UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

School of Chemistry

Synthesis of the Pedamide Fragment of Onnamide F

By

William John Buffham

Thesis submitted for the degree of Doctor of Philosophy

June 2008

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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SYNTHESIS OF THE PEDAMIDE FRAGMENT OF ONNAMIDE F

By William John Buffham

This thesis is concerned with the synthesis of two key fragments of onnamide F, a marine natural product isolated from the sponge *Trachycladus laevispirulifer*. Onnamide F has been shown to be a particularly potent inhibitor of fungal growth and the development of parasitic larvae.

Onnamide F has not been synthesised previously, but synthetic approaches to the structurally related natural products pederin, mycalamides A and B, theopederin D, onnamide A and psymberin / irciniastatin A are discussed in Chapter 1.

Chapter 2 details a racemic synthesis of the central tetrahydropyran fragment of onnamide F. The realisation of an asymmetric synthesis of the pedamide fragment based on the aforementioned synthesis is described in Chapter 3. Details of key ring-hydroxylation, expansion and cyclisation reactions are presented, including discussion of the influence of internal steric and kinetic factors on their stereochemical course.

Optimisation of the key cyclisation reaction that delivers the required functionalised THP system proved challenging and required modification of the original synthetic target. This work, and synthesis of a key conjugated diene fragment are discussed in Chapter 4. Some initial research towards a formal synthesis of the related natural product psymberin is described in Chapter 5.

List of Contents

Authors Declaration

The research described in this thesis was carried out under the supervision of Prof. D. C. Harrowven at the University of Southampton between October 2004 and October 2007. No part of this thesis has previously been submitted for a degree.

Acknowledgements

Top of the list for a "thank you" is my supervisor, Professor David Harrowven for his constant advice, support, interest and for never being too busy to talk about a problem. Thank you also to David and his family for the Christmas parties and socials at their home over the years!

Second mention goes to my housemates: Jon, Iain and Paul. It's been really fun living with you guys these last few years even if the house was occasionally disgusting. The fact that we still talk about past nights out and remember the venues long gone reminds me that we'll always stay mates!

Massive thanks to past and present inhabitants of Lab 30:3007 – Sally, Simon, Philip, Stephen, Lana, Dave, Ian, Sarah and Kerri. Thank you all for being such good mates, we've always had fun both in and out of work and I've really enjoyed working with you. Especially big thanks to Sally and Simon for being great friends with me throughout our three years and to Philip and Stephen for being generally entertaining!

People that don't fall in to those categories but also need thanking are George, Louise, Helen, Martin and Laura for being my friends for years, Mishal for talking constantly and Allison for being the Hydrogen Lady and sorting Jon out! I'm really going to miss Wednesday dinners, I'll have to find some new people to feed me. Plus, people kept raising the bar every week, there should have been a limit on cost and time.

A huge thanks to Dr. Nigel Swain at Pfizer for his advice and help throughout my PhD. Another thank you to all there who looked after me during my CASE placement and showed me the pubs in Canterbury, especially Alex G, Martin and Lesa but also Kate, Alex H, Denise, Steven, Fran and Sarah. I also need to thank Dr. Richard Brown at Southampton for providing me with both a different perspective on my research and advice when things weren't working. Thank you also to Dr. Jeremy Hinks, who taught me the basics of practical organic chemistry as an undergraduate and thanks to the undergrads who have made the last three years entertaining at times as well!

Also thank you to Joan Street and Neil Wells for the NMR service, John Langley and Julie Herniman for the mass spec service and Mark Light for running my X-ray samples. Thanks to Karl, Graham, Tony and Pat for running stores and the tea room.

Finally, I think my family deserve a really big thank you for supporting me in my decisions and always being there to listen when things are bad.

William Buffham.
June 2008.

Abbreviations

Ac	Acetyl
Am	Amyl
amu	Atomic mass units
Ar	Aryl (unless defined)
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOC-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
bp	Boiling point
Bu	Butyl
Bz	Benzoyl
CDI	Carbonyldiimidazole
Celite®	Diatomaceous earth
CHN	Carbon, hydrogen, nitrogen elemental analysis
CI	Chemical ionisation
Conc	Concentrated
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	Diastereomeric excess
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2PYR$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DHQ-PHN	Hydroquinine-9-phenanthryl ether
$(DHQ)_2PYR$	Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL, DIBAL-H	Di*iso*butylaluminium hydride
DIPT	Di*iso*propyltartrate
DMAP	4-Dimethylaminopyridine

DMDO	Dimethyldioxirane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*'-Dimethyl-*N*,*N*'-propylene urea
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
EI	Electron ionisation
Equiv	Equivalents
ES	Electrospray
Et	Ethyl
Ether	Diethyl ether
FT	Fourier transform
GC	Gas chromatography
h	Hours
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HRMS	High resolution mass spectrum
Ipc	*iso*pinocampheyl
IR	Infra-red
J	NMR coupling constant
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium di*iso*propylamide
LiHMDS	Lithium hexamethyldisilazide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LRMS	Low resolution mass spectrum
*m*CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
min	Minutes
MOM	Methoxymethyl

MoOPD	Oxidoperoxymolybdenum(pyridine)(DMPU), MoO_5.Py.DMPU
MoOPH	Oxidoperoxymolybdenum(pyridine)(HMPA), MoO_5.Py.HMPA
mp	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
n.O.e.	Nuclear Overhauser effect
Oxone®	DuPont product, potassium peroxymonosulfate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Petrol	Petroleum ether, bp 40-60°C
Ph	Phenyl
PMB	*para*-Methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium-*para*-toluene sulfonate
Pr	Propyl
Py	Pyridine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
R	Alkyl (unless defined)
Rac	Racemic
RT	Room temperature
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBAOH	Tetra-*n*-butylammonium hydroxide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCCA	Trichloro*iso*cyanuric acid
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TES	Triethylsilyl

Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
tfc	3-(Trifluoromethylhydroxymethylene)-(+)-camphorate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Tri*iso*propylsilyl
TMS	Trimethylsilyl
Tol	*p*-Tolyl
TPAP	Tetra-*n*-propylammonium perruthate
Trityl	Triphenylmethyl
Troc	Trichloroethyloxycarbonyl
Ts	Toluenesulfonyl

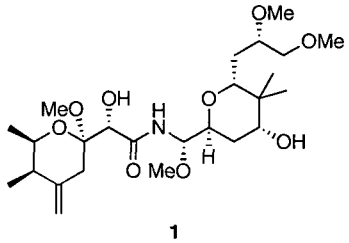
Chapter 1 Introduction

Marine organisms are often a valuable source of complex natural products with multiple stereogenic centres and an array of functional groups. Organisms that produce these compounds include plants such as algae and phytoplankton, and animals such as molluscs, sponges and corals. There are many new marine natural products discovered and described each year, with 656 new compounds identified in 2003 and a similar number for other recent years.[1]

1.1 The Pederin Class of Natural Products

1.1.1 Pederin

Several compounds with related structures have been isolated from both marine and land-based sources, such as the onnamides, mycalamides, theopederins, icadamides, irciniastatins, psymberin and pederin. The first of these to be isolated was pederin (**1**), found in beetles of the genus *Paederus*, which exploit its potent toxicity as a chemical defence.[2-4] Pederin causes inflammation and blistering of the skin and is also active against human cancer cell lines, prompting studies towards its total synthesis.[5]



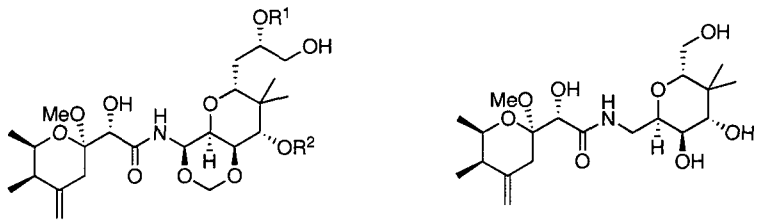
1

Figure 1.1.1: Pederin

The mycalamides, onnamides, theopederins and icadamides are all isolated from marine sponges of various genera. Since they are structurally similar to pederin, it has been suggested that the biosynthesis of these compounds is due to symbiotic bacteria rather than biosynthesis by the organism itself.[6]

1.1.2 Mycalamides A – D

Mycalamide A (**2**) was isolated from a sponge of the genus *Mycale* collected from a reef in New Zealand. Before purification was complete, the sponge extract mixture was tested and shown to possess strong *in vivo* antiviral activity. The pure natural product also demonstrated strong activity *in vitro* against herpes simplex and polio viruses.[7] Mycalamide B (**3**, also from *Mycale*) and mycalamide D (**5**, from *Stylinos* and *Mycale*) have very similar structures to mycalamide A and similar antiviral activity.[8,9]



2 R^1 = H, R^2 = Me
3 R^1 = R^2 = Me
5 R^1 = R^2 = H

4

Figure 1.1.2: Mycalamides A – D

Mycalamide C (**4**, from *Stylinos*) lacks the acetal present in mycalamides A, B and D and has a simpler side chain, but is otherwise similar. Mycalamide C (**4**) also possesses some cytotoxic activity.[9] Since the mycalamides have exhibited protein synthesis inhibition characteristics, in common with pederin and some onnamides, they may be useful antibiotic compounds.[8]

1.1.3 Theopederins A – L

Theopederins A – J (**6 – 11**, **14 – 17**) have been isolated from a species of *Theonella* sponge from Japan and show a strong resemblance to both the onnamides and mycalamides.[10,11] Theopederins K and L (**12**, **13**) were collected from a *Discodermia* sponge in Honduras and introduce new side chain structures to the class.[12] All theopederins displayed cytotoxic activity against tumour cell lines *in vitro* and some also showed antimicrobial properties.

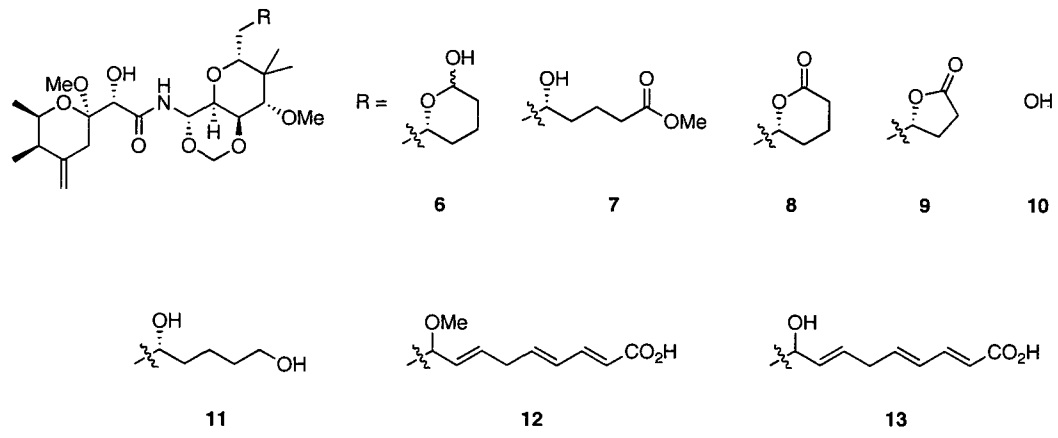


*Figure 1.1.3: Theopederins A – F (**6 – 11**) and K – L (**12, 13**).*

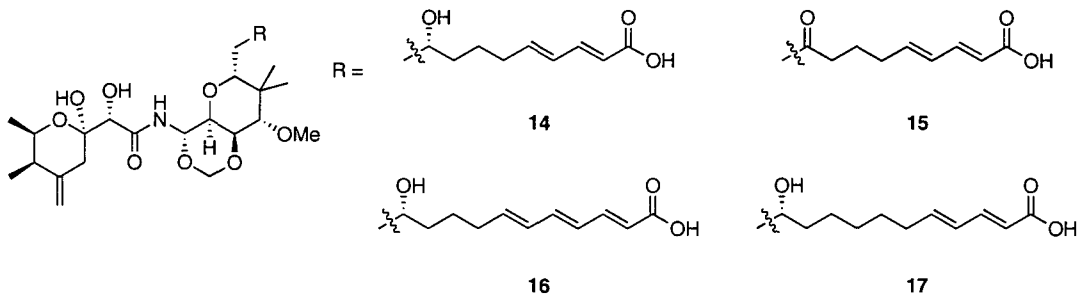


*Figure 1.1.4: Theopederins G – J (**14 – 17**).*

1.1.4 Icadamides A – C

Icadamides A (**18**) and B (**19**) have been isolated from the sponge *Leiosella* and were active against human colon cancer cells *in vitro*. Both compounds were also active against leukaemia and lung tumours *in vivo*.[13] Icadamide C (**20**) was recently isolated from the *Discodermia calyx* sponge and contains structural features common to both the theopederins and onnamides, particularly onnamide A (**25**).[14]

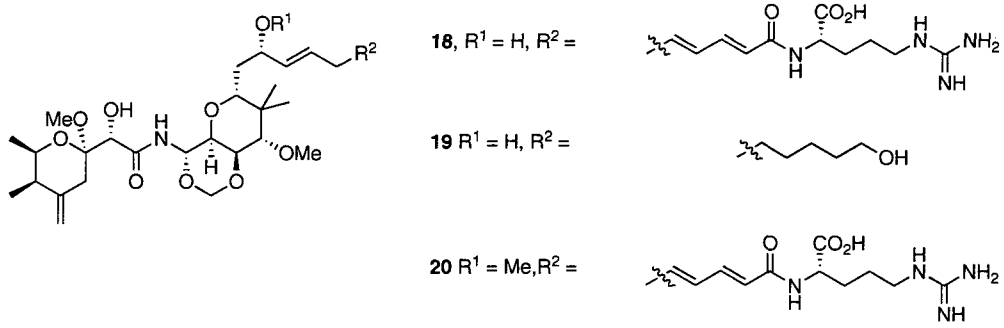


Figure 1.1.5: Icadamides A – C.

1.1.5 Psymberin and Irciniastatin

Psymberin (**21**) and irciniastatins A (**22**) and B (**23**) are natural products isolated from the sponges *Psammocinia* and *Ircinia ramose* respectively. Psymberin and irciniastatin A share a tetrahydropyran fragment common to many members of the pederin class of natural products (Figure 1.1.6).[15,16] Upon synthesis of the natural products, it was suggested that structures **21** and **22** are in fact the same compound (**24**).[17]

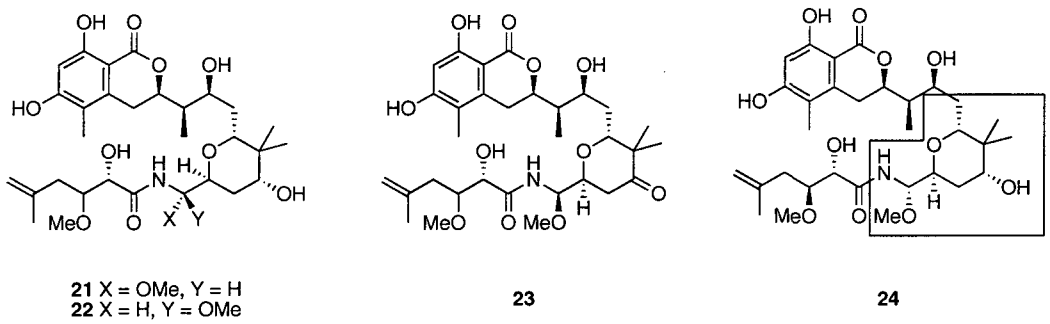


*Figure 1.1.6: Psymberin (**21**) and irciniastatins A (**22**) and B (**23**) as originally identified, together with their corrected common structure, **24**. The THP targeted in this thesis is highlighted.*

Psymberin (**24**) proved to be active against several human cancer cell lines, particularly selected colon, melanoma and breast cancers. Both psymberin (**24**) and irciniastatin B (**23**) were also active against human cancer cell lines with psymberin displaying potency against lung cancer and leukaemia and irciniastatin B being more potent against pancreas, breast and central nervous system cancer cell lines. Psymberin (**24**) also displayed some very weak antimicrobial and antibacterial activity.[15,16]

1.1.6 Onnamides A – E

Onnamide A (**25**) was isolated from a species of the sponge *Theonella* and has been shown to possess potent antiviral activity against herpes simplex, vesicular stomatitis virus and coronavirus.[18] Also isolated from a sponge of the same genus were onnamides B (**26**), C (**27**), D (**28**) and E (**29**).[19]

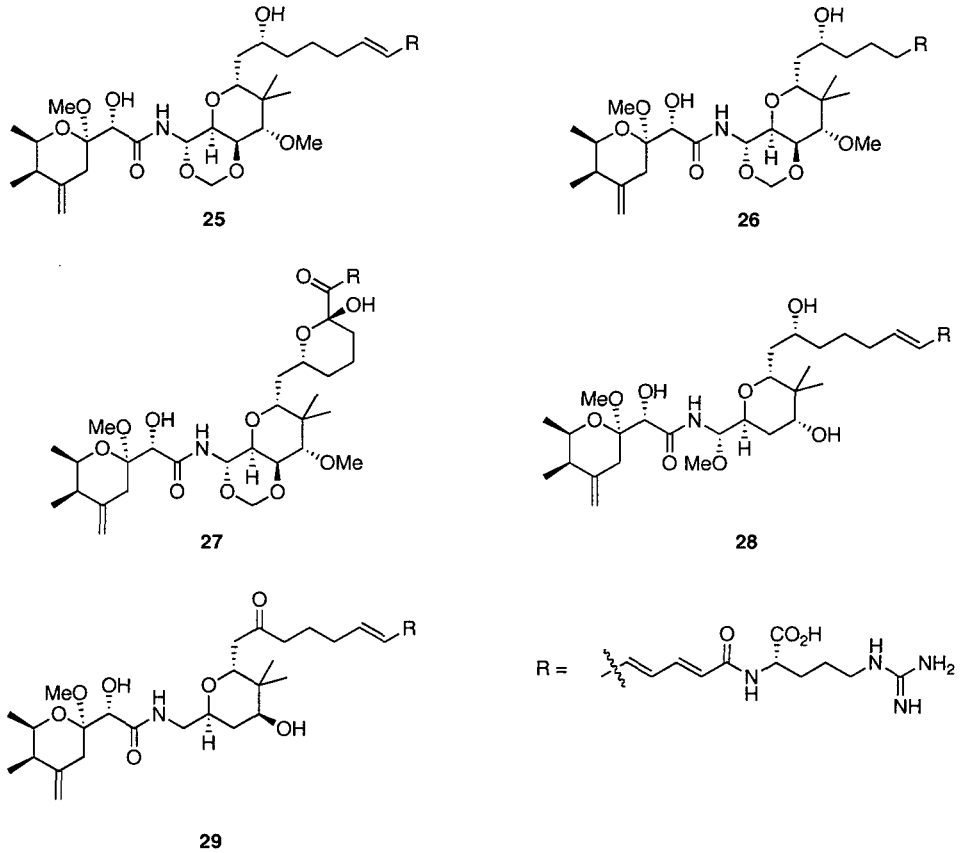
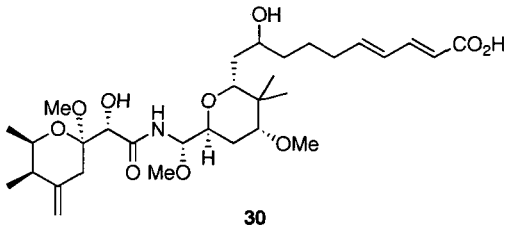


Figure 1.1.7: Onnamides A - E

1.1.7 Onnamide F

All of these compounds display potent cytotoxicity against cancer cells *in vitro*, increasing interest in their total synthesis.[19] A related structure is onnamide F, the synthetic target of this work. Onnamide F (**30**) was isolated from the sponge *Trachycladus laevispirulifer*, found on the south coast of Australia. It shares many structural features with the other onnamides, particularly onnamide D (**28**).[20] It also has a side chain of the type present in theopederin G (**14**).



30

Figure 1.18: Onnamide F.

The discovering authors were unable to determine the stereochemistry of the side chain alcohol, which may be answered by its total synthesis. A biological assay showed onnamide F to be a potent inhibitor of both the development of parasitic nematode larvae and fungal growth. Interestingly, a simple analogue prepared by esterification of the acid functionality was a more potent inhibitor in the nematode assay.

1.2 Disconnection Strategy

The disconnection strategy adopted in this study is outlined in Figure 1.2.1. Disconnection of the central amide bond and removal of the unsaturated side chain leaves three synthetic targets (**32**, **36** and **37**), allowing for convergent synthesis. This work concentrates on synthesis of the central tetrahydropyran ring (**37**) and the unsaturated side chain (**32**).

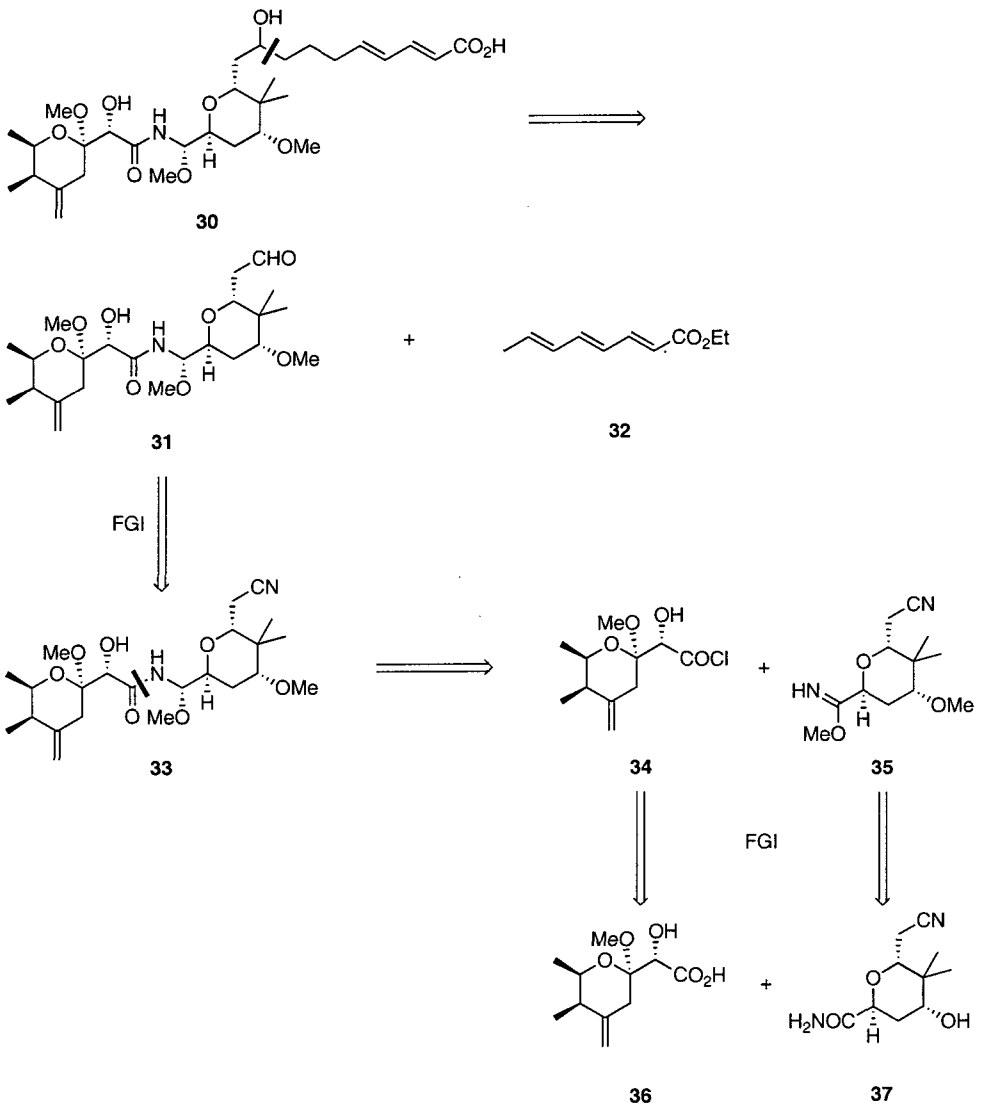


Figure 1.2.1: Disconnection strategy for onnamide F.

