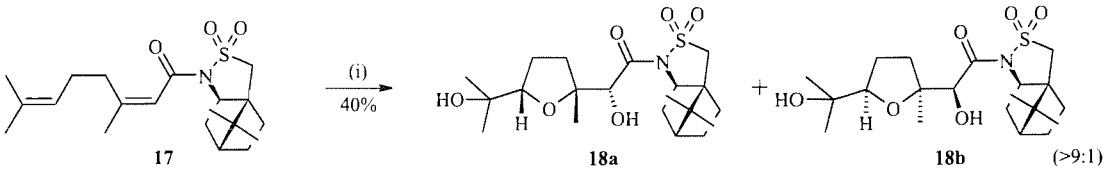
An enantioselective version of the oxidative cyclisation with permanganate was then investigated; Walba *et al.* have reported asymmetric induction in the oxidative cyclisation using 1,5-dienes bearing a chiral auxiliary.[15] Initial attempts were performed using Evans' oxazolidinone (scheme 1.7).[16] Oxazolidinone-functionalized dienoate **15** was prepared by addition of the lithiated oxazolidinone to the corresponding acid chloride. Oxidative cyclisation of dienoate **15** afforded non racemic THFs **16a,b** in a 3:1 ratio and in a good yield, with the major diastereoisomer **16a** resulting from an attack on the *Re* face of the conjugated double bond.



Conditions and reagents: (i) $KMnO_4$, acetone/water (10:1), pH = 7.5, CO_2 bubbling, –30°C, 30 min.

Scheme 1.7: Oxidative cyclisation of enantiomerically enriched dienoate **15**.

The moderate diastereoselectivity was consistent with previous observations of Evans *et al.* showing that Lewis acid catalysis and chelation were probably required to reach high face selectivity.[17] This low selectivity issue was solved by switching from the Evans' oxazolidinone to Oppolzer's camphorsultam auxiliary.[18,19] Diene **17** was prepared by addition of the sodiated (2*R*)-camphorsultam to the corresponding acid chloride (scheme 1.8). Oxidative cyclisation of diene **17** yielded the corresponding THF adducts **18a,b** in an improved 9:1 ratio and moderate yield. The major diastereoisomer **18a** resulted from the attack of the *Re* face of the conjugated double bond, the same facial preference was observed previously by Oppolzer *et al.* in dihydroxylation reactions.[18]

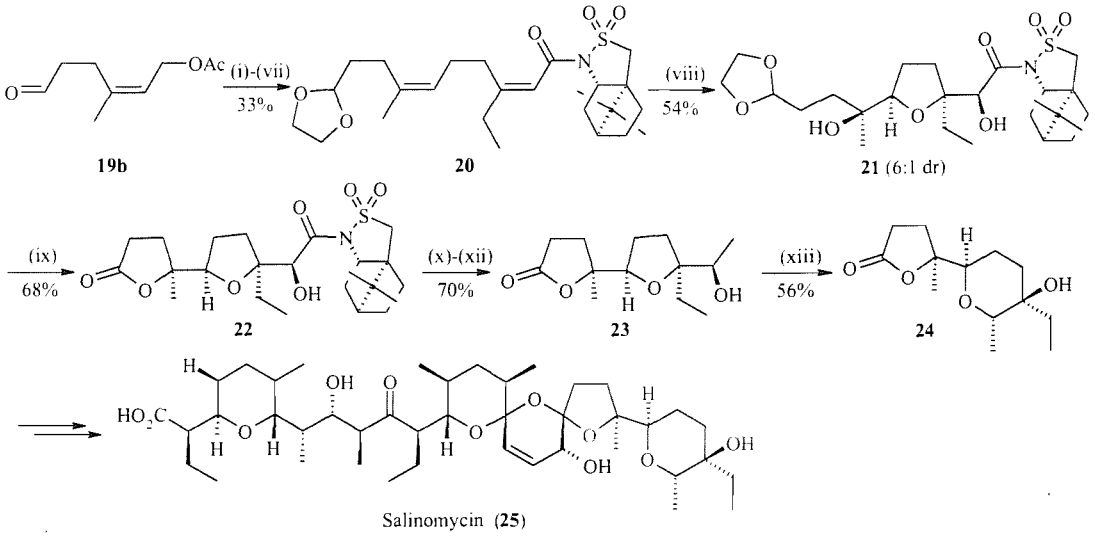


17 18a 18b

Conditions and reagents: (i) $KMnO_4$, acetone/water (10:1), pH = 7.5, CO_2 bubbling, –30°C, 30 min.

Scheme 1.8: Oxidative cyclisation of enantiomerically enriched dienoate **17**.

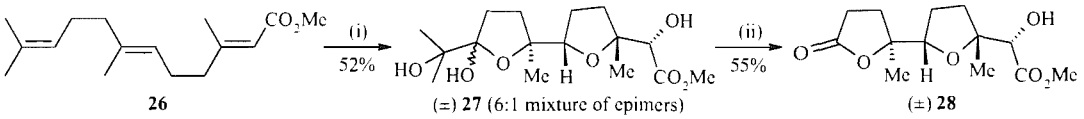
Permanganate oxidative cyclisation has been widely used in natural product synthesis in racemic[14,20,21] and asymmetric versions. The first application of permanganate oxidative cyclisation of a polyene bearing the Oppolzer sultam in total synthesis was reported by Kocienski *et al.*[22] Known aldehyde **19b** was converted in seven steps in the requisite 1,5-diene precursor **20** in good overall yield (scheme 1.9). The replacement of the CO_2 bubbling during the oxidation step by a phosphate buffer (pH 6) improved Walba conditions[15] critically. The desired oxidative cyclisation product **21** was obtained in good yield and diastereoselectivity (dr 6:1). It is interesting to notice that if the reaction was run in the absence of added acetic acid, inferior results were obtained. Treatment of THF adduct **21** with excess ozone gave intermediate hydroxy esters which cyclised using PTSA to afford the corresponding lactone **22** in good yield. The minor diastereoisomer obtained during the oxidation cyclisation step was successfully separated from lactone **22** at this stage. The sultam moiety was reductively removed, the primary alcohol selectively tosylated and subsequently removed *via* a radical reaction with Bu_3SnH to provide lactone **23**. The corresponding mesylate was prepared and underwent silver carbonate promoted solvolytic ring expansion to afford the desired oxane derivative **24**.



Conditions and reagents: (i) $HOCH_2CH_2OH$, PTSA, PhH, reflux (-H_20), 3h; (ii) K_2CO_3, MeOH, r.t., 6.5h; (iii) MsCl, LiCl, 2,6-lutidine, DMF, 0 to 15°C, 3.5h; (iv) $LiC{\equiv}CCH_2Li$, THF, –65 to –10°C, 2.25h; (v) (a) BuLi, THF, –78°C; (b) $ClCO_2Me$, –90 to –10 °C, 3.5h; (vi) Et_2CuLi, THF, –85°C, 3h; (vii) (a) NaOH, MeOH; (b) $(COCl)_2$; (c) (*2S*)-bornane-10,2-sultam, BuLi; (viii) $KMnO_4$, pH 6 acetate buffer, acetone-AcOH-water, –35°C, 5h; (ix) (a) O_3, EtOAc, –80°C, 70 min; (b) PTSA, CH_2Cl_2, r.t., 8h; (x) $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, –10°C, 2h; (xi) TsCl, Et_3N, CH_2Cl_2, r.t., 41h; (xii) NaI, Bu_3SnH, AIBN, DME, 80°C, 7.5h; (xiii) (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 30 min; (b) Ag_2CO_3, acetone-water, reflux, 27h.

Scheme 1.9: $KMnO_4$ oxidative cyclisation of dienoate **20**

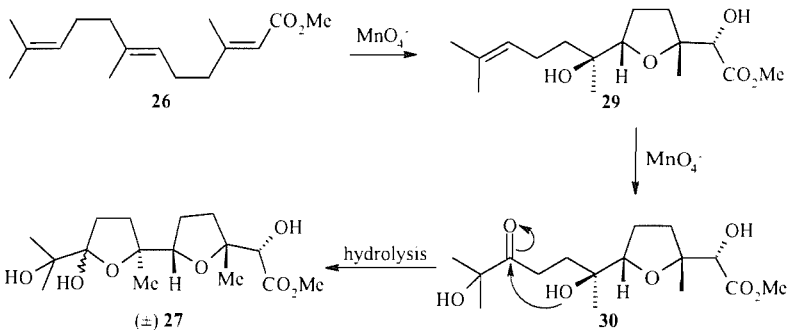
Brown *et al.* have described that permanganate oxidation of 1,5,9-trienes provided regioselectively substituted octahydro-2,2'-bifuranyl systems.[23] Methyl (*E,E*)-farnesoate **26** was easily prepared from farnesol and oxidised by potassium permanganate in buffered aqueous acetone to afford lactol **27** as an mixture of epimers (6:1) (scheme 1.10). Cleavage of the vicinal diol with lead tetraacetate yielded racemic lactone **28** in moderate yield.



Conditions and reagents: (i) $KMnO_4$, acetone, water, AcOH, acetate buffer (pH = 6.5), –30°C; (ii) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Scheme 1.10: Synthesis of racemic lactone **28** *via* $KMnO_4$ oxidative cyclisation

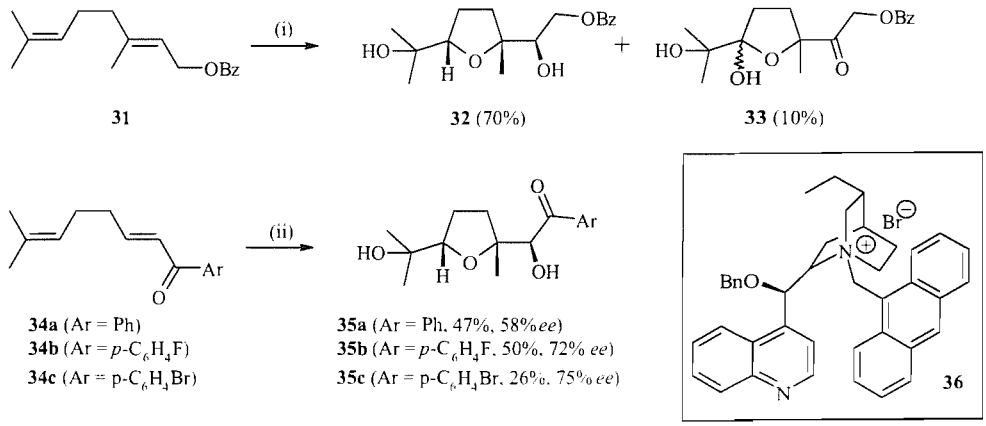
The mechanism of the polycyclisation is in line with the mechanism proposed by Baldwin *et al.*[11] Lactol **27** is formed by oxidation of the remaining double bond to the corresponding hydroxy-ketone **30** and lactol formation (scheme 1.11).



Conditions and reagents: (i) $KMnO_4$, acetone, water, AcOH, acetate buffer (pH = 6.5), –30°C; (ii) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Scheme 1.11: Mechanism of $KMnO_4$ oxidative cyclisation on trienoate **26**.

Brown *et al.* have reported the permanganate promoted oxidative cyclisation of 1,5-dienes using phase-transfer catalysis,[24] oxidation of geranyl benzoate **31** with stoichiometric $KMnO_4$ in presence of AcOH and phase-transfer catalyst Adogen 464 afforded racemic THF **32** in good yield (scheme 1.12). An asymmetric oxidation was also attempted on dienes **34a-c** using a chiral phase-transfer catalyst **36** affording the corresponding THF **35a-c** in moderate yield and good *ee*.

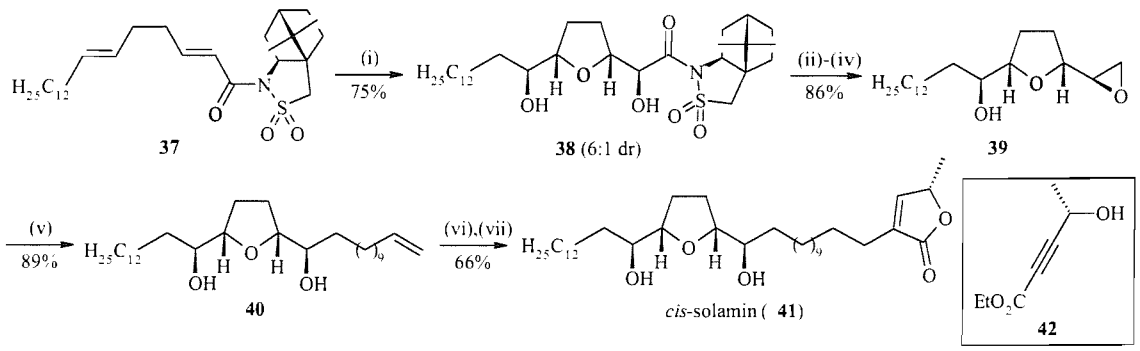


Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (4 eq.), Adogen 464 (0.4 eq.)/Et_2O; (ii) $KMnO_4$ (powdered, 1.6 eq.), AcOH (6.5 eq.), **8** (0.1 eq.)/CH_2Cl_2, –30°C.

Scheme 1.12: $KMnO_4$ oxidative cyclisation under phase transfer conditions

Brown *et al.* have described the synthesis of *cis*-solamin (**41**) using permanganate mediated oxidative cyclisation.[25,26] Diene **37** was treated with powdered potassium permanganate in a mixed solvent system of acetone and AcOH and provided the desired mono-THF adduct **38** in good yield and diastereoselectivity (scheme 1.13). After removal of the sultam auxiliary using $NaBH_4$ and tosylation of the primary alcohol, treatment of the resulting tosylate with DBU

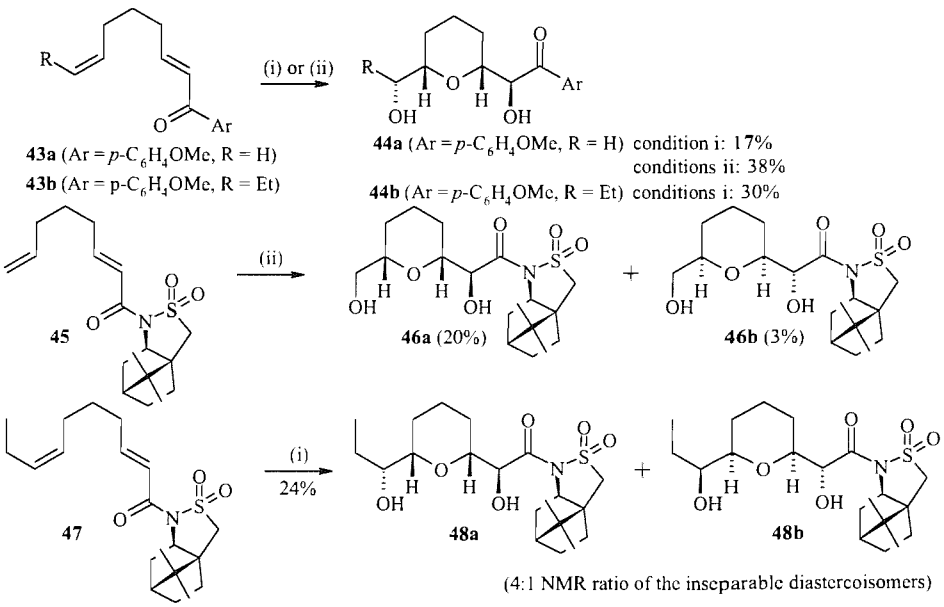
gave the epoxide **39**. Cuprate addition to epoxide **39** afforded mono-THF **40** that underwent a formal Alder-ene reaction with alkyne **42** and subsequent diimide reduction of the double bond to afford *cis*-solamin (**41**) in good yield.



Conditions and reagents: (i) $KMnO_4$ (1.3 eq.), acetone/AcOH (3:2); (ii) $NaBH_4$, THF, H_2O; (iii) Bu_2SnO, C_6H_6 then TsCl, TBAB; (iv) DBU, CH_2Cl_2; (v) CH_2=$CH(CH_2)_9$)MgBr, CuI, THF, –60 to –20°C; (vi) **42**, CpRu(cod)Cl, MeOH, reflux; (vii) $TsNHNH_2$, NaOAc, THF/H_20, 60°C.

Scheme 1.13: Synthesis of *cis*-solamin (**41**).

Brown *et al.* have described the permanganate mediated synthesis of *cis*-2,6-*bis*-hydroxyalkyl-tetrahydropyrans.[27] Racemic 1,6-dienes **43a,b** and dienoyl sultams **45** and **47** underwent oxidative cyclisation with permanganate to afford the corresponding exclusively *cis*-THP adducts in moderate yields (scheme 1.14).

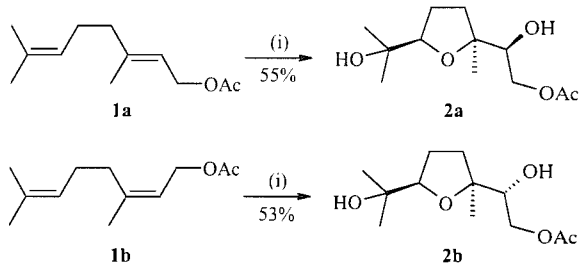


Conditions and reagents: (i) $KMnO_4$ (1.4 eq.), AcOH/acetone (2:3), –15°C; (ii) $KMnO_4$ (1.4 eq.), AcOH (16 eq.), Adogen 464 (10 mol%)/CH_2Cl_2, –60°C.

Scheme 1.14: Synthesis of *cis*-2,6-disubstituted-THP.

1-I-2 Osmium Tetroxide Catalysed Oxidation

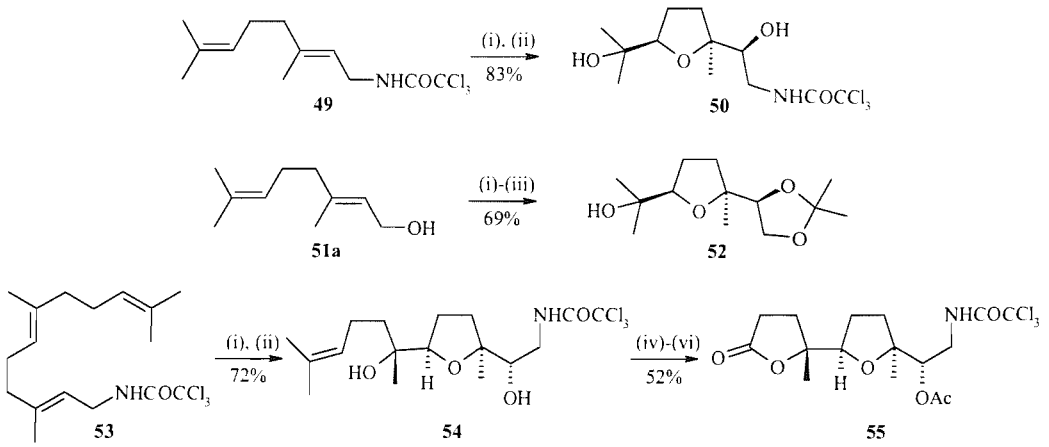
The first example of an osmium tetroxide oxidative cyclisation was published by Piccialli *et al.*[28] Geranyl and neryl acetates **1a,b** were oxidised using catalytic OsO_4 in presence of sodium periodate as co-oxidant and the corresponding 2,5-*cis*-disustituted THFs **2a,b** were obtained in moderate yields (Scheme 1.15).



Conditions and reagents: (i) OsO_4 (5 mol %), $NaIO_4$ (4 eq.), DMF, –10°C, 16h.

Scheme 1.15: First example of OsO_4 mediated oxidative cyclisation.

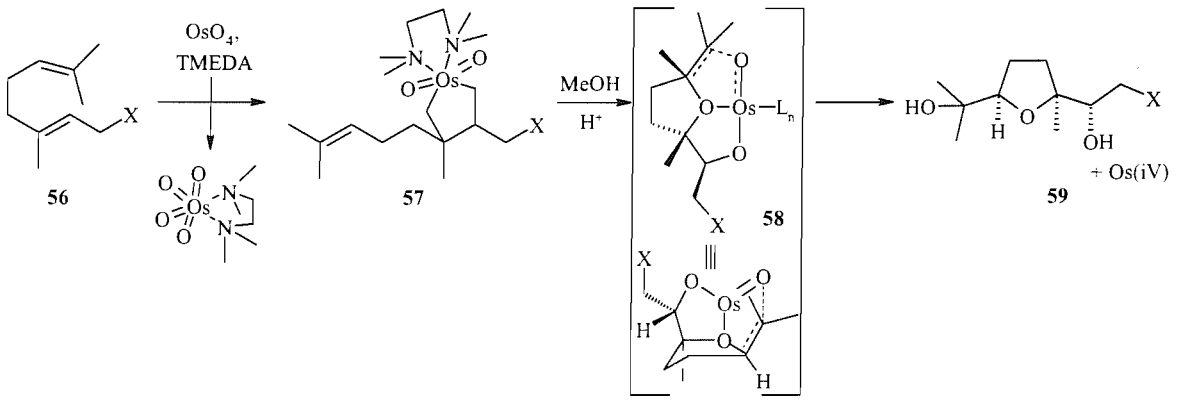
This methodology has been developed further by Donohoe *et al.*; they have reported the synthesis of 2,5-*cis*-disustituted THFs from oxidation using OsO_4 and TMEDA.[29] OsO_4 is combined with TMEDA to form a hydrogen bond acceptor reagent. Directed oxidative cyclisation of 1,5-dienes **49** and **51a** afforded the corresponding 2,5-*cis*-disubstituted THFs **50** and **52** in good yields (Scheme 1.16). It is interesting to note that *bis*-THF systems could also be prepared. OsO_4 mediated oxidative cyclisation of the 1,5-diene unit of triene **53** afforded the resulting THF **54**. After protection of the secondary alcohol and cleavage of the alkene using Lemieux conditions the resulting lactol was oxidised to the lactone **55** with Jones reagent in moderate yield.



Conditions and reagents: (i) OsO_4 (1 eq.), TMEDA (1 eq.), CH_2Cl_2, –78°C; (ii) MeOH, HCl; (iii) $Me_2C(OMe)_2$, (iv) Ac_2O; (v) OsO_4 (cat.), quinuclidine, $NaIO_4$; (vi) CrO_3, H_2SO_4, acetone.

Scheme 1.16: Directed oxidation by OsO_4 / TMEDA

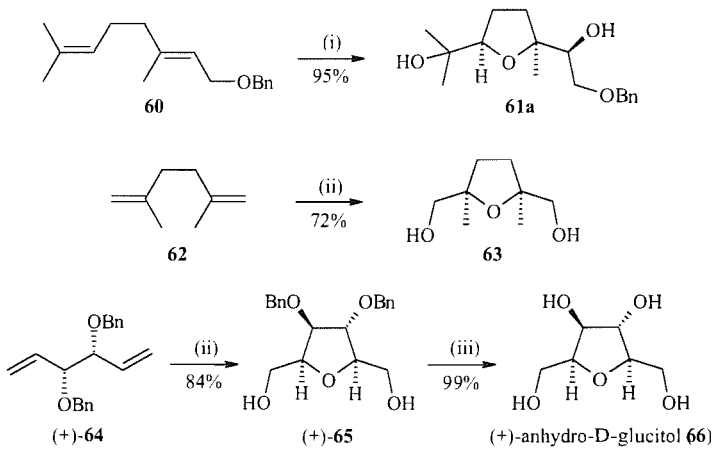
The mechanism of this reaction followed the one proposed by Baldwin (scheme 1.5).[11] The reaction starts with a regioselective dihydroxylation of the polyene, controlled by hydrogen bonding (Scheme 1.17). The Os atom then undergoes a [3+2] cycloaddition with the remaining double bond. It is thought that the acid serves to promote whatever ligand exchange is necessary to allow cyclisation to occur. Alternatively, acid could, by protonation of the oxo ligands make the metal a better electrophile and more reactive during the cyclisation. The *cis* stereoselectivity of this reaction is explained by the transition structure **58**.



Scheme 1.17: Possible mechanism of OsO_4 oxidative cyclisation

Although the yields of this reaction were good, the use of stoichiometric transition metals was a major drawback. Donohoe *et al.* have recently shown that this reaction can be achieved under catalytic conditions using catalytic OsO_4 (5%), Me_3NO (4 eq.) and either CSA (6 eq.)

or TFA (excess) to lower the pH.[30] Under these improved conditions, the dihydroxylation/ oxidative cyclisation provided better yields than when using stoichiometric osmium (Scheme 1.18). Enantiomerically pure adducts could also be obtained. To illustrate the utility of this method, (+)-anhydro-D-glucitol (**66**) was prepared from readily available diene (+)-**64** in good yield.

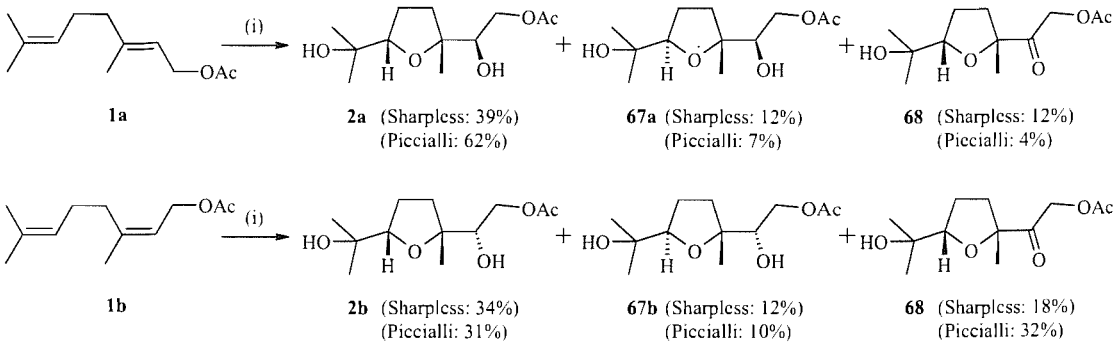


Conditions and reagents: (i) OsO_4 (5%), Me_3NO (4 eq.), TFA (excess), acetone/water (9:1), –78°C; (ii) OsO_4 (5%), Me_3NO (4 eq.), CSA (6 eq.), CH_2Cl_2, –78°C; (iii) H_2, Pd/C, EtOH.

Scheme 1.18: Oxidative cyclisation using catalytic osmium tetroxide

1-I-3 Ruthenium tetroxide oxidative cyclisation

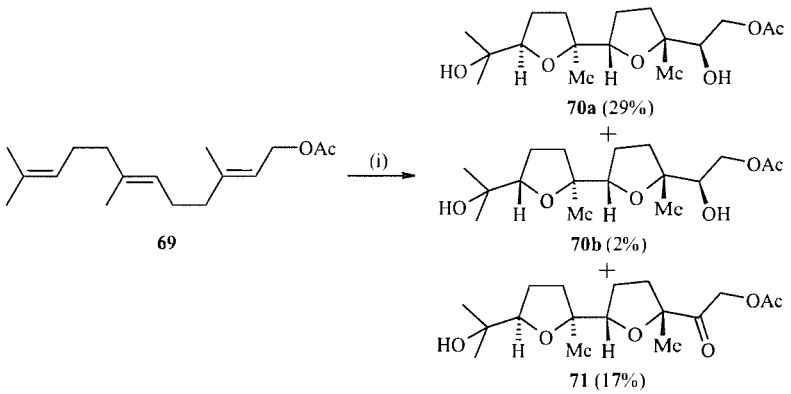
Sharpless *et al.* have reported the first oxidative cyclisation of 1,5-dienes with ruthenium tetroxide.[31] As a part of a study to improve the catalytic conversion of primary alcohols to carboxylic acids with ruthenium, they discovered that the oxidation of geranyl and neryl acetates **1a,b** with their procedure led to the formation of THF adducts **2a,b**, **67a,b** and **68** (scheme 1.19). The 2,5-disubstituted THFs were obtained as mixtures of *cis* and *trans* isomers (3:1 ratio) and a non negligible amount of the *cis*-THF-ketone **68**. Piccialli *et al.* later investigated this reaction and reported a method improving the *cis* stereoselectivity of the process.[32]



Conditions and reagents: (i) Sharpless: $RuCl_3.(H_2O)_n$ (2.2 mol%), $NaIO_4$ (3.1 eq.), CCl_4, H_2O, MeCN, 25°C, 15 min; Picialli: $RuO_2.2H_2O$ (4 mol%), $NaIO_4$ (4 eq.), EtOAc/CH_3CN/H_2O (3:3:1), 0°C, 4 min.

Scheme 1.19: Oxidative cyclisation of neryl and geranyl acetates **1a,b** with RuO_4.

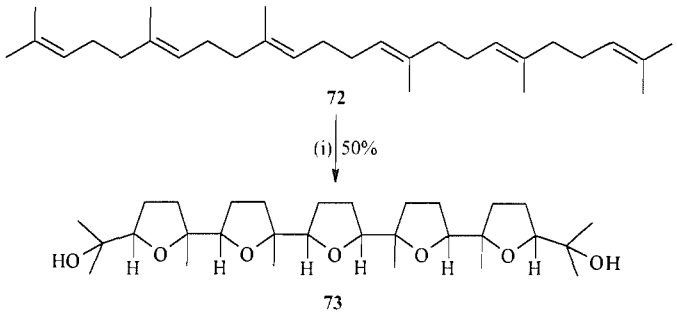
Piccialli *et al.* have reported the construction of *bis*, *tri* and even *penta*-THF units *via* ruthenium tetroxide oxidative cyclisation.[33-35] Oxidation of farnesyl acetate **69** with catalytic $RuO_2.H_2O$ in presence of $NaIO_4$ afforded *bis-cis*-THF diol **70a,b** with high *cis*-selectivity with ketone **71** as the major side-product (scheme 1.20).



Conditions and reagents: (i) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (4 eq.), EtOAc/CH_3CN/H_2O (3:3:1), 0°C, 30 min.

Scheme 1.20: Oxidative cyclisation of farnesyl acetate with RuO_4.

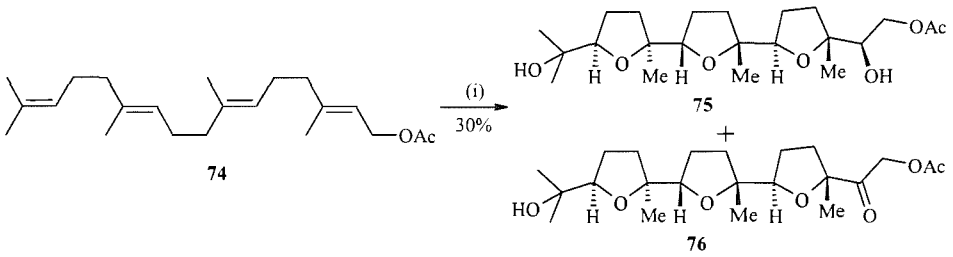
Squalene **72** was oxidised to the *penta*-THF **73** in good yield (scheme 1.21). The relative configuration of the *penta*-THF diol **73** has yet to be determined, although NMR analysis has showed that it possessed a non-*meso* structure.



Conditions and reagents: (i) $RuO_2.2H_2O$ (20mol%), $NaIO_4$ (8 eq.), $EtOAc/CH_3CN/H_2O$ (3:3:1), 0°C, 30 min.

Scheme 1.21: Construction of a *penta*-THF diol *via* ruthenium oxidative cyclisation.

Polycyclisation of geranylgeranyl acetate **74** afforded a mixture of *tri*-THF diol **75** and the corresponding *tri*-THF ketone **76** (2:1) in moderate yield (scheme 1.22). The determination of the relative configuration of *tri*-THF unit **75** was established by a combination of 600MHz 2D NMR studies and chemical correlation work. The relative configuration was also confirmed *via* the preparation of **75** *via* using mechanistically established methods.



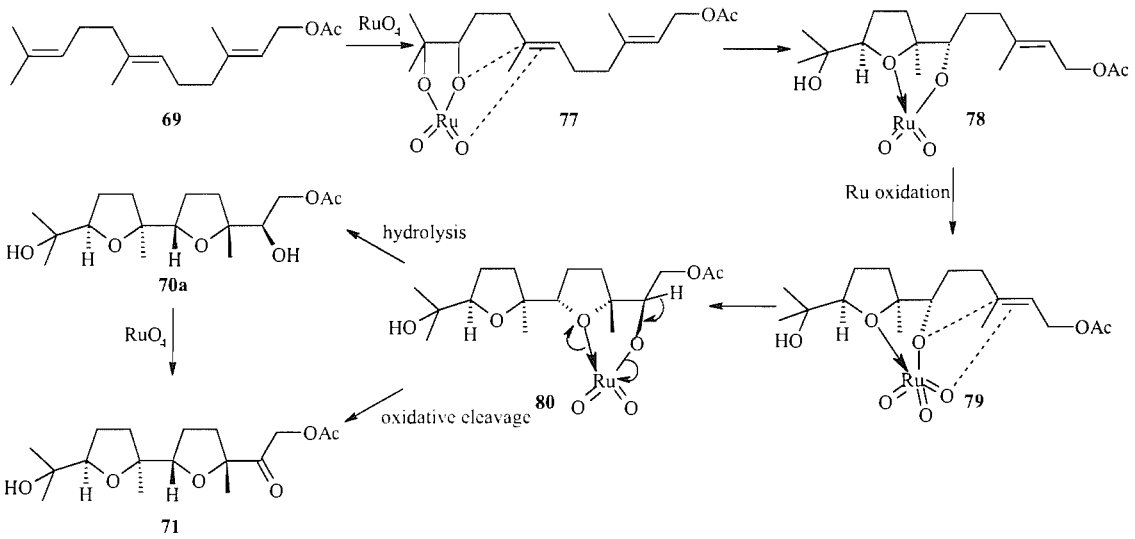
Conditions and reagents: (i) $RuO_2.2H_2O$ (20 mol%), $NaIO_4$ (5 eq.), $EtOAc/CH_3CN/H_2O$ (3:3:1), 0°C, 30 min.

Scheme 1.22: Oxidative cyclisation of geranylgeranyl acetate **74** with RuO_4.

It is thought that the mechanism of this reaction followed the same path as described for permanganate oxidations. In Sharpless publication, they stated that the difference of selectivity between permanganate and ruthenium is probably due to the differences in bond lengths: the longer bonds in the case of the second-row transition metal ruthenium apparently allow incursion of the pathway leading to *trans*-products.[31]

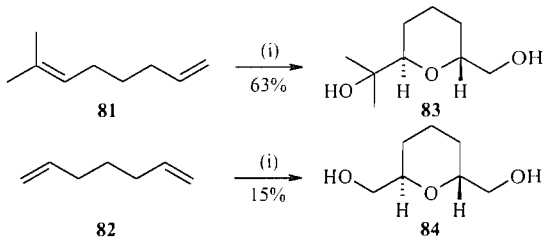
Further studies carried out by Piccialli *et al.* have attempted to establish the mechanism of this reaction for the polycyclisation step.[33-35] It is thought that the formation of Ru^{VI} diester **77** *via* interaction of RuO_4 and the most electron-rich double bond is followed by the closure of the

first THF ring through a [3+2] cycloaddition of the O–Ru=O portion of **77** onto the nearest double bond (scheme 1.23).[33] Intermediate **78** is obtained after hydrolysis. After re-oxidation of the Ru atom to an active oxidation level, species **79** is generated. This explains the requirement for an additional amount of $NaIO_4$ when the number of double bonds increases; each oxidation step requires one equivalent of $NaIO_4$. Intermediate **79** undergoes a second [3+2] cycloaddition of the O–Ru=O portion of **79** onto the last double bond to afford species **80** from which *bis*-THF **70a** is released *via* hydrolysis and ketone **71** by oxidative cleavage (see arrows). It is thought also that over-oxidation of **70a** by RuO_4 leads to the formation of ketone **71**, which explains the high proportion of ketone **71** obtained in this reaction.



Scheme 1.23: Mechanistic hypothesis of the RuO_4 mediated oxidation on triene **61**.

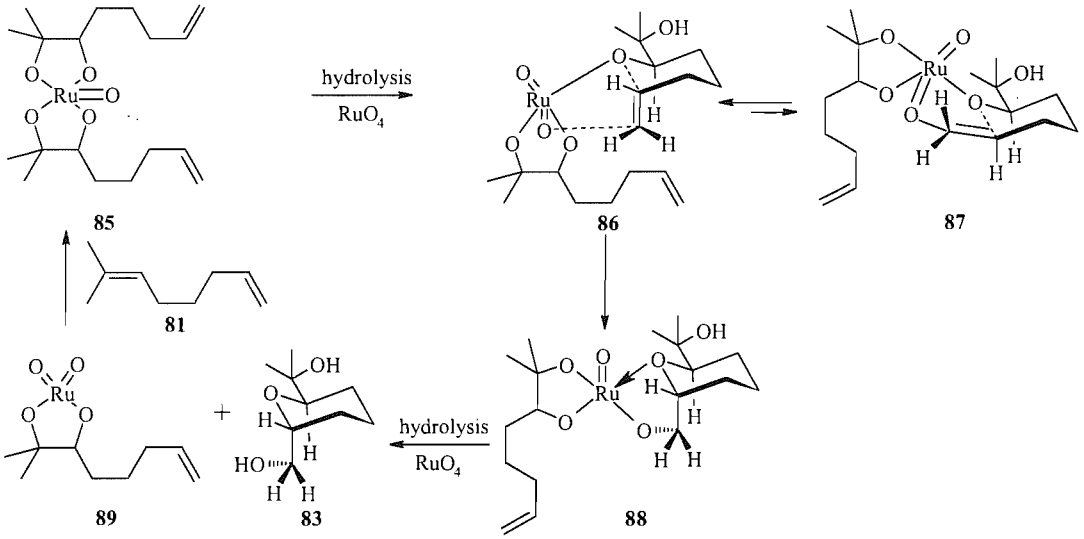
Piccialli *et al.* have also reported the RuO_4-catalysed oxidative cyclisation of 1,6-dienes to *trans*-2,6-disubstituted-THPs.[36] Dienes **81** and **82** were oxidised with ruthenium to afford the corresponding *trans*-THPs **83** and **84** in poor to good yield and good selectivity (scheme 1.24).



Conditions and reagents: (i) $RuO_2.2H_2O$ (5 mol%), $NaIO_4$ (4 eq.), $EtOAc/CH_3CN/H_2O$ (3:3:1), 0°C, 4 min.

Scheme 1.24: Oxidative cyclisation of geranylgeranyl acetate **74** with RuO_4.

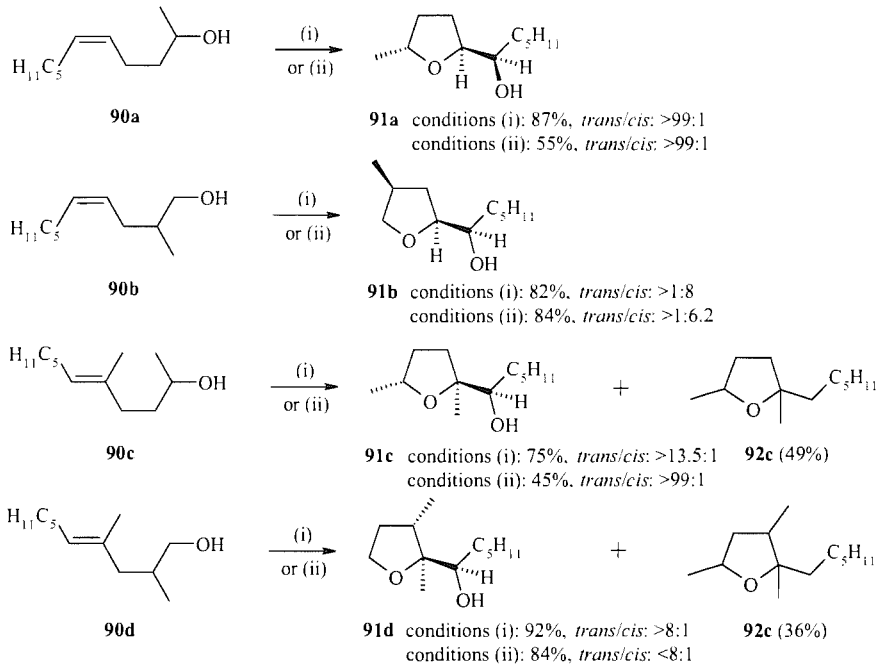
The *trans* stereoselectivity can be explained by applying the mechanistic model proposed by McDonald *et al.*[37] It is thought that after the addition of RuO_4 to the diene **81**, RuO_4 reacts with another molecule of diene to form Ru^{VI} diester **85** (scheme 1.25). Partial hydrolysis of diester **85** followed by ruthenium oxidation leads to intermediate species **86** and **87**. Intermediate **86** is favoured by a smaller number of destabilising *gauche* interactions. Intermediate species **88** is formed *via* a [3+2] cycloaddition and *trans*-THF **83** is obtained after hydrolysis. Monomeric ruthenate ester **89** is then regenerated *via* ruthenium oxidation.



Scheme 1.25: Mechanistic hypothesis of the RuO_4 mediated oxidation on 1,6-diene **81**

1-I-4 Rhenium oxide induced oxidative cyclisation of γ-hydroxy olefins

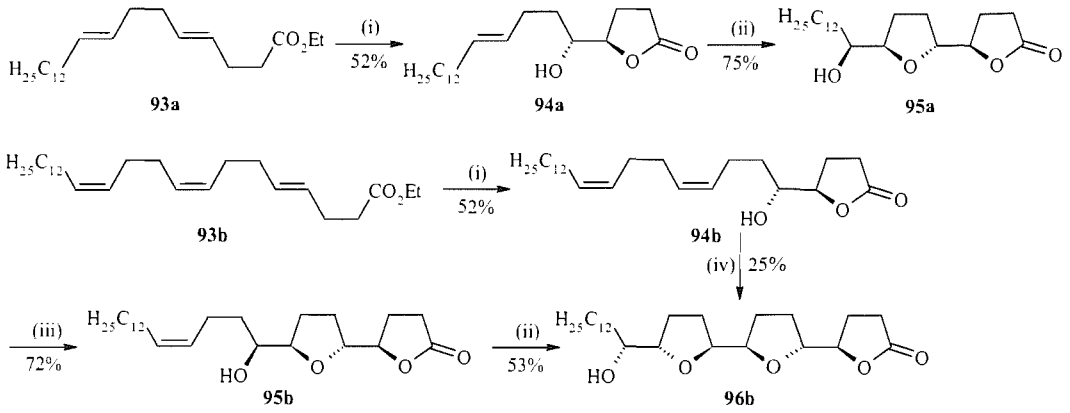
Kennedy *et al.* have reported the synthesis of THF adducts *via* rhenium oxide oxidation on 5-hydroxyalkenes. Alkenes **90a-d** were oxidised successfully by stoichiometric Re_2O_7 in presence of 2,6-lutidine and NaOOH to afford the corresponding *trans*-THFs **91a-d** in good yield and selectivity along with the non-oxidative cyclisation products **92c,d** (scheme 1.26).[38-40] The catalytic version of this reaction, using H_5IO_6 as a cooxidant, gave a slight decrease in yield and selectivity.[41]



Conditions and reagents: (i) Re_2O_7 (3 eq.), 2,6-lutidine (3 eq.), NaOOH, CH_2Cl_2, r.t., 11h; (ii) Re_2O_7 (50mol%), H_5IO_6 (1.3 eq.), $NaHSO_3$, CH_2Cl_2, r.t., 15h.

Scheme 1.26: Oxidative cyclisation of 5-hydroxyalkenes with rhenium oxide

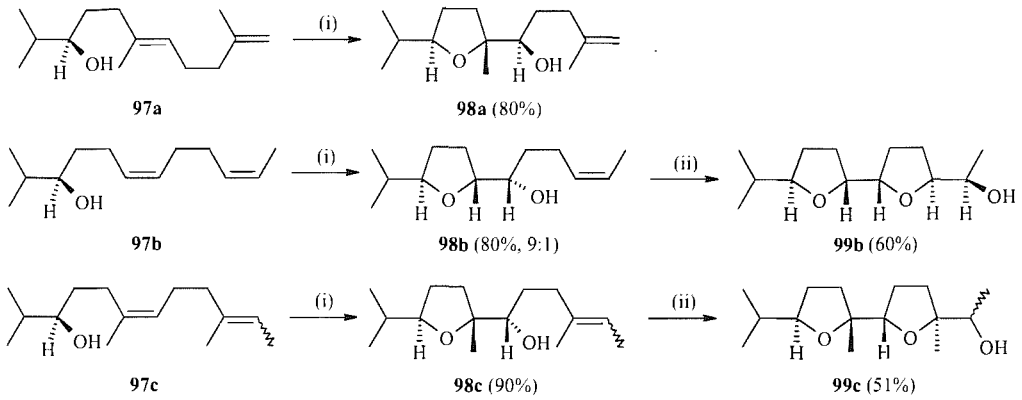
Sinha *et al.* applied Kennedy oxidation to the asymmetric polycyclisation of polyenes.[42] Polyenes **93a,b** were treated with AD-mix-β to afford the corresponding hydroxylatones **94a,b** (scheme 1.27). Oxidation of **94a** with Re_2O_7 produced bicyclic lactone **95a** as a single diastereoisomer. Selective monocyclisation of hydroxylactone **94b** to give product **95b** was achieved by replacing periodic acid by 2,6-lutidine. It seems that reactions proceed much slower with 2,6-lutidine than with periodic acid, probably *via* coordination to the metal. Bicyclic lactone **95b** was treated with the more reactive mixture of Re_2O_7 and periodic acid to produce the tricyclic lactone **96b** in good yield. Tandem oxidative cyclisation with Re_2O_7 and H_5IO_6 of hydroxy lactone **94b** was also achieved to afford **96b** in moderate yield.



Conditions and reagents: (i) AD-mix- β; (ii) Re_2O_7 (1.5 eq.), H_5IO_6 (2 eq.), $NaHSO_3$, CH_2Cl_2, r.t., 35 min; (iii) Re_2O_7 (2 eq.), 2,6-lutidine (4 eq.), CH_2Cl_2, r.t., 15h; (iv) Re_2O_7 (3 eq.), H_5IO_6 (4 eq.), $NaHSO_3$, CH_2Cl_2, r.t., 2h.

Scheme 1.27: Combined osmium-rhenium approach to polycyclisation of polyenes

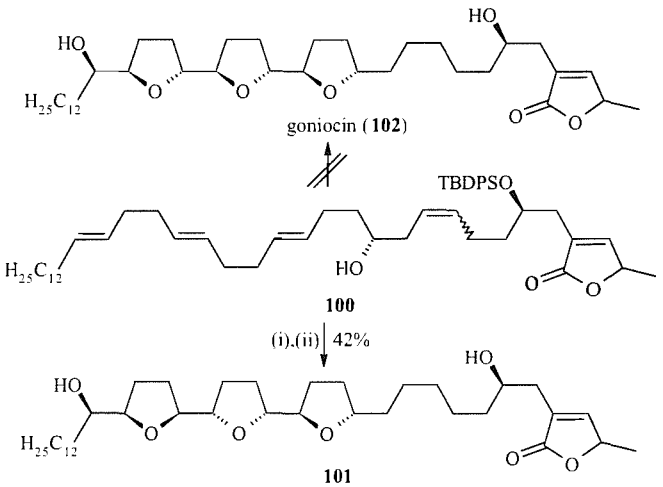
McDonald *et al.* have reported that attempts to oxidise of trisubstituted dienes **97a,b** using the previous methods were unsuccessful and led to a complex reaction mixture including oxidative cyclisation and acid-catalysed cyclohydration by-products.[43] During the course of the reaction, the formation of perrhenic acid could be responsible for nonoxidative cyclohydration of trisubstituted alkene substrates *via* tertiary carbenium ion intermediates. They therefore decided to change the leaving group from perrhenate (O_3ReO^-) to a less acidic organic carboxylate (RCO_2^-). Oxidation of dienes **97a-c** with (tridfluoroacetyl)perrhenate gave the monocyclic *trans*-THFs **98a-c** in good yield and excellent selectivity (scheme 1.28). THFs **98b,c** were converted to the *bis*-THFs **99b,c** *via* rhenium oxide oxidation. It is interesting to note that (dichloroaceetyl)perrhenate combined with excess dichloroacetic acid was more effective in the cyclisation of monocyclic THFs **98a-c** to the corresponding *bis*-THFs **99b,c**.



Conditions and reagents: (i) $(CF_3CO_2)ReO_3$, 2,6-lutidine (3 eq.), CH_2Cl_2, 20°C; (ii) $(Cl_2CHCO_2)ReO_3$, $(Cl_2CHCO)_2O$, CH_2Cl_2, 20°C.

Scheme 1.28: Rhenium oxide-induced tandem *syn*-oxidative cyclisations of hydroxydienes

Sinha *et al.* have reported the synthesis of *tri*-THF in a one step rhenium oxide oxidative cyclisation toward the synthesis of goniocin.[44] Triene **100** was oxidised and hydrogenation followed by deprotection afforded *tri*-THF **101** in good yield and selectivity (scheme 1.29). Surprisingly, the NMR data did not correspond to the analysis of natural product goniocin (**102**) and showed that the stereochemistry of **101** was *trans-threo-cis-threo-cis-threo*.

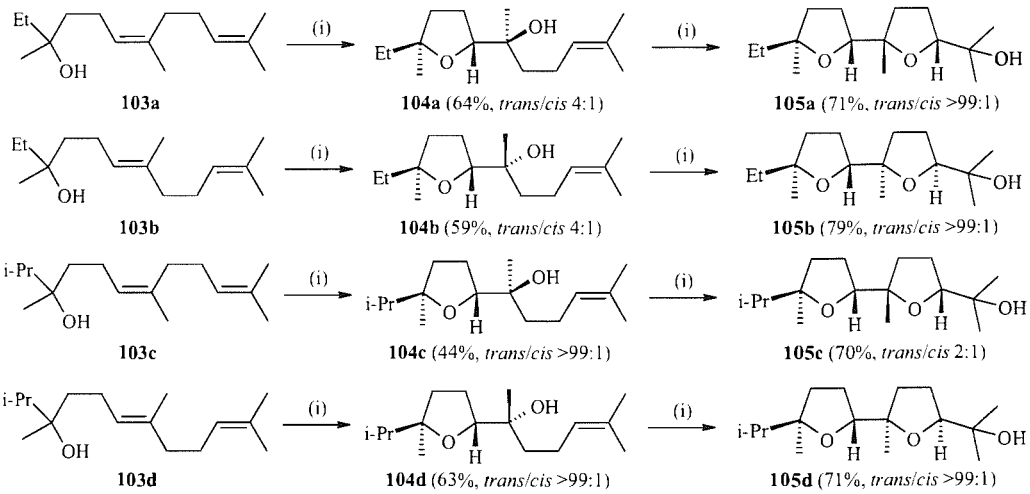


Conditions and reagents: (i) Re_2O_7, TFAA, THF r.t., 1h, concentration under vacuum and washing with cold pentane, then alcohol **1**, CH_2Cl_2, TFAA, 0°C to r.t., 3h; (ii) (a) H_2, Wilkinson's catalyst (20%, w/w), C_6H_6-EtOH (4:1), r.t., 4h; (b) 4% AcCl in MeOH, CH_2Cl_2 (1:1, v/v), r.t., 16h.

Scheme 1.29: Synthesis of 17,18-*bis*-*epi*-goniocin **101**

Similar observations have been noted by Morimoto *et al.*[45,46] who have described the sequential oxidative cyclisation of tertiary alcohols **103a,b** and to afford *bis*-THFs **105a,b**

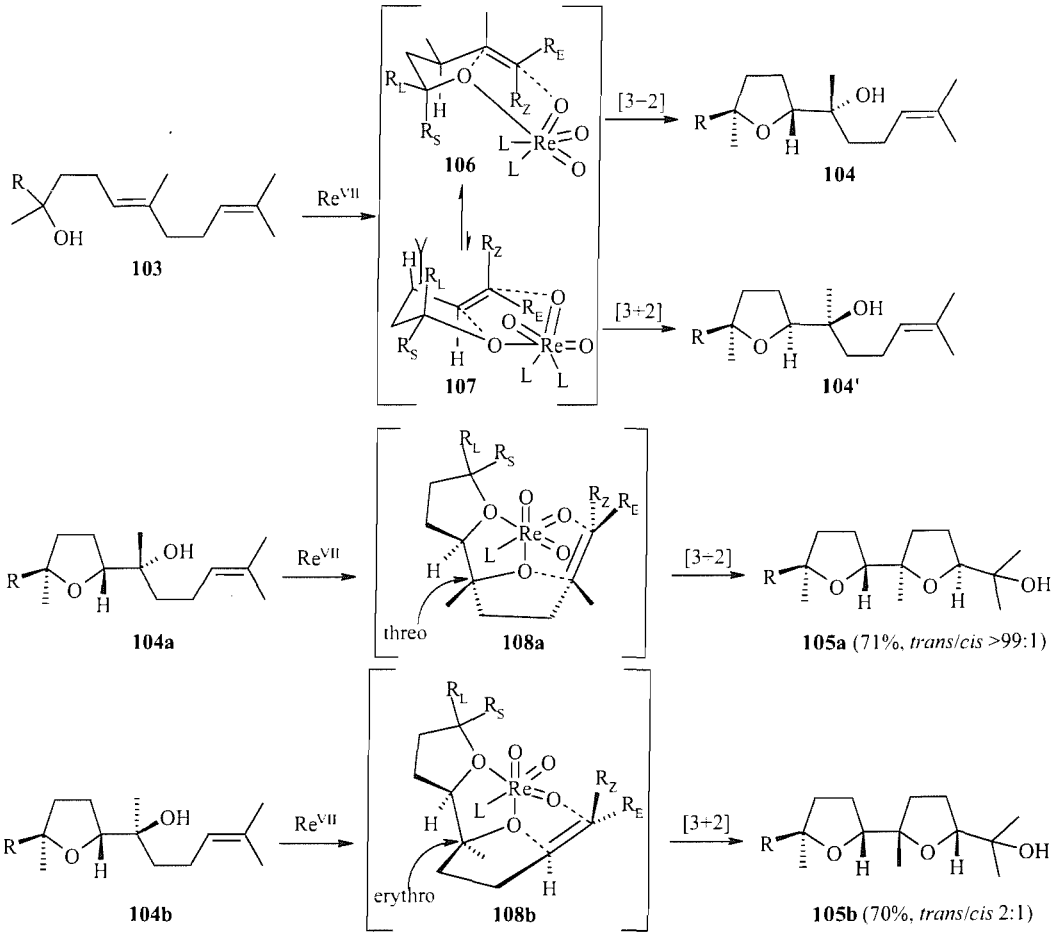
where the second ring is *cis*-2,5-disubstituted (scheme 1.30). The sequential rhenium oxide oxidation of tertiary alcohols to *bis*-THFs have been reported when alcohols **103a-d** were oxidised to the corresponding monocyclic *trans*-THFs **104a-d** in good yield and selectivity. *Re*-oxidation of *trans*-THFs **104a-d** with rhenium oxide gave *bis*-THFs **105a-d** in good yield. But surprisingly, *cis*-selectivity was obtained for the second THF ring.



Conditions and reagents: (i) $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$ (4 eq.), CH_2Cl_2, molecular sieves 4Å, –45°C, 8h.

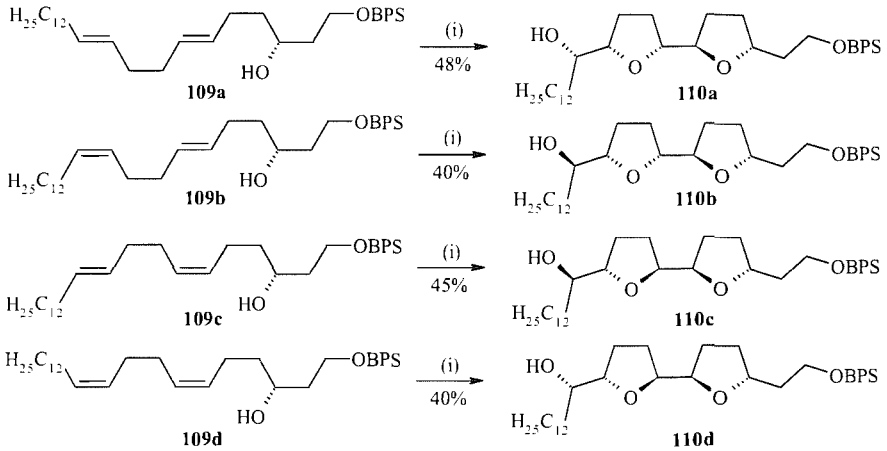
Scheme 1.30: Synthesis of *bis*-THFs *via* rhenium oxide oxidative cyclisation

It is thought that the formation of the first *trans*-THF ring is controlled by steric effects, the intermediate **107** experiences steric hindrance due to the interaction between R_L and H_a, while the preferred pseudoequatorial position of R_L and the alkene favours alkylorhenium intermediate **106** (scheme 1.31). The *trans*-THF **104** is then obtained *via* a [3+2] cycloaddition on the double bond. The reversal of diastereoselectivity in the second oxidation is apparently due to the presence of the THF ring α to the hydroxy group and therefore is controlled by chelation. The intramolecular coordination of the THF ring with rhenium oxide could lead to the formation of the chelated intermediates **108a,b**. During the second [3+2] cycloaddition, the least strained approach of the rhenium oxo moieties toward the double bond leads to the formation of the *cis*-THF. The reason for the low *cis*-selectivity of **105c** is unclear; although, it seems that **104c** has difficulty in forming a rigid chelation structure.



Scheme 1.31: Morimoto's investigation on the selectivity of rhenium oxidative cyclisation.

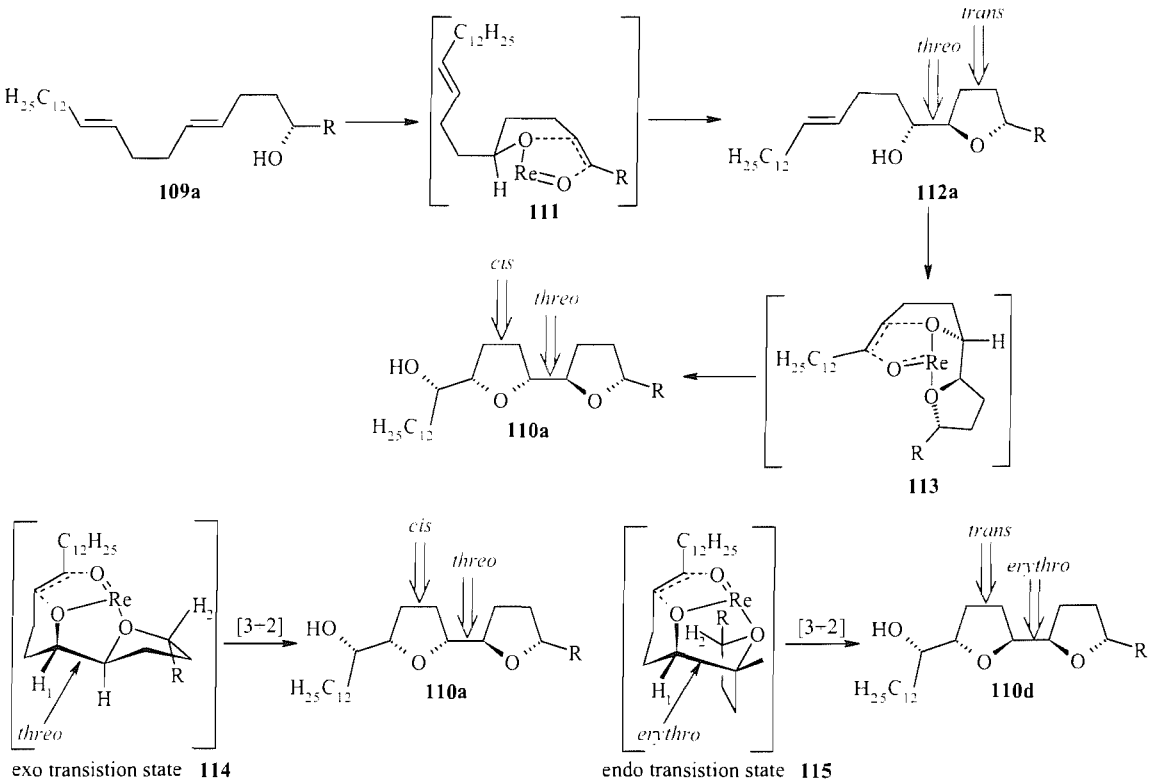
Further studies by Sinha *et al.* showed that the tandem rhenium oxide mediated oxidative cyclisation of dienes **109a,b** afforded *cis-trans-bis*-THFs **110a,b** however oxidation of dienes **109c,d** gave all *trans bis*-THFs **110c,d** (scheme 1.32).[47] The formation of all *trans-bis*-THF was surprising and might mean that Morimoto's explanation was not complete and other factors should be taken in account for the selectivity of the polycyclisation with rhenium oxide.



Conditions and reagents: (i) $(CF_3CO_2)ReO_3$ (2.5 eq.), TFAA (3 eq.), CH_2Cl_2; 6h; (ii) $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$ (4 eq.), CH_2Cl_2, molecular sieves 4Å, –45°C, 8h.

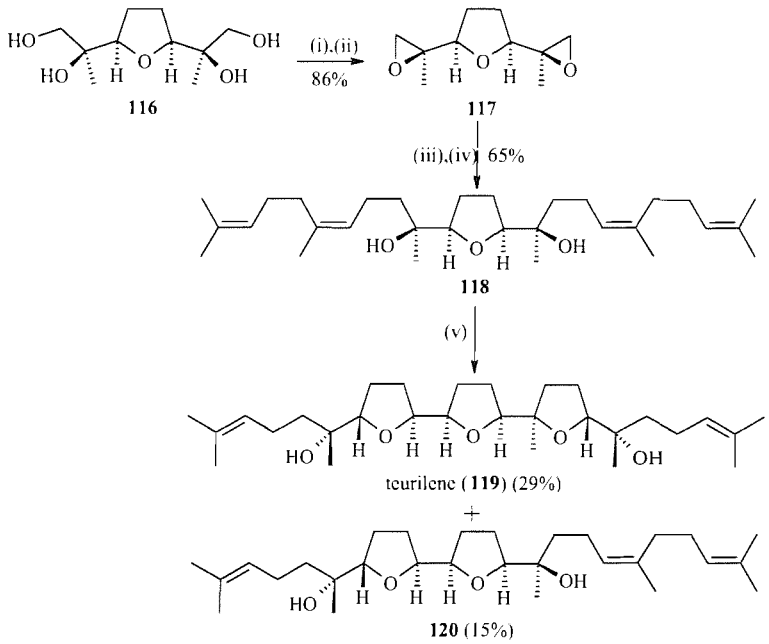
Scheme 1.32: Investigation on the selectivity of rhenium oxide oxidative cyclisation.

Sinha's model for the formation of the first *trans*-THF and the second *cis*-THF is consistent with Morimoto's conclusions (scheme 1.33). During the second oxidation, the neighbouring THF becomes a bidentate ligand to rhenium and the cyclisation proceeds *via* transition state **113** to give the second *cis*-THF fragment. However, they believe that the coordinating efficiency of this ligand depends on the relative configuration of the THF and alcohol moieties. When the relative configuration is *threo*, the reaction goes *via* sterically favoured *exo*-transition state **114** to give *cis*-selectivity during the [3+2] cycloaddition. Alternatively, when the vicinal oxygen functions have an *erythro* relationship, the reaction proceeds *via* the disfavoured *endo* transition state **115** that favours a non-chelated intermediate like **111** and leads to *trans*-selectivity. The low selectivity obtained by Morimoto *et al.* with *erythro* substrate **105c**, could be explained by an *endo* transition state such as **115**.



Scheme 1.33: Sinha investigation on the selectivity of rhenium oxide oxidative cyclisation.

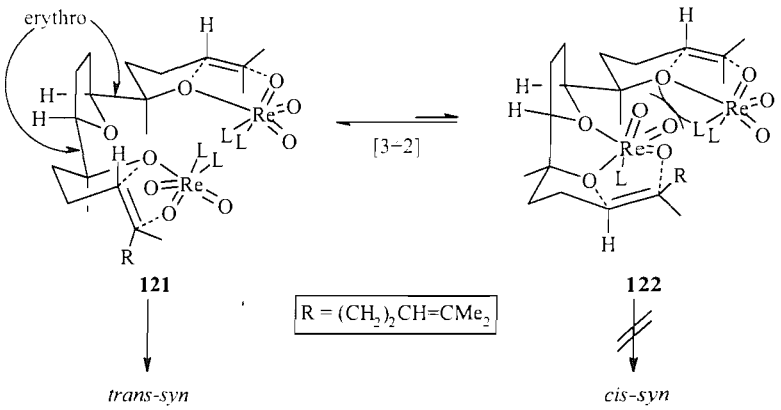
Morimoto *et al.* have applied these rules to the synthesis of teurilene (**119**).[46,48] Mesylation of THF **116** and subsequent basic treatment yielded the *meso bis*-epoxide **117** (scheme 1.34). *Bis*-epoxide **117** was then treated with lithiated neryl sulphide in presence of TMEDA and the sulphide moieties were subsequently removed under Bouvault-Blanc conditions to afford mono-THF **118**. Oxidation with rhenium oxide provided a mixture of the desired product teurilene (**119**) in poor yield and the monocyclised alcohol **120** as by-product.



Conditions and reagents: (i) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h (ii) K_2CO_3, MeOH, r.t., 1h; (iii) neryl sulfide, *n*-BuLi, TMEDA, THF, –78°C, 1h; (iv) Na, THF, *i*-PrOH, reflux, 12h; (v) $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$, TFAA, CH_2Cl_2/CH_3CN, –45°C, 8h.

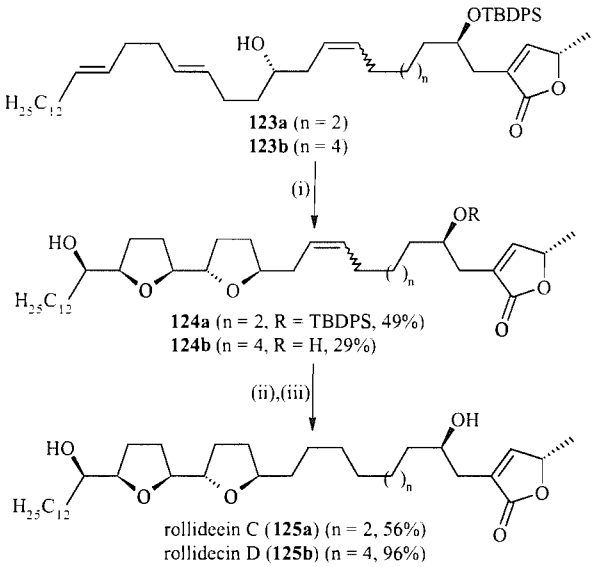
Scheme 1.34: Synthesis of teurilene *via* rhenium oxide oxidative cyclisation

The rhenium oxidative cyclisation only gave the *trans-syn* isomer diastereoselectively as a result of steric control. It is thought that reaction of mono-THF **118** with rhenium gives the bisalkoxyrhenium intermediate **121** (scheme 1.35). The chelation control model **122** is disfavoured by the steric repulsion between the two rhenium complexes. These results are consistent with Sinha's rule that if the vicinal oxygens functions formed are in an *erythro* relative configuration, the next cyclisation has a *trans*-selectivity.



Scheme 1.35: Transition state leading to the *trans-syn*-diastereoselectivity.

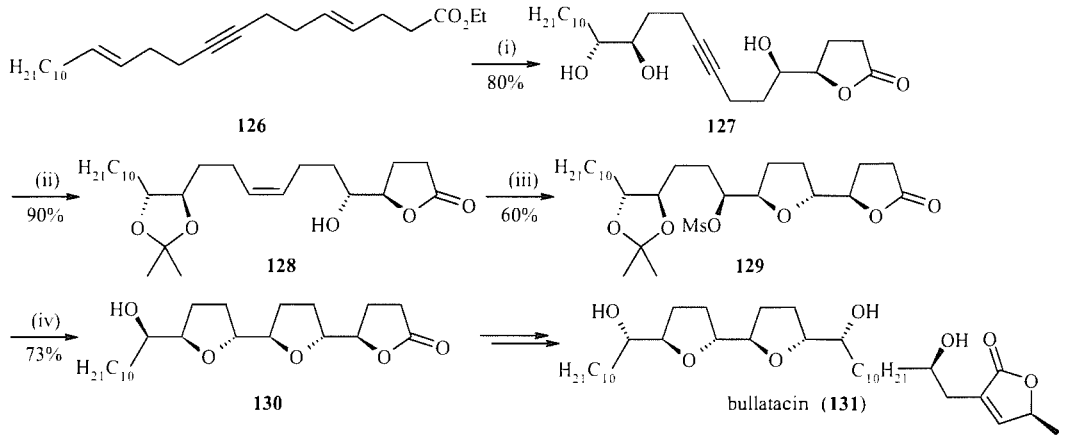
Sinha *et al.* have also applied the stereoselectivity rules in the total synthesis of rollidecins C and D.[49] Trienes **123a,b** underwent rhenium-mediated oxidative cyclisation to yield corresponding *bis*-THFs **124a,b** (scheme 1.36). Cleavage of the TBDPS group of **124b** was achieved during the cyclisation step by leaving the reaction on for a longer period of time. Hydrogenation of **124b** afforded the desired rollidecin D (**125b**) in good yield. Hydrogenation and subsequent deprotection of the TBDPS group of *bis*-THF **124a** yielded rollidecin C (**125a**).



Conditions and reagents: (i) Re_2O_7, TFAA, THF r.t., 1h, concentration under vacuum and washing with cold pentane, then alcohol **14**, CH_2Cl_2, TFAA, 0°C to r.t., 3h. The same procedure was used for compound **15** with the exception that the mixture was left at r.t. overnight; (ii) H_2, Wilkinson's catalyst (20%, w/w), C_6H_6-EtOH (4:1), r.t., 4h; (iii) 4% AcCl in MeOH, CH_2Cl_2 (1:1, v/v), r.t., 16h.

Scheme 1.36: Synthesis of rollidencin C (**125a**) and D (**125b**).

Sinha *et al.* have reported the synthesis of *bis*-THF segments *via* the "naked" carbon skeleton strategy.[50] Sharpless asymmetric dihydroxylation of skeleton **126** followed by a base-acid treatment gave the trihydroxylactone **127** (scheme 1.37). After protection of the vicinal diol, the alkyne was partially hydrogenated to yield *cis*-olefin **128**. Kennedy's oxidative cyclisation with Re_2O_7 and mesylation of the resulting alcohol produced *bis*-THF lactone **129**. Acidic hydrolysis of the vicinal diol and subsequent Williamson-type etherification afforded *tri*-THF lactone **130,** precursor to bullatacin (**131**). They have also applied this method to the synthesis of goniocin and cyclogoniodenin T.[51]

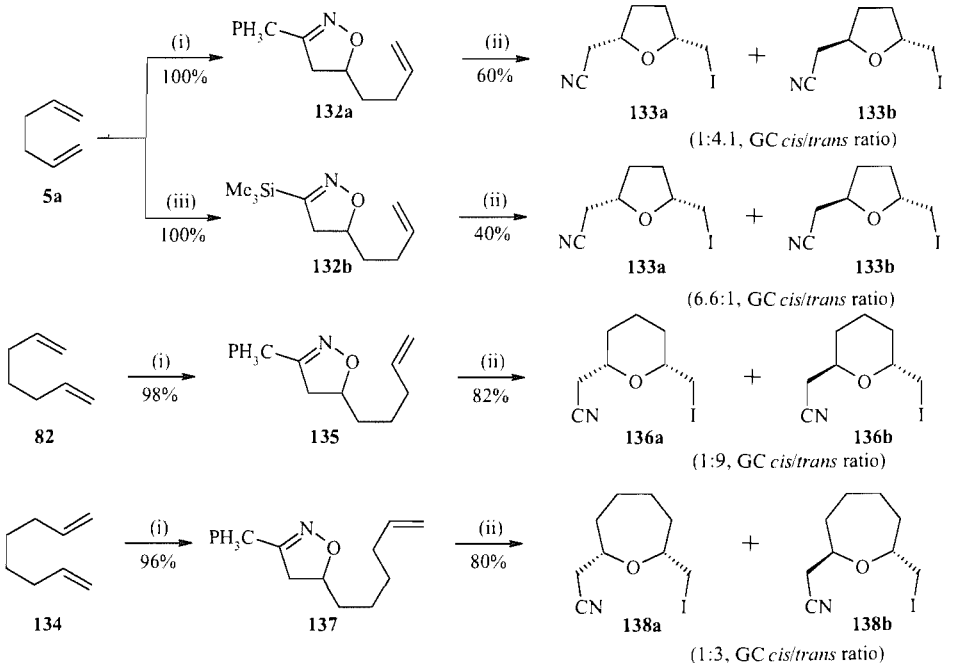


Conditions and reagents: (i) (a) AD-mix-β, $MeSO_2NH_2$, t-BuOH/H_2O (1:1), 0°C, 16h; (b) aqueous KOH, MeOH, 60°C, 2h, then HCl (3N); (c) TsOH (5%), CH_2Cl_2, 30 min; (ii) (a) dimethoxypropane, acetone, TsOH (cat), 0 to 25°C, 30 min; (b) 5% Pd/$CaCO_3$/lead (10%, w/w), hexane/cyclohexene/Et_3N (2:2:1), –10°C, 12h; (iii) (a) Re_2O_7, lutidine, CH_2Cl_2, 2h; (b) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h; (iv) (a) TsOH (20% w/w), MeOH/H_2O (4:1), 60°C, 16h; (b) pyridine, 100°C, 2h.

Scheme 1.37: Preparation of THF rings by "naked" carbon skeleton approach.

1-I-5 Oxidative cyclisation of 1,5-dienes *via* a nitrile oxide intermediate

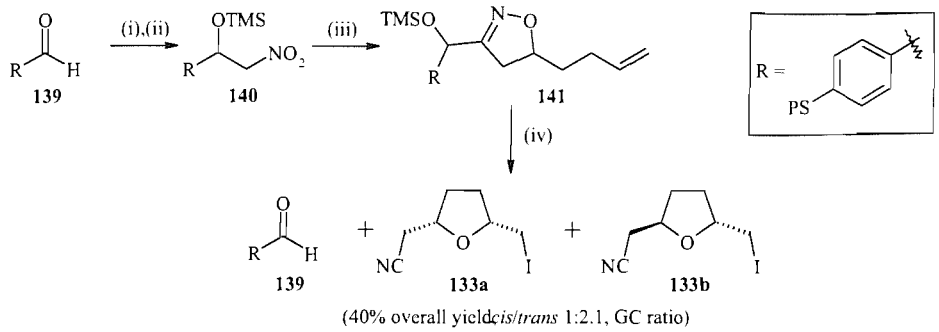
Kurth *et al.* have reported the preparation of 2,5-disubstituted-THFs *via* the exposure of 1,5-hexadienes to a tandem 1,3-dipolar cycloaddition/electrophilic cyclisation sequence.[52] Cycloaddition between 1,5-hexadiene **5a** (5 eq.) and triphenylacetonitrile oxide (prepared from triphenylmethyl chloride and silver fulminate) furnished isoxazoline **132a** in quantitative yield (scheme 1.38). Treatment of heterocycle **132** with iodine resulted in electrophilic cyclisation and afforded THF adducts **133a,b** in moderate yield and 1:4.1 ratio. The synthesis of (3-trimethylsilyl)isoxazoline **132b** was carried out using a similar one-pot process involving cycloaddition of 1,5-hexadiene **5a** and trimethylsilylcarbonitrile oxide (generated *in situ* from trimetylsilyl bromide and mercury fulminate). After treatment with iodine, heterocycle **132b** underwent cyclisation and afforded THF adducts **133a,b** in moderate yield but this time with *cis* selectivity (ratio 6.6:1). It is interesting to note that when this methodology was applied to dienes **82** and **134** the corresponding THP **136a,b** and oxepane **138a,b** were obtained in good yield and excellent *trans*-selectivity for the THP examples. The reaction was attempted on deca-1,9-diene but although the corresponding isoxazoline was obtained, it failed to cyclise.



Conditions and reagents: (i) Ph_3CCNO; (ii) I_2, CH_2Cl_2; (iii) Me_3SiCNO.

Scheme 1.38: Synthesis oxygen heterocycles utilising a cyclisation-fragmentation strategy.

Kurth *et al.* adapted this methodology on a polymer support and incorporated a cyclisation-based traceless linker strategy.[53,54] Aldehyde **139** was prepared from oxidation of commercially available 2% cross-linked Merrifield polymer (scheme 1.39). Aldehyde **139** then underwent nitroaldol condensation and subsequent protection of the resulting alcohol with a TMS group yielded polymer-supported trimethylsilyl ether **140**. Phenyl isocyanate-mediated dehydration of the nitroalkane moiety presumably generated the polymer-bound nitrile oxide, which then underwent an intermolecular 1,3-dipolar cycloaddition with 1,5-hexadiene **5a** to give the polymer-bound isoxazoline **141**. Finally, electrophilic cyclisation of the isoxazoline **141** with iodine monochloride regenerated the polymer-bound aldehyde **139** and afforded THF adduct **133a,b** in overall good yield and a moderate *cis/trans* selectivity (1:2.1).



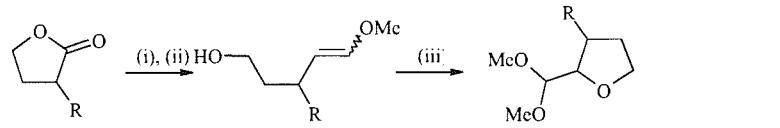
Conditions and reagents: (i) CH_3NO_2, Et_3N, EtOH/THF, 25°C, 15h; (ii) Me_3SiCl, Et_3N, 0°C to 25°C, THF; (iii) 1,5-hexadiene (3 eq.), PhNCO, Et_3N, benzene, 80°C in sealed tube, 4 days; (iv) ICl, CH_2Cl_2, –78°C, 30 min.

Scheme 1.39: Synthesis of 2,5-disubstituted THFs using a cyclisation-fragmentation strategy

1-II Oxidation-cyclisation of unsaturated alcohols

1-II-1 Use of anodic coupling reaction

Moeller *et al.* have reported the first example of THF rings prepared *via* anodic oxidation reactions based on reversing the polarity of enol ethers and its application to the synthesis of naturals products.[55] Previous studies have shown that the addition of an enol ether radical cation to an olefinic nucleophile led to the formation of a radical at the terminating end of the cyclisation.[56] The compatibility of oxygen nucleophiles with the anodic cyclisation reactions was first examined using simple alcohols (scheme 1.40). After reduction of the lactones **142a,b** to the lactols with DIBAL, enol ethers **143a,b** were prepared *via* a Wittig reaction. The enol ethers **143a,b** were then oxidized at a constant current of 8mA in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum auxiliary electrode; 0.03 M tetraethylammonium tosylate in 30% MeOH/THF was used as electrolyte along with 2,6-lutidine as a proton scavenger. After the passage of 2.0 F/mol of charge, desired THFs **144a,b** were obtained in excellent yield and stereoselectivity.

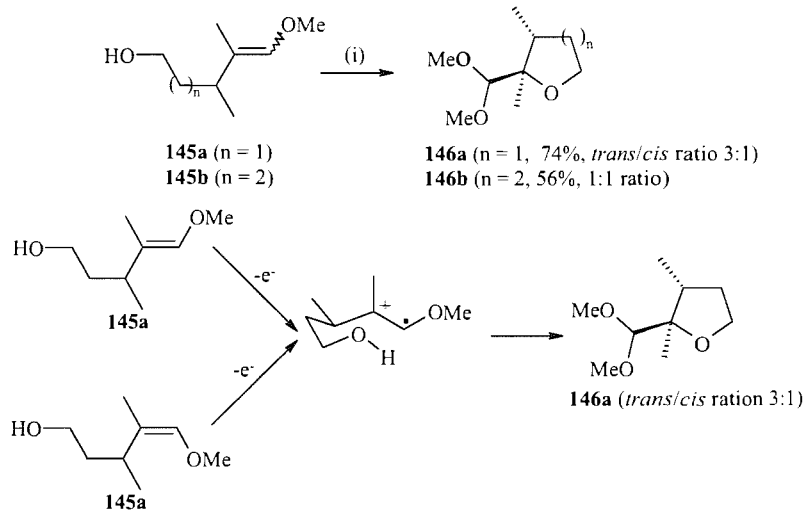


142a (R = Me)
142b (R = Bn)
143a (R = Me, 35%)
143b (R = Bn, 61%)
144a (R = Me, 96%, 5:1, *trans/cis*)
144b (R = Bn, 95%, 10:1, *trans/cis*)

Conditions and reagents: (i) DIBAL-H, THF –20°C; (ii) PH_3P=CHOMe, THF, 0°C, 16h; (iii) RVC anode, Pt cathode, 30% MeOH/THF, 0.03 M Et_4NOTs, 2,6-lutidine, 2F/mole 8mA.

Scheme 1.40: Synthesis of THF *via* anodic oxidation reactions.

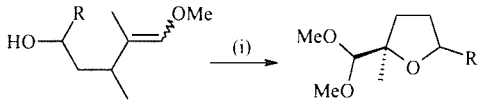
This methodology could also be applied to enol ethers bearing a trisubstituted double bond and generating a quaternary chiral center. Enol ether **145a** was synthesised along similar lines to **143a,b**, with addition of MeLi to the lactone prior to the preparation of the alcohol (scheme 1.41). After oxidation, the desired THF **146a** was obtained in good yield and moderate selectivity. This difference in selectivity was intriguing and Moeller *et al.* decided to investigate the stereoselectivity of the reaction.[57] When this oxidation was attempted on alcohol **145b**, the resulting THP **146b** was obtained in a 1:1 ratio; this lack of selectivity suggested a kinetic control of the reaction. Separation of the *cis* and *trans* isomers of enol ether **145a** and oxidation of each enol stereoisomer led to THF **146a** in the same *trans* selectivity (3:1). The stereoselectivity of this reaction did not depend of the stereochemistry of the enol ether, confirming earlier observations made on carbon-carbon bond forming reactions.[58]



Conditions and reagents: (i) RVC anode, Pt cathode, 30% MeOH/THF, 0.03 M Et_4NOTs, 2F/mole 8mA.

Scheme 1.41: Synthesis of THF and THP *via* anodic oxidation reactions.

The stereoselectivity could result from steric interactions between the forming dimethoxyacetal group and the neighbouring methyl group. This hypothesis was disproved by the preparation and oxidation of alcohols **145c-e** that yielded the corresponding THF **146c-e** (scheme 1.42). The degree of selectivity obtained had little to do with steric effects. The remaining possibility was that the formation of the *trans*-product was favoured by a stereoelectronic effect, following Baldwin rules.[59-61]

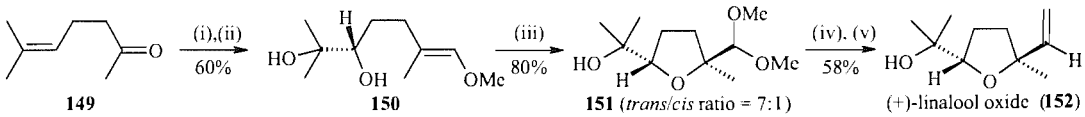


145c (R = *t*-Bu) **146c** (R = *t*-Bu, 84%, *trans/cis* ratio 5:1)
145d (R = i-Pr) **146d** (R = i-Pr, 87%, *trans/cis* ratio 4:1)
145e (R = Me) **146e** (R = Me, 71% *trans/cis* ratio 2.5:1)

Conditions and reagents: (i) RVC anode, Pt cathode, 30% MeOH/THF, 0.03 M Et_4NOTs, 2F/mole 8mA.

Scheme 1.42: Synthesis of 2,5-disubstituted THF *via* anodic oxidation reactions.

This methodology was applied to the synthesis of two natural products, linalool oxide[62] and (+)-nemorensic acid.[57,63] Diol **150** was obtained *via* a sequential asymmetric dihydroxylation and Wittig reaction on ketone **149** (scheme 1.43). Anodic oxidation reaction afforded the THF **150** in good yield and selectivity. Hydrolysis of acetal **150** and subsequent Wittig reaction on the resulting aldehyde yielded (+)-linalool oxide (**152**).

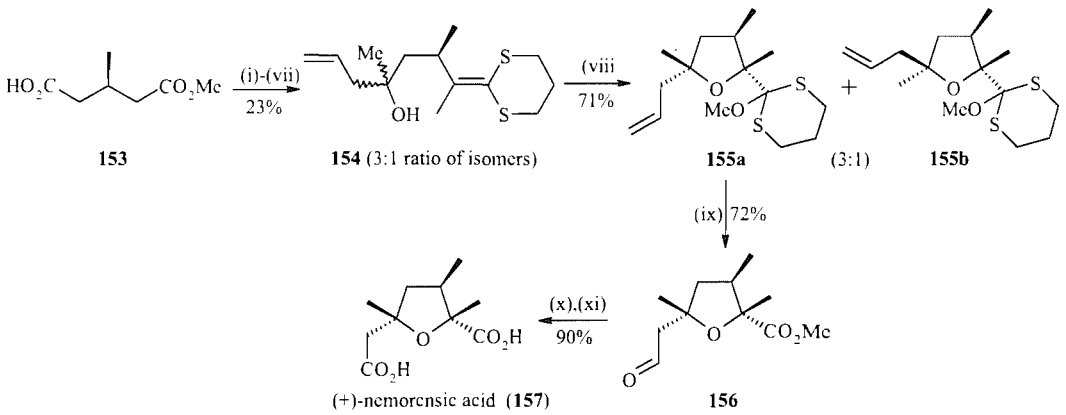


149 **150** **151** (*trans/cis* ratio = 7:1) (+)-linalool oxide (**152**)

Conditions and reagents: (i) $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH:H_2O (1:1), 0°C, 6h; (ii) PH_3P=CHOMe, THF, 0°C to 25°C, 16h; (iii) RVC anode, Pt cathode, 30% MeOH/THF, 0.03 M Et_4NOTs, 2F/mole 8mA; (iv) 50% TFA/H_2O, $CHCl_3$, 25°C; (v) PH_3P=CH_2, THF, 0°C to 25°C, 16h.

Scheme 1.43: Synthesis of (+)-linalool oxide (**152**).

Alcohol **154** was synthesised in seven steps from methyl (*R*)-(+)-3-methylglutarate **153** and oxidised to afford THFs **155a,b** in good yield (scheme 1.44).[64] After separation, THF **155a** was treated under ozonolysis conditions to yield THF **156**. Oxidation of the aldehyde moiety and saponification of the ester group afforded the desired (+)-nemorensic acid **157** in good yield.

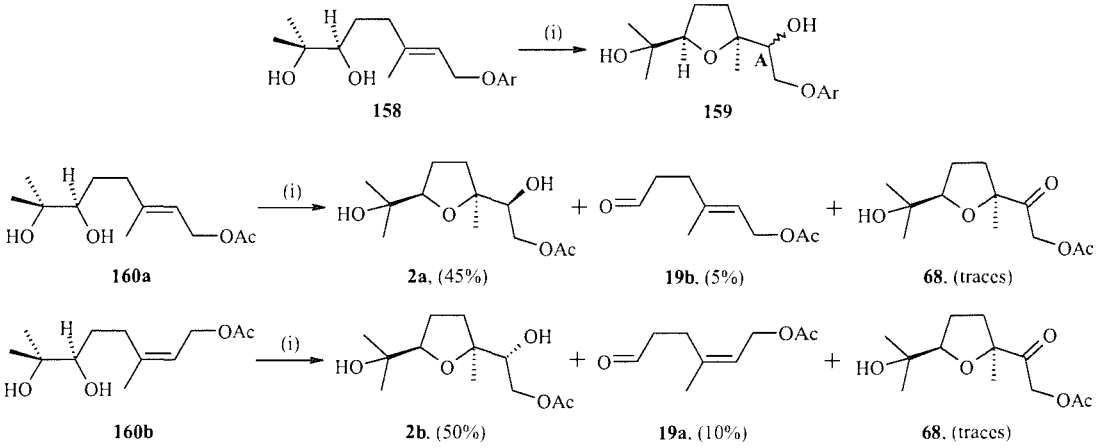


Conditions and reagents: (i) BH_3Me_2S, THF; (ii) LDA, MeI, THF; (iii) Me_3Al, $SH(CH_2)_3SH$, CH_2Cl_2, reflux, 12h (iv) TFAA, DMSO, CH_2Cl_2, Et_3N; (v) MeLi, Et_2O; (vi) TFAA, DMSO, CH_2Cl_2, Et_3N; (vii) (-)-$Ipc_2BCH_2CH{=}CH_2$, Et_2O; (viii) RVC anode, Pt cathode, 30% MeOH/THF, 0.03 M Et_4NOTs, 2F/mole 8mA; (ix) (a) O_3, CH_2Cl_2; (b) Me_2S; (x) $KMnO_4$, *t*-BuOH, 5% NaH_2PO_4; (xi) NaOH, H_2O.

Scheme 1.44: Synthesis of (+)-nemorensic acid (**157**).

1-II-2 Chromium promoted oxidative cyclisation

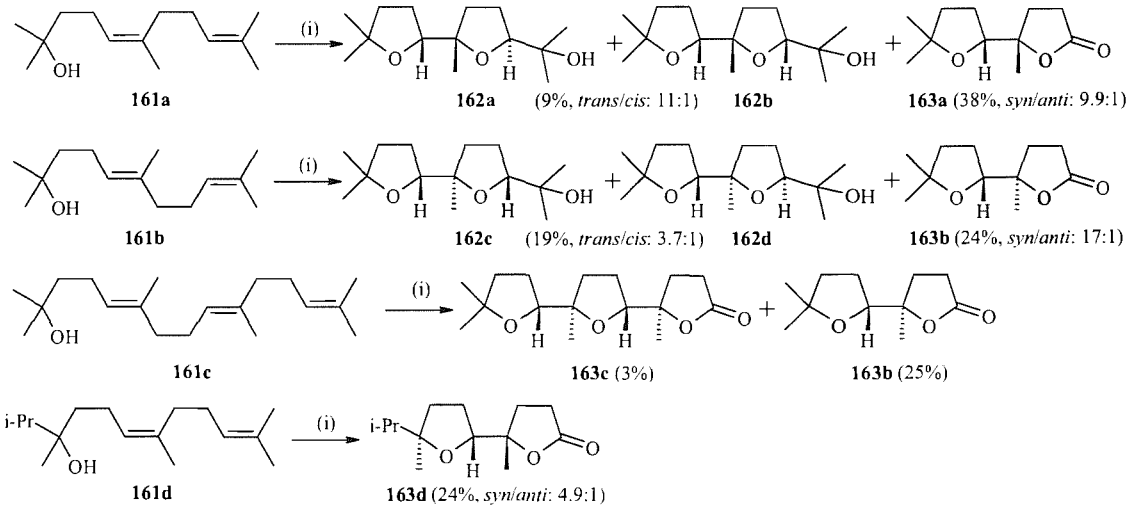
Casida *et al.* have showed that Collins oxidation of diol **158** afforded *cis*-THF **159** (scheme 1.45).[65] Unfortunately, the relative stereochemistry of chiral center A was not reported. Walba *et al.* have completed this study and described a novel related process involving the Cr^{VI} promoted oxidative cyclisation of 5,6-dihydroxyalkene.[66] Geranyl and neryl acetate diols **160a,b** were prepared by acid hydrolysis of the corresponding epoxides obtained *via* selective *m*-CPBA oxidation[65] and oxidisation with Collins reagent gave corresponding racemic *cis*-THF diols **2a,b** in moderate yields. Small quantities of known aldehydes **19a,b**[67] were also isolated with traces of ketone **68**. Pyridinium chlorochromate oxidation of diol **160b** gave similar results while bipyridinium chlorochromate afforded aldehyde **19b** as a major product. Analysis of the crude mixtures showed that the oxidative cyclisation process occurred with >99.5% stereoselectivity.



Conditions and reagents: (i) CrO_3, pyridine, 5 min.

Scheme 1.45: First example of chromium mediated oxidative cyclisation.

McDonald *et al.* have reported synthesis of polycyclic alcohols and lactones *via* PCC oxidative cyclisation.[68] Hydroxy polyenes **161a-d** were oxidised to afford a mixture of desired *bis*-THF alcohols **162a-d** and bicyclic lactones **163a-d** in overall moderate yield and good selectivity (scheme 1.46). Oxidation with Pyridium dichromate (PDC) was also achieved but in lower yield.

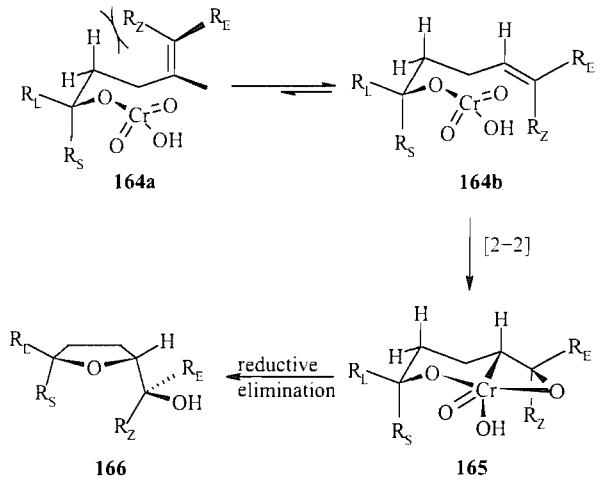


Conditions and reagents: (i) PCC (5 eq.), celite, AcOH, CH_2Cl_2, 20°C, 14h.

