UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Chemistry

Towards Onnamide F; A Nematocide from the Marine Sponge *Trachycladus laevispirulifer*

by

Simon C. Rainbow

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ABSTRACT

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TOWARDS ONNAMIDE F; A NEMATOCIDE FROM THE MARINE SPONGE *TRACHYCLADUS LAEVISPIRULIFER*

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Onnamide F is a recently isolated natural product from the southern Australian marine sponge, *Trachycladus laevispirulifer*, that has shown significant antifungal and nematocidal activity.[1] Onnamide F contains a tetrahydropyran substructure, known as pederic acid, and an amide bond linkage to a second tetrahydropyran. To date no total synthesis of onnamide F has been reported.

A range of tetrahydropyrans with structural similarities to pederic acid were synthesised using a new Lewis acid mediated cyclisation reaction. Additionally, a diastereoselective route to tetrahydropyrans containing the *exo*-methylene functionality at C4 has been developed.

A useful new route to the pederic acid precursor pederamide has been established. The tetrahydropyran skeleton was formed by a new Lewis aicd mediated cyclisation reaction between 3,4-Dimethylpent-4-en-2-ol and *trans*-cinnamaldehyde, promoted by benzyltriethylammonium aluminium chloride. Further transformations gave us the opportunity to establish the correct oxidation level at the anomeric centre. Methyl ether formation followed by removal of the acetate group furnished a secondary alcohol which could be resolved via formation of the (+)-acetylmandelate ester. The enantiomerically pure tetrahydropyran was subjected to a Dess-Martin oxidation. Treatment with TMSCN followed by borax induced hydrolysis gave pederamide and its diastereoisomer.

List of Contents.

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Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
app	Apparent
aq	Aqueous
Bn	Benzyl
Bz	Benzoyl
BINOL	(+)-1,1'-Binaphthalene-2,2'-diol
Boc	*tert*-Butoxycarbonyl
Borax	disodium tetraborate
br	Broad
Bu	Butyl
conc	Concentrated
*m*CPBA	*meta*-Chloroperoxybenzoic acid
d	Doublet
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	Dihydropyran
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMPU	*N,N'*-Dimethyl-*N,N'*-propylene urea
DMSO	Dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Equiv	Equivalents
Et	Ethyl
h	Hours
HMDS	Hexamethyl disilazane
HMPA	Hexamethylphosphoramide

HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
IR	Infrared
LA	Lewis acid
LDA	Lithium diisopropylamide
LICKOR	Lithium-potassium alkoxide reagents
LRMS	Low resolution mass spectrometry
m	Multiplet
m.p.	Melting point
MAC	Masked acyl cyanides
Me	Methyl
Ms	Methanesulfonyl
MS	Mass spectrometry
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
n.O.e	Nuclear overhauser effect
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Piv	Pivaloyl
PMA	phosphomolybdic acid
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	Parts per million
PPy	Polypyrrole
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid
py	pyridine
q	Quartet
quant.	Quantitative yield
rt	room temperature

s	Singlet
SEM	2-Trimethylsilylethoxymethoxy
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Tf (OTf)	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	*p*-Toluenesulphonyl
UV	Ultraviolet
VAZO®	1,1'-Azobis(cyclohexanecarbonitrile)

1. Introduction.

Onnamide F **1.1** is a recently isolated natural product from the southern Australian marine sponge, *Trachycladus laevispirulifer*, that has shown significant antifungal and nematocidal activity.[1] Vuong *et al.* determined the structure of **1.1** using detailed spectroscopic analysis and chemical conversion to methyl ester **1.2** (Figure 1.1).[1] Onnamide F contains a common structural motif previously described in a number of natural products exhibiting interesting pharmacological activities, including the beetle chemical defense agent pederin **1.3**,[2,3] and the sponge metabolites the onnamides,[4] mycalamides [5-8] and theopederins.[9,10]

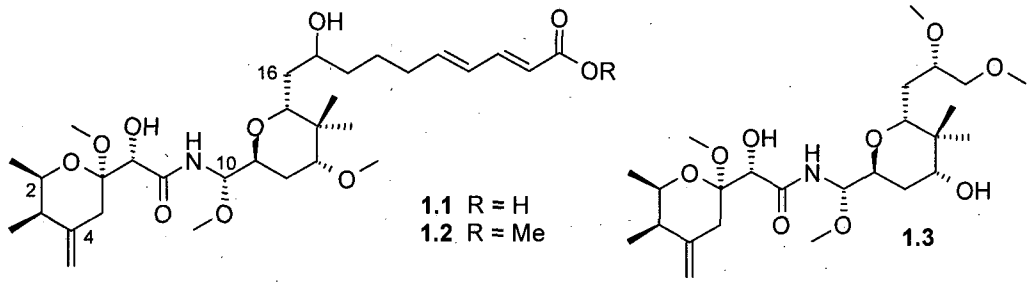
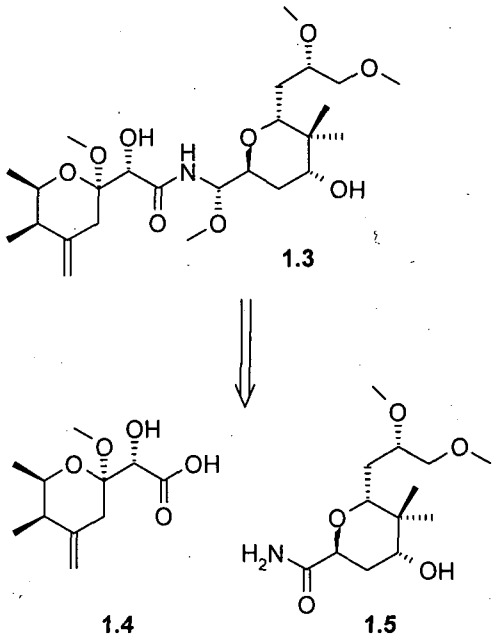


Figure 1.1. Structure of Onnamide F and Pederin.[1]

All of these related natural products include a tetrahydropyran substructure, known as pederic acid **1.4**, and an amide bond linkage to a second tetrahydropyran. The substituents on the second THP vary in each of the natural products. To date no total synthesis of onnamide F has been reported, though many syntheses of related natural products have been described.[11-34] In the majority of these syntheses, a convergent strategy is employed whereby the key fragments are connected through the amide bond (Scheme 1.1).

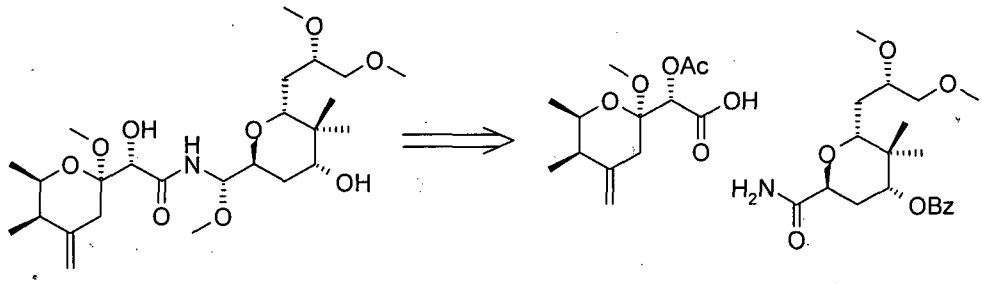


Scheme 1.1. The Retrosynthesis of Pederin.

1.1. The First Total Synthesis of Pederin.

Pederin **1.3** is a potent insect toxin isolated from the Staphylinid beetle *Paederus fuscipes*. It exhibits remarkable physiological activities, including inhibition of mitosis in HeLa cells and blocking protein synthesis in 80S ribosomes at a concentration of 1-10 ng/mL.[35-37] In 1952 the toxin was isolated by Pavan and Bo.[2,3] It was not until 1968 that the correct structure was elucidated and named pederin.

The first total synthesis of pederin **1.3** was achieved by Matsumoto and co-workers.[15] The pioneering work carried out by this group was designed to avoid problems associated with the high acid lability of the homoallylic acetal array in the pederic acid ring. The stereoselective synthesis of the two tetrahydropyran moieties, (+)-acetylpederic acid **1.7** and (+)-benzoylpedamide **1.8** was successfully achieved.[11,38,39] A convergent strategy was used to connect the tetrahydropyran moieties through an *N*-(1-methoxyalkyl)amide linkage (Scheme 1.2).



1.3 1.7 1.8

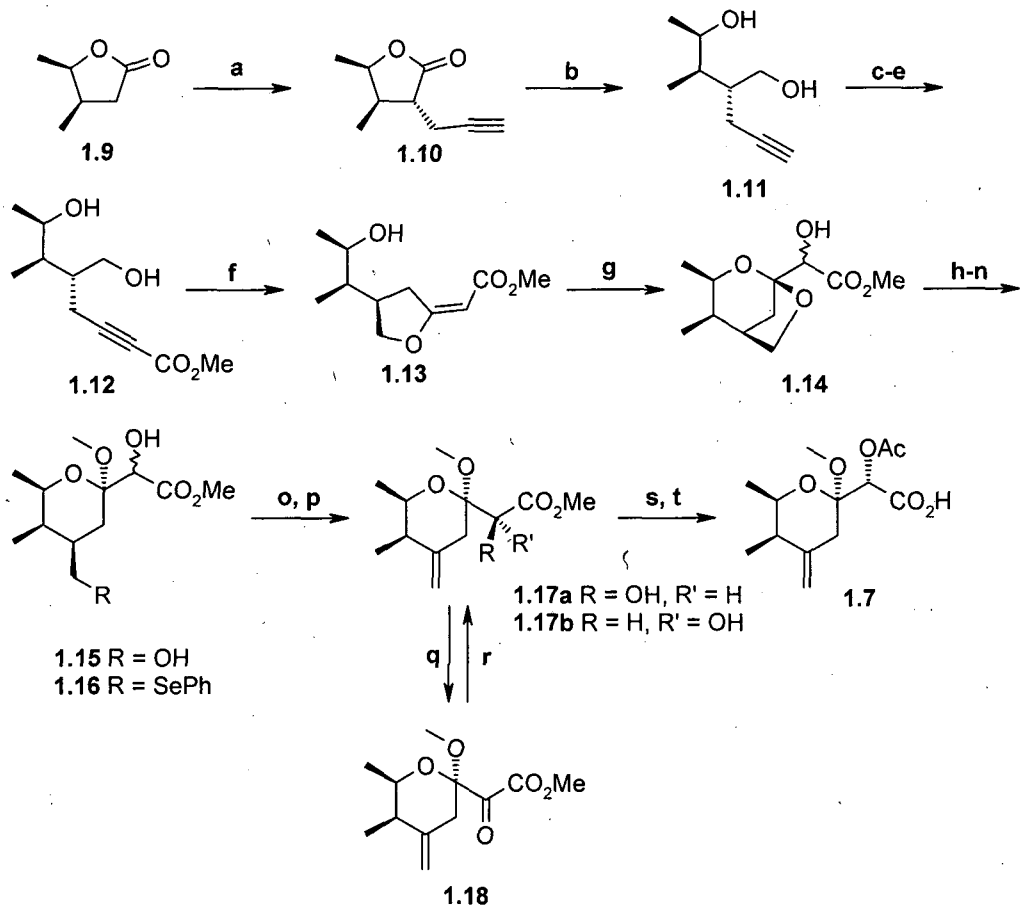
Scheme 1.2. Matsumoto's Retrosynthesis of Pederin

γ-Lactone **1.9** was the starting point of the synthesis of (+)-acetylpederic acid **1.7** (Scheme 1.3). This species was synthesized from enantiomerically pure *trans*-2,3-epoxybutane according to the Meinwald protocol.[40] Treatment of **1.9** with LDA, followed by alkylation with propargyl bromide gave lactone **1.10**. Reduction of **1.10** with $LiAlH_4$ in diethyl ether at reflux afforded diol **1.11**. Conversion of **1.11** to ester **1.12** was accomplished in 72% overall yield by deprotonation then treatment with methyl chloroformate after protection of the alcohol functionalities as DHP ethers. Cyclisation of this intermediate to the unsaturated ester **1.13** was achieved in a *Z*:*E* ratio of 1:3 by treatment with triethylamine at reflux.

A 1:1 mixture of **1.14** was then generated by oxidation of **1.13** with *m*CPBA. After protecting the alcohol of **1.14** as a benzoyl ester, the tetrahydrofuran ring was selectively opened using 1N HCl in THF at reflux. Subsequent protection of the newly formed primary alcohol with benzoyl chloride allowed methylation of the alcohol at the anomeric centre. Tetrahydropyran **1.15** was then formed after debenzoylation with sodium methoxide. Selective tosylation of the primary alcohol of **1.15** and subsequent treatment with phenylselenolate anion[41] in absolute methanol gave selenide **1.16** in 55% yield.

Oxidation of **1.16** with 30% H_2O_2 in THF, followed by thermally induced elimination of phenylselenic acid in a mixture of benzene and triethylamine (1:1) afforded a 1:1 mixture of methyl pederate **1.17a** and its C2 epimer **1.17b**. Ketone **1.18** was obtained in 90% yield by oxidation of **1.17** with Collins reagent. Reduction of **1.18** with sodium borohydride in methanol at −78 °C proceeded in a stereoselective manner, giving methyl pederate **1.17a** in an improved diastereomeric

ratio of 5:1. Conversion of methyl pederate **1.17** to (+)-acetylpederic acid **1.7** was achieved by reacting with acetic anhydride and pyridine, then subsequent saponification of the ester functionality.



Reagents and conditions: - (a) i. LDA, THF, −78 °C; ii. $BrCH_2CCH$, 93%; (b) $LiAlH_4$, Et_2O, reflux, 95%; (c) DHP-TsOH, CH_2Cl_2; (d) *n*BuLi, $ClCO_2Me$, THF, −78 °C; (e) TsOH, MeOH, 72%; (f) NEt_3, reflux, *Z*:*E* = 1:3; (g) *m*CPBA, CH_2Cl_2, 49% (2 steps), dr = 1:1; (h) BzCl-py; (i) 1N HCl, THF, reflux; (j) BzCl-py; (k) MeOH-AcCl; (l) MeOH-NaOMe; (m) TsOH, MeOH; (n) NaSePh, MeOH, 55%; (o) H_2O_2, THF; (p) PhH/NEt_3 (1:1), reflux, R:R' = 1:1, 78%; (q) $CrO_3.py_2$, CH_2Cl_2, 90%; (r) $NaBH_4$, MeOH, −78 °C, R:R' = 5:1, 90%; (s) Ac_2O, py; (t) 1N HCl.

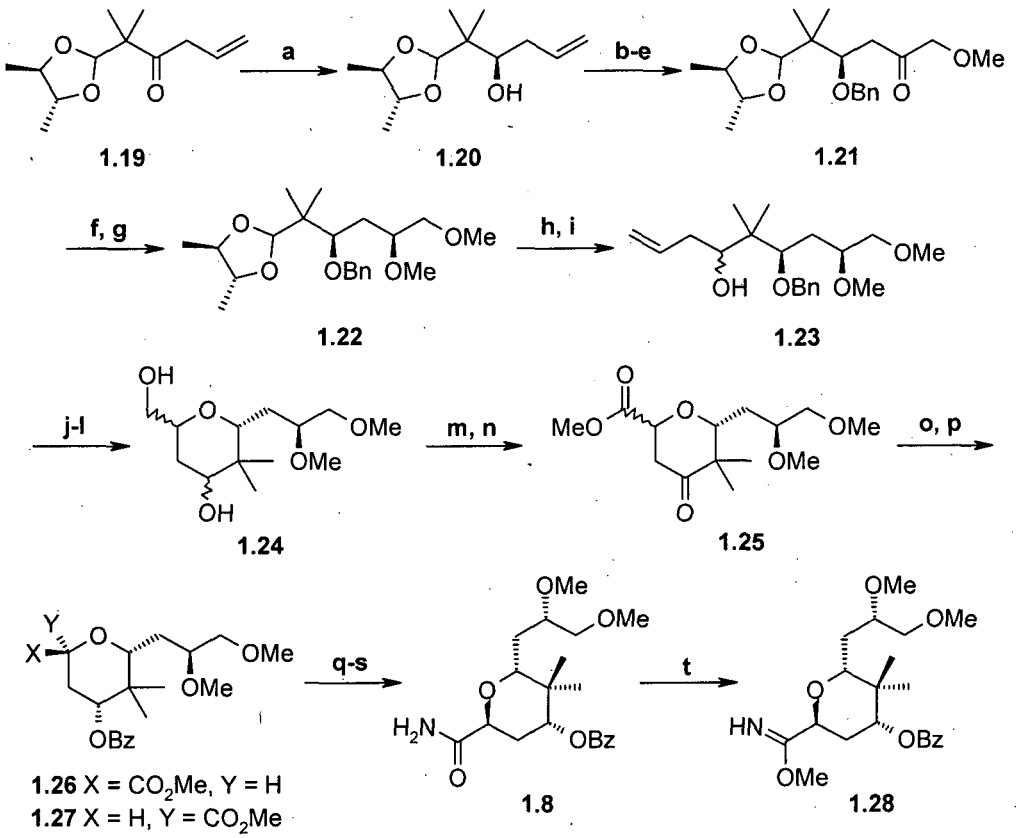
Scheme 1.3. Matsumoto's Synthesis of (+)-acetylpederic acid.

The starting point of the synthesis of the second tetrahydropyran, (+)-benzoylpedamide **1.8** is the formation of the optically active ketone **1.19** (Scheme 1.4). This was achieved in 51% overall yield from 3-hydroxy-2,2-dimethylpropanal, through protection of the aldehyde, oxidation of the alcohol, Grignard addition of allylmagnesium bromide and oxidation to ketone **1.19**.[38,39] Stereoselective reduction

with lithium aluminium hydride gave alcohol **1.20** in 74% diastereomeric excess. The alcohol **1.20** was converted into dialkoxyketone **1.21** in 76% overall yield by protection of the alcohol as benzyl ether, *m*CPBA epoxidation, ring opening with sodium methoxide and Collins oxidation. Reduction of **1.21** with lithium tri-*tert*-butoxyaluminium hydride followed by methylation of the resulting alcohol gave optically active acetal **1.22** in 88% yield.

Demasking of **1.22** with 3N HCl and allylmagnesium bromide addition, next afforded alcohol **1.23** as a 1:1 epimeric mixture. Removal of the benzyl protecting group was then accomplished by sodium in liquid ammonia. The resulting diol was converted to tetrahydropyran **1.24** by *m*CPBA oxidation and treatment with acid. The stereochemistry of the secondary alcohol of THP **1.24** was established by converting **1.24** to ketoester **1.25**, through Jones oxidation and esterification. Reduction of **1.25** with sodium borohydride afforded predominantly the desired α-alcohol and, after protection as its benzoate ester, a 1:1 mixture of **1.26** and **1.27** was obtained.

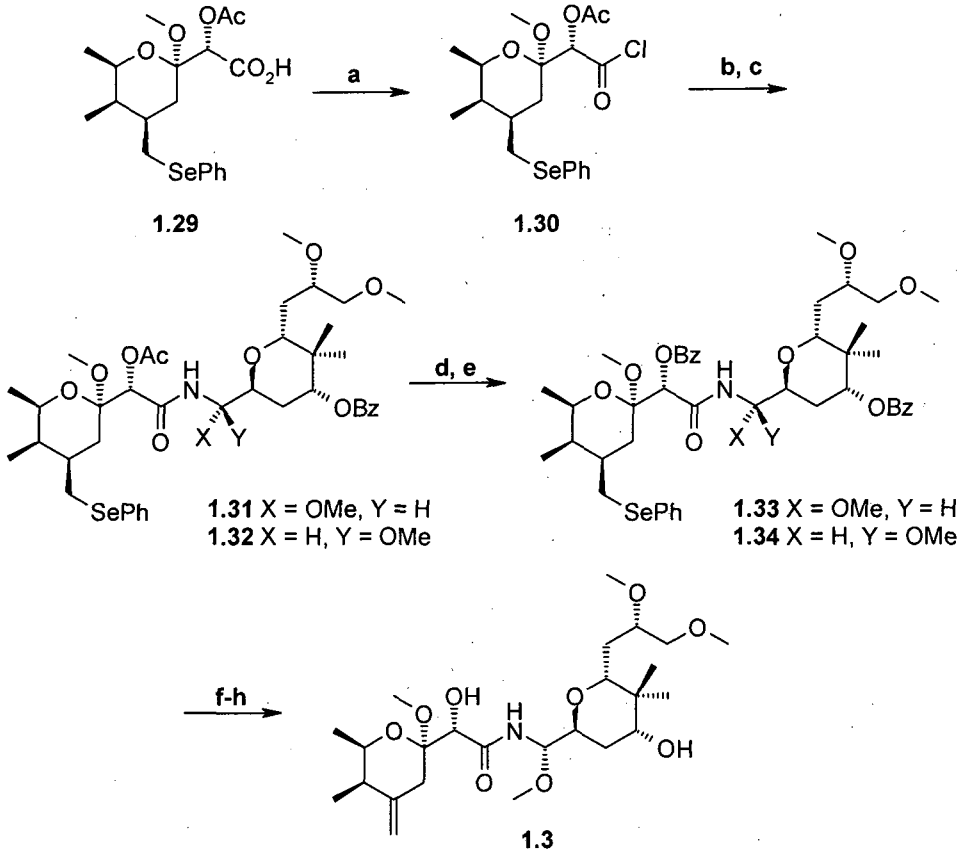
Conversion of the undesirable epimer **1.27** to **1.26** could be achieved by enolisation and a thermodynamically controlled protonation. **1.26** and **1.27** were thus obtained in an improved ratio of 9:2 and separated by silica gel chromatography. Transformation of ester **1.26** to (+)-benzoylpedamide **1.8** was accomplished in 79% overall yield through saponification of the ester, conversion of the resulting carboxylic acid to its acid chloride and subsequent amidation. In preparation for the coupling of the tetrahydropyran moieties, **1.8** was converted to imidate **1.28** by treatment with Meerwein salt.[42]



Reagents and conditions: - (a) $LiAlH_4$, Et_2O/PhMe (1:1), −123 °C, 74% de, 98%; (b) BnCl, *t*AmONa, DMSO, RT, 2 h; (c) *m*CPBA, CH_2Cl_2, RT, 12 h; (d) NaOMe, MeOH, RT, 2 days; (e) $CrO_3.py_2$, CH_2Cl_2, RT, 30 min, 76% (4 steps); (f) $Li(tBu)_3AlH_3$, Et_2O, −78 °C, 30 min, *syn*:*anti* (10:1), 95%; (g) MeI, NaH, PhH, reflux, 2 h, 93%; (h) 3N HCl, $(CH_3)_2CO$, reflux, 5 h; (i) CH_2CHCH_2MgBr, Et_2O, RT, 10 min, 78% (2steps); (j) Na, NH_3(l), −78 °C, 20 min, 74%; (k) *m*CPBA, CH_2Cl_2, RT, 12 h; (l) $TsOH.H_2O$, PhH, reflux, 12 h, 86% (2 steps); (m) Jones reagent, $(CH_3)_2CO$, RT, 12 h; (n) CH_2N_2, Et_2O, RT; (o) $NaBH_4$, EtOH, −78 °C, 30 min, 68% (3 steps); (p) PhCOCl, py, RT, 12 h, **1.26**:**1.27** (1:1), 94%; (q) NEt_3, H_2O, MeOH, RT, 12 h; (r) $SOCl_2$, DMF, CH_2Cl_2, reflux, 3 h; (s) NH_3, CH_2Cl_2, 0 °C, 30 min, 79% (3 steps); (t) $Me_3O.BF_4$, CH_2Cl_2, RT, 12 h.

Scheme 1.4. Matsumoto's Synthesis of (+)-Benzoylpedamide.

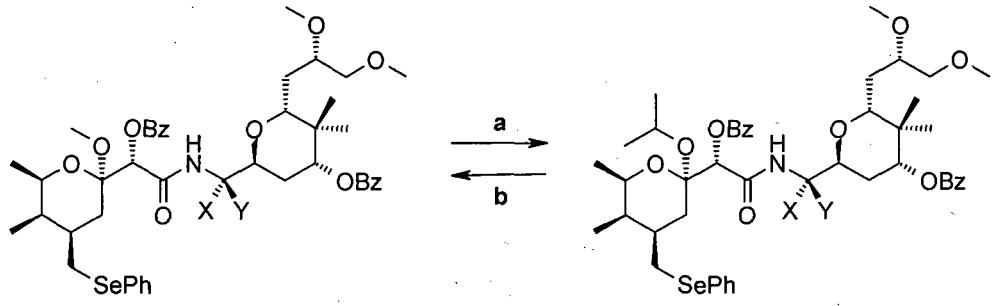
With both tetrahydropyran fragments to hand, Matsumoto devised a coupling strategy, since employed by many others to complete the synthesis of pederin (Scheme 1.5).[15] The (+)-acetylselenopederic acid fragment **1.29** was converted to the corresponding acid chloride **1.30** with thionyl chloride. Treatment of acid chloride **1.30** with imidate **1.28** in the presence of triethylamine, followed by reduction of the intermediate methyl *N*-acylimidate, gave an epimeric mixture of *N*-(1-methoxyalkyl) amides **1.31** and **1.32**.



Reagents and conditions: - (a) $SOCl_2$, py, CH_2Cl_2, RT, 5 min; (b) **1.28**, NEt_3, CH_2Cl_2, RT, 2 h; (c) $NaBH_4$, EtOH, −20 °C, 30 min, 72% (3 steps); (d) 1 M, LiOH, MeOH, RT, 3 h; (e) BzCl, DMAP, py, RT, 81% (2 steps), (f) $NaIO_4$, MeOH, RT, 1 h; (g) NEt_3, PhH, reflux, 30 min; (h) 1 M, LiOH, MeOH, RT, 3 h, 75%.

Scheme 1.5. Matsumoto's Synthesis of Pederin **1.3**.

It was found that conversion of the acetoxy compounds **1.31** and **1.32** to the corresponding benzoyl esters **1.33** and **1.34** was essential for successful separation of the epimers. After separation by preparative TLC, compounds **1.33** and **1.34** were obtained in 81% yield (**1.33**:**1.34** = 2:7). This disappointing stereoselectivity was improved by carrying out a kinetically controlled resolution (Scheme 1.6). The *epi*-pederin derivative **1.34** was first treated with acetyl chloride in isopropanol to afford **1.36** after 7 days. Kinetically controlled methoxylation of **1.36** with acetyl chloride in methanol proceeded in a stereoselective manner to give a 4:1 mixture of **1.33** and **1.34** in 74% yield.



1.33 X = OMe, Y = H
1.34 X = H, Y = OMe

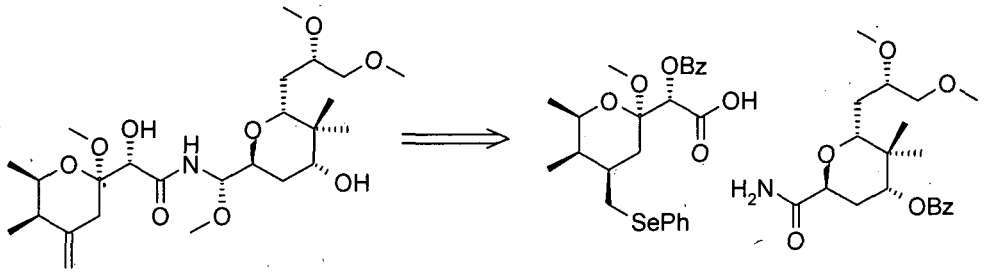
1.35 X = O^{i}Pr, Y = H, Z = ^{i}Pr
1.36 X = H, Y = O^{i}Pr, Z = ^{i}Pr

Reagents and conditions: - (a) AcCl, ^{i}PrOH, RT, 7 days; (b) AcCl, MeOH, RT, 4.5 h.

Scheme 1.6. Kinetic Resolution of Pederin Derivatives.

1.2. The Nakata Synthesis of Pederin.

Nakata, Oishi and co-workers developed a total synthesis of pederin,[13] employing a convergent strategy similar to that of Matsumoto (Scheme 1.7).[15] The (+)-benzoylselenopederic acid fragment **1.37** was synthesized from optically active (+)-β-keto imide **1.38**, which in turn was prepared using Evans' methodology.[43] Stereoselectivity was set in the pederic acid fragment by employing this methodology and the subsequent syn-directing reduction of **1.38** using $Zn(BH_4)_2$.



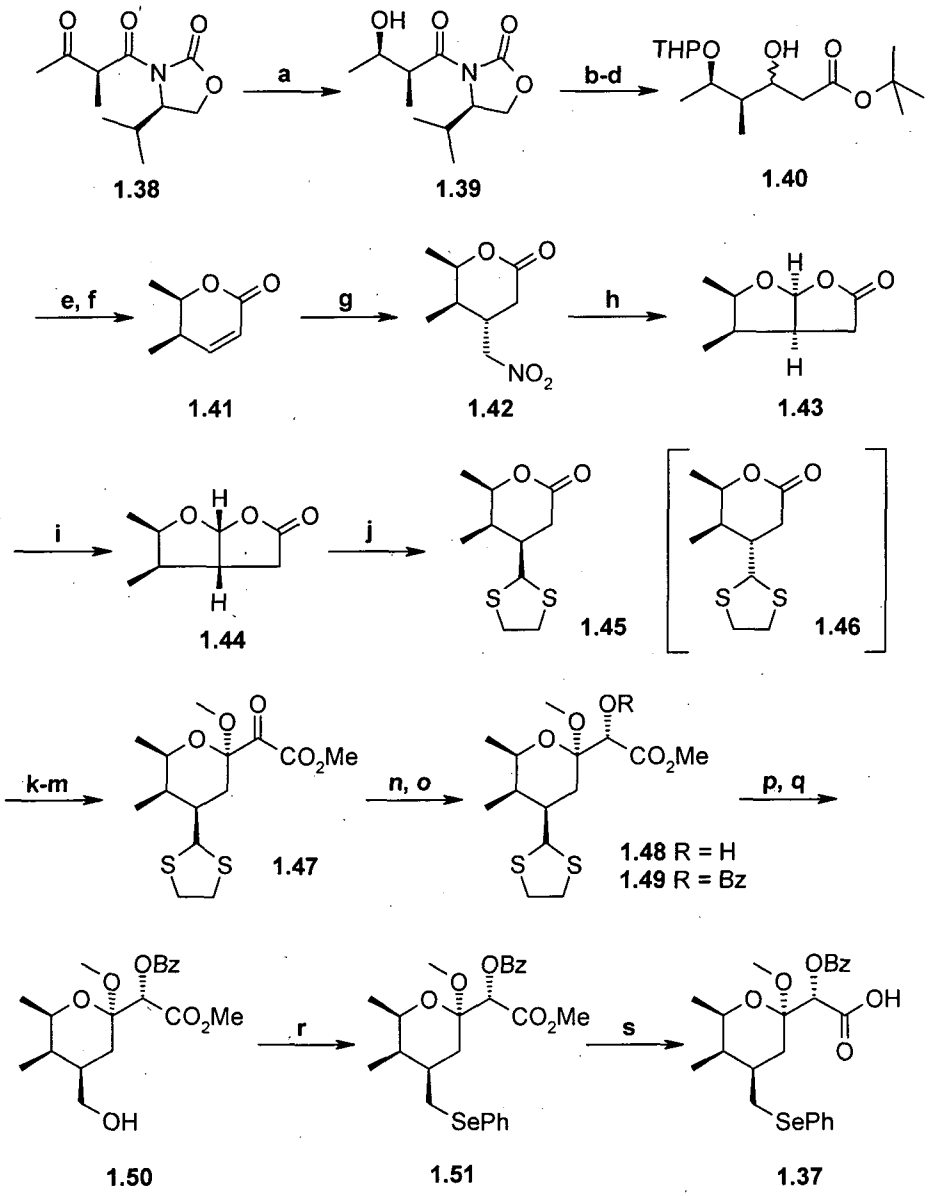
1.3 **1.37** **1.8**

Scheme 1.7. A Retrosynthesis of Pederin

The reduction of (+)-β-keto imide **1.38** was achieved using $Zn(BH_4)_2$ in CH_2Cl_2 at −25 °C, giving the desired syn-**1.39** quantitatively in >30:1 diastereoselectivity (Scheme 1.8). Imide **1.39**, after protection of the alcohol as the THP ether, was reduced with DIBAL-H and the resulting aldehyde treated with the lithium enolate of *tert*-butyl acetate in THF generating β-hydroxy ester **1.40** in 80% yield. Reaction of **1.40** with TsOH in MeOH and subsequent treatment with TsOH in refluxing benzene

gave α-β-unsaturated lactone **1.41** (81%). Michael addition of the anion of nitromethane to **1.41**, generated with Triton-B, gave lactone **1.42** in 92% yield.[12] Conversion of the nitromethyl group of **1.42** to its corresponding aldehyde with $TiCl_3$ and triethylamine also induced cyclisation to bicyclic lactone **1.43**. Treatment with HCl in CH_2Cl_2 isomerised **1.43** exclusively to the more stable lactone **1.44** (70% from **1.42**). On treatment with ethanedithiol and boron trifluoride diethyletherate, **1.44** was converted into thioacetal **1.45** (81%). The isomer **1.46** was obtained from **1.43** in the same way.

Introduction of the α-keto ester side chain of **1.47** was accomplished by Claisen condensation with the lithium enolate of $MeOC(Me)_2OCH_2CO_2Me$ followed by methanolysis of the resultant hemiacetal and lactol functions. Finally, a Moffatt oxidation of the secondary alcohol gave **1.47** (91% from **1.45**). Stereoselective reduction of **1.47** with $Zn(BH_4)_2$ in Et_2O at −78 °C yielded the desired alcohol **1.48** quantitatively with 17:1 diastereoselectivity. Benzoylation of **1.48** afforded **1.49** (86%), allowing confirmation of stereochemistry by x-ray crystallography. Removal of the thioacetal protecting group and $Zn(BH_4)_2$ reduction of the resulting aldehyde to alcohol **1.50** proceeded in 91% yield. Phenylselenation of **1.50** was accomplished using PhSeCN[44] and tributylphosphine yielding **1.51** (94%) without hydrolyzing the benzoate group. Saponification of the methyl ester to acid **1.37** was achieved in quantitative yield on treatment of **1.51** with PrSLi in HMPA.[45]



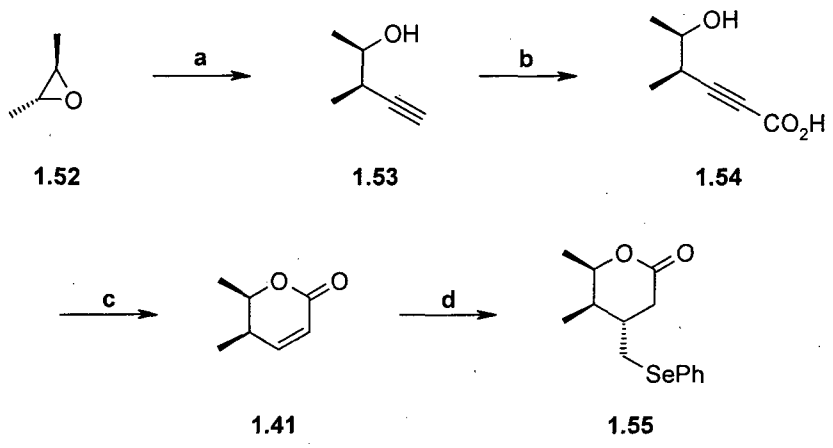
Reagents and conditions: - (a) $Zn(BH_4)_2$, CH_2Cl_2, −25 °C, 100%; (b) DHP, TsOH; (c) DIBAL-H, PhMe, −78 °C; (d) LDA, *t*BuOAc, THF, −78 °C, 80% (3 steps); (e) TsOH, MeOH; (f) TsOH, PhMe, reflux, 81%; (g) $MeNO_2$, Triton B, 92%; (h) $TiCl_3$, NEt_3; (i) HCl, CH_2Cl_2, 70%; (j) $HSCH_2CH_2SH$, $BF_3.Et_2O$, CH_2Cl_2, RT, 81%; (k) LDA, $MeOC(Me)_2OCH_2CO_2Me$, THF, −78 °C; (l) CSA, $CH(OMe)_3$, CH_2Cl_2, MeOH; (m) DMSO, DCC, Py, TFA, Et_2O, 91%; (n) $Zn(BH_4)_2$, Et_2O, −78 °C, 100%; (o) PhCOCl, DMAP, py, 86%; (p) HgO, $HgCl_2$, MeCN; (q) $Zn(BH_4)_2$, Et_2O, 91%; (r) PhSeCN, Bu_3P, THF, 0 °C, 94%; (s) PrSLi, HMPA, RT, 100%.

Scheme 1.8. Nakata's Synthesis of (+)-Benzoylselenopederic acid.

1.3. The Kocienski Approach to Pederin.

The first approach of Kocienski and co-workers to pederin,[14,16,17] employed a convergent strategy in the same mould as previous groups (Scheme 1.7).[13,15] Again the synthesis started with the formation of the two tetrahydropyran fragments, benzoylpedamide **1.8** and benzoylselenopederic acid **1.68**. The selenide protected *exo*-alkene functionality was removed in the final steps after coupling of the fragments. This was done to avoid problems caused by the acid sensitivity of the group.

Formation of the benzoylselenopederic acid fragment **1.68** was achieved by synthesising two principal fragments, the selenolactone **1.55** and the glycolic acid derivative **1.60**. Selenolactone **1.55** was prepared from *trans*-2,3-epoxybutane **1.52** (Scheme 1.9). Ring opening of **1.52** was successfully accomplished using lithium acetylide in HMPA (82%). Deprotonation of the resulting alkyne **1.53** followed by addition of carbon dioxide generated carboxylic acid **1.54** in 96% yield. Hydrogenation of **1.54** to the corresponding α,β-unsaturated alkene using a poisoned palladium catalyst, followed by Kugelrohr distillation induced cyclisation to lactone **1.41** (85%). Michael addition of the phenylselenomethane anion to lactone **1.41** gave selenolactone **1.55** in 89% yield.[46]

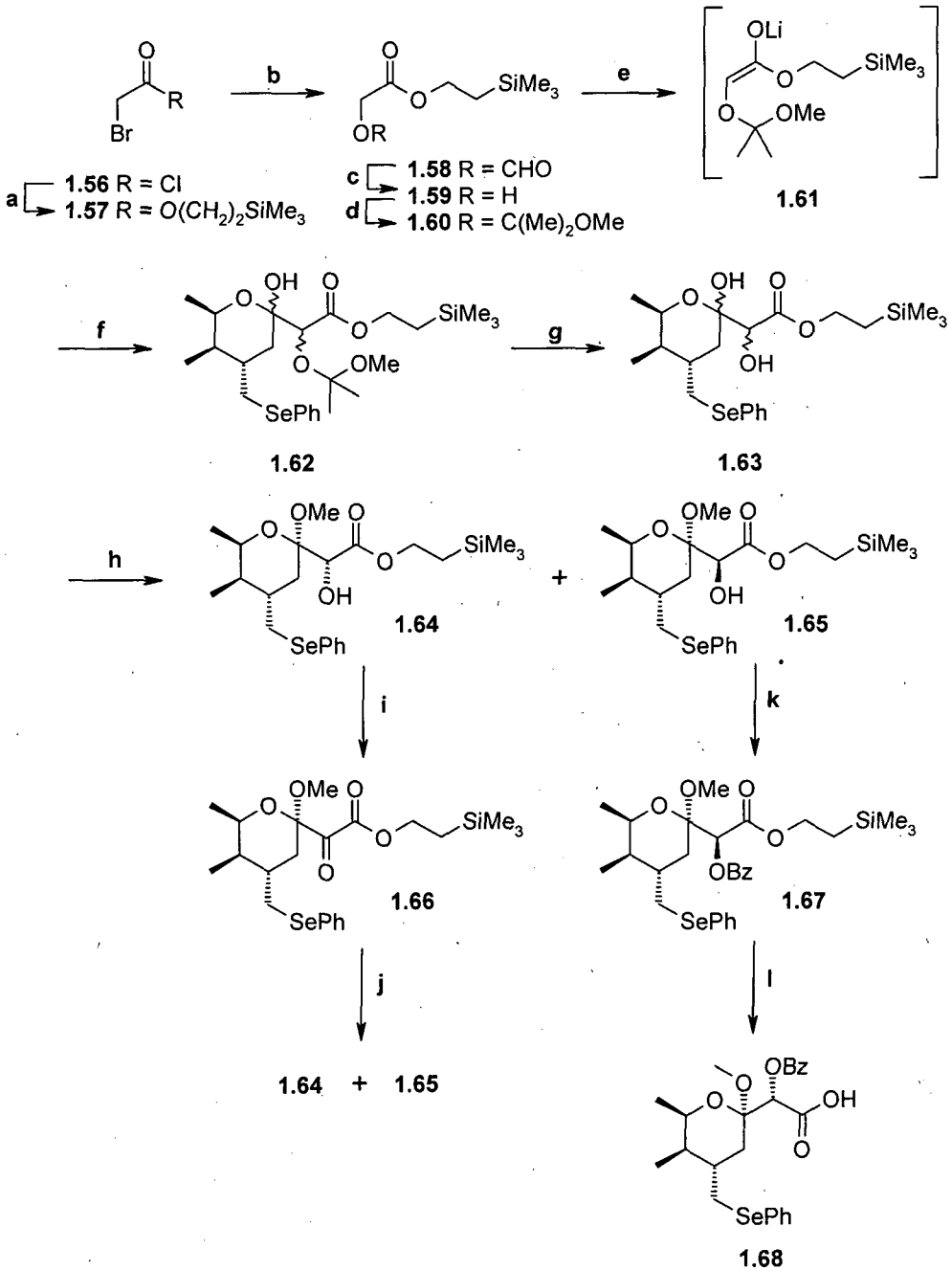


Reagents and conditions: - (a) Lithium acetylide, HMPA, RT, 6 days, 82%; (b) *n*BuLi, CO_2, −78 °C, 20 min, 96%; (c) H_2, $Pd/BaSO_4$, quinoline, Kugelrohr, 85%; (d) $PhSeCH_2Li$, THF, HMPA, −78 °C, 1 h, 89%.

Scheme 1.9. Kocienski's Synthesis of Selenolactone **1.55**.

Advancement of selenolactone **1.55** to benzoylselenopederic acid **1.68** required incorporation of the glycolate side chain onto the ring (Scheme 1.10). Acid chloride **1.56** was converted to ester **1.57** using $Me_3Si(CH_2)_2OH$ and pyridine in CH_2Cl_2 (89%). Addition of sodium formate to **1.57** in DMF and heating to 50 °C for 15 h gave **1.58** in quantitative yield. Triethylamine in methanol facilitated formation of alcohol **1.59** (86%) and thence acetal **1.60** (96%).

Formation of lithium enolate **1.61** followed by addition of selenolactone **1.55** at −78 °C gave **1.62**. Yields were variable due to proton abstraction by the glycolate enolate competing with the desired nucleophilic addition. Hydrolysis of the acetal with aqueous acid gave a complex mixture of diastereoisomeric diols **1.63**, which, on exposure to acidic methanol gave a 1:1 mixture of **1.64** and the desired intermediate **1.65** (61%). These isomers could be separated by column chromatography, however, in practice it proved more convenient to oxidize the mixture to the corresponding α-keto ester **1.66** then reduce *in situ* with BH_3-NH_3 complex in THF at low temperature.[47] In this way the diastereoisomer ratio **1.64**:**1.65** could be improved to 1:7. The alcohol **1.65** was then separated and converted to the crystalline benzoate derivative **1.67**. Tetra-*n*-butylammonium fluoride in THF next facilitated removal of the trimethylsilyl ester, giving benzoylselenopederic acid **1.68**.

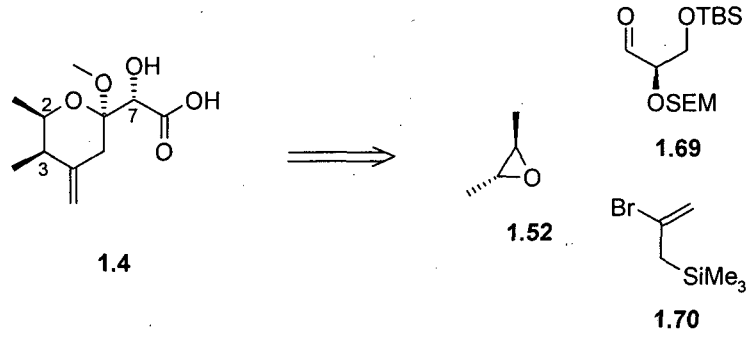


Reagents and conditions: - (a) $Me_3Si(CH_2)_2OH$, py, CH_2Cl_2, 0 °C, 89%; (b) HCOONa, DMF, 50 °C, 15 h, 100%; (c) NEt_3, MeOH, 5 °C, 30 min, 86%; (d) 2-methoxypropene, HCl, CH_2Cl_2, 0 °C, 2 h; (e) LDA, THF, −78 °C, 1 h; (f) **1.55**, −78 °C, 2.5 h; (g) H_3O^+, THF, RT, 20 min; (h) TsOH, MeOH, RT, 3.5 h, 61%; (i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 70 °C, 1.5 h, 90%; (j) $NH_3.BH_3$, THF, −78 °C, 1.5 h, 100%; (k) PhCOCl, DMAP, py, CH_2Cl_2, RT, 60 min; (l) TBAF, THF, RT, 20 min, 100%.

Scheme 1.10. Kocienski's Synthesis of Benzoylselenopederic acid **1.68**.

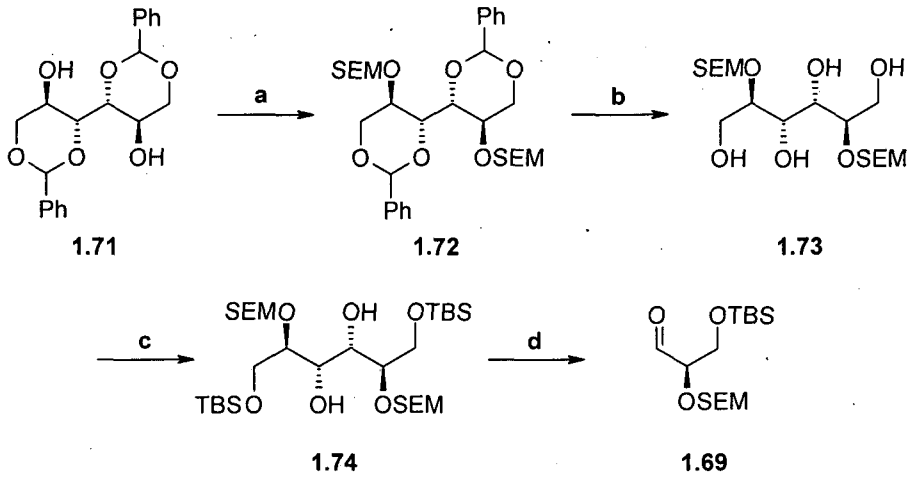
1.4. Breitfelder's Synthesis of Pederic Acid.

Breitfelder *et al.*[19] used a number of protecting group manipulations to form the desired pederic acid fragment **1.4**. Their strategy introduces the stereogenic centre at C(7) from chiral building block **1.69**, while the stereogenic centres at C(2) and C(3) were derived from enantiomerically pure *trans*-2,3-epoxybutane **1.70** (Scheme 1.11).



Scheme 1.11. Breitfelder's Pederic Acid Retrosynthesis.

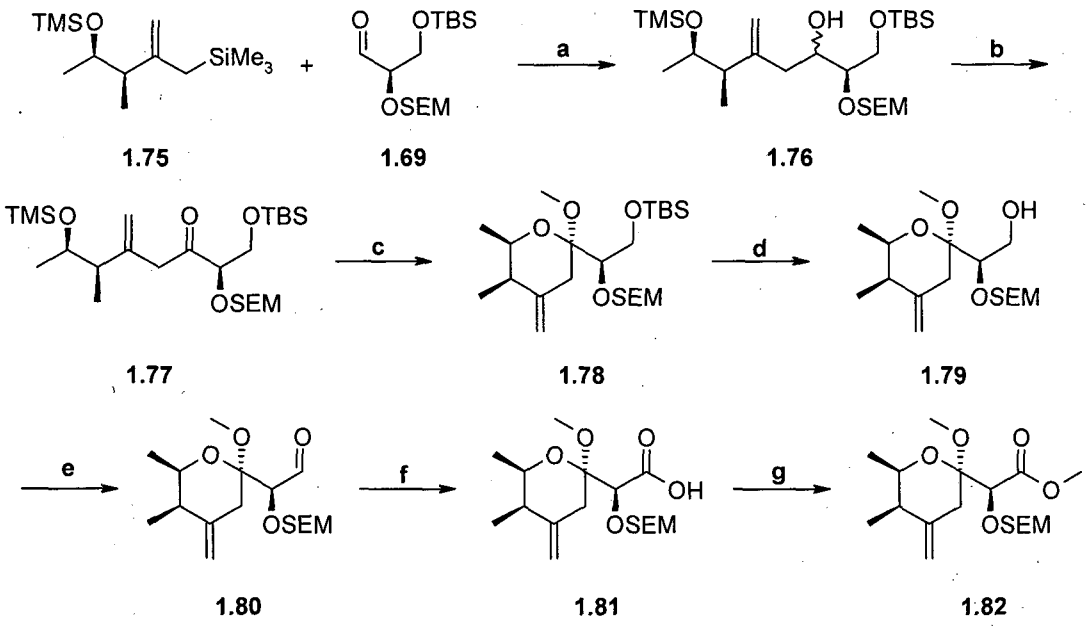
The glyceraldehyde building block **1.69** was prepared from 1,3:4,6-di-*O*-benzylidene-D-mannitol (**1.71**) according to Scheme 1.12. SEM protection followed by hydrogenation gave tetrol **1.73**, which after protection of the primary alcohol functions as silyl ethers afforded diol **1.74**. Cleavage with lead tetraacetate gave aldehyde **1.69**, which was used without further purification due to its tendency to racemize.[19]



Reagents and conditions: - (a) SEMCl, $^{i}Pr_2NEt$, 0 °C, 3 d, 92-99%; (b) H_2, $Pd(OH)_2$, EtOH, 12 h, 98%; (c) TBSCl, 1*H*-imidazole, 0 °C to RT, 12 h, 99%; (d) $Pb(OAc)_4$, $NaHCO_3$, 0 °C, 20 min 97%.

Scheme 1.12. Breitfelder's Synthesis of Methyl Protected Pederic Acid.

Building block **1.75** (Scheme 1.13) was prepared from *trans*-2,3-epoxybutane and alkene **1.70** according to the Kocienski protocol.[16] The $SnCl_4$-mediated reaction of **1.75** with aldehyde **1.69** gave adduct **1.76**, of which one diastereoisomer predominated by 10:1. This stereogenic centre was later destroyed by Dess-Martin oxidation to ketone **1.77**. PPTS catalysed acetalisation was carried out on ketone **1.77** to afford the tetrahydro-2*H*-pyran ring **1.78**. Removal of the TBS alcohol protecting group followed by TPAP oxidation of the resulting primary alcohol **1.79** led to aldehyde **1.80**. Breitfelder avoided epimerisation of aldehyde **1.80** by carrying out the $NaClO_2$ oxidation on crude material. The resulting acid **1.81** was found to be unstable on storage, but could be characterised as the methyl ester **1.82**.

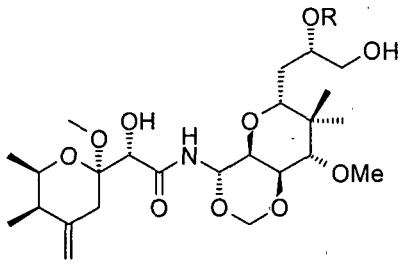


Reagents and conditions: - (a) $SnCl_4$, Et_3N, −78 °C, 61-84%; (b) Dess-Martin, DCM, 1 h, 88-99%; (c) PPTS, MeOH, RT, 70-81%; (d) Bu_4NF, THF, 0 °C, 4 h, 82-93 %; (e) $Pr_4N^+ RuO_4^-$, CH_2Cl_2, RT, 50 min, 88-94%; (f) $NaClO_2$, RT, 20 min, 95%; (g) CH_2N_2, Et_2O, 0 °C, 30 min, 96%.

Scheme 1.13. Breitfelder's Synthesis of Methyl Protected Pederic Acid.

1.5. Syntheses of Pederic Acid within the Mycalamide Series.

Mycalamides A **1.83** and B **1.84** are metabolites isolated from the marine sponge of genus *Mycale*. They have both shown significant in vitro antiviral activity.[6,7] They are structurally similar to onnamide F and have the pederic acid subunit in common. In addition they have a more complex trioxadecalin ring system, connected to the pederic acid fragment through the familiar amide bond (Figure 1.2).

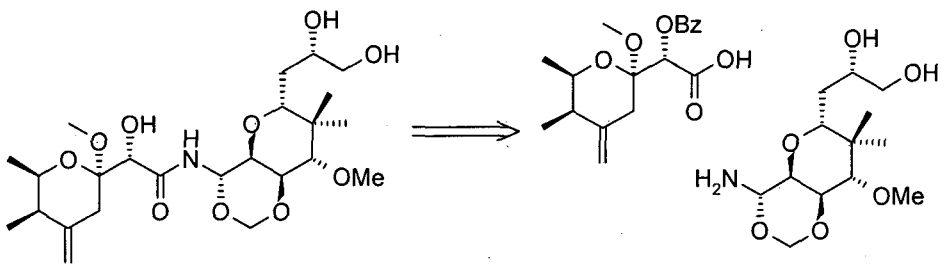


1.83 R = H, Mycalamide A
1.84 R = Me, Mycalamide B

Figure 1.2. The Structure of Mycalamides A and B.

1.6. Rawal's Synthesis of Benzoylpederic Acid.

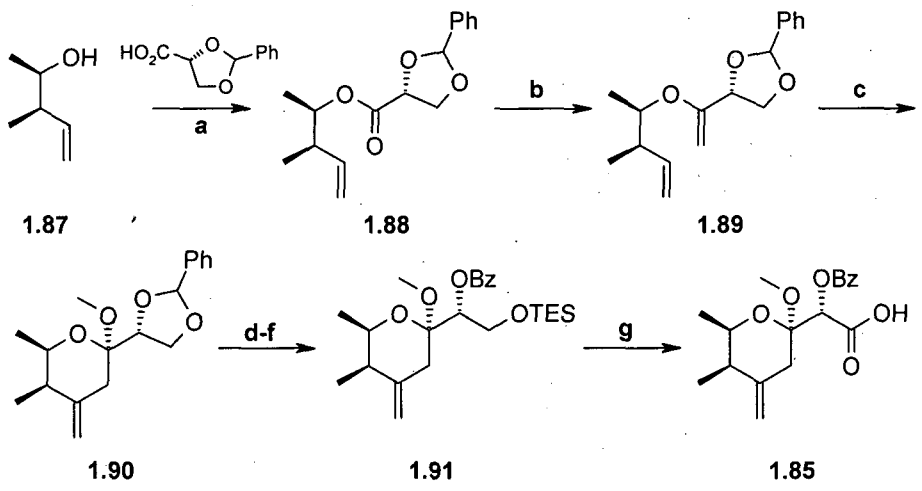
An elegant total synthesis of mycalamide A **1.83** was achieved by Rawal and co-workers using the usual convergent strategy (Scheme 1.14).[28] The key step in the synthesis of benzoylpederic acid **1.85** was a Wacker/Heck palladium catalysed cyclisation.



1.83 **1.85** **1.86**

Scheme 1.14. A Retrosynthesis of Mycalamide A.

The synthesis of benzoylpederic acid **1.85** begins from the known homoallylic alcohol **1.87** (Scheme 1.15), synthesized in 2 steps using Brown chemistry.[48] Esterification with benzylidene protected glyceric acid[49] using EDC gave ester **1.88**. Methylenation[50] with Cp_2TiMe_2 next generated enol ether **1.89** in 85% yield. Syringe pump addition of **1.89** to a mixture of MeOH, TMOF, propylene oxide, benzoquinone and $PdCl_2$ in THF/DMF (20/1) gave tetrahydropyran **1.90** as a 5.7:1 mixture of diastereoisomers. Removal of the benzylidene group and selective protection of the primary alcohol followed by benzoyl protection of the secondary hydroxyl gave **1.91**. Slow addition of **1.91** to a mixture of PDC in DMF transformed the TES-protected hydroxyl directly to acid **1.85**. For characterisation purposes benzoylpederic acid **1.85** was converted to the corresponding methyl ester.

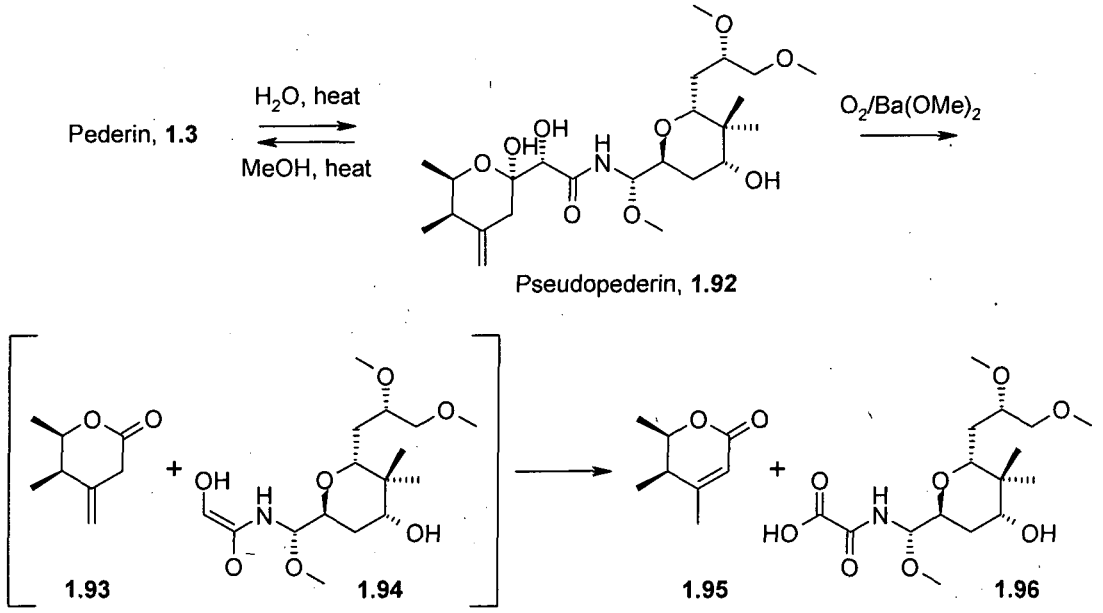


Reagents and conditions: - (a) EDC, DMAP, CH_2Cl_2, 91%; (b) Cp_2TiMe_2, PhMe, 80 °C, 85%; (c) $PdCl_2$, benzoquinone, MeOH, TMOF, propylene oxide, THF/DMF (20/1), dr = 5.7:1, 78%; (d) Na, $NH_3(l)$, EtOH, 93%; (e) TESCl, DIPEA, CH_2Cl_2, 93%; (f) BzCl, DMAP, DIPEA, CH_2Cl_2, 94%; (g) PDC, DMF, 83%.

Scheme 1.15. Rawal's Synthesis of Benzoylpederic acid.