Fragments **36** and **37** will be joined by reaction of acid chloride **34** with imidate **35**. An *in situ* reduction would introduce the required stereochemistry of the central

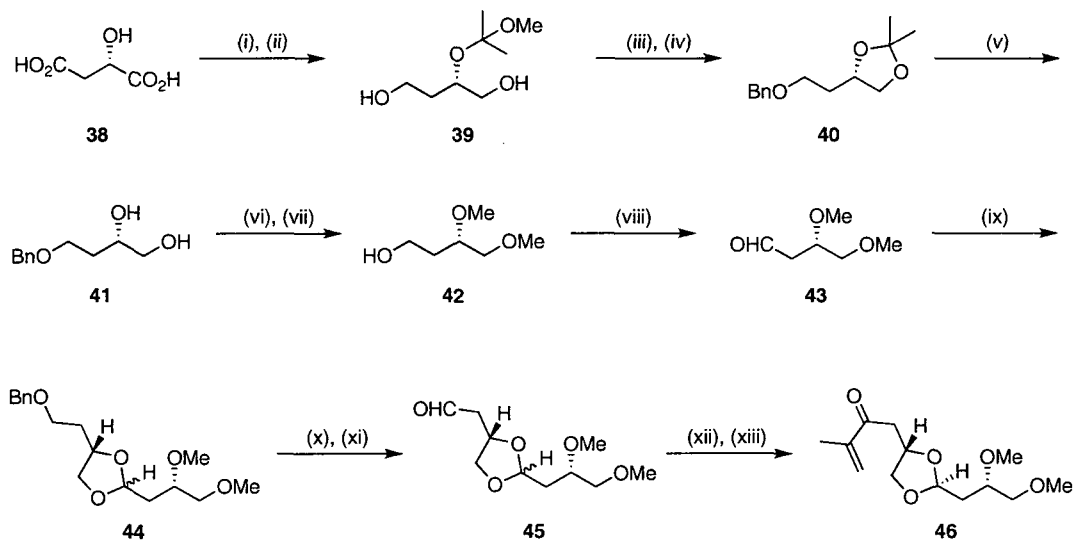
methyl ether.[21] The unsaturated side chain **32** would be attached via an aldol condensation with addition of a bulky aluminium complex to control the regioselectivity.[22] The triene would then be converted into a diene by hydrogenation in the presence of Wilkinson's catalyst.

1.3 Previous Syntheses

Onnamide F has not been synthesised previously, but total syntheses of pederin, mycalamides A and B, theopederin D, onnamide A and psymberin / irciniastatin A have been completed. Numerous approaches to the pederic acid fragment **36** have also been published.[23-30]

1.3.1 Aldol

Kocienski's first total synthesis of pederin used an intramolecular Mukaiyama aldol condensation as a key step in the construction of tetrahydropyran ring **50**. Following known[31] protecting steps (i) to (iii), (*S*)-malic acid (**38**) was efficiently transformed into the key compound **41**, which was used twice in the synthesis of advanced fragment **46** (Scheme 1.3.1).[32,33]

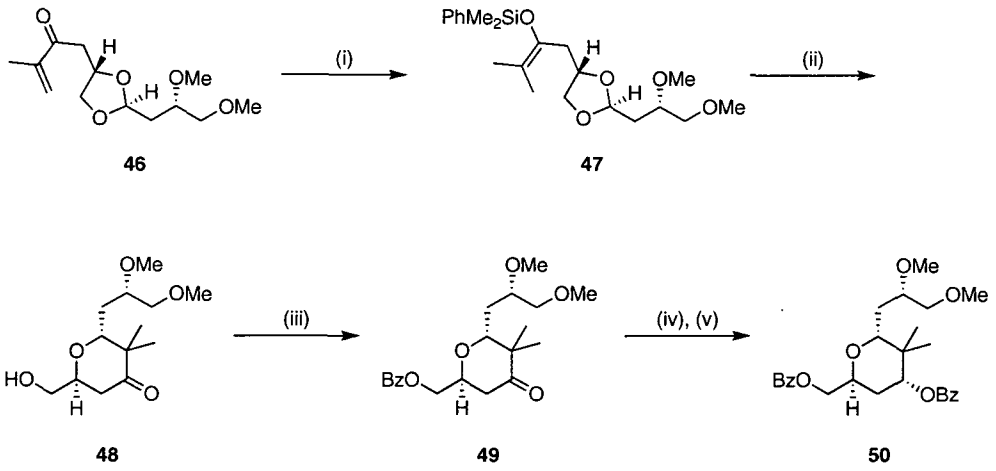


*Scheme 1.3.1: Synthesis of Mukaiyama aldol precursor **46**.*

Reagents and Conditions: (i) 2-methoxypropene, $POCl_3$, RT. (ii) $LiAlH_4$, THF, reflux. (iii) $BF_3.OEt_2$, Et_2O, RT. (steps i-iii [31]) (iv) BnBr, NaH, NaI, THF, RT, 88%. (v) HCl (2 M), THF, reflux, 100%. (vi) MeI, NaH, THF, RT, 93%. (vii) H_2, Pd / C, EtOH, RT, 96%. (viii) Swern oxidation, 98%. (ix) **41**, *p*-TsOH, $MgSO_4$, CH_2Cl_2, RT, 66%. (x) Na / NH_3 (l), Et_2O, –78 °C, 88%. (xi) PCC, CH_2Cl_2, RT, 50%. (xii) $H_2C{=}C(CH_3)MgBr$, THF, 0 °C, 88%. (xiii) PCC, CH_2Cl_2, RT, 54%.

The key step involved formation of silyl enol ether **47**, which upon treatment with $TiCl_4$ underwent a Mukaiyama aldol condensation reaction to give **48** (Scheme

1.3.2).[32] Ketone **48** was advanced to **50** by a protection, reduction and protection sequence, but unfortunately reduction of ketone **49** gave a 1:1 mixture of the corresponding diastereomeric alcohols. The diastereoselectivity of the aldol condensation also favoured the undesired product, so Kocienski reported a modified synthesis of **50** in 1984 which addressed some of the problems.[32,34,35]



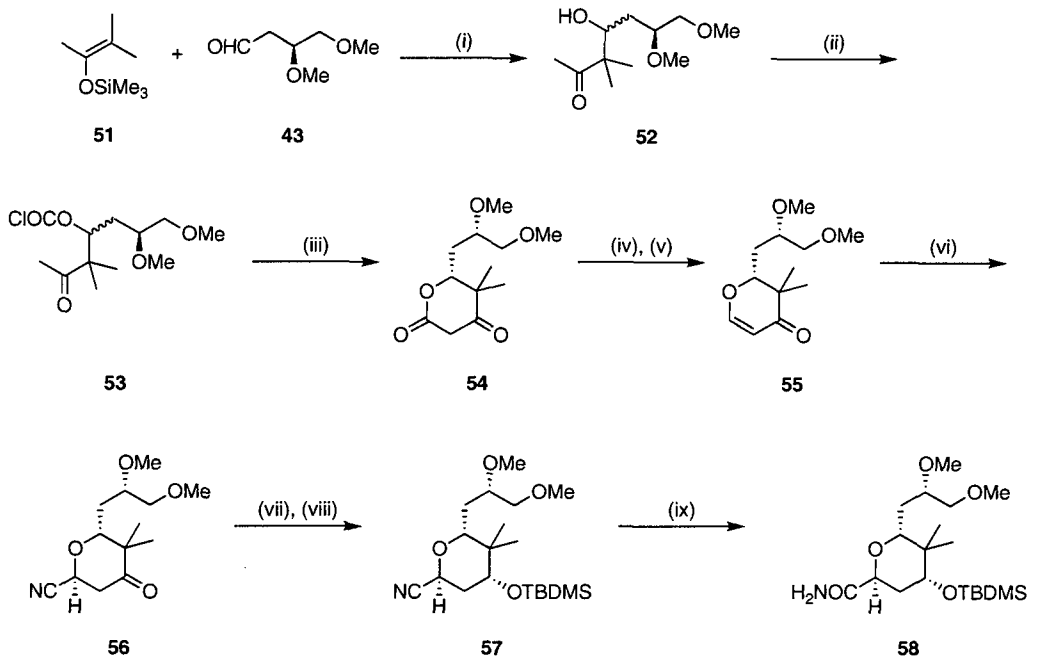
*Scheme 1.3.2: Synthesis of **50** via aldol condensation.*

Reagents and Conditions: (i) $PhMe_2SiH$, $RhCl(PPh_3)_3$, neat, 55 °C, 90%. (ii) $TiCl_4$, CH_2Cl_2, –78 °C, 18%, *d.r.* 4:5. (iii) BzCl, DMAP, pyridine, RT, 58%. (iv) $NaBH_4$, EtOH, RT, *d.r.* 1:1. (v) BzCl, DMAP, pyridine, RT, 34% (2 steps).

1.3.2 Intramolecular acylation

Kocienski described an alternate approach to pederin that made use of an intramolecular acylation to form the required tetrahydropyran ring.[32,34,35] The remaining stereochemistry was established by a Michael addition and reduction of a ketone (Scheme 1.3.3). The synthesis began with aldehyde **43**, derived from (*S*)-malic acid.

The intramolecular acylation product **54** was separable from the unwanted diastereoisomer and transformed into α,β-unsaturated ketone **55**. Michael-type addition of cyanide was efficient, with a *d.r.* of 30:1. Reduction of ketone **56** also displayed high diastereoselectivity (25:1) and excellent yield, offering a short route to fragment **58** and intermediate **55** which was used in the synthesis of a mycalamide B derivative.[36]

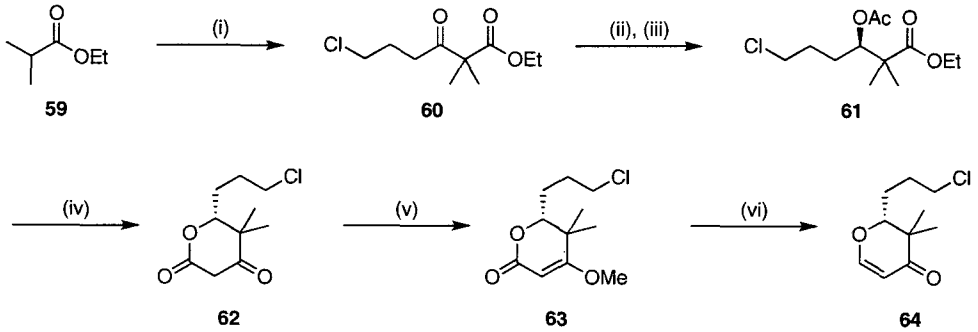


*Scheme 1.3.3: Synthesis of **58** via intramolecular acylation.*

Reagents and Conditions: (i) $TiCl_4$, CH_2Cl_2, –85 °C, 91%. (ii) $COCl_2$, pyridine, $PhCH_3$, 0 °C, 93%. (iii) LDA, THF, –78 °C, 80%, separate, *d.r.* 2:1 from step (i). (iv) Me_2SO_4, K_2CO_3, acetone, reflux, 99%. (v) DIBAL-H, $PhCH_3$, –70 °C, 70%. (vi) TMS-CN, $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 95%, *d.r.* 30:1. (vii) $NaBH_4$, $CeCl_3$, MeOH, –80 °C, 99%, *d.r.* 25:1. (viii) TBDMS-Cl, imidazole, DMAP, DMF, reflux, 94%. (ix) H_2O_2, K_2CO_3, EtOH, RT, 74%.

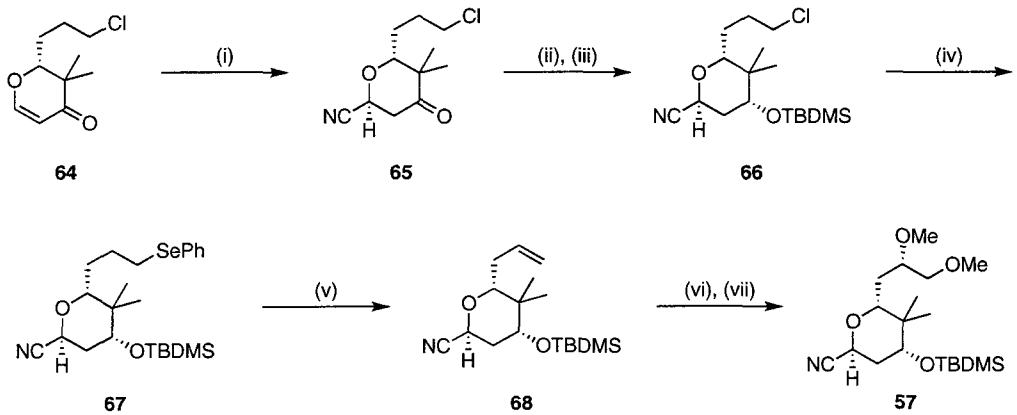
1.3.3 Dieckmann Cyclisation

Kocienski *et al.* have additionally published syntheses of mycalamide B and theopederin D and a formal total synthesis of pederin, each using common fragment **64**. The key step in its construction is a Dieckmann cyclisation of **61** to **62** (Scheme 1.3.4).[37,38]



*Scheme 1.3.4: Synthesis of **64** in the total synthesis of mycalamide B, theopederin D and pederin.*
Reagents and Conditions: (i) (a) LDA, THF –78 °C. (b) $Cl(CH_2)_3COCl$, 93%. (ii) Ru(BINAP), H_2, MeOH, HCl, 40 °C, 93%, 94% *e.e.* (iii) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, 76%. (iv) LDA, THF, –78 °C, 78%. (v) Me_2SO_4, K_2CO_3, 18-crown-6, CH_2Cl_2, RT, 99%. (vi) DIBAL-H, CH_2Cl_2, –78 °C, 85%.

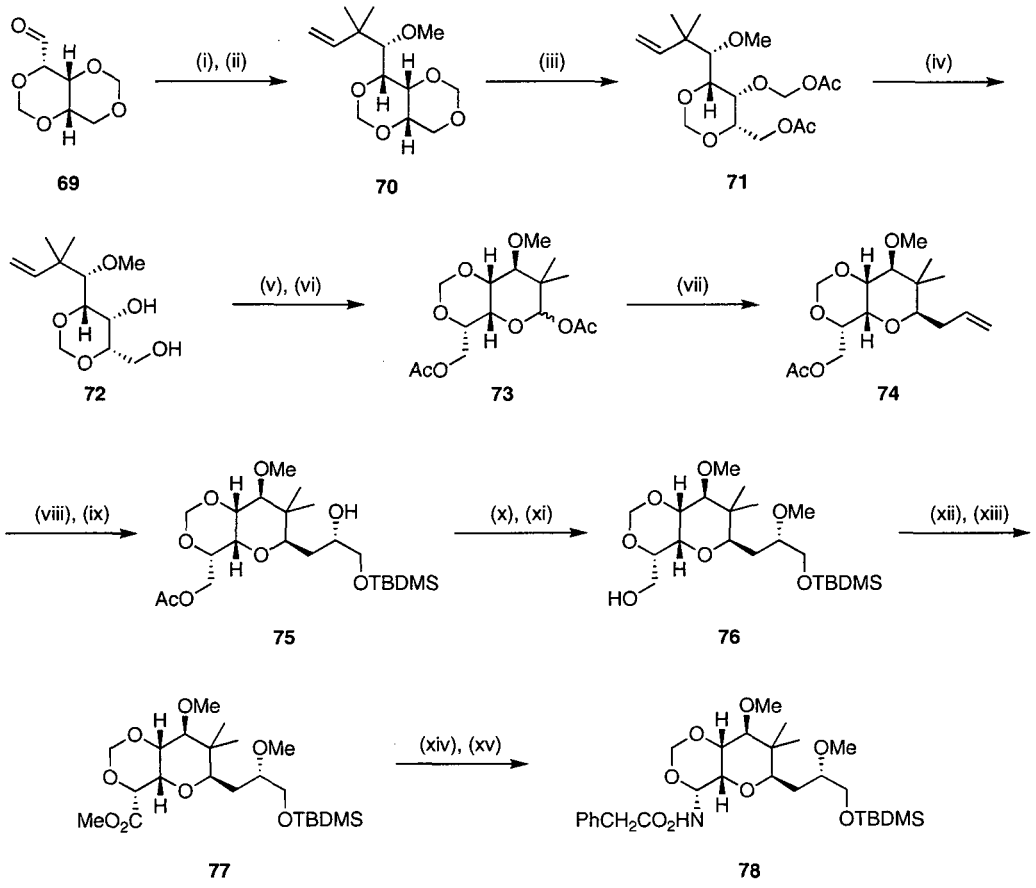
Other notable reactions in the synthesis of **57** are the efficient asymmetric hydrogenation of keto-ester **60** and the use of an asymmetric dihydroxylation of alkene **68** to elaborate the side chain. The route from **64** to the pederin fragment **57** is detailed in Scheme 1.3.5.[37] The short sequence benefits from good selectivities and yields. The use of a selenide to introduce the unsaturated side chain is particularly effective.



*Scheme 1.3.5: Conversion of **64** into **57** for the formal total synthesis of pederin.*
Reagents and Conditions: (i) TMS-CN, TMS-OTf, CH_2Cl_2, 0 °C, 92%, *d.r.* 99:1. (ii) $NaBH_4$, $CeCl_3$, MeOH, –95 °C to –60 °C, 99%, *d.r.* 30:1. (iii) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%. (iv) PhSeNa, EtOH, reflux, 91%. (v) (a) $NaIO_4$, MeOH, H_2O, RT. (b) NEt_3, $PhCH_3$ (1:1), reflux, 96%. (vi) K_2OsO_4, DHQ-PHN, $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH, H_2O, 0 °C, 78%, *d.r.* 3:2. (vii) MeI, NaH, 18-crown-6, THF, RT, 91%.

1.3.4 Lactol Formation

Formation and modification of a lactol has been used successfully to form the central ring system of mycalamide B by Hoffmann *et al.*[39,40] The synthesis began with an internally controlled prenylation of aldehyde **69**, with subsequent protection, cleavage and hydrolysis giving diol **72**. Lactol **73** was formed by ozonolysis of the alkene and reaction with acetic anhydride. The acetate was displaced with allyltrimethylsilane and $BF_3.OEt_2$ to give **74** as a single diastereoisomer (Scheme 1.3.6).



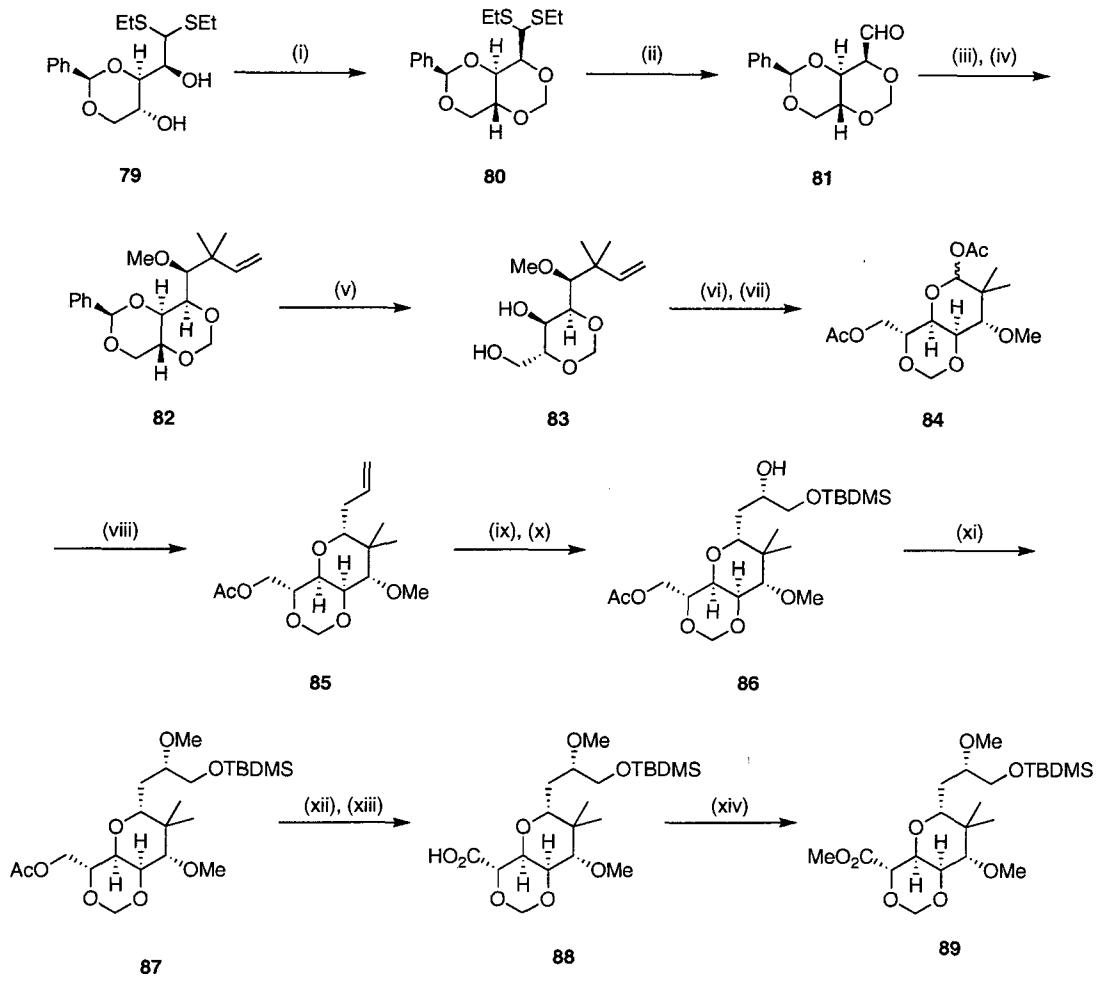
Scheme 1.3.6: Lactol based method to mycalamide B fragment ***78****.*

Reagents and Conditions: (i) $(CH_3)_2C{=}CHCH_2SnBu_3$, $TiCl_4$, 4 Å mol sieves, CH_2Cl_2, 0 °C, 87%, 95% *d.e.* (ii) MeI, NaH, THF, RT, 93%. (iii) $(CF_3CO)_2O$, AcOH, RT. (iv) K_2CO_3, MeOH, H_2O, RT, 65% (2 steps). (v) (a) O_3, CH_2Cl_2, –78 °C. (b) PPh_3, –78 °C to RT. (vi) Ac_2O, pyridine, CH_2Cl_2, RT, 79% (2 steps). (vii) Allyltrimethylsilane, $BF_3.OEt_2$, 4 Å mol sieves, MeCN, 0 °C, 99%. (viii) $K_2OsO_4.2H_2O$, DHQ-PHN, $K_3Fe(CN)_6$, K_2CO_3. ^tBuOH, H_2O, 0 °C, 78%, *d.r.* 2:1. (ix) TBDMS-Cl, imidazole, DMF, 0 °C to RT, separate diastereoisomers, 60%. (x) CH_2N_2, SiO_2, Et_2O, 0 °C, 92%. (xi) K_2CO_3, MeOH, H_2O, 96%. (xii) Swern oxidation, 92%. (xiii) I_2, KOH, MeOH, 69%. (xiv) KOH, H_2O, 93%. (xv) $(PhO)_2P(O)N_3$, BnOH, NEt_3, PhH, 80 °C, 62%.