Scheme 1.46: First example of chromium mediated polycyclisation.

Mc Donald *et al.* proposed that the chromium oxidation mechanism is based on a [2+2] cycloaddition, where the steric effects favour the chair-like conformer in which the alkene is in pseudoequatorial position (scheme 1.47).[68]. *Trans*-THF adduct then is obtained after a reductive elimination. However, the different mechanisms shown previously for the metal

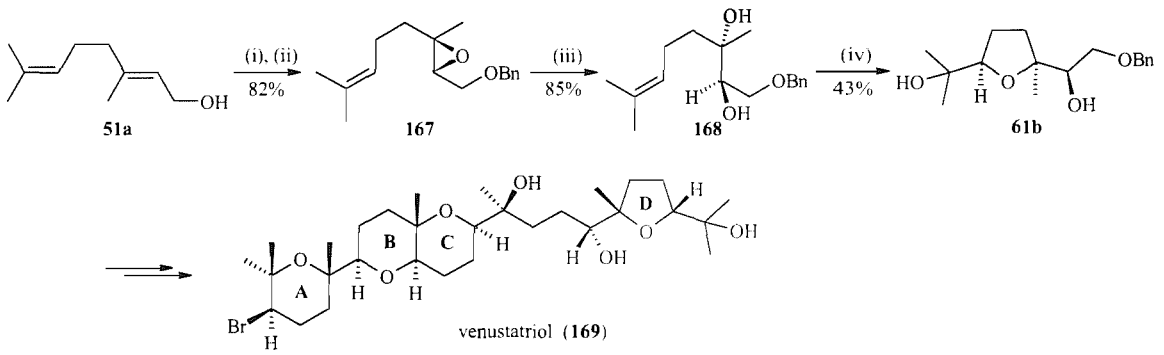
oxidative cyclisation led to believe that chromium probably works along similar lines *i.e. via* [3+2] cycloadditions (scheme 1.5, 1.17).



Conditions and reagents: (i) PCC (5 eq.), celite, AcOH, CH_2Cl_2, 20°C, 14h.

Scheme 1.47: Model of *syn*-oxidative cyclisation.

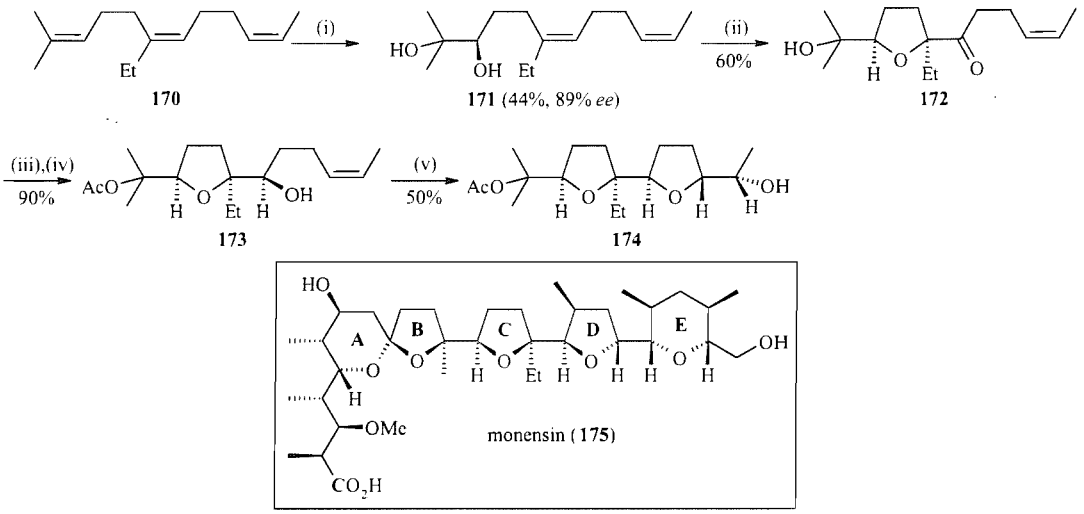
This method was applied toward the synthesis of venustatriol by Corey *et al.*[69] Ring D was prepared *via* oxidation with pyridimium chlorochromate (scheme 1.48). Epoxidation of geraniol **51a** with (–)-diethyl (2*R*,3*R*)-tartrate, Ti(O*i*Pr)$_4$ and *t*-BuOOH in the presence of molecular sieves afforded the (2*R*,3*R*)-epoxide, that was subsequently converted to the corresponding benzyl ether **167**. After cleavage of the epoxide, diol **168** was oxidised with stoichiometric pyridium chlorochromate and afforded stereoselectively the THF **61b** in moderate yield.



Conditions and reagents: (i) (–)-diethyl (2*R*,3*R*)-tartrate, Ti(O*i*Pr)$_4$, *t*-BuOOH, molecular sieves, CH_2Cl_2, (ii) NaH (1eq.), BnBr (1.1 eq.), THF, 23°C, 14 h; (iii) perchloric acid, THF/H_2O (6:1), 23°C, 14h; (iv) PCC (1.05 eq.), CH_2Cl_2, 23°C, 10h.

Scheme 1.48: Preparation of THF **61b** *via* chromium oxidation.

McDonald *et al.* have described a potential biomimetic approach to the *bis*-THF region of monensin (**175**) *via* the combination of the chromium catalysed oxidative cyclisation and rhenium oxidation.[70] Triene **170** was treated with AD-mix-β and the resulting diol **171** oxidised with Collins reagent to yield the THF ketone **172** (scheme 1.49). The alcohol moiety was protected and the ketone reduced to afford THF **173** in good yield. Oxidative cyclisation of THF **173** gave *bis*-THF **174** in moderate yield. Compound **174** corresponds to the C and D rings of monensin (**175**).

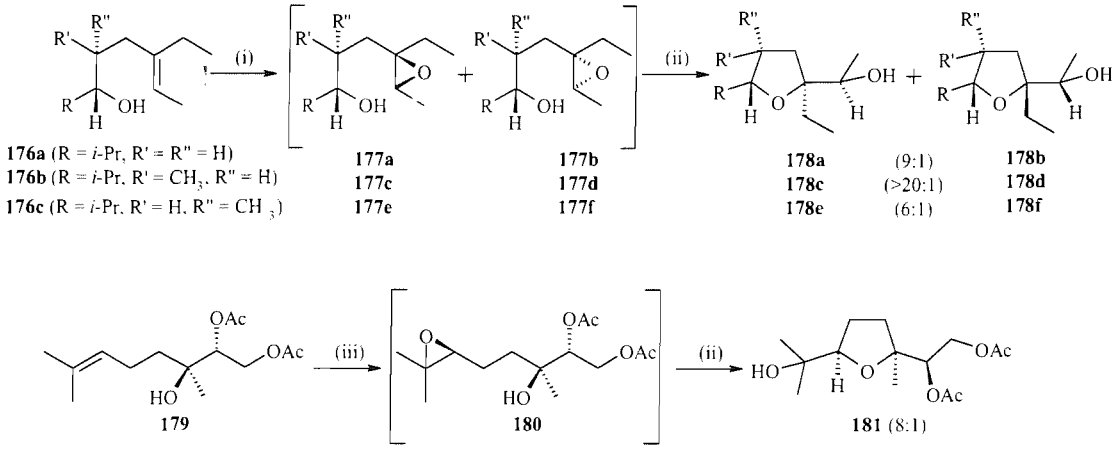


Conditions and reagents: (i) AD-mix β, t-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0°C, 8h; (ii) $CrO_3(py)_2$, CH_2Cl_2, r.t., 15 min; (iii) Ac_2O, DMAP, Et_3N, r.t., 30h; (iv) $CeCl_3 \cdot H_2O$, $NaBH_4$, EtOH, –78 to 20°C, 1h; $(Cl_2CHCO_2)ReO_3$, $(Cl_2CHCO)_2O$, CH_2Cl_2, 0°C to r.t., 12h.

Scheme 1.49: Synthesis of *bis*-THF *via* chromium and rhenium oxidative cyclisations.

1-II-3 Vanadium catalysed oxidation-cyclisation

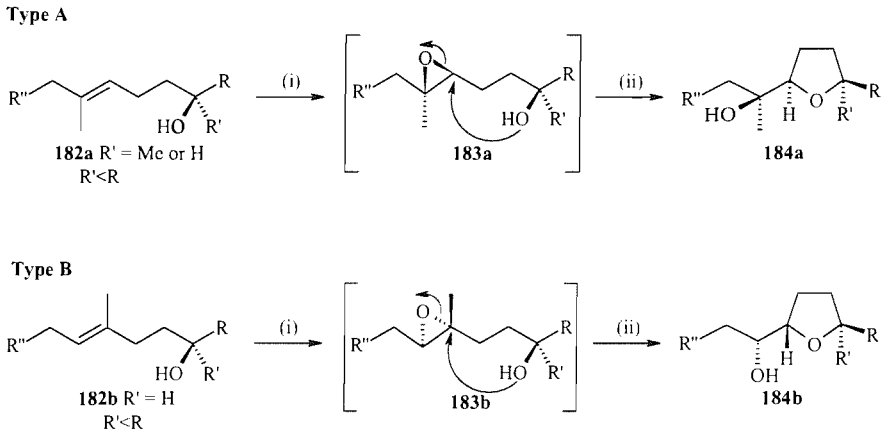
Kishi *et al.* have reported the first stereocontrolled synthesis of THFs *via* vanadium catalysed epoxidation-cyclisation of γ,δ-unsaturated alcohols.[71] Alcohols **176a-d** were treated with a mixture of $VO(acac)_2$ and *t*-BuOOH to yield the corresponding THFs **178a,c,e** in excellent *trans* stereoselectivity (scheme 1.50). Further studies by Shirahama *et al.* showed that the stereoselectivity of this reaction depended on the γ,δ-unsaturated alcohol precursor and that *cis*-THF could be prepared.[72-74] Vanadyl acetylacetonate catalysed oxidation of bishomoallyl alcohol **179** afforded *cis*-THF **181** in good selectivity.[73]



Conditions and reagents: (i) $VO(acac)_2$, t-BuOOH, PhH, r.t.; (ii) AcOH; (iii) $VO(acac)_2$, t-BuOOH, PhH, NaOAc, r.t..

Scheme 1.50: THF synthesis *via* vanadium catalysed cyclisation.

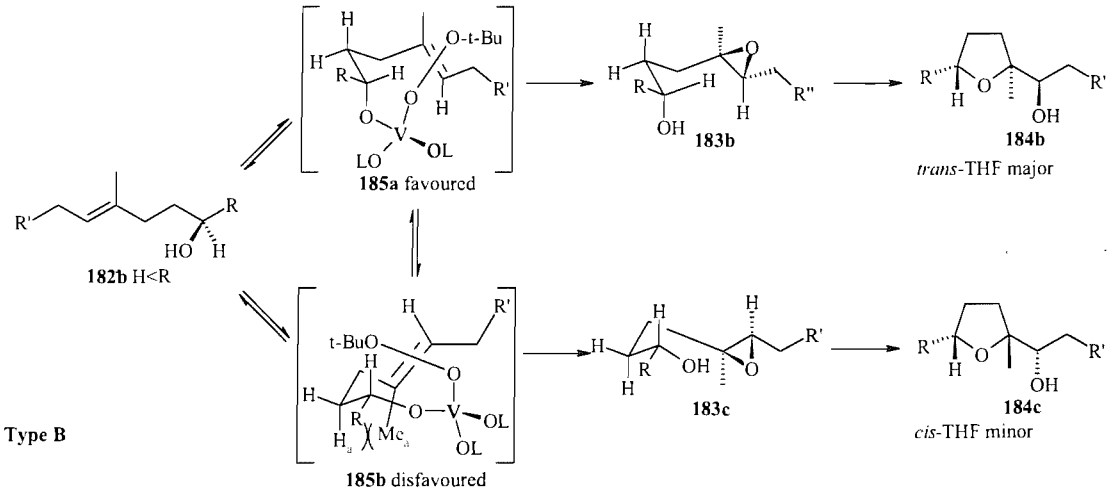
Vanadium catalysed oxidation could therefore be divided in two types (scheme 1.51). In type A, 4-substituted-4-en-1-ol **182a** gave *trans*-2,5,5-trisubstituted THF **184b** through an *anti* epoxide intermediate, while in type B 5-substituted-4-en-1-ol **182b** gave *cis*-2,5-disubstituted THF **184b** through a *syn* epoxide. It is also interesting to note that the stereoselectivity of this reaction did not depend on the stereochemistry of the double bond.



Scheme 1.51: Selectivities in $VO(acac)_2$ catalysed oxidation.

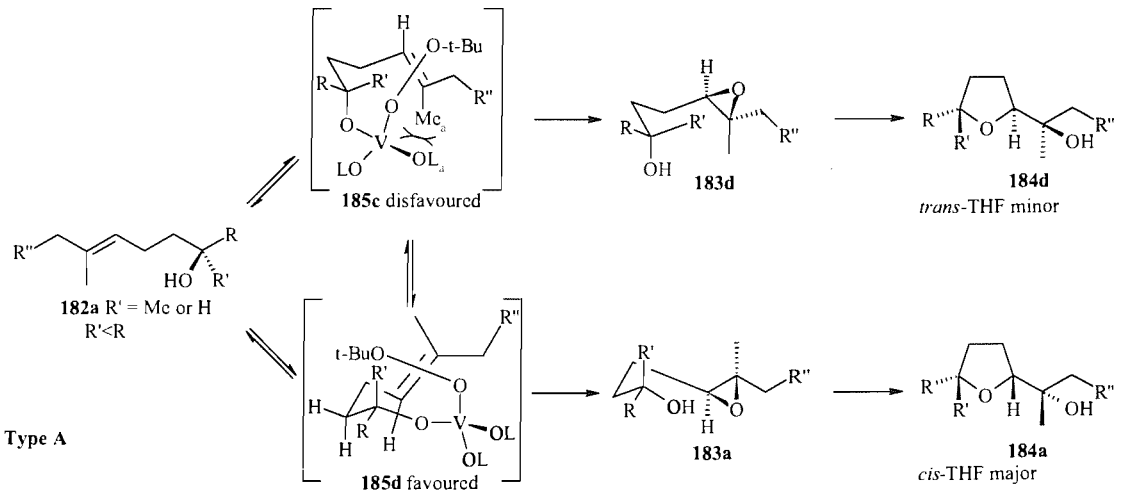
It is thought that the stereoselectivity is due to steric factors. It follows the model proposed by Sharpless *et al.* for epoxidation.[75] In type B, the transition state of the minor epoxide **185b** experiences steric compression due to the interaction between H_a, R and Me_a (scheme 1.52). In contrast, the $A^{1,3}$ strain is minimised in the transition state **185a** of major epoxide **183b**. This steric compression becomes more important for R' = CH_3 than for R' = H, explaining the

decrease of stereoselectivity between examples **178c** and **178e** (scheme 1.51). The observed selectivity is also solvent dependent. Hanassian *et al.* have reported that the use of noncoordinating solvent such as hexanes led to improve the selectivity (9:1 *cis/trans*) in comparison to CH_2Cl_2, benzene or toluene (4-5:1 *cis/trans*).



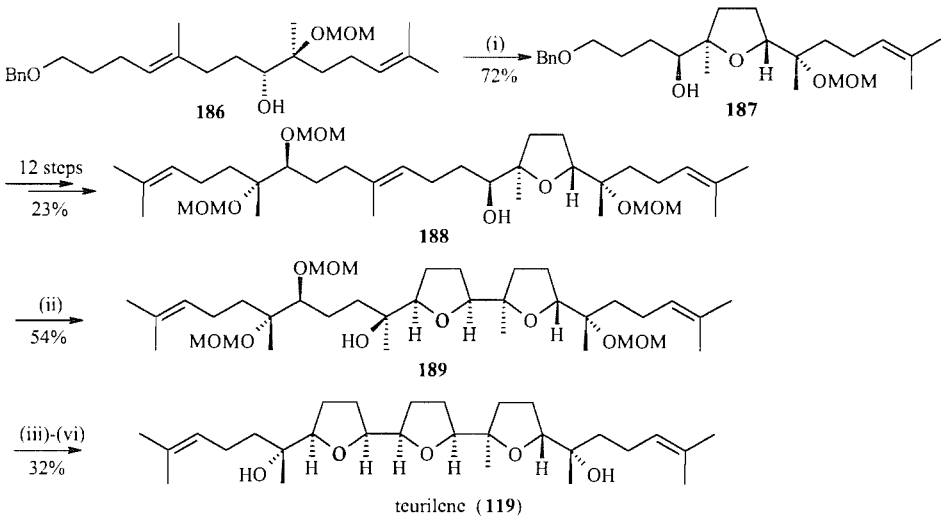
Scheme 1.52: Steric effects on type B selectivity.

In type A, the transition state **185c** which leads to the minor epoxide **183d** can experience steric compression between the vinylic methyl group Me_a and the tertiary oxygen bound to the catalyst OL_a (scheme 1.53).[76] Minimisation of this steric compression favours the transition state **185d** of the *cis* isomer **183a**.



Scheme 1.53: Steric effects on type A selectivity.

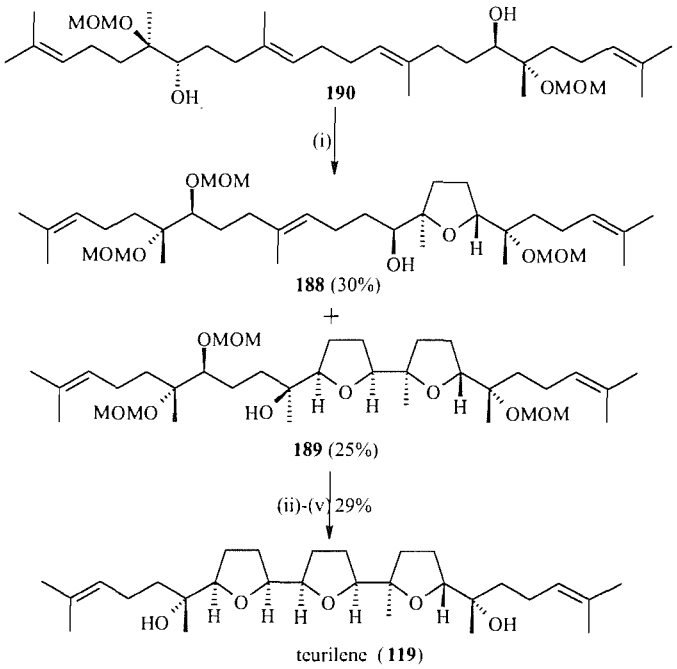
Vanadium catalysed oxidation has been applied to the preparation of mono, *bis*, *tri* and *penta* THF fragments used in total syntheses.[77,78] Shirahama *et al.* have reported the synthesis of teurilene *via* two different methods, both involving vanadium epoxidation-cyclisation.[73] The first one, involved a step-by-step construction of the *bis*-THF segment, while in the second approach, oxidation was carried out in one step. Diene **186** was oxidised to the corresponding *trans*-THF **187** in good yield and stereoselectivity (scheme 1.54). THF **188** was obtained in twelve steps and oxidised with $VO(acac)_2$ to afford *bis*-THF **189** in good yield. All the MOM groups were then removed by acid, the secondary alcohol of resulting tetrol was mesylated and converted to the corresponding epoxide. Teurilene (**119**) was obtained after exposure of the epoxide to acid with formation of the third THF ring.



Conditions and reagents: (i) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, r.t., 3.5h; (ii) (i) $VO(acac)_2$, *t*-BuOOH, AcOH, PhH, 50°C, 5h; (iii) HCl, MeOH, r.t., 12h; (iv) MsCl, Et_3N, CH_2Cl_2, –40°C, 2h; (v) K_2CO_3, MeOH, r.t., 30 min; (vi) HCl, H_2O, Et_2O, r.t., 1h.

Scheme 1.54: Synthesis of teurilene (**119**) *via* step-by-step THF unit construction.

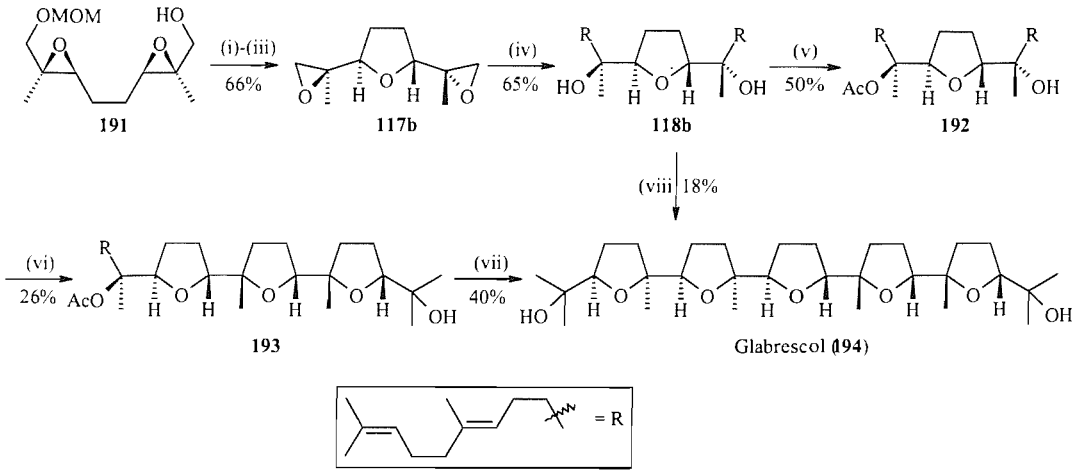
Tetraene **190** was exposed to $VO(acac)_2$ and simultaneous type A and B oxidation-cyclisation took place to afford *bis*-THF **189** in moderate yield along with mono-THF **188** (scheme 1.55).[72,73] *Bis*-THF **189** was then converted to teurilene (**119**) in the same way that was shown previously.



Conditions and reagents: (i) $VO(acac)_2$, *t*-BuOOH, AcOH, PhH, 50°C, 7h; (ii) HCl, MeOH, r.t., 12h; (iii) MsCl, Et_3N, CH_2Cl_2, –40°C, 2h; (iv) K_2CO_3, MeOH, r.t., 30 min; (v) HCl, H_2O, Et_2O, r.t., 1h.

Scheme 1.55: Synthesis of teurilene (**119**) *via* double cyclisation.

Morimoto *et al.* have described the synthesis of glabrescol, a *penta*-THF diol *via* vanadium oxidation.[79] By replacing AcOH by TFA, they have dramatically improved the results obtained by Shirahama *et al.*. Diepoxide **191** was prepared using Sharpless asymmetric epoxidation and converted to THF ring **117b** in good overall yield (scheme 1.56). Introduction of the geranyl side chains and monoacetylation of diol **118b** yielded alcohol **192**, double cyclisations of alcohol **192** using the optimised conditions afforded *tri*-THF **193** as a major product after deacetylation. Repetition on the oxidation step on *tri*-THF **193** gave glabrescol (**194**) in good yield. The conversion of diol **118b** into glabrescol (**194**) was also achieved directly *via* vanadium oxidation and in moderate yield and selectivity.

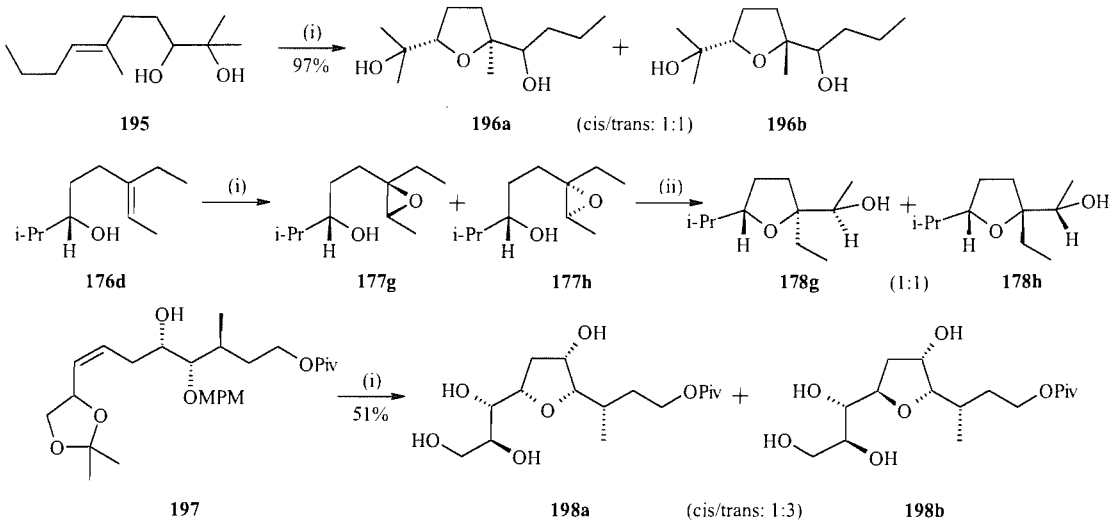


Conditions and reagents: (i) NaOH (1M, aq.), 1,4-dioxane, reflux, 1h, then acidified by HCl (pH 2), reflux, 10 min; (ii) MsCl, Py, CH_2Cl_2, 0°C to r.t., 1h; (iii) K_2CO_3, MeOH, r.t., 15 min; (iv) (a) genaryl phenyl sulphide, BuLi, TMEDA, THF, –78°c, 1 h; (b) Na, *i*-PrOH, THF, reflux; (v) Ac_2O, Py, DMAP, CH_2Cl_2, r.t., 24h; (vi) (a) $VO(acac)_2$ (0.02 eq.) *t*-BuOOH (2.5 eq.), TFA (2 eq.), CH_2Cl_2, r.t., 30 min; (b) $LiAlH_4$, THF, 0°C, 1h; (vii) $VO(acac)_2$ (0.02 eq.) *t*-BuOOH (2.5 eq.), TFA (2 eq.), CH_2Cl_2, r.t., 30 min; (viii) $VO(acac)_2$ (0.05 eq.) *t*-BuOOH (5 eq.), TFA (2 eq.), CH_2Cl_2, r.t., 30 min.

Scheme 1.56: Synthesis of glablescol (**194**) *via* sequential double cyclisations.

1-II-4 Use of *m*-CPBA

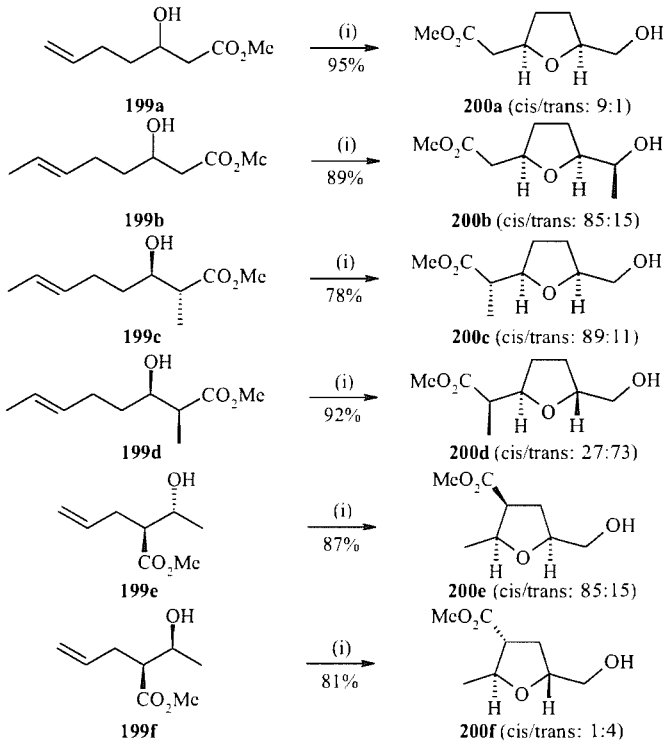
Casida *et al.* have reported that the reaction between ethyldiol **195** and *m*-CPBA afforded a 1:1 mixture of the *cis* and *trans* THFs **196a** and **196b** (scheme 1.57).[65] During the studies on vanadium induced oxidation, Kishi *et al.* showed that *m*-CPBA oxidised 5-hydroxyalkene **176d** to give a 1:1 mixture of THF **178g,h**,[71] they discovered that stereoselectivity could also be obtained with the oxidation of diene **197** providing the *trans*-THF **198b** in moderate selectivity.[80]



Conditions and reagents: (i) *m*-CPBA (1.5 eq.), CH_2Cl_2, 0°C to 25°C, 4h.

Scheme 1.57: Cyclisation of hydroxy alkenes using *m*-CPBA

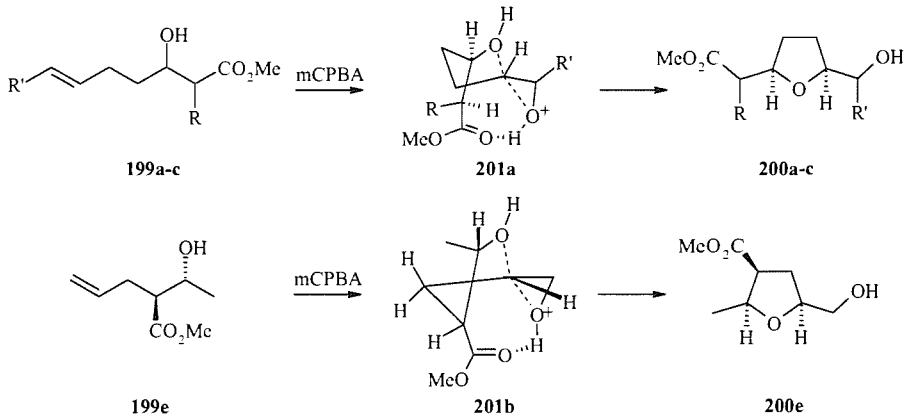
Iqbal *et al.* have described the synthesis of 2,5-disubstituted-THF using *m*-CPBA.[81] The stereochemistry of the reaction is controlled by a remotely placed methoxycarbonyl group.[82] Alkenes **199a-f** were treated with *m*-CPBA and the desired THF **200a-f** were obtained in good yield and selectivity (scheme 1.58).



Conditions and reagents: (i) *m*-CPBA (1.5 eq.), CH_2Cl_2, 0°C to 25°C, 4h.

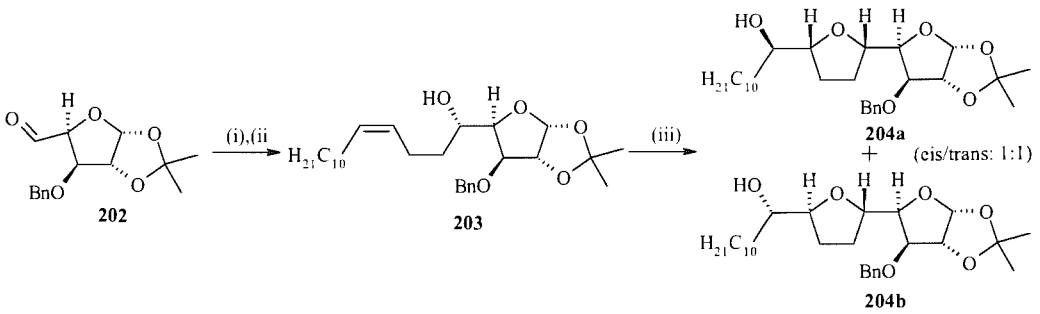
Scheme 1.58: Cyclisation of hydroxy alkenes using *m*-CPBA

Cis-selectivity obtained for THFs **200a-c,e** could be explained by an involvement of the ester group during the cyclisation. It is thought that the electrophilic cyclisation of alcohols **199a,c** goes *via* transition state **201a**, the hydrogen bonding lowers the activation energy and therefore is responsible for the high *cis* selectivity (scheme 1.59). In a similar manner, *cis* stereoselectivity is obtained for alcohol **199e** *via* hydrogen bonding between the protonated oxirane and the carbonyl of the ester group shown in transition state **201b**. The *trans* selectivity obtained for the cyclisation of **199d,f** could be explained by the non-involvement of the ester group due to steric interactions.



Scheme 1.59: Cyclisation of hydroxy alkenes using *m*-CPBA

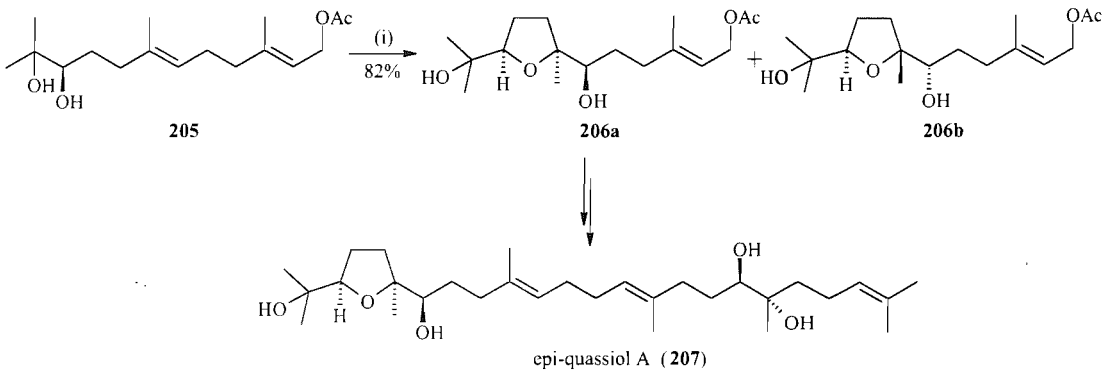
m-CPBA has been used toward the synthesis of natural products but in a non-stereospecific manner. Gesson *et al.* has*ve reported the synthesis of *bis*-THF adducts **204a,b** *via* *m*-CPBA induced cyclisation of the 5-hydroxy-alkene unit in compound **203** (scheme 1.60).[83] *Bis*-THF **204b** is a useful intermediate toward the synthesis of natural compound uvaricin.



Conditions and reagents: (i) 1-bromo-3-tetradecyne, Mg; (ii) Lindlar reduction; (iii) (a) *m*-CPBA, CH_2Cl_2; (b) AcOH, CH_2Cl_2, 20°C, 12h.

Scheme 1.60: *m*-CPBA induced synthesis of THFs **204a,b**.

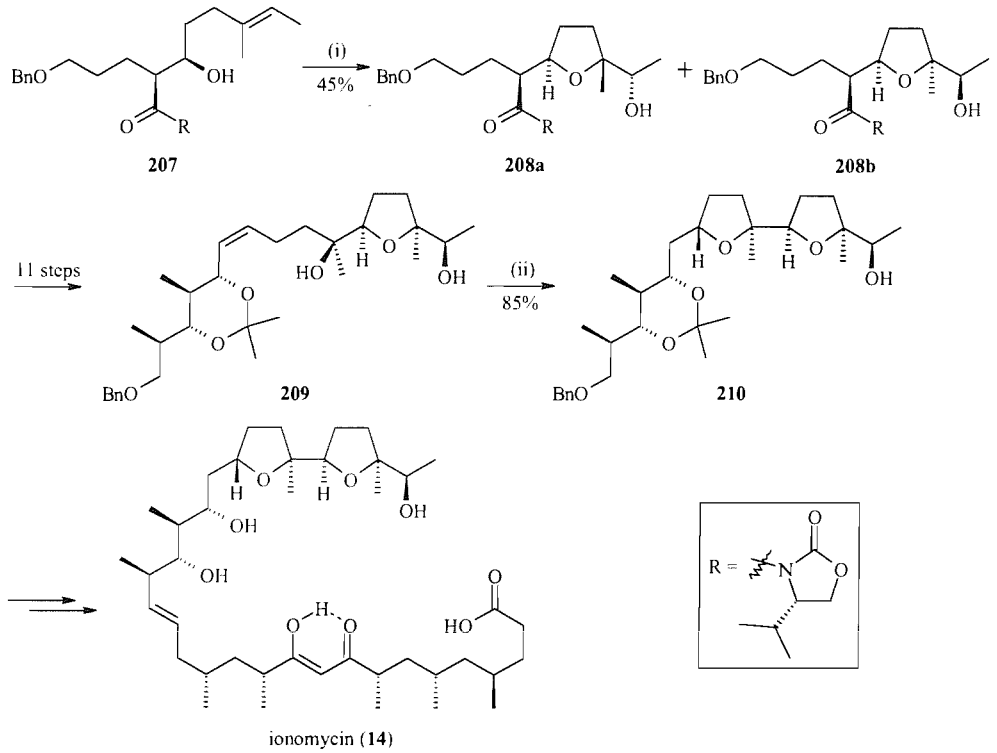
Kodama *et al.* have reported the asymmetric cyclisation of enantiomerically pure dihydroxy-diene **205** using *m*-CPBA.[84] Diene **205** was prepared from farnesol and treated with *m*-CPBA to afford two diastereomeric THFs **206a,b** in a 1:1 ratio (scheme 1.61). THF **206a** was used in the synthesis of *epi*-quassiol A (**207**).



Conditions and reagents: (i) 1-bromo-3-tetradecyne, Mg; (ii) Lindlar reduction; (iii) (a) *m*-CPBA, CH_2Cl_2; (b) AcOH, CH_2Cl_2, 20°C, 12h.

Scheme 1.61: *m*-CPBA-induced synthesis of THFs **206a,b**.

Evans *et al.* have described the synthesis of the *bis*-THF units present in ionomycin (**14**) *via* *m*-CPBA oxidation followed by mercuric acetate cyclisation.[85] Non-selective oxidation of alcohol **207** with *m*-CPBA gave a 1:1 mixture of THFs **208a,b** that were separable by chromatography (scheme 1.62). After conversion of the desired THF **208a** into THF **209** in 11 steps, internal oxymercuration with $Hg(OAc)_2$ gave *bis*-THF **210** in good yield and excellent selectivity (*trans/cis*: 93:7).

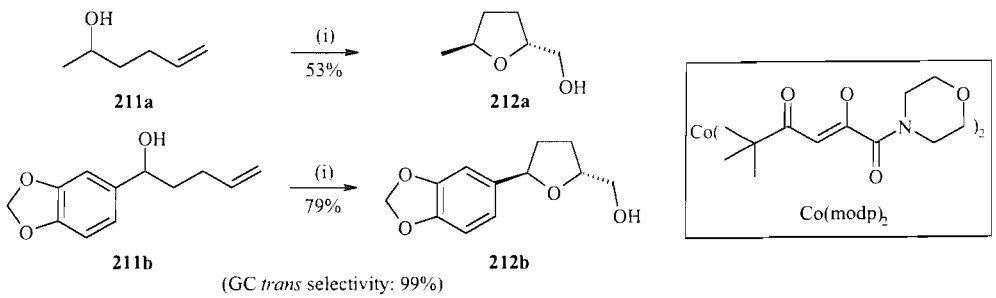


Conditions and reagents: (i) *m*-CPBA, EtOAc, 0 to 20°C, 24h, then AcOH, 10h; (ii) (a) $Hg(OAc)_2$, CH_2Cl_2, –78 to 20°C, 13h; (b) $NaBH_4$, NaOH, $MeOH/H_2O$ (6:1), 20°C, 30 min.

Scheme 1.62: Synthesis of *bis*-THF *via m*-CPBA oxidation and mercuricyclisation.

1-II-5 Oxidative cyclisation of hydroxy alkenes catalysed by cobalt (II) complex

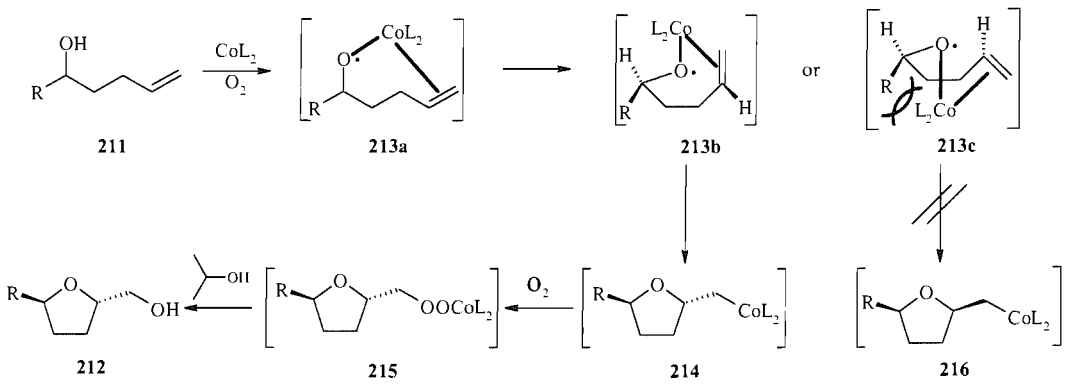
Mukaiyama *et al.* have described the successful cobalt mediated oxidative cyclisation of 5-hydroxy-1-alkenes.[86] Alcohols **211a,b** were oxidised[87] with O_2 in presence of *bis*(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II) ($Co(modp)_2$) to afford 2,5-disubstituted-THFs **212a,b** in good yield and excellent *trans* stereoselectivity (scheme 1.63).



Conditions and reagents: (i) $Co(modp)_2$ (20mol%), 2-propanol, molecular sieves, O_2, *t*-BuOOH, 50°C, 30 min.

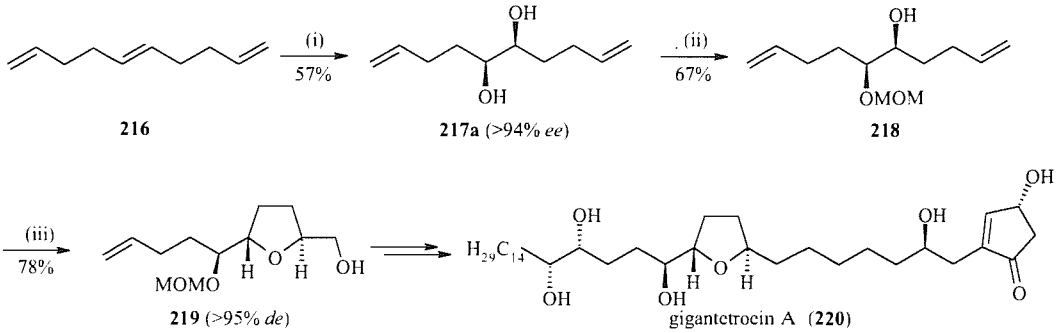
Scheme 1.63: Oxidative cyclisation of hydroxy alkenes catalysed by $Co(modp)_2$

It is thought that mechanistically the cyclisation starts by the formation of radical intermediate **213a** from the reaction between the alkene, the cobalt complex and O_2 (scheme 1.64). Radical **213b** then interacts with Co complex in the coordination sphere and is converted to the cyclised intermediate **214**. Insertion of O_2 into the cobalt-carbon bond of compound **53** forms intermediate **215** that undergoes reductive cleavage and yields the THF product **212** and cobalt peroxide. It is thought that hydroperoxyde accelerates the generation of the radical intermediate **213a**. The *trans* selectivity of this reaction is due to the position taken by groups R and CoL_2 during the cyclisation of intermediate **214**; R and CoL_2 are *trans* to each other because of steric repulsion between them.



Scheme 1.64: Mechanism of oxidative cyclisation catalysed by $Co(modp)_2$

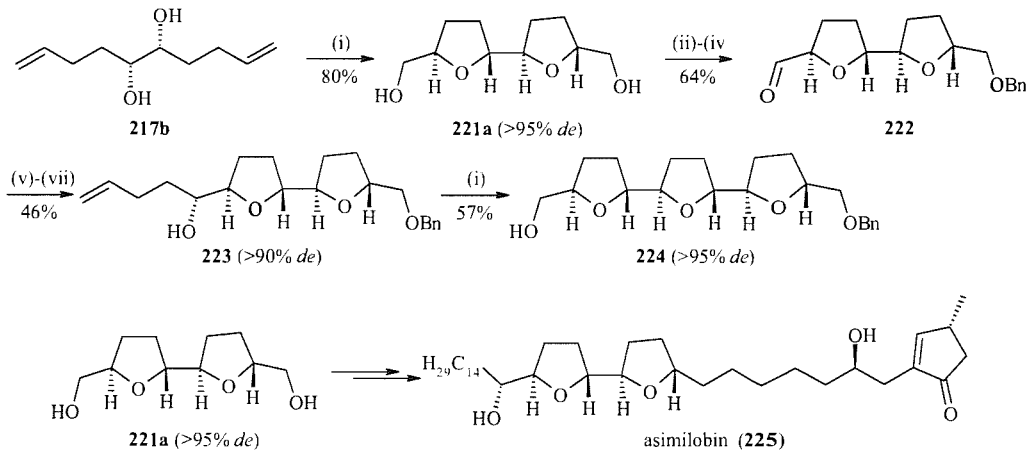
This methodology has been studied intensively by Shi *et al.*[88-91] They described the stereocontrolled construction of mono, *bis*, *tri* and *tetra trans*-THF units from a key triene precursor (scheme 1.65). Triene **216** underwent a Sharpless AD reaction and the obtained diol **217a** was subsequently mono-protected by MOMCl. Oxidation of alcohol **218** using $Co(modp)_2$ under an oxygen atmosphere afforded mono-THF **219** in good yield and excellent diastereoselectivity (*de* calculated from NMR studies). THF **219** was then converted to acetogenin gigantetrocin A (**220**) in 15 steps.[89]



Conditions and reagents: (i) $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH:H_2O (1:1), 0°C, 12h; (ii) NaH, MOMCl, THF, 25°C, 24h; (iii) $Co(modp)_2$ (20mol%), TBHP, O_2, *i*-PrOH, 60°C, 4h.

Scheme 1.65: Mono-THF synthesis *via* cobalt oxidation.

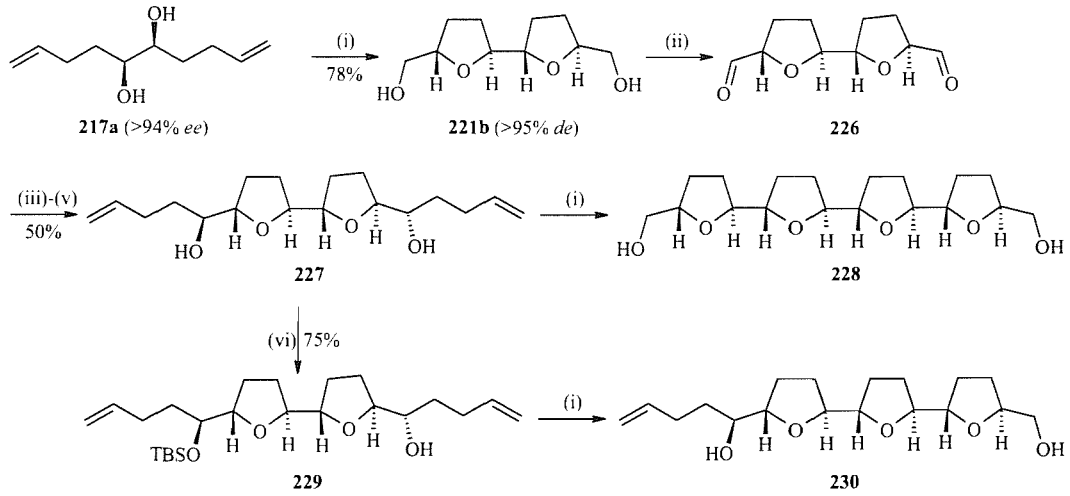
Using this strategy, adjacent *trans-bis*-THF and *tri*-THF could also be easily synthesised and used toward the synthesis of natural products. Diol **217b** was obtained by Sharpless AD on triene **216** and was oxidised with $Co(modp)_2$ to yield *trans/threo/trans bis*-THF ring **221a** (scheme 1.66). After mono-protection with a benzyl group and the remaining alcohol was converted to the aldehyde **222** *via* a Swern oxidation. The aldehyde **222** was coupled with (3-buten-1-yl)magnesium bromide and underwent another Swern oxidation to afford the corresponding ketone that was subsequently reduced by L-selectride to give the enol **223** in overall good yield and excellent diastereoselectivity. Oxidation of enol **223** with $Co(modp)_2$ afforded *tri*-THF unit **224** in good yield.[91] It is interesting to note that *bis*-THF segment **221a** was converted to the acetogenin asimilobin (**225**) in 12 steps.[90]



Conditions and reagents: (i) $Co(modp)_2$ (20mol%), TBHP, O_2, *i*-PrOH, 50°C, 4h; (ii) NaH, BnBr, THF, 25°C, 12h; (iii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, –78°c to 25°C, 3 h; (iv) CH_2=$CHCH_2CH_2MgBr$, THF, –20°C, 90 min; (v) L-selectride, THF, –78°C, 1h.

Scheme 1.66: *Bis* and *tri*-THF fragments synthesis *via* cobalt oxidation.

This methodology has allowed Shi *et al.* to synthesise *tetra*-THF using a similar method to the one seen previously. Diol **217a** was oxidised with $Co(modp)_2$ to yield *trans/threo/trans bis*-THF ring **221b** (scheme 1.67). After a Swern oxidation, the dial **226** was coupled with two equivalents of (3-buten-1-yl)magnesium bromide and underwent another Swern oxidation to afford the corresponding dione. Subsequent reduction using L-selectride gave the diendiol **227** in overall moderate yield and with a 2.6:1 diastereoselectivity; the two diastereoisomers were separated by column on silica gel. Diendiol **227** was then converted the usual manner to afford the C_2-symmetric *tetra*-THF unit **228** in excellent *trans*-selectivity. Compound **227** was also mono-protected with TBDMSCl and *bis*-THF **229** was oxidised to afford *tri*-THF **230**.



Conditions and reagents: (i) $Co(modp)_2$ (20mol%), TBHP, O_2, *i*-PrOH, 50°C, 4h; (ii) NaH, BnBr, THF, 25°C, 12h; (iii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2,–78°c to 25°C, 3 h; (iv) CH_2=$CHCH_2CH_2MgBr$, THF, –20°C, 90 min; (v) L-selectride, THF, –78°C, 1h; (vi) TBDMSCl, imidazole, THF, 25°C, 25h.

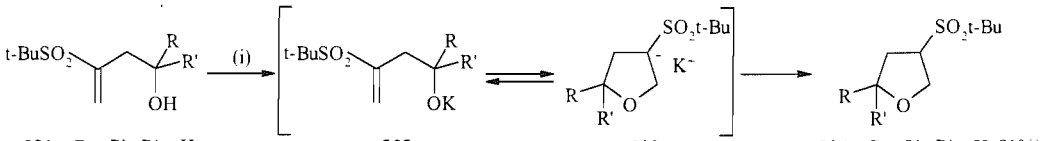
Scheme 1.67: *Tri* and *tetra*-THF fragments synthesis *via* cobalt oxidation.

Evans *et al.* have described the synthesis of (–)-mucocin using $Co(modp)_2$ catalysed oxidation to construct the mono-THF unit.[92] This synthesis will be described later.

1-II-6 1,4-Addition to α,β-unsaturated sulfones

Knochel *et al.* have reported that γ-functionalized unsaturated sulfones cyclised under basic conditions to provide THF fragments *via* a 5-*endo*-trig process.[93] Sulfones **231a-c** were treated with catalytic potassium hydride and afforded the corresponding THFs **234a-c** in good yield (scheme 1.68). It is thought that the deprotonation of the hydroxy-sulfone **231** gives the corresponding alcoholate **232**, which is in equilibrium with the potassium carbanion **233**.

Species **233** takes the hydroxy proton from another molecule of **232**, this leads to the formation of THF adduct **234** and intermediate **232**, which restarts the catalytic cycle.



231a (R = Ph, R' = H)
231b (R = Et, R' = Et)

232

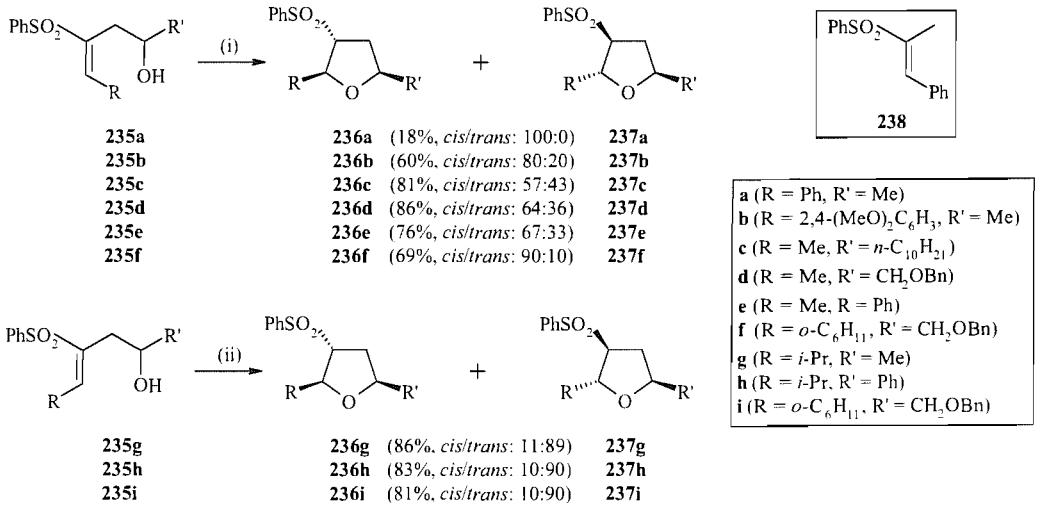
233

234a (R = Ph, R' = H, 81%)
234b (R = Et, R' = Et, 88%)

Conditions and reagents: (i) KH (mol%), THF, 25°C, 10 min.

Scheme 1.68: 5-*endo*-trigonal ring closures of unsaturated sulfones.

Craig *et al.* have developed the methodology further and applied it to the synthesis of 2,5-disubstituted THF.[94,95] Treatment of sulfones **235a-i** with stoichiometric potassium *tert*-butoxide afforded the mixture of THFs **236a-i** and **237a-i** in diverse yields and ratios (scheme 1.69). The low yield encountered from the reaction of **235a** may be due to the predominant formation of by-product **238**. Although, the cyclisation of most *E*-substrates only gave a modest *cis*-selectivity, the *Z*-isomers underwent efficient cyclisation with high *trans*-selectivity.



235a	**236a** (18%, *cis/trans*: 100:0)	**237a**
235b	**236b** (60%, *cis/trans*: 80:20)	**237b**
235c	**236c** (81%, *cis/trans*: 57:43)	**237c**
235d	**236d** (86%, *cis/trans*: 64:36)	**237d**
235e	**236e** (76%, *cis/trans*: 67:33)	**237e**
235f	**236f** (69%, *cis/trans*: 90:10)	**237f**

238

a (R = Ph, R' = Me)
b (R = 2,4-(MeO)$_2$C$_6$H$_3$, R' = Me)
c (R = Me, R' = *n*-C$_{10}$H$_{21}$)
d (R = Me, R' = CH$_2$OBn)
e (R = Me, R = Ph)
f (R = *o*-C$_6$H$_{11}$, R' = CH$_2$OBn)
g (R = *i*-Pr, R' = Me)
h (R = *i*-Pr, R' = Ph)
i (R = *o*-C$_6$H$_{11}$, R' = CH$_2$OBn)

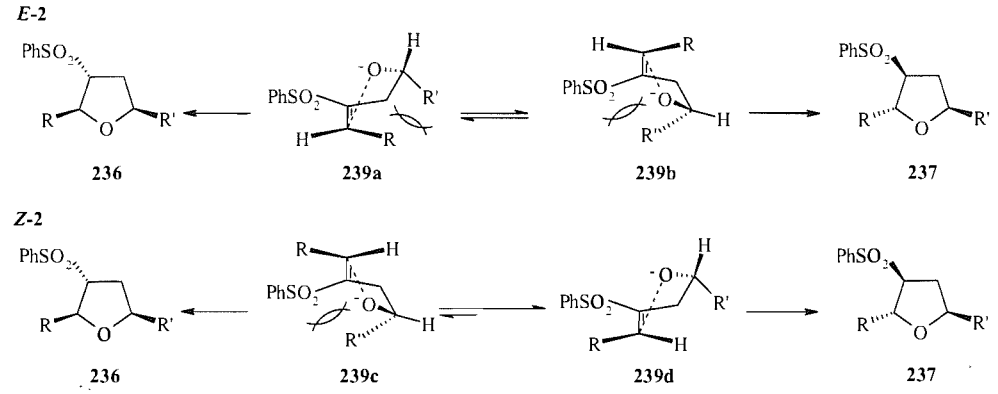
235g	**236g** (86%, *cis/trans*: 11:89)	**237g**
235h	**236h** (83%, *cis/trans*: 10:90)	**237h**
235i	**236i** (81%, *cis/trans*: 10:90)	**237i**

Conditions and reagents: (i) *t*BuOK (1 eq.), *t*BuOH (5 eq.), THF (0.033 M), 25°C, 6 to 23 min; (ii) *t*BuOK (1 eq.), *t*BuOH (10 eq.), THF (0.033 M), 25°C, 6 to 23 min. **235f** was oxidised using conditions (ii) and **235g** using conditions (i).

Scheme 1.69: Synthesis of 2,5-disubstituted THFs *via* 5-*endo*-trigonal ring reactions.

It is thought that the modest *syn*-selectivity observed in most cases is due to the destabilising interactions observed in both of the conformers **239a** and **239b** leading respectively to the *syn* and *anti* THFs **236** and **237** (scheme 1.70). On the other hand, if the same model is applied to

the *Z*-substrates, it indicates that the reactions would be selective for *anti* THF **237** since there is no major destabilising interaction in conformer **239d**.

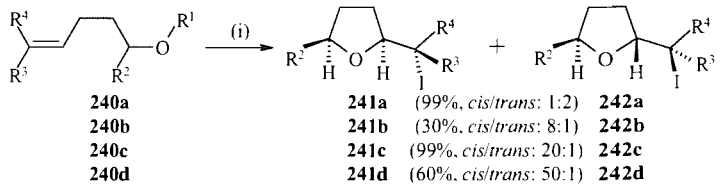


01.71: Interaction models of the 5-*endo-trig* cyclisation reaction.

1-III Cyclisation of unsaturated alcohols

1-III-1 Haloetherification

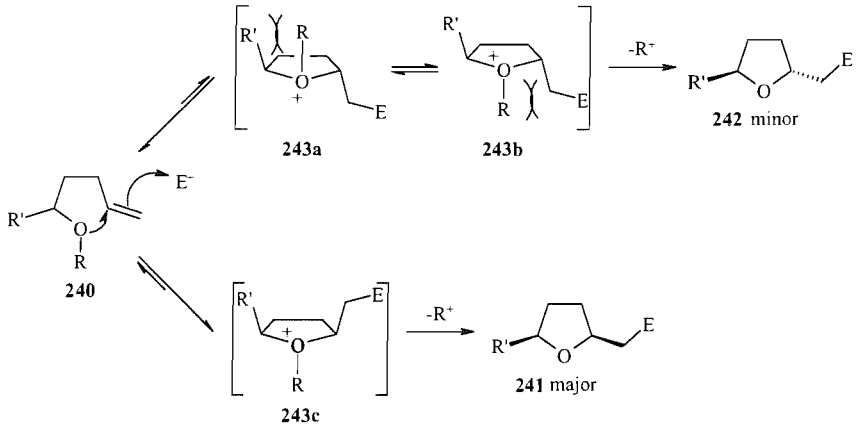
Bartlett *et al.* reported the stereocontrolled synthesis of *cis* and *trans* disubstituted THF *via* the cyclisation of alkenes with iodine.[96] Alkenes **240a-d** were treated with iodine and the corresponding 2,5-disubstituted THFs **241a-d** and **242a-d** were obtained in good yield (scheme 1.71). When the alcohol was protected, the reaction gave stereoselectively *cis*-isomers; on the other hand, unprotected alcohol **241a** produced the *trans*-isomer **242a** as the major product.



Conditions and reagents: (i) I_2, CH_3CN, 0°C; addition of $NaHCO_3$ for entry **a** and cyclisation performed at 21°C for entry **d**.

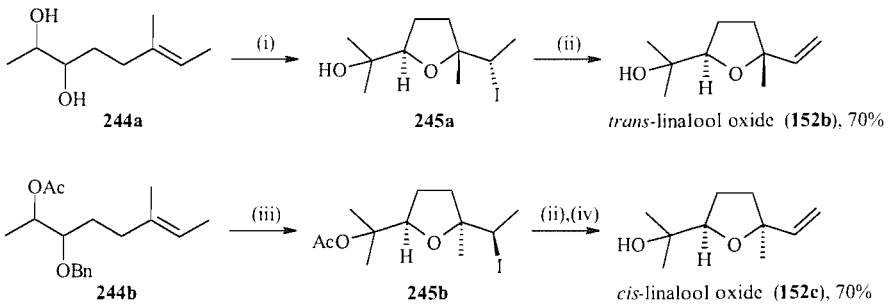
Scheme 1.71: THF synthesis *via* halocyclisation

It is thought that the mechanism of this reaction goes *via* the formation of an oxonium ion intermediate (scheme 1.72). The alkyl substituent should be bulky enough to have a significant steric effect. But when R is too large, it can prevent cyclisation and therefore leads to reduced yields (*e.g.* **241b**). The limiting factor of this reaction is the loss of the alkyl group R from the oxonium ion intermediates **243a-c**. It should be slow in comparison to the reversal of their formation to favour **243c** thermodynamically as well as kinetically. The 2,6-dichlorobenzyl substituent seems to represent the optimal combination of steric and electronic properties for promoting a transition state that avoids 1,2-steric interactions, accommodates 1,3-interactions and allows an easy fragmentation of the intermediate oxonium ion.



Scheme 1.72: Mechanism of the halocyclisation.

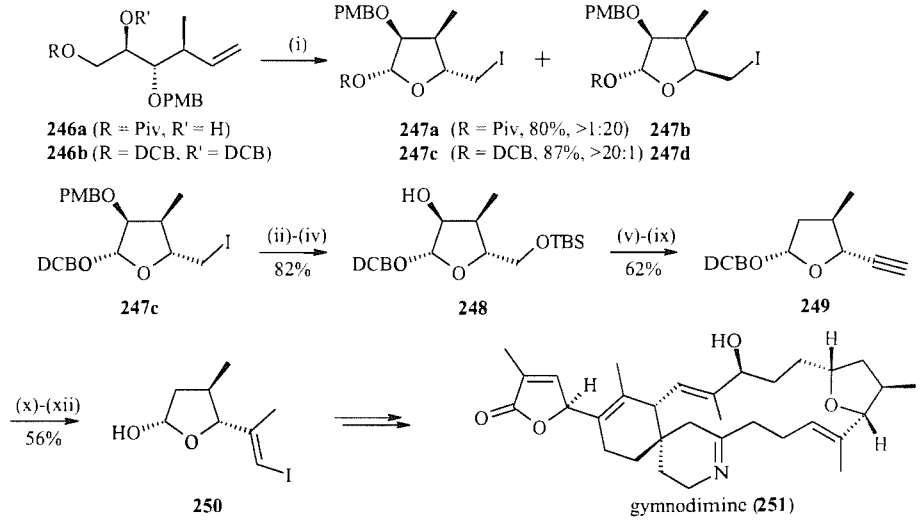
Bartlett *et al.* have applied these observations to the syntheses of racemic *cis* and *trans* linalool oxides **152b,c**.[96] Iodocyclisation of alkenes **244a,b** and elimination of HI and cleavage of the acetate group in **245b** afforded the corresponding *trans* and *cis*-linalool oxides **152b,c** in good yield and selectivity (scheme 1.73).



Conditions and reagents: (i) I_2, CH_3CN, $NaHCO_3$, 0°C; (ii) *t*-BuOK, DMF, 25°C; (iii) I_2, CH_3CN, 0°C; (iv) NaOH.

Scheme 1.73: Synthesis of *trans* and *cis* linalool oxides **152b,c** *via* iodocyclisation.

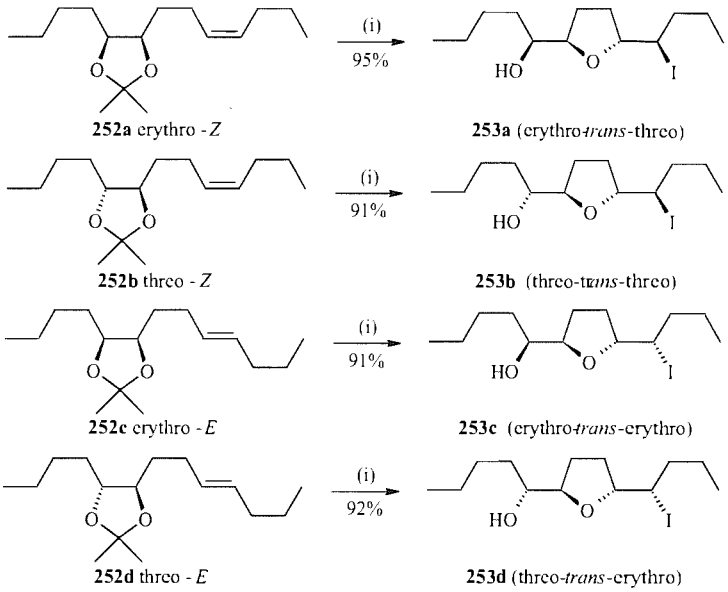
Bartlett's conditions for the iodocyclisation were applied toward the synthesis of gymnodimine (**251**) by White *et al.*[97] Alkene **246a** was treated with iodine and afforded the THF **247b** in good yield and selectivity (scheme 1.74). It is interesting to note that when iodocyclisation was performed on alkene **246b**, opposite selectivity was obtained. Displacement of the iode in THF **247c** with cesium trifluoroacetate was followed by the cleavage of the trifluoroacetate ester and the sequential protection of the resulted primary alcohol and cleavage of the *p*-methoxybenzyl group to yield mono-THF **248**. After reductive deoxygenation and deprotection of the silyl group, the primary alcohol was oxidised to the aldehyde, which reacted with diethyl diazomethylphosphonate to give the alkyne **249**. THF **249** underwent stannylcupration-methylation followed by metal-halogen exchange and the removal of the dichlorobenzyl group to provide THF **250** in moderate yield.



Conditions and reagents: (i) I_2, CH_3CN, –20°C; (ii) $CsOCOCF_3$, DMF, 90°C, 36h, then Et_2NH, 3h; (iii), TBSCl, imidazole; (iv) DDQ, CH_2Cl_2; (v) $(Im)_2C{=}S$, toluene, 100°C; (vi) *n*-Bu_3SnH, AIBN, toluene, 100°C; (vii) TBAF, THF; (viii) $(COCl_2)$, DMSO, Et_3N, –78°C; (ix) $N_2CHP(O)(OEt)_2$, *t*-BuOK; (x) n-$Bu_3SnCu(CN)Li$, MeI, DMPU-THF; (xi) I_2, Et_2O; (xii) Me_3SiCl, NaI, MeCN.

Scheme 1.74: Iodocyclisation toward the synthesis of gymnodimine (**251**)

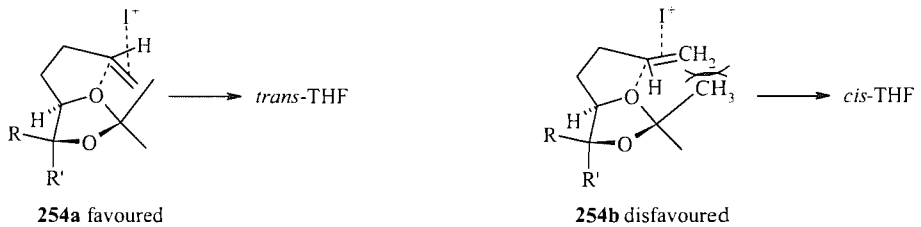
Mootoo *et al.* have investigated iodocyclisation intensively and showed that 5,6-*O*-isopropylidene acetals on treatment with iodonium ion, gave exclusively the *trans*-2,5-disubstituted THF.[98] Alkenes **252a-d** were treated with iodonium dicollidine perchlorate (IDCP) to afford the corresponding THF adducts **253a-d** in excellent yield and *trans* selectivity (no *cis* isomer was obtained) (scheme 1.75).



Conditions and reagents: (i) IDCP (2.5 eq.), CH_2Cl_2/H_2O, r.t., 5 min.

Scheme 1.75: Synthesis of *trans*-THF *via* iodocyclisation.

It is thought that the high streoselectivity of this reaction is due to the formation of a THF-oxonium ion intermediate which has a fused [5.5.0]oxahydrindan type geometry (scheme 1.76). Intermediate **254a** that leads to the *cis*-isomer is disfavoured by steric effects.

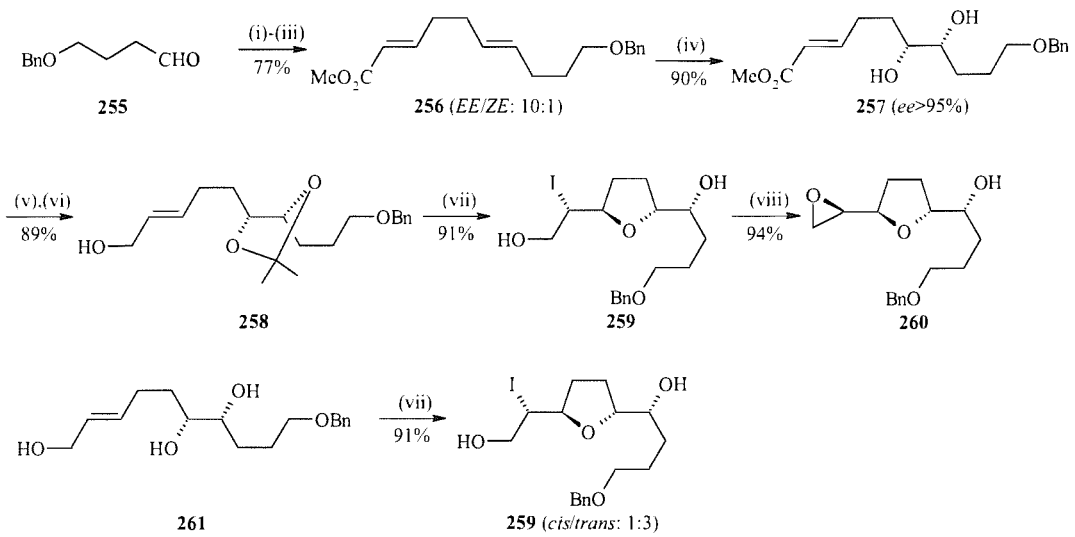


254a favoured **254b** disfavoured

Scheme 1.76: THF-oxonium in intermediates **254a** and **254b**.

Mootoo *et al.* combined iodocyclisation with Sharpless asymmetric dihydroxylation to synthesise *trans*-THF fragments that could be used as intermediates in acetogenin synthesis.[99] Diene **256** was prepared from 4-(benzyl-oxy)butanal **255** and treated with AD-mix-β to afford diol **257** in good yield and excellent *ee* (scheme 1.77). Isopropylidenation of the diol moiety followed by reduction of the ester group gave alcohol **258** in good yield. Treatment of alkene **258** with IDCP provided a single *trans*-THF-iodide product **259** in good yield. It is interesting to note that attempted iodocyclisation of triol **261** led to a mixture of *cis* and *trans*-THFs (1:3), this result confirmed previous observations.[98] THF **259** was treated with potassium

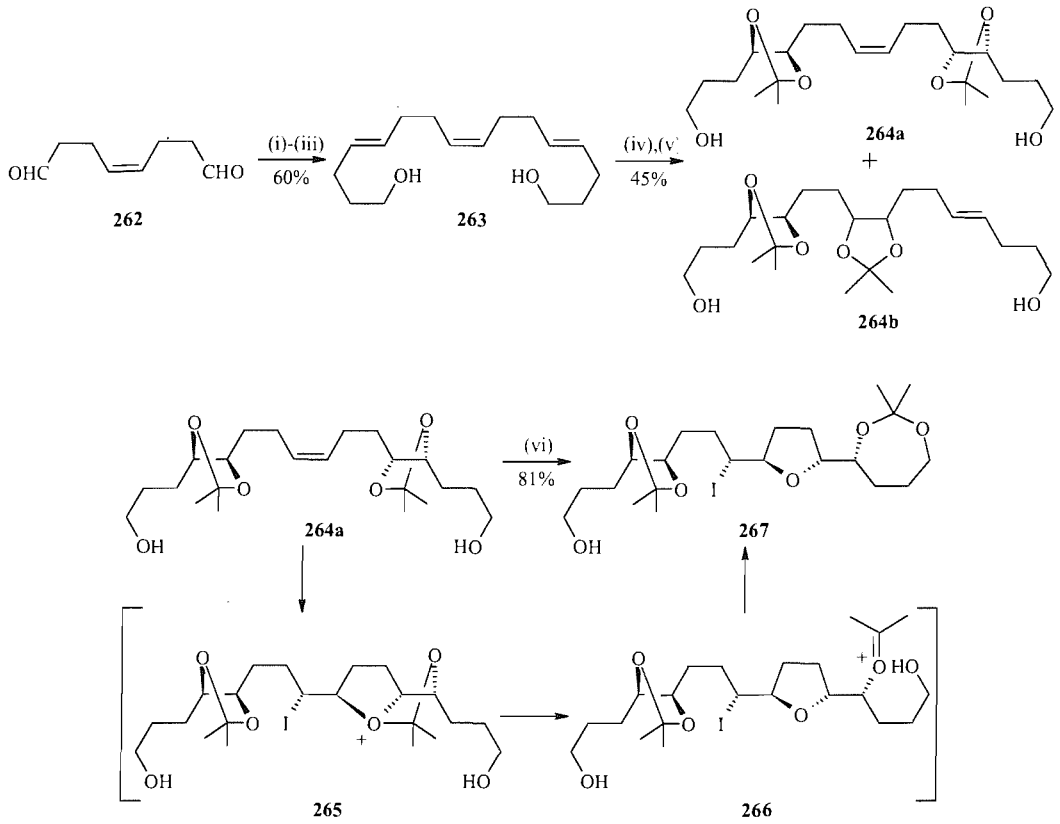
carbonate to yield the desired epoxy-THF **260**, that could be used for elaboration into a variety of mono and *bis*-THF acetogenins.



Conditions and reagents: (i) vinyl magnesium bromide, THF, 0°C, 20 min; (ii) *n*-butyl vinyl ether, $Hg(OAc)_2$, reflux, 18h; (iii) $Ph_3P{=}CHCO_2Me$, CH_3CN, 60°C, 40 min; (iv) AD-mix-β, t-BuOH/H_2O (1:1), 0°C, 3 days; (v) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 30 min; (vi) DIBALH, CH_2Cl_2, –40°C, 30 min; (vii) IDCP (2.5 eq.), 1% aq. CH_3CN, r.t., 5 min; (viii) K_2CO_3, MeOH, r.t., 5 min.

Scheme 1.77: Asymmetric synthesis of *trans*-THFs *via* iodocyclisation.

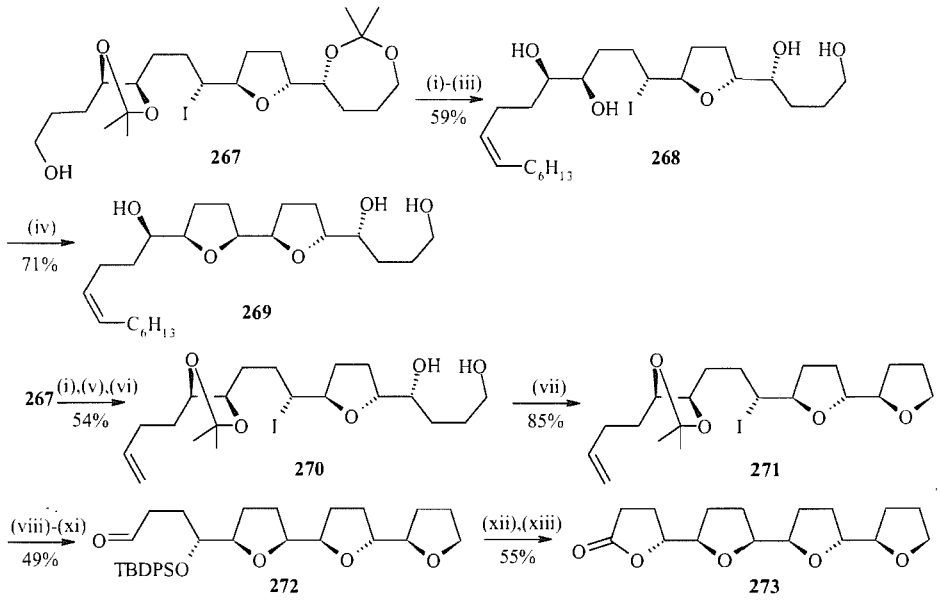
Mootoo *et al.* have then developed the construction of *bis*-THF units *via* iodocyclisation. Treatment of triene **263** with AD-mix-β and subsequent acetonation provided the desired *bis*-isoproplylidene alkene **264a** and side-product **264b** as a 5:1 mixture and in moderate yield (scheme 1.78). Alkene **264a** was treated with IDCP and afforded THF **267** in good yield and excellent selectivity. It is thought that the seven-member ring **267** is formed *via* capture of the oxocarbenium **266** by the neighbouring primary alcohol.



Conditions and reagents: (i) vinyl magnesium bromide, THF, 0°C, 1h; (ii) $CH_3C(OEt)_3$, $EtCO_2H$, 138 to 140°C, 2h; (iii) DIBALH, CH_2Cl_2, –78°C, 1h; (iv) AD-mix-*β*, $MeSO_2NH_2$, t-BuOH/H_2O (1:1), r.t. to –3°C, 20h; (v) 2,2-dimethoxypropane, CSA, DMF, 0°C to r.t., 30 min; (vi) IDCP (1.5 eq.), CH_3CN, r.t., 10 min.

Scheme 1.78: Preparation of *trans*-THF **267** *via* iodocyclisation.

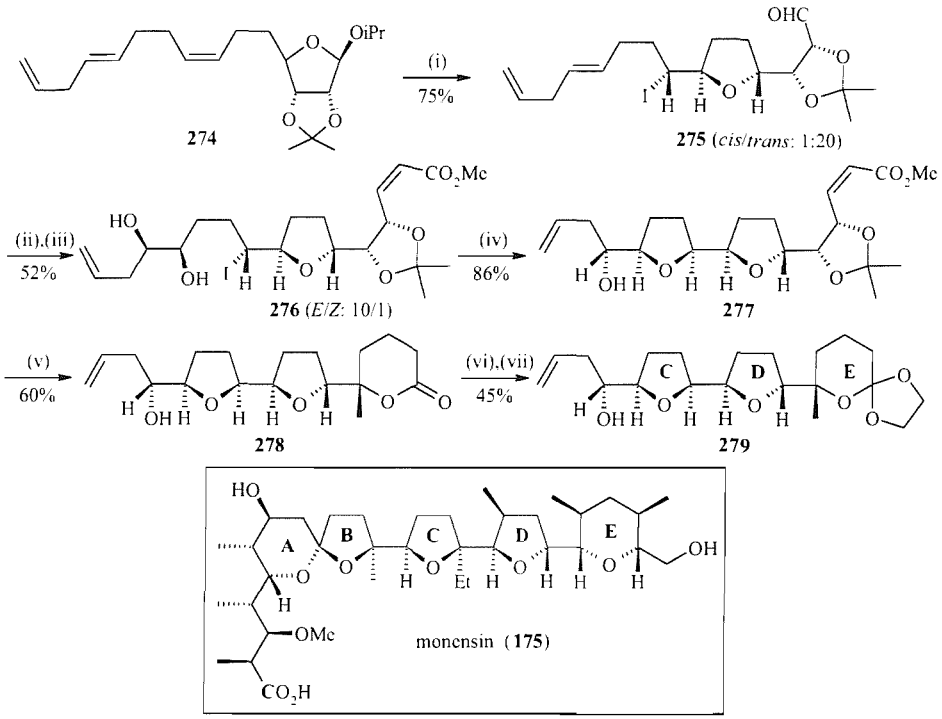
THF **267** was used as a key precursor to the synthesis of *bis*, *tri* and *tetra*-THFs. After conversion of THF **267** to THF **268**, subsequent treatment with dibutyltin oxide afforded *bis*-THF product **269** in good yield (scheme 1.79). THF **270** was easily prepared from THF **267** and underwent Mitsunobu etherification to yield *bis*-THF **271**. Acetonide hydrolysis of *bis*-THF **271** and subsequent dibutyl tin oxide etherification followed by sequential silylation and ozonolysis provided aldehyde **272**. This underwent $NaClO_2$ oxidation to a resulting carboxylic acid which cyclise under acidic conditions to yield lactone **273**.



Conditions and reagents: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C, 1h; (ii) $C_6H_{13}CH{=}PPh_3$, NaHMDS, toluene, r.t. to –78°C, 90 min; (iii) H_2SO_4, MeOH, r.t., 14h; (iv) Bu_2SnO, benzene, reflux, 17h; (v) $CH_2{=}PPh_3$, toluene NaHMDS, r.t. to –78°C, 90 min; (vi) 2,2-dimethoxypropane, CSA, DMF, 0°C to r.t., 3h; (vii) PPh_3, DEAD, CH_2Cl_2, r.t., 2h; (viii) $BF_3{\cdot}EtO_2$, THF/H_2O (20:3), r.t., 2 days; (ix) Bu_2SnO, benzene, reflux, 17h; (x) TBDPSCl, imidazole, DMF, 50°C, 3h; (xi) O_3, PPh_3, CH_2Cl_2/MeOH (4:1), –78°C to r.t., 1h; (xii) $NaH_2PO_4{\cdot}H_2O$, CH_3CN/H_2O (5:1), H_2O_2 (30% aq.) aq. $NaClO_2$, 0°C to r.t., 1h; (xiii) HCl (6N, aq.) THF, r.t., 2 days.

Scheme 1.79: Conversion of *trans*-THF **267** in *bis*, *tri* and *tetra*-THFs.

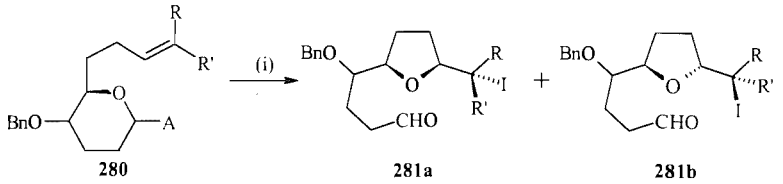
It is interesting to note that high *trans*-selectivity could also be obtained *via* the iodoetherification of C5 allylated ribo-furanoside.[100] Triene **274** was treated with IDCP to give the corresponding *trans*-THF adduct **275** in good yield and selectivity (scheme 1.80). THF **275** was then converted to *bis*-THF furanone segment **279**, an advanced precursor toward the synthesis of monensin (**175**). After olefination of aldehyde **275**, the resulting ester was treated with AD-mix β to give diol **276** in moderate yield and selectivity. Treatment with dibutyltin oxide afforded the *bis*-THF **277** in good yield. Reduction with dissolved magnesium and subsequent acidic hydrolysis provided lactone **278** in good yield. Protection of the lactone as an orthoester followed by configurational inversion of the homoallylic alcohol *via* the Mitsunobu conditions afforded desired *bis*-THF furanone **279**.



Conditions and reagents: (i) IDCP, CH_2Cl_2, then $Na_2S_2O_3$ (aq. sol.); (ii) $Ph_3{=}CHCO_2Me$, CH_3CN, reflux; (iii) AD-mix-β, $MeSO_2NH_2$, t-BuOH/H_2O (1:1), r.t. to –3°C; (iv) Bu_2SnO, benzene, Dean-Stark, reflux; (v) (a) Mg, MeOH, reflux; (b) CSA, CH_2Cl_2, MS 4Å, reflux; (vi) ethylene glycol, CSA, Dowex 50WX8-400, benzene, $MgSO_4$, reflux; (vii) (a) PPh_3, DEAD, *p*-NO_2-$C_6H_4CO_2H$, toluene; (b) NaOH (3N, aq. sol.), EtOH, reflux.

Scheme 1.80: Preparation of *bis*-THF furanone segment **279** *via* iodocyclisation.

Mootoo *et al.* have also developed a methodology leading to the formation of *cis*-THF *via* iodocyclisation using IDCP of monosaccharide alkenes.[101,102] Alkenes **280** were treated with IDCP and the corresponding THFs **281a,b** were obtained in good yield (scheme 1.81). Two generalisations emerged from these results, *cis*-selectivity increase with the aglycone size and *Z*-alkenes are less *cis*-selective than the *E*-isomers.

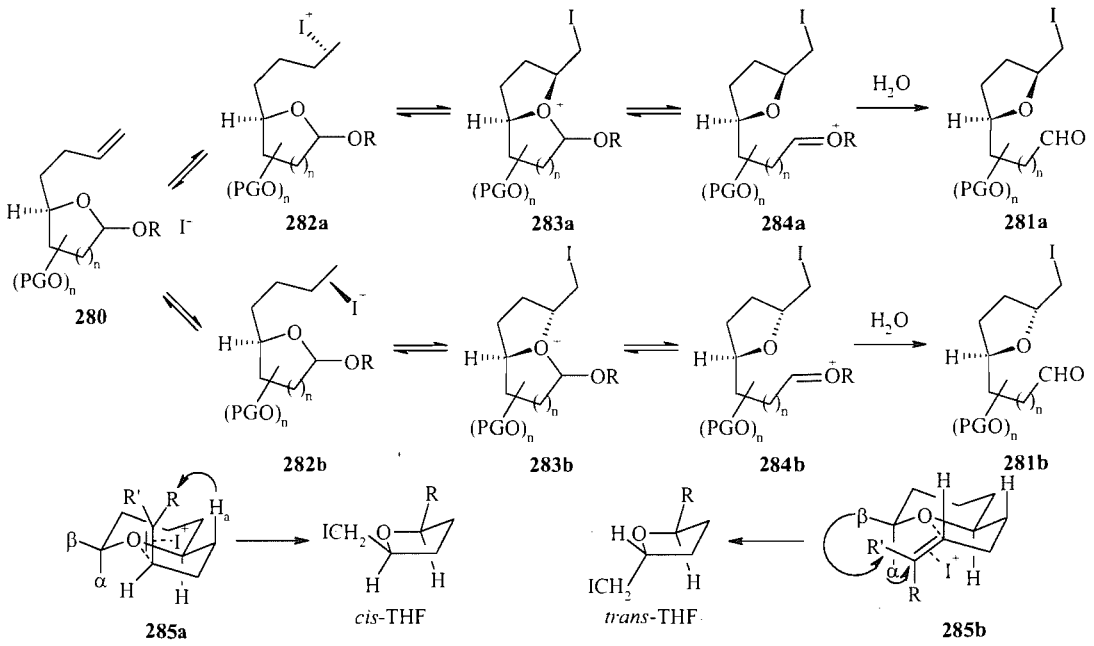


Sugar substitution	R = R' = H	*Z*: R = Pr, R' = H	*E*: R = H, R' = Pr
	cis/*trans*, yield	*cis*/*trans*, yield	*cis*/*trans*, yield
A = α-OC(CH$_2$)$_3$; α-OBn	3.5:1	1:1.5	3.5:1
A = α/β-OCPh$_3$; α-OBn	*cis* only; 80%	8:1; 81%	20:1; 78%
A = α-OC(CH$_2$)$_3$; β-OBn	3.5:1	1:1	8:1
A = α/β-OCPh$_3$; β-OBn	10:1; 87%	*cis* only; 91%	*Cis* only; 79%

Conditions and reagents: (i) IDCP, CH_2Cl_2, /H_2O, 10 min.

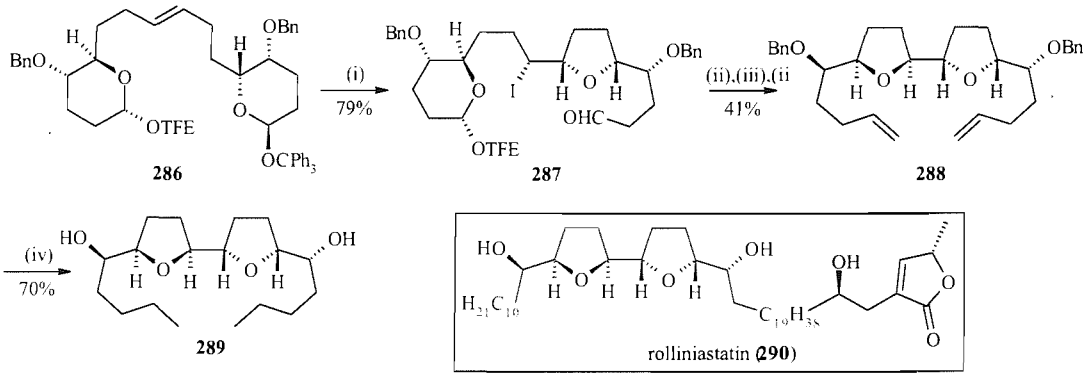
Scheme 1.81: Preparation of *cis*-THF **281a** *via* iodocyclisation.

It is thought that the reaction proceeds *via* the formation of bicyclic THF-oxonium intermediate **283**. The bicyclic nature of intermediate **283** allows communication of chirality from the monosaccharide template to the newly formed stereogenic center in the THF product (scheme 1.82). Fragmentation of intermediate **283** leads to species **284** that undergoes hydrolysis to give THF adducts **281**. It is thought that conformer **285a** with the alkene complex up is preferred to a down orientation, as depicted in conformer **285b**. The lower *cis*-selectivity encountered with the *Z* isomer could be explained by the destabilizing $A^{1,3}$ interaction between R and H_a in conformer **285a**.



Scheme 1.82: Mechanism of the iodocyclisation on monosaccharide alkenes.

This result was applied to a synthesis of the *bis*-THF core of the acetogenin rolliniastratin (**290**).[103] Iodoetherification of alkene **286** gave exclusively *cis*-THF **287** in good yield (scheme 1.83). After olefination of the aldehyde **287** with methylene triphenylphosphorane and acid hydrolysis to provide the intermediate lactol, treatment with methylene triphenylphosphorane led to the cyclisation of the second THF unit as well as olefination of the aldehyde to afford **288** in good yield. *Bis*-THF **288** was finally converted by hydrogenolysis to the bibutylated *bis*-hydroxymethyl-*bis*-THF diol **289**.

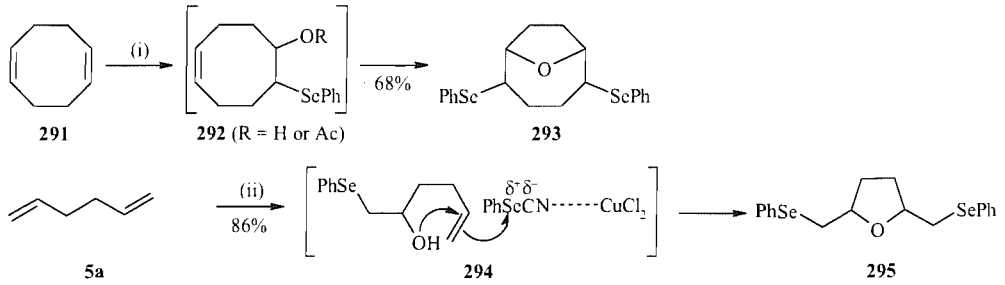


Conditions and reagents: (i) IDCP, CH_2Cl_2/H_2O, r.t., 20 min; (ii) $Ph_3P{=}CH_2$, THF, –78°C to r.t., 1 h; (iii) $BF_3{\cdot}Et_2O$, THF/H_2O (10:1), r.t., 2 days; (iv) HCOOH, H_2, Pd/C, MeOH, r.t., 16 h.

Scheme 1.83: Toward the synthesis of rolliniastratin (**290**) *via* iodocyclisation.

1-III-2 Selenocyclisation

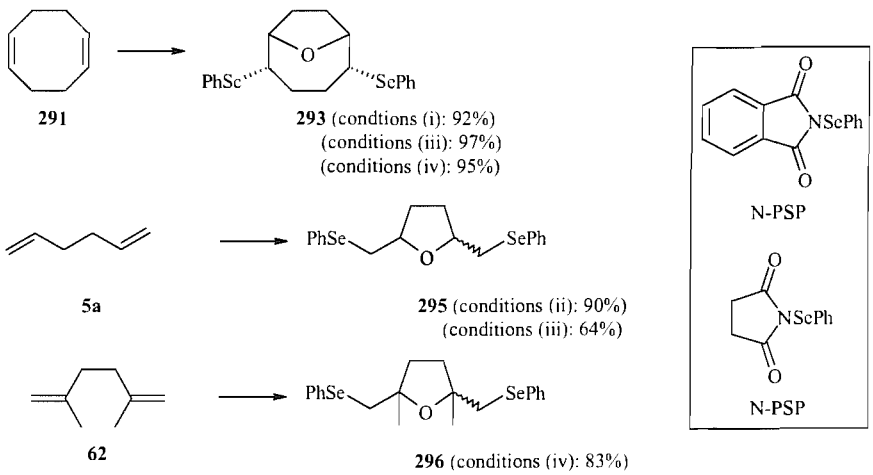
Uemura *et al.* have reported the cyclisation of cyclo-octa-1,5-diene **291** using stoichiometric phenyl selenocyanate to the corresponding THF **293** (scheme 1.84).[104] The reaction proceeds *via* the alkoxy or hydroxy-selenation of one of the double bond, followed by intramolecular attack of the phenyl selenocyanate. This reaction was applied to 1,5-hexadiene **5a** to give the corresponding 2,5-*bis*(phenylselenomethyl)tetrahydrofuran **295** in good yield.[105] The authors did not discuss the stereoselectivity of the reaction.