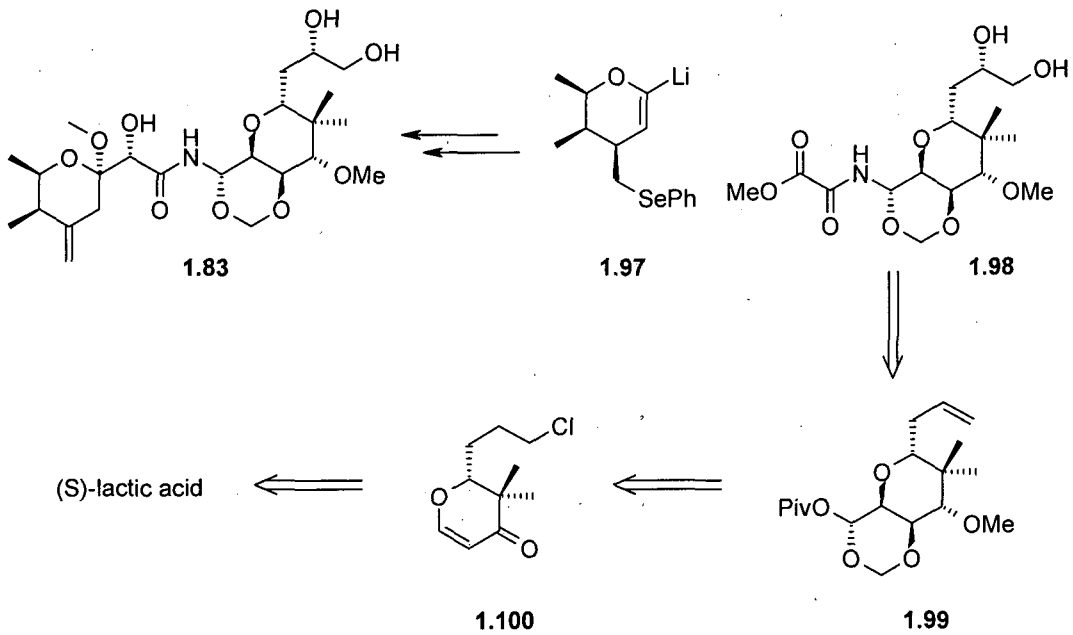
1.7. Lithiated dihydropyran approaches.

An alternative approach to the synthesis of the pederin family of natural products has been undertaken by Kocienski *et al.*[18,29-31,33] It is of particular note for the unique manner in which the troublesome *N*-acyl aminal bridge is constructed. The work drew inspiration from the degradation studies of Quilico and co-workers leading to their structural elucidation of pederin (Scheme 1.16).[51] They noted that Pseudopederin **1.92**, the hydrolysis product of pederin, undergoes a retroaldol reaction on heating in the presence of base and air to give **1.96**, with the *N*-acyl aminal group still intact. These transformations suggested an alternate disconnection, to α-dicarbonyl **1.98** and the lithiated dihydropyran **1.97** (Scheme 1.17).



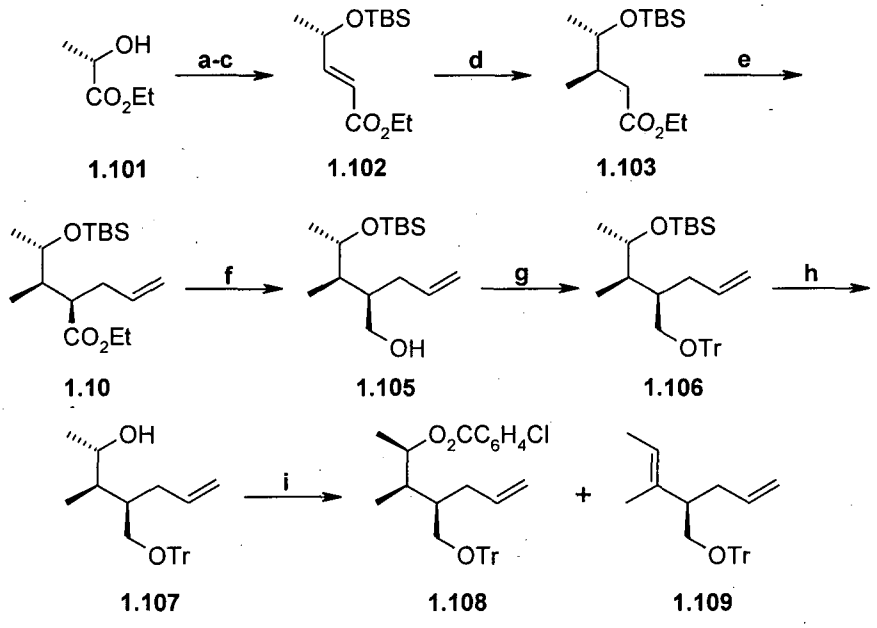
Scheme 1.16. Structural Elucidation of Pederin.

The new strategy employed the metallated dihydropyran **1.97** as an acyl anion equivalent. Its reaction with α-keto ester **1.98** establishes all the requisite carbon atoms at the correct oxidation level.



Scheme 1.17. Kocienski's Retrosynthesis of Mycalamide A.

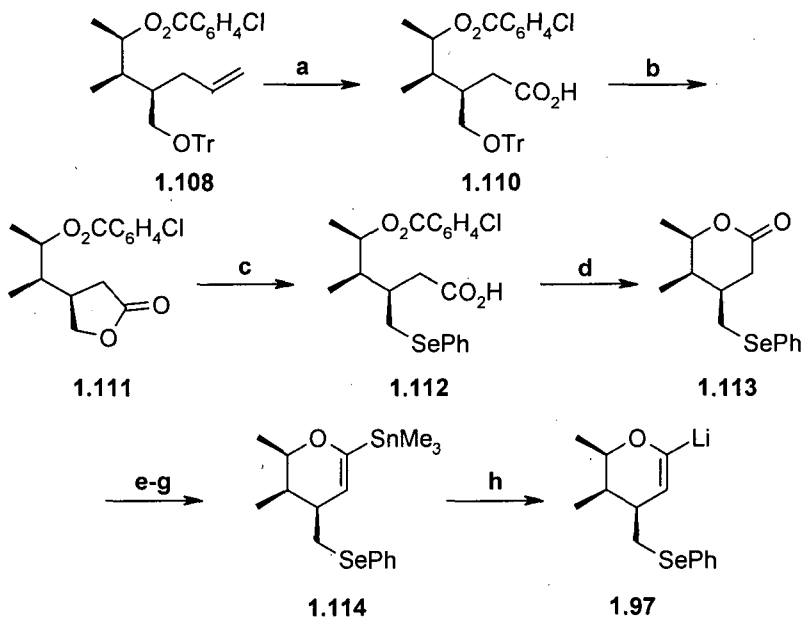
Ethyl (*S*)-lactate **1.101** was transformed into the α,β-unsaturated ester **1.102** by TBS protection of the alcohol, DIBAL-H reduction and Horner-Emmons olefination[52] (Scheme 1.18). Conjugate addition of lithium dimethylcuprate to ester **1.102** in the presence of HMPA and TMSCl generated adduct **1.103** with excellent diastereoselectivity.[53] Allylation of the potassium enolate of ester **1.103** then introduced a third stereogenic centre giving **1.104** in 80% yield (dr = 22:1). DIBAL-H reduction of ester **1.104** to alcohol **1.105** followed by trityl protection (to **1.106**) and silyl deprotection gave alcohol **1.107**. A Mitsunobu esterification with *p*-chlorobenzoic acid formed ester **1.108** in 76% yield with only 5% of the elimination product **1.109** observed as a byproduct.



Reagents and conditions: - (a) TBSCl, NEt_3, DMAP; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 71% (3 steps); (d) Me_2CuLi, TMSCl, HMPA, THF, −95 to −50 °C, dr = 24:1, 75%; (e) KHMDS, allyl bromide, THF, −78 °C, dr = 22:1, 80%; (f) DIBAL-H, CH_2Cl_2, 5 °C, 100 min, 89%; (g) Ph_3CCl, NEt_3, DMAP, CH_2Cl_2, RT, 12 h, 94%; (h) TBAF, THF, reflux, 5 h, 97%; (i) $p ClC_6H_4CO_2H$, DIAD, PPh_3, THF, −10 to 0 °C, 3 h, 76% **1.108**, 5% **1.109**.

Scheme 1.18.

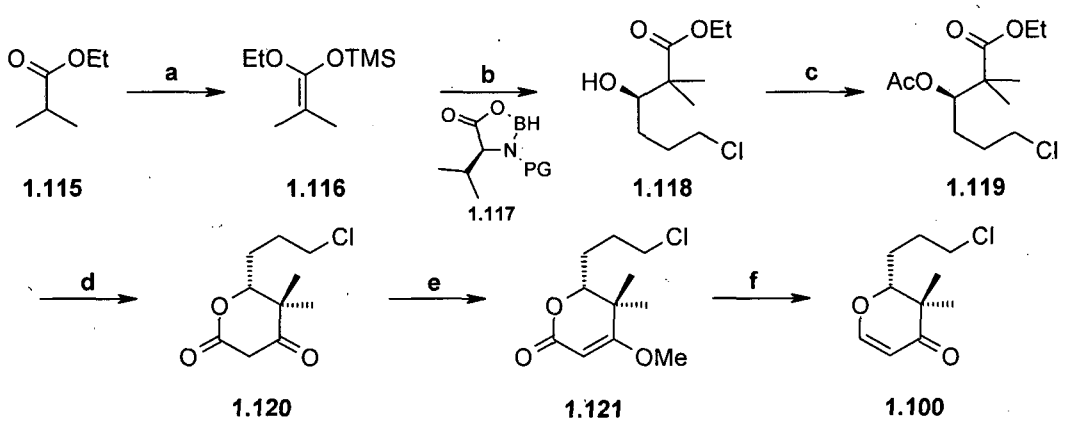
Oxidative cleavage of alkene **1.108** followed by TsOH treatment achieved simultaneous deprotection of the trityl group and cyclisation to lactone **1.111** (Scheme 1.19). Selenide **1.112** was then formed by addition of the phenylseleno anion to lactone **1.111**. They achieved saponification of ester **1.112** to the corresponding acid using an "ate" complex derived from addition of *n*BuLi to DIBAL-H.[54] This method suppressed epimerisation at the C2 position which was seen when NaOH was used. The resultant hydroxy acid was lactonised under acidic conditions to give **1.113** in 72% yield. Lactone **1.113** was next converted to the corresponding enol triflate, then coupled under palladium catalysis with Me_6Sn_2 to give enol stannane **1.114**. Transmetallation of **1.114** to the corresponding organolithium **1.97** was accomplished quantitatively at −78 °C with *n*BuLi.



Reagents and conditions: - (a) $RuCl_3.H_2O$, $NaIO_4$, MeCN, CCl_4, H_2O, RT, 7 h, 95%; (b) TsOH, MeOH, RT, 4 h, 71%; (c) PhSeNa, EtOH, reflux, 10 h, 80%; (d i) [*i*$Bu_2Al(H)Bu$]Li, CH_2Cl_2, THF, −78 °C; (d ii) HCl, RT, 24 h, 72%; (e) KHMDS, HMPA, THF; (f) $PhN(Tf)_2$; (g) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, THF, 70% (3 steps); (h) *n*BuLi, THF, −78 °C, 15 min, 100%.

Scheme 1.19. Kocienski's Synthesis of Lithiated Dihydropyran **1.97**.

Dihydropyranone **1.100** (Scheme 1.20) is a key intermediate in Kocienski's synthetic strategy because it can be converted into the simple monocyclic system of pederin, as well as the more complex trioxadecalin ring system of the mycalamides, onnamides and theopederins. The starting point was ethyl isobutyrate **1.115**, which was converted with LDA and TMSCl to enol ether **1.116**. The asymmetric aldol condensation of **1.116** with 4-chlorobutanal to β-hydroxy ester **1.118** was accomplished using the borane reagent **1.117** according to the method of Kiyooka.[55,56] Dieckmann cyclisation of the acetate **1.119** gave β-keto lactone **1.120**. *O*-Methylation under phase transfer catalysed conditions afforded enol ether **1.121**. Reduction of the remaining ketone functionality using DIBAL-H generated the desired dihydropyranone **1.100**.



Reagents and conditions: - (a) LDA, TMSCl, THF, 91%; (b) $Cl(CH_2)_3CHO$, THF, −78 °C, 1.5 h, er = 97:3, 95%; (c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, 12 h, 76%; (d) LDA, THF, −78°C, 1.5 h, 78%; (e) Me_2SO_4, K_2CO_3, 18-c-6, CH_2Cl_2, RT, 12 h, 99%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 85%.

Scheme 1.20.

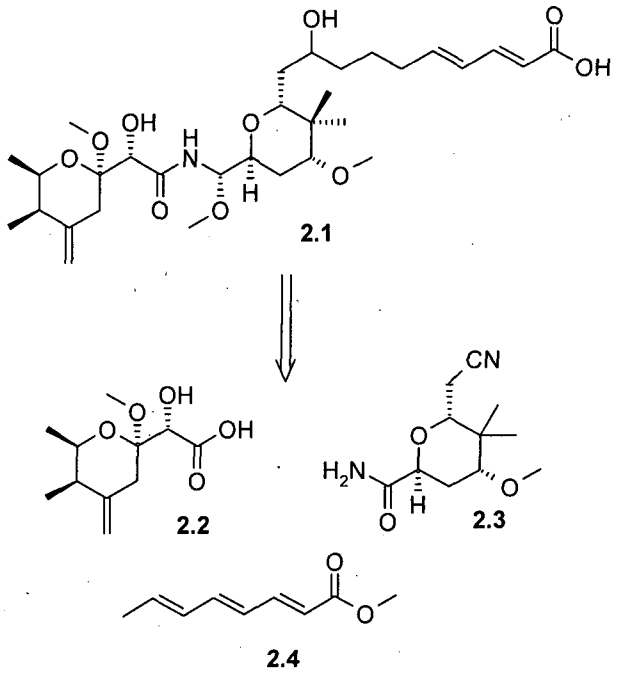
1.8. Summary.

The natural product onnamide F has not been previously synthesised. However, many syntheses of related natural products have been described.[11-34] The majority of these syntheses employ a convergent strategy, whereby the key fragments are connected through the amide bond. However, an interesting alternative method has been developed by Kocienski *et al.*[18,29-31,33] It is of particular note for the unique manner in which the troublesome *N*-acyl aminal bridge is constructed. An alternate disconnection, to α-dicarbonyl **1.98** and the lithiated dihydropyran **1.97** was suggested.

The pederic acid fragment, common to all the related natural products is the usual starting point of previous syntheses. Matsumoto,[15] Kocienski[14,16,17] and Breitfelder[19] synthesised pederic acid from enantiomerically pure *trans*-2,3-epoxybutane. Other groups, including Nakata,[13] used Evans aldol chemistry[57,58] to set the desired stereochemistry in their pederic acid synthesis. Rawal and co-workers synthesized benzoylpederic acid using a Wacker/Heck palladium catalysed cyclisation.[28] Our synthesis of onnamide F begins with the formation of the pederic acid fragment.

2. Early Work Towards Pederic Acid.

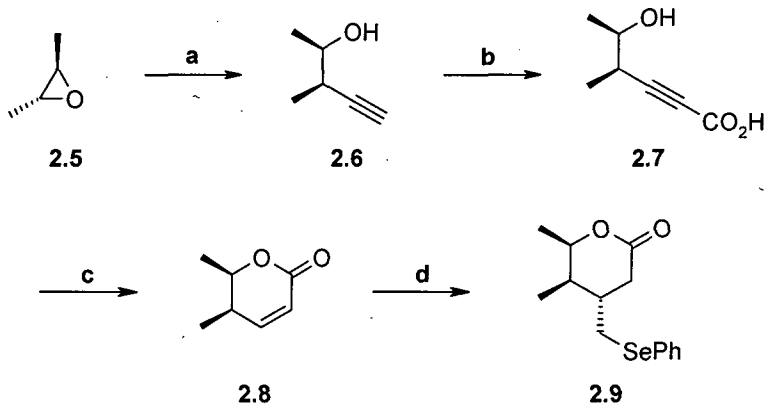
We propose to synthesise onnamide F by the convergent strategy depicted in Scheme 2.1. This gives three key fragments; tetrahydropyran **2.2**, pederic acid **2.3** and triene **2.4**. Our first approach to pederic acid was closely related to that of Kocienski *et al.*[16]



Scheme 2.1. The Retrosynthesis of Onnamide F.

2.1. Towards δ-lactone 2.9.

The ring opening of epoxide **2.5** using lithium acetylide ethylenediamine complex gave the alcohol **2.6** (Scheme 2.2). The literature procedure used the highly toxic and carcinogenic HMPA as solvent.[16] We employed the less harmful solvent DMPU as an alternative and were pleased to find that alcohol **2.6** was given in an excellent yield of 98%.

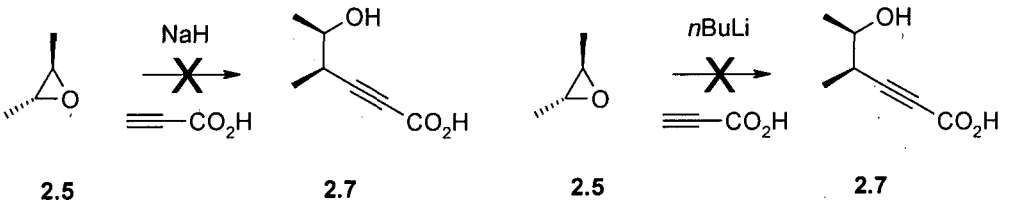


Reagents and conditions: - (a) lithium acetylide ethylenediamine complex, DMPU, 20 °C, 6 days, 98%; (b) (i) *n*BuLi, THF, 45 min, −78 °C (ii) diisopropylamine, 15 min, 0 °C (iii) CO_2, 20 min, −78 °C, 63%; (c) Pd/$BaSO_4$, quinoline, H_2, EtOH, RT, 1 h, 68%; (d) $(PhSe)_2CH_2$, *n*BuLi, THF/HMPA, 3 h, −78 °C, 40%.

Scheme 2.2. Formation of δ-lactone **2.9**.

Deprotonation of alkynol **2.6** was accomplished using *n*BuLi at low temperature. More than two equivalents of base were required as both the alcohol and alkyne functionalities had to be deprotonated. When treated with carbon dioxide the alkynyl anion reacted to form carboxylic acid **2.7** in 63% yield. Hydrogenation of acid **2.7** to the corresponding α,β-unsaturated hydroxy acid was successfully realised using a poisoned paladium catalyst. Kugelrohr distillation of the crude olefinic acid under reduced pressure resulted in lactonisation to **2.8** in 68% yield. Treatment of this lactone with phenylselenomethyllithium, formed by the addition of butyllithium to bis-(phenylseleno)methane at −78 °C afforded selenide **2.9** in 40% yield, together with unreacted bis-(phenylseleno)methane.[59]

Alternative methods of synthesising hydroxy acid **2.7** directly from *trans*-2,3-epoxybutane were investigated. The first involved the deprotonation of propiolic acid with sodium hydride to form the alkynyl anion intermediate. This was then reacted with epoxide **2.5** in the hope of generating **2.7**. However, after acid/base extraction ^{1}H NMR indicated only recovered propiolic acid starting material with no trace of desired product observed. A similar reaction incorporating butyllithium to deprotonate propiolic acid was also attempted, and this too proved unsuccessful.



2.5 2.7 2.5 2.7

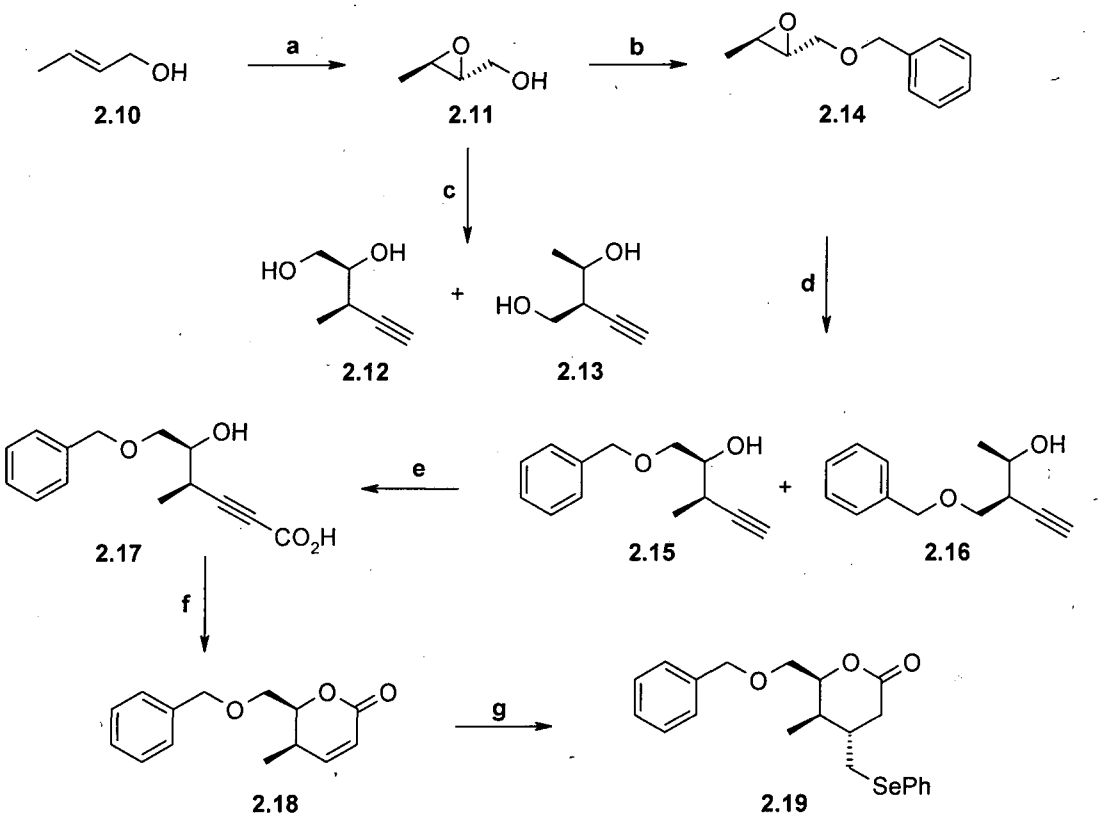
Scheme 2.3. Attempts to Form **2.7**.

2.2. Alternative Formation of Pederic Acid.

In parallel, a route based on work by Kobayashi *et al.* [60] was investigated in order to set the desired absolute stereochemistry (Scheme 2.3). Thus, epoxidation of 2-buten-1-ol **2.10** to oxirane **2.11** using ^{t}BuOOH and a vanadium catalyst initially proceeded in poor yield. It was found that the poor yield was due to the high solubility of the product in water.[61,62] The yield was significantly improved by carrying out a continuous aqueous extraction overnight. Similar problems were encountered when scaling-up this reaction. In this case removing the aqueous work-up allowed the product to be isolated in high yield.

Ring opening of epoxy alcohol **2.11** was initially attempted using the lithium acetylide ethylenediamine complex in DMPU. After stirring for 6 days, the desired product **2.12** was formed together with its regioisomer **2.13** (1:1, 85%). These were co-polar and could not be separated by column chromatography.

It was reasoned that protection of the alcohol as its benzyl ether might improve regioselectivity. Protection of the epoxy alcohol **2.11** was carried out by deprotonation with NaH and reaction with benzyl iodide (formed *in situ* from benzyl bromide and TBAI). The benzyl protected epoxide **2.14** was formed in 78% yield[63] and the reaction could be carried out on a larger scale without problem. Ring opening of **2.14** with lithium acetylide ethylenediamine complex[60] gave a 2:1 mixture of the desired alkyne **2.15** and its regioisomer **2.16**. Importantly, these could be separated easily using column chromatography allowing isolation of the desired regioisomer **2.15** in 55% yield.



Reagents and conditions: a) ^{t}BuOOH, $V(acac)_3$, CH_2Cl_2, RT, 4 h, 89%; (b) BnBr, TBAI, NaH, THF, −20 °C, 3 h, 78%; (c) lithium acetylide ethylenediamine complex, DMPU, 20 °C, 4 days, 89%, 1:1-**2.12**:**2.13**; (d) lithium acetylide ethylenediamine complex, DMPU, 20 °C, 4 days, 55%, 2:1-**2.15**:**2.16**; (e) (i) *n*BuLi, THF, 45 min, −78 °C (ii) diisopropylamine, 15 min, 0 °C (iii) CO_2, 20 min, −78 °C, 85%; (f) (i) $Pd/BaSO_4$, quinoline, H_2, EtOH, RT, 30 min, (ii) Toluene, reflux, 18 h, 59%; (g) $(PhSe)_2CH_2$, *n*BuLi, THF/HMPA, −78 °C, 3 h, 34%.

Scheme 2.3. Alternative Formation of Pederic Acid

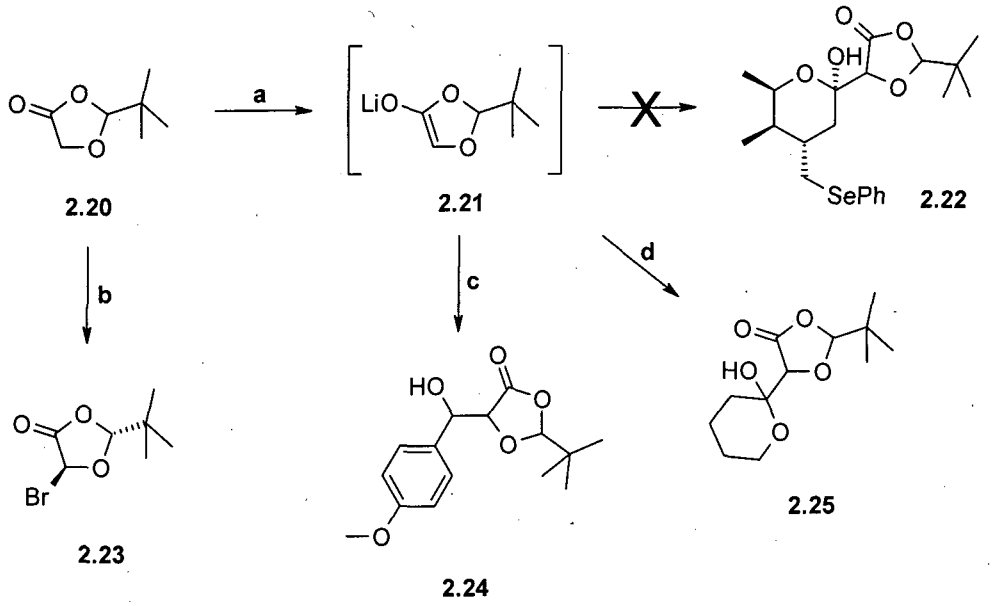
Double deprotonation of alkynyl alcohol **2.15** was accomplished using an excess of *n*BuLi at low temperature. Initially, quenching with CO_2 produced a mixture of pentanoic acid and carboxylic acid **2.17** that could not be separated easily. This problem was resolved by the addition of diisopropylamine to the dianion, thus converting the excess *n*BuLi to LDA. On warming to 0 °C the desired carboxylic acid **2.17** was afforded in 85% yield and high purity.

Initial attempts to reduce alkyne **2.17** to the corresponding α,β-unsaturated hydroxy acid using a poisoned palladium catalyst proved problematic. Conducting the hydrogenation reaction using a 2:1 ratio of catalyst to quinoline resulted in some over

reduction of the alkyne **2.17** to the corresponding alkane regardless of the duration of the reaction. Optimisation led us to reverse the ratio to at least 2:1 quinoline to catalyst whereupon over-hydrogenation was eradicated. Heating the resulting hydroxy acid at reflux overnight in toluene induced lactonisation. While an acid wash facilitated removal of the quinoline. In this way the desired lactone **2.18** was obtained in 59% yield. Scale-up proved problematic due to difficulties in monitoring the reaction. Although over-hydrogenation could be avoided, it proved very difficult to force the reaction to completion. Interestingly, the prolonged reaction times needed induced lactonisation, so heating at reflux overnight was no longer necessary. Coupling of the benzyl protected lactone **2.18** with bis(phenylseleno)methane to afford the selenide δ-lactone **2.19** was accomplished using the previously described procedure but gave a low yield of 34%.[59]

2.3. Incorporating the Side Chain of Pederic Acid.

Having achieved a synthesis of the tetrahydropyran ring, our attention now turned to the incorporation of the hydroxyacetic acid side chain. To that end, trimethylacetaldehyde was reacted with trimethylsilyl trimethylsiloxyacetate at –78 °C in the presence of 10 mol% trimethylsiloxy triflate affording the racemic dioxolanone **2.20** in good yield.[64,65] The lithium enolate **2.21** was then formed by dropwise addition of **2.20** to a solution of LDA in THF (Scheme 2.4) and selenide lactone **2.9** added. This failed to give the expected adduct **2.22**, returning only both starting materials on work-up.



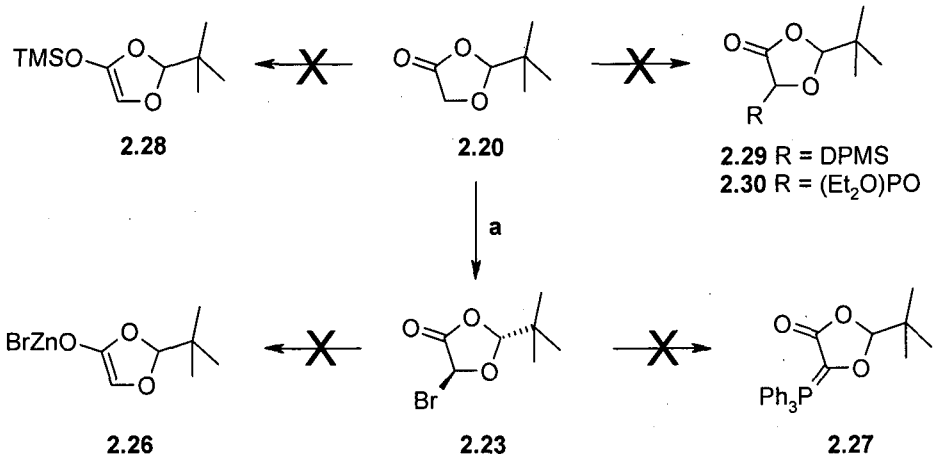
Reagents and conditions: a) LDA, THF, −78 °C, 40 min; (b) NBS, benzoyl peroxide, $(CH_2Cl)_2$, 80 °C, 3 h, 67%; (c) *para*-anisaldehyde, THF, −35 °C, 2 h, 28%, dr = 5:1; (d) δ-valerolactone, THF, −35 °C, 2 h, 15%.

Scheme 2.4. The Reactions of 2-(1,1-Dimethylethyl)-1,3-dioxolan-4-one.

The failure of this reaction led us to suspect that formation of enolate **2.21** had not been successful. Therefore we decided to prove its intermediacy by trapping it with a simple aldehyde. The desired enolate **2.21** was generated as before, then *para*-anisaldehyde added at −78 °C. The desired alcohol ester **2.24** was observed, albeit in a disappointing 28% yield and accompanied by traces of the starting material. The enolate was then reacted with *δ*-valerolactone to form lactol **2.25**. LRMS indicated a successful reaction, though the NMR spectra were too complicated to be accurately interpreted due to the presence of at least 4 diastereoisomers. A low yield of 15% was also obtained.

Alternative methods of coupling were investigated. Bromination of **2.20** to **2.23** was achieved in good yield by reaction with *N*-bromosuccinimide at reflux in 1,2-dichloroethane.[66] Attempts to form the corresponding Wittig salt **2.27** proved unsuccessful,[67] possibly due to steric encumbrance and adverse electronic effects. Formation of the Reformatsky reagent **2.26** was also unsuccessful with only degraded starting materials recovered (Scheme 2.5). Efforts to synthesise silanes **2.28** and **2.29** were made, but in both cases the reactions failed, returning only the dioxolanone starting materials.[68] While treatment of 2-(1,1-dimethylethyl)-1,3-

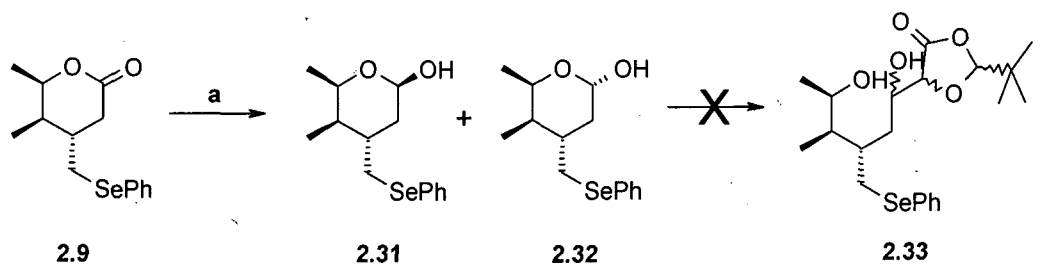
dioxolan-4-one **2.20** with LDA followed by addition of diethyl phosphorochloridite failed to form the desired phosphonate carbanion **2.30**.[69] Here too, unreacted starting materials accounted for much of the mass balance.



Reagents and conditions: a) NBS, benzoyl peroxide, $(CH_2Cl)_2$, 80 °C, 3 h, 67%

Scheme 2.5. Investigating the Coupling Reaction of **2.20** and **2.23**.

The reduction of lactone **2.9** to the lactols **2.31** and **2.32** with DIBAL-H at −78 °C proved successful, giving an inseperable mixture of diasteroisomers in 80% yield (Scheme 2.6). However, attempts to couple these lactols with lithium enolate **2.21** failed to give the desired product **2.33**, returning only recovered starting material and unidentified degradation products.

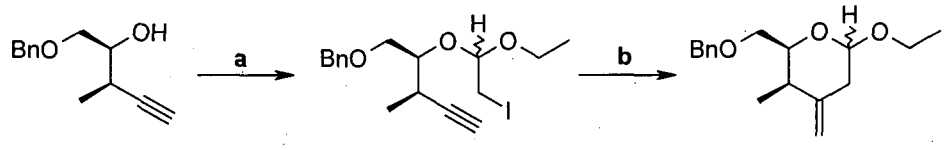


Reagents and conditions: a) DIBAL-H, PhMe, −78 °C, 12 h, 80%, dr = 1:1.

Scheme 2.6. Reduction of lactone **2.9**.

2.4. Alternative Method of Forming Pederic Acid.

These frustrations led us to explore an alternative approach to the pederic acid fragment **2.2**, based on a radical cyclisation strategy (Scheme 2.7). Attempts to synthesise iodoacetal **2.34** and effect its radical cyclisation to **2.35** proved problematic. 3-Butyn-1-ol was reacted with ethyl vinyl ether and *N*-iodosuccinimide to generate iodoacetal **2.34** in 78% yield. All attempts to cyclise to tetrahydropyran **2.35** met with failure, alkyne **2.15** was isolated as the sole product.

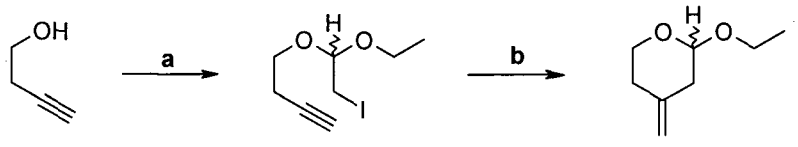


2.15 **2.34** **2.35**

Reagents and conditions: (a) $EtOCHCH_2$, NIS, CH_2Cl_2, 24 h, 78%. (b) proposed- $n$$Bu_3SnH$, VAZO, 70 °C, 2 h.

Scheme 2.7. A Radical Cyclisation Approach.

At this stage we decided to examine hydroxy alkyne **2.36** as a model. Iodoacetal **2.37** was generated in 99% yield by reacting **2.36** with ethyl vinyl ether and NIS. The tributyltin hydride mediated radical cyclisation reaction of **2.37** failed to generate the desired alkene **2.38**, instead giving a complex product mixture. After purification by column chromatography using K_2CO_3 to remove tributyltin residues, the main component of the reaction mixture was 3-butyn-1-ol, **2.36** (Scheme 2.8).



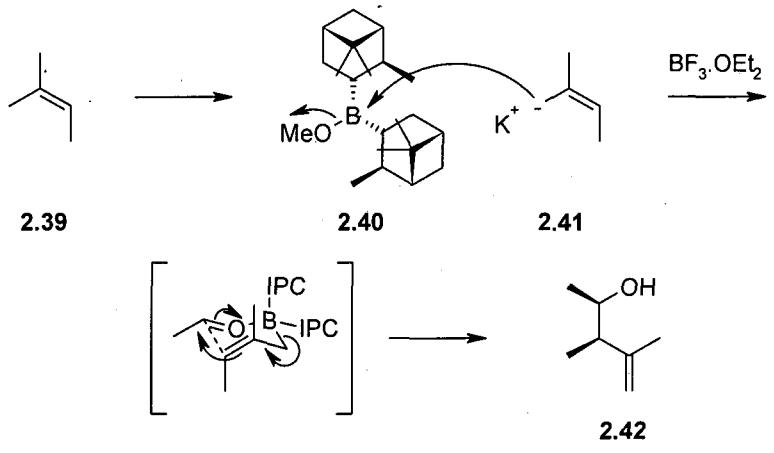
2.36 **2.37** **2.38**

Reagents and conditions: (a) $EtOCHCH_2$, NIS, CH_2Cl_2, 24 h, 99%; (b) proposed- $n$$Bu_3SnH$, VAZO, 70 °C, 2 h.

Scheme 2.8. Radical Cyclisation Model Studies.

2.5. LICKOR superbase reactions.

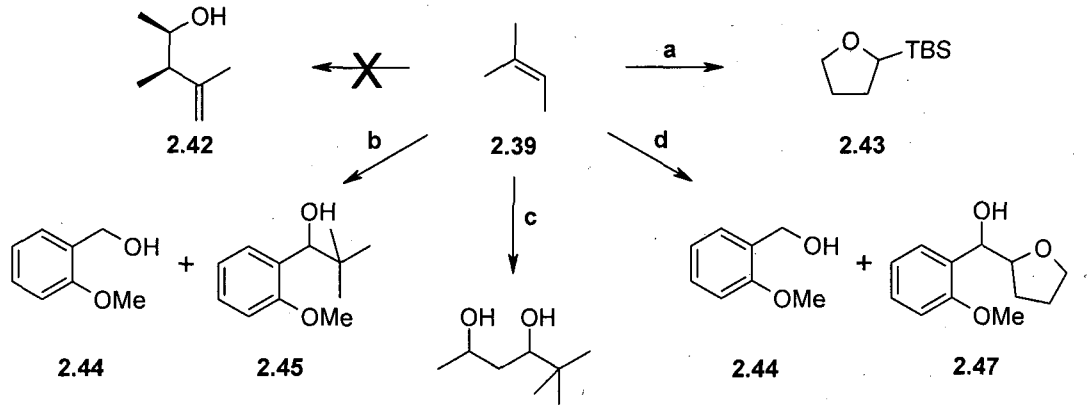
We envisaged a new route to the pederic acid skeleton, from the homoallylic alcohol **2.42**. Our plan was to deprotonate alkene **2.39** using a "superbase"[70] to generate alkyl anion **2.41** (Scheme 2.9). Addition of diisopinocamphenylborane,[48] **2.40**, $BF_3.OEt_2$ and ethanal should then give homoallylic alcohol **2.42** in high enantiomeric excess.



2.39 **2.40** **2.41** **2.42**

Scheme 2.9. Proposed Formation of Homoallylic Alcohol **2.42**.

Initial attempts to prepare homoallylic alcohol **2.42** from commercially available alkene **2.39** were not successful. Reactions were difficult to monitor, and it was unclear whether the LICKOR superbase was effecting deprotonation of **2.39** to **2.41**.[70] We thus decided to trap anion **2.41** with a simple aldehyde (Scheme 2.10). The *t*BuLi/KO*t*Bu mixture was generated in THF as before at −78 °C, then 2-methyl-2-butene and *o*-anisaldehyde were added sequentially. The desired alkene was not observed. Rather, a mixture of products was isolated, including alcohol **2.44**, arising from a Cannizzaro reaction,[71] and the α-substituted THF **2.47**. The reaction was repeated using TBSCl to trap the anion and gave α-silyl tetrahydrofuran **2.43** in poor yield.



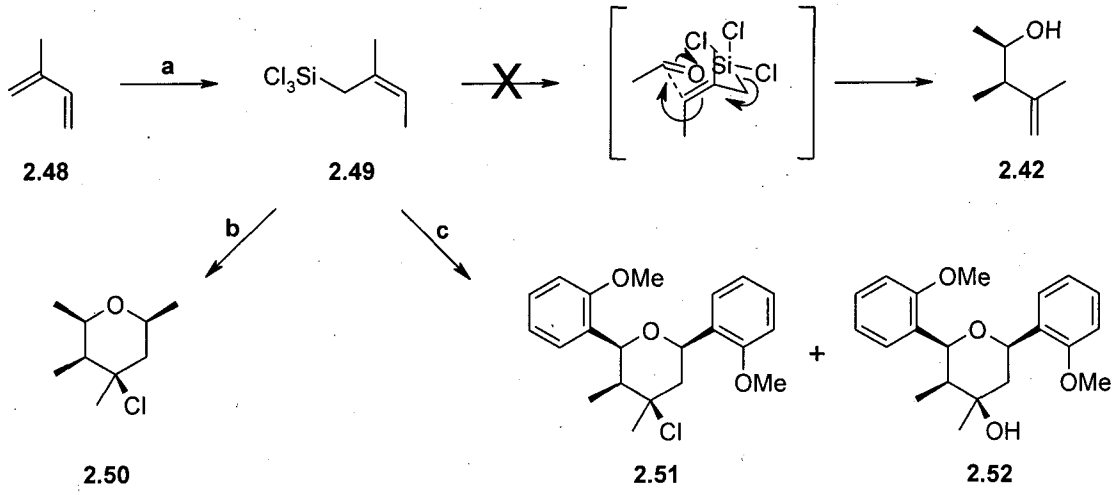
Reagents and conditions: - (a) *t*BuLi, KO*t*Bu, TBSCl, THF, −78 °C to RT, 16 h, 17-66%; (b) *t*BuLi, KO*t*Bu, *o*-anisaldehyde, pentane, −78 °C to RT, 16 h, 45% **2.44**, 28% **2.45**; (c) *t*BuLi, KO*t*Bu, CH_3CHO, pentane, −78 °C to RT, 16 h, 37%; (d) *t*BuLi, KO*t*Bu, *o*-anisaldehyde, THF, −78 °C to RT, 16 h, 17-66%.

Scheme 2.10. Unwanted Products of LICKOR Reactions with **2.39**.

To prevent the side reactions involving THF, the LICKOR superbase was formed in pentane at −78 °C.[72] The alkene **2.39** was added and the reaction mixture warmed to RT before re-cooling to −78°C. Addition of 2-methoxybenzaldehyde followed by an aqueous work-up gave alcohol **2.44**, the product of a Cannizzaro reaction.[71] A further by-product was alcohol **2.45**, arising from direct addition of *t*BuLi to the aldehyde. In a final attempt to form the hydroxy alkene **2.42**, the reaction was carried out with acetaldehyde. In this instance the major product isolated was **2.46**, the result of acetaldehyde self condensation followed by addition of *tert*-butyl lithium.

2.6. Further attempts to form 2.42.

Our failure to generate homoallylic alcohol **2.42** using LICKOR superbase methodology led us to an alternative strategy. We planned to synthesise **2.42** from isoprene **2.48** via **2.49**. Trichlorosilane **2.49** was obtained from the reaction of **2.48** with trichlorosilane, triphenylphosphine and catalytic bis(benzonitrile)palladium dichloride in 86% yield (Scheme 2.11).[73] Dropwise addition of **2.49** to acetaldehyde and boron trifluoride diethyl etherate at −78 °C did not generate the desired hydroxyl alkene **2.42**, giving instead tetrahydropyran **2.50** in 19% yield.



Reagents and conditions: - (a) $SiCl_3H$, PPh_3, $(PhCN)_2PdCl_2$, 70 °C, 5 h, 86%; (b) acetaldehyde, $BF_3.OEt_2$, CH_2Cl_2, −78 °C, 5 h, dr = 3:2, 19%; (c) *o*-anisaldehyde, $BF_3.OEt_2$, CH_2Cl_2, −78 °C, 5 h, **2.51**:**2.52** = 1:1, 30%;.

Scheme 2.11. Cyclisations from Isoprene.

The identity of the product proved hard to elucidate, so the reaction was repeated with *o*-anisaldehyde. In this case two products were formed, **2.51** and **2.52**. Fortunately the former was a crystalline solid, so an x-ray crystal structure was obtained. This showed it to be tetrahydropyran **2.51**. By analogy, we deduced that the second product of the reaction was the corresponding alcohol **2.52** and that the acetaldehyde reaction had produced THP **2.50**.

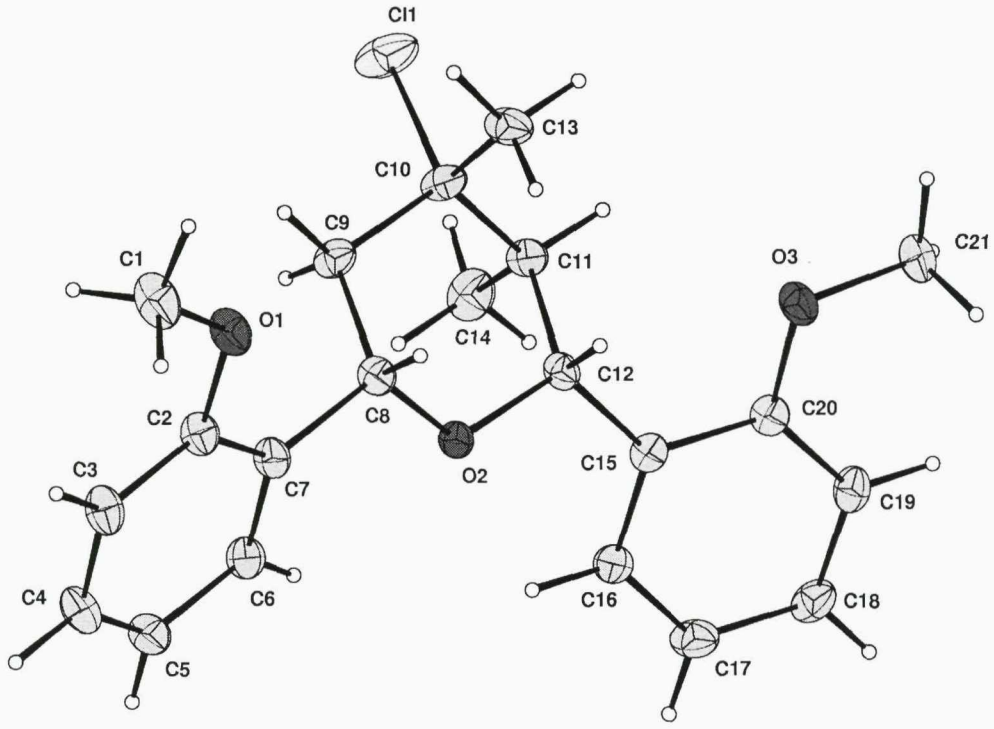
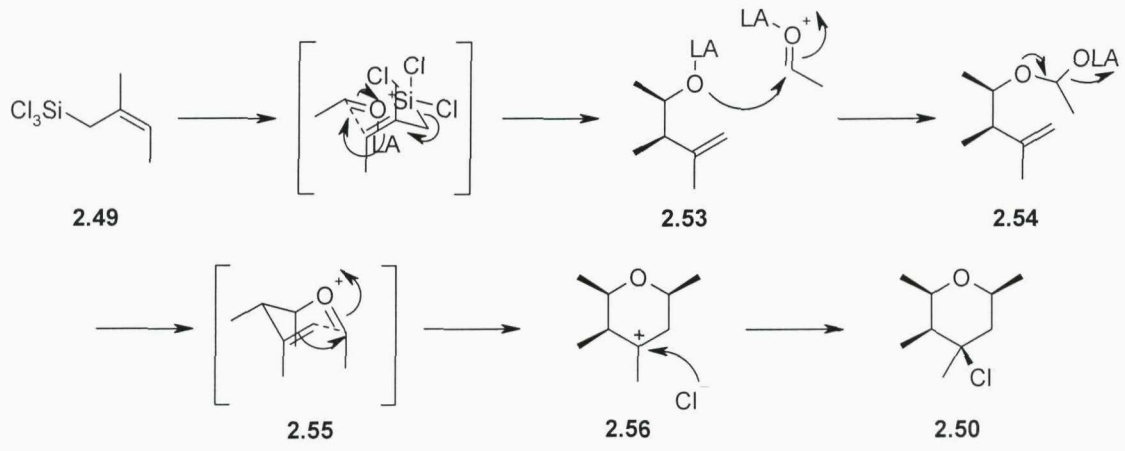


Figure 2.1. X-Ray Crystal Structure of THP **2.51**.

A plausible mechanism for the formation of tetrahydropyrans **2.50** - **2.52** is shown in Scheme 2.12. Addition of trichlorosilane **2.49** to acetaldehyde first induces their union to **2.53**. This adduct now adds to a second molecule of acetaldehyde to give intermediate **2.54**. Collapse to the oxonium ion next induces cyclisation *via* the chair-like transition state to produce tetrahydropyran cation **2.56**. Capture by chloride completes the sequence to give **2.50**.



Scheme 2.12. Mechanism of Lewis Acid Mediated Cyclisation.

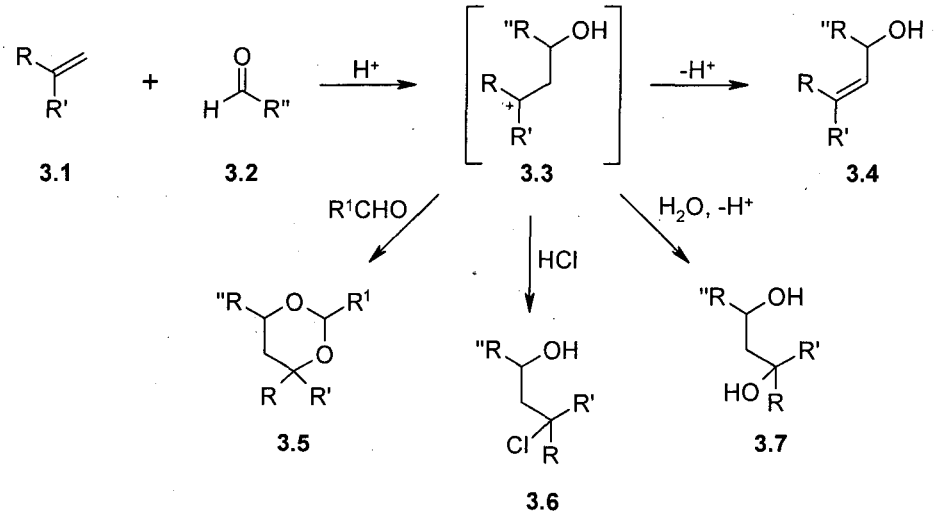
Since **2.50-2.52** are close analogs of the tetrahydropyran found in pederic acid we decided to investigate the cyclisation reaction further. In particular, our plan was to synthesise homoallylic alcohol **2.53** and investigate its union with various aldehydes under Lewis acid mediated cyclisation conditions.

3. The Lewis Acid Mediated Cyclisation.

3.1. Background.

3.1.1. The Prins Reaction.

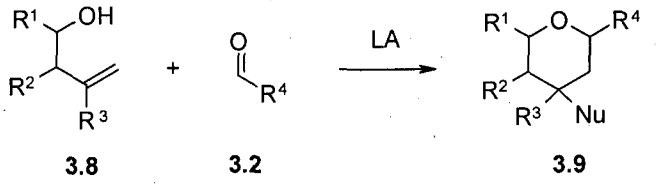
The condensation of olefins with aldehydes in the presence of an acid catalyst is usually called the Prins reaction.[74,75] A number of different products have been generated from these reactions, including homoallylic alcohols, 1,3-dioxanes[76] and 1,3-glycols (Scheme 3.1). An acid catalysed addition of alkene **3.1** to aldehyde **3.2** generates the intermediate cation **3.3**. This then collapses by deprotonation or reaction with nucleophiles to generate a wide range of products. The reaction proceeds with a variety of carbonyl compounds, alkenes and acid sources, including Lewis acids.[76-78]



Scheme 3.1. Products of the Prins Reaction.

Tetrahydropyrans can be generated from the acid catalysed cyclisation reaction of homoallylic alcohols with aldehydes (Scheme 3.2).[79-87] Many acid catalysts can be used, including strong mineral acids and Lewis acids. Many aldehydes and different

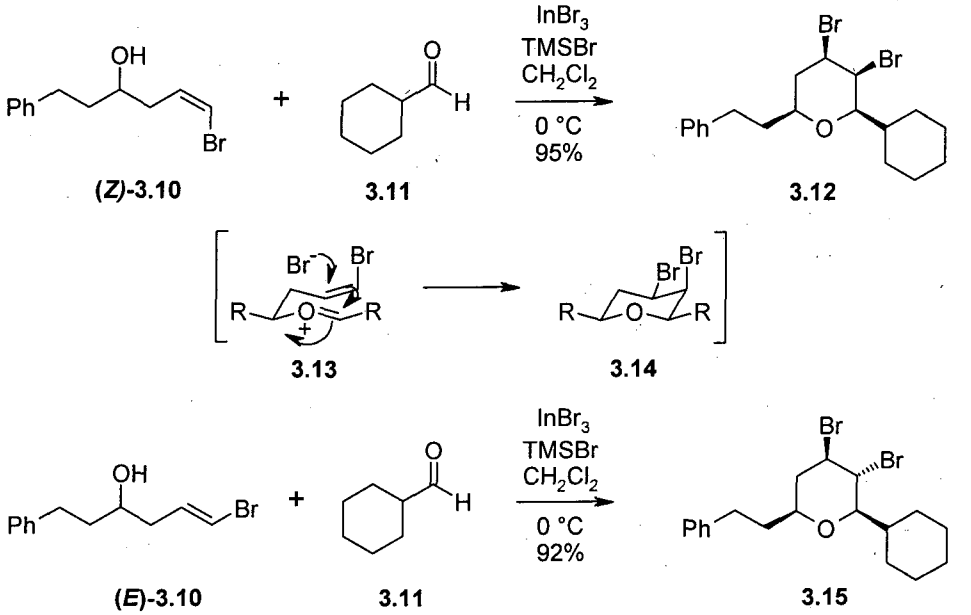
homoallylic alcohols have been used to synthesise a broad range of functionalised tetrahydropyrans. Furthermore, these reactions often proceed with excellent diastereoselectivity, though this is dependent on the starting materials used.



3.8 **3.2** **3.9**

Scheme 3.2. Tetrahydropyran Formation.

Loh and co-workers[87] developed an interesting strategy to construct tetrasubstituted THP rings using indium based Lewis acids (Scheme 3.3).[88] Indium tribromide was found to be the most efficient Lewis acid in the synthesis of a number tetrahydropyrans. Cyclisation of **(*Z*)-3.10** with aldehyde **3.11** gave the corresponding dibrominated THP **3.12** with high stereocontrol. The reaction proceeds via the chair like transition state **3.13**. Interestingly, the reaction of **(*E*)-3.10** with **3.11** gives the *trans* dibrominated THP **3.15**, with TMSBr used as a source of Br^-.



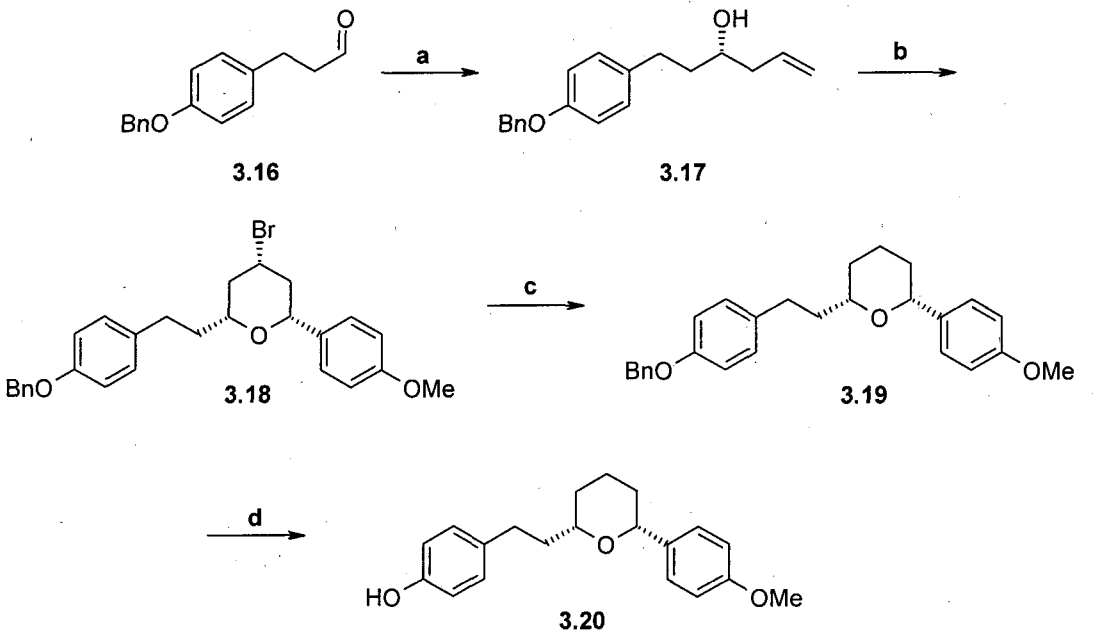
(*Z*)-3.10 **3.11** **3.12**

3.13 **3.14**

(*E*)-3.10 **3.11** **3.15**

Scheme 3.3. Loh's Tetrasubstituted THP formation.[87]

The synthetic value of this reaction has been demonstrated in two natural product syntheses.[89,90] The synthesis of (−)-centrolobine **3.20** was achieved in 4 steps from aldehyde **3.16**.[89] Asymmetric allylation of **3.16** to the homoallylic alcohol **3.17** proceeded smoothly in moderate yield and good enantiomeric excess. Initial attempts to carry out the Lewis acid mediated cyclisation with $In(OTf)_3$ proved problematic, due to epimerisation of the THP **3.18**. By using a weaker Lewis acid, $InBr_3$, Loh found that the cyclisation reaction proceeded with retention of enantiomeric purity. Reduction of the bromide under radical conditions, and benzyl deprotection, gave (−)-centrolobine **3.20**.



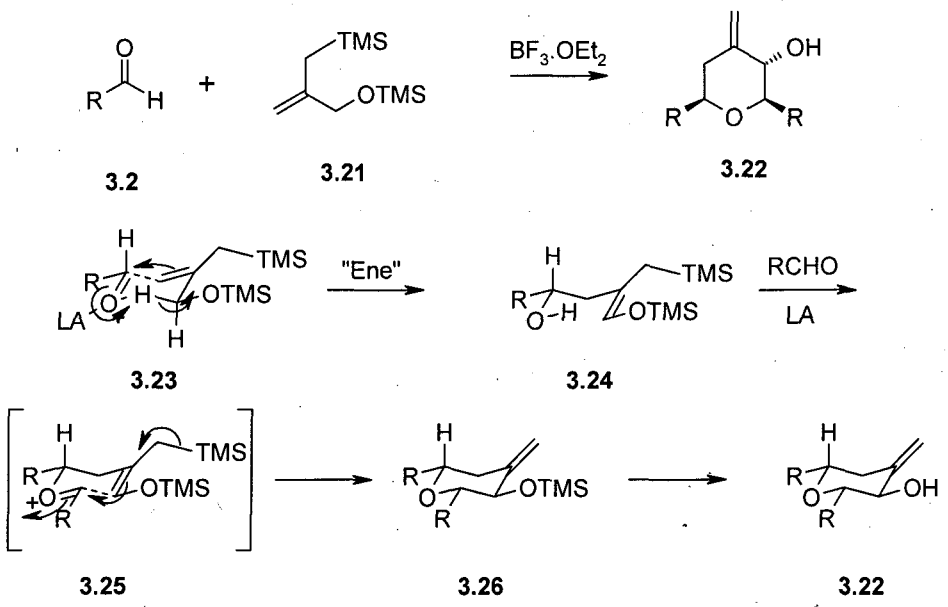
Reagents and conditions: - (a) $InCl_3$, (*R*)-BINOL, allyl-$SnBu_3$, CH_2Cl_2, −78 °C to 25 °C, 24 h, 68%, 84% ee; (b) $InBr_3$, TMSBr, *p*-anisaldehyde, CH_2Cl_2, −78 °C, 1 h, 83%; (c) Bu_3SnH, ABCCN, PhH, reflux, 24 h, 98%; (d) H_2, Pd/C, MeOH/EtOAc, 7 h, 71%, 84% ee.