Dihydroxylation of **74**, followed by a sequence of protections and hydrolysis gave **76**. The primary alcohol in **76** was oxidised with a Swern oxidation and converted to an ester, before saponification and conversion to **78** *via* a Curtius rearrangement (Scheme 1.3.6).[39,40]

Unfortunately, the sequence delivered the wrong stereochemistry at the carbon adjacent to the nitrogen in **78**. The authors planned to epimerise the stereocentre adjacent to the ester at compound **77** but it did not prove possible, but alteration of the route to set the correct stereochemistry at this centre earlier in the synthesis was successful.

To complete the synthesis with the correct stereochemistry, the diol in **79** was alkylated and the aldehyde unmasked to give **81**, which was subjected to a Grignard addition to afford **82** as a single diastereoisomer. Removal of the bridging phenyl group in **82** and subsequent lactol formation *via* ozonolysis and acetate displacement as above afforded **85** as a single diastereoisomer. Dihydroxylation, protection and conversion of the acetate to ester **89** completed the synthesis (Scheme 1.3.7).[40]

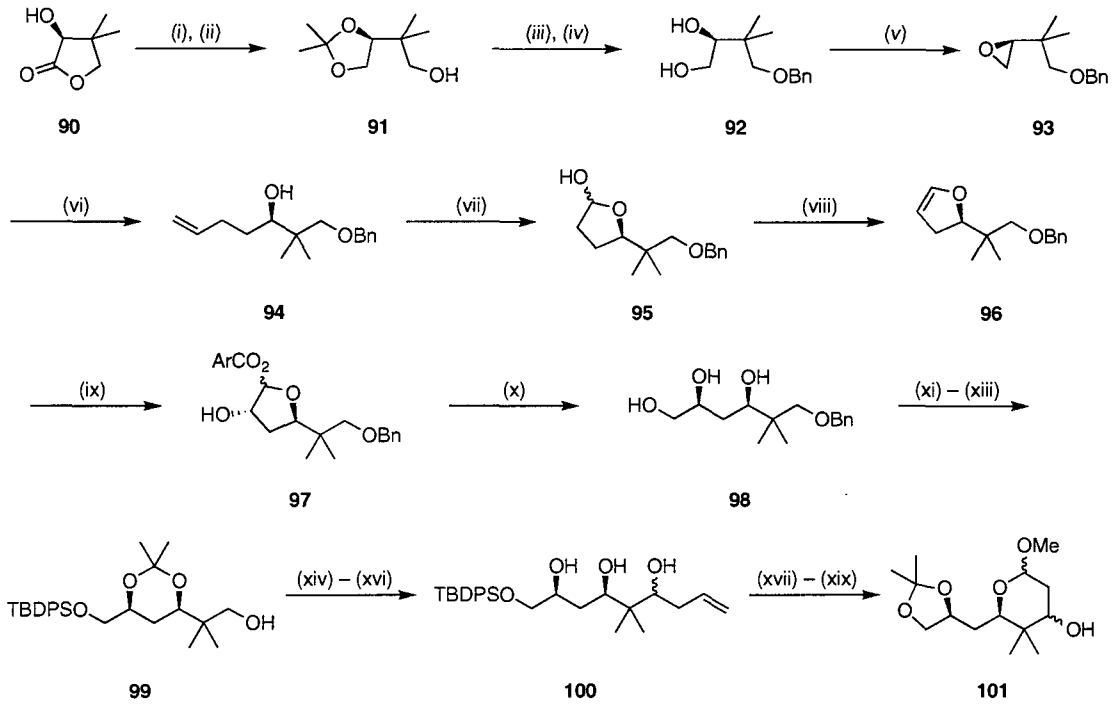


*Scheme 1.3.7: Synthesis of **89** with correct stereochemistry.*

Reagents and Conditions: (i) CH_2BrCl, NaOH, TBAB, H_2O, dioxane, 60 °C, 62%. (ii) $HgCl_2$, $AgNO_3$, Ag_2O, MeCN, H_2O, 0 °C, 100%. (iii) $(CH_3)_2C{=}CHCH_2MgCl$, $MgBr_2$, THF, –30 °C, 94%, single diastereoisomer. (iv) MeI, NaH, DMF, RT, 91%. (v) 80% AcOH, RT, 82%. (vi) (a) O_3, CH_2Cl_2, –78 °C. (b) PPh_3, –78 °C to RT. (vii) Ac_2O, pyridine, CH_2Cl_2, RT, 96% (2 steps). (viii) Allyltrimethylsilane, $BF_3.OEt_2$, 4 Å mol sieves, MeCN, 0 °C, 84%, single diastereoisomer. (ix) $K_2OsO_4.2H_2O$, DHQ-PHN, $K_3Fe(CN)_6$, K_2CO_3. ^{t}BuOH, H_2O, 0 °C, 92%, *d.r.* 2:1. (x) TBDMS-Cl, imidazole, DMF, 0 °C to RT, separate diastereoisomers, 42%. (xi) CH_2N_2, SiO_2, Et_2O, 0 °C, 82%. (xii) K_2CO_3, MeOH, H_2O, RT, 96%. (xiii) $RuCl_3$, $K_2S_2O_8$, KOH, ^{t}BuOH, H_2O, RT. (xiv) CH_2N_2, SiO_2, Et_2O, 77% (2 steps).

Nakata reported a formal total synthesis of mycalamide A using lactol intermediates to both set stereochemistry and form the THP ring (Scheme 1.3.8).[41] The synthesis began from the known epoxide **93**, which was synthesised in five steps.[42] Grignard-copper iodide addition to **93** was followed by osmium tetroxide mediated oxidative cleavage of the alkene to form lactol **95**. Dehydration of **95**, followed by reaction

with *m*CPBA and $LiAlH_4$ reduction of **97** yielded triol **98**. A sequence of protection and deprotection steps gave **99**, in which the alcohol was oxidised *via* a Swern oxidation and the resultant aldehyde subjected to Grignard addition and subsequent removal of the acetonide to afford **100**. Ozonolysis and subsequent protection afforded lactol **101**.

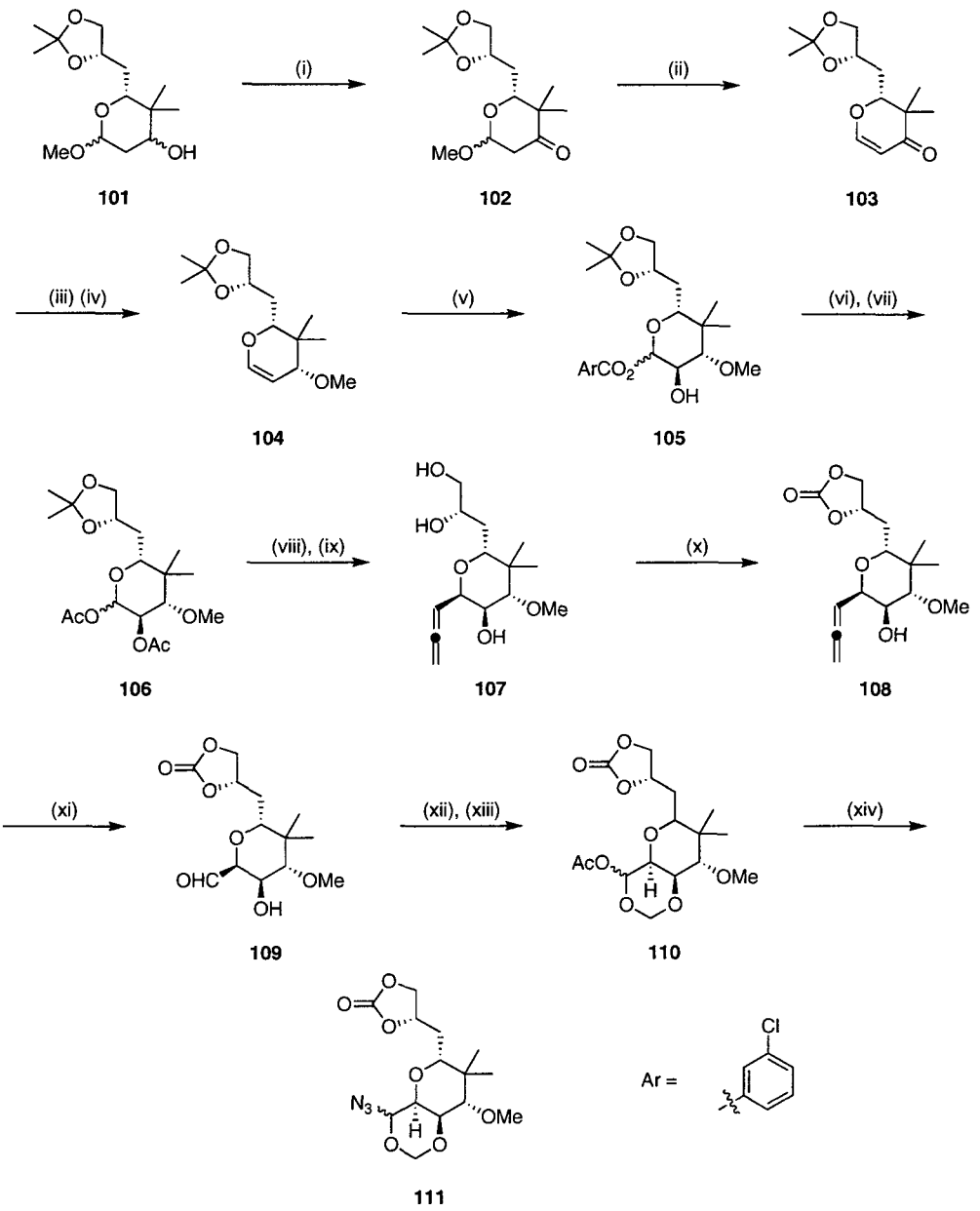


Scheme 1.3.8: THP synthesis via lactols.

Reagents and Conditions: (i) $LiAlH_4$. (ii) Acetone, CSA. (iii) BnBr, NaH. (iv) AcOH, H_2O. (v) NaH, *p*-TsCl. (vi) Allylmagnesium chloride, CuI, THF, –23 °C to RT, 99%. (vii) (a) OsO_4, NMO, acetone, H_2O, ^tBuOH, RT. (b) $NaIO_4$, THF, H_2O, RT, 74% (2 steps). (viii) MsCl, NEt_3, $^iPr_2NEt$, CH_2Cl_2, reflux, 67%. (ix) *m*CPBA, CH_2Cl_2, RT. (x) $LiAlH_4$, THF, reflux, 84%, *d.r.* 14:1 (2 steps). (xi) TBDPS-Cl, imidazole, DMF, RT, 92%. (xii) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, RT, 90%. (xiii) H_2, $Pd(OH)_2$, THF, RT, 85%. (xiv) Swern oxidation, 92%. (xv) Allylmagnesium chloride, THF, 0 °C. (xvi) AcOH, H_2O. (xvii) (a) O_3, MeOH, –78 °C. (b) Me_2S, –78°C to RT. (xviii) $HC(OMe)_3$, CSA, MeOH, RT. (xix) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, RT, 80% (5 steps).

PDC oxidation of the alcohol in **101** and elimination of methanol from the product gave **103**, which was reduced with sodium borohydride-cerium trichloride and the resultant alcohol protected. Oxidation of **104**, followed by a sequence of hydrolysis, acetate formation, displacement of the lactol acetate and removal of the protecting groups afforded allene **107**. The side chain diol of **107** was joined using CDI and ozonolysis afforded aldehyde **109**. Reaction of **109** with paraformaldehyde, and

finally acetate formation and displacement with TMS azide completed the synthesis of fragment **111** (Scheme 1.3.9). These steps introduced the ring and diol required for synthesis of mycalamide A. [41]

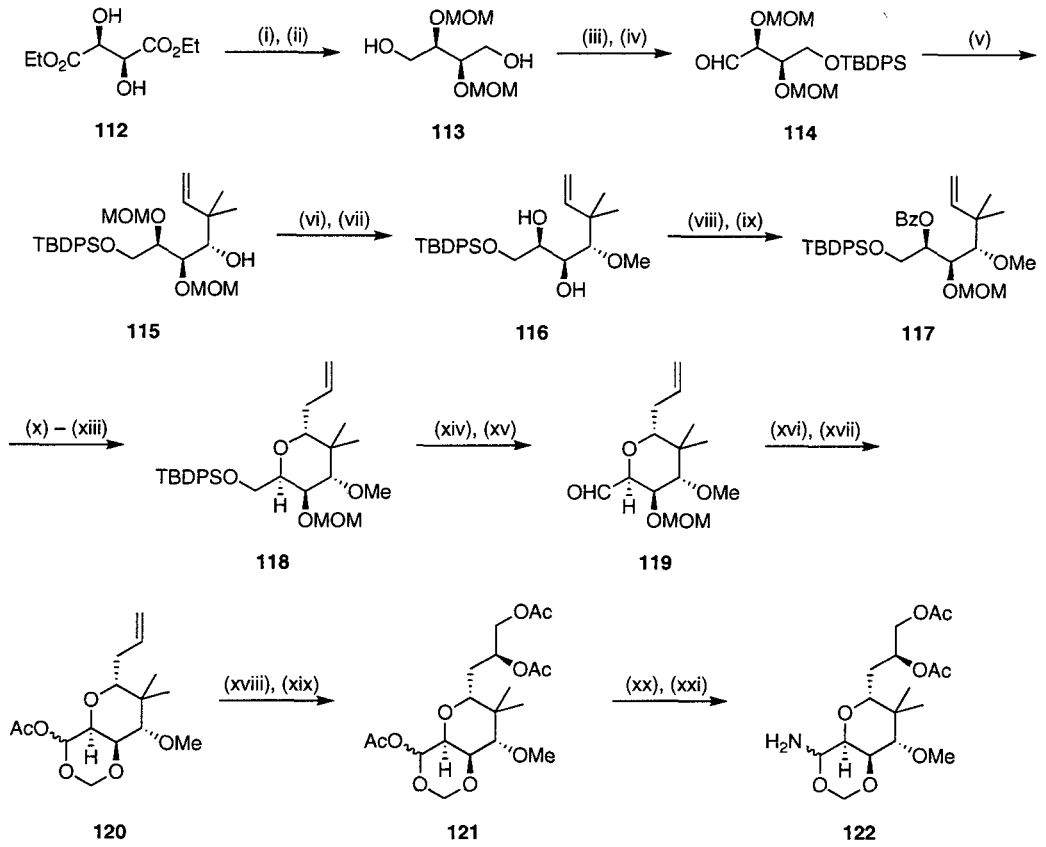


*Scheme 1.3.9: Completion of mycalamide A fragment **111**.*

Reagents and Conditions: (i) PDC, CH_2Cl_2, RT. (ii) TBAF, THF, RT, 50% (2 steps). (iii) $NaBH_4$, $CeCl_3$, MeOH, –78 °C to RT. (iv) MeI, KH, THF, 0 °C, 90% (2 steps). (v) *m*CPBA, CH_2Cl_2, RT. (vi) K_2CO_3, MeOH, RT. (vii) Ac_2O, pyridine, RT, 88% (3 steps). (viii) HC≡CHCH$_2$-TMS, TMS-OTf, MeCN, 0 °C, 73%. (ix) K_2CO_3, MeOH, RT. (x) CDI, PhH, RT, 57% (2 steps). (xi) (a) O_3, MeOH, –78 °C. (b) Me_2S, –78 °C to RT. (xii) Paraformaldehyde, HCl (conc.), PhH, 10 °C. (xiii) Ac_2O, pyridine, RT. (xiv) TMS-N_3, TMS-OTf, MeCN, 0 °C, 48% (4 steps).

From **111**, hydrogenolysis of the azide to the amine gives the required coupling partner for mycalamide A. Nakata used a related approach to produce mycalamide A analogues from carbohydrate derivatives (Scheme 1.3.17). The route was also modified for large scale synthesis but the key reactions remained the same.[41]

Rawal made use of a lactol to form the required THP in the total synthesis of mycalamide A.[30] Diethyl tartrate (**112**) was MOM protected, reduced, mono silyl protected and the remaining alcohol oxidised *via* a Swern oxidation to aldehyde **114**. Zinc-mediated addition of prenyl (tributyl)stannane gave **115** with an excellent *d.r.* of 50:1, to which a protection / deprotection sequence was applied, resulting in mono-MOM protected **117**. Ozonolysis to form a lactol, acetate formation and displacement with allyltrimethylsilane afforded **118** as a single diastereoisomer, with deprotection, Swern oxidation and reaction with paraformaldehyde giving **120**. Dihydroxylation of the alkene and protection of the resultant diol gave **121**, which was advanced to **122** by displacement of the lactol acetate with TMS azide, followed by catalytic hydrogenation (Scheme 1.3.10).

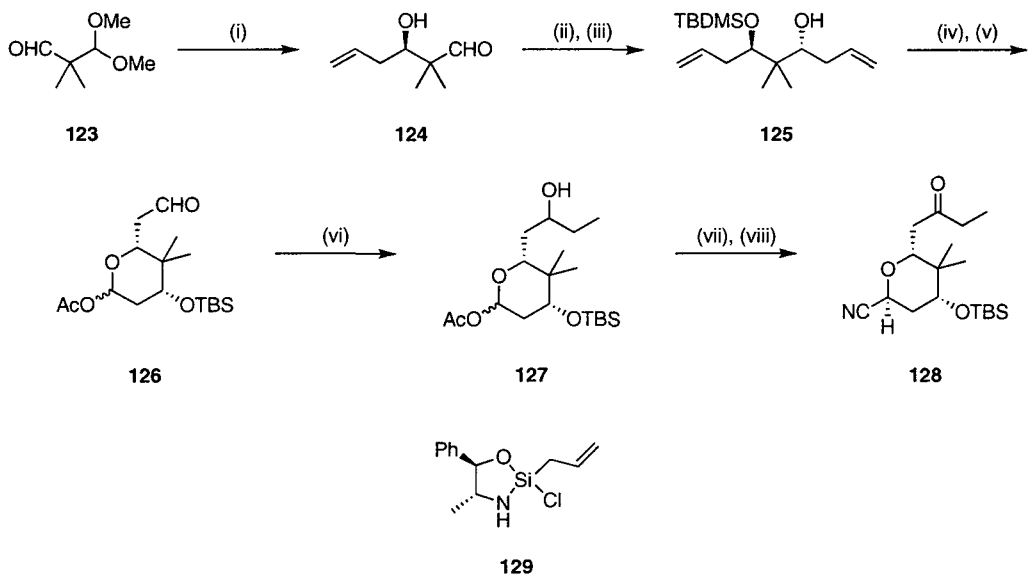


*Scheme 1.3.10: Synthesis of fragment **122** for the total synthesis of mycalamide A.*

Reagents and Conditions: (i) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, quant. (ii) $LiAlH_4$, Et_2O, 86%. (iii) ^nBuLi, TBDPS-Cl, THF, quant. (iv) Swern oxidation, 90%. (v) $(CH_3)_2C{=}CHCH_2SnBu_3$, $ZnBr_2$, CH_2Cl_2, –78 °C to 0 °C, 90%, *d.r.* 50:1. (vi) NaH, MeI, THF, 98%. (vii) $ZnBr_2$, ^nBuSH, CH_2Cl_2, RT, 98%. (viii) BzCl, $^iPr_2NEt$, CH_2Cl_2, RT. 80%. (ix) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, RT, 91%. (x) K_2CO_3, MeOH, RT, 83%. (xi) (a) O_3, CH_2Cl_2, –78 °C. (b) Me_2S, CH_2Cl_2, –78 °C to RT. (xii) Ac_2O, DMAP, pyridine, RT. (xiii) Allyltrimethylsilane, $BF_3.OEt_2$, CH_2Cl_2, 66% overall, single diastereoisomer. (xiv) TBAF, THF, 91%. (xv) Swern oxidation. (xvi) Paraformaldehyde, HCl (conc.), THF. (xvii) Ac_2O, DMAP, pyridine, CH_2Cl_2, 63%, *d.r.* 5.4:1. (xviii) OsO_4, $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, ^tBuOH, H_2O, –3 °C, 83%, *d.r.* 5:1. (xix) Ac_2O, $^iPr_2NEt$, DMAP, CH_2Cl_2, 92%. (xx) TMS-N_3, TMS-OTf, MeCN, –78 °C to 0 °C, quant. (xxi) H_2, Pd / C, EtOAc, 90%.

Interestingly, the only use of an external source of chirality is the ligand used in dihydroxylation of **120**, the remainder of the reactions are successfully used to generate chiral centres with internal stereocontrol. The steps required to introduce the diol and central ring are similar to those used by Kishi in the first total syntheses of mycalamides A and B (Schemes 1.3.14 and 1.3.15).