Conditions and reagents: (i) PhSeCN (2 eq.), $CuCl_2$, THF/H_2O (9:1), reflux, 5h; (ii) PhSeCN (2 eq.), $CuCl_2$, $MeCN/H_2O$ (5:1), 76°C, 8h.

Scheme 1.84: Selenocyclisation of 1,5-cod **291** and 1,5-hexadiene **5a**.

Further investigations using the seleno reagent were carried out by Uemura and Nicolaou's groups to improve the reaction. [105-109] Uemura *et al.* have reported the preparation of 2,5-disubtituted THFs **293** and **295** using phenylselenyl chloride in aqueous acetonitrile in good yield (scheme 1.85).[109] On the other hand, Nicolaou *et al.* have investigated the use of *N*-phenylselenophthalimide (N-PSP) or *N*-phenylselenosuccinimide (N-PSS) as a source of "PhSeOH" to carry out the same reaction and obtained the desired THFs **293**, **295** and **296** in good yield.[106-108]

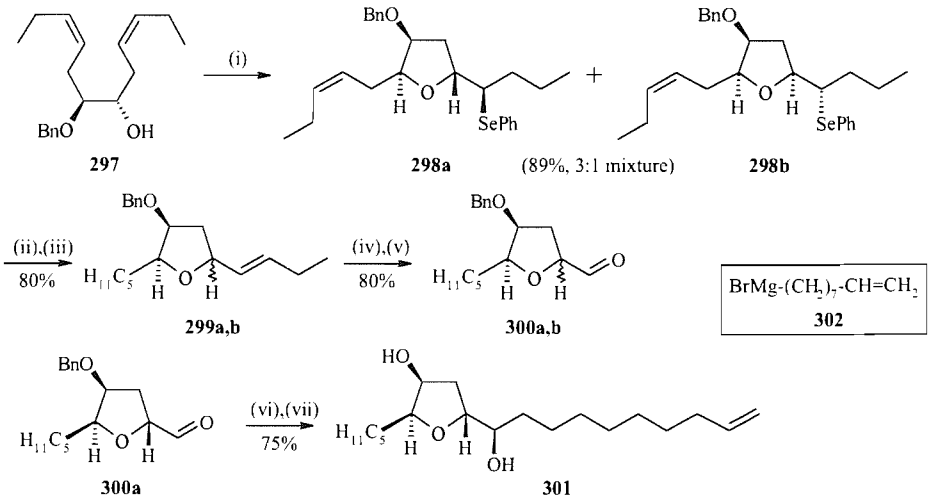


Conditions and reagents: Uemura: (i) PhSeCl (2 eq.), $MeCN/H_2O$ (5:1), 25°C, 24h; (ii) PhSeCl (2 eq.), $MeCN/H_2O$ (5:1), 76°C, 5h; Nicolaou: (iii) NPSP (2.6 eq.), H_2O (1.5 eq.), PTSA (0.1 eq.), CH_2Cl_2, 25°C, 18h; (iv) NPSS (2.6 eq.), H_2O (1.5 eq.), PTSA (0.1 eq.), CH_2Cl_2, 25°C, 18h.

Scheme 1.85: Selenocyclisation of dienes to the corresponding THFs.

Takano *et al.* applied this method to the synthesis of a natural product (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**301**).[110] Enantiomerically pure diene **297** was treated with

phenylselenyl chloride to afford the THF adducts **298a,b** as a 3:1 mixture and in good yield (scheme 1.86). After reduction of the double bond with 2,4,6-triisopropylbenzenesulfonyl hydrazide, the resulting selenide intermediate was converted to the olefins **299a,b** in overall good yield. Dihydroxylation of the THFs **299a,b** and subsequent cleavage with lead tetraacetate yielded the aldehydes **300a,b**. After separation, aldehyde **300a** was treated with Grignard reagent **302** and the benzyl moiety was removed to afford the marine lipid (**301**).

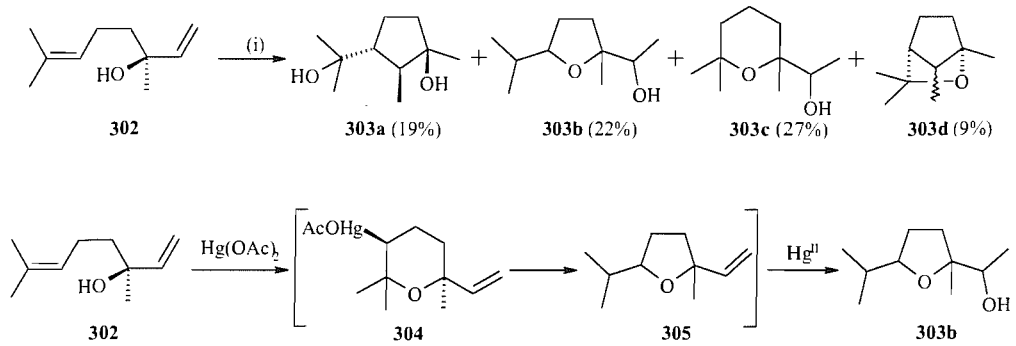


Conditions and reagents: (i) PhSeCl, CH_2Cl_2, –78°C; (ii) 2,4,6-triisopropylbenzenesulfonyl hydrazide, THF, reflux; (iii) H_2O_2 (30%), THF, r.t.; (iv) OsO_4 (10 mol%), NMO, acetone/H_2O, r.t.; (v) $Pb(OAc)_4$, THF – 30°C; (vi) **302**, Et_2O, –78°C; (vii) Li, NH_3, reflux.

Scheme 1.86: Synthesis of marine natural product (**301**).

1-III-3 Mercuricyclisation

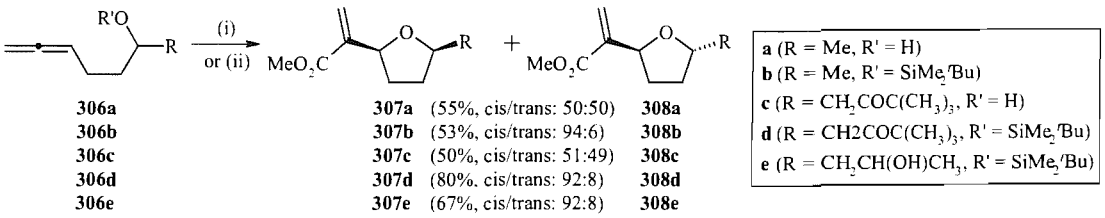
Itô *et al.* have reported the formation of a THF derivative as a side-product of the synthesis of cyclonerodiol from linalool **302**.[111] Linalool **302** was treated with $Hg(OAc)_2$ to afford a mixture of products **303a-d** (scheme 1.87). The stereochemistry of THF **303b** was not described. Investigation of this reaction showed that the first step is the formation of species **304**, it is thought that intermediate **304** rearranges to THF **305**, which is attacked by another molecule of Hg^{II} to give hydroxyether **303b**.



Conditions and reagents: (i) $Hg(OAc)_2$, THF/H_2O, r.t., 12h.

Scheme 1.87: Oxymercuration of linalool **302**.

Walkup *et al.* have applied this method to the synthesis of THF units *via* intramolecular oxymercuration of allenes.[112] γ-Hydroxy-allene **306a** was treated with $Hg(OAc)_2$ and gave the corresponding THFs **307a** and **308a** in moderate yield but no selectivity was exhibited (scheme 1.88). They therefore decided to adapt Bartlett's[96] strategy of using a bulky ether group to direct the stereochemistry of the electrophilic cyclisation. Oxymercuration of allenes **306b-e** afforded the THFs **307b-e** with high *cis*-selectivity.

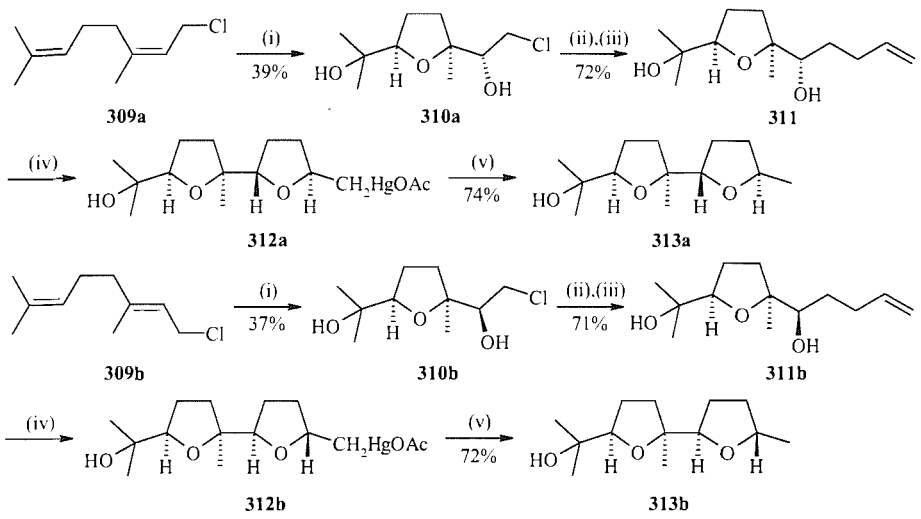


306a	**307a** (55%, cis/trans: 50:50)	**308a**
306b	**307b** (53%, cis/trans: 94:6)	**308b**
306c	**307c** (50%, cis/trans: 51:49)	**308c**
306d	**307d** (80%, cis/trans: 92:8)	**308d**
306e	**307e** (67%, cis/trans: 92:8)	**308e**

Conditions and reagents: (i) (a) $Hg(OAc)_2$, CH_2Cl_2, 25°C, 8 to 10h; (b) $PdCl_2$ (0.1 eq.), $CuCl_2$ (3 eq.), CH_3OH, CO (1 atm), 25°C, 8 to 10h; (ii) (a) $Hg(OCOCF_3)_2$, 25°C, 2 to 4h; (b) $PdCl_2$ (0.1 eq.), $CuCl_2$ (3 eq.), CH_3OH, CO (1 atm), 25°C, 8 to 10h.

Scheme 1.88: Oxymercuration on γ-Hydroxy-allenes **306a-e**.

Chastrette *et al.* have described the synthesis *bis*-THF products from 1,5-dienes.[113] They have applied Klein's permanganate oxidative cyclisation to neryl and geranyl chloride **309a,b** to afford the corresponding THF adducts **310a,b** (scheme 1.89). After treatment of THFs **310a,b** with potassium hydroxide, the resulting epoxides reacted with allylmagnesium bromide to give THFs **311a,b**. Cyclisation of the hydroxy-alkene units present in THFs **312a,b** with mercuric acetate and subsequent reduction of the organomercuric moiety afforded the corresponding *bis*-THFs **313a,b** in good yield and selectivity.

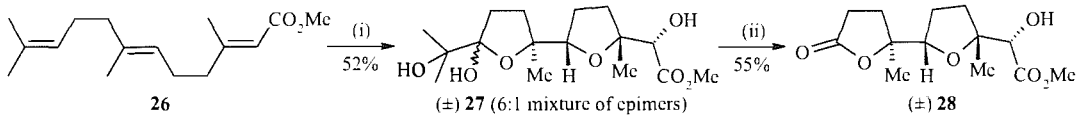


Conditions and reagents: (i) $KMnO_4$, acetone/H_2O (9:1), CO_2 bubbling, −10°C, 2h; (ii) powdered KOH, Et_2O, reflux, 5h; (iii) allylmagnesium bromide, Et_2O, r.t.; (iv) $Hg(OAc)_2$, THF/H_2O (1:1), r.t., 1h; (v) $NaBH_4$, NaOH.

Scheme 1.89: Synthesis of *bis*-THF *via* permanganate oxidation and mercuricyclisation.

Chapter 2: Stereoselective synthesis of *bis*-adjacent *Cis*-2,5-disubstituted THFs

As was discussed previously in chapter 1, preliminary results carried out in our group showed that permanganate oxidation of 1,5,9-trienes provided substituted octahydro-2,2'-bifuranyl systems regioselectively (scheme 1.10).[23]

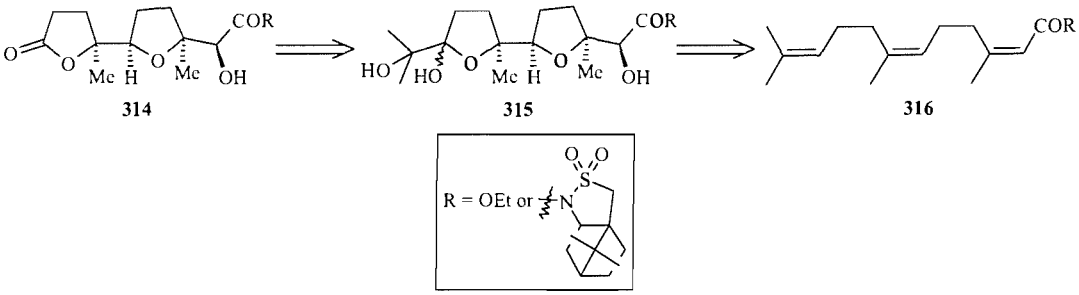


26 (±) **27** (6:1 mixture of epimers) (±) **28**

Conditions and reagents: (i) $KMnO_4$, acetone, water, AcOH, acetate buffer (pH = 6.5), –30°C; (ii) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Scheme 1.10: Oxidative cyclisation of enantiomerically enriched dienoate **26**.

To demonstrate the versatility and convenience of the triene oxidation method as a stereocontrolled route to polyether fragments, we proposed to prepare and oxidise the four stereoisomers of ethyl farnesoate to construct the corresponding racemic octahydro-2,2'-bifuranyl systems (scheme 2.1). An asymmetric version of this reaction was also to be attempted on trienes bearing the Oppolzer's sultam chiral auxiliary.



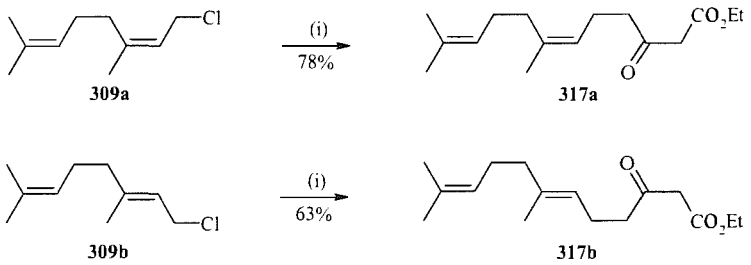
314 **315** **316**

Scheme 2.1: Retrosynthetic analysis of octahydro-2,2'-bifuranyl systems.

2-I 1,5,9-Trienes synthesis

The relative stereochemistry of the final product depends on that of the initial triene. Therefore the triene synthesis should allow access to any of the four possible stereoisomers stereoselectively. The requisite trienes were synthesised using a slight modification of methodology developed by Weiler *et al.*,[114,115] with the central double bond stereochemistry originating from neryl or geranyl chloride **309a,b** (scheme 2.2).

The β-ketoesters were synthesised by alkylation of the dianion of ethyl acetoacetate with neryl chloride or geranyl chloride **309a,b**.[116] Neryl and geranyl chlorides **309a,b** were prepared easily from corresponding commercially available nerol and geraniol **51a,b**.[22] The dianion was produced by treating ethyl acetoacetate with a slight excess of NaH and *n*-BuLi; the alkylating agent **309a** or **309b** was then added to afford the corresponding β-keto esters **317a,b** in moderate yields (scheme 2.2).

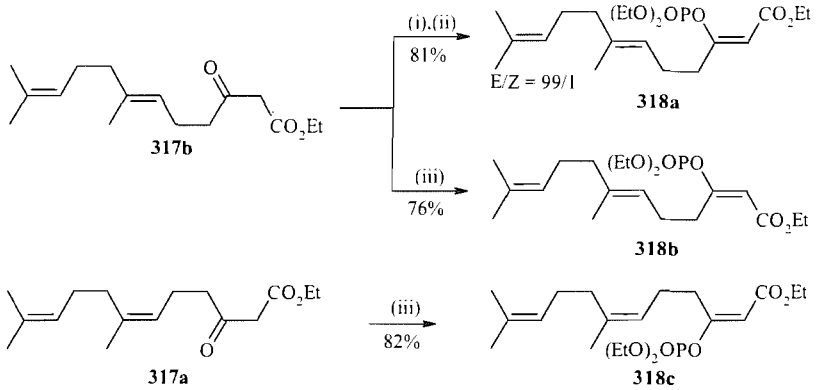


Conditions and reagents: (i) ethyl acetoacetate, NaH, then *n*-BuLi, THF, 0°C to 25°C, 30 min; (ii) geranyl chloride, THF, 0°C to 25°C, 30 min.

Scheme 2.2: Preparation of the β-ketoesters **317a** and **317b**.

The β-ketoester **317a** underwent stereoselective enol phosphate formation by treatment with LiHMDS and $(EtO)_2POCl$ to provide the 2-(*Z*) enol phosphate **318a** in good yield and selectivity (crude isomer ratio: 2*Z*:2*E* > 49:1 by ^1H NMR) (scheme 2.3).[117] It is thought that the coordination of the metal ion (Li) with the ester group in the enolate species is responsible for the predominance of the *Z*-isomer. The experiment was also conducted in Et_2O, a non polar solvent, which favours tight binding between the keto-enolate and the counterion.

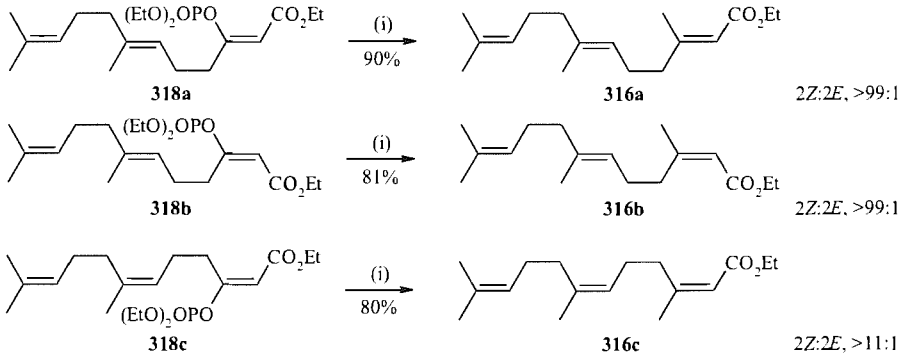
The 2-(*E*)-enol phosphates **318a,c** were synthesised from the corresponding β-ketoesters **317a,b** along similar lines, with the exception that the enolization was performed in DMPU with Et_3N as the base and a catalytic amount DMAP to afford the corresponding 2-(*E*)-enol phosphates **318,c** (crude isomer ratio: 2*Z*:2*E* > 49:1 by ^1H NMR) in good yield (scheme 2.3). The *E*-isomer is obtained predominately when a polar solvent and a base without a Lewis acidic counterion are used.



Conditions and reagents: (i) LiHMDS, THF, 0°C; (ii) $PO(OEt)_2Cl$, THF, 0°C to 25°C, 4h; (iii) Et_3N, DMPU, DMAP, $PO(OEt)_2Cl$, –20°C to 25°C, 12 h.

Scheme 2.3: Synthesis of the *E* and *Z* enol-phosphates **318a-c**.

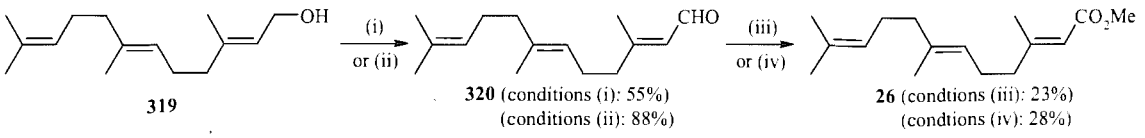
Stereoselective alkylation of enol phosphates **318a-c** was carried out using the copper methyl Grignard reagent $Me_2CuLiMgCl$.[114,115] Enol phosphates **318a-c** were treated with $Me_2CuLiMgCl$, formed by reaction of CuI with MeLi and MeMgCl, to afford the corresponding desired trienes **316a-c** in very good yields and selectivities (scheme 2.4).



Conditions and reagents: (i) CuI, MeLi, MeMgCl, THF, –30°C, 4 h. (ratios obtained by GC).

Scheme 2.4: Synthesis of the 1,5,9-trienes **316a-c**.

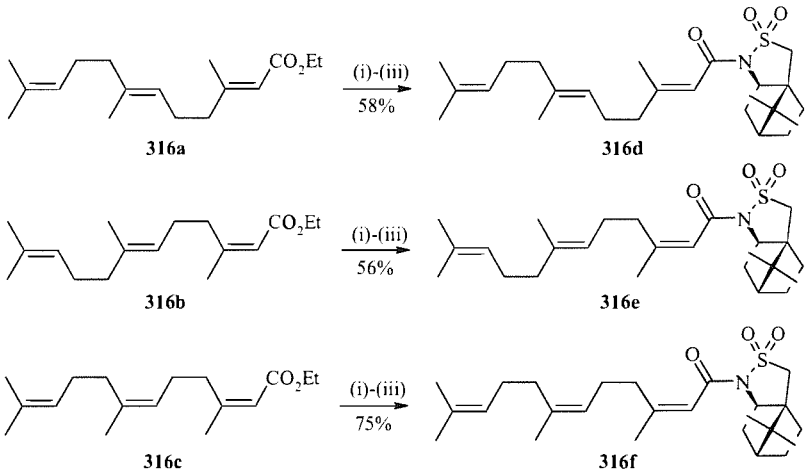
Methyl ester trienoate (2*E*,6*E*) methyl-farnesoate was also synthesised. Farnesol **319** was oxidised with either MnO_2 or $BaMnO_4$ to afford farnesal **320** in good yield.[23,118] Treatment of farnesal **320** with MnO_2 or $BaMnO_4$ and an excess of NaCN in MeOH afforded (2*E*,6*E*) methyl-farnesoate **26** in poor yield (scheme 2.5).



Conditions and reagents: (i) MnO_2 (20 eq), hexane, r.t., 2 days; (ii) $BaMnO_4$ (10 eq), CH_2Cl_2, r.t., 3 days; (iii) MnO_2, NaCN, MeOH, r.t., 24 h; (iv) $BaMnO_4$, NaCN, MeOH, r.t., 24 h.

Scheme 2.5: Synthesis of (2*E*,6*E*) methyl-farnesoate **26**.

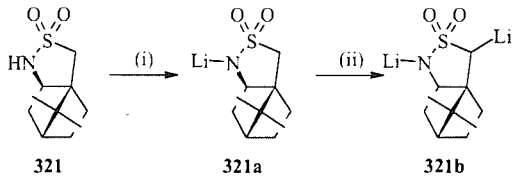
To demonstrate that the overall approach could provide enantiomerically enriched polyether fragments, the Oppolzer camphorsultam auxiliary was introduced into the trienoates **316a-c**.[15,22] Basic hydrolysis of the unsaturated esters **316a-c** and activation of the resulting carboxylic acids with pentafluorophenol in presence of DCC produced the corresponding pentafluorophenyl esters, which underwent substitution with lithiated (2*R*)-10,2-camphorsultam to afford the corresponding trienes **316d-f** in moderate yields (scheme 2.6).



Reagents and conditions: (i) NaOH, $NaHCO_3$, water, MeOH, reflux, 16 h; (ii) pentafluorophenol, DCC, EtOAc, 25°C, 24 h; (iii) *n*-BuLi, (2*R*)-10,2-camphorsultam, THF, –78°C to 25°C.

Scheme 2.6: Syntheses of trienes **316d-f** bearing a chiral auxiliary.

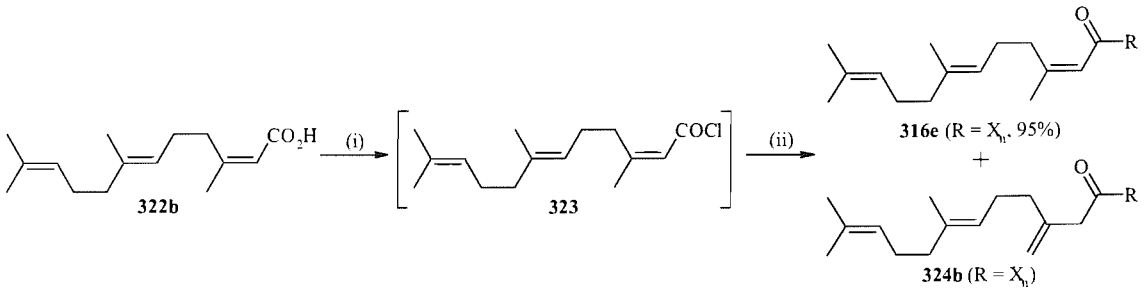
It is interesting to note that if a slight excess of *n*-BuLi was present during the lithiation of the (2*R*)-10,2-camphorsultam, the unreactive dianion **321b** could be obtained which lowered the yield of the reaction (scheme 2.7). It was therefore decided to attempt the preparation of the anion of the sultam with a less reactive base (*e.g.* NaH).



Conditions and reagents: (i) *n*-BuLi; (ii) *n*-BuLi.

Scheme 2.7: Formation of dianion **321b** with *n*-BuLi.

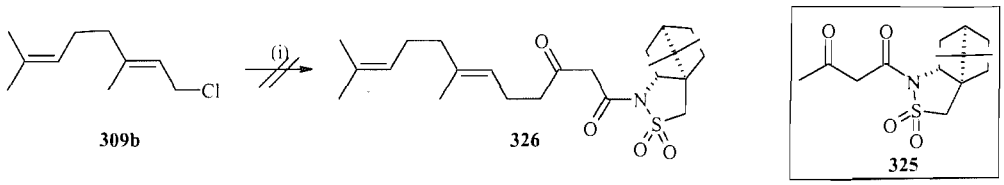
Liddle *et al.* have described a method using an acid chloride intermediate prepared *in situ* from the corresponding carboxylic acid.[119] Following Liddle's work, acid **322b** was treated with a catalytic amount of DMF and a slight excess of $(COCl)_2$ to provide the acid chloride **323**, which was immediately treated with the sodiated sultam to afford the triene **316e** in excellent yields (scheme 2.8). Purification of triene **316e** was revealed to be difficult because of the presence of by-product **324b**. It is thought that the acidic conditions during the preparation of the acid chloride were responsible for the formation of the by-product **324b**.



Conditions and reagents: (i) $(COCl)_2$, DMF, toluene, 0°C to r.t., 1 h; (ii) NaH, sultam, CH_2Cl_2, 0°C to r.t., 1 h.

Scheme 2.8: Preparation of triene **316e**.

In an attempt to shorten the synthesis of the 1,5,9-trienes bearing the camphorsultam **316d-f**, it was attempted to attach the camphorsultam auxiliary earlier in the synthesis by treating geranyl chloride **309b** with the dianion of *N*-(3-oxobutanoyl)bornane-10,2-sultam **325** (scheme 2.9);[120] unfortunately, the desired diene **326** was not obtained and only degradation was observed.



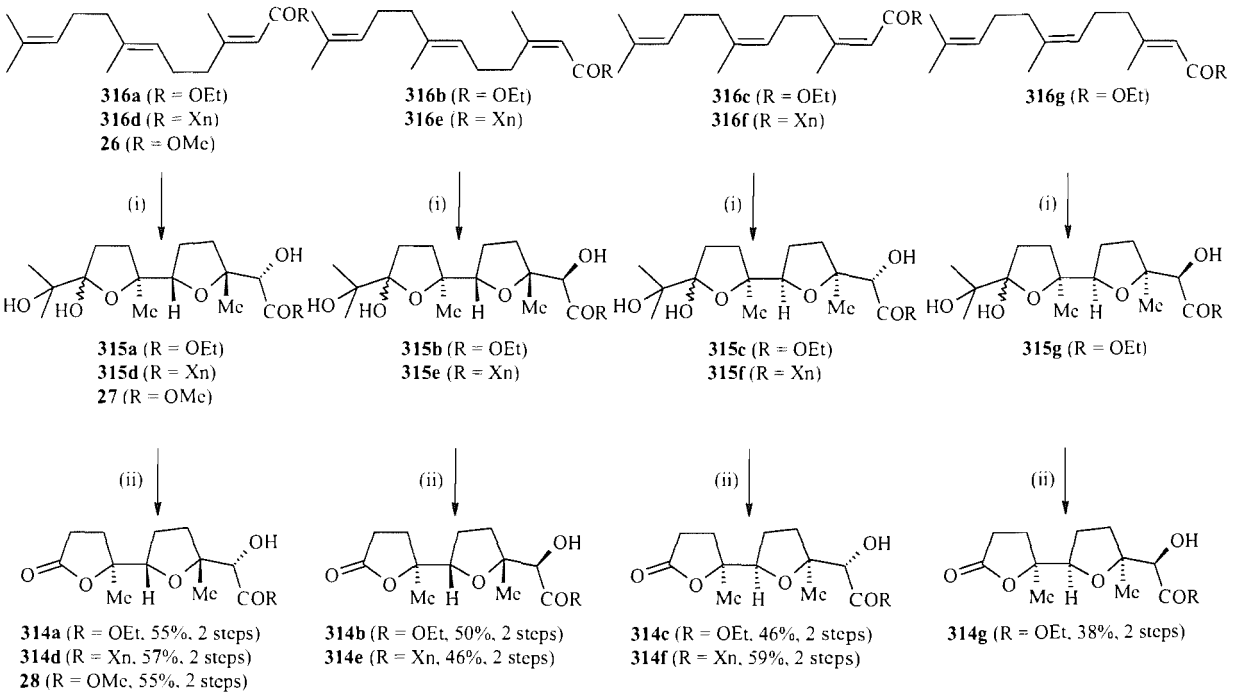
309b 326 325

Conditions and reagents: (i) ethyl acetoacetate, NaH, then *n*-BuLi, THF, 0°C to 25°C, 30 min; (ii) **325**, THF, 0°C to 25°C, 30 min.

Scheme 2.9: Attempted synthesis of diene **326**.

2-II Permanganate oxidation of 1,5,9-trienes

Permanganate mediated oxidative cyclisation was performed on the 1,5,9-trienes **316a-g** synthesised previously with optimised quantities of reactants, *i.e.* 3 eq. of $KMnO_4$ (1 eq. per double bond), 4.2 eq. of AcOH (1.4 eq. per double bond) and a pH 6.24 buffer.[23] 1,5,9-Trienes **316a-g** and **26** were oxidised to afford the corresponding lactols **315a-g** and **27**, which were used without further purification in the next step (scheme 2.10). Careful cleavage of lactols **315a-g** and **27** using $Pb(OAc)_4$ afforded the desired lactones **314a-g** and **28** in reasonable overall yields and stereoselectivity (scheme 2.10).[121] It was found that cleavage using $NaIO_4/SiO_2$ reagent provided a milder, more convenient and higher-yield method for achieving the same transformation.[122,123] Lactols **315a-g** and **27** were therefore treated with an excess of the $NaIO_4/SiO_2$ reagent prepared following the method described Zhong *et al.* and provided the resulting lactones **314a-g** and **28** in good yields and stereoselectivity (scheme 2.10).[124] It is interesting to note that in the oxidative cyclisation of the trienes bearing the sultam **316d-f** only one diastereoisomer of the corresponding lactols **315d-f** was formed (as judged from the crude ^1H NMR).



Conditions and reagents: (i) 3 eq. $KMnO_4$, 4.2 eq. AcOH, phosphate buffer (pH = 6.24), water, acetone, –25°C, 40 min; (ii) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0°C, 15 min; (iii) $NaIO_4$ (on silica gel), CH_2Cl_2, r.t., 45 min.

Scheme 2.10: Permanganate oxidative cyclisation on trienes **316a-g** and **26**.

Confirmation of the relative stereochemical assignment was obtained from x-ray crystallographic analysis of the lactone **314b**, which crystallised as a single diastereoisomer (Figure 2.1).

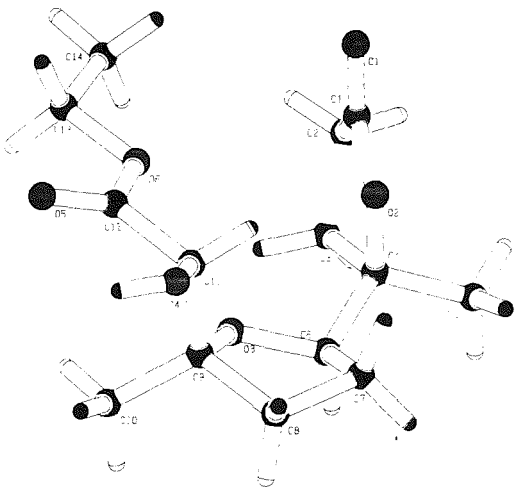


Figure 2.1: X-ray structure of lactone **314b**.

Lactone **314d** was successfully recrystallised in a mixture EtOAc/hexane to afford small white needles suitable for x-ray structural determination permitting the confirmation of the predicted stereochemistry (figure 2.2).

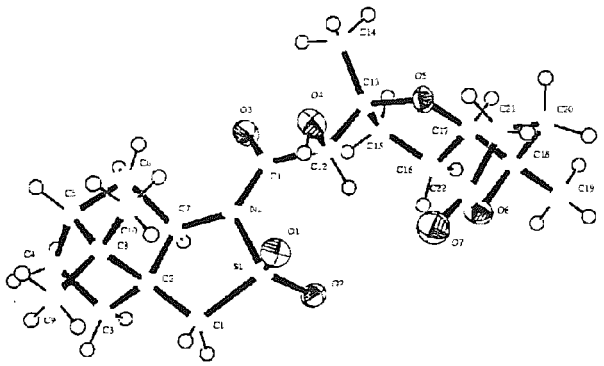


Figure 2.2: X-ray of lactone **314d**.

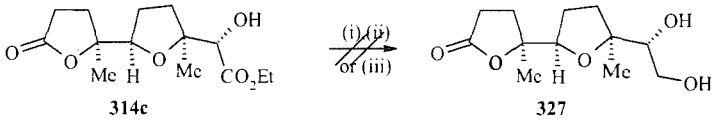
2-III Efforts to selectively cleave the ester group

To demonstrate the utility of the THF lactones **314a-g** and **28** described above, manipulation of the structure was attempted to prepare an intermediate useful for further elaboration. In order to retain the maximum structural and stereochemical complexity, reduction of the ester group or the sultam moiety was investigated. The reduction of the ester moiety would allow the possibility of chain homologation. Many of methods used commonly to reduce ester groups, like the use of $LiAlH_4$ or DIBAL, were not antiicpated to be compatible with substrates **314a-g** due to possibilities of reduction of the lactone moiety.[19,125,126] The method to be used must allow differentiation of the ester and lactone groups.

Kocienksi *et al.* have shown that it is possible to directly reduce an α-hydroxy *N*-acyl-sultam auxiliary in the presence of a lactone.[22] The hydroxy group is believed to coordinate to the borane and direct the subsequent reduction using $NaBH_4$. It was thought that this method could also be applied to the reduction of the ester group. Lactone **314c** was treated at 0°C with borane dimethylsulfide complex, followed after 30 min by $NaBH_4$ (scheme 2.11). Unfortunately, no desired product was obtained and starting material was recovered. It was thought that maybe the formation of the complex between the hydroxy group and $BH_3.SMe_2$ was not complete; therefore after treatment of the lactone with $BH_3.SMe_2$, the reaction was

warmed to room temperature and left to react for 12 hours before addition of $NaBH_4$. Unfortunately, again only decomposition was observed.

The cleavage was also attempted using two different types of enzymes, a protease (novozym 435) and a lipase (lipase PS "Amnino"); unfortunately starting material was recovered from both experiments.



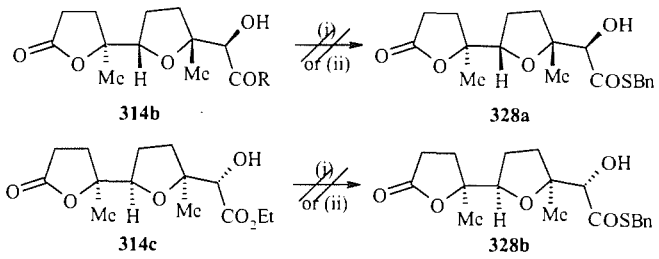
Conditions and reagents: (i) $NaBH_4$, $BH_3.SMe_2$, Et_2O, r.t., 24h; (ii) $NaBH_4$, BH_3. SMe_2, Et_2O, 0°C, 2h; (iii) protease or lipase, H_2O/*t*-BuOH (9:1), 25°C to 60°C, 5 days.

Scheme 2.11: Attempts to cleave the ester moiety from lactone **314c**.

An alternative was the cleavage of both lactone and ester groups with a thiol nucleophile. The lactone ring should then undergo reclosure under mild conditions and reduction of the thioester should be possible using Raney Ni (scheme 2.12).[127] Two methods were attempted to prepare the thioester **328a,b**. The first method was based on the use of the "ate" complex $BnSAlMe_3^-Li^+$ to convert the ethyl ester moiety to the *S*-benzyl esters.[19,128] The method employed the "ate" complex $BnSAlMe_3^-Li^+$ prepared *in situ* from $AlMe_3$ and BnSLi. In the second method, lactones **314b,c** were treated with $AlMe_3$ and BnSH.[129] These methods were attempted under different experimental conditions (table 2.1). Unfortunately, no desired product was obtained and only starting material or decomposition was observed (scheme 2.12). It was therefore decided to abandon our efforts to cleave the ester group and focus on the application of the permanganate mediated oxidative cyclisation methodology to the synthesis of natural products.

	lactone	eq. of *n*-BuLi	eq. of $AlMe_3$	eq. of BnSH	**Observations**
1	**314b**	2.0	2.0	2.0	starting material recovered
2	**314c**	3.0	3.0	3.0	starting material recovered
3	**314b**	0	3.0	3.0	degradation
4	**314c**	0	3.5	3.5	degradation

Table 2.1: Experimental conditions for the ester cleavage.



Conditions and reagents: (i) $AlMe_3$, n-BuLi, BnSH, Et_2O, toluene, 0°C, 120 min; (ii) $AlMe_3$, BnSH, CH_2Cl_2, 0°C to r.t., 48 h.

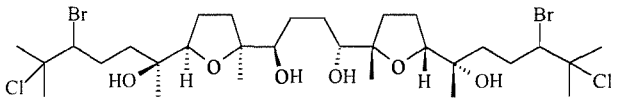
Scheme 2.12: Attempts to cleave the ester group from lactone **314c**.

2-IV Conclusion and further work

A short, efficient and stereoselective synthesis of perhydro-2,2-bifuranyl systems has been achieved from readily accessible trienes using oxidative cyclisation methodology. Excellent levels of asymmetric induction were obtained during the permanganate oxidative cyclisation of trienes bearing the Oppolzer's sultam auxiliary. Unfortunately, the efforts to convert lactones **314a-g** to useful intermediates for further elaboration toward natural products synthesis have been yet unsuccessful.

Chapter 3: Toward the synthesis of intricatetraol.

Suzuki *et al.* have isolated intricatetraol, a halogenated triterpene alcohol from the red alga *Laurencia intricata* (figure 3.1).[130] Intricatetraol is unique because it possesses C2 symmetry and it is the first example of a halogenated triterpenoid with chlorine atoms from the alga genus *Laurencia.* Unfortunately, the absolute configuration of the halogen atoms on intricatetraol has not been established yet. To our knowledge, there is no published work.

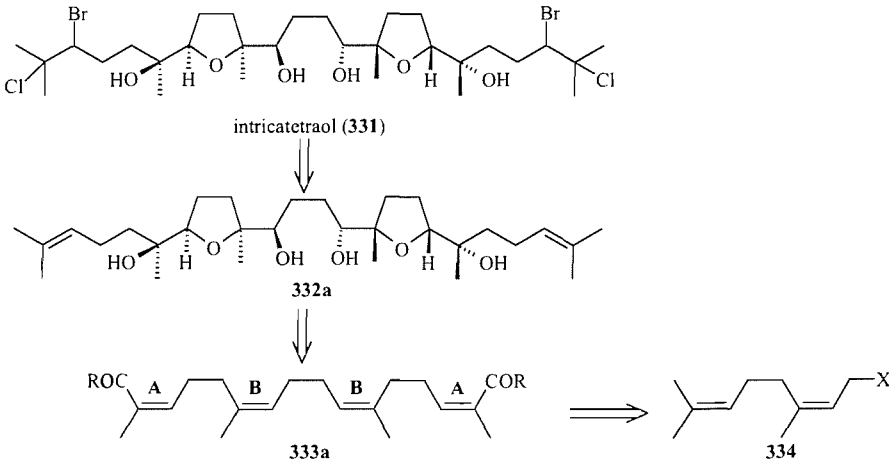


intricatetraol (331)

Figure 3.1: Intricatetraol (**331**).

3-I First Approach to intricatetraol

In this chapter, our efforts towards the synthesis of intricatetraol are discussed. Two different approaches were attempted. The first approach is centred on the construction of the *bis*-THF diol core **332a** *via* permanganate tandem oxidative cyclisation of tetraene precursor **333a** (scheme 3.1). Tetraene **333a** is prepared by the coupling of 1,5-dienes **334**.



Scheme 3.1: Retrosynthetic approach to intricatetraol (**331**).

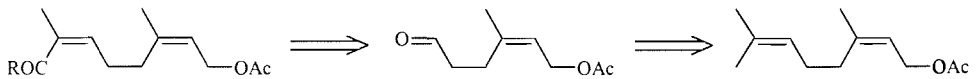
To our knowledge, permanganate oxidative cyclisation of polyenes possessing a trisubstituted double bond bearing an ester group and an α-methyl has not been described previously. According to the established reactivity of the permanganate ion,[9-13] the double bond **A** should be attacked first (scheme 3.1). It raised the question whether the presence of the methyl group

would prevent or retard the attack of the permanganate. It was therefore decided to investigate the oxidative cyclisation of a series of structurally related model 1,5-dienes before attempting to oxidise the desired tetraene.

3-I-1 Model study on simple 1,5-dienes

3-I-1-1 Synthesis of model 1,5-dienes

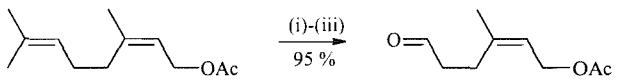
A model 1,5-diene **335** was easily prepared from the commercially available neryl acetate **1b** (scheme 3.2).



335 **19b** **1b**

Scheme 3.2: Retrosynthetic scheme to 1,5-diene **335**.

Neryl acetate **1b** was treated with *m*-CPBA to afford the corresponding epoxide in quantitative yield; subsequent conversion to the corresponding diol was carried out in quantitative yield *via* acidic hydrolysis. Aldehyde **19b** was obtained, in good yield, after cleavage of the diol with $NaIO_4$ (scheme 3.3).

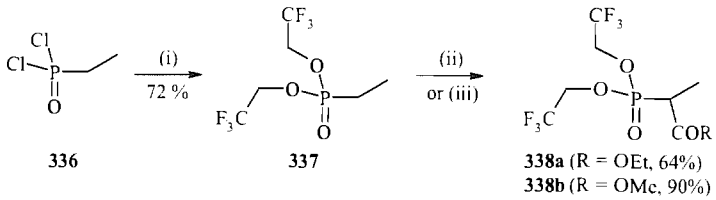


1b **19b**

Conditions and reagents: (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 1h; (ii) H_2SO_4 (10% aq. sol.), water, r.t., 3h; (iii) $NaIO_4$, acetone/water, r.t., 4h.

Scheme 3.3: Synthesis of the aldehyde **19b**.

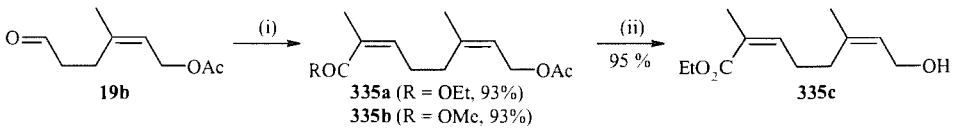
Still *et al.*[131] have described the use of a fluorinated phosphonate to permit the stereoselective formation of the *Z*-isomer during Wittig-Horner-Emmons reactions. It is thought that the electron withdrawing effects of the OCH_2CF_3 groups minimise the lifetime of the oxaphosphetane sufficiently to restrict any thermodynamic equilibration to the *E*-compound. Ethylphosphonic dichloride **336** was treated with fluoroethanol and triethylamine to provide the phosphonate **337** in moderate yield, which was converted to the desired phosphonates **338a** or **338b** by treatment with LiHMDS and ethyl or methyl chloroformate (scheme 3.4).[132]



Conditions and reagents : (i) CF_3CH_2OH, Et_3N, THF, 10°C to r.t., 12 h; (ii) *n*-BuLi, HMDS, $ClCO_2Et$, HCl, THF, –78°C to 0°C, 1 h; (iii) *n*-BuLi, HMDS, $ClCO_2Me$, HCl, THF, –78°C to 0°C, 1h

Scheme 3.4: Synthesis of fluorinated phosphonates **338a,b**.

The aldehyde **19b** was treated with the fluorinated phosphonates **338a** or **338b** in presence of KHMDS and a stoichiometric amount of 18-crown-6 to provide the corresponding dienes **335a,b** in good yield and selectivity; only a single isomer was observed by ^1H NMR and GC (scheme 3.5). Hydroxy-diene **335c** was also prepared in good yield by basic hydrolysis of diene **335a**.



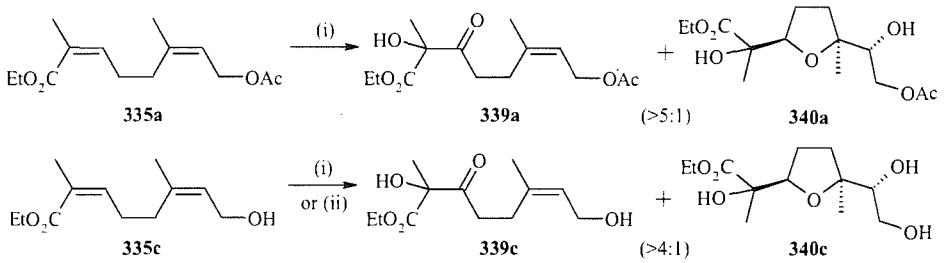
Conditions and reagents: (i) $(CF_3CH_2O)_2P(O)CH_2CH_3COR$ **338a** (R=OEt) or **338b** (R=OMe), 18-crown-6, KHMDS, THF, –78°C, 90 min; (ii) K_2CO_3, MeOH, overnight, –20°C to r.t..

Scheme 3.5: Synthesis of dienes **335a-c**.

3-I-1-2 Attempted oxidative cyclisation of dienes 335a-c

Permanganate oxidative cyclisation using the previously reported conditions was attempted on diene **335a**.[23] Unfortunately, the reaction gave a mixture consisting of hydroxy ketone **339a** as the major product and desired THF **340a** as the minor product (crude ratio: **339a**:**340a** > 5:1 by ^1H NMR). The same result was obtained when the oxidation was attempted on diene **335c** (scheme 3.6).

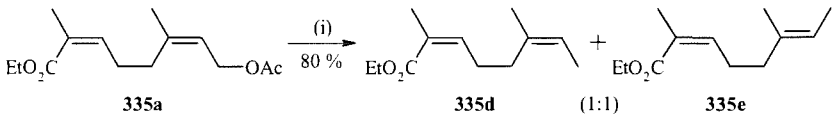
As an alternative, the reaction was conducted on diene **335c** under phase transfer conditions, in CH_2Cl_2 with potassium permanganate and Adogen 464© as a phase transfer catalyst, but no improvement was observed (crude ratio: **339c**:**340c** > 4:1 by ^1H NMR) (scheme 3.6).[24] It is thought that the presence of an electron withdrawing group on the second double bond may disfavour cyclisation of the intermediate on the second double bond, cleavage of the manganese diester intermediate leads to the formation of hydroxy ketones.



Conditions and reagents: (i) $KMnO_4$ (2 eq.), AcOH (2.8 eq.), buffer, acetone/water, –25 °C, 2 h; (ii) $KMnO_4$ (powered, 2 eq.), Adogen 464 (0.05 eq.), AcOH (8 eq.) , CH2Cl2, –30°C, 2h.

Scheme 3.6: Attempts of oxidative cyclisation on 1,5-dienes **335a,c**.

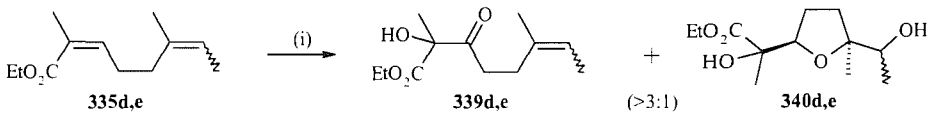
Previous work has shown that palladium was an efficient way to reduce allylic acetates (–CH_2OAc → –CH_3).[133,134] Cleavage was achieved by treatment of diene **335a** with a catalytic amount of $Pd(acac)_2$ in the presence of dppe and $NMe_4BH(OAc)_3$ (scheme 3.7).[135] Unfortunately, isomerisation of the double bond occurred and the dienes **335d,e** were obtained as a 1:1 *E/Z* mixture, but in good yield.



Conditions and reagents: (i) $Pd(acac)_2$, dppe, $NMe_4BH(OAc)_3$, CH_2Cl_2, r.t., 36 h.

Scheme 3.7: Synthesis of dienes **335d,e**.

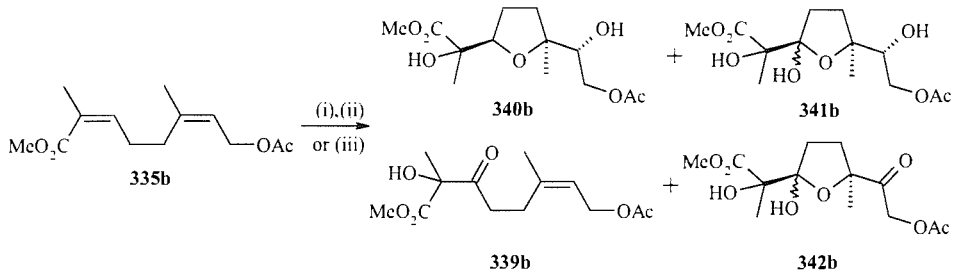
Permanganate oxidative cyclisation was attempted on the mixture of dienes **40a,b**, but the hydroxy ketone **339d** was also obtained predominately (Scheme 3.8).



Conditions and reagents: (i) $KMnO_4$ (2 eq.), AcOH (2.8 eq.), buffer, acetone/water, –25 °C, 1 h.

Scheme 3.8: Attempted oxidative cyclisation on dienes **335d,e**.

This result proved that the withdrawing effect of the acetate may not be the only reason why the reaction did not go to completion. A different approach to the oxidative cyclisation reaction was also attempted. The use of powdered permanganate in a mixture of acetone and acetic acid as solvent in a 3:2 ratio, with 5% Adogen 464© as phase transfer catalyst gave the desired product **340b** in good yield and selectivity (scheme 3.9).[26] A comparative study was set up to optimise this step (table 3.1).



Scheme 3.9: Oxidative Cyclisation of diene **335b**.

Conditions	**340b**	**339b**	**341b**	**342b**
(i)	70 %	-	15 %	-
(ii)	72 %	-	10 %	-
(iii)	18 %	-	40 %	34 %

(i) $KMnO_4$ (powered, 2 eq.), Adogen 464 (0.05 eq.), AcOH/acetone (2:3), –30°C to 0°C, 2h30.

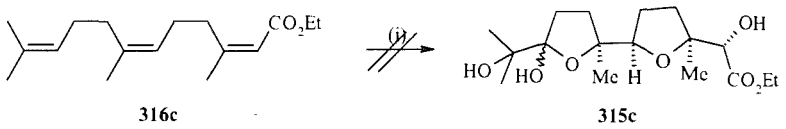
(ii) $KMnO_4$ (powered, 2 eq.), AcOH/acetone (2:3), –30°C to 0°C, 2h30.

(iii) $KMnO_4$ (2 eq. of a 0.4 M aqueous sol.), AcOH (2.8 eq.), buffer (0.5 mL), acetone, -30°C to 0°C, 2h30.

Table 3.1: Comparative study for the optimisation of the oxidative cyclisation step.

As expected, conditions (iii) gave by-products in majority, but when using conditions (i) and (ii), the desired product **340b** was obtained in good yield. Therefore, conditions (ii) will be used for oxidative cyclisation work on this type of diene system.

Due to the improved yields obtained for the oxidative cyclisation of 1,5-diene **335b**, it was decided to re-examine the oxidative cyclisation of triene **316c** (scheme 3.10). Unfortunately, the desired product **315c** was not obtained, only degradation of the starting material occurred.

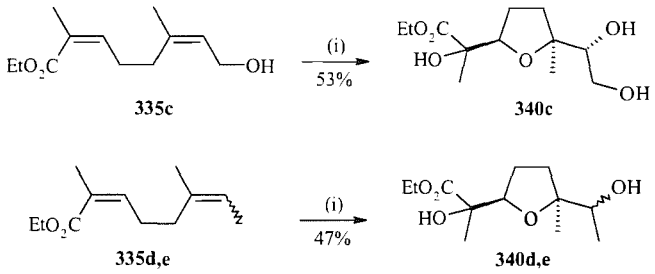


316c 315c

Conditions and reagents: (i) $KMnO_4$ (powered), adogen 464, AcOH/acetone (2:3), –25°C to 10°C, 4 h.

Scheme 3.10: Attempted oxidative cyclisation of triene **316c**.

The oxidative cyclisation step was attempted on diene **335c** leading to the corresponding 2,5-disubstituted THF **340c** as major product (crude ^1H and ^{13}C NMR). Oxidative cyclisation of the isomeric mixture of dienes **335d,e** afforded the corresponding 2,5-disubstituted THF products **340a,b** in moderate yield and as an approximately 1:1 ratio of diastereoisomers (scheme 3.11).



335c 340c

335d,e 340d,e

Conditions and reagents: (i) $KMnO_4$ (powdered), AcOH/acetone (2:3), –25°C to 10°C, 2h 30 min.

Scheme 3.11: Oxidative cyclisation of dienes **335c-e**.

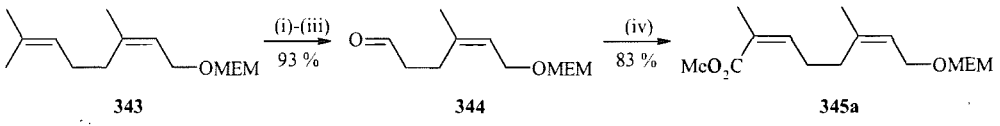
The syntheses of different racemic 2,5-*cis*-disubstituted THFs from simple 1,5-dienes bearing a trisubstituted double bond with an ester group and an α-methyl has been achieved successfully with an improved oxidation procedure. Previous work showed that the Oppolzer camphorsultam has given good diastereoselectivity during the oxidative cyclisation step. Oxidative cyclisation of model 1,5-dienes bearing the camphorsultam was therefore the next logical progression.

3-I-1-3 Synthesis of model 1,5-dienes bearing Oppolzer's chiral auxiliary

A MEM protecting group would be employed in the 1,5-diene synthesis, replacing the acetate group. This would provide a substrate which was stable to basic conditions encountered during the proposed synthesis.

Diene **345a** was synthesised using the method previously reported for the synthesis of diene **335a**. The MEM group was inserted at the start of the synthesis by treatment of nerol **51b**

with MEMCl and diisopropylethylamine to give the protected alcohol **343**.[136] After epoxidation of the protected alcohol **343** with *m*-CPBA followed by acidic hydrolysis, the corresponding diol was obtained in quantitative yield. The synthesis of the key aldehyde **344** was completed by cleavage of the diol with $NaIO_4$ in good yield (scheme 3.12). Aldehyde **344** was treated with methyl-phosphonic acid *bis*-(2,2,2-trifluoro-ethyl) ester in presence of KHMDS and a stoichiometric amount of 18-crown-6 to provide diene **345a** in good yield and excellent stereoselectivity (only the *cis* isomer was observed by ^1H NMR and GC).

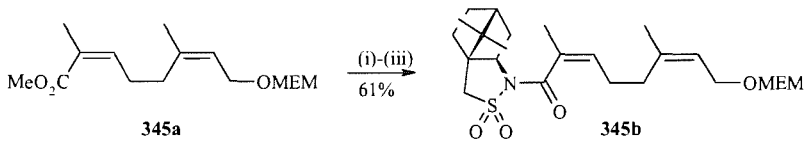


343 **344** **345a**

Conditions and reagents : (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 1h; (ii) H_2SO_4 (10% aq. sol.), water, r.t., 3h; (iii) $NaIO_4$, acetone/water, rt, 4h, (iv) $(CF_3CH_2O)_2P(O)CH_2CH_3CO_2Me$, 18-crown-6, KHMDS, THF, –78°C, 90 min.

Scheme 3.12: Synthesis of diene **345a**.

(2*R*)-camphor sultam was attached to diene **345a** using the method seen previously (scheme 2.6). Basic hydrolysis of the unsaturated ester **345a** and activation of the resulting carboxylic acid with pentafluorophenol in presence of DCC produced the pentafluorophenyl ester, which underwent substitution with lithiated (2*R*)-10,2-camphorsultam to afford the corresponding diene **345b** in moderate yields (scheme 3.13).



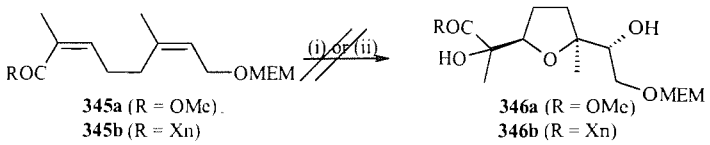
345a **345b**

Reagents and conditions : (i) NaOH, $NaHCO_3$, water, MeOH, reflux, 18h; (ii) pentafluorophenol, DCC, EtOAc, r.t., 24h; (iii) *n*-BuLi, (2*R*)-10,2-camphorsultam, CH_2Cl_2, –78 °C to r.t., 2h.

Scheme 3.13: Synthesis of diene **345b** bearing a chiral auxiliary.

3-I-1-4 Attempted oxidative cyclisation of dienes 345a,b

Oxidative cyclisation on the dienes **345a,b** was then attempted using the two different procedures described previously. Unfortunately, the reaction produced an unknown major by-product and none of the desired THFs **346a,b** (scheme 3.14).



345a (R = OMe)
345b (R = Xn)

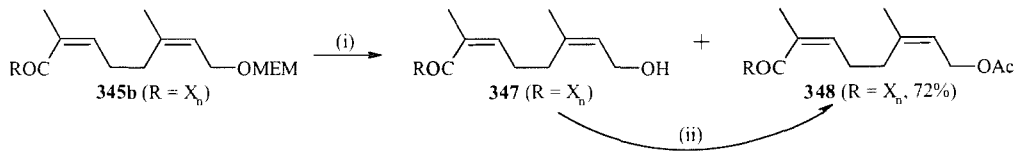
346a (R = OMe)
346b (R = Xn)

Reagents and conditions : (i) $KMnO_4$ (powered, 2 eq.), AcOH/acetone (2:3), –30°C to 0°C, 2.5h; (ii) $KMnO_4$ (2 eq. of a 0.4 M aqueous sol.), AcOH (2.8 eq.), buffer (0.5 mL), acetone, –30°C to 0°C, 1h.

Scheme 3.14: Attempted oxidative cyclisation of dienes **345a,b**.

The exact structure of the by-product has not been elucidated. It is thought that the permanganate is chelating to the MEM group which directs attack on the proximal double bond and cleavage of the MEM group. To prevent this problem, it was planned to remove the MEM group in diene **345b** and replaced it with by an acetyl group. With reference to previous results (scheme 3.9) the oxidative cyclisation of this type of diene was anticipated to be successful.

Diene **345b** was treated with a catalytic amount of $FeCl_3$, acetic anhydride and Et_3N to afford a mixture of alcohol **346** and diene **348**;[136] after treatment *in situ* of this mixture with DMAP, acetic anhydride and Et_3N to convert the unreacted alcohol **347**, diene **348** was obtained in good yield (scheme 3.15).



345b (R = X_n)

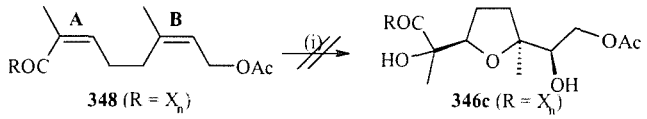
347 (R = X_n)

348 (R = X_n, 72%)

Reagents and conditions : (i) $FeCl_3$, Ac_2O, Et_3N, CH_2Cl_2, –60°C; (ii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, r.t.

Scheme 3.15: Synthesis of diene **348**.

Encouraged by the previous results, the oxidative cyclisation of diene **348** was attempted. Unfortunately, the desired THF **346c** was not obtained and the formation of side-products formation was noted (scheme 3.16). Cyclisation did not proceed, possibly because the sultam may block the attack of the permanganate on double bond **B** because of its spatial position due to the presence of the methyl group on the double bond **A**. The use of an alternative chiral auxiliary should be investigated to obtain a solution to this problem.



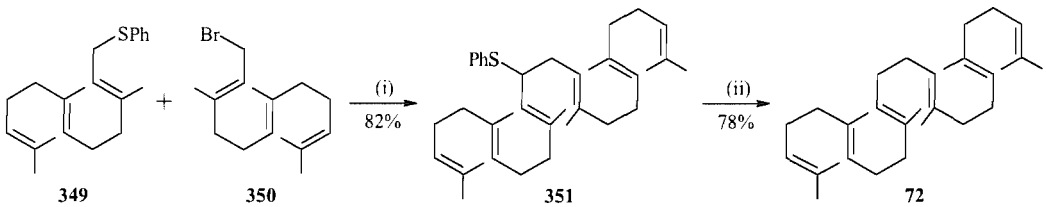
348 (R = X_n) 346c (R = X_n)

Reagents and conditions: (i) $KMnO_4$ (powered, 2 eq.), AcOH/acetone (2:3), −30°C to 0°C, 2.5h.

Scheme 3.16: Attempted synthesis of 2,5-disubstituted THF **346c**.

3-I-2 Preparation of the tetraene precursor 333a

Biellmann *et al.* have reported the synthesis of squalene **72** *via* a nucleophilic substitution of bromide **350** by the carbanion derived from sulphide **349** (scheme 3.17).[137] The reaction proceeded in good yield and no isomerisation of the double bond occurred. To conclude the synthesis, the sulphide group was removed using lithium in ethylamine.

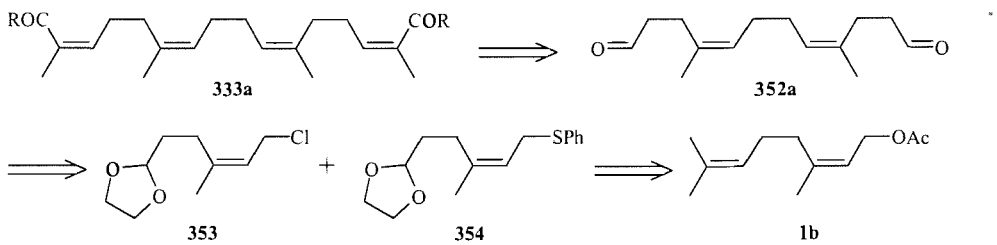


349 350 351 72

Reagents and conditions : (i) DABCO, *n*-BuLi, −18°C to r.t., 30 min; (ii) Li, ethylamine −15°C, 2.5h..

Scheme 3.17: Synthesis of squalene **72**.

We decided to apply this method to the synthesis of tetraene **333a.** Tetraene **333a** was to be obtained *via* a Still-Gennari reaction on dialdehyde **352**. Diene **352a** was to be prepared by coupling alkenes **353** and **354** (scheme 3.18). Alkenes **353** and **354** were to be derived from neryl acetate **1b**.

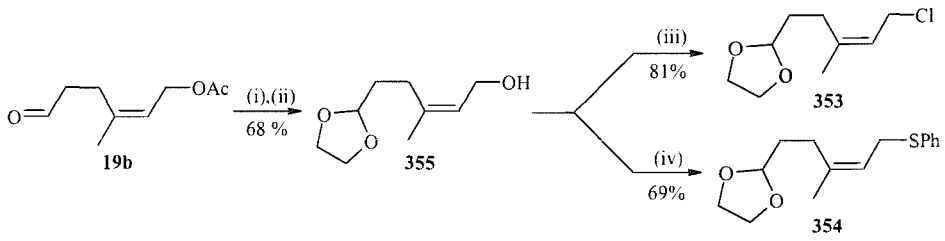


333a 352a 353 354 1b

Scheme 3.18: Retrosynthetic approach to tetraene **333a**.

3-I-2-1 Synthesis of compounds 353 and 354

Aldehyde **19b** was protected as its 1,3-dioxolane derivative **355** by treatment with PTSA and 1,2-ethanediol using a Dean-Stark apparatus (scheme 3.19).[22] Subsequent hydrolysis with K_2CO_3 and MeOH afforded the corresponding allylic alcohol **356** in moderate yield. Treatment of the alcohol **356** with lithium chloride, 2,6-lutidine and MsCl afforded the corresponding allylic chloride **353** in good yield. Allylic alcohol **356** was then treated with phenyl disulfide and tributyl phosphine to give the corresponding phenyl sulfide **354** in moderate yield (scheme 3.19).



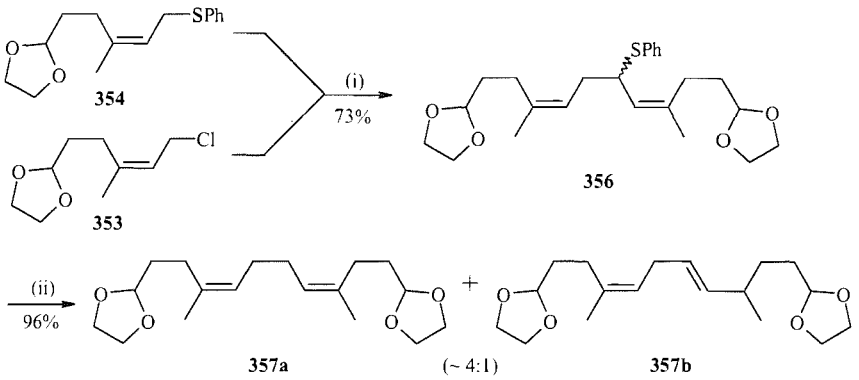
Conditions and reagents : (i) PTSA, 1,2-ethanediol, toluene, reflux, overnight; (ii) K_2CO_3, methanol, r.t., overnight; (iii) LiCl, MsCl, 2,6-lutidine, DMF, 0°C to 15°C, 4h; (iv) $(PhS)_2$, Bu_3P, pyridine, 0°C to r.t., 2h.

Scheme 3.19: Synthesis of the precursors **353** and **354**.

3-I-2-2 Coupling of precursors 353 and 354

The coupling adduct **356** was obtained as a mixture of diastereoisomers by treatment of the allylic chloride **353** with the lithiated allylic phenyl sulfide **354** in presence of DABCO (scheme 3.20).[138] It has been reported the DABCO acts as a ligand in this reaction, leading to improved stereoselectivity. It is thought that DABCO coordinates the newly formed lithiated allylic phenyl sulfide, preventing isomerisation of the double bond. It was shown that the temperature of the reaction has also a critical effect on the stereoselectivity of the reaction. When the reaction mixture was allowed to warm to –50°C, a significant amount of the *cis,trans*-isomer was obtained (*cis,cis*:*cis,trans* 1.3:1 mixture by NMR and GC).

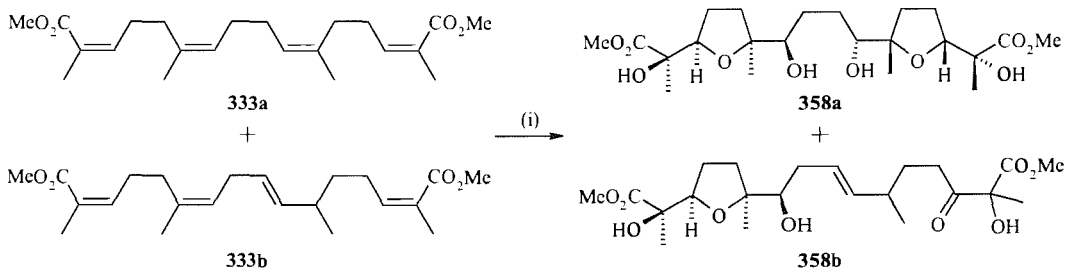
The phenyl sulphide group was subsequently removed by treatment with sodium metal in presence of *iso*-propanol to give the corresponding diene **357a** and a side-product **357b** (resulting from the translocation of one of the double bonds in a 4:1 ratio) but in good yield (scheme 3.20).[48]



Conditions and reagents : (i) DABCO, *n*-BuLi, –78°C, 5h; (ii) Na, THF/isopropanol (3:2), reflux, 5h.

Scheme 3.20: Synthesis of the diene **357a**.

The separation of dienes **357a** and **357b** was not possible by normal chromatography on silica gel; however it has been reported that effective separation of this related isomers could be achieved using silica impregnated with $AgNO_3$.[48,138] Attempts were made to separate product **357a** from its side-product **357b** using $AgNO_3$ impregnated silica, unfortunately, separation was not complete, but the ratio was improved from 4:1 to 5:1. It was decided to go through the synthesis using the mixture of dienes. The minor tetraene **333b** will not be able to undergo the double oxidative cyclisation and the product should be separable from *bis*-THF **3** expected from oxidation of the major tetraene **333a** (scheme 3.21).

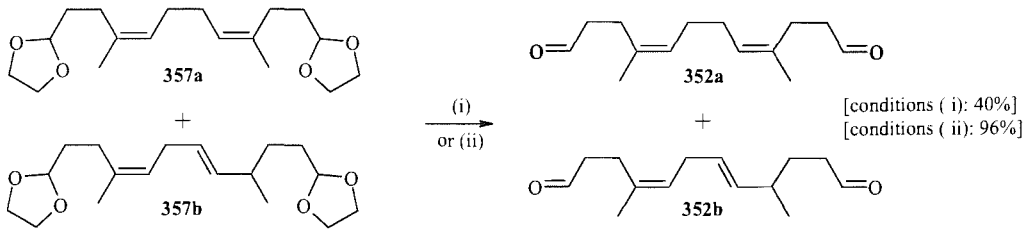


Conditions and reagents: (i) $KMnO_4$ oxidation.

Scheme 3.21: Expected products from oxidation of the mixture of tetraene isomers.

The deprotection of the cyclic acetals was then attempted on the mixture of dienes **357a,b**. Treatment of the dienes **357a,b** with HCl in THF/acetone afforded the corresponding dialdehydes **352a,b**. Unfortunately, this reaction proceeded slowly and the formation of many by-products was observed (scheme 3.22).[139] Another method of deprotection was attempted using toluene sulfonic acid in water/acetone, but only decomposition was observed.[140] Therefore milder deprotection conditions were investigated. Marko *et al.* have reported the

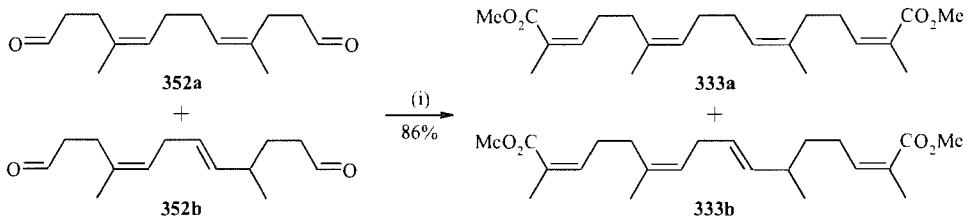
deprotection of cyclic acetal using ceric ammonium nitrate in the presence of a basic buffer.[141] Treatment of the diacetals **357a,b** with a catalytic amount of CAN in a 1:1 mixture of MeCN and a buffer solution (pH 8) afforded the corresponding dialdehydes **352a,b** in excellent yield (scheme 3.22).



Conditions and reagents: (i) HCl, THF/acetone/water, r.t. to 50°C, 4 days; (ii) CAN, buffer pH 8, MeCN, 3 days, 60°C.

Scheme 3.22: Synthesis of the dialdehyde **352a**.

The Still-Gennari conditions seen previously were applied to the aldehydes **352a,b**. Treatment of aldehydes **352a,b** with the fluorinated phosphonate **338b** in the presence of KHMDS and 18-crown-6 afforded the corresponding tetraenes **333a,b** in good yield and with excellent stereoselectivity; only the *cis-cis* isomer was observed by ^{1}H NMR and GC (scheme 3.23).



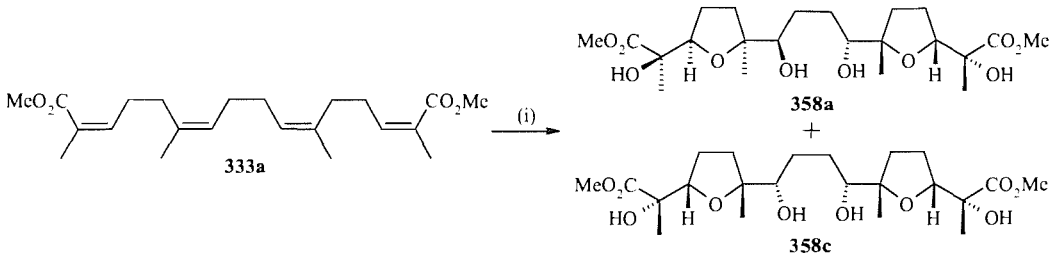
Conditions and reagents: (i) $(CF_3CH_2O)_2P(O)CH_2CH_3CO_2Me$ **338b**, 18-crown-6, KHMDS, THF, -78 °C, 2h.

Scheme 3.23: Synthesis of tetraene **333a**.

3-I-2-3 Attempted oxidative cyclisation of tetraenes 333a,b

Oxidative cyclisation on the tetraenes **333a,b** was attempted using the improved conditions (scheme 3.9). Unfortunately, the desired *bis*-THF **358a** was not obtained. The major by-product resulted from cleavage of the tetraene during the oxidation. Different conditions were then investigated, observing mainly degradation of the starting material (table 3.2). Oxidative cyclisation was successful only when 2.5 eq. of powered $KMnO_4$ in a mixture of acetone/AcOH (3:2) was used (scheme 3.24). The crude NMR showed characteristic peaks for the THF rings and mass spectrometry confirmed the formation of the desired products

358a,b. Unfortunately, purification by chromatography on silica gel has been unsuccessful, resulting in a loss of material; this is thought to be due to the high polarity of products **358a,b**.



Conditions and reagents: (i) $KMnO_4$, AcOH, solvent, additive (see table 3.2).

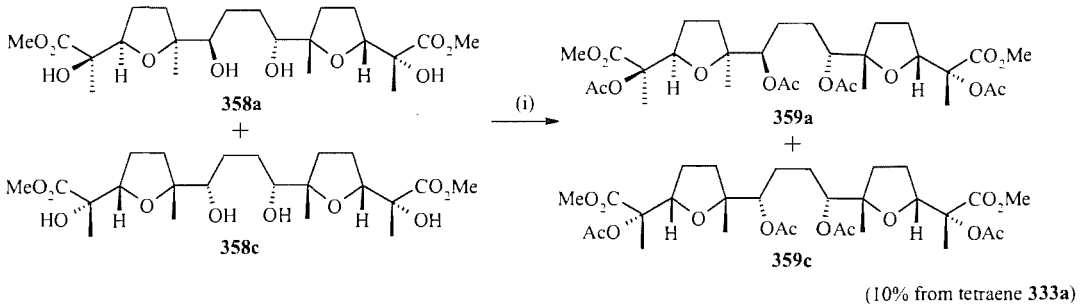
Scheme 3.24: Attempted oxidative cyclisation on tetraene **333a**.

(i)	$KMnO_4$	Solvent	AcOH	T (°C)	Time	Observations
1[a]	4 eq. powdered	acetone	co-solvent[b]	–30°C to 0°C	2h30	degradation
2	4 eq. powdered	acetone	co-solvent[b]	–30°C to 0°C	2h30	degradation
3	4 eq. 0.4 M aq. sol.	acetone/buffer	2.8 eq	–30°C to 0°C	2h30	degradation
4	3.5 eq. powdered	acetone	co-solvent[b]	–30°C to –10°C	1h30	degradation
5	3.5 eq. 0.4 M aq. sol.	acetone/buffer	2.8 eq	–30°C to –10°C	1h30	degradation
6	2.5 eq. powdered	acetone	co-solvent[b]	–30°C to –10°C	1h30	**358a,b** (25%, crude)

[a] Reaction carried out with the addition of 10 mol% adogen 464; [b] AcOH/acetone (2:3).

Table 3.2: Results of the oxidative cyclisation of tetraene **333a** under different conditions

In order to overcome this problem, the alcohol groups of crude *bis*-THFs **358a,c** were protected and protected product **22** was successfully purified, confirming the formation of the *bis*-THFs **358a,c** (scheme 3.25).[142] Unfortunately, the yield of this step was quite poor probably because of the formation of the mono, *bis* and *tri*-protected adducts.



Conditions and reagents: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 24h.

Scheme 3.25: Protection of *bis*-THFs **358a,c**.

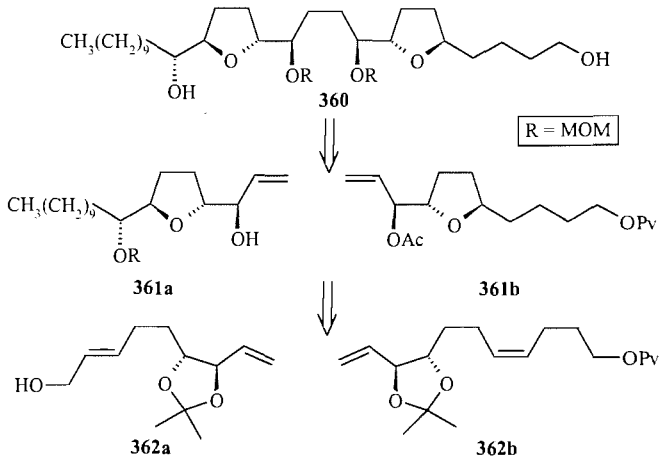
The results obtained for the oxidative cyclisation of the tetraene **333a** has not been as good as expected, and unfortunately, the oxidative cyclisations carried out on simple 1,5-dienes **345b** and **348** bearing the sultam have not been successful, which is a major obstacle for the asymmetric approach. This route was therefore abandoned, although investigation on the replacement of the camphor-sultam by an alternative chiral auxiliary will be attempted later in the laboratory.

3-II Second approach to intricatetraol

An alternative approach to the synthesis of intricatetraol (**331**) was adopted where the *bis*-THF core **332a** was to be formed *via* the coupling of two THF rings. The revised approach would rely on a metathesis reaction to couple the two THF-containing fragments. Recently, two total syntheses of non-adjacent *bis*-THFs containing natural products have been published using a related strategy.[92,143] This approach will provide an interesting alternative toward the synthesis of intricatetraol (**331**).

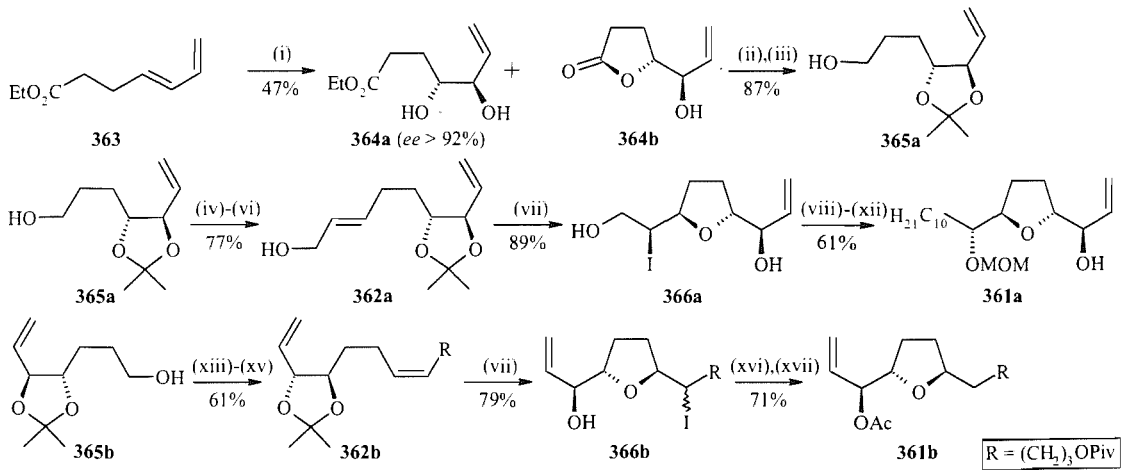
3-II-1 Previous use of metathesis toward the synthesis of non adjacent *bis*-THF products

Mootoo *et al.* have described the synthesis of a precursor of bullatanocin *via* iodoetherifcation of hydroxy alkenes and olefin cross metathesis (scheme 3.26).[143] The mono-THFs **361** and **362** were prepared *via* iodocyclisation of alkenes **363** and **364**.



Scheme 3.26: Mootoo's retrosynthetic scheme of *bis*-THF core **360**.

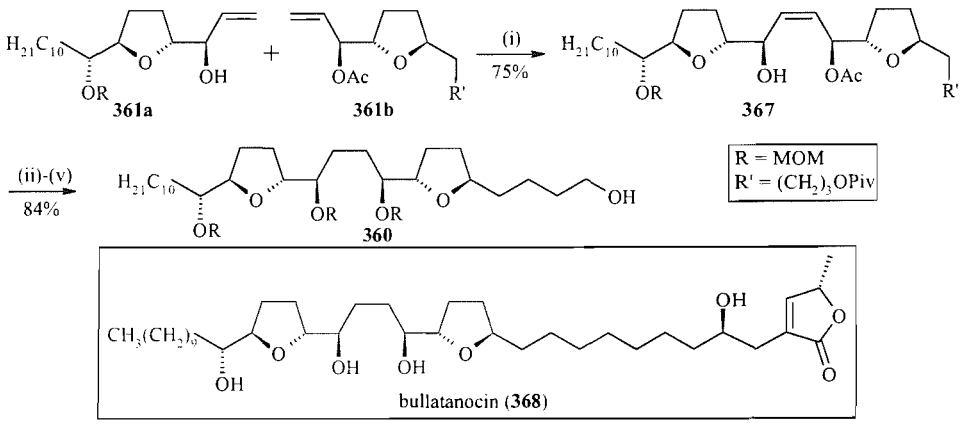
Treatment of 1,3-diene **363** with AD-mix β by Mootoo *et al.* gave a 1:1 mixture of diol **364a** (*ee* > 92%) and the derived lactone **364b** in moderate yield (scheme 3.27). Reduction of the mixture and subsequent acetonation afforded alkene **365a**. Synthesis of alkene **365b** was carried out along similar lines, using AD-mix α instead of AD-mix β to provide **365b** in moderate yield and *ee* > 95%. The aldols **365a,b** were converted to the corresponding aldehydes which underwent Wittig olefination with $Ph_3P{=}CHCO_2Me$ and $Ph_3P{=}CH(CH_2)_3OLi$, respectively. DIBAL reduction or pivaloylation of the olefination products provided the dienes **362a,b**. Iodocyclisation of diene **362a** with IDCP gave *trans*-THF **366a** as a single isomer in good yield. THF **366a** was treated with sodium methoxide followed by alcohol silylation to produce a silyoxy-epoxide intermediate. This epoxide was opened with nonyl magnesium bromide, the resulting alcohol protected with MOMCl and the silyl group removed to afford THF **361a** in good yield. Treatment of diene **362b** with IDCP provided the desired THF **366b** in good yield and selectivity. After reduction of the iodide with Bu_3SnH, the secondary alcohol was acetylated to afford THF **361b** in good yield.



Conditions and reagents : (i) AD-mix β, *t*-BuOH/H_2O (1:1), $MeSONH_2$; (ii) DIBALH, THF, –78°C; (iii) $(MeO)_2CMe_2$, CSA, CH_2Cl_2; (iv) PCC, CH_2Cl_2; (v) $Ph_3P{=}CHCO_2Me$; (vi) DIBALH, THF, –78°C; (vii) IDCP, CH_3CN/H_2O; (viii) K_2CO_3, MeOH; (ix) TBDMSCl, imidazole, CH_2Cl_2; (x) $CH_3(CH_2)_8MgBr$, CuBr, THF; (xi) MOMCl, *i*-Pr_2Net, CH_2Cl_2; (xii) Bu_4NF, THF; (xiii) Swern oxidation; (xiv) $Ph_3P{=}CH(CH_2)_3OLi$, toluene, –78°C; (xv) PivCl, pyridine, DMAP; (xvi) Bu_3SnH, toluene, AIBN, reflux; (xvii) Ac_2O, EtOAc, DMAP.

Scheme 3.27: Synthesis of THF **361a,b**.

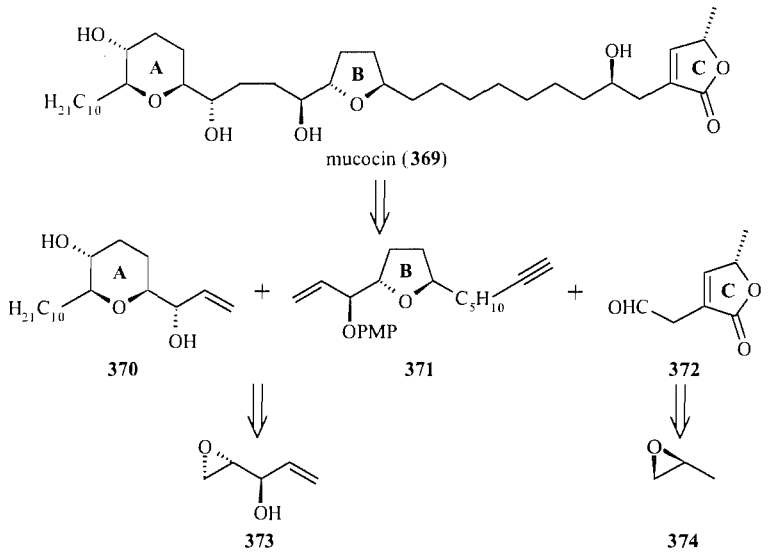
The cross metathesis of THF **361a,b** was carried out using an excess of ester **361b** to prevent the formation of homodimers and *bis*-THF **367** was obtained in good yield (76% related to THF **361a** and 75% related to THF **361b**) (scheme 3.28). After hydrogenation of *bis*-THF **367**, sequential hydrolysis of the acetate group, protection of the resulting alcohol with MOMCl and removal of the pivaloate group afforded the *bis*-THF **360** precursor of bullatanocin (**368**).



Conditions and reagents: (i) **361a**:**361b** (1:3), Grubbs' catalyst (10 mol%), 18h, r.t., then Grubbs' catalyst (10 mol%), 18h, r.t; (ii) H_2, Pd/C, EtOAc; (iii) K_2CO_3, MeOH; (iv) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (v) NaOMe, MEOH.

Scheme 3.28: Synthesis of *bis*-THF **360**.

Evans *et al.* have described the total synthesis of (–)-mucocin (**369**) using a temporary silicon-tethered ring-closing metathesis cross-coupling reaction (scheme 3.29).[92] Alkyne **371** and aldehyde **372** are coupled *via* enantioselective addition. Precursors **370** and **371** are prepared from a common intermediate, epoxide **373** and aldehyde **372** from epoxide **374**.



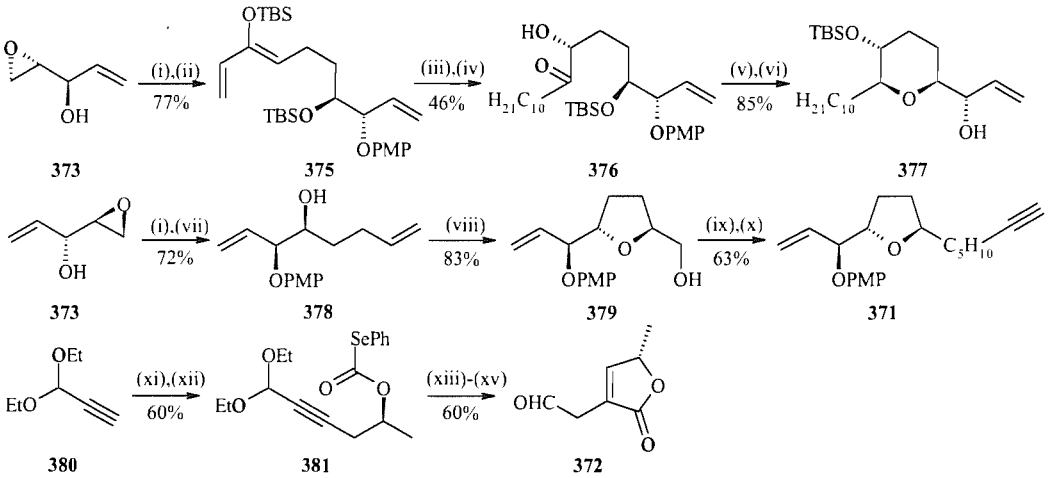
Scheme 3.29: Retrosynthetic route to (–)-mucocin (**369**).

After a Mitsunobu inversion of the allylic alcohol **373** using *p*-methoxyphenol, the epoxide was opened and the resulting secondary alcohol was protected *in situ* with TBSOTf to afford triene **375** in good yield (scheme 3.30). Sharpless asymmetric dihydroxylation of the triene **7** using AD-mix *β* (*ds*≥99:1 by HPLC) followed by the conjugate addition of the cuprate derived from octylmagnesium bromide provided alcohol **376**. Reductive etherification of ketone **376** with bismuth tribromide, subsequent protection of the secondary alcohol with TBSOTf and cleavage of the PMP group afforded pyran **377** in good yield.

Mitsunobu inversion of epoxide **373** followed by the epoxide opening with the cuprate derived from allylmagnesium bromide gave diene **378**. *Trans*-THF **379** (*ds*≥19:1) was obtained in good yield *via* cobalt catalysed oxidative cyclisation of alcohol **378**. Conversion of primary alcohol **379** to the corresponding triflate, followed by cuprate displacement and *in situ* deprotection of trimethylsilyl group furnished THF **371**.

Treatment of epoxide **374** with the carbanion derived from alkyne **380** gave the secondary alcohol that was converted to the selenocarbonate **381** in moderate yield. Treatment of selenocarbonate **381** with Bu_3SnH, provided the γ-butyrolactone; metal-catalysed

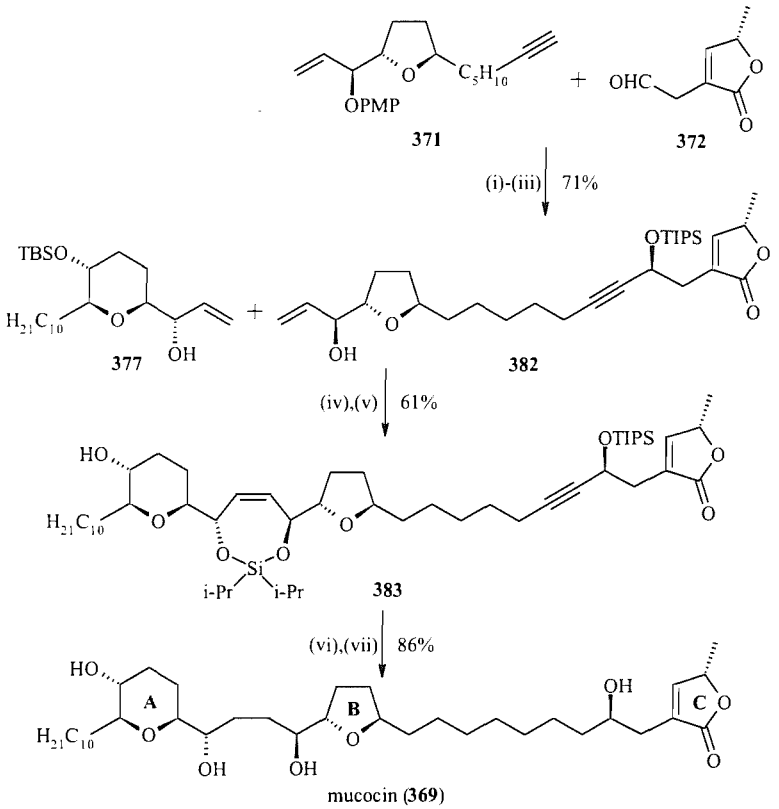
isomerisation of the exo-cyclic olefin and hydrolysis of the diethyl acetal afforded the aldehyde **372** in good yield.