Scheme 3.4. Loh's Synthesis of (-)-Centrolobine.[89]

3.1.2. The Intramolecular Silyl-Modified Sakurai Reaction.

A new methodology which allows the one-step preparation of *exo*-methylene tetrahydropyrans has been developed.[91-99] The silyl-modified Sakurai reaction prepares homoallylic ethers directly from carbonyl compounds.[91] An intramolecular variant of this reaction has been used to synthesise trisubstituted tetrahydropyrans possessing an *exo*-methylene unit **3.22** (Scheme 3.5). The proposed mechanism

starts with an *ene*-type reaction *via* the chair-like transition state **3.23**.[93] Further condensation of the free hydroxyl function with the unreacted aldehyde then generates the oxonium cation **3.25** which undergoes intramolecular Lewis acid mediated cyclisation producing THP **3.26**. The chair-like transition state during the cyclisation accounts for the observed stereochemistry, only one diastereoisomer being formed.

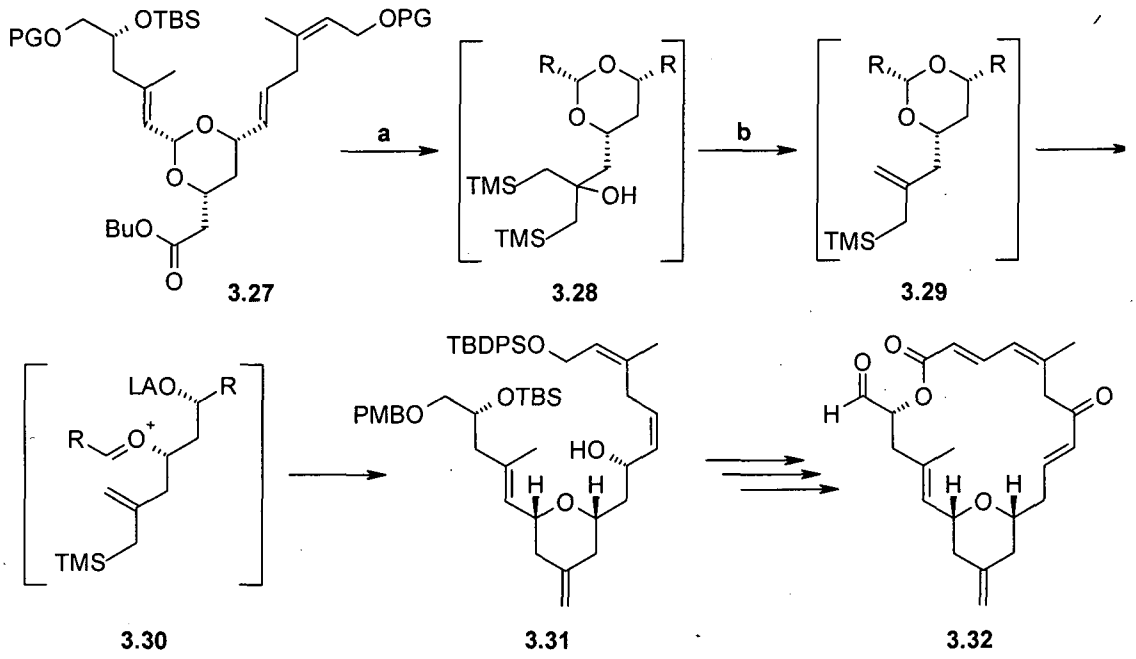


Scheme 3.5. The Intramolecular Silyl-Modified Sakurai Reaction.[93]

The reaction has been exemplified in approaches to several natural products.[94,97,98,100] Notably, Floreancig and co-workers[98] completed the total synthesis of (+)-dactylolide **3.32**, using the aforementioned Lewis acid mediated cyclisation to incorporate the *exo*-methylene tetrahydropyran.

Treatment of acetal **3.27** with excess $TMSCH_2MgBr$ and $CeCl_3$ surprisingly gave the THP **3.31** as the major product (Scheme 3.6). This resulted from the initial formation of allylsilane **3.29**, followed by acetal ionisation to the oxocarbenium species **3.30** and cyclisation. Although giving the desired natural product precursor, Floreancig found this method extremely capricious. A more reliable protocol was therefore devised, in which the addition of the Grignard reagent and $CeCl_3$ was followed by an aqueous $NaHCO_3$ quench. The resulting crude tertiary alcohol **3.28** was then dissolved in CH_2Cl_2 and treated with pyridinium triflate and $MgSO_4$ to

effect allylsilane formation and cyclisation to **3.31**. This mild process provided the (+)-dactylolide precursor **3.31** in 75% yield from **3.27**.[98]



Reagents and conditions: - (a) Me_3SiCH_2MgCl, $CeCl_3$, THF, −78 °C to RT; (b) Py.HOTf, $MgSO_4$, CH_2Cl_2, 75%.

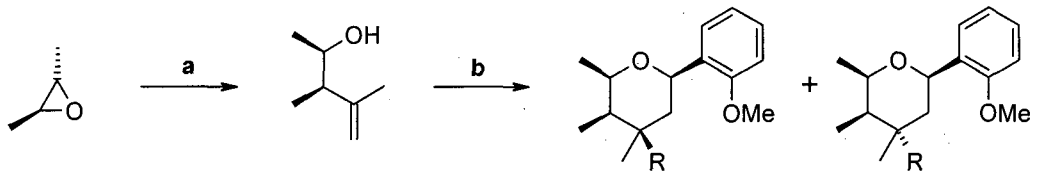
Scheme 3.6. The Total Synthesis of (+)-Dactylolide.[98]

3.1.3. Our Plan.

In order to generate the THP skeleton present in pederic acid, we planned to carry out the Lewis acid mediated cyclisation with homoallylic alcohol **3.35**. We were aiming to find conditions that would generate the *exo*-methylene functionality present in pederic acid.

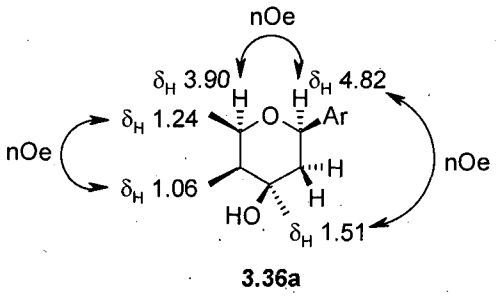
3.2. Results and Discussion.

Ring opening of *trans*-2,3-epoxybutane **3.34** to homoallylic alcohol **3.35** was completed smoothly using isopropenylmagnesium bromide and copper chloride at −40 °C in 91% yield (Scheme 3.7).[101] Dropwise addition of homoallylic alcohol **3.35** to a solution of *o*-anisaldehyde and boron trifluoride diethyl etherate in CH_2Cl_2 at −78 °C gave two diastereoisomers of tetrahydropyran **3.36**. The major product **3.36a** was shown by n.O.e studies to have *rel*-(2*R*,3*S*,4*R*,6*R*) stereochemistry, differing from its partner **3.36b** in respect of the alcohol configuration at C4. A minor by-product was also observed, in which the hydroxyl function was replaced by a fluoride group.



Reagents and conditions: - (a) Isopropenylmagnesium bromide, CuCN, Et_2O, −40 °C, 14 h, 91%; (b) *o*-anisaldehyde, $BF_3.OEt_2$, CH_2Cl_2, −78 °C, 5 h, 38%, dr = 3:2 (**3.36a**:**3.36b**, **3.37a**:**3.37b**).

Scheme 3.7. Lewis Acid Mediated Cyclisation.

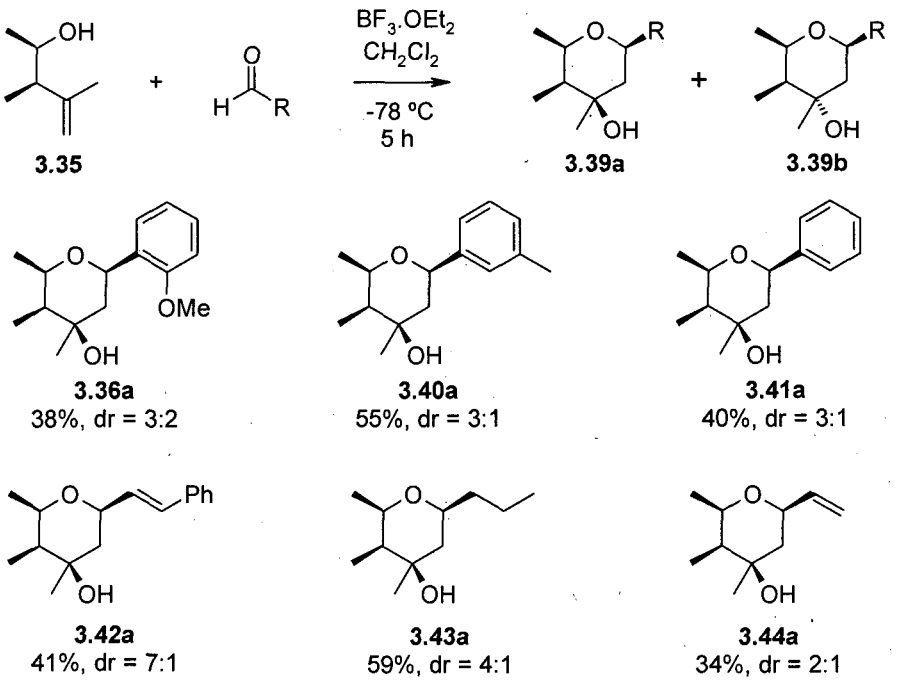


3.36a

Figure 3.1. N.O.e Studies on **3.36a**.

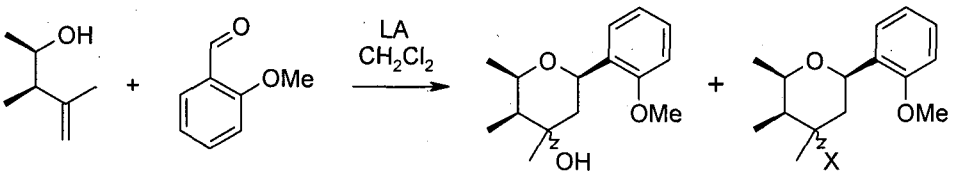
Optimal conditions for the initial reactions were found to be 2 molar equivalents of aldehyde and $BF_3.OEt_2$ with respect to **3.35**. The reactions proceeded best in CH_2Cl_2, although results in toluene were comparable. To test the reproducibility of this interesting Lewis acid mediated cyclisation, the reaction was repeated with a range of aldehydes with the results summarised in Scheme 3.8. All reactions were

carried out in CH_2Cl_2 at −78 °C, using boron trifluoride diethyl etherate as the Lewis acid.



Scheme 3.8. $BF_3.OEt_2$ Mediated Cyclisation Results.

In order to use this reaction in our synthesis of pederic acid, its efficiency needed to be improved. Thus, we decided to examine a variety of Lewis acids in the hope of achieving better yields and improved diastereoselectivity. However, our ultimate aim was to generate a product with the *exo*-methylene subunit of pederic acid in place. The cyclisation reaction was repeated with a range of Lewis acids, and the results are summarised in Table 3.1. All reactions gave alcohol **3.36** as the main product, with a minor product **3.46** observed where X is the halide from the Lewis acid. The best result was obtained with aluminium trichloride, giving an improved yield of 50%. However none of the Lewis acids gave the desired *exo*-methylene product.



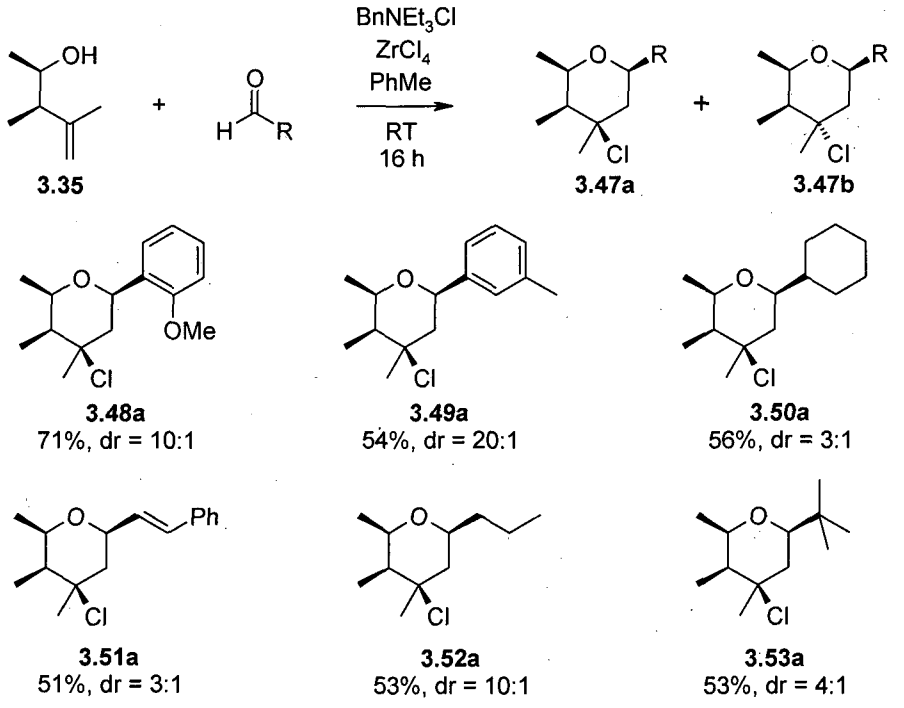
3.35 **3.45** **3.36** **3.46a** X = Cl **3.46b** X = F

			% Yield	
Lewis acid	**Time h**	**Temp °C**	**3.36**	**3.46a/b**
BF_3OEt_2	5	−78	38	3
BF_3	5	−78	34	4
$TiCl_4$	5	−78	29	2
$SnCl_4$	5	−78	35	6
$InCl_3$	16	25	13	2
$Yb(OTf)_3$	16	25	49	0
$AlCl_3$	16	25	50	12
$ZnCl_2$	16	25	27	3

Table 3.1. Lewic Acid mediated Cyclisation.

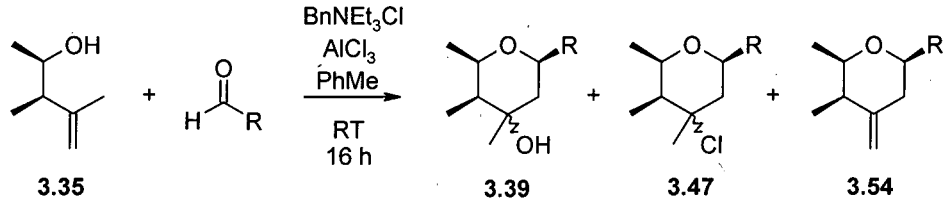
Attempts to form an ionic Lewis acid were successfully made by treating a CH_2Cl_2 solution of benzyltriethylammonium chloride with aluminium chloride at 0 °C. The reaction was allowed to warm to RT and stirred overnight. After removal of the solvent *in vacuo*, the resulting sticky white crystalline solid was found to be the ionic Lewis acid $[BnEt_3]^+AlCl_4^-$.[102] Similar Lewis acids were made using titanium tetrachloride and zirconium tetrachloride. All were extremely hygroscopic and had to be formed under anhydrous conditions and stored under vacuum.

Dropwise addition of homoallylic alcohol **3.35** to a solution of $[BnNEt_3]^+ZrCl_5^-$ and an aldehyde in toluene gave the diastereoisomers **3.47a** and **3.47b** (Scheme 3.9). The reaction works well using the pre-formed Lewis acid and gave similar yields when generated *in situ*. Notably, with this ionic Lewis acid, a significant improvement in yield and diastereoselectivity was observed compared to the aluminium chloride mediated cyclisations.



Scheme 3.9. $[BnNEt_3]^+ZrCl_5^-$ Mediated Cyclisation Results.

When the reaction was conducted using $[BnNEt_3]^+AlCl_4^-$, under the aforementioned conditions we generate alcohols **3.39**, chlorides **3.47** and the desired *exo*-methylene THP **3.54** (Table 3.2) The reaction was again repeated with a range of aromatic and aliphatic aldehydes. In all cases examined, compounds **3.47** and **3.54** were given in a 1:1 ratio, with the alcohol **3.39** given as a minor product. The best result was obtained using *trans*-cinnamaldehyde, generating the *exo*-methylene product in 40% yield. Again the Lewis acid can be generated *in situ* to simplify the experimental procedure. We have encountered problems with the aqueous work-up in all reactions using aluminium based Lewis acids. The aluminium salts generated have a strong tendancy to form emulsions on work-up. These problems were eliminated by carrying out a wash with 10% aqueous Rochelle's salt solution.

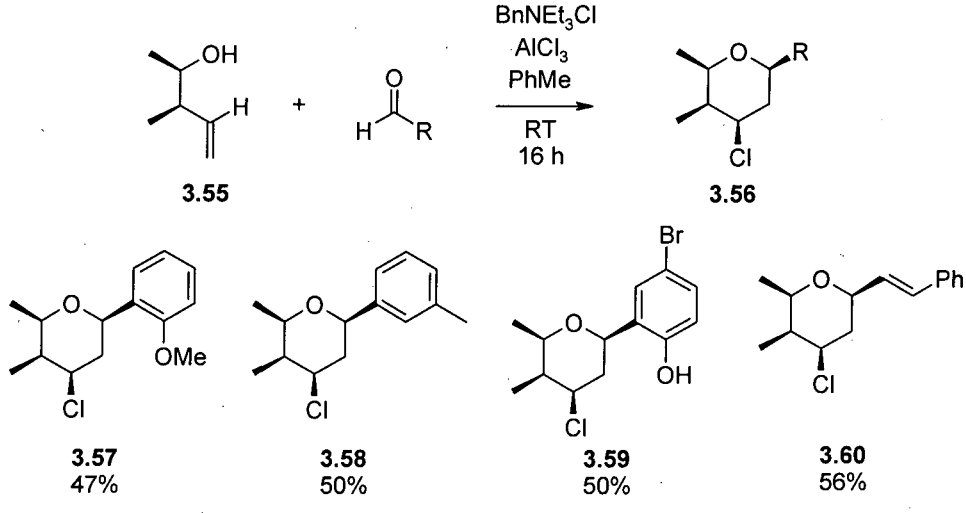


3.35 3.39 3.47 3.54

RCHO	3.39		3.47		3.54
	% Yield	dr	% Yield	dr	% Yield
o-PhOMe	7	3:2	27	8:1	27
m-PhMe	6	3:1	32	20:1	32
C_6H_{11}	6	2:1	28	3:1	28
$(CH)_2Ph$	5	5:1	40	3:1	40
C_3H_7	2	4:1	35	10:1	35
C_4H_9	3	3:1	31	4:1	31

Table 3.2. $[BnNEt_3]^+AlCl_4^-$ Mediated Cyclisation Results.

Formation of homoallylic alcohol **3.55** was accomplished by opening *trans*-2,3-epoxybutane with vinylmagnesium bromide. $[BnNEt_3]^+AlCl_4^-$ mediated cyclisation of **3.55** with various aromatic aldehydes gave THP **3.56** in moderate yield with complete diastereoselectivity (Scheme 3.10).

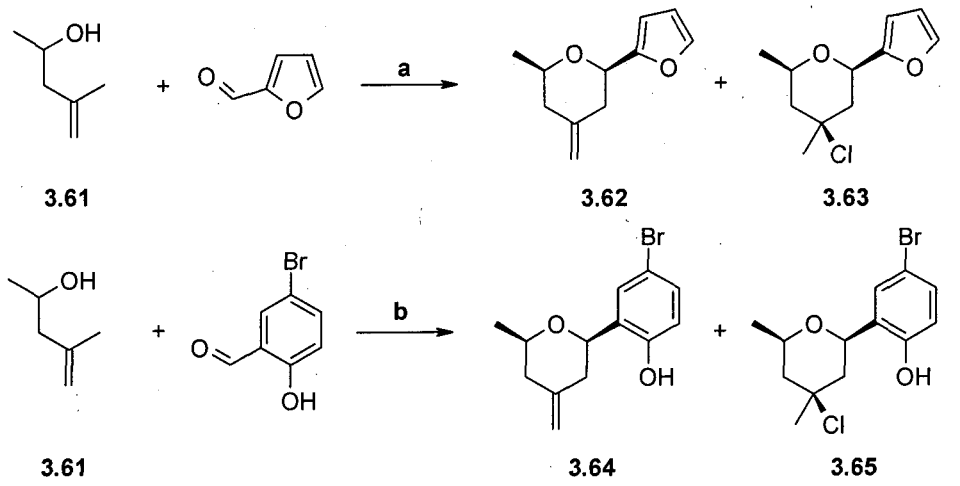


3.55 **3.56**

3.57 47% **3.58** 50% **3.59** 50% **3.60** 56%

Scheme 3.10. $[BnNEt_3]^+AlCl_4^-$ Mediated Cyclisation Results.

Further investigation into this interesting reaction led us to try the Lewis acid mediated cyclisation with homoallylic alcohol **3.61**. This was formed in the usual way, by ring opening of the epoxide with isopropenylmagnesium bromide. The cyclisation reaction was then attempted using $[BnNEt_3]^+AlCl_4^-$. 2-furaldehyde and 5-bromosalicylaldehyde both gave a 1:1 mixture of the chloride and *exo*-methylene isomers in good yield (Scheme 3.11). Tetrahydropyrans **3.64** and **3.65** were inseparable by column chromatography.

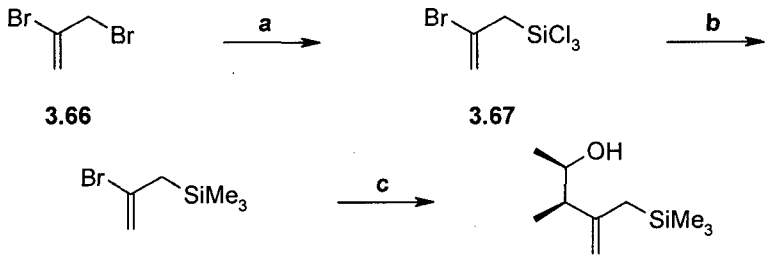


Reagents and conditions: - (a) (i) $AlCl_3$, $BnNEt_3Cl$, PhMe, 0 °C to RT, 30 min (ii) $CHOC_4H_3O$, **3.61**, 16 h, 94%, **3.62**:**3.63** = 1:1; (b) (i) $AlCl_3$, $BnNEt_3Cl$, PhMe, 0 °C to RT, 30 min (ii) CHOPhBrOH, **3.61**, 16 h, 66%, **3.64**:**3.65** = 1:1.

Scheme 3.11. $[BnNEt_3]^+AlCl_4^-$ Mediated Cyclisation Results.

We had obtained some encouraging results in the formation of the *exo*-methylene tetrahydropyrans **3.54**. However, we were still plagued by the problem of product mixtures and the formation of the undesired alcohol **3.39** and chloride **3.47**. In order to eliminate these by-products, we decided to employ the silylated homoallylic alcohol **3.69**.[93] The synthesis of **3.69** started with dropwise addition of trichlorosilane to alkene **3.66** (Scheme 3.12). The reaction was extremely exothermic so great care had to be taken, particularly during scale-up. Crude trichlorosilane **3.67** was obtained on removal of the solvent by distillation and used in the next reaction without further purification. Addition of methylmagnesium bromide to **3.67** followed by Kugelrohr distillation, gave **3.68** in 41% yield over the

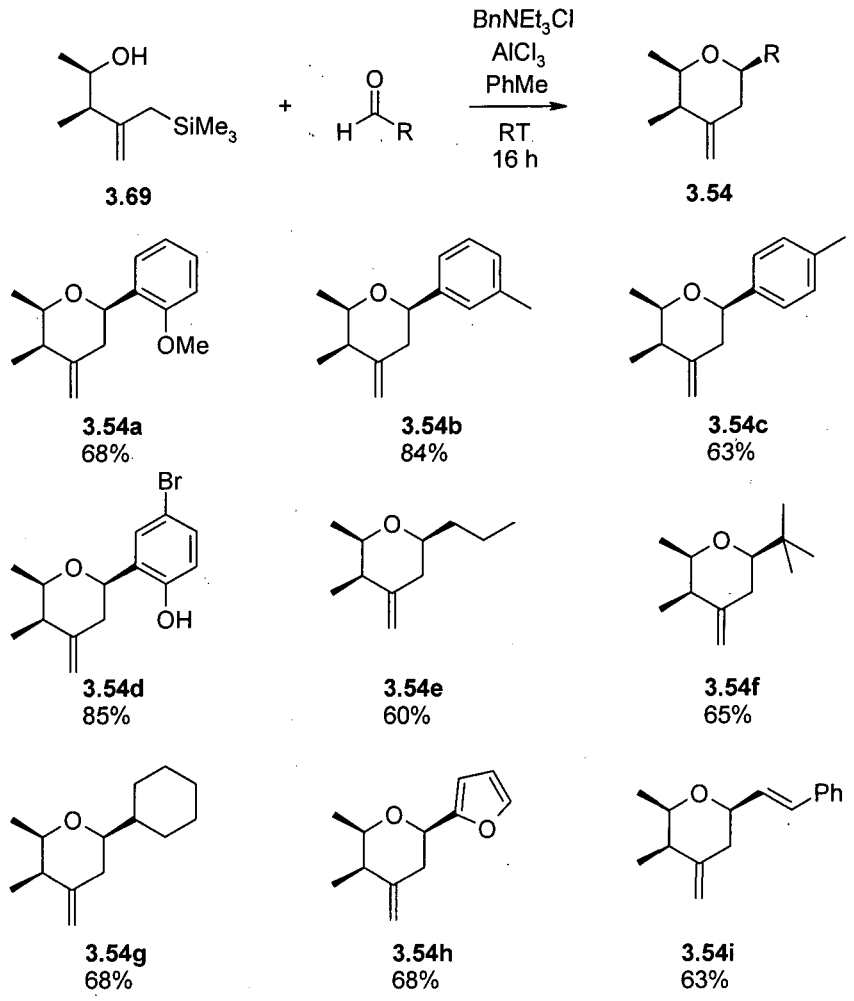
2 steps. Ring opening of *trans*-2,3-epoxybutane with the Grignard reagent formed from **3.68**, gave homoallylic alcohol **3.69** in 33% yield.



Reagents and conditions: - (a) Cl_3SiH, NEt_3, $CuCl_2$, Et_2O, 0 °C, 16 h; (b) CH_3MgBr, Et_2O, 0 °C, 16 h, 41% (2 steps); (c) Mg (s), *trans*-2,3-epoxybutane, CuCN, Et_2O, THF, −40 °C, 16 h, 33%.

Scheme 3.12. The Synthesis of Homoallylic Alcohol **3.69**.[103]

Cyclisation of homoallylic alcohol **3.69** with various aldehydes using $[BnNEt_3]^+AlCl_4^-$ as the Lewis acid on each occasion gave *exo*-methylene tetrahydropyran **3.54** as the sole isolated product (Scheme 3.13). The high yields (60-85%) and excellent diastereoselectivity were gratifying as they were suitable for exploration in our synthesis of pederic acid. The *trans*-cinnamaldehyde product **3.54i** was shown by n.O.e studies to have *rel*-(2*R*,3*R*,6*R*) stereochemistry.



Scheme 3.13. *Exo*-methylene THP Formation.

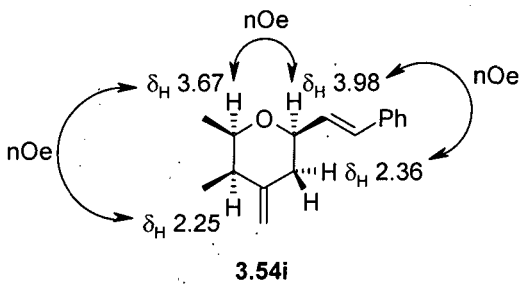
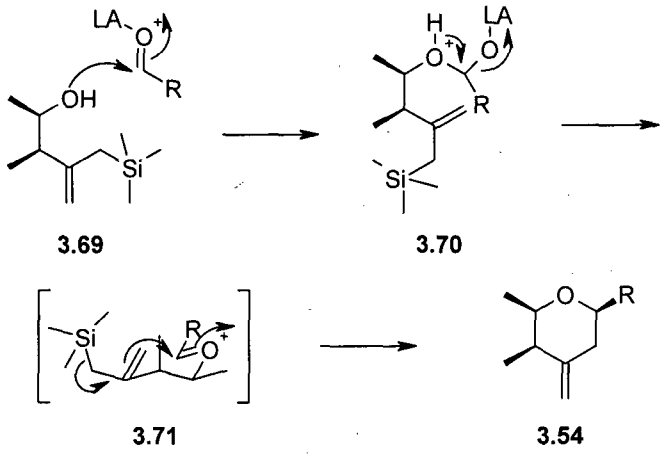


Figure 3.2. n.O.e Studies on **3.54i**.

A plausible mechanism for the formation of *exo*-methylene THP **3.54** is shown in Scheme 3.14. Addition of homoallylic alcohol **3.69** to the Lewis acid co-ordinated aldehyde induces their union to **3.70**. Formation of the oxonium ion **3.71** and cyclisation *via* the chair-like transition state gives the *exo*-methylene THP **3.54**.



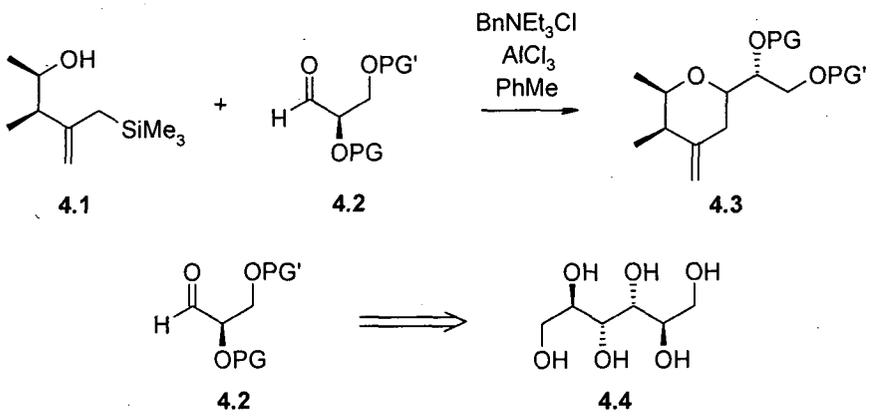
Scheme 3.14. Mechanism of *exo*-Methylene Formation.

We have established a diastereoselective route to tetrahydropyrans containing the *exo*-methylene functionality at C4. The method seemed ideally suited for an approach to pederic acid and our efforts in that regard are described in the following chapter.

4. Towards Pederic Acid.

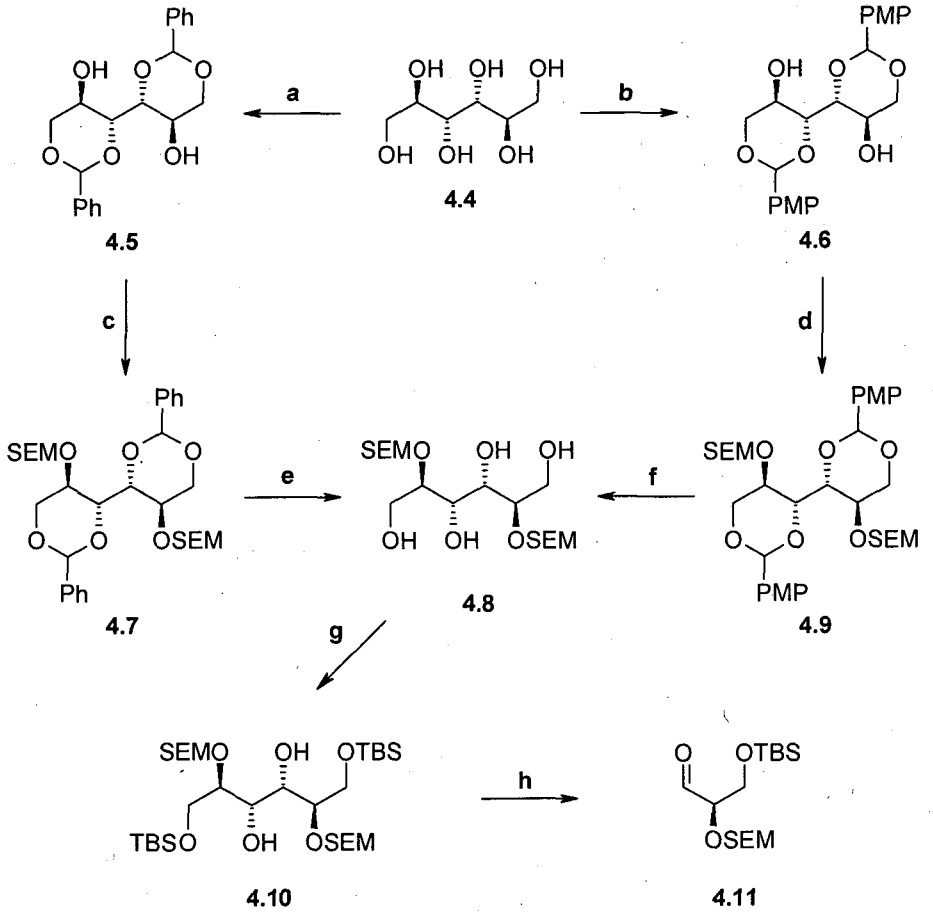
4.1. D-Mannitol Route.

We planned to use the Lewis acid mediated cyclisation to generate the tetrahydropyran skeleton in pederic acid (Scheme 4.1). We sought to react homoallylic alcohol **4.1** with an aldehyde of the general structure **4.2**. The stereogenic centres present in D-mannitol make it a convenient precursor to aldehyde **4.2**. Indeed, Breitfelder and co-workers have developed a synthesis of aldehyde **4.11** using this starting material.[19]



Scheme 4.1. Lewis Acid Mediated Cyclisation.

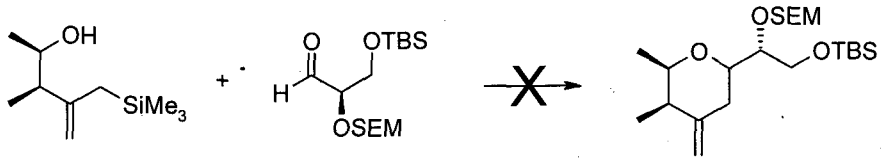
The synthesis of aldehyde **4.11** from D-mannitol began with the protection of the 1,3- and 4,6-diol functionalities as benzylidene acetals **4.5** using benzaldehyde and concentrated H_2SO_4 (Scheme 4.2).[19] SEM protection of the secondary alcohols led to **4.7** in 73% yield. Deprotection of the benzylidene acetals to tetrol **4.8** proved problematic, though a yield of 63% was obtained using hydrogenation at elevated pressure in acetic acid with a palladium catalyst. It was found that changing the diol protecting group from the benzylidene acetal to the *p*-methoxybenzylidene acetal **4.6** allowed deprotection to be achieved at atmospheric pressure in an improved yield of 72%.[104] TBS protection of the primary alcohol functionalities gave diol **4.10** in 86% yield, which was cleaved with lead(IV) acetate and $NaHCO_3$ to the desired aldehyde **4.11** in 82% yield after purification.



Reagents and conditions: - (a) Benzaldehyde, H_2SO_4, DMF, RT, 72 h, 30%; (b) *p*-anisaldehyde, trimethylorthoformate, H_2SO_4, DMF, 60 °C, 4 h, 26%; (c) $^iPr_2NEt$, SEMCl, CH_2Cl_2, RT, 72 h, 73%; (d) $^iPr_2NEt$, SEMCl, CH_2Cl_2, RT, 72 h, 94%; (e) H_2 (2 atm), 5% Pd/C, AcOH, RT, 4 h, 63%; (f) H_2 (1 atm), 5% Pd/C, AcOH, RT, 10 h, 72%; (g) 1*H*-imidazole, TBSCl, CH_2Cl_2, RT, 16 h, 86%; (h) $NaHCO_3$, $Pb(OAc)_4$, CH_2Cl_2, −78 °C, 20 min, 82%.

Scheme 4.2. The Synthesis of Aldehyde **4.11**.

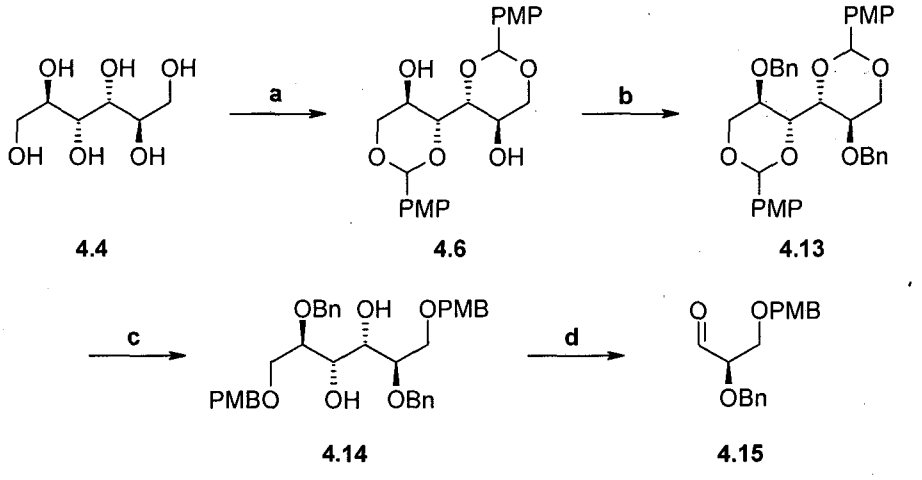
Attempted coupling of aldehyde **4.11** and homoallylic alcohol **4.1** failed to generate the desired THP **4.12** under a host of reaction conditions. The failure of the cyclisation reaction suggested that the silyl protecting groups in aldehyde **4.11** were not stable to Lewis acids, prompting us to change these to acid stable benzyl ethers.



4.1 4.11 4.12

Scheme 4.3. Attempted Lewis Acid Mediated Cyclisation.

The 1,3- and 4,6-diol functionalities were protected as *p*-methoxybenzylidene acetals **4.6** as previously described.[104] Protection of the secondary alcohols as benzyl ethers proceeded smoothly using benzyl bromide, TBAI and sodium hydride in 85% yield.[63] Selective reduction of the *p*-methoxybenzylidene acetals **4.13** to diol **4.14** leaving *p*-methoxybenzyl ether protecting groups on the primary alcohols, was achieved using $NaCNBH_3$ and TFA at 80 °C in 43% yield.[105] Cleavage of diol **4.14** with lead(IV) acetate gave the desired aldehyde **4.15** in 77% yield (Scheme 4.4).



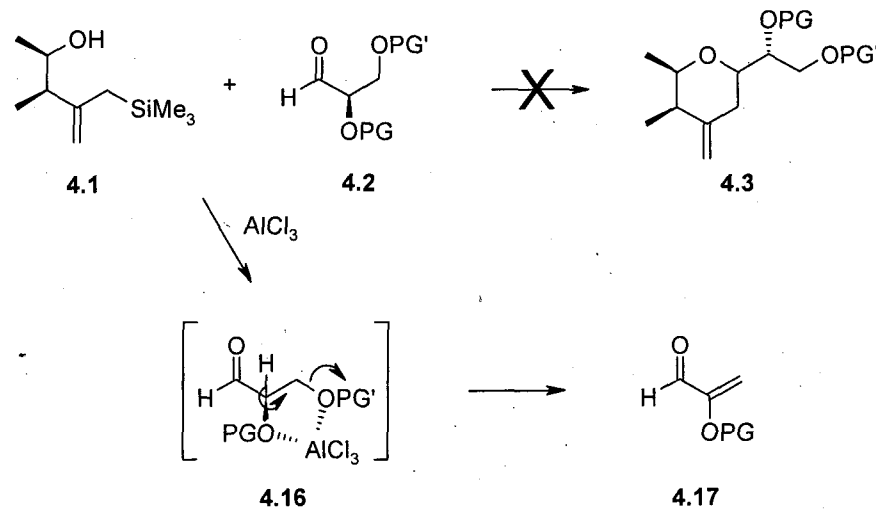
4.4 4.6 4.13

4.14 4.15

Reagents and conditions: - (a) *p*-anisaldehyde, trimethyl orthoformate, H_2SO_4, DMF, 60 °C, 4 h, 26%; (b) BnBr, TBAI, NaH, DMF, 0 °C, 12 h, 85%; (c) $NaCNBH_3$, TFA, DMF, 80 °C, 6 h, 43%; (d) $NaHCO_3$, $Pb(OAc)_4$, CH_2Cl_2, −78 °C, 20 min, 77%.

Scheme 4.4. Formation of aldehyde **4.15**.

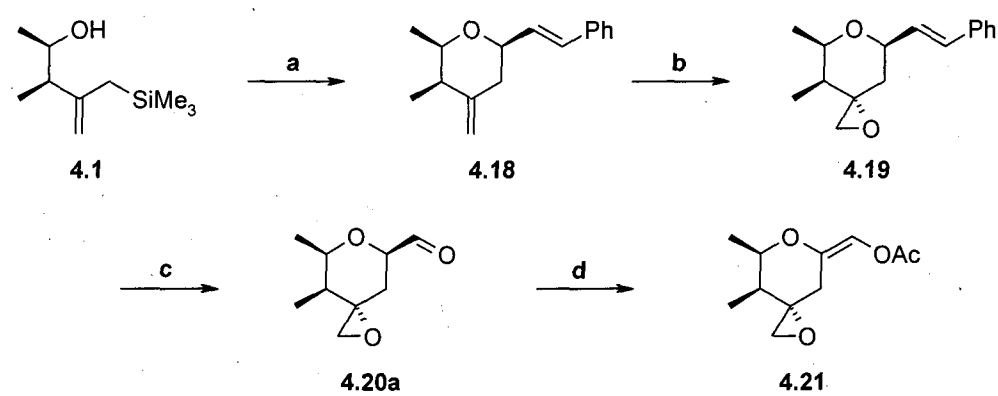
Lewis acid mediated cyclisation of homoallylic alcohol **4.1** with aldehyde **4.15** failed, yielding only products of degradation. It therefore seems likely that aldehydes such as **4.15** undergo β-elimination through intermediate **4.16** to give the unstable α,β-unsaturated aldehyde **4.17** (Scheme 4.5).



Scheme 4.5. β-Elimination Pathway.

4.2. *trans*-Cinnamaldehyde Route.

Having failed to form the pederic acid skeleton from these D-mannitol derived aldehydes, we began to consider methods of constructing the side chain from the *trans*-cinnamaldehyde derived tetrahydropyran **4.18** (Scheme 4.6).



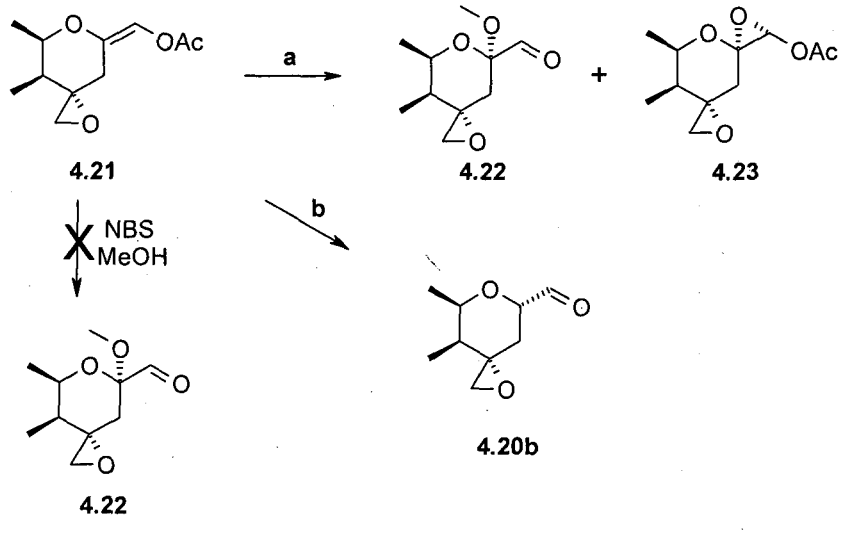
Reagents and conditions: - (a) *trans*-cinnamaldehyde, $[BnNEt_3]^+AlCl_4^-$, CH_2Cl_2, RT, 16 h, 63%; (b) *m*CPBA, CH_2Cl_2, RT, 16 h, dr = 20:1, 75%; (c) O_3 (1 – 2% in O_2), CH_2Cl_2/MeOH (84:16), PPh_3, 1.5 h, −78 °C, 62%; (d) K_2CO_3, CH_3CN, Ac_2O, 80 °C, 12 h, *Z*:*E* = 10:1, 65%.

Scheme 4.6. Formation of Alkene **4.21**.

Dropwise addition of homoallylic alcohol **4.1** to a stirred mixture of $[BnNEt_3]^+AlCl_4^-$ and *trans*-cinnamaldehyde in toluene gave THP **4.18** in 63% yield after stirring for 16 h. On scale-up the original work-up procedure gave a messy emulsion when toluene was used as the reaction solvent. It was found that by adding Rochelle's salt

to the aqueous washes and using CH_2Cl_2 as the reaction solvent this could be eradicated. Protection of the *exo*-cyclic alkene at C4 was next accomplished through selective epoxidation using *m*CPBA in CH_2Cl_2. The desired epoxide **4.19** was formed in 75% yield together with 7% of double epoxidised material and 13% recovered starting material **4.18**. Ozonolysis of the remaining alkene **4.19** in CH_2Cl_2/MeOH (84:16) gave the unstable aldehyde **4.20a** in 62% yield. Following purification by column chromatography this aldehyde was exposed to potassium carbonate in acetonitrile before acetic anhydride was added. Heating the resulting solution at 80 °C for 12 h [106] gave acetate **4.21** in 65% yield.

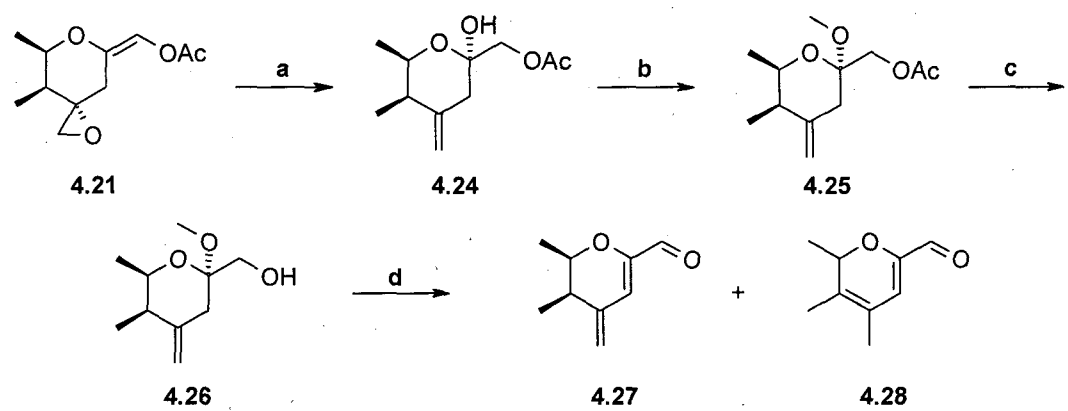
We next sought to effect the oxidation of the vinyl acetate in order to introduce the anomeric centre at C2 of the tetrahydropyran (Scheme 4.7). Epoxidation[107] of **4.21** with *m*CPBA gave a complex product mixture from which aldehyde **4.22** and epoxide **4.23** could be isolated, but not separated by chromatography. Optimisation of the reaction for **4.22**, and attempts to transform the mixture to **4.22** by treatment with acidic methanol failed to establish a usable protocol. Likewise, bromination of **4.21** proved problematic, leading to degradation of **4.21**.[108] While attempted dihydroxylation with osmium tetroxide induced hydrolysis to aldehyde **4.20b**.[109]



Reagents and conditions: - (a) *m*CPBA, CH_2Cl_2/MeOH (4:1), RT, 16 h, 67%; (b) OsO_4, NMO, MeOH,/H_2O (4:1), RT, 30 min, 86%.

Scheme 4.7. Problematic Oxidations.

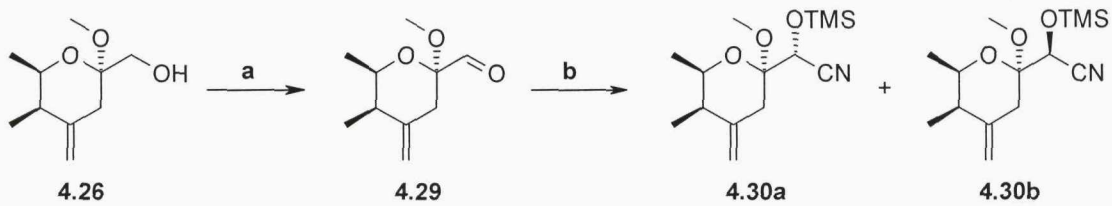
These difficulties were eventually resolved through treatment of **4.21** with zinc powder, sodium iodide and sodium acetate in aqueous acetic acid (Scheme 4.8).[110] Under these conditions the vinyl acetate was smoothly hydrated to install the anomeric centre, and the epoxide reduced to reveal the *exo*-cyclic alkene at C4. Methanolysis of the thus formed alcohol **4.24** with PPTS in methanol proceeded in quantitative yield to give acetal **4.25**. Removal of the acetate group with sodium methoxide next afforded alcohol **4.26** in excellent yield.[111] Preliminary attempts to effect the oxidation of alcohol **4.26** to aldehyde **4.29** using the Swern procedure resulted in a 1:1 mixture of unstable aldehydes **4.27** and **4.28**, presumably via elimination of methanol from the desired product.



Reagents and conditions: - (a) NaI, $NaOAc.3H_2O$, Zn, $AcOH/H_2O$ (10:1), 0 °C, 40 min, 53%; (b) MeOH, PPTS, RT, 16 h, 99%; (c) NaOMe, MeOH, RT, 2 h, 98%; (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 45 min, **4.27**:**4.28** = 1:1, 96%.

Scheme 4.8. Advancement to Alcohol **4.26**.

Pleasingly, Dess-Martin periodinane[112] oxidation of alcohol **4.26** gave the desired aldehyde **4.29** in high yield (Scheme 4.9). Addition of TMSCN to the crude reaction mixture induced the formation of a separable 1:1 mixture of diastereoisomeric cyanohydrins **4.30a** and **4.30b**.



4.26 **4.29** **4.30a** **4.30b**

Reagents and conditions: - (a) Dess-Martin periodinane, 0 °C, 1 h, 84%; (b) TMSCN, CH_2Cl_2, 16 h, RT, dr = 1:1, 80%.

Scheme 4.9. Cynaohydrin Formation.

It was impossible to identify the desired cyanohydrin diastereoisomer by ^1H NMR spectroscopy. Fortunately, one of the diastereoisomers was a crystalline solid and so an X-ray crystal structure was obtained. This was shown to be cyanohydrin **4.30b** with the wrong configuration at the newly established stereogenic centre (Figure 4.1).

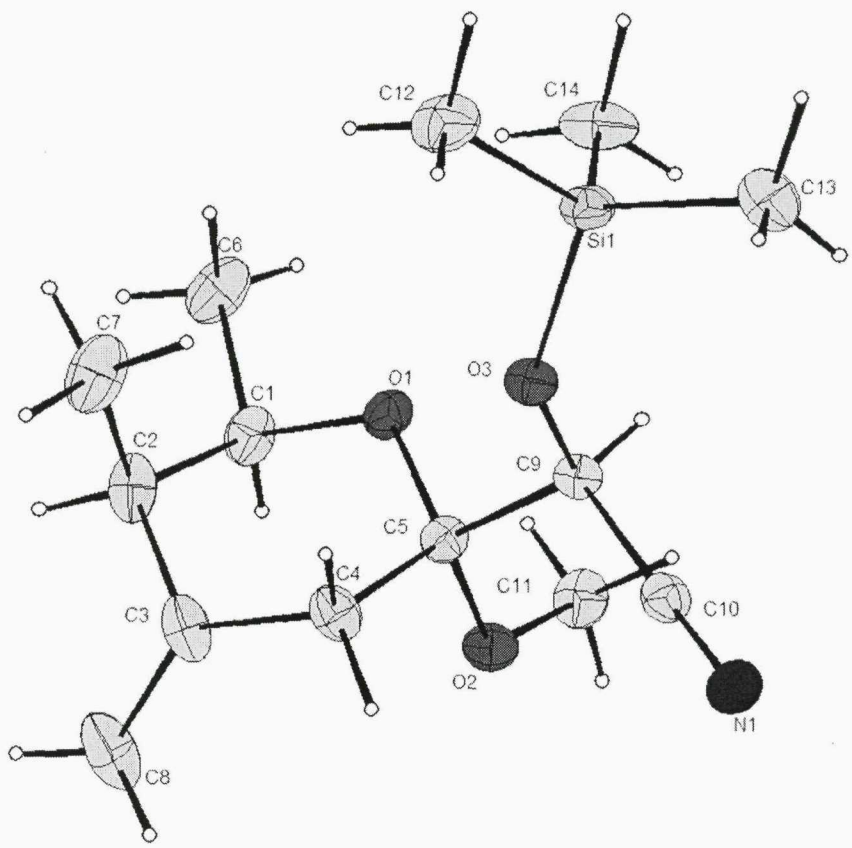
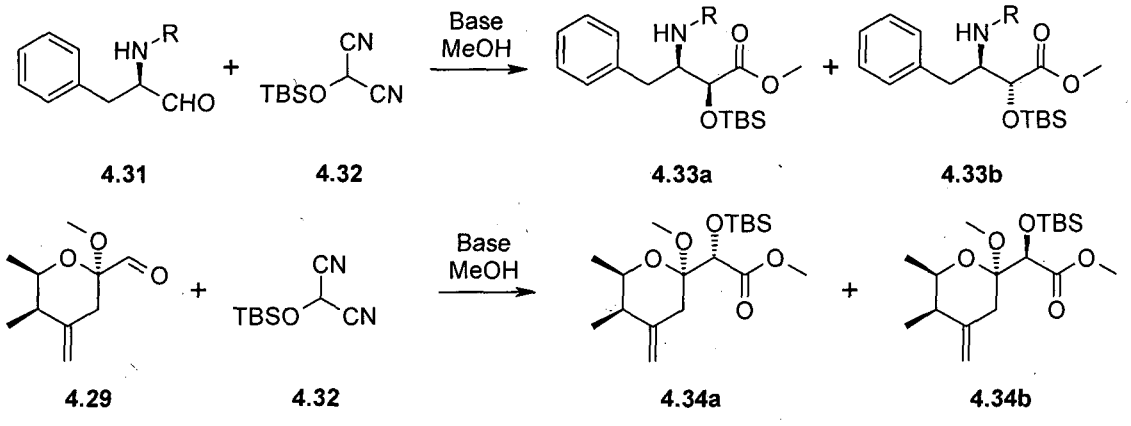


Figure 4.1. X-Ray Crystal Structure of Cyanohydrin **4.30b**.

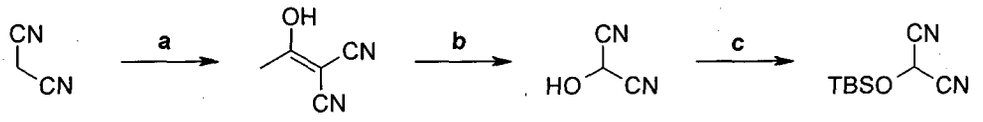
4.3. MAC Reagents.

Masked acyl cyanides (MAC reagents) such as **4.32**, are useful synthons in the formation of amino acids. Nemoto and co-workers have recently reported a one-pot reaction to synthesise β-amino acids **4.33a** and **4.33b** from aldehyde **4.31** and MAC reagent **4.32**.[113] A yield of 86% was accomplished when the reaction was carried out in diethyl ether at 0 °C, using PPy as the base. Our plan envisioned the use of this method to convert our aldehyde **4.29** directly to the methyl ester of pederic acid **4.34a** (Scheme 4.10).



Scheme 4.10. Ester Formation from MAC Reagent **4.32**.[113]

In order to harness this methodology, we needed to synthesise the MAC reagent **4.32** (Scheme 4.11). The attempted formation of **4.32** using Nemoto's procedure proved highly problematic.[114] Confirmation of formation of **4.36** was extremely difficult due to solubility issues and the lack of information given by ^{1}H NMR spectroscopy. The intermediate alcohol **4.37** was unstable according to Nemoto and could not be isolated. Our attempted formation of **4.37** was carried out using *m*CPBA in acetic acid. The crude product was then protected as the TBS ether. However, none of the desired product was obtained, only hydrolysed TBSCl. The oxidation reaction was repeated, this time using peracetic acid solution. Again the reaction failed to generate the desired MAC reagent **4.32**. We believed that the excess acetic acid was interfering with the TBS protection. But, with no way of confirming formation of any of the intermediates, this was little more than conjecture on our part.



4.35 **4.36** **4.37** **4.32**

Reagents and conditions: - (a) CH_3COCl, NEt_3, THF, 16 h, RT, 97%; (b) AcOOH, AcOH, H_2O, 2 h, RT; (c) TBSCl, Imidazole, DMF, 5 min, 0 °C, 79% (2 steps).

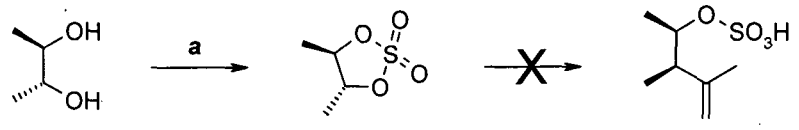
Scheme 4.11. Nemoto's Synthesis of **4.32**.[114]

We contacted Hisao Nemoto directly to obtain detailed experimental procedures for his synthesis of **4.32**. We were extremely disappointed to find he was unable to assist us in the synthesis of the MAC reagent due to pending patents on the procedure. Other methods of synthesising MAC reagents are available, but these require lengthy and time consuming preparations.[115] We therefore sought an alternative method of finishing our pederic acid synthesis.

4.4. Cyclic Sulfates and Chiral Resolution.

In order to synthesise onnamide F, an enantioselective route to pederic acid must be established. It is possible to synthesise both enantiomers of *trans*-2,3-epoxybutane, but the synthesis is not trivial and the shortest literature route involves four steps.[116] It has been reported that cyclic sulfates react in a similar fashion to epoxides. If true, a simple route to homoallylic alcohols **4.1** and **4.10** can be envisioned from the cyclic sulfate (**4.39**) of diol **4.38** (Scheme 4.12).[117]

Formation of cyclic sulfate **4.39** was achieved in a two step sequence through treatment firstly with thionyl chloride, then ruthenium chloride and sodium periodate.[118] All attempts to effect scission of the cyclic sulfate **4.39** with isopropenylmagnesium bromide failed. From this, and a lack of literature precedent, we conclude that cyclic sulfates are less reactive than epoxides in reaction with Grignard reagents. These results prompted us to examine the use of a chiral resolution technique.

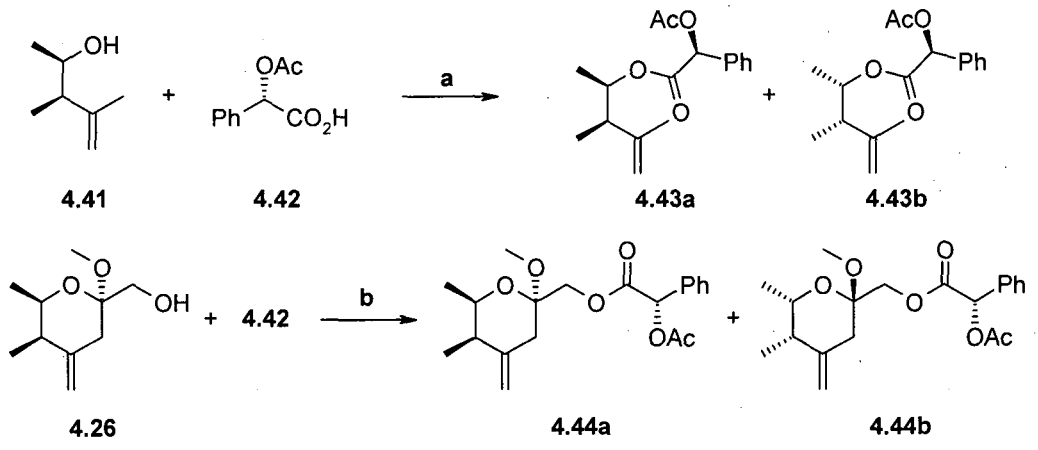


4.38 **4.39** **4.40**

Reagents and conditions: - (a) (i) $SOCl_2$, CCl_4, reflux, 30 min; (ii) $RuCl_3.H_2O$, $NaIO_4$, 0 °C, 1.5 h, 96%.