The lactol-based approach was recently used in the synthesis of psymberin (**24**), reported by De Brabander *et al.*[17] Synthesis of the tetrahydropyran moiety with the required stereochemistry was achieved in a very short sequence from known aldehyde **123**. Two sequential asymmetric additions of silane **129** first to **123** and then to product **124** afforded **125** after mono TBDMS protection with very good selectivity. Ozonolysis and acetate formation gave **126**, which was subjected to diethyl zinc addition, giving **127**. Displacement of the acetate with TMS cyanide and oxidation of the secondary alcohol with Dess-Martin periodinane completed the synthesis of **128** (Scheme 1.3.11).

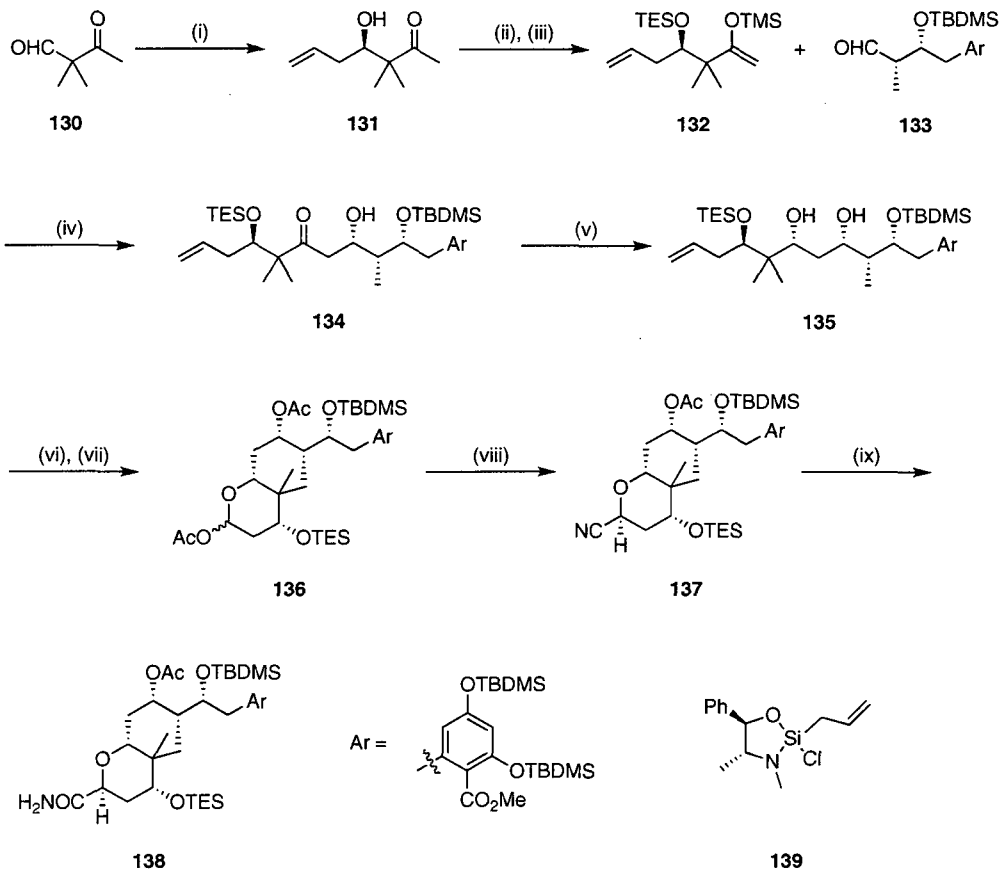


*Scheme 1.3.11: Synthesis of fragment **128** in the total synthesis of psymberin.*

Reagents and Conditions: (i) **129**, $PhCH_3$, –15 °C, 69%, 94% *e.e.* (ii) **129**, $PhCH_3$, –15 °C, 79%, *d.r.* 17:1. (iii) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 92%. (iv) (a) O_3, CH_2Cl_2, –78 °C. (b) PPh_3, RT, 99%. (v) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C, 81%. (vi) *N,N'*-(1*R*,2*R*-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide), $Ti(O^iPr)_4$, Et_2Zn, $PhCH_3$, –15 °C, 84% (mixture). (vii) TMS-CN, ZnI_2, MeCN, 0 °C, 91%. (viii) DMP, CH_2Cl_2, RT, 95%.

Another approach to a fragment of psymberin was published in 2005 by Floreancig *et al.*[43] The route differs from those previously mentioned in assembling the majority of the carbon framework as an acyclic precursor to the lactol. Asymmetric allylation of keto-aldehyde **130** with silane **139** resulted in homoallylic alcohol **131** in 94% *e.e.* Protection and silyl enol-ether formation, followed by a Mukaiyama aldol reaction with aldehyde **133** resulted in **134** with a *d.r.* of 6:1. Stereocontrolled reduction of the

ketone, ozonolysis to form the lactol and acetate formation afforded **136**. The acetate was displaced with TMS cyanide to give **137** as a single diastereoisomer, and the nitrile was converted to the amide using the Parkin platinum catalyst, which avoided deprotection of the alcohols (Scheme 1.3.12).

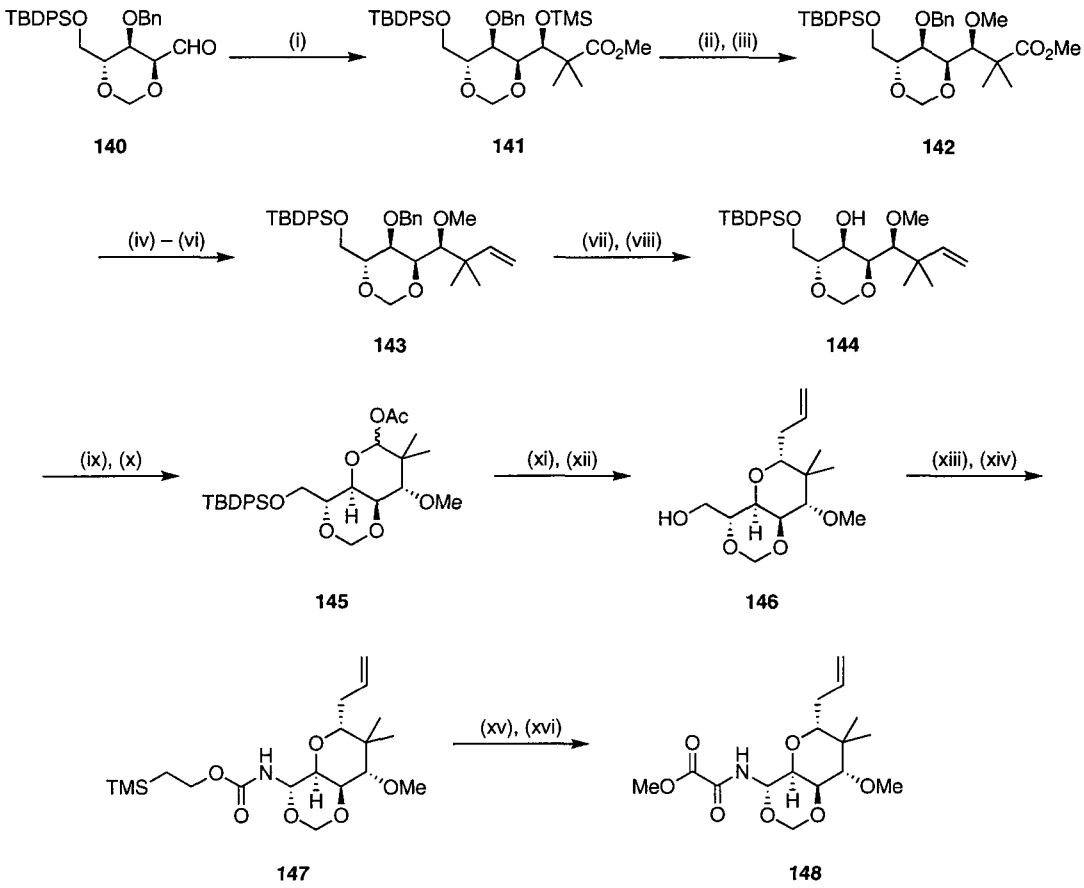


Scheme 1.3.12: THP synthesis en route to a psymberin fragment.

Reagents and Conditions: (i) **139**, $PhCH_3$, –15 °C, 90%, 94% *e.e.* (ii) TES-Cl, imidazole, DMF, RT. (iii) TMS-OTf, NEt_3, Et_2O, 0 °C, 100% (2 steps). (iv) $BF_3.OEt_2$, CH_2Cl_2, –78 °C, 95%, *d.r.* 6:1. (v) Et_2BOMe, $NaBH_4$, THF, –78 °C, 74%, *d.r.* not reported. (vi) (a) O_3, CH_2Cl_2, –78 °C. (b) PPh_3, –78 °C to RT, 76%. (vii) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, 76%. (viii) TMS-CN, $BF_3.OEt_2$, CH_2Cl_2, –78 °C, 97%, single diastereoisomer. (ix) $(Me_2PO)HPt(Me_2POH)$, EtOH, H_2O, 80 °C, 96%.

A recent synthesis of mycalamide A by Toyota *et al.* takes a different approach: the central ring of the mycalamides is constructed first and the tetrahydropyran unit then formed *via* a lactol (Scheme 1.3.13).[44,45] **140** was synthesised in an eight step sequence and elaborated to **141** *via* a Mukaiyama aldol reaction, giving **141** in 89% yield and as a single diastereoisomer. Synthesis of **148** was completed using some steps similar to those published by Kishi.[46,47] Deprotection / protection gave **142**,

which was converted into **143** by a Wittig olefination reaction with the corresponding aldehyde. Birch reduction, followed by DDQ oxidation to restore aromaticity to the TBDPS group afforded **144**, which was converted into lactol **145** by ozonolysis and acetate formation. Acetate displacement with allyltrimethylsilane, conversion to **147** *via* a Curtius rearrangement, alkylation and finally deprotection afforded **148**.



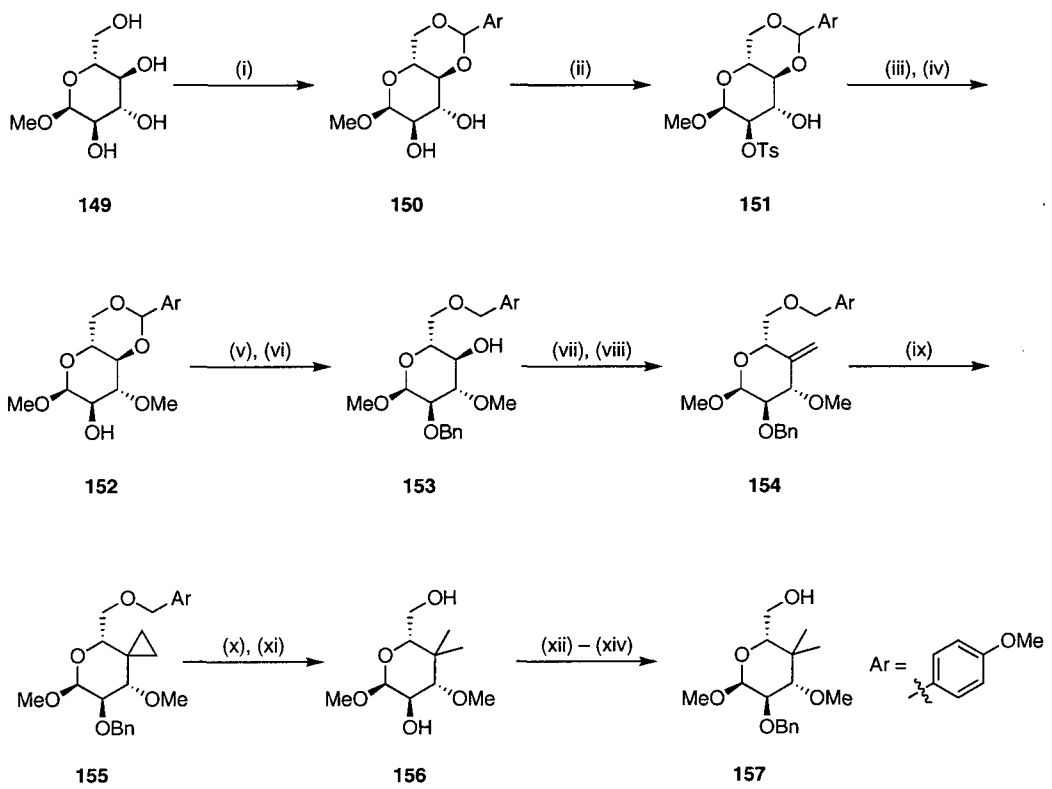
*Scheme 1.3.13: Synthesis of mycalamide B fragment **148** via a lactol.*

Reagents and Conditions: (i) $(CH_3)_2C{=}C(OSiMe_3)(OMe)$, $Yb(OTf)_3$, TMS-Cl, CH_2Cl_2, –78 °C, 89%, single diastereoisomer. (ii) CSA, MeOH, RT, 84%. (iii) MeI, NaH, THF 0 °C, 95%. (iv) DIBAL-H, THF, 0 °C, 100%. (v) SO_3.py, DMSO, NEt_3, RT, 97%. (vi) $Ph_3P^+MeBr^-$, BuLi, THF, 0 °C, 100%. (vii) Li, NH_3 (l), THF, –78 °C. (viii) DDQ, PhH, RT, 74% (2 steps). (ix) (a) O_3, MeOH, –78 °C. (b) Me_2S. (x) Ac_2O, pyridine, RT, 99% (2 steps). (xi) Allyltrimethylsilane, $BF_3.OEt_2$, 4 Å mol sieves, MeCN, 0 °C. (xii) TBAF, THF, RT, 86% (2 steps). (xiii) Jones oxidation. (xiv) $(PhO)_2P(O)N_3$, TMS-$(CH_2)_2OH$, NEt_3, 4 Å mol sieves, THF, 65 °C, 78% (2 steps). (xv) LiHMDS, MeO_2CCOCl, DMAP, THF, –78 °C, 78%. (xvi) TBAF, THF, 0 °C, 93%.

1.3.5 Carbohydrate Derivatives

Modified pyranoses have been used as starting materials for syntheses of natural products of the class discussed in this thesis. This has the advantages that some of the stereochemistry is already in place and the pyranose is an advanced intermediate.

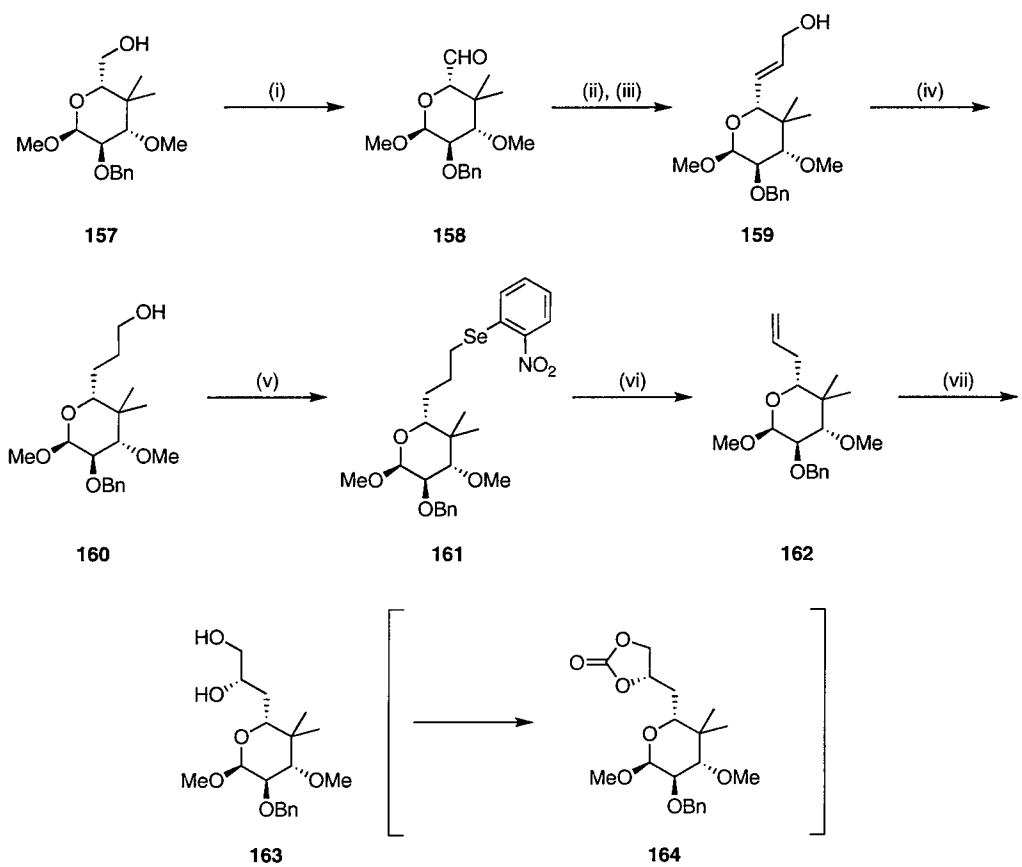
The first reported synthesis of mycalamides A and B was Kishi's,[47] beginning with methyl α-D-glucopyranoside (**149**) which was converted into the protected form **153** over six steps. Following conversion of **153** to **154** *via* oxidation and Wittig olefination, cyclopropane **155** was formed by reaction with diazomethane and a palladium catalyst. **155** was converted to **156** by two sequential hydrogenations, followed by a protection / deprotection sequence to give **157** (Scheme 1.3.14).



Scheme 1.3.14: Carbohydrate modification in the synthesis of mycalamides A and B.

Reagents and Conditions: (i) $MeOC_6H_4CH(OMe)_2$, *p*-TsOH. (ii) $^n(Bu_2)SnO$, then TsCl, NEt_3. (iii) MeI, Ag_2O. (iv) Na(Hg). (v) BnBr, NaH. (vi) $NaCNBH_3$, TFA, 65% (6 steps to **153**). (vii) Swern oxidation. (viii) $CH_3P^+Ph_3Br^-$. (ix) CH_2N_2, $Pd(OAc)_2$, Et_2O, RT. (x) H_2, $Pd(OH)_2$ / C, EtOAc, RT. (xi) H_2, PtO_2, AcOH, RT. (xii) TBDPS-Cl, imidazole, CH_2Cl_2, RT. (xiii) BnBr, NaH, THF, RT. (xiv) TBAF, THF, RT, 62% (7 steps to **157**).

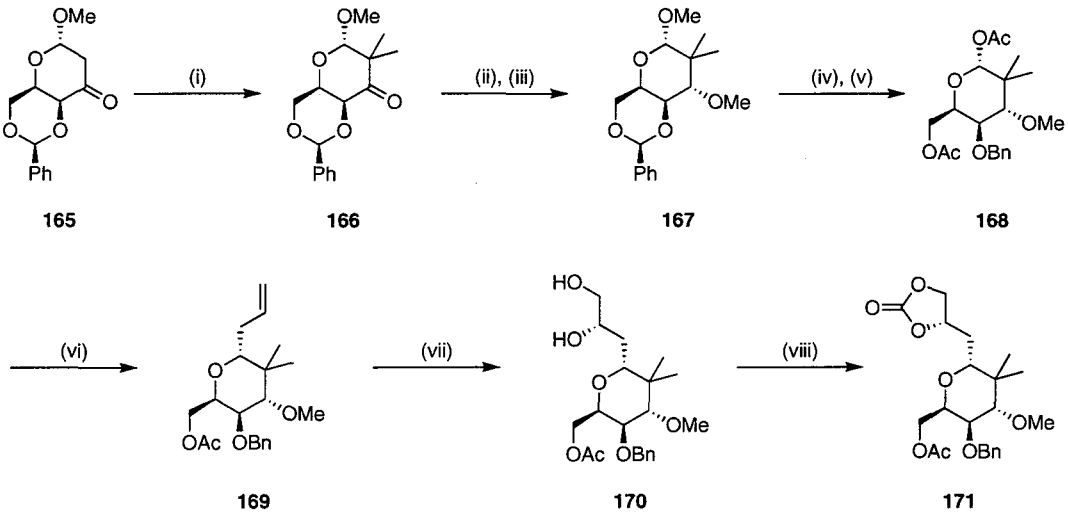
From **157**, the next steps were to introduce the required side chain functionality on the ring for the mycalamides. The authors found that direct methods, such as vinylation of a triflate or iodide derived from **157** were not successful and that a five-step sequence was required (Scheme 1.3.15, full information not given in reference). Following oxidation, olefination and subsequent reduction, **160** was converted into selenide **161** and eliminated by treatment with *m*CPBA to give **162**. Dihydroxylation provided the functionality present in mycalamide A (**2**). Further modification was necessary to introduce the central OCH_2O bridging ring present in many of the natural products and provide functionality to couple to the pederic acid fragment.[47]



Scheme 1.3.15: Altering ring functionality.

Reagents and Conditions: (i) Swern oxidation. (ii) Horner-Emmons olefination. (iii) DIBAL-H, CH_2Cl_2, –78 °C. (iv) H_2, Rh on Al_2O_3, EtOAc, RT. (v) *o*-$O_2NC_6H_4SeCN$, $^nBu_3P$, PhH. (vi) *m*CPBA, 79% (6 steps to **162**). (vii) OsO_4, *N,N'*-bis (2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, –90 °C. (Separated as carbonate **164**, 75% 2 steps).

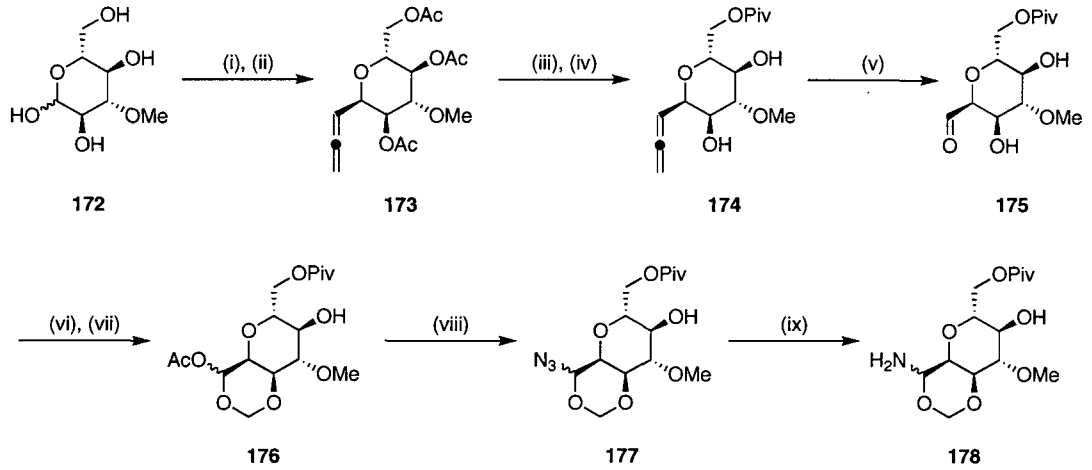
Kishi also used a carbohydrate derivative in the first total synthesis of onnamide A.[46] This synthesis began with **165**, which was methylated by enolate formation and treatment with methyl iodide and HMPA. Reduction of the ketone and protection of the resultant alcohol was followed by removal of the benzyl group, acetate formation and displacement with allyltrimethylsilane, to afford **169**. Dihydroxylation and cyclisation of the diol with CDI gave **171** (Scheme 1.3.16).