Conditions and reagents : (i) *p*-$MeCOC_6H_4OH$, DIAD, PPh_3, THF, 0°C; (ii) $(CH_2{=}CH)_2CHOTBS$, *n*-BuLi, THF, –78°C, then TBSOTf, 2,6-lutidine, –78 to 0 °C; (iii) AD-mix *β*, *t*-BuOH/H_2O (1:1), $MeSONH_2$; (iv) *n*-octylMgBr, CuCN, THF, –78°C; (v) $BiBr_3$, t-$BuMe_2SiH$, MeCN, 0°C, then 2,6-lutidine, TBSOTf, 0°C; (vi) $(NH_4)_2Ce(NO_3)_6$, MeCN/H_2O, –5°C (vii) $CH_2{=}CHCH_2MgBr$, CuCN, Et_2O, –78°C; (viii) $Co(modp)_2$, O_2, *t*-BuOOH, iPrOH; (ix) Tf_2O, Et_3N, CH_2Cl_2, –78°C; (x) $TMSC{\equiv}C(CH_2)_4MgBr$, CuI THF, –20 to –10°C, then MeOH, TBAF, –20°C to r.t.; (xi) *S*-propylene oxide **6**, *n*-BuLi, HMPA, THF; (xii) $COCl_2$, Et_3N, C_6H_6, 0°C to r.t., then PhSeH, pyridine, THF/C_6H_6, 0°C to r.t.; (xiii) n-Bu_3SnH, AIBN, C_6H_6, reflux; (xiv) $Rh(CO)(PPh_3)_3$, C_6H_6, 85°C; (xv) HCOOH, pentane, 0°C.

Scheme 3.30: Synthesis of precursors **371**, **372** and **377**.

Enatioselective addition of the alkynyl zinc reagent prepared from THF **371** to aldehyde **372** gave the propargylic alcohol (*ds* = 20:1 by HPLC), subsequent protection with TIPSOTf and cleavage of the PMP ether afforded THF **382** in good yield (scheme 3.31). Treatment of alcohol **382** with excess of diisoproplydichlorosilane followed by the removal of the excess silylating reagent and addition of pyran **377** furnished the mixed *bis*-alkoxy silane that underwent ring-closing metathesis with stoichiometric Grubbs' catalyst to afford compound **383** in good yield. After the removal of all silicon groups with HF, chemoselective reduction with diimide gave (–)-mucocin (**369**) in good yield.

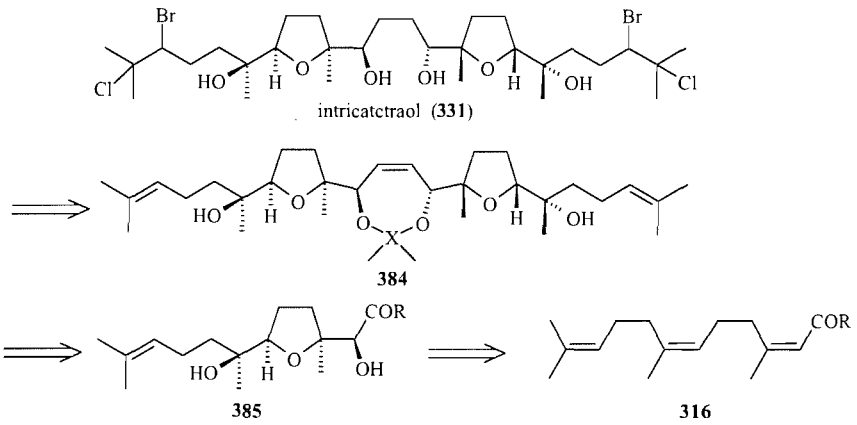


Conditions and reagents : (i) Et_2Zn, toluene, reflux, then (*R*)-BINOL, $Ti(Oi\text{-}Pr)_4$, THF, **4**, 0°C; (ii) TIPSOTf, pyridine, DMAP, THF, 0°C; (iii) $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O$, −10°C; (iv) **382**, $i\text{-}Pr_2SiCl_2$ (xs), CH_2Cl_2, imidazole, 0°C to r.t., then **377**, imidazole, 0°C to r.t.; (v), Grubb' catalyst (1.8 eq.), 1.2-DCE, reflux; (vi) HF/MeCN, CH_2Cl_2, r.t.; (vii) $TsNHNH_2$, NaOAc, 1,2-DME/H_2O, reflux.

Scheme 3.31: Evans' synthesis of mucocin (**369**).

3-II-2 Approach toward intricatetraol *via* metathesis

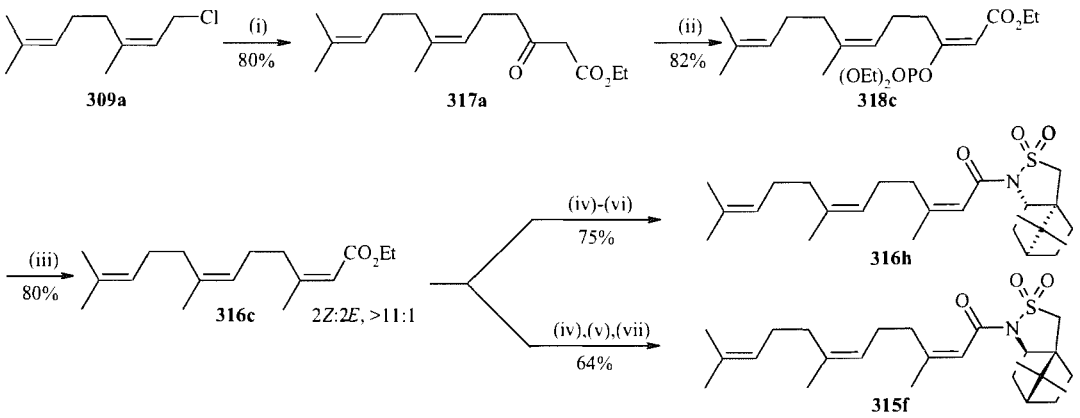
It is proposed to synthesise intricatetraol (**331**) using a tethered ring-closing cross metathesis reaction to construct the *bis*-THF core **384** (scheme 3.32). The mono-THF precursor **385** will be obtained by selective permanganate mediated oxidative cyclisation of the corresponding triene **316** bearing a chiral auxiliary.



Scheme 3.32: Second approach to intricatetraol (**331**).

3-II-2-1 Selective oxidative cyclisation of 1,5,9-trienes 316c,f,h

The synthesis of trienes **316c,f,h** has been previously described strarting from nerol **51b** (scheme 3.33). The correct absolute stereochemistry should be obtained by using the (2*S*)-camphorsultam auxiliary.

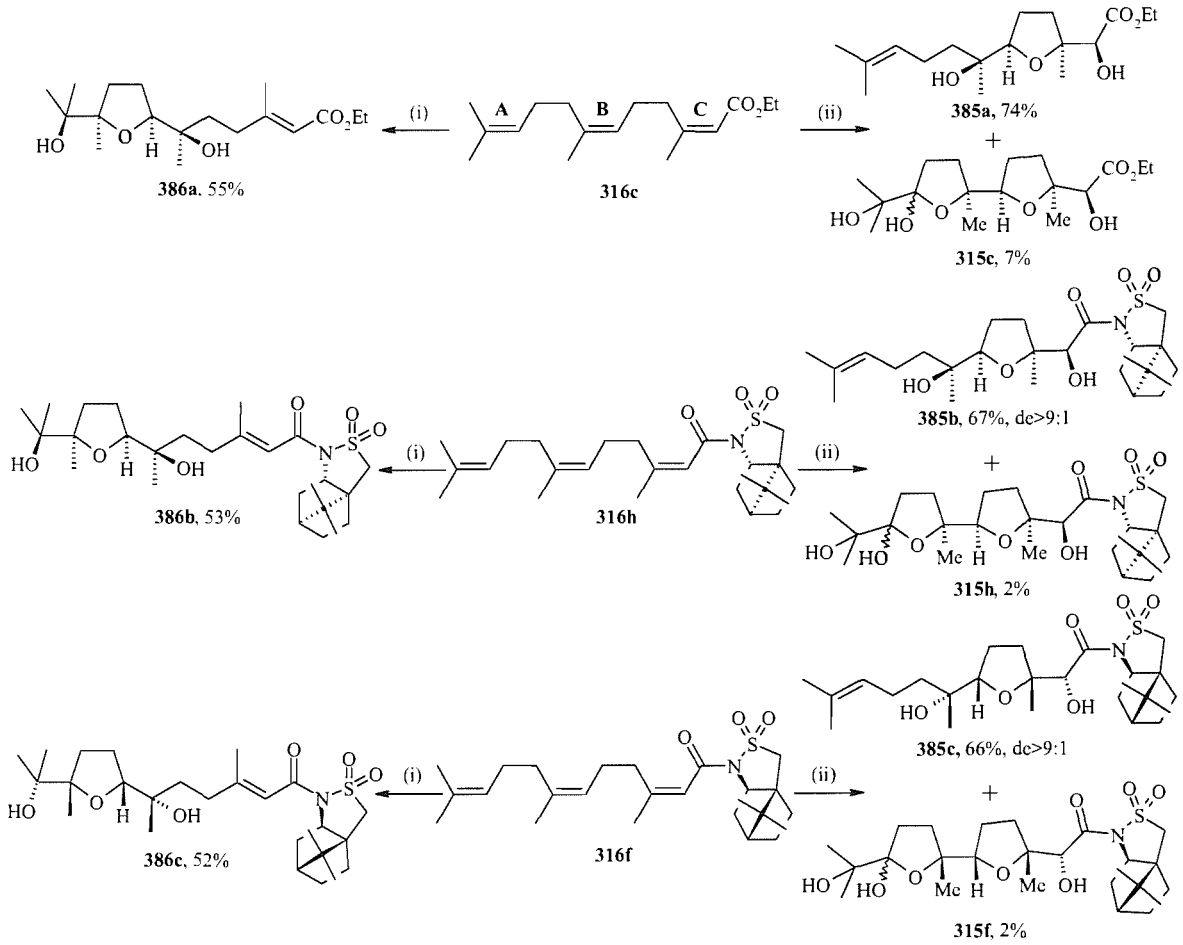


Conditions and reagents : (i) ethyl acetoacetate, NaH, then *n*-BuLi, THF, 0 to 25°C, 30 min; (ii) Et_3N, DMPU, DMAP, $PO(OEt)_2Cl$, –20 to 25°C, 12 h; (iii) MeCu, MeMgCl, THF, –30°C, 4 h; (iv) NaOH, $NaHCO_3$, water, MeOH, reflux, 16 h; (v) pentafluorophenol, DCC, EtOAc, 25°C, 24 h; (vi) *n*-BuLi, (2*S*)-10,2-camphorsultam, THF, –78°C to 25°C, 18h; (vii) *n*-BuLi, (2*R*)-10,2-camphorsultam, THF, –78°C to 25°C, 18h.

Scheme 3.33: Synthesis of trienes **316c,f,h**.

Oxidative cyclisation of trienes **316c,f,h** were attempted using 1.5 eq. of powered $KMnO_4$ in a mixture of acetone/AcOH (3:2), surprisingly, products **386a-c** were obtained in good yield instead of the desired products **385a-c** (scheme 3.34). It is thought that the important concentration of acid in the reaction may cause strong hydrogen oxygen interactions between

the acid and the permanganate ion, which could become more electrophile and therefore favoured the attack on the double bond **A**. However, within the group, these oxidation conditions have been applied successfully to similar type of trienes bearing disubstituted double bonds. Therefore, alternative conditions were investigated and treatment of trienes **316c,f,h** with 1.7 eq. of $KMnO_4$ (aq. sol.) and 2.8 eq. of AcOH in acetone in presence of a buffer (pH = 6.24) afforded the desired products **385a-c** in good yield with a small amount of the corresponding THF lactols **17c,f,h** as minor by-products (scheme 3.34). Oxidative cyclisation of trienes **316h,f** was achieved with an excellent level of asymmetric induction.

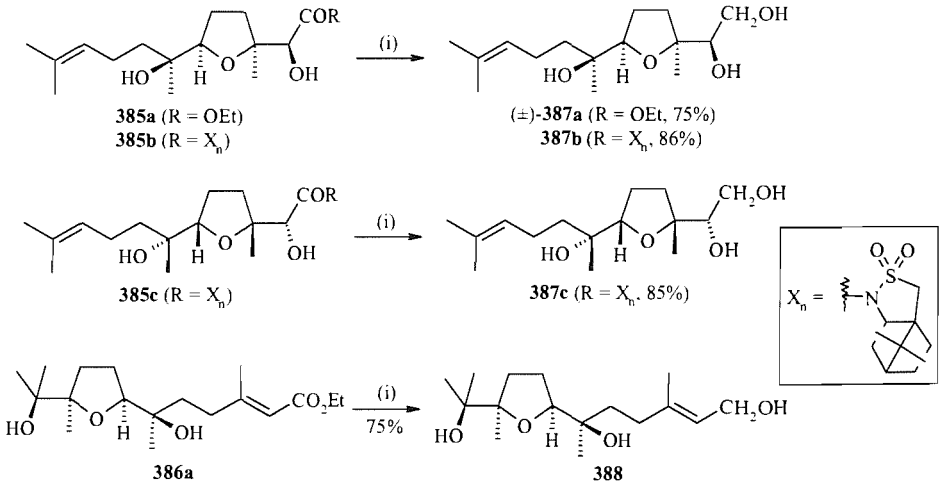


Conditions and reagents: (i) $KMnO_4$ (powdered, 1.5 eq.), AcOH/acetone (2:3), –30°C to 0°C, 1h; (ii) $KMnO_4$ (1.7 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer (0.5 mL), acetone, –30°C to 0°C, 2h.

Scheme 3.34: Formation of mono-THFs **385a-c**.

3-II-2-2 Reduction of mono-THFs to the corresponding triols

Mono-THFs **385a-c** and **386a** were reduced using $LiAlH_4$ in THF affording the corresponding triols **387a,b** and **388** in good yield (Scheme 3.35).[126] Triol **387b** is known in the literature and the data were identical to that reported, which confirmed the predicted diastereoselectivity for the oxidative cyclisation of the triene bearing the sultam.[144]



Conditions and reagents: (i) $LiAlH_4$, THF, –78°C to r.t., 24h.

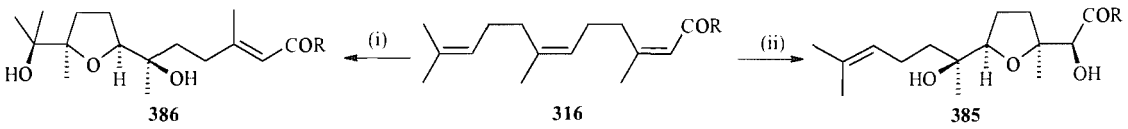
Scheme 3.35: Synthesis of triols **387a-c** and **388**.

The direct reduction of the sultam moiety of mono-THF **385b** to the aldehyde was attempted by treatment with DIBAL, but the desired product was not obtained, starting material was recovered and the chiral centre next to the sultam appeared to have undergone epimerization.[19]

3-III Conclusion and further work

The synthesis of all *cis*-tetraene **333a** was achieved *via* a versatile method in moderate yield, but it was not possible to obtain a pure sample as by-product **333b** was carried on through the synthesis. Oxidative cyclisation on tetraenes **333a,b** mainly led to degradation and when the desired *bis*-THFs **358a,c** were obtained, it was not possible to obtain a pure sample due to purification issues. Selective permanganate oxidative cyclisation of trienes **316c,f,h** afforded the corresponding mono-THFs **385a-c** in good yield and high diastereoselectivity. It is interesting to note that it is possible to selectively prepare mono-THF **385** or mono-THF **386**

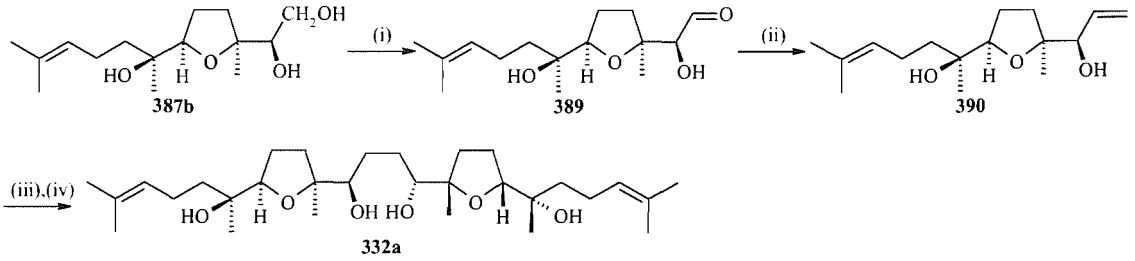
from the same triene precursor **316** by simply changing the conditions of oxidation with permanganate (scheme 3.36).



Conditions and reagents: (i) $KMnO_4$ (powered, 1.5 eq.), AcOH/acetone (2:3), –30°C to 0°C, 1h; (ii) $KMnO_4$ (1.7 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer (0.5 mL), acetone, –30°C to 0°C, 2h.

Scheme 3.36: Selective oxidation of triene **316**.

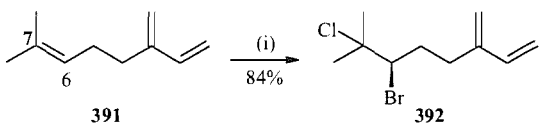
In order to move towards the synthesis of intricatetraol (**331**), selective oxidation of the primary alcohol moiety of mono-THF **387b** with TEMPO will be attempted to produce the aldehyde **389**, which will undergo olefination to afford diol **390** (scheme 3.37).[145-149] THF **390** will then undergo a metathesis and the disubstituted double bond will be subsequently reduced to afford *bis*-THF **332a**.



Conditions and reagents: (i) TEMPO, NaOCl; (ii) $MePPH_3Br$, NaHMDS; (iii) Grubbs' catalyst; (iv) HF/MeCN.

Scheme 3.37: Toward the synthesis of intricatetraol (**331**).

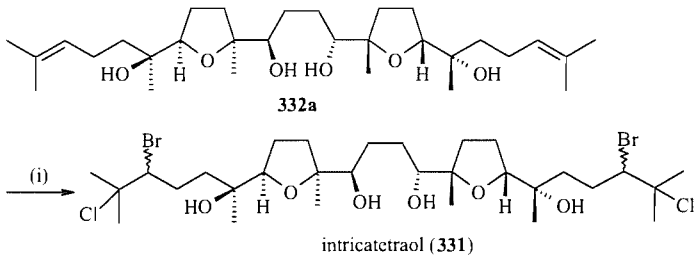
Sotokawa *et al.* have shown that tetraalkylammonium dichlorobromate (R_4NBrCl_2) can be employed for selective conversion of trisubstituted double bonds to the corresponding dihalogen.[150] Treatment of diene **391** with stoichiometric Bu_4NBrCl_2 afforded the dihalogen **392** in good yield and selectivity (>43:1) following Markovnikov selectivity (scheme 3.38).



Conditions and reagents: (i) Bu_4NBrCl_2 (1 eq.), CH_2Cl_2, 0°C, 1h.

Scheme 3.38: Synthesis of diene **392**.

We propose to attempt the conversion of *bis*-THF **332a** to intricatetraol (**331**) along similar lines (scheme 3.39). The main core of *bis*-THF **332a** should induce the desired regiochemistry. As discussed previously, the absolute configuration of the brome group is as yet unknown; the selective bromochlorination of *bis*-THF **332a** should provide precious indication about the absolute configuration of the natural product intricatetraol (**331**).



332a

intricatetraol (**331**)

Conditions and reagents: (i) Bu_4NBrCl_2.

Scheme 3.39: Synthesis of intricatetraol (**331**).

Chapter 4: Synthesis of *trans*-THFs and application toward the synthesis of eurylene

In this chapter, our efforts on the synthesis of *trans*-disubstituted THFs *via* permanganate oxidative cyclisations and their application toward the synthesis of eurylene are summarized. Itokawa *et al.* have reported the isolation of eurylene a squalene-type triterpene from the woods of *Eurycoma longifolia.*[151,152] The absolute configuration of eurylene (**393**) was elucidated by spectroscopic data, chemical evidence and X-ray analysis (figure 4.1). Although the left hand and right-hand segments of eurylene are structurally and functionally similar, the molecule is not symmetrical because of stereochemical differences; it is therefore a challenging target for total synthesis.

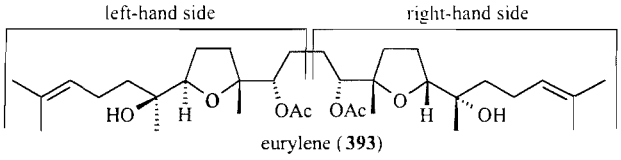
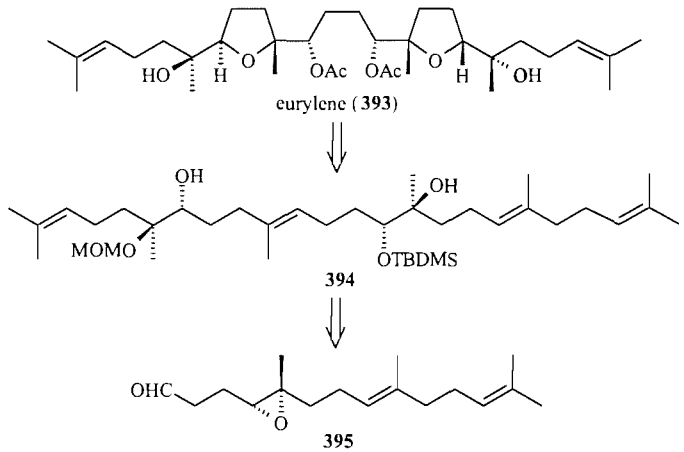


Figure 4.1: Eurylene (**393**).

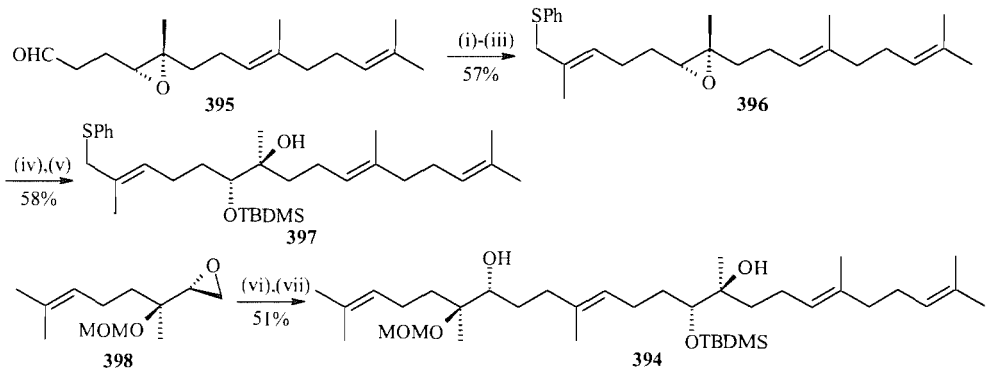
4-I Previous syntheses of eurylene (393)

Shirahama *et al.* have described the first total synthesis of eurylene (**393**) *via* a double vanadium catalysed oxidation of two *bis*-homoallyl alcohol systems present in tetraene **394** (scheme 4.1).[125]



Scheme 4.1: Shirahama's retrosynthetic analysis of eurylene (**393**).

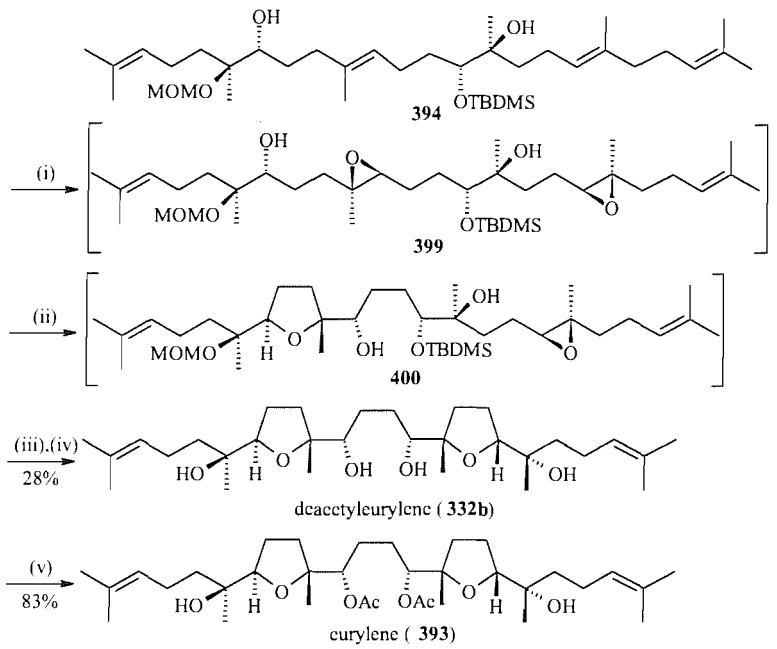
Horner-Emmons olefination of aldehyde **395** with sodium triethyl 2-phosphonopropionate and reduction of the ester moiety with DIBAL afforded the primary alcohol that was converted to the corresponding sulphide **396** by nucleophilic substitution with diphenyl sulphide (scheme 4.2). After cleavage of the epoxide with catalytic perchloric acid, the resulting secondary alcohol was protected using TBDMSOTf to give the tertiary alcohol **397**. Oxirane **398** was treated with the lithio derivative of compound **397** and subsequently desulfurised under Birch conditions to afford *bis*-homoallyl alcohol **394**.



Conditions and reagents: (i) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, THF, 0°C, 15 min; (i) DIBAL, toluene, –78°C, 15 min; (iii) PhSSPh, *n*-Bu_3P, CH_2Cl_2, r.t., 30 min; (iv) $HClO_4$ (cat.), THF/H_2O (6:1), reflux, 1h; (v) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –20°C, 20 min; (vi) **396**, *n*-BuLi, TMEDA, HMPA, THF, –20°C, 30 min; (vii) Li NH_3/EtOH (1:1), –78°C, 4h.

Scheme 4.2: Synthesis of tetraene **394**.

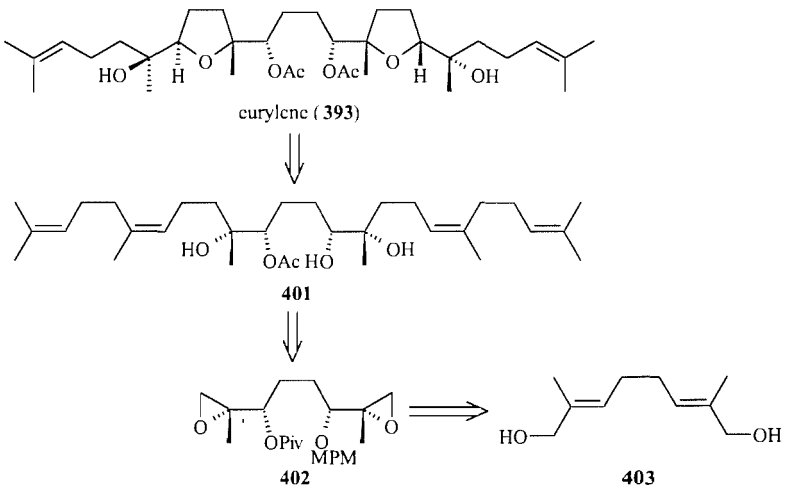
Vanadium catalysed oxidation of alcohol **394** gave the unstable bisepoxide **399** (scheme 4.3). Acid catalysed cyclisation of the left hand epoxide afforded intermediate **400**, deprotection of the TBDMS group and subsequent acid treatment afforded de-acetyleurylene (**332b**). Finally, acetylation of the alcohol groups provided eurylene (**393**) in good yield.



Conditions and reagents: (i) TBHP, $VO(acac)_2$ (cat.), MS 3Å, benzene, r.t., 3h, then Me_2S, r.t., 30 min; (ii) CSA (cat.), r.t., 2h; (iii) TBAF, THF, reflux, 2h; (iv) HCl (cat.), THF/H_2O (10:1), reflux, 15 min; (v) Ac_2O, pyridine, r.t., 50h .

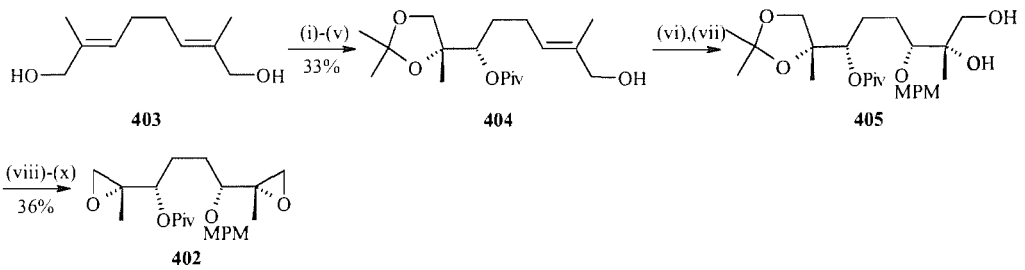
Scheme 4.3: Synthesis of eurylene (**393**) *via* vanadium catalysed oxidation.

Morimoto *et al.* have reported the total synthesis of eurylene (**393**) using a combination of rhenium and chromium oxidation to construct the *trans* and *cis*-THF units respectively from triol precursor **401** (scheme 4.4).[153] Triol **401** derives from di-epoxide **402** that can be prepared by Sharpless asymmetric epoxidation of the readily available diol **403**.



Scheme 4.4: Morimoto's retrosynthetic analysis of eurylene (**393**).

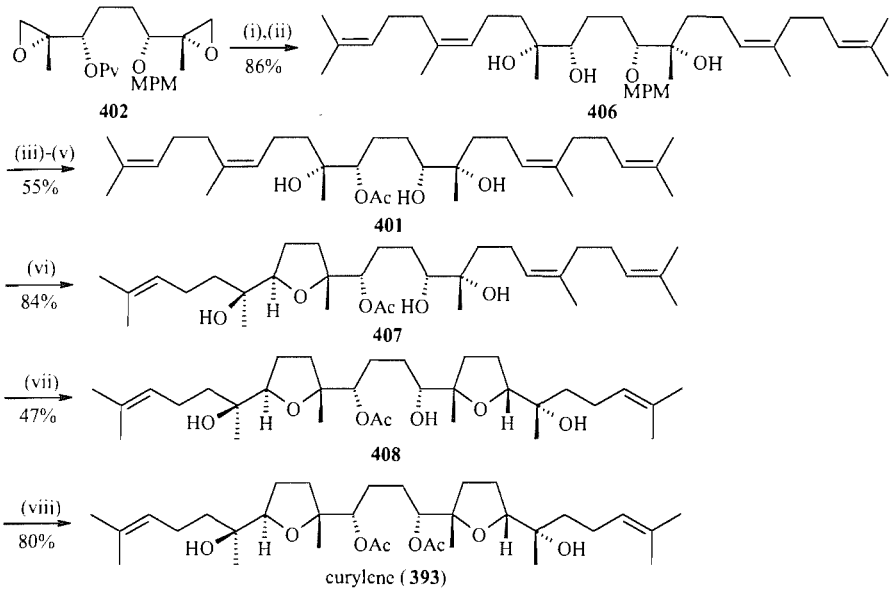
After mono-protection of diol **403** with TBSCl and Sharpless epoxidation of the remaining allylic alcohol using (–)-diethyl D-tartrate (98% *ee*), a titanium-assisted epoxide-opening reaction with introduction of the pivaloate group afford the corresponding 1,2-diol intermediate (scheme 4.5). Silylation of the primary alcohol, acetonide formation and desilylation provided the allylic alcohol **404** in good overall yield. Asymmetric epoxidation using (+)-diethyl L-tartrate and subsequent $Ti(OMPM)_4$-mediated epoxide-opening reaction with *p*-anise alcohol gave a mixture of the desired 1,2-diol **405** and a 1,3-diol derivative in a 3:1 ratio. After sequential deprotection of the actetonide and mesylation of the primary alcohol groups, subsequent basic treatment of the dimesylate intermediate afforded the desired di-epoxide **402** in overall good yield.



Conditions and reagents: (i) TBSCl, imidazole, CH_2Cl_2, r.t., 1h; (ii) TBHP, $Ti(OiPr)_4$, D-(–)-DET, MS 4 Å, CH_2Cl_2, –20°C, 2h; (iii) $Ti(OiPr)_4$, PvOH, benzene, 0°C, 2h; (iv) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0°C, 2h; (v) Bu_4NF, THF, r.t., 3h; (vi) TBHP, $Ti(OiPr)_4$, L-(+)-DET, MS 4 Å, CH_2Cl_2, –20°C, 3h; (vii) $Ti(OMPM)_4$, MPMOH, benzene, 60°C, 12h; (viii) $AcOH/H_2O$ (4/1), r.t., 5h; (ix) MsCl, pyridine, CH_2Cl_2, 0°C to r.t., 5h; (x) K_2CO_3, MeOH, r.t., 1h.

Scheme 4.5: Synthesis of di-epoxide **402**.

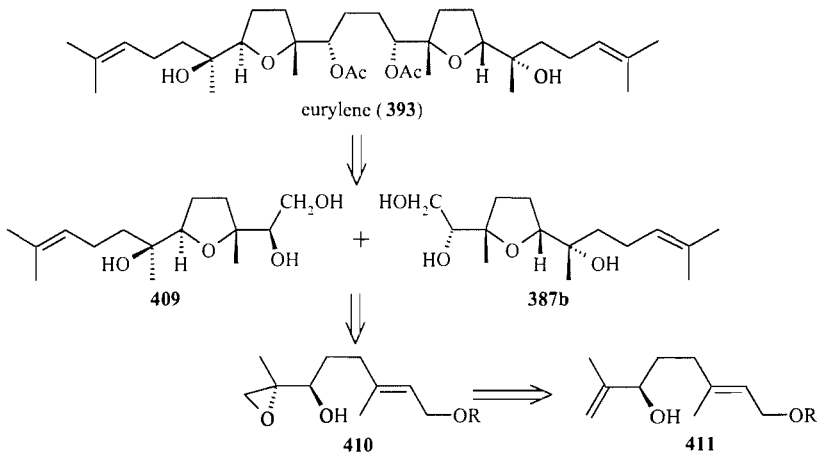
Treatment of di-epoxide **402** with the lithio derivative of neryl phenyl sulphide and subsequent desulfurisation under Bouvault-Blanc conditions gave triol **406** in good yield (scheme 4.6). Selective acetylation of the secondary alcohol and removal of the MPM group afforded the triol **401** in good yield. Treatment of triol **401** with $[(CF_3CO_2)ReO_3 \cdot 2CH_3CN]$ furnished the expected *trans*-THF **407** in good yield and diastereoselectivity. Treatment of mono-THF **407** with PCC afforded (+)-14-deacetyleurylene (**408**) with complete *cis*-diastereoselectivity. The synthesis of (+)-eurylene (**393**) was completed by selective acetylation of *bis*-THF (**408**).



Conditions and reagents: (i) neryl phenyl sulphide, *n*-BuLi, TMEDA, THF, –78°C, 30 min, then 0°C, 2h; (ii) Na, THF/*i*PrOH (2/1), reflux, 15h; (iii) Ac_2O, pyridine, r.t., 12h; (iv) DDQ, MS 4 Å, CH_2Cl_2, 0°C, 2h; (v) AcOH/H_2O (4/1), r.t., 16h; (vi) $[(CF_3CO_2)ReO_3{\cdot}2CH_3CN]$, TFAA, CH_2Cl_2/CH_3CN (9/1), –40°C, 1.5h; (vii) PCC, CH_2Cl_2, r.t., 30 min; (viii) Ac_2O, pyridine, r.t., 40h.

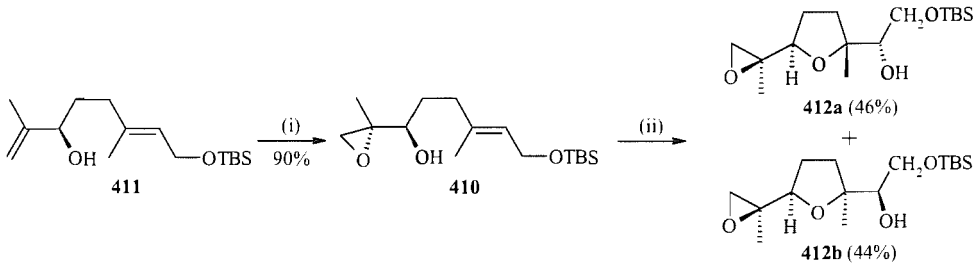
Scheme 4.6: Synthesis of (+)-eurylene (**393**).

Hioki *et al.* have described the synthesis of eurylene (**393**) *via* the coupling of two mono-THF moieties **387b** and **409**.[144] These diastereomeric segments **387b** and **409** were accessible from a common precursor **410**, by the non-stereoselective THF ring formation followed by addition of a prenyl group (scheme 4.7).



Scheme 4.7: Hioki's retrosynthetic analysis of eurylene (**393**).

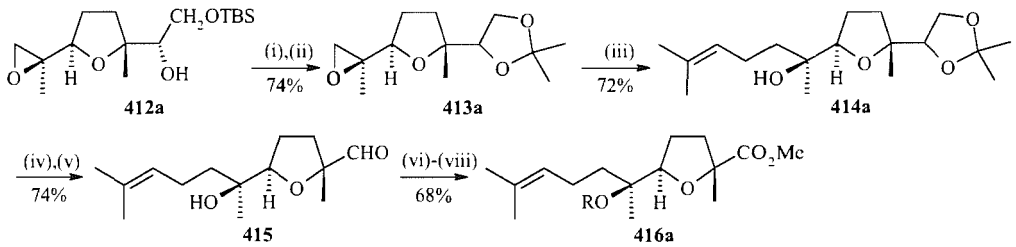
(*R*)-allylic alcohol **411** was first converted into the epoxide **410** in excellent yield and diastereoselectivity (scheme 4.8). Treatment of epoxide **410** with *m*-CPBA afforded desired mono-THFs **412a,b** in almost equal amount and overall good yield. The stereochemistry of products **412a,b** was determined by NOE experiments.



Conditions and reagents: (i) $VO(acac)_2$, *t*-BuOOH, benzene; (ii) *m*-CPBA, r.t., CH_2Cl_2.

Scheme 4.8: Synthesis of mono-THFs **412a,b**.

Mono-THF **412a** was converted to **413a** by sequential deprotection and protection of the resulting diol (scheme 4.9). Treatment of acetonide **413a** with prenylmagnesium chloride and cuprous iodide afforded alcohol **414a** in good yield. Hydrolysation of the acetonide group and cleavage of the resulting diol gave the corresponding aldehyde **415**. Further oxidation and esterification of aldehyde **415** followed by the silylation of the tertiary alcohol afforded the left-hand segment **416a** in good yield.

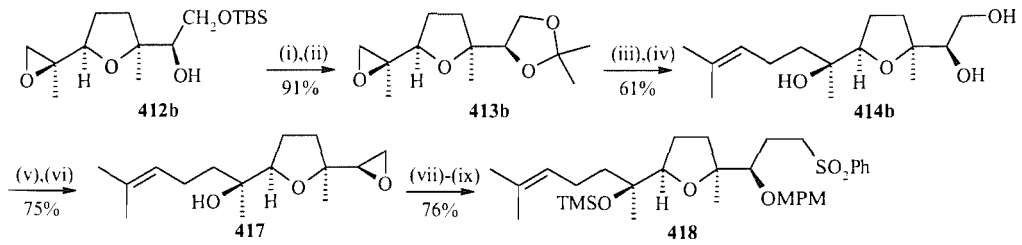


Conditions and reagents: (i) *n*-Bu_4NF, THF; (ii) DMP, PPTS, CH_2Cl_2; (iii) Me_2=$CHCH_2MgCl$, CuI, THF, –15°C to 0°C; (iv) PPTS, EtOH, (v) $NaIO_4$, aq. THF; (vi) $NaClO_2$, 2-methyl-2-butene, $NaHPO_4$, aq. *t*-BuOOH; (vii) MeI, K_2CO_3, DMF; (viii) TMSCl, imidazole, DMF.

Scheme 4.9: Synthesis of the left-hand segment **416**.

In a similar way to the left-hand segment, mono-THF **412b** was transformed into the diol **414b** in moderate yield (scheme 4.10). Diol **414b** was selectively converted into the monomesylate that yielded epoxide **417** after treatment with potassium carbonate. The lithiated methylphenyl sulfone was then treated with **417** and the two alcohols groups were

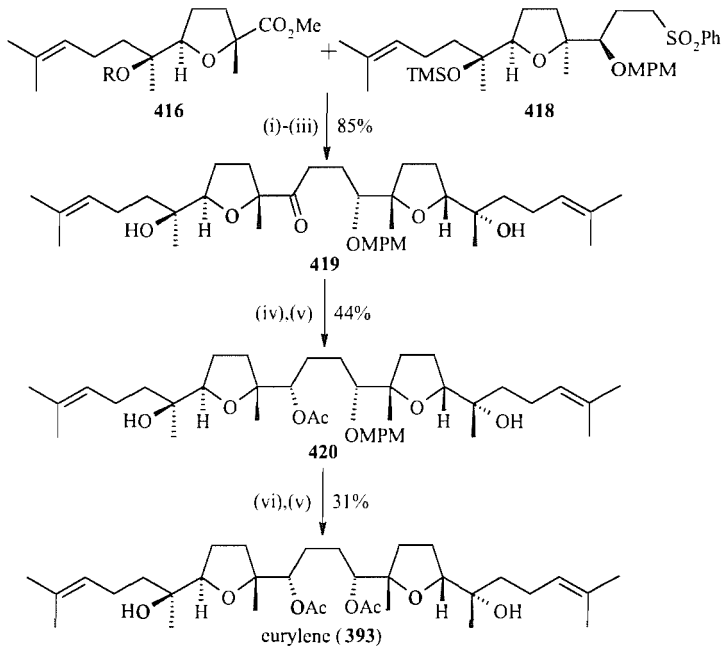
selectively protected as MPM ether and TMS groups to complete the synthesis of the right-hand segment **418**.



Conditions and reagents: (i) *n*-Bu_4NF, THF; (ii) DMP, PPTS, CH_2Cl_2; (iii) Me_2=$CHCH_2MgCl$, CuI, THF, –15°C to 0°C; (iv) PPTS, EtOH, (v) MsCl, pyridine; (vi) K_2CO_3, MeOH; (vii) $MeSO_2Ph$, *n*-BuLi, DMPU, THF, –78°C to 0°C; (viii) MPMCl, NaH, TDMF; (ix) TMSCl, imidazole, DMF.

Scheme 4.10: Synthesis of the right-hand segment **418**.

Coupling of the lithio-anion of THF **416** and THF **418** afforded the corresponding *bis*-THF in good yield. After reductive desulfonylation and deprotection of the TMS groups, ketone **419** was obtained in good yield. Reduction of the ketone **419** with $LiAlH_4$ or DIBAL led to the corresponding epimeric alcohols as a 1:1 mixture. The mixture was acetylated and separated to provide pure **420**. Deprotection of the MPM groups with DDQ and acetylation of the resulting alcohol afforded eurylene (**393**) in moderate yield (scheme 4.11).

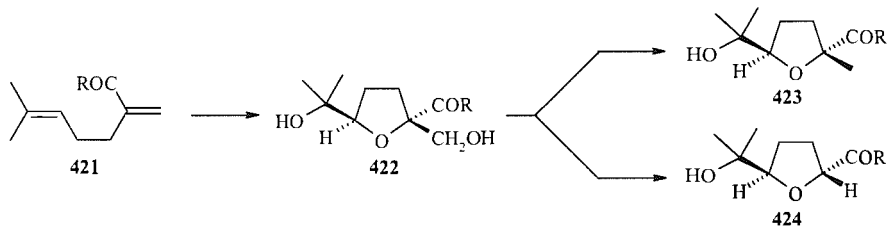


Conditions and reagents: (i) LiHMDS, DMPU, THF, –78°C to –30°C; (ii) SmI_2, THF-MeOH (5:1), –78°C; (iii) HCl (1M, aq. sol.), MeO; (iv) $NaBH_4$, MeOH; (v) Ac_2O, pyridine, 50°C; (vi) DDQ, CH_2Cl_2/$NaHCO_3$ (10:1).

Scheme 4.11: Synthesis of eurylene (**393**).

4-II Strategy for the synthesis of 2,5-*trans*-disubstituted THFs

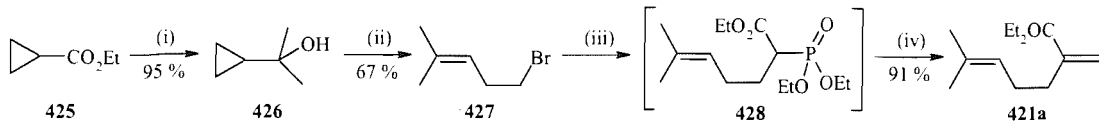
The different strategies described for the synthesis of intricatetraol could not be applied to eurylene because it is unsymmetrical and possesses a *trans*-THF fragment (figure 4.1). The direct oxidative cyclisation of 1,5-dienes with potassium permanganate could only afford *cis*-THF fragments. Therefore, the development of a strategy using potassium permanganate to synthesize *trans*-THFs would provide a useful extension of our methodology. We imagined that *trans*-THFs **423** could be prepared from *cis*-THF diols **422** by means of a selective deoxygenation reaction (scheme 4.12). *cis*-THFs **422** could also lead to *trans*-THFs **424** *via* a sequential selective oxidation to the corresponding aldehyde and decarbonylation. The requisite *cis*-THF diols should be obtained by permanganate promoted oxidative cyclisation of appropriate 1,5-dienes **421** bearing a terminal double bond.



Scheme 4.12: Synthesis of *trans*-THFs *via* oxidative cyclisation with $KMnO_4$.

4-II-1 Synthesis of the precursor 2,5-*cis*-disubstituted THFs

Ethyl cyclopropanecarboxylate **425** was treated with 2 eq. of MeMgI to afford the alcohol **426** in good yield (scheme 4.13). Tertiary alcohol **426** was then opened by treatment with $MgBr_2$ prepared *in situ* from Mg turnings and 1,2-dibromoethane to afford bromide **427** in moderate yield. According to the method of Vasil'ev *et al.*,[154] a Horner-Wittig reagent **428** was synthesised from **427** *via* a nucleophilic substitution on the triethyl phosphonoacetate anion formed *in situ*; reagent **428** was used in a Horner-Wittig-Emmons type reaction with formaldehyde to afford the desired diene **421** in good yield.

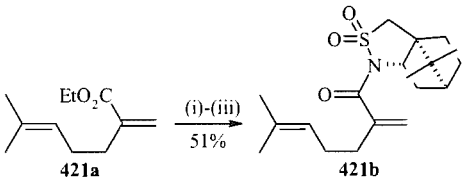


425 426 427 428 421a

Conditions and reagents: (i) MeMgI, Et_2O, r.t. to reflux, 1h; (ii) $MgBr_2$, Et_2O, reflux, 3h; (iii) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMSO, 6h, 60°C; (iv) CH_2O, K_2CO_3, 6h, r.t. to 50°C.

Scheme 4.13: Synthesis of the diene precursor **421a**.

The (2*S*)-Oppolzer sultam was attached to diene **421a** using the ester hydrolysis, activation sequence described previously (scheme 2.6). Basic hydrolysis of diene **421a** and activation of the resulting carboxylic acids with pentafluorophenol in presence of DCC produced the corresponding pentafluorophenyl diene, which underwent substitution with lithiated (2*S*)-10,2-camphorsultam to afford the corresponding diene **421b** in satisfactory yields (scheme 4.14).

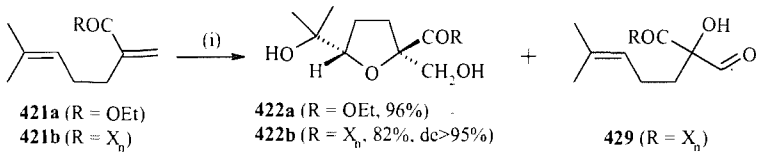


421a 421b

Conditions and reagents: (i) NaOH, $NaHCO_3$, water, MeOH, reflux, 16h; (ii) pentafluorophenol, DCC, EtOAc, 25°C, 24h; (iii) *n*-BuLi, (2*S*)-10,2-camphorsultam, THF, –78°C to 25°C, 18h.

Scheme 4.14: Synthesis of diene **421b** bearing the sultam.

The oxidative cyclisation was carried out on diene **421a** using the optimised conditions developed previously to afford the desired 2,5-*cis*-disubstituted THF **422a** in excellent yield (scheme 4.15). It is interesting to note that the reaction product does not require purification; only the desired product was seen by NMR. When the reaction was attempted on diene **421b**, the desired THF **422b** was obtained in good yield and diastereoselectivity (*de*>95% by ^1H NMR), the hydroxy aldehyde **429** was obtained as the only significant by-product. This by-product was not observed during the oxidation of diene **421a**. It is thought that the presence of the sultam may slow down the reaction by hindering the attack on the second double bond.



421a (R = OEt)
421b (R = X_n)

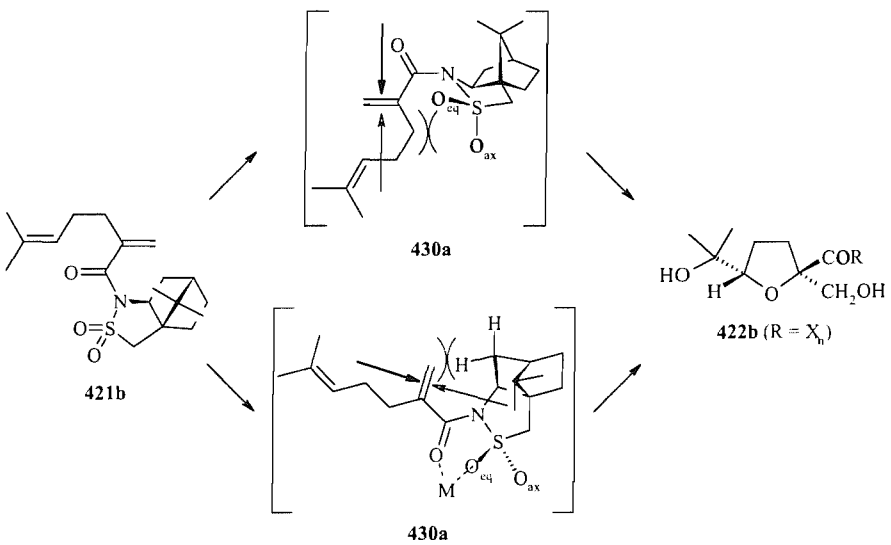
422a (R = OEt, 96%)
422b (R = X_n, 82%, dc>95%)

429 (R = X_n)

Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer pH 6.24, acetone, –30°C to 0°C, 1h.

Scheme 4.15: Permanganate promoted oxidative cyclisation of dienes **421a,b**.

The selectivity obtained with the Oppolzer's camphor sultam could be explained by two different conformation models (scheme 4.16). In conformation **430a,** if the potassium coordinates with the equatorial oxygen atom, the lower side of the double bond is blocked by the camphor structure and the attack has to take place on the upper side. On the other hand, in reactive conformation **430b**, if no chelation occurs, the anti-position of the carbonyl and the NSO_2 moiety is favoured because of steric and stereoelectronic reasons. Even if the camphor structure is too far to shield the double bond effectively, the axial oxygen atom blocked the lower side and the attack takes place on the upper side. Both of these models lead to the same stereoselectivity and rationalises the high diastereoselectivity obtained during the oxidative cyclisation on diene **421b**.



Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer pH 6.24, acetone, –30°C to 0°C, 1h.

Scheme 4.16: Proposal to rationalise the diastereoselectivity obtained with the sultam.

THF **422b** was successfully recrystallized for a mixture $EtOAc/CH_2Cl_2$ to afford **422b** as small transparent prisms suitable for X-ray structural determination, thus permitting the confirmation of the predicted stereochemistry (figure 4.2).

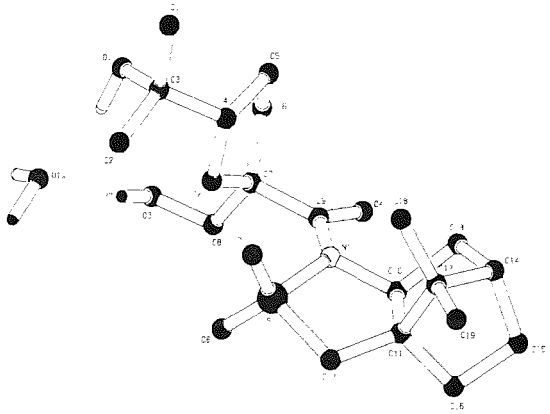
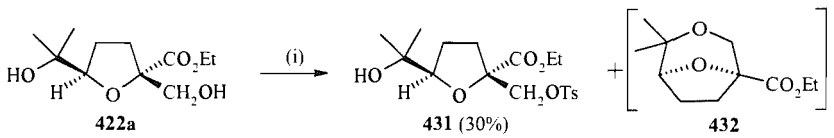


Figure 4.2: X-Ray structure of THF **422b**.

4-II-2 Reductive deoxygenation of the primary alcohol

Reductive deoxygenation is commonly realised by conversion of the free primary alcohol to the corresponding tosylate, followed by *in situ* iodide exchange and radical reduction.[155] The THF **422a** was treated with TsCl, DMAP and triethylamine in CH_2Cl_2; only the desired compound **431** was visible in the crude NMR albeit in poor yield (scheme 4.17).

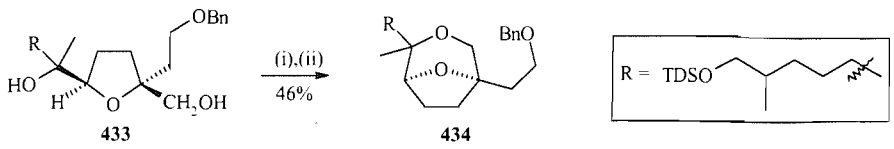


422a **431** (30%) **432**

Conditions and reagents: (i) TsCl, DMAP, Et_3N, CH_2Cl_2.

Scheme 4.17: Attempted synthesis of tosylate **431**.

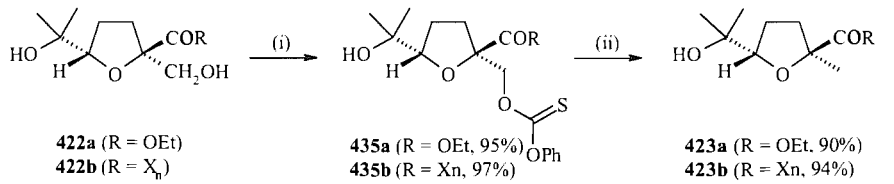
It is believed that the tertiary alcohol present on the molecule underwent an intramolecular nucleophilic substitution with the newly formed tosylate to afford product **432**, which was lost due to its volatility. The synthesis of this type of bicyclic compound from THF diols has previously been reported by Walba *et al.* (Scheme 4.18).[156] In their synthesis, activation of the tertiary alcohol **433** *via* preparation of the corresponding sodiated anion was needed to obtain the intramolecular nucleophilic substitution. It seemed that the tertiary alcohol present on THF **422a** was reactive enough to attack the tosylate group without prior activation.



Conditions and reagents: (i) TsCl, py, r.t., 10h; (ii) NaH/DMF, r.t., 13h.

Scheme 4.18: Synthesis of 3,8-Dioxabicyclo[3.2.1]octane precursor **434** by Walba.

It was thought that xanthate chemistry could provide a solution to this issue; indeed xanthate moieties are not such good leaving groups as tosylates. Zard *et al.* have reported that xanthate chemistry is quite versatile and can be used with many different functional groups present on the molecule.[157-160] THFs **422a,b** were treated with chlorothioformate, pyridine and catalytic DMAP to afford the desired xanthates **435a,b** in excellent yield (scheme 4.19).[161] Xanthate **435a,b** underwent a radical reaction with Bu_3SnH and catalytic AIBN to produce the 2,5-*trans*-disubstituted THF **423a,b** in excellent yield.[162]



Conditions and reagents: (i) PhOC(S)Cl, pyridine, DMAP, CH_2Cl_2, r.t., 2h; (ii) Bu_3SnH, AIBN, toluene, reflux, 5h.

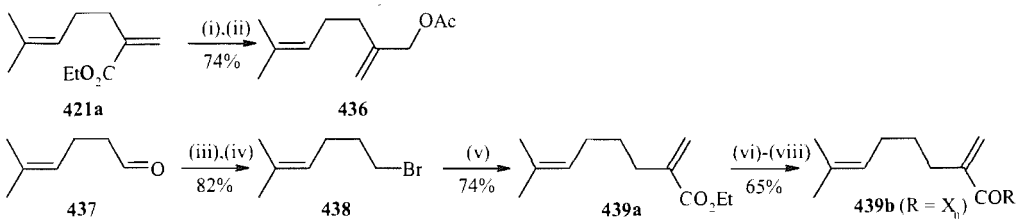
Scheme 4.19: Synthesis of 2,5-*trans*-disubstituted THF **423a,b**.

2,5-*Trans*-disubstituted THF **423a** was obtained in 6 steps from commercially available ethyl cyclopropanecarboxylate **425** in an overall yield of 43% and THF **423b** was obtained in 10 steps from commercially available ethyl cyclopropanecarboxylate **425** in an overall yield of 22%.

4-II-3 Attempted synthesis of *trans*-THF 445 and *trans*-THP 446

The application of the above methodology was investigated using other dienes. Diene **436** was prepared easily from diene **421a** by reduction with DIBAL and subsequent acetylation of the primary alcohol with acetic anhydride (scheme 4.20). Reduction of aldehyde **437** to the alcohol with $NaBH_4$ and subsequent treatment with CBr_4 gave the corresponding bromide **438** in good yield. The phosphonate derived from bromide **438** underwent a Horner-Wittig-Emmons type reaction with formaldehyde to afford the desired diene **439a** in good yield.

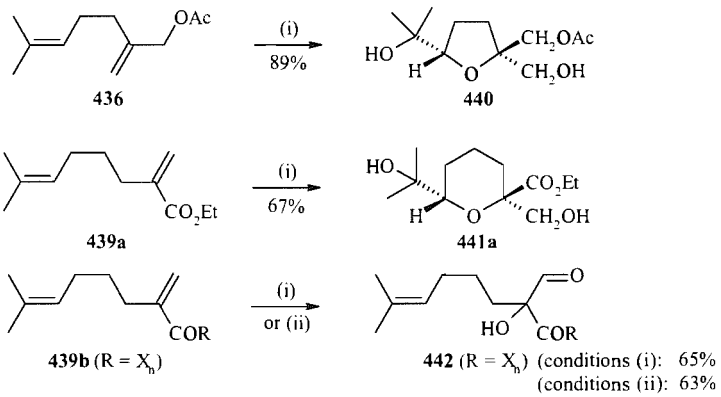
Diene **439a** was converted to diene **439b** bearing the (2*S*)-camphorsultam by the method described previously.



Conditions and reagents: (i) DIBALH,CH_2Cl_2, –30°C, 3h; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 2h; (iii) NaBH4, H2O, r.t., 1h; (iv) CBr_4, PPh_3, CH_2Cl_2, r.t., 3h; (v) (a) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMSO, 60°C, 6h; (b) CH_2O, K_2CO_3, r.t. to 50°C, 6h; (vi) NaOH, $NaHCO_3$, water, MeOH, reflux, 16h; (vii) pentafluorophenol, DCC, EtOAc, 25°C, 24h; (viii) *n*-BuLi, (2*S*)-10,2-camphorsultam, THF, –78°C to 25°C, 18h.

Scheme 4.20: Synthesis of dienes **436** and **439a,b**.

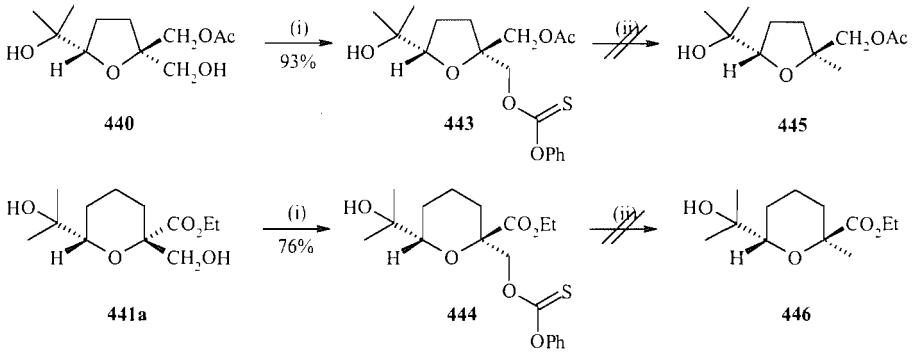
Oxidative cyclisation of dienes **436** and **439a** afforded the corresponding THF **440** and THP **441a** in good yield (scheme 4.21). Unfortunately, treatment of diene **439b** with permanganate failed to give the desired THP **441b** and led to the formation of the hydroxy aldehyde **442**.



Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer pH 6.24, acetone, –30°C to 0°C, 1h; (ii) $KMnO_4$ (powered, 2 eq.), AcOH/acetone (2:3), –30°C to 0°C, 1h to 2h.

Scheme 4.21: Oxidative cyclisation of dienes **436** and **439a,b**.

THF **440** and THP **441a** were converted to the corresponding xanthates **443** and **444** in good yield (scheme 4.22). Attempts of deoxygenation using the method described previously did not lead to the desired *trans* products **445** and **446**, instead the reaction afforded the free alcohol products **440** and **441a**. It is thought that the Bu_3SnH used to carry out the reaction contained water or Bu_3SnOH which caused the cleavage of the xanthate group.

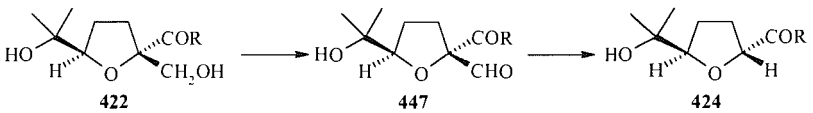


Conditions and reagents: (i) PhOC(S)Cl, pyridine, DMAP, CH_2Cl_2, r.t., 2h; (ii) Bu_3SnH, AIBN, toluene, reflux, 5h or 1 day.

Scheme 4.22: Attempted synthesis of *trans*-THF **445** and *trans*-THP **446**.

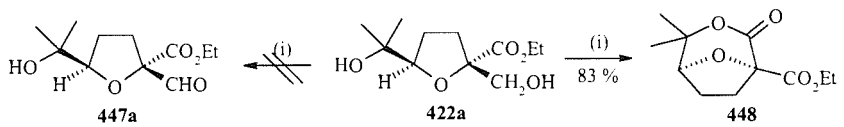
4-II-4 Attempted reductive removal of the hydroxymethyl group

It was also decided to extend this methodology to the synthesis of *trans*-THFs bearing two hydrogens at the 2 and 5 positions of the *cis*-THF diols **422** (scheme 4.23). This strategy involved replacing the hydroxymethyl group with a hydrogen, by selective oxidation of the primary alcohol to an aldehyde followed by stereospecific decarbonylation.



Scheme 4.23: Strategic approach to the synthesis of *trans*-THF **424**.

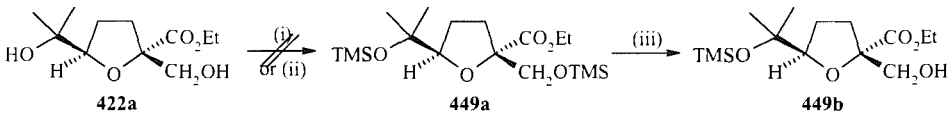
When THF **422a** was treated with a catalytic amount of TPAP and NMO in CH_2Cl_2, the bicyclic product **448** was obtained in good yield instead of the desired aldehyde **447a** (scheme 4.24). It is thought that the tertiary alcohol present is reactive enough to cyclise onto the newly formed aldehyde. The same type of side-reaction was encountered when it was attempted to convert THF **422a** to the corresponding tosylate **431** (scheme 4.17).



Conditions and reagents: (i) TPAP, molecular sieves 4Å, MNO, CH_2Cl_2, r.t., 1h.

Scheme 4.24: Attempted synthesis of aldehyde **447a**.

Two approaches were attempted to solve this problem. The first approach involved the protection of the tertiary alcohol in compound **422a** to prevent any formation of side-product. It was decided to protect both of the alcohols with a trimethylsilyl group that could be easily removed from the primary alcohol under mild basic conditions. THF **422a** was treated with TMSCl with triethylamine in dichloromethane; unfortunately the reaction did not go to completion and starting material was recovered (scheme 4.25).[163] When THF **422a** was treated with TMSOTf in presence of 2,6-lutidine, degradation occured.[164]

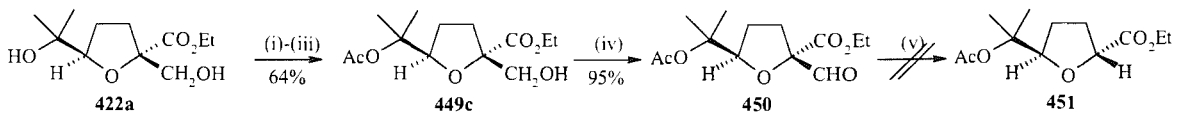


422a **449a** **449b**

Conditions and reagents: (i) TMSCl, Et_3N, CH_2Cl_2, r.t., 48h; (ii) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to r.t.,12h.

Scheme 4.25: Attempted protection of the tertiary alcohol group present in THF **422a**.

The second strategy involved the sequential protection of the primary alcohol, then the tertiary alcohol, followed by the selective deprotection of the primary alcohol. THF **422a** was treated with TBDMSCl and an excess of imidazole to afford the mono-protected THF,[165] that was subsequently treated with Ac_2O, Et_3N and a catalytic amount of DMAP to give the *bis*-protected THF. THF **449c** was obtained in good yield by treatment of *bis*-protected THF with HCl.[166] Oxidation of the primary alcohol of THF **449c** with TPAP in presence of NMO afforded aldehyde **450** in good yield (scheme 4.26). Different methods were attempted to carry out the selective decarbonylation. Treatment with Wilkinson's catalyst under different conditions was attempted. Unfortunately, the desired *trans*-THF **451** was not obtained and only degradation was observed.[167]



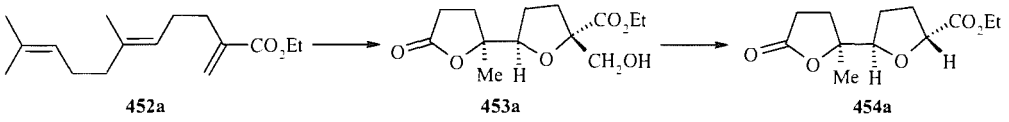
422a **449c** **450** **451**

Conditions and reagents: (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0°C to r.t., 3 days; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 24h; (iii) HCl, water/CH_2Cl_2, r.t., 24h; (iv) TPAP, NMO, crushed molecular sieves, r.t., 1h; (v) Wilkinson's catalyst, toluene, r.t., 3 days or Wilkinson's catalyst, toluene, reflux, 24h or Wilkinson's catalyst, xylene, 24h, r.t. to reflux.

Scheme 4.26: Attempted synthesis of 2,5-*trans*-disubstituted THF **451**.

As an alternative to the protection of the tertiary alcohol, it was chosen to investigate the oxidative cyclisation of the triene **452a**, which would afford THF lactone **453a** with a masked

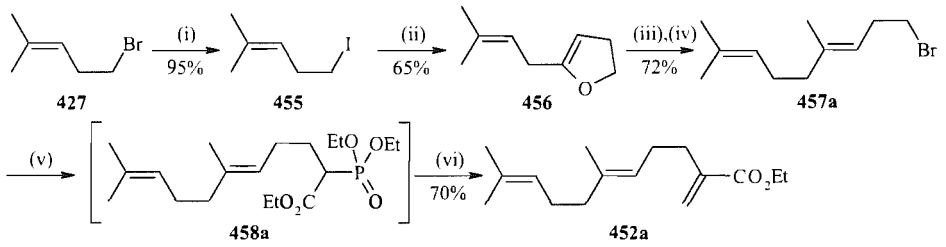
tertiary alcohol (scheme 4.27). *cis*-THF lactone **453a** could then be converted to the *trans*-THF lactone **454a**.



452a **453a** **454a**

Scheme 4.27: Alternative strategy involving THF-lactones.

Treatment of bromide **427** with sodium iodide gave iodide **455** in good yield (scheme 4.28).[168] Alkene **455** was treated with 2,3-dihydrofuran and *n*-BuLi to afford the desired dihydrofuran **456** in moderate yield.[169] After conversion of dihydrofuran **456** into homogeraniol using MeMgBr and a catalytic amount of *bis*(triphenylphosphine)nickel dichloride, subsequent treatment with CBr_4 and triphenylphosphine afforded the corresponding homogeranyl bromide **457a** in good yield. Horner-Wittig reagent **458a** was synthesised from **457a** *via* a nucleophilic substitution on the triethyl phosphonoacetate anion formed *in situ*; this reagent was used in a Horner-Wittig-Emmons type reaction with formaldehyde to afford the desired diene **452a** in good yield.

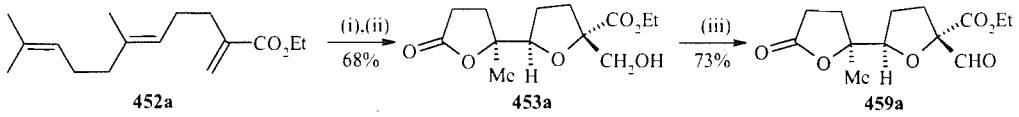


427 **455** **456** **457a** **458a** **452a**

Conditions and reagents: (i) NaI, acetone, r.t., 1 day; (ii) 2,3-dihydrofuran, *n*-BuLi, THF, –50 °C to r.t., 18h; (iii) MeMgBr, $((PPh_3)_2)NiCl_2$, toluene, reflux, 1h; (iv) CBr_4, PPh_3, CH_2Cl_2, 3h; (v) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMSO, 60°C, 6h; (vi) CH_2O, K_2CO_3, r.t. to 50°C, 6h.

Scheme 4.28: Synthesis of triene **452a**.

Triene **452a** was oxidised and subsequently cleaved with $NaIO_4$ on SiO_2 to afford lactone **453a** in good yield (scheme 4.29). Lactone **453a** was treated with catalytic TPAP with NMO in CH_2Cl_2 to afford the aldehyde **459a**. Decarbonylation using Wilkinson's catalyst was attempted but only degradation was observed.



452a 453a 459a

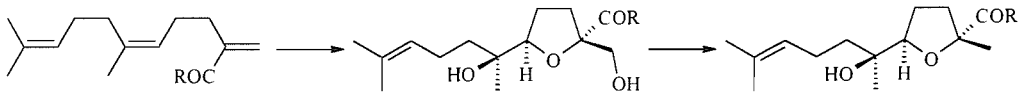
Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer pH 6.24, acetone, –30°C to 0°C, 1h; (ii) $NaIO_4$ (on SiO_2), CH_2Cl_2, r.t., 1h; (iii) TPAP, NMO, crushed molecular sieves, r.t., 1h.

Scheme 4.29: Toward the synthesis of 2,5-*trans*-disubstituted-THF-lactone.

It was therefore decided to abandon our efforts toward the synthesis of *trans*-THFs **424** and focus on the application of the synthesis of *trans*-THFs **423** toward the synthesis of eurylene (**393**).

4-III Toward the synthesis of eurylene

It was decided to develop the synthesis of the two fragments **416** and **387b** already synthesized by Hioki *et al.* using oxidative cyclisation with potassium permanganate and therefore achieve the formal synthesis of eurylene (**393**) (scheme 4.7 and 4.9). After permanganate promoted selective oxidative cyclisation of triene **452**, *trans*-THF **416** should be prepared from *cis*-THF **460** *via* the strategy developed to synthesize *trans*-THFs **423** (scheme 4.30).

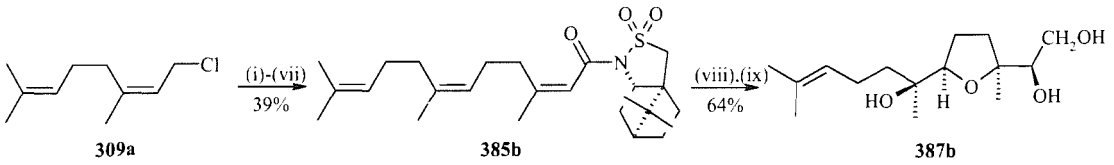


452 460 416

Scheme 4.30: Synthesis of a *trans*-THF adduct **416**.

4-III-1 Synthesis of fragment 387b

Triol **387b** was synthesised previously as part of our efforts toward the synthesis of intricatetraol (scheme 3.35) . This synthesis was repeated from commercially available nerol in 10 steps with a good overall yield (Scheme 4.31).



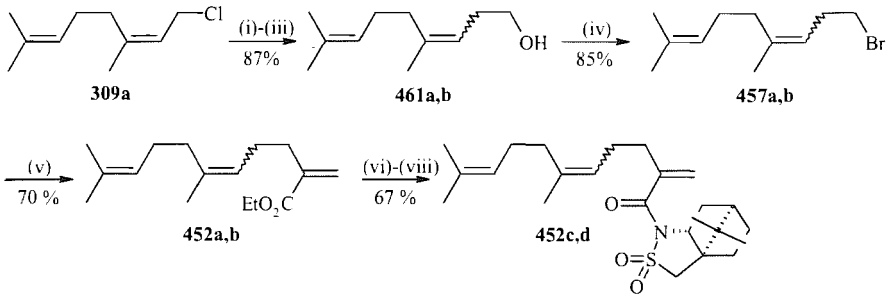
309a 385b 387b

Conditions and reagents: (i) MsCL, LiCl, THF, 25°C, 2h; (ii) ethyl acetoacetate, NaH, then *n*-BuLi, THF, 0°C to 25°C, 30 min; (iii) Et_3N, DMPU, DMAP, $PO(OEt)_2Cl$, –20°C to 25°C, 12h; (iv) MeCu, MeMgCl, THF, –30°C, 4h; (v) NaOH, $NaHCO_3$, water, MeOH, reflux, 16h; (vi) pentafluorophenol, DCC, EtOAc, 25°C, 24h; (vii) *n*-BuLi, (2*S*)-10,2-camphorsultam, THF, –78°C to 25°C, 18h; (viii) $KMnO_4$ (1.7 eq. of a 0.4 M aq. solution), AcOH (2.8 eq.), buffer (0.5 mL), acetone, –30°C to 0°C, 2h; (ix) $LiAlH_4$, THF, –78°C to r.t., 24h.

Scheme 4.31: Synthesis of right-half segment **387b** of eurylene (**393**).

4-III-2 Toward the synthesis of fragment 416

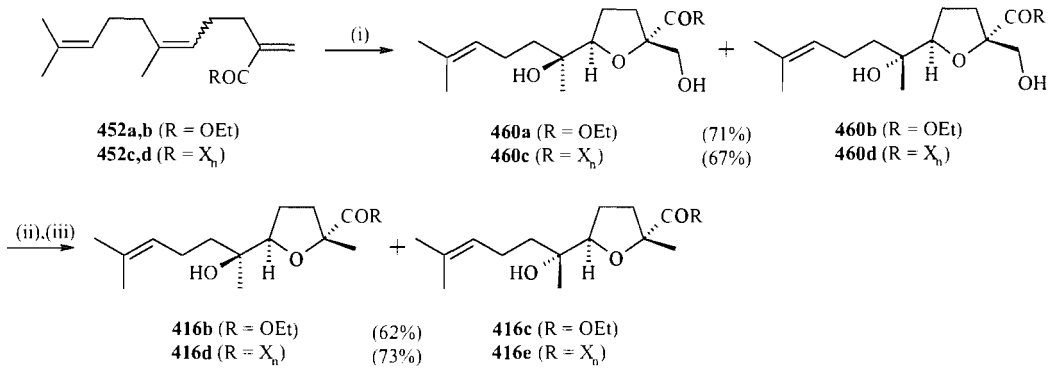
Neryl chloride **309a** was treated with NaCN in DMF to afford the corresponding cyanide which was converted into the carboxylic acid *via* a basic hydrolysis. After reduction of the carboxylic acid with $LiAlH_4$ alcohol **461** was obtained in overall good yield (scheme 4.32). Unfortunately, carbon NMR analysis revealed that isomerisation had occurred and that the product was a 2:1 mixture of homonerol **461b** and homogeraniol **461a**. Isomerisation happened during the preparation of the carboxylic acid. Conversion of the cyanide to the corresponding aldehyde was attempted but was unfortunately unsuccessful. Due to time constraints, it was not possible to find a new route for the effective preparation of pure homonerol **461a**. It was therefore decided to carry on with the synthesis using the mixture to test subsequent routes. Alcohols **461a,b** were treated with PPh_3 and CBr_4 to afford the corresponding bromides **457a,b**. As seen previously, phosphonates were prepared *in situ* with bromides **457a,b** and sodiated triethyl phosphonoacetate prior to a Horner-Wittig-Emmons reaction with formaldehyde to afford the desired trienes **452a,b** in good yield. Trienes **452a,b** were converted to the corresponding trienes **452c,d** bearing the (2*R*)-camphorsultam by the method described previously.



Conditions and reagents: (i) MeMgI, Et_2O, r.t. to reflux, 1h; (ii) MgI_2, Et_2O, reflux, 3h; (iii) 2,3-dihydrofuran, *n*-BuLi, THF, –50°C to r.t., 18h; (iv) MeMgBr, $((PPh_3)_2)NiCl_2$, toluene, reflux, 1h; (v) CBr_4, PPh_3, CH_2Cl_2, r.t., 3h; (vi) (a) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMSO, 60°C, 6h; (b) CH_2O, K_2CO_3, r.t. to 50°C, 6h.

Scheme 4.32: Synthesis of the trienes **452a-d**.

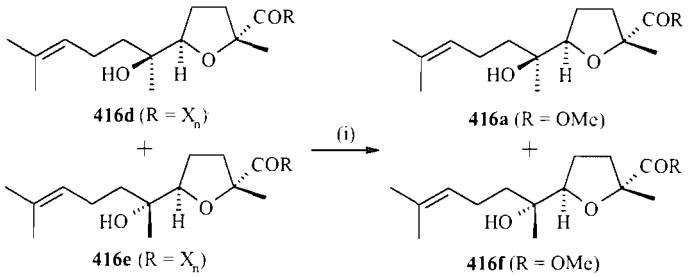
Trienes **452a-d** underwent selective oxidative cyclisation and the corresponding mono-THFs **460a-d** were obtained in good yield (scheme 4.33). The primary alcohols **460a-d** were treated with chlorothioformate, pyridine and catalytic DMAP to afford the desired mono-THFs **461a-d** in good yield. Mono-THFs **461a-d** were converted to the corresponding 2,5-*trans*-THFs **416b-e** by radical reaction with tributyltin hydride and AIBN in good yields.



Conditions and reagents: (i) $KMnO_4$ (2 eq. of a 0.4 M aq. sol.), AcOH (2.8 eq.), buffer pH 6.24, acetone, –30°C to 0°C, 1h; (ii) PhOC(S)Cl, pyridine, DMAP, CH_2Cl_2, r.t., 2h; (iii) Bu_3SnH, AIBN, toluene, reflux, 5h.

Scheme 4.33: Synthesis of *trans*-THFs **416b-e**.

The synthesis was concluded by a transesterification of the sultam moiety to a methyl ester by treatment of *trans*-THFs **416d,e** with catalytic potassium carbonate in methanol, although the crude NMR and mass spectrometry confirmed the formation of THF **416a** and by-product **416f**, no product was retrieved after purification on silica gel (scheme 4.34). Insufficient time was available to repeat this reaction.



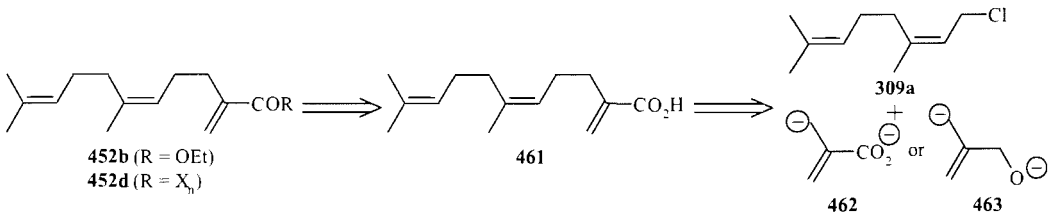
Conditions and reagents: (i) K_2CO_3, MeOH, 1 day.

Scheme 4.34: Synthesis of fragments **416a,f**.

4-III Conclusion and further work

A novel permanganate mediated route to *trans*-THFs has been accomplished in good overall yields ans showed great potential. The method was applied toward the synthesis of a fragment of eurylene (**393**) and a formal synthesis of eurylene was achieved by the formation of THFs **416a** and **387b** in good yield and selectivity.

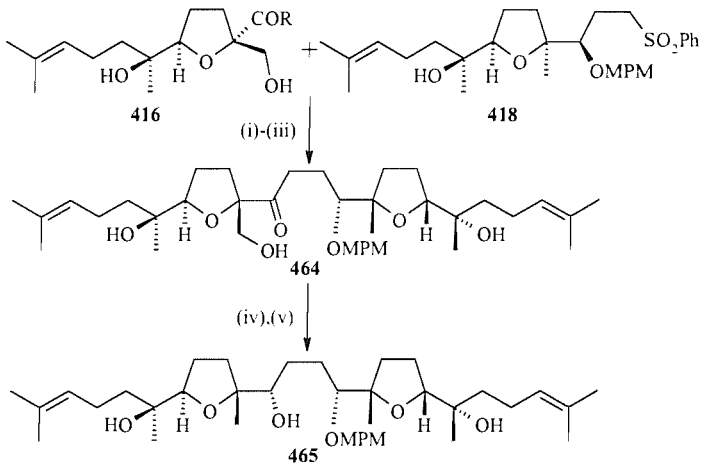
The preparation of isomerically pure homoneryl bromide **457b** proved to be difficult; it would therefore be interesting to investigate the synthesis of triene **452** *via* a route that does not involve homoneryl bromide **457b**. It was shown previously that the reaction of neryl and geranyl chlorides **309a,b** with the dianion of ethyl acetoacetate afforded the corresponding β-keto esters **317a,b** (scheme 2.13). Triene **452** could be prepared along similar lines, using the dianion of methacrylic acid **462** or of methallyl alcohol **463** (scheme 4.35). The acid **461** resulting from the nucleophilic substitution should be easily converted to the corresponding ester **452b** or to triene **452d** bearing the Oppolzer sultam.



Scheme 4.35: Alternative retrosynthesis to trienes **452b,d**

In the total synthesis reported by Hioki *et al.*, the lack of selectivity observed for the reduction of the ketone **419** was a major drawback (scheme 4.11).[144] To improve this step, it is proposed couple segments **416** and **418** and reduce the ketone moiety before the cleavage of the

hydroxymethyl group present in *bis*-THF **464** (scheme 4.36). The presence of the free alcohol may serve to direct the reduction of the ketone to the desired alcohol.



Scheme 4.36: Toward the synthesis of eurylene (**393**).

Chapter 5: Concluding remarks

A short, efficient and stereoselective synthesis of perhydro-2,2-bifuranyl systems has been achieved from readily accessible trienes using permanganate mediated oxidative cyclisation in good yields. Excellent levels of asymmetric induction were obtained through the use of Oppolzer's sultam auxiliary. Unfortunately, efforts to convert THF-lactones to useful intermediates for further elaboration toward natural products synthesis have been unsuccessful.

Permanganate promoted oxidative cyclisations double bonds bearing an ester group and an α-methyl group were achieved in good yields. Unfortunately, the application of this method to the tandem oxidation of an all *cis*-tetraene was proven to be difficult and mainly led to degradation. However, selective oxidation of 1,5,9-trienes provided the corresponding mono-THFs in good yield and excellent diastereoselectivity. These mono-THFs should be useful intermediates for the synthesis of intricatetraol.

A series of *cis*-THF diols were converted to the corresponding *trans*-THF fragments in good yields and with high diastereoselectivities. This new methodology was applied to the synthesis of the left-hand side of eurylene. Selective permanganate mediated oxidative cyclisation followed by the conversion of the resulting *cis*-mono-THF to the desired *trans*-mono-THF proceeded smoothly and in good yield. Unfortunately, the presence of the minor isomer in the bromide precursor of the 1,5,9-triene afforded mixtures throughout the synthesis.

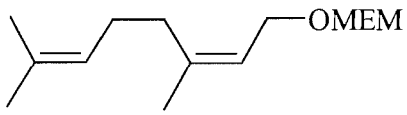
Chapter 6: Experimental

I General procedures

All chemicals were used as received from standard chemical suppliers unless otherwise stated. Triethylamine was distilled from calcium hydride and stored over sodium hydroxide. All non aqueous reactions were performed in oven or flame dried apparatus under argon atmosphere using distilled dry solvents.[170] Reactions were monitored by analytical TLC using aluminium plates precoated with silica gel 60 (Merk). Flash column chromatography was performed on silica gel with particle size 40-63 μm. NMR spectra were collected on Bruker AM300, AC300 or DPX400 spectrometers. Chemical shifts are given in ppm, ^{1}H NMR coupling constant J are given in Hz and rounded to the nearest 0.1 Hz. ^{1}H NMR spectra were recorded using residual isotopic solvent ($CHCl_3$, δ_H at 7.27 ppm) as internal reference. ^{13}C NMR spectra were recorded using $CDCl_3$ (δ_C at 77.0 ppm) as internal reference. IR spectra were recorded on Nicolet Impact 400 IRFT Spectrometer from diffuse reflectance. The following abbreviations have been used: s, strong; m, medium; w, weak; b, board. Nominal mass spectra were recorded on a Fisons VG single quadrupole mass spectrometer in electrospray ionisation mode or using a GC-MS method on a Thermoquest trace MS single Quadrupole mass spectrometer. The GC column used a RTX5 capillary column with helium carrier gas, the reagent gas being ammonia and the source temperature 200°C for the chemical ionisation mode used.. Melting points were uncorrected. IUPAC nomenclature is adopted throughout.

II Experimental procedures

(2*Z*)-1-[(2-Methoxyethoxy)methoxy]-3,7-dimethylocta-2,6-diene (343)

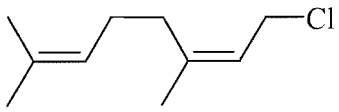


$C_{14}H_{26}O_3$.
M = 242.36 g.mol^{-1}.

According to the method Behnke *et al.*,[136] diisopropylethylamine (8.81 mL, 50.57 mmol) was added dropwise to a solution of nerol **51b** (5.00 g, 32.42 mmol) in CH_2Cl_2 (30 mL) and the mixture was cooled to 0°C. MEMCl (5.8 mL, 50.57 mmol) was then added dropwise and the resulting solution was allowed to warm up to room temperature over 3 hours. The reaction mixture was then diluted in CH_2Cl_2 (50 mL) and washed with an aqueous solution of HCl (1M, 2 x 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product **343** as a pale yellow oil (7.70 g, 31.77 mmol, 98%). The product was used in the next step without further purification.

IR (cm^{-1})	2964 (b), 2936 (b), 2884 (b), 1720 (s), 1451 (w), 1375 (w), 1105 (b) and 1049 (b)
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.36 (1H, td, *J* = 6.9 and 1.3 Hz, C**H**CH_2O), 5.09 (1H, m, C**H**$C(CH_3)_2$), 4.72 (2H, s, OCH_2O), 4.07 (2H, dd, *J* = 6.9 and 1.1 Hz, $CHCH_2O$), 3.73-3.69 (2H, m, OCH_2), 3.58-3.56 (2H, m, OCH_2), 3.40 (3H, s, OCH_3), 2.11-2.04 (4H, m, 2 x CH_2), 1.76 (3H, br q, *J* = 1.3 Hz, CH_3), 1.68 (3H, s, CH_3), 1.60 (3H, s, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	141.0 (CH=**C**CH_3), 131.9 (CH=**C**$(CH_3)_2$), 123.8 (C=**C**H), 121.1 (C=**C**H), 94.7 (OCH_2O), 71.8 (CH_2OCH_3), 66.6 (OCH_2CH_2), 63.6 ($CHCH_2O$), 58.9 (OCH_3), 32.1 (CH_2C), 26.7 (CH_2CH), 25.6 (CH_3), 23.4 (CH_3), 17.6 (CH_3).
LRMS (ES+ ionisation)	281.3 ($[M+K]^+$, 18%), 130.1 (100%).

Neryl chloride (309a)[171]

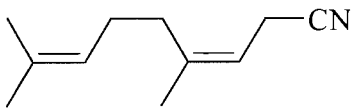


$C_{10}H_{17}Cl$.
M = 172.70 g.mol^{-1}.

To a solution of nerol (15.0 g, 0.097 mol) in 2,6-lutidine (13.4 mL, 0.115 mol) was added LiCl (94.24 g, 0.1 mol), in dry DMF (60 mL). The mixture was cooled to 0°C and MsCl (8.54 mL, 0.11 mol) was added dropwise to the solution. The resulting mixture was stirred for 2 hours, dissolved in Et_2O (100 mL), washed with water (5 x 25 mL), HCl (2M aq. sol., 3 x 15 mL), brine (30 mL) and $NaHCO_3$ (sat. aq. sol., 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product a pale yellow oil (16.0 g, 0.092 mol, 93%). The spectroscopic data were in agreement with the literature.[171] The crude product was used in the next step without further purification.

IR (cm^{-1})	2964 (b), 2916 (b), 2851 (b), 1659 (s), 1446 (s), 1380 s), 1244 (s), 1172 (s), 826 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.46 (1H, t, J = 7.8 Hz, CC**H**CH_2Cl), 5.11 (1H, br s, C**H**$C(CH_3)_2$), 4.08 (2H, d, J = 7.9 Hz, CH_2**CH_2**Cl), 2.13 (4H, m, 2 x CH_2), 1.78 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.62 (3H, s, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	142.7 (**C**CH_3), 132.4 (**C**$(CH_3)_2$), 123.4 (**C**HCH_2), 121.1 (**C**$HC(CH_3)_2$), 41.0 (**C**H_2Cl), 31.9 (CH_2**C**H_2C), 26.5 (**C**H_2CH), 25.7 (**C**H_3), 23.5 (2 x **C**H_3).
LRMS (ES+ ionisation)	196.2 ([M+Na]$^+$, 19%), 149.1 (100%).

(*Z*)-4,8-Dimethylnona-3,7-dienenitrile (466)[172]



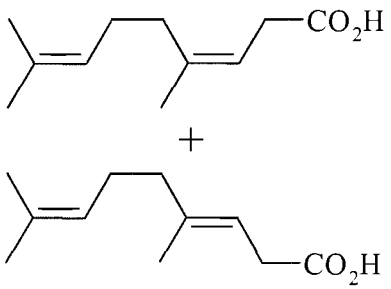
$C_{11}H_{17}N$.
M = 163.26 g.mol^{-1}.

According to the method of Mori *et al.*,[172] neryl chloride **309a** (9.54 g, 55.3 mmol), was added dropwise to a suspension of NaCN (9.50 g, 193.9 mmol), in dry DMF (120 mL) at 0°C. The resulting mixture was stirred at room temperature for 20 hours and then poured into ice-water and extracted with Et_2O (4 x 70 mL). The combined organic phases were washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude

product as an orange oil (15.0 g). After purification on silica gel (300 mL, Et_2O/hexane, 5:95) the title product **466** was obtained as a colourless oil (7.31 g, 44.8 mmol, 81%). The spectroscopic data were in agreement with the literature.[172]

IR (cm^{-1})	2969 (s), 2916 (s), 2859 (s), 2249 (m), 1738 (m), 1448 (s), 1378 (s), 1217 (m), 919 (m), 824 (m).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.17 (1H, t, J = 7.1 Hz, C**H**CH_2CN), 5.07 (1H, tdd, J = 7.1, 2.7 and 1.3Hz, $(CH_3)_2C$=C**H**), 3.04 (1H, dd, J =2.4 and 1.3 Hz, CH**H**CN), 3.02 (1H, dd, J = 2.4 and 1.3 Hz, CH**H**CN), 2.12-2.03 (4H, m, CH_2CH and CH_2C), 1.75 (3H, dd, J = 2.7 and 1.3 Hz, CH_3), 1.70 (3H, d, J = 1.3 Hz, CH_3), 1.62 (3H, d, J = 1.3 Hz, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	142.1 ((CH_3)C), 132.6 ($(CH_3)_2$C), 123.1 ((CH_3)C=CH), 118.5 (CN), 112.4 ($(CH_3)_2$C=CH), 31.9 ($CH_2C(CH_3)$), 25.8 (CH_2CH), 25.6 (CH_3), 23.1 (CH_3), 17.6 (CH_3), 16.1 (CH_2CN).

(*Z*)-4,8-Dimethylnona-3,7-dienoic acid (467b) and (*E*)-4,8-dimethylnona-3,7-dienoic acid (467a) [172]

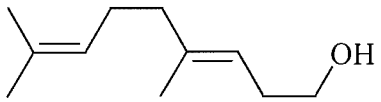


$C_{11}H_{18}O_2$.
M = 182.26 g.mol^{-1}.