Scheme 4.12. Cyclic Sulfate Synthesis.

Formation of the acetylmandelate esters **4.43a** and **4.43b** in a 1:1 mixture from homoallylic alcohol **4.41** was achieved using a DCC coupling reaction with carboxylic acid **4.42** (Scheme 4.13).[119] Unfortunately separation of these diastereoisomers proved impossible. The acetylmandelate esters **4.44a** and **4.44b** were also prepared from alcohol **4.26**, and in this instance separation of the resulting diastereoisomers was possible.



4.41 **4.42** **4.43a** **4.43b**

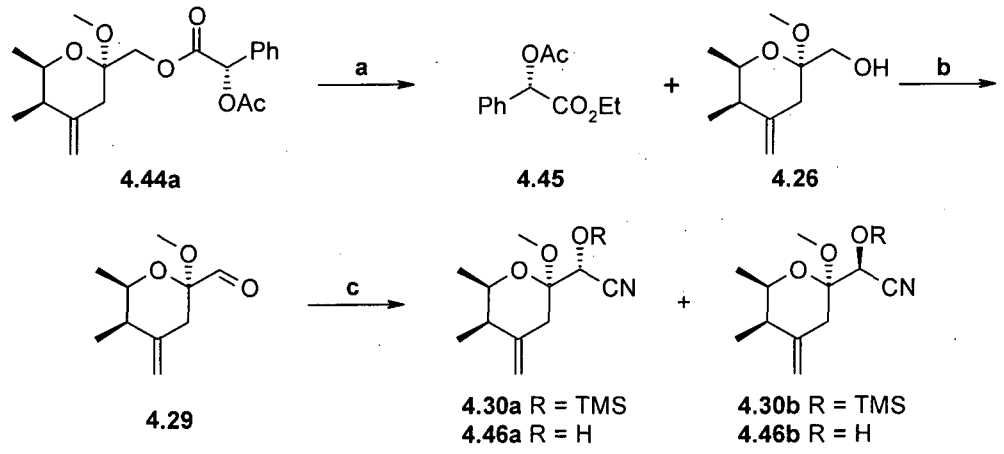
4.26 **4.44a** **4.44b**

Reagents and conditions: - (a) DCC, DMAP, CH_2Cl_2, 0 °C, 16 h, dr = 1:1, 79%; (b) DCC, DMAP, CH_2Cl_2, 0 °C, 16 h, dr = 1:1, 88%.

Scheme 4.13. Chiral Resolution of Secondary Alcohols.

4.5. The Synthesis of Pederamide.

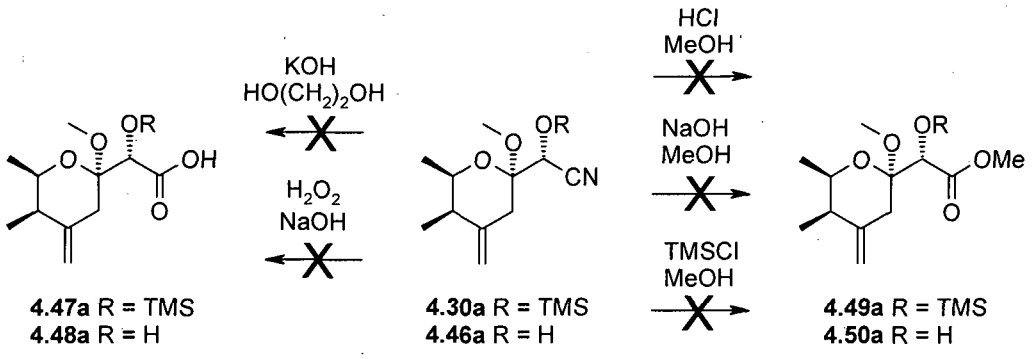
Saponification of the ester **4.44a** to enantiomerically pure alcohol **4.26** and ester **4.45** was accomplished using potassium carbonate in ethanol. Dess-Martin oxidation[112] to aldehyde **4.29** followed by treatment with TMSCN gave a separable 4:4:5:5 mixture of TMS protected cyanohydrins **4.30a** and **4.30b**, and cyanohydrins **4.46a** and **4.46b** (Scheme 4.14).



Reagents and conditions: - (a) K_2CO_3, EtOH, 2 h, RT, 87% **4.26**, 2% **4.38**; (b) Dess-Martin periodinane, 0 °C, 1 h, 84%; (c) TMSCN, CH_2Cl_2, 16 h, RT, dr = 1:1, 40% **4.30**, 52% **4.46**.

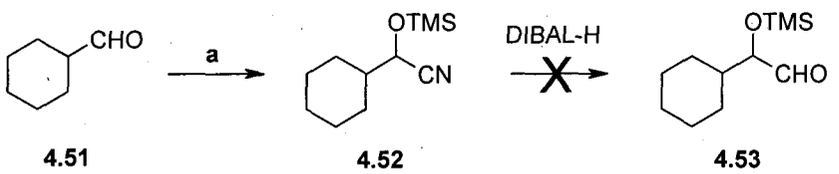
Scheme 4.14. Enantiomerically Enriched Route.

All attempts to hydrolyse the cyanohydrins **4.30a** and **4.46a** to carboxylic acids **4.47a** and **4.48a** met with failure (Scheme 4.15). Potassium hydroxide in ethylene glycol[120] induced removal of the TMS group and elimination of cyanide to aldehyde **4.29** in low yield. Hydrogen peroxide and sodium hydroxide in ethanol[121] failed to react, with only recovered starting material obtained. Treatment of **4.30a** with HCl in methanol also induced cleavage of the silyl ether to alcohol **4.46a**, with prolonged exposure leading to decomposition, presumably due to oxonium ion formation and subsequent elimination. Reaction of **4.46a** with sodium hydroxide in methanol[122] likewise gave decomposition products. While addition of TMSCl in MeOH[123] to **4.30a** gave alcohol **4.46a**.



Scheme 4.15. Problematic Cyanohydrin Hydrolyses.

We next carried out model studies on cyanohydrin trimethylsilyl ether **4.52** due to the precious nature of **4.30a** and **4.46a**, synthesised by the addition of TMSCN to NMO and cyclohexanecarboxaldehyde **4.51**.[124] All attempts to reduce the nitrile to the corresponding aldehyde **4.53** using DIBAL-H[125] failed, with no reaction observed under the conditions employed (Scheme 4.16).

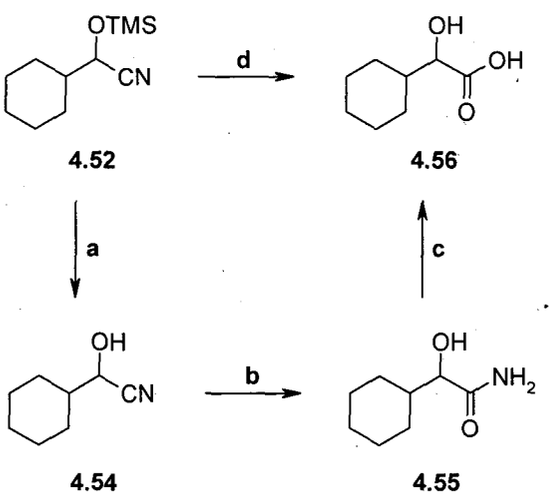


4.51 **4.52** **4.53**

Reagents and conditions: - (a) NMO, TMSCN, CH_2Cl_2, RT, 1 h, 99%.

Scheme 4.16. Model Studies.

Basic hydrolysis of cyanohydrin trimethylsilyl ether **4.52** was achieved using disodium tetraborate (Scheme 4.17).[126] Thus, addition of borax to **4.52** in THF/H_2O (1:1) effected removal of the silyl group on heating at 80 °C for 1 h. Longer reaction times initially induced hydrolysis of the nitrile to the corresponding primary amide **4.55**, which could be isolated and purified, or hydrolysed *in situ* by the addition of sodium hydroxide to carboxylic acid **4.56**.



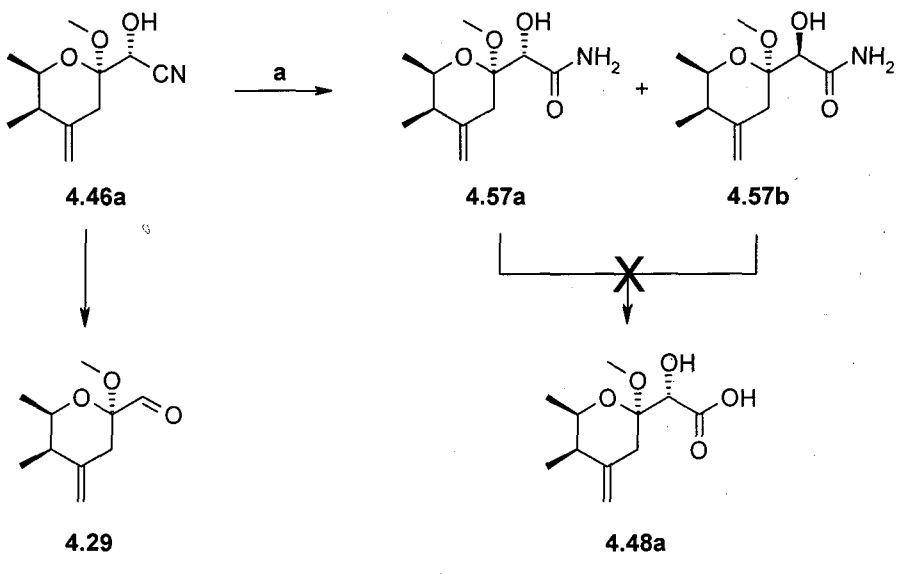
4.52 **4.56**

4.54 **4.55**

Reagents and conditions: - (a) Borax, THF/H_2O (1:1), 80 °C, 1 h, 60%; (b) Borax, THF/H_2O (1:1), 80 °C, 16 h, 94%; (c) NaOH (3 M), THF/H_2O (1:1), 80 °C, 24 h, 94%; (d) (i) Borax, THF/H_2O (1:1), 80 °C, 16 h, (ii) NaOH (3 M), 80 °C, 24 h, 83% (2 steps).

Scheme 4.17. The Successful Hydrolysis of **4.52**.

Hydrolysis of cyanohydrin **4.46a** with disodium tetraborate[126] generated an inseparable 1:1 mixture of diastereomeric primary amides **4.58a** and **4.58b** in 47% yield (Scheme 4.19). The low yield was possibly due to the competing elimination of cyanide to give the unstable aldehyde **4.29**. The direct formation of pederic acid **4.48a** from cyanohydrin **4.46a** was also attempted by prolonged treatment of **4.46a** with disodium tetraborate. The primary amides **4.57a** and **4.57b** were observed by tlc after 1 h. The reaction mixture was then treated with sodium hydroxide, leading to a polar product presumed to be pederic acid. However, concentration *in vacuo* induced decomposition, reflecting the instability of pederic acid **4.48a** when the alcohol functionality and carboxylic acid are both unprotected.



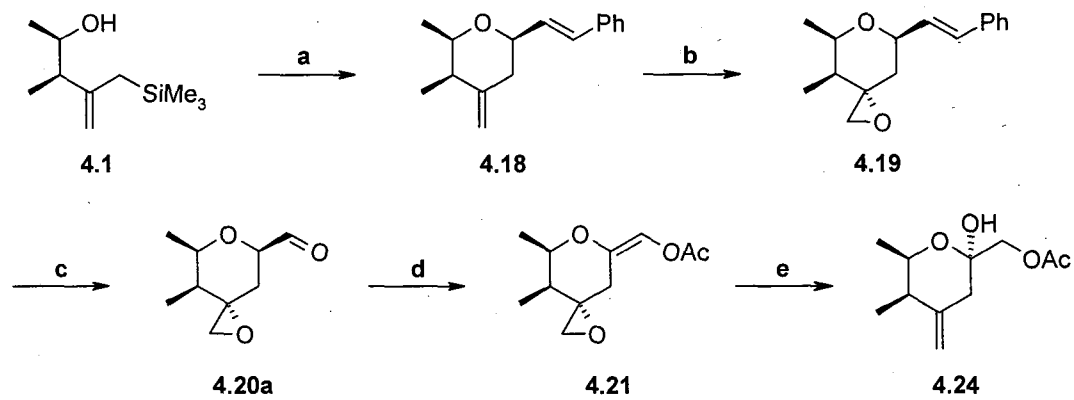
Reagents and conditions: - (a) Borax, THF/H_2O (1:1), 80 °C, 1 h, dr = 1:1, 47%.

Scheme 4.19. The Synthesis of Pederamide.

4.6. Conclusions.

We have developed a useful new route to pederamide **4.57a**. The tetrahydropyran skeleton was formed by a new Lewis acid mediated cyclisation reaction between homoallylic alcohol **4.1** and *trans*-cinnamaldehyde promoted by benzyltriethylammonium aluminium chloride (Scheme 4.20). The cyclisation generates THP **4.18** with the desired *exo*-methylene subunit in place. After protection of the *exo*-methylene as an epoxide, the remaining alkene functionality was ozonolysed to aldehyde **4.20a**. Treatment with acetic anhydride[106] to enol

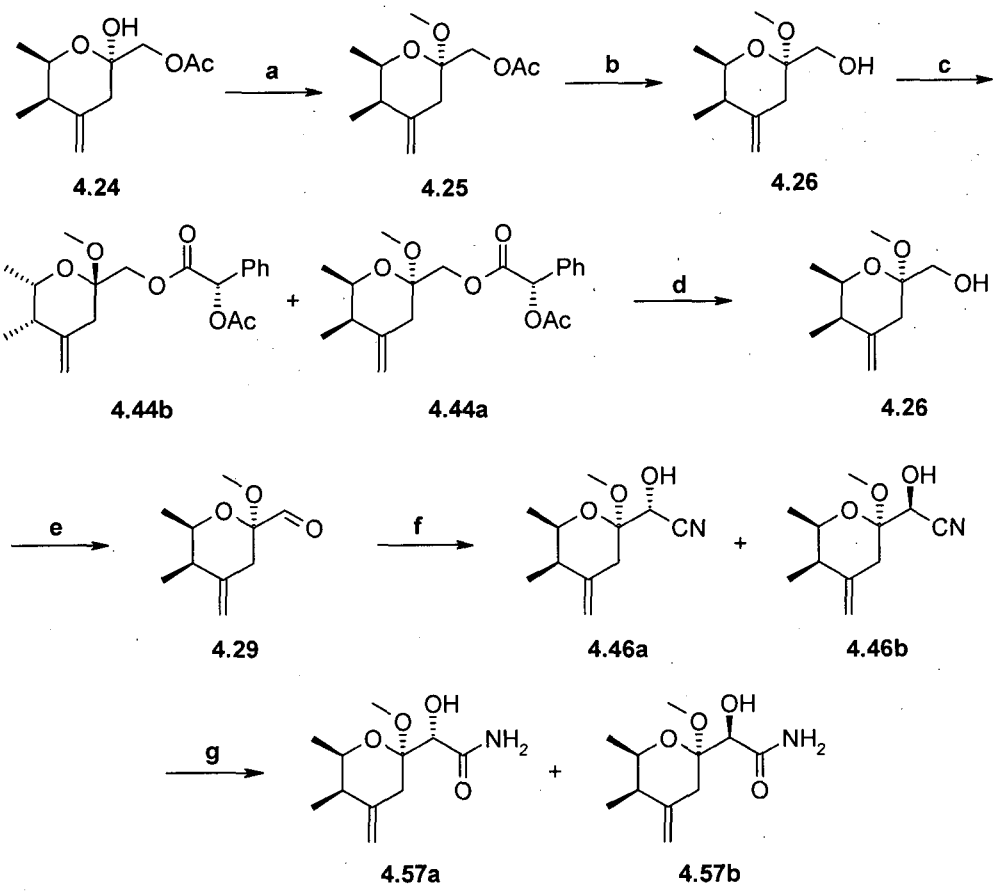
acetate **4.21** gave us the opportunity to unmask the exocyclic alkene and establish the correct oxidation level at the anomeric centre using NaI and zinc dust in buffered aqueous acetic acid.[110]



Reagents and conditions: - (a) *trans*-cinnamaldehyde, $[BnNEt_3]^+AlCl_4^-$, CH_2Cl_2, RT, 16 h, 63%; (b) *m*CPBA, CH_2Cl_2, RT, 16 h, dr = 20:1, 75%; (c) O_3 (1-2% in O_2), CH_2Cl_2/MeOH (84:16), PPh_3, 1.5 h, −78 °C, 62%; (d) K_2CO_3, CH_3CN, Ac_2O, 80 °C, 12 h, *Z*:*E* = 10:1, 65%; (e) NaI, $NaOAc.3H_2O$, Zn, AcOH/H_2O (10:1), 0 °C, 40 min, 53%.

Scheme 4.20. Towards Pederamide.

Methyl ether formation followed by removal[111] of the acetate group furnished alcohol **4.26** which could be resolved via formation of the (+)-acetylmandelate ester. The enantiomerically pure (2*R*,5*R*,6*R*)-triethylene tetrahydropyran **4.26** was subjected to a Dess-Martin oxidation.[112] Treatment with TMSCN next gave a separable 1:1 mixture of cyanohydrins **4.46** which, on borax induced hydrolysis[126] gave pederamide **4.57a** and its diastereoisomer **4.57b** (Scheme 4.21).

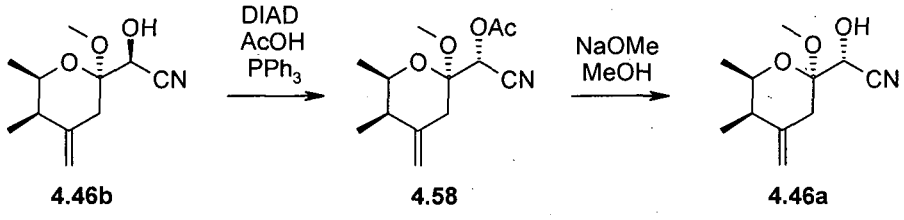


Reagents and conditions: - (a) MeOH, PPTS, RT, 16 h, 99%; (b) NaOMe, MeOH, RT, 2 h, 98%; (c) **4.42**, DCC, DMAP, CH_2Cl_2, 0 °C, 16 h, dr = 1:1, 88%; (d) K_2CO_3, EtOH, 2 h, RT, 87% **4.26**, 2% **4.38**; (e) Dess-Martin periodinane, 0 °C, 1 h, 84%; (f) TMSCN, CH_2Cl_2, 16 h, RT, dr = 1:1, 40% **4.30**, 52% **4.46**; (g) Borax, THF/H_2O (1:1), 80 °C, 1 h, dr = 1:1, 47%.

Scheme 4.21. The Synthesis of Pederamide.

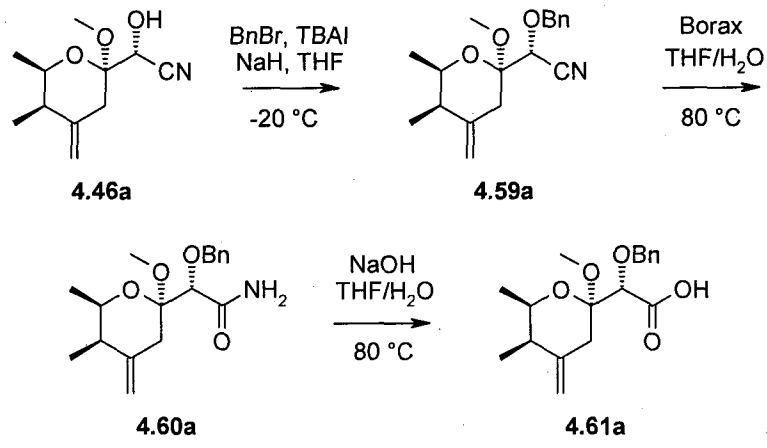
4.7. Future Work.

The undesirable cyanohydrin diastereoisomer **4.46b** has reduced the efficiency of our route to pederic acid. We propose an inversion of **4.46b** to **4.46a** using a Mitsunobu esterification reaction (Scheme 4.22).[127]



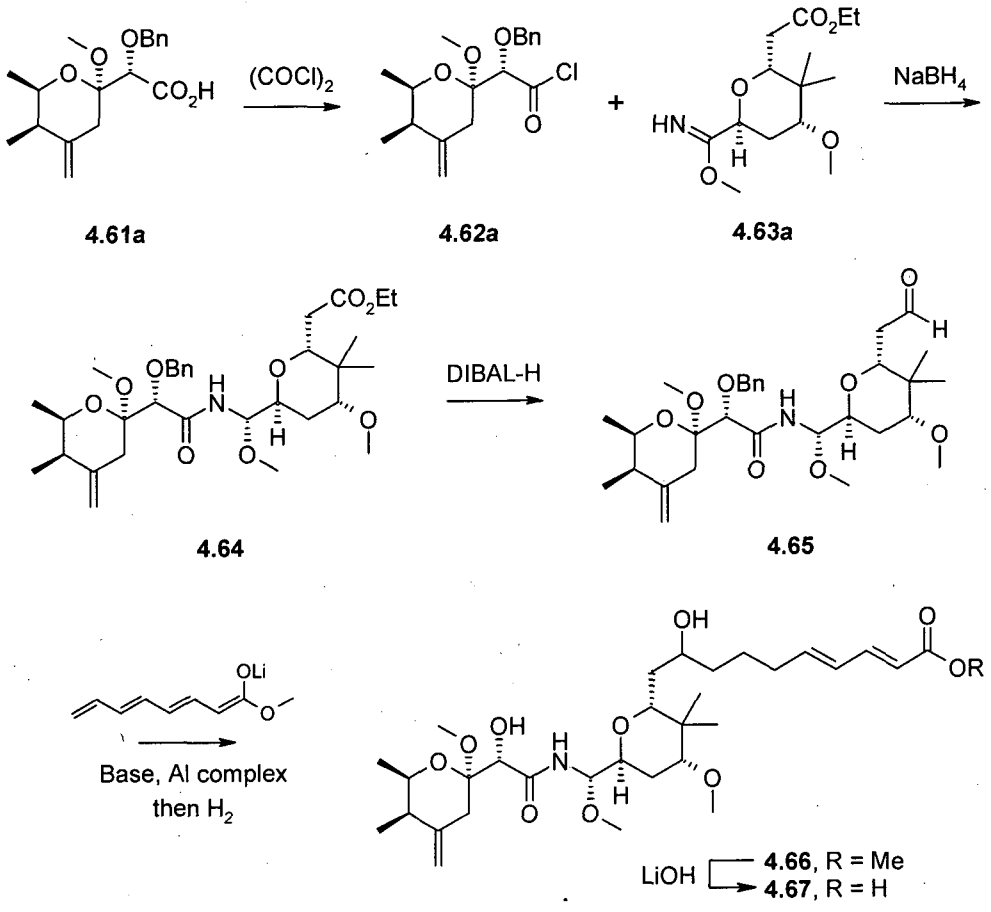
Scheme 4.22. Proposed Mitsunobu Reaction.

In the next phase of this programme, the plan is to protect cyanohydrin **4.46a** as its benzyl ether **4.59a** (Scheme 4.23). Borax hydrolysis to benzyl pederamide **4.60a**, followed by treatment with sodium hydroxide will furnish benzyl protected pederic acid **4.61a** which is known to be a stable entity.



Scheme 4.23. The Formation of Benzyl Protected Pederic Acid.

With **4.61a** to hand we plan to effect its coupling to imidate **4.63a** prepared by Will Buffham in the Harrowven group, via acid chloride **4.62a**. *In situ* sodium borohydride reduction will then give ester **4.64**, a precursor to aldehyde **4.65**. Introduction of the final eight carbon fragment will be attempted by means of a new coupling reaction developed by Saito *et al.*, in which aldehyde **4.65** and the lithiated ester are linked to form **4.66**.[128] The stereochemical course of that reaction is difficult to predict. As the configuration at that stereocentre in onnamide F has yet to be determined, this is of little consequence as either diastereoisomer of alcohol **4.67** can be used to access the other. The synthesis of **1** will be completed by directed alkene hydrogenation and saponification of the ester functionalities (Scheme 4.24).



Scheme 4.24. The Synthesis of Onnamide F.

5. Experimental.

5.1. General.

All reactions were performed in oven-dried glassware and when required under an inert atmosphere of nitrogen or argon. TLC was performed using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm. The plates were visualized under a UV lamp (254 nm) and by staining with either 20% phosphomolybdic acid in ethanol or 10% aqueous potassium permanganate. Column chromatography was achieved using Apollo silica gel (0.040-0.063 mm, 230-400 mesh), which was slurry packed and run under low pressure.

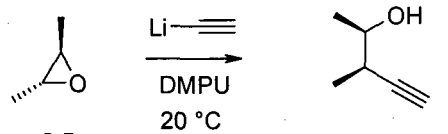
Infrared spectroscopy was performed using a Bio-Rad FT-IR goldengate spectrometer. Adsorption maxima (ν_{max}) are quoted as wavenumbers (cm^{-1}) and the following abbreviations used to describe their intensity: w – weak, m – medium, s – strong, br – broad.

Nuclear magnetic resonance spectroscopy was performed using a Bruker Avance 300 MHz spectrometer or a Bruker DPX 400 MHz spectrometer run in a $CDCl_3$, CD_3OD, $(CD_3)_2CO$ or $(CD_3)_2SO$ solution. Chemical shifts are quoted as δ-values in ppm downfield of TMS (0 ppm) and referenced to the solvent peak. Coupling constants (*J*) are given in Hz and signals are described using the notation: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, br – broad.

Mass spectrometry was performed using electron ionization (EI) and chemical ionization (CI) on a Thermoquest Trace GCMS spectrometer; and by electrospray positive (ES^+) ionization on a Waters ZMD spectrometer. High resolution EIMS was performed on a VG Analytical 70-250-Se spectrometer and high resolution ESMS performed on a Bruker Apex III spectrometer. Melting points were determined using a Griffin melting point apparatus.

All solvents were distilled prior to use. Toluene, THF and 1,2-dimethoxyethane were distilled from sodium with benzophenone as an indicator, and dichloromethane distilled from calcium hydride. Other solvents and reagents were purified according to standard laboratory methods.[129]

***rel*-(2*R*,3*R*)-3-Methyl-4-pentyne-2-ol**



2.5
$C_4H_{10}O$
MW = 72.11

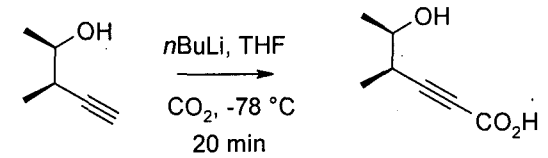
2.6
$C_6H_{10}O$
MW = 98.15

Hydroxyalkyne **2.6** was prepared according to the method of Kocienski *et al.*[16] To lithium acetylide ethylenediamine complex (90%, 17.13 g, 0.186 mol) in DMPU (70 mL) at 0 °C was added in one portion *trans*-2,3-epoxybutane (4.63 mL, 0.052 mol). The reaction mixture was warmed slowly to 20 °C and stirred under nitrogen for 6 days. It was then cautiously poured into 2 M HCl (200 mL) and extracted with diethyl ether (5 x 70 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by vacuum distillation (69-73 °C, 2 mm Hg) afforded **2.6** as a colourless oil (4.99 g, 0.051 mol, 98%).

FT-IR (ν/cm^{-1})	3298 (m), 2975 (m), 2934 (w), 1711 (m), 1088 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 3.75 (1 H, m, C**H**OH), 2.60 (1 H, qd, J = 6.0, 5.0 Hz, CH_3C**H**), 2.40 (1 H, br s, CC**H**), 2.08 (1 H, d, J = 1.5 Hz, O**H**), 1.25 (3 H, d, J = 6.0 Hz, C**H**$_3$), 1.15 (3 H, d, J = 6.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 85.7 (**C**CH), 70.5 (C**C**H), 70.3 (CH_3**C**HOH), 33.9 (CH_3**C**HCCH), 19.4 (**C**H$_3$CHOH), 16.1 (**C**H$_3$CHCCH) ppm.

Data consistent with literature values (traces of DMPU impurity remain in spectra).[16]

***rel*-(4*R*,5*R*)-4-Methyl-5-hydroxy-2-hexynoic acid**



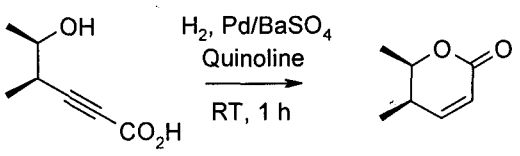
2.6
$C_6H_{10}O$
MW = 98.15

2.7
$C_7H_{10}O_3$
MW = 142.16

Carboxylic acid **2.7** was prepared according to the method of Kocienski *et al.*[16] To a stirred solution of alcohol **2.6** (1.59 g, 16.2 mmol) in THF (35 mL) at −78 °C was added dropwise *n*BuLi (2.5 M in hexanes, 15.6 mL). The solution was stirred for 45 min, then a solution of diisopropylamine (0.94 mL, 6.7 mmol) in THF (5 mL) was added dropwise and the reaction mixture warmed to 0 °C. After 15 min the solution was cooled to −78 °C then dry CO_2 (g) was bubbled through the solution for 20 min forming a thick gel. This was carefully poured into ice/2 M HCl (~1:1, 100 mL) and extracted with diethyl ether (3 x 50 mL). After adding saturated NaCl (100 mL) the aqueous phase was further extracted with chloroform (3 x 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (5-20% MeOH/CH_2Cl_2, 5% AcOH) gave **2.7** as a pale orange crystalline solid (1.45 g, 10.2 mmol, 63%).

m.p.	95-97 °C (ether/petrol), lit. 95-96 °C (ether/hexanes)[16]
FT-IR (ν/cm^{-1})	2960 (m), 2935 (m), 2234 (w), 1703 (s), 1259 (m).
^{1}H NMR ($(CD_3)_2SO$)	δ_H (300 MHz): 4.88 (1 H, br s, **OH**), 3.55 (1 H, quintet, J = 6.2 Hz, **CH**OH), 2.58 (1 H, m, CH_3**CH**), 2.50 (1 H, m, **OH**), 1.14 (3 H, d, J = 6.0 Hz, **C**H_3), 1.10 (3 H, d, J = 7.0 Hz, **C**H_3) ppm.
^{13}C NMR ($(CD_3)_2SO$)	δ_C (75 MHz): 154.3 (**C**O_2H), 90.1 (CHC**C**CO_2H), 75.2 (CH**C**CCO_2H), 68.6 (**C**OH), 33.6 (CH_3**C**CH), 20.3 (**C**H_3CHOH), 16.0 (**C**H_3CHC) ppm.

(±)-*cis*-5,6-Dimethyl-5,6-dihydro-2*H*-pyran-2-one



2.7
$C_7H_{10}O_3$
MW = 142.16

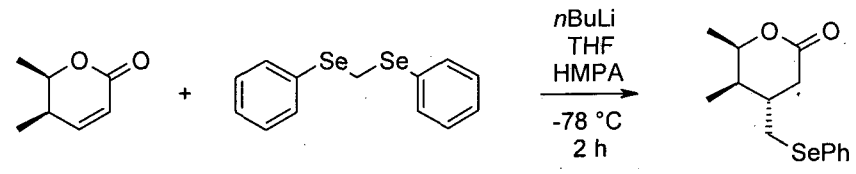
2.8
$C_7H_{10}O_2$
MW = 126.16

Lactone **2.8** was prepared according to the method of Kocienski *et al.*[16] To a stirred solution of acid **2.7** (0.50 g, 3.52 mmol) in ethanol (10 mL) was added $Pd/BaSO_4$ (5%, 0.07 g) and quinoline (0.04 g). After stiring under an atmosphere of hydrogen (1 atm) for 1 h, the reaction mixture was filtered through a pad of celite, concentrated *in vacuo*, resolvated in diethyl ether (10 mL), washed with 2 M HCl (10 mL) and concentrated *in vacuo* to yield the hydroxy acid precursor to **2.8**. Kugelrohr distillation (170-180 °C, 1.5 mmHg) followed by column chromatography (20-100% ether/petrol) yielded pure **2.8** as a colourless oil (0.30 g, 2.38 mmol, 68%).

FT-IR (ν/cm^{-1})	2976 (w), 1724 (s), 1703 (s), 1450 (w), 1385 (m), 1247 (s), 1127 (s), 1088 (s), 988 (m), 821 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 6.91 (1 H, dd, J = 9.7, 5.9 Hz, CH=C**H**), 5.95 (1 H, dd, J = 9.7, 0.9 Hz, C**H**=CH), 4.62 (1 H, qd, J = 6.6, 3.7 Hz, C**H**O), 2.36 (1 H, m, CH_3C**H**), 1.35 (3 H, d, J = 6.6 Hz, C**H**$_3$), 1.05 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 164.6 (**C**=O), 151.6 (**C**HCHCO), 119.7 (CH**C**HCO), 76.3 (CH_3**C**HO), 33.0 (CH_3**C**H), 17.1 (**C**H$_3$CHO), 11.2 (**C**H$_3$) ppm.

Data consistent with literature values.[16]

***rel*-(4*S*,5*R*,6*R*)--5,6-Dimethyl-4-phenylselenomethyltetrahydro-2*H*-pyran-2-one**



2.8
$C_7H_{10}O_2$
MW = 126.16

$C_{13}H_{12}Se_2$
MW = 326.16

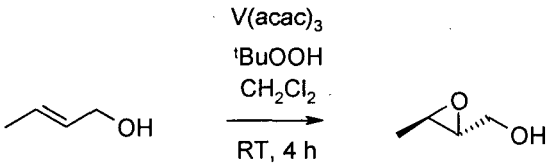
2.9
$C_{14}H_{18}O_2Se$
MW = 297.26

To a stirred solution of $(PhSe)_2CH_2$ (1.68 g, 5.15 mmol) in THF (5 mL) at –78 °C was added dropwise *n*BuLi (1.86 M in hexane, 2.98 mL, 5.55 mmol). The solution was stirred for 2 h, then HMPA (1 mL) added. The resulting solution was re-cooled to –78 °C and a solution of lactone **2.8** (0.50 g, 3.96 mmol) in THF/HMPA (0.2/0.5 mL) added dropwise over 30 min. The solution was poured into 2 M HCl (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with saturated $NaHCO_3$ (15 mL), H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33-100% diethyl ether/petrol) yielded **2.9** as a yellow oil (0.46 g, 1.55 mmol, 40%).

FT-IR (ν/cm^{-1})	2969-2921 (br. w), 1729 (s), 1576 (w), 1381 (m), 1251 (m), 1072 (m), 735 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.52-7.49 (2 H, m, 2 x Ar C**H**), 7.28-7.26 (3 H, m, 3 x Ar C**H**), 4.50 (1 H, qd, J = 6.6, 3.3 Hz, OC**H**), 2.98 (2 H, qd, J = 11.3, 6.7 Hz, C**H**$_2$Se), 2.67 (1 H, dd, J = 16.7, 6.7 Hz, C**H**HC=O), 2.37 (1 H, dd, J = 16.7, 9.3 Hz, CH**H**C=O), 1.99-1.81 (2 H, m, CH_3C**H**, C**H**), 1.28 (3 H, d, J = 6.6 Hz, C**H**$_3$), 0.95 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 172.1 (**C**=O), 133.1 (2 x Ar **C**H), 129.4 (2 x Ar **C**H), 129.3 (Ar **C**H), 127.5 (Ar **C**), 75.9 (CH_3**C**HO), 37.4 (CH_3**C**H), 36.9 (CH_2**C**HCH_2), 34.3 (**C**H$_2$CO$_2$), 33.9 (**C**H$_2$Se), 17.0 (**C**H$_3$CHO), 13.9, (**C**H$_3$CH) ppm.

Data consistent with literature values.[16]

***rel*-(2*S*,3*R*)-2-Hydroxymethyl-3-methyloxirane**



2.10
C_4H_8O
MW = 72.11

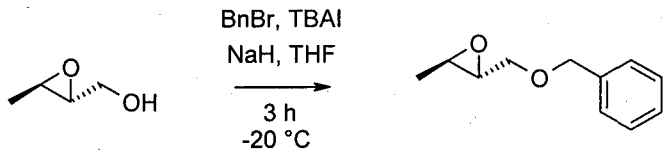
2.11
$C_4H_8O_2$
MW = 88.11

Epoxide **2.11** was prepared according to the procedure of Sharpless *et al.*[62] To a vigorously stirred green solution of 2-buten-1-ol (10.10 g, 0.14 mol) and vanadium(III) acetylacetonate (400 mg) in CH_2Cl_2 (150 mL) was added *tert*-butylhydroperoxide (70% in H_2O, 25.5 g, 0.20 mol). The reaction mixture was stirred at RT for 4 h, then extracted with diethyl ether (3 x 100 mL). The ether extracts were combined, washed with saturated $NaHCO_3$ (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33-100% ether/petrol) yielded epoxyalcohol **2.11** (10.96 g, 0.12 mol, 89%) as a colourless oil.

FT-IR (ν/cm^{-1})	3430 (br. m), 2984 (w), 2926 (w), 2871 (w), 1450 (w), 1034 (s), 986 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 3.90 (1 H, dd, J = 14.6, 3.0 Hz, C**H**HOH), 3.62 (1 H, dd, J = 14.6, 5.2 Hz, CH**H**OH), 3.04 (1 H, qd, J = 6.2, 2.6 Hz, CH_3C**H**), 2.89 (1 H, m, C**H**CH_2), 2.01 (1 H, br. s, O**H**), 1.34 (3 H, d, J = 5.2 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 61.6 (**C**H_2), 59.4 (**C**HCH_3), 56.0 (**C**HCH_2), 17.1 (**C**H_3) ppm.

Data consistent with literature values.[130]

***rel*-(2*S*,3*R*)-2-Benzyloxymethyl-3-methyloxirane**



2.11
$C_4H_8O_2$
MW = 88.11

2.14
$C_{11}H_{14}O_2$
MW = 178.23

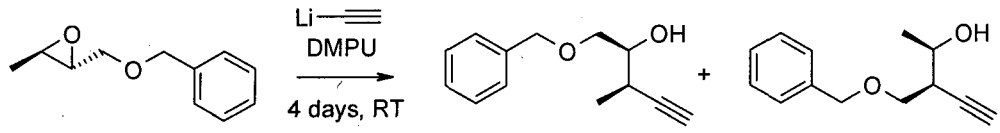
Epoxide **2.14** was prepared according to the procedure of Kobayashi *et al.*[60] To a solution of alcohol **2.11** (3.00 g, 34.0 mmol), benzyl bromide (6.99 g, 41.0 mmol) and tetrabutylammonium iodide (1.26 g, 3.40 mmol) in THF (100 mL) at −20 °C under argon was added sodium hydride (60% dispersion in mineral oil, 1.50 g, 37.0 mmol). After stirring for 3 h, saturated NH_4Cl (60 mL) was added, then the solution was extracted with diethyl ether (4 x 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33-100% petrol/ether) yielded **2.14** (4.73 g, 26.5 mmol, 78%) as a colourless oil.

FT-IR (ν/cm^{-1}) 2987 (w), 2856 (w), 2364 (w), 1452 (m), 1087 (s).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz,): 7.37-7.29 (5 H, m, Ar**H**), 4.62 (1 H, d, J = 11.9 Hz, C**H**HPh), 4.55 (1 H, d, J = 11.9 Hz, CH**H**Ph), 3.70 (1 H, dd, J = 11.4, 3.3 Hz, C**H**HOBn), 3.50 (1 H, dd, J = 11.4, 5.0 Hz, CH**H**OBn), 2.95-2.88 (2 H, m, C**H**CH), 1.34 (3 H, d, J = 5.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 138.0 (Ar **C**), 128.4 (2 x Ar **C**H), 127.7 (2 x Ar **C**H), 127.6 (Ar **C**H), 73.3 (CH**C**H$_2$OBn), 70.4 (O**C**H$_2$Ph), 57.9 (CH$_3$**C**HOCH), 52.1 (CHO**C**HCH$_2$), 17.3 (**C**H$_3$) ppm.

***rel*-(2*S*,3*R*)-1-Benzyloxy-3-methylpent-4-yn-2-ol (2.15) & *rel*-(2*R*,3*S*)-3-benzyloxymethylpent-4-yn-2-ol (2.16)**



2.14
$C_{11}H_{14}O_2$
MW = 178.23

2.15
$C_{13}H_{16}O_2$
MW = 204.27

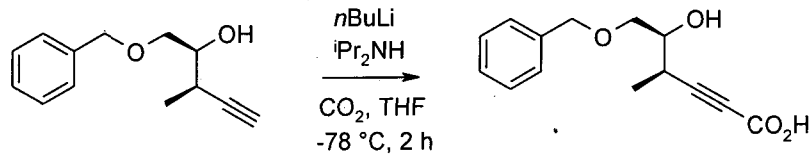
2.16
$C_{13}H_{16}O_2$
MW = 204.27

Hydroxyalkyne **2.15** was prepared according to the procedure of Kobayashi *et al.*[60] To lithium acetylide ethylenediamine complex (90%, 7.63 g, 0.083 mol) in DMPU (70 mL) at 0 °C was added in one portion **2.14** (4.00 g, 0.024 mol). The reaction mixture was warmed slowly to 20 °C and stirred under nitrogen for 4 days. It was then cautiously poured into 2 M HCl (100 mL) and extracted with diethyl ether (5 x 60 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*, yielding a crude mixture of regioisomers. Purification by column chromatography (25-100% ether/petrol) yielded firstly **2.15** (1.81 g, 8.9 mmol, 37%) then **2.16** (0.91 g, 4.5 mmol, 19%), both as yellow oils.

Spectroscopic data obtained on major regioisomer **2.15**.

FT-IR (ν/cm^{-1})	3419 (w), 3294 (m), 2864(m), 1734 (w), 1452 (s), 1136 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.37-7.29 (5 H, m, Ar**H**), 4.59 (2 H, s, C**H**$_2$Ph), 3.79-3.68 (2 H, m, OC**H**$_2$), 3.61 (1 H, m, C**H**OH), 2.64 (1 H, qd, J = 6.9, 2.4 Hz, CH_3C**H**), 2.47 (1 H, d, J = 4.4 Hz, O**H**), 2.10 (1 H, d, J = 2.4 Hz, C**H**), 1.28 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 137.9 (Ar **C**), 128.5 (2 x Ar **C**H), 127.8 (2 x Ar **C**H), 127.7 (Ar **C**H), 85.5 (CHC**C**H), 73.5 (BnOC**H**$_2$CH), 73.1 (**C**H), 72.2 (PhC**H**$_2$O), 70.3 (**C**H), 29.4 (**C**H), 16.9 (C**H**$_3$) ppm.

***rel*-(2*S*,3*R*)-6-Benzyloxy-5-hydroxy-4-methylhex-2-ynoic acid**



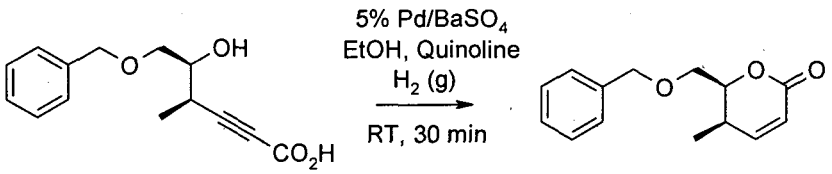
2.15
$C_{13}H_{16}O_2$
MW = 204.27

2.17
$C_{14}H_{16}O_4$
MW = 248.28

To a stirred solution of alcohol **2.15** (0.80 g, 3.92 mmol) in THF (15 mL) at −78 °C was added dropwise *n*BuLi (2.31 M in hexanes, 4.07 mL). The solution was stirred for 45 min, a solution of diisopropylamine (0.22 mL, 1.57 mmol) in THF (1 mL) was added dropwise then the reaction mixture was warmed to 0 °C. After 15 min the solution was cooled to −78 °C then dry CO_2 (g) was bubbled through the solution for 20 min forming a thick gel. This was carefully poured into ice/2 M HCl (~1:1, 35 mL) and extracted with diethyl ether (3 x 20 mL). After saturation with NaCl (aq) (50 mL) the aqueous residue was further extracted with chloroform (3 x 10 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (5-20% MeOH/CH_2Cl_2, 5% AcOH) yielded **2.17** as a viscous brown oil (0.83 g, 3.42 mmol, 85%).

FT-IR (ν/cm^{-1})	3394-2910 (m), 2603 (w), 2231 (s), 1728 (s), 1453 (s), 1294 (s), 1088 (s), 909 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.40-7.29 (5 H, m, Ar**H**), 6.12 (2 H, br.s, 2 x O**H**), 4.58 (2 H, s, C**H**$_2$Ph), 3.79 (1 H, qd, J = 6.7, 3.4 Hz, C**H**CH$_3$), 3.71 (1 H, dd, J = 9.7, 3.4 Hz, BnOC**H**H), 3.61 (1 H, dd, J = 9.7, 6.7 Hz, BnOCH**H**), 2.84-2.80 (1 H, m, C**H**OH), 1.31 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 156.6 (**C**OOH), 137.4 (Ar **C**), 128.5 (2 x Ar **C**H), 128.0 (2 x Ar **C**H), 127.9 (Ar **C**H), 91.8 (**C**COOH), 74.4 (CH**C**C), 73.6 (BnO**C**H$_2$), 72.5 (**C**HOH), 71.6 (Ph**C**H$_2$O), 29.6 (**C**H), 15.6 (**C**H$_3$) ppm.
LRMS	m/z (ES$^+$) 249 ([M + H]$^+$ 100%).

***rel*-(5*R*,6*S*)-6-Benzyloxymethyl-5-methyl-5,6-dihydropyran-2-one**



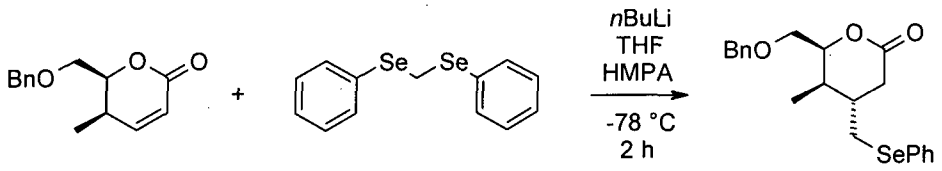
2.17
$C_{14}H_{16}O_4$
MW = 248.28

2.18
$C_{14}H_{16}O_3$
MW = 232.28

To a stirred solution of carboxylic acid **2.17** (0.27 g, 1.09 mmol) in ethanol (8 mL) was added Pd/$BaSO_4$ (5%, 0.05 g) and quinoline (0.12 g). After stirring under an atmosphere of hydrogen (1 atm) for 30 min the reaction mixture was filtered through a pad of celite, concentrated *in vacuo,* resolvated in toluene (10 mL) and heated at reflux for 16 h. The solution was cooled to RT, then washed with 2 M HCl (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (33-100% ether/petrol) yielded **2.18** as a yellow oil (0.15 g, 0.65 mmol, 59%).

FT-IR (ν/cm^{-1})	2917 (w), 2875 (w), 1701 (s), 1453 (m), 1376 (m), 1244 (s), 1074 (s), 997 (s), 820 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.40-7.31 (5 H, m, Ar**H**), 6.96 (1 H, dd, J = 9.7, 6.2 Hz, CH=C**H**), 5.97 (1 H, dd, J = 9.7, 0.9 Hz, C**H**=CH), 4.69-4.53 (3 H, m, C**H**, CH_2Ph), 3.75 (1 H, dd, J = 9.9, 6.2 Hz, OC**H**H), 3.64 (1 H, dd, J = 9.9, 7.1 Hz, OCH**H**), 2.58 (1 H, qd, J = 6.4, 2.8 Hz, CH_3C**H**), 1.03 (3 H, d, J = 6.4 Hz, CH_3) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 163.7 (**C**=O), 151.2 (**C**HCHCO), 137.5 (Ar **C**), 128.4 (2 x Ar **C**H), 127.8 (2 x Ar **C**H), 127.7 (Ar **C**H), 120.0 (CH**C**HCO), 77.9 (O**C**H), 73.6 (BnOCH_2), 68.6 (PhCH_2O), 30.1 (**C**HCH_3), 11.3 (CH_3) ppm.
LRMS	m/z (ES^+) 255 ($[M + Na]^+$, 100%).
HRMS	m/z (ES^+) found: 255.0994, $[M + Na]^+$. $C_{14}H_{16}O_3Na$ requires 255.0991.

***rel*-(4*S*,5*R*,6*S*)-6-Benzyloxymethyl-5-methyl-4-phenylselenylmethyl-tetrahydropyran-2-one**



2.18
$C_{14}H_{16}O_3$
MW = 232.28

$C_{13}H_{12}Se_2$
MW = 326.16

2.19
$C_{21}H_{24}O_3Se$
MW = 403.38

To a stirred solution of $(PhSe)_2CH_2$ (0.70 g, 2.13 mmol) in THF (5 mL) at –78 °C was added dropwise *n*BuLi (1.90 M in hexane, 1.22 mL, 2.32 mmol). The solution was stirred for 2 h, then HMPA (4 mL) added. A solution of lactone **2.18** (0.45 g, 1.94 mmol) in THF (1.5 mL) was then added dropwise over 30 min to the reaction mixture. The solution was poured into 2 M HCl (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding crude **2.19** (1.02 g, 2.53 mmol). Purification by column chromatography (33-100% diethyl ether/petrol) yielded **2.19** (0.27 g, 0.66 mmol, 34%) as a yellow oil.

FT-IR (ν/cm^{-1}) 3055 (w), 2961-2870 (w), 1732 (s), 1577 (w), 1436 (m), 1372 (m), 1250 (m), 1072 (s), 997 (m), 733 (s).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.51-7.47 (2 H, m, 2 x Ar C**H**), 7.37-7.24 (8 H, m, 8 x Ar C**H**), 4.59-4.44 (3 H, m, OC**H**, OC**H**$_2$Ph), 3.68 (1 H, dd, J = 10.3, 5.9 Hz, OC**H**H), 3.57 (1 H, dd, J = 10.3, 4.8 Hz, OCH**H**), 3.01 (1 H, dd, J = 12.4, 5.9 Hz, C**H**HSe), 2.93 (1 H, dd, J = 12.4, 6.6 Hz, CH**H**Se), 2.69 (1 H, dd, J = 16.5, 6.6 Hz, C**H**HC=O), 2.33 (1 H, m, CH**H**C=O), 2.10-1.94 (2 H, m, CH_3C**H**C**H**), 0.92 (3 H, d, J = 6.8 Hz, C**H**$_3$) ppm.

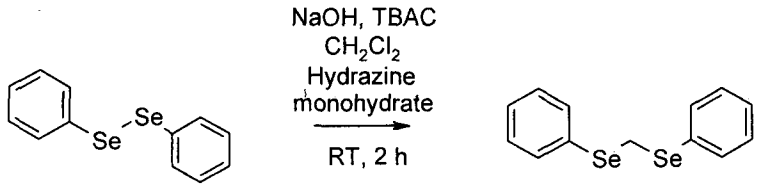
^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 171.7 (**C**=O), 137.6 (Ar **C**), 133.2 (2 x Ar **C**H), 129.4 (Ar **C**), 129.3 (2 x Ar **C**H), 128.5 (2 x Ar **C**H), 127.9 (2 x Ar **C**H), 127.8 (Ar **C**H), 127.5 (Ar **C**H), 78.5 (O**C**H), 73.7 (Ph**C**H$_2$O),

69.2 ($BnOCH_2$), 37.8 ($CHCH_3$), 34.6 ($CHCH_2SePh$), 34.5 ($CH_2C=O$), 33.9 (CH_2SePh), 14.3 (CH_3) ppm.

LRMS m/z (ES^+) 427 ($[M + Na]^+$, 100%).

HRMS m/z (ES^+) found: 427.0781 $[M + Na]^+$. $C_{21}H_{24}O_3NaSe$ requires 427.0783.

Bis-(phenylseleno)-methane



$C_{12}H_{10}Se_2$
MW = 312.13

$C_{13}H_{12}Se_2$
MW = 326.16

To a vigorously stirred mixture of powdered sodium hydroxide (2.00 g, 50.0 mmol), tetrabutylammonium chloride (0.56 g, 2.0 mmol) and diphenyl diselenide (3.12 g, 10.0 mmol) in THF (20 mL) was added hydrazine monohydrate (0.58 mL, 12.0 mmol) dropwise. The mixture was stirred for 30 min, then CH_2Cl_2 (2.02 mL, 24.0 mmol) was added dropwise over 1 h. After a further 1 h, water (20 mL) was added then the mixture extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20-100% petrol/chloroform) yielded bis(phenylseleno)methane as a yellow oil (1.92 g, 5.90 mmol, 59%).

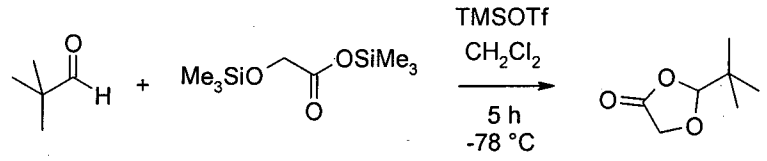
FT-IR (ν/cm^{-1}) 3051-2930 (br m), 1574 (s), 1473 (s), 1434 (s), 1129 (s), 1020 (s).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.57-7.51 (6 H, m, 6 x Ar**H**), 7.30-7.26 (4 H, m, 4 x Ar**H**), 4.23 (2 H, s, CH_2) ppm.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 133.0 (4 x Ar **C**H), 130.8 (2 x Ar **C**), 129.2 (4 x Ar **C**H), 127.6 (2 x Ar **C**H), 21.0 (CH_2) ppm.

Data consistent with literature values.[131]

2-(1,1-Dimethylethyl)-1,3-dioxolan-4-one



$C_5H_{10}O$
MW = 86.13

$C_8H_{20}O_3Si_2$
MW = 220.42

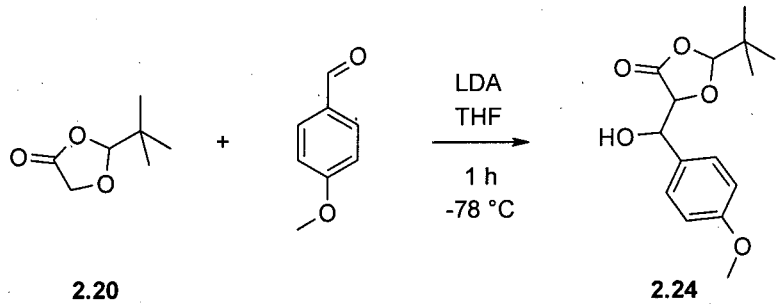
2.20
$C_7H_{12}O_3$
MW = 144.17

Dioxolanone **2.20** was prepared according to the procedure of Pearson and co-workers.[64] To a stirred solution of trimethylacetaldehyde (4.50 g, 52.0 mmol), TMSOTf (0.47 mL, 2.6 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added trimethylsilyl trimethylsiloxyacetate (16.31 mL, 68.0 mmol) dropwise. The reaction mixture was stirred at –78 °C for 5 h then washed with H_2O (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (12-50% diethyl ether/petrol) yielded **2.20** (5.72 g, 40.0 mmol, 76%) as a volatile clear oil.

FT-IR (ν/cm^{-1})	2964 (w), 1802 (s), 1206 (s), 1092 (s), 953 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 5.24 (1 H, s, C**H**), 4.33 (1 H, dd, J = 15.0, 0.7 Hz, C**H**H), 4.24 (1 H, dd, J = 15.0, 0.7 Hz, CH**H**), 0.97 (9 H, s, (C**H**$_3$)$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 171.6 (**C**=O), 111.9 (**C**H), 64.4 (**C**H$_2$), 35.0 (**C**(CH$_3$)$_3$), 23.2 ((**C**H$_3$)$_3$) ppm.
LRMS	m/z (EI) 145 ([M + H]$^+$, 58%), 87 (100), 69 (76), 57 (88).

Data consistent with literature values.[65]

2-*tert*-Butyl-5-[hydroxy-(4-methoxyphenyl)-methyl]-[1,3]dioxolan-4-one



2.20
$C_7H_{12}O_3$
MW = 144.17

$C_8H_8O_2$
MW = 136.15

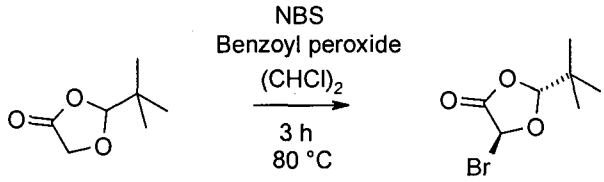
2.24
$C_{15}H_{20}O_5$
MW = 280.32

*n*BuLi (1.86 M in hexanes, 5.54 mL, 10.30 mmol) was added dropwise to a solution of diisopropylamine (1.43 mL, 10.30 mmol) in THF (80 mL) at –78 °C. The resulting solution was allowed to warm to 0 °C, then immediately re-cooled to –78 °C and **2.20** (1.38 g, 9.55 mmol) added dropwise. After 45 min, *p*-anisaldehyde (1.00 g, 7.34 mmol) in THF (3 mL) was added dropwise to the reaction mixture and the temperature allowed to warm to –25 °C, where it was maintained for 1 h. The reaction mixture was poured into a 1:1 solution of saturated NH_4Cl/H_2O (200 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10-100% diethyl ether/petrol) yielded **2.24** as a 5:1 mixture of diastereoisomers, initially as a yellow oil (0.58 g, 2.07 mmol, 28%) which crystallised upon standing.

m.p.	63-65 °C (ether/petrol)
FT-IR (ν/cm^{-1})	3477 (br w), 2960 (m), 1786 (s), 1512 (m), 1355 (m), 1247 (s), 1200 (s), 1104 (s), 1030 (s), 977 (s), 832 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz) Signals attributed to the major diastereoisomer: 7.40-7.32 (2 H, m, 2 x Ar C**H**), 6.95-6.89 (2 H, m, 2 x Ar C**H**), 5.44 (1 H, d, J = 1.9 Hz, OC**H**), 5.06 (1 H, s, OC**H**O), 4.47 (1 H, dd, J = 4.3, 1.9 Hz, C**H**OH), 3.82 (3 H, s, OC**H**$_3$), 2.48 (1 H, d, J = 4.3 Hz, O**H**), 0.96 (9 H, s, (C**H**$_3$)$_3$) ppm Other selected signals attributed to the minor diastereoisomer; 5.31 (1 H, d, J = 1.9 Hz, OC**H**), 5.02 (1 H, s, OC**H**O), 4.58 (1 H, dd, J = 4.3,

	1.9 Hz, CHOH), ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 172.0 (**C**=O), 159.8 (Ar **C**), 131.4 (Ar **C**), 128.1 (2 x Ar **C**H), 114.0 (2 x Ar **C**H), 112.3 (O**C**HO), 78.9 (**C**HOH), 73.6 (**C**HC=O), 55.3 (O**C**H_3), 35.5 (**C**$(CH_3)_3$), 23.2 ((**C**$H_3)_3$) ppm.
LRMS	m/z (ES^+) 303 ($[M + Na]^+$ 100%).
HRMS	m/z (ES^+) found: 303.1211, $[M + Na]^+$. $C_{15}H_{20}O_5Na$ requires 303.1203.
Elemental	Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.34, H, 7.28.