Scheme 1.3.16: Synthesis of fragment of onnamide A.

Reagents and Conditions: (i) (a) LiTMP, Et_2O, –25 °C. (b) MeI, HMPA, THF, –5 °C, 30 – 60%. (ii) $NaBH(OAc)_3$, $CeCl_3$, MeOH, 0 °C. (iii) MeI, NaH, THF, RT, 78% (2 steps). (iv) $LiAlH_4$, $AlCl_3$, Et_2O, CH_2Cl_2, reflux. (v) Ac_2O, $BF_3.OEt_2$, 0 °C to RT, 75 – 80% (2 steps). (vi) Allyltrimethylsilane, TMS-OTf, $BF_3.OEt_2$, MeCN, 0 °C, 93%. (vii) OsO_4, *N,N'*-bis (2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, –90 °C. (viii) CDI, PhH, reflux, 65% (2 steps).

Nakata's synthesis of mycalamide A analogues also made use of carbohydrate chemistry.[26] Drawing on Kishi's synthesis, the required fragment was completed in 11 steps from 3-*O*-methyl-α-D-glucopyranose **172** and provides insight into the steps not fully disclosed by Kishi (Scheme 1.3.17).



*Scheme 1.3.17: Synthesis of fragment **178** for mycalamide A analogues.*

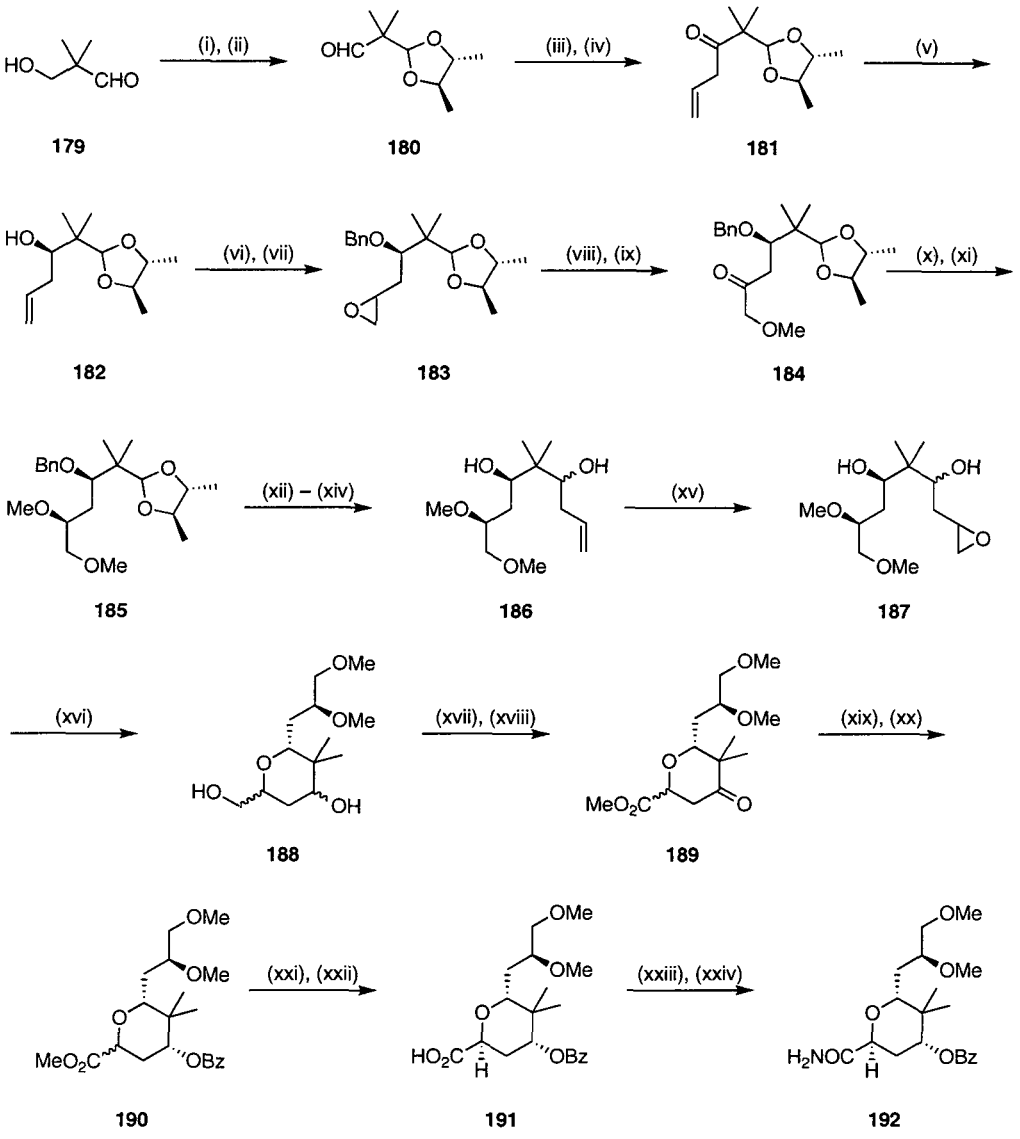
Reagents and Conditions: (i) Ac_2O, pyridine, RT. (ii) $HC{\equiv}CHCH_2$-TMS, TMS-OTf, $BF_3.OEt_2$, MeCN, 0 °C, 68% (2 steps). (iii) K_2CO_3, MeOH, RT. (iv) PivCl, pyridine, CH_2Cl_2, 91% (2 steps). (v) (a) O_3, MeOH, –78 °C. (b) Me_2S, 0 °C. (vi) Paraformaldehyde, CSA, CH_2Cl_2, 0 °C. (vii) Ac_2O, pyridine, RT, 74% (3 steps). (viii) TMS-N_3, TMS-OTf, MeCN, 0 °C, 88%. (ix) H_2, Pd / C (10%), EtOAc, RT.

Following acetate formation, subsequent displacement and ozonolysis, **175** was reacted with paraformaldehyde. Acetate formation, displacement with TMS azide and reduction completed the synthesis of fragment **178**.

1.3.6 Epoxide Opening

Opening of an epoxide has also been successfully used to form a ring system in several syntheses, with the advantage that stereochemistry can be introduced into the ring system if the epoxide is formed *via* an enantioselective method, e.g. Sharpless asymmetric epoxidation.

The first such synthesis was reported by Matsumoto in the synthesis of pedamide, one of the fragments of pederin.[48,49] Aldehyde **179** was protected and a sequence of oxidation, allyl Grignard addition and oxidation gave ketone **181**. Extensive experimentation was needed to control the $LiAlH_4$ reduction of **181** in 74% *e.e.*, followed by a sequence of standard transformations to **184**. Reduction of the ketone, followed by protection with methyl iodide, removal of the acetal and reaction of the resultant aldehyde with allyl Grignard to afford **186** after de-benzylation (Scheme 1.3.18).

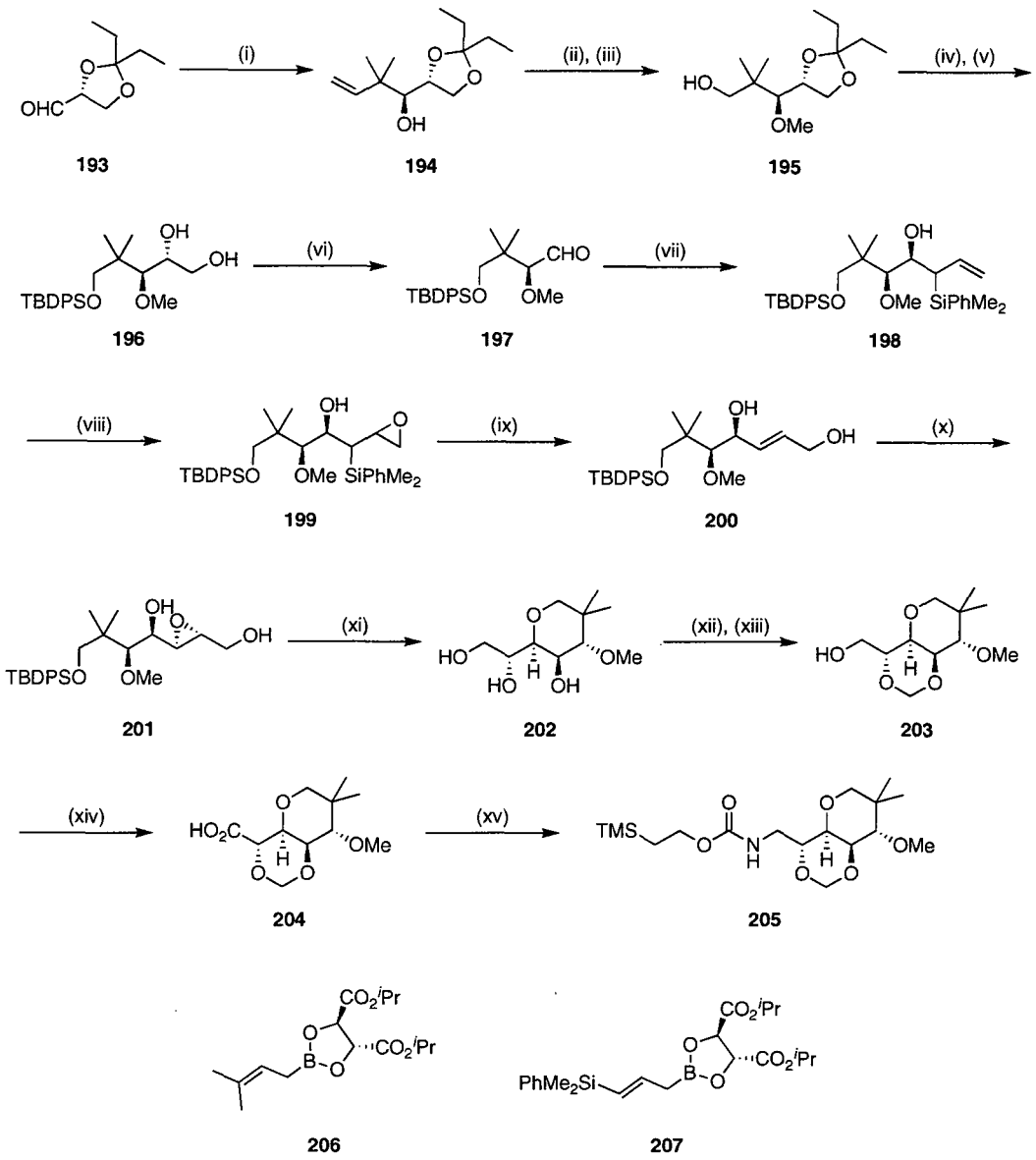


*Scheme 1.3.18: Synthesis of pedamide **192** via epoxide opening.*

Reagents and Conditions: (i) (2*R*,3*R*)-2,3-butanediol, *p*-TsOH, PhH, reflux. (ii) PCC, CH_2Cl_2, RT. (iii) Allylmagnesium bromide, Et_2O, RT. (iv) Jones oxidation, 0 °C, 51% (4 steps). (v) $LiAlH_4$, Et_2O : $PhCH_3$ (1:1), –123 °C, 98%, 74% *e.e.* (vi) BnCl, ^{t}AmONa, DMSO, RT. (vii) *m*CPBA, CH_2Cl_2, RT. (viii) NaOMe, MeOH, RT. (ix) Collins oxidation, CH_2Cl_2, RT, 76% (4 steps). (x) $Li(^tBuO)_3AlH$, Et_2O, –78 °C, 95%. (xi) MeI, NaH, PhH, reflux, 93% (2 steps). (xii) HCl (3 M), acetone, reflux. (xiii) Allylmagnesium bromide, Et_2O, RT, 78% (2 steps). (xiv) Na, NH_3 (l), –78 °C, 74%. (xv) *m*CPBA, CH_2Cl_2, RT. (xvi) *p*-TsOH, PhH, reflux, 86% (2 steps) (xvii) Jones oxidation, RT. (xviii) CH_2N_2, Et_2O, RT. (xix) $NaBH_4$, EtOH, –78 °C, 89% (3 steps). (xx) BzCl, pyridine, RT, 94%. (xxi) (a) LDA, THF, –78 °C. (b) AcOH, –78 °C, 54%. (xxii) NEt_3, H_2O, MeOH, RT. (xxiii) $SOCl_2$, DMF, CH_2Cl_2, reflux. (xxiv) NH_3, CH_2Cl_2, 0 °C, 79% (3 steps).

Epoxide **187** was formed by reaction of **186** with *m*CPBA and cyclised by treating with acid to give key intermediate **188**. A series of oxidation, protection, reduction and protection afforded **190**, which was converted into **191** by careful de / reprotonation, followed by hydrolysis of the ester. After any racemic material was removed by addition of a seed crystal and the synthesis was completed by conversion of the acid to a primary amide by a standard acid chloride formation and reaction with ammonia protocol (Scheme 1.3.18).[48,49] The synthesis proved to be an efficient strategy and the approach was used in the first total synthesis of pederin.[21]

Roush reported the use of the addition of an alcohol to an epoxide to form a tetrahydropyran ring in an approach to onnamide A and mycalamides A and B.[50] Use of prenylborane **206** developed by Roush *et al.* allowed asymmetric prenylation of aldehyde **193** in good yield and with excellent selectivity (*d.r.* 99:1). Protection and ozonolysis with a reductive work up afforded **195**, which after protection / deprotection and oxidative cleavage with sodium periodate gave **197**. Addition of borane **207** afforded **198** in good yield (86%) and with a *d.r.* of 99:1. The epoxide was generated by exposure of **198** to DMDO and converted into **200** by treatment with acidic methanol. A Sharpless asymmetric epoxidation provided **201** with a *d.r.* of 99:1, which was cyclised to **202** by treatment with HF. Protection of the primary alcohol of **202** and alkylation of the remaining alcohols yielded **203** after deprotection with acetic acid. Jones oxidation and a Curtius rearrangement completed the synthesis of **205** (Scheme 1.3.19).

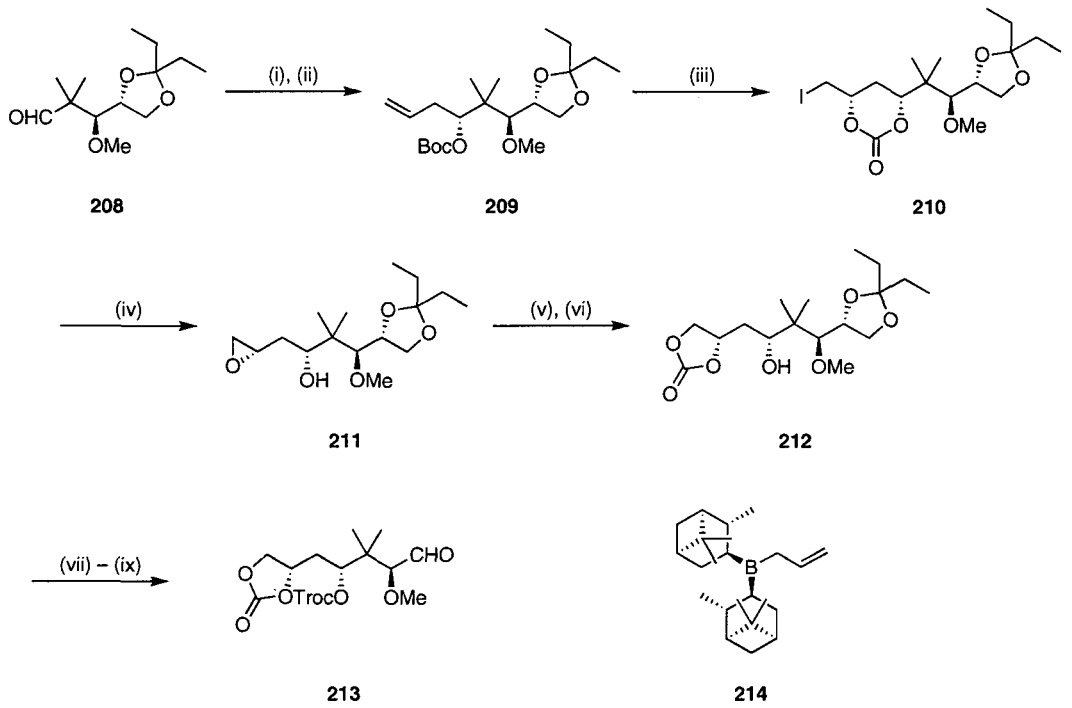


Scheme 1.3.19: Towards a fragment of onnamide A and mycalamides A and B.

Reagents and Conditions: (i) **206**, 4 Å mol sieves, $PhCH_3$, –78 °C, 79%, *d.r.* 99:1. (ii) MeI, NaH, DMF, RT, 93%. (iii) (a) O_3, CH_2Cl_2, MeOH (3:2), –78 °C. (b) $NaBH_4$, EtOH, 86%. (iv) TBDPS-Cl, imidazole, DMF, 60 °C, 86%. (v) HCO_2H, MeOH, RT. (vi) $NaIO_4$, THF, H_2O, RT, 78% (2 steps). (vii) **207**, 4 Å mol sieves, $PhCH_3$, –78 °C, 86%, *d.r.* 99:1. (viii) DMDO, acetone, K_2CO_3, RT. (ix) AcOH, MeOH, 86% (2 steps). (x) $Ti(O^iPr)_4$, (–)-DIPT, ^tBuOOH, CH_2Cl_2, –20 °C, 92%, *d.r.* 99:1. (xi) HF, MeCN, RT, 86%. (xii) Trityl chloride, $^iPr_2NEt$, CH_2Cl_2, RT, 85%. (xiii) (a) $BrCH_2Cl$, NaH, DMF. (b) AcOH, 60 °C, 49%. (xiv) Jones oxidation, 91%. (xv) $(PhO)_2P(O)N_3$, TMS-$(CH_2)_2OH$, NEt_3, THF, reflux, 79%.

For a complete synthesis, the correct side chain diol or diether would need to be present. Roush *et al.* published a modified synthesis two years later of a route to

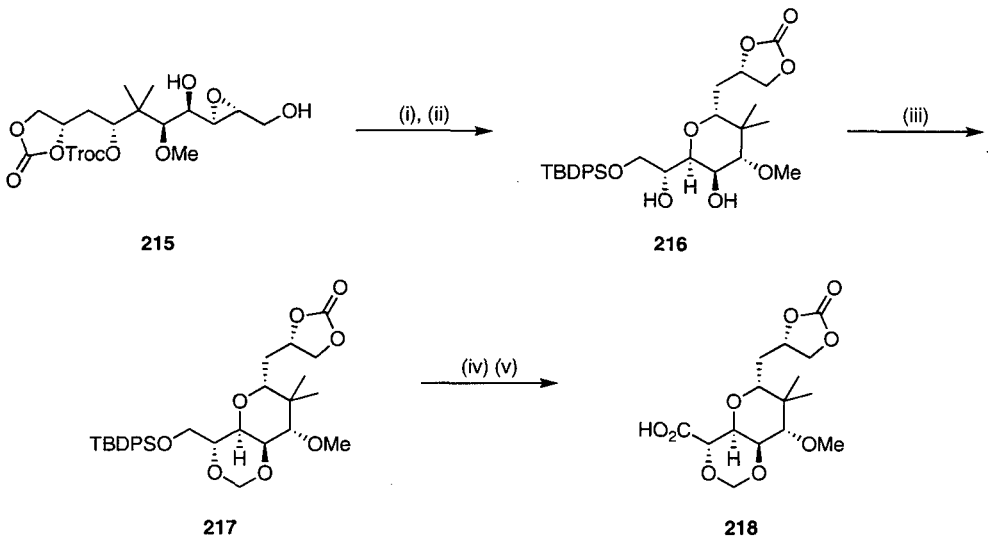
carboxylic acid **218** and related compounds (Schemes 1.3.20 and 1.3.21),[51] which they then used to complete the total synthesis of mycalamide A.[52]



Scheme 1.3.20: Modified synthetic route to mycalamide A fragment.

Reagents and Conditions: (i) **214**, Et_2O, –95 °C, 89%, *d.r.* 98:1. (ii) (a) BuLi, THF, 0 °C. (b) BOC-ON, RT, 95%. (iii) IBr, CH_2Cl_2 –78 °C. (iv) NaOH (sat.), dioxane, H_2O, RT, 77% (2 steps). (v) NaOAc, DMF, H_2O, 65 °C. (vi) $(Cl_3CO)_2CO$, pyridine, CH_2Cl_2, –78 °C, 64% (2 steps). (vii) Troc-Cl, pyridine, CH_2Cl_2, 0 °C. (viii) AcOH, H_2O (4:1), 80 °C. (ix) KIO_4, THF, H_2O, 65% (3 steps).

Aldehyde **213** was then advanced as before (Scheme 1.3.19) through asymmetric addition to the aldehyde, epoxidation, Peterson elimination and Sharpless epoxidation to give epoxide **215**. From epoxide **215**, acidic zinc removed the Troc group and induced cyclisation which gave **216** after silyl protection. Formation of the CH_2 bridge, deprotection and oxidation of the alcohol to a carboxylic acid gave **218** (Scheme 1.3.21).[51,52]

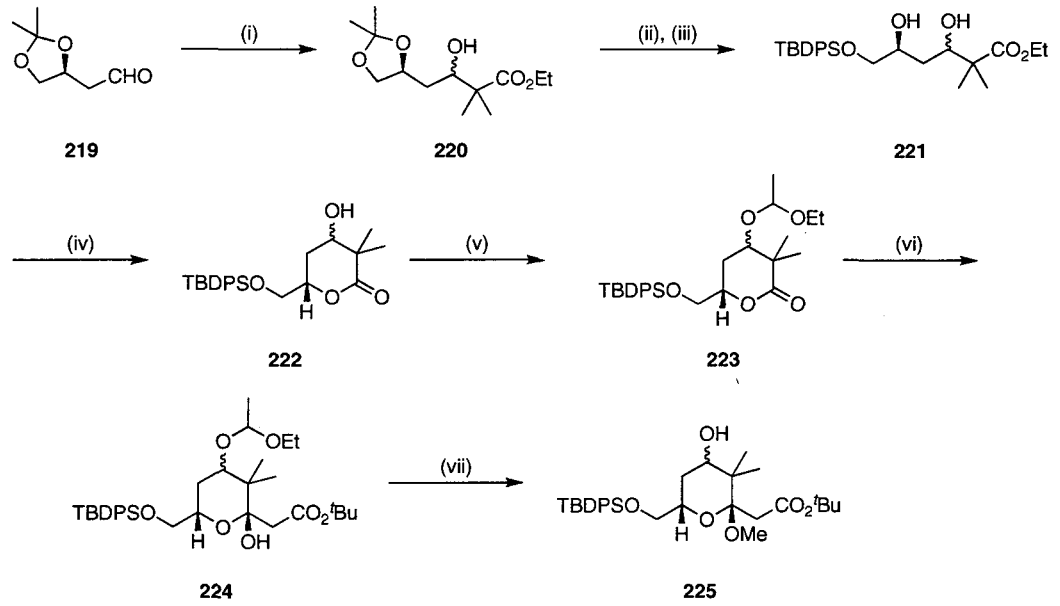


*Scheme 1.3.21: Completion of fragment **218**.*

Reagents and Conditions: (i) Zn, AcOH, 50 °C, 84%. (ii) TBDPS-Cl, imidazole, DMF, RT, 74%. (iii) P_2O_5, $(MeO)_2CH_2$, RT, 88%. (iv) TBAF, AcOH, THF. (v) Jones oxidation, 86%.