According to the method of Mori *et al.*,[172] a solution of KOH (7.20 g, 126.0 mmol), in water (10 mL) was added to a solution of neryl cyanide **466** (6.20 g, 38.0 mmol) in MeOH (40 mL) and the mixture was stirred and heated at reflux for 20 h. The solvent was removed *in vacuo* and the residue was diluted in $NaHCO_3$ (sat. aq. sol., 30 mL) and extracted with Et_2O (3 x 40 mL). The aqueous layer was acidified with HCl (20 mL, 2N aq. solution) and extracted further with Et_2O (3 x 40 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil (6.65 g, 36.5 mmol, 96%), mixture of the title product **467b** and its *E* isomer **467a** (*Z*:*E* ≥3:1, by ^{1}H NMR). The mixture was used in the next step without further purification.

IR (cm^{-1})	2968 (w), 2918 (m), 2857 (w), 1708 (s), 1441 (w), 1377 (m), 1217 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	9.32 (1H, br s, COO**H**), 5.32 (1H, tdd, J = 7.2, 2.5 and 1.3 Hz, C**H**CH_2COOH), 5.09 (1H, m, (CH_3)C=C**H**), 3.08 (2H, d, J = 7.2 Hz, C**H**$_2$COOH), 2.07 (4H, m, 2 x C**H**$_2$), 1.68 (3H, s, C**H**$_3$), 1.64 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	178.3 (**C**OOH), 139.5 ((CH_3)**C**=CH), 132.0 ($(CH_3)_2$**C**), 131.6 ($(CH_3)_2$**C**), 123.8 ($(CH_3)_2$**C**=CH), 115.8 ((CH_3)C=**C**H), 115.1 ((CH_3)C=**C**H), 39.5 (**C**H_2CO), 32.1 (**C**H_2CH), 26.4 (**C**H_2C), 25.6 (**C**H_3), 23.3 (**C**H_3), 17.6 (**C**H_3).

Homogeraniol (461a)[169]



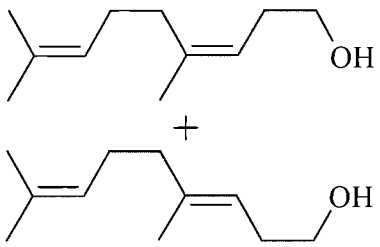
$C_{11}H_{20}O$.
M = 168.28 g.mol^{-1}.

According to the method of Kocieñski *et al.*,[169] to a stirred solution of *bis*(triphenylphosphine)nickel dichloride (145 mg, 0.22 mmol) in dry toluene (20 mL) was added MeMgBr (3 M in Et_2O, 4.4 mL). The resulting mixture was stirred for 30 minutes before the dropwise addition of a solution of 5-(4-Methyl-pent-3-enyl)-2,3-dihydro-furan **456** (700 mg, 4.401 mmol) in dry toluene (10 mL). The resulting solution was heated to reflux for 40 min, then poured in NH_4Cl (sat. aq. sol., 20 mL) with vigorous stirring, after cooling to room temperature. The mixture was stirred until decoloration and then extracted with ether (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude compound as a yellow oil. Purification on silica gel (50 g, EtOAc/hexane, 1:9) gave the title product **461a** as a colourless oil (460 mg, 2.72 mmol, 62%). The spectroscopic data were in agreement with the literature. [169]

IR (cm^{-1})	3328 (b), 2964 (s), 2926 (s), 2915 (s), 1735 (s), 1725 (m), 1436 (m), 1375 (s), 1214 (m), 1049 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.15-5.08 (2H, m, 2 x C**H**C), 3.64 (2H, q, J = 6.2 Hz, C**H**$_2$OH), 2.31 (2H, q, J = 6.7 Hz, C**H**$_2$), 2.10 (5H, m, 2 x C**H**$_2$ and O**H**),

	1.69 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.60 (3H, s, CH_3),
^{13}C-NMR	138.9 ($(CH_3)\mathbf{C}$=CH), 131.6 ($\mathbf{C}(CH_3)_2$), 124.1 ($\mathbf{C}$H=C(CH_3)),
(75MHz, $CDCl_3$, ppm)	119.9 ($\mathbf{C}$H=C(CH_3)$_2$), 62.4 ($\mathbf{C}H_2$OH), 39.8 ($\mathbf{C}H_2$C(CH_3)), 31.6 ($\mathbf{C}H_2CH_2$OH), 25.6 ($\mathbf{C}H_2CH_2$C(CH_3)), 25.6 ($\mathbf{C}H_3$), 22.6 ($\mathbf{C}H_3$), 17.6 ($\mathbf{C}H_3$).

Homonerol (461b) and homegeraniol (461a) [169]



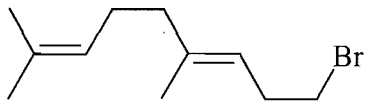
$C_{11}H_{20}O$.

M = 168.28 g.mol^{-1}.

According to the method of Scheideman *et al.*,[173] the mixture of acids **467a,b** (3.42 g, 18.76 mmol) in Et_2O (40 mL) was added dropwise to a suspension of $LiAlH_4$ (0.74 g, 18.76 mmol) in Et_2O (20 mL) at 0°C. The resulting solution was warmed to room temperature and stirred for 3 hours. Excess $LiAlH_4$ was quenched with NaOH (2M aq. sol., 5 mL). After filtering through celite, the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the mixture of alcohols **461a,b** (*Z*:*E* ≥3:1, by ^{1}H NMR) as a pale yellow oil (2.95 g, 17.53 mmol, 93%). The mixture was used in the next step without further purification.

IR (cm^{-1})	3354 (b), 2965 (s), 2617 (s), 1737 (w), 1672 (s), 1443 (s), 1376 (s), 1217 (w), 1047 (s).
^{1}H-NMR	5.09-5.07 (2H, m, 2 x C**H**C), 3.61 (2H, td, *J* = 6.6 and 1.1 Hz,
(400MHz, $CDCl_3$, ppm)	CH_2OH), 2.28 (2H, q, *J* = 6.6 Hz, CH_2), 2.06 (5H, m, 2 x CH_2 and O**H**), 1.65 (6H, s, 2 x CH_3), 1.60 (3H, s, CH_3).
^{13}C-NMR	138.8 ($(CH_3)\mathbf{C}$=CH), 131.8 ($\mathbf{C}(CH_3)_2$), 131.6 ($\mathbf{C}(CH_3)_2$), 124.0
(100MHz, $CDCl_3$, ppm)	($\mathbf{C}$H=C(CH_3)), 120.7 ($\mathbf{C}$H=C(CH_3)$_2$), 119.9 ($\mathbf{C}$H=C(CH_3)$_2$), 62.6 ($\mathbf{C}H_2$OH), 62.3 ($\mathbf{C}H_2$OH), 39.8 ($\mathbf{C}H_2$C(CH_3)), 32.0 ($\mathbf{C}H_2CH_2$OH), 31.5 ($\mathbf{C}H_2CH_2$OH), 26.5 ($\mathbf{C}H_2CH_2$C(CH_3)), 25.6 ($\mathbf{C}H_3$), 23.4 ($\mathbf{C}H_3$), 17.6 ($\mathbf{C}H_3$), 16.1 ($\mathbf{C}H_3$).

Homogeranyl bromide (457a) [174]

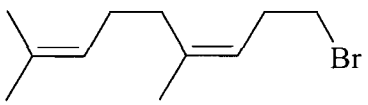


$C_{11}H_{19}Br$.
M = 231.18 g.mol^{-1}.

To a solution of homogeraniol **461a** (0.35 g, 2.08 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (1.80 g, 5.40 mmol) in one batch. The resulting solution was stirred for 15 min before the addition of PPH_3 (1.65 g, 5.40 mmol) in 4 portions. The resulting solution was stirred for 90 min. Water (40 mL) was then added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil and a white solid. Purification on silica gel (40 g, hexane/CH_2Cl_2, 1:3) afforded the title product **457a** as a colourless oil (0.35 mg, 1.50 mmol, 72%). The spectroscopic data were in agreement with the literature.[174]

IR (cm^{-1})	2966 (m), 2914 (m), 2855 (m), 1738 (m), 1443 (s), 1376 (s), 1267 (s), 1204 (m), 1105 (s), 1033 (s), 833 (m).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.15-5.10 (2H, m, 2 x C**H**C), 3.35 (2H, q, J = 7.3 Hz, C**H$_2$**Br), 2.59 (2H, q, J = 7.3 Hz, C**H$_2$**CH$_2$Br), 2.08 (4H, m, 2 x C**H$_2$**), 1.69 (3H, s, C**H$_3$**), 1.64 (3H, s, C**H$_3$**)., 1.61 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	138.6 (**C**CH$_3$), 131.6 (**C**(CH$_3$)$_2$), 124.0 (**C**HC(CH$_3$)$_2$), 120.8 (**C**H(CH$_2$)$_2$Br), 32.8 (**C**H$_2$C), 31.7 (**C**H$_2$Br), 31.5 (**C**H$_2$CH$_2$Br), 26.5 (**C**H$_2$CH$_2$), 26.5 (**C**H$_3$), 25.7 (**C**H$_3$), 17.7 (**C**H$_3$).
LRMS (GC-EIMS)	232 (([M]$^+$, 2%)

Homoneryl bromide (457b)

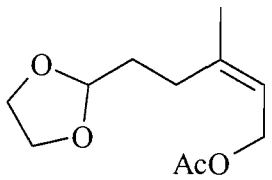


$C_{11}H_{19}Br$.
M = 231.18 g.mol^{-1}.

Following the procedure used for the synthesis of homogeranyl bromide **457a**, the mixture of alcohols **461a,b** (4.90 g , 29.11 mmol) was converted to the crude bromide. Purification on SiO_2 (300 mL, hexane/Et_2O, 98:2) gave the title product **457b** as a pale yellow oil (6.27 g, 27.12 mmol, 93%).

IR (cm^{-1})	2966 (m), 2914 (m), 2855 (m), 1739 (m), 1443 (s), 1376 (s), 1267 (s), 1205 (m), 1105 (s), 1033 (s), 984 (m), 833 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.16-5.13 (2H, m, 2 x C**H**C), 3.33 (2H, t, J = 7.3 Hz, C**H$_2$**Br), 2.57 (2H, q, J = 7.3 Hz, C**H$_2$**CH$_2$Br), 2.06 (4H, m, 2 x C**H$_2$**), 1.73 (3H, s, C**H$_3$**), 1.70 (3H, s, C**H$_3$**), 1.55 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	138.6 (**C**CH$_3$), 131.9 (**C**(CH$_3$)$_2$), 123.9 (**C**HC(CH$_3$)$_2$), 121.6 (**C**H(CH$_2$)$_2$Br), 32.9 (**C**H$_2$C), 32.1 (**C**H$_2$Br), 31.6 (**C**H$_2$CH$_2$Br), 26.4 (**C**H$_2$CH$_2$), 26.7 (**C**H$_3$), 23.3 (**C**H$_3$), 17.6 (**C**H$_3$).
LRMS (GC-EIMS)	232 (([M]$^+$, 5%)

(2*Z*)-5-(1,3-Dioxolan-2-yl)-3-methylpent-2-en-1-yl acetate (468) [22]



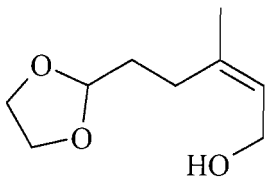
$C_{11}H_{18}O_4$.
M = 214.26 g.mol^{-1}.

According to the method of Kocieñski *et al.*,[22] a mixture of aldehyde **19b** (2.0 g, 11.75 mmol), ethane-1,2-diol (1.23 mL, 22.33 mmol), PTSA (30 mg) and toluene (80 mL) was refluxed for 6 hours with removal of water (~ 0.5 mL) using a Dean-Stark trap. The cooled mixture was washed with $NaHCO_3$ (sat. aq. sol., 30 mL) and the combined aqueous layers were extracted with Et_2O (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product **468** as a yellow oil (1.85 g, 8.63 mmol, 73%), which was used in the next step without further purification. The spectroscopic data were in agreement with the literature.[22]

IR (cm^{-1})	2969 (b), 2880 (b), 1739 (s), 1451 (w), 1384 (w), 1243 (s), 1134 (s), 1020 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.32 (1H, td, J = 7.0 and 1.0 Hz, C**H**CH$_2$O), 4.80 (1H, t, J = 4.8 Hz, OC**H**O), 4.55 (2H, d, J = 7.0 Hz, C**H$_2$**O), 4.00-3.87 (2H, m, OC**H$_2$**), 3.83-3.77 (2H, m, OC**H$_2$**), 2.18 (2H, dd, J = 11.0 and 8.0 Hz, C**H$_2$**), 2.01 (3H, s, C**H$_3$**), 1.72-1.65 (2H, m, C**H$_2$**), 1.72 (3H, d, J = 1.0 Hz, C**H$_3$**).
^{13}C-NMR	171.1 (**C**O), 141.8 (**C**CH$_3$), 119.6 (**C**HCCH$_3$), 103.8 (O**C**HO),

(75MHz, $CDCl_3$, ppm)	65.0 (OCH_2), 61.0 (CH_2O), 31.9 (CH_2), 26.3 (CH_2), 23.3 (CH_3), 21.3 (2 x CH_3).
LRMS (ES+ ionisation)	232.1 ($[M+NH_4]^+$, 32%), 153.1 (100%).

(2*Z*)-5-(1,3-Dioxolan-2-yl)-3-methylpent-2-en-1-ol (355) [22]



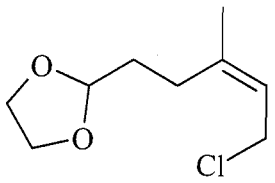
$C_9H_{16}O_3$.

M = 172.22 g.mol^{-1}.

According to the method of Kocieñski *et al.*,[22] crude acetate **468** (900 mg, 4.20 mmol) was dissolved in MeOH (30 mL) and K_2CO_3 (50 mg) was added in one portion. The resulting mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was dissolved in Et_2O (40 mL); the resulting suspension was washed with water (50 mL) and brine (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil (1.0 g), which was purified on silica gel (250 mL, EtOAc/hexane, 3:7) to afford the title product **355** as a colourless oil (670 mg, 3.89 mmol, 93%). Spectroscopic data were in agreement with the literature.

IR (cm^{-1})	3415 (br), 2969 (b), 2878 (b), 1670 (w), 1448 (s), 1408 (s), 1210 (s), 1138 (s), 1020 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.44 (1H, td, *J* = 7.0 and 1.0 Hz, $CHCH_2O$), 4.79 (1H, t, *J* = 4.8 Hz, OCHO), 4.03 (2H, d, *J* = 7.0 Hz, CH_2O), 4.02-3.87 (2H, m, OCH_2), 3.83-3.74 (2H, m, OCH_2), 2.35 (1H, s, OH), 2.18 (2H, t, *J* = 7.0 Hz, CH_2), 1.77-1.67 (2H, m, CH_2), 1.70 (3H, d, *J* = 1.0 Hz, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	138.8 (CCH_3), 125.1 ($CHCCH_3$), 103.9 (OCHO), 62.9 (OCH_2), 58.4 (CH_2O), 31.8 (CH_2), 26.1 (CH_2), 23.2 (2 x CH_3).

2-[(*Z*)-5-Chloro-3-methylpent-3-enyl]-1,3-dioxolane (353) [22]

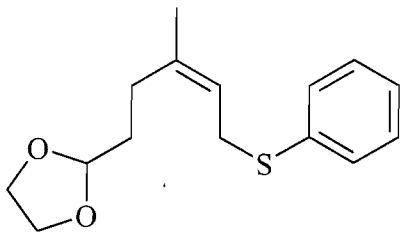


$C_9H_{15}ClO_2$.
M = 190.67 g.mol^{-1}.

Allylic alcohol **355** (200 mg, 1.16 mmol) was dissolved in DMF (20 mL) and cooled down to 0°C, before the addition of LiCl (150 mg, 3.48 mmol) and 2,6-lutidine (0.55 mL, 4.64 mmol) followed by the dropwise addition of MsCl (0.30 mL, 3.48 mmol). The reaction was stirred for 3.5 h during which time the temperature rose to 15°C. The mixture was diluted with Et_2O (20 mL) and washed with water (2 x 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (240 mg) which was purified on silica gel (75 mL, Et_2O/hexane, 1:9) to afford the title compound **353** as a colourless oil (180 mg, 0.94 mmol, 81%). Spectroscopic data were in agreement with the literature.[22]

IR (cm^{-1})	2974 (b), 2883 (b), 1734 (s), 1380 (w), 1223 (w), 1134 (s), 1034 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.46 (1H, td, *J* = 8.2 and 0.8 Hz, C**H**CH_2Cl), 4.85 (1H, t, *J* = 4.8 Hz, OC**H**O), 4.11 (2H, d, *J* = 8.2 Hz, C**H$_2$**Cl), 4.02-3.94 (2H, m, OC**H$_2$**), 3.91-3.85 (2H, m, OC**H$_2$**), 2.24 (2H, dd, *J* = 10.0 and 7.7 Hz, C**H$_2$**), 1.80-1.74 (2H, m, C**H$_2$**), 1.78 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	141.8 (**C**CH_3), 121.6 (**C**HCCH_3), 103.8 (**C**HO), 65.0 (**C**H_2), 40.8 (**C**H_2Cl), 31.9 (**C**H_2), 26.0 (**C**H_2), 23.3 (2 x **C**H_3).
LRMS (ES+ ionisation)	228.2 ([M+K]$^+$, 100%).

2-(3-Methyl-(*Z*)-5-phenylsulfanyl-pent-3-enyl)-[1,3]-dioxolane (354) [138]



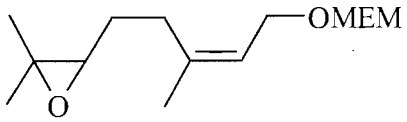
$C_{15}H_{20}O_2S$.
M = 264.39 g.mol^{-1}.

According to the method of Hioki *et al.*,[138] diphenyl sulphide (1.28 g, 5.81 mmol) was added in one portion to an ice-cold solution of allylic alcohol **355** (200 mg, 1.16 mmol) in pyridine (20 mL) and the resulting solution was stirred for 5 minutes. Tributyl phosphine (1.2 mL, 4.65

mmol) was added dropwise and the resulting mixture was warmed to room temperature and stirred for 2 h. Water (35 mL) was then added and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (3.0 g), which was purified on silica gel (50 mL, hexane, then EtOAc/hexane, 1:9) to afford the title compound **354** as a colourless oil (213 mg, 0.81 mmol, 69%). Spectroscopic data were in agreement with the literature.[138]

IR (cm^{-1})	2959 (b), 2922 (b), 2879 (b), 1734 (s), 1446 (w), 1370 (w), 1238 (s), 11438 (w), 1025 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	7.35-7.32 (2H, m, C**H**=C), 7.28-7.24 (2H, m, C**H**=CH), 7.16 (1H, tt, J = 7.2 and 1.3 Hz, C**H**), 5.33 (1H, tt, J = 7.7 and 0.5 Hz, C**H**CH_2S), 4.82 (1H, t, J = 4.7 Hz, OC**H**O), 3.99-3.91 (2H, m, O**C**H_2), 3.88-3.80 (2H, m, O**C**H_2), 3.57 (2H, dd, J = 7.7 and 1.0 Hz, **C**H_2S), 2.14 (2H, dd, J = 10.2 and 7.7 Hz, **C**H_2), 1.72-1.64 (2H, m, **C**H_2), 1.72 (3H, d, J = 1.3 Hz, **C**H_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	139.0 (**C**CH_3), 136.8 (**C**S), 129.6 (2 x **C**H, arom), 128.9 (2 x **C**H arom), 125.9 (**C**H, arom), 120.4 (**C**H**C**CH_3), 104.0 (O**C**HO), 64.9 (O**C**H_2), 32.0 (**C**H_2CH), 31.8 (**C**H_2S), 26.0 (**C**H_2C), 23.2 (2 x **C**H_3).

3-((3*Z*)-5-[(2-Methoxyethoxy)methoxy]-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (469)

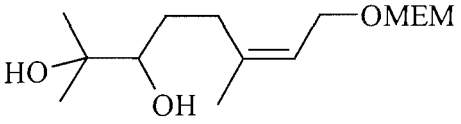


$C_{14}H_{26}O_4$.
M = 258.36 g.mol^{-1}.

To an ice cold stirred solution of diene **343** (5.00 g, 20.63 mmol) in CH_2Cl_2 (100 mL), $NaHCO_3$ (sat. aq. sol., 3.74 g, 44.00 mmol) was added in one portion followed by the portionwise addition of mCPBA (5.31 g, 60%, 22.69 mmol). The resulting mixture was stirred 45 minutes, washed with water (2 x 100 mL), $NaHCO_3$ (sat. aq. sol., 2 x 100 mL), water (2 x 75 mL) and brine (3 x 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to obtain the title compound **469** (4.91g, 19.02 mmol, 92%) as a colourless oil that was used in the next step without further purification.

IR (cm^{-1})	2974 (b), 2936 (b), 2870 (b), 1739 (s), 1446 (w), 1370 (s), 1200 (w), 1110 (b), 1039 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.40 (1H, br t, J = 6.7 Hz, CHCH$_2$O), 4.72 (2H, s, OCH$_2$O), 4.09 (2H, d, J = 6.7 Hz, CHCH$_2$O), 3.74-3.68 (2H, m, OCH$_2$), 3.58-3.54 (2H, m, OCH$_2$), 3.39 (3H, s, OCH$_3$), 2.69 (1H, d, J = 6.1 Hz, CHOC), 2.29-2.19 (2H, m, CH$_2$), 1.78 (3H, s, CH$_3$), 1.72-1.58 (1H, m, CHH), 1.35-1.19 (1H, m, CHH), 1.31 (3H, s, CH$_3$), 1.27 (3H, s, CH$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	140.1 (CH=CCH$_3$), 121.1 (C=CH), 94.7 (OCH$_2$O), 71.7 (CH$_2$OCH$_3$), 66.7 (OCH$_2$CH$_2$), 63.8 (CHCH$_2$O), 63.4 (CHOC), 59.0 (OCH$_3$), 58.3 (C(CH$_3$)$_2$), 28.8 (CH$_2$C), 27.6 (CH$_2$CH), 24.8 (CH$_3$), 23.4 (CH$_3$), 18.7 (CH$_3$).
LRMS (ES+ ionisation)	297.3 ([M+K]$^+$, 100%), 276.3 ([M+NH$_4$]$^+$, 48%), 299.3 ([M+MeCN]$^+$, 25%), 281.2 ([M+Na]$^+$, 22%).

(6*Z*)-8-[(2-Methoxyethoxy)methoxy]-2,6-dimethyloct-6-ene-2,3-diol (470)



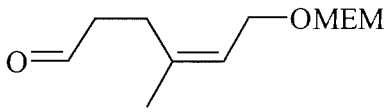
$C_{14}H_{28}O_5$.
M = 276.37 g.mol^{-1}.

Epoxide **469** (6.00 g, 23.2 mmol) was dissolved in water (50 mL) and a solution of H_2SO_4 (10% sol. in water, 1.3 mL) was added dropwise. The resulting mixture was stirred at room temperature for 3 hours, until the solution turned homogeneous. The aqueous phase was extracted with EtOAc (60 mL). The organic phase was washed $NaHCO_3$ (sat. aq. sol., 30 mL), the combined aqueous phases were extracted further with EtOAc (3 x 50 mL). The combined organic phase were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **470** as a colourless oil (6.23 g, 22.5 mmol, 96%). The product was used in the next step without further purification.

IR (cm^{-1})	3428 (b), 2969 (b), 2931 (b), 2874 (b), 1720 (s), 1455 (w), 1380 (s), 1110 (b), 1039 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.40 (1H, br t, J = 6.7 Hz, CHCH$_2$O), 4.72 (2H, s, OCH$_2$O), 4.09 (2H, d, J = 6.7 Hz, CHCH$_2$O), 3.74-3.68 (2H, m, OCH$_2$), 3.58-

	3.54 (2H, m, OCH_2), 3.39 (3H, s, OCH_3), 2.69 (1H, d, J = 6.1 Hz, CHOC), 2.29-2.19 (2H, m, CH_2), 1.78 (3H, s, CH_3), 1.72-1.58 (1H, m, CHH), 1.35-1.19 (1H, m, CHH), 1.31 (3H, s, CH_3), 1.27 (3H, s, CH_3). OH peaks were not observed.
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	140.1 ($CH=CCH_3$), 121.1 ($C=CH$), 94.7 (OCH_2O), 71.7 (CH_2OCH_3), 66.7 (OCH_2CH_2), 63.8 ($CHCH_2O$), 63.4 (CHOC), 59.0 (OCH_3), 58.3 ($C(CH_3)_2$), 28.8 (CH_2C), 27.6 (CH_2CH), 24.8 (CH_3), 23.4 (CH_3), 18.7 (CH_3).
LRMS (ES+ ionisation)	315.3 ($[M+K]^+$, 100%).

(4*Z*)-6-[(2-Methoxyethoxy)methoxy]-4-methylhex-4-enal (344)



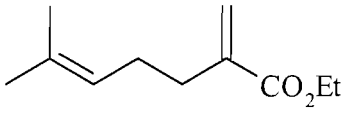
$C_{11}H_{20}O_4$.
M = 216.28 g.mol^{-1}.

To a solution of diol **470** (4.00 g, 17.40 mmol) in acetone (50 mL) was added a solution of $NaIO_4$ (7.45 g, 34.8 mmol) in water (20 mL) at room temperature. The resulting white solution was stirred for 3.5 h before the solid was filtered off and some of the acetone was removed *in vacuo*. The aqueous phase was extracted with Et_2O (5 x 40 mL), the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford quantitatively the title compound **344** (3.75g, 17.34 mmol, 100%) as a yellow oil. The product was used in the next step without further purification.

IR (cm^{-1})	2969 (b), 2926 (b), 2879 (b), 1725 (s), 1451 (w), 1361 (w), 1110 (b), 1044 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.78 (1H, t, J = 1.6 Hz, CHO), 5.42 (1H, dt, J = 6.9 and 0.7 Hz, $CHCH_2O$), 4.72 (2H, s, OCH_2O), 4.08 (2H, dd, J = 6.9 and 0.8 Hz, $CHCH_2O$), 3.72-3.69 (2H, m, OCH_2), 3.56-3.53 (2H, m, OCH_2), 3.39 (3H, s, OCH_3), 2.45 (2H, tt, J = 8.2 and 1.3 Hz, CH_2), 2.43 (2H, br t, J = 7.9 Hz, CH_2), 1.76 (3H, br d, J = 1.0 Hz, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	201.5 (CHO), 139.0 ($CH=CCH_3$), 122.4 ($C=CH$), 94.5 (OCH_2O), 71.7 (CH_2OCH_3), 66.7 (OCH_2CH_2), 63.2 ($CHCH_2O$), 58.9

	(OCH_3), 42.2 (CH_2CHO), 24.4 (CH_2CH) and 23.1 (CH_3).
LRMS (ES+ ionisation)	255.2 ($[M+K]^+$, 100%), 234.2 ($[M+NH_4]^+$, 50%).

6-Methyl-2-methylene-hept-5-enoic acid ethyl ester (421a) [154]

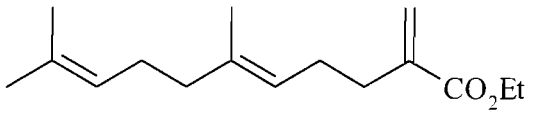


$C_{11}H_{18}O_2$.
M = 182.26 g.mol^{-1}.

According to the method of Vasil'ev *et al.*,[154] NaH (295 mg, 7.37 mmol) was dispersed in DMSO (10 mL) before the dropwise addition of triethyl phosphonoacetate (1.46 mL, 7.37 mmol). Once the gas evolution has ceased, bromide **427** (720 mg , 4.42 mmol) was added in one portion and the mixture was stirred for 5 hours at 50°C then cooled to room temperature. K_2CO_3 (2.1 g, 15.35 mmol) was added in one portion followed by CH_2O (23% aq, 62.4 mL). The resulting mixture was stirred at room temperature overnight then at 60°C for 3.5 hours. The reaction was cooled to room temperature, diluted in water (35 mL) and extracted with Et_2O (4 x 40 mL). The combined organic phases were washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow oil (950 mg). Purification on silica gel (50 g, hexane/EtOAc, 98:2) afforded the title compound **421a** as a colourless oil (650 mg, 3.57 mmol, 81%).

IR (cm^{-1})	2978 (m), 2922 (m), 2865 (w), 1720 (s), 1635 (m), 1446 (m), 1299 (m), 1176 (s), 1134 (m), 1034 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.13 (1H, s, CC**H**H), 5.50 (1H, s, CC**H**H), 5.10 (1H, br t, J = 7.0 Hz, C**H**), 4.21 (2H, q, J = 7.2 Hz, O**CH$_2$**), 2.32 (2H, t, J = 7.4 Hz, **CH$_2$**), 2.15 (2H, q, J = 7.4 Hz, **CH$_2$**), 1.67 (3H, s, **CH$_3$**), 1.59 (3H, s, **CH$_3$**), 1.30 (3H, t, J = 7.2 Hz, OCH$_2$**CH$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	167.3 (**C**OO), 140.6 (**C**CO$_2$Et), 132.2 (**C**(CH$_3$)$_2$), 124.5 (**C**CH$_2$), 123.4 (**C**H), 60.5 (O**C**H$_2$), 32.0 (**C**H$_2$), 27.0 (**C**H$_2$), 25.6 (**C**H$_3$), 17.6 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).
LRMS (GC-EIMS)	182 ($[M]^+$, 62%).

(*E*)-ethyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (452a)

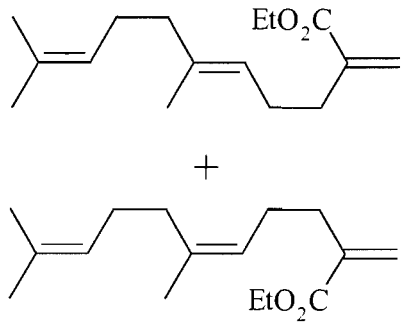


$C_{16}H_{26}O_2$.
M = 250.38 g.mol^{-1}.

Following the procedure used for the synthesis of **421a**, bromide **457a** (150 mg , 0.65 mmol) was converted to the triene **452a** obtained as a colourless oil (120 mg, 0.48 mmol, 74%) after purification on SiO_2 (25 g, hexane/EtOAc, 95:5).

IR (cm^{-1})	2964 (m), 2922 (s), 2846 (m), 1740 (s), 14446 (m), 1375 (m), 1271 (w), 1102 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	6.15 (1H, d, J = 1.5 Hz, CC**H**H), 5.52 (1H, q, J = 1.5 Hz, CC**H**H), 5.13 (1H, tq, J = 7.3 and 1.3 Hz, C**H**CCH$_3$), 5.08 (1H, tt, J = 7.0 and 1.3 Hz, C**H**C(CH$_3$)$_2$), 4.20 (2H, q, J = 7.2 Hz, OC**H$_2$**), 2.34 (2H, t, J = 7.2 Hz, C**H$_2$**C), 2.19 (2H, dd, J = 15.1 and 7.3 Hz, CH$_2$C**H$_2$**CH), 2.08 (2H, m, C**H$_2$**), 2.04 (2H, m, C**H$_2$**), 1.69 (3H, d, J = 1.3 Hz, C**H$_3$**), 1.60 (6H, s, C**H$_3$**), 1.30 (3H, t, J = 7.2 Hz, OCH$_2$C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	167.4 (**C**OO), 140.6 (**C**COOEt), 136.1 (**C**CH$_3$), 131.4 (**C**(CH$_3$)$_2$), 124.5 (**C**CH$_2$), 124.4 (CH$_3$**C**CH), 123.4 ((CH$_3$)$_2$)**C**CH), 60.7 (O**C**H$_2$), 39.8 (**C**H$_2$), 32.2 (**C**H$_2$), 26.9 (**C**H$_2$), 26.8 (**C**H$_2$), 25.8 (**C**H$_3$), 17.8 (**C**H$_3$), 16.1 (**C**H$_3$), 14.4 (OCH$_2$**C**H$_3$).
LRMS (GC-EIMS)	250 ([M]$^+$, 10%).

(*Z*)-Ethyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (452b) and (*E*)-ethyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (452a)

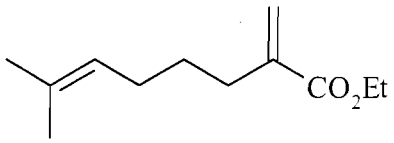


$C_{16}H_{26}O_2$.
M = 250.38 g.mol^{-1}.

Following the procedure used for the synthesis of **421a**, mixture of bromides **457a,b** (1.52 g , 6.61 mmol) was converted to a inseparable mixture of trienes **452a,b** obtained as a colourless oil (1.46 g, 5.82 mmol, 88%), after purification on SiO_2 (25 g, hexane/EtOAc, 95:5).

IR (cm^{-1})	2954 (m), 2922 (s), 2853 (m), 1740 (s), 1453 (m), 1376 (m), 1267 (w), 1205 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.14 (1H, s, CC**H**H), 5.52 (1H, s, CC**H**H), 5.12 (2H, m, C**H**CH$_3$ and C**H**(CH$_3$)$_2$), 4.22 (2H, q, *J* = 7.3 Hz, OC**H$_2$**), 2.32 (2H, ddd, *J* = 8.5, 7.3 and 5.3 Hz, C**H$_2$**C), 2.17 (2H, dd, *J* = 7.8 and 1.0 Hz, CH$_2$C**H$_2$**CH), 2.06-1.99 (4H, m, 2 x C**H$_2$**), 1.69 (3H, s, C**H$_3$**), 1.60 (6H, s, C**H$_3$**), 1.30 (3H, t, *J* = 7.3 Hz, OCH$_2$C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	167.3 (**C**OO), 140.7 (**C**COOEt), 135.9 (**C**CH$_3$), 131.2 (**C**(CH$_3$)$_2$), 124.5 (**C**CH$_2$), 124.4 (**C**CH$_2$), 124.1 (CH$_3$**C**CH), 123.3 ((CH$_3$)$_2$)**C**CH), 60.5 (O**C**H$_2$), 39.7 (**C**H$_2$), 32.2 (**C**H$_2$), 26.8 (**C**H$_2$), 26.6 (**C**H$_2$), 25.6 (**C**H$_3$), 17.6 (**C**H$_3$), 16.0 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).
LRMS (GC-EIMS)	250 ([M]$^+$, 12%).

Ethyl 7-methyl-2-methyleneoct-6-enoate (439a)

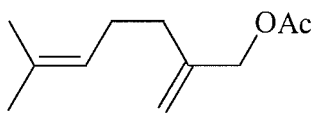


$C_{12}H_{20}O_2$.
M = 196.15 g.mol^{-1}.

Following the procedure used for the synthesis of **421a**, bromide **438** (250 mg , 1.412 mmol) was converted to triene **439a** obtained as a colourless oil (206 mg, 1.050 mmol, 74%), after purification on SiO_2 (50 mL, hexane / Et_2O, 95:5).

IR (cm^{-1})	2970 (w), 2934 (m), 2860 (w), 1720 (s), 1368 (m), 1216 (m), 1178 (m), 1135 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.13 (1H, s, CC**H**H), 5.51 (1H, q, *J* = 1.5 Hz, CC**H**H), 5.12 (1H, ttd, *J* = 7.3, 4.3 and 2.8 Hz, C**H**CH$_3$), 4.20 (2H, q, *J* = 7.0 Hz, OC**H$_2$**), 2.32 (2H, dt, *J* = 8.5 and 7.7 Hz, C**H$_2$**C), 2.00 (2H, q, *J* = 7.3 Hz, C**H$_2$**CH), 1.69 (3H, s, C**H$_3$**), 1.60 (3H, s, C**H$_3$**), 1.51 (2H, td, *J* = 15.3 and 7.5 Hz, C**H$_2$**CH$_2$CH), 1.31 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	167.4 (**C**OO), 141.0 (**C**COOEt), 131.8 (**C**(CH$_3$)$_2$), 124.2 ((CH$_3$)$_2$)**C**CH), 124.1 (C=**C**H$_2$), 60.5 (O**C**H$_2$), 31.4 (C**C**H$_2$), 28.6 (**C**H$_2$), 26.7 (**C**H$_2$), 25.7 (**C**H$_3$), 17.7 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).

6-Methyl-2-methylenehept-5-enyl acetate (436) [154]



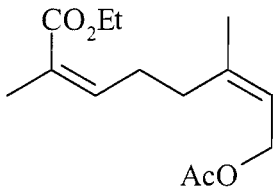
$C_{11}H_{18}O_2$.
M = 182.13 g.mol^{-1}.

According to the method of Vasil'ev *et al.*,[154] DIBALH (1.5 M sol. in toluene, 17.25 mL, 25.85 mmol) was added dropwise to a solution of diene **421a** (2.14 g, 11.75 mmol) in hexane (30 mL) at –30°C. The resulting mixture was stirred at this temperature for 3 hours and warmed to 0°C before addition of MeOH (2 mL) and water (15 mL). Cold HCl (2M aq. sol., 3 mL) was added to dissolve the solid formed. The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic phases were washed with $NaHCO_3$ (sat. aq. sol., 3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the corresponding alcohol (1.52 g, 10.85 mmol, 92%) that was used directly in the next step. The alcohol (1.50 g, 10.70

mmol) was dissolved in CH_2Cl_2 (20 mL) before the addition of triethylamine (7.40 mL, 54.00 mmol) followed by Ac_2O (2.20 mL, 0.202 mmol) and DMAP (10 mg, 0.07 mmol). the reaction was stirred for 48 hours, Et_2O (30 mL) was added and the mixture was washed with H_2O (30 mL) and brine (30 mL). The combined aqueous phases were extracted with Et_2O (3 x 30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (2.50 g). Purification on silica gel (350 mL, hexane/Et_2O, 4:1) afforded the title product **436** as a colourless oil (1.85 g, 10.16 mmol, 95%).

IR (cm^{-1})	2969 (w), 2928 (w), 2858 (w), 1741 (s), 1441 (w), 1374 (m), 1225 (s), 1027 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.11 (1H, tdd, J = 7.0, 2.9 and 1.5 Hz, $(CH_3)_2CCH$), 5.04 (1H, s, CCHH), 4.96 (1H, s, CCHH), 4.53 (2H, s, OCH_2), 2.17-2.09 (4H, m, 2 x CH_2), 2.10 (3H, s, $C(O)CH_3$), 1.70 (3H, s, CH_3), 1.62 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	170.7 (COO), 143.8 ($C=CH_2$), 132.1 ($C(CH_3)_2$), 123.6 ($CHC(CH_3)_2$), 112.3 ($C=CH_2$), 66.9 (OCH_2), 33.2 (CH_2), 26.2 (CH_2), 25.6 (CH_3), 20.9 (CH_3), 17.7 (CH_3).
LRMS (GC-EIMS)	182 ($[M]^+$, 65%).

(2*Z*,6*Z*)-Ethyl 8-acetoxy-2,6-dimethylocta-2,6-dienoate (335a)



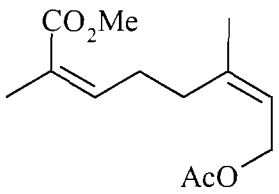
$C_{14}H_{22}O_4$.
M = 254.33 g.mol^{-1}.

According to the method of Marshall *et al.*,[175] to a solution of phosphonate **338a** (104 mg, 0.329 mmol) and 18-crown-6 (135 mg, 0.51 mmol) in THF (10 mL) at –78°C was added dropwise KHMDS (0.68 mL, 0.5 M solution in toluene, 0.34 mmol) followed by the dropwise addition of aldehyde **19b** (50 mg, 0.296 mmol). The resulting solution was stirred at –78°C for 90 minutes, then quenched with NH_4Cl (sat. aq. sol., 15 mL). The aqueous phase was extracted with Et_2O (10 mL) and EtOAc (2 x 15 mL). The combined organic phases were washed with water (2 x 10 mL) and brine (2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil (70 mg). Purification on

silica gel (20 g, EtOAc/hexane, 1:9) afforded the title compound as a colourless oil (60 mg, 0.354 mmol, 93%).

IR (cm^{-1})	2977 (b), 2931 (b), 1739 (s), 1714 (s), 1448 (s), 1378 (s), 1233 (b), 1024 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.88 (1H, tq, J = 7.4 and 1.5 Hz, CC**H**), 5.39 (1H, t, J = 7.2 Hz, OCH_2CH), 4.56 (2H, d, J = 7.4 Hz, C**H$_2$**OH), 4.20 (2H, q, J = 7.2 Hz, OC**H$_2$**), 2.57 (2H, q, J = 7.5 Hz, CHC**H$_2$**), 2.21 (2H, t, J = 7.7 Hz, C**H$_2$**C), 2.06 (3H, s, OCC**H$_3$**), 1.89 (3H, s, C**H$_3$**), 1.77 (3H, s, C**H$_3$**), 1.30 (3H, t, J = 7.2 Hz, OCH_2CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	171.0 (**C**OO), 168.0 (**C**OO), 141.8 (**C**H), 141.4 (**C**CH_3), 127.8 (**C**CH_3), 119.6 (**C**HCH_2), 60.9 (**C**HCH_2), 60.1 (OCH_2), 31.5 (**C**H_2), 27.8 (**C**H_2), 23.2 (**C**H_3), 21.0 (**C**H_3), 20.6 (**C**H_3), 14.2 (OCH_2CH_3).
LRMS (ES+ ionisation)	785.2 ($[3M+Na]^+$, 5%), 531.3 ($[2M+Na]^+$, 100%), 277.2 ($[M+Na]^+$, 80%)
HRMS	Calculated : $C_{14}H_{22}O_4Na$ = 277.1410. Found : 277.1407.

(2*Z*,6*Z*)-methyl 8-acetoxy-2,6-dimethylocta-2,6-dienoate (335b) [175]

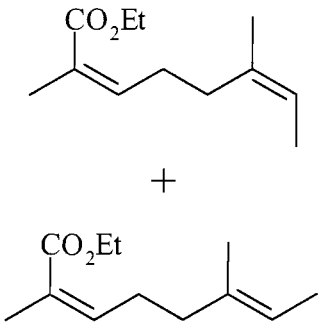


$C_{13}H_{20}O_4$.
M = 240.30 g.mol^{-1}.

According to the method of Marshall *et al.*,[175] to a solution of the phosphonate **338b** (1.14 g, 3.42 mmol) and 18-crown-6 (1.13 g, 4.63 mmol) in THF (30 mL) at –78°C was added dropwise KHMDS (7.2 mL, 0.5 M solution in toluene, 3.60 mmol) followed by the dropwise addition of aldehyde **19b** (525 mg, 3.08 mmol). The resulting solution was stirred at –78°C for 90 minutes and then quenched with NH_4Cl (sat. aq. sol., 45 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic phases were washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (750 mg). Purification on silica gel (150 mL, EtOAc/hexane, 1:9) afforded the title compound **335b** as a colourless oil (690 mg, 2.87 mmol, 93%).

IR (cm^{-1})	3030 (w), 2950 (m), 2851 (w), 1740 (s), 1716 (s), 1455 (m), 1436 (m), 1380 (m), 1361 (m), 1238 (s), 1125 (m).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.89 (1H, t, J = 7.4 Hz, C(O)CC**H**), 5.36 (1H, t, J = 7.0 Hz, OCH_2CH), 4.54 (2H, d, J = 7.2 Hz, CH_2OH), 3.71 (3H, s, OCH_3), 2.55 (2H, q, J = 7.5 Hz, $CHCH_2$), 2.21 (2H, t, J = 7.6 Hz, CH_2C), 2.03 (3H, d, J = 1.8 Hz, $OCCH_3$), 1.87 (3H, s, CH_3), 1.74 (3H, s, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	171.0 (**C**$OOCH_2$), 168.1 (**C**OO), 141.9 (**C**H), 141.8 (**C**CH_3), 127.4 (**C**CH_3), 119.6 (**C**HCH_2), 60.9 (**C**HCH_2), 51.2 (OCH_3), 31.4 (CH_2), 27.8 (CH_2), 23.2 (CH_3), 20.9 (CH_3), 20.6 (CH_3).
LRMS (ES+ ionisation)	263.2 ($[M+Na]^+$, 55%), 258.3 (($[M+NH_4]^+$, 25%), 128.1 (100%)

(2*Z*,6*Z*)-Ethyl 2,6-dimethylocta-2,6-dienoate (335d) and (2*Z*,6*E*)-ethyl 2,6-dimethylocta-2,6-dienoate (335e)



$C_{12}H_{20}O_2$.
M = 196.29 g.mol^{-1}.

A solution of diene **335a** (50 mg, 0.204 mmol), $Pd(acac)_2$ (12 mg, 0.040 mmol), dppe (50 mg, 0.121 mmol) and $nMe_4BH(OAc)_3$ (526 mg, 2.002 mmol) in THF (5 mL) was stirred for 36 hours. The solvent was removed *in vacuo* and the resulting crude product was purified on silica gel (75 mL, CH_2Cl_2/hexane, 15:85) to afford the title compound, a pale yellow oil, as a inseparable mixture of dienes **335d,e** (30 mg, 0.153 mmol, 76%).

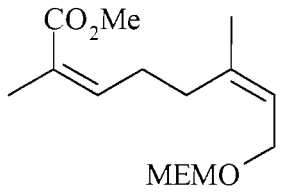
IR (cm^{-1})	2978 (m), 2922 (m), 2855 (w), 1711 (s), 455 (m), 1239 (m), 1182 (s), 1129 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.91 (1H, br s, C**H**=CO), 5.24 (1H, app t, J = 6.2 Hz, C**H**=CCH_2), 4.21 (2H, app q, J = 7.2 Hz, OCH_2), 2.55 (2H, br t, J = 6.5 Hz, CH_2CH=C), 2.14 (1H, t, J = 7.8 Hz, $CHHC(CH_3)$), 2.08 (1H, t, J

= 7.4 Hz, CHHC(CH_3)), 1.91 (3H, s, CH_3), 1.61 (1.5H, s, CH_3 *cis*), 1.59 (1.5H, s, CH_3 *trans*), 1.57 (3H, s, CH_3), 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3).

^{13}C-NMR (75MHz, $CDCl_3$, ppm) 168.2 (COO), 142.5 (CH=CCH_2), 142.2 (CH=CCH_2), 135.1 ($C(CH_3)$), 135.0 ($C(CH_3)$), 127.3 ($C(CH_3)$), 127.1 ($C(CH_3)$), 119.6 ($CHCH_3$), 118.9 ($CHCH_3$), 60.0 (OCH_2), 39.1 ($CH_2C(CH_3)$), 28.0 (CH_2CH), 27.7 (CH_2CH), 15.5 (CH_3), 14.3 (OCH_2CH_3), 13.3 (CH_3), 13.2 (CH_3).

LRMS (GC-EIMS) 196 ($[M]^+$, 20%).

Methyl (2*Z*,6*Z*)-8-[(2-methoxyethoxy)methoxy]-2,6-dimethylocta-2,6-dienoate (345a)



$C_{15}H_{26}O_5$.
M = 286.37 g.mol^{-1}.

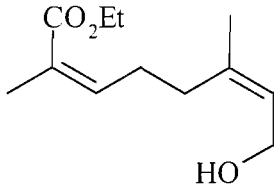
According to the method of Marshall *et al.*,[175] to a solution of the phosphonate $(CF_3CH_2O)_2P(O)CH_2CH_3CO_2Me$ (1.70 g, 5.12 mmol) and 18 crown 6 (1.83 g, 6.92 mmol) in THF (40 mL) at –78°C was added dropwise KHMDS (10.7 mL, 0.5 M solution in toluene, 5.34 mmol) followed by the dropwise addition of aldehyde **344** (1.00 g, 4.61 mmol). The resulting solution was stirred at –78°C for 90 minutes and then quenched with NH_4Cl (sat. aq. sol., 45 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic phases were washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (1.40 g). Purification on silica gel (200 mL, EtOAc/hexane, 1:4) afforded the title compound **345a** as a colourless oil (1.10 g, 3.84 mmol, 83%).

IR (cm^{-1}) 2931 (b), 2874 (b), 1725 (s), 1455 (w), 1365 (w), 1214 (s), 1129 (b), 1105 (b), 1044 (b).

^{1}H-NMR (300MHz, $CDCl_3$, ppm) 5.90 (1H, tq, J = 7.6 and 1.6 Hz, C**H**CCO_2Me), 5.38 (1H, td, J = 6.9 and 1.3 Hz, OCH_2CH), 4.68 (2H, s, OCH_2O), 4.06 (2H, dd, J = 6.9 and 0.7 Hz, OCH_2CH), 3.72 (3H, s, $COOCH_3$), 3.70-3.67 (2H, m, OCH_2), 3.56-3.54 (2H, m, OCH_2), 3.36 (3H, s, OCH_3),

	2.55 (2H, qq, J = 7.4 and 1.3 Hz, CHC**H**$_2$), 2.17 (2H, t, J = 7.7 Hz, C**H**$_2$C), 1.87 (3H, q, J = 1.3 Hz, C**H**$_3$) 1.72 (3H, br d, J = 1.3 Hz, C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	168.2 (**C**OO), 142.1 (CH_2**C**CH_3), 140.2 (**C**H=CCH_3), 127.3 (**C**CH_3), 121.7 (**C**H=CCH_3), 94.6 (O**C**H_2O), 71.8 (CH_3O**C**H_2), 66.7 (O**C**H_2CH_2), 63.5 (O**C**H_2CH), 58.9 (O**C**H_3), 51.2 (COO**C**H_3), 31.5 (**C**H_2), 27.9 (**C**H_2), 23.2 (**C**H_3), 20.6 (**C**H_3).
LRMS (ES+ ionisation)	304.4 ($[M+NH_4]^+$, 100%), 325.2 ($[M+K]^+$, 42%).

Ethyl (2*Z*, 6*E*)-8-hydroxy-2,6-dimethyl-2,6-octadienoate (335c)



$C_{12}H_{20}O_3$.
M = 212.29 g.mol^{-1}.

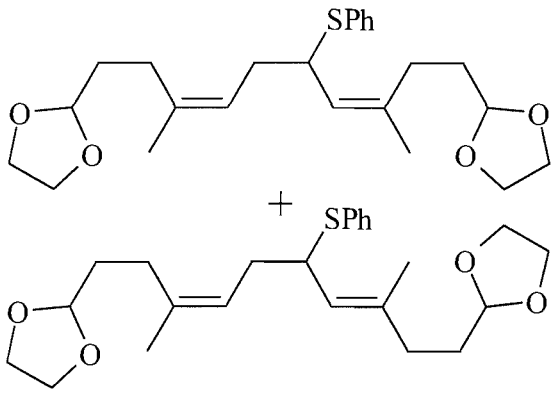
According to the method of Marshall *et al.*,[175] a solution of acetate **335a** (50 mg, 0.197 mmol) and a catalytic amount of K_2CO_3 in dry methanol (1 mL) at –20°C was stirred overnight. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **335c** as a colourless oil (40 mg, 0.188 mmol, 95%), which was used without further purification in the next step.

IR (cm^{-1})	3300 (b), 2979 (b), 2929 (b), 1730 (s), 1445 (s), 1374 (s), 1225 (b) and 1020 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.85 (1H, qq, J = 7.7 and 1.5 Hz, C**H**CH_2CH_2), 5.37 (1H, td, J = 7.0 and 1.2 Hz, C**H**CH_2OH), 4.10 (2H, q, J = 7.1 Hz, OC**H**$_2$), 4.04 (2H, d, J = 6.9 Hz, C**H**$_2$OH), 2.48 (2H, qt, J = 7.8 and 1.2 Hz, C**H**$_2$), 2.10 (2H, q, J = 7.8 Hz, C**H**$_2$C), 1.82 (3H, s, C**H**$_3$), 1.67 (3H, s, C**H**$_3$), 1.24 (3H, t, J = 7.1 Hz, OCH_2C**H**$_3$). O**H** peak was not observed.
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	167.9 (**C**OO), 141.8 (**C**HCH_2CH_2), 138.5 (**C**CH_2), 127.6 (**C**HCH_2OH), 125.0 (**C**CH), 60.1 (O**C**H_2), 58.6 (**C**H_2OH), 31.3 (**C**H_2C), 25.6 (**C**H_2CH), 23.3 (**C**H_3), 20.5 (**C**H_3), 14.2

(OCH_2CH_3).

LRMS (ES+ ionisation) 447.3 ($[2M+Na]^+$, 20%).

[(*Z*)-1-((*Z*)-5-[1,3]-Dioxolane-2-methyl-pent-1-enyl)-7-[1,3]-Dioxolane -4-methyl-hept-3-enylsulfanyl]-benzene (356) and [(*Z*)-1-((*E*)-5-[1,3]-dioxolane-2-methyl-pent-1-enyl)-7-[1,3]-Dioxolane -4-methyl-hept-3-enylsulfanyl]-benzene (356b)



$C_{24}H_{32}O_4S$.

M = 418.60 g.mol^{-1}.

Method 1:

Allylic phenyl sulphide **354** (2.22 g, 8.4 mmol) was dissolved in THF (75 mL) and cooled to –78°C. DABCO (942 mg, 8.4 mmol) was added in one portion and the resulting solution was stirred for 5 minutes. *n*-BuLi (12.5 mL, 29.4 mmol) was added dropwise and the mixture was stirred 5 minutes. Allylic chloride **353** (1 g, 5.24 mmol) in THF (40 mL) was added dropwise and the orange resulting solution was warmed at –50°C over 5 hours. The reaction was quenched by the addition of NH_4Cl (aq. sat. sol., 30 mL) followed by the addition of water (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude compound as a yellow oil (4 g), which was purified on silica gel (200 mL, EtOAc/hexane, 15:85). Compound **356** was obtained as a colourless oil (550 mg, 1.32 mmol, 25%), compound **356b** was obtained as a colourless oil (430 mg, 1.03 mmol, 20%) and a mixture of compound **356** and **356b** as a colourless (280 mg, 0.67 mmol, 13%).

Method 2:

Allylic phenyl sulphide **354** (400 mg, 1.51 mmol) was dissolved in THF (30 mL) and cooled to –78°C. DABCO (170 mg, 1.51 mmol) was added in one portion and the resulting solution was stirred for 5 minutes. *n*-BuLi (4 mL, 5.29 mmol) was added dropwise and the mixture was stirred 5 minutes. Allylic chloride **353** (165 mg, 0.865 mmol) in THF (10 mL) was added

dropwise and the orange resulting solution was stirred at –78°C for 5 hours. The reaction was quenched by the addition of NH_4Cl (aq. sat. sol., 30 mL) followed by the addition of water (50 mL) and Et_2O (50 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude compound as a yellow oil (1 g), which was purified on silica gel (250 mL, EtOAc/hexane, 15:85). The title product **356** was obtained as a colourless oil (250 mg, 0.597 mmol, 69%).

Compound **356**:

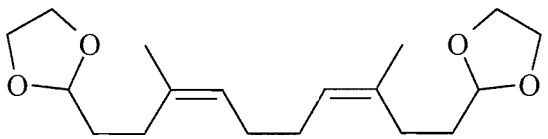
IR (cm^{-1})	2964 (b), 2922 (b), 2884 (b), 1744 (s), 1432 (w), 1375 (w), 1145 (s), 1039 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	7.44-7.41 (2H, m, 2 x C**H**=CH, arom), 7.29-7.21 (3H, m, C**H**=CH and 2 x C**H**=CH, arom), 5.16 (1H, td, *J* = 7.2 and 1.1 Hz, C**H**CH_2S), 5.07 (1H, dd, *J* = 10.3 and 1.1 Hz, C**H**CH_2), 4.80 (1H, t, *J* = 4.8 Hz, OC**H**O), 4.75 (1H, t, *J* = 4.8 Hz, OC**H**O), 3.99-3.90 (5H, m, C**H**S and 2 x OC**H_2**), 3.88-3.78 (4H, m, 2 x OC**H_2**), 2.38-2.22 (2H, m, C**H_2**), 2.09 (2H, t, *J* = 7.9 Hz, C**H_2**), 2.09-1.82 (2H, m, C**H_2**) 1.72-1.42 (2H, m, C**H_2**) 1.69 (3H, s, C**H_3**), 1.67 (3H, d, *J* = 1.1 Hz, C**H_3**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	137.2 (CH_2CH=**C**CH_3), 136.3 (CH_2CH=**C**CH_3), 135.0 (**C**S), 133.5 (C=**C**H), 128.5 (**C**H), 127.0 (**C**H), 126.5 (CH_2**C**H=C), 122.2 (**C**HCCH_3), 104.2 (O**C**HO), 104.1 (O**C**HO), 64.8 (O**C**H_2), 47.1 (**C**HS), 33.7 (SCH**C**H_2), 32.0 (**C**H_2CHO), 31.9 (**C**H_2CHO), 26.3 (**C**H_2C), 23.3 (**C**H_3), 23.0 (**C**H_3).
LRMS (ES+ ionisation)	457.2 ($[M+K]^+$, 75%), 587.3 (100%).
HRMS	Calculated : $C_{24}H_{32}O_4SNa$ = 441.2070. Found : 441.2072.

Compound **356b**:

IR (cm^{-1})	2960 (b), 2925 (b), 2883 (b), 1746 (s), 1431 (w), 1374 (w), 1147 (s), 1041 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	7.43-7.41 (2H, m, 2 x C**H**=CH, arom), 7.28-7.24 (3H, m, C**H**=CH and 2 x C**H**=CH, arom), 5.19 (1H, td, *J* = 7.0 and 1.3 Hz, C**H**CH_2S), 5.08 (1H, dd, *J* = 10.3 and 1.1 Hz, C**H**CH_2), 4.85 (1H,

	t, J = 4.8 Hz, OC**H**O), 4.76 (1H, t, J = 4.8 Hz, OC**H**O), 4.00-3.92 (5H, m, C**H**S and 2 x OC**H**$_2$), 3.89-3.81 (4H, m, 2 x OC**H**$_2$), 2.44-2.35 (2H, m, C**H**$_2$), 2.14 (2H, dd, J = 7.8 and 1.1 Hz, C**H**$_2$), 2.04-1.84 (2H, m, C**H**$_2$) 1.77-1.53 (2H, m, C**H**$_2$) 1.67 (3H, s, C**H**$_3$) and 1.57 (3H, d, J = 1.1 Hz, C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	137.2 (CH_2CH=**C**CH_3), 136.2 (CH_2CH=**C**CH_3), 134.9 (**C**S), 133.5 (C=**C**H), 128.5 (**C**H), 127.1 (**C**H), 126.3 (CH_2**C**H=C), 121.2 (**C**HCCH_3), 104.2 (O**C**HO), 104.0 (O**C**HO), 64.8 (O**C**H_2), 47.0 (**C**HS), 33.9 (SCH**C**H_2), 32.3 (**C**H_2CHO), 31.9 (**C**H_2CHO), 26.3 (**C**H_2C), 23.1 (**C**H_3) and 16.3 (**C**H_3).
LRMS (ES+ ionisation)	457.3 ($[M+K]^+$, 18%), 481.5 ($[M+Na+K]^+$, 12%), 146.5 (100%).

2-((3*Z*,7*Z*)-3,8-Dimethyl-deca-3,7-dienyl)-di-([1,3]-dioxolane) (357a)



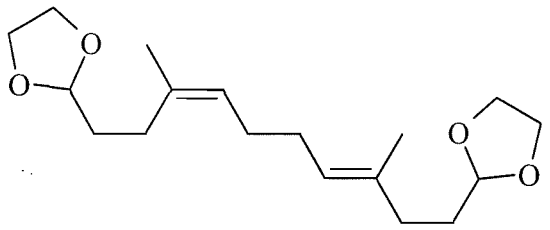
$C_{18}H_{30}O_4$.
M = 310.44 g.mol^{-1}.

According to the method of Morimoto *et al.*,[48] a solution of **356** (250 mg, 0.574 mmol) in a mixture of dry THF (20 mL) and iso-propanol (10 mL) was warmed up to reflux, before the addition of sodium metal (100 mg, 4.35 mmol). Additional sodium metal (total 700 mg) was added in small portions during 4 hours. After cooling to room temperature, the reaction was quenched by addition of water (5 mL) and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude compound as a yellow oil (300 mg). Purification on silica gel (150 mL, hexane/EtOAc, 9:1) afforded the title compound **357a** and a small amount of by-product **357b** in a 5:1 ratio (178 mg, 0.573 mmol, 100%).

IR (cm^{-1})	2959 (b), 2922 (b), 2874 (b), 1450 (w), 1138 (s), 1039 (b), 732 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.14 (2H, br s, 2 x C**H**CH_2), 4.82 (2H, t, J = 4.8 Hz, OC**H**O), 4.02-3.92 (4H, m, 4 x OC**H**$_2$), 3.91-3.80 (4H, m, 2 x OC**H**$_2$), 2.16-2.08 (4H, m, 2 x C**H**$_2$), 2.03 (4H, br t, J = 3.1 Hz, 2 x C**H**$_2$), 1.75-1.67 (4H, m, 2 x C**H**$_2$), 1.69 (6H, d, J = 1.1 Hz, 2 x C**H**$_3$).

^{13}C-NMR (75MHz, $CDCl_3$, ppm)	134.4 (2 x CH_2CH=**C**CH_3), 125.5 (2 x CH_2**C**H=CCH_3), 104.4 (2 x O**C**HO), 64.9 (2 x O**C**H_2), 32.2 (2 x **C**H_2CHO), 28.1 (2 x **C**H_2CH), 26.2 (2 x **C**H_2C) and 23.3 (2 x **C**H_3).
LRMS (GC-MSEI)	310 ($[M]^+$, 18%).

2-((3*Z*,7*E*)-10-(1,3-Dioxolan-2-yl)-3,8-dimethyldeca-3,7-dienyl)-1,3-dioxolane (357c)

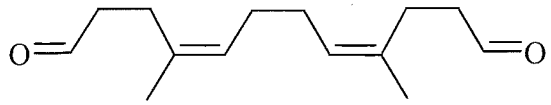


$C_{18}H_{30}O_4$.
M = 310.44 g.mol^{-1}.

According to the method of Morimoto *et al.*,[48] a solution of **356b** (300 mg, 0.717 mmol) in a mixture of dry THF (20 mL) and iso-propanol (10 mL) was warmed up to reflux, before the addition of sodium metal (100 mg, 4.35 mmol). Additional sodium metal (total 900 mg) was added in small portions during 4 hours. After cooling to room temperature, the reaction was quenched by addition of water (10 mL) and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic phase were washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude compound as a yellow oil (400 mg). Purification on silica gel (150 mL, hexane/EtOAc, 9:1) afforded the title compound **357c** and a small amount of by-product **357d** in a 4:1 ratio (222 mg, 0.709 mmol, 99%).

IR (cm^{-1})	2959 (b), 2922 (b), 2874 (b), 1450 (w), 1138 (s), 1039 (b), 732 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.15 (2H, q, J = 7.7 Hz , 2 x C**H**CH_2), 4.81 (2H, m, 2 x OC**H**O), 3.95-3.89 (4H, m, 4 x OC**H$_2$**), 3.87-3.77 (4H, m, 2 x OC**H$_2$**), 2.13-2.04 (4H, m, 2 x C**H$_2$**), 2.00 (4H, br s, 2 x C**H$_2$**), 1.74-1.67 (4H, m, 2 x C**H$_2$**), 1.69 (3H, d, J = 1.1 Hz, C**H$_3$**), 1.58 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	135.6 (CH_2CH=**C**CH_3), 134.4 (CH_2CH=**C**CH_3), 125.5 (CH_2**C**H=CCH_3), 124.4 (CH_2**C**H=CCH_3), 104.3 (O**C**HO), 104.2 (O**C**HO), 64.8 (O**C**H_2), 33.8 (**C**H_2CHO), 32.3 (**C**H_2CHO), 28.3 (**C**H_2CH), 27.9 (**C**H_2CH), 26.1 (**C**H_2C), 23.3 (**C**H_3).
LRMS (ES+ ionisation)	311.1 ($[M+H]^+$, 50%), 411.3 (100%).

(4*Z*,8*Z*)-4,9-Dimethyl-dodeca-4,8-dienedial (352a)

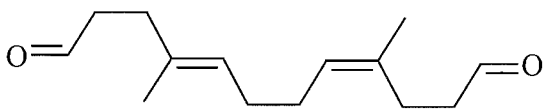


$C_{14}H_{22}O_2$.
M = 222.33 g.mol^{-1}.

According to the method of Markò *et al.*,[141] solid cerium ammonium nitrate (43 mg, 8 mol%) was added to a stirred solution of dienes **352a,b** (300 mg, 0.966 mmol) in MeCN (20 mL) and borate-HCl buffer 5 Merck (pH 8, 20 mL). The faintly yellow solution was heated at 60°C for 3 days. After cooling to room temperature, water (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were combined, dried ($NaSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (450 mg). Purification on silica gel (100 mL, hexane/EtOAc, 4:1) afforded the title compound **352a** and a small amount of by-product **352b** in a 5:1 ratio as a colourless oil (207 mg, 0.931 mmol, 96%).

IR (cm^{-1})	2959 (b), 2917 (b), 2851 (b), 2718 (b), 1720 (s), 1450 (w), 1101 (s), 1011 (b), 973 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.78 (2H, t, *J* = 1.8 Hz, 2 x **CH**O), 5.18 (2H, br s, 2 x **CH**CH_2), 2.16-2.12 (4H, m, 2 x **C**H_2), 2.03 (4H, br t, *J* = 3.2 Hz, 2 x **C**H_2), 1.75-1.70 (4H, m, 2 x **C**H_2), 1.69 (6H, d, *J* = 1.1 Hz, 2 x **C**H_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	202.2 (2 x **C**HO), 133.3 (2 x CH=**C**CH_3), 126.2 (2 x **C**H=CCH_3), 42.2 (2 x **C**H_2CHO), 28.1 (2 x **C**H_2C), 24.3 (2 x **C**H_2CH), 23.0 (2 x **C**H_3).
LRMS (ES+ ionisation)	261.2 ([M+K]$^+$, 75%), 487.4 (100%).
HRMS	Calculated: $C_{14}H_{22}O_2Na$ = 245.1512. Found : 245.1509.

(4*E*,8*Z*)-4,9-Dimethyl-dodeca-4,8-dienedial (352c)



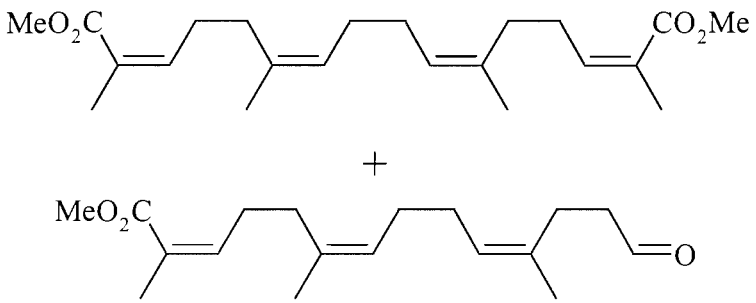
$C_{14}H_{22}O_2$.
M = 222.33 g.mol^{-1}.

According to the method of Markò *et al.*,[141] solid cerium ammonium nitrate (28 mg, 8 mol%) was added to a stirred solution of diene **357c** (200 mg, 0.644 mmol) in MeCN (10 mL) and borate-HCl buffer 5 Merck (pH 8, 10 mL). The faintly yellow solution was heated at 60°C for

3 days. After cooling to room temperature, water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were combined, dried ($NaSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (300 mg). Purification on silica gel (100 mL, hexane/EtOAc, 4:1) afforded the title compound **352c** and a small amount of by-product **352d** in a 4:1 ratio as a colourless oil (135 mg, 0.607 mmol, 94%).

IR (cm^{-1})	2959 (b), 2917 (b), 2860 (b), 2718 (b), 1720 (s), 1445 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.75 (1H, t, J = 1.8 Hz, 2 x **CHO**), 9.75 (1H, t, J = 1.8 Hz, **CHO**), 5.15 (2H, br s, 2 x **CH**CH_2), 2.55-2.47 (4H, m, 2 x **C**H_2), 2.41-2.30 (4H, m, 2 x **C**H_2), 2.03 (2H, br t, J = 3.2 Hz, 2 x **C**H_2), 1.69 (3H, d, J = 1.1 Hz, 2 x **C**H_3), 1.61 (3H, s, **C**H_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	202.5 (**C**HO), 202.2 (**C**HO), 133.4 (CH=**C**CH_3), 133.2 (CH=**C**CH_3), 126.2 (**C**H=CCH_3), 125.0 (**C**H=CCH_3), 42.4 (**C**H_2CHO), 42.2 (**C**H_2CHO), 31.8 (**C**H_2C), 28.1 (**C**H_2C), 24.3 (**C**H_2CH), 23.0 (**C**H_3).
LRMS (ES+ ionisation)	261.2 ($[M+K]^+$, 75%), 487.4 (100%).

**(2*Z*,6*Z*,10*Z*,14*Z*)-Dimethyl 2,6,11,15-tetramethylhexadeca-2,6,10,14-tetraenedioate (333a) and (2*Z*,6*Z*,10*Z*)-methyl 13-formyl-2,6,11-trimethyltrideca-2,6,10-trienoate (471a)



$C_{22}H_{34}O_4$.
M = 362.51 g.mol^{-1}.

$C_{18}H_{28}O_3$.
M = 292.42 g.mol^{-1}.

Method 1:

According to the method of Marshall *et al.*,[175] to a solution of the phosphonate **338b** (690 mg, 2.070 mmol) and 18-crown-6 (720 mg, 2.723 mmol) in THF (20 mL) at –78°C was added dropwise KHMDS (4.5 mL, 0.5 M solution in toluene, 2.500 mmol) followed by the dropwise addition of aldehydes **352a,b** (200 mg, 0.900 mmol) in THF (15 mL). The resulting solution was stirred at –78°C for 2 hours and then quenched with NH_4Cl (sat. aq. sol., 20 mL). The

aqueous phase was extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (1.40 g). Purification on silica gel (250 mL, EtOAc/hexane, 1:4) afforded the title compound **333a** and a small amount of by-product **333b** in a 4:1 ratio as a colourless oil (105 mg, 0.290 mmol, 32%) and the title compound **471a** as a colourless oil (140 mg, 0.478 mmol, 53%).

Method 2:

According to the method of Marshall *et al.*,[175] to a solution of the phosphonate **338b** (347 mg, 1.04 mmol) and 18-crown-6 (355 mg, 1.35 mmol) in THF (10 mL) at –78°C was added dropwise KHMDS (3.2 mL, 0.5 M solution in toluene, 1.60 mmol) followed by the dropwise addition of aldehydes **352a,b** (100 mg, 0.45 mmol) in THF (15 mL). The resulting solution was stirred at –78°C for 2 hours and then quenched with NH_4Cl (sat. aq. sol., 20 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (1.40 g). Purification on silica gel (250 mL, EtOAc/hexane, 1:4) afforded the title compound **333a** and a small amount of by-product **333b** in a 4:1 ratio as a colourless oil (140 mg, 0.386 mmol, 86%).

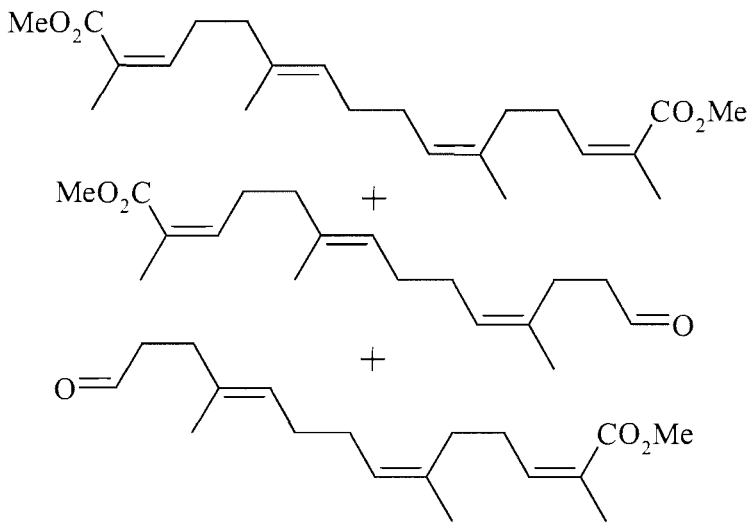
Compound **333a**:

IR (cm^{-1})	2950 (b), 2922 (b), 2860 (b), 1725 (s), 1455 (w), 1432 (w), 1205 (b), 1129 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.92 (2H, tdd, J = 7.3, 2.8 and 1.2 Hz, 2 x COCC**H**CH_2), 5.17 (2H, br s, 2 x CC**H**CH_2), 3.73 (6H, s, 2 x O**C**H_3), 2.54 (4H, qd, J = 7.3 and 1.2 Hz, 2 x C**H**$_2$), 2.11 (4H, t, J = 7.6 Hz, 2 x C**H**$_2$), 2.01 (4H, br t, J = 3.3 Hz, 2 x C**H**$_2$), 1.89 (6H, t, J = 1.3 Hz, 2 x C**H**$_3$) 1.60 (6H, s, 2 x C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	168.4 (2 x **C**OOCH$_3$), 142.7 (2 x **C**H=CCH$_3$), 134.4 (2 x CH=**C**CH$_3$), 127.0 (2 x CH=**C**CH$_3$), 125.6 (2 x **C**H=CCH$_3$), 51.1 (2 x O**C**H$_3$), 31.4 (2 x **C**H$_2$C), 28.3 (2 x **C**H$_2$CH), 27.9 (2 x **C**H$_2$CH), 23.2 (2 x **C**H$_3$), 20.5 (2 x **C**H$_3$).
LRMS (ES+ ionisation)	385.5 ($[M+Na]^+$, 85%), 417.5 (100%).
HRMS	Calculated: $C_{22}H_{34}O_4Na$ = 385.2349. Found : 385.2361.

Compound **471a**:

IR (cm^{-1})	2945 (b), 2921 (b), 2895 (b), 2718 (b), 1720 (s), 1445 (w), 1365 (b), 1209 (b), 1124 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.78 (1H, t, J = 1.7 Hz, C**H**O), 5.92 (1H, tq, J = 7.4 and 1.5 Hz, COCC**H**CH_2), 5.27-5.15 (2H, m, 2 x CC**H**CH_2), 3.73 (3H, s, OCH_3), 2.54 (4H, m, 2 x C**H$_2$**), 2.35 (2H, t, J = 7.7 Hz, C**H$_2$**), 2.11 (2H, t, J = 7.7 Hz, C**H$_2$**), 2.01 (4H, br t, J = 3.3 Hz, 2 x C**H$_2$**), 1.89 (3H, t, J = 1.3 Hz, C**H$_3$**), 1.69 (6H, s, 2 x C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	202.4 (**C**HO), 168.7 (**C**OOCH$_3$), 142.8 (**C**H=CCH$_3$), 134.4 (CH=**C**CH$_3$), 133.1 (CH=**C**CH$_3$), 127.0 (CH=**C**CH$_3$), 126.6 (**C**H=CCH$_3$), 125.6 (**C**H=CCH$_3$), 51.2 (O**C**H$_3$), 42.3 (**C**H$_2$CHO), 31.3 (**C**H$_2$C), 28.2 (**C**H$_2$C), 27.9 (**C**H$_2$CH), 24.3 (**C**H$_2$CH), 23.2 (**C**H$_3$), 23.1 (**C**H$_3$), 20.7 (**C**H$_3$).
LRMS (ES+ ionisation)	331.3 ([M+K]$^+$, 100%).

(2*Z*,6*Z*,10*E*,14*Z*)-Dimethyl 2,6,11,15-tetramethylhexadeca-2,6,10,14-tetraenedioate (333c), (2*Z*,6*E*,10*Z*)-methyl 13-formyl-2,6,11-trimethyltrideca-2,6,10-trienoate (471b) and (2*Z*,6*Z*,10*E*)-methyl 13-formyl-2,6,11-trimethyltrideca-2,6,10-trienoate (471c)



$C_{22}H_{34}O_4$.
M = 362.51 g.mol^{-1}.

$C_{18}H_{28}O_3$.
M = 292.42 g.mol^{-1}.

According to the method of Marshall *et al.*,[175] to a solution of the phosphonate $(CF_3CH_2O)_2P(O)CH_2CH_3CO_2Me$ (311 mg, 0.931 mmol) and 18 crown 6 (324 mg, 1.223 mmol) in THF (15 mL) at –78°C was added dropwise KHMDS (2.3 mL, 0.5 M solution in toluene, 1.125 mmol) followed by the dropwise addition of the aldehydes **352c,d** (90 mg, 0.405 mmol) in THF (10 mL). The resulting solution was stirred at –78°C for 2 hours and

then quenched with NH_4Cl (sat. aq. sol., 20 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and EtOAc (3 x 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (1.10 g). Purification on silica gel (100mL, EtOAc/hexane, 1:4) afford the title compound **333c** and a small amount of by-product **333d** in a 4:1 ratio as a colourless oil (60 mg, 0.166 mmol, 41%) and an inseparable mixture of compounds **471b,c** as a colourless oil (65 mg, 0.222 mmol, 55%).

Compound **333c**:

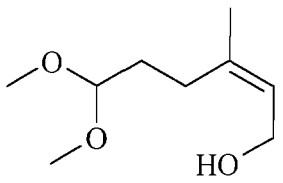
IR (cm^{-1})	2945 (b), 2922 (b), 2851 (b), 1716 (s), 1450 (w), 1436 (w), 1200 (b), 1124 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.92 (2H, tq, *J* = 7.2 and 1.7 Hz, 2 x COCC**H**CH_2), 5.17 (2H, br s, 2 x CC**H**CH_2), 3.74 (6H, s, 2 x O**C**H_3), 2.57-2.51 (4H, m, 2 x CH_2), 2.15-2.11 (4H, m, 2 x CH_2), 2.02 (4H, br t, *J* = 3.3 Hz, 2 x CH_2) 1.89 (6H, t, *J* = 1.5 Hz, 2 x CH_3), 1.69 (3H, d, *J* = 1.1 Hz, CH_3), 1.60 (3H, s, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	168.5 (**C**$OOCH_3$), 143.2 (**C**H=CCH_3), 142.8 (**C**H=CCH_3), 134.5 (CH=**C**CH_3), 127.0 (CH=**C**CH_3), 126.7 (CH=**C**CH_3), 125.7 (**C**H=CCH_3), 124.9 (**C**H=CCH_3), 51.2 (**O**CH_3), 39.1 (**C**H_2CH), 28.4 (**C**H_2C), 28.1 (**C**H_2CH), 28.0 (**C**H_2CH), 23.2 (**C**H_3), 20.7 (**C**H_3), 20.6 (**C**H_3).
LRMS (ES+ ionisation)	385.5 ($[M+Na]^+$, 85%), 417.5 (100%).

Compounds **471b,c**:

IR (cm^{-1})	2945 (b), 2921 (b), 2895 (b), 2718 (b), 1720 (s), 1445 (w), 1365 (b), 1209 (b), 1124 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.79 (1H, t, *J* = 1.7 Hz, C**H**O), 9.78 (1H, t, *J* = 1.7 Hz, C**H**O), 5.93 (2H, br s, 2 x COCC**H**CH_2), 5.17 (4H, br s, 2 x CC**H**CH_2), 3.74 (6H, s, 2 x O**C**H_3), 2.55-2.50 (8H, m, 4 x CH_2), 2.37-2.35 (4H, m, 2 x CH_2), 2.11 (4H, br s, 2 x CH_2), 2.14-2.01 (8H, m, 4 x CH_2), 1.89 (6H, t, m, 2 x CH_3) and 1.69 (6H, s, 2 x CH_3), 1.27 (6H, s, 2 x CH_3).
^{13}C-NMR	202.6 (**C**HO), 202.3 (**C**HO), 168.7 (**C**$OOCH_3$),

(75MHz, $CDCl_3$, ppm)	143.1(**C**H=CCH$_3$), 142.7 (**C**H=CCH$_3$), 134.7 (CH=**C**CH$_3$), 133.2 (CH=**C**CH$_3$), 126.5 (CH=**C**CH$_3$), 125.5 (**C**H=CCH$_3$), 125.3 (**C**H=CCH$_3$), 124.6 (**C**H=CCH$_3$), 51.2 (O**C**H$_3$), 42.3 (**C**H$_2$CHO), 42.1 (**C**H$_2$CHO), 31.9 (**C**H$_2$C), 31.4 (**C**H$_2$C), 28.4 (**C**H$_2$C), 28.2 (**C**H$_2$C), 28.0 (**C**H$_2$CH), 27.9 (**C**H$_2$CH), 24.3 (**C**H$_2$CH), 23.2 (**C**H$_3$), 23.1 (**C**H$_3$), 20.6 (**C**H3), 20.7 (**C**H$_3$).
LRMS (ES+ ionisation)	331.3 ([M+K]$^+$, 100%), 622.5 ([2M+K]$^+$, 35%).

(*Z*)-6,6-Dimethoxy-3-methyl-hex-2-en-1-ol (472) [176]



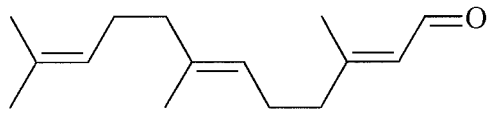
$C_9H_{18}O_3$.
M = 174.2 g.mol^{-1}.

According the method of Germain *et al.*,[176] to aldehyde **19b** (7.00 g, 41.12 mmol) in MeOH (300 mL) was added 4M hydrogen chloride in dioxane (2.1 mL, 8.24 mmol). The mixture was stirred at room temperature for 4 hours before the addition of K_2CO_3 (2.25 g, 16.34 mmol). The mixture was stirred overnight and solvents were removed. NH_4Cl (sat. aq. sol., 50 mL) was added and the aqueous phase extracted with EtOAc (5 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the crude product as an orange oil (8 g). Purification on silica gel (200 mL, EtOAc/hexane, 2:3) afforded the title product **472** as a yellow oil (6.30 g, 36.17 mmol, 88%). Spectroscopic data were in agreement with that reported in the literature.[176]

IR (cm^{-1})	3409 (b), 2959 (b), 2926 (b), 2822 (b), 1663 (s), 1446 (w), 1124 (w), 1053 (b).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.46 (1H, t, *J* = 7.2 Hz, C**H**C), 4.31 (1H, t, *J* = 5.9 Hz, OC**H**CH$_2$), 4.05 (2H, d, *J* = 7.2 Hz, C**H$_2$**OH), 3.27 (6H, s, 2 x OC**H$_3$**), 2.45 (1H, br s, O**H**), 2.11 (2H, t, *J* = 7.2 Hz, C**H$_2$**), 1.67 (3H, s, C**H$_3$**), 1.67-1.65 (2H, m, C**H$_2$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	138.6 (CH=**C**CH$_3$), 125.0 (**C**H=CCH$_3$), 102.9 (**C**O), 58.3 (**C**H$_2$OH), 52.1 (O**C**H$_3$), 29.6 (**C**H$_2$CH), 26.4 (**C**H$_2$C), 22.9 (2 x **C**H$_3$).

LRMS (ES+ ionisation) 196.9 ($[M+Na]^+$, 15%), 379.3 (100%).

(2*E*,6*E*) Farnesal (320) [118,177]



$C_{15}H_{24}O$.
M = 220.36 g.mol^{-1}.

Method 1:

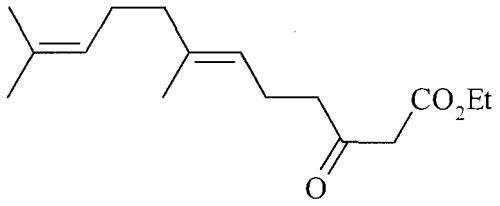
According to the method of Cane *et al.*,[177] farnesol **319** (100 mg, 0.45 mmol) was dissolved in hexane (5 mL) and MnO_2 (1.7 g) was added in one portion. The solution was left to stir overnight. Celite was then added, the solids were filtered off and the solvents were evaporated. The residue was dissolved in hexane, filtered through a pad of silica and concentrated *in vacuo* to give the crude product as a yellow oil (98 mg). Purification on silica gel (15 g, EtOAc/hexane, 1:9) afforded the title product **320** as a yellow oil (54 mg, 0.25 mmol, 56%) as well as recovered starting material (41 mg, 0.18 mmol, 40%).

Method 2:

Acording to the method of Zoller *et al.*,[118] farnesol **319** (302 mg, 1.36 mmol) was dissolved in dry CH_2Cl_2 (15 mL) before the addition of $BaMnO_4$ (3.50 g, 13.6 mmol). The resulting mixture was stirred for 4 days. The solution was filtered on a pad of celite and concentrated *in vacuo* to give the title product **320** as a yellow oil (262 mg, 1.19 mmol, 88%). Spectroscopic data were in agreement with that reported in the literature.[118,177]

IR (cm^{-1})	2967 (s), 2917 (s), 2850 (s), 1678 (s), 1628 (w), 1439 (m), 1379 (m), 1193 (m), 1119 (m).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.97 (1H, d, *J* = 8.1 Hz, C**H**O), 5.86 (1H, d, *J* = 7.4 Hz, =C**H**CHO), 5.06 (2H, m, 2 × =C**H**), 2.12 (3H, s, C**H**$_3$=CHCHO), 2.22-2.09 (4H, m, C**H**$_2$C**H**$_2$), 2.05-2.00 (4H, m, C**H**$_2$C**H**$_2$), 1.59 (3H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.56 (3H, s, C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	191.3 (**C**HO), 163.9 ((CH$_3$)**C**=CH-CHO), 136.5 ((CH$_3$)**C**=C), 131.4 ((CH$_3$)$_2$**C**=C), 127.4 (C=**C**-CHO), 124.1 ((CH$_3$)$_2$C=**C**H), 122.4 (CH$_3$C=**C**H), 40.6 (**C**H$_2$), 39.6 (**C**H$_2$), 26.6 (**C**H$_2$), 25.7 (**C**H$_3$), 25.6 (**C**H$_2$), 17.7 (**C**H$_3$), 17.6 (**C**H$_3$), 16.0 (**C**H$_3$).

Ethyl (6*E*)-7,11-dimethyl-3-oxo-6, 10-dodecadienoate (317b) [178]

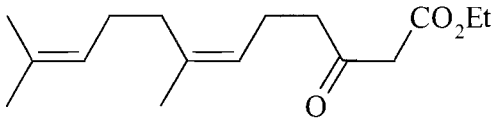


$C_{16}H_{26}O_3$.
M = 266.39 g.mol^{-1}.

To an ice-cooled suspension of sodium hydride (1.16 g of a 60% dispersion in mineral oil, 29.0 mmol) in dry THF (20 mL) was added dropwise ethyl acetoacetate (3.75 mL, 29.0 mmol). After 10 mins, *n*-BuLi (14.3 mL of a 2.1 M solution in hexanes, 29.0 mmol) was added and the mixture was stirred for a further 15 min. A solution of geranyl chloride **309b** (4.75 g, 27.5 mmol) in dry THF (25 mL) was added to the reaction and the resulting orange mixture allowed to warm to room temperature. After 30 min a solution of HCl (20 mL of 3.5 M aq.) and Et_2O (50 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with water until neutral, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a rusty orange oil. Purification on SiO_2 (300 mL, Et_2O/hexane, 1:33, then 1:10 and 1:3) gave the title compound **317b** as a light gold oil (3.69 g, 14.0 mmol, 52%). Spectroscopic data were in agreement with that reported in the literature.[178]

IR (cm^{-1})	2966 (m), 2914 (m), 2858 (m), 1741 (s), 1716 (s), 1649 (m), 1629 (m), 1445 (m), 1404 (m), 1368 (m), 1312 (s) and 1235 (s)
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.08 (2H, tt, J = 6.0 and 1.1 Hz, =C**H**), 4.20 (2H, q, J = 7.0 Hz, O**CH$_2$**), 3.42 (2H, s, COC**H$_2$**CO), 2.57 (2H, t, J = 7.0 Hz, CH$_2$C**H$_2$**CO), 2.30 (2H, q, J = 7.1 Hz, =CHC**H$_2$**), 2.15-2.0 (4H, m, =CHC**H$_2$**C**H$_2$**C=), 1.69 (3H, s, C**H$_3$**), 1.61 (3H, s, C**H$_3$**), 1.59 (3H, s, C**H$_3$**), 1.29 (3H, t, J = 7.2 Hz, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	202.6 (**C**O), 167.2 (**C**OO), 136.7 ((CH$_3$)**C**=), 131.4 ((CH$_3$)$_2$**C**=), 124.1 ((CH$_3$)$_2$=**C**H), 122.1 (C(CH$_3$)=**C**H), 61.3 (O-**C**H$_2$), 49.4 (CO**C**H$_2$CO), 43.0 (**C**H$_2$CO), 39.6 (=**C**(CH$_3$)CH$_2$), 26.6 (=CH**C**H$_2$), 25.7 (**C**H$_3$), 22.1 (COCH$_2$**C**H$_2$), 17.6 (**C**H$_3$), 16.0 (**C**H$_3$), 14.1 (O-CH$_2$**C**H$_3$).

Ethyl (6*Z*)-7,11-dimethyl-3-oxo-6, 10-dodecadienoate (317a) [178]

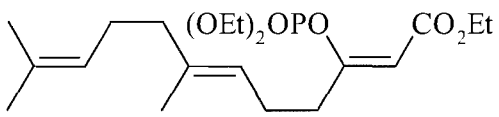


$C_{16}H_{26}O_3$.
M = 266.39 g.mol^{-1}.

Following the method used for the preparation of β–keto ester **317b**, neryl chloride **309a** (10.0 g, 57.90 mmol) afforded the title compound **317a** as a yellow oil (12.1 g, 45.42 mmol, 78%) after purification on silica gel (300 mL, Et_2O/hexane, 2:3). Spectroscopic data were in agreement with that reported in the literature.[178]

IR (cm^{-1})	2960 (m), 2920 (m), 2864 (m), 1740 (s), 1718 (s), 1651 (m), 1627 (m), 1439 (m), 1401 (m), 1367 (m), 1311 (s), 1234 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.10 (2H, m, C=C**H**), 4.18 (2H, q, *J* = 7.2 Hz, O**C**$\mathbf{H_2}$), 3.42 (2H, s, COC$\mathbf{H_2}$CO), 2.55 (2H, t, *J* = 7.5 Hz, CH_2C$\mathbf{H_2}$CO), 2.30 (2H, q, *J* = 7.3 Hz, =CHC$\mathbf{H_2}$), 2.03 (4H, m, =CHC$\mathbf{H_2}$C$\mathbf{H_2}$C=), 1.69 (6H, s, C$\mathbf{H_3}$), 1.60 (3H, s, C$\mathbf{H_3}$), 1.26 (3H, t, *J* = 7.2 Hz, OCH_2C$\mathbf{H_3}$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	202.6 (**C**OCH_2), 167.3 (**C**OO), 136.8 ((CH_3)**C**), 131.7 ($(CH_3)_2$**C**), 124.2 ($(CH_3)_2$C=**C**H), 123.1 ((CH_3)C=**C**H), 61.4 (O**C**H_2), 49.4 (CO**C**H_2CO), 43.3 (CH_2**C**H_2CO), 32.0 (**C**H_2C(CH_3)), 26.6 (**C**$H_2$$CH_2$CO), 25.8 ($(\mathbf{C}H_3)_2$C), 23.4 (**C**$H_3$), 22.0 (**C**$H_3$), 17.7 (**C**$H_3$), 14.2 ($OCH_2$**C**$H_3$).
LRMS (ES+ ionisation)	267 ($[M+H]^+$, 90%).

Ethyl (2*Z*, 6*E*)-3-[(diethoxyphophosryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (318a)



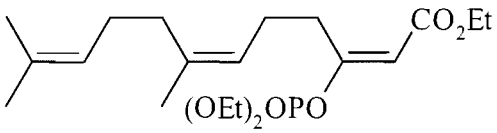
$C_{20}H_{35}O_6P$.
M = 402.44 g.mol^{-1}.

To an ice-cooled solution of LiHMDS (4.12 mL of a 1.0 M solution in THF, 4.12 mmol) in dry THF (20 mL) was added a solution of β-keto ester **317a** (1.00 g, 3.75 mmol) in dry THF (15 mL). After 15 mins $(EtO)_2POCl$ (0.6 mL, 4.12 mmol) was added dropwise and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with NH_4Cl (sat. aq. sol., 20 mL) and the organic layer was separated then washed with NH_4Cl (sat. aq. sol., 2 × 20 mL) and with $NaHCO_3$ (sat. aq. sol., 3 x 20 mL), dried ($MgSO_4$), filtered

and concentrated *in vacuo* to give a yellow oil. Purification on SiO_2 (85 g, Et_2O/hexane, 2:3) afforded title compound **318a** as a pale yellow oil (1.20 g, 3.03 mmol, 81%).