***rel*-(3*S*,5*S*)-5-Bromo-2-(1,1-dimethylethyl)-1,3-dioxolane-4-one**



2.20
$C_7H_{12}O_3$
MW = 144.17

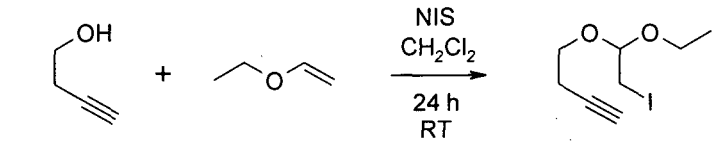
2.23
$C_7H_{11}O_3Br$
MW = 223.07

2.23 was prepared according to the procedure of Beckwith and co-workers.[66] **2.20** (0.50 g, 3.47 mmol), *N*-bromosuccinimide (0.68 g, 3.83 mmol) and benzoyl peroxide (0.02 g) in 1,2-dichloroethane (20 mL) were heated at reflux for 3 h. The mixture was cooled to 0 °C and filtered. The filtrate was concentrated *in vacuo* then purified by column chromatography (5-50% diethyl ether/petrol) to yield **2.23** as an orange oil (0.52 g, 2.31 mmol, 67%).

FT-IR (ν/cm^{-1})	3544-3222 (br w), 2966 (w), 1800 (s), 1483 (w), 1297 (m), 1204 (s), 1167 (m), 1084 (s), 1044 (m), 955 (s), 888 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 6.47 (1 H, s, C**H**Br), 5.38 (1 H, s, C**H**), 1.02 (9 H, s, (C**H**$_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 166.0 (**C**=O), 109.7 (O**C**HO), 73.9 (**C**HBr), 33.8 (**C**$(CH_3)_3$), 23.2 ((**C**$H_3)_3$) ppm.
LRMS	m/z (ES^+) 256 ($[M + Na]^+$, 100%).

Data consistent with literature values.[66]

4-(1-Ethoxy-2-iodoethoxy)-but-1-yne



2.36
C_4H_6O
MW = 70.09

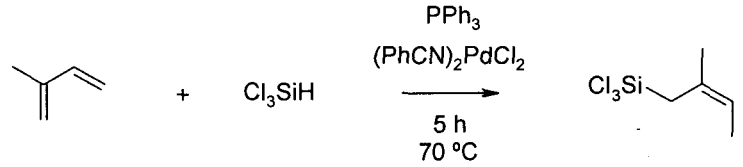
C_4H_8O
MW = 72.11

2.37
$C_8H_{13}IO_2$
MW = 268.10

A solution of 3-butyn-1-ol (0.20 g, 2.85 mmol), ethyl vinyl ether (0.41 g, 5.65 mmol) and NIS (1.27 g, 5.65 mmol) in CH_2Cl_2 (30 mL) was stirred at ambient temperature for 24 h. The mixture was concentrated *in vacuo*, diluted with petroleum ether (30 mL), filtered and concentrated *in vacuo* to yield crude **2.37** (0.84 g). Purification by column chromatography (33-100% diethyl ether/petroleum ether) yielded **2.37** (0.76 g, 2.84 mmol, 99%) as an orange oil.

FT-IR (ν/cm^{-1})	3293 (w), 2970-2880 (w), 1417 (w), 1336 (w), 1115 (s), 1042 (s), 993 (s), 637 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.70 (1 H, t, J = 5.6 Hz, OC**H**O), 3.77-3.54 (4 H, m, 2 x OC**H**$_2$), 3.24 (2 H, d, J = 5.6 Hz, C**H**$_2$I), 2.53-2.48 (2 H, m, C**H**$_2$C), 2.00 (1 H, s, CC**H**), 1.25 (3 H, t, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 101.9 (O**C**HO), 81.0 (**C**CH), 69.5 (C**C**H), 64.2 (O**C**H$_2$CH$_3$), 62.4 (CH$_2$**C**H$_2$O), 20.0 (**C**H$_2$I), 15.1 (**C**H$_3$), 4.9 (**C**H$_2$CCH) ppm.
LRMS	m/z (EI) 267 (M^+, 5%), 199 (88), 171 (86), 141 (16), 127 (100), 99 (12), 75 (26), 66 (58), 53 (80).
HRMS	m/z (EI) found 267.9884 $[M]^+$, $C_8H_{13}IO_2$ requires 267.9716.

Trichloro-((*Z*)-2-methylbut-2-enyl)-silane



2.48
C_5H_8
MW = 68.12

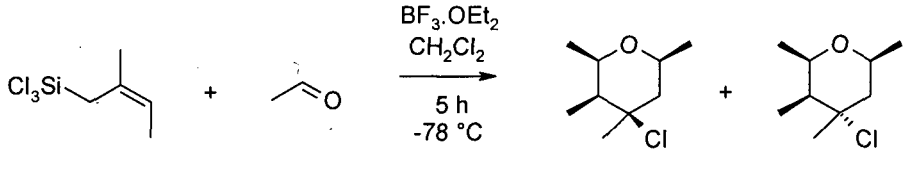
MW = 135.45

2.49
$C_5H_9Cl_3Si$
MW = 203.57

Trichlorosilane **2.49** was prepared by the method of Ojima *et al.*[73] Isoprene (5.99 mL, 60.0 mmol), trichlorosilane (6.67 mL, 66.0 mmol), triphenylphosphine (0.08 g, 0.30 mmol) and *bis*-(benzonitrile)palladium dichloride (0.05 g, 0.14 mmol) were placed in a pressure tube and degassed under argon for 15 min. The tube was sealed, heated at 70 °C for 5 h, then cooled to RT. Distillation (163-165 °C/ 760 mm Hg) yielded **2.49** as a colourless oil (10.51 g, 51.6 mmol, 86%).

FT-IR (ν/cm^{-1}):	2976 (br w), 1442 (w), 1380 (w), 1336 (w), 1222 (w), 1179 (w), 1026 (w), 955 (w), 807 (m), 752 (s), 720 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 5.43 (1 H, q, J = 6.8 Hz, CC**H**), 2.39 (2 H, s, C**H**$_2$), 1.83 (3 H, s, CC**H**$_3$), 1.61 (3 H, d, J = 6.8 Hz, CHC**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 126.5 (**C**CH), 122.6 (C**C**H), 29.7 (**C**H$_3$CH), 25.4 (**C**H$_3$CCH$_2$Si), 14.3 (CH$_2$Si) ppm.

***rel*-(2*R*,3*S*,4*RS*,6*S*)-4-Chloro-2,3,4,6-tetramethyltetrahydropyran-4-ol**



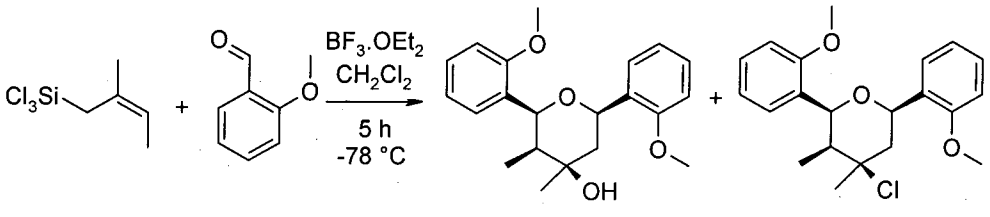
2.49 $C_5H_9Cl_3Si$ MW = 203.57 | C_2H_4O MW = 44.05 | **2.50a** $C_9H_{17}ClO$ MW = 176.69 | **2.50b** $C_9H_{17}ClO$ MW = 176.69

To a solution of acetaldehyde (0.31 mL, 5.50 mmol) and **2.49** (1.02 g, 5.00 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added boron trifluoride diethyl etherate (0.76 mL, 6.00 mmol) dropwise. The reaction mixture was stirred at −78 °C for 5 h, then poured into a saturated solution of $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding a yellow oil. Purification by column chromatography (25-50% diethyl ether/petrol) yielded firstly **2.50a** then **2.50b** as a brown oil (0.15 g, 0.95 mmol, dr = 3:2).

Spectroscopic data shown for the major diastereoisomer only, as the minor diastereoisomer decomposed before analysis could be carried out.

FT-IR (ν/cm^{-1}):	3442 (br w), 2980 (br w), 1600 (w), 1589 (w), 1494 (m), 1460 (w), 1438 (w), 1372 (w), 1285 (w), 1240 (s), 1157 (m), 1087 (s), 1050 (m), 1028 (m), 920 (m), 846 (w), 860 (w), 751 (s), 658 (w).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.29 (1 H, qd, J = 6.5, 2.0 Hz, OC**H**CH), 3.93 (1 H, m, OC**H**CH_2), 1.78-1.51 (3 H, m, C**H**, C$\mathbf{H}_2$), 1.63 (3 H, s, CClC$\mathbf{H}_3$), 1.19 (3 H, d, J = 6.2 Hz, C$\mathbf{H}_3$CHO), 1.15 (3 H, d, J = 6.5 Hz, C$\mathbf{H}_3$CHO), 0.92 (3 H, d, J = 7.1 Hz, C$\mathbf{H}_3$CH) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 75.4 (**C**Cl), 71.3 (O**C**H), 69.9 (O**C**H), 45.2 (CH_3**C**HC), 43.2 (**C**H_2), 32.0 (CCl**C**H_3), 21.5 (**C**H_3CHO), 19.1 (**C**H_3CHO), 9.2 (**C**H_3CH) ppm.
LRMS	m/z (ES$^+$) 181 ([M(^{35}Cl) + Na]$^+$, 50%).

rel-(2_S_,3_S_,4_R_,6_R_)-2,6-bis-(2-Methoxyphenyl)-3,4-dimethyl-4-hydroxytetrahydropyran-4-ol (2.51) & _rel_-(2_S_,3_S_,4_R_,6_R_)-2,6-bis-(2-methoxyphenyl)-3,4-dimethyl-4-chlorotetrahydropyran-4-ol (2.52)



2.49
$C_5H_9Cl_3Si$ MW = 203.57

$C_8H_8O_2$ MW = 136.15

2.51
$C_{21}H_{26}O_4$
MW = 342.44

2.52
$C_{21}H_{25}ClO_3$
MW = 360.88

To a stirred solution of *o*-anisaldehyde (0.41 g, 3.00 mmol) and **2.49** (0.70 g, 3.44 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added boron trifluoride diethyl etherate (0.76 mL, 6.00 mmol) dropwise. The reaction mixture was stirred at −78 °C for 5 h, then poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* yielding a crude yellow oil. Purification by column chromatography (25-50%

diethyl ether/petrol) yielded firstly chloride **2.52** (0.19 g, 0.53 mmol, 15%) then alcohol **2.51** (0.18 g, 0.53 mmol, 15%) as white crystalline solids.

Spectroscopic data for alcohol **2.51**

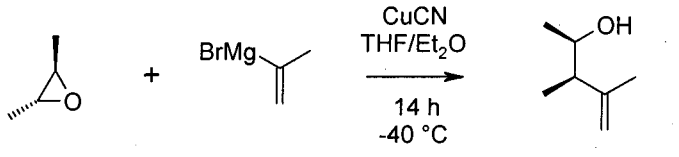
m.p.	203-205 °C (diethyl ether/petrol)
FT-IR (ν/cm^{-1}):	3434 (br w), 2973 (br w), 1603 (w), 1589 (w), 1494 (m), 1458 (w), 1438 (w), 1372 (w), 1285 (w), 1240 (s), 1157 (m), 1087 (s), 1050 (m), 1028 (m), 941 (m), 846 (w), 860 (w), 817 (w), 789 (w).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.71 (1 H, dd, J = 7.5, 1.4 Hz, Ar C**H**), 7.58 (1 H, dd, J = 7.5, 1.4 Hz, Ar C**H**), 7.32-7.19 (2 H, m, 2 x Ar C**H**), 7.10-7.01 (2 H, m, 2 x Ar C**H**), 6.86 (2 H, dd, J = 7.8, 5.9 Hz, 2 x Ar C**H**), 5.14 (1 H, d, J = 1.7 Hz, OC**H**Ar), 4.98 (1 H, dd, J = 11.6, 2.5 Hz, OC**H**Ar), 3.81 (6 H, s, OC**H**$_3$), 2.11 (1 H, qd, J = 7.0, 1.7 Hz, CH$_3$C**H**), 1.89-1.69 (2 H, m, C**H**$_2$), 1.68 (3 H, s, C**H**$_3$COH), 1.50 (1 H, br s, O**H**), 0.81 (3 H, d, J = 7.0 Hz, C**H**$_3$CH) ppm. nOe (400 MHz, $CDCl_3$); irradiation of the signal at δ_H 5.14 led to nOe enhancement at 4.98 and 2.11. Irradiation of the signal at δ_H 4.98 led to nOe enhancement at 5.14 and 1.89-1.69. Irradiation of the signal at δ_H 1.68 led to nOe enhancement at 2.11, 1.89-1.69 and 0.81.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 154.2 (Ar **C**), 153.8 (Ar **C**), 130.3 (Ar **C**), 128.7 (Ar **C**), 126.6 (Ar **C**H), 126.1 (Ar **C**H), 126.1 (Ar **C**H), 125.0 (Ar **C**H), 119.5 (Ar **C**H), 118.9 (Ar **C**H), 108.9 (Ar **C**H), 108.4 (Ar **C**H), 73.5 (O**C**HCHAr), 70.8 (O**C**HCH$_2$Ar), 70.5 (**C**CH$_3$OH), 54.1 (O**C**H$_3$) 53.9 (O**C**H$_3$), 41.0 (CH$_3$**C**H), 40.2 (**C**H$_2$), 25.6 (**C**H$_3$COH), 6.8 (**C**H$_3$CH) ppm.
LRMS	m/z (ES$^+$) 365 ([M + Na]$^+$, 78%).
HRMS	m/z (ES$^+$) found 365.4326 [M + Na]$^+$, $C_{21}H_{26}O_4Na$ requires 365.4292.

Spectroscopic data for chloride **2.52**

m.p.	140-142 °C (diethyl ether/petrol)
FT-IR (ν/cm^{-1}):	2936 (br. w), 2836 (m), 1603 (m), 1590 (m), 1493 (s), 1464 (m), 1361 (m).
^{1}H NMR	δ_H (300 MHz): 7.71 (1 H, dd, J = 7.5, 1.4 Hz, Ar C**H**), 7.58 (1 H, dd,

($CDCl_3$)	J = 7.5, 1.4 Hz, Ar C**H**), 7.32-7.19 (2 H, m, 2 x Ar C**H**), 7.11-7.00 (2 H, m, 2 x Ar C**H**), 6.86 (2 H, dd, J = 7.8, 5.9 Hz, 2 x Ar C**H**), 5.28 (1 H, d, J = 1.5 Hz, OC**H**CHAr), 5.08 (1 H, dd, J = 8.6, 5.4 Hz, OC**H**Ar), 3.84 (3 H, s, OC**H**$_3$), 3.83 (3 H, s, OC**H**$_3$), 2.40 (1 H, qd, J = 7.0, 1.5 Hz, CH_3C**H**), 2.28-2.20 (2 H, m, C**H**$_2$), 2.14 (3 H, s, C**H**$_3$CCl), 1.04 (3 H, d, J = 7.0 Hz, C**H**$_3$CH) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 155.6 (Ar **C**), 155.2 (Ar **C**), 130.9 (Ar **C**), 129.8 (Ar **C**), 128.4 (Ar **C**H), 127.9 (Ar **C**H), 127.5 (Ar **C**H), 126.4 (Ar **C**H), 121.1 (Ar **C**H), 120.5 (Ar **C**H), 110.3 (Ar **C**H), 109.9 (Ar **C**H), 74.0 (O**C**H), 74.0 (**C**ClCH$_3$), 72.1 (O**C**H), 55.6 (O**C**H$_3$), 55.5 (O**C**H$_3$), 44.0 (CH_3**C**H), 43.7 (**C**H$_2$), 30.0 (**C**H$_3$), 11.4 (**C**H$_3$) ppm.
LRMS	m/z (ES$^+$) 385 ([M(^{35}Cl) + Na]$^+$, 30%).
Elemental	Anal. Calcd for $C_{21}H_{25}ClO_3$: C, 69.89; H, 6.98. Found: C, 69.94, H, 7.03.

***rel*-(2*R*,3*R*)-3,4-Dimethylpent-4-en-2-ol**



3.34
C_4H_8O
MW = 72.11

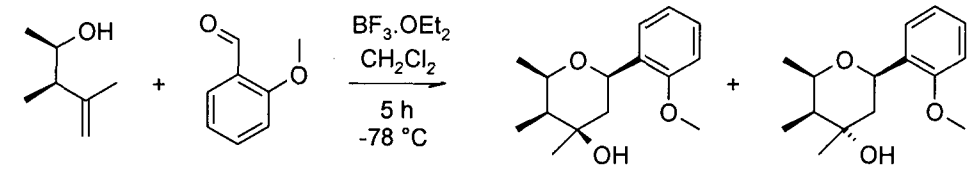
C_3H_5BrMg
MW = 145.24

3.35
$C_7H_{14}O$
MW = 114.19

Homoallylic alcohol **3.35** was prepared according to the procedure of Driver *et al.*[132] Copper cyanide (1.52 g, 16.8 mmol) was added to a solution of *trans*-2,3-epoxybutane (4.98 mL, 55.4 mmol) in diethyl ether (30 mL) at −40 °C. A solution of isopropenylmagnesium bromide (0.5 M in THF, 205 mL) was added dropwise to the reaction mixture over 1 h. The mixture was allowed to warm to RT over 12 h, then stirred for a further 2 h at RT, before saturated NH_4Cl (150 mL) was added dropwise to the black solution. The mixture was extracted with diethyl ether (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding **3.35** as an orange oil (5.77 g, 50.5 mmol, 91%).

FT-IR (ν/cm^{-1}):	3362 (br w), 2968 (m), 1646 (m), 1453 (m), 1374 (m), 1157 (w), 1087 (s), 1035 (s), 907 (s), 898 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.84 (1 H, s, C=C**H**H), 4.77 (1 H, s, C=CH**H**), 3.78 (1 H, app. quint, J = 6.5 Hz, CH_3C**H**OH), 2.11 (1 H, app. quint, J = 6.5 Hz, CH_3C**H**), 1.73 (3 H, s, C**H**$_3$CCH_2), 1.57 (1 H, br s, O**H**), 1.18 (3 H, d, J = 6.5 Hz, C**H**$_3$CHOH), 1.07 (3 H, d, J = 6.5 Hz, C**H**$_3$CH) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 148.1 (**C**CH_2), 111.3 (C**C**H_2), 68.8 (CH_3**C**HOH), 48.0 (CH_3**C**HC), 21.0 (**C**H_3CCH_2), 21.0 (**C**H_3CHOH), 13.6 (**C**H_3CH) ppm.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-6-(2-Methoxyphenyl)-2,3,4-trimethyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | $C_8H_8O_2$ MW = 136.15 | **3.36a** $C_{15}H_{22}O_3$ MW = 250.34 | **3.36b** $C_{15}H_{22}O_3$ MW = 250.34

To a solution of *o*-anisaldehyde (0.48 g, 3.6 mmol) and boron trifluoride diethyletherate (0.44 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added **3.35** (0.20 g, 1.8 mmol) in CH_2Cl_2 (1.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* yielding crude **3.36**. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded firstly **3.36a** (0.10 g, 0.42 mmol, 23%) then **3.36b** (0.07 g, 0.28 mmol, 16%) as yellow oils.

Spectroscopic data shown for the major diastereoisomer only, as the minor diastereoisomer decomposed before analysis could be carried out.

FT-IR (ν/cm^{-1}):	3434 (br w), 2973 (br w), 1603 (w), 1589 (w), 1494 (m), 1458 (w), 1438 (w), 1372 (w), 1285 (w), 1240 (s), 1157 (m), 1087 (s), 1050

(m), 1028 (m), 941 (m), 846 (w), 860 (w), 817 (w), 789 (w), 751 (s).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 7.50 (1 H, dd, J = 7.7, 1.7 Hz, Ar C**H**), 7.23 (1 H, td, J = 7.7, 1.7 Hz, Ar C**H**), 6.98 (1 H, td, J = 7.7, 0.8 Hz, Ar C**H**), 6.86 (1 H, dd, J = 7.7, 0.8 Hz, Ar C**H**), 4.82 (1 H, dd, J = 11.0, 2.9 Hz, OC**H**Ar), 3.90 (1 H, qd, J = 6.4, 2.2 Hz, OC**H**CH_3), 3.80 (3 H, s, OC**H**$_3$), 1.72-1.59 (3 H, m, CH_3C**H**, C**H**$_2$), 1.51 (3 H, s, CC**H**$_3$OH), 1.42 (1 H, br s, O**H**), 1.24 (3 H, d, J = 6.4 Hz, C**H**$_3$CH), 1.06 (3 H, d, J = 6.9 Hz, C**H**$_3$CH) ppm.

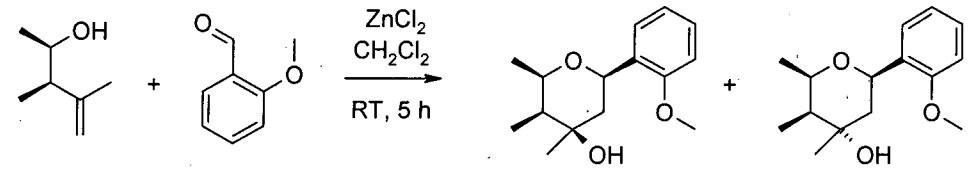
nOe (400 MHz, $CDCl_3$); irradiation of the signal at δ_H 4.82 led to nOe enhancement at 3.90, 1.72-1.59 and 1.51. Irradiation of the signal at δ_H 1.51 led to nOe enhancement at 3.90, 1.72-1.59 and 1.06. Irradiation of the signal at δ_H 1.24 led to nOe enhancement at 1.06.

^{13}C NMR ($CDCl_3$) δ_C (100 MHz): 155.5 (Ar **C**), 131.1 (Ar **C**), 128.0 (Ar **C**H), 126.3 (Ar **C**H), 120.9 (Ar **C**H), 110.2 (Ar **C**H), 73.2 (O**C**HCH$_2$), 71.6 (**C**OH), 71.4 (CH_3**C**HO), 55.3 (O**C**H$_3$), 44.6 (CH_3**C**H), 41.3 (**C**H$_2$), 27.0 (**C**H$_3$COH), 19.4 (**C**H$_3$CHO), 6.7 (**C**H$_3$CH) ppm.

LRMS m/z (ES^+) (233 $[MH - OH]^+$, 70%).

HRMS m/z (ES^+) found: 273.1460, $[M + Na]^+$. $C_{15}H_{22}O_3Na$ requires 273.1461.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-6-(2-Methoxyphenyl)-2,3,4-trimethyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | $C_8H_8O_2$ MW = 136.15 | **3.36a** $C_{15}H_{22}O_3$ MW = 250.34 | **3.36b** $C_{15}H_{22}O_3$ MW = 250.34

To a solution of *o*-anisaldehyde (0.48 g, 3.6 mmol) and zinc(II) chloride (0.48 g, 3.6 mmol) in CH_2Cl_2 (10 mL) was added **3.35** (0.20 g, 1.8 mmol) in CH_2Cl_2 (1.0 mL) dropwise. The reaction mixture was stirred at RT for 5 h then poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined

organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded firstly **3.36a** (0.07, 0.29 mmol, 16%) then **3.36b** (0.05 g, 0.20 mmol, 11%) as yellow oils.

Spectroscopic data shown for the major diastereoisomer only, as the minor diastereoisomer decomposed before analysis could be carried out.

FT-IR (ν/cm^{-1}): 3434 (br w), 2973 (br w), 1603 (w), 1589 (w), 1494 (m), 1458 (w), 1438 (w), 1372 (w), 1285 (w), 1240 (s), 1157 (m), 1087 (s), 1050 (m), 1028 (m), 941 (m), 846 (w), 860 (w), 817 (w), 789 (w), 751 (s).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 7.50 (1 H, dd, J = 7.7, 1.7 Hz, Ar C**H**), 7.23 (1 H, td, J = 7.7, 1.7 Hz, Ar C**H**), 6.98 (1 H, td, J = 7.7, 0.8 Hz, Ar C**H**), 6.86 (1 H, dd, J = 7.7, 0.8 Hz, Ar C**H**), 4.82 (1 H, dd, J = 11.0, 2.9 Hz, OC**H**Ar), 3.90 (1 H, qd, J = 6.4, 2.2 Hz, OC**H**CH_3), 3.80 (3 H, s, O**C**H_3), 1.72-1.59 (3 H, m, CH_3C**H**, CH_2), 1.51 (3 H, s, CC**H**$_3$OH), 1.42 (1 H, br s, O**H**), 1.24 (3 H, d, J = 6.4 Hz, C**H**$_3$CH), 1.06 (3 H, d, J = 6.9 Hz, C**H**$_3$CH) ppm.

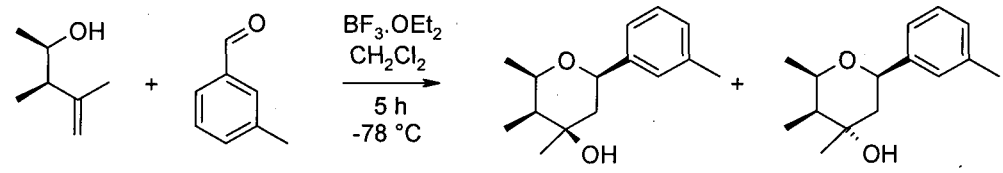
nOe (400 MHz, $CDCl_3$); irradiation of the signal at δ_H 4.82 led to nOe enhancement at 3.90, 1.72-1.59 and 1.51. Irradiation of the signal at δ_H 1.51 led to nOe enhancement at 3.90, 1.72-1.59 and 1.06. Irradiation of the signal at δ_H 1.24 led to nOe enhancement at 1.06.

^{13}C NMR ($CDCl_3$): δ_C (100 MHz): 155.5 (Ar **C**), 131.1 (Ar **C**), 128.0 (Ar **C**H), 126.3 (Ar **C**H), 120.9 (Ar **C**H), 110.2 (Ar **C**H), 73.2 (O**C**HCH$_2$), 71.6 (**C**OH), 71.4 (O**C**HCH$_3$), 55.3 (O**C**H$_3$), 44.6 (CH_3**C**H), 41.3 (**C**H$_2$), 27.0 (**C**H$_3$COH), 19.4 (**C**H$_3$CHO), 6.7 (**C**H$_3$CH) ppm.

LRMS m/z (ES^+) 233 ($[MH - OH]^+$, 70%).

HRMS m/z (ES^+) found: 273.1460, $[M + Na]^+$. $C_{15}H_{22}O_3Na$ requires 273.1461.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-2,3,4-Trimethyl-6-*m*-tolyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 + C_8H_8O MW = 120.15

3.40a $C_{15}H_{22}O_2$ MW = 234.34 + **3.40b** $C_{15}H_{22}O_2$ MW = 234.34

To a solution of *m*-tolualdehyde (0.20 mL, 1.80 mmol) and boron trifluoride diethyl etherate (0.22 mL, 1.80 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added **3.35** (0.10 g, 0.90 mmol) in CH_2Cl_2 (0.5 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded an inseparable 3:1 mixture of **3.40a** and **3.40b** as a colourless oil (0.12 g, 0.51 mmol, 55%).

FT-IR (ν/cm^{-1}): 3426 (br w), 2975 (m), 2924 (w), 2882 (w), 1610 (w), 1455 (m), 1372 (s), 1326 (m), 1291 (w), 1155 (s), 1101 (s), 1014 (m), 944 (m), 888 (m), 863 (m), 777 (s), 700 (s), 660 (m).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz) Signals attributed to the major diastereoisomer: 7.25–6.90 (4 H, m, Ar C**H**), 4.31 (1 H, dd, J = 11.9, 2.6 Hz, OC**H**Ar), 3.81 (1 H, qd, J = 6.4, 2.2 Hz, OC**H**CH_3), 2.26 (3 H, s, ArC**H**$_3$), 1.78-1.40 (3 H, m, CH_3C**H**, CH_2), 1.43 (3 H, s, C**H**$_3$COH), 1.16 (3 H, d, J = 6.4 Hz, OCHC**H**$_3$), 0.99 (3 H, d, J = 7.0 Hz, C**H**$_3$CH) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.65 (1 H, dd, J = 11.7, 2.7 Hz, OC**H**Ar), 4.25 (1 H, qd, J = 6.6, 2.4 Hz, OC**H**CH_3), 1.13 (3H, d, J = 6.6 Hz, OCHC**H**$_3$), 0.92 (3 H, d, J = 7.1 Hz, C**H**$_3$CH) ppm.

^{13}C NMR ($CDCl_3$) δ_C (100 MHz) Signals attributed to the major diastereoisomer: 142.3 (Ar **C**), 138.0 (Ar **C**) 128.3 (Ar **C**H), 128.2 (Ar **C**H), 126.7 (Ar **C**H), 123.1 (Ar **C**H), 77.5 (O**C**HAr), 73.3 (O**C**HCH$_3$), 71.6 (CH$_3$**C**OH), 44.5 (CH$_3$**C**H), 42.6 (**C**H$_2$), 27.2 (**C**H$_3$COH), 21.5(Ar**C**H$_3$), 19.4

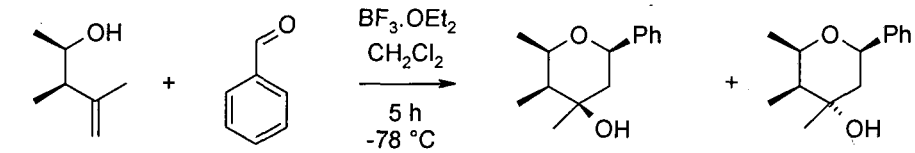
($OCHCH_3$), 6.7 (CH_3CH) ppm.

Signals attributed to the minor diastereoisomer: 143.0 (Ar **C**), 137.9 (Ar **C**) 128.3 (Ar **C**H), 128.0 (Ar **C**H), 126.7 (Ar **C**H), 123.1 (Ar **C**H), 77.3 (**O**CHAr), 75.6 ($O\mathbf{C}HCH_3$), 72.2 ($CH_3\mathbf{C}OH$), 44.1 ($CH_3\mathbf{C}H$), 41.8 ($\mathbf{C}H_2$), 29.6 ($\mathbf{C}H_3COH$), 21.5 ($Ar\mathbf{C}H_3$), 18.9 ($OCH\mathbf{C}H_3$), 9.0 ($\mathbf{C}H_3CH$) ppm.

LRMS m/z (ES^+) 257 ($[M + Na]^+$, 55%).

HRMS m/z (ES^+) found: 257.1510, $[M + Na]^+$. $C_{15}H_{22}O_2Na$ requires 257.1512.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-2,3,4-Trimethyl-6-phenyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | C_7H_6O MW = 106.12 | **3.41a** $C_{14}H_{20}O_2$ MW = 220.31 | **3.41b** $C_{14}H_{20}O_2$ MW = 220.31

To a solution of benzaldehyde (0.18 mL, 1.80 mmol) and boron trifluoride diethyl etherate (0.22 mL, 1.80 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added **3.35** (0.10 g, 0.90 mmol) in CH_2Cl_2 (0.5 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded an inseparable 3:1 mixture of **3.41a** and **3.41b** as a colourless oil (0.08 g, 0.36 mmol, 40%).

FT-IR (ν/cm^{-1}): 3420 (br w), 2974 (m), 2883 (w), 1495 (w), 1452 (m), 1372 (m), 1300 (w), 1156 (m), 1090 (s), 1010 (m), 941 (m), 894 (w), 866 (w), 818 (w), 761 (w), 743 (w), 698 (s), 579 (m), 540 (w).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz) Signals attributed to the major diastereoisomer: 7.65-7.20 (5 H, m, 5 x Ar C**H**), 4.35 (1 H, dd, J = 11.7, 2.6 Hz, OC**H**Ph), 3.81 (1 H, qd, J = 6.4, 2.2 Hz, $OC\mathbf{H}CH_3$), 1.85-1.43 (3 H, m, $CH_3C\mathbf{H}$,

CH_2), 1.43 (3 H, s, CH_3COH), 1.16 (3 H, d, J = 6.4 Hz, $OCHCH_3$), 0.99 (3 H, d, J = 6.7 Hz, CH_3CH) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.68 (1 H, dd, J = 11.9, 2.7 Hz, OCHPh), 4.25 (1 H, qd, J = 6.6, 2.4 Hz, $OCHCH_3$), 1.12 (3 H, d, J = 6.6 Hz, $OCHCH_3$), 0.90 (3 H, d, J = 6.8 Hz, CH_3CH) ppm.

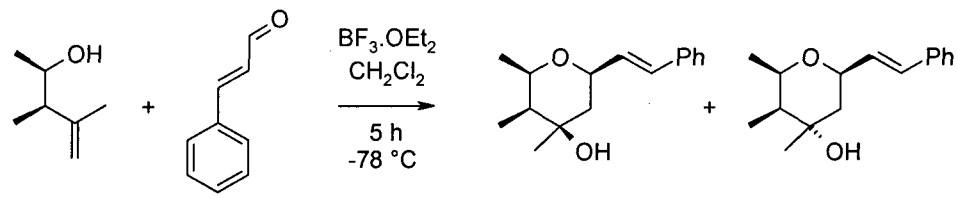
^{13}C NMR ($CDCl_3$) δ_C (75 MHz) Signals attributed to the major diastereoisomer: 142.3 (Ar **C**), 128.2 (2 x Ar **C**H), 127.3 (2 x Ar **C**H), 125.7 (Ar **C**H), 77.2 (**O**CHPh), 73.1 ($OCHCH_3$), 71.4 (CH_3COH), 44.3 (CH_3CH), 42.5 (CH_2), 27.0 (CH_3COH), 19.1 ($OCHCH_3$), 6.5 (CH_3CH) ppm.

Signals attributed to the minor diastereoisomer: 143.0 (Ar **C**), 129.9 (2 x Ar **C**H), 128.1 (2 x Ar **C**H), 127.1 (Ar **C**H), 75.4 (**O**CHPh), 72.0 ($OCHCH_3$), 70.7 (CH_3COH), 43.9 (CH_3CH), 41.7 (CH_2), 29.4 (CH_3COH), 18.6 ($OCHCH_3$), 8.8 (CH_3CH) ppm.

LRMS m/z (ES^+) 243 ($[M + Na]^+$, 42%).

HRMS m/z (ES^+) found: 243.1360, $[M + Na]^+$. $C_{14}H_{20}O_2Na$ requires 243.1356.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-2,3,4-Trimethyl-6-((*E*)-styryl)-tetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | C_9H_8O MW = 132.16 | **3.42a** $C_{16}H_{22}O_2$ MW = 246.35 | **3.42b** $C_{16}H_{22}O_2$ MW = 246.35

To a solution of *trans*-cinnamaldehyde (0.23 mL, 1.80 mmol) and boron trifluoride diethyl etherate (0.22 mL, 1.80 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added **3.35** (0.10 g, 0.90 mmol) in CH_2Cl_2 (0.5 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried

($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded an inseparable 7:1 mixture of **3.42a** and **3.42b** as a yellow oil (0.09 g, 0.37 mmol, 41%).

FT-IR (ν/cm^{-1}): 3430 (br w), 2976 (w), 2882 (w), 1560 (w), 1495 (w), 1450 (w), 1373 (m), 1301 (w), 1154 (m), 1084 (s), 1029 (m), 1006 (m), 965 (s), 936 (m), 909 (m), 865 (w), 810 (w), 710 (s), 692 (s), 663 (w).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz) Signals attributed to the major diastereoisomer: 7.42-7.19 (5 H, m, 5 x Ar C**H**), 6.62 (1 H, d, J = 15.9 Hz, CHC**H**Ph), 6.25 (1 H, dd, J = 15.9, 6.2 Hz, C**H**CHPh), 4.08 (1 H, ddd, J = 6.2, 2.7, 1.1 Hz, OC**H**CHCH), 3.83 (1 H, qd, J = 6.3, 2.0 Hz, OC**H**CH_3), 1.75-1.49 (3 H, m, CH_3C**H**, C**H**$_2$), 1.48 (3 H, s, C**H**$_3$COH), 1.29 (1 H, s, O**H**), 1.24 (3 H, d, J = 6.3 Hz, OCHC**H**$_3$), 1.03 (3 H, d, J = 7.0 Hz, C**H**$_3$CH) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.43 (1 H, m, OC**H**CHCH), 4.28 (1 H, qd, J = 6.5, 2.2 Hz, OC**H**CH_3), 1.22 (3 H, d, J = 6.5 Hz, OCHC**H**$_3$), 0.98 (3 H, d, J = 7.1 Hz, C**H**$_3$CH) ppm.

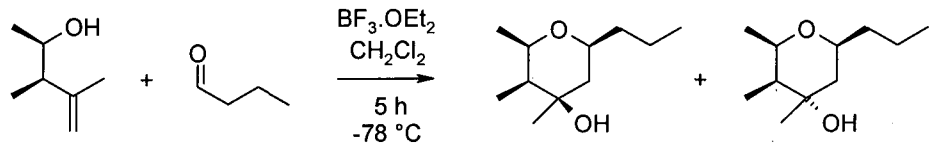
^{13}C NMR ($CDCl_3$): δ_C (100 MHz) Signals attributed to the major diastereoisomer: 136.9 (Ar **C**), 130.9 (Ar **C**H), 130.0 (2 x Ar **C**H), 128.6 (**C**HCHPh), 127.8 (2 x Ar **C**H), 126.7 (CH**C**HPh), 76.0 (O**C**HCHCHPh), 73.1 (O**C**HCH$_3$), 71.5 (**C**OH), 44.7 (CH$_3$**C**H), 40.8 (**C**H$_2$), 27.4 (**C**H$_3$COH), 19.5 (OCH**C**H$_3$), 6.8 (**C**H$_3$CH) ppm.

Signals attributed to the minor diastereoisomer: 137.0 (Ar **C**), 130.6 (Ar **C**H), 129.8 (2 x Ar **C**H), 128.5 (**C**HCHPh), 127.6 (2 x Ar **C**H), 126.6 (CH**C**HPh), 75.9 (O**C**HCHCHPh), 74.3 (O**C**HCH$_3$), 70.7 (**C**OH), 44.3 (CH$_3$**C**H), 39.9 (**C**H$_2$), 29.9 (**C**H$_3$COH), 19.0 (OCH**C**H$_3$), 9.1 (**C**H$_3$CH) ppm.

LRMS m/z (ES^+) 269 ($[M + Na]^+$, 74%).

HRMS m/z (ES^+) found: 269.1510, $[M + Na]^+$. $C_{16}H_{22}O_2$ requires 269.1512.

***rel*-(2*R*,3*S*,4*RS*,6*S*)-2,3,4-Trimethyl-6-propyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | C_4H_8O MW = 72.11 | **3.43a** $C_{11}H_{22}O_2$ MW = 186.30 | **3.43b** $C_{11}H_{22}O_2$ MW = 186.30

To a solution of butyraldehyde (0.18 mL, 2.0 mmol) and boron trifluoride diethyl etherate (0.25 mL, 2.0 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added **3.35** (0.11 g, 1.0 mmol) in CH_2Cl_2 (0.5 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30-70% diethyl ether/hexanes) yielded firstly **3.43a** (0.09 g, 0.47 mmol, 47%) then **3.43b** (0.02 g, 0.12 mmol, 12%) as a colourless oil.

Spectroscopic data shown for the major diastereoisomer only, as the minor diastereoisomer decomposed before analysis could be carried out.

FT-IR (ν/cm^{-1}): 3384 (br w), 2959 (m), 2933 (m), 2873 (m), 1455 (m), 1371 (m), 1332 (w), 1302 (w), 1164 (m), 1130 (m), 1096 (s), 1079 (m), 1025 (m), 1003 (w), 936 (m), 905 (w), 866 (m), 839 (w), 807 (w).

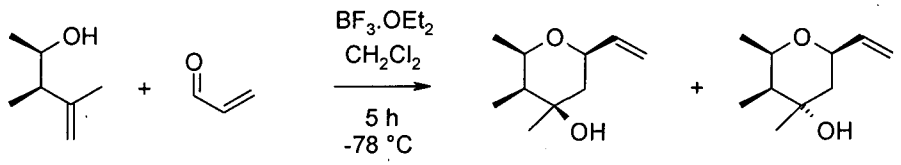
^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 4.10 (1 H, qd, J = 6.6, 2.2 Hz, OC**H**CH_3), 3.65 (1 H, m, OC**H**CH_2), 1.61 (1 H, br s, O**H**), 1.58-1.26 (7 H, m, 3 x C**H**$_2$, CH_3C**H**), 1.22 (3 H, s, COHC**H**$_3$), 1.12 (3 H, d, J = 6.6 Hz, OCHC**H**$_3$), 0.91 (3 H, t, J = 7.1 Hz, CH_2CH_2C**H**$_3$), 0.87 (3 H, d, J = 7.1 Hz, C**H**$_3$CH) ppm.

^{13}C NMR ($CDCl_3$): δ_C (100 MHz): 73.0 (O**C**HCH$_2$), 72.1 (**C**OH), 70.5 (O**C**HCH$_3$), 40.4 (CH$_3$**C**H), 39.7 (C**C**H$_2$), 38.3 (OCH**C**H$_2$), 29.7 (**C**H$_3$COH), 18.8 (OCH**C**H$_3$), 18.7 (**C**H$_2$CH$_3$), 14.1 (**C**H$_3$CH), 9.0 (**C**H$_3$CH$_2$) ppm.

LRMS m/z (CI) 169 ([MH – OH]$^+$, 100%).

HRMS m/z (EI) found 168.15163 $[MH - H_2O]^+$, $C_{11}H_{21}O$ requires 168.15142.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-2,3,4-Trimethyl-6-vinyltetrahydropyran-4-ol**



3.35 $C_7H_{14}O$ MW = 114.19 | C_3H_4O MW = 56.06 | **3.44a** $C_{10}H_{18}O_2$ MW = 170.25 | **3.44b** $C_{10}H_{18}O_2$ MW = 170.25

To a solution of acrolein (0.82 mL, 12.3 mmol) and boron trifluoride diethyl etherate (1.55 mL, 12.3 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added **3.35** (0.70 g, 6.13 mmol) in CH_2Cl_2 (2 mL) dropwise. The reaction mixture was stirred at −78 °C for 5 h then poured into a saturated solution of $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/hexanes) yielded an inseparable 2:1 mixture of **3.44a** and **3.44b** as a yellow oil (0.35 g, 2.06 mmol, 34%).

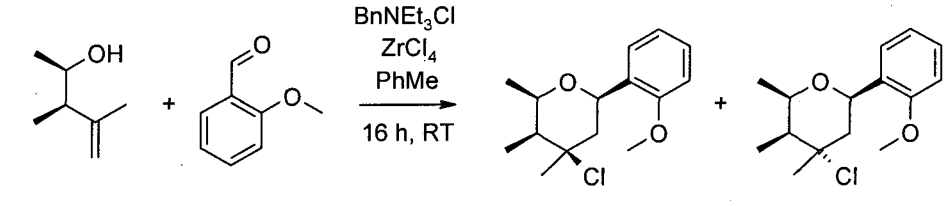
FT-IR (ν/cm^{-1}): 3422 (br w), 2977 (m), 2936 (w), 2886 (w), 1647 (w), 1454 (w), 1373 (m), 1320 (w), 1140 (m), 1081 (s), 1023 (s), 989 (s), 910 (s), 886 (m), 861 (m), 816 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz) Signals attributed to the major diastereoisomer: 5.85 (1 H, ddd, J = 16.8, 10.5, 5.9 Hz, C**H**=CH_2), 5.30-5.07 (2 H, m, CH=C**H**$_2$), 3.89 (1 H, m, OC**H**CH=C), 3.76 (1 H, qd, J = 6.6, 2.0 Hz, OC**H**CH_3), 1.63-1.31 (3 H, m, CH_3C**H**, C**H**$_2$), 1.42 (3 H, s, C**H**$_3$COH), 1.25 (1 H, s, O**H**), 1.19 (3 H, d, J = 6.6 Hz, OCHC**H**$_3$), 0.97 (3 H, d, J = 7.0 Hz, C**H**$_3$CH) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.22 (1 H, m, OC**H**CH=C), 4.20 (1 H, qd, J = 6.6, 2.3 Hz, OC**H**CH_3), 1.15 (3 H, d, J = 6.6 Hz, OCHC**H**$_3$), 0.89 (3 H, d, J = 7.1 Hz, C**H**$_3$CH) ppm.

^{13}C NMR ($CDCl_3$)	δ_C (100 MHz) Signals attributed to the major diastereoisomer: 139.3 (=**C**H), 115.3 (=**C**H_2), 74.4 (O**C**HCH$_3$), 72.0 (**C**OH), 70.6 (O**C**HCHCH$_2$), 44.2 (CH_3**C**H), 39.5 (C**C**H_2CH), 29.8 (**C**H_3COH), 18.9 (OCH**C**H_3), 9.0 (**C**H_3CH) ppm. Signals attributed to the minor diastereoisomer: 138.8 (=**C**H), 115.6 (=**C**H_2), 76.1 (O**C**HCH$_3$), 72.9 (O**C**HCHCH$_2$), 71.4 (**C**OH), 44.6 (CH_3**C**H), 40.3 (C**C**H_2CH), 27.4 (**C**H_3COH), 19.4 (OCH**C**H_3), 6.8 (**C**H_3CH) ppm.
LRMS	m/z (CI) 171 ($[MH]^+$, 45%), 153 (71), 109 (50), 72 (27).
HRMS	m/z (CI) found: 170.13068, $[M]^+$. $C_{10}H_{18}O_2$ requires 170.13030.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-4-Chloro-6-(2-methoxyphenyl)-2,3,4-trimethyltetrahydropyran**



3.35		**3.48a**	**3.48b**
$C_7H_{14}O$	$C_8H_8O_2$	$C_{15}H_{21}ClO_2$	$C_{15}H_{21}ClO_2$
MW = 114.19	MW = 136.15	MW = 268.79	MW = 268.79

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *o*-anisaldehyde (0.12 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) in toluene (1 mL) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (50:1 petroleum ether/diethyl ether) yielded an inseparable 10:1 mixture of **3.48a** and **3.48b** as a white waxy solid (0.08 g, 0.31 mmol, 71%).

FT-IR (ν/cm^{-1}): 2976 (m), 2918 (br. w), 2880 (w), 2841 (w), 1589 (m), 1491 (s), 1464 (m), 1438 (m), 1390 (m), 1331 (w), 1282 (s), 1236 (s), 1088 (s), 1049 (w), 1034 (m), 943 (m), 837 (w), 759 (s).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz) Signals attributed to the major diastereoisomer: 7.50 (1 H, dd, J = 7.7, 1.7 Hz, Ar C**H**), 7.23 (1 H, td, J = 7.7, 1.7 Hz, Ar C**H**), 6.98 (1 H, td, J = 7.7, 0.8 Hz, Ar C**H**), 6.86 (1 H, dd, J = 7.7, 0.8 Hz, Ar C**H**), 5.23 (1 H, dd, J = 10.9, 2.4 Hz, OC**H**Ar), 4.50 (1 H, qd, J = 6.5, 2.1 Hz, OC**H**CH_3), 3.84 (3 H, s, OC**H**$_3$), 2.04 (1 H, app. ddd, J = 14.4, 2.4, 1.6 Hz, C**H**H), 1.84-1.69 (2 H, m, CH_3C**H**, CH**H**), 1.65 (3 H, s, ArOC**H**$_3$), 1.23 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.04 (3 H, d, J = 7.2 Hz, C**H**$_3$) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.81-4.71 (2 H, m, OC**H**Ar, OC**H**CH_3), 3.83 (3 H, s, OC**H**$_3$), 1.14 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

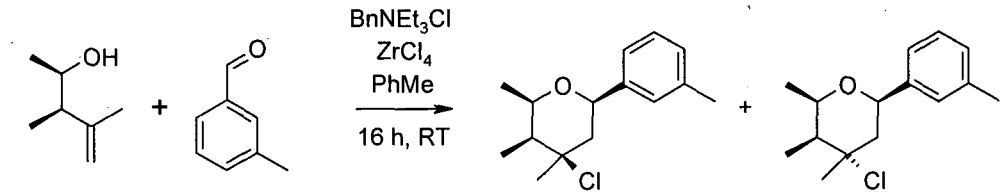
^{13}C NMR ($CDCl_3$) δ_C (100 MHz) Signals attributed to the major diastereoisomer: 156.0 (Ar **C**), 131.2 (Ar **C**), 128.3 (Ar **C**H), 126.6 (Ar **C**H), 121.0 (Ar **C**H), 110.5 (Ar **C**H), 75.4 (**C**CH_3), 71.8 (O**C**HCH_3), 70.7 (O**C**HAr), 55.6 (O**C**H_3), 45.4 (**C**H_3), 42.0 (**C**H_2), 32.0 (CH_3**C**H), 19.3 (**C**H_3), 9.3 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer: 156.0 (Ar **C**), 131.2 (Ar **C**), 128.3 (Ar **C**H), 126.6 (Ar **C**H), 121.0 (Ar **C**H), 107.6 (Ar **C**H), 75.3 (**C**CH_3), 71.8 (O**C**HCH_3), 70.7 (O**C**HAr), 55.6 (O**C**H_3), 42.8 (**C**H_3), 37.7 (**C**H_2), 29.9 (CH_3**C**H), 18.9 (**C**H_3), 12.4 (**C**H_3) ppm.

LRMS m/z (ES^+) 291 ([M(^{35}Cl) + Na]$^+$, 100%).

HRMS m/z (ES^+) found: 291.1120, [M + Na]$^+$. $C_{15}H_{21}{}^{35}ClNaO_2$ requires 291.1122.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-4-Chloro-2,3,4-trimethyl-6-*m*-tolyltetrahydropyran**



3.35 $C_7H_{14}O$ MW = 114.19 + C_8H_8O MW = 120.15

3.49a $C_{15}H_{21}ClO$ MW = 252.79 + **3.49b** $C_{15}H_{21}ClO$ MW = 252.79

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *m*-tolualdehyde (0.10 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (50:1 petroleum ether/diethyl ether) yielded an inseparable 20:1 mixture of **3.49a** and **3.49b** as a yellow waxy solid (0.06 g, 0.24 mmol, 54%).

FT-IR (ν/cm^{-1}): 2976 (m), 2929 (br. m), 1489 (w), 1447 (m), 1421 (w), 1378 (m), 1329 (m), 1280 (w), 1201 (m), 1160 (m), 1101 (s), 1087 (s), 1032 (m), 1002 (w), 945 (w), 837 (w), 779 (s), 700 (s).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz) Signals attributed to the major diastereoisomer: 7.28-7.04 (4 H, m, 4 x Ar C**H**), 4.83 (1 H, dd, J = 10.0, 3.5 Hz, OC**H**Ar), 4.47 (1 H, qd, J = 6.5, 2.1 Hz, OC**H**CH_3), 2.36 (3 H, s, C**H**$_3$), 1.98-1.74 (3 H, m, C**H**$_2$, CH_3C**H**), 1.68 (3 H, s, C**H**$_3$), 1.24 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.04 (3 H, d, J = 7.2 Hz, C**H**$_3$) ppm.

Other selected signals attributed to the minor diastereoisomer: 4.31 (1 H, dd, J = 10.2, 3.3 Hz, OC**H**Ar), 4.02 (1 H, qd, J = 6.6, 2.0 Hz, OC**H**CH_3), 1.14 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (100 MHz) Signals attributed to the major diastereoisomer: 142.4 (Ar **C**), 138.2 (Ar **C**), 128.5 (Ar **C**H), 128.5 (Ar **C**H), 126.9 (Ar **C**H),

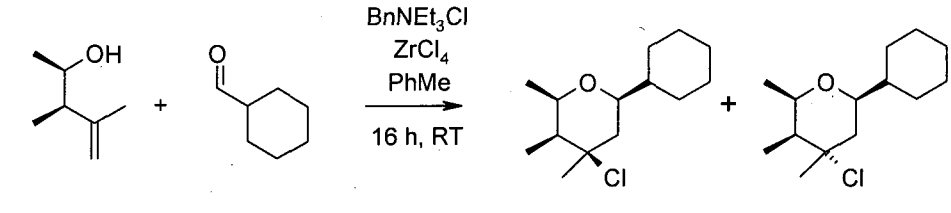
123.3 (Ar **C**H), 76.2 (O**C**HCH$_3$), 75.3 (**C**CH$_3$), 71.9 (O**C**HAr), 45.2 (**C**CH$_3$), 43.5 (**C**H$_2$), 32.0 (Ar**C**H$_3$), 21.7 (CH$_3$**C**H), 19.2 (**C**H$_3$), 9.3 (**C**H$_3$) ppm.

Signals attributed to the minor diastereoisomer: 142.4 (Ar **C**), 138.2 (Ar **C**), 128.5 (Ar **C**H), 128.5 (Ar **C**H), 126.9 (Ar **C**H), 123.3 (Ar **C**H), 76.2 (O**C**HCH$_3$), 75.3 (**C**CH$_3$), 72.0 (O**C**HAr), 45.1 (**C**CH$_3$), 42.9 (**C**H$_2$), 31.8 (Ar**C**H$_3$), 21.7 (CH$_3$**C**H), 19.0 (**C**H$_3$), 9.4 (**C**H$_3$) ppm.

LRMS m/z (ES$^+$) 275 ([M(^{35}Cl) + Na]$^+$, 70%).

HRMS m/z (EI) found: 252.1251, [M]$^+$. $C_{15}H_{21}{}^{35}ClO$ requires 252.1281.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-4-Chloro-6-cyclohexyl-2,3,4-trimethyltetrahydropyran**

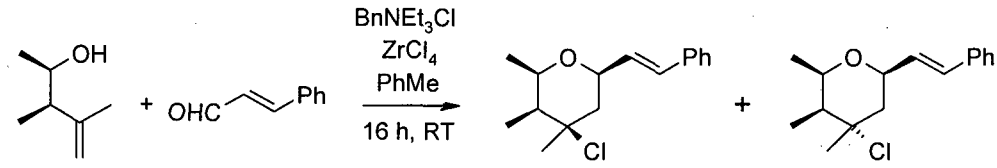


3.35 $C_7H_{14}O$ MW = 114.19 | $C_7H_{12}O$ MW = 112.17 | **3.50a** $C_{14}H_{25}ClO$ MW = 244.81 | **3.50b** $C_{14}H_{25}ClO$ MW = 244.81

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), cyclohexanecarboxaldehyde (0.11 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (100:1 petroleum ether/diethyl ether) yielded an inseparable 3:1 mixture of **3.50a** and **3.50b** as a yellow oil (0.06 g, 0.25 mmol, 56%).

FT-IR (ν/cm^{-1}):	2976 (m), 2924 (br s), 2852 (m), 1449 (m), 1377 (m), 1330 (w), 1198 (w).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz) Signals attributed to the major diastereoisomer: 4.22 (1 H, qd, J = 6.5, 2.0 Hz, OC**H**CH_3), 3.51 (1 H, ddd, J = 10.9, 6.7, 2.3 Hz, OC**H**), 2.05-1.87 (2 H, m, C**H**, C**H**H), 1.64 (3 H, s, CC**H**$_3$), 1.79-1.51 (5 H, m), 1.45-1.16 (5 H, m), 1.13 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.08-0.93 (2 H, m, C**H**, CH**H**), 0.89 (3 H, d, J = 7.2 Hz, C**H**$_3$) ppm. Other selected signals attributed to the minor diastereoisomer: 3.78 (1 H, qd, J = 6.6, 2.1 Hz, OC**H**CH_3), 3.19 (1 H, ddd, J = 10.8, 6.8, 2.2 Hz, OC**H**), 1.15 (3 H, d, J = 6.6 Hz, C**H**$_3$).
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz) Signals attributed to the major diastereoisomer: 78.1 (O**C**H), 75.9 (**C**Cl), 71.3 (O**C**H), 45.6 (**C**H), 42.6 (**C**H$_3$CCl), 38.4 (**C**H$_2$), 32.3 (**C**H), 29.4 (**C**H$_2$), 28.6 (**C**H$_2$), 26.8 (**C**H$_2$), 26.4 (**C**H$_2$), 26.3 (**C**H$_2$), 19.0 (**C**H$_3$), 9.2 (**C**H$_3$) ppm. Signals attributed to the minor diastereoisomer: 79.3 (O**C**H), 75.0 (**C**Cl), 71.9 (O**C**H), 46.4 (**C**H), 43.0 (**C**H$_3$CCl), 40.0 (**C**H$_2$), 32.3 (**C**H), 30.4 (**C**H$_2$), 29.3 (**C**H$_2$), 26.8 (**C**H$_2$), 26.4 (**C**H$_2$), 26.3 (**C**H$_2$), 19.8 (**C**H$_3$), 9.9 (**C**H$_3$) ppm.
LRMS	m/z (CI) 245 ([MH(^{35}Cl)]$^+$, 30%), 169 (100%), 160 (22), 135 (32), 125 (76), 95 (60), 69 (50), 55 (68), 41 (66).
HRMS	m/z (EI) found: 243.1508 [M − H]$^+$, $C_{14}H_{24}{}^{35}ClO$ requires 243.1516.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-4-Chloro-2,3,4-trimethyl-6-((*E*)-styryl)-tetrahydropyran**



3.35 $C_7H_{14}O$ MW = 114.19 | C_9H_8O MW = 132.16 | **3.51a** $C_{16}H_{21}ClO$ MW = 264.80 | **3.51b** $C_{16}H_{21}ClO$ MW = 264.80

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C

under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *trans*-cinnamaldehyde (0.11 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (60:1 petroleum ether/diethyl ether) yielded an inseparable 3:1 mixture of **3.51a** and **3.51b** as a yellow oil (0.06 g, 0.22 mmol, 51%).

FT-IR (ν/cm^{-1}): 2977 (m), 2935 (br. m), 1448 (m), 1377 (m), 1355 (w), 1330 (w), 1198 (w), 1158 (m), 1089 (s), 1028 (m), 1007 (m), 964 (s), 915 (w), 849 (w), 744 (s).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz) Signals attributed to the major diastereoisomer: 7.43-7.19 (5 H, m, 5 x Ar C**H**), 6.64 (1 H, d, J = 16.0 Hz, CH=C**H**Ph), 6.22 (1 H, dd, J = 16.0, 6.5 Hz, C**H**=CHPh), 4.51 (1 H, ddd, J = 10.9, 6.5, 3.2 Hz, OC**H**CH=CH), 4.40 (1 H, qd, J = 6.5, 2.1 Hz, OC**H**CH_3), 1.94-1.72 (3 H, m, C$\mathbf{H}_2$, CH_3C**H**), 1.68 (3 H, s, CC$\mathbf{H}_3$), 1.22 (3 H, d, J = 6.5 Hz, C$\mathbf{H}_3$), 0.98 (3 H, d, J = 7.2 Hz, C$\mathbf{H}_3$) ppm.

Other selected signals attributed to the minor diastereoisomer: 6.62 (1 H, d, J = 16.0 Hz, CH=C**H**Ph), 6.18 (1 H, dd, J = 16.0, 6.5 Hz, C**H**=CHPh), 4.15 (1 H, m, OC**H**CH=CH), 3.95 (1 H, qd, J = 6.6, 2.2 Hz, OC**H**CH_3), 1.24 (3 H, d, J = 7.2 Hz, C$\mathbf{H}_3$) ppm.