1.3.7 Lactone Formation

Nakata used a lactone as the basis of the ring with addition to the carbonyl to add functionality.[53] Aldehyde **219** (derived from (*S*)-malic acid) was converted into **220** by an aldol reaction, which after protecting group manipulation was followed by acid-induced cyclisation to lactone **222**. The alcohol of **222** was alkylated to protect it during the addition to the lactone carbonyl, giving **225** after deprotection (Scheme 1.3.22).

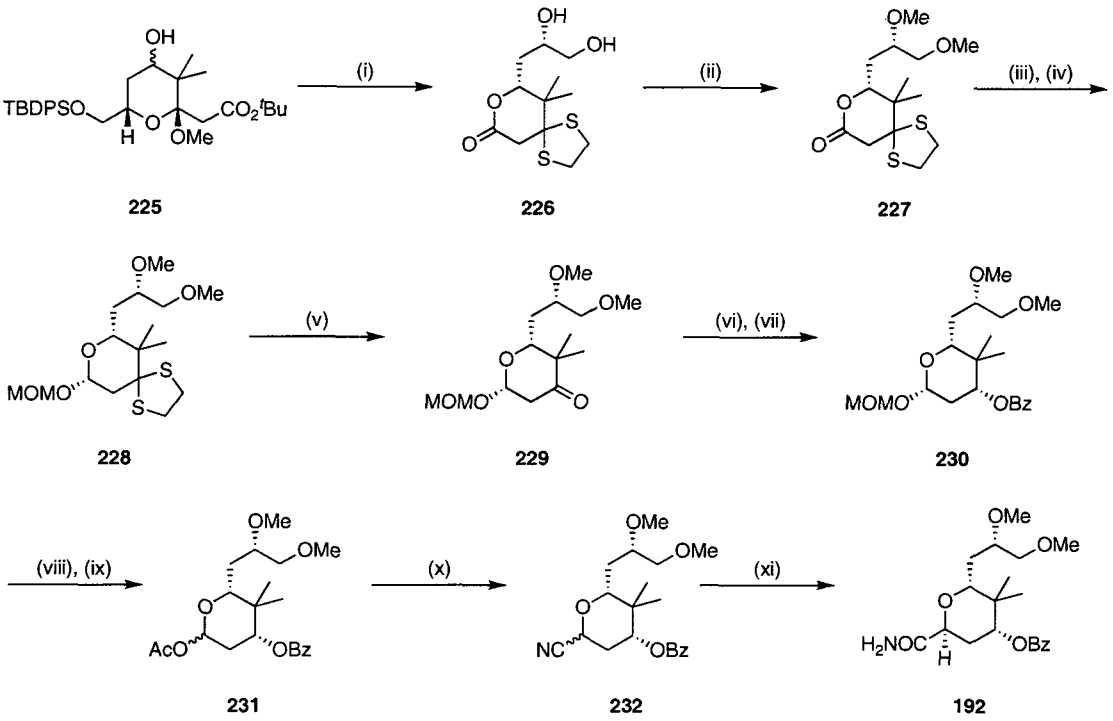


219 220 221 222 223 224 225

*Scheme 1.3.22: Synthesis of **225** via a lactone.*

Reagents and Conditions: (i) $(CH_3)_2CHCO_2Et$, LDA, THF –78 °C, 74%. (ii) *p*-TsOH, MeOH. (iii) TBDPS-Cl, imidazole, DMF. (iv) CSA, PhH, 72% (3 steps). (v) H_2C=CHOEt, PPTS, CH_2Cl_2. (vi) ^{t}BuOAc, LDA, THF, –78 °C. (vii) $CH(OMe)_3$, CSA, CH_2Cl_2, MeOH, 38% (3 steps).

Acetal **225** was converted into another lactone (**226**) by treatment with ethane dithiol and $BF_3.OEt_2$ to enable both elaboration of the ring and setting of the stereochemistry. Methylation of the diol, reduction of the lactone and MOM protection afforded **228**. Removal of the thiol enabled reduction of the resultant ketone with $LiAlH_4$, giving **230** as a single diastereoisomer after benzoyl protection. Removal of the MOM protecting group and reaction with acetic anhydride was followed by displacement of the resultant acetate with TMS cyanide to give **232**. The nitrile was converted into amide **192** using $TiCl_4$ (Scheme 1.3.23).



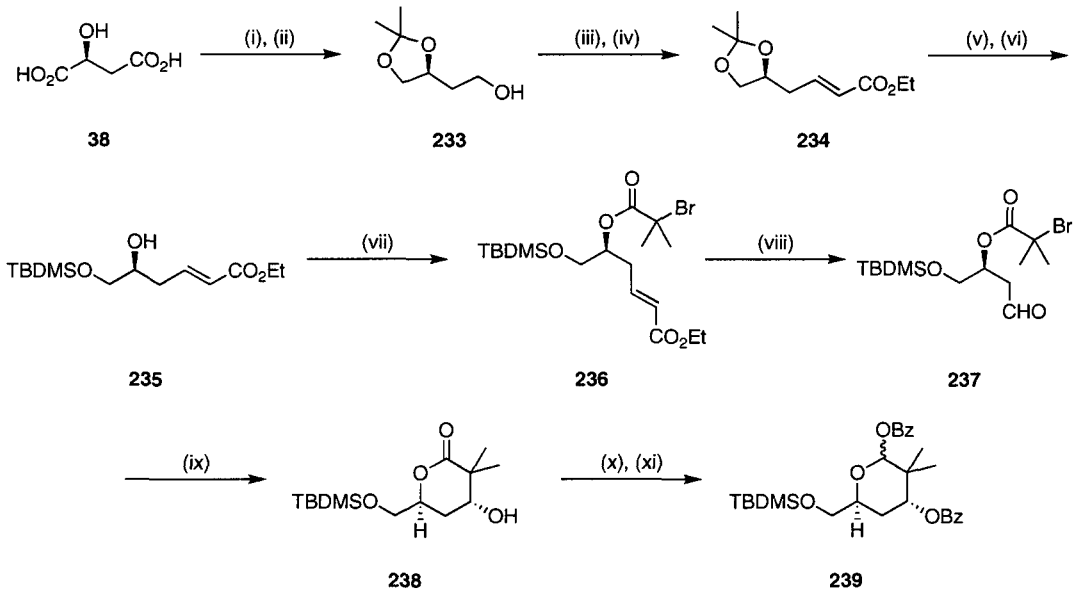
*Scheme 1.3.23: Further elaboration of **225** to **192**.*

Reagents and Conditions: (i) $HSCH_2CH_2SH$, $BF_3.OEt_2$, –30 °C, 83%. (ii) CH_2N_2, SiO_2, Et_2O, 83%. (iii) DIBAL-H, $PhCH_3$, –78 °C. (iv) CH_3OCH_2Br, $^iPr_2NEt$, CH_2Cl_2, 88% (2 steps). (v) NBS, $AgNO_3$, Na_2CO_3, MeCN, H_2O, 87%. (vi) $LiAlH_4$, Et_2O, 0 °C, 98%, single diastereoisomer. (vii) BzCl, pyridine, 100%. (viii) HCl (6 M), THF, 50 °C. (ix) Ac_2O, pyridine, 86%. (x) TMS-CN, $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 94%. (xi) $TiCl_4$, AcOH, H_2O, 87%.

192 is the required fragment for the synthesis of pederin, which Nakata successfully completed *via* this synthesis.[24] It is also similar to the target fragment (**37**) for onnamide F (**30**).

1.3.8 Samarium Diiodide Cyclisation

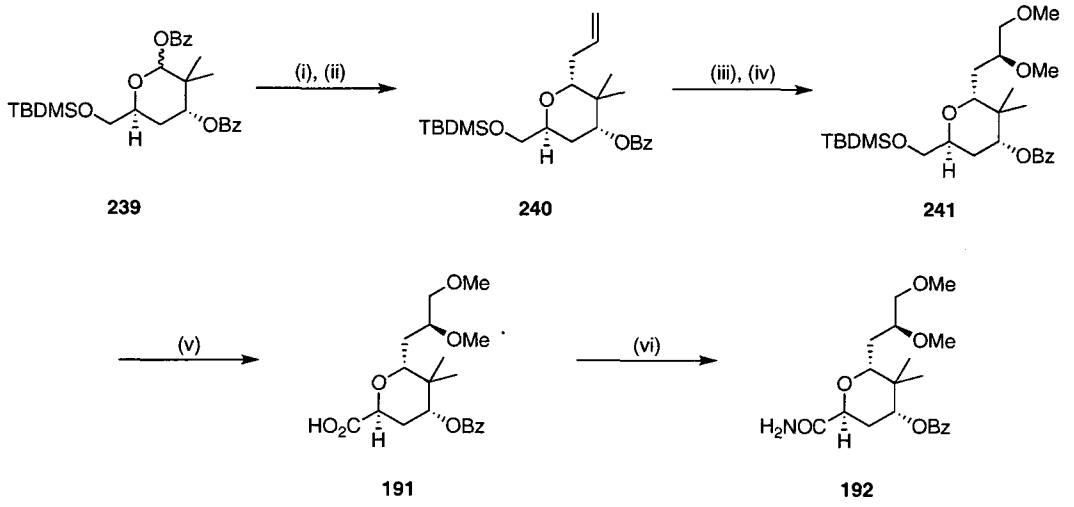
Nakata continued with the use of lactones in the synthesis of pederin.[54] From (*S*)-malic acid (**38**), reduction of the acid functionalities, acetal protection, Swern oxidation and a Wittig olefination gave **234**. Removal of the acetal and subsequent silyl protection were followed by acylation to form **236**, which was converted into **237** by ozonolysis. Samarium diiodide mediated cyclisation gave **238**, which was reduced to the corresponding lactol and protected with benzoyl chloride to give **239** (Scheme 1.3.24).



*Scheme 1.3.24: Use of SmI_2 to form lactone **238**.*

Reagents and Conditions: (i) $BH_3.SMe_2$, THF. (ii) *p*-TsOH, acetone, 91% (2 steps). (iii) Swern oxidation. (iv) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 89%. (v) HCl (1 M), THF, RT. (vi) TBDMS-Cl, pyridine, 99% (2 steps). (vii) $BrC(CH_3)_2COBr$, NEt_3, CH_2Cl_2, RT, 100%. (viii) (a) O_3, CH_2Cl_2 –78 °C. (b) Me_2S, –78 °C to RT. (ix) SmI_2, THF, 0 °C to RT, 85% (2 steps). (x) DIBAL-H, CH_2Cl_2, –78 °C. (xi) BzCl, pyridine, 0 °C to RT, 89% (2 steps).

From protected lactol **239**, familiar steps were used to complete the synthesis. Displacement of the benzoate with allyltrimethylsilane and silyl protection yielded **240**. Dihydroxylation and methylation of the diol advanced **240** to **241**, which was in turn oxidised to **191** *via* a Jones oxidation and converted to the amide **192** (Scheme 1.3.25).[54]



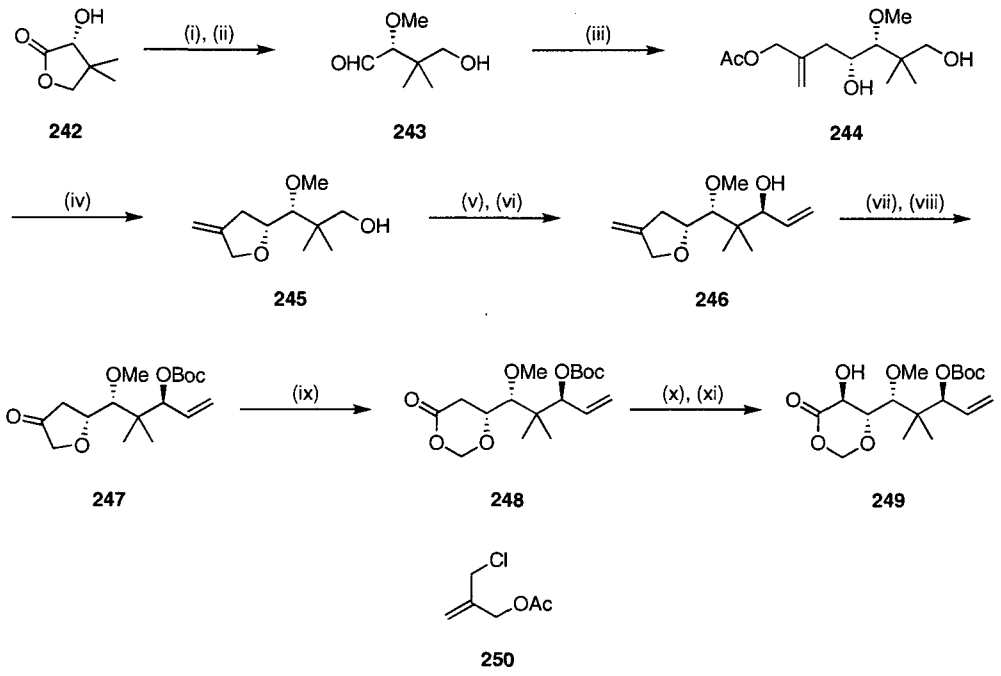
*Scheme 1.3.25: Completion of fragment **192**.*

Reagents and Conditions: (i) Allyltrimethylsilane, TMS-OTf, $BF_3.OEt_2$, MeCN, 0 °C, 91%. (ii) TBDMS-Cl, imidazole, CH_2Cl_2, 0 °C to RT, 100%. (iii) OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^tBuOH, H_2O, 90%, *d.r.* 3.1:1. (iv) MeI, NaH, DMF, 0 °C to RT. (v) Jones oxidation, acetone, 0 °C to RT. (vi) PyBOP, HOBt, $^iPr_2NEt$, NH_4Cl, DMF, 0 °C, 86% (3 steps).

192 was obtained in 35% overall yield from (*S*)-malic acid and the total synthesis of pederin was completed using steps already developed for the coupling between **192** and the pederic acid fragment.[54]

1.3.9 Palladium-Catalysed Cyclisation

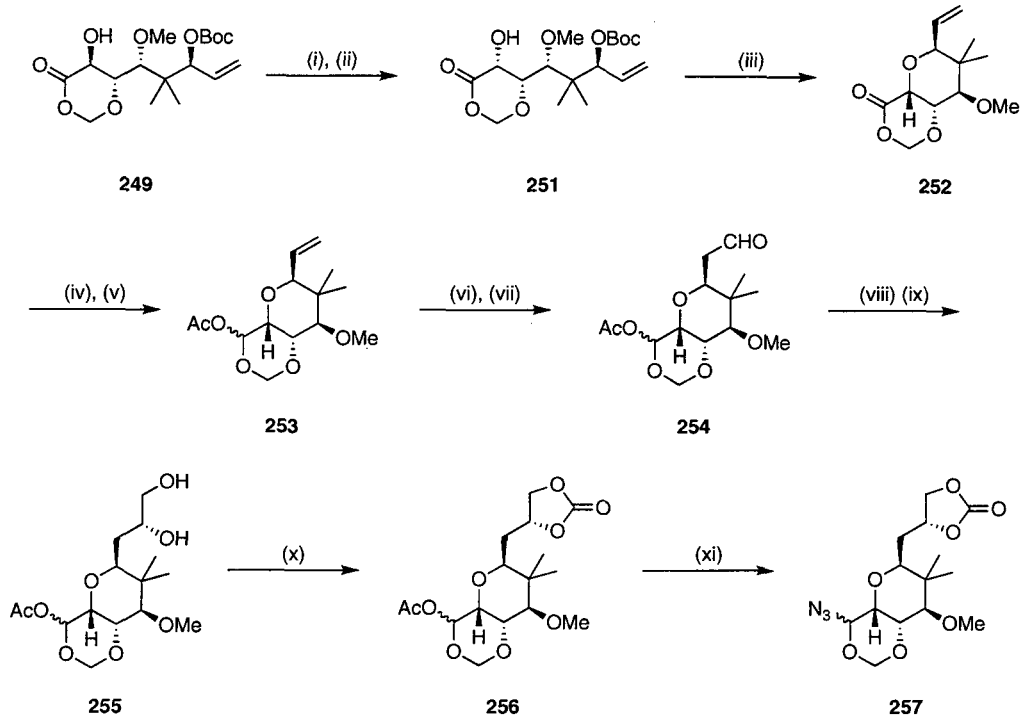
Trost's approach to (–)-mycalamide A was *via* a palladium-induced cyclisation of an alcohol onto an alkene.[55] This method was used in the formation of both rings of the required fragment, starting from lactone **242**. The alcohol functionality of **242** was protected as the methyl ether and the lactone subjected to DIBAL reduction. The resulting aldehyde was reacted with **250** in the presence of indium to afford **244** in 62% yield with a *d.r.* of 5:1. Palladium catalysed cyclisation afforded **245** in excellent yield, which was then oxidised *via* a Swern oxidation and reacted with vinylmagnesium bromide to give **246**. Boc protection, osmium mediated oxidative cleavage and Baeyer-Villiger oxidation provided one of the rings of mycalamide A (**248**). A Rubottom oxidation introduced the alcohol in **249** (Scheme 1.3.26).



Scheme 1.3.26: Palladium-mediated cyclisation of mycalamide A central ring.

Reagents and Conditions: (i) MeI, Ag_2O, MeCN, 58 °C, 86%, 98% *e.e.* (ii) DIBAL-H, CH_2Cl_2 –78 °C. (iii) **250**, In powder, NH_4Cl, H_2O, 62% (2 steps), *d.r.* 5:1. (iv) $PdCl_2(dppf)$, BEt_3, NEt_3, THF, reflux, 99%. (v) Swern oxidation, 90%. (vi) Vinylmagnesium bromide, $MgBr_2.Et_2O$ complex, CH_2Cl_2, –78 °C to RT, 96%. (vii) ^{n}BuLi, $(Boc)_2O$, THF, 0 °C to RT, 87%. (viii) (a) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^{t}BuOH, H_2O. (b) $NaIO_4$, THF, H_2O, 91%. (ix) *m*CPBA, 30% Li_2CO_3, CH_2Cl_2, RT, 98%. (x) (a) TBDMS-OTf, NEt_3, CH_2Cl_2 –78 °C. (b) DMDO, acetone, CH_2Cl_2, 4 Å mol sieves, –5 °C, 68%. (xi) $NBu_4Ph_3SiF_2$, $PhCO_2H$, THF 50 °C, 83%.

The second ring was introduced *via* the sequence shown in Scheme 1.3.27. After activation of the alcohol by conversion to the triflate, inversion was effected by treatment with sodium nitrite to give **251**. A further palladium catalysed cyclisation yielded **252** in 58% yield, with DIBAL reduction of the lactone and acetate formation giving **253**. Hydroboration of the alkene and PCC oxidation of the resultant alcohol advanced **253** to **254**. A Wittig olefination, dihydroxylation and cyclisation of the product with triphosgene gave **256**. The acetate was then displaced with TMS azide to complete the synthesis of **257**.[55]



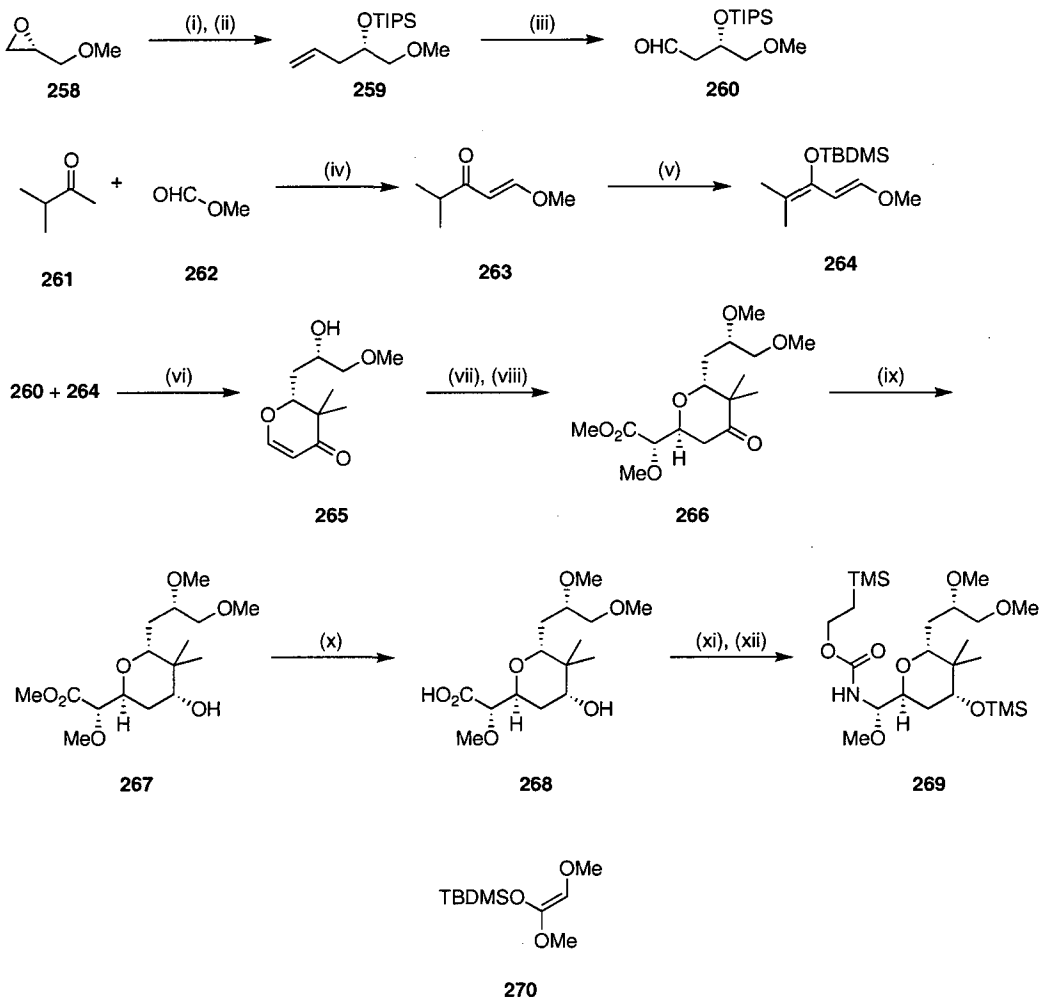
*Scheme 1.3.27: Completion of synthesis of fragment **257**.*

Reagents and Conditions: (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C. (ii) $NaNO_2$, DMF, RT, 75% (2 steps). (iii) $Pd_2(dba)_3CHCl_3$, dppf, dichloroethane, 70 °C, 58%. (iv) DIBAL-H, CH_2Cl_2 –78 °C. (v) Ac_2O, pyridine, DMAP, –78 °C to RT, 100% (2 steps). (vi) 9-BBN, $RhCl(PPh_3)_3$, THF, 0 °C to RT. (vii) PCC, 4 Å mol sieves, CH_2Cl_2, 45 °C, 48%. (viii) $H_2C{=}PPh_3$, $PhCH_3$, –40 °C to –20 °C, 97%. (ix) OsO_4, $(DHQD)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH, H_2O, 74% - quant, *d.r.* 4.1:1 – 9:1. (x) Triphosgene, pyridine, CH_2Cl_2, –78 °C, 73 – 84%. (xi) TMS-OTf, TMS-N_3, MeCN, 0 °C, 68%, *d.r.* 1.6:1.