IR (cm^{-1})	2981 (w), 2919 (w), 2858 (w), 1721 (m), 1665 (m), 1445 (w), 1373 (w), 1281 (m), 1199 (m), 1143 (m), 1025 (s), 984 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.32 (1H, s, =C**H**COO), 5.09-5.02 (2H, qt, *J* = 6.2 and 1.1 Hz, =C**H**), 4.22 (4H, qu, *J* = 7.0 Hz, P-OC**H**$_2$), 4.13 (2H, q, *J* = 7.0 Hz, O-C**H**$_2$CH$_3$), 2.42 (2H, t, *J* = 7.4 Hz, C**H**$_2$C(OP)=), 2.25 (2H, q, *J* = 7.4 Hz, =CH$_2$C**H**$_2$), 2.07-1.93 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.65 (3H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.57 (3H, s, C**H**$_3$), 1.34 (6H, dt, *J* = 7.4 and 1.1 Hz, PO-CH$_2$C**H**$_3$), 1.25 (3H, t, *J* = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	163.7 ((PO)**C**=), 161.4 (**C**OO), 136.9 ((CH$_3$)**C**==, 131.4 ((CH$_3$)$_2$**C**=), 124.1 ((CH$_3$)$_2$C=**C**H), 121.8 (=**C**H), 105.3 ((PO)C=**C**H), 105.2 ((PO)C=**C**H), 64.7 (d, *J* = 5.6 Hz, P-O**C**H$_2$), 59.8 (O-**C**H$_2$), 39.6 (**C**H$_2$C=), 35.2 (**C**H$_2$C(OP)=), 26.6 (=CH**C**H$_2$), 25.6 (**C**H$_3$), 24.8 (=CH**C**H$_2$), 17.6 (**C**H$_3$), 16.1 (d, *J* = 6.7 Hz , P-OCH$_2$**C**H$_3$), 16.0 (P-OCH$_2$**C**H$_3$), 14.2 (O- CH$_2$**C**H$_3$).

Ethyl (2*E*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (318c)

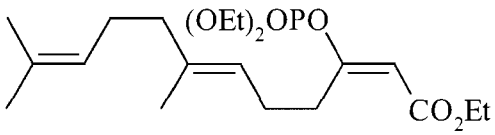


$C_{20}H_{35}O_6P$.
M = 402.44 g.mol^{-1}.

To an ice-cooled solution of DMAP (102 mg, 0.84 mmol) and Et_3N (1.2 mL, 8.4 mmol) in DMPU (15 mL) was added a solution of β-keto ester **317b** (2.00 g, 7.5 mmol) in DMPU (9.0 mL). After 50 mins the mixture was cooled to –20 °C and $(EtO)_2POCl$ (1.3 mL, 8.9 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. The mixture was diluted with Et_2O (30 mL) and acidified with HCl (2N, 40 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the organic layers combined, washed with saturated $CuSO_4$ solution (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting rusty orange oil (crude ratio 2*E*:2*Z* > 49:1 by 1H NMR) was purified on SiO_2 (250 g, Et_2O/hexane, 1:4 then 1:1) to give the title product **318c** as a pale yellow oil (2.15 g, 5.34 mmol, 71%).

IR (cm^{-1}) †	2976 (w), 2914 (w), 2853 (w), 1716 (m), 1644 (m), 1445 (w), 1373 (w), 1281 (m), 1122 (m), 1030 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.82 (1H, d, *J* = 1.5 Hz, =C**H**COO), 5.15 (1H, td, *J* = 7.0 and 1.5 Hz, =C**H**), 5.12-5.07 (1H, m, =C**H**), 4.17 (4H, qu, *J* = 7.4 Hz, P-OC**H**$_2$), 4.12 (2H, q, *J* = 7.1 Hz, O-C**H**$_2$), 2.79 (2H, dt, *J* = 7.7 and 1.5 Hz, =CHC**H**$_2$), 2.25 (2H, q, *J* = 7.6 Hz, C**H**$_2$C(CH_3)=), 1.98-2.10 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.66 (6H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.35 (6H, td, *J* = 7.4 and 1.5 Hz, P-OCH_2C**H**$_3$), 1.25 (3H, t, *J* = 7.4 Hz, O-CH_2C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	166.2 (**C**OO), 166.1 (**C**(OP)=), 136.5 (**C**(CH_3)=), 131.5 ((CH_3)$_2$**C**=), 124.2 (=**C**H), 123.2 (=**C**H), 105.4 (**C**HCOO), 64.8 (d, *J* = 5.6 Hz P-O**C**H_2), 60.0 (O-**C**H_2), 32.0 (**C**H_2C(CH_3)=), 31.9 (**C**H_2C(OP)=), 26.5 (=CH**C**H_2), 25.7 ((CH_3)$_2$**C**=), 25.2 (**C**H_3C=), 23.3 (=CH**C**H_2), 17.6 ((CH_3)$_2$C=), 16.1 (d, *J* = 6.7 Hz, P-OCH_2**C**H_3), 16.0 (P-OCH_2**C**H_3), 14.2 (O-CH_2**C**H_3).
LRMS (ES+ ionisation)	425.3 ($[M+Na]^+$, 38%), 420.3 ($[M+NH_4]^+$, 100%), 403.3 ($[M+H]^+$, 100%).
HRMS (ESI)	Calculated : $C_{20}H_{36}O_6P$ = 403.2244. Found : 403.2242.

Ethyl (2*E*, 6*E*)-3-[(diethoxyphophoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (318b)



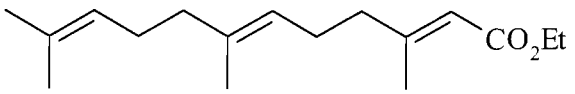
$C_{20}H_{35}O_6P$.
M = 402.44 g.mol^{-1}.

Following the procedure for the preparation of the *E*-enol phosphate **318c**, the β-keto ester **317a** (2.00 g, 7.5 mmol) afforded a crude gold green oil (crude ratio 2*E*:2*Z* > 49:1 by 1H NMR), which was purified on SiO_2 (180 g, Et_2O/hexane, 2:5) to give **318b** as a very pale yellow oil (2.30 g, 5.7 mmol, 76%).

IR (cm^{-1})	2976 (w), 2914 (w), 2853 (w), 1716 (m), 1644 (m), 1445 (w), 1373 (w), 1281 (m), 1122 (m), 1030 (s).
^{1}H-NMR	5.84 (1H, d, *J* = 1.8 Hz, =C**H**COO), 5.14 (1H, td, *J* = 7.4 and 1.5

(300MHz, $CDCl_3$, ppm)	Hz, =C**H**), 5.07 (1H, t, *J* = 5.9 Hz, =C**H**), 4.18 (4H, qu, *J* = 7.4 Hz, P-OC**H**$_2$), 4.14 (2H, q, *J* = 7.1 Hz, O-C**H**$_2$), 2.80 (2H, td, *J* = 7.7 and 1.1 Hz, C**H**$_2$C(PO)=), 2.26 (2H, q, *J* = 7.4 Hz, =CHC**H**$_2$), 2.11-1.92 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.67 (6H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.35 (6H, t, *J* = 1.1 and 7.0 Hz, P-OCH$_2$C**H**$_3$), 1.25 (3H, t, *J* = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	166.2 (**C**OO), 166.1 (**C**(OP)=), 136.5 (**C**(CH$_3$)=), 131.5 ((CH$_3$)$_2$**C**=), 124.2 (=**C**H), 123.2 (=**C**H), 105.4 ((PO)C=**C**H), 64.8 (d, *J* = 6.7 Hz, P-O**C**H$_2$), 64.7 (P-O**C**H$_2$), 60.0 (O-**C**H$_2$), 39.8 (**C**H$_2$C(CH$_3$)=), 31.9 (**C**H$_2$C(OP)=), 31.9 (=CH**C**H$_2$), 26.7 ((**C**H$_3$)$_2$C=), 25.8 (=CH**C**H$_2$), 25.2 (**C**H$_3$)C=),17.6 ((**C**H$_3$)$_2$C=), 16.1 (d, *J* = 6.7 Hz , P-OCH$_2$**C**H$_3$), 14.2 (O-CH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	425.2 ($[M+Na]^+$, 100%).
HRMS	Calculated : $C_{20}H_{36}O_6P$ = 425.2063. Found : 425.2071.

General procedure for the methylcopper-catalysed Grignard substitution of enol phosphates: Ethyl (2*E*, 6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (316a)



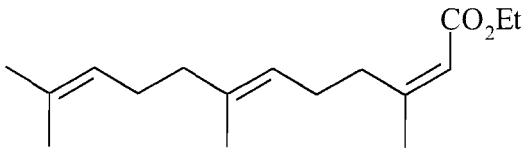
$C_{17}H_{28}O_2$.
M = 264.39 g.mol^{-1}.

MeLi (3.0 mL of a 1.6 M solution in Et_2O, 4.1 mmol) was added dropwise to a suspension of CuI (800 mg, 4.21 mmol) in THF (15 mL) at 0°C. The orange mixture was stirred at 0°C for 15 mins, before cooling to –30 °C. MeMgCl (2.3 mL of a 3 M solution in THF, 6.8 mmol) was added dropwise maintaining the temperature below –25 °C. After 30 min the resulting light brown suspension was treated with a solution of enol phosphate **318a** (550 mg, 1.37 mmol) in THF (20 mL), and the mixture stirred at –30°C for 3 h, then quenched by pouring quickly onto an ice-cold NH_4Cl (sat. aq. sol.) and ammonia solution. The organic layer was diluted with Et_2O (20 mL) and washed with a mixture of NH_4Cl (sat. aq. sol.) and ammonia solution until the blue colouring disappeared. The organic layer was washed with brine (3 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow/orange oil. Purification on SiO_2 (20 g, Et_2O/hexane, 1:10) afforded the title product **316a** as a colourless

oil (350 mg, 1.32 mmol, 96%, ratio 2*Z*:2*E*, >99:1 by GC). Spectroscopic data were in agreement with that reported in the literature.[179]

IR (cm^{-1})	2971 (w), 2919 (w), 2853 (w), 1716 (s), 1650 (m), 1445 (m), 1378 (m), 1224 (s), 1143 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.67 (1H, s, =C**H**COO), 5.08 (2H, m, =C**H**), 4.14 (2H, q, J = 7.4 Hz, O**CH$_2$**), 2.20-2.15 (4H, m, =CHC**H$_2$**C**H$_2$**), 2.16 (3H, s, **CH$_3$**C=CHCOO), 2.04 (2H, t, J = 6.2 Hz, **CH$_2$**C(CH$_3$)=), 2.02-1.96 (2H, m, =CHC**H$_2$**), 1.68 (3H, s, C**H$_3$**), 1.60 (6H, s, 2 x C**H$_3$**), 1.27 (3H, t, J = 7.4 Hz, O-CH$_2$C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	166.9 (**C**OO), 159.8 (**C**=CHCOO), 136.1 (CH$_3$**C**=), 131.4 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**H), 122.9 (CH$_3$C=**C**H), 115.6 (=**C**HCOO), 59.4 (O**C**H$_2$), 40.9 (**C**H$_2$C(CH$_3$)=), 39.7 (**C**H$_2$C(CH$_3$)=), 26.7 (=CH**C**H$_2$), 25.9 (=CH**C**H$_2$), 25.7 (**C**H$_3$), 18.8 (**C**H$_3$), 17.6 (**C**H$_3$), 16.0 (**C**H$_3$C=CHCOO), 14.3 (O-CH$_2$**C**H$_3$).

Ethyl (2*Z*, 6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (316b) [178]



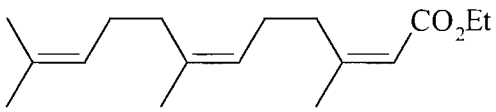
$C_{17}H_{28}O_2$.
M = 264.39 g.mol^{-1}.

Following the General procedure for the methylcopper-catalysed Grignard substitution of enol phosphate **318a**, enol phosphate **318b** (660 mg, 1.64 mmol) afforded **316b** as a colourless oil (420 mg, 1.59 mmol, 97%, ratio 2*E*:2*Z*, >99:1 by GC). ^{1}H-NMR data were in agreement with that reported in the literature.[178]

IR (cm^{-1})	2971 (m), 2914 (m), 2858 (w), 1716 (s), 1650 (m), 1445 'm), 1373 (m), 1240 (w), 1209 (w), 1153 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.65 (1H, s, =C**H**COO), 5.17 (1H, td, J = 7.0 and 1.1 Hz, =C**H**), 5.09 (1H, tt, J = 5.5 and 1.1 Hz, =C**H**), 4.12 (2H, q, J = 7.4 Hz, O**CH$_2$**), 2.64 (2H, t, J = 7.4 Hz, **CH$_2$**C(CH$_3$)=), 2.16 (2H, q, J =

	7.4 Hz, =CHC**H**$_2$), 2.12-1.95 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.89 (3H, s, C**H**$_3$C=CHCO$_2$Et), 1.68 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.26 (3H, t, J = 7.0 Hz, OCH$_2$C**H**$_3$).
^{13}C-NMR (75MHz, CDCl$_3$, ppm)	166.3 (**C**OO), 160.1 (**C**=CHCOO), 135.7 (CH$_3$**C**=), 131.3 ((CH$_3$)$_2$**C**=), 124.3 (CH$_3$**C**=), 123.5 ((CH$_3$)$_2$**C**=), 116.2 (=**C**HCOO), 59.4 (O**C**H$_2$), 39.7 (**C**H$_2$C(CH$_3$)=), 33.4 (**C**H$_2$C(CH$_3$)=), 26.7 (=CH**C**H$_2$), 25.6 (**C**H$_3$), 25.3 (**C**H$_3$), 17.6 (**C**H$_3$), 15.9 ((**C**H$_3$)C=CHCOO), 14.3 (OCH$_2$**C**H$_3$).

Ethyl (2*Z*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (316c) [180]

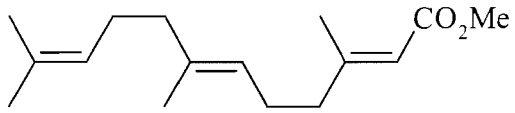


C$_{17}$H$_{28}$O$_2$.
M = 264.39 g.mol^{-1}.

Following the general procedure for the methylcopper-catalysed Grignard substitution of enol phosphate **318a**, enol phosphate **318c** (1.0 g, 2.5 mmol) afforded **316c** as a pale yellow oil (520 mg, 2.0 mmol, 80%, ratio 2E:2Z, >11:1 by GC). ^{1}H NMR data were in agreement with that reported in the literature.[180]

IR (cm^{-1})	2971 (m), 2919 (m), 2853 (w), 1716 (s), 1644 (m), 1450 (m), 1378 (m), 1240 (m), 1163 (s), 1143 (s).
^{1}H-NMR (300MHz, CDCl$_3$, ppm)	5.66 (1H, s, =C**H**COO), 5.17 (1H, td, J = 7.4 and 1.5 Hz, =C**H**), 5.14-5.10 (1H, m, =C**H**), 4.13 (2H, q, J = 7.0 Hz, OC**H**$_2$), 2.64 (2H, t, J = 7.4 Hz, =C(CH$_3$)C**H**$_2$), 2.16 (2H, q, J = 7.0 Hz, =CHC**H**$_2$), 2.05-2.04 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.88 (3H, s, C**H**$_3$C=CHCO$_2$Et), 1.69 (6H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.27 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (75MHz, CDCl$_3$, ppm)	166.3 (**C**OO), 160.0 (**C**=CHCOO), 135.8 (**C**=CH), 131.5 ((CH$_3$)$_2$**C**=), 124.4 (=**C**H), 124.3 (=**C**H), 116.2 (=**C**HCOO), 59.4 (O**C**H$_2$), 33.6 (**C**H$_2$C=CH), 31.9 (**C**H$_2$C=CH), 26.6 (=CH**C**H$_2$), 25.7 (**C**H$_3$), 25.4 (**C**H$_3$), 23.4 (**C**H$_3$C=CHCO$_2$Et), 17.6 (**C**H$_3$), 14.3 (OCH$_2$**C**H$_3$).

(*E*,*E*) Methyl Farnesoate (26) [177]



$C_{16}H_{26}O_2$.
M = 250.38 g.mol^{-1}.

Method 1 :

According to the method of Cane *et al.*,[177] farnesal **320** (82 mg, 0.36 mmol) was dissolved in dry MeOH (5.4 mL) before the sequential addition of NaCN (105 mg, 2.1 mmol), MnO_2 (700 mg, 8.05 mmol) and AcOH (35 µL, 0.55 mmol) at room temperature. The resulting mixture was stirred for 24 hours. The reaction mixture was filtered through a pad of celite and diluted with ether (15 mL). The organic phase was washed with $NaHCO_3$ (sat. aq. sol., 3 ×20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a dark yellow oil (100 mg). Purification silica gel (30g, hexane/Et_2O, 9:1) afforded the title product **26** as a colourless oil (17 mg, 0.08 mmol, 23%). The spectroscopic data were in good agreement with that reported in the literature.[177]

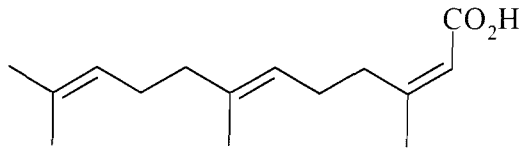
Method 2 :

Farnesal **320** (81 mg, 0.36 mmol) was dissolved in dry MeOH (5.5 mL) before the sequential additionof NaCN (100 mg, 2.0 mmol), $BaMnO_4$ (1.97 g, 7.70 mmol) and AcOH (40 µL, 0.57 mmol) at room temperature. The resulting mixture was stirred for 24 hours. The reaction mixture was filtered through a pad of celite and diluted with ether (15 mL). The organic phase was washed with $NaHCO_3$ (sat. aq. sol., 4 ×15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a dark yellow oil (95 mg). Purification silica gel (30g, hexane/Et_2O, 9:1) afforded the title product **26** as a colourless oil (20 mg, 0.10 mmol, 28%). The spectroscopic data were in good agreement with that reported in the literature.[177]

IR (cm^{-1})	2917 (m), 2853 (m), 1712 (s), 1649 (m), 1436 (m), 1385 (w), 1355 (w), 1257 (m), 1227 (s), 1148 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.68 (1H, s, =C**H**-COOCH$_3$), 5.09 (2H, m, 2 × =C**H**), 3.69 (3H, s, -OC**H$_3$**), 2.17 (3H, s, C**H$_3$**C=CHCOOCH$_3$), 2.08-1.98 (2H, m, C**H$_2$**C=CHCOOCH$_3$), 1.69 (3H, s, C**H$_3$**), 1.61 (6H, s 2 × C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	167.3 (**C**OO), 160.3 ((CH$_3$)**C**=C), 136.2 ((CH$_3$)**C**=C), 131.4 ((CH$_3$)$_2$**C**=C), 124.2 (C=**C**H), 122.8 (C=**C**H), 115.2 (**C**HCOO),

50.8 (OCH_3), 40.9 (CH_2), 39.7 (CH_2), 26.6 (CH_2), 25.9 (CH_3), 25.7 (CH_2), 18.8 (CH_3), 17.7 (CH_3), 16.0 (CH_3).

General procedure for the basic hydrolysis of the ester moiety of the trienoates: (2*Z*, 6*E*)-3,7,11-trimetryl-2,6,10-dodecatrienoic acid (322b) [181]

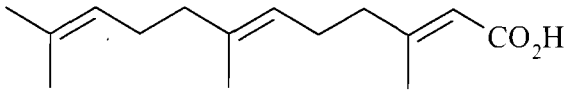


$C_{15}H_{24}O_2$.
M = 236.39 g.mol^{-1}.

According to the method of Kulkarni *et al.*,[181] at room temperature, a solution of NaOH (230 mg, 5.7 mmol) and $NaHCO_3$ (sat. aq. sol., 40 mg, 0.45 mmol) in water (2.7 mL) was added to a solution of trienoate **316b** (235 mg, 0.89 mmol) in MeOH (2 mL). The resulting solution was heated to reflux and stirred for 24 hours. The reaction was cooled, washed with hexane (20 mL) and carefully neutralised with HCl (2 M, 15 mL) taking care to keep the temperature at 0°C. The aqueous layer was extracted with ether (4 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product **322b** as a yellow oil (180 mg, 0.76 mmol, 76%) which was used without further purification. Spectroscopic data were in agreement with that reported in the literature.[181]

IR (cm^{-1})	2964 (b), 2922 (b), 1687 (s), 1635 (s), 1441 (s), 1248 (s), 925 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.65 (1H, d, *J* = 1.5 Hz, =C**H**COO), 5.15 (1H, td, *J* = 7.3 and 1.1 Hz, =C**H**), 5.10 (1H, br s, O**H**), 5.09 (1H, tt, *J* = 7.0 and 1.1 Hz, =C**H**), 2.66 (2H, t, *J* = 7.4 Hz, C**H$_2$**C(CH_3)=), 2.20 (4H, m, =CHC**H$_2$**C**H$_2$**), 2.12-1.95 (2H, m, =CHC**H$_2$**), 1.94 (3H, m, C**H$_3$**C=CHCO$_2$Et), 1.69 (3H, s, C**H$_3$**), 1.63 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	171.8 (**C**OO), 163.7 (**C**=CHCOO), 136.3 (CH_3**C**=), 131.4 ((CH_3)$_2$**C**=), 124.3 (CH_3**C**=), 123.3 ((CH_3)$_2$**C**=), 115.7 (=**C**HCOO), 41.5 (**C**H$_2$C(CH_3)=), 39.7 (**C**H$_2$C(CH_3)=), 26.7 (=CH**C**H$_2$), 25.7 (**C**H$_3$), 25.3 (**C**H$_3$), 17.7 (**C**H$_3$), 16.0 ((CH_3)C=CHCOO).
LRMS (ES- ionisation)	384.8 ([M+2Na]$^{2-}$, 100%).

(2*E*, 6*E*)-3,7,11-Trimetryl-2,6,10-dodecatrienoic acid (322a) [181]

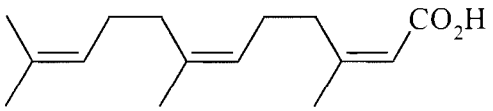


$C_{15}H_{24}O_2$.
M = 236.39 g.mol^{-1}.

Following the general procedure for the basic hydrolysis of the ester moiety, trienoate **316a** (600 mg, 2.27 mmol) afforded the crude acid **322a** as a yellow oil (415 mg, 1.76 mmol, 78%). Spectroscopic data were in agreement with that reported in the literature.[181]

IR (cm^{-1})	2964 (b), 2925 (b), 1685 (s), 1634 (s), 1443 (s), 1247 (s), 925 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.70 (1H, s, =C**H**COO), 5.09 (2H, m, 2 × =C**H**), 5.08 (1H, br s, O**H**), 2.18 (3H, s, C**H$_3$**), 2.20-2.00 (8H, m, 4 × C**H$_2$**), 1.69 (3H, s, C**H$_3$**), 1.61 (6H, s, 2 × C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	172.3 (**C**OO), 163.2 (**C**=CHCOO), 136.3 (CH_3**C**=), 131.4 ((CH_3)$_2$**C**=), 124.1 (CH_3**C**=), 122.7 (**C**H=), 115.1 (=**C**HCOO), 41.2 (**C**H$_2$C(CH_3)=), 39.6 (**C**H$_2$C(CH_3)=), 26.6 (=CH**C**H$_2$), 25.9 ((=CH**C**H$_2$), 25.7 (**C**H$_3$), 19.1 (**C**H$_3$), 17.7 (**C**H$_3$), 16.0 ((CH_3)C=CHCOO).
LRMS (CI - GCMS)	236 ([M]$^+$, 100%).

(2*Z*, 6*Z*)-3,7,11-Trimetryl-2,6,10-dodecatrienoic acid (322c)



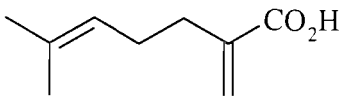
$C_{15}H_{24}O_2$.
M = 236.39 g.mol^{-1}.

Following the general procedure for the basic hydrolysis of the ester moiety, trienoate **316c** (4.00 g, 15.13 mmol) afforded the crude acid **322c** as a yellow oil (3.29 g, 13.91 mmol, 92%) which was used without further purification.

IR (cm^{-1})	2964 (b), 2922 (b), 1687 (s), 1635 (s), 1441 (s), 1248 (s), 925 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.69 (1H, s, =C**H**COO), 5.15 (1H, t, J = 7.3 Hz, =C**H**), 5.15 (1H, br s, O**H**), 5.12 (1H, m, =C**H**), 2.66 (2H, t, J = 7.8 Hz,

	$CH_2C(CH_3)$=), 2.18 (4H, m, =CHC**H**$_2$C**H**$_2$), 2.12-1.95 (2H, m, =CHC**H**$_2$), 1.93 (3H, s, C**H**$_3$C=CHCO$_2$H), 1.69 (6H, s, 2 x C**H**$_3$), 1.62 (3H, s, C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	170.4 (**C**OO), 163.4 (**C**=CHCOO), 136.1 (CH_3**C**=), 131.5 ((CH_3)$_2$**C**=), 124.3 (CH_3C=**C**H), 124.2 ((CH_3)$_2$C=**C**H), 115.4 (=**C**HCOO), 33.9 (**C**H$_2$C(CH_3)=), 31.9 (**C**H$_2$C(CH_3)=), 26.6 (=CH**C**H$_2$), 26.6 (**C**H$_3$), 25.7 (**C**H$_3$), 23.3 (**C**H$_3$), 17.6 ((CH_3)**C**=CHCOO).
LRMS (ES- ionisation)	384.8 ($[M+2Na]^{2-}$, 9%).

6-Methyl-2-methylenehept-5-enoic acid (473)

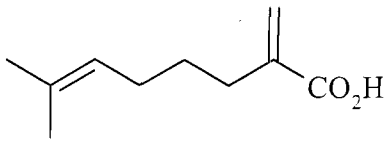


$C_9H_{14}O_2$.
M = 154.2 g.mol^{-1}.

Following the general procedure for the basic hydrolysis of the ester moiety, dienoate **421a** (100 mg, 0.649 mmol) afforded the crude product **473** as a yellow oil (82 mg, 0.532 mmol, 82%) which was used without further purification.

IR (cm^{-1})	3335 (b), 2953 (b), 2922 (b), 2854 (b) 1735 (s), 1606 (s), 1455 (s), 1377 (s), 1104 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.13 (1H, br s, CH**H**CCOO), 5.47 (1H, br s, CH**H**CCOO), 5.10 (1H, br s, O**H**), 5.08 (1H, m, =C**H**C(CH_3)$_2$), 2.26 (2H, m, C**H**$_2$C=CH$_2$), 2.12 (2H, m, =CHC**H**$_2$), 1.67 (3H, s, C**H**$_3$), 1.57 (3H, s, C**H**$_3$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	172.8 (**C**OO), 146.3 (**C**COO), 124.5 ((CH_3)$_2$**C**=), 118.2 (**C**H$_2$=C), 115.5 (**C**H=C), 31.9 (**C**H$_2$CCH$_2$=), 29.7 (**C**H$_2$C(CH_3)$_2$), 25.6 (CH_3), 22.7 (**C**H$_3$).
LRMS (ES+ ionisation)	176.3 ($[M+Na]^+$, 20%), 128.8 (100%).

7-Methyl-2-methyleneoct-6-enoic acid (474)

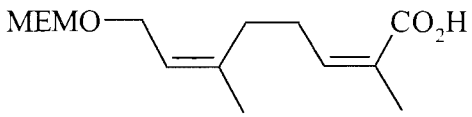


$C_{10}H_{16}O_2$.
M = 168.12 g.mol^{-1}.

Following the general procedure for the basic hydrolysis of the ester, dienoate **439a** (460 mg, 2.347 mmol) afforded the crude product **474** as a yellow oil (380 mg, 2.260 mmol, 96%) which was used without further purification.

IR (cm^{-1})	3335 (b), 2953 (b), 2922 (b), 2854 (b), 1735 (s), 1606 (s), 1455 (s), 1377 (s), 1104 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	10.88 (1H, br s, O**H**), 6.29 (1H, d, *J* = 1.5 Hz, C=C**H**H), 5.65 (1H, dd, *J* = 2.8 and 1.3 Hz, C=C**H**H), 5.12 (1H, tdd, *J* = 7.1, 2.9 and 1.5 Hz, C**H**=C), 2.31 (2H, ddd, *J* = 8.6, 7.1 and 0.9 Hz, CH_2CH_2CH=C), 2.03 (2H, app q, *J* = 7.3 Hz, $CH_2CH_2CH_2CH$=C), 1.70 (3H, q, *J* = 1.3 Hz, CH_3), 1.61 (3H, d, *J* = 0.9 Hz, CH_3), 1.54 (2H, m, , CH_2CH_2CH=C).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	172.9 (COO), 140.2 (**C**=CH_2), 131.9 (**C**$(CH_3)_2$), 126.8 (C=**C**H_2), 124.1 (**C**H=C$(CH_3)_2$), 31.0 (CH_2CCO), 28.4 (CH_2CH_2CCO), 27.5 (**C**H_2CH=C), 25.7 (CH_3), 17.7 (CH_3).
LRMS (ES+ ionisation)	190.1 (M+Na]$^+$, 25%), 128.8 (100%).

(2*Z*,6*Z*)-8-[(2-Methoxyethoxy)methoxy]-2,6-dimethylocta-2,6-dienoic acid (475)



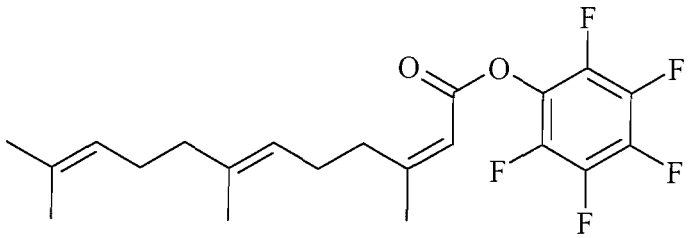
$C_{14}H_{24}O_5$.
M = 272.37 g.mol^{-1}.

Following the general procedure for the basic hydrolysis of the ester moiety, the diene **345a** (980 mg, 3.42 mmol) afforded the title product **475** as a colourless oil (860 mg, 3.16 mmol, 92%), which was used without further purification.

IR (cm^{-1})	2926 (b), 2879 (b), 1716 (s), 1687 (s), 1451 (s), 1379 (w), 1210 (w), 1167 (w), 1115 (s), 1053 (s).

^{1}H-NMR (300MHz, $CDCl_3$, ppm)	6.07 (1H, qq, *J* = 7.9 and 1.5 Hz, CC**H**), 5.36 (1H, td, *J* = 6.9 and 1.3 Hz, OCH_2CH), 4.72 (2H, s, OCH_2O), 4.01 (2H, dd, *J* = 6.9 and 1.0 Hz, OCH_2CH), 3.73-3.70 (2H, m, OCH_2), 3.64-3.62 (2H, m, OCH_2), 3.47 (3H, s, OCH_3), 2.55 (2H, qq, *J* = 7.9 and 1.5 Hz, $CHCH_2$), 2.19-2.15 (2H, m, CH_2C), 1.92 (3H, q, *J* = 1.3 Hz, CH_3), 1.77 (3H, q, *J* = 1.3 Hz, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	172.2 (**C**OO), 144.0 (**C**H=CCO_2H_3), 140.2 (CH_2CCH_3), 127.2 (**C**CH_3), 121.8 (**C**H=CCH_3), 94.6 (OCH_2O), 71.9 (CH_3OCH_2), 66.6 (OCH_2CH_2), 63.5 (OCH_2CH), 58.9 (OCH_3), 31.6 (CH_2), 28.4 (CH_2), 23.4 (CH_3), 20.5 (CH_3).
LRMS (ES+ ionisation)	311.2 ($[M+K]^+$, 100%), 583.4 ($[2M+K]^+$, 75%), 290.3 ($[M+NH_4]^+$, 45%), 567.4 ($[2M+Na]^+$, 37%), 295.2 ($[M+Na]^+$, 33%), 562.5 ($[2M+NH_4]^+$, 22%).

General procedure for the activation of the carboxylic acid with pentafluorophenol: pentafluorophenyl (2*Z*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (476b)



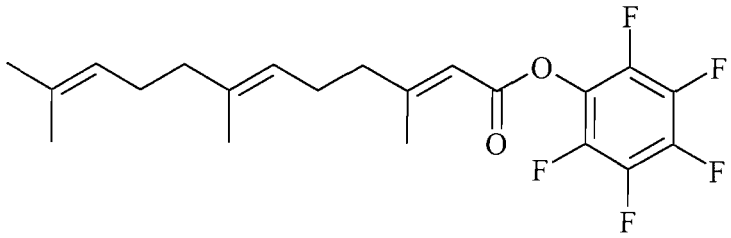
$C_{21}H_{23}F_5O_2$.
M = 402.19 g.mol^{-1}.

To a solution of acid **322b** (172 mg, 0.73 mmol) and pentafluorophenol (160 mg, 0.85 mmol) in EtOAc (6 mL) was added dropwise a solution of DCC (170 mg, 0.83 mmol) in EtOAc (8 mL). After 24 h, the mixture was diluted in hexane (40 mL) and the solids removed by filtration. The organic layer was washed with $NaHCO_3$ (sat. aq. sol., 2 × 40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil (350 mg). Purification on SiO_2 (40 g, CH_2Cl_2/hexane, 3:10) gave the title ester **476b** as a yellow oil (285 mg, 0.71 mmol, 97%).

IR (cm^{-1})	2969 (b), 2917 (b), 2851 (b), 1763 (s), 1635 (s), 1517 (s), 1441 (w), 1105 (s), 997 (w).
^{1}H-NMR	5.97 (1H, d, *J* = 1.1 Hz, =C**H**COO), 5.15 (1H, qt, *J* = 7.3 and 1.1

(300MHz, $CDCl_3$, ppm)	Hz, =C**H**), 5.10 (1H, br s, -O**H**), 5.08 (1H, tt, *J* = 6.6 and 1.5 Hz, =C**H**), 2.71 (2H, t, *J* = 7.4 Hz, $CH_2C(CH_3)$=), 2.27 (4H, m, =CHCH_2CH_2), 2.15-1.97 (2H, m, =CHCH_2), 2.05 (3H, m, CH_3C=CHCO$_2$Et), 1.68 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.60 (3H, s, CH_3).
^{13}C-NMR	168.7 (**C**OO), 161.6 (**C**=CHCOO), 136.7 (CH_3**C**=), 131.7
(75MHz, $CDCl_3$, ppm)	((CH_3)$_2$**C**=), 124.5 (CH_3**C**=), 123.1 ((CH_3)$_2$**C**=), 112.9 (=**C**HCOO), 41.6 (**C**$H_2C(CH_3)$=), 39.9 (**C**$H_2C(CH_3)$=), 34.4 (=CH**C**H_2), 26.9 (**C**H_3), 25.9 (2 × **C**H_3), 18.0 (**C**H_3), 16.4 ((**C**H_3)C=CHCOO), aromatic carbons not observed.
LRMS (ES+ ionisation)	443.5 ([M+ MeCN]$^+$, 5%), 153.3 (100%).
HRMS (HREI)	Calcd for $C_{21}H_{23}O_2F_5$: 402.1618. Found: 402.1617.

Pentafluorophenyl (2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (476a)



$C_{21}H_{23}F_5O_2$.
M = 402.19 g.mol^{-1}.

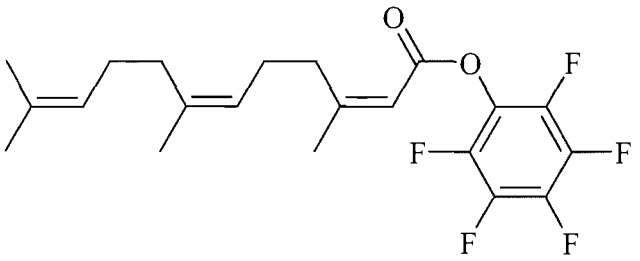
Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, acid **322a** (203 mg, 0.86 mmol) afforded the title ester **476a** as a yellow oil (342 mg, 0.85 mmol, 99%).

IR (cm^{-1})	2960 (b), 2910 (b), 2856 (b), 1763 (s), 1635 (s), 1518 (s), 1450 (w), 1104 (s), 1001 (w).
^{1}H-NMR	5.97 (1H, d, *J* = 1.2 Hz, =C**H**COO), 5.13 (1H, td, *J* = 6.8 and 1.2
(300MHz, $CDCl_3$, ppm)	Hz, =C**H**), 5.10 (1H, td, *J* = 6.8 and 1.4 Hz, =C**H**), 2.25 (3H, d, *J* = 1.3 Hz, CH_3), 2.31-2.24 (4H, m, 2 × CH_2), 2.08-2.02 (4H, m, 2 × CH_2), 1.69 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.62 (3H, s, CH_3).
^{13}C-NMR	167.8 (**C**OO), 161.7 (**C**=CHCOO), 136.7 (CH_3**C**=), 131.5
(75MHz, $CDCl_3$, ppm)	((CH_3)$_2$**C**=), 124.1 (CH_3**C**=), 122.3 ((CH_3)$_2$**C**=), 112.1 (=**C**HCOO), 41.3 (**C**$H_2C(CH_3)$=), 39.6 (**C**$H_2C(CH_3)$=), 29.7 (=CH**C**H_2), 26.6 (**C**H_3), 25.8 (**C**H_3), 17.6 (**C**H_3), 16.0

((**C**H$_3$)C=CHCOO), aromatic carbons not observed.

LRMS (ES+ ionisation) 443.5 ([M+ MeCN]$^+$, 5%), 153.3 (100%).

Pentafluorophenyl (2*Z*,6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (476c)



C$_{21}$H$_{23}$F$_5$O$_2$.
M = 402.19 g.mol^{-1}.

Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, acid **322c** (3.00 g, 12.69 mmol) afforded the title ester **476c** as a yellow oil (4.91 g, 12.21 mmol, 96%), after purification on SiO_2 (200 mL, CH_2Cl_2/hexane, 3:10).

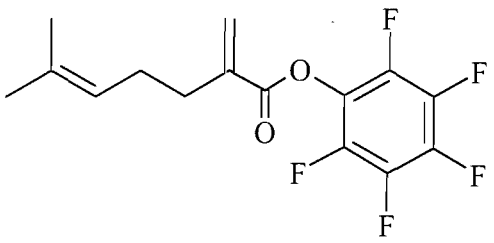
IR (cm^{-1}) 2962 (b), 2944 (b), 2883 (b), 1678 (s), 1632 (s), 1451 (w), 1328 (w), 1202 (s), 1132 (s),1105 (s), 997 (w), 538 (s).

^{1}H-NMR (300MHz, CDCl$_3$, ppm) 5.97 (1H, d, *J* = 1.3 Hz, =C**H**COO), 5.15 (1H, td, *J* = 7.2 and 1.3 Hz, =C**H**), 5.09 (1H, m, =C**H**), 2.70 (2H, t, *J* = 7.6 Hz, C**H$_2$**C(CH$_3$)=), 2.27 (2H, dd, *J* = 15.3 and 7.7 Hz, =CHCH$_2$C**H$_2$**), 2.10-2.00 (4H, m, =CHC**H$_2$**), 2.04 (3H, d, *J* = 1.3 Hz, C**H$_3$**C=CHCO$_2$Et), 1.69 (3H, d, *J* = 1.3 Hz, C**H$_3$**), 1.68 (3H, s, C**H$_3$**), 1.60 (3H, s, C**H$_3$**).

^{13}C-NMR (75MHz, CDCl$_3$, ppm) 168.2 (**C**OO), 161.1 (**C**=CHCOO), 143.0 (2 x C=**C**F), 140.8 (**C**=CF), 139.6 (2 x **C**F=CF), 136.5 (CH$_3$**C**=), 136.2 (CF=**C**F), 131.6 ((CH$_3$)$_2$**C**=), 124.2 (CH$_3$**C**=), 123.6 ((CH$_3$)$_2$**C**=), 112.6 (=**C**HCOO), 34.3 (**C**H$_2$C(CH$_3$)=), 31.8 (**C**H$_2$C(CH$_3$)=), 26.6 (=CH**C**H$_2$), 26.4 (**C**H$_3$), 26.0 (**C**H$_3$), 25.6 (**C**H$_3$), 23.3 (**C**H$_3$), 17.5 ((**C**H$_3$)C=CHCOO).

LRMS (ES+ ionisation) 443.5 ([M+ MeCN]$^+$, 5%), 153.3 (100%).

Perfluorophenyl 6-methyl-2-methylenehept-5-enoate (477)

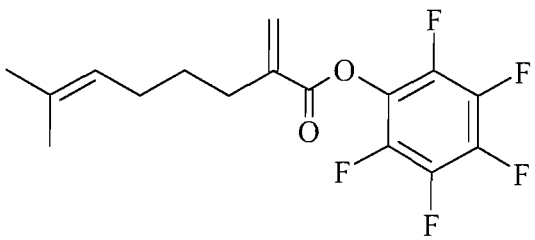


$C_{15}H_{13}F_5O_2$.
M = 320.3 g.mol^{-1}.

Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, acid **473** (80 mg, 0.519 mmol) afforded the title ester **477** as a yellow oil (150 mg, 0.468 mmol, 90%) after purification on SiO_2 (50 mL, CH_2Cl_2/hexane, 3:10).

IR (cm^{-1})	2970 (b), 2921 (b), 2871 (b), 1780 (s), 1519 (s), 1441 (w), 1147 (s), 1078 (s), 996 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.49 (1H, s, =CH**H**CCOO), 5.87 (1H, s, =CH**H**CCOO), 5.14 (1H, t, *J* = 7.0 Hz, C=C**H**), 2.46 (2H, t, *J* = 7.3 Hz, C**H$_2$**C=), 2.25 (2H, q, =CHC**H$_2$**), 1.72 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	163.0 (**C**OO), 142.6 (**C**F), 140.7 (**C**F), 140.1 (**C**F), 137.8 (**C**=CH$_2$), 137.0 (**C**F), 135.1 (**C**F), 133.1 ((CH$_3$)$_2$**C**=), 129.4 (**C**H=C(CH$_3$)$_2$), 122.6 (CH=**C**H$_2$), 32.1 (**C**H$_2$C=CH$_2$), 26.8 (**C**H$_2$CHC(CH$_3$)$_2$), 25.6 (**C**H$_3$), 17.7 (**C**H$_3$).
LRMS (CI+ ionisation)	320.1 ([M]$^+$, 100%), 321.1 ([M+H]$^+$,25%).

Perfluorophenyl 7-methyl-2-methyleneoct-6-enoate (478)



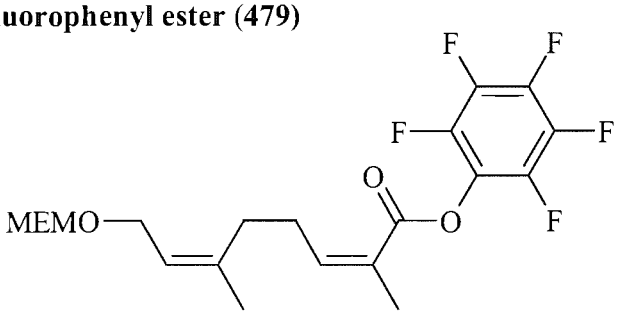
$C_{16}H_{15}F_5O_2$.
M = 334.3 g.mol^{-1}.

Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, acid **474** (400 mg, 2.381 mmol) gave the title ester **478** as a yellow oil (717 mg, 2.145 mmol, 90%) after purification on SiO_2 (100 mL, CH_2Cl_2/hexane, 1:5).

IR (cm^{-1})	2930 (w), 2360 (w), 1760 (s), 1510 (s), 1441 (w), 1145 (m), 1080

	(s), 1045 (m), 994 (s).
^{1}H-NMR	6.49 (1H, s, C=C**H**H), 5.87 (1H, d, *J* = 1.3 Hz, C=C**H**H), 5.14
(400MHz, $CDCl_3$, ppm)	(1H, tddd, *J* = 7.1, 4.3, 2.8 and 1.5 Hz, C**H**=C), 2.43 (2H, dd, *J* = 7.8 and 7.1 Hz, CH_2CH_2CH=C), 2.06 (2H, appq, *J* = 7.3 Hz, $CH_2CH_2CH_2CH$=C), 1.71 (3H, q, *J* = 1.0 Hz, CH_3), 1.62 (3H, s, CH_3), 1.59 (2H, m, CH_2CH_2CH=C).
^{13}C-NMR	163.0 (**C**OO), 142.6 (**C**F, d, *J* = 11.6 Hz), 141.0 (**C**F, d, *J* = 11.6
(100MHz, $CDCl_3$, ppm)	Hz), 140.6 (**C**=CF, d, *J* = 5.8 Hz), 138.3 (**C**=CH_2), 138.2 (**C**F, d, *J* = 11.6 Hz), 136.7 (**C**F), 132.2 (**C**$(CH_3)_2$), 128.9 (C=**C**H_2), 122.8 (**C**H=C$(CH_3)_2$), 31.5 (**C**H_2CCO), 28.3 (**C**H_2CH_2CCO), 27.4 (**C**H_2CH=C), 25.7 (**C**H_3), 17.7 (**C**H_3).

(2*Z*,6*Z*)-8-(2-Methoxy-ethoxymethoxy)-2,6-dimethyl-octa-2,6-dienoic acid pentafluorophenyl ester (479)



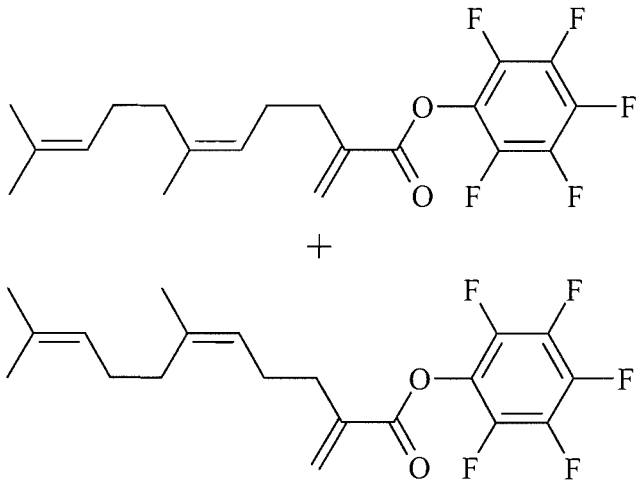
$C_{20}H_{23}F_5O_5$.
M = 438.40 g.mol^{-1}.

Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, acid **475** (200 mg, 0.734 mmol) afforded the title ester **479** as a pale yellow oil (290 mg, 0.662 mmol, 90%), which was used in the next step without further purification.

IR (cm^{-1})	2922 (b), 2874 (b), 1749 (w), 1517 (s), 1063 (w), 1039 (w), 1001 (s).
^{1}H-NMR	6.27 (1H, td, *J* = 7.4 and 1.3 Hz, CC**H**), 5.42 (1H, t, *J* = 7.2 Hz,
(300MHz, $CDCl_3$, ppm)	OCH_2C**H**), 4.71 (2H, s, O**C**H_2O), 4.08 (2H, dd, *J* = 7.2 and 1.1 Hz, O**C**H_2CH), 3.71-3.69 (2H, m, O**C**H_2), 3.58-3.55 (2H, m, O**C**H_2), 3.40 (3H, s, O**C**H_3), 2.65 (2H, dt, *J* = 7.5 and 1.3 Hz, CH**C**H_2), 2.24 (2H, t, *J* = 7.4 Hz, C**H**$_2$C), 2.08 (3H, q, *J* = 1.3 Hz, C**H**$_3$), 1.75 (3H, q, *J* = 1.3 Hz, C**H**$_3$).

^{13}C-NMR (75MHz, $CDCl_3$, ppm)	162.9 (**C**OO), 148.3 (**C**CO_2CH_3), 142.2-136.4 (5 x **C**F), 139.7 (**C**H=CCO_2CH_3), 125.1 (**C**=CF), 127.7 (**C**CH_3), 122.1 (**C**H=CCH_3), 94.6 (OCH_2O), 71.8 (CH_3OCH_2), 66.7 (OCH_2CH_2), 63.4 (OCH_2CH), 59.0 (OCH_3), 31.1 (CH_2), 28.3 (CH_2), 23.1 (CH_3), 20.4 (CH_3).
LRMS (ES+ ionisation)	477.4 ($[M+K]^+$, 100%), 461.4 ($[M+Na]^+$, 55%).

(*Z*)-Perfluorophenyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (481b) and (*E*)-perfluorophenyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoate (481a)



$C_{20}H_{21}F_5O_2$.
M = 388.4 g.mol^{-1}.

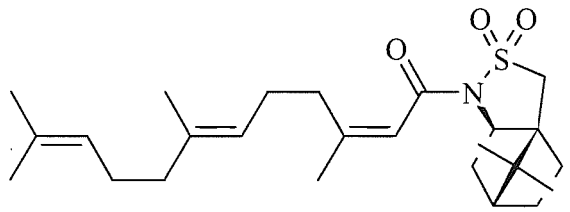
Following the general procedure for the activation of the carboxylic acid with pentafluorophenol, the mixture of acids **480a,b** (525 mg, 2.361 mmol) was converted to an inseparable mixture of esters **481a,b** obtained as a yellow oil (860 mg, 2.214 mmol, 94%), after purification on SiO_2 (50 mL, CH_2Cl_2 / hexane, 3:10).

IR (cm^{-1})	2969 (m), 2924 (m), 2858 (m), 1760 (s), 1518 (s), 1450 (w), 1377 (w), 1146 (m), 1074 (s), 995 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.49 (1H, s, C=C**H**H), 5.87 (1H, d, J = 1.0 Hz, C=C**H**H), 5.16-5.10 (2H, m, **CH**CH_3 and **CH**$(CH_3)_2$), 2.47 (2H, q, J = 7.3 Hz, CH_2C), 2.29 (2H, m, CH_2CH_2CH), 2.10-2.00 (4H, m, 2 x CH_2), 1.69 (3H, s, CH_3), 1.62 (6H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	162.9 (**C**OO), 142.6 (**C**F), 140.1 (**C**F), 139.2 (**C**=CF), 137.9 (**C**(CH_3)), 137.7 (**C**(CH_3)), 136.7 (**C**=CH_2), 131.7 (**C**$(CH_3)_2$),

131.4 ($\mathbf{C}(CH_3)_2$), 129.4 ($C=\mathbf{C}H_2$), 124.2 ($\mathbf{C}H=C(CH_3)_2$), 123.3 ($\mathbf{C}H=C(CH_3)$), 122.5 ($CH=\mathbf{C}(CH_3)$), 39.7 ($\mathbf{C}H_2CCO$), 32.3 ($\mathbf{C}H_2$), 31.9 ($\mathbf{C}H_2$), 31.6 ($\mathbf{C}H_2$), 26.6 ($\mathbf{C}H_2$), 25.6 ($\mathbf{C}H_3$), 23.3 ($\mathbf{C}H_3$), 17.6 ($\mathbf{C}H_3$).

LRMS (GC-EIMS) 388 ($[M]^+$, 9%).

***N*-((*2Z,6E*)-3,7,11-Trimethyl-dodeca-2,6,10-trienoyl)-(2*R*)-camphor-10,2-sultam (316e)**



$C_{25}H_{39}NO_3S$.
M = 433.66 g.mol^{-1}.

Method 1 :

To a solution of (2*R*)-10,2-camphorsultam (50 mg, 0.221 mmol) in dry THF (3 mL) was added *n*-BuLi (0.16 mL of 1.6 M in hexanes, 0.256 mmol) at –78°C. The solution was allowed to warm to –20°C over 1 h whereupon a solution of the activated ester **476b** (90 mg, 0.21 mmol) in dry THF (3 mL) was added dropwise. The solution was then allowed to warm to room temperature. After 40 min. the reaction was diluted in Et_2O (15 mL) and quenched with NH_4Cl (sat. aq. sol., 25 mL). The organic phase was washed with $NaHCO_3$ (sat. aq. sol., 3 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (220 mg). Purification on SiO_2 (25 g, hexane/CH_2Cl_2, 4:1 then 1:4) afforded the title triene **316e** as a colourless oil (56 mg, 0.13 mmol, 61%).

Method 2 :

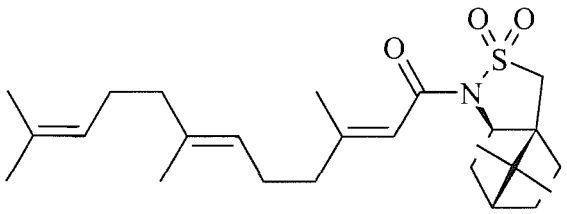
According to the method of Liddle *et al.*[119] to a dispersion of NaH (24 mg, 0.55 mmol), in dry toluene (4 mL) at 0°C, a solution of (2*R*)-10,2-camphorsultam (80 mg, 0.36 mmol) in dry toluene (2 mL) was added dropwise and the resulting mixture was allowed to warm at room temperature for 1 hour.

To a solution of acid **322b** (102 mg, 0.42 mmol) in dry CH_2Cl_2 (1 mL) was added a drop of DMF followed by the dropwise addition of oxalyl chloride (0.2 mL). Degazement occurred, the reaction was stirred for 1 hour at room temperature, evaporated to dryness and the resulting residue was dissolved in dry toluene (6 mL). This solution was added dropwise to the mixture of sultam and NaH in toluene, which was prior cooled to 0°C. The resulting mixture was allowed to warm to room temperature and was stirred overnight. The reaction

was quenched by pouring in NH_4Cl (sat. aq. sol., 30 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (3 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (250 mg). Purification on silica gel (20 g, eluting CH_2Cl_2/hexane, 3:2, then CH_2Cl_2/hexane, 4:1) afforded the title product **316e** as a colourless oil (171 mg, 0.40 mmol, 94%).

$[\alpha]^{20}_D$	−10.8 (*c* 0.3, $CDCl_3$).
IR (cm^{-1})	2960 (b), 2914 (b), 1674 (s), 1632 (s), 1461 (w), 1372 (s), 1331 (s), 1268 (s), 1240 (s) and 1133 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	6.32 (1H, s, =C**H**CON), 5.18 (1H, dd, *J* = 7.5 and 6.2 Hz, =C**H**), 5.10 (1H, dd, *J* = 7.7 and 5.9 Hz, =C**H**), 3.93 (1H, dd, *J* = 6.3 and 6.2 Hz, C**H**N), 3.59 (1H, d, *J* = 13.7 Hz, C**H**HSO$_2$), 3.42 (1H, d, *J* = 13.8 Hz, CH**H**SO$_2$), 2.61-1.88 (8H, m, 4 × C**H$_2$**), 1.97 (3H, s, C**H$_3$**), 1.61 (6H, s, 2 × C**H$_3$**), 1.43-1.36 (2H, m, C**H$_2$**CCH$_2$S), 1.16 (3H, s, C**H$_3$**C), 0.98 (3H, s, C**H$_3$**C).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	163.9 (**C**ON), 163.0 (**C**=CHCON), 135.7 (CH$_3$**C**=), 131.3 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**H), 123.5 (CH$_3$C=**C**H), 116.0 (=**C**HCON), 65.2 (CHN), 53.2 (**C**H$_2$SO$_2$), 48.1 (**C**CH$_2$SO$_2$), 47.7 (**C**(CH$_3$)$_2$), 44.7 (**C**HC(CH$_3$)$_2$), 39.6 (**C**H$_2$CHN), 32.8 (**C**H$_2$CH$_2$CCH$_2$S), 26.6 (**C**H$_2$CCH$_2$S), 26.5 (=CH**C**H$_2$), 25.9 (=CH**C**H$_2$), 25.7 (=CH**C**H$_2$), 22.6 (**C**H$_3$), 20.8 (**C**H$_3$), 19.9 (**C**H$_3$), 17.7 (**C**H$_3$), 16.0 (**C**H$_3$CCHCON).
LRMS (ES+ ionisation)	889.3 ([2M+Na]$^+$, 22%), 456.2 ([M+Na]$^+$, 34%), 434.3 ([M+H]$^+$, 39%).

***N*-((*2E,6E*)-3,7,11-Trimethyl-dodeca-2,6,10-trienoyl)-(2*R*)-camphor-10,2-sultam (316d)**

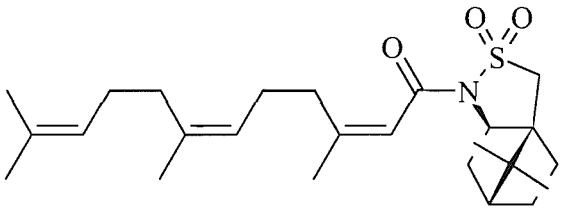


$C_{25}H_{39}NO_3S$.
M = 433.66 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, the activated ester **476a** (80 mg, 0.199 mmol) afforded the title triene **316d** as a colourless oil (55 mg, 0.127 mmol, 64%).

$[\alpha]^{20}_D$	−11.3 (*c* 0.3, $CDCl_3$).
IR (cm^{-1})	2955 (b), 2935 (b), 2910 (b), 1681 (s), 1632 (s), 1453 (w), 1329 (m), 1268 (s), 1236 (s) 1133 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	6.33 (1H, d, *J* = 1.2 Hz, =C**H**CON), 5.09 (1H, tt, *J* = 6.6 and 1.3 Hz, =C**H**), 5.08 (1H, tq, *J* = 8.2 and 1.4 Hz, =C**H**), 3.93 (1H, dd, *J* = 7.3 and 5.4 Hz, C**H**N), 3.46 (1H, d, *J* = 13.7 Hz, CH_2SO_2), 3.43 (1H, d, *J* = 13.7 Hz, CH_2SO_2), 2.16 (3H, d, *J* = 1.3 Hz, CH_3C=CHCON), 2.22-1.87 (8H, m, CH_2), 1.68 (3H, d, *J* = 1.2 Hz , CH_3), 1.60 (6H, s, 2 × CH_3), 1.43-1.36 (2H, m, CH_2CCH_2S), 1.18 (3H, s, CH_3C), 0.97 (3H, s, CH_3C).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	164.6 (**C**ON), 162.5 (**C**=CHCON), 136.1 (CH_3**C**=), 131.3 ($(CH_3)_2$**C**=), 124.3 ($(CH_3)_2C$=**C**H), 122.8 (CH_3C=**C**H), 115.5 (=**C**HCON), 65.0 (CHN), 53.1 (CH_2SO_2), 48.2 (CCH_2SO_2), 47.7 ($C(CH_3)_2$), 44.7 ($CHC(CH_3)_2$), 38.7 (CH_2CHN), 32.8 ($CH_2CH_2CCH_2S$), 26.6 (CH_2CCH_2S), 26.5 (=CHCH_2), 26.0 (=CHCH_2), 25.7 (=CHCH_2), 20.8 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 17.7 (CH_3), 16.0 ($CH_3CCHCON$).
LRMS (ES+ ionisation)	889.2 ($[2M+Na]^+$, 4%), 434.2 ($[M+H]^+$, 12%).
HRMS (ES+ ionisation)	Calcd for $C_{25}H_{39}NO_3SNa$: 456.2543. Found: 456.2550.

_N_-((_2Z,6Z_)-3,7,11-Trimethyl-dodeca-2,6,10-trienoyl)-(2_R_)-camphor-10,2-sultam (316f)



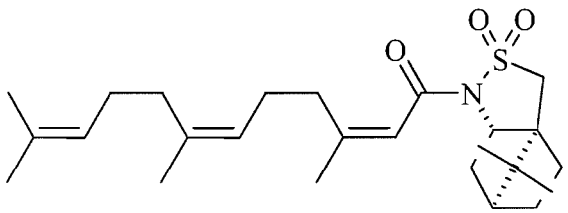
$C_{25}H_{39}NO_3S$.
M = 433.66 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using (2*R*)-10,2-camphorsultam, the activated ester **476c** (170 mg, 0.424 mmol) afforded the title triene **316f** as a colourless oil (135 mg, 0.311 mmol, 73%), after purification on SiO_2 (150 mL, hexane/CH_2Cl_2, 4:1 then 1:4).

$[\alpha]_D$	−35.1 (*c* 0.1, CH_2Cl_2).
IR (cm^{-1})	2963 (b), 2918 (b), 1679 (s), 1632 (s), 1450 (w), 1330 (s), 1268

	(s), 1238 (s) 1202 (s), 1113 (s).
^{1}H-NMR	6.30 (1H, s, =C**H**CON), 5.16 (1H, td, *J* = 7.2 and 1.1 Hz, =C**H**),
(300MHz, $CDCl_3$, ppm)	5.13 (1H, m, =C**H**), 3.91 (1H, dd, *J* = 6.6 and 5.8 Hz, C**H**N), 3.47 (1H, d, *J* = 13.8 Hz, C**H$_2$**SO_2), 3.40 (1H, d, *J* = 13.6 Hz, C**H$_2$**SO_2), 2.67-2.49 (2H, m, C**H$_2$**), 2.20-2.03 (9H, m, C**H**CH_2 and C**H$_2$**), 1.92-1.87 (2H, m, C**H$_2$**), 1.94 (3H, d, *J* = 1.3 Hz, C**H$_3$**C=CHCON), 1.68 (6H, s, 2 × C**H$_3$**), 1.60 (3H, s, C**H$_3$**), 1.47-1.31 (2H, m, C**H$_2$**CCH_2S), 1.18 (3H, s, C**H$_3$**C), 0.96 (3H, s, C**H$_3$**C).
^{13}C-NMR	163.8 (**C**ON), 162.8 (**C**=CHCON), 135.8 (CH_3**C**=), 131.4
(75MHz, $CDCl_3$, ppm)	((CH_3)$_2$**C**=), 124.3 ((CH_3)$_2$C=**C**H), 124.3 ((CH_3)C=**C**H), 116.0 (=**C**HCON), 65.0 (CHN), 53.1 (**C**H_2SO_2), 48.1 (**C**CH_2SO_2), 48.1 (**C**HC(CH_3)$_2$), 47.7 (**C**(CH_3)$_2$), 44.6 (**C**H_2CHN), 38.7 (CH_2**C**H_2CCH_2S), 34.7 (**C**H_2CCH_2S), 32.8 (=CH**C**H_2), 31.9 (=CH**C**H_2), 26.6 (=CH**C**H_2), 25.9 (**C**H_3), 25.7 (**C**H_3), 25.7 (**C**H_3), 23.3 (**C**H_3), 20.8 (**C**H_3), 19.8 (**C**H_3), 17.6 (CH_3**C**HCON).
LRMS (GC-EI)	433 (4%).

***N*-((*2Z,6Z*)-3,7,11-Trimethyl-dodeca-2,6,10-trienoyl)-(2*S*)-camphor-10,2-sultam (316h)**



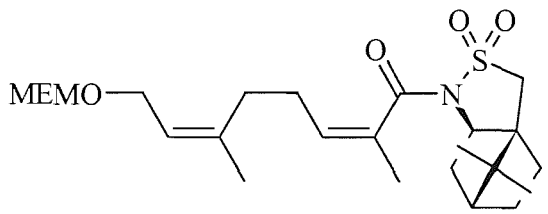
$C_{25}H_{39}NO_3S$.
M = 433.66 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using (2*S*)-10,2-camphorsultam, activated ester **476c** (4.50 g, 11.19 mmol) afforded the title triene **316h** as a colourless oil (4.13 g, 9.52 mmol, 85%) after purification on SiO_2 (250 mL, hexane/CH_2Cl_2 ,4:1 then 1:4).

$[\alpha]^{20}_D$	+37.4 (*c* 0.2, CH_2Cl_2).
IR (cm^{-1})	2926 (b), 2910 (b), 2855 (b), 1736 (s), 1372 (s), 1235 (w), 1038 (m).
^{1}H-NMR	6.30 (1H, s, =C**H**CON), 5.16 (1H, td, *J* = 1.3 and 7.3 Hz, =C**H**),

(400MHz, $CDCl_3$, ppm)	5.12 (1H, m, =C**H**), 3.93 (1H, dd, *J* = 5.5 and 7.0 Hz, C**H**N), 3.47 (1H, d, *J* = 13.8 Hz, C**H**$_2$$SO_2$), 3.41 (1H, d, *J* = 13.8 Hz, C**H**$_2$$SO_2$), 2.65-2.51 (2H, m, C**H**$_2$), 2.18 (1H, m, C**H**$_2$), 2.09-1.85 (10H, m, C**H**$_2$), 1.94 (3H, s, C**H**$_3$C=CHCON), 1.62 (6H, s, 2 × C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.44-1.32 (2H, m, C**H**$_2$$CCH_2S$), 1.17 (3H, s, C**H**$_3$C), 0.96 (3H, s, C**H**$_3$C).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	163.9 (**C**ON), 162.6 (**C**=CHCON), 135.8 (CH_3**C**=), 131.3 ((CH_3)$_2$**C**=), 124.4 ((CH_3)$_2$C=**C**H), 124.3 ((CH_3)C=**C**H), 116.1 (=**C**HCON), 65.0 (CHN), 53.1 (**C**H$_2$$SO_2$), 48.1 (**C**$CH_2SO_2$), 48.1 (**C**HC($CH_3$)$_2$), 47.7 (**C**($CH_3$)$_2$), 44.7 (**C**$H_2$CHN), 38.7 (**C**$H_2$$CH_2CCH_2S$), 34.7 (**C**$H_2$$CCH_2S$), 32.8 (=CH**C**$H_2$), 31.9 (=CH**C**$H_2$), 26.6 (=CH**C**$H_2$), 25.8 (**C**$H_3$), 25.6 (**C**$H_3$), 23.3 (**C**$H_3$), 20.8 (**C**$H_3$), 19.8 (**C**$H_3$), 17.6 (**C**$H_3$CCHCON).
LRMS (ES+ ionisation)	889.9 ([2M+Na]$^+$, 20%), 456.4 ([M+Na]$^+$, 100%).

***N*-((2*Z*,6*Z*)-8-(2-Methoxy-ethoxymethoxy)-2,6-dimethyl-octa-2,6-dienoyl)-(2*R*)-camphor-10,2-sultam (345b)**



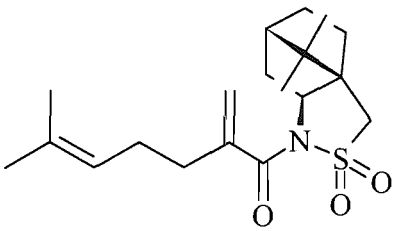
$C_{24}H_{39}NO_6S$.
M = 469.64 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using (2*R*)-10,2-camphorsultam, the activated ester **479** (270 mg, 0.616 mmol) afforded the title product **345b** as a colourless gum (210 mg, 0.447 mmol, 73%) after purification on silica gel (small, EtOAc/hexane, 3:7).

IR (cm^{-1})	2959 (b), 2940 (b), 2884 (b), 1682 (s), 1455 (w), 1337 (s), 1280 (s), 1138 (s), 1110 (s) 1049 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	5.57 (1H, tt, *J* = 6.9 and 1.6 Hz, COCC**H**), 5.37 (1H, td, *J* = 6.9 and 1.3 Hz, CH_2CC**H**), 4.72 (2H, s, OC**H**$_2$O), 4.06 (2H, d, *J* = 7.0 Hz, OC**H**$_2$CH), 3.93 (1H, t, *J* = 6.5 Hz, CHN), 3.71-3.68 (2H, m, OC**H**$_2$), 3.58-3.56 (2H, m, OC**H**$_2$), 3.46 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 3.39 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 3.40 (3H, s,

	OCH_3), 2.24-2.21 (6H, m, 3 x CH_2), 1.95 (3H, d, J = 1.3 Hz, CH_3), 1.91-1.87 (3H, m, CH and CH_2), 1.71 (3H, s, CH_3), 1.45 (2H, m, CH_2), 1.18 (3H, s, CH_3), 0.98 (3H, s, CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	170.4 (CON), 140.1 (CH_3CCON), 133.8 (CH=CCON), 130.9 (CH_3CCH), 121.7 (CH=CCH_3), 94.7 (OCH_2O), 71.8 (CH_3OCH_2), 66.7 (OCH_2CH_2), 65.0 (NCH), 63.6 (OCH_2CH), 59.0 (OCH_3), 53.1 (CH_2SO_2), 48.3 (SO_2CH_2C), 47.7 ($C(CH_3)$), 44.7 (CH_2CH_2CH), 38.4 ($CHCH_2CH$), 33.0 (CCH_2), 31.2 (CCH_2), 28.5 (CH_2CHCCO), 26.5 ($CHCH_2CH_2$), 23.2 (CH_3), 20.8 (CH_3), 20.4 (CH_3) 19.9 (CH_3).
LRMS (ES+ ionisation)	487.4 ($[M+NH_4]^+$,100%), 508.3 ($[M+K]^+$, 21%), 956.4 ($[2M+NH_4]^+$, 18%).

***N*-(6-Methyl-2-methylene-hept-5-enoyl)-(2*S*)-camphor-10,2-sultam (421b)**



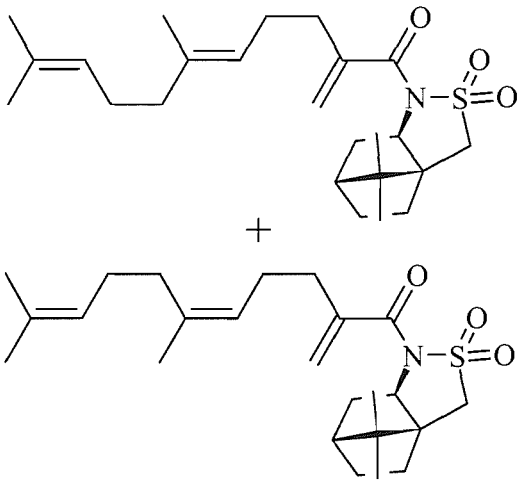
$C_{19}H_{29}NO_3S$.
M = 351.5 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using (2*S*)-10,2-camphorsultam, the activated ester **477** (1.15 g, 3.59 mmol) afforded the title product **421b** as a colourless oil (1.20 g, 3.42 mmol, 95%) after purification on silica gel (150 mL, hexane/CH_2Cl_2, 2:3).

IR (cm^{-1})	2991 (w), 2961 (m), 2884 (w), 1744 (w), 1680 (s), 1454 (w), 1334 (s), 1198 (s), 1132 (s), 1113 (m), 1065 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.76 (1H, s, C=CHH), 5.64 (1H, dd, J = 1.5 and 1.2 Hz, C=CHH), 5.13 (1H, tddd, J = 7.0, 4.3, 2.8 and 1.5 Hz, $CHC(CH_3)_2$), 4.05 (1H, dd, J = 7.8 and 4.8 Hz, CHN), 3.51 (1H, d, J = 13.6 Hz, $CHHSO_2$), 3.41 (1H, d, J = 13.6 Hz, $CHHSO_2$), 2.45-2.28 (2H, m, $CH_2C=CH_2$), 2.23-2.17 (2H, m, $CH_2CH_2C=CH_2$), 2.09-1.92 (4H, m, 2 x CH_2, sultam), 1.90 (1H, m, $CHC(CH_3)_2$, sultam), 1.69 (3H, d, J = 1.3 Hz, CH_3), 1.62 (3H, s, CH_3), 1.46-1.34 (2H, m, CH_2CCH_2S, sultam), 1.23 (3H, s, CH_3), 1.00 (3H, s, CH_3).

^{13}C-NMR (100MHz, $CDCl_3$, ppm)	171.2 (**C**ON), 143.2 (**C**=CH_2), 132.2 ($(CH_3)_2$**C**), 123.6 (C=**C**H_2), 123.4 ($(CH_3)_2$C=**C**H), 65.6 (**C**HN), 53.6 (CH_2SO_2), 47.9 (**C**CH_2SO_2), 47.7 ($(CH_3)_2$**C**, sultam), 45.2 (**C**H$C(CH_3)_2$, sultam), 38.4 (**C**H_2C=CH_2), 33.2 (**C**H_2CH$C(CH_3)_2$, sultam), 32.6 (**C**H_2CH$C(CH_3)_2$, sultam), 26.5 (CH**C**H_2), 26.3 (**C**H_2CCH_2SO_2), 25.6 (**C**H_3), 21.2 (**C**H_3), 19.9 (**C**H_3), 17.7 (**C**H_3).
LRMS (GC-EIMS)	351 ($[M]^+$, 7%).

***N*-((*Z*)-Ethyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoyl)-(2*R*)-camphor-10,2-sultam (452d) and *N*-((*E*)-ethyl 6,10-dimethyl-2-methyleneundeca-5,9-dienoyl)-(2*R*)-camphor-10,2-sultam (452c)**



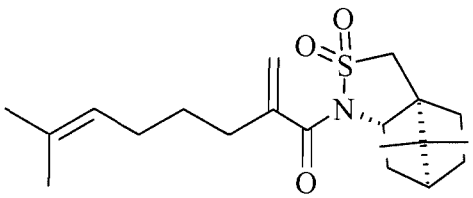
$C_{24}H_{37}NO_3S$.
M = 419.63 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using the (2*R*)-10,2-camphorsultam, the mixture of activated esters **481a,b** (860 mg, 2.221 mmol) was converted to an inseparable mixture of trienes **452c,d** obtained as a colourless oil (855 mg, 2.038 mmol, 92%) after purification on silica gel (100 mL, hexane/CH_2Cl_2, 3:7).

IR (cm^{-1})	2960 (m), 2924 (m), 2882 (m), 1679 (s), 1442 (m), 1338 (s), 1195 (s), 1132 (s), 1111 (s), 1063 (s), 767 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.75 (1H, s, C=C**H**H), 5.63 (1H,dd, *J* = 3.8 and 1.2 Hz, C=C**H**H), 5.15 (1H, m, C**H**CCH_3), 5.09 (1H, m, C**H**$C(CH_3)_2$), 4.04 (1H, m, C**H**N), 3.51 (1H, d, *J* = 13.8 Hz, C**H**HSO_2), 3.39 (1H, d, *J* = 13.5 Hz, C**H**HSO_2), 2.44-2.25 (2H, m, C**H**$_2$C=CH_2), 2.23-2.17 (2H, dd, *J* = 14.8 and 7.3 Hz, C**H**$_2$C**H**$_2$C=CH_2), 2.09-1.87 (8H, m, 4 x

	CH_2), 2.04 (3H, s, CH_3), 1.89 (1H, br s, $CHC(CH_3)_2$, sultam), 1.68 (3H, d, J = 1.5 Hz, CH_3), 1.61 (3H, s, CH_3), 1.45-1.34 (2H, m, CH_2CCH_2S, sultam), 1.23 (3H, s, CH_3), 1.00 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	171.1 (CON), 143.1 (C=CON), 135.9 (CH_3C=), 135.8 (CH_3C=), 131.5 ($(CH_3)_2C$=), 131.2 ($(CH_3)_2C$=), 124.3 ($(CH_3)_2C$=CH), 124.1 ($(CH_3)_2C$=CH), 123.5 (CH_2CCON), 123.3 (CH_3C=CH), 65.5 (CHN), 53.6 (CH_2SO_2), 47.9 (CCH_2SO_2), 47.7 ($C(CH_3)_2$), 45.2 ($CHC(CH_3)_2$), 39.6 (CH_2CHN), 38.4 ($CH_2CH_2CCH_2S$), 33.2 (CH_2CCH_2S), 32.7 (=CCH_2), 32.5 (=CCH_2), 31.9 (=$CHCH_2$), 26.7 (=CCH_2), 26.5 (=CCH_2), 26.4 (=$CHCH_2$), 26.2 (=$CHCH_2$), 26.0 (=$CHCH_2$), 25.6 (CH_3), 23.3 (CH_3), 21.2 (CH_3), 19.9 (CH_3), 17.6 (CH_3).
LRMS (GC-EIMS)	419 ($[M]^+$, 3%).

_N_-(7-Methyl-2-methyleneoct-6- enoyl)-(2_S_)-camphor-10,2-sultam (439b)



$C_{20}H_{31}NO_3S$.
M = 365.53 g.mol^{-1}.

Following the procedure used for the synthesis of **316e**, using (2*S*)-10,2-camphorsultam, the activated ester **478** (400 mg, 1.197 mmol) afforded the title product **439b** as a colourless oil (395 mg, 1.081 mmol, 90%) which was purified on silica gel (small, CH_2Cl_2/hexane, 3:2).

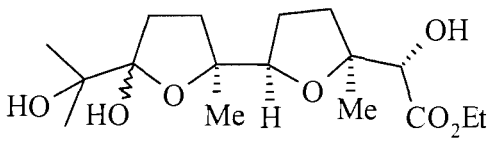
IR (cm^{-1})	2961 (m), 2925 (m), 2884(w), 1744 (m), 1680 (s), 1454 (w), 1334 (s), 1198 (m), 1132 (m), 1113 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.75 (1H, s, C=C**H**H), 5.63 (1H, s, C=C**H**H), 5.12 (1H, tdd, J = 7.0, 2.8 and 1.5 Hz, $CHC(CH_3)_2$), 4.04 (1H, dd, J = 7.8 and 4.8 Hz, CHN), 3.51 (1H, d, J = 13.6 Hz, $CHHSO_2$), 3.39 (1H, d, J = 13.6 Hz, $CHHSO_2$), 2.41 (1H, dd, J = 15.3 and 7.8 Hz, $CHHC=CH_2$), 2.30 (1H, dd, J = 15.3 and 7.8 Hz, $CHHC=CH_2$), 2.08-1.85 (6H, m, $CH_2CH_2CH_2C=CH_2$ and 2 x CH_2, sultam), 1.90 (1H, m, $CHC(CH_3)_2$, sultam), 1.68 (3H, s, CH_3), 1.60 (3H, s,

	CH_3), 1.58-1.50 (2H, m, $CH_2CH_2C{=}CH_2$), 1.45-1.34 (2H, m, CH_2CCH_2S, sultam), 1.23 (3H, s, CH_3), 1.00 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	171.1 (CON), 143.5 ($C{=}CH_2$), 131.7 ($(CH_3)_2C$), 124.2 ($(CH_3)_2C{=}CH$), 123.6 ($C{=}CH_2$), 65.6 (CHN), 53.6 (CH_2SO_2), 47.9 (CCH_2SO_2), 47.7 ($(CH_3)_2C$, sultam), 45.2 ($CHC(CH_3)_2$, sultam), 38.4 ($CH_2C{=}CH_2$), 33.2 ($CH_2CHC(CH_3)_2$, sultam), 32.1 ($CH_2CHC(CH_3)_2$, sultam), 27.8 ($CHCH_2$), 27.6 ($CH_2CCH_2SO_2$), 26.5 ($CHCH_2CH_2$), 25.7 (CH_3), 21.2 (CH_3), 19.9 (CH_3), 17.7 (CH_3).
LRMS (ES+ ionisation)	753.3 ($[2M+Na]^+$, 4%), 748.4 ($[2M+NH_4]^+$, 4%), 429.1 ($[M+Na+MeCN]^+$, 8%), 383.1 ($[M+NH_4]^+$, 7%), 366.1 (($[M+H]^+$, 12%), 128.8 (100%).

Silica gel supported sodium periodate reagent

According to the method described by Zhong *et al.*,[25] $NaIO_4$ (2.57 g) was dissolved in water (5 mL) with an internal temperature of 70°C. To this solution, silica gel (10 g) was added with vigorous shaking to obtain a free flowing powder (12 g).

General procedure for the $KMnO_4$ oxidation of 1,5,9-trienoates : (±)-Ethyl (2*R)-2-hydroxy-2-[(2*S**,2'*R**,5*R**)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl] ethanoate (315c)**

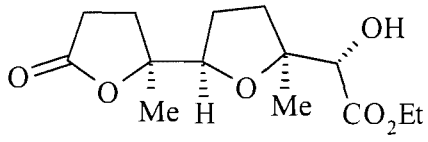


$C_{17}H_{30}O_7$.
M = 346.39 g.mol^{-1}.

To a vigorously stirred mixture of trieneoate **316c** (360 mg, 1.36 mmol) and phosphate buffer (4 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (20 mL) at –20 °C was added a solution of $KMnO_4$ (10.2 mL of 0.4 M (aq.), 4.10 mmol) containing AcOH (330 μL). The purple mixture was stirred rapidly for 30-60 min during which time it turned dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts and the aqueous layer was saturated with NaCl then extracted using CH_2Cl_2 (6 x 30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude title lactol **315c** (510 mg) as a colourless oil that was

used in the next reaction without further purification. Selected data for major epimer: ^{13}C NMR (100 MHz) 173.0, 109.4, 86.4, 84.7, 84.1, 76.2, 73.5, 62.3, 34.7, 33.1, 29.4, 27.6, 25.1, 24.8, 24.0, 22.5, 14.3.

(±)-Ethyl (2*R)-2-hydroxy-2-[(2*S**,2'*R**,5*R**)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl] ethanoate (314c)**



$C_{14}H_{22}O_6$.
M = 286.39 g.mol^{-1}.

General procedure for glycol cleavage using $Pb(OAc)_4$:

To a stirred solution of lactol **315c** (90 mg, 0.26 mmol)in dry CH_2Cl_2 (10 mL) was added Na_2CO_3 (47 mg, 0.44 mmol) followed by $Pb(OAc)_4$ (165 mg, 0.36 mmol). After 20 minutes celite was added and the mixture stirred for a further 15 min. The solids were then removed by filtration through a short plug of SiO_2, washing with EtOAc. The resulting solution was washed with $NaHCO_3$ (sat. aq. sol., 2 x 20 mL). The aqueous layer was saturated with NaCl and re-extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Purification on SiO_2 (15 g, EtOAc/CH_2Cl_2, 1:5) afforded the title compound **314c** as a colourless oil (35 mg, 0.13 mmol, 50% from **316c**).

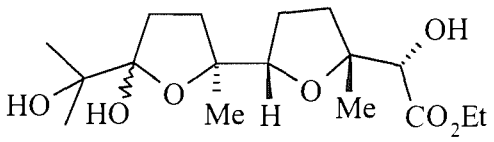
General procedure for glycol cleavage using $NaIO_4$-SiO_2 reagent:

To a vigorously stirred suspension of $NaIO_4$-SiO_2 reagent (6 g) in dry CH_2Cl_2 (20mL) was added a solution of crude lactol **315c** (510 mg) in dry CH_2Cl_2 (10 mL). The resulting mixture was stirred for 40 min before the solids were removed by filtration and washed with $CHCl_3$ (4 x 40 mL). The organic filtrate was concentrated *in vacuo* to give a yellow oil (400 mg). Purification on SiO_2 (35 g, CH_2Cl_2/EtOAc, 85:15) afforded the title lactone **314c** as a colourless oil (0.63 mmol, 180 mg, 46% from **316c**).

IR (cm^{-1})	3483 (b), 2971 (w), 2940 (w), 2873 (w), 1767 (s), 1737 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.26 (2H, q, *J* = 7.0 Hz, OC**H$_2$**), 4.07 (1H, dd, *J* = 9.6 and 5.9 Hz, C**H**CH$_2$), 4.03 (1H, d, *J* = 7.0 Hz, C**H**OH), 3.05 (1H, d, *J* = 7.0 Hz, O**H**), 2.79 (1H, ddd, *J* = 17.5, 10.3 and 7.4 Hz, CH**H**), 2.54 (1H, ddd, *J* = 17.5, 10.3 and 5.1 Hz, CH**H**), 2.40-2.26 (2H, m,

	CH_2), 1.99-1.82 (2H, m, CH_2), 1.80-1.59 (2H, m, CH_2), 1.38 (3H, s, CH_2CCH_3), 1.32 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.23 (3H, s CH_2CCH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	177.0 (CCOO), 174.0 (COO), 87.2 (CC-CH_3), 84.6 (CC-CH_3), 83.2 (CH-OH), 76.0 (CCH), 62.0 (O-CH_2), 34.2 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 27.1 (CH_2), 23.7 (CH_3), 22.7 (CH_3), 14.1 (O-CH_2CH_3 CH_3).
LRMS (ES+ ionisation)	595.1 ($[2M+Na]^+$, 61%), 309.1 ($[M+Na]^+$, 49%), 304.1 ($[M+NH_4]^+$, 100%).

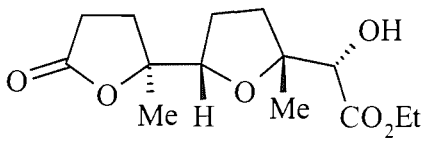
Ethyl (2*R)-2-hydroxy-2-[(2*R**,2'*R**,5*S**)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl] ethanoate (315a)**



$C_{17}H_{30}O_7$.
M = 346.39 g.mol^{-1}.

Following the general procedure for the $KMnO_4$ oxidation of trienoates, trienoate **316a** (97 mg, 0.38 mmol) afforded the crude title lactol **315a** (140 mg) as a colourless oil that was used in the next reaction without further purification. Selected data: ^{13}C NMR (75 MHz, selected signals from crude) 173.3, 109.5, 86.1, 84.8, 83.2, 76.7, 73.2, 61.2, 36.6, 32.4, 31.7, 27.5, 24.4, 23.9, 23.7, 23.5, 14.1

(±)-Ethyl (2*R)-2-hydroxy-2-[(2*R**,2'R*,5*S**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl] ethanoate (314a)**



$C_{14}H_{22}O_6$.
M = 286.39 g.mol^{-1}.

Method 1 :

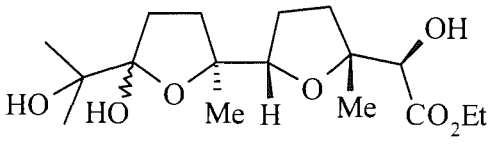
Following the general procedure for the $Pb(OAc)_4$ cleavage, crude **315a** (110 mg, 0.31 mmol) afforded the title lactone **314a** as a pale yellow oil (37 mg, 0.14 mmol, 46% from **316a**).

Method 2 :

Following the procedure used for the $NaIO_4$-SiO_2 cleavage, crude **315a** (20 mg) afforded the title lactone **314a** as a colourless oil (10 mg, 0.035 mmol, 55% from **316a**).

IR (cm^{-1})	3483 (b), 2983 (w), 2935 (w), 2863 (w), 1768 (s), 1734 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.28 (1H, dd, J = 10.8 and 7.1 Hz, OCH_2), 4.23 (1H, dd, J = 10.8 and 7.1 Hz, OCH_2), 3.99 (1H, s, CHOH), 3.94 (1H, dd, J = 8.3 and 6.7 Hz, $CHCH_2$), 2.91 (1H, br s, OH), 2.89-2.78 (1H, m, CHH), 2.49 (1H, ddd, J = 17.5, 10.5 and 4.0 Hz, CHH), 2.44 (1H, ddd, J = 12.8, 10.5 and 4.0 Hz, CHH), 2.35 (1H, ddd, J = 12.5, 9.0 and 4.8Hz, CHH), 2.14-1.88 (3H, m), 1.70 (1H, td, J = 12.6 and 8.3 Hz, CHH), 1.36 (3H, s, CH_2CCH_3), 1.30 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.18 (3H, s CH_2CCH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	177.9 (CCOO), 172.1 (COO), 85.7 ($CCCH_3$), 85.0 ($CCCH_3$), 84.5 (CHOH), 76.4 (CCH), 61.6 (OCH_2), 35.3 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 24.2 (CH_3), 22.4 (CH_3), 14.1 (OCH_2CH_3).
(ES+ ionisation)	595.1 ($[2M+Na]^+$, 100%), 309.0 ($[M+Na]^+$, 28%), 304.1 ($[M+NH_4]^+$, 70%)
HRMS	Calcd for $C_{14}H_{22}O_6$: 287.1495. Found: 287.1495 (87, $[M+H]^+$).

(±)-Ethyl (2*R)-2-hydroxy-2-[(2*S**,2'*S**,5*R**)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl] ethanoate (315b)**

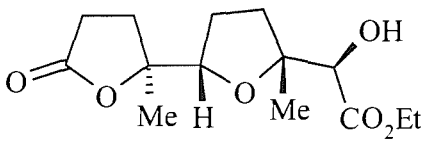


$C_{17}H_{30}O_7$.

M = 346.39 g.mol^{-1}.

Following the general procedure for the $KMnO_4$ oxidation of trienoates, trienoate **316b** (200 mg, 0.76 mmol) afforded the crude title lactol **315b** (240 mg) as a colourless oil that was used in the next reaction without further purification. ^{13}C NMR (75 MHz, selected signals from crude) 171.8, 109.7, 85.0, 84.8, 82.9, 77.3, 73.3, 61.5, 33.4, 32.7, 31.9, 28.0, 24.7, 24.5, 24.2, 24.0, 14.3; MS (ES) *m/z* (relative intensity) 715.4 (49, $[2M+Na]^+$), 369 (100, $[M+Na]^+$).

(±)-Ethyl (2*R)-2-hydroxy-2-[(2*S**,2'*R**,5*R**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl] ethanoate (314b)**



$C_{14}H_{22}O_6$.
M = 286.39 g.mol^{-1}.

Method 1 :

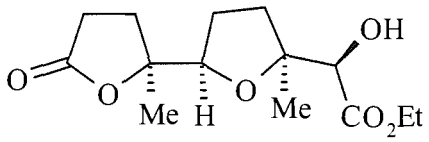
Following the general procedure for the $Pb(OAc)_4$ cleavage, crude **315b** (60 mg, from 0.19 mmol of **316b**) afforded the title lactone **314b** (24 mg, 0.09 mmol, 44% from **316b**) as a colourless oil which solidified on standing. Recrystallisation from EtOAc/hexane gave colourless needles suitable for x-ray structural determination.

Method 2 :

Following the procedure used for the $NaIO_4$-SiO_2 cleavage, crude **315b** (55 mg, from 0.174 mmol of **316b**) afforded the title lactone **314b** as a colourless oil (25 mg, 0.087 mmol, 50% from **316b**).

mp (uncorrected)	54-59°C
IR (cm^{-1})	3473 (b), 2976 (w), 2930 (w), 2873 (w), 1767 (s), 1731 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.28 (2H, q, *J* = 7.3 Hz, OC**H$_2$**), 4.02 (1H, d, *J* = 6.3 Hz, C**H**OH), 3.95 (1H, dd, *J* = 8.5 and 7.0 Hz, C**H**CH$_2$), 3.01 (1H, d, *J* = 6.0 Hz, O**H**), 2.87 (1H, app. ddd, *J* = 17.8, 9.8 and 7.2 Hz, C**H**H), 2.52-2.41 (2H, m, C**H$_2$**), 2.35 (1H, ddd, *J* = 12.8, 8.8 and 5.0 Hz, CH**H**), 2.07-1.87 (3H, m, C**H$_2$** and C**H**H), 1.69 (1H, td, *J* = 12.8 and 8.3 C**H**H), 1.36 (3H, s, CH$_2$CC**H$_3$**), 1.32 (3H, t, *J* = 7.0 Hz, OCH$_2$C**H$_3$**), 1.20 (3H, s CH$_2$CC**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	177.6 (**C**COO), 173.1 (**C**OO), 85.5 (**C**CCH$_3$), 84.7 (C**C**CH$_3$), 84.6 (**C**HOH), 75.6 (**C**CH), 61.9 (O**C**H$_2$), 34.6 (**C**H$_2$), 31.8 (**C**H$_2$), 29.5 (**C**H$_2$), 26.0 (**C**H$_2$), 24.3 (**C**H$_3$), 22.0 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	595.1 ([2M+Na]$^+$, 100%), 309.0 ([M+Na]$^+$, 28%), 304.1 ([M+NH$_4$]$^+$, 70%).

(±)-Ethyl (2*R)-2-hydroxy-2-[(2*R**,2'*S**,5*S**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl] ethanoate (314g)**

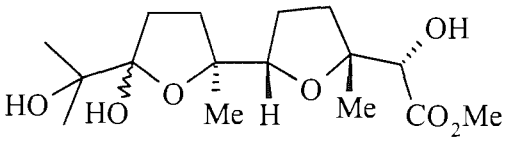


$C_{14}H_{22}O_6$.
M = 286.39 g.mol^{-1}.

To a vigorously stirred suspension of $NaIO_4$-SiO_2 reagent (250 mg) in dry CH_2Cl_2 (3mL), pure lactol **315g** (15 mg, 0.043 mmol) in dry CH_2Cl_2 (1 mL) was added in one portion. The resulting mixture was stirred for 45 minutes. The mixture was filtered and the silica gel was washed with $CHCl_3$ (3 × 15 mL). The solution was concentrated *in vacuo* to give the crude product as a yellow oil (25 mg). Purification on silica gel (25 g, CH_2Cl_2/EtOAc, 85:15) afforded the title product **314g** as a yellow oil (9 mg, 0.031 mmol, 72% for one step).

IR (cm^{-1})	3411 (b), 2976 (w), 2940 (w), 1767 (s), 1731 (s), 1455 (m), 1373 (m), 1081 (s), 944 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.31 (1H, dq, *J* = 7.4 and 4.4 Hz, OC**H$_2$**), 4.24 (1H, qd, *J* = 7.4 and 4.0 Hz, OC**H$_2$**), 4.02 (1H, dd, *J* = 9.0 and 6.6 Hz, C**H**OH) 4.01 (1H, d, *J* = 6.4, C**H**CH$_2$), , 3.10 (1H, d, *J* = 6.4 Hz, O**H**), 2.73 (1H, ddd, *J* = 18.2, 10.6 and 8.1 Hz, C**H**H), 2.52 (1H, ddd, *J* = 18.1, 10.5 and 5.0 Hz, CH**H**), 2.45-2.28 (2H, m, C**H$_2$**), 2.00-1.80 (2H, m, C**H$_2$**), 1.80-1.63 (2H, m, C**H$_2$**), 1.39 (3H, s, CH$_2$CC**H$_3$**), 1.34 (3H, t, *J* = 4.0 Hz, OCH$_2$C**H$_3$**), 1.26 (3H, s CH$_2$CC**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	177.1 (**C**COO), 172.7 (**C**OO), 87.3 (**C**CCH$_3$), 85.1 (**C**CCH$_3$), 83.4 (**C**HOH), 76.2 (**C**CH), 62.1 (O**C**H$_2$), 35.4 (**C**H$_2$), 29.4 (**C**H$_2$), 28.5 (**C**H$_2$), 28.1 (**C**H$_2$), 23.9 (**C**H$_3$), 23.8 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	595.1 ([2M+Na]$^+$, 48%), 325.0 ([M+K]$^+$, 21%), 309.14 ([M+Na]$^+$, 38%), 304.2 ([M+NH$_4$]$^+$, 100%).