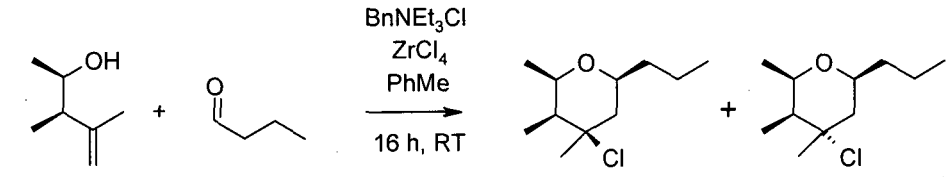
^{13}C NMR ($CDCl_3$) δ_C (100 MHz) Signals attributed to the major diastereoisomer: 137.0 (Ar **C**), 131.1 (Ar **C**H), 129.7 (2 x Ar **C**H), 128.7 (**C**H=CH), 127.8 (2 x Ar **C**H), 126.7 (CH=**C**H), 75.0 (**C**CH_3), 74.7 (O**C**HCH_3), 71.5 (O**C**HCH=), 45.2 (CH_3**C**H), 41.6 (**C**H_2), 32.1 (**C**CH_3), 19.1 (**C**H_3), 9.2 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer: 136.9 (Ar **C**), 131.1 (Ar **C**H), 129.5 (2 x Ar **C**H), 128.0 (**C**H=CH), 127.8 (2 x Ar **C**H), 126.7 (CH=**C**H), 75.8 (O**C**HCH_3), 73.2 (**C**CH_3), 72.1 (O**C**HCH=), 46.0 (CH_3**C**H), 43.0 (**C**H_2), 30.1 (**C**CH_3), 19.9 (**C**H_3), 9.9 (**C**H_3) ppm.

LRMS m/z (CI) 229 ([MH – HCl]$^+$, 68%), 211 (18), 185 (62), 157 (100), 133 (20), 117 (10), 91 (10).

HRMS m/z (EI) found: 264.1287, $[M]^+$. $C_{16}H_{21}{}^{35}ClO$ requires 264.1281.

***rel*-(2*R*,3*S*,4*RS*,6*S*)-4-Chloro-2,3,4-trimethyl-6-propyltetrahydropyran**



3.35 $C_7H_{14}O$ MW = 114.19 | C_4H_8O MW = 72.11 | **3.52a** $C_{11}H_{21}ClO$ MW = 204.74 | **3.52b** $C_{11}H_{21}ClO$ MW = 204.74

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), butyraldehyde (0.08 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (75:1 petroleum ether/diethyl ether) yielded an inseparable 10:1 mixture of **3.52a** and **3.52b** as a colourless oil (0.05 g, 0.23 mmol, 53%).

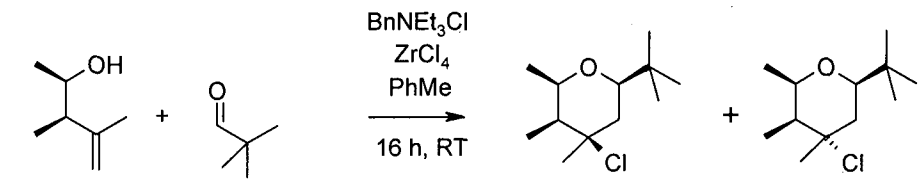
FT-IR (ν/cm^{-1}): 2976 (br w), 2959 (br w), 2933 (br w), 2905 (br w), 2872 (br w), 1448 (m), 1373 (m), 1332 (m).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz) Signals attributed to the major diastereoisomer: 4.25 (1 H, qd, J = 6.5, 2.0 Hz, OC**H**CH_3), 3.77 (1 H, m, OC**H**), 1.75-1.67 (2 H, m, C**H**$_2$), 1.63 (3 H, s, C**H**$_3$CCl), 1.60-1.32 (5 H, m, CH_3C**H**, 2 x C**H**$_2$), 1.14 (3 H, d, J = 6.5 Hz, C**H**$_3$), 0.92 (3 H, t, J = 7.4 Hz, CH_2C**H**$_3$), 0.91 (3 H, d, J = 7.3 Hz, C**H**$_3$) ppm.

Other selected signals attributed to the minor diastereoisomer: 3.81 (1 H, qd, J = 6.6, 2.2 Hz, OC**H**CH_3), 3.46-3.39 (1 H, m, OC**H**), 1.16 (3 H, d, J = 6.6 Hz, C**H**$_3$), 0.93 (3 H, d, J = 7.2 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$)	δ_C (100 MHz) Signals attributed to the major diastereoisomer: 75.5 (**C**Cl), 73.7 (O**C**HCH$_3$), 71.3 (O**C**H), 45.5 (**C**H$_3$CCl), 41.5 (**C**H$_2$), 38.0 (**C**H$_2$), 32.1 (CH$_3$**C**H), 19.0 (CH$_2$**C**H$_3$), 18.9 (**C**H$_2$CH$_3$), 14.3 (**C**H$_3$), 9.2 (**C**H$_3$) ppm. Signals attributed to the minor diastereoisomer: 74.9 (O**C**HCH$_3$), 73.8 (**C**Cl), 72.0 (O**C**H), 46.3 (**C**H$_3$CCl), 43.1 (**C**H$_2$), 38.3 (**C**H$_2$), 30.3 (CH$_3$**C**H), 19.8 (CH$_2$**C**H$_3$), 18.9 (**C**H$_2$CH$_3$), 14.3 (**C**H$_3$), 9.9 (**C**H$_3$) ppm.
LRMS	m/z (CI) 205 ([MH(^{35}Cl)]$^+$, 30%), 169 ([MH – HCl]$^+$, 100%), 160 (22), 135 (32), 125 (76), 95 (60), 69 (50), 55 (68), 41 (66).
HRMS	m/z (EI) found: 204.1283, [M]$^+$. $C_{11}H_{21}{}^{35}ClO$ requires 204.1281.

***rel*-(2*R*,3*S*,4*RS*,6*R*)-6-*tert*-Butyl-4-chloro-2,3,4-trimethyltetrahydropyran**

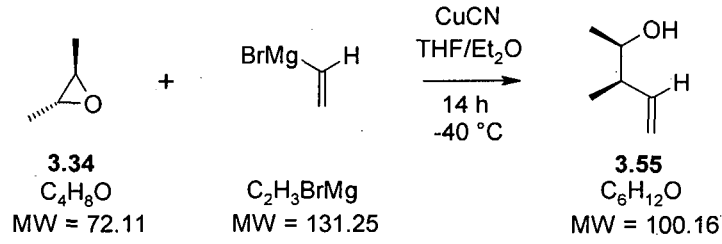


3.35 $C_7H_{14}O$ MW = 114.19 + $C_5H_{10}O$ MW = 86.13 → **3.53a** $C_{12}H_{23}ClO$ MW = 218.77 + **3.53b** $C_{12}H_{23}ClO$ MW = 218.77

Zirconium tetrachloride (0.21 g, 0.88 mmol) was added to a solution of benzyltriethylammonium chloride (0.20 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), trimethylacetaldehyde (0.10 mL, 0.88 mmol) and homoallylic alcohol **3.35** (0.05 g, 0.44 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (75:1 petroleum ether/diethyl ether) yielded an inseparable 4:1 mixture of **3.53a** and **3.53b** as a colourless oil (0.05 g, 0.23 mmol, 53%).

FT-IR (ν/cm^{-1}):	2976 (br m), 2955 (br m), 1479 (br w), 1447 (br w), 1363 (m), 1101 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz) Signals attributed to the major diastereoisomer: 4.21 (1 H, qd, J = 6.5, 2.0 Hz, OC**H**CH_3), 3.39 (1 H, dd, J = 10.7, 2.7 Hz, OC**H**), 1.65 (3 H, s, C**H**$_3$CCl), 1.75-1.12 (3 H, m, C**H**CH_3, C**H**$_2$), 1.10 (3 H, d, J = 6.5 Hz, C**H**$_3$), 0.91 (9 H, s, C(C**H**$_3$)$_3$), 0.88 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm. Other selected signals attributed to the minor diastereoisomer: 3.37 (1 H, qd, J = 6.6, 2.1 Hz, OC**H**CH_3), 3.03 (1 H, dd, J = 10.6, 2.6 Hz, OC**H**), 1.14 (3 H, d, J = 6.6 Hz, C**H**$_3$), 0.89 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz) Signals attributed to the major diastereoisomer: 81.0 (O**C**HCH$_3$), 76.4 (**C**Cl), 71.2 (O**C**H), 45.3 (**C**H$_3$CCl), 35.7 (**C**H$_2$), 33.9 (**C**(CH$_3$)$_3$), 32.5 (CH$_3$**C**H), 26.1 ((**C**H$_3$)$_3$), 19.0 (**C**H$_3$), 9.2 (**C**H$_3$) ppm. Signals attributed to the minor diastereoisomer: 82.3 (O**C**HCH$_3$), 76.4 (**C**Cl), 72.0 (O**C**H), 46.8 (**C**H$_3$CCl), 37.4 (**C**H$_2$), 34.2 (**C**(CH$_3$)$_3$), 30.9 (CH$_3$**C**H), 26.1 ((**C**H$_3$)$_3$), 19.8 (**C**H$_3$), 10.1 (**C**H$_3$) ppm.
LRMS	m/z (CI) 219 ([MH(^{35}Cl)]$^+$, 38%), 183 ([MH – HCl]$^+$, 66%), 161 (72), 139 (20), 125 (100), 97 (60), 69 (40), 55 (50), 41 (60).
HRMS	m/z (EI) found: 218.9856, [M]$^+$. $C_{12}H_{23}{}^{35}ClO$ requires 218.9685.

***rel*-(1*R*,2*R*)-3-Methylpent-4-en-2-ol**



3.34
C_4H_8O
MW = 72.11

C_2H_3BrMg
MW = 131.25

3.55
$C_6H_{12}O$
MW = 100.16

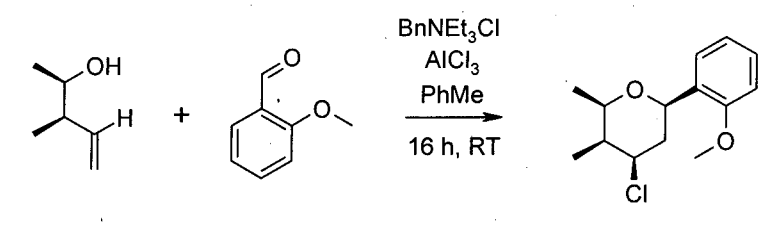
Copper cyanide (0.38 g, 4.20 mmol) was added to a solution of *trans*-2,3-epoxybutane (1.24 mL, 13.9 mmol) in diethyl ether (20 mL) at −40 °C. A solution of vinylmagnesium bromide (1.00 M in THF, 25.7 mL) was added dropwise to the

reaction mixture over 1 h. The mixture was allowed to warm to RT over 12 h, then stirred for a further 2 h at RT, before saturated NH_4Cl (100 mL) was added dropwise to the black solution. The mixture was extracted with diethyl ether (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by Kugelrohr distillation (110-120 °C, 760 mmHg) yielded **3.55** as a colourless oil (1.10 g, 11.0 mmol, 79%).

FT-IR (ν/cm^{-1}):	3394 (br. w), 2965 (m), 1632 (w), 1458 (m), 1417 (w), 1374 (w), 1247 (s), 1157 (m), 1053 (br. m), 835 (s), 768 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 5.80 (1 H, m, C**H**=CH_2), 5.17-5.03 (2 H, m, CH=C**H**$_2$), 3.71 (1 H, m, CH_3C**H**OH), 2.26 (1 H, m, CH_3C**H**), 1.51 (1 H, br s, O**H**), 1.17 (3 H, d, J = 6.3 Hz, C**H**$_3$), 1.04 (3 H, d, J = 6.9 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 140.7 (**C**H=CH_2), 115.7 (CH=**C**H$_2$), 71.0 (CH_3**C**HOH), 45.0 (CH_3**C**H), 20.2 (**C**H$_3$), 14.9 (**C**H$_3$) ppm.

Data consistent with literature values.[133]

***rel*-(2*R*,3*S*,4*R*,6*R*)-4-Chloro-6-(2-methoxyphenyl)-2,3-dimethyltetrahydropyran**



3.55
$C_6H_{12}O$
MW = 100.16

$C_8H_8O_2$
MW = 136.14

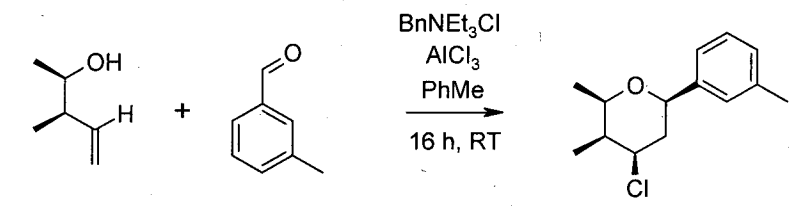
3.57
$C_{14}H_{19}ClO_2$
MW = 254.76

Aluminium trichloride (0.13 g, 1.00 mmol) was added to a solution of benzyltriethylammonium chloride (0.23 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *o*-anisaldehyde (0.14 g, 1.00 mmol) and homoallylic alcohol **3.55** (0.05 g, 0.50 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min, then extracted with diethyl ether (3 x 5 mL). The combined

organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (50:1 petroleum ether/diethyl ether) yielded **3.57** as a colourless oil (0.06 g, 0.24 mmol, 47%).

FT-IR (ν/cm^{-1}):	2923 (br. s), 2854 (m), 2358 (br. m), 1743 (w), 1603 (w), 1493 (s), 1463 (s), 1435 (m), 1390 (m), 1372 (w), 1299 (m), 1286 (m), 1246 (s), 1170 (w), 1155 (m), 1095 (s), 1071 (s), 1026 (m), 1017 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.50 (1 H, dd, J = 7.6, 1.7 Hz, Ar C**H**), 7.28-7.19 (1 H, m, Ar C**H**), 6.99 (1 H, app. td, J = 7.6, 0.8 Hz, Ar C**H**), 6.85 (1 H, dd, J = 8.3, 0.8 Hz, Ar C**H**), 4.79 (1 H, dd, J = 11.3, 2.4 Hz, OC**H**Ar), 4.43 (1 H, dt, J = 12.6, 4.4 Hz, C**H**Cl), 3.82 (3 H, s, OC**H**$_3$), 3.78 (1 H, qd, J = 6.4, 1.9 Hz, OC**H**CH$_3$), 2.17 (1 H, app. dddd, J = 13.0, 4.4, 2.4, 1.1 Hz, C**H**H), 2.04-1.98 (1 H, m, CH$_3$C**H**), 1.83 (1 H, app. td, J = 12.6, 11.3 Hz, CH**H**), 1.29 (3 H, d, J = 6.4 Hz, C**H**$_3$), 1.14 (3 H, d, J = 6.9 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 155.7 (Ar **C**), 130.5 (Ar **C**), 128.5 (Ar **C**H), 126.5 (Ar **C**H), 121.1 (Ar **C**H), 110.4 (Ar **C**H), 76.0 (O**C**HCH$_3$), 73.8 (O**C**H), 62.2 (**C**HCl), 55.5 (O**C**H$_3$), 40.4 (CH$_3$**C**H), 37.3 (**C**H$_2$), 19.4 (**C**H$_3$), 6.1 (**C**H$_3$) ppm.
LRMS	m/z (CI) 255 ([MH(^{35}Cl)]$^+$, 100%), 219 (38), 175 (40), 137 (42), 121 (6), 91 (18).
HRMS	m/z (EI) found: 254.1080, [M]$^+$. $C_{14}H_{19}{}^{35}ClO_2$ requires 254.1074.

***rel*-(2*R*,3*S*,4*R*,6*R*)-4-Chloro-2,3-dimethyl-6-*m*-tolyltetrahydropyran**



3.55
$C_6H_{12}O$
MW = 100.16

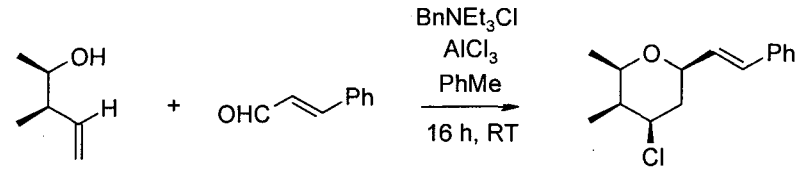
C_8H_8O
MW = 120.15

3.58
$C_{14}H_{19}ClO$
MW = 238.76

Aluminium trichloride (0.13 g, 1.00 mmol) was added to a solution of benzyltriethylammonium chloride (0.23 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *m*-tolualdehyde (0.12 mL, 1.00 mmol) and homoallylic alcohol **3.55** (0.05 g, 0.50 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (40:1 petroleum ether/diethyl ether) yielded **3.58** as a colourless oil (0.06 g, 0.25 mmol, 50%).

FT-IR (ν/cm^{-1}):	2977 (m), 2924 (br. s), 2853 (m), 1610 (w), 1489 (w), 1458 (m), 1387 (m), 1360 (w), 1324 (w), 1298 (m), 1188 (w), 1166 (m), 1098 (s), 1073 (m), 1041 (w), 1015 (m), 1015 (m), 924 (w), 783 (s), 701 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.31-7.03 (4 H, m, 4 x Ar C**H**), 4.40 (1 H, dt, J = 12.3, 4.6 Hz, C**H**Cl), 4.37 (1 H, dd, J = 10.4, 3.1 Hz, OC**H**Ar), 3.76 (1 H, qd, J = 6.5, 1.9 Hz, OC**H**CH_3), 2.36 (3 H, s, ArC**H**$_3$), 2.11-1.95 (3 H, m, CH_3C**H**, C**H**$_2$), 1.28 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.15 (3 H, d, J = 6.9 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (101 MHz): 141.6 (Ar **C**), 138.3 (Ar **C**), 128.7 (Ar **C**H), 128.6 (Ar **C**H), 126.8 (Ar **C**H), 123.2 (Ar **C**H), 79.7 (O**C**HCH$_3$), 76.1 (O**C**H), 61.9 (**C**HCl), 40.3 (CH_3**C**H), 38.6 (**C**H$_2$), 21.6 (Ar**C**H$_3$), 19.4 (**C**H$_3$), 6.1 (**C**H$_3$) ppm.
LRMS	m/z (CI) 238 ([M(^{35}Cl)]$^+$, 28%), 203 ([M – Cl]$^+$, 40), 159 (56), 118 (100), 105 (12), 83 (40).
HRMS	m/z (EI) found: 238.1134, [M]$^+$. $C_{14}H_{19}{}^{35}ClO$ requires 238.1124.

rel-(2*R*,3*S*,4*R*,6*R*)-4-Chloro-2,3-dimethyl-6-((*E*)-styryl)-tetrahydropyran



3.55
$C_6H_{12}O$
MW = 100.16

C_9H_8O
MW = 132.16

3.60
$C_{15}H_{19}ClO$
MW = 250.77

Aluminium trichloride (0.13 g, 1.00 mmol) was added to a solution of benzyltriethylammonium chloride (0.23 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *trans*-cinnamaldehyde (0.13 mL, 1.00 mmol) and homoallylic alcohol **3.55** (0.05 g, 0.50 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (40:1 petroleum ether/diethyl ether) yielded **3.60** as a colourless oil (0.07 g, 0.28 mmol, 56%).

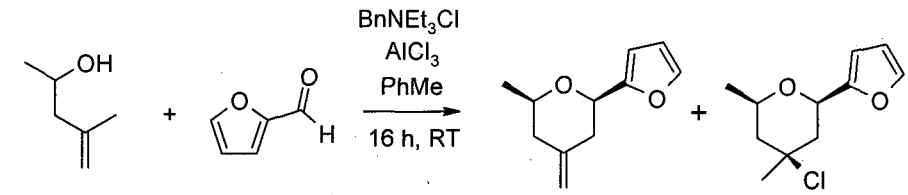
FT-IR (ν/cm^{-1}):	2978 (br. m), 2927 (br. m), 2852 (m), 1495 (w), 1449 (m), 1368 (m), 1297 (m), 1268 (w), 1168 (m), 1126 (w), 1089 (s), 1067 (m), 1029 (w), 1012 (m), 965 (s), 937 (m), 861 (m), 766 (m), 746 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.45-7.19 (5 H, m, 5 x Ar C**H**), 6.61 (1 H, d, J = 16.0 Hz, CH=C**H**Ph), 6.20 (1 H, dd, J = 16.0, 6.2 Hz, C**H**=CHPh), 4.33 (1 H, dt, J = 12.1, 4.7 Hz, C**H**Cl), 4.05 (1 H, ddd, J = 6.2, 2.7, 1.1 Hz, OC**H**), 3.69 (1 H, qd, J = 6.5, 1.9 Hz, OC**H**CH_3), 2.08-1.80 (3 H, m, CH_3C**H**, C**H**$_2$), 1.28 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.08 (3 H, d, J = 6.9 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 136.8 (Ar **C**), 131.3 (Ar **C**H), 129.0 (2 x Ar **C**H), 128.7 (**C**H=CH), 128.0 (2 x Ar **C**H), 126.8 (CH=**C**H), 78.0 (O**C**HCH=CH), 75.8 (O**C**HCH$_3$), 61.6 (**C**HCl), 40.3 (CH_3**C**H), 36.9 (**C**H$_2$), 19.3

(CH_3), 6.0 (CH_3) ppm.

LRMS m/z (CI) 250 ([M(^{35}Cl)]$^+$, 74%), 215 (84), 197 (20), 171 (20), 133 (32), 109 (100), 91 (38).

HRMS m/z (EI) found: 250.5440, $[M]^+$. $C_{15}H_{19}{}^{35}ClO$ requires 250.5399.

***rel*-(2*R*,6*R*)-2-Furan-2-yl-6-methyl-4-methylenetetrahydropyran (3.62) & *rel*-(2*R*,4*S*,6*R*)-4-chloro-2-furan-2-yl-4,6-dimethyltetrahydropyran (3.63)**



3.61 $C_6H_{12}O$ MW = 100.16 | $C_5H_4O_2$ MW = 96.09 | **3.62** $C_{11}H_{14}O_2$ MW = 178.23 | **3.63** $C_{11}H_{15}ClO_2$ MW = 214.69

Aluminium trichloride (0.13 g, 1.00 mmol) was added to a solution of benzyltriethylammonium chloride (0.23 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), 2-furaldehyde (0.09 mL, 1.00 mmol) and homoallylic alcohol **3.55** (0.05 g, 0.50 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (48:1 petroleum ether/diethyl ether) yielded firstly **3.62** (0.05 g, 0.27 mmol, 47%) then **3.63** (0.05 g, 0.27 mmol, 47%) as colourless oils.

Spectroscopic data for exo-alkene **3.62**

FT-IR (ν/cm^{-1}): 2975 (m), 2935 (m), 2886 (m), 2851 (m), 1655 (m), 1504 (m), 1444 (w), 1348 (s).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 7.40 (1 H, dd, J = 1.8, 0.8 Hz, OC**H**=CH), 6.37-6.28 (2 H, m, C**H**C**H**), 4.81 (2 H, app. t, J = 1.8 Hz, CC**H**$_2$), 4.40 (1 H, dd,

J = 11.4, 2.8 Hz, OC**H**), 3.59 (1 H, qdd, J = 12.3, 6.2, 2.2 Hz, OC**H**CH_3), 2.59-2.40 (2 H, m, $OCHCH_3C$**H**H, $OCHCH_3CH$**H**), 2.28 (1 H, dt, J = 12.3, 2.2 Hz, OCHC**H**H), 2.07 (1 H, m, OCHCH**H**), 1.30 (3 H, d, J = 6.2 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 154.7 (**C**=CH), 144.1 (**C**CH_2), 142.5 (O**C**H=CH), 110.3 (**C**HCH), 109.4 (C**C**H_2), 106.8 (CH**C**H), 75.1 (O**C**HCH_3), 73.8 (O**C**), 42.4 (**C**H_2), 38.6 (**C**H_2), 22.1 (**C**H_3) ppm.

LRMS m/z (CI) 179 ($[MH]^+$, 100%), 134 (62), 121 (24), 105 (12), 94 (14), 67 (6).

HRMS m/z (EI) found: 178.0997, $[M]^+$. $C_{11}H_{14}O_2$ requires 178.0994.

Spectroscopic data for **3.63**

FT-IR (ν/cm^{-1}): 2971 (m), 2927 (w), 2871 (w), 1505 (m), 1445 (m), 1371 (s), 1151 (s).

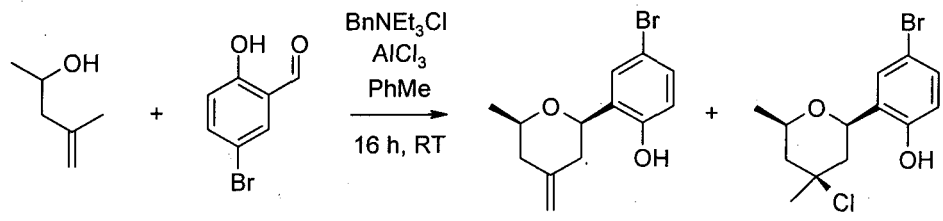
^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 7.39 (1 H, dd, J = 1.8, 0.8 Hz, OC**H**=CH), 6.39-6.26 (2 H, m, C**H**C**H**), 4.91 (1 H, dd, J = 12.5, 2.2 Hz, OC**H**), 4.10 (1 H, qdd, J = 10.7, 6.3, 2.0 Hz, OC**H**CH_3), 2.12 (1 H, dt, J = 12.5, 2.2 Hz, OCHC**H**H), 2.06-1.91 (2 H, m, OCHCH**H**, OCH**H**$CHCH_3$), 1.70 (3 H, s, C**H**$_3$CCl), 1.52 (1 H, dd, J = 14.1, 10.7 Hz, OCH**H**$CHCH_3$), 1.28 (3 H, d, J = 6.3 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 154.2 (**C**=CH), 142.5 (O**C**H=CH), 110.3 (CH**C**H), 107.2 (**C**HCH), 70.2 (O**C**H), 69.5 (**C**Cl), 69.3 (O**C**H), 47.7 (**C**H_2), 44.0 (**C**H_2), 34.2 (**C**H_3), 21.4 (**C**H_3) ppm.

LRMS m/z (CI) 215 ($[MH(^{35}Cl)]^+$, 86%), 179 (100), 161 (12), 135 (62), 121 (24), 95 (26), 82 (20), 55 (8).

HRMS m/z (EI) found: 214.0752, $[M]^+$. $C_{11}H_{15}{}^{35}ClO_2$ requires 214.0747.

4-Bromo-2-(*rel*-(2*R*,6*R*)-6-methyl-4-methylenetetrahydropyran-2-yl)-phenol (3.64) & 4-bromo-2-(*rel*-(2*R*,4*S*,6*R*)-4-chloro-4,6-dimethyltetrahydropyran-2-yl)-phenol (3.65)



3.61 $C_6H_{12}O$ MW = 100.16

$C_7H_5BrO_2$ MW = 201.02

3.64 $C_{13}H_{15}BrO_2$ MW = 283.17

3.65 $C_{13}H_{16}BrClO_2$ MW = 319.63

Aluminium trichloride (0.13 g, 1.00 mmol) was added to a solution of benzyltriethylammonium chloride (0.23 g, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), 5-bromosalicylaldehyde (0.20 g, 1.00 mmol) and homoallylic alcohol **3.61** (0.05 g, 0.50 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (40:1 petroleum ether/diethyl ether) yielded an inseparable 1:1 mixture of **3.64** and **3.65** (0.09 g, 0.33 mmol, 66%) as colourless oils.

FT-IR (ν/cm^{-1}): 3343 (br m), 2971 (m), 2898 (w), 1655 (m), 1579 (m), 1482 (s), 1374 (s).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 8.28 (1 H, s, ArO**H**), 8.16 (1 H, s, ArO**H**), 7.27 (1 H + 1 H, app. dd, J = 8.5, 2.5 Hz, 2 x Ar C**H**), 7.11 (1 H + 1 H, s, 2 x Ar C**H**), 6.77 (1 H + 1 H, app. dd, J = 8.5, 4.8 Hz, 2 x Ar C**H**), 5.04 (1 H, dd, J = 11.0, 2.2 Hz, OC**H**Ar), 4.86 (2 H, s, C=C**H**$_2$), 4.53 (1 H, dd, J = 8.3, 6.1 Hz, OC**H**Ar), 4.17 (1H, qdd, J = 13.6, 6.2, 2.4 Hz, OC**H**CH$_3$), 3.65 (1H, qdd, J = 12.1, 6.1, 2.3 Hz, OC**H**CH$_3$), 2.47-2.40 (1 H + 1 H, m, OCHC**H**HCH$_3$), 2.39-2.31 (1 H + 1 H, m, OCHCH**H**CH$_3$), 2.16-1.98 (1H + 1 H, m, OCHArC**H**$_2$), 1.90 (1 H, dd,

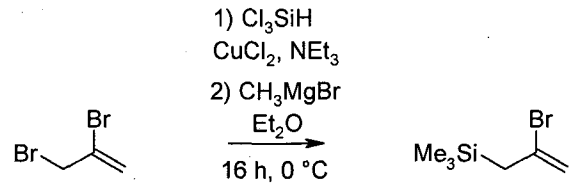
J = 14.3, 11.0 Hz, OCHArC**H**H), 1.68 (3 H, s, CC**H**$_3$), 1.54 (1 H, app. dd, J = 14.3, 11.0 Hz, OCHArCH**H**), 1.35 (3H, d, J = 6.2 Hz, C**H**$_3$), 1.34 (3H, d, J = 6.1 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 155.0 (Ar **C**), 154.9 (Ar **C**), 142.7 (2 x Ar **C**), 131.9 (2 x Ar **C**H), 129.6 (Ar **C**H), 129.5 (Ar **C**H), 127.7 (Ar **C**), 127.2 (Ar **C**), 119.3 (2 x Ar **C**H), 111.7 (**C**=CH$_2$), 110.5 (C=**C**H$_2$), 81.3 (O**C**HCH$_3$), 77.4 (O**C**HCH$_3$), 76.1 (O**C**H), 71.1 (O**C**H), 68.5 (**C**Cl), 47.5 (**C**H$_2$), 33.9 (CC**H**$_3$), 46.1 (**C**H$_2$), 42.1 (**C**H$_2$), 40.7 (**C**H$_2$), 22.0 (**C**H$_3$), 21.3 (**C**H$_3$) ppm.

LRMS m/z (CI) 283 ([M(^{79}Br)]$^+$, 42%), 266 (10), 239 (12), 225 (100), 200 (12), 159 (84), 144 (10), 115 (12), 82 (16).

HRMS m/z (EI) found: 284.0222, [M]$^+$. $C_{13}H_{15}{}^{79}BrO_2$ requires 284.0235.

(2-Bromoallyl)-trimethylsilane



3.66
$C_3H_4Br_2$
MW = 199.87

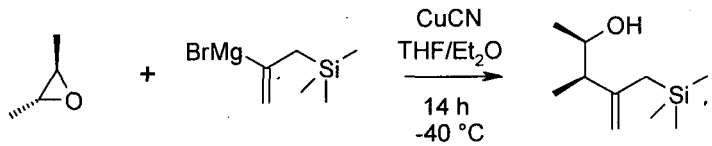
3.68
$C_6H_{13}BrSi$
MW = 193.16

Trimethylsilane **3.68** was prepared according to the procedure of Nishiyama and co-workers.[103] Trichlorosilane (27.3 mL, 0.27 mol) was added dropwise to a stirred solution of 2,3-dibromopropene (45.0 g, 0.23 mol), triethylamine (31.4 mL, 0.23 mol) and copper(II) chloride (1.50 g, 11.1 mmol) in diethyl ether (210 mL) at 0 °C. The reaction mixture was stirred at RT for 16 h, then the diethyl ether removed by distillation. The resulting brown oil was used in the next reaction without further purification. A solution of methylmagnesium bromide in diethyl ether (3.0 M, 262.5 mL) was added dropwise to a solution of the crude (2-bromoallyl)-trichlorosilane (57.2 g, 0.23 mol) in diethyl ether (200 mL) at 0 °C. The reaction mixture was stirred for 16 h at RT, poured into saturated NH_4Cl (400 mL) then extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with brine

(500 mL), dried ($MgSO_4$) and concentrated by distillation. Purification by Kugelrohr distillation (66-68 °C, 39 mmHg) yielded **3.68** as a colourless oil (17.9 g, 92.7 mmol, 41%).

FT-IR (ν/cm^{-1}):	2958 (m), 1630 (w), 1460 (w), 1417 (w), 1374 (w), 1247 (s), 1157 (m), 1053 (br. m), 835 (s), 768 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 5.32 (1 H, s, =C**H**H), 5.23 (1 H, s, =CH**H**), 2.12 (2 H, s, $(CH_3)_3SiC\mathbf{H}_2$), 0.13 (9 H, s, $Si(C\mathbf{H}_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 131.4 (**C**Br), 114.1 ($C\mathbf{C}H_2$), 33.6 ($Si\mathbf{C}H_2$), −1.3 ($Si(\mathbf{C}H_3)_3$) ppm.
LRMS	m/z (CI) 194 ($[MH]^+$, 6%), 177 (28), 137 (34), 113 (24), 90 (16), 73 (100).

***rel*-(2*R*,3*R*)-3-Methyl-4-trimethylsilanylmethylpent-4-en-2-ol**



3.34
C_4H_8O
MW = 72.11

3.72
$C_6H_{13}BrMgSi$
MW = 205.37

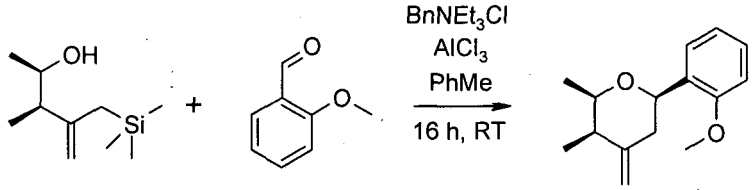
3.69
$C_{10}H_{22}OSi$
MW = 186.37

Homoallylic alcohol **3.69** was prepared according to the procedure of Kocienski and co-workers.[16] Copper(I) cyanide (0.35 g, 3.96 mmol) was added to a solution of *trans*-2,3-epoxybutane (1.18 mL, 13.2 mmol) in diethyl ether (20 mL) at −40 °C. A solution of **3.70** (1.32 M in THF, 20.0 mL) was added dropwise to the reaction mixture over 1 h. The mixture was allowed to warm to RT over 12 h, then stirred for a further 2 h at RT, before saturated NH_4Cl (100 mL) was added dropwise to the black solution. The mixture was extracted with diethyl ether (3 x 50 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether/petroleum ether) yielded **3.69** as a colourless oil (0.79 g, 4.24 mmol, 33%).

FT-IR (ν/cm^{-1}):	3392 (br. w), 2955 (m), 1629 (w), 1458 (w), 1417 (w), 1374 (w), 1247 (s), 1157 (m), 1053 (br. m), 835 (s), 768 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.74-4.67 (2 H, m, =C**H**$_2$), 3.81 (1 H, m, C**H**OH), 1.99 (1 H, app. qdd, J = 7.0, 6.9, 3.8 Hz, CH_3C**H**C), 1.69-1.43 (3 H, m, O**H**, C**H**$_2$), 1.20 (3 H, d, J = 6.3 Hz, C**H**$_3$), 1.04 (3 H, d, J = 6.9 Hz, C**H**$_3$), 0.04 (9H, s, Si(C**H**$_3$)$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 150.8 (**C**=CH$_2$), 107.6 (=**C**H$_2$), 67.8 (CH_3**C**HOH), 47.4 (CH_3**C**HC), 27.6 (**C**H$_2$Si), 20.6 (**C**H$_3$), 12.3 (**C**H$_3$), −1.2 (Si(**C**H$_3$)$_3$) ppm.

Data consistent with literature values.[16]

rel-(2_R_,3_R_,6_R_)-6-(2-Methoxyphenyl)-2,3-dimethyl-4-methylenetetrahydropyran



3.69
$C_{10}H_{22}OSi$
MW = 186.37

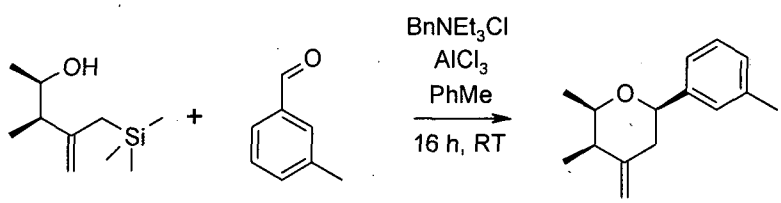
$C_8H_8O_2$
MW = 136.15

3.54a
$C_{15}H_{20}O_2$
MW = 232.33

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *o*-anisaldehyde (0.06 g, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (50:1 petroleum ether/diethyl ether) yielded **3.54a** as a colourless oil (0.03 g, 0.14 mmol, 68%).

FT-IR (ν/cm^{-1}):	2975 (m), 2933 (br. m), 1651 (w), 1493 (s), 1462 (m), 1438 (m), 1367 (w), 1372 (w), 1239 (s), 1208 (w), 1157 (m), 1092 (s), 1073 (m), 1050 (m), 1030 (m), 1018 (m), 940 (m), 751 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.56 (1 H, dd, J = 7.6, 1.7 Hz, Ar C**H**), 7.23 (1 H, m, Ar C**H**), 7.00 (1 H, td, J = 7.6, 0.8 Hz, Ar C**H**), 6.86 (1 H, dd, J = 8.2, 0.8 Hz, Ar C**H**), 4.78 (1 H, app. t, J = 1.8 Hz, CC**H**H), 4.72 (1 H, dd, J = 11.1, 3.8 Hz, OC**H**Ar), 4.70 (1 H, app. t, J = 1.8 Hz, CCH**H**), 3.82 (3 H, s, OC**H**$_3$), 3.75 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH$_3$), 2.35-2.24 (3 H, m, C**H**, OCHC**H**$_2$), 1.23 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.13 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (101 MHz): 155.9 (Ar **C**), 151.3 (Ar **C**), 131.7 (**C**=CH$_2$), 128.2 (Ar **C**H), 126.6 (Ar **C**H), 121.1 (Ar **C**H), 110.5 (Ar **C**H), 107.4 (C=**C**H$_2$), 76.8 (O**C**HAr), 75.2 (O**C**HCH$_3$), 55.6 (O**C**H$_3$), 42.8 (CH$_3$**C**H), 37.6 (**C**H$_2$), 18.9 (**C**H$_3$), 12.6 (**C**H$_3$) ppm.
LRMS	m/z (CI) 233 ([MH]$^+$, 32%), 188 (100), 159 (32), 137 (36), 121 (32), 107 (14), 91 (36), 81 (26), 65 (10).
HRMS	m/z (CI) found: 232.1465, [M]$^+$. $C_{15}H_{20}O_2$ requires 232.1463.

***rel*-(2*R*,3*R*,6*R*)-2,3-Dimethyl-4-methylene-6-*m*-tolyltetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

C_8H_8O
MW = 120.15

3.54b
$C_{15}H_{20}O$
MW = 216.33

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *m*-tolualdehyde (0.05 mL, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added.

After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (80:1 petroleum ether/diethyl ether) yielded **3.54b** as a colourless oil (0.04 g, 0.18 mmol, 84%).

FT-IR (ν/cm^{-1}): 2975 (m), 2922 (br. m), 1650 (w), 1610 (w), 1489 (w), 1448 (m), 1371 (m), 1320 (w), 1201 (w), 1161 (m), 1129 (w), 1091 (s), 1052 (w), 1021 (m), 1000 (w), 944 (w), 913 (m), 890 (s), 779 (s), 700 (s).

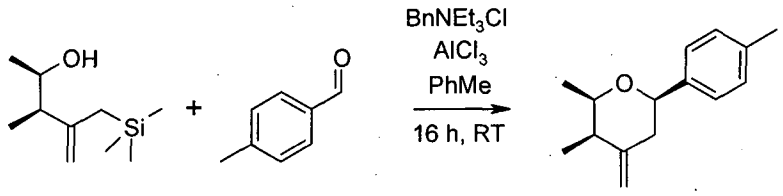
^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.31-7.07 (4 H, m, 4 x Ar C**H**), 4.81 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.71 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.30 (1 H, dd, J = 11.5, 2.7 Hz, OC**H**Ar), 3.74 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH_3), 2.45 (1 H, dd, J = 13.7, 2.7 Hz, OCHC**H**H), 2.37 (3 H, s, Ar$C\mathbf{H}_3$), 2.28 (1 H, qd, J = 7.0, 2.5 Hz, $CH_3C\mathbf{H}$), 2.25 (1 H, dd, J = 13.7, 2.7 Hz, OCHCH**H**), 1.23 (3 H, d, J = 6.5 Hz, $C\mathbf{H}_3$), 1.14 (3 H, d, J = 7.0 Hz, $C\mathbf{H}_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 151.0 (Ar **C**), 142.9 (Ar **C**), 129.2 (Ar **C**H), 128.4 (Ar **C**H), 126.8 (Ar **C**H), 125.5 (**C**=CH_2), 123.2 (Ar **C**H), 107.6 (C=**C**H_2), 81.3 (**O**CHAr), 76.9 (**O**CHCH_3), 42.7 (Ar**C**H_3), 38.8 (**C**H_2), 21.6 (CH_3**C**H), 18.8 (**C**H_3), 12.6 (**C**H_3) ppm.

LRMS m/z (CI) 217 ($[MH]^+$, 20%), 172 (100), 157 (44), 145 (68), 118 (20), 91 (22), 81 (40), 68 (10).

HRMS m/z (EI) found: 216.1518, $[M]^+$. $C_{15}H_{20}O$ requires 216.1514.

***rel*-(2*R*,3*R*,6*R*)-2,3-Dimethyl-4-methylene-6-*p*-tolyltetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

C_8H_8O
MW = 120.15

3.54c
$C_{15}H_{20}O$
MW = 216.33

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *p*-tolualdehyde (0.05 mL, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (80:1 petroleum ether/diethyl ether) yielded **3.54c** as a colourless oil (0.03 g, 0.13 mmol, 63%).

FT-IR (ν/cm^{-1}): 2975 (m), 2923 (br. m), 2357 (w), 1650 (w), 1516 (w), 1448 (m), 1371 (m), 1320 (w), 1201 (w), 1161 (m), 1129 (w), 1078 (s), 1052 (w), 1033 (m), 1000 (w), 944 (w), 913 (m), 807 (s).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 7.29 (2 H, d, J = 8.0 Hz, 2 x Ar C**H**), 7.16 (2 H, d, J = 8.0 Hz, 2 x Ar C**H**), 4.81 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.71 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.31 (1 H, dd, J = 11.5, 2.6 Hz, OC**H**Ar), 3.73 (1 H, qd, J = 6.5, 2.4 Hz, OC**H**CH_3), 2.45 (1 H, m, OCHC**H**H), 2.36 (3 H, s, ArC**H**$_3$), 2.28 (1 H, qd, J = 7.0, 2.4 Hz, CH_3C**H**), 2.24 (1 H, dd, J = 13.7, 2.6 Hz, OCHCH**H**), 1.23 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.13 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

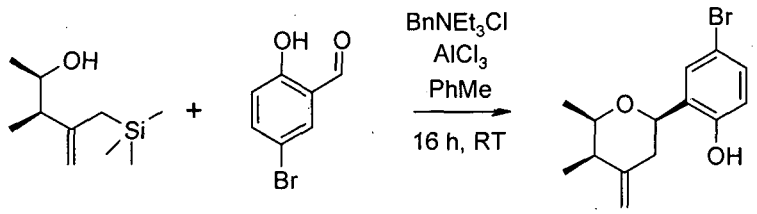
^{13}C NMR ($CDCl_3$): δ_C (75 MHz): 151.0 (Ar **C**), 140.0 (Ar **C**), 137.3 (**C**=CH_2), 129.2 (2 x Ar **C**H), 126.1 (2 x Ar **C**H), 107.5 (C=**C**H_2), 81.0 (O**C**H), 76.9

(OCH), 42.7 (ArCH$_3$), 38.8 (CH$_2$), 21.3 (CH$_3$CH), 18.8 (CH$_3$), 12.6 (CH$_3$) ppm.

LRMS m/z (CI) 217 ([MH]$^+$, 52%), 172 (100), 157 (40), 145 (86), 118 (16), 91 (20), 81 (30), 68 (6).

HRMS m/z (EI) found: 216.1513, [M]$^+$. $C_{15}H_{20}O$ requires 216.1514.

4-Bromo-2-(*rel*-(2*R*,5*R*,6*R*)-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-phenol



3.69
$C_{10}H_{22}OSi$
MW = 186.37

$C_7H_5O_2Br$
MW = 201.02

3.54d
$C_{14}H_{17}O_2B$
MW = 297.19

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), 5-bromosalicyladehyde (0.09 g, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (40:1 petroleum ether/diethyl ether) yielded **3.54d** as a colourless oil (0.05 g, 0.18 mmol, 85%).

FT-IR (ν/cm^{-1}): 3336 (br. m), 2974 (m), 1652 (m), 1579 (m), 1482 (s), 1450 (w), 1374 (s), 1244 (s), 1155 (m), 1130 (w), 1113 (w), 1084 (s), 1048 (m), 1016 (s), 939 (m), 892 (s), 816 (m), 780 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 8.40 (1 H, s, Ar C**H**), 7.28-7.09 (2 H, m, Ar C**H**, ArO**H**), 6.78 (1 H, d, J = 8.7 Hz, Ar C**H**), 4.88 (1 H, app. t, J = 1.7

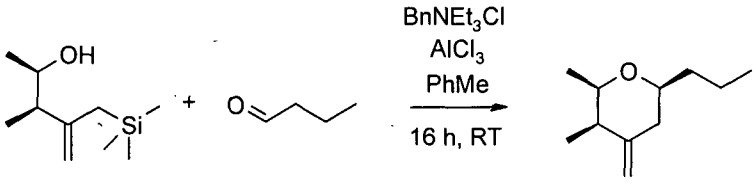
Hz, =C**H**H), 4.79 (1 H, app. t, J = 1.7 Hz, =CH**H**), 4.54 (1 H, dd, J = 12.1, 2.9 Hz, OC**H**Ar), 3.81 (1 H, qd, J = 6.4, 2.5 Hz, OC**H**CH_3), 2.63 (1 H, dd, J = 13.8, 2.9 Hz, C**H**H), 2.33 (1 H, qd, J = 7.0, 2.5 Hz, CH_3C**H**), 2.27 (1 H, dd, J = 13.8, 2.9 Hz, CH**H**), 1.26 (3 H, d, J = 6.4 Hz, C**H**$_3$), 1.12 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 154.9 (Ar **C**), 148.4 (Ar **C**), 131.9 (Ar **C**H), 129.4 (Ar **C**H), 127.8 (Ar **C**), 119.3 (Ar **C**H), 111.7 (**C**=CH_2), 109.6 (C=**C**H_2), 81.8 (O**C**HCH$_3$), 78.1 (O**C**H), 42.2 (**C**H_2), 36.7 (CH_3**C**H), 18.5 (**C**H_3), 12.4 (**C**H_3) ppm.

LRMS m/z (CI) 297 ([M]$^+$, 22%), 254 (20), 225 (50), 173 (100), 158 (10), 145 (18), 115 (10), 91 (18), 81 (46), 68 (10).

HRMS m/z (EI) found: 296.0407, [M]$^+$. $C_{14}H_{17}O_2{}^{79}Br$ requires 296.0412.

***rel*-(2*R*,3*R*,6*S*)-2,3-Dimethyl-4-methylene-6-propyltetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

C_4H_8O
MW = 72.11

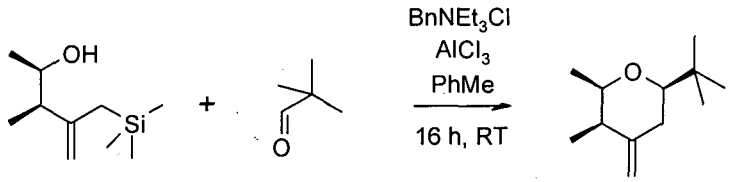
3.54e
$C_{11}H_{20}O$
MW = 168.28

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), butyraldehyde (0.04 mL, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was stirred for 16 h before being poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in*

vacuo. Purification by column chromatography (100:1 petroleum ether/diethyl ether) yielded **3.54e** as a colourless oil (0.02 g, 0.13 mmol, 60%).

FT-IR (ν/cm^{-1}):	3070 (w), 2960 (br. s), 2935 (br. s), 1280 (w), 1651 (m), 1454 (m), 1372 (s), 1327 (s), 1195 (w), 1168 (s), 1126 (s), 1093 (s), 1035 (m), 1003 (w), 976 (w), 929 (m), 889 (s), 820 (w).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.71 (1 H, app. t, J = 1.8 Hz, =C**H**H), 4.62 (1 H, app. t, J = 1.8 Hz, =CH**H**), 3.52 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH_3), 3.25 (1 H, m, OC**H**CH_2), 2.17 (1 H, qd, J = 7.0, 2.5 Hz, CH_3C**H**), 2.10-1.95 (2 H, m, CC**H**$_2$CH), 1.67-1.29 (4 H, m, C**H**$_2$C**H**$_2CH_3$), 1.15 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.02 (3 H, d, J = 7.0 Hz, C**H**$_3$), 0.92 (3 H, t, J = 7.1 Hz, CH_2C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 151.4 (**C**=CH_2), 107.1 (C=**C**H_2), 78.9 (**O**CH), 76.4 (**O**CH), 42.9 (CH_3**C**H), 38.7 (**C**H_2), 36.7 (**C**H_2), 18.9 (**C**H_2), 18.7 (**C**H_3), 14.3 (**C**H_3), 12.6 (**C**H_3) ppm.
LRMS	m/z (CI) 169 ([MH]$^+$, 66%), 155 (4), 125 (34), 109 (20), 95 (100), 81 (60), 67 (22), 55 (14), 41 (30).
HRMS	m/z (EI) found: 168.1517 [M]$^+$, $C_{11}H_{20}O$ requires 168.1514.

***rel*-(2*R*,3*R*,6*R*)-6-*tert*-Butyl-2,3-dimethyl-4-methylenetetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

$C_5H_{10}O$
MW = 86.13

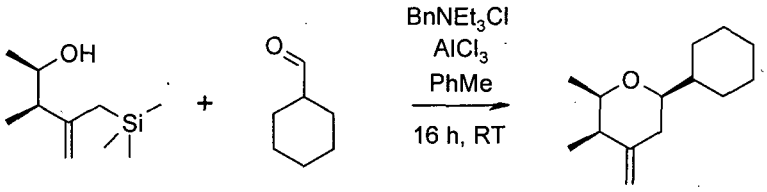
3.54f
$C_{12}H_{22}O$
MW = 182.31

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), trimethylacetaldehyde (0.05 mL,

0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (100:1 petroleum ether/diethyl ether) yielded **3.54f** as a colourless oil (0.03 g, 0.14 mmol, 65%).

FT-IR (ν/cm^{-1}):	2954 (br. m), 2669 (w), 1651 (m), 1479 (w), 1395 (w), 1361 (w), 1362 (w), 1323 (m), 1157 (m), 1099 (s), 1032 (s), 931 (w), 887 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.71 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.62 (1 H, app. t, J = 1.9 Hz, =CH**H**), 3.46 (1 H, qd, J = 6.4, 2.4 Hz, OC**H**CH_3), 2.89 (1 H, dd, J = 11.5, 2.7 Hz, OC**H**C$(CH_3)_3$), 2.22-2.07 (2 H, m, C**H**H, CH_3C**H**), 1.97 (1 H, dd, J = 13.2, 2.7 Hz, CH**H**), 1.12 (3 H, d, J = 6.4 Hz, C**H**$_3$), 0.98 (3 H, d, J = 6.7 Hz, C**H**$_3$), 0.92 (9 H, s, C$(CH_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 152.4 (**C**=CH_2), 106.9 (C=**C**H_2), 86.3 (O**C**HCH_3), 76.3 (O**C**H), 42.9 (CH_3**C**H), 34.3 (**C**$(CH_3)_3$), 30.8 (**C**H_2), 26.1 (C$(CH_3)_3$), 18.6 (**C**H_3), 12.5 (**C**H_3) ppm.
LRMS	m/z (CI) 183 ($[MH]^+$, 70%), 165 (22), 125 (100), 109 (32), 96 (58), 81 (80), 67 (24), 55 (20), 41 (54).
HRMS	m/z (EI) found: 182.1670 $[M]^+$, $C_{12}H_{22}O$ requires 182.1657.

***rel*-(2*R*,3*R*,6*R*)-6-Cyclohexyl-2,3-dimethyl-4-methylenetetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

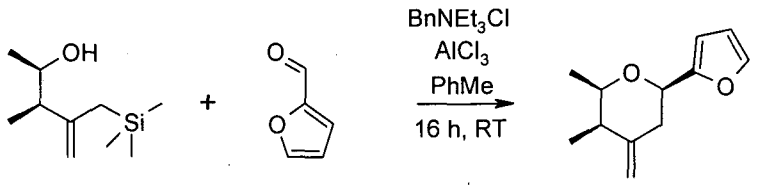
$C_7H_{12}O$
MW = 112.17

3.54g
$C_{14}H_{24}O$
MW = 208.35

Aluminium trichloride (0.06 g, 0.43 mmol) was added to a solution of benzyltriethylammonium chloride (0.10 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), cyclohexanecarboxaldehyde (0.05 mL, 0.43 mmol) and homoallylic alcohol **3.69** (0.04 g, 0.21 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 10 mL), stirred for 15 min and extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (100:1 petroleum ether/diethyl ether) yielded **3.54g** as a colourless oil (0.03 g, 0.14 mmol, 68%).

FT-IR (ν/cm^{-1}):	2947 (w), 2924 (br. s), 2852 (s), 1469 (m), 1448 (m), 1406 (m), 1351 (m), 1233 (w), 1190 (m), 1161 (s), 1125 (s), 1092 (s), 1068 (s), 1031 (w), 965 (m), 889 (s), 841 (m), 817 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.71 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.62 (1 H, app. t, J = 1.9 Hz, =CH**H**), 3.48 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH$_3$), 2.99 (1 H, ddd, J = 10.9, 6.7, 3.1 Hz, OC**H**CH), 2.17 (1 H, qd, J = 7.0, 2.5 Hz, CH$_3$C**H**), 2.14-1.17 (12 H, m, 5 x C**H**$_2$, OCHC**H**H, OCHC**H**), 2.01 (1 H, dd, J = 13.3, 3.1 Hz, OCHCH**H**), 1.13 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.01 (3 H, d, J = 6.7 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 151.8 (**C**=CH$_2$), 107.0 (C=**C**H$_2$), 83.5 (O**C**HCH$_3$), 76.4 (O**C**H), 43.2 (CH$_3$**C**H), 43.1 (OCH**C**H), 33.5 (OC**C**H$_2$), 29.6 (**C**H$_2$), 28.6 (**C**H$_2$), 26.9 (**C**H$_2$), 26.5 (**C**H$_2$), 26.4 (**C**H$_2$), 18.7 (**C**H$_3$), 12.5 (**C**H$_3$) ppm.
LRMS	m/z (CI) 209 ([MH]$^+$, 30%), 191 (14), 164 (24), 149 (60), 135 (88), 107 (22), 95 (68), 81 (100), 67 (38), 55 (56).
HRMS	m/z (EI) found: 208.1141 [M]$^+$, $C_{14}H_{24}O$ requires 208.1095.

***rel*-(2*R*,3*R*,6*R*)-6-Furan-2-yl-2,3-dimethyl-4-methylenetetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

$C_5H_4O_2$
MW = 96.09

3.54h
$C_{12}H_{16}O_2$
MW = 192.26

Aluminium trichloride (0.71 g, 5.36 mmol) was added to a solution of benzyltriethylammonium chloride (1.22 g, 5.36 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), 2-furaldehyde (0.44 mL, 5.36 mmol) and homoallylic alcohol **3.69** (0.50 g, 2.68 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (50 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 60 mL), stirred for 15 min and extracted with diethyl ether (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (45:1 petroleum ether/diethyl ether) yielded **3.54h** as a yellow oil (0.35 g, 1.82 mmol, 68%).

FT-IR (ν/cm^{-1}): 2979 (m), 2941 (br. m), 1653 (m), 1504 (m), 1451 (m), 1381 (m), 1372 (m), 1344 (m), 1316 (m), 1233 (w), 1158 (s), 1128 (w), 1092 (s), 1073 (s), 1019 (s), 966 (w), 892 (s), 806 (m), 734 (s).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 7.40 (1 H, dd, J = 1.8, 0.8 Hz, CH=C**H**), 6.34 (1 H, dd, J = 3.2, 1.8 Hz, C**H**=CH), 6.30 (1 H, dt, J = 3.2, 0.8 Hz, C**H**CH=CH), 4.82 (1 H, app t, J = 1.9 Hz, =C**H**H), 4.73 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.39 (1 H, dd, J = 12.0, 2.7 Hz, OC**H**), 3.73 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH_3), 2.72 (1 H, m, C**H**H), 2.34-2.20 (2 H, m, CH**H**, CH_3C**H**), 1.22 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.10 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

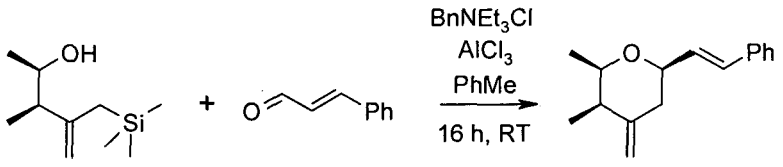
^{13}C NMR ($CDCl_3$): δ_C (75 MHz): 154.8 (**C**=CH), 150.0 (**C**=CH_2), 142.4 (=**C**H), 110.2 (=**C**H), 108.3 (=CH_2), 106.8 (=**C**H), 76.9 (O**C**H), 74.2 (O**C**HCH_3),

42.7 (CH_3CH), 34.5 (CH_2), 18.7 (CH_3), 12.5 (CH_3) ppm.

LRMS m/z (EI) 192 ($[M]^+$, 6%), 148 (100), 119 (44), 94 (98), 81 (62), 65 (20).

HRMS m/z (EI) found: 192.1142 $[M]^+$, $C_{12}H_{16}O_2$ requires 192.1150.

***rel*-(2*R*,3*R*,6*R*)-2,3-Dimethyl-4-methylene-6-((*E*)-styryl)-tetrahydropyran**



3.69
$C_{10}H_{22}OSi$
MW = 186.37

C_9H_8O
MW = 132.16

3.54i
$C_{16}H_{20}O$
MW = 228.34

Aluminium trichloride (7.16 g, 53.7 mmol) was added to a solution of benzyltriethylammonium chloride (12.23 g, 53.7 mmol) in CH_2Cl_2 (300 mL) at 0 °C under argon. The mixture was allowed to warm to RT then stirred for 30 min before removal of the solvent *in vacuo*. Toluene (3 mL), *trans*-cinnamaldehyde (6.77 mL, 53.7 mmol) and homoallylic alcohol **3.69** (5.00 g, 26.8 mmol) were sequentially added. After 16 h the reaction mixture was poured into saturated $NaHCO_3$ (250 mL). The resulting emulsion was then poured into a solution of Rochelle's salt (1 M, 300 mL), stirred for 15 min and extracted with diethyl ether (3 x 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (45:1 petroleum ether/diethyl ether) yielded **3.54i** as a yellow oil (3.86 g, 16.9 mmol, 63%).

FT-IR (ν/cm^{-1}): 2974 (m), 2850 (br. w), 1651 (w), 1619 (w), 1494 (w), 1449 (m), 1371 (m), 1318 (w), 1247 (m), 1163 (m), 1113 (w), 1090 (s), 1018 (w), 963 (m), 937 (w), 846 (s), 743 (s), 720 (w).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.47-7.18 (5 H, m, 5 x Ar C**H**), 6.62 (1 H, d, J = 16.0 Hz, CHC**H**Ph), 6.28 (1 H, dd, J = 16.0, 6.3 Hz, C**H**CHPh), 4.80 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.71 (1 H, app. t, J = 1.9 Hz, =CH**H**), 3.98

(1 H, app. dddd, J = 11.4, 6.3, 2.7, 1.5 Hz, OC**H**), 3.67 (1 H, qd, J = 6.4, 2.6 Hz, OC**H**CH_3), 2.36 (1 H, td, J = 11.4, 1.5 Hz, C**H**H), 2.25 (1 H, qd, J = 7.0, 2.6 Hz, CH_3C**H**), 2.17 (1 H, dd, J = 16.5, 2.7 Hz, CH**H**), 1.22 (3 H, d, J = 6.4 Hz, C**H**$_3$), 1.09 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

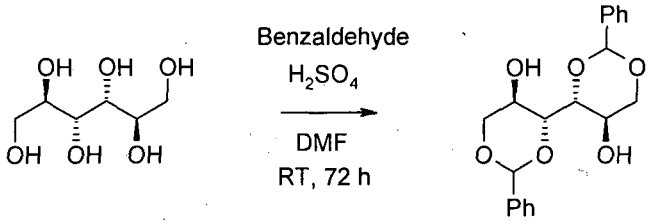
nOe (400 MHz, $CDCl_3$); irradiation of the signal at δ_H 3.98 led to nOe enhancement at 6.62, 3.67 and 2.36. Irradiation of the signal at δ_H 3.67 led to nOe enhancement at 3.98, 2.25 and 1.22.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 150.4 (Ar **C**), 137.0 (**C**=CH_2), 130.9 (2 x Ar **C**H), 130.4 (2 x Ar **C**H), 128.7 (**C**H=CH), 127.7 (Ar **C**H), 126.7 (CH=**C**H), 107.8 (C=**C**H_2), 79.7 (O**C**HCH), 76.5 (O**C**HCH_3), 42.7 (CH_3**C**H), 36.9 (**C**H_2), 18.8 (**C**H_3), 12.5 (**C**H_3) ppm.