1.3.10 Hetero Diels-Alder and Conjugate Addition

Rawal *et al.* recently reported a unique approach to the synthesis of pederin using a hetero Diels-Alder reaction to form the ring and introduce one of the stereocentres.[5] The synthesis started with epoxide **258**, which was opened with vinylmagnesium bromide, the alcohol protected and the alkene cleaved by ozonolysis to afford **260**. The other fragment (**264**) required for the hetero Diels-Alder reaction was prepared by reaction of **261** and **262** to afford **263** in 47% yield after elimination. Treatment of **263** with TBDMS chloride resulted in **264** in 95% yield. **260** and **264** were reacted together using an aluminium Lewis acid and an HF quench to afford **265** in 65% yield and with excellent selectivity (*d.r.* 92:8). Methylation of the alcohol and reaction with **270** in the presence of scandium triflate gave **266** in 85% yield with excellent

selectivity (20:1). L-selectride reduction also proved selective, providing **267** with a *d.r.* of 12:1. Saponification of the ester in **267** and reaction of the resultant acid with TMS ethanol and DPPA afforded **269** in 72% yield after silyl protection (Scheme 1.3.28).



*Scheme 1.3.28: Short synthesis of **269** via hetero Diels-Alder reaction.*

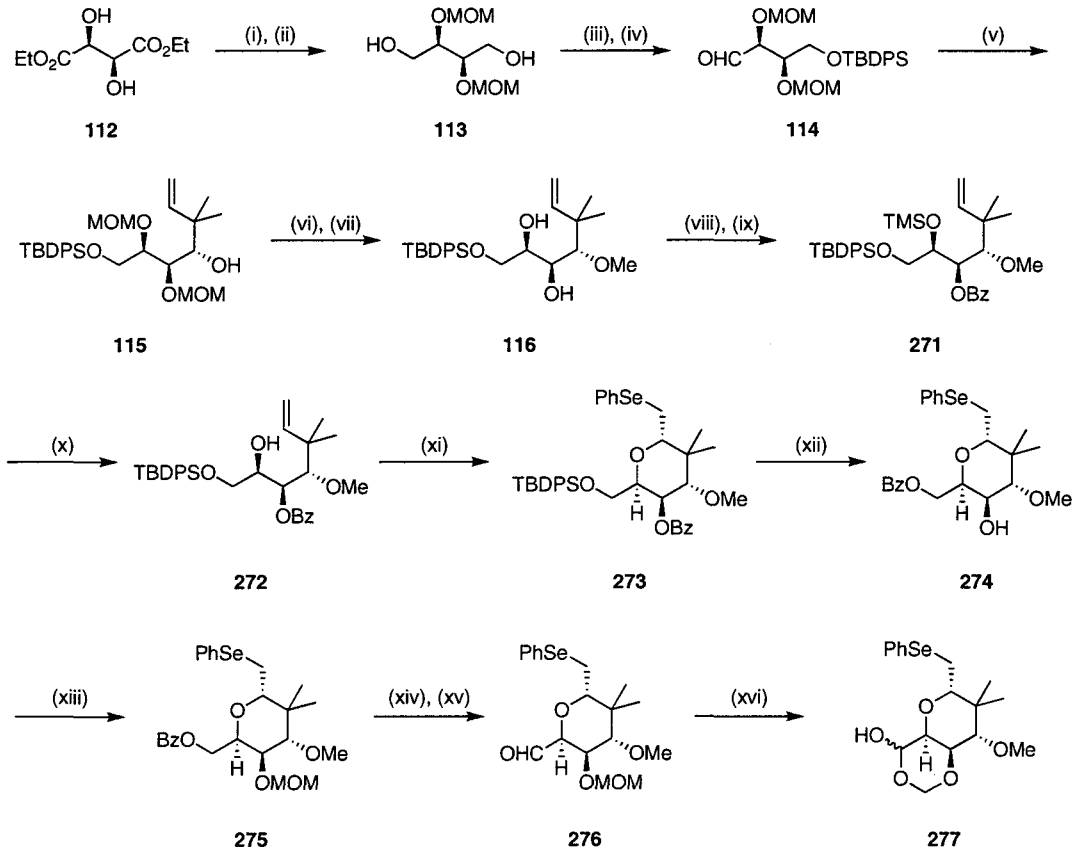
Reagents and Conditions: (i) Vinylmagnesium bromide, CuI, THF, –78 °C to 0 °C. (ii) TIPS-Cl, imidazole, CH_2Cl_2, RT, 85% (2 steps). (iii) (a) O_3, CH_2Cl_2, –78 °C. (b) PPh_3, –78 °C to RT, 83%. (iv) (a) NaOMe, Et_2O, reflux. (b) Me_2SO_4, DMSO, 0 °C, 47%. (v) TBDMS-Cl, NEt_3, Et_2O, 0 °C, 95%. (vi) (a) Al(2,6-diphenylphenoxide)$_2$Me (0.2 equiv.), TMS-OTf, CH_2Cl_2, –78 °C to –45 °C. (b) 10% HF in MeCN quench, 65%, *d.r.* 92:8. (vii) MeI, NaHMDS, THF, –78 °C to 0 °C, 87%. (viii) (a) **270**, $Sc(OTf)_3$, CH_2Cl_2, –78 °C to RT. (b) 10% HF in MeCN quench, 85%, *d.r.* 20:1. (ix) L-selectride, THF, –78 °C, 92%, *d.r.* 12:1. (x) NaOH, MeOH, RT, quant. (xi) TMS-CH_2CH_2OH, DPPA, NEt_3, 4 Å mol sieves, THF, reflux, 75%. (xii) TMS-Cl, imidazole, DMF, RT, 72%.

This approach proved to be a very efficient strategy; the synthesis was completed in a short sequence from commercially available starting materials. **269** had all of the required stereochemistry for pederin, including the chiral methyl ether adjacent to the carbamate. This is often introduced *via* an imidate,[21,56] but in this case, only coupling to pederic acid and deprotection were required to complete the total synthesis.[5]

1.3.11 Michael Addition

In another synthesis reported by Rawal *et al.*, modification of a tartrate, subsequent Michael addition to a terminal double bond and formation of a selenide was used to form the required THP ring of the mycalamides.[57] After MOM protection and reduction of diethyl tartrate, **113** was mono silyl protected and the remaining alcohol oxidised to aldehyde **114**. Addition of prenyl (tributyl)stannane afforded **115** in 90% yield with excellent selectivity (50:1). Following several protecting group modifications, **272** was cyclised to selenide **273** with a *d.r.* of 1.8:1. Further manipulation of the protecting groups, including migration of the benzoyl group, and Swern oxidation afforded **277** after ring formation with paraformaldehyde (Scheme 1.3.29).

This synthesis makes good use of the chirality present in the tartrate starting material and has an advantage in that the selenide offers the opportunity to further functionalise the molecule by introducing the required side chains for the mycalamides. The steps to convert **277** into a suitable coupling partner have been previously reported.[47]

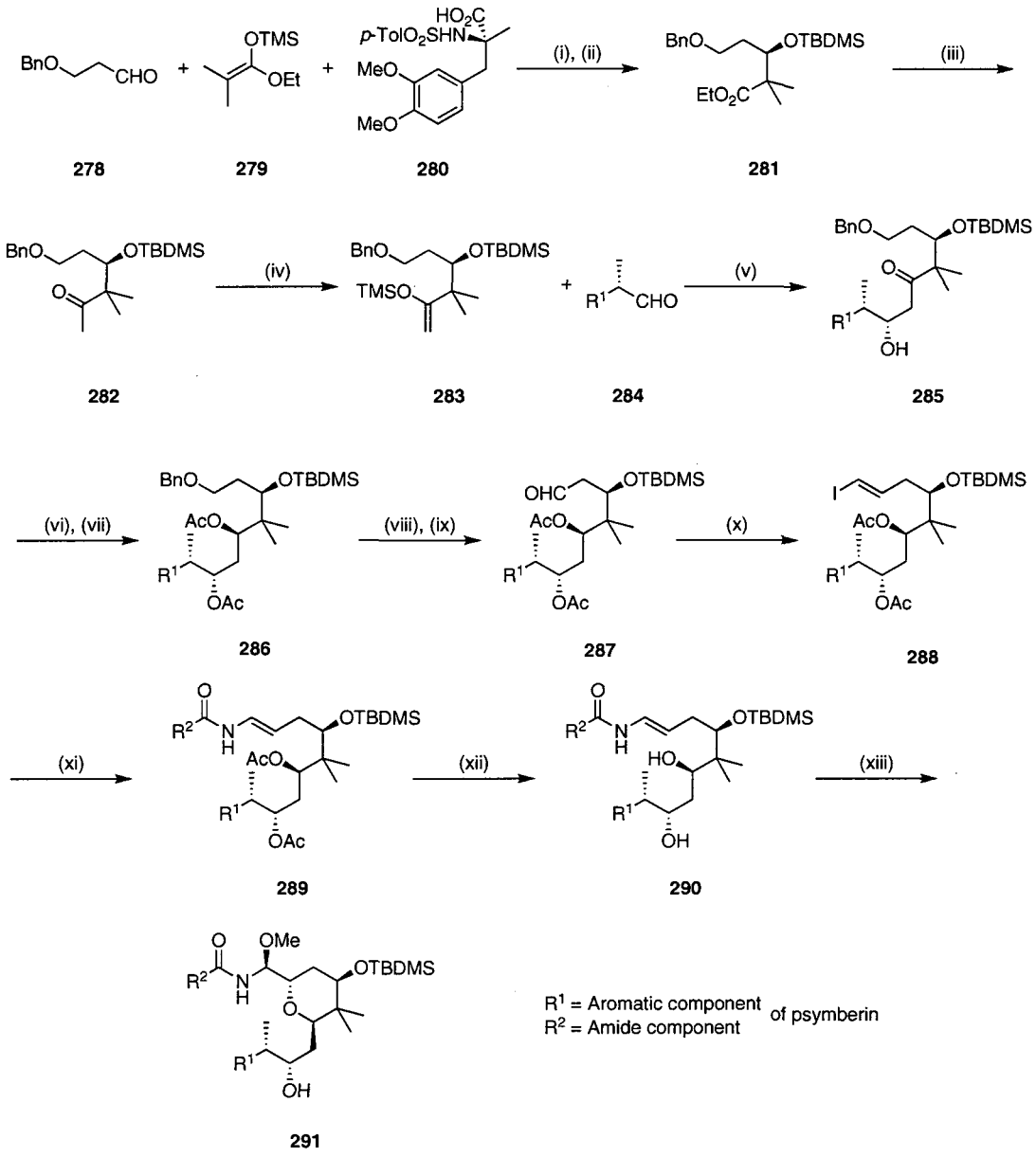


Scheme 1.3.29: Synthesis of 277 via Michael addition.

Reagents and Conditions: (i) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, quant. (ii) $LiAlH_4$, Et_2O, reflux, 86%. (iii) ^nBuLi, TBDPS-Cl, THF, 0°C, quant. (iv) Swern oxidation, 90%. (v) $(CH_3)_2C{=}CHCH_2SnBu_3$, $ZnBr_2$, CH_2Cl_2, –78 °C to 0 °C, 90%, *d.r.* 50:1. (vi) MeI, NaH, THF, RT, 98%. (vii) PPTS, ^{i}PrOH, reflux, 80%. (viii) TMS-Cl, NEt_3, THF, RT, 93%. (ix) BzCl, DMAP, pyridine, 95%. (x) PPTS, MeOH, 96%. (xi) *N*-phenylselenophthalimide, CSA, CH_2Cl_2, RT, 78%, *d.r.* 1.8:1. (xii) TBAF, THF, RT, 84%. (xiii) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, RT, 98%. (xiv) NaOH (2 M), MeOH, RT, 98%. (xv) Swern oxidation, 69%. (xvi) Paraformaldehyde, HCl (conc.), Et_2O, 0 °C, 92%.

The second synthesis to use Michael addition was the total synthesis of psymberin reported by Huang *et al.* in 2007.[58] A ligand-controlled Masamune aldol condensation was used to connect **278** and **279** in excellent yield (95%) and *e.e.* (98%). Ester **281** was treated with TMS-CH_2Li to give ketone **282** in one step, which was then transformed into silyl enol ether **283**. An aldol reaction between **283** and aldehyde **284** gave ketone **285** with selectivity of 5:1, the ketone in **285** was reduced with catecholborane (*d.r.* 15:1) and the resultant alcohol protected as the acetate (**286**). Following deprotection and DMP oxidation, Takai vinyl iodide formation gave **288**, which was reacted with the appropriate amide and the acetate hydrolysed to give

290. Exposure of **290** to a hypervalent iodine reagent induced cyclisation to form **291** with 1:1 selectivity (Scheme 1.3.30).



*Scheme 1.3.30: Synthesis of **291** in the total synthesis of psymberin.*

Reagents and Conditions: (i) BH_3.THF, CH_3CH_2CN, –78 °C, 95%, 98% *e.e.* (ii) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%. (iii) TMS-CH_2Li, pentane, 0 °C, 95%. (iv) TMS-OTf, NEt_3, CH_2Cl_2, 0 °C, 100%. (v) $BF_3.OEt_2$, CH_2Cl_2, –78 °C, 91%, *d.r.* 5:1. (vi) Catecholborane, THF, 0 °C, 92%, *d.r.* 15:1. (vii) Ac_2O, DMAP, pyridine, RT, 78%. (viii) H_2, Pd / C, EtOH, RT, 100%. (ix) DMP, CH_2Cl_2, 0 °C to RT, 95%. (x) $CrCl_2$, CHI_3, THF, 0 °C, 90%, E:Z 5:1. (xi) R^2CONH_2, $MeNH(CH_2)_2NHMe$, $CsCO_3$, $PhCH_3$, 70 °C, 95%. (xii) NaOMe, MeOH, RT, then protection of R^1, 95% (2 steps). (xiii) $PhI(OAc)_2$, MeOH, hexafluoro*iso*propanol, 0 °C to RT, 72%, *d.r.* 1:1.

1.4 Retrosynthetic Analysis and Synthetic Approach

Disconnection of onnamide F led to three fragments (Figure 1.2.1). Retrosynthetic analysis of two of these fragments (**37** and **32**) is detailed in Figure 1.4.1.

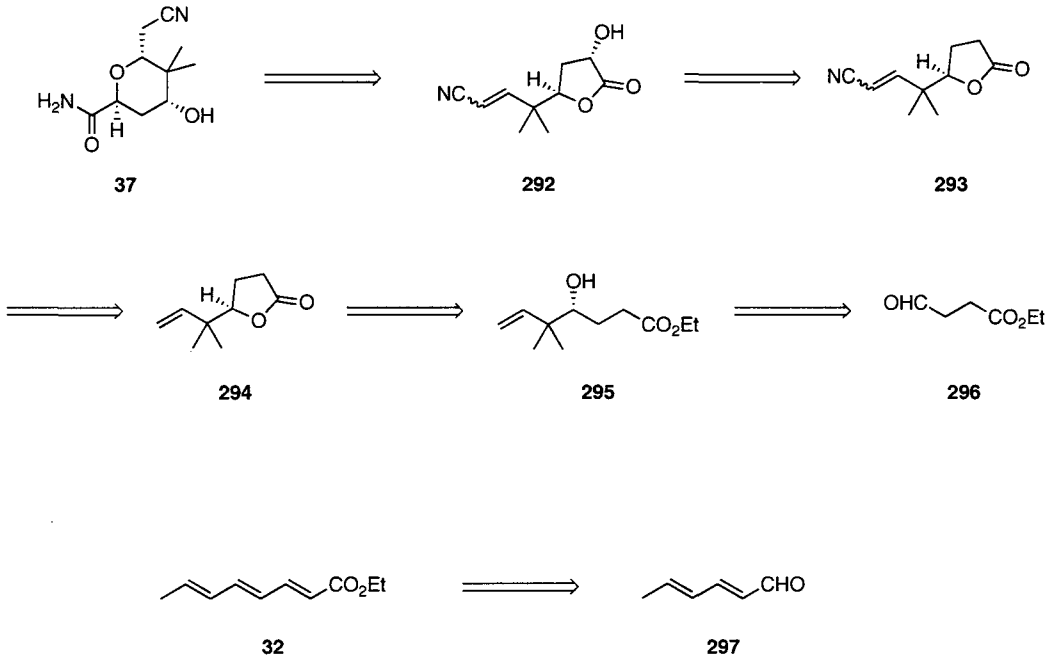
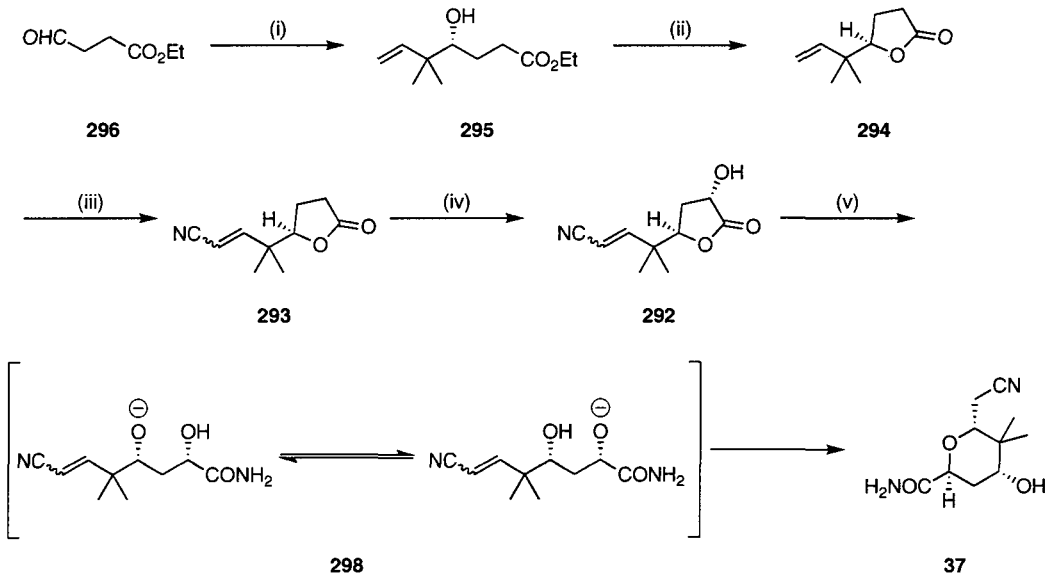


Figure 1.4.1: Retrosynthetic analysis of fragments 37 and 32.

The synthetic approach to **37** and **32** (Scheme 1.4.1) uses both externally controlled asymmetric reactions and steric factors of the five-membered ring to influence the resulting stereochemistry.

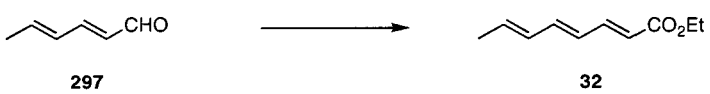


Scheme 1.4.1: Proposed synthesis of fragment ***37****.*

Reagents and Conditions: (i) (3,3-Dimethylallyl)di*iso*pinocampheylborane. (ii) PPTS. (iii) Acrylonitrile, Grubbs I or II catalyst. (iv) (a) LiTMP. (b) MoOPH. (v) NH_3.

The proposed sequence begins with asymmetric prenylation of aldehyde **296** using Brown's chiral borane technique.[59,60] The resulting alcohol would be cyclised to form the lactone **294**. Successful cross-metathesis with acrylonitrile using Grubbs catalyst would give substituted alkene **293**.[61-63] When **293** is treated with a base to form the enolate followed by addition of MoOPH,[64] α-hydroxylation should take place on the opposite face of the ring to the bulky prenyl group at C5, providing the required *S* stereocentre at C3 (**292**). Lactone **292** will be opened with ammonia and, after proton transfer, can undergo Michael addition to the unsaturated nitrile to deliver fragment **37** in only five steps.

Unsaturated chain **32** is known in the literature and can be synthesised in one step *via* a Wittig or Horner-Wadsworth-Emmons reaction (Scheme 1.4.2).[65]



Scheme 1.4.2: Synthesis of unsaturated chain ***32****.*

Reagents and Conditions: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF.

Chapter 2 Results - Racemic Synthesis of Nitrile Fragment 37

2.1 Starting material synthesis

The synthetic approach to fragment **37** began with preparation of starting aldehyde **296**, which is not commercially available but is known in the literature.[66] One obvious route, hydrolysis of γ-butyrolactone and oxidation of the resulting alcohol, was largely unsuccessful, so reduction of acid chloride **299** was used as a start point for the synthesis (Scheme 2.1.1).

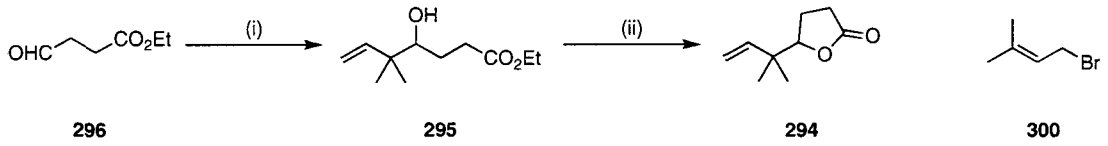
299 **296**

*Scheme 2.1.1: Synthesis of starting aldehyde **296**.*
Reagents and Conditions: Et_3SiH, Pd / C, neat, 0 °C, 2 h, 72%.