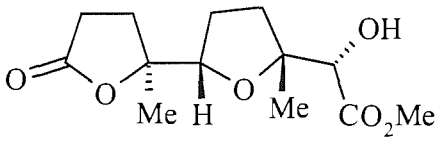
(±)-Methyl (2*R)-2-hydroxy-2-[(2*R**,2'*R**,5*S**)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl] ethanoate (27)**



$C_{16}H_{28}O_7$.
M = 332.40 g.mol^{-1}.

Following the general procedure described for the $KMnO_4$ oxidation of trienoates, methyl (*E,E*)-farnesoate **26** (15 mg, 0.060 mmol) afforded the crude title lactol **27** as an oily solid (25 mg) that was used in the next reaction without further purification. ^{13}C NMR (75 MHz, selected signals from crude) : 173.9, 109.6, 84.8, 84.1, 83.2, 77.1, 73.1, 52.0, 36.8, 32.3, 31.8, 27.7, 24.5, 23.9, 23.7.

(±)-Methyl (2*R)-2-hydroxy-2-[(2*R**,2'*R**,5*S**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl) ethanoate (28)**



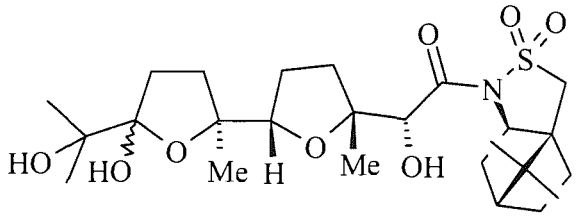
$C_{13}H_{20}O_6$.
M = 272.30 g.mol^{-1}.

Following the procedure used for the $NaIO_4$-SiO_2 cleavage, crude lactol **27** (25 mg) afforded the title lactone **28** as a colourless oil (9 mg, 0.033 mmol, 55% from **26**).

IR (cm^{-1})	3420 (b), 2960 (w), 1760 (s), 1737 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.02 (1H, d, *J* = 8.4 Hz, C**H**OH) 3.93 (1H, dd, *J* = 8.6 and 6.7 Hz, C**H**CH$_2$), 3.78 (3H, s), 2.99 (1H, d, *J* = 8.4 Hz, O**H**), 2.82 (1H, app. ddd, *J* = 17.8, 10.6 and 8.3 Hz, C**H**H), 2.55-2.38 (2H, m, C**H$_2$**), 2.33 (1H, ddd, *J* = 17.1, 9.0 and 4.8 Hz, CH**H**), 2.11-1.88 (3H, m, C**H**H and C**H$_2$**), 1.69 (1H, td, *J* = 12.5 and 8.5 Hz, CH**H**), 1.37 (3H, s, CH$_2$CC**H$_3$**), 1.25 (3H, s, CH$_2$CC**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	178.0 (**C**COO), 172.6 (**C**OO), 85.7 (**C**C-CH$_3$), 85.1 (**C**C-CH$_3$), 84.7 (**C**H-OH), 76.6 (**C**CH), 52.4 (O-**C**H$_2$), 35.3 (**C**H$_2$), 32.2 (**C**H$_2$), 29.6 (**C**H$_2$), 27.0 (**C**H$_2$), 24.4 (**C**H$_3$), 23.0 (**C**H$_3$).
LRMS (ES+ ionisation)	567.4 ([2M+Na]$^+$, 70%), 295.4 ([M+Na]$^+$, 100%), 273.2 (67 [M+H]$^+$, 37%).

HRMS (ES+ ionisation) Calculated : $C_{13}H_{20}O_6Na$ = 295.1152. Found : 295.1155.

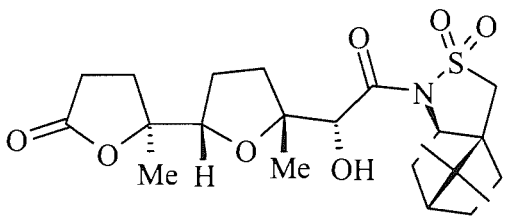
***N*-[(2*R*)-2-Hydroxy-2-((2*R*,2'*R*,5*S*)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2*R*)-camphor-10,2-sultam (315e)**



$C_{25}H_{41}NO_8S$.
M = 515.57 g.mol^{-1}.

Following the general procedure described for the $KMnO_4$ oxidation of trienoates, oxidation of **316e** (22 mg, 0.05 mmol) afforded the crude lactol **315e** as a pale yellow oil (30 mg) that was used in the next reaction without further purification. Selected data: ^{13}C NMR (75 MHz, selected signals from crude) 172.1, 109.7, 85.6, 85.3, 82.1, 75.9, 72.4, 65.4, 53.1, 48.7, 47.8, 44.8, 38.7, 32.9, 32.1 (x2), 29.8, 26.6, 24.9, 24.0, 23.8, 23.1, 21.1, 20.0.

***N*-[(2*R*)-2-Hydroxy-2-((2*R*,2'*R*,5*S*)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2*R*)-camphor-10,2-sultam (314e)**



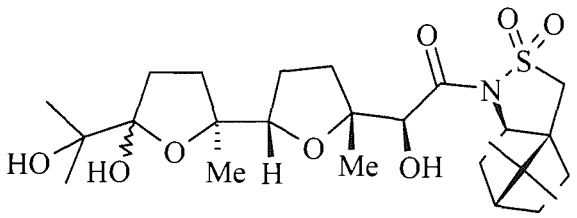
$C_{22}H_{33}NO_7S$.
M = 455.57 g.mol^{-1}.

Following the procedure described for the $NaIO_4$-SiO_2 cleavage, the crude lactol **315e** (30 mg) afforded the title lactone **314e** as a colourless oil (13 mg, 0.03 mmol, 60% from **316e**) after purification on SiO_2 (25 mL, CH_2Cl_2/EtOAc, 9:1).

$[\alpha]^{20}_D$	–57.3 (*c* 0.4, $CDCl_3$)
IR (cm^{-1})	3483 (b), 2983 (w), 2935 (w), 2863 (w), 1768 (s), 1734 (s), 1455 (m), 1380 (m), 1095 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.02 (1H, s, C**H**-OH), 3.88 (2H, m, C**H**N and C**H**CH_2), 3.51 (1H, d, *J* =13.8 Hz, C**H**HSO_2), 3.46 (1H, d, *J* =13.8 Hz, CH**H**SO_2), 2.82 (1H, dd, *J* = 21.6 and 9.8 Hz, C**H**H), 2.60 (1H, dd, *J* = 24.6 and 10.0 Hz, CH**H**), 2.26-1.89 (5H, m), 1.69 (1H, dd, *J* = 12.0

	and 10.0 Hz, CHH), 1.57-1.43 (6H, m), 1.40 (2H, m), 1.30 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.11 (3H, s, CH_3), 0.97 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	177.3 (CCOO), 168.2 (CON), 86.5 ($CC-CH_3$), 85.0 ($CC-CH_3$), 84.5 (CH-OH), 75.2 (CCH), 65.0 (CHN), 53.1 (CH_2SO_2), 48.5 (CCH_2SO_2), 47.8 ($C(CH_3)_2$), 44.5 ($CHC(CH_3)_2$), 38.1 (CH_2CHN), 36.8 (CH_2), 32.8 ($CH_2CH_2CCH_2S$), 31.2 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 24.0 (CH_3), 23.6 (CH_3), 21.0 (CH_3), 19.7 (CH_3).
LRMS (ES+ ionisation)	933.0 ($[2M+Na]^+$, 16%), 478.2 ($[M+Na]^+$, 28%), 128.8 (100%).

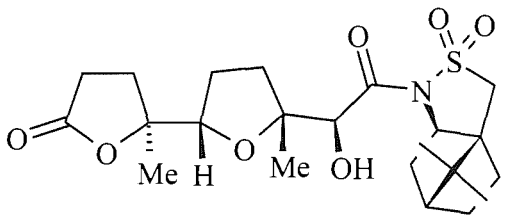
_N_-[(2_S_)-2-Hydroxy-2-((2_R_,2'_R_,5_S_)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2_R_)-camphor-10,2-sultam (315d)



$C_{25}H_{41}NO_8S$.
M = 515.57 g.mol^{-1}.

Following the general procedure described for the $KMnO_4$ oxidation of trienoates, oxidation of **316d** (30 mg, 0.069 mmol) afforded the crude lactol **315d** as a pale yellow oil (40 mg). Selected data: ^{13}C NMR (100 MHz) 174.2, 109.5, 84.8, 83.9, 83.4, 75.7, 73.0, 65.2, 53.1, 48.4, 47.7, 44.6, 38.0, 32.8, 32.2, 31.5, 27.4, 26.4, 24.4, 24.0, 23.9, 23.6, 20.9, 19.8.

_N_-[(2_S_)-2-Hydroxy-2-((2_R_,2'_R_,5_S_)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2_R_)-camphor-10,2-sultam (314d)

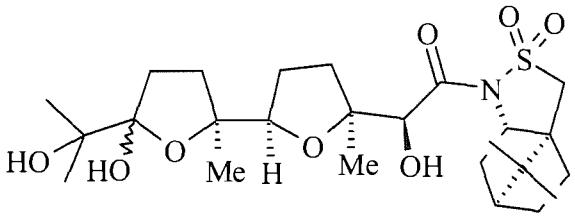


$C_{22}H_{33}NO_7S$.
M = 455.57 g.mol^{-1}.

Following the procedure described for the $NaIO_4$-SiO_2 cleavage, the crude lactol **315d** (40 mg) afforded the title lactone **314d** as a colourless glass (18 mg, 0.04 mmol, 58% from **316d**) after purification on SiO_2 (25 mL, CH_2Cl_2/EtOAc, 9:1). Crystallisation gave colourless needles suitable for x-ray structural determination.

$[\alpha]^{20}_D$	–49.5 (*c* 0.3, $CDCl_3$)
Mp (EtOAc/hexane)	151-154°C
IR (cm^{-1})	3499 (w), 2959 (b), 2936 (b), 2874 (b), 1763 (s), 1701 (s), 1375 (m), 1038 (w), 911 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.50 (1H, br s, C**H**OH), 4.00 (1H, dd, *J* = 7.8 and 5.1 Hz, C**H**N), 3.93 (1H, dd, *J* = 9.4 and 6.2 Hz, C**H**CH_2), 3.52 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.43 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.15 (1H, br s, O**H**), 2.94-2.85 (1H, m, C**H**H), 2.51 (1H, dt, *J* = 4.4 and 2.8 Hz, C**H**H), 2.33 (1H, ddd, *J* = 12.6, 9.1 and 3.4 Hz, C**H**H) 2.30-1.86 (8H, m, 4 x C**H**$_2$), 1.74 (1H, ddd, *J* = 12.6, 9.3 and 8.4 Hz, C**H**H), 1.51-1.45 (3H, m, C**H**H and C**H**$_2$), 1.35 (6H, s, C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 0.96 (3H, s, C**H**$_3$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	178.2 (**C**COO), 169.8 (**C**ON), 85.4 (**C**C-CH_3), 84.4 (**C**C- CH_3), 84.3 (**C**H-OH), 75.0 (**C**CH), 65.2 (**C**HN), 52.9 (**C**H_2SO_2), 48.6 (**C**CH_2SO_2), 47.7 (**C**$(CH_3)_2$), 44.7 (**C**H$C(CH_3)_2$), 38.1 (**C**H_2CHN), 34.8 (**C**H_2), 32.7 (**C**$H_2CH_2CCH_2S$), 32.1 (**C**H_2), 29.5 (**C**H_2), 26.6 (**C**H_2), 26.3 (**C**H_2), 24.4 (**C**H_3), 23.6 (**C**H_3), 21.0 (**C**H_3), 19.9 (**C**H_3).
LRMS (ES+ ionisation)	933.2 ($[2M+Na]^+$, 6%), 478.2 ($[M+Na]^+$, 5%), 456.2 ($[M+H]^+$, 16%) 153.3 (100%).
HRMS (ES+ ionisation)	Calculated : $C_{22}H_{33}NO_7SNa$ = 478.1870. Found : 478.1869.

***N*-[(2*R*)-2-Hydroxy-2-((2*R*,2'*R*,5*S*)-5'-hydroxy-5'-(1-hydroxy-1-methyl-ethyl)-5,2'-dimethyl-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2*S*)-camphor-10,2-sultam (315h)**

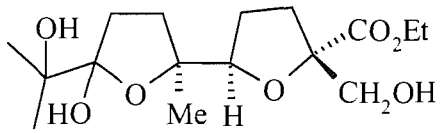


$C_{25}H_{41}NO_8S$.

M = 515.57 g.mol^{-1}.

Following the general procedure described for the $KMnO_4$ oxidation of trienoates, oxidation of **316h** (100 mg, 0.231 mmol) afforded the crude lactol **315h** as a pale yellow oil (125 mg) that was used in the next reaction without further purification. Selected data: ^{13}C NMR (100 MHz, selected signals from crude) 169.5, 109.3, 86.9, 84.8, 82.9, 75.4, 73.9, 65.3, 53.1, 48.7, 47.8, 44.6, 38.2, 33.7, 32.8, 29.7, 27.0, 25.6, 24.7, 24.1, 23.9, 23.4, 21.0, 20.8, 19.8.

(±)-(2*R,5*S**)-Ethyl tetrahydro-5-((2*R**)-tetrahydro-5-hydroxy-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (482a)**

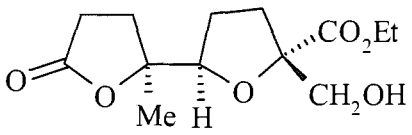


$C_{16}H_{28}O_7$.
M = 332.40 g.mol^{-1}.

To a stirred solution of triene **452a** (80 mg, 0.32 mmol) in a mixture of acetone (3 mL) and AcOH (2 mL) at –30°C was added in one batch powered $KMnO_4$ (152 mg, 0.96 mmol). The solution was stirred for 1 hour maintaining the temperature between –30°C and –10°C. The solution was poured into an ice-cold sat. sol. of $Na_2S_2O_5$ (10 mL), discolouring the brown solution. The aqueous phase was extracted with EtOAc (2 x 10 mL), Et_2O (2 x 10 mL), EtOAc (2 x 10 mL). The aqueous phase was then neutralised with $NaHCO_3$ (sat. aq. sol., 10 mL) and extracted further with EtOAc (2 x 10 mL); these organic phases were washed with brine (10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (150 mg). Purification on silica gel (50 mL, EtOAc/CH_2Cl_2, 1:4) afforded the title product **482a** as a pale yellow oil (70 mg, 0.211 mmol, 66%).

IR (cm^{-1})	3491 (b), 2952 (w), 2931 (w), 2885 (w), 1737 (s), 1370 (m), 1101 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.22 (2H, q, J = 7.2 Hz, OC**H$_2$**), 4.17-4.13 (2H, m, CC**H** and O**H**), 3.82 (1H, d, J = 11.8 Hz, CH**H**OH), 3.76 (1H, d, J = 11.8 Hz, C**H**HOH), 2.59-2.48 (1H, m, CCH**H**), 2.35-1.83 (9H, m, CCH**H** and 3 x C**H$_2$** and 2 x O**H**), 1.30 (6H, s, 2 x C**H$_3$**), 1.27 (3H, t, J = 7.3 Hz, OCH$_2$C**H$_3$**), 1.27 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	174.3 (**C**OO), 109.4 (**C**(CH$_3$)$_2$), 98.4 (C**C**-CH$_3$), 85.4 (**C**H-OH), 84.4 (CCCH$_3$), 73.0 (**C**OH), 66.0 (O**C**H$_2$), 61.2 (**C**H$_2$OH), 32.6 (**C**H$_2$), 32.4 (**C**H$_2$), 31.8 (**C**H$_2$), 26.0 (**C**H$_2$), 24.4 (**C**H$_3$), 24.0 (**C**H$_3$), 23.8 (**C**H$_3$), 14.6 (O-CH$_2$**C**H$_3$ **C**H$_3$).
LRMS (ES+ ionisation)	687.6 ([2M+Na]$^+$, 100%), 355.3 ([M+Na]$^+$, 25%).
HRMS	Calculated: $C_{18}H_{27}O_7Na$ = 355.1727 Found: 355.1722.

(±)-(2*R,5*S**)-Ethyl tetrahydro-5-((*R**)-tetrahydro-2-methyl-5-oxofuran-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (453a)**

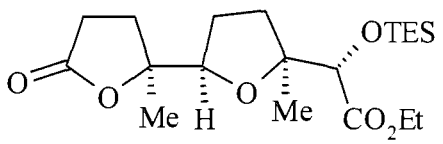


$C_{13}H_{20}O_6$.
M = 272.31 g.mol^{-1}.

Following the procedure used for the $NaIO_4$-SiO_2 cleavage, lactol **482a** (65 mg, 0.196 mmol) afforded the title lactone **753a** as a colourless oil (0.183 mmol, 50 mg, 93%) after purification on SiO_2 (25 g, CH_2Cl_2/EtOAc, 75:25).

IR (cm^{-1})	3483 (b), 2971 (w), 2940 (w), 2873 (w), 1767 (s), 1737 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.25 (2H, q, *J* = 7.3 Hz, OC**H**$_2$), 4.18 (1H, t, *J* = 7.0 Hz, C**H**O), 3.85 (1H, dd, *J* = 11.5 and 5.3 Hz, CH**H**OH), 3.67 (1H, dd, *J* = 11.8 and 4.5 Hz, C**H**HOH), 2.81-2.79 (1H, m, CCH**H**), 2.84-2.49 (1H, m, CCH**H**), 2.51 (1H, dt, *J* = 10.5 and 4.2 Hz, CH**H**C), 2.16-1.94 (6H, 2 x C**H**$_2$ and C**H**H and O**H**), 1.39 (3H, s, C**H**$_3$), 1.30 (3H, t, *J* = 7.3 Hz, OCH$_2$C**H**$_3$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	177.9 (**C**OO, THF), 173.5 (**C**OO), 87.3 (**C**CH$_2$OH), 86.3 (**C**HO, THF), 85.5 (**C**CH$_3$), 66.4 (O**C**H$_2$CH$_3$), 61.3 (**C**H$_2$OH), 31.9 (**C**H$_2$), 29.7 (**C**H$_2$), 26.0 (2 x **C**H$_2$), 24.1 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	567.3 ([2M+Na]$^+$, 35%), 295.3 ([M+Na]$^+$, 100%).
HRMS	Calculated: $C_{13}H_{20}O_6Na$ = 295.1152 Found: 295.1149.

(±)-Ethyl (2*R)-2- triethylsilanyloxy -2-[(2*S**,2'*R**,5*R**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl) ethanoate (483a)**



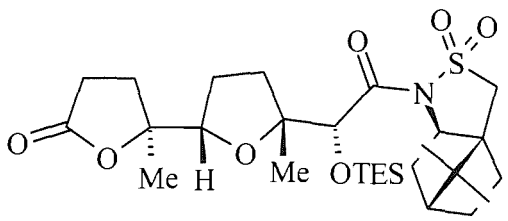
$C_{20}H_{36}O_6Si$.
M = 400.59 g.mol^{-1}.

According to the method of Ishiyama *et al.*,[182] lactone **314c** (50 mg, 0.17 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and cooled to 0°C before the dropwise addition of 2,6-lutidine (0.03 mL, 0.36 mmol) followed by the dropwise addition of TESOTf (0.05 mL, 0.27 mmol). The resulting solution was allowed to warm at room temperature and stirred for one hour. The reaction was quenched by the addition of NH_4Cl (sat. aq. sol., 10 mL) and the

aqueous phase was extracted with EtOAc (5 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (200 mg). Purification on SiO_2 (25 g, CH_2Cl_2/EtOAc, 19:1) afforded the pure product **483a** as a yellow oil (58 mg, 0.15 mmol, 88%).

IR (cm^{-1})	2950 (w), 2905 (m), 2872 (w), 1772 (s), 1746 (s), 1457 (m), 1375 (w), 1242 (w) 1137 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.14 (2H, m, OC**H**$_2$), 4.07 (1H, m, C**H**CH$_2$), 4.06 (1H, s, C**H**-OTES), 2.78 (1H, ddd, *J* = 18.0, 10.5 and 2.9 Hz, C**H**H), 2.59-2.21 (3H, m, C**H**$_2$ and C**H**H), 1.96-1.79 (2H, m, C**H**$_2$), 1.67-1.56 (2H, m, C**H**$_2$), 1.37 (3H, s, C**H**$_3$), 1.32 (3H, t, *J* = 7.2 Hz, O CH$_2$C**H**$_3$), 1.22 (3H, s, CH$_2$CC**H**$_3$), 0.96 (9H, t, *J* = 7.8 Hz, SiCH$_2$C**H**$_3$), 0.60 (6H, q, *J* = 7.7 Hz, SiC**H**$_2$CH$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	176.3 (**C**COO), 174.2 (**C**OO), 87.3 (**C**CH$_3$), 85.1 (**C**CH$_3$), 82.8 (**C**HOH), 76.4 (**C**CH), 60.8 (O**C**H$_2$), 34.6 (**C**H$_2$), 29.5 (**C**H$_2$), 28.7 (**C**H$_2$), 27.2 (**C**H$_2$), 23.4 (**C**H$_3$), 21.8 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 6.7 (3 x Si**C**H$_2$), 4.5 (3 x SiCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	823.2 ([2M+Na]$^+$, 80%), 423.2 (100, [M+Na]$^+$), 401.1 ([M+H]$^+$, 100%).

***N*-[(2*R*)-2-Triethylsilanyloxy -2-((2*R*,2'*R*,5*S*)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl)ethanoyl]-(2*R*)-camphor-10,2-sultam (483b)**



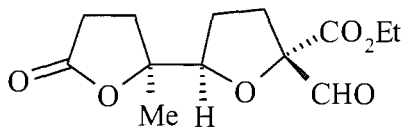
$C_{28}H_{47}NO_6SSi$.
M = 569.84 g.mol^{-1}.

Following the procedure for the preparation of the protected lactone **483a**, lactone **314e** (20 mg, 0.04 mmol) afforded the title product **483b** as a yellow oil (20 mg, 0.035 mmol, 88%).

$[\alpha]^{20}_D$	–61.1 (*c* 0.5, $CDCl_3$)
IR (cm^{-1})	2959 (b), 2916 (b), 2870 (b), 1768 (s), 1697 (s), 1455 (w), 1327 (s), 1230 (s), 1130 (s), 751 (w).

^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.77 (1H, s, C**H**OTES), 3.88 (1H, dd, *J* = 7.5 and 5.5 Hz, C**H**N), 3.78 (1H, dd, *J* = 8.4 and 6.4 Hz, C**H**CH_2, THF), 3.58 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 3.48 (1H, d, *J* = 13.7 Hz, C**H**HSO_2), 2.68-2.05 (7H, m, C**H**C$(CH_3)_2$ and 3 x C**H$_2$**), 1.89-1.63 (6H, m, 3 x C**H$_2$**), 1.37 (3H, s, C**H$_3$**), 1.31 (3H, s, C**H$_3$**), 1.17 (3H, s, C**H$_3$**), 0.97 (3H, s, C**H$_3$**), 0.93 (9H, t, *J* = 7.9 Hz, $SiCH_2C\mathbf{H}_3$), 0.64 (6H, q, *J* = 7.9 Hz, $SiC\mathbf{H}_2CH_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	174.2 (**C**CON), 170.5 (**C**ON), 85.7 (**C**CH_3), 85.6 (**C**CH_3), 81.8 (**C**HOTES), 75.0 (**C**CH), 66.0 (**C**HN), 52.8 ($\mathbf{C}H_2SO_2$), 48.1 ($\mathbf{C}CH_2SO_2$), 47.5 ($\mathbf{C}(CH_3)_2$), 44.7 ($\mathbf{C}HC(CH_3)_2$), 387 ($\mathbf{C}H_2CHN$), 34.4 ($\mathbf{C}H_2$), 33.2 ($\mathbf{C}H_2CH_2CCH_2S$), 30.4 ($\mathbf{C}H_2$), 29.4 ($\mathbf{C}H_2$), 26.3 ($\mathbf{C}H_2$), 24.7 ($\mathbf{C}H_3$), 21.6 ($\mathbf{C}H_3$), 21.0 ($\mathbf{C}H_3$), 19.9 ($\mathbf{C}H_3$), 6.8 (3 x $Si\mathbf{C}H_2$), 4.8 (3 x $SiCH_2\mathbf{C}H_3$).
LRMS (ES+ ionisation)	1161.1 ($[2M+K]^+$, 4%), 592.2 ($[M+Na]^+$, 34%), 570.2 ($[M+H]^+$, 12%).

(±)-(2*R,5*S**)-Ethyl 2-formyl-tetrahydro-5-((*R**)-tetrahydro-2-methyl-5-oxofuran-2-yl)furan-2-carboxylate (459a)**



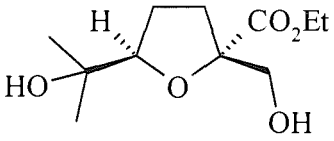
$C_{13}H_{18}O_6$.
M = 270.28 g.mol^{-1}.

To a solution of THF **453a** (20 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) containing 50 mg of crushed molecular sieves, was added NMO (17 mg, 0.127 mmol) and TPAP (5 mg). The resulting solution was stirred for 45 minutes, filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo* to afford the crude compound as a pale yellow oil (25 mg). Purification on silica gel (15 g, EtOAc/CH_2Cl_2, 2:3) afforded the title product **459a** as a yellow oil (15 mg, 0.055 mmol, 76%).

IR (cm^{-1})	2960 (w), 2915 (w), 2895 (w), 1772 (s), 1760 (s), 1742 (s), 1450 (m), 1130 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	9.52 (1H, s, C**H**O), 4.27 (1H, dd, *J* = 7.0 and 1.5 Hz, C**H**OC), 4.25 (2H, q, *J* = 7.3 Hz, O**CH$_2$**), 2.90 (1H, dt, *J* = 8.0 and 4.8 Hz,

	CHHC), 2.55 (2H, m, CHH and CHH), 2.27 (1H, tt, J = 8.0 and 4.8 Hz, CHHC), 2.09-1.94 (4H, m, 2 x CH_2), 1.38 (3H, s, CH_3), 1.30 (3H, t, J = 7.3 Hz, OCH_2CH_3).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	196.6 (CHO), 177.9 (CCOO), 177.1 (COO), 90.1 ($CCCH_3$), 87.3 (CHOH), 85.1 ($CCCH_3$), 62.2 (OCH_2), 31.7 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 25.6 (CH_2), 24.3 (CH_3), 14.1 (OCH_2CH_3).
LRMS (ES+ ionisation)	563.5 ($[2M+Na]^+$, 25%), 558.5 ($[2M+NH_4]^+$, 49%), 288.4 ($[M+NH_4]^+$, 100%).

(±)-(2*R,5*S**)-Ethyl tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (422a)**



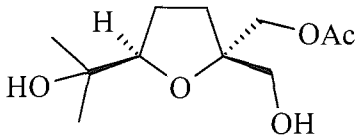
$C_{11}H_{20}O_5$.
M = 232.28 g.mol^{-1}.

To a vigorously stirred mixture of diene **421a** (520 mg, 2.857 mmol) and phosphate buffer (1.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (40 mL) at –20 °C was added a solution of $KMnO_4$ (14.3 mL of 0.4 M (aq), 5.714 mmol) containing AcOH (0.322 mL, 8.00 mmol). The purple mixture was stirred rapidly for 20 min during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 40 mL), then with Et_2O (40 mL), saturated with NaCl and extracted further with EtOAc (2 x 40 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil. Purification on silica gel (20 g, CH_2Cl_2/EtOAc, 1:1) afforded the title product **422a** as a colourless oil (636 mg, 2.738 mmol, 96%). The crude compound could be used without further purification in the next step.

IR (cm^{-1})	3409 (b), 2969 (s), 2936 (s), 2874 (m), 1734 (s), 1465 (w), 1370 (s), 1110 (s), 1053 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.20 (2H, m, OCH_2), 4.04 (1H, br t, J = 7.4 Hz, CCH), 3.89 (1H, d, J = 11.4 Hz, CHHOH), 3.74 (1H, d, J = 11.4 Hz, CHHOH), 3.18 (2H, br s, 2 x OH), 2.17 (2H, m, CH_2), 1.92 (2H, br q, J = 7.4 Hz, $CHCH_2$), 1.28 (3H, s, CH_3), 1.27 (3H, t, J = 7.1 Hz,

	OCH_2CH_3), 1.13 (3H, s, CH_3).
^{13}C-NMR	174.1 (**C**OO), 87.6 (O**C**H), 86.7 (**C**$(CH_3)_2$), 71.5 (O**C**CH_2), 66.0
(100MHz, $CDCl_3$, ppm)	(OCH_2), 61.3 (CH_2OH), 32.0 (CH_2C), 27.5 (CH_3), 26.1 ($CHCH_2$), 24.9 (CH_3), 14.2 (OCH_2CH_3).
LRMS (ES+ ionisation)	487.2 ($[2M+Na]^+$, 75%), 465.2 ($[2M+H]^+$, 18%).
HRMS	Calcd for $C_{11}H_{20}O_5Na$: 255.1203. Found: 255.1202.

(±)-((2*R,5*S**)-Tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furan-2-yl)methyl acetate (440)**

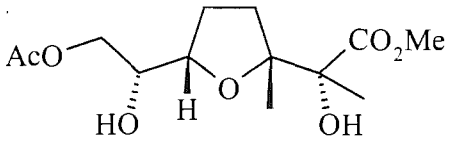


$C_{11}H_{20}O_5$.
M = 232.27 g.mol^{-1}.

Following the procedure for the preparation of THF **422a**, oxidative cyclisation of diene **436** (70 mg, 0.385 mmol) afforded THF **440** as a colourless oil (80 mg, 0.344 mmol, 89%) after purification on silica gel (50 mL, CH_2Cl_2/EtOAc, 2:1).

IR (cm^{-1})	3495 (b), 2976 (m), 2886 (m), 1743 (m), 1491 (w), 1288 (m), 1201 (s), 1046 (m).
^{1}H-NMR	4.07 (2H, s, CH_2OAc), 3.87 (1H, t, J = 7.0 Hz, CHO, THF), 3.62
(400MHz, $CDCl_3$, ppm)	(1H, d, J = 11.4 Hz, CHHOH), 3.51 (1H, d, J = 11.4 Hz, CHHOH), 2.81 (1H, br s, OH), 2.39 (1H, br s, OH), 2.09 (3H, s, OCH_3), 2.08-1.80 (2H, m, CH_2), 1.92 (2H, br q, J = 7.4 Hz, $CHCH_2$), 1.28 (3H, s, CH_3), 1.13 (3H, s, CH_3).
^{13}C-NMR	170.8 (CH_3COO), 86.2 (CCH_2OH, THF), 83.8 ($CHCH_2$, THF),
(100MHz, $CDCl_3$, ppm)	71.7 ($C(CH_3)_2$), 66.2 (CH_2OAc), 65.4 (CH_2OH), 30.2 (CH_2C, THF), 27.3 (CH_3), 26.1 (CH_2CH, THF), 24.8 (CH_3), 20.6 (CH_3).
LRMS (ES+ ionisation)	487.4 ($[2M+Na]^+$, 12%), 296.0 ($[M+Na+MeCN]^+$, 70%), 254.9 ($[M+Na]^+$, 100%).
HRMS	Calcd for $C_{11}H_{20}O_5Na$: 255.1203. Found: 255.1199.

(±)-2-[5-(2-Acetoxy-1-hydroxy-ethyl)-2-methyl-tetrahydro-furan-2-yl]-2-hydroxy-propionic acid methyl ester.

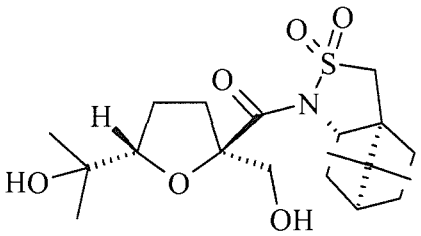


$C_{13}H_{22}O_7$.
M = 290.31 g.mol^{-1}.

Powdered $KMnO_4$ (67 mg, 0.42 mmol) was added in one portion to a solution of triene **4a** (50 mg, 0.21 mmol), in Acetone/AcOH (3:2, 3 mL, 2 mL) at –30°C. The purple mixture was rapidly stirred for 2 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 20 mL), then with Et_2O (20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (80 mg). Purification on SiO_2 (25 g) eluting with CH_2Cl_2 / EtOAc (50:50) gave the title mono-THF **16a** as a colourless oil (44 mg, 0.151 mmol, 72%).

IR (cm^{-1})	3030 (b), 2945 (m), 2912 (w), 2878 (w), 1740 (s), 1716 (s), 1470 (m), 1440 (m), 1380 (m), 1120 (m).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.25 (1H, dd, *J* = 11.5 and 2.5 Hz, C**H**HOCOCH$_3$), 4.20 (1H, dd, *J* = 7.8 and 6.3 Hz, C**H**O, THF), 3.98 (1H, dd, *J* = 11.5 and 7.8 Hz, C**H**HOCOCH$_3$), 3.89 (1H, dd, *J* = 7.0 and 2.5 Hz, C**H**OH), 3.79 (3H, s, OC**H**$_3$), 3.55 (1H, O**H**), 2.22 (1H, ddd, *J* = 12.3, 9.3 and 7.3 Hz, CH**H**C, THF), 2.11 (3H, s, OCC**H**$_3$), 2.04-1.84 (2H, m, C**H**$_2$CHO, THF), 1.53 (1H, ddd, *J* = 12.3, 8.8 and 5.8 Hz, , CH**H**C, THF), 1.48 (C**H**$_3$), 1.21 (C**H**$_3$).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	175.4 (**C**OO), 171.3 (CH$_3$**C**O), 85.8 (**C**OH), 81.6 (**C**HO, THF), 76.7 (O**C**, THF), 74.9 (**C**HOH), 65.6 (**C**H$_2$OCO), 52.9 (**C**H$_3$OCO), 31.2 (**C**H$_2$C, THF), 27.2 (**C**H$_2$CHO), 23.6 (**C**H$_3$), 23.5 (**C**H$_3$), 20.9 (OC**C**H$_3$).
LRMS (ES+ ionisation)	604.4 ([2M+Na]$^+$, 25%), 313.1 ([M+Na]$^+$, 100%).

***N*-[(2*S*,5*R*)- Tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furanoyl]-2-(2*S*)-camphor-10,2-sultam (422b)**



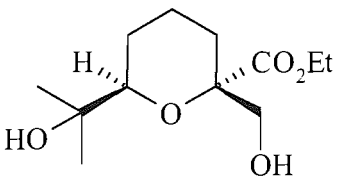
$C_{19}H_{31}NO_6S$.
M = 401.3 g.mol^{-1}.

To a vigorously stirred mixture of diene **421b** (420 mg, 1.196 mmol) and phosphate buffer (1.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (25 mL) at –30 °C was added a solution of $KMnO_4$ (6.0 mL of 0.4 M (aq), 2.40 mmol) containing AcOH (0.192 mL, 3.35 mmol). The purple mixture was rapidly stirred for 90 min during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 20 mL), then with Et_2O (20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil (600 mg, *de* > 9:1, from crude ^{1}H NMR). Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 4:1) gave the major diastereoisomer **422b** as a colourless glass (395 mg, 0.984 mmol, 82%). Recrystallisation from CH_2Cl_2/hexane gave transparent crystals suitable for x-ray structural determination.

$[\alpha]_D$	20.5 (*c* 0.4, CH_2Cl_2).
Mp (EtOAc/hexane)	49 - 54°C
IR (cm^{-1})	3422 (b), 2969 (b), 2942 (b), 2920 (b), 1674 (s), 1458 (w), 1340 (s), 1287 (m), 1166 (s), 1141 (s) and 1062 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.17 (1H, dd, *J* = 8.5 and 7.0 Hz, C**H**O, THF), 4.10 (1H, dd, *J* = 8.3 and 4.0 Hz, NC**H**), 4.01 (1H, d, *J* = 11.3 Hz, C**H**HO), 3.67 (1H, d, *J* = 11.1 Hz, C**H**HO), 3.55 (1H, d, *J* = 13.6 Hz, CH**H**SO_2), 3.42 (1H, d, *J* = 13.3 Hz, C**H**HSO_2), 2.97 (1H, br s, O**H**), 2.69 (1H, br s, O**H**), 2.32 (1H, ddd, *J* = 12.8, 7.5 and 4.7 Hz, C**H**HCHO, THF), 2.17 (1H, t, *J* = 8.8 Hz, C**H**HCHO, THF), 2.07 (1H, dd, *J* = 13.9 and 8.8 Hz, C**H**HCHN), 1.96-1.82 (5H, m, 2 x CH_2 and C**H**HCHN), 1.63 (2H, m, CH_2), 1.37-1.32 (2H, m, CH_2CCH_2S), 1.27 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.17 (3H, s,

	CH_3), 1.00 (3H, s, CH_3).
^{13}C-NMR	176.8 (**C**OO), 89.1 ($(CH_3)_2$**C**OH), 88.5 (O**C**H, THF), 71.5 (**C**O,
(100MHz, $CDCl_3$, ppm)	THF), 67.8 (N**C**H), 67.1 (**C**H_2OH), 54.9 (**C**H_2SO_2), 47.7
	(CCH_2SO_2), 47.5 ($(CH_3)_2$**C**), 45.5 (**C**HCH_2), 39.3 (**C**H_2CO,
	THF), 35.0 (**C**H_2CH_2CH), 33.7 (CH_2**C**H_2CH), 27.5 (**C**H_3C),
	26.1, (**C**H_2CHO, THF), 24.0 (**C**H_3), 21.8 (**C**H_3) and 20.0 (**C**H_3).
LRMS (ES+ ionisation)	825.8 ($[2M+Na]^+$, 25%), 424.4 ($[M+Na]^+$, 100%).
HRMS	Calcd for $C_{19}H_{31}NO_6SNa$: 424.1764. Found: 424.1767.

(±)-(2*R,6*S**)-Ethyl tetrahydro-2-(hydroxymethyl)-6-(2-hydroxypropan-2-yl)-2H-pyran-2-carboxylate (441a)**



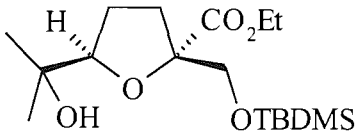
$C_{12}H_{22}O_5$.
M = 246.3 g.mol^{-1}.

To a vigorously stirred mixture of dienoate **439a** (82 mg, 0.418 mmol) and phosphate buffer (0.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (10 mL) at –30°C was added a solution of $KMnO_4$ (2.09 mL of 0.4 M (aq), 0.834 mmol) containing AcOH (67 μL, 1.170 mmol). The purple mixture was stirred rapidly for 2.5 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (3 x 30 mL), then with Et_2O (2 x 20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (200 mg) as a yellow oil. Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 1:1) gave the title product **441a** as a colourless oil (69 mg, 0.280 mmol, 67%).

IR (cm^{-1})	3420 (b), 2978 (m), 2935 (m), 2907 (m), 1711 s), 1370 (m), 1218
	(s), 1187 (s), 1111 (s), 1065 (s), 1021 (s).
^{1}H-NMR	4.32 (2H, dq, J = 7.3 and 4.3 Hz, OC**H**$_2$CH$_3$), 3.78 (1H, dd, *J* =
(400MHz, $CDCl_3$, ppm)	10.8 and 9.0 Hz, C**H**HO), 3.62 (1H, br dd, *J* = 10.8 and 5.3 Hz,
	C**H**HO), 3.61 (1H, m, C**H**O, THF), 2.58 (2H, br s, 2 x O**H**), 1.80-1.68 (2H, m, C**H**$_2$), 1.65-1.51 (2H, m, C**H**$_2$), 1.38-1.30 (2H, m,

	CH_2), 1.37 (6H, s, 2 x CH_3), 1.34 (3H, t, J = 7.3 Hz, OCH_2CH_3).
^{13}C-NMR	174.9 (**C**OO), 88.8 (**C**C=O), 78.3 (**O**CH, THF), 76.1 (**C**OH), 67.8
(100MHz, $CDCl_3$, ppm)	(CH_2OH), 62.5 (OCH_2CH_3), 35.2 (CH_2CH_2CH, THF), 34.0 (CH_2CH_2CH, THF), 26.5 (2 x CH_3), 17.4 (CH_2CH_2C, THF), 14.2 (OCH_2CH_3).
LRMS (ES+ ionisation)	310.1 ($[M+MeCN+Na]^+$, 24%), 269.1 ($[M+Na]^+$, 100%).

(±)-(2*S,5*R**)-Ethyl tetrahydro-2-(*tert*-Butyl-dimethyl-silanyloxymethyl methyl)-5-(2-hydroxypropan-2-yl)furan-2-carboxylate (484)**



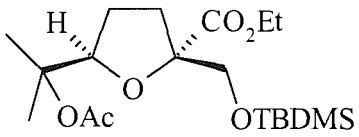
$C_{17}H_{34}O_5Si$.
M = 346.54 g.mol^{-1}.

To a ice-cold stirred solution of THF **422a** (30 mg, 0.129 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (72 µL, 0.516 mmol) followed by TBDMSCl (30 mg, 0.195 mmol) and DMAP (1.6 mg, 0.013 mmol). After warming up to room temperature, the reaction was stirred for 3 days, before the addition of Et_2O (10 mL). the mixture was washed with NH_4Cl (sat. aq. sol., 10 mL), H_2O (10 mL) and brine (10 mL). The combined aqueous phases were extracted with Et_2O (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (45 mg). Purification on SiO_2 (25 mL, CH_2Cl_2/EtOAc, 4:1) afforded the title product **484** as a colourless oil (40 mg, 0.115 mmol, 89%).

IR (cm^{-1})	3470 (b), 2959 (b), 2936 (b), 2860 (b), 1730 (w), 1460 (s), 1261 (s), 1110 (w), 845 (s), 779 (s).
^{1}H-NMR	4.24-4.15 (2H, m, OCH_2), 4.04 (1H, dd, J = 7.5 and 4.2 Hz,
(400MHz, $CDCl_3$, ppm)	CC**H**), 3.90 (1H, d, J = 10.5 Hz, CH**H**OH), 3.87 (1H, d, J = 10.5 Hz, C**H**HOH), 2.28-2.21 (1H, m, CCH**H**), 2.08-1.97 (3H, m, $CHCH_2$ and O**H**), 1.96-1.88 (1H, m, CCH**H**), 1.29 (3H, s, CH_3), 1.27 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.12 (3H, s, CH_3), 0.95 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$).
^{13}C-NMR	173.7 (**C**OO), 87.6 (O**C**H), 87.0 ($C(CH_3)_2$), 71.6 ($OCCH_2$), 65.5
(100MHz, $CDCl_3$, ppm)	(OCH_2), 61.0 (CH_2OH), 31.2 (CH_2C), 27.7 (CH_3), 25.9 (CH_3),

	25.9 ($CHCH_2$), 24.8 (CH_3), 18.4 (SiC), 14.2 (OCH_2CH_3), 1.0 (2 x $SiC(CH_3)_2$), –5.5 (3 x $SiCC(CH_3)_3$).
LRMS (ES+ ionisation)	715.4 ($[2M+Na]^+$, 8%), 369.1 ($[M+Na]^+$, 100%).
HRMS	Calculated: $C_{17}H_{34}O_5SiNa$ = 369.2068 Found: 369.2062.

(±)-(2*R,5*S**)-Ethyl tetrahydro-2-(*tert*-Butyl-dimethyl-silanyloxymethyl methyl)-5-(2-acetoxypropan-2-yl)furan-2-carboxylate (485)**



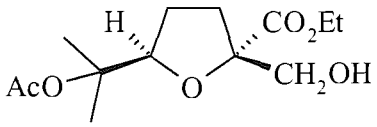
$C_{19}H_{36}O_6Si$.
M = 388.57 g.mol^{-1}.

To a stirred solution of THF **484** (35 mg, 0.101 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (70 µL, 0.510 mmol) followed by Ac_2O (20 µL, 0.202 mmol) and DMAP (2 mg, 0.014 mmol). The reaction was stirred for 48 hours before addition of Et_2O (10 mL). The mixture was washed with H_2O (10 mL) and brine (10 mL) and the combined aqueous phases were extracted with Et_2O (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (40 mg), Purification on SiO_2 (25 mL, CH_2Cl_2/EtOAc, 6:1) afforded the title product **485** as a colourless oil (30 mg, 0.077 mmol, 76%).

IR (cm^{-1})	3470 (b), 2959 (b), 2936 (b), 2860 (b), 1730 (w), 1460 (s), 1261 (s), 1110 (w), 845 (s), 779 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.22-4.19 (3H, m, CC**H** and OCH_2), 3.88 (1H, d, J = 10.5 Hz, CHHOH), 3.80 (1H, d, J = 10.5 Hz, C**H**HOH), 2.28-2.21 (1H, m, CCH**H**), 2.08-1.97 (2H, m, $CHCH_2$), 1.98 (3H, s, OCH_3), 1.96-1.78 (1H, m, CCH**H**), 1.50 (3H, s, CH_3), 1.30 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.26 (3H, s, CH_3), 0.88 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	173.5 (COO), 170.3 (COO), 87.7 (OCH), 85.4 ($C(CH_3)_2$), 82.8 ($OCCH_2$), 66.9 (OCH_2), 61.0 (CH_2OH), 31.3 (CH_2C), 29.7 (CH_3), 25.9 (CH_3), 25.8 ($CHCH_2$), 22.6 (CH_3), 22.4 (CH_3), 18.3 (SiC), 14.2 (OCH_2CH_3), 1.0 (2 x $SiC(CH_3)_2$), –5.5 (3 x $SiCC(CH_3)_3$).

LRMS (ES+ ionisation)	427.2 ($[M+K]^+$, 15%), 411.2 ($[M+Na]^+$, 25%), 411.2 ($[M+NH_4]^+$, 100%).

(±)-(2*S,5*R**)-Ethyl 5-(2-acetoxypropan-2-yl)-tetrahydro-2-(hydroxymethyl)furan-2-carboxylate (449c)**

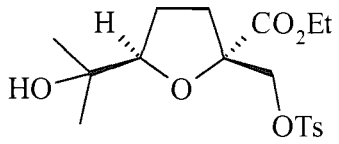


$C_{13}H_{22}O_6$.
M = 274.31 g.mol^{-1}.

A solution of HCl (5 mL of 1 M (aq)) was added to a stirred solution of THF **485** (750 mg, 1.925 mmol) at room temperature. The reaction was stirred overnight and neutralised with $NaHCO_3$. The aqueous phase was extracted with Et_2O (4 x 20 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a pale yellow oil (720 mg). Purification on SiO_2 (200 mL, CH_2Cl_2/EtOAc, 4:1) afforded the title product **449c** as a colourless oil (395 mg, 1.827 mmol, 95%).

IR (cm^{-1})	3545 (b), 2996 (b), 2941 (b), 2925 (b), 1738 (s), 1366 (w), 1216 (m), 1204 (m), 1091 (s), 1023 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.21 (2H, qd, *J* = 7.1 and 4.8 Hz, OC**H$_2$**), 4.17 (1H, t, *J* = 7.0 Hz, CC**H**O), 3.50 (1H, d, *J* = 7.0 Hz, CH**H**OH), 3.45 (1H, d, *J* = 7.2 Hz, C**H**HOH), 2.42 (1H, br s, O**H**), 2.34-1.94 (3H, m, C**H**H and C**H$_2$**, THF), 2.25 (3H, s, C**H$_3$**), 1.63 (1H, m, CH**H**, THF), 1.59 (3H, s, C**H$_3$**), 1.48 (3H, s, C**H$_3$**), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	173.7 (**C**OO), 170.1 (CH_3**C**O), 87.0 (**C**HO, THF), 86.7 (**C**(CH_3)$_2$), 82.5 (O**C**CH$_2$, THF), 65.8 (COO**C**H$_2$), 61.2 (**C**H$_2$OH), 31.8 (**C**H$_2$CO, THF), 26.1 (**C**H$_2$CHO, THF), 22.6 (2 x **C**H$_3$C), 22.5 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	297.1 ($[M+Na]^+$, 100%), 275.1 ($[M+H]^+$, 7%).

(±)-((2*R,5*S**)-2-(Ethoxycarbonyl)-tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl)methyl 4-methylbenzenesulfonate (431)**

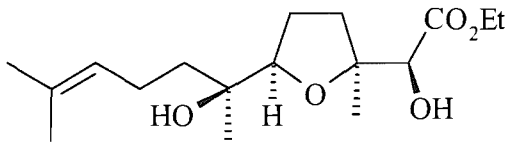


$C_{18}H_{26}O_7S$.
M = 386.5 g.mol^{-1}.

To a solution of THF **422a** (36 mg, 0.155 mmol), Et_3N (0.35 mL, 0.24 mmol) and a trace of DMAP in CH_2Cl_2 (3 mL) at 0°C was added TsCl (40 mg, 0.176 mmol). The mixture was stirred for 4 h at 0°C and then diluted with EtOAc (10 mL) and washed with water (2 x 10 mL), HCl (2 x 10 mL, 2M aq. sol.), $NaHCO_3$ (sat. aq. sol., 2 x 10 mL) and brine (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (90 mg). Purification on silica gel (20 g, CH_2Cl_2/EtOAc, 4:1) gave the title product **431** as a pale yellow oil (19 mg, 0.049 mmol, 32%).

IR (cm^{-1})	3527 (b), 2978 (m), 2926 (m), 2898 (w), 1735 (s), 1588 (w), 1366 (s), 1194 (s), 1172 (s), 969 (s), 807 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.80 (2H, d, *J* = 8.2 Hz, SCC**H** x 2, arom), 7.35 (2H, d, *J* = 8.2 Hz, (CH_3)CC**H** x 2, arom), 4.34 (1H, d, *J* = 10.2 Hz, C**H**HO), 4.22 (1H, d, *J* = 10.2 Hz, C**H**HO), 4.17 (2H, qd, *J* = 7.2 and 2.6 Hz, O**CH_2**CH_3), 4.05 (1H, t, *J* = 7.3 Hz, C**H**O, THF), 2.45 (3H, CH=CC**H_3**), 2.21 (1H, br s, O**H**), 2.18-1.85 (4H, C**H_2** x 2, THF), 1.27 (3H, t, *J* = 7.3 Hz, OCH_2C**H_3**), 1.26 (3H, C**H_3**), 1.10 (3H, C**H_3**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	171.9 (**C**OO), 145.1 ((CH_3)**C**=CH), 132.8 (2 x S**C**=CH), 129.9 (**C**H=C$(CH_3)_3$), 127.9 (2 x **C**H=CS), 88.3 (**C**HO, THF), 84.0 (**C**O, THF), 71.3 (**CH_2**OS), 70.7 (**C**$(CH_3)_2$), 61.6 (OCH_2CH_3), 32.5 (**CH_2**CO, THF), 27.4 (**CH_3**), 25.5 (**CH_2**CHO, THF), 24.6 (**CH_3**), 21.6 (**CH_3**), 14.1 (OCH_2**C**H_3).
LRMS (ES+ ionisation)	810.9 ($[2M+K]^+$, 40%), 794.9 ($[2M+Na]^+$, 100%), 425.1 ($[M+K]^+$, 60%).
HRMS	Calcd for $C_{18}H_{24}O_6SNa$: 409.1297. Found: 409.1281.

(±)-(2*R)-Ethyl-2-((2*R**,5*S**)-tetrahydro-5-((*R**)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)-2-hydroxyacetate (385a)**

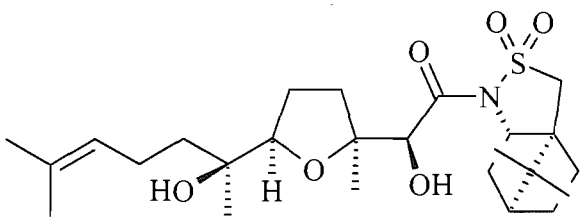


$C_{17}H_{30}O_7$.
M = 314.2 g.mol^{-1}.

To a vigorously stirred mixture of trieneoate **316c** (100 mg, 0.379 mmol) and phosphate buffer (0.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (15 mL) at –30°C was added a solution of $KMnO_4$ (1.6 mL of 0.4 M (aq), 0.644 mmol) containing AcOH (61 μL, 1.061 mmol). The purple mixture was rapidly stirred for 2 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 20 mL), then with Et_2O (20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (110 mg) as a colourless oil. Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 90:10) gave the title mono-THF **385a** as a colourless oil (0.280 mmol, 88 mg, 74%) and the bis-lactol **315c** as a by product (0.026 mmol, 9 mg, 7%).

IR (cm^{-1})	3430 (b), 2974 (b), 2932 (b), 2874 (b), 1734 (s), 1451 (w), 1375 (w), 1270 (m), 1204 (m), 1091 (s), 1023 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.10 (1H, t, *J* = 7.0 Hz, C**H**=C(CH$_3$)$_2$), 4.28 (2H, m, OC**H$_2$**), 4.06 (1H, s, C**H**OH), 3.87 (1H, dd, *J* = 9.6 and 6.0 Hz, C**H**O, THF), 3.11 (2H, br s, 2 x O**H**), 2.32 (1H, m, C**H$_2$**COH), 2.06-1.93 (3H, m, C**H$_2$**, THF), 1.87 (1H, m, C**H$_2$**), 1.76-1.65 (2H, m, C**H$_2$**), 1.68 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.45 (1H, m, C**H$_2$**), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H$_3$**), 1.27 (3H, s, C**H$_3$**), 1.26 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	173.2 (**C**OO), 131.6 (**C**(CH$_3$)$_2$), 124.4 (**C**HC(CH$_3$)$_2$), 85.9 (OCH, THF), 83.8 (**C**OH), 75.1 (**C**HOH), 72.4 (OCCH$_2$, THF), 61.9 (OCH$_2$), 37.8 (**C**H$_2$COH), 35.2 (**C**H$_2$C, THF), 25.6 (**C**H$_3$), 25.4 (CH**C**H$_2$CH$_2$), 24.9 (**C**H$_3$), 22.4 (**C**H$_3$), 22.2 (OCH**C**H$_2$, THF), 17.6 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	337.4 ([M+Na]$^+$, 100%).
HRMS	Calcd for $C_{17}H_{30}O_5Na$: 337.1985. Found: 337.1981.

***N*-[(*S*)-2-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-oyl)]-2-hydroxy-(2*S*)-camphor-10,2-sultam (385b)**



$C_{25}H_{41}NO_6S$.
M = 483.7 g.mol^{-1}.

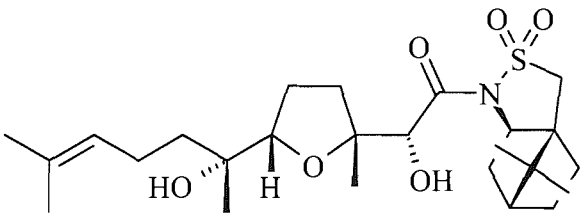
To a vigorously stirred mixture of trieneoate **316h** (600 mg, 1.384 mmol) and phosphate buffer (1.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (40 mL) at –30°C was added a solution of $KMnO_4$ (5.9 mL of 0.4 M (aq), 2.353 mmol) containing AcOH (222 μL, 3.875 mmol). The purple mixture was rapidly stirred for 2 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (3 x 40 mL), then with Et_2O (2 x 30 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (540 mg) as a colourless oil. Purification on SiO_2 (150 mL, CH_2Cl_2/EtOAc, 9:1) gave the major diastereoisomer **385b** as a colourless solid glass (0.924 mmol, 447 mg, 67%), the minor diastereoisomer as a colourless oil (0.052 mmol, 25 mg, 4%), and the bis-lactol **315h** as a by product (0.029 mmol, 15 mg, 2%).

Major diastereoisomer **385b**:

$[\alpha]_D$	–29.8 (c 0.1, CH_2Cl_2).
Mp (EtOAc/hexane)	47-51°C
IR (cm^{-1})	3432 (b), 2964 (b), 2937 (b), 2882 (b), 1701 (s), 1454 (w), 1329 (w), 1270 (m), 1219 (m), 1134 (s), 1060 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.12 (1H, tdd, *J* = 7.0, 2.8 and 1.3 Hz, C**H**=C$(CH_3)_2$), 4.63 (1H, s, C**H**OH), 3.92 (1H, dd, *J* = 7.5 and 4.8 Hz, C**H**N), 3.85 (1H, t, *J* = 7.3 Hz, C**H**O, THF), 3.79 (1H, br s, O**H**), 3.55 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.45 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.13 (1H, br s, O**H**), 2.27 (1H, ddd, *J* = 9.3, 6.0 and 3.3 Hz, CH**H**CO, THF), 2.18 (1H, m, C**H**H), 2.10-1.99 (3H, m, C**H**C and C**H$_2$**CH=C), 1.97-1.86 (5H, m, CHHCHO, THF and C**H$_2$**COH and C**H$_2$**), 1.79 (1H, ddd, *J* = 10.6, 6.5 and 4.0 Hz, CHHCO,

	THF), 1.68 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.51-1.30 (4H, m, CHHCO, THF and CHH and CH_2), 1.30 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.17 (3H, s, CH_3), 0.98 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	170.1 (COO), 131.6 ($C(CH_3)_2$), 124.5 ($CHC(CH_3)_2$), 83.9 (OCH, THF), 75.6 (CHOH), 73.4 (COH), 65.2 (CHN), 53.0 (CH_2SO_2), 48.7 (CCH_2SO_2), 47.8 ($C(CH_3)_2$), 44.6 ($CHCH_2$), 38.3 (CH_2), 38.1 (CH_2), 33.3 (CH_2CO, THF), 32.8 (CH_2), 26.4 (CH_2), 26.0 (CH_2CHO, THF), 25.6 (CH_3), 24.4 (CH_3), 24.1 (CH_3), 22.2 (CH_2), 20.8 (2 x CH_3), 19.8 (CH_3), 17.6 (CH_3).
LRMS (ES+ ionisation)	990.0 ($[2M+Na]^+$, 60%), 506.4 ($[M+Na]^+$, 100%).
HRMS	Calcd for $C_{25}H_{41}NO_6SNa$: 506.2547. Found: 506.2551.

_N_-[(_R_)-2-((2_R_,5_S_)-Tetrahydro-5-((_R_)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-oyl)]-2-hydroxy-(2_R_)-camphor-10,2-sultam (385c)



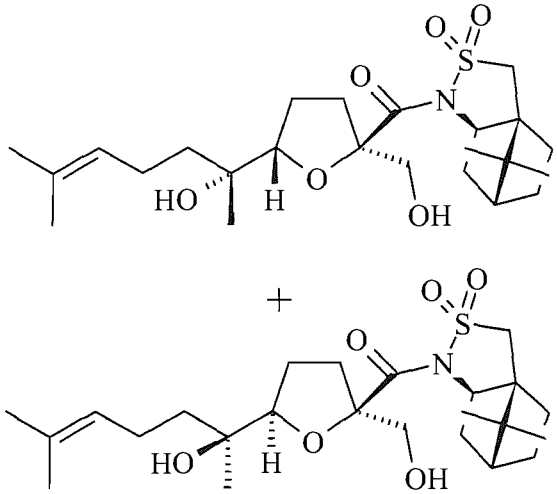
$C_{25}H_{41}NO_7S$..
M = 483.7 g.mol^{-1}.

To a vigorously stirred mixture of trieneoate **316f** (300 mg, 0.692 mmol) and phosphate buffer (1 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (20 mL) at –30°C was added a solution of $KMnO_4$ (2.9 mL of 0.4 M (aq), 1.176 mmol) containing AcOH (111 μL, 1.938 mmol). The purple mixture was rapidly stirred for 2 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 20 mL), then with Et_2O (20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (450 mg, *de* > 9:1) as a colourless oil. Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 9:1) gave the major diastereoisomer **385c** as a colourless oil (0.459 mmol, 222 mg, 66%), the minor diastereoisomer as a colourless oil (0.021 mmol, 10 mg, 3%), and the bis-lactol **315f** as a by product (0.010 mmol, 5 mg, 2%).

Major diastereoisomer **385c**:

$[\alpha]_D$	39.4 (c 0.1, CH_2Cl_2).
IR (cm^{-1})	3456 (b), 2964 (b), 2936 (b), 2884 (b), 1702 (s), 1454 (w), 1331 (w), 1270 (m), 1219 (m), 1135 (s), 1061 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.11 (1H, ddt, *J* = 7.0, 2.8 and 1.3 Hz, C**H**=C(CH_3)$_2$), 4.64 (1H, s, C**H**OH), 3.93 (1H, dd, *J* = 7.8 and 5.0 Hz, C**H**N), 3.85 (1H, t, *J* = 7.0 Hz, C**H**O, THF), 3.61 (1H, br s, O**H**), 3.55 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.45 (1H, d, *J* = 13.8 Hz, C**H**HSO$_2$), 3.11 (1H, br s, O**H**), 2.28 (1H, ddd, *J* = 9.5, 6.3 and 3.0 Hz, CH**H**CO, THF), 2.18 (1H, m, C**H**H), 2.11-2.00 (3H, m, C**H**C and C**H$_2$**CH=C), 1.98-1.87 (5H, m, C**H**HCHO, THF and C**H$_2$**COH and C**H$_2$**), 1.77 (1H, ddd, *J* = 10.3, 6.3 and 4.0 Hz, C**H**HCO, THF), 1.68 (3H, d, *J* = 1.0 Hz, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.51-1.32 (4H, m, C**H**HCO, THF and C**H**H and C**H$_2$**), 1.30 (3H, s, C**H$_3$**), 1.27 (3H, s, C**H$_3$**), 1.17 (3H, s, C**H$_3$**), 0.98 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	170.1 (**C**OO), 131.6 (**C**(CH$_3$)$_2$), 124.5 (**C**HC(CH$_3$)$_2$), 83.9 (O**C**H, THF), 75.6 (**C**HOH), 73.4 (**C**OH), 65.2 (**C**HN), 53.0 (**C**H$_2$SO$_2$), 48.7 (**C**CH$_2$SO$_2$), 47.8 (**C**(CH$_3$)$_2$), 44.6 (**C**HCH$_2$), 38.3 (**C**H$_2$), 38.1 (**C**H$_2$), 33.3 (**C**H$_2$CO, THF), 32.8 (**C**H$_2$), 26.4 (**C**H$_2$), 26.0 (**C**H$_2$CHO, THF), 25.6 (**C**H$_3$), 24.4 (**C**H$_3$), 24.1 (**C**H$_3$), 22.2 (2 x **C**H$_2$), 20.8 (**C**H$_3$), 19.8 (**C**H$_3$), 17.6 (**C**H$_3$).
LRMS (ES+ ionisation)	990.0 ([2M+Na]$^+$, 55%), 506.4 ([M+Na]$^+$, 100%).

***N*-[(2*S*,5*R*)-Ethyl tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-oyl]-2--(2*S*)-camphor-10,2-sultam (460c) and *N*-[(2*S*,5*R*)-ethyl tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-oyl]-2--(2*S*)-camphor-10,2-sultam (460d)**



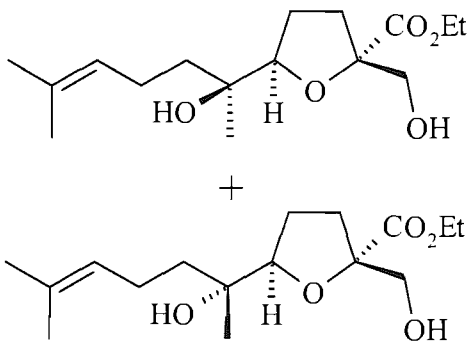
$C_{24}H_{39}NO_6S$.
M = 469.6 g.mol^{-1}.

To a vigorously stirred mixture of trieneoates **452c,d** (150 mg, 0.358 mmol) and phosphate buffer (1.0 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (15 mL) at –30°C was added a solution of $KMnO_4$ (1.5 mL of 0.4 M (aq), 0.608 mmol) containing AcOH (57 μL, 1.002 mmol). The purple mixture was rapidly stirred for 1.5 hours during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (3 x 30 mL), then with Et_2O (2 x 20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (200 mg) as a colourless oil. Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 9:1) gave an inseparable mixture of products **460c,d** as a colourless oil (108 mg, 0.230 mmol, 64%).

$[\alpha]_D$	–22.6 (*c* 0.8, CH_2Cl_2)
IR (cm^{-1})	3458 (b), 2968 (m), 2943 (m), 2881 (m), 1738 (m), 1677 (s), 1455 (m), 1339 (s), 1289 (m), 1200 (m), 1166 (s), 1140 (s), 1062 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.12 (1H, ddd, *J* = 14.8, 7.3 and 2.5 Hz, C**H**C$(CH_3)_2$), 4.21 (1H, m, C**H**O, THF), 4.09 (1H, dd, *J* = 7.3 and 4.0 Hz, NC**H**), 3.99 (1H, dd, *J* = 11.0 and 5.0 Hz, C**H**HO), 3.69 (1H, d, *J* = 11.0 Hz,

	CHHO), 3.56 (1H, dd, J = 13.3 and 3.5 Hz, CH**H**SO_2), 3.43 (1H, d, J = 13.6 Hz, CH**H**SO_2), 2.81 (O**H**), 2.33 (1H, ddd, J = 12.8, 8.3 and 4.8 Hz, C**H**HCHO, THF), 2.19-1.83 (10H, m, O**H** and C**H**CH_2CHN and 4 x CH_2), 1.61-1.25 (5H, m, O**H**, 2 x CH_2), 1.69 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.09 (3H, s, CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	176.8 (**C**ON), 131.4 (**C**$CH_3)_2$), 124.8 (**C**H$CCH_3)_2$), 124.5 (**C**H$CCH_3)_2$), 89.2 (CH_3**C**O, THF), 87.7 (**C**HO, THF), 73.5 (CH_3**C**OH), 73.4 (CH_3**C**OH), 67.8 (**C**HN), 67.0 (**C**H_2OH), 54.8 (**C**H_2SO_2), 47.8 (**C**H$(CH_3)_2$), 47.5 (**C**H$(CH_3)_2$), 45.6 (**C**H$(CH_3)_2$), 39.5 (**C**H_2COH), 39.4 (**C**H_2CO, THF), 37.3 (**C**H_2CHO, THF), 35.1 (**C**H_2CCH_2S), 33.7 (CH_2**C**H_2CH), 26.2 (**C**H_2CHN), 25.7 (CH_3), 22.1 (CH_3), 22.1 (**C**H_2CH), 21.8 (CH**C**H_2CH_2), 21.8 (CH_3), 21.6 (CH_3), 19.9 (CH_3), 17.7 (CHCH_2**C**H_2).
LRMS (ES+ ionisation)	956.5 ($[2M+NH_4]^+$, 12%), 487.2 ($[M+NH_4]^+$, 100%), 470.1 ($[M+H]^+$, 42%).
HRMS	Calcd for $C_{25}H_{41}NO_6SNa$: 506.2547. Found: 506.2551.

(±)-(2*R,5*S**)-Ethyl tetrahydro-5-((*R**)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (460a) and (2*R**,5*S**)-Ethyl tetrahydro-5-((*S**)-2-hydroxy-6-methylhept-5-en-2-yl)-2-(hydroxymethyl)furan-2-carboxylate (460b)**



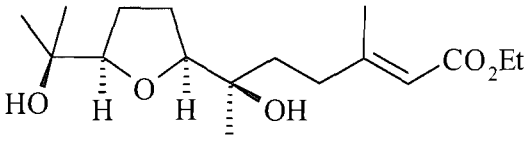
$C_{16}H_{28}O_5$.
M = 300.4 g.mol^{-1}.

To a vigorously stirred mixture of trieneoates **452a,b** (235 mg, 0.939 mmol) and phosphate buffer (0.5 mL, KH_2PO_4 : NaH_2PO_4, 8 : 2, pH 6.2) in acetone (20 mL) at –30°C was added a solution of $KMnO_4$ (3.3 mL of 0.4 M (aq), 1.314 mmol) containing AcOH (150 μL, 2.630 mmol). The purple mixture was rapidly stirred for 1 hour during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to

dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 30 mL), then with Et_2O (30 mL), saturated with NaCl and extracted further with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (300 mg) as a colourless oil. Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 4:1) gave a inseparable mixture of mono-THFs **460a,b** as a colourless oil (205 mg, 0.682 mmol, 73%).

IR (cm^{-1})	3381 (b), 2973 (m), 2925 (m), 2877 (m), 1729 (s), 1448 (w), 1376 (w), 1102 (s), 1056 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.16 (1H, m, C**H**=C(CH_3)$_2$), 4.23 (2H, m, OC**H$_2$**), 3.87 (1H, dd, *J* = 8.3 and 6.8 Hz, C**H**O, THF), 3.86 (1H, dd, *J* = 11.0 and 3.3 Hz, C**H**HO), 3.74 (1H, dd, *J* = 11.3 and 3.3 Hz, C**H**HO), 2.97 (1H, br s, O**H**), 2.43 (1H, br s, O**H**), 2.21-2.06 (4H, m, 2 x C**H$_2$**), 2.02-1.85 (2H, m, C**H$_2$**), 1.70-1.35 (2H, m, C**H$_2$**), 1.68 (3H, d, *J* = 1.2 Hz, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.29 (3H, t, *J* = 7.3 Hz, OCH$_2$C**H$_3$**), 1.10 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	174.0 (**C**OO), 131.9 (**C**(CH$_3$)$_2$), 131.6 (**C**(CH$_3$)$_2$), 124.4 (**C**HC(CH$_3$)$_2$), 124.2 (**C**HC(CH$_3$)$_2$), 87.0 (O**C**H, THF), 86.3 (O**C**CH$_2$, THF), 86.2 (O**C**H, THF), 73.4 (**C**OH), 73.2 (**C**OH), 66.2 (C**C**H$_2$OH), 61.2 (O**C**H$_2$), 40.0 (**C**H$_2$COH), 38.1 (**C**H$_2$COH), 32.1 (CH**C**H$_2$CH$_2$), 32.0 (CH**C**H$_2$CH$_2$), 25.8 (**C**H$_2$C, THF), 25.6 (**C**H$_3$), 22.5 (OCH**C**H$_2$, THF), 22.1 (**C**H$_3$), 22.1 (OCH**C**H$_2$, THF), 17.6 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	623.5 ([2M+Na]$^+$, 8%), 618.5 ([2M+NH$_4$]$^+$, 8%), 318.1 ([M+NH$_4$]$^+$, 100%).
HRMS	Calcd for $C_{16}H_{28}O_5Na$: 323.1829. Found: 323.1828.

(±)-(*R,*E*)-Ethyl 6-((2*S**,5*R**)-tetrahydro-5-(2-hydroxypropan-2-yl)-5-methylfuran-2-yl)-6-hydroxy-3-methylhept-2-enoate (386a)**



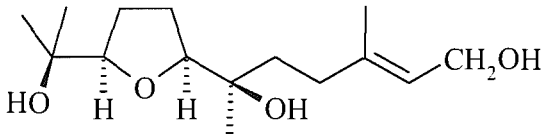
$C_{17}H_{30}O_7$.
M = 314.2 g.mol^{-1}.

Powdered $KMnO_4$ (155 mg, 0.984 mmol) was added in one portion to a solution of triene **316c** (200 mg, 0.758 mmol), in acetone/AcOH (3:2, 6 mL, 4 mL) at –30°C. The purple mixture was stirred rapidly for 1 hour during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated $Na_2S_2O_5$ (aq.) to dissolve all of the manganese salts. The aqueous layer was extracted with EtOAc (2 x 20 mL), then with Et_2O (20 mL), saturated with NaCl and extracted further with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (250 mg). Purification on SiO_2 (100 mL, CH_2Cl_2/EtOAc, 7:3) gave the title mono-THF **386a** as a colourless oil (0.414 mmol, 130 mg, 55%) and the bis-lactol **315c** as a by product (0.072 mmol, 25 mg, 9%).

IR (cm^{-1})	3475 (b), 2973 (b), 2941 (b), 2877 (b), 1712 (s), 1646 (s), 1449 (w), 1376 (w), 1231 (m), 1167 (m), 1078 (s) and 1035 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.74 (1H, br s, C**H**=COO), 4.14 (2H, q, *J* = 7.2 Hz, OC**H$_2$**), 3.83 (1H, t, *J* = 6.9 Hz, C**H**O, THF), 3.49 (1H, dd, *J* = 10.8 and 1.8 Hz, C**H**OH), 3.11 (1H, ddd, *J* = 12.6, 9.5 and 7.3 Hz, C**H**HCHOH), 2.36 (1H, ddd, *J* = 12.3, 7.5 and 4.5 Hz, C**H**HC=CH), 2.18 (1H, m, C**H**HC(CH$_3$), THF), 2.04-1.90 (2H, m, C**H$_2$**CH, THF), 1.76 (1H, m, C**H**HC(CH$_3$)=CH), 1.52-1.31 (4H, m, C**H**HCHOH and C**H**HC(CH$_3$), THF and 2 x O**H**), 1.44 (3H, s, C**H$_3$**), 1.26 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H$_3$**), 1.24 (3H, s, C**H$_3$**), 1.16 (3H, s, C**H$_3$**), 1.10(3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	167.3 (**C**OO), 159.7 (**C**(CH$_3$)$_2$), 117.2 (**C**HCOO), 85.8 (O**C**CH$_3$, THF), 85.0 (H**C**O, THF), 75.2 (**C**HOH), 71.7 (HC=**C**CH$_3$), 60.0 (O**C**H$_2$), 32.1 (**C**H$_2$CO, THF), 30.2 (**C**H$_2$CCHCOO), 29.9 (OCH**C**H$_2$, THF), 27.7 (**C**H$_3$CO, THF), 25.1 (**C**H$_3$), 24.9 (**C**H$_3$), 23.5 (2 x **C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).

LRMS (ES+ ionisation)	667 ($[2M+K]^+$, 5%), 651.6 ($[2M+Na]^+$, 15%), 629.6 ($[2M+H]^+$, 8%), 353.1 ($[M+K]^+$, 20%), 337.2 ($[M+Na]^+$, 100%), 315.2 ($[M+H]^+$, 85%).
HRMS	Calcd for $C_{17}H_{30}O_5Na$: 337.1985. Found: 337.1981.

(±)-(*R,*E*)-6-((2*S**,5*R**)-Tetrahydro-5-(2-hydroxypropan-2-yl)-5-methylfuran-2-yl)-3-methylhept-2-ene-1,6-diol (388)**



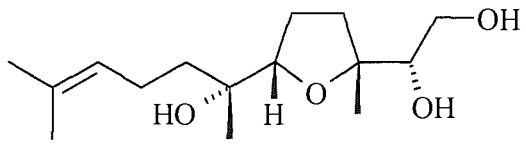
$C_{15}H_{28}O_4$.
M = 272.4 g.mol^{-1}.

According to the method of Davies *et al.*,[126] a solution of THF **386a** (70 mg, 0.223 mmol) in THF (5 mL) was cooled to –78°C, before the addition of $LiAlH_4$ (1M in THF, 223 µL, 0.223 mmol). The resulting mixture was allowed to warm at room temperature and stirred for 24 h. NaOH (2 mL) was added cautiously under vigorous stirring and the reaction was heated to reflux for 30 min before being filtered though Celite, washed with Et_2O (2 x 20 mL) and concentrated *in vacuo* to give the crude product (65 mg) as a colourless oil. Purification on SiO_2 (75 mL, CH_2Cl_2/EtOAc, 9:1) gave the title triol **388** as a colourless oil (0.168 mmol, 46 mg, 75%).

IR (cm^{-1})	3395 (b), 2969 (b), 2926 (b), 2873 (b), 1739 (s), 1455 (w), 1375 (w), 1167 (m), 1081 (s), 1002 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.60 (1H, t, *J* = 7.3 Hz, C**H**=C(CH_3)), 4.23 (1H, dd, *J*= 8.3 and 11.8 Hz, C**H**HOH), 4.00 (1H, dd, *J*= 7.0 and 12.0 Hz, C**H**HOH), 3.84 (1H, dt, *J* = 2.8 and 7.0 Hz, C**H**O, THF), 3.55 (1H, br s, O**H**), 3.54 (1H, dd, *J* = 1.8 and 11.0 Hz, C**H**OH), 2.71 (1H, br s, O**H**), 2.57 (1H, ddd, *J* = 6.5, 10.0 and 13.3 Hz, C**H**HCHOH), 2.17-2.05 (2H, m, C**H**HCH_2COH and C**H**HCO, THF), 1.98-1.88 (2H, m, CH_2CHO, THF), 1.74 (3H, s, CH=C(CH_3)), 1.68 (1H, m, C**H**HCH_2COH), 1.55-1.38 (3H, m, C**H**HCO, THF and C**H**HCOH and O**H**), 1.26 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.13 (3H, s, CH_3).
^{13}C-NMR	140.4 (CH=**C**(CH_3)), 125.1 (**C**H=C(CH_3)), 86.2 (O**C**CH_3, THF),

(100MHz, $CDCl_3$, ppm)	84.5 (HCO, THF), 75.0 (CHOH), 72.0 ($HOC(CH_3)_2$), 58.1 (CH_2OH), 31.4 (CH_2CO, THF), 29.3 ($CH_2C(CH_3)$), 27.7 (CH_2CHOH), 27.6 ($CH=C(CH_3)$), 26.8 (CH_2CHO, THF), 25.6 (CH_3), 23.8 (CH_3), 22.8 (CH_3).
LRMS (ES+ ionisation)	567.2 ($[2M+Na]^+$, 10%), 545.3 ($[2M+K]^+$, 25%), 295.0 ($[M+Na]^+$, 100%), 273.0 ($[M+H]^+$, 70%).

(*S*)-1-((2*R*,5*S*)-Tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)ethane-1,2-diol (387c)

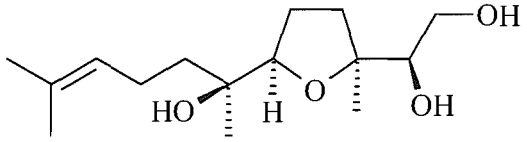


$C_{15}H_{28}O_4$.
M = 272.4 g.mol^{-1}.

Following the procedure for the preparation of mono-THF **388**, diol **385c** (150 mg, 0.310 mmol) was reduced to afford the desired triol **387c** (72 mg, 0.264 mmol, 85%).

$[\alpha]_D$	–10.7 (c 1.0, $CHCl_3$)
IR (cm^{-1})	3361 (b), 2967 (m), 2931 (m), 2875 (m), 1451 (m), 1375 (m), 1071 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.11 (1H, tt, *J* = 7.0 and 1.5 Hz, C**H**=$C(CH_3)_2$), 3.84 (1H, t, *J* = 7.3 Hz Hz, C**H**O, THF), 3.71 (1H, br dd, *J* = 4.5 and 3.5 Hz, C**H$_2$**OH), 3.55 (1H, dd, *J*= 11.8 and 7.8 Hz, C**H**OH), 2.40 (2H, br s, 2 x O**H**), 2.15 (1H, ddd, *J* = 12.3, 9.0 and 5.3 Hz, CH**H**COH), 2.10-1.87 (3H, m, C**H**H and C**H$_2$**), 1.61-1.32 (4H, m, 2 x C**H$_2$**), 1.69 (3H, s, C**H$_3$**), 1.63 (3H, s, C**H$_3$**), 1.28 (3H, s, C**H$_3$**), 1.20 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	132.1 ($C(CH_3)_2$), 124.2 ($CHC(CH_3)_2$), 84.7 (OCH, THF), 83.8 (COH), 77.1 (CHOH), 74.0 ($OCCH_2$, THF), 63.3 (CH_2OH), 38.5 (CH_2COH), 32.6 (CH_2C, THF), 26.4 ($CHCH_2CH_2$), 25.7 (CH_3), 24.2 (CH_3), 23.7 (CH_3), 22.6 ($OCHCH_2$, THF), 17.7 (CH_3).
LRMS (ES+ ionisation)	567.4 ($[2M+Na]^+$, 8%), 563.5 ($[2M+NH_4]^+$, 25%), 336.1 ($[M+CH_3CN + Na]^+$, 25%), 295.1 ($[M+Na]^+$, 100%).

(*R*)-1-((2*S*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2-yl)ethane-1,2-diol (387b) [144]

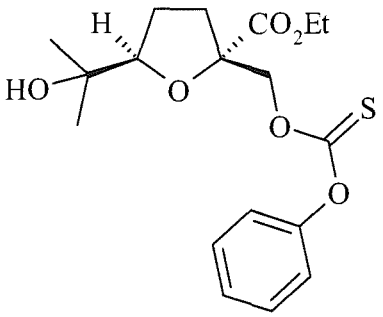


$C_{15}H_{28}O_4$.
M = 272.4 g.mol^{-1}.

Following the procedure for the preparation of mono-THF **388**, diol **385b** (110 mg, 0.227 mmol) was reduced to afford the desired triol **387b** (53 mg, 0.195 mmol, 86%). Spectroscopic data were good agreement with that reported in the literature.[144]

$[\alpha]_D$	6.8 (c 1.3, $CHCl_3$)
IR (cm^{-1})	3361 (b), 2967 (m), 2931 (m), 2875 (m), 1451 (m), 1375 (m), 1071 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.09 (1H, tt, *J* = 7.0 and 1.5 Hz, C**H**=C$(CH_3)_2$), 3.87 (1H, t, *J* = 7.0 Hz Hz, C**H**O, THF), 3.78 (1H, dd, *J* = 11.5 and 6.0 Hz, C**H**HOH), 3.71 (1H, dd, *J* = 11.5 and 6.0 Hz, C**H**HOH), 3.51 (1H, dd, *J* = 6.5 and 3.0 Hz, C**H**OH), 3.01 (3H, br s, 3 x O**H**), 2.32 (1H, ddd, *J* = 12.0, 9.5 and 4.5 Hz, CH**H**COH), 2.17-1.93 (3H, m, CH**H**COH and C$\mathbf{H_2}$, THF), 1.87 (1H, m, C$\mathbf{H_2}$), 1.71-1.32 (3H, m, C**H**H and C$\mathbf{H_2}$), 1.68 (3H, s, C$\mathbf{H_3}$), 1.61 (3H, s, C$\mathbf{H_3}$), 1.26 (3H, s, C$\mathbf{H_3}$), 1.18 (3H, s, C$\mathbf{H_3}$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	132.0 (**C**$(CH_3)_2$), 124.2 (**C**H**C**$(CH_3)_2$), 84.6 (O**C**H, THF), 83.8 (**C**OH), 76.7 (**C**HOH), 73.9 (O**C**CH_2, THF), 63.3 (**C**H_2OH), 38.5 (**C**H_2COH), 32.6 (**C**H_2C, THF), 26.2 (CH**C**H_2CH_2), 25.7 (**C**H_3), 24.2 (**C**H_3), 23.8 (**C**H_3), 22.2 (OCH**C**H_2, THF), 17.6 (**C**H_3).
LRMS (ES+ ionisation)	567.4 ($[2M+Na]^+$, 15%), 336.1 ($[M+CH_3CN+Na]^+$, 52%), 295.1 ($[M+Na]^+$, 100%).

(±)-*O*-((2*R,5*S**)-2-(Ethoxycarbonyl)-tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate (435a)**



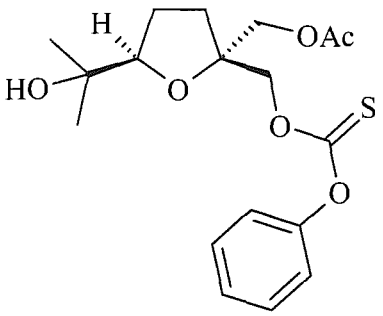
$C_{18}H_{24}O_6S$.
M = 368.5 g.mol^{-1}.

According to the method of Ireland *et al.*,[161] to a solution of THF **422a** (50 mg, 0.215 mmol), pyridine (1.29 mmol, 105 µL) and a trace of DMAP in CH_2Cl_2 (3mL) was added chlorothioformate (110 µL, 0.778 mmol). The bright yellow mixture was stirred for 3 h, diluted with CH_2Cl_2 (20 mL) and washed with HCl (10 mL, 2M aq. sol.) and water (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (90 mg). Purification on silica gel (100 mL, CH_2Cl_2/EtOAc, 15:85) gave the title product **435a** as a pale yellow oil (75 mg, 0.203 mmol, 94%).

IR (cm^{-1})	3445 (b), 2976 (b), 1736 (s), 1376 (w), 1293 (m), 1201 (s), 1113 (s), 1019 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.43 (2H, t, *J* = 8.0 Hz, OC**H**=CH x 2, arom), 7.30 (1H, d, *J* = 7.5 Hz, C**H**=CH, arom), 7.10 (2H, d, *J* = 8.0 Hz, OCH=C**H** x 2, arom), 4.86 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.82 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.31-4.20 (2H, m, OC**H$_2$**CH$_3$), 4.15 (1H, t, *J* = 7.3 Hz, CC**H**), 2.45 (1H, br s, O**H**), 2.26-1.94 (4H, m, C**H$_2$**), 1.31 (3H, s, C**H$_3$**), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**), 1.18 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	195.1 (**C**=S), 172.3 (**C**OO), 153.4 (O**C**=CH, arom), 129.5 (2 x OC=**C**H, arom), 126.6 (HC=**C**-CH, arom), 121.8 (2 x OCCH=**C**H, arom), 88.2 (O**C**H), 84.6 (**C**C=O), 75.4 (SCO**C**H$_2$), 71.1 (**C**OH), 61.6 (O**C**H$_2$), 32.9 (OC**C**H$_2$), 27.4 (**C**H$_3$), 25.7 (**C**H$_3$), 24.7 (CH**C**H$_2$) and 14.2 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	432.0 ([M+MeCN]$^+$, 20%), 391.0 ([M+Na]$^+$, 60%), 386.1

	($[M+NH_4]^+$, 100%).
HRMS	Calcd for $C_{18}H_{24}O_6SNa$: 391.1186. Found: 391.1183.

(±)-*O*-((2*R,5*R**)-2-(Acetoxymethyl)-tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate (443)**



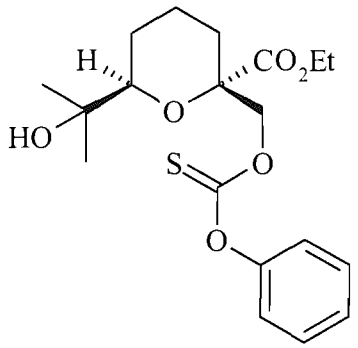
$C_{18}H_{24}O_6S$.
M = 368.44 g.mol^{-1}.

Following the procedure for the preparation of THF **435a**, THF **440** (350 mg, 1.507 mmol) was converted to the crude xanthate **443** (420 mg). Purification on silica gel (120 mL, CH_2Cl_2/EtOAc, 1:1) afforded the title product **443** as a pale yellow oil (515 mg, 1.398 mmol, 93%).

IR (cm^{-1})	3495 (b), 2976 (w), 3886 (w), 1743 (m), 1491 (w), 1376 (w), 1288 (m), 1201 (s), 1046 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.43 (2H, tdd, *J* = 7.3, 1.7 and 2.6 Hz, OCH=C**H** x 2, arom), 7.31 (1H, t, *J* = 7.3 Hz, C**H**=CH, arom), 7.10 (2H, d, *J* = 7.7 Hz, OC**H**=CH x 2, arom), 4.58 (1H, d, *J* = 11.1 Hz, C**H**HOC=S), 4.55 (1H, d, *J* = 11.1 Hz, C**H**HOOC=S), 4.20 (1H, d, *J* = 11.5 Hz, C**H**HOC=O), 4.09 (1H, d, *J* = 11.5 Hz, C**H**HOOC=O), 4.15 (1H, dd, *J* = 5.8 and 8.7 Hz, CC**H**, THF), 2.12 (3H, s, OC**H$_3$**), 2.11-1.88 (4H, m, C**H$_2$**), 1.59 (1H, s, O**H**), 1.26 (3H, s, C**H$_3$**), 1.16 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	195.0 (**C**=S), 170.1 (CH_3**C**OO), 153.4 (2 x O**C**=CH, arom), 129.0 (2 x OC=**C**H, arom), 126.9 (HC=**C**-CH, arom), 121.1 (OCCH=**C**H), 89.3 (**C**CH_2O, THF), 85.2 (O**C**H, THF), 76.1 (**C**H_2O), 75.1 (**C**OH), 64.8 (**C**H_2OAc), 32.9 (CH_2), 25.3 (**C**H_3), 24.1 (**C**H_2CH, THF), 24.8 (**C**H_3), 20.6 (**C**H_3).
LRMS (ES+ ionisation)	391.0 ($[M+Na]^+$, 100%).

HRMS Calcd for $C_{18}H_{24}O_6SNa$: 391.1186. Found: 391.1193.

(±)-*O*-((2*R,6*S**)-2-(Ethoxycarbonyl)-tetrahydro-6-(2-hydroxypropan-2-yl)-2*H*-pyran-2-yl)methyl *O*-phenyl carbonothioate (444)**

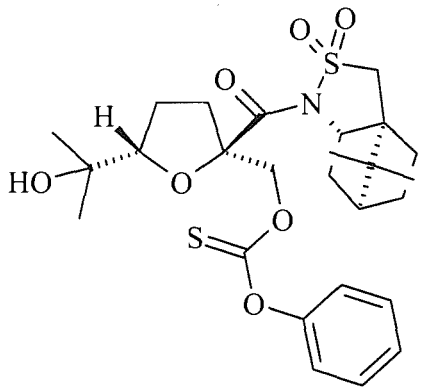


$C_{19}H_{26}O_6S$.
M = 382.4 g.mol^{-1}.

Following the procedure for the preparation of THF **435a**, THP **441a** (120 mg, 0.490 mmol) was converted to the crude xanthate **444** (170 mg). Purification on silica gel (75 mL, CH_2Cl_2/EtOAc, 1:4) afforded the title product **444** as a pale yellow oil (142 mg, 0.371 mmol, 76%).

IR (cm^{-1})	3471 (b), 2979 (m), 2937 (m), 1742 (m), 1710 (m), 1472 (w), 1309 (s), 1210 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.41 (2H, ddd, *J* = 8.0, 7.8 and 2.3 Hz, OC**H**=CH x 2, arom), 7.30 (1H, d, *J* = 7.8 Hz, C**H**=CH, arom), 7.09 (2H, br d, *J* = 8 Hz, OCH=C**H** x 2, arom), 4.65 (1H, d, *J* = 10.8 Hz, C**H**HO), 4.59 (1H, d, *J* = 10.8 Hz, C**H**HO), 4.42-4.29 (3H, m, CC**H** and O**C**$\mathbf{H_2}$CH$_3$), 3.48 (1H, br s, O**H**), 2.08 (1H, ddd, *J* = 14.3, 10.8 and 5.3 Hz, C**H**H), 1.89-1.42 (5H, m, C**H**H and 2 x C$\mathbf{H_2}$), 1.38 (6H, s, 2 x C$\mathbf{H_3}$), 1.33 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\mathbf{H_3}$).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	199.7 (**C**=S), 176.6 (**C**OO), 153.3 (2 x O**C**=CH, arom), 129.5 (2 x OC=**C**H, arom), 126.6 (HC=**C**-CH, arom), 121.7 (OCCH=**C**H), 88.2 (**C**C=O), 77.6 (O**C**H, THF), 76.1 (**C**H$_2$O), 75.2 (**C**OH), 62.8 (O**C**H$_2$), 35.1 (**C**H$_2$CH$_2$CH, THF), 34.2 (CH$_2$**C**H$_2$CH, THF), 26.6 (2 x **C**H$_3$), 17.3 (**C**H$_2$CH$_2$C, THF), 14.0 (OCH$_2$**C**H$_3$).
LRMS (ES+ ionisation)	421.1 ([M+K]$^+$, 100%).

***N*-[*O*-((2*S*,5*R*)-2-(Methyl *O*-phenyl carbonothioatyl)-tetrahydro-5-(2-hydroxypropan-2-yl)furan-2-yl]-2-(2*S*)-camphor-10,2-sultam (435b)**



$C_{26}H_{35}NO_7S_2$.
M = 537.7 g.mol^{-1}.

According to the method of Ireland *et al.*,[161] to a solution of THF **422b** (70 mg, 0.174 mmol), pyridine (83 µL, 1.04 mmol) and a trace of DMAP in CH_2Cl_2 (3 mL) was added chlorothioformate (85 µL, 0.626 mmol). The bright yellow mixture was stirred for 3 h, diluted with CH_2Cl_2 (20 mL) and washed with HCl (2 x 10 mL, 2M aq. sol.) and water (2 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (110 mg). Purification on silica gel (120 mL, CH_2Cl_2/EtOAc, 85:15) gave the title product **435b** as a pale yellow oil (91 mg, 0.169 mmol, 97%).