LRMS m/z (CI) 228 ([M]$^+$, 48%), 211 (14), 185 (66), 169 (22), 157 (100), 133 (32), 81 (26).

HRMS m/z (EI) found: 228.1513, [M]$^+$. $C_{16}H_{20}O$ requires 228.1514.

(4*R*,5*R*,4'*R*,5'*R*)-2,2'-Diphenyl-[4,4']bi[[1,3]dioxanyl]-5,5'-diol



4.4
$C_6H_{14}O_6$
MW = 182.17

4.5
$C_{20}H_{22}O_6$
MW = 358.39

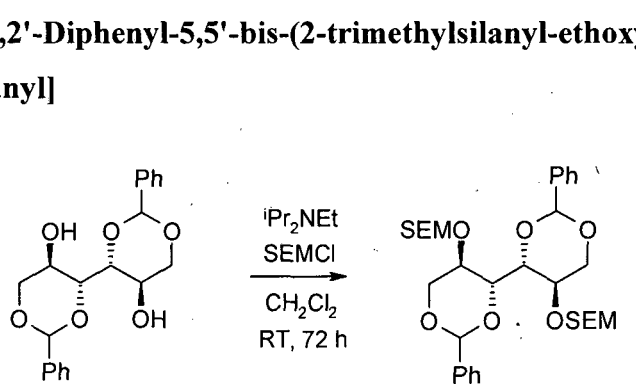
Benzylidene ether **4.5** was prepared according to the procedure of Baggett and co-workers.[134] Concentrated sulfuric acid (2 mL) was added to a suspension of D-mannitol (10.0 g, 55.0 mmol) and benzaldehyde (12.0 mL, 0.11 mol) in DMF (30 mL). After 72 h the reaction mixture was poured into an ice/water (300 mL) solution containing K_2CO_3 (3.0 g) and *iso*-hexane (50 mL). After vigorous stirring a sticky white solid was obtained. The filtrate was collected and washed with *iso*-hexane. The crude product was dispersed in chloroform (50 mL), heated at reflux for 15 min

then cooled to 4 °C for 24 h. The resulting product was isolated by filtration and dried under vacuum yielding white crystals (5.86 g, 16.4 mmol, 30%).

m.p.	185-187 °C (MeOH), lit.[134] m.p. = 192-193 °C.
$[\alpha]_D^{27}$	−8.5 (c = 3.00, $CHCl_3$) (lit.[134] $[\alpha]_D^{26}$ = −9.1 (c = 1.5, $CHCl_3$)).
FT-IR (ν/cm^{-1}):	3480 (w), 1461 (w), 1449 (w), 1410 (w), 1396 (w), 1364 (m), 1311 (w), 1224 (w), 1100 (m), 1071 (s), 1049 (s), 970 (s), 927 (m), 779 (m), 747 (s), 739 (s), 699 (s).
^{1}H NMR ($(CD_3)_2SO$)	δ_H (300 MHz): 7.44-7.33 (10 H, m, 10 x Ar C**H**), 5.51 (2 H, s, 2 x OC**H**O), 5.34 (2 H, d, J = 5.9 Hz, 2 x O**H**), 4.16 (2 H, dd, J = 10.5, 5.2 Hz, 2 x C**H**H), 3.91 (2 H, d, J = 9.1 Hz, 2 x C**H**), 3.83-3.74 (2 H, m, 2 x C**H**OH), 3.55 (2 H, t, J = 10.5 Hz, 2 x CH**H**) ppm.
^{13}C NMR ($(CD_3)_2SO$)	δ_C (100 MHz): 138.2 (2 x Ar **C**), 128.5 (2 x Ar **C**H), 128.0 (4 x Ar **C**H), 126.1 (4 x Ar **C**H), 100.1 (2 x O**C**HO), 78.1 (2 x **C**H), 71.0 (2 x **C**H$_2$), 58.8 (2 x **C**HOH) ppm.

Spectroscopic data consistent with literature values.[134]

(4*R*,5*R*,4'*R*,5'*R*)-2,2'-Diphenyl-5,5'-bis-(2-trimethylsilanyl-ethoxymethoxy)-[4,4']bi[[1,3]dioxanyl]



4.5
$C_{20}H_{22}O_6$
MW = 358.39

4.7
$C_{32}H_{50}O_8Si_2$
MW = 618.92

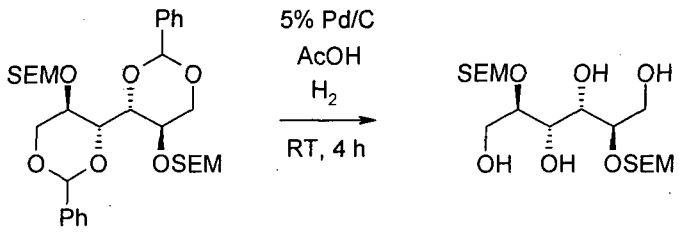
Silyl ether **4.7** was prepared according to the procedure of Breitfelder and co-workers.[19] Diisopropylethylamine (16.9 mL, 97.1 mmol) was added to a suspension of **4.5** (5.8 g, 16.2 mmol) in CH_2Cl_2 (250 mL). A solution of (trimethylsilyl)ethoxymethyl chloride (17.1 mL, 97.1 mmol) in CH_2Cl_2 (30 mL) was added dropwise at 0 °C. The reaction mixture was warmed to RT and stirred for 72

h. The red solution was washed with saturated $NaHCO_3$ (400 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20-25% diethyl ether/hexane) yielded **4.7** as a white crystalline solid (7.4 g, 11.9 mmol, 73%).

m.p.	45-47 °C (lit.[19] m.p. = 45 °C).
$[\alpha]_D^{27}$	+14.5 (c = 2.90, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = +29.7 (c = 1.33, $CHCl_3$)).
FT-IR (ν/cm^{-1}):	2952 (w), 2878 (w), 1451 (w), 1413 (w), 1370 (w), 1248 (m), 1217 (w), 1093 (s), 1056 (s), 1029 (s), 973 (m), 936 (m), 857 (s), 830 (s), 746 (s), 733 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.51-7.28 (10 H, m, 10 x Ar C**H**), 5.50 (2 H, s, 2 x OC**H**O), 4.74 (2 H, d, J = 4.0 Hz, 2 x OC**H**HO), 4.71 (2 H, d, J = 4.0 Hz, 2 x OCH**H**O), 4.49 (2 H, dd, J = 12.0, 8.0 Hz, 2 x C**H**H), 4.11 (2 H, m, 2 x C**H**), 4.01 (2 H, d, J = 8.0 Hz, 2 x C**H**), 3.73-3.65 (4 H, m, 2 x C**H**$_2$), 3.55-3.47 (2 H, m, 2 x CH**H**), 0.94-0.87 (4 H, m, 2 x C**H**$_2$Si), 0.00 (18 H, s, 2 x (C**H**$_3$)$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 137.7 (2 x Ar **C**), 128.9 (2 x Ar **C**H), 128.4 (4 x Ar **C**H), 126.2 (4 x Ar **C**H), 101.0 (2 x O**C**HO), 95.3 (2 x O**C**H$_2$O), 77.6 (2 x **C**H), 70.4 (2 x O**C**H$_2$CH), 66.6 (2 x **C**H), 65.6 (2 x **C**H$_2$), 18.1 (2 x **C**H$_2$Si), −1.4 (2 x Si(**C**H$_3$)$_3$) ppm.

Spectroscopic data consistent with literature values.[19]

(2*R*,3*S*,4*S*,5*R*)-2,5-*bis*-(2-Trimethylsilanylethoxymethoxy)-hexane-1,3,4,6-tetraol



4.7
$C_{32}H_{50}O_8Si_2$
MW = 618.92

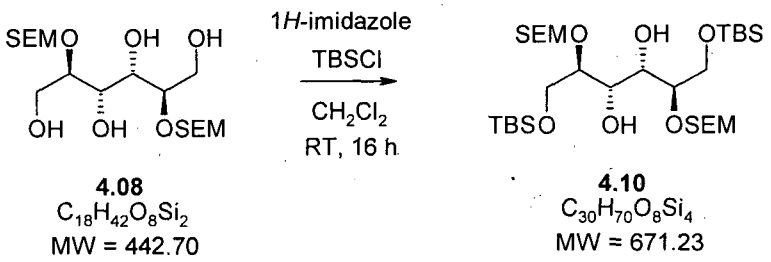
4.8
$C_{18}H_{42}O_8Si_2$
MW = 442.70

To a solution of **4.7** (0.20 g, 0.32 mmol) in acetic acid (5 mL) was added 5% Pd/C (0.06 g). The reaction mixture was degassed by ultrasonication and subjected to a 3 bar atmosphere of hydrogen whilst stirring for 4 h. The mixture was filtered through a pad of celite, washed through with CH_2Cl_2 (15 mL) and concentrated *in vacuo*. Purification by column chromatography (7% MeOH/CH_2Cl_2) yielded **4.8** as a white crystalline solid (0.09 g, 0.20 mmol, 63%).

m.p.	72-74 °C (lit.[19] m.p. = 71-72 °C).
$[\alpha]_D^{27}$	+20.5 (*c* = 2.60, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = +18.9 (*c* = 1.99, $CHCl_3$)).
FT-IR (ν/cm^{-1}):	3409 (br. w), 2955 (w), 2909 (w), 1454 (w), 1419 (w), 1382 (w), 1249 (m), 1187 (w), 1159 (w), 1092 (m), 1057 (m), 1039 (m), 1000 (s), 925 (m), 857 (s), 831 (s), 758 (m).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.80-4.68 (4 H, m 4 x OCH_2O), 3.94-3.75 (4 H, m, 4 x C**H**), 3.72-3.55 (8 H, m, 4 x CH_2), 3.28 (4 H, br. s, 4 x O**H**), 0.96-0.91 (4 H, m, 4 x CH_2Si), 0.00 (18 H, s, 2 x $Si(CH_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 95.7 (2 x OCH_2O), 80.8 (2 x OCH_2OCH), 69.5 (2 x **C**HOH), 66.1 (2 x CH_2OH), 63.1 (2 x OCH_2CH_2Si), 18.0 (2 x CH_2Si), −1.5 (2 x $Si(CH_3)_3$) ppm.
LRMS	m/z (ES^-) 441 ($[M-H]^-$, 100%).

Spectroscopic data consistent with literature values.[19]

(2*R*,3*S*,4*S*,5*R*)-1,6-bis-(*tert*-Butyldimethylsilanyloxy)-2,5-bis-(2-trimethylsilanylethoxymethoxy)-hexane-3,4-diol



4.08
$C_{18}H_{42}O_8Si_2$
MW = 442.70

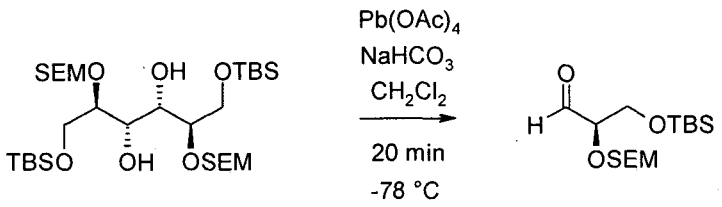
4.10
$C_{30}H_{70}O_8Si_4$
MW = 671.23

Diol **4.10** was prepared according to the procedure of Breitfelder and co-workers.[19] At 0 °C 1*H*-imidazole (0.31 g, 4.52 mmol) was added to a solution of **4.08** (0.50 g, 1.13 mmol) in CH_2Cl_2 (40 mL). After 15 min a solution of *tert*-butyldimethylsilyl chloride (0.68 g, 4.52 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture. The solution was allowed to warm to RT and stirred for 16 h. MeOH (4 mL) was added to the reaction mixture and the solvents removed *in vacuo*. Purification by column chromatography (20-33% diethyl ether/hexanes) yielded **4.10** as a colourless oil (0.65 g, 0.97 mmol, 86%).

$[\alpha]_D^{28}$	−26.7 (c = 2.50, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = −18.5 (c = 1.62, $CHCl_3$)).
FT-IR (ν/cm^{-1}):	2954 (w), 2859 (w), 1472 (w), 1250 (m), 1056 (m), 1021 (m), 938 (w), 810 (s), 775 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.82 (2 H, d, J = 6.6 Hz, 2 x OC**H**HO), 4.77 (2 H, d, J = 6.6 Hz, 2 x OCH**H**O), 3.93 (2 H, dd, J = 12.0, 4.0 Hz, 2 x OC**H**HCH), 3.85 (2 H, d, J = 8.0 Hz, 2 x C**H**OH), 3.80-3.70 (4 H, m, 2 x OCH**H**CH, 2 x OCH_2C**H**), 3.63 (4 H, m, 2 x OC**H**$_2CH_2Si$), 3.54 (2 H, br s, 2 x O**H**), 0.97-0.92 (4 H, m, 2 x OCH_2C**H**$_2Si$), 0.89 (18 H, s, 2 x $C(C$**H**$_3)_3$), 0.07 (12 H, s, 2 x $Si(C$**H**$_3)_2$), 0.01 (18 H, s, 2 x $Si(C$**H**$_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 95.8 (2 x O**C**H_2O), 78.8 (2 x OCH_2O**C**H), 69.5 (2 x **C**HOH), 65.7 (2 x **C**H_2OSi), 64.4 (2 x O**C**H_2CH_2Si), 25.9 (2 x $C(C$**H**$_3)_3$), 18.3 (2 x **C**$(CH_3)_3$), 18.1 (2 x OCH_2**C**H_2Si), −1.2 (2 x $Si(C$**H**$_3)_3$), −5.4 (2 x $Si(C$**H**$_3)_2$) ppm.
LRMS	m/z (ES^+) 671 ($[MH]^+$, 60%).

Spectroscopic data consistent with literature values.[19]

(*R*)-3-(*tert*-Butyldimethylsilanyloxy)-2-(2-trimethylsilanylethoxymethoxy)-propionaldehyde



4.10
$C_{30}H_{70}O_8Si_4$
MW = 671.23

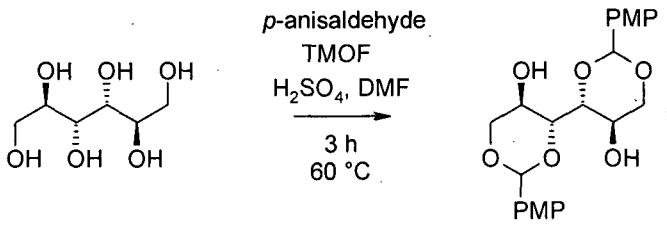
4.11
$C_{15}H_{34}O_4Si_2$
MW = 334.61

Aldehyde **4.11** was prepared according to the procedure of Breitfelder and co-workers.[19] To a solution of **4.10** (0.65 g, 0.97 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added $NaHCO_3$ (0.24 g, 2.91 mmol) followed by $Pb(OAc)_4$ (0.50 g, 1.12 mmol). The reaction mixture was stirred for 20 min, then filtered through a pad of Celite and washed with CH_2Cl_2 (50 mL). The filtrate was dried (K_2CO_3), filtered, concentrated *in vacuo*, resolvated with hexanes (20 mL) and concentrated *in vacuo*. Purification by column chromatography (25% diethyl ether/hexanes) yielded **4.11** as a colourless oil (0.53 g, 1.58 mmol, 82%).

$[\alpha]_D^{27}$	+11.2 (*c* = 2.60, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = + 6.1 (*c* = 3.45, $CHCl_3$)).
FT-IR (ν/cm^{-1}):	2954 (w), 2930 (w), 2890 (w), 2890 (w), 1737 (m), 1473 (w), 1362 (w), 1250 (m), 1112 (m), 1058 (m), 1031 (m), 938 (w), 820 (s), 776 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 9.67 (1 H, d, *J* = 1.3 Hz, C**H**O), 4.80 (2 H, s, OC**H**$_2$O), 4.01 (1 H, app. dt, *J* = 4.9, 1.3 Hz, C**H**CH$_2$O), 3.90 (2 H, dd, *J* = 4.9, 0.7 Hz, CHC**H**$_2$O), 3.76-3.58 (2 H, m, OC**H**$_2$CH$_2$Si), 0.99-0.80 (11 H, m, C**H**$_2$Si, SiC(C**H**$_3$)$_3$), 0.05 (6 H, s, Si(C**H**$_3$)$_2$), 0.00 (9 H, s, Si(C**H**$_3$)$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 202.4 (**C**HO), 94.9 (O**C**H$_2$O), 82.5 (**C**HCH$_2$O), 65.7 (CH**C**H$_2$O), 62.9 (O**C**H$_2$CH$_2$Si), 25.8 (C(**C**H$_3$)$_3$), 18.2 (**C**(CH$_3$)$_3$), 18.0 (OCH$_2$**C**H$_2$Si), −1.5 (Si(C**H**$_3$)$_3$), −5.5 (Si(C**H**$_3$)$_2$) ppm.

Spectroscopic data consistent with literature values.[19]

(4*R*,5*R*,4'*R*,5'*R*)-2,2'-bis-(4-Methoxyphenyl)-[4,4']bi[[1,3]dioxanyl]-5,5'-diol



4.4
$C_6H_{14}O_6$
MW = 182.17

4.6
$C_{22}H_{26}O_8$
MW = 418.45

Diol **4.6** prepared according to the procedure of Peters and co-workers.[104] To a solution of D-mannitol (12.5 g, 68.6 mmol) in DMF (45 mL) was added *p*-anisaldehyde (16.7 mL, 137.2 mmol), trimethylorthoformate (22.5 mL, 205.8 mmol) and conc. sulfuric acid (2 mL). The reaction mixture was heated to 60 °C for 2 h, then allowed to cool to RT. The reaction mixture was poured into an ice/water solution (400 mL) containing K_2CO_3 (7.5 g). The sticky cream precipitate was collected, washed with hexanes (250 mL), then azeotroped with toluene (100 mL). Chloroform (50 mL) was added to the precipitate and the mixture heated at reflux for 1 h. On cooling to RT the resulting precipitate was collected by filtration and washed with cold chloroform (50 mL) to yield **4.6** (7.55 g, 18.0 mmol, 26%) as a white crystalline solid.

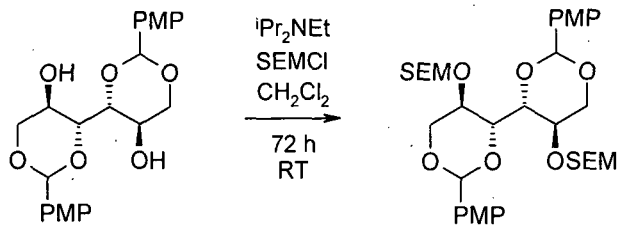
m.p.	222-224 °C ($CHCl_3$) (lit.[104] m.p. = 224-225 °C, MeOH)
$[\alpha]_D^{28}$	−12.6 (*c* = 2.90, $CHCl_3$)
FT-IR (ν/cm^{-1}):	1739 (w), 1614 (w), 1516 (m), 1465 (w), 1420 (m), 1367 (m), 1303 (m), 1257 (m), 1224 (m), 1170 (m), 1103 (w), 1034 (s), 971 (s), 810 (s), 787 (m).
^{1}H NMR ($(CD_3)_3SO$)	δ_H (400 MHz): 7.34 (4 H, d, *J* = 8.0 Hz, 4 x Ar C**H**), 6.91 (4 H, d, *J* = 8.0 Hz, 4 x Ar C**H**), 5.45 (2 H, s, 2 x OC**H**O), 5.31 (2 H, d, *J* = 4.0 Hz, 2 x O**H**), 4.13 (2 H, dd, *J* = 12.0, 4.0 Hz, 2 x C**H**H), 3.87 (2 H, d, *J* = 8.0 Hz, 2 x C**H**OH), 3.82-3.75 (2 H, m, OC**H**), 3.74 (6 H, s, 2 x OC**H**$_3$), 3.51 (2 H, t, *J* = 12.0 Hz, 2 x CH**H**) ppm.
^{13}C NMR	δ_C (100 MHz): 159.3 (2 x Ar **C**), 130.6 (2 x Ar **C**), 127.4 (4 x Ar

((CD$_3$)$_3$SO) **C**H), 113.3 (4 x Ar **C**H), 100.1 (2 x O**C**HO), 78.0 (2 x **C**HOH), 71.0 (2 x **C**H$_2$O), 58.8 (2 x O**C**H), 55.1 (2 x O**C**H$_3$) ppm.

LRMS m/z (ES$^+$) 419 ([MH]$^+$, 100%).

Spectroscopic data consistent with literature values.[104]

(4*R*,5*R*,4'*R*,5'*R*)-2,2'-bis-(4-Methoxyphenyl)-5,5'-bis-(2-trimethylsilanylethoxymethoxy)-[4,4']bi[[1,3]dioxanyl]



4.6
$C_{22}H_{26}O_8$
MW = 418.45

4.9
$C_{34}H_{54}O_{10}Si_2$
MW = 678.98

Diisopropylethylamine (2.50 mL, 14.4 mmol) was added to a suspension of **4.6** (2.0 g, 4.8 mmol) in CH_2Cl_2 (80 mL). A solution of (trimethylsilyl)ethoxymethyl chloride (2.52 mL, 14.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to RT and stirred for 72 h. The resulting red solution was washed with saturated $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20-40% diethyl ether/hexane) yielded **4.9** as a clear gelatinous oil (3.05 g, 4.5 mmol, 94%).

$[\alpha]_D^{28}$ +16.4 (c = 2.50, $CHCl_3$).

FT-IR (ν/cm^{-1}): 2952 (br w), 1698 (w), 1614 (w), 1600 (m), 1517 (m), 1463 (w), 1390 (w), 1302 (w), 1248 (s), 1217 (w), 1160 (m), 1100 (m), 1025 (s), 935 (m), 857 (m), 829 (s), 785 (w), 765 (w), 732 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 7.46-7.40 (4 H, m, 4 x Ar C**H**), 6.92-6.84 (4 H, m, 4 x Ar C**H**), 5.45 (2 H, s, 2 x OC**H**O), 4.73 (2 H, d, J = 6.8 Hz, 2 x OC**H**HO), 4.71 (2 H, d, J = 6.8 Hz, 2 x OCH**H**O), 4.45 (2 H, dd, J = 10.6, 5.1 Hz, 2 x OC**H**CH$_2$), 4.12-4.02 (2 H, m, 2 x OC**H**HCH$_2$), 3.98

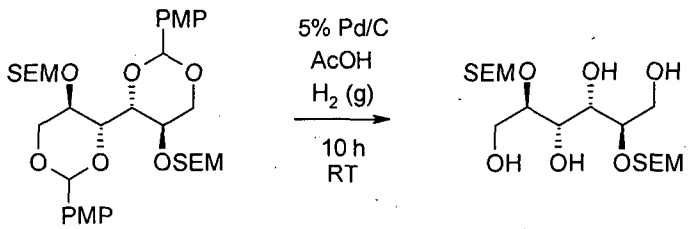
(2 H, d, J = 11.5 Hz, 2 x OC**H**), 3.81 (6 H, s, 2 x OC**H**$_3$), 3.73-3.62 (4 H, m, 2 x OCHC**H**$_2$), 3.56-3.47 (2 H, m, 2 x OCH**H**CH$_2$), 0.98-0.84 (4 H, m, 2 x OCH$_2$C**H**$_2$Si), 0.02 (18 H, s, 2 x Si(C**H**$_3$)$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (100 MHz): 160.0 (2 x Ar **C**), 130.3 (2 x Ar **C**), 127.4 (4 x Ar **C**H), 113.6 (4 x Ar **C**H), 100.7 (2 x O**C**HO), 95.3 (2 x O**C**H$_2$O), 77.5 (2 x O**C**H), 70.4 (2 x **C**H$_2$O), 66.6 (2 x O**C**HCH$_2$), 65.6 (2 x O**C**H$_2$CH$_2$), 55.3 (2 x O**C**H$_3$), 18.1 (2 x OCH$_2$**C**H$_2$Si), −1.4 (2 x Si(**C**H)$_3$) ppm.

LRMS m/z (ES$^+$) 679 ([MH]$^+$, 100%).

HRMS m/z (ES$^+$) found: 679.3332 [MH]$^+$, $C_{34}H_{55}O_{10}Si_2$ requires 679.3328.

(2*R*,3*S*,4*S*,5*R*)-2,5-bis-(2-Trimethylsilanylethoxymethoxy)-hexane-1,3,4,6-tetraol



4.9
$C_{34}H_{54}O_{10}Si_2$
MW = 678.98

4.8
$C_{18}H_{42}O_8Si_2$
MW = 442.70

To a solution of **4.9** (1.50 g, 2.21 mmol) in glacial acetic acid (50 mL) was added 5% Pd/C (0.25 g). The reaction mixture was degassed by ultrasonication, then subjected to a 3 bar atmosphere of hydrogen whilst stirring for 10 h. The mixture was filtered through a pad of Celite, washed through with CH_2Cl_2 (150 mL) and concentrated *in vacuo*. Purification by column chromatography (5% MeOH/CH_2Cl_2) yielded **4.8** (0.71 g, 1.60 mmol, 72%) as a white crystalline solid.

m.p. 72-74 °C (lit.[19] m.p. = 71-72 °C).

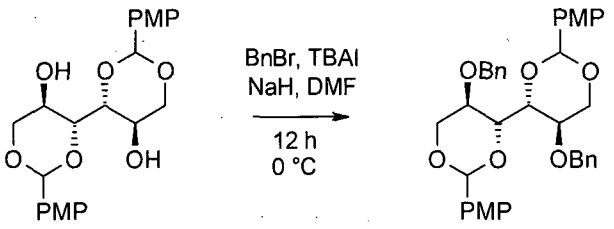
$[\alpha]_D^{27}$ +20.5 (c = 2.60, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = +18.9 (c = 1.99, $CHCl_3$)).

FT-IR 3409 (br. w), 2955 (w), 2909 (w), 1454 (w), 1419 (w), 1382 (w),

(ν/cm^{-1}):	1249 (m), 1187 (w), 1159 (w), 1092 (m), 1057 (m), 1039 (m), 1000 (s), 925 (m), 857 (s), 831 (s), 758 (m).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.80-4.68 (4 H, m 4 x OCH_2O), 3.94-3.75 (4 H, m, 4 x CH), 3.72-3.55 (8 H, m, 4 x CH_2), 3.28 (4 H, br. s, 4 x OH), 0.96-0.91 (4 H, m, 4 x CH_2Si), 0.00 (18 H, s, 2 x $Si(CH_3)_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 95.7 (2 x OCH_2O), 80.8 (2 x OCH_2OCH), 69.5 (2 x CHOH), 66.1 (2 x CH_2OH), 63.1 (2 x OCH_2CH_2Si), 18.0 (2 x CH_2Si), −1.5 (2 x $Si(CH_3)_3$) ppm.
LRMS	m/z (ES^-) 441 ($[M-H]^-$, 100%).

Spectroscopic data consistent with literature.[19]

(4*R*,5*R*, 4'*R*,5'*R*)-5,5'-bis-Benzyloxy-2,2'-bis-(4-methoxyphenyl)-[4,4']bi[[1,3]dioxanyl]



4.6
$C_{22}H_{26}O_8$
MW = 418.45

4.13
$C_{36}H_{38}O_8$
MW = 598.70

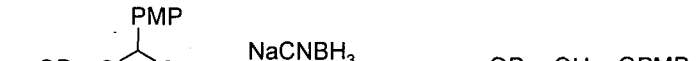
Benzyl ether **4.13** was prepared according to the procedure of Peters and co-workers.[104] To a solution of **4.6** (5.00 g, 12.0 mmol) in DMF (30 mL) was added tetrabutylammonium iodide (1.30 g, 36.0 mmol) and benzyl bromide (3.60 mL, 29.9 mmol). The mixture was cooled to 0 °C and sodium hydride (60% in mineral oil, 1.60 g, 29.9 mmol) was added. After stirring for 12 h the reaction mixture was poured into saturated NH_4Cl (100 mL), extracted with diethyl ether (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-35% diethyl ether/hexane) yielded **4.13** (6.13 g, 10.2 mmol, 85%) as a white foam.

$[\alpha]_D^{27}$	+ 8.4 (c = 2.60, $CHCl_3$)
FT-IR	2868 (br.w), 1615 (m), 1588 (w), 1517 (m), 1455 (w), 1373 (w), 1303

(ν/cm^{-1}):	(w), 1247 (s), 1219 (w), 1171 (m), 1101 (s), 1028 (s), 980 (m), 934 (m), 827 (s), 738 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.31-7.16 (14 H, m, 14 x Ar C**H**), 6.82-6.77 (4 H, m, 4 x Ar C**H**), 5.29 (2 H, s, 2 x OC**H**O), 4.57 (4 H, s, 2 x OC**H**$_2$Ph), 4.31 (2 H, dd, J = 10.8, 4.9 Hz, 2 x C**H**OCH), 4.07-3.91 (4 H, m, 2 x CHC**H**$_2$O), 3.81 (6 H, s, 2 x OC**H**$_3$), 3.65 (2 H, t, J = 10.5 Hz, 2 x CHC**H**CH$_2$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 159.9 (2 x Ar **C**), 137.9 (2 x Ar **C**), 130.2 (2 x Ar **C**), 128.4 (4 x Ar **C**H), 127.9 (4 x Ar **C**H), 127.9 (4 x Ar **C**H), 127.5 (4 x Ar **C**H), 113.4 (2 x Ar **C**H), 100.9 (2 x O**C**HO), 77.4 (2 x O**C**H), 72.6 (2 x O**C**H$_2$CH), 69.5 (2 x O**C**H$_2$Ph), 66.8 (2 x O**C**H), 55.2 (2 x O**C**H$_3$) ppm.
LRMS	m/z (ES$^+$) 599 ([MH]$^+$, 100%).

Spectroscopic data consistent with literature.[104]

(2*R*,3*S*,4*S*,5*R*)-2,5-bis-Benzyloxy-1,6-bis-(4-methoxybenzyloxy)-hexane-3,4-diol



4.13
$C_{36}H_{38}O_8$
MW = 598.70

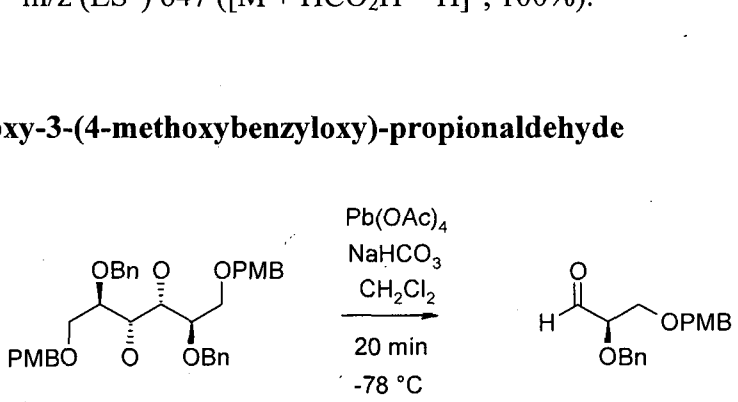
4.14
$C_{36}H_{42}O_8$
MW = 602.73

Diol **4.14** was prepared according to the procedure of Peters and co-workers.[104] To a solution of **4.13** (1.26 g, 2.10 mmol), powdered molecular sieves (1.26 g, 3 Å) and sodium cyanoborohydride (1.39 g, 21.0 mmol) in DMF (20 mL) was added TFA (2.4 mL, 21.0 mmol) in DMF (5 mL). The reaction mixture was heated to 80 °C for 6 h. After cooling to RT, the mixture was partitioned between diethyl ether (20 mL) and H_2O (30 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*.

Purification by column chromatography (25-50% ethyl acetate/hexanes) yielded **4.14** (0.55 g, 0.91 mmol, 43%) as a colourless oil.

$[\alpha]_D^{27}$	−10.4 (c = 2.90, $CHCl_3$).
FT-IR (ν/cm^{-1}):	3476 (br w), 2866 (br w), 1612 (m), 1586 (w), 1512 (s), 1454 (m), 1394 (w), 1362 (w), 1302 (m), 1245 (s), 1173 (m), 1075 (br s), 1030 (s), 818 (s), 736 (s), 697 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.34-7.21 (16 H, m, 16 x Ar C**H**), 6.88-6.81 (4 H, m, 4 x Ar C**H**), 4.72 (2 H, d, J = 11.6 Hz, 2 x OC**H**HArO), 4.58 (2 H, d, J = 11.6 Hz, 2 x OCH**H**ArO), 4.48 (4 H, s, 2 x C**H**$_2$Ph), 3.94 (2 H, app. br t, J = 5.7 Hz, 2 x C**H**OH), 3.79 (6 H, s, 2 x OC**H**$_3$), 3.78-3.60 (4 H, m, 2 x CHC**H**$_2$O), 3.08 (2 H, br d, J = 5.9 Hz, 2 x O**H**) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 159.2 (2 x Ar **C**), 138.2 (2 x Ar **C**), 130.0 (2 x Ar **C**), 129.3 (4 x Ar **C**H), 128.3 (4 x Ar **C**H), 128.1 (4 x Ar **C**H), 127.9 (4 x Ar **C**H), 113.7 (2 x Ar **C**H), 79.1 (2 x **C**HOH), 73.1 (2 x **C**H$_2$), 72.9 (2 x **C**H$_2$), 69.9 (2 x CH**C**HCH$_2$), 69.8 (2 x **C**H$_2$), 55.2 (2 x O**C**H$_3$) ppm.
LRMS	m/z (ES^-) 647 ([M + HCO_2H − H]$^-$, 100%).

(*R*)-2-Benzyloxy-3-(4-methoxybenzyloxy)-propionaldehyde



4.14
$C_{36}H_{42}O_8$
MW = 602.73

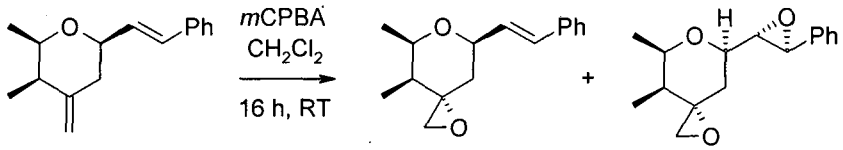
4.15
$C_{18}H_{20}O_4$
MW = 300.36

To a solution of **4.14** (0.30 g, 0.50 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added $NaHCO_3$ (0.13 g, 1.49 mmol) followed by $Pb(OAc)_4$ (0.26 g, 0.58 mmol). The reaction mixture was stirred for 20 min, then filtered through a pad of Celite and washed through with CH_2Cl_2 (30 mL). The filtrate was dried (K_2CO_3), concentrated *in vacuo*, then resolvated with hexanes (20 mL) and concentrated *in vacuo*.

Purification by column chromatography (25% ethyl acetate/hexanes) yielded **4.15** (0.23 g, 0.77 mmol, 77%) as a colourless oil.

$[\alpha]_D^{27}$	+6.7 (c = 3.00, $CHCl_3$).
FT-IR (ν/cm^{-1}):	2862 (br w), 1733 (s), 1612 (m), 1512 (s), 1455 (m), 1361 (w), 1302 (w), 1250 (s), 1174 (m), 1085 (s), 1029 (s), 928 (w), 817 (s), 737 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 9.70 (1 H, d, J = 1.1 Hz, C**H**O), 7.38-7.21 (7 H, m, 7 x Ar C**H**), 6.89-6.85 (2 H, m, 2 x Ar C**H**), 4.73 (1 H, d, J = 12.0 Hz, OC**H**HAr), 4.67 (1 H, d, J = 12.0 Hz, OCH**H**Ar), 4.50 (1 H, d, J = 12.0 Hz, OC**H**HPh), 4.46 (1 H, d, J = 12.0 Hz, OCH**H**Ph), 3.96 (1 H, t, J = 3.7 Hz, C**H**), 3.79 (3 H, s, OC**H**$_3$), 3.78-3.71 (2 H, m, CHC**H**$_2$O) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (100 MHz): 202.2 (**C**HO), 159.3 (Ar **C**), 137.1 (Ar **C**), 129.6 (Ar **C**), 129.4 (2 x Ar **C**H), 128.5 (2 x Ar **C**H), 128.1 (2 x Ar **C**H), 128.0 (2 x Ar **C**H), 113.8 (Ar **C**H) 82.6 (**C**H), 73.2 (O**C**H$_2$PMP), 72.7 (O**C**H$_2$Ph), 68.7 (CH**C**H$_2$O), 55.2 (O**C**H$_3$) ppm.
LRMS	m/z (ES$^+$) 323 ([M + Na]$^+$, 100%).

***rel*-(3*S*,4*S*,5*R*,7*R*)-4,5-Dimethyl-7-((*E*)-styryl)-1,6-dioxaspiro[2.5]octane (4.19) & *rel*-(3*S*,4*S*,5*R*,7*R*)-4,5-dimethyl-7-((2*S*,3*S*)-3-phenyloxiranyl)-1,6-dioxaspiro[2.5]octane (4.19a)**



4.18
$C_{16}H_{20}O$
MW = 228.34

4.19
$C_{16}H_{20}O_2$
MW = 244.34

4.19a
$C_{16}H_{20}O_3$
MW = 260.34

To a stirred solution of **4.18** (7.90 g, 34.6 mmol) in CH_2Cl_2 (300 mL) was added *m*CPBA (77%, 8.55 g, 38.1 mmol). The reaction mixture was stirred at RT for 16 h then washed with saturated $NaHCO_3$ (500 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding crude **4.19**. Purification by column chromatography (2-10% diethyl

ether/petroleum ether) yielded firstly **4.19** (5.50 g, 22.5 mmol, 75%, dr = 20:1) then **4.19a** (0.52 g, 2.00 mmol, 7%, dr = 10:1) as yellow oils.

Spectroscopic data for **4.19**.

FT-IR (ν/cm^{-1}):	2975 (br. m), 2923 (br. m), 1712 (m), 1637 (w), 1450 (m), 1375 (m), 1316 (w), 1165 (m), 1090 (s), 1070 (m), 966 (s), 932 (m), 866 (w), 792 (w), 748 (s).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 7.48-7.16 (5 H, m, 5 x Ar C**H**), 6.63 (1 H, d, J = 16.3 Hz, CHC**H**Ph), 6.23 (1 H, dd, J = 16.3, 6.3 Hz, C**H**CHPh), 4.37 (1 H, app. dddd, J = 11.8, 6.3, 2.6, 1.2 Hz, OC**H**CHCHPh), 4.05 (1 H, qd, J = 6.5, 2.2 Hz, OC**H**CH_3), 2.70 (1 H, d, J = 4.5 Hz, CC**H**H) , 2.68 (1 H, d, J = 4.5 Hz, CCH**H**), 2.18 (1 H, dd, J = 13.8, 11.8 Hz, C**H**H), 1.22 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.19 (1 H, m, CH**H**), 1.13 (1 H, m, CH_3C**H**), 1.09 (3 H, d, J = 5.1 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 136.9 (Ar **C**), 131.0 (2 x Ar **C**H), 129.9 (2 x Ar **C**H), 128.7 (**C**HCHPh), 127.8 (Ar **C**H), 126.7 (CH**C**HPh), 76.5 (O**C**H), 73.9 (O**C**HCH_3), 61.0 (**C**CH_2), 53.2 (C**C**H_2), 40.8 (CH_3**C**H), 35.0 (**C**H_2), 18.4 (**C**H_3), 10.4 (**C**H_3) ppm.
LRMS	m/z (CI) 244 (M^+, 70%), 227 (78), 215 (28), 201 (100), 183 (84), 155 (64), 131 (86), 115 (80), 104 (66).
HRMS	m/z (CI) found: 244.1458, $[M]^+$. $C_{16}H_{20}O_2$ requires 244.1463.

Spectroscopic data for **4.19a**.

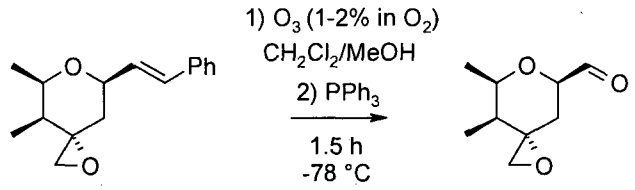
FT-IR (ν/cm^{-1}):	2976 (m), 2915 (br. w), 2863 (br. w), 1548 (w), 1497 (w), 1456 (m), 1405 (w), 1375 (m), 1301 (m), 1244 (m), 1170 (m), 1094 (s), 1020 (m), 921 (s), 890 (s), 847 (m), 756 (s), 697 (s), 647 (m), 508 (m).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 7.39-7.22 (5 H, m, 5 x Ar C**H**), 3.98 (1 H, qd, J = 6.5, 2.3 Hz, OC**H**CH_3), 3.86 (1 H, d, J = 2.0 Hz, OCHC**H**Ph), 3.73 (1 H, ddd, J = 12.1, 5.6, 2.5 Hz, OC**H**CH_2), 3.09 (1 H, dd, J = 5.6, 2.0 Hz, OC**H**CHPh), 2.69 (1 H, d, J = 4.4 Hz, CC**H**HO), 2.67 (1 H, d, J = 4.4 Hz, CCH**H**O), 2.23 (1 H, dd, J = 13.7, 12.1 Hz, C**H**H), 1.21 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.16-1.08 (2 H, m, CH_3C**H**, CH**H**), 1.06 (3 H, d, J = 5.6 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (75 MHz): 137.1 (Ar **C**), 128.6 (2 x Ar **C**H), 128.4 (2 x Ar **C**H), 125.8 (Ar **C**H), 75.7 (O**C**HCH$_3$), 73.9 (OCH**C**HPh), 64.1 (O**C**HCH$_2$), 60.7 (**C**CH$_2$), 55.6 (O**C**HCHPh), 53.2 (C**C**H$_2$), 40.7 (CH$_3$**C**H), 31.1 (**C**H$_2$), 18.1 (**C**H$_3$), 10.3 (**C**H$_3$) ppm.

LRMS m/z (CI) 261 ([MH]$^+$, 64%), 243 (42), 217 (36), 199 (18), 183 (10), 154 (12), 141 (100), 123 (26), 91 (88), 69 (14), 55 (24).

HRMS m/z (ES$^+$) found: 315.1564, [M + Na + MeOH]$^+$. $C_{17}H_{24}NaO_4$ requires 315.1567.

***rel*-(3*S*,5*R*,7*R*,8*S*)-7,8-Dimethyl-1,6-dioxaspiro[2.5]octane-5-carbaldehyde**



4.19
$C_{16}H_{20}O_2$
MW = 244.34

4.20
$C_9H_{14}O_3$
MW = 170.21

Ozone (1-2% in O_2) was bubbled through a solution of **4.19** (5.50 g, 22.5 mmol) in CH_2Cl_2/MeOH (84:16, 320 mL) at −78 °C. After 1 h, triphenylphosphine (11.81 g, 45.0 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture at −78 °C and stirred for 30 min. The mixture was allowed to warm to RT and the solvent removed *in vacuo*. Purification by column chromatography (2-4% MeOH/CH_2Cl_2) yielded **4.20** as an unstable colourless oil (2.37 g, 14.0 mmol, 62%).

FT-IR (ν/cm^{-1}): 2976 (br. m), 2923 (br. w), 2855 (br. w), 2360 (m), 1736 (s), 1454 (w), 1378 (m), 1299 (m), 1241 (w), 1163 (m), 1099 (s), 1027 (m), 933 (s), 907 (s), 842 (w), 789 (w), 741 (m).

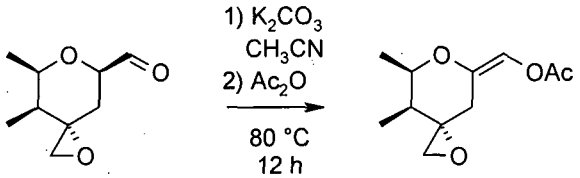
^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 9.70 (1 H, d, J = 3.0 Hz, C**H**O), 4.17 (1 H, dd, J = 12.3, 3.0 Hz, OC**H**), 4.04 (1 H, qd, J = 6.5, 2.4 Hz, OC**H**CH$_3$), 2.73 (1 H, d, J = 4.4 Hz, OCHH), 2.69 (1 H, d, J = 4.4 Hz, OCH**H**), 2.09 (1 H, dd, J = 13.9, 12.3 Hz, C**H**H), 1.32-1.07 (2 H, m, C**H**, CH**H**),

1.24 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.05 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 201.2 (**C**HO), 79.9 (O**C**HCH$_3$), 74.5 (O**C**H), 60.3 (**C**CH$_2$), 53.4 (**C**H$_2$), 40.9 (CH$_3$**C**H), 29.3 (**C**H$_2$), 18.0 (**C**H$_3$), 10.2 (**C**H$_3$) ppm.

LRMS: m/z (CI) 171 ([MH]$^+$, 44%), 141 (78), 127 (100), 109 (12), 97 (56), 69 (16).

***rel*-(3*S*,7*R*,8*S*)-7,8-Dimethyl-1,6-dioxaspiro[2.5]oct-(5*E*)-ylidenemethyl acetate**



4.20
$C_9H_{14}O_3$
MW = 170.21

4.21
$C_{11}H_{16}O_4$
MW = 212.25

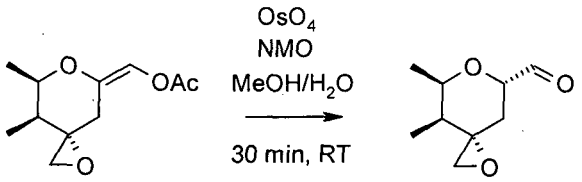
Potassium carbonate (9.33 g, 67.5 mmol) was added to a stirred solution of aldehyde **4.20** (3.83 g, 22.5 mmol) in CH_3CN (250 mL). After 15 min acetic anhydride (6.38 mL, 67.5 mmol) was added. The reaction mixture was heated to 80 °C for 12 h,[106] then cooled to RT and concentrated *in vacuo*. The resulting solid was partitioned between diethyl ether (100 mL) and H_2O (200 mL). The aqueous phase was extracted with diethyl ether (3 x 100 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (22% diethyl ether/petroleum ether) yielded **4.21** (2.96 g, 14.0 mmol, 65%) as a yellow oil.

FT-IR (ν/cm^{-1}): 2978 (br. w), 1747 (s), 1703 (w), 1419 (w), 1372 (m), 1325 (m), 1217 (s), 1148 (m), 1100 (s), 1080 (s), 1051 (w), 1006 (m), 991 (m), 970 (m), 960 (m), 895 (w), 822 (w), 750 (s).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 6.60 (1 H, d, J = 1.5 Hz, =C**H**), 4.23 (1 H, qd, J = 6.5, 2.7 Hz, OC**H**CH$_3$), 2.75-2.70 (3 H, m, C**H**H, C**H**$_2$), 2.17 (3 H, s, OC**H**$_3$), 1.80 (1 H, d, J = 14.9 Hz, CH**H**), 1.44 (1 H, qd, J = 7.3, 2.7 Hz, CH$_3$C**H**), 1.29 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.07 (3 H, d, J = 7.3 Hz,

	CH_3) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (101 MHz): 168.1 (**C**=O), 138.1 (**C**=CH), 118.9 (C=**C**H), 76.2 (O**C**HCH$_3$), 59.9 (O**C**CH$_2$), 52.5 (O**C**H$_2$), 40.3 (**C**H$_3$CO$_2$), 29.9 (**C**H$_2$), 20.9 (CH$_3$**C**H), 17.5 (**C**H$_3$), 9.9 (**C**H$_3$) ppm.
LRMS	m/z (CI) 212 (M^+, 12%), 183 (6), 170 (84), 152 (46), 140 (26), 123 (68), 95 (30), 67 (28), 55 (44).
HRMS	m/z (CI) found: 213.1122, $[MH]^+$, $C_{11}H_{17}O_4$ requires 213.1121.

***rel*-(3*S*,5*S*,7*R*,8*S*)-7,8-Dimethyl-1,6-dioxaspiro[2.5]octane-5-carbaldehyde**



4.21
$C_{11}H_{16}O_4$
MW = 212.25

4.20b
$C_9H_{14}O_3$
MW = 170.21

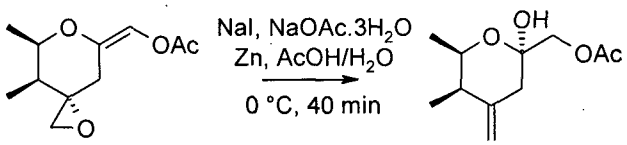
Osmium tetroxide in *tert*-butyl alcohol (2.5% w/v, 0.24 mL, 0.024 mmol) was added to a solution of **4.21** (0.05 g, 0.24 mmol) and NMO (0.06 g, 0.47 mmol) in MeOH/H_2O (4:1, 5 mL).[109] After 30 min saturated $NaHCO_3$ (10 mL) was added and the mixture stirred for a further 10 min. The mixture was extracted with ethyl acetate (2 x 10 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (1.5% MeOH/CH_2Cl_2) yielded aldehyde **4.20b** (0.035 g, 0.21 mmol, 86%) as an unstable brown oil.

FT-IR (ν/cm^{-1}):	2978 (br. w), 1755 (s), 1703 (w), 1419 (w), 1372 (m), 1325 (m), 1217 (s), 1148 (m), 1100 (s), 1080 (s), 1051 (w), 1006 (m), 991 (m), 970 (m), 960 (m), 895 (w), 822 (w), 750 (s).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 9.88 (1 H, d, J = 0.5 Hz, C**H**O), 4.28 (1 H, dd, J = 7.3, 3.0 Hz, OC**H**CHO), 4.24 (1 H, qd, J = 6.5, 2.9 Hz, OC**H**CH$_3$), 2.69 (2 H, m, C**H**$_2$O), 2.33 (1 H, dd, J = 14.2, 7.1 Hz, C**H**H), 1.68 (1 H, app. ddd, J = 14.2, 2.9, 1.0 Hz, CH**H**), 1.30 (1 H, m, CH$_3$C**H**), 1.24 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.03 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 203.2 (**C**HO), 78.0 (O**C**HCH$_3$), 71.4 (O**C**H), 59.0 (O**C**CH$_2$), 52.8 (O**C**H$_2$), 39.7 (CH$_3$**C**HC), 28.5 (**C**H$_2$), 17.5 (**C**H$_3$), 9.7 (**C**H$_3$) ppm.

LRMS m/z (ES$^+$) 225 ([M + MeOH + Na]$^+$, 100%).

***rel*-(2*R*,5*R*,6*R*)-2-Hydroxy-5,6-dimethyl-4-methylenetetrahydropyran-2-ylmethyl acetate**



4.21
$C_{11}H_{16}O_4$
MW = 212.25

4.24
$C_{11}H_{18}O_4$
MW = 214.26

Sodium iodide (9.44 g, 63.0 mmol) and sodium acetate (3.54 g, 26.0 mmol) were added to a solution of vinyl acetate **4.21** (0.60 g, 2.83 mmol) in AcOH/H_2O (38 mL, 10:1).[110] After cooling to 0 °C, zinc dust (4 x 0.35 g, 4 x 5.35 mmol) was added to the reaction mixture in four portions at 10 min intervals. The reaction mixture was warmed to RT then filtered through a pad of Celite, washing through with $CHCl_3$ (3 x 10 mL). The filtrate was washed with H_2O (50 mL), and the aqueous phase extracted with $CHCl_3$ (3 x 20 mL). The combined organic phases were washed with saturated K_2CO_3 (100 mL) and H_2O (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25-50% diethyl ether/petroleum ether) yielded **4.24** (0.32 g, 1.49 mmol, 53%) as a colourless oil.

FT-IR (ν/cm^{-1}): 3459 (br. m), 2974 (br. m), 1742 (s), 1655 (w), 1429 (w), 1376 (s), 1238 (br. s), 1177 (m), 1125 (w), 1082 (s), 1048 (s), 1004 (m), 927 (m), 888 (m), 812 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 4.92 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.79 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.16 (1 H, qd, J = 6.5, 2.7 Hz, OC**H**CH$_3$), 4.14 (1 H, d, J = 11.3 Hz, C**H**HOAc), 4.02 (1 H, d, J = 11.3 Hz, CH**H**OAc), 2.72 (1 H, app. d, J = 1.5 Hz, O**H**), 2.47 (1 H, dd, J =

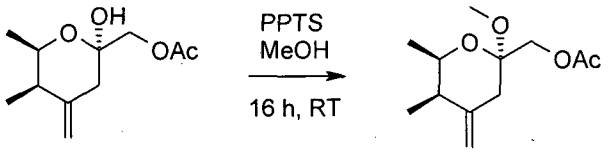
13.8, 1.5 Hz, C**H**H), 2.25 (1 H, qd, J = 7.0, 2.7 Hz, CH_3C**H**), 2.18 (1 H, d, J = 13.8 Hz, CH**H**), 2.13 (3 H, s, COC**H**$_3$), 1.13 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.03 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 171.0 (**C**=O), 146.5 (**C**CH_2), 110.7 (C=**C**H_2), 95.6 (**C**OH), 69.6 (**C**H_2O), 69.0 (O**C**HCH_3), 41.9 (**C**H_3CO_2), 36.3 (CH_2), 21.1 (CH_3**C**HC), 18.1 (**C**H_3), 11.7 (**C**H_3) ppm.

LRMS m/z (CI) 197 ([MH – H_2O]$^+$, 100%), 155 (78), 136 (72), 121 (44), 109 (20), 93 (26), 79 (16), 67 (16), 55 (10), 43 (48).

HRMS m/z (EI) found: 196.1096 [M – H_2O]$^+$, $C_{11}H_{16}O_3$ requires 196.1099.

rel-(2_R_,5_R_,6_R_)-2-Methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-ylmethyl acetate



4.24
$C_{11}H_{18}O_4$
MW = 214.26

4.25
$C_{12}H_{20}O_4$
MW = 228.29

PPTS (0.02 g, 0.08 mmol) was added to a solution of **4.24** (0.50 g, 2.33 mmol) in MeOH (20 mL) at RT. After 16 h the reaction mixture was partitioned between diethyl ether (30 mL) and saturated K_2CO_3 (50 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (10% diethyl ether/petroleum ether) to yield **4.25** (0.53 g, 2.31 mmol, 99%) as a clear oil.

FT-IR (ν/cm^{-1}): 2972 (br. w), 1747 (s), 1655 (w), 1453 (w), 1376 (m), 1331 (w), 1297 (w), 1235 (s), 1161 (m), 1123 (w), 1080 (m), 1048 (s), 1032 (s), 1003 (w), 890 (m), 790 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 4.84 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.73 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.23 (1 H, d, J = 11.7 Hz, C**H**HOAc), 4.00 (1 H, d, J = 11.7 Hz, CH**H**OAc), 3.91 (1 H, qd, J = 6.7, 2.6 Hz, OC**H**CH_3), 3.21 (3 H, s, OC**H**$_3$), 2.44 (1 H, app. dt, J = 14.2, 2.1 Hz,

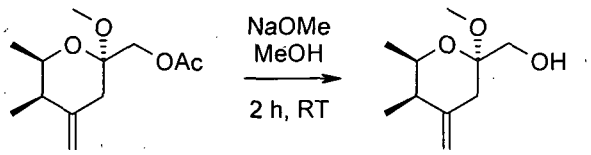
CHH), 2.25 (1 H, d, J = 14.2 Hz, CHH), 2.22 (1 H, qd, J = 7.0, 2.6 Hz, CH_3CH), 2.11 (3 H, s, $COCH_3$), 1.14 (3 H, d, J = 6.7 Hz, CH_3), 1.03 (3 H, d, J = 7.0 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 170.7 (C=O), 146.8 ($C=CH_2$), 109.8 ($C=CH_2$), 98.4 ($COCH_3$), 68.8 ($OCHCH_3$), 64.5 (CH_2O), 48.6 (OCH_3), 41.6 ($COCH_3$), 36.4 (CH_2), 21.1 (CH_3CH), 18.0 (CH_3), 12.0 (CH_3) ppm.

LRMS m/z (CI) 197 ($[MH - MeOH]^+$, 100%), 155 (56), 137 (94), 109 (26), 81 (56), 43 (50).

HRMS m/z (ES^+) found: 251.1255 $[M + Na]^+$, $C_{12}H_{20}NaO_4$ requires 251.1254.

(*rel*-(2*R*,5*R*,6*R*)-2-Methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-methanol



4.25
$C_{12}H_{20}O_4$
MW = 228.29

4.26
$C_{10}H_{18}O_3$
MW = 186.25

NaOMe in MeOH[111] (1 M, 9.0 mL, 9.00 mmol) was added to a solution of **4.25** (0.55 g, 2.41 mmol) in MeOH (20 mL) at RT. After 2 h the reaction mixture was poured into saturated NH_4Cl (40 mL). The aqueous phase was extracted with diethyl ether (3 x 15 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33% diethyl ether/petroleum ether) yielded alcohol **4.26** (0.44 g, 2.36 mmol, 98%) as a colourless oil.

FT-IR (ν/cm^{-1}): 3432 (br. w), 2971 (w), 2938 (br. w), 1653 (w), 1452 (w), 1372 (m), 1329 (w), 1223 (m), 1146 (m), 1089 (s), 1052 (br. s), 1025 (s), 968 (w), 941 (w), 915 (w), 889 (m), 858 (m), 790 (m).

^{1}H NMR δ_H (300 MHz): 4.85 (1 H, app. t, J = 1.9 Hz, =CHH), 4.74 (1 H, app.

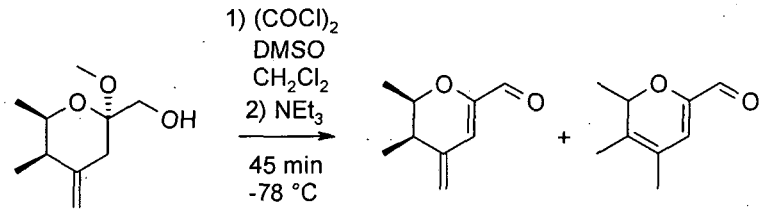
(CDCl$_3$) t, J = 1.9 Hz, =CH**H**), 3.93 (1 H, qd, J = 6.6, 2.7 Hz, OC**H**CH$_3$), 3.61 (1 H, dd, J = 11.3, 6.4 Hz, C**H**HOH), 3.54 (1 H, dd, J = 11.3, 6.4 Hz, CH**H**OH), 3.23 (3 H, s, OC**H**$_3$), 2.60 (1 H, app. dt, J = 14.4, 2.0 Hz, C**H**H), 2.27-2.17 (2 H, m, CH$_3$C**H**, CH**H**), 1.71 (1 H, app. t, J = 6.4 Hz, O**H**), 1.16 (3 H, d, J = 6.6 Hz, C**H**$_3$), 1.03 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR (CDCl$_3$) δ_C (101 MHz): 147.2 (**C**=CH$_2$), 109.7 (C=**C**H$_2$), 99.6 (O**C**O), 69.0 (O**C**H$_3$), 64.5 (**C**H$_2$OH), 48.6 (O**C**HCH$_3$), 41.6 (CH$_3$**C**H), 35.6 (**C**H$_2$), 18.0 (**C**H$_3$), 12.0 (**C**H$_3$) ppm.