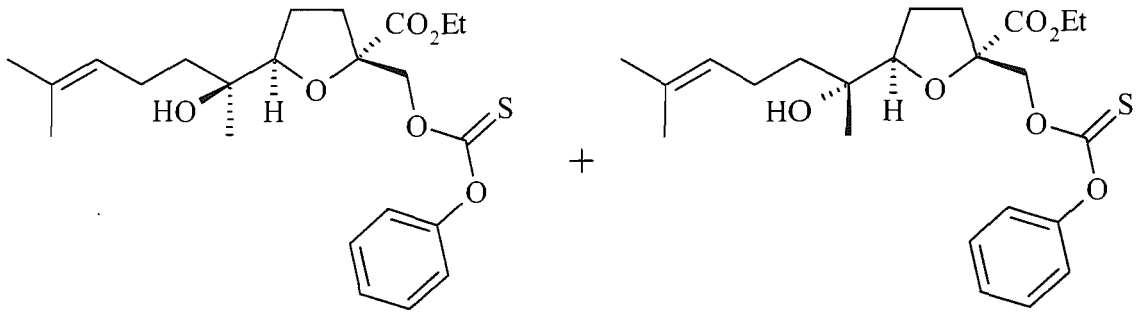
IR (cm^{-1})	3521 (b), 2964 (b), 2884 (b), 1678 (s), 1490 (w), 1339 (s), 1287 (s), 1199 (s), 1143 (s), 1052 (w).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.41 (2H, br t, *J* = 7.8 Hz, OC**H**=CH x 2, arom), 7.28 (1H, m, C**H**=CH, arom), 7.11 (2H, d, *J* = 7.8 Hz, OCH=C**H** x 2, arom), 4.98 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.84 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.16 (1H, dd, *J* = 8.8 and 6.5 Hz, NC**H**), 4.10 (1H, dd, *J* = 7.5 and 4.2 Hz, C**H**O, THF), 3.53 (1H, d, *J* = 13.6 Hz, CH**H**SO_2), 3.48 (1H, d, *J* = 13.3 Hz, C**H**HSO_2), 2.45 (1H, ddd, *J* = 13.0, 8.8 and 4.2 Hz, C**H**HCHO, THF), 2.31 (1H, td, *J* = 13.3 and 8.8 Hz, C**H**HCHO, THF), 2.11-2.03 (2H, m, C**H$_2$**), 1.99 (6H, m, 3 x C**H$_2$**), 1.37-1.34 (2H, m, C**H$_2$**C**H$_2$**S), 1.27 (3H, s, C**H$_3$**), 1.22 (3H, s, C**H$_3$**), 1.12 (3H, s, C**H$_3$**), 1.00 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	195.1 (**C**=S), 175.2 (**C**OO), 153.5 (2 x **O**C=CH, arom), 129.5 (2 x OC=**C**H, arom), 126.5 (HC=**C**-CH, arom), 121.9

(OCCH=CH), 88.9 (OCH, THF), 87.4 ($(CH_3)_2COH$), 75.4 (CH_2OCS), 71.3 (CO, THF), 67.6 (NCH), 54.6 (CH_2SO_2), 47.9 (CCH_2SO_2), 47.5 ($(CH_3)_2C$), 45.5 ($CHCH_2$), 39.3 (CH_2CH), 35.3 (CH_2CHO, THF), 33.7 (CH_2CO, THF), 27.3 (CH_3C), 26.1 (CH_2CH_2CH), 26.0 (CH_2CH_2CH), 24.0 (CH_3), 21.8 (CH_3), 20.0 (CH_3).

LRMS (ES+ ionisation) 1098.0 ($[2M+Na]^+$, 100%), 1093.0 ($[2M+NH_4]^+$, 20%), 576.4 ($[M+K]^+$, 100%), 560.2 ($[M+Na]^+$, 40%), 555.4 ($[M+NH_4]^+$, 100%).

HRMS Calcd for $C_{26}H_{35}NO_7S_2Na$: 560.1747. Found: 560.1749.

(±)-*O*-((2*S,5*R**)-2-(Ethoxycarbonyl)-tetrahydro-5-((*S**)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate (486a) and (±)-*O*-((2*S**,5*R**)-2-(ethoxycarbonyl)-tetrahydro-5-((*R**)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)methyl *O*-phenyl carbonothioate (486b)**



$C_{23}H_{32}O_6S$.

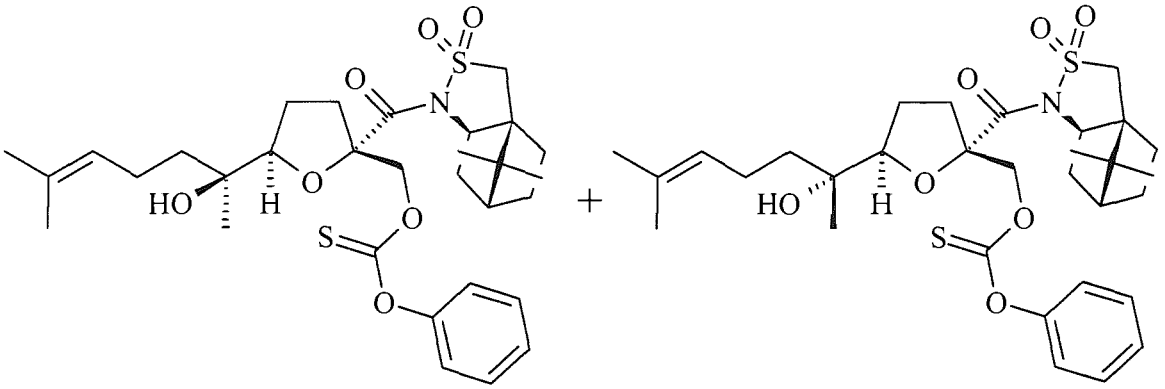
M = 436.56g.mol^{-1}.

Following the method used for the preparation of THF **435a**, the mixture of THFs **460a,b** (77 mg, 0.256 mmol), was converted to an inseparable mixture of products **486a,b**, obtained as a pale yellow oil (105 mg, 0.240 mmol, 94%) after purification on silica gel (100 mL, CH_2Cl_2/EtOAc, 95:5).

IR (cm^{-1}) 3496 (b), 2968 (m), 2904 (m), 2880 (m), 1736 (m), 1490 (m), 1377 (m), 1294 (s), 1201 (s), 1113 (m).

^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.42 (2H, t, *J* = 8.0 Hz, OC**H**=CH x 2, arom), 7.30 (1H, dd, *J* = 7.5 and 1.8 Hz, C**H**=CH, arom), 7.10 (2H, d, *J* = 7.8 Hz, OCH=C**H** x 2, arom), 5.15 (1H, m, C**H**=C$(CH_3)_2$), 4.86 (1H, d, *J* = 11.3 Hz, C**H**HO), 4.82 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.33-4.21 (2H, m, OC**H_2**), 4.17 (1H, dd, *J* = 8.0 and 6.8 Hz, C**H**O, THF), 2.26-1.94 (7H, m, 3 x C**H_2** and O**H**), 1.68-1.36 (2H, m, **C**H_2COH) 1.69 (3H, s, C**H_3**), 1.63 (3H, s, C**H_3**), 1.31 (3H, t, *J* = 7.0 Hz, OCH_2C**H_3**), 1.12 (3H, s, C**H_3**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	195.2 (**C**=S), 172.3 (**C**OO), 153.4 (2 x O**C**=CH, arom), 131.8 (**C**$(CH_3)_2$), 131.5 (**C**$(CH_3)_2$), 129.6 (2 x OC=**C**H, arom), 126.6 (HC=**C**-CH, arom), 124.5 (**C**HC$(CH_3)_2$), 124.4 (**C**HC$(CH_3)_2$), 121.8 (OCCH=**C**H, arom), 87.7 (O**C**H, THF), 86.9 (O**C**H, THF), 84.3 (O**C**CH_2, THF), 75.5 (C**C**H_2OCS), 72.9 (**C**OH), 72.8 (**C**OH), 61.6 (O**C**H_2CH_3), 40.0 (**C**H_2COH), 37.8 (**C**H_2COH), 32.9 (CH**C**H_2CH_2), 32.8 (CH**C**H_2CH_2), 25.7 (**C**H_3), 25.5 (**C**H_2C, THF), 25.2 (**C**H_2C, THF), 22.5 (OCH**C**H_2, THF), 22.1 (OCH**C**H_2, THF), 21.7 (**C**H_3), 17.6 (**C**H_3), 14.2 (OCH_2**C**H_3).
LRMS (ES+ ionisation)	454.1 ($[M+NH_4]^+$, 100%).
HRMS	Calcd for $C_{23}H_{32}O_6SNa$: 459.1812. Found: 459.1810.

***N*-[*O*-((2*S*,5*R*)-2-(Methyl *O*-phenyl carbonothioatyl)-tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)]-2-camphor-10,2-sultam (486c) and *N*-[*O*-((2*S*,5*R*)-2-(methyl *O*-phenyl carbonothioatyl)-tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)furan-2-yl)]-2-camphor-10,2-sultam (486d)**



$C_{31}H_{43}NO_7S_2$.

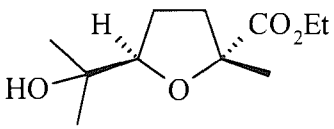
M = 605.8 g.mol^{-1}.

According to Ireland *et al.*,[161] to a solution of the mixture of THFs **460c,d** (110 mg, 0.234 mmol), pyridine (114 μL, 1.321 mmol) and a trace of DMAP in CH_2Cl_2 (3 mL) was added chlorothioformate (120 μL, 0.884 mmol). The bright yellow mixture was stirred for 3h and then diluted with CH_2Cl_2 (20 mL) and washed with HCl (2 x 10 mL, 2M aq. sol.) and water (2 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil (180 mg). Purification on silica gel (140 mL, CH_2Cl_2/EtOAc, 95:5) gave an inseparable mixture of products **485c,d** as a pale yellow oil (130 mg, 0.214 mmol, 91%).

$[\alpha]_D$	–31.3 (*c* 0.5, CH_2Cl_2)
IR (cm^{-1})	3485 (b), 2959 (m), 2932 (w), 2882 (w), 1753 (m), 1678 (m), 1593 (w), 1490 (m), 1346 (m), 1257 (s), 1206 (s), 1166 (m).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	7.35 (2H, tdd, *J* = 7.3, 2.0 and 2.5 Hz, OC**H**=CH x 2, arom), 7.25 (1H, dd, *J* = 2.5 and 1.3 Hz, C**H**=CH, arom), 7.21 (2H, m, OCH=C**H** x 2, arom), 5.13 (1H, ddd, *J* = 7.0, 2.8 and 1.3 Hz, C**H**C(CH$_3$)$_2$), 4.63 (1H, d, *J* = 11.0 Hz, C**H**HO), 4.60 (1H, d, *J* = 11.0 Hz, CHHO), 4.21 (1H, dd, *J* = 9.3 and 6.0 Hz, C**H**O, THF), 4.13 (1H, dd, *J* = 7.8 and 4.8 Hz, NC**H**), 3.54 (1H, d, *J* = 13.6 Hz, CH**H**SO$_2$), 3.47 (1H, d, *J* = 13.6 Hz, C**H**HSO$_2$), 3.28 (O**H**),

	2.31 (1H, m, C**H**HCHO, THF), 2.14-2.05 (4H, m, 2 x C**H**$_2$), 1.95-1.84 (5H, m C**H**CH$_2$CHN and 2 x C**H**$_2$), 1.74 (1H, dd, J = 11.6 and 5.7 Hz, C**H**HCHO, THF), 1.62-1.49 (2H, m, C**H**$_2$), 1.36 (2H, m, C**H**$_2$), 1.70 (3H, s, C**H**$_3$), 1.56 (3H, s, C**H**$_3$), 1.27 (3H, s, C**H**$_3$), 1.06 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$).
^{13}C-NMR (100MHz, CDCl$_3$, ppm)	196.5 (**C**=S), 175.3 (**C**OO), 154.4 (2 x O**C**=CH, arom), 131.1 (**C**CH$_3$)$_2$), 129.4 (2 x OC=**C**H, arom), 126.0 (HC=**C**-CH, arom), 125.3 (**C**HCCH$_3$)$_2$), 121.3 (OCCH=**C**H), 89.1 (CH$_3$**C**O, THF), 87.9 (**C**HO, THF), 72.3 (CH$_3$**C**OH), 71.0 (CH$_3$**C**OH), 67.5 (**C**HN), 54.7 (**C**H$_2$SO$_2$), 47.9 (**C**HC(CH$_3$)$_2$, sultam), 47.6 (**C**HC(CH$_3$)$_2$), 45.4 (**C**HC(CH$_3$)$_2$), 39.5 (**C**H$_2$COH), 39.2 (**C**H$_2$CO, THF), 35.3 (**C**H$_2$CHO, THF), 33.6 (**C**H$_2$CCH$_2$S), 26.2 (**C**H$_2$CHN), 25.8 (**C**H$_3$), 25.2 (**C**H$_2$CH), 22.1 (CH**C**H$_2$CH$_2$), 21.8 (**C**H$_3$), 21.3 (**C**H$_3$), 19.9 (**C**H$_3$), 17.7 (**C**H$_3$).
LRMS (ES+ ionisation)	1235.7 ([2M+Na]$^+$, 7%), 1230.0 ([2M+NH$_4$]$^+$, 12%), 644.3 ([M+K]$^+$, 18%), 628.3 ([M+Na]$^+$, 97%), 623.3 ([M+NH$_4$]$^+$, 100%).

(±)-(2*R,5*R**)-Ethyl tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuran-2-carboxylate (423a)**



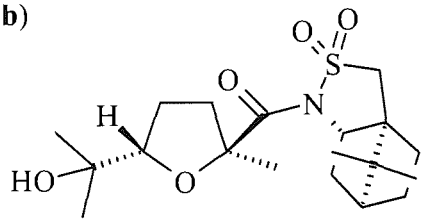
C$_{11}$H$_{20}$O$_4$.
M = 216.2 g.mol^{-1}.

According to Lopez *et al.*,[162] to a solution of THF **435a** (40 mg, 0.108 mmol) in toluene (2 mL) was added SnBu$_3$H (35 μL, 0.130 mmol) followed by AIBN (3 mg, 0.022 mmol). The reaction was heated up to reflux and stirred for 4 hours. The solvents were then removed *in vacuo* and the crude mixture (85 mg) was purified by column chromatography (100 mL, CH$_2$Cl$_2$/EtOAc, 4:1) to yield the title product **423a** as a colourless oil (21 mg, 0.097 mmol, 90%).

IR (cm^{-1})	3496 (b), 2980 (b), 2965 (b), 2937 (b), 1731 (s), 1645 (w), 1373 (w), 1271 (w), 1176 (s), 1123 (s), 1023 (s).

^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.20 (2H, dq, *J* = 7.3 and 3.8 Hz, OCH_2), 3.98 (1H, t, *J* = 7.3 Hz, CCHO, THF), 2.33-2.26 (1H, m, CHHCHO, THF), 1.91-178 (3H, m, CHHCHO and CCH_2), 1.76 (1H, br s, OH), 1.50 (3H, s, CH_3), 1.29 (3H, t, *J* = 7.3 Hz, OCH_2CH_3), 1.15 (6H, s, 2 x CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	175.1 (COO), 87.0 ($C(CH_3)_2$), 83.7 (OCH, THF), 71.0 ($OCCH_3$, THF), 61.0 (OCH_2), 36.7 (CH_2CO, THF), 27.1 (CH_2CHO, THF), 25.9 (CH_3), 24.4 (CH_3), 14.2 (OCH_2CH_3).
LRMS (ES+ ionisation)	280.0 ($[M+Na+MeCN]^+$, 100%), 239 ($[M+Na]^+$, 75%), 234.0 ($[M+NH_4]^+$, 67%).
HRMS	Calcd for $C_{11}H_{20}O_4Na$: 239.1254. Found: 239.1251.

***N*-[(2*R*,5*R*)-Tetrahydro-5-(2-hydroxypropan-2-yl)-2-methylfuranoyl-2-(2*S*)-camphor-10,2-sultam (423b)**



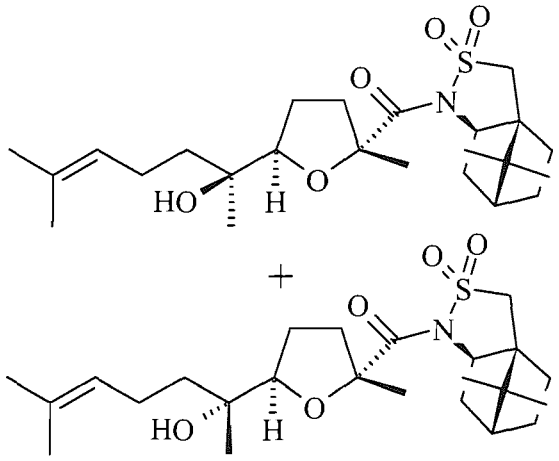
$C_{19}H_{31}NO_5S$.
M = 385.5 g.mol^{-1}.

According to Lopez *et al.*,[162] to a solution of THF **435b** (70 mg, 0.130 mmol) in toluene (3 mL) was added $SnBu_3H$ (53 μL, 0.195 mmol) followed by AIBN (4 mg, 0.026 mmol), the reaction was heated up to reflux and stirred for 4 hours. The solvents were then removed *in vacuo* and the crude mixture (85 mg) was purified by column chromatography (100 mL, CH_2Cl_2/EtOAc, 1:4) to yield the title product **423b** as a colourless glass (47 mg, 0.122 mmol, 94%).

$[\alpha]_D$	17.4 (*c* 0.8, CH_2Cl_2).
IR (cm^{-1})	3422 (b), 29569 (b), 2942 (b), 2920 (b), 1674 (s), 1458 (w), 1340 (s), 1287 (m), 1166 (s), 1141 (s) and 1062 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	4.08 (1H, dd, *J* = 7.8 and 4.0 Hz, NCH), 4.02 (1H, t, *J* = 7.6 Hz, CHO, THF), 3.54 (1H, d, *J* = 13.5 Hz, $CHHSO_2$), 3.41 (1H, d, *J* = 13.3 Hz, $CHHSO_2$), 2.76 (1H, br s, OH), 2.34 (1H, ddd, *J* = 16.3, 8.3 and 8.0 Hz, CHHCHO, THF), 2.09-1.99 (5H, m, CH_2CHN and $CHCH_2CHN$ and CH_2CO), 1.97-1.85 (3H, m, CHHCHO and $CHCH_2$), 1.54 (3H, CH_3), 1.37-1.33 (2H, m,

	$CH_2CCH_2SO_2$), 1.23 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.16 (6H, s, 2 x CH_3).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	178.5 (**C**ON), 87.8 (**C**HO, THF), 86.0 (CH_3**C**O, THF), 71.2 (($C(CH_3)_2$OH), 67.7 (**C**HN), 54.6 (CH_2SO_2), 47.8 ($CC(CH_3)_2$), 47.5 ($C(CH_3)_2$), 45.6 ($CHC(CH_3)_2$), 39.5 (CH_2CO), 33.9 (CH_2CO, THF), 26.8 (CH_3), 26.2 (CH_2CCH_2S), 25.9 (CH_3), 24.5 (CH_2CHN), 23.5 (CH_2CH), 21.9 (CH_3), 19.9 (2 x CH_3).
LRMS (ES+ ionisation)	560.1 ($[M+Na]^+$, 60%), 555.2 ($[M+NH_4]^+$, 100%).
HRMS	Calcd for $C_{26}H_{35}NO_7S_2Na$: 560.1747. Found: 560.1749.

***N*-[(2*R*,5*R*)-Tetrahydro-5-((*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-2- methylfuranoyl-2-(2*R*)-camphor-10,2-sultam (416d) and *N*-[(2*R*,5*R*)-tetrahydro-5-((*R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2- methylfuranoyl-2-(2*R*)-camphor-10,2-sultam (416e)**



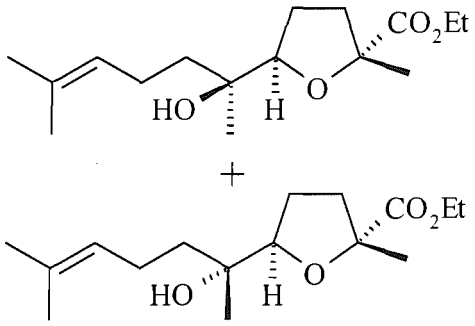
$C_{25}H_{39}NO_5S$.
M = 453.64 g.mol^{-1}.

According to Lopez *et al.*,[162] to a solution of the mixture of THFs **460c,d** (60 mg, 0.099 mmol) in toluene (2 mL) was added $SnBu_3H$ (33 μL, 0.121 mmol) followed by AIBN (3 mg, 0.020 mmol), the reaction was heated up to reflux and stirred for 4 hours. The solvents were then removed *in vacuo* and the crude mixture (75 mg) was purified by column chromatography (50 mL SiO_2 containing 10% KF, CH_2Cl_2/EtOAc, 1:2) to yield a inseparable mixture of products **416d,e** as a colourless glass (40 mg, 0.088 mmol, 89%).

$[\alpha]_D$	–24.2 (*c* 0.7, CH_2Cl_2)
IR (cm^{-1})	3440 (b), 2968 (m), 2940 (m), 2897 (m), 1738 (m), 1675 (s), 1458 (m), 1339 (s), 1289 (m), 1200 (m), 1166 (s), 1140 (s), 1062 (s).

^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.12 (1H, ddd, *J* = 12.8, 5.5 and 2.8 Hz, C**H**C(CH_3)$_2$), 4.07 (1H, dd, *J* = 7.8 and 4.0 Hz, NC**H**), 4.07 (1H, m, C**H**O, THF), 3.55 (1H, dd, *J* = 13.6 and 3.3 Hz, CH**H**SO_2), 3.40 (1H, d, *J* = 13.6 Hz, C**H**HSO_2), 2.46 (1H, br s, O**H**), 2.35 (1H, ddd, *J* = 13.3, 8.3 and 5.5 Hz, C**H**HCHO, THF), 2.22-1.83 (6H, m, 3 x C**H$_2$**), 1.85 (1H, br s, C**H**CH_2CHN), 1.79-1.72 (4H, m, 2 x C**H$_2$**), 1.48 (1H, ddd, *J* = 10.0, 6.8 and 3.0 Hz, C**H**HCHO, THF), 1.52-1.25 (2H, m, C**H$_2$**CCH_2SO_2), 1.68 (3H, s, C**H$_3$**), 1.62 (3H, s, C**H$_3$**), 1.56 (6H, s, 2 x C**H$_3$**), 1.23 (3H, s, C**H$_3$**), 1.00 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	178.5 (**C**ON), 131.4 (**C**CH_3)$_2$), 131.2 (**C**CH_3)$_2$), 124.9 (**C**H**C**CH_3)$_2$), 87.7 (**C**HO, THF), 86.9 (**C**HO, THF), 86.0 (CH_3**C**O, THF), 73.0 (CH_3**C**OH), 72.8 (CH_3**C**OH), 67.7 (**C**HN), 54.6 (**C**H_2SO_2), 47.9 (**C**(CH_3)$_2$), 47.5 (**C**C(CH_3)$_2$), 45.6 (**C**HC(CH_3)$_2$), 39.5 (**C**H_2COH), 39.4 (**C**H_2CO, THF), 26.2 (**C**H_2CCH_2S), 25.9 (**C**H_2CHO, THF), 25.7 (**C**H_3), 25.3 (**C**H_2CHN), 24.4 (**C**H_3), 23.9 (**C**H_3), 22.1 (**C**H_2CH), 21.8 (CH**C**H_2CH_2), 21.8 (**C**H_3), 20.9 (**C**H_3), 19.9 (**C**H_3), 17.6 (CHCH_2**C**H_2).
LRMS (ES+ ionisation)	929.6 ($[2M+Na]^+$, 18%), 920.6 ($[2M+NH_4]^+$, 26%), 476.2 ($[M+Na]^+$, 28%), 471.2 ($[M+NH_4]^+$, 100%), 454.2 ($[M+H]^+$, 66%).
HRMS	Calcd for $C_{24}H_{39}NO_5SNa$: 476.2441. Found: 476.2449.

(±)-(2*R,5*R**)-Ethyl tetrahydro-5-((*S**)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2 carboxylate (416b) and (±)-(2*R**,5*R**)-ethyl tetrahydro-5-((*R**)-2-hydroxy-6-methylhept-5-en-2-yl)-2-methylfuran-2 carboxylate (416c)**



$C_{16}H_{28}O_4$.

M = 284.39 g.mol^{-1}.

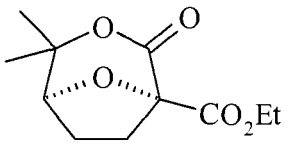
According to Lopez *et al.*,[162] to a solution of the mixture of THF **460a,b** (100 mg, 0.271 mmol) in toluene (5 mL) was added $SnBu_3H$ (90 µL, 0.331 mmol) followed by AIBN (8 mg, 0.052 mmol). The reaction was heated up to reflux and stirred for 4 hours. The solvents were then removed *in vacuo* and the crude mixture (125 mg) was purified by column chromatography (100 mL SiO_2 containing 10% KF, CH_2Cl_2/EtOAc, 1:1) to yield a inseparable mixture of products **416b,c** as a colourless glass (53 mg, 0.186 mmol, 69%).

IR (cm^{-1})	3381 (b), 2973 (m), 2925 (m), 2877 (w), 1729 (s), 1448 (m), 1376 (m), 1271 (m), 1190 (m), 1102 (s), 1056 (s).
^{1}H-NMR (400MHz, $CDCl_3$, ppm)	5.13 (1H, br s, C**H**C(CH_3)$_2$), 4.19 (2H, m, OC**H$_2$**CH$_3$), 4.00 (1H, dt, *J* = 7.0 and 9.5 Hz, C**H**O, THF), 2.31 (1H, m, C**H**HC, THF), 2.10 (2H, m, C**H$_2$**CH$_2$COH), 1.97-1.77 (3H, m, C**H$_2$**CHO, THF and C**H**HCO, THF), 1.37-1.32 (2H, m, C**H$_2$**COH), 1.62 (3H, s, C**H$_3$**), 1.58 (3H, s, C**H$_3$**), 1.57 (1H, br s, O**H**), 1.49 (3H, s, C**H$_3$**), 1.29 (3H, t, *J* = 7.3 Hz, OCH$_2$C**H$_3$**), 1.10 (3H, s, C**H$_3$**).
^{13}C-NMR (100MHz, $CDCl_3$, ppm)	175.2 (**C**OOCH$_2$CH$_3$), 131.8 (**C**(CH$_3$)$_2$, minor), 131.4 (**C**(CH$_3$)$_2$), 124.6 (**C**HC(CH$_3$)$_2$), 86.1 (**C**HO, THF, minor), 85.7 (**C**HO, THF), 83.5 (**C**O, THF), 72.8 (CH$_3$**C**OH), 60.9 (COO**C**H$_2$CH$_3$), 40.1 (CH**C**H$_2$), 37.1 (**C**H$_2$CO, THF, minor), 36.6 (**C**H$_2$CO, THF, minor), 25.6 (**C**H$_3$), 25.6 (**C**H$_3$), 24.5 (**C**H$_2$CHO, THF), 24.0 (**C**H$_2$CHO, THF, minor), 22.4 (**C**H$_3$), 21.5 (**C**H$_3$), 17.6 (CHCH$_2$**C**H$_2$), 14.2 (**C**H$_3$).
LRMS (ES+ ionisation)	591.5 ([2M+Na]$^+$, 8%), 307.1 ([M+Na]$^+$, 8%), 302.1 ([M+NH$_4$]$^+$,

100%).

HRMS Calcd for $C_{16}H_{28}O_4Na$: 307.1880. Found: 307.1883.

17,4-Dimethyl-2-oxo-3,8-dioxa-bicyclo[3.2.1]octane-1-carboxylic acid ethyl ester (448)

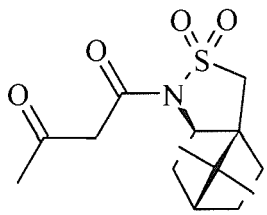


$C_{11}H_{16}O_5$.
M = 228.25 g.mol^{-1}.

To a solution of THF **422a** (50 mg, 0.216 mmol) in CH_2Cl_2 (5 mL) containing 200 mg of crushed molecular sieves, was added NMO (49 mg, 0.377 mmol) and TPAP (29 mg). The resulting solution was stirred for 45 minutes, , filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo* to afford the crude compound as a pale yellow oil (55 mg). Purification on silica gel (15 g, EtOAc/CH_2Cl_2, 2:3) afforded the title product **448** as a yellow oil (40 mg, 0.175 mmol, 81%).

IR (cm^{-1})	2983 (b), 2921 (b), 2841 (d), 1753 (s), 1327 (w), 1167 (w), 1103 (w).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.40-4.26 (3H, m, OCH_2 and CH), 2.51-2.10 (4H, m, 2 x CH_2), 1.63 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.35 (3H, t, J = 7.2 Hz, OCH_2CH_3)
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	166.3 (COO), 166.0 (COO), 85.6 (CCO), 83.7 (CHCO), 80.2 (CHCO), 62.4 (OCH_2), 32.8 (CH_2CO), 27.2 (CH_3), 23.8 (CH_3), 22.7 (CH_2), 14.0 (CH_3).
LRMS (ES+ ionisation)	479.2 ([2M+Na]$^+$, 30%), 292 (100%), 267.1 ([M+K]$^+$, 15%), 229.1 ([M+H]$^+$, 33%).

***N*-(3-oxobutanoil)bornane-10,2-(2*R*)-sultam (487) [120]**



$C_{14}H_{21}ONO_4S$.
M = 299.39 g.mol^{-1}.

According to the method described by Marco *et al.*,[120] (2*R*)-10,2-camphorsultam (500mg, 2.3 mmol) was dissolved in toluene (5 mL) and dioxinone (500 mg, 3.5 mmol) was added in a

preheated bath at 130°C. The solution was stirred for 50 minutes and allowed to cool to room temperature. Solvents were removed under reduced pressure to give a sticky orange residue, which was purified on silica gel (45 g, hexane/EtOAc, 9:1 then 4:1). The product was obtained as an orange oil which was crystallised in a mixture hexane/EtOAc (98:2) to give the title product **487** as transparent needles (628 mg, 2.1 mmol, 91%). The structure was confirmed by X-ray crystallography. The spectroscopic data were in good agreement with literature.[120]

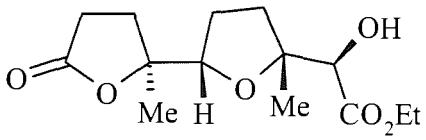
IR (cm^{-1})	3281 (w), 2959 (b), 2879 (b), 1730 (s), 1692 (s), 1630 (s), 1455 (s), 1342 (w), 1134 (s), 997 (s).
^{1}H-NMR (300MHz, $CDCl_3$, ppm)	4.10 (1H, d, *J* = 16.9 Hz, CH**H**CO), 3.91 (1H, dd, *J* = 7.9 and 4.8 Hz, C**H**NSO_2), 3.71 (1H, d, *J* = 16.9 Hz, CH**H**CO), 3.49 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 3.42 (1H, d, *J* = 13.8 Hz, CH**H**SO_2), 2.26-2.06 (2H, m, C**H$_2$**), 2.02 (3H, s, C**H$_3$**CO), 1.93-1.91 (3H, m, C**H**C$(CH_3)_2$, C**H$_2$**), 1.46-1.36 (2H, m, C**H$_2$**), 1.16 (3H, s, C**H$_3$**), 0.97 (3H, s, C**H$_3$**).
^{13}C-NMR (75MHz, $CDCl_3$, ppm)	200.1 (**C**OCH_3), 178.7 (**C**ON), 65.0 (**C**HNSO_2), 52.8 (**C**H_2SO_2), 50.7 (**C**H_2CO), 48.6 (**C**CH_2SO_2), 47.8 (C$(CH_3)_2$), 44.7 (**C**HC$(CH_3)_2$), 38.6 (**C**H_2CHN), 32.7 (**C**$H_2CH_2CCH_2S$), 30.3 (**C**H_3CO), 26.5 (**C**H_2), 21.9 (**C**H_3), 20.8 (**C**H_3), 19.9 (**C**H_3).
LRMS (ES+ ionisation)	621.3 ($[2M+Na]^+$, 6%), 300.2 ($[M+H]^+$, 9%).

Chapter 7: Appendix

X-Ray:

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Ethyl (2*S)-2-hydroxy-2-[(2*R**,2'*S**,5*S**)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl] ethanoate (314b)**



Empirical formula	$C_{14}H_{22}O_6$	
Formula weight	286.32	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 9.3133(3) Å	α = 90°
	b = 15.4441(4) Å	β = 90°
	c = 9.8424(3) Å	γ = 90°
Volume	1415.69(7) Å^3	
Z	4	
Density (calculated)	1.343 Mg / m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	616	
Crystal	Plate; colourless	
Crystal size	0.26 × 0.22 × 0.10 mm^3	

θ range for data collection	3.29 – 27.49°
Index ranges	$-10 \le h \le 12$, $-19 \le k \le 20$, $-12 \le l \le 12$
Reflections collected	14735
Independent reflections	3218 [$R_{int} = 0.0585$]
Completeness to $\theta = 27.49°$	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9896 and 0.9733
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3218 / 1 / 186
Goodness-of-fit on F^2	1.024
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0340$, $wR2 = 0.0767$
R indices (all data)	$R1 = 0.0435$, $wR2 = 0.0810$
Absolute structure parameter	0.7(7)
Extinction coefficient	0.0098(16)
Largest diff. peak and hole	0.174 and –0.170 e Å^{-3}

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	3738(2)	–661(1)	2416(2)	19(1)	1
C2	5029(2)	–964(1)	3196(2)	23(1)	1
C3	5245(2)	–267(1)	4268(2)	21(1)	1
C4	4585(2)	541(1)	3598(2)	18(1)	1
C5	5689(2)	1053(1)	2788(2)	24(1)	1
C6	3783(2)	1134(1)	4571(2)	17(1)	1
C7	2834(2)	1820(1)	3898(2)	21(1)	1
C8	1644(2)	1941(1)	4944(2)	22(1)	1
C9	1438(2)	1032(1)	5517(2)	19(1)	1
C10	963(2)	1014(1)	6996(2)	27(1)	1
C11	400(2)	505(1)	4602(2)	19(1)	1
C12	133(2)	–399(1)	5159(2)	21(1)	1
C13	1039(2)	–1800(1)	5515(2)	31(1)	1
C14	2280(2)	–2334(1)	5057(2)	32(1)	1
O1	2997(1)	–1071(1)	1644(1)	26(1)	1
O2	3520(1)	186(1)	2642(1)	20(1)	1
O3	2845(1)	638(1)	5438(1)	19(1)	1
O4	–937(1)	936(1)	4454(1)	25(1)	1
O5	–964(1)	–605(1)	5723(1)	33(1)	1
O6	1241(1)	–934(1)	4962(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.2056(19)	O1–C1–C2	128.06(14)
C1–O2	1.3416(17)	O2–C1–C2	109.88(13)
C1–C2	1.502(2)	C1–C2–C3	103.87(12)
C2–C3	1.521(2)	C1–C2–H2A	111.0
C2–H2A	0.9900	C3–C2–H2A	111.0
C2–H2B	0.9900	C1–C2–H2B	111.0
C3–C4	1.539(2)	C3–C2–H2B	111.0
C3–H3A	0.9900	H2A–C2–H2B	109.0
C3–H3B	0.9900	C2–C3–C4	102.98(12)
C4–O2	1.4733(17)	C2–C3–H3A	111.2
C4–C6	1.520(2)	C4–C3–H3A	111.2
C4–C5	1.523(2)	C2–C3–H3B	111.2
C5–H5A	0.9800	C4–C3–H3B	111.2
C5–H5B	0.9800	H3A–C3–H3B	109.1
C5–H5C	0.9800	O2–C4–C6	107.18(11)
C6–O3	1.4412(17)	O2–C4–C5	108.24(12)
C6–C7	1.531(2)	C6–C4–C5	110.42(12)
C6–H6	1.0000	O2–C4–C3	103.89(11)
C7–C8	1.524(2)	C6–C4–C3	114.52(12)
C7–H7A	0.9900	C5–C4–C3	112.09(12)
C7–H7B	0.9900	C4–C5–H5A	109.5
C8–C9	1.526(2)	C4–C5–H5B	109.5
C8–H8A	0.9900	H5A–C5–H5B	109.5
C8–H8B	0.9900	C4–C5–H5C	109.5
C9–O3	1.4468(17)	H5A–C5–H5C	109.5
C9–C10	1.521(2)	H5B–C5–H5C	109.5
C9–C11	1.551(2)	O3–C6–C4	110.55(11)
C10–H10A	0.9800	O3–C6–C7	105.91(11)
C10–H10B	0.9800	C4–C6–C7	115.37(13)
C10–H10C	0.9800	O3–C6–H6	108.3
C11–O4	1.4190(17)	C4–C6–H6	108.3
C11–C12	1.520(2)	C7–C6–H6	108.3
C11–H11	1.0000	C8–C7–C6	102.26(12)
C12–O5	1.2053(19)	C8–C7–H7A	111.3
C12–O6	1.3358(18)	C6–C7–H7A	111.3
C13–O6	1.4573(17)	C8–C7–H7B	111.3
C13–C14	1.489(2)	C6–C7–H7B	111.3
C13–H13A	0.9900	H7A–C7–H7B	109.2
C13–H13B	0.9900	C7–C8–C9	103.20(12)
C14–H14A	0.9800	C7–C8–H8A	111.1
C14–H14B	0.9800	C9–C8–H8A	111.1
C14–H14C	0.9800	C7–C8–H8B	111.1
O4–H4	0.8400	C9–C8–H8B	111.1
O1–C1–O2	122.00(14)	H8A–C8–H8B	109.1

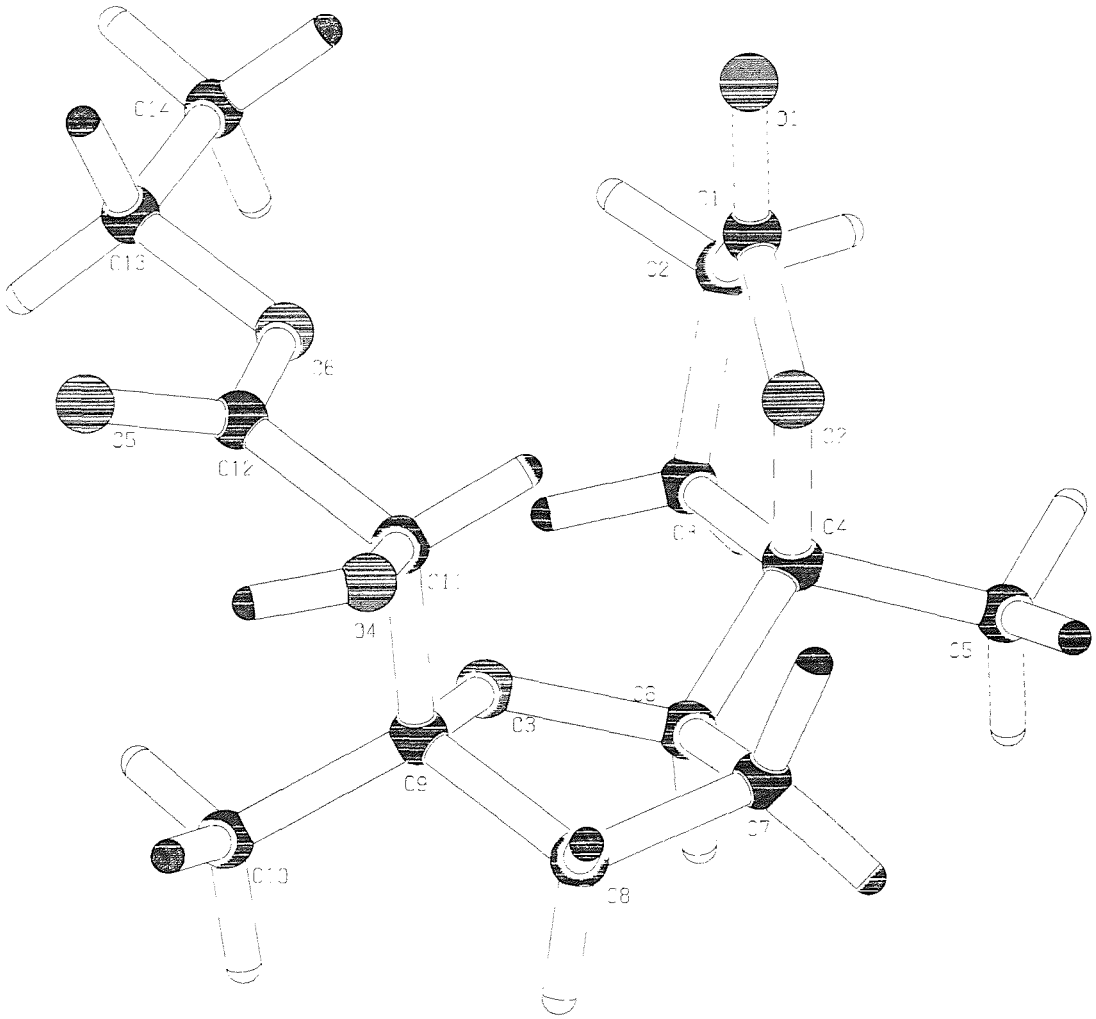
O3–C9–C10	107.92(12)	O5–C12–C11	123.14(13)
O3–C9–C8	104.60(11)	O6–C12–C11	112.88(12)
C10–C9–C8	113.97(13)	O6–C13–C14	107.15(13)
O3–C9–C11	108.25(11)	O6–C13–H13A	110.3
C10–C9–C11	111.43(12)	C14–C13–H13A	110.3
C8–C9–C11	110.28(13)	O6–C13–H13B	110.3
C9–C10–H10A	109.5	C14–C13–H13B	110.3
C9–C10–H10B	109.5	H13A–C13–H13B	108.5
H10A–C10–H10B	109.5	C13–C14–H14A	109.5
C9–C10–H10C	109.5	C13–C14–H14B	109.5
H10A–C10–H10C	109.5	H14A–C14–H14B	109.5
H10B–C10–H10C	109.5	C13–C14–H14C	109.5
O4–C11–C12	108.91(12)	H14A–C14–H14C	109.5
O4–C11–C9	111.12(11)	H14B–C14–H14C	109.5
C12–C11–C9	111.97(12)	C1–O2–C4	111.57(11)
O4–C11–H11	108.2	C6–O3–C9	110.99(10)
C12–C11–H11	108.2	C11–O4–H4	109.5
C9–C11–H11	108.2	C12–O6–C13	114.43(12)
O5–C12–O6	123.98(14)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	17(1)	21(1)	19(1)	1(1)	3(1)	1(1)
C2	20(1)	24(1)	25(1)	−1(1)	0(1)	3(1)
C3	19(1)	24(1)	20(1)	−1(1)	−1(1)	4(1)
C4	15(1)	22(1)	17(1)	−1(1)	−3(1)	−1(1)
C5	21(1)	27(1)	22(1)	−1(1)	2(1)	−2(1)
C6	14(1)	20(1)	18(1)	−1(1)	0(1)	−3(1)
C7	18(1)	19(1)	25(1)	3(1)	1(1)	−2(1)
C8	20(1)	17(1)	30(1)	−2(1)	1(1)	0(1)
C9	15(1)	20(1)	22(1)	−1(1)	1(1)	2(1)
C10	19(1)	36(1)	25(1)	−7(1)	2(1)	−2(1)
C11	15(1)	20(1)	22(1)	0(1)	−1(1)	1(1)
C12	18(1)	21(1)	24(1)	−2(1)	−1(1)	−1(1)
C13	26(1)	19(1)	48(1)	6(1)	5(1)	−1(1)
C14	26(1)	22(1)	48(1)	−1(1)	−1(1)	2(1)
O1	22(1)	25(1)	31(1)	−7(1)	−5(1)	0(1)
O2	19(1)	20(1)	20(1)	−2(1)	−5(1)	0(1)

O3	14(1)	21(1)	22(1)	3(1)	2(1)	−1(1)
O4	17(1)	28(1)	30(1)	4(1)	−2(1)	3(1)
O5	23(1)	24(1)	53(1)	2(1)	13(1)	−2(1)
O6	19(1)	18(1)	34(1)	1(1)	4(1)	0(1)



***N*-[(2*S*,5*R*)- tetrahydro-2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)furanoyl]-2-camphor-10,2-sultam (422b)**

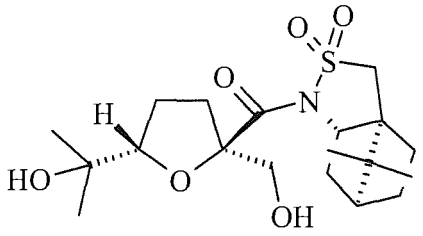


Table 1. Crystal data and structure refinement.

Empirical formula	$C_{19}H_{31}NO_6S$	
Formula weight	401.3	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 14.3472(14) Å	$\alpha = 90°$
	b = 17.3099(13) Å	$\beta = 90°$
	c = 8.1910(10) Å	$\gamma = 90°$
Volume	2034.2(4) Å^3	
Z	4	
Density (calculated)	1.370 Mg / m^3	
Absorption coefficient	0.200 mm^{-1}	
F(000)	904	
Crystal	Slab; colourless	
Crystal size	0.46 × 0.42 × 0.18 mm^3	
θ range for data collection	3.69 – 27.50°	
Index ranges	$-18 \le h \le 18$, $-22 \le k \le 22$, $-10 \le l \le 10$	
Reflections collected	22230	
Independent reflections	4655 [R_{int} = 0.0410]	
Completeness to $\theta = 27.50°$	99.6 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9649 and 0.9135	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4655 / 1 / 381	
Goodness-of-fit on F^2	1.037	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0316, $wR2$ = 0.0723	
R indices (all data)	$R1$ = 0.0385, $wR2$ = 0.0749	
Absolute structure parameter	0.00(5)	
Extinction coefficient	0.0050(11)	
Largest diff. peak and hole	0.244 and –0.222 e Å^{-3}	

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f*
C1	6510(1)	11488(1)	3888(2)	22(1)	1
C2	6612(2)	10267(1)	2269(2)	28(1)	1
C3	7046(1)	10740(1)	3631(2)	19(1)	1
C4	7080(1)	10266(1)	5206(2)	18(1)	1
C5	7598(1)	10632(1)	6651(2)	26(1)	1
C6	8507(1)	10176(1)	6755(2)	22(1)	1
C7	8223(1)	9385(1)	6101(2)	17(1)	1
C8	9025(1)	8907(1)	5364(2)	23(1)	1
C9	7805(1)	8883(1)	7460(2)	17(1)	1
C10	6670(1)	8001(1)	8651(2)	16(1)	1
C11	5739(1)	7619(1)	8190(2)	16(1)	1
C12	5760(1)	7468(1)	6368(2)	18(1)	1
C13	6450(1)	8427(1)	10261(2)	22(1)	1
C14	5454(1)	8144(1)	10643(2)	22(1)	1
C15	5506(1)	7275(1)	11018(2)	24(1)	1
C16	5671(1)	6904(1)	9315(2)	22(1)	1
C17	4987(1)	8165(1)	8945(2)	19(1)	1
C18	4913(1)	8983(1)	8245(2)	23(1)	1
C19	4002(1)	7821(1)	8891(3)	26(1)	1
N1	6966(1)	8498(1)	7259(2)	15(1)	1
O1	7977(1)	10963(1)	3191(2)	26(1)	1
O2	7567(1)	9548(1)	4850(1)	17(1)	1
O3	9529(1)	9309(1)	4153(2)	31(1)	1
O4	8222(1)	8817(1)	8755(1)	24(1)	1
O5	5838(1)	8808(1)	4844(1)	20(1)	1
O6	7136(1)	7903(1)	4385(1)	21(1)	1
S1	6445(1)	8218(1)	5455(1)	15(1)	1
O1S	9038(1)	9795(1)	1161(2)	30(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C3	1.520(2)	C4–O2	1.4545(19)
C1–H1A	0.94(2)	C4–C5	1.535(2)
C1–H1B	1.02(2)	C4–H4	1.069(18)
C1–H1C	0.95(2)	C5–C6	1.527(3)
C2–C3	1.517(2)	C5–H5A	1.02(2)
C2–H2A	0.90(2)	C5–H5B	1.00(2)
C2–H2B	1.00(2)	C6–C7	1.526(2)
C2–H2C	0.99(2)	C6–H6A	1.005(16)
C3–O1	1.437(2)	C6–H6B	0.96(2)
C3–C4	1.529(2)	C7–O2	1.4196(19)

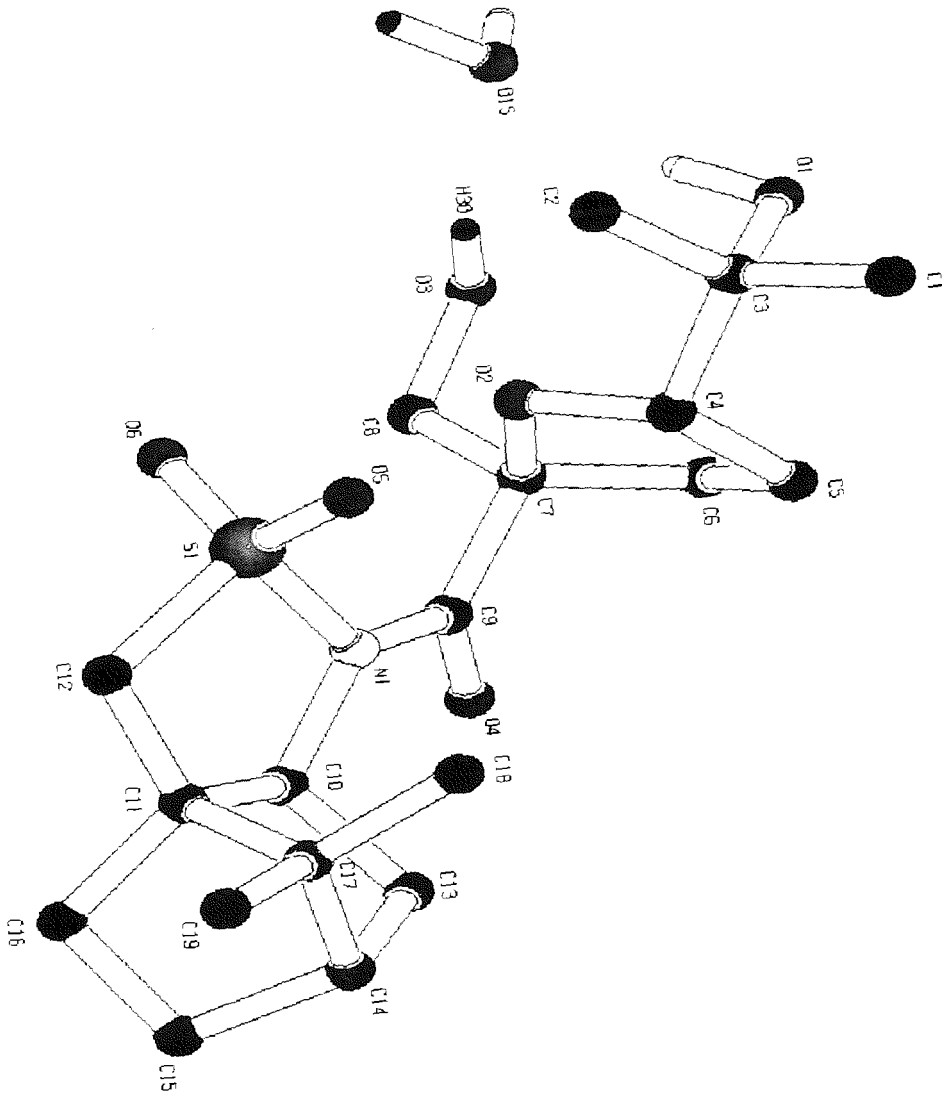
C7–C9	1.534(2)	H1A–C1–H1C	111.9(18)
C7–C8	1.540(2)	H1B–C1–H1C	105.3(16)
C8–O3	1.410(2)	C3–C2–H2A	110.6(12)
C8–H8A	0.99(2)	C3–C2–H2B	108.8(13)
C8–H8B	1.005(16)	H2A–C2–H2B	108.2(18)
C9–O4	1.223(2)	C3–C2–H2C	108.0(12)
C9–N1	1.385(2)	H2A–C2–H2C	110.1(17)
C10–N1	1.491(2)	H2B–C2–H2C	111.2(18)
C10–C11	1.537(2)	O1–C3–C2	109.99(15)
C10–C13	1.543(2)	O1–C3–C1	105.95(14)
C10–H10	0.976(17)	C2–C3–C1	110.77(15)
C11–C12	1.515(2)	O1–C3–C4	109.02(13)
C11–C16	1.546(2)	C2–C3–C4	110.11(14)
C11–C17	1.563(2)	C1–C3–C4	110.90(14)
C12–S1	1.7915(17)	O2–C4–C3	107.77(12)
C12–H12A	0.940(18)	O2–C4–C5	105.94(13)
C12–H12B	0.983(18)	C3–C4–C5	116.39(14)
C13–C14	1.543(2)	O2–C4–H4	114.0(9)
C13–H13A	0.96(2)	C3–C4–H4	114.1(9)
C13–H13B	0.952(19)	C5–C4–H4	98.3(9)
C14–C15	1.537(2)	C6–C5–C4	104.09(14)
C14–C17	1.545(2)	C6–C5–H5A	109.8(12)
C14–H14	0.991(18)	C4–C5–H5A	109.1(12)
C15–C16	1.554(2)	C6–C5–H5B	110.6(12)
C15–H15A	0.931(19)	C4–C5–H5B	111.9(12)
C15–H15B	1.00(2)	H5A–C5–H5B	111.1(17)
C16–H16A	1.00(2)	C7–C6–C5	102.45(14)
C16–H16B	0.969(18)	C7–C6–H6A	110.3(9)
C17–C18	1.530(2)	C5–C6–H6A	107.2(9)
C17–C19	1.533(2)	C7–C6–H6B	111.4(13)
C18–H18A	1.02(2)	C5–C6–H6B	113.9(12)
C18–H18B	1.00(2)	H6A–C6–H6B	111.1(15)
C18–H18C	0.97(2)	O2–C7–C6	104.61(13)
C19–H19A	1.02(2)	O2–C7–C9	112.15(12)
C19–H19B	1.02(2)	C6–C7–C9	110.92(14)
C19–H19C	0.98(2)	O2–C7–C8	108.67(13)
N1–S1	1.7256(13)	C6–C7–C8	114.77(14)
O1–H1O	0.94(3)	C9–C7–C8	105.85(13)
O3–H3O	0.902(10)	O3–C8–C7	113.22(14)
O5–S1	1.4312(12)	O3–C8–H8A	108.1(11)
O6–S1	1.4321(12)	C7–C8–H8A	108.2(11)
O1S–H1S	0.71(3)	O3–C8–H8B	107.2(9)
O1S–H2S	1.09(4)	C7–C8–H8B	115.2(9)
C3–C1–H1A	110.8(14)	H8A–C8–H8B	104.3(14)
C3–C1–H1B	107.8(12)	O4–C9–N1	118.89(15)
H1A–C1–H1B	109.1(19)	O4–C9–C7	119.42(14)
C3–C1–H1C	111.7(11)	N1–C9–C7	121.69(14)

N1–C10–C11	107.94(12)	C11–C16–H16A	109.2(11)
N1–C10–C13	115.85(14)	C15–C16–H16A	112.0(11)
C11–C10–C13	103.75(13)	C11–C16–H16B	111.0(11)
N1–C10–H10	105.6(10)	C15–C16–H16B	114.2(11)
C11–C10–H10	110.8(10)	H16A–C16–H16B	108.0(15)
C13–C10–H10	112.9(11)	C18–C17–C19	106.50(15)
C12–C11–C10	107.39(13)	C18–C17–C14	112.95(14)
C12–C11–C16	116.74(14)	C19–C17–C14	114.64(14)
C10–C11–C16	104.65(13)	C18–C17–C11	117.32(14)
C12–C11–C17	120.52(14)	C19–C17–C11	112.97(14)
C10–C11–C17	104.06(12)	C14–C17–C11	92.38(12)
C16–C11–C17	101.81(13)	C17–C18–H18A	106.9(12)
C11–C12–S1	107.27(11)	C17–C18–H18B	110.3(11)
C11–C12–H12A	111.6(11)	H18A–C18–H18B	111.0(16)
S1–C12–H12A	108.4(11)	C17–C18–H18C	114.0(12)
C11–C12–H12B	116.2(10)	H18A–C18–H18C	107.6(18)
S1–C12–H12B	104.1(10)	H18B–C18–H18C	107.0(16)
H12A–C12–H12B	108.8(15)	C17–C19–H19A	113.5(11)
C14–C13–C10	102.19(13)	C17–C19–H19B	109.6(11)
C14–C13–H13A	115.6(12)	H19A–C19–H19B	108.0(16)
C10–C13–H13A	109.8(12)	C17–C19–H19C	112.0(13)
C14–C13–H13B	112.4(12)	H19A–C19–H19C	105.5(17)
C10–C13–H13B	110.7(11)	H19B–C19–H19C	108.0(17)
H13A–C13–H13B	106.3(17)	C9–N1–C10	115.75(13)
C15–C14–C13	107.91(14)	C9–N1–S1	127.86(11)
C15–C14–C17	102.96(14)	C10–N1–S1	111.67(10)
C13–C14–C17	102.21(13)	C3–O1–H1O	107.4(18)
C15–C14–H14	115.6(10)	C7–O2–C4	110.13(12)
C13–C14–H14	113.6(10)	C8–O3–H3O	112(3)
C17–C14–H14	113.2(10)	O5–S1–O6	118.63(7)
C14–C15–C16	103.42(13)	O5–S1–N1	111.31(7)
C14–C15–H15A	110.7(11)	O6–S1–N1	109.32(7)
C16–C15–H15A	111.0(11)	O5–S1–C12	109.23(8)
C14–C15–H15B	108.7(11)	O6–S1–C12	110.99(8)
C16–C15–H15B	109.6(11)	N1–S1–C12	94.81(7)
H15A–C15–H15B	113.0(15)	H1S–O1S–H2S	101(3)
C11–C16–C15	102.36(13)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	22(1)	18(1)	27(1)	3(1)	−2(1)	1(1)
C2	37(1)	24(1)	24(1)	1(1)	−10(1)	0(1)
C3	18(1)	18(1)	20(1)	2(1)	−1(1)	−2(1)
C4	20(1)	18(1)	17(1)	0(1)	1(1)	3(1)
C5	30(1)	26(1)	23(1)	−3(1)	−5(1)	5(1)
C6	22(1)	21(1)	24(1)	1(1)	−3(1)	−5(1)
C7	15(1)	20(1)	15(1)	3(1)	−4(1)	−2(1)
C8	17(1)	27(1)	23(1)	7(1)	4(1)	1(1)
C9	15(1)	18(1)	19(1)	0(1)	1(1)	0(1)
C10	18(1)	19(1)	12(1)	3(1)	1(1)	−1(1)
C11	18(1)	14(1)	15(1)	−1(1)	2(1)	−1(1)
C12	23(1)	15(1)	16(1)	−2(1)	1(1)	−2(1)
C13	27(1)	25(1)	14(1)	−3(1)	2(1)	−5(1)
C14	26(1)	23(1)	17(1)	−2(1)	8(1)	0(1)
C15	28(1)	26(1)	18(1)	5(1)	4(1)	−1(1)
C16	28(1)	18(1)	20(1)	4(1)	3(1)	−2(1)
C17	21(1)	16(1)	21(1)	0(1)	6(1)	1(1)
C18	24(1)	17(1)	28(1)	1(1)	7(1)	5(1)
C19	23(1)	27(1)	29(1)	4(1)	5(1)	0(1)
N1	16(1)	18(1)	11(1)	1(1)	−1(1)	−1(1)
O1	23(1)	23(1)	33(1)	2(1)	9(1)	−3(1)
O2	17(1)	17(1)	16(1)	2(1)	−2(1)	3(1)
O3	21(1)	42(1)	29(1)	12(1)	7(1)	2(1)
O4	23(1)	31(1)	18(1)	6(1)	−6(1)	−5(1)
O5	18(1)	20(1)	22(1)	5(1)	−5(1)	−2(1)
O6	24(1)	24(1)	15(1)	−2(1)	4(1)	1(1)
S1	17(1)	16(1)	13(1)	0(1)	−1(1)	0(1)


O15
O1
C2
C1
H30
O3
C3
O2
C4
C8
C5
O6
O5
C7
C6
S1
C9
N1
O4
C12
C18
C10
C11
C17
C13
C19
C16
C14
C15

***N*-[(2*S*)-2-hydroxy-2-((2*R*,2'*R*,5*S*)-2',5-dimethyl-5'-oxo-octahydro-[2,2']bifuranyl-5-yl)ethanoyl] camphor-10,2-sultam (314d)**

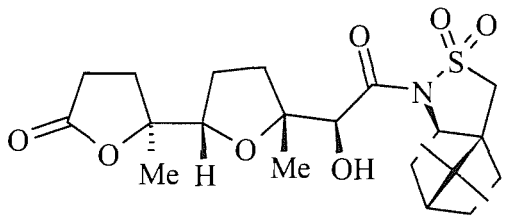


Table 1. Crystal data and structure refinement.

Empirical formula	$C_{22}H_{33}NO_7S$	
Formula weight	455.55	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.9402(7) Å	α = 90°
	b = 7.8852(5) Å	β = 95.159(2)°
	c = 11.9838(9) Å	γ = 90°
Volume	1123.71(13) Å^3	
Z	2	
Density (calculated)	1.346 Mg / m^3	
Absorption coefficient	0.187 mm^{-1}	
F(000)	488	
Crystal	Needle; Colourless	
Crystal size	0.32 × 0.02 × 0.01 mm^3	
θ range for data collection	3.10 – 25.03°	
Index ranges	$-14 \le h \le 14$, $-9 \le k \le 9$, $-11 \le l \le 14$	
Reflections collected	7943	
Independent reflections	3821 [R_{int} = 0.0905]	
Completeness to θ = 25.03°	99.8 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9981 and 0.9425	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3821 / 1 / 286	
Goodness-of-fit on F^2	1.002	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0738, $wR2$ = 0.1040	
R indices (all data)	$R1$ = 0.1480, $wR2$ = 0.1235	
Absolute structure parameter	0.04(14)	
Extinction coefficient	0.0129(18)	
Largest diff. peak and hole	0.261 and –0.256 e Å^{-3}	

Special details: All hydrogen atoms were fixed.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f*
S1	6366(1)	12052(2)	11058(1)	28(1)	1
O1	6444(3)	13730(4)	10595(3)	34(1)	1
O4	8401(3)	14891(5)	11997(3)	39(1)	1
O2	5705(3)	11872(5)	11990(3)	32(1)	1
N1	7685(3)	11302(5)	11399(4)	24(1)	1
O3	9176(3)	11007(4)	12672(3)	39(1)	1
O6	5897(3)	16091(5)	13977(3)	35(1)	1
O5	8246(3)	15607(4)	14300(3)	31(1)	1
O7	5732(3)	17033(6)	12204(3)	48(1)	1
C2	7065(4)	9576(7)	9797(5)	26(1)	1
C7	7890(4)	9661(7)	10859(5)	26(1)	1
C17	7546(5)	15348(7)	15198(5)	32(2)	1
C18	6534(4)	16507(6)	15041(5)	30(2)	1
C8	7777(4)	10241(6)	8851(5)	29(1)	1
C9	7203(5)	9977(6)	7672(5)	37(2)	1
C1	5996(4)	10493(6)	10015(5)	27(1)	1
C13	8697(4)	14014(6)	13929(5)	29(1)	1
C11	8382(4)	11860(7)	12320(4)	28(1)	1
C12	8090(4)	13628(6)	12786(5)	30(1)	1
C5	8744(5)	8987(7)	9175(5)	36(2)	1
C10	8120(4)	12131(7)	8906(5)	40(2)	1
C14	9968(4)	14238(7)	13913(5)	43(2)	1
C20	6876(5)	18371(6)	14922(5)	30(2)	1
C4	8151(4)	7258(7)	9143(5)	38(2)	1
C3	6961(4)	7702(6)	9514(5)	29(2)	1
C22	6130(4)	17201(8)	13162(5)	34(1)	1
C16	7302(5)	13452(7)	15204(5)	41(2)	1
C6	9068(4)	9448(7)	10420(5)	37(2)	1
C21	6876(5)	18592(7)	13652(5)	36(2)	1
C19	5771(5)	16220(8)	15969(5)	45(2)	1
C15	8388(5)	12721(7)	14810(5)	41(2)	1

Table 3. Bond lengths [Å] and angles [°].

S1–O2	1.431(3)	N1–C7	1.477(6)
S1–O1	1.441(4)	O3–C11	1.207(6)
S1–N1	1.698(4)	O6–C22	1.358(7)
S1–C1	1.780(5)	O6–C18	1.462(6)
O4–C12	1.445(6)	O5–C17	1.435(6)
O4–H4	0.8400	O5–C13	1.452(6)
N1–C11	1.393(6)	O7–C22	1.210(6)

C2–C1	1.509(7)	C21–H21A	0.9900
C2–C3	1.519(7)	C21–H21B	0.9900
C2–C7	1.540(7)	C19–H19A	0.9800
C2–C8	1.566(8)	C19–H19B	0.9800
C7–C6	1.554(7)	C19–H19C	0.9800
C7–H7	1.0000	C15–H15A	0.9900
C17–C18	1.513(7)	C15–H15B	0.9900
C17–C16	1.524(7)	O2–S1–O1	116.8(2)
C17–H17	1.0000	O2–S1–N1	110.0(2)
C18–C19	1.517(7)	O1–S1–N1	108.8(2)
C18–C20	1.535(7)	O2–S1–C1	111.1(2)
C8–C9	1.528(7)	O1–S1–C1	112.6(3)
C8–C5	1.543(7)	N1–S1–C1	95.4(2)
C8–C10	1.545(8)	C12–O4–H4	109.5
C9–H9A	0.9800	C11–N1–C7	120.8(4)
C9–H9B	0.9800	C11–N1–S1	123.8(4)
C9–H9C	0.9800	C7–N1–S1	112.8(3)
C1–H1A	0.9900	C22–O6–C18	111.0(4)
C1–H1B	0.9900	C17–O5–C13	111.3(4)
C13–C12	1.522(7)	C1–C2–C3	116.8(4)
C13–C14	1.530(7)	C1–C2–C7	108.9(4)
C13–C15	1.537(7)	C3–C2–C7	105.1(4)
C11–C12	1.553(7)	C1–C2–C8	119.2(5)
C12–H12	1.0000	C3–C2–C8	101.7(4)
C5–C4	1.535(7)	C7–C2–C8	103.6(4)
C5–C6	1.550(8)	N1–C7–C2	106.3(4)
C5–H5	1.0000	N1–C7–C6	115.7(4)
C10–H10A	0.9800	C2–C7–C6	104.3(4)
C10–H10B	0.9800	N1–C7–H7	110.1
C10–H10C	0.9800	C2–C7–H7	110.1
C14–H14A	0.9800	C6–C7–H7	110.1
C14–H14B	0.9800	O5–C17–C18	109.4(4)
C14–H14C	0.9800	O5–C17–C16	105.5(5)
C20–C21	1.531(7)	C18–C17–C16	116.3(5)
C20–H20A	0.9900	O5–C17–H17	108.4
C20–H20B	0.9900	C18–C17–H17	108.4
C4–C3	1.567(7)	C16–C17–H17	108.4
C4–H4A	0.9900	O6–C18–C17	108.6(4)
C4–H4B	0.9900	O6–C18–C19	107.9(4)
C3–H3A	0.9900	C17–C18–C19	110.1(5)
C3–H3B	0.9900	O6–C18–C20	104.8(4)
C22–C21	1.499(8)	C17–C18–C20	111.9(4)
C16–C15	1.532(7)	C19–C18–C20	113.2(5)
C16–H16A	0.9900	C9–C8–C5	114.1(4)
C16–H16B	0.9900	C9–C8–C10	105.4(4)
C6–H6A	0.9900	C5–C8–C10	114.7(4)
C6–H6B	0.9900	C9–C8–C2	113.3(4)

C5–C8–C2	92.6(4)
C10–C8–C2	116.8(4)
C8–C9–H9A	109.5
C8–C9–H9B	109.5
H9A–C9–H9B	109.5
C8–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
C2–C1–S1	107.0(4)
C2–C1–H1A	110.3
S1–C1–H1A	110.3
C2–C1–H1B	110.3
S1–C1–H1B	110.3
H1A–C1–H1B	108.6
O5–C13–C12	106.8(4)
O5–C13–C14	107.5(4)
C12–C13–C14	113.9(5)
O5–C13–C15	104.2(4)
C12–C13–C15	111.2(5)
C14–C13–C15	112.6(5)
O3–C11–N1	119.7(5)
O3–C11–C12	124.7(5)
N1–C11–C12	115.5(5)
O4–C12–C13	108.7(4)
O4–C12–C11	107.7(4)
C13–C12–C11	113.5(4)
O4–C12–H12	108.9
C13–C12–H12	108.9
C11–C12–H12	108.9
C4–C5–C8	103.3(4)
C4–C5–C6	107.9(5)
C8–C5–C6	102.0(4)
C4–C5–H5	114.1
C8–C5–H5	114.1
C6–C5–H5	114.1
C8–C10–H10A	109.5
C8–C10–H10B	109.5
H10A–C10–H10B	109.5
C8–C10–H10C	109.5
H10A–C10–H10C	109.5
H10B–C10–H10C	109.5
C13–C14–H14A	109.5
C13–C14–H14B	109.5
H14A–C14–H14B	109.5
C13–C14–H14C	109.5
H14A–C14–H14C	109.5
H14B–C14–H14C	109.5
C21–C20–C18	103.0(5)
C21–C20–H20A	111.2
C18–C20–H20A	111.2
C21–C20–H20B	111.2
C18–C20–H20B	111.2
H20A–C20–H20B	109.1
C5–C4–C3	102.8(4)
C5–C4–H4A	111.2
C3–C4–H4A	111.2
C5–C4–H4B	111.2
C3–C4–H4B	111.2
H4A–C4–H4B	109.1
C2–C3–C4	102.9(4)
C2–C3–H3A	111.2
C4–C3–H3A	111.2
C2–C3–H3B	111.2
C4–C3–H3B	111.2
H3A–C3–H3B	109.1
O7–C22–O6	121.6(6)
O7–C22–C21	128.4(6)
O6–C22–C21	110.0(5)
C17–C16–C15	101.6(5)
C17–C16–H16A	111.5
C15–C16–H16A	111.5
C17–C16–H16B	111.5
C15–C16–H16B	111.5
H16A–C16–H16B	109.3
C5–C6–C7	101.3(4)
C5–C6–H6A	111.5
C7–C6–H6A	111.5
C5–C6–H6B	111.5
C7–C6–H6B	111.5
H6A–C6–H6B	109.3
C22–C21–C20	104.6(5)
C22–C21–H21A	110.8
C20–C21–H21A	110.8
C22–C21–H21B	110.8
C20–C21–H21B	110.8
H21A–C21–H21B	108.9
C18–C19–H19A	109.5
C18–C19–H19B	109.5
H19A–C19–H19B	109.5
C18–C19–H19C	109.5
H19A–C19–H19C	109.5
H19B–C19–H19C	109.5
C16–C15–C13	102.9(4)
C16–C15–H15A	111.2

C13–C15–H15A	111.2	C13–C15–H15B	111.2
C16–C15–H15B	111.2	H15A–C15–H15B	109.1

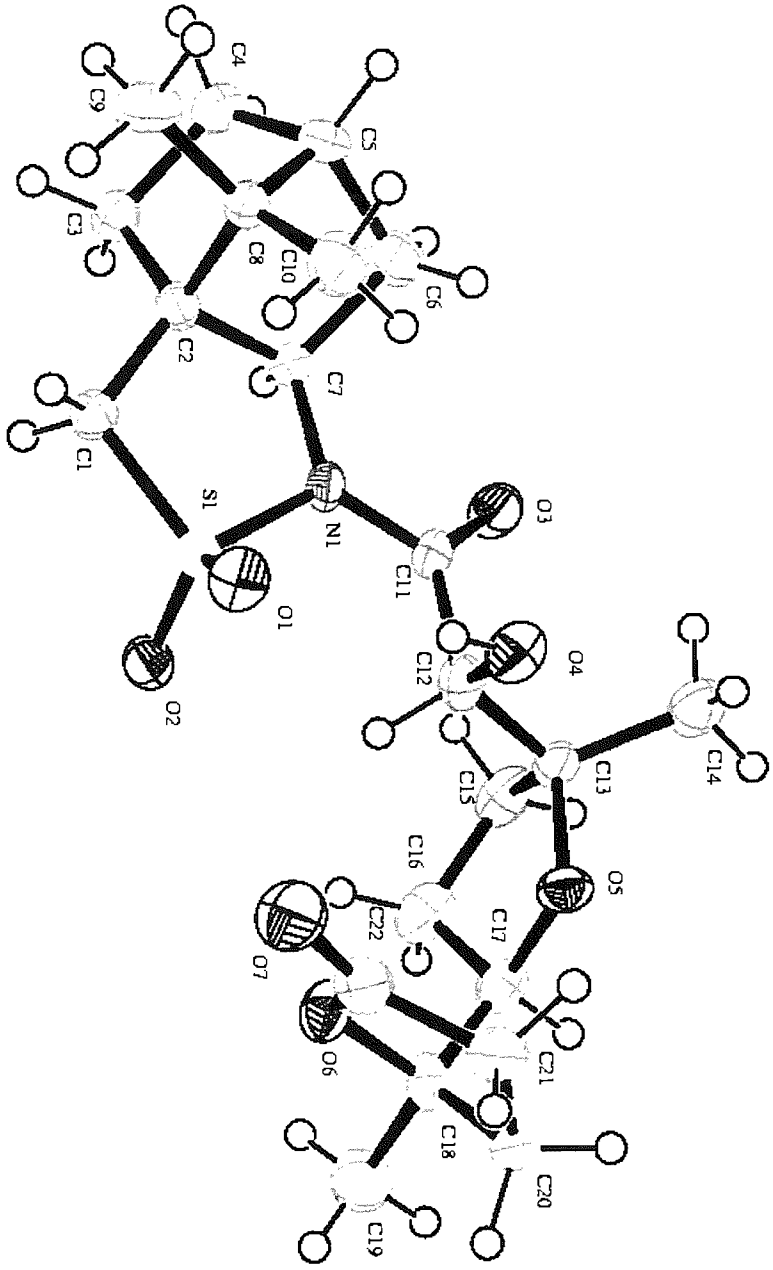
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	25(1)	28(1)	31(1)	−1(1)	0(1)	2(1)
O1	37(2)	27(2)	38(3)	6(2)	−2(2)	2(2)
O4	44(3)	38(2)	33(3)	−2(2)	0(2)	−4(2)
O2	26(2)	41(2)	29(2)	−1(2)	3(2)	−1(2)
N1	18(2)	24(2)	29(3)	−2(2)	−4(2)	−2(2)
O3	33(2)	34(2)	47(3)	−10(2)	−9(2)	10(2)
O6	34(2)	42(3)	28(3)	0(2)	−3(2)	−7(2)
O5	34(2)	26(2)	33(3)	−6(2)	4(2)	5(2)
O7	47(2)	61(3)	35(3)	−2(3)	−5(2)	6(3)
C2	20(3)	35(3)	24(4)	0(3)	2(3)	−1(3)
C7	27(3)	26(3)	25(4)	−5(3)	4(3)	−1(2)
C17	36(3)	33(3)	26(4)	−2(3)	−1(3)	−4(3)
C18	24(3)	35(3)	29(4)	3(3)	−2(3)	−4(2)
C8	27(3)	35(3)	25(4)	−6(3)	4(3)	−8(3)
C9	47(4)	36(4)	29(4)	1(3)	13(3)	4(3)
C1	26(3)	25(3)	29(4)	−2(3)	2(3)	−1(3)
C13	25(3)	22(3)	38(4)	−9(3)	−6(3)	7(2)
C11	24(3)	26(3)	32(4)	−6(3)	1(3)	−6(3)
C12	27(3)	25(3)	37(4)	2(3)	−1(3)	−2(3)
C5	27(3)	51(4)	32(4)	−13(3)	7(3)	4(3)
C10	40(3)	43(3)	38(4)	3(4)	7(3)	−8(3)
C14	38(4)	34(3)	55(5)	−12(3)	−6(3)	6(3)
C20	28(3)	29(3)	32(4)	−9(3)	4(3)	2(3)
C4	34(3)	40(4)	39(4)	−15(3)	1(3)	2(3)
C3	29(3)	26(3)	31(4)	−2(3)	−2(3)	0(2)
C22	32(3)	36(3)	33(4)	1(4)	−4(3)	8(3)
C16	54(4)	34(3)	33(4)	2(3)	4(3)	−10(3)
C6	28(3)	35(3)	47(4)	−6(3)	1(3)	8(3)
C21	37(4)	37(3)	33(4)	−2(3)	4(3)	4(3)
C19	44(4)	61(4)	32(4)	−2(3)	9(3)	−5(3)
C15	49(4)	29(3)	42(5)	−3(3)	−12(3)	1(3)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f*
H4	7885	14986	11476	58	1
H7	7743	8707	11376	31	1
H17	7987	15651	15919	39	1
H9A	7695	10392	7119	55	1
H9B	6492	10605	7593	55	1
H9C	7054	8767	7547	55	1
H1A	5443	9686	10282	32	1
H1B	5660	11038	9320	32	1
H12	7260	13690	12841	36	1
H5	9381	9059	8690	44	1
H10A	8649	12360	8345	60	1
H10B	8480	12390	9654	60	1
H10C	7450	12840	8755	60	1
H14A	10120	15122	13372	64	1
H14B	10303	13166	13696	64	1
H14C	10295	14569	14661	64	1
H20A	6326	19140	15230	36	1
H20B	7631	18588	15306	36	1
H4A	8551	6448	9670	45	1
H4B	8094	6770	8379	45	1
H3A	6365	7500	8899	35	1
H3B	6793	7029	10177	35	1
H16A	6642	13161	14680	49	1
H16B	7176	13047	15964	49	1
H6A	9507	10514	10491	44	1
H6B	9502	8527	10818	44	1
H21A	6575	19718	13415	43	1
H21B	7646	18476	13417	43	1
H19A	5136	17012	15879	68	1
H19B	6195	16411	16697	68	1
H19C	5489	15053	15932	68	1
H15A	8260	11582	14475	49	1
H15B	8986	12644	15437	49	1


C4
C9
C5
C3
C8
C10
C6
C2
C7
C1
S1
N1
O3
C11
O1
O4
O2
C12
C14
C13
C15
C16
O5
C22
C17
O7
O6
C21
C18
C20
C19

Chapter 8: References

1. Chavez, D.; Acevedo, L. A.; Mata, R. J. *J. Nat. Prod.* **1998**, *61*, 419-423.
2. Leboeuf, M.; Cave, A.; Bhaumik, P. K.; Mukherjee, B.; Mukherjee, R. *Phytochemistry* **1982**, *21*, 2783-2813.
3. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504-540.
4. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275-306.
5. Fang, X. P.; Rieser, M. J.; Gu, Z. M.; Zhao, G. X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27-67.
6. Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711-54.
7. Kötz, A.; Steche, T. *J. Parkt. Chem.* **1924**, *107*, 193-195.
8. Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353-2358.
9. Walba, D. M.; Wand, M.; Wilkes, M. *J. Am. Chem. Soc.* **1979**, *101*, 4396-4397.
10. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120-8.
11. Baldwin, J. E.; Crossley, M. J.; Lehtonen, E. M. M. *J. Chem. Soc., Chem. Comm.* **1979**, 918-920.
12. Lee, D. G.; Brownridge, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 3033-4.
13. Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940-941.
14. Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731-734.
15. Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624-5625.
16. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
17. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*.
18. Oppolzer, W.; Barras, J. P. *Helv. Chim. Acta* **1987**, *70*, 1666-1675.
19. Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; DeBrabander, J. *Helv. Chim. Acta* **1997**, *80*, 1319-1337.
20. Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531-3534.
21. Gale, J. B.; Yu, J. G.; Hu, X. F. E.; Khare, A.; Ho, D. K.; Cassady, J. M. *Tetrahedron Lett.* **1993**, *34*, 5847-5850.
22. Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc. Perkin Trans. 1* **1998**, 9-39.

23. Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *Chem. Commun.* **2000**, 1735-1736.
24. Brown, R. C. D.; Keily, J. F. *Angew. Chem. Int. Ed.* **2001**, *40*, 4496-4498.
25. Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715-3718.
26. Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368-3374.
27. Cecil, A. R. L.; Brown, R. C. D. *Tetrahedron Lett.* **2004**, *45*, 7269-7271.
28. de Champdoré, M.; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781-9784.
29. Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971-974.
30. Donohoe, T. J.; Butterworth, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 948-951.
31. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3937-3938.
32. Piccialli, V.; Cavallo, N. *Tetrahedron Lett.* **2001**, *42*, 4695-4699.
33. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2002**, *43*, 9265-9269.
34. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2003**, *44*, 3429.
35. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. *Tetrahedron Lett.* **2003**, *44*, 5499-5503.
36. Piccialli, V. *Tetrahedron Lett.* **2000**, *41*, 3731-3733.
37. McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683-7686.
38. Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729-3732.
39. Tang, S. H.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299-5302.
40. Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133-5136.
41. Tang, S. H.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303-5306.
42. Sinha, S. C.; Sinhabagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447-1448.
43. McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750-5751.
44. Sinha, S. C.; Sinha, A.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014-12015.
45. Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633-1634.
46. Morimoto, Y.; Kinoshita, T.; Iwai, T. *Chirality* **2002**, *14*, 578-586.
47. Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 9076-9077.
48. Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792-6797.

49. D'Souza, L. J.; Sinha, S. C.; Lu, S.-F.; Keinam, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255-5262.
50. Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035-6051.
51. Sinha, S. C.; Sinha, A.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017-4018.
52. Kurth, M. J.; Rodriguez, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7577-7578.
53. Beebe, X.; Kurth, M. J.; Schore, N. E. *J. Am. Chem. Soc.* **1992**, *114*, 10061-10062.
54. Beebe, X.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4196-4203.
55. Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636-5637.
56. Hudson, C. M.; Moeller, K. D. *J. Am. Chem. Soc.* **1994**, *116*, 3347-3356.
57. Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101-10111.
58. Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372-7375.
59. Deslongchamps, P. *Stereoelectronics Effects in Organic Synthesis* **1983**, Pergamon Press: Oxford U.K. , 32-33.
60. Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153-156.
61. Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065-5066.
62. Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685-2688.
63. Liu, B.; Moeller, K. D. *Tetrahedron Lett.* **2001**, *42*, 7163-7165.
64. Sun, Y.; Liu, B.; Kao, J.; D.A., d. A.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 1729-1732.
65. Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food. Chem.* **1974**, *22*, 379-385.
66. Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727-730.
67. Stork, G.; Cgregson, M.; Grieco, P. A. *Tetrahedron Lett.* **1969**, 1391-1392.
68. McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921-7922.
69. Corey, E. J.; Ha, D. C. *Tetrahedron Lett.* **1988**, *29*, 3171-3174.
70. McDonald, F. E.; Schultz, C. C. *Tetrahedron* **1997**, *53*, 16435-16448.
71. Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2741-2744.
72. Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5947-5948.
73. Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299-2311.

74. Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1987**, *28*, 5665-5668.

75. Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587-1590.

76. Hanessian, S.; Cooke, N. G.; Dehoff, B. S.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276-5290.

77. Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2473.

78. Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083-1085.

79. Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124-7125.

80. Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M.; Yoon, S. K. *Tetrahedron Lett.* **1992**, *33*, 1553-1556.

81. Iqbal, J.; Pandey, A.; Chauhan, B. P. S. *Tetrahedron* **1991**, *47*, 4143-4154.

82. Ting, P. C.; Barlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668-2669.

83. Bertrand, P.; Gesson, J. P. *Tetrahedron Lett.* **1992**, *33*, 5177-5180.

84. Kodama, M.; Yoshio, S.; Tabata, T.; Deguchi, Y.; Sekiya, Y. *Tetrahedron Lett.* **1997**, *38*, 4627-4630.

85. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

86. Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 67-70.

87. Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449-451.

88. Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron Lett.* **1999**, *40*, 977-981.

89. Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 667-670.

90. Wang, Z.-M.; Tian, S.-K.; Shi, M. *Eur. J. Org. Chem.* **2000**, 349-356.

91. Tian, S.-K.; Wang, T. L.; Jiang, J.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2551-2562.

92. Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.

93. Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455-4458.

94. Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695-698.

95. Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, *55*, 13471-13494.

96. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963-3964.

97. White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4109-4112.

98. Zhang, H. P.; Mootoo, D. R. *J. Org. Chem.* **1995**, *60*, 8134-8135.

99. Zhang, H. P.; Seepersaud, M.; Seepersaud, S.; Mootoo, D. R. *J. Org. Chem.* **1998**, *63*, 2049-2052.

100. Dabideen, D.; Mootoo, D. R. *Tetrahedron Lett.* **2003**, *44*, 8365-8368.

101. Wilson, P.; Shan, W.; Mootoo, D. R. *J. Carbohydr. Chem.* **1994**, *13*, 133.

102. Zhang, H. P.; Wilson, P.; Shan, W.; Ruan, Z. M.; Mootoo, D. R. *Tetrahedron Lett.* **1995**, *36*, 649-652.

103. Ruan, Z. M.; Dabideen, D.; Blumenstein, M.; Mootoo, D. R. *Tetrahedron* **2000**, *56*, 9203-9211.

104. Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *J. Chem. Soc., Chem. Comm.* **1979**, 610-611.

105. Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *Chem. Lett.* **1979**, 1359-1360.

106. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835-4841.

107. Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704-3706.

108. Scarborough Jr., R. M.; Smith III, A. B.; Barnette, W. E.; Nicolaou, K. C. *J. Org. Chem.* **1979**, *44*, 1742-744.

109. Uemura, S.; Toshimitsu, A.; Aoai, T.; Okano, M. *Tetrahedron Lett.* **1980**, *21*, 1533-1536.

110. Hatakeyma, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333-1336.

111. Matsuki, Y.; Komada, M.; Ito, S. *Tetrahedron Lett.* **1979**, *42*, 4081-4084.

112. Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023-1026.

113. Amouroux, R.; Folefoc, G.; Chastrette, F.; Chastrette, M. *Tetrahedron Lett.* **1981**, *22*, 2259-2262.

114. Alderice, M.; Spino, C.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1643-1648.

115. Alderice, M.; Spino, C.; Weiler, L. *Can. J. Chem.* **1993**, *71*, 1955-1961.

116. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *95*, 1082-1083.

117. Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431-1433.

118. Zoller, T.; Uguen, D.; DeCian, A.; Fischer, J.; Sable, S. *Tetrahedron Lett.* **1997**, *38*, 3409-3412.

119. Liddle, J.; Huffman, J. W. *Tetrahedron* **2001**, *57*, 7607-7612.

120. Marco, J. L.; Martin, N.; Martinezgrau, A.; Seoane, C.; Albert, A.; Cano, F. H. *Tetrahedron* **1994**, *50*, 3509-3528.

121. Weijard, J.; Wolf, F. J. *Organic Syntheses, Coll. Vol. 4*, 124.

122. Shing, T. K. M.; Wong, C. H.; Yip, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1323-1340.

123. Marco-Contelles, J.; Destabel, C.; Gallego, P.; Chiara, J. L.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 1354-1362.

124. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622-2624.

125. Ujihara, K.; Shirahama, H. *Tetrahedron Lett.* **1996**, *37*, 2039-2042.

126. Davies, S. G.; Epstein, E. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555-1565.

127. Liu, H.-J.; Luo, W. *Can. J. Chem.* **1992**, *70*, 128-134.

128. Miyata, O.; Fujiwara, Y.; Nishiguchi, A.; Honda, H.; Shinada, T.; Ninomiya, I.; Naito, T. *Synlett* **1994**, 637-638.

129. Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960-3961.

130. Suzuki, M.; Matsuo, Y.; Takeda, S.; Suzuki, T. *Phytochemistry* **1993**, *33*, 651-656.

131. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

132. Patois, C.; Savignac, P.; Aboutjaudet, E.; Collignon, N. *Synth. Commun.* **1991**, *21*, 2391-2396.

133. Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27-30.

134. Greca, M. D.; Monaco, P.; Pollio, A.; Previtera, L. *Phytochemistry* **1992**, *31*, 4119-4124.

135. Fischer, M. *PhD Thesis*, University of Southampton **2002**.

136. Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Muller, D.; Thormann, H.-J. *Tetrahedron* **2000**, *56*, 1081-1095.

137. Biellmann, J.; Ducep, J. *Tetrahedron* **1971**, *27*, 5861-5872.

138. Hioki, H.; Ooi, H.; Hamano, M.; Mimura, Y.; Yoshio, S.; Kodama, M.; Ohta, S.; Yanai, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 1235-1246.

139. Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616-2617.

140. Wipf, P.; Reeves, J. T.; Balachandran, R.; Guiliano, K. A.; Hamel, E.; Day, B. W. *J. Am. Chem. Soc.* **2000**, *122*, 9391-9395.

141. Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem. Int. Ed.* **1999**, *38*, 3207-3209.

142. McDonald, F. E.; Bravo, F. W., X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515-2523.

143. Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475-3478.

144. Hioki, H.; Yoshio, S.; Motosue, M.; Oshita, Y.; Nakamura, Y.; Mishima, D.; Fukuyama, Y.; Kodama, M.; Ueda, K.; Katsu, T. *Org. Lett.* **2004**, *6*, 961-964.

145. Polt, R.; Sames, D.; Chruma, J. *J. Org. Chem.* **1999**, *64*, 6147-6158.

146. Inoue, M.; Wang, J.; Wang, G.-X.; Ogasawara, Y.; Hirama, M. *Tetrahedron* **2003**, *59*, 5645-5659.

147. Smith III, A. B.; Wood, J. L.; Wong, W. Y.; Gould, A. E.; Rizzo, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 7425-7426.

148. Leanna, R. M.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029-5032.

149. Tanaka, H.; Sawayama, A. M.; Wandless, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 6864-6865.

150. Sotokawa, T.; Noda, T.; Pi, S.; Hirama, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 3430-3431.

151. Itokawa, H.; Kishi, E.; Morita, H.; Takeya, K.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1803-1804.

152. Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765-771.

153. Morimoto, Y.; Muragaki, K.; Iwai, T.; Morishita, Y.; Kinoshita, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4082-4084.

154. Vasil'ev, A. A.; Engman, L.; Serebryakov, E. P. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2211-2216.

155. Tsvetkov, Y. E.; Shashkov, A. S.; Knirel, Y. A.; Zahringer, U. *Carbohydr. Res.* **2001**, *335*, 221-243.

156. Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404-5406.

157. Cordero Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 3717-3719.

158. Bacqué, E.; Pautrat, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2312-2313.

159. Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877-5880.

160. Quiclet-Sire, B.; Wendeborn (née Bertrand), F.; Zard, S. Z. *Chem. Commun.* **2002**, 2214-2215.

161. Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166-7172.

162. Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949-6950.

163. Fernandez, C. N., O.; Rivas, E.; Montenegro, G.; Fontenla, J.A.; Fernandez-Mayoralas, A. *Carbohydr. Res.* **2000**, *327*, 353-?

164. Shimizu, H.; Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2001**, *57*, 1903-1908.

165. Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523-2533.

166. Horita, K.; Noda, I.; Tanaka, K.; Miura, T.; Oikawa, K.; Yonemitsu, O. *Tetrahedron* **1993**, *49*, 5979-5996.

167. O'Connor, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 2075-5077.

168. Smitt, O.; Högderg, H.-E. *Tetrahedron* **2002**, *58*, 7691-7700.

169. Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215-1217.

170. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, **1996**.

171. Naruta, N. *J. Org. Chem.* **1980**, *45*, 4097-4104.

172. Mori, K.; Fumaki, Y. *Tetrahedron* **1985**, *41*, 2369-2377.

173. Scheideman, M.; Shapland, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 10502-10503.

174. Oehlschlager, A. C.; Singh, S. M.; Sharma, S. *J. Org. Chem.* **1991**, *56*, 3856-3861.

175. Marshall, J. A.; Lebreton, J.; Dehoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883-3889.

176. Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269-5278.

177. Cane, D. E.; Iyengar, R.; Shiao, M. S. *J. Am. Chem. Soc.* **1981**, *103*, 914-931.

178. Gibbs, R. A.; Krishnan, U.; Dolence, J. M.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 7821-7829.

179. Fernandez, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235-246.

180. Xie, H.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. *J. Org. Chem.* **2000**, *65*, 8552-8563.

181. Yashwant, S.; Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568-1576.

182. Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1163-1166.