LRMS m/z (CI) 155 ([MH – MeOH]$^+$, 96%), 137 (26) , 125 (100), 109 (22), 95 (34), 81 (12), 67 (16), 55 (24).

HRMS m/z (CI) found: 155.0996, [MH – MeOH]$^+$. $C_9H_{15}O_3$ requires 155.0994.

***rel*-(5*R*,6*R*)-5,6-Dimethyl-4-methylene-5,6-dihydro-4*H*-pyran-2-carbaldehyde (4.27) & 4,5,6-trimethyl-6*H*-pyran-2-carbaldehyde (4.28)**



4.26
$C_{10}H_{18}O_3$
MW = 186.25

4.27
$C_9H_{12}O_2$
MW = 152.19

4.28
$C_9H_{12}O_2$
MW = 152.19

To a solution of oxalyl chloride (0.08 mL, 0.97 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO in CH_2Cl_2 (2 M, 0.97 mL, 1.93 mmol) dropwise. The mixture was stirred for 10 min at −78 °C and then alcohol **4.26** (0.09 g, 0.48 mmol) in CH_2Cl_2 (8 mL) was added dropwise. After stirring for a further 15 min at −78 °C triethylamine (0.54 mL, 3.87 mmol) was added The reaction mixture was allowed to warm to RT over 30 min then poured into saturated $NaHCO_3$ (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (18-40% diethyl ether/petroleum ether) yielded firstly **4.27** (0.035 g, 0.23 mmol, 48%) then **4.28** (0.035 g, 0.23 mmol, 48%) as unstable yellow oils.

Both aldehydes were unstable and degraded before full analysis could be carried out.

Spectroscopic data for aldehyde **4.27**

FT-IR (ν/cm^{-1}): 3441 (br. w), 2979 (w), 2926 (br. w), 1701 (s), 1635 (w), 1456 (m), 1417 (w), 1386 (m), 1338 (w), 1279 (br. m), 1080 (br. s), 1002 (m), 966 (w), 888 (w), 731 (w).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 9.22 (1 H, s, C**H**O), 6.26 (1 H, app. d, J = 0.5 Hz, =C**H**), 5.23 (1 H, d, J = 0.8 Hz, =C**H**H), 5.09 (1 H, d, J = 0.8 Hz, =CH**H**), 4.20 (1 H, qd, J = 6.5, 2.7 Hz, OC**H**CH_3), 2.55 (1 H, qd, J = 7.1, 2.7 Hz, CH_3C**H**), 1.32 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.05 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

The ^{1}H NMR spectrum exhibits additional signals attributed to CH_2Cl_2, diethyl ether and petroleum ether.

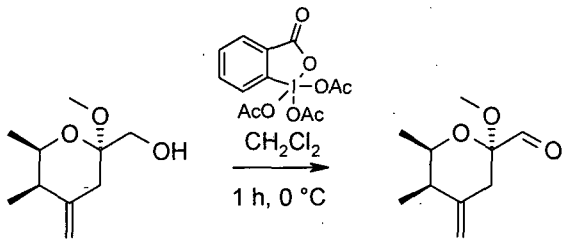
Spectroscopic data for aldehyde **4.28**

FT-IR (ν/cm^{-1}): 3400 (br. m), 2980 (w), 2922 (br. w), 1698 (br. s), 1447 (m), 1379 (m), 1272 (m), 1135 (m), 1071 (br. s), 1013 (br. s), 855 (w), 732 (w).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 9.16 (1 H, s, C**H**O), 5.95 (1 H, s, =C**H**), 4.79 (1 H, q, J = 6.5 Hz, CH_3C**H**), 1.81 (3 H, s, C**H**$_3$C), 1.74 (3 H, s, C**H**$_3$C), 1.30 (3 H, d, J = 6.5 Hz, C**H**$_3$CH) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 185.9 (**C**HO), 148.0 (=**C**), 133.2 (=**C**CH_3), 124.2 (C=**C**H), 122.4 (=**C**CH_3), 76.7 (O**C**HCH_3), 17.9 (OCH**C**H_3), 16.4 (**C**H_3C), 15.9 (**C**H_3C) ppm.

(2*R*,5*R*,6*R*)-2-Methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-carbaldehyde



4.26
$C_{10}H_{18}O_3$
MW = 186.25

4.29
$C_{10}H_{16}O_3$
MW = 184.24

To a stirred suspension of Dess-Martin periodinane[112] (0.47 g, 1.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added alcohol **4.26** (0.17 g, 0.91 mmol) in CH_2Cl_2 (5 mL). After 1 h the reaction mixture was diluted with diethyl ether (15 mL) and poured into saturated $NaHCO_3$ (30 mL) containg an excess of $Na_2S_2O_3$ (1.0 g). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the resulting white powdery solid was dry-loaded onto silica. Purification by column chromatography (25% diethyl ether/petroleum ether) yielded aldehyde **4.29** (0.14 g, 0.76 mmol, 84%) as a yellow oil.

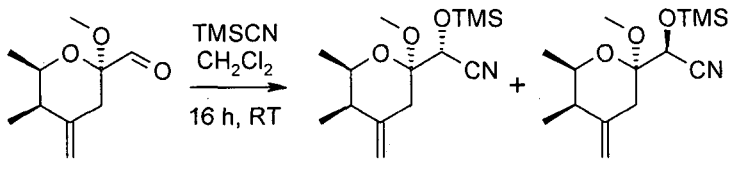
The aldehyde was unstable and degraded before full analysis could be carried out.

$[\alpha]_D^{27}$	−63.2 (c = 0.5, $CHCl_3$).
FT-IR (ν/cm^{-1}):	2979 (w), 2926 (br. w), 1711 (s), 1635 (w), 1459 (m), 1437 (m), 1386 (m), 1338 (w), 1279 (br. w), 1145 (m) 1082 (br. s), 1002 (m), 966 (w), 888 (w), 731 (w).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 9.50 (1 H, s, C**H**O), 4.92 (1 H, app. t, J = 1.8 Hz, =C**H**H), 4.79 (1 H, app. t, J = 1.8 Hz, =CH**H**), 4.01 (1 H, qd, J = 6.6, 2.6 Hz, OC**H**CH$_3$), 3.26 (3 H, s, OC**H**$_3$), 2.38 (1 H, app. dt, J = 14.1, 2.1 Hz, C**H**H), 2.28 (1 H, qd, J = 7.0, 2.6 Hz, CH$_3$C**H**), 2.17 (1 H, d, J = 14.1 Hz, CH**H**), 1.23 (3 H, d, J = 6.6 Hz, C**H**$_3$), 1.06 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (101 MHz): 198.6 (**C**HO), 144.9 (**C**=CH$_2$), 111.2 (C=**C**H$_2$), 99.8 (OCO), 69.7 (CH$_3$**C**H), 50.9 (O**C**H$_3$), 41.4 (CH$_3$**C**H), 33.4 (**C**H$_2$),

17.9 (CH_3), 11.9 (CH_3) ppm.

The ^1H and ^{13}C NMR spectra exhibit additional signals attributed to CH_2Cl_2, diethyl ether and petroleum ether.

(*RS*)-((2*R*,5*R*,6*R*)-2-Methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-trimethylsilanyloxyacetonitrile



4.29
$C_{10}H_{16}O_3$
MW = 184.24

4.30a
$C_{14}H_{25}NO_3Si$
MW = 283.45

4.30b
$C_{14}H_{25}NO_3Si$
MW = 283.45

To a stirred solution of aldehyde **4.29** (0.14 g, 0.76 mmol) in CH_2Cl_2 (5 mL) at RT was added TMSCN (0.17 mL, 1.37 mmol) dropwise. After 16 h the solvent was removed *in vacuo*. Purification by column chromatography (5% diethyl ether/petroleum ether) yielded firstly **4.30a** (0.09 g, 0.30 mmol, 40%) then **4.30b** (0.09 g, 0.30 mmol, 40%) as colourless oils.

Spectroscopic data for cyanohydrin **4.30a**

$[\alpha]_D^{27}$ -77.1 ($c = 0.5$, $CHCl_3$).

FT-IR (ν/cm^{-1}): 2973 (br. w), 2900 (br. w), 1658 (w), 1455 (w), 1426 (w), 1380 (w), 1325 (w), 1255 (m), 1231 (m), 1180 (w), 1148 (s), 1102 (s), 1047 (m), 1018 (m), 950 (w), 885 (m), 871 (s), 846 (s), 793 (w), 778.

^1H NMR ($CDCl_3$) δ_H (400 MHz): 4.88 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.78 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.53 (1 H, s, C**H**CN), 3.88 (1 H, qd, J = 6.6, 2.5 Hz, OC**H**CH_3), 3.19 (3 H, s, OCH_3), 2.69 (1 H, app. dt, J = 14.4, 2.1 Hz, C**H**H), 2.39 (1 H, d, J = 14.4 Hz, CH**H**), 2.25 (1 H, qd, J = 7.0, 2.5 Hz, CH_3C**H**), 1.16 (3 H, d, J = 6.6 Hz, CH_3), 1.10 (3 H, d, J = 7.0 Hz, CH_3), 0.25 (9 H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 146.2 (**C**=CH_2), 119.2 (**C**N), 110.4 (C=**C**H_2), 99.8 (**O**CO), 70.2 (CH_3**C**H), 63.8 (**C**HCN), 48.5 (OCH_3), 41.9 (CH_3**C**H),

33.8 ($\mathbf{C}H_2$), 17.8 ($\mathbf{C}H_3$), 11.8 ($\mathbf{C}H_3$), −0.1 ($Si(\mathbf{C}H_3)_3$) ppm.

LRMS m/z (CI) 284 ($[MH]^+$, 4%), 252 ($[M - MeOH]^+$, 82%), 239 (76), 224 (26), 209 (12), 181 (6), 155 (100), 140 (10), 123 (66), 111 (24), 95 (60), 81 (38), 73 (72).

HRMS m/z (ES^+) found: 306.1497, $[M + Na]^+$, $C_{14}H_{25}NNaO_3Si$ requires 306.1496.

Spectroscopic data for cyanohydrin **4.30b**

$[\alpha]_D^{27}$ −19.0 (c = 0.6, $CHCl_3$).

FT-IR (ν/cm^{-1}): 2975 (br. w), 1655 (w), 1442 (w), 1375 (w), 1323 (w), 1251 (m), 1232 (m), 1175 (m), 1146 (m), 1126 (m), 1098 (m), 1077 (s), 1039 (s), 1017 (m), 996 (m), 967 (m), 879 (s), 843 (s), 790 (m), 755 (m).

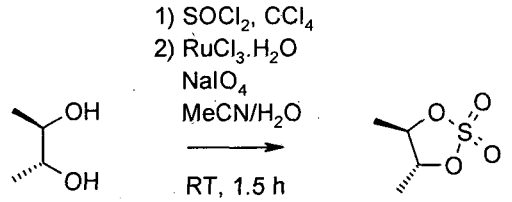
^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 4.87 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.77 (1 H, app. t, J = 1.9 Hz. =CH**H**), 4.51 (1 H, s, C**H**CN), 3.89 (1 H, qd, J = 6.5, 2.6 Hz, OC**H**CH_3), 3.31 (3 H, s, O$\mathbf{C}H_3$), 2.79 (1 H, app. dt, J = 14.2, 2.1 Hz, C**H**H), 2.26 (1 H, d, J = 14.2 Hz, CH**H**), 2.21 (1 H, qd, J = 6.9, 2.6 Hz, CH_3C**H**), 1.15 (3 H, d, J = 6.5 Hz, C$\mathbf{H}_3$), 1.01 (3 H, d, J = 6.9 Hz, C$\mathbf{H}_3$), 0.24 (9 H, s, $Si(C\mathbf{H}_3)_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 146.2 (**C**=CH_2), 117.9 (**C**N), 110.4 (C=**C**H_2), 99.7 (O**C**O), 70.2 (O**C**HCH_3), 64.9 (**C**HCN), 49.0 (O**C**H_3), 41.3 (CH_3**C**H), 32.4 (**C**H_2), 17.9 (**C**H_3), 11.7 (**C**H_3), −0.2 ($Si(C\mathbf{H}_3)_3$) ppm.

LRMS m/z (CI) 284 ($[MH]^+$, 4%), 252 ($[M - MeOH]^+$, 70%), 239 (70), 224 (26), 194 (12), 155 (100), 140 (10), 123 (66), 111 (24), 95 (60), 81 (38), 73 (72).

HRMS m/z (ES^+) found: 306.1488, $[M + Na]^+$, $C_{14}H_{25}NNaO_3Si$ requires 306.1496.

(4*R*,5*R*)-4,5-Dimethyl-[1,3,2]dioxathiolane 2,2-dioxide



4.38
$C_4H_{10}O_2$
MW = 90.12

4.39
$C_4H_8O_4S$
MW = 152.17

Thionyl chloride (0.97 mL, 0.013 mol) was added to a solution of **4.38** (1.00 g, 0.011 mol) in carbon tetrachloride (12 mL). The mixture was heated at reflux for 30 min, then cooled to 0 °C. Acetonitrile (12 mL), water (18 mL), ruthenium trichloride (0.01 g) and sodium periodate (3.52 g, 0.017 mol) were added sequentially to the reaction mixture, which was then warmed to RT. After 1.5 h the reaction mixture was partitioned between diethyl ether (30 mL) and H_2O (50 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL), then the combined organic phases were washed with H_2O (50 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (40% diethyl ether/petroleum ether) yielded **4.39** (1.60 g, 10.51 mmol, 96%) as a colourless oil.

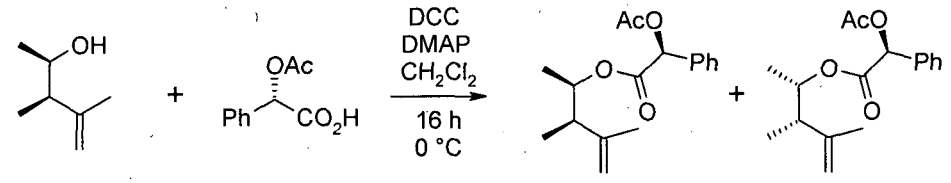
FT-IR (ν/cm^{-1}): 2991 (br w), 1445 (w), 1371 (s), 1291 (w), 1203 (s), 1122 (m), 1027 (s), 983 (w), 911 (s), 847 (m), 816 (s).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 4.75-4.62 (2 H, m, 2 x OC**H**CH_3), 1.56 (6 H, d, J = 3.6 Hz, 2 x OCHC**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 85.3 (O**C**HCH_3), 16.7 (OCH**C**H_3) ppm.

Spctroscopic data consistent with literature values.[118]

(*S*)-Acetoxyphenylacetic acid (3*R*,4*R*)-2,3-dimethylpent-1-en-4-yl ester (4.43a) & (*S*)-acetoxyphenylacetic acid (3*S*,4*S*)-2,3-dimethylpent-1-en-4-yl ester (4.43b)



4.41 $C_7H_{14}O$ MW = 114.19 + **4.42** $C_{10}H_{10}O_4$ MW = 194.19 → **4.43a** $C_{17}H_{22}O_4$ MW = 290.36 + **4.43b** $C_{17}H_{22}O_4$ MW = 290.36

DCC (2.38 g, 11.6 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred suspension of (*S*)-(+)-acetylmandelic acid (2.45 g, 12.6 mmol), DMAP (0.12 g, 1.00 mmol) and alcohol **4.41** (1.20 g, 10.5 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The reaction mixture was warmed to RT. After 16 h, the reaction was filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (10:1 petroleum ether/diethyl ether) to give an inseparable 1:1 mixture of **4.43a** and **4.43b** (2.42 g, 8.33 mmol, 79%) as a colourless oil.

FT-IR (ν/cm^{-1}): 2979 (br. w), 1740 (s), 1647 (w), 1496 (w), 1455 (m), 1372 (m), 1271 (w), 1229 (s), 1209 (s), 1179 (s), 1081 (m), 1052 (m), 1025 (w), 1003 (w), 965 (w), 894 (m), 736 (m).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 7.52-7.44 (2 H + 2 H, m, 4 x Ar C**H**), 7.42-7.34 (3 H + 3 H, m, 6 x Ar C**H**), 5.90 (1 H + 1 H, s, 2 x C**H**OAc), 5.01-4.85 (1 H + 1 H, m, 2 x OC**H**CH$_3$), 4.78 (1 H, app. t, 1.9 Hz, =C**H**H), 4.76 (1 H, s, =C**H**H), 4.66 (1 H, app. t, 1.9 Hz, =CH**H**), 4.59 (1 H, s, =CH**H**), 2.30 (1 H, app. quintet, *J* = 7.0 Hz, CH$_3$C**H**), 2.21 (3 H + 3 H, s, 2 x CO$_2$C**H**$_3$), 2.20-2.17 (1 H, m, CH$_3$C**H**), 1.68 (3 H, s, CC**H**$_3$), 1.53 (3 H, s, CC**H**$_3$), 1.21 (3 H, d, *J* = 6.3 Hz, OCHC**H**$_3$), 1.06 (3 H, d, *J* = 6.4 Hz, OCHC**H**$_3$), 1.02 (3 H, d, *J* = 7.0 Hz, C**H**$_3$CH), 0.74 (3 H, d, *J* = 7.0 Hz, C**H**$_3$CH) ppm.

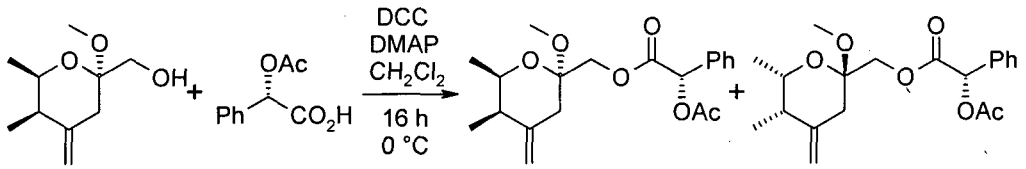
^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 170.5 (**C**=O), 168.7 (**C**=O), 146.6 (**C**=O), 146.4 (**C**=O), 134.3 (Ar **C**), 134.1 (Ar **C**), 129.3 (4 x Ar **C**H), 128.9 (2 x Ar **C**H), 127.9 (2 x Ar **C**H), 127.7 (2 x Ar **C**H), 112.5 (C=**C**H$_2$), 112.3 (C=**C**H$_2$), 77.4 (2 x **C**=CH$_2$) 75.0 (O**C**HCH$_3$), 74.9 (O**C**HCH$_3$), 74.8

(2 x **C**HOAc), 46.6 ($CO_2\mathbf{C}H_3$), 46.5 ($CO_2\mathbf{C}H_3$), 20.9 (2 x $CH_3\mathbf{C}H$), 20.1 (2 x $C\mathbf{C}H_3$), 18.6 ($\mathbf{C}H_3$), 18.1 ($\mathbf{C}H_3$), 15.8 ($\mathbf{C}H_3$), 15.2 ($\mathbf{C}H_3$) ppm.

LRMS m/z (CI) 291 ($[MH]^+$, 100%), 231 (6), 187 (10), 149 (10), 118 (6), 97 (94), 81 (14).

HRMS m/z (ES^+) found: 313.1416, $[M + Na]^+$, $C_{17}H_{22}NaO_4$ requires 313.1410.

(*S*)-Acetoxyphenylacetic acid (2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-ylmethyl ester (4.44a) & (*S*)-acetoxyphenylacetic acid (2*S*,5*S*,6*S*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-ylmethyl ester (4.44b)



4.26 $C_{10}H_{18}O_3$ MW = 186.25 | **4.42** $C_{10}H_{10}O_4$ MW = 194.19 | **4.44a** $C_{20}H_{26}O_6$ MW = 362.43 | **4.44b** $C_{20}H_{26}O_6$ MW = 362.43

DCC (0.61 g, 2.95 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a stirred suspension of (S)-(+)-acetylmandelic acid (0.63 g, 3.22 mmol), DMAP (0.03 g, 0.26 mmol) and alcohol **4.26** (0.50 g, 2.68 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was warmed to RT. After 16 h the reaction was filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (6:1 petroleum ether/diethyl ether) giving **4.44** as a 1:1 mixture of diastereoisomers (0.85 g, 2.35 mmol, 88%) as a colourless oil. Repeated column chromatography (6:1 petroleum ether/diethyl ether) effected separation of these diastereoisomers.

Spectroscopic data for first diastereoisomer.

$[\alpha]_D^{27}$ +2.7 (c = 0.45, $CHCl_3$).

FT-IR (ν/cm^{-1}): 2971 (br. w), 2924 (br. w), 1745 (s), 1655 (w), 1497 (w), 1455 (w), 1374(m), 1329 (w), 1297 (w), 1229 (s), 1158 (s), 1122 (w), 1081 (m),

1050 (s), 892 (m), 860 (w), 790 (w), 738 (m).

^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.62-7.31 (5 H, m, 5 x Ar C**H**), 5.98 (1 H, s, C**H**OAc), 4.80 (1 H, app. t, J = 1.8 Hz, =C**H**H), 4.63 (1 H, app. t, J = 1.8 Hz, =CH**H**), 4.30 (1 H, d, J = 11.6 Hz, OC**H**H), 4.01 (1 H, d, J = 11.6 Hz, OCH**H**), 3.84 (1 H, qd, J = 6.6, 2.5 Hz, OC**H**CH_3), 3.08 (3 H, s, OC**H**$_3$), 2.27 (1 H, m, C**H**H), 2.22 (3 H, s, C**H**$_3CO_2$), 2.16 (1 H, qd, J = 7.0, 2.5 Hz, CH_3C**H**), 2.03 (1 H, m, CH**H**), 1.11 (3 H, d, J = 6.6 Hz, C**H**$_3$), 0.95 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

Additional signals in the ^{1}H NMR spectrum were attributed to the presence of acetone and water.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 170.4 (**C**=O), 167.5 (**C**=O), 146.7 (**C**=CH_2), 133.4 (Ar **C**), 129.0 (2 x Ar **C**H), 128.2 (2 x Ar **C**H), 127.7 (Ar **C**H), 109.8 (C=**C**H_2), 98.1 (O**C**O), 75.5 (**C**HOAc), 68.8 (OC**H**CH_3), 65.1 (**C**H_2O), 48.5 (O**C**H_3), 41.5 (CH_3**C**H), 35.9 (**C**H_2), 20.9 (CO**C**H_3), 17.9 (**C**H_3), 12.0 (**C**H_3) ppm.

LRMS m/z (CI) 331 ([M – MeOH]$^+$, 70%), 154 (16), 139 (100), 106 (26), 91 (20), 81 (4).

HRMS m/z (ES$^+$) found: 385.1617, [M + Na]$^+$, $C_{20}H_{26}NaO_6$ requires 385.1622.

Spectroscopic data for second diastereoisomer

$[\alpha]_D^{27}$ +75.7 (c = 0.66, $CHCl_3$).

FT-IR (ν/cm^{-1}): 2971 (br. w), 2924 (br. w), 1745 (s), 1655 (w), 1497 (w), 1455 (w), 1374(m), 1329 (w), 1297 (w), 1229 (s), 1158 (s), 1122 (w), 1081 (m), 1050 (s), 892 (m), 860 (w), 790 (w), 738 (m).

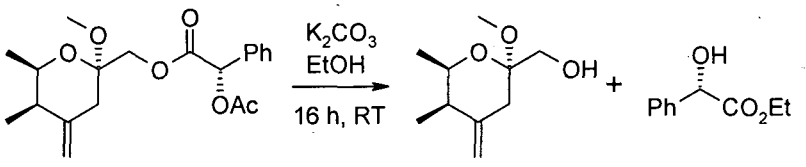
^{1}H NMR ($CDCl_3$) δ_H (300 MHz): 7.63-7.30 (5 H, m, 5 x Ar C**H**), 5.98 (1 H, s, C**H**OAc), 4.79 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.61 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.18 (1 H, d, J = 11.5 Hz, OC**H**H), 4.12 (1 H, d, J = 11.5 Hz, OCH**H**), 3.85 (1 H, qd, J = 6.6, 2.6 Hz, OC**H**CH_3), 3.17 (3 H, s, O**C**H_3), 2.27 (1 H, app. dt, J = 14.1, 1.9 Hz, C**H**H), 2.21 (3 H, s, C**H**$_3CO_2$), 2.15 (1 H, qd, J = 7.0, 2.6 Hz, CH_3C**H**), 1.99 (1 H, m, CH**H**), 1.07 (3 H, d, J = 6.6 Hz, C**H**$_3$), 0.89 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 170.4 (**C**=O), 168.6 (**C**=O), 146.7 (**C**=CH_2), 133.8 (Ar **C**), 129.5 (Ar **C**H), 128.9 (2 x Ar **C**H), 127.9 (2 x Ar **C**H), 109.8 (C=**C**H_2), 98.1 (O**C**O), 74.7 (**C**HOAc), 68.7 (OC**H**CH_3), 65.2 (O**C**H_2), 48.6 (O**C**H_3), 41.5 (CH_3**C**H), 36.1 (**C**H_2), 20.9 (CO**C**H_3), 17.9 (**C**H_3), 11.9 (**C**H_3) ppm.

LRMS m/z (CI) 331 ([MH – MeOH]$^+$, 70%), 154 (16), 139 (100), 106 (26), 91 (20).

HRMS m/z (ES$^+$) found: 385.1617, [M + Na]$^+$, $C_{20}H_{26}NaO_6$ requires 385.1622.

((2*R*,5*R*,6*R*)-2-Methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-methanol



4.44a $C_{20}H_{26}O_6$ MW = 362.43 | **4.26** $C_{10}H_{18}O_3$ MW = 186.25 | **4.45** $C_{10}H_{12}O_3$ MW = 180.21

Potassium carbonate (0.72 g, 5.24 mmol) was added to a stirred solution of ester **4.44a** (0.38 g, 1.05 mmol) in ethanol (30 mL) at RT. After 16 h the reaction mixture was partitioned between saturated NH_4Cl (50 mL) and diethyl ether (10 mL). The aqueous phase was extracted with diethyl ether (2 x 10 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33% diethyl ether/petroleum ether) yielded firstly alcohol **4.26** (0.17 g, 0.91 mmol, 87%) then ester **4.45** (0.02 g, 0.11 mmol, 2%) as colourless oils.

Spectroscopic data for alcohol **4.26**

$[\alpha]_D^{27}$ +90.5 (c = 0.5, $CHCl_3$).

FT-IR (ν/cm^{-1}): 3432 (br. w), 2971 (w), 2938 (br. w), 1653 (w), 1452 (w), 1372 (m), 1329 (w), 1223 (m), 1146 (m), 1089 (s), 1052 (br. s), 1025 (s), 968 (w), 941 (w), 915 (w), 889 (m), 858 (m), 790 (m).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 4.85 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.74 (1 H, app. t, J = 1.9 Hz, =CH**H**), 3.93 (1 H, qd, J = 6.6, 2.7 Hz, OC**H**CH_3), 3.61 (1 H, dd, J = 11.3, 6.4 Hz, C**H**HOH), 3.54 (1 H, dd, J = 11.3, 6.4 Hz, CH**H**OH), 3.23 (3 H, s, OC**H**$_3$), 2.60 (1 H, app. dt, J = 14.4, 2.0 Hz, C**H**H), 2.27-2.17 (2 H, m, CH_3C**H**, CH**H**), 1.71 (1 H, app. t, J = 6.4 Hz, O**H**), 1.16 (3 H, d, J = 6.6 Hz, C**H**$_3$), 1.03 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (101 MHz): 147.2 (**C**=CH_2), 109.7 (C=**C**H_2), 99.6 (O**C**O), 69.0 (O**C**HCH_3), 64.5 (**C**H_2OH), 48.6 (O**C**H_3), 41.6 (CH_3**C**H), 35.6 (**C**H_2), 18.0 (**C**H_3), 12.0 (**C**H_3) ppm.

LRMS m/z (CI) 155 ($[MH - MeOH]^+$, 96%), 137 (26) , 125 (100), 109 (22), 95 (34), 81 (12), 67 (16), 55 (24).

HRMS m/z (CI) found: 155.0996, $[MH - MeOH]^+$, $C_9H_{15}O_3$ requires 155.0994.

Spectroscopic data for ester **4.45**

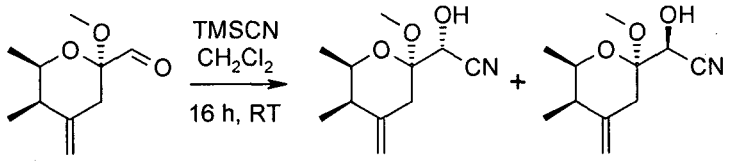
FT-IR (ν/cm^{-1}): 3460 (br. w), 2982 (w), 1729 (s), 1495 (w), 1454 (m), 1368 (w), 1209 (s), 1182 (s), 1093 (s), 1066 (s), 1019 (m), 940 (w), 864 (w), 731 (s).

^{1}H NMR ($CDCl_3$): δ_H (300 MHz): 7.71-7.08 (5 H, m, 5 x Ar C**H**), 5.17 (1 H, s, PhC**H**OH), 4.28 (1 H, dq, J = 7.1, 3.7 Hz, C**H**$_2$$CH_3$), 4.17 (1 H, dq, J = 7.1, 3.7 Hz, C**H**$_2$$CH_3$), 3.52 (1 H, br. s, O**H**), 1.23 (3 H, t, J = 7.1 Hz, CH_2C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$): δ_C (75 MHz): 173.8 (**C**=O), 138.6 (Ar **C**), 128.7 (2 x Ar **C**H), 128.6 (2 x Ar **C**H), 126.7 (Ar **C**H), 73.1 (**C**H), 62.4 (**C**H_2), 14.2 (**C**H_3) ppm.

Spectroscopic data consistent with literature values.

(*R*)-Hydroxy-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-acetonitrile (4.46a) & (*S*)-hydroxy-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-acetonitrile (4.46b)



4.29
$C_{10}H_{16}O_3$
MW = 184.24

4.46a
$C_{11}H_{17}NO_3$
MW = 211.26

4.46b
$C_{11}H_{17}NO_3$
MW = 211.26

To a stirred solution of aldehyde **4.29** (0.17 g, 0.91 mmol) in CH_2Cl_2 (5 mL) at RT was added TMSCN (0.17 mL, 1.37 mmol) dropwise. After 16 h the solvent was removed *in vacuo*. Purification by column chromatography (22% diethyl ether/petroleum ether) yielded firstly **4.46b** (0.05 g, 0.24 mmol, 26%) then **4.46a** (0.05 g, 0.24 mmol, 26%) as colourless oils.

Spectroscopic data for cyanohydrin **4.46a**.

$[\alpha]_D^{27}$ −83.2 (c = 0.5, $CHCl_3$).

FT-IR (ν/cm^{-1}): 3419 (br. m), 2974 (m), 2916 (m), 1656 (w), 1454 (w), 1427 (w), 1380 (m), 1327 (w), 1230 (m), 1173 (w), 1141 (m), 1082 9s), 1075 (s), 1041 (s), 1017 (m), 945 (w), 909 (m), 881 (m), 791 (w).

^{1}H NMR ($CDCl_3$) δ_H (400 MHz): 4.91 (1 H, app. t, J = 1.9 Hz, =C**H**H), 4.79 (1 H, app. t, J = 1.9 Hz, =CH**H**), 4.56 (1 H, d, J = 4.2 Hz, C**H**OH), 3.92 (1 H, qd, J = 6.5, 2.5 Hz, OC**H**CH$_3$), 3.26 (3 H, s, OC**H**$_3$), 2.75 (1 H, app. dt, J = 14.2, 2.1 Hz, C**H**H), 2.49 (1 H, d, J = 4.2 Hz, O**H**), 2.36 (1 H, d, J = 14.2 Hz, CH**H**), 2.28 (1 H, qd, J = 7.1, 2.5 Hz, CH$_3$C**H**), 1.19 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.09 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): 145.3 (**C**=CH$_2$), 118.0 (**C**N), 110.9 (C=**C**H$_2$), 99.4 (O**C**O), 70.7 (O**C**HCH$_3$), 64.2 (**C**HOH), 48.9 (O**C**H$_3$), 41.6 (CH$_3$**C**H), 33.7 (**C**H$_2$), 17.8 (**C**H$_3$), 11.8 (**C**H$_3$) ppm.

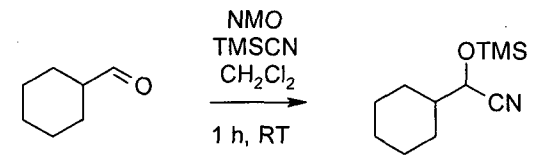
LRMS m/z (ES$^+$) 234 ([M + Na]$^+$, 100%).

HRMS m/z (ES$^+$) found: 234.1105, [M + Na]$^+$, $C_{11}H_{17}NNaO_3$ requires 234.1101.

Spectroscopic data for cyanohydrin **4.46b**.

$[\alpha]_D^{27}$	−36.5 (c = 0.5, $CHCl_3$).
FT-IR (ν/cm^{-1}):	3418 (br. m), 2975 (m), 2939 (m), 1656 (w), 1453 (w), 1428 (w), 1380 (m), 1328 (w), 1232 (m), 1171 (m), 1143 (m), 1117 (m), 1072 (s), 1039 (s), 1013 (m), 960 (m), 898 (m), 877 (m).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.92 (1 H, app. t, J = 1.8 Hz, =C**H**H), 4.81 (1 H, app. t, J = 1.8 Hz, =CH**H**), 4.56 (1 H, d, J = 4.0 Hz, C**H**OH), 3.96 (1 H, qd, J = 6.5, 2.7 Hz, CH_3C**H**), 3.35 (3 H, s OC**H**$_3$), 2.75 (1 H, app. dt, J = 14.3, 2.1 Hz, C**H**H), 2.71 (1 H, d, J = 4.0 Hz, O**H**), 2.36 (1 H, d, J = 14.3 Hz, CH**H**), 2.27 (1 H, qd, J = 7.0, 2.7 Hz, CH_3C**H**), 1.20 (3 H, d, J = 6.5 Hz, C**H**$_3$), 1.04 (3 H, d, J = 7.0 Hz, C**H**$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (101 MHz): 145.2 (**C**=CH_2), 117.1 (**C**N), 111.2 (C=**C**H_2), 99.1 (O**C**O), 70.8 (O**C**HCH_3), 64.7 (**C**HOHCN), 49.7 (O**C**H_3), 41.1 (CH_3**C**H), 33.5 (**C**H_2), 17.9 (**C**H_3), 11.9 (**C**H_3) ppm.
LRMS	m/z (ES^+) 234 ($[M + Na]^+$, 100%).
HRMS	m/z (ES^+) found: 234.1105, $[M + Na]^+$, $C_{11}H_{17}NNaO_3$ requires 234.1101.

Cyclohexyltrimethylsilanyloxyacetonitrile



4.51
$C_7H_{12}O$
MW = 112.17

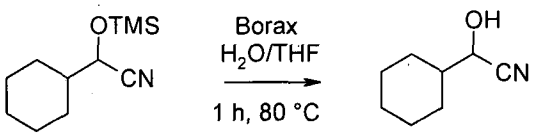
4.52
$C_{11}H_{21}NOSi$
MW = 211.38

Cyanohydrin **4.52** was prepared according to the procedure of Kim and co-workers.[124] TMSCN (0.84 mL, 6.69 mmol) was added dropwise to a stirred solution of NMO (20 mol%, 0.10 g, 0.89 mmol) and aldehyde **4.51** (0.54 g, 4.46 mmol) in CH_2Cl_2 (20 mL) at RT. After 1 h the solvent was removed *in vacuo* giving a brown oil. Purification by column chromatography (60:1-30:1 petroleum ether/diethyl ether) yielded cyanohydrin **4.52** (0.93 g, 4.40 mmol, 99%) as a colourless oil.

FT-IR (ν/cm^{-1}):	2929 (m), 2855 (m), 1452 (m), 1253 (s), 1110 (s), 1092 (m), 1070 (m), 1016 (w), 975 (w), 933 (w), 899 (m), 839 (s), 752 (m).
^{1}H NMR ($CDCl_3$)	δ_H (300 MHz): 4.15 (1 H, d, J = 6.3 Hz, C**H**CN), 2.04-1.47 (6 H, m, 3 x C**H**$_2$), 1.42-0.90 (5 H, m, C**H**, 2 x C**H**$_2$), 0.20 (9 H, s, Si(C**H**$_3$)$_3$) ppm.
^{13}C NMR ($CDCl_3$)	δ_C (75 MHz): 119.6 (**C**N), 66.7 (**C**HCN), 43.1 (**C**HCHCN), 28.3 (**C**H$_2$), 28.1 (**C**H$_2$), 26.2 (**C**H$_2$), 25.7 (2 x **C**H$_2$), −0.3 (Si(**C**H$_3$)$_3$) ppm.

Spectroscopic data consistent with literature values.[124]

Cyclohexylhydroxylacetonitrile



4.52
$C_{11}H_{21}NOSi$
MW = 211.38

4.54
$C_8H_{13}NO$
MW = 139.20

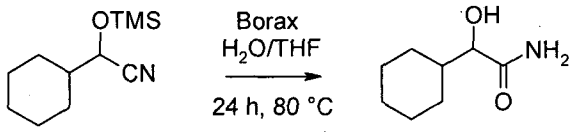
To a stirred solution of cyanohydrin **4.52** (0.05 g, 0.24 mmol) in H_2O/THF (1:1, 2 mL) was added disodium tetraborate[126] (0.09 g, 0.24 mmol). The reaction mixture was heated at 80 °C for 1 h then cooled to RT and poured into H_2O (10 mL). The aqueous phase was extracted with diethyl ether (3 x 5 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (33% diethyl ether/petroleum ether) yielded cyanohydrin **4.54** as a colourless oil (0.02 g, 0.14 mmol, 60%).

FT-IR (ν/cm^{-1}):	3422 (br. m), 2927 (s), 2855 (s), 2247 (w), 1641 (w), 1451 (s), 1312 (w), 1276 (w), 1233 (w), 1186 (w), 1143 (w), 1086 (m), 1059 (s), 1042 (s),993 (w), 970 (m), 925 (w), 894 (w), 881 (w).
^{1}H NMR ($CDCl_3$)	δ_H (400 MHz): 4.28 (1 H, t, J = 6.2 Hz, C**H**OHCN), 2.64 (1 H, d, J = 6.2 Hz, CHO**H**CN), 2.00-1.61 (6 H, m, 3 x C**H**$_2$), 1.40-1.00 (5 H, m, 2 x C**H**$_2$, C**H**) ppm.

^{13}C NMR (CDCl$_3$)	δ_C (101 MHz): 119.4 (**C**N), 66.6 (**C**HOH), 42.5 (**C**HCHOH), 28.3 (**C**H$_2$), 28.0 (**C**H$_2$), 26.1 (**C**H$_2$), 25.6 (2 x **C**H$_2$) ppm.

Spectroscopic data consistent with literature values.[124]

2-Cyclohexyl-2-hydroxyacetamide



4.52
$C_{11}H_{21}NOSi$
MW = 211.38

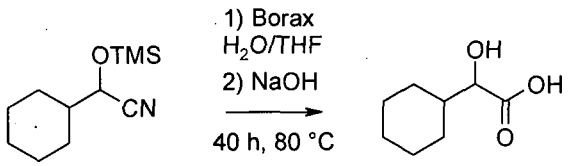
4.55
$C_8H_{15}NO_2$
MW = 157.21

To a stirred solution of cyanohydrin **4.52** (0.10 g, 0.47 mmol) in H$_2$O/THF (1:1, 4 mL) was added disodium tetraborate[126] (0.36 g, 0.95 mmol). The reaction mixture was heated at 80 °C for 24 h then cooled to RT and poured into H$_2$O (10 mL). The aqueous phase was extracted with diethyl ether (3 x 5 mL), then the combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by column chromatography (6% MeOH/CH$_2$Cl$_2$) yielded amide **4.55** (0.07 g, 0.44 mmol, 94%) as a white crystalline solid.

m.p.	145-147 °C (lit.[135] m.p. = 139-142 °C).
FT-IR (ν/cm^{-1}):	2931 (s), 2853 (m), 2577 (m), 2531 (m), 2413 (m), 1611 (s), 1449 (s), 1340 (w), 1106 (s), 1087 (m), 1055 (w), 1015 (w), 995 (m), 960 (w), 909 (m), 826 (w), 742 (w).
^{1}H NMR (MeOD)	δ_H (400 MHz): 3.81 (1 H, d, J = 3.6 Hz, OC**H**), 1.90-1.47 (6 H, m, 3 x C**H**$_2$), 1.44-1.04 (5 H, m, 2 x C**H**$_2$, C**H**) ppm.
^{13}C NMR (MeOD)	δ_C (101 MHz): 179.9 (**C**=O), 76.9 (**C**HOH), 42.9 (**C**H), 30.7 (**C**H$_2$), 27.6 (**C**H$_2$), 27.4 (**C**H$_2$), 27.3 (2 x **C**H$_2$) ppm.

Spectroscopic data consistent with literature values.[135]

Cyclohexylhydroxyacetic acid



4.52
$C_{11}H_{21}NOSi$
MW = 211.38

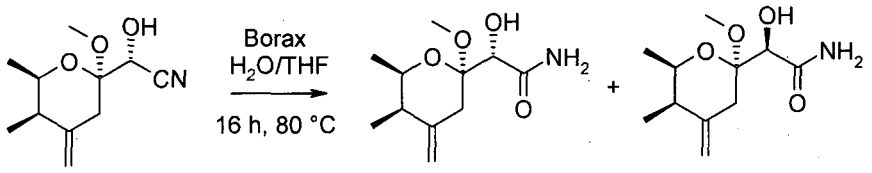
4.56
$C_8H_{14}O_3$
MW = 158.20

To a stirred solution of cyanohydrin **4.52** (0.10 g, 0.47 mmol) in H_2O/THF (1:1, 4 mL) was added disodium tetraborate[126] (0.36 g, 0.95 mmol). The reaction mixture was heated at 80 °C for 16 h then cooled to RT. NaOH (aq) (3M, 0.64 mL, 1.90 mmol) was added and the solution heated at 80 °C for 24 h. After cooling to RT the reaction mixture was poured into H_2O (5 mL). The organic phase was washed with HCl (2M, 10 mL), then the aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* yielding a white solid. Purification by column chromatography (10% MeOH/CH_2Cl_2) gave acid **4.56** (0.07 g, 0.44 mmol, 94%) as a white crystalline solid.

m.p.	140-142 °C (lit.[136] m.p. = 139-142 °C).
FT-IR (ν/cm^{-1}):	3197 (br. w), 2927 (s), 2855 (m), 1792 (s), 1452 (m), 1322 (w), 1284 (m), 1266 (s), 1240 (s), 1124 (m), 1090 (m), 1044 (m), 1033 (w), 1020 (m), 965 (m), 941 (w), 914 (w), 895 (w), 850 (w), 816 (m).
^{1}H NMR ($CO(CD_3)_2$)	δ_H (400 MHz): 3.96 (1 H, d, J = 3.8 Hz, CHO**H**), 3.04 (1 H, br. s, CO_2**H**), 1.85-1.46 (6 H, m, 3 x C**H**$_2$), 1.39-1.03 (5 H, m, 2 x C**H**$_2$, C**H**) ppm.
^{13}C NMR ($CO(CD_3)_2$)	δ_C (101 MHz): 175.7 (**C**O_2H), 75.3 (**C**HOH), 42.7 (**C**HCHOH), 27.4 (**C**H$_2$), 27.1 (**C**H$_2$), 27.0 (**C**H$_2$), 26.9 (2 x **C**H$_2$) ppm.

Spectroscopic data consistent with literature values.[136]

(*S*)-2-Hydroxy-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-acetamide (4.57a) & (*R*)-2-hydroxy-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-acetamide (4.57b)



4.46a
$C_{14}H_{25}NO_3Si$
MW = 283.45

4.57a
$C_{11}H_{19}NO_4$
MW = 229.38

4.57b
$C_{11}H_{19}NO_4$
MW = 229.38

To a stirred solution of cyanohydrin **4.46a** (8 mg, 0.028 mmol) in H_2O/THF (1:1, 1 mL) was added disodium tetraborate[126] (22 mg, 0.056 mmol). The reaction mixture was heated to 80 °C for 16 h then cooled to RT and poured into H_2O (5 mL). The aqueous phase was extracted with diethyl ether (3 x 3 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (4% MeOH/CH_2Cl_2) yielded an inseparable 1:1 mixture of **4.57a** and **4.57b** (3 mg, 0.013 mmol, 47%) as a colourless oil.

FT-IR (ν/cm^{-1}): 3450 (br. m), 2921 (s), 2851 (m), 1681 (s), 1592 (w), 1454 (m), 1377 (m), 1323 (m), 1261 (m), 1227 (w), 1171 (w), 1138 (m), 1073 (s), 1041 (s), 1012 (s), 923 (w), 890 (m), 750 (m), 721 (w).

^{1}H NMR ($CDCl_3$): δ_H (400 MHz): 6.79 (1 H + 1 H, br. s, 2 x N**H**H), 5.68 (1 H, br. s, NH**H**), 5.56 5.68 (1 H, br. s, NH**H**), 4.87 (1 H + 1 H, app. t, J = 1.9 Hz, 2 x C=C**H**H), 4.76 (1 H + 1 H, app. t, J = 1.9 Hz, 2 x C=CH**H**), 4.27 (1 H, d, J = 3.4 Hz, C**H**OH), 4.19 (1 H, d, J = 3.2 Hz, C**H**OH), 4.05 (1 H, qd, J = 6.7, 2.8 Hz, OC**H**CH$_3$), 4.01 (1 H, qd, J = 6.6, 2.6 Hz, OC**H**CH$_3$), 3.89 (1 H, d, J = 3.4 Hz, CHO**H**), 3.64 (1 H, d, J = 3.2 Hz, CHO**H**), 3.36 (3 H, s, OC**H**$_3$), 3.34 (3 H, s, OC**H**$_3$), 2.62 (1 H, app. dt, J = 14.4, 2.3 Hz, C**H**H), 2.40-2.23 (2 H + 2 H, m, 2 x CH$_3$C**H**, 2 x CH**H**), 2.21-2.19 (1 H, m, C**H**H), 1.26 (3 H, d, J = 6.6 Hz, C**H**$_3$), 1.19 (3 H, d, J = 6.7 Hz, C**H**$_3$), 1.05 (3 H, d, J = 7.0 Hz, C**H**$_3$), 0.98 (3 H, d, J = 7.1 Hz, C**H**$_3$) ppm.

Additional signals in the ^{1}H NMR spectrum were attributed to traces of petroleum ether and CH_2Cl_2.

^{13}C NMR ($CDCl_3$) δ_C (101 MHz): unseen (2 x **C**ONH_2), 145.4 (2 x **C**OCH_3), 111.1 (C=**C**H_2), 110.5 (C=**C**H_2), 100.2 (**C**=CH_2), 100.1 (**C**=CH_2), 72.4 (O**C**HCH_3), 70.5 (O**C**HCH_3), 69.8 (**C**HOH), 69.6 (**C**HOH), 49.9 (O**C**H_3), 48.6 (O**C**H_3), 41.6 (CH_3**C**H), 41.4 (CH_3**C**H), 29.7 (**C**H_2), 29.6 (**C**H_2), 18.2 (**C**H_3), 18.1 (**C**H_3), 12.3 (**C**H_3), 12.0 (**C**H_3) ppm.

LRMS m/z (CI) 198 ($[M - MeOH]^+$, 56%), 180 (38), 153 (100), 135 (10), 123 (16), 107 (14), 95 (18), 81 (38), 67 (20), 55 (14), 41 (30).

HRMS m/z (ES^+) found: 252.3228, $[M + Na]^+$, $C_{11}H_{19}NNaO_4$ requires 252.3117.

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Appendix

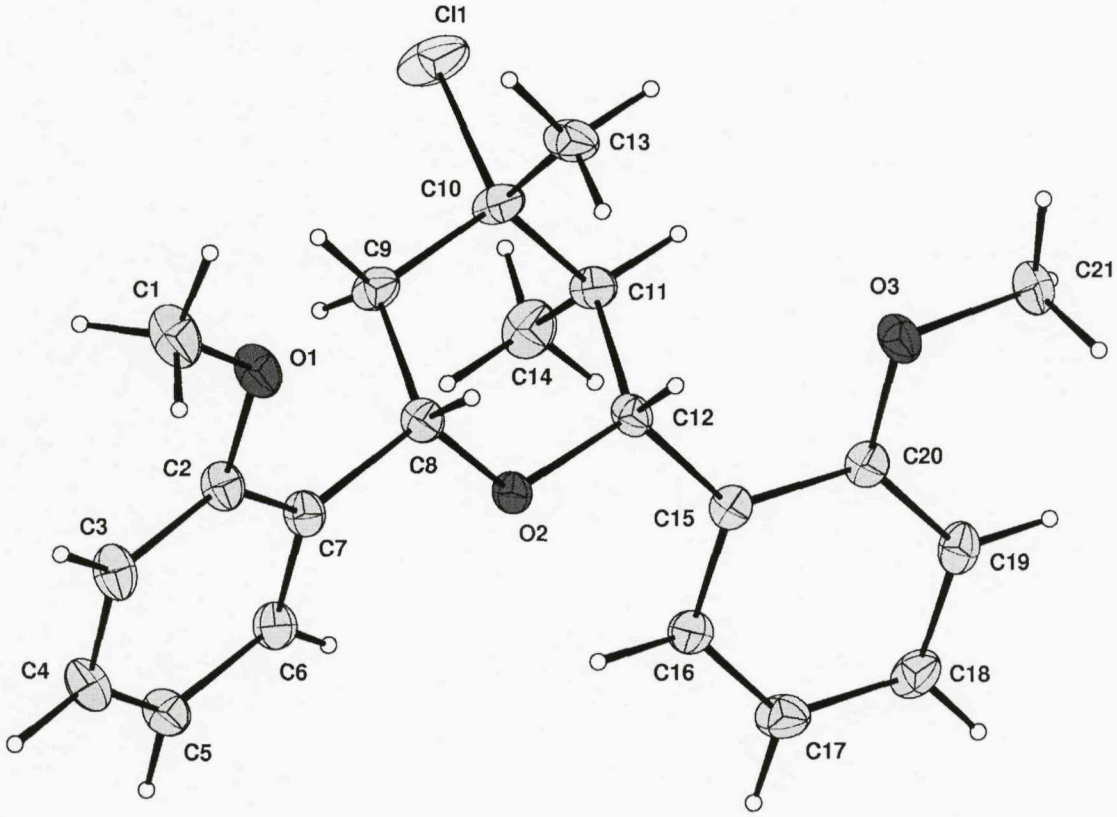
Crystal structure data for compound 2.51.

Table 1. Crystal data and structure refinement details.

Identification code	**2005sot1412 (SCR/4395/59/1)**
Empirical formula	$C_{21}H_{25}ClO_3$
Formula weight	360.86
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*C2/c*
Unit cell dimensions	a = 18.9809(8) Å
	b = 8.2916(2) Å β =97.533(2)°
	c = 23.8378(10) Å
Volume	3719.3(2) Å^3
Z	8
Density (calculated)	1.289 Mg / m^3
Absorption coefficient	0.222 mm^{-1}
F(000)	1536
Crystal	Needle; Colourless
Crystal size	0.25 × 0.03 × 0.03 mm^3
θ range for data collection	2.94 – 27.48°
Index ranges	$-24 \le h \le 24$, $-10 \le k \le 10$, $-30 \le l \le 30$
Reflections collected	25303
Independent reflections	4272 [R_{int} = 0.0747]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9934 and 0.9366
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4272 / 0 / 230
Goodness-of-fit on F^2	1.048
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0652, *wR2* = 0.1564
R indices (all data)	*R1* = 0.1072, *wR2* = 0.1754
Largest diff. peak and hole	0.749 and –0.616 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	–2144(2)	6402(4)	1773(2)	46(1)	1
C14	1683(2)	7598(4)	1448(1)	45(1)	1
C2	–1301(1)	8542(3)	1752(1)	30(1)	1
C3	–1704(2)	9585(3)	2037(1)	35(1)	1
C4	–1452(2)	11126(4)	2169(1)	36(1)	1
C5	–809(2)	11634(3)	2024(1)	33(1)	1
C6	–412(1)	10586(3)	1734(1)	31(1)	1
C7	–649(1)	9048(3)	1595(1)	28(1)	1
C8	–234(1)	7908(3)	1269(1)	28(1)	1
C9	164(1)	6627(3)	1657(1)	31(1)	1
C10	624(1)	5592(3)	1321(1)	33(1)	1
C11	1127(1)	6674(3)	1030(1)	31(1)	1
C12	654(1)	7884(3)	657(1)	26(1)	1
C13	194(2)	4448(3)	912(1)	39(1)	1
C15	1077(1)	9004(3)	324(1)	26(1)	1
C16	1143(2)	10625(3)	450(1)	32(1)	1
C17	1524(2)	11648(3)	138(1)	37(1)	1
C18	1834(2)	11028(3)	–306(1)	37(1)	1
C19	1781(1)	9403(3)	–441(1)	33(1)	1
C20	1402(1)	8395(3)	–125(1)	28(1)	1
C21	1663(2)	6075(3)	–660(1)	36(1)	1
O1	–1496(1)	6989(2)	1607(1)	36(1)	1
O2	262(1)	8850(2)	1003(1)	27(1)	1
O3	1314(1)	6773(2)	–224(1)	35(1)	1
Cl1	1159(1)	4277(1)	1831(1)	56(1)	1



Thermal ellipsoids drawn at the 35% probability level.

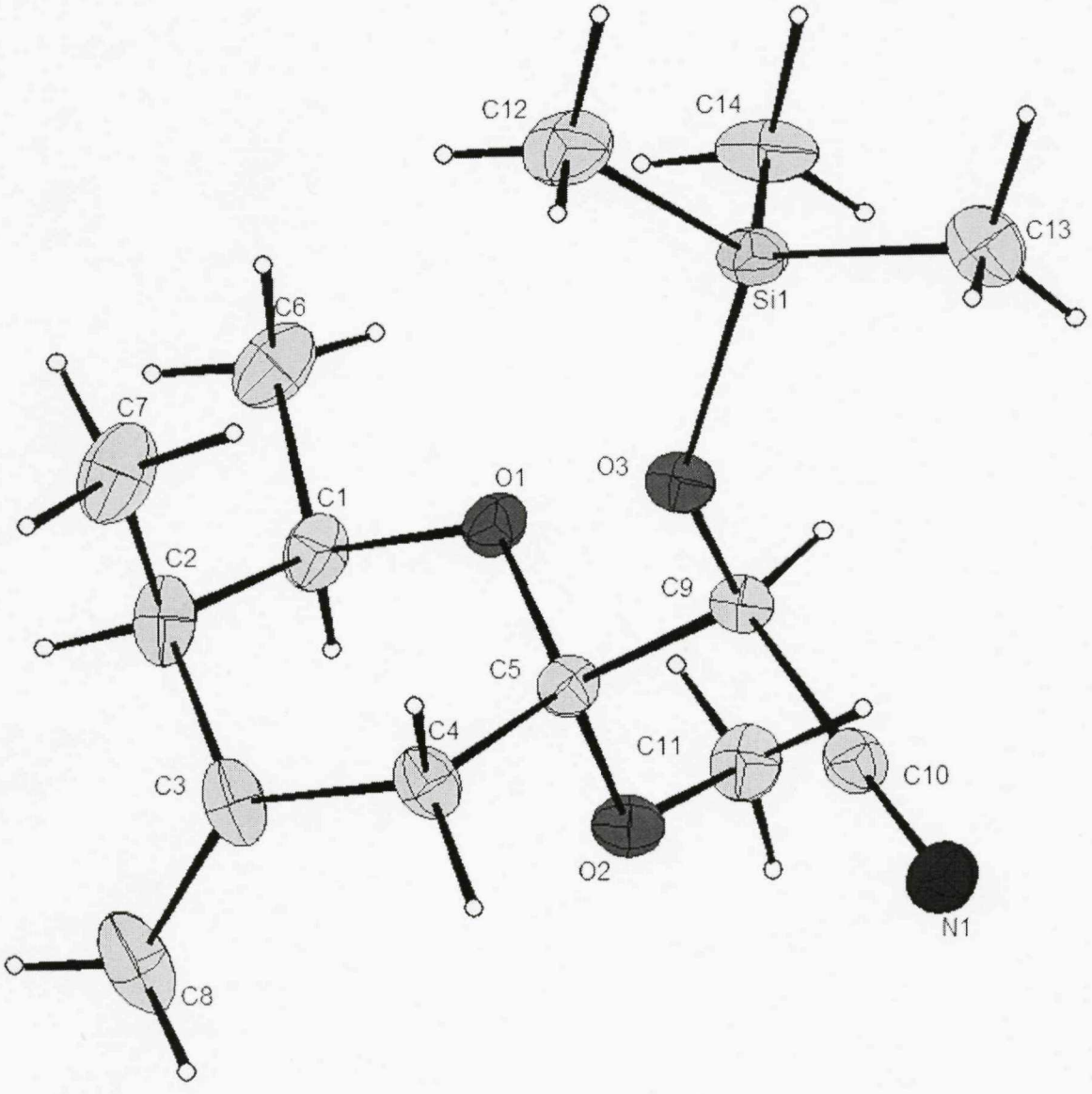
Crystal structure data for compound 4.30b.

Table 1. Crystal data and structure refinement.

Identification code	**2007sot1049**	
Empirical formula	$C_{14}H_{25}NO_3Si$	
Formula weight	283.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 7.9853(3) Å	α=94.357(2)°
	b = 8.1232(4) Å	
	β=100.072(2)°	
	c = 13.5392(6) Å	γ=105.729(2)°
Volume	825.24(6) Å^3	
Z	2	
Density (calculated)	1.141 Mg / m^3	
Absorption coefficient	0.146 mm^{-1}	
F(000)	308	
Crystal	Block; Colourless	
Crystal size	0.14 × 0.10 × 0.06 mm^3	
θ range for data collection	3.18 – 27.48°	
Index ranges	$-10 \le h \le 10$, $-10 \le k \le 10$, $-17 \le l \le 17$	
Reflections collected	13668	
Independent reflections	3767 [R_{int} = 0.0542]	
Completeness to θ = 27.48°	99.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9913 and 0.9798	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3767 / 0 / 178	
Goodness-of-fit on F^2	1.114	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0636, *wR2* = 0.1119	
R indices (all data)	*R1* = 0.0894, *wR2* = 0.1240	
Largest diff. peak and hole	0.268 and –0.274 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.*
Si1	5735(1)	3973(1)	2078(1)	23(1)	1
O1	1839(2)	512(2)	2291(1)	22(1)	1
O2	1835(2)	−2114(2)	1434(1)	23(1)	1
O3	5409(2)	1909(2)	2277(1)	21(1)	1
N1	6169(3)	−1315(3)	894(2)	29(1)	1
C1	510(3)	−117(3)	2888(2)	25(1)	1
C2	1409(3)	−454(4)	3914(2)	31(1)	1
C3	2391(3)	−1753(3)	3723(2)	28(1)	1
C4	3689(3)	−1202(3)	3042(2)	24(1)	1
C5	2846(3)	−606(3)	2094(2)	20(1)	1
C6	−462(3)	1240(4)	2932(2)	34(1)	1
C7	2640(4)	1189(4)	4568(2)	39(1)	1
C8	2126(4)	−3230(4)	4100(2)	43(1)	1
C9	4264(3)	514(3)	1584(2)	19(1)	1
C10	5321(3)	−545(3)	1193(2)	21(1)	1
C11	738(3)	−1883(3)	536(2)	26(1)	1
C12	6623(4)	5182(3)	3364(2)	36(1)	1
C13	7395(4)	4536(4)	1276(2)	40(1)	1
C14	3600(4)	4285(3)	1471(2)	35(1)	1



N.B. As well as the configuration shown (C1, C2, C5 = R, C9 = S), the crystal structure also contains the opposite enantiomer (C1, C2, C5 = S, C9 = R) and thus is a racemic mixture. This is the only other enantiomer present in this structure.