Upon treatment of acid chloride **299** with triethylsilane in the presence of palladium on carbon,[67,68] aldehyde **296** was isolated in moderate to good yield. Purification by column chromatography was necessary to remove triethylsilyl chloride from the product, but this had to be performed quickly as extended contact with silica caused degradation, as did distillation of the crude product. Alternative reductions using $NaBH(OAc)_3$ as a hydride source or hydrogen gas with a metal catalyst either failed or resulted in over-reduction.

2.2 *Iso*prenylation of aldehyde **296** to lactone **294**

To facilitate the development of a racemic synthesis of nitrile **37**, a robust route to lactone **294** was required that could deliver this material in quantity. The most straightforward method was *via* addition of a prenylzinc species (generated from prenyl bromide, zinc dust and ammonium chloride in a THF / water solvent mixture) to aldehyde **296** (Scheme 2.2.1).[69]



296 **295** **294** **300**

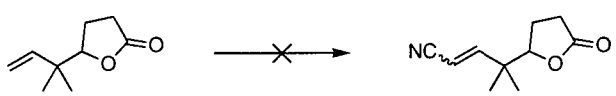
*Scheme 2.2.1: Synthesis of racemic lactone **294**.*

Reagents and Conditions: (i) Zn dust, prenyl bromide (**300**), NH_4Cl, H_2O, THF, RT, 2 h, 85% (crude). (ii) TFA (cat.), CH_2Cl_2, reflux, 1 h, 90%.

This resulted in an unstable hydroxy ester **295** which cyclised to **294** on treatment with TFA in CH_2Cl_2 at reflux. The *iso*prenylation reaction proved reliable, high yielding and held several advantages over the corresponding Grignard additions. In particular, it allowed the use of an aqueous solvent mixture, resulting in rapid and easy reagent formation and reduced side-reactions such as homocoupling.

2.3 Introduction of unsaturated nitrile functionality

The initial plan was to introduce the nitrile functionality *via* a cross-metathesis reaction between **294** and acrylonitrile, facilitated by a suitable catalyst. Grubbs' I and II catalysts offered the combination of reasonable stability and commercial availability, with literature reports indicating that metathesis reactions involving acrylonitrile are possible, if rather challenging.[62,63] Mixtures of lactone **294**, acrylonitrile and Grubbs' catalyst were subjected to various traditional reaction conditions without success (Scheme 2.3.1).



294 **293**

Scheme 2.3.1: Attempted cross-metathesis reactions.

Reagents and Conditions: 1. Acrylonitrile, Grubbs I, CH_2Cl_2, reflux, 16 h.[63]

2. Acrylonitrile, Grubbs II, CuCl, CH_2Cl_2, reflux, 16 h.[62]

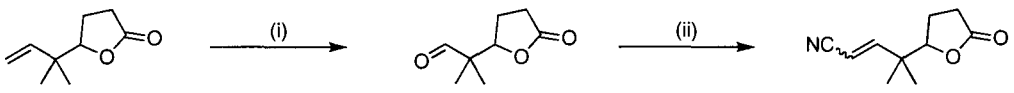
After thermal methods failed, microwave irradiation was employed in an attempt to achieve a successful conversion. Unfortunately, this failed to afford nitrile **293** with

all reactions returning the starting material **294**. The reaction conditions tried are detailed in Table 2.3.1.

Entry	Conditions
1	Grubbs II (2 mol%), CH_2Cl_2, 120 °C, 15 min.
2	Grubbs II (5 mol%), $PhCH_3$, 150 °C, 15 min.
3	Grubbs I, (5 mol%), $PhCH_3$, 150 °C, 15 min.
4	Grubbs II (5 mol%), CuCl (20 mol%), CH_2Cl_2, 120 °C, 15 min.

Table 2.3.1: Microwave assisted cross-metathesis.
All reactions were run with 2 equiv. of acrylonitrile at 0.04 M with a fixed hold time.

Literature reports suggest that the use of Schrock's molybdenum catalyst might be advantageous,[61] but as this species is very air sensitive and requires a glove box for handling, a robust two-step procedure for the conversion of alkene **294** to nitrile **293** was examined (Scheme 2.3.2). Ozonolysis of **294** afforded aldehyde **301** in 51% yield after chromatography.



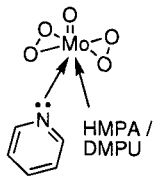
294 **301** **293**

*Scheme 2.3.2: Synthesis of **293** via oxidative cleavage and Wittig olefination.*
Reagents and Conditions: (i) (a) O_3, CH_2Cl_2, –78 °C, 30 min. (b) PPh_3, –78 °C to RT, 1 h, 51%.
(ii) ^tBuOK, $Br^-Ph_3P^+CH_2CN$, THF, 0 °C to RT, 16 h, 95%, *E*:*Z* 6:1.

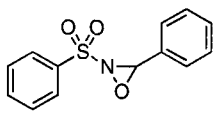
The Wittig reaction between **301** and acetonitriletriphenylphosphonium bromide proceeded cleanly and efficiently, yielding a 6:1 mixture of (*E*) and (*Z*)-nitrile **293** in 95% yield after column chromatography.

2.4 Hydroxylation of lactone **293** *via* electrophilic oxygen reagents

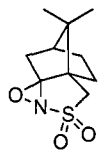
The next task was to effect the diastereoselective α-hydroxylation of lactone **293** with an electrophilic hydroxylating reagent. Several reagents exist which are capable of introducing an alcohol adjacent to a carbonyl. These are mainly based around MoOPH (**303**), developed by Vedejs, and various oxaziridine reagents (e.g. **304** and **305**), developed by Davis (Figure 2.4.1).



303



304

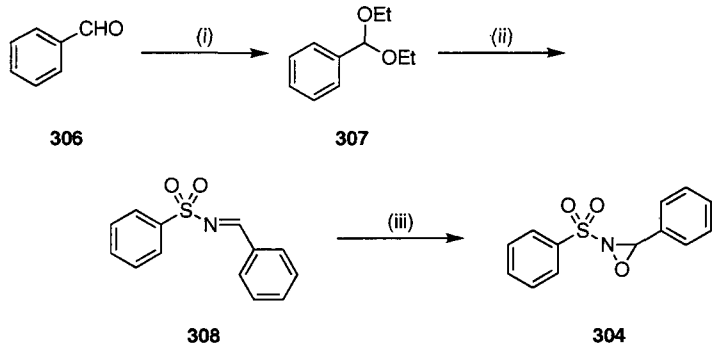


305

Figure 2.4.1: α-hydroxylation reagents.

MoOPH and the related DMPU analogue, MoOPD are quickly synthesised from MoO_3 in a two-step protocol.[64,70,71] Attempts to effect the hydroxylation of the enolate of lactone **294** with MoOPD were unsuccessful, even when the reaction was allowed to warm from –78 °C to room temperature. This may, in part, be due to the low solubility of these reagents in THF and the need to add them as solids to the pre-formed enolate.[64]

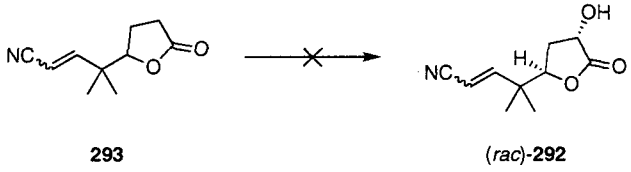
The oxaziridines **304** and **305** are also easy to prepare and have better solubility in organic solvents, better stability and lower toxicity. Oxaziridine **304** was easily prepared from benzaldehyde by the literature method (Scheme 2.4.1) and was stored under nitrogen at –18 °C until needed to minimise decomposition.[72-74]



*Scheme 2.4.1: Synthesis of oxaziridine **304**.*

Reagents and Conditions: (i) $(EtO)_3CH$, NH_4Cl, EtOH, reflux, 1.5 h, quant. (ii) Benzenesulfonamide, neat, 170 °C, 30 min, 62%. (iii) Oxone, K_2CO_3, $PhCH_3$, H_2O, RT, 3 h, 76%.

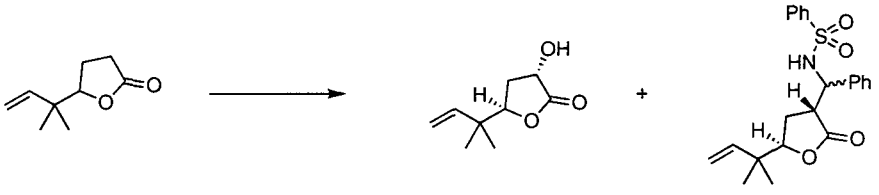
When nitrile **293** was sequentially treated with LiTMP and oxaziridine **304** (Scheme 2.4.2),[75] none of the desired product (*rac*)-**292** could be identified by NMR or TLC, and only a very polar compound was detected.



*Scheme 2.4.2: Initial attempts at α-hydroxylation of **293**.*

Reagents and Conditions: (i) LiTMP, THF, –78 °C, 1 h. (ii) Oxaziridine **304**, THF, –78 °C, 2 h.

With the failure of this reaction, the order of synthesis was altered to add the alcohol functionality before the nitrile. Hydroxylation of lactone **294** did proceed with oxaziridine **304**, albeit in very low yield (Scheme 2.4.3).[75] It did not prove possible to purify (*rac*)-**309** when prepared via this method.



294 (*rac*)-**309** **310**

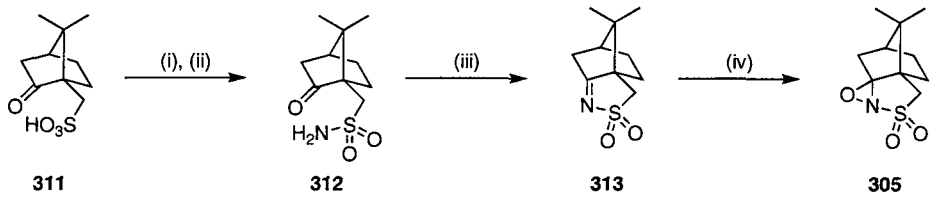
*Scheme 2.4.3: Hydroxylation of lactone **294**.*

Reagents and Conditions: (i) LiTMP or KHMDS, THF –78 °C, 1 h. (ii) Oxaziridine **304**, THF, –78 °C, 15 min, 9%.

Replacement of LiTMP with KHMDS to deprotonate the lactone had no effect on the yield and severe purification problems were encountered in all cases. Upon reaction, oxaziridine **304** re-forms the precursor sulfonimine **308**, which decomposes on silica gel to benzaldehyde and benzenesulfonamide. As a result, lactone (*rac*)-**309** could not be isolated in its pure form following column chromatography. Addition of HCl to the reaction mixture hydrolyse **308** before work up was unsuccessful as benzenesulfonamide further interfered with purification.

An additional problem described in the literature was also evidenced. Sulfonimine **308** is reactive to enolates and upon formation, competes with oxaziridine **304** with formation of **310** as a significant by product. The identity of **310** was confirmed by ^{1}H-^{1}H COSY NMR (the stereochemistry depicted is assumed).

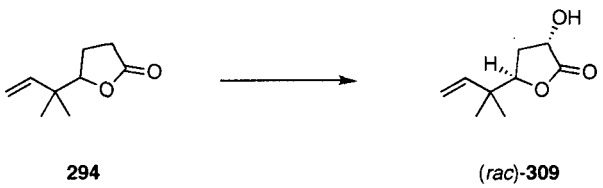
By products of this type have been noted by both Fry and Davis.[75,76] Davis recommended the use of camphorsulfonyl oxaziridine **305** to overcome this problem, as the sulfonimine **313**, formed upon reaction is inert to organometallic nucleophiles and enolates.[76] The chiral nature of the reagent could also offer an opportunity to influence the diastereoselectivity of the reaction. Consequently, the syntheses of **305** and its enantiomer were completed in four steps from camphorsulfonic acid by the literature procedure (Scheme 2.4.4).[77]



*Scheme 2.4.4: Synthesis of reagent **305**.*

Reagents and Conditions: (i) Oxalyl chloride, DMF (cat.), CH_2Cl_2, 0 °C, 16 h. (ii) NH_3, CH_2Cl_2, H_2O, 0 °C, 22 h, 91% (2 steps). (iii) Amberlyst-15 resin, $PhCH_3$, Dean and Stark, reflux, 6 h, 77%. (iv) Oxone, K_2CO_3, $PhCH_3$, H_2O, 0 °C to RT, 72 h, 75%.

Formation of the enolate of lactone **294** and subsequent treatment with (+) or (–)-**305** resulted in the successful formation of hydroxylactone (*rac*)-**309** in yields varying from 40 – 81% (Scheme 2.4.5).[78-80] The effects of differing bases (LiTMP, LiHMDS, LDA, NaHMDS, KHMDS) and the two oxaziridine enantiomers were investigated to attempt to improve yields and selectivity (Table 2.4.1).



*Scheme 2.4.5: Successful synthesis of (rac)-**309** without by products.*

Reagents and Conditions: (i) Base, THF, –78 °C, 1 h. (ii) (+) or (–)-**305**, THF, –78 °C, 15 min to 1 h.

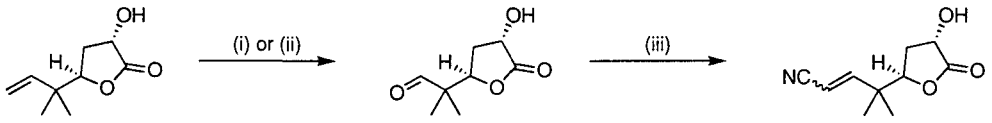
Entry	Base	Oxaziridine	Yield	*Anti*:*Syn* (typical)
1	LiTMP	(–)-**305**	16 – 81%	3:1
2	LiTMP	(+)-**305**	26 – 54%	3:1
3	LiHMDS	(+)-**305**	9 – 34%	3:1
4	LDA	(+)-**305**	29%	3:1
5	NaHMDS	(+)-**305**	37%	1:1
6	KHMDS	(–)-**305**	Generated mixture of products	

Table 2.4.1: Results of varying reagents in hydroxylation reactions. All reaction conditions were as Scheme 2.4.5.

The original hypothesis was correct; hydroxylation does indeed favour the face of the lactone ring opposite to the bulky *iso*prenyl group. As Table 2.4.1 indicates, diastereomeric ratios of around 3:1 are consistent in the hydroxylation reaction, but yields vary greatly. Base selection is important as NaHMDS decreased the diastereoselectivity and KHMDS delivered the least satisfactory result. Addition of DMPU lowered the yield to 26%, with diastereoselectivity remaining at 3:1. In this racemic series, the low yield (~40%) was accepted to enable further study on subsequent reactions. Application of oxaziridine **305** to the nitrile lactone **293** (Scheme 2.4.2) completely failed, indicating that the nitrile is incompatible with the required reaction conditions, possibly due to the α,β-unsaturated nitrile as a good Michael acceptor undergoing addition by the metal amide base.[81]

2.5 Formation of nitrile lactone (*rac*)-**292**

The oxidative cleavage-Wittig olefination strategy was applied next to hydroxylactone (*rac*)-**309** (Scheme 2.5.1). Ozonolysis was superior to ruthenium tetroxide mediated cleavage in that there were fewer problems with work-up and purification. Unfortunately, under identical conditions to those in Scheme 2.3.2, the Wittig olefination reaction afforded a 35% yield of pure material.



(*rac*)-**309** (*rac*)-**314** (*rac*)-**292**

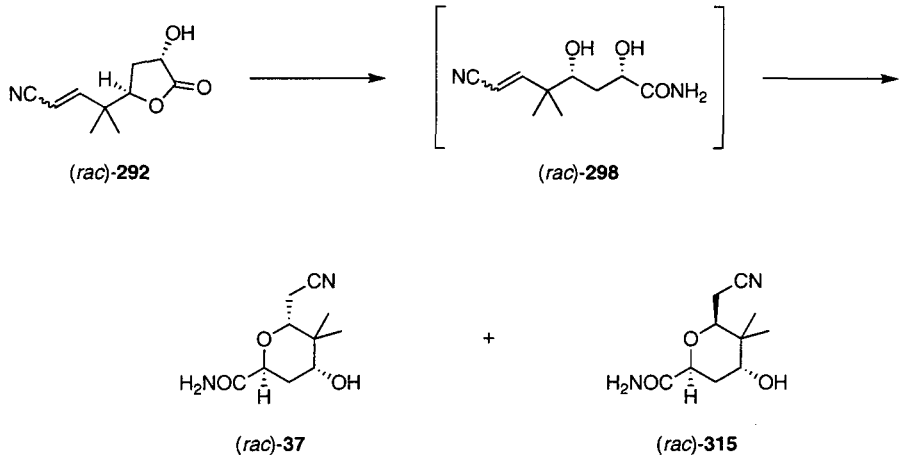
*Scheme 2.5.1: Oxidative cleavage and Wittig olefination of lactone (rac)-**309**.*

Reagents and Conditions: (i) (a) O_3, CH_2Cl_2, –78 °C, 15 min. (b) PPh_3, –78 °C to RT, 1 h, 28 – 71%. (ii) $RuCl_3$, $NaIO_4$, MeCN, H_2O, RT, 4.5 h, 51%. (iii) ^tBuOK, $Br^-Ph_3P^+CH_2CN$, THF, 0 °C to RT, 48 h, 35%, *E*:*Z* 8:1.

2.6 The key ring expansion of nitrile lactone (*rac*)-**292** with ammonia

Nitrile (*rac*)-**292** was, in the first instance, treated with a mixture of aqueous ammonia and dioxane at room temperature for 24 hours. Gratifyingly, this reaction resulted in the formation of two diastereomeric tetrahydropyrans (*rac*)-**37** and (*rac*)-**315**, albeit in

low yield (Scheme 2.6.1). The open-chain intermediate (*rac*)-**298** was not isolated from the reaction.



Scheme 2.6.1: Synthesis of tetrahydropyran fragments (rac)-37 and (rac)-315.

Reagents and Conditions: NH_3, dioxane, H_2O, RT, 24 h, 9% (*rac*)-**37**, 19% (*rac*)-**315**.

Further analysis showed that the desired product (*rac*)-**37** was produced as the minor diastereoisomer under these conditions. Since the reaction had not delivered the required diastereoselectivity, extensive experimentation was conducted to improve the reaction outcome (Chapter 4).

2.7 NMR experiments

A range of NMR experiments were used to confirm the stereochemistry of (*rac*)-**37** and (*rac*)-**315**. The n.O.e. experiments and key coupling constants for structures (*rac*)-**37** and (*rac*)-**315** are summarised in Table 2.7.1 and Figures 2.7.1 and 2.7.2. 2D NMR experiments were used to aid assignment of both ^{1}H and ^{13}C data.

Irradiation site	(*rac*)-**37** δ_H / ppm	(*rac*)-**315** δ_H / ppm	n.O.e. effect in (*rac*)-**37**	n.O.e. effect in (*rac*)-**315**
H-1	4.47	4.32	Enhance methyl	Enhance **H**-2 and **H**-3
H-2	3.62	4.00	None	Enhance **H**-1 and methyl
H-3	3.43	3.56	Enhance methyl	Enhance methyl
CH_2CN	2.83	N/A	Enhance methyl	N/A
Ring CH_2	2.27, 1.84	N/A	None	N/A
Methyl groups	0.97, 0.91	N/A	Enhance **H**-1 and **H**-2	N/A

*Table 2.7.1: n.O.e. experiment results for (rac)-**37** and (rac)-**315** (solvent d_3-MeOD).*

The n.O.e. experiment results indicate a through-space interaction between **H**-1 and **H**-2 in (*rac*)-**315**, showing that the protons are *syn* across the oxygen. This interaction is not present in (*rac*)-**37**, indicating the correct product (Figure 2.7.1).

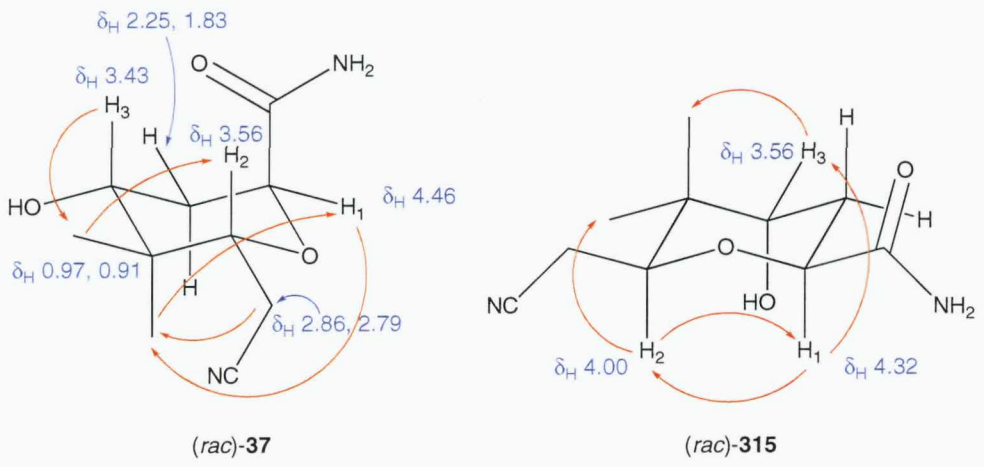
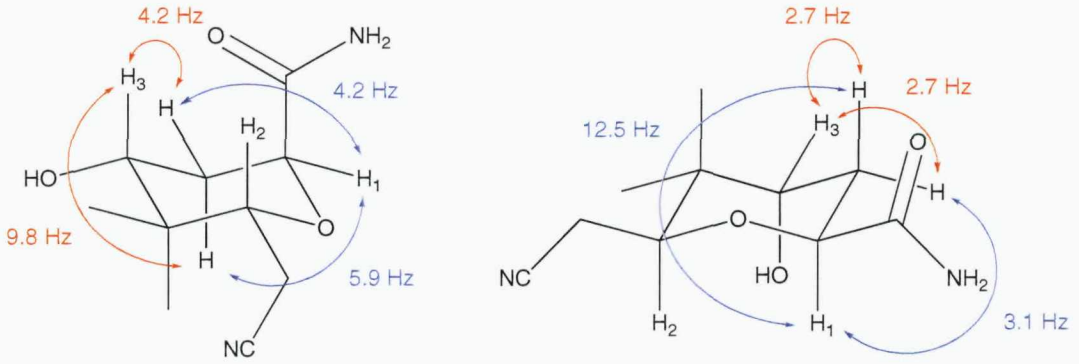


*Figure 2.7.1: Key n.O.e. interactions and chemical shifts for (rac)-**37** and (rac)-**315** in CD_3OD.*

Analysis of the coupling constants of the protons labelled **H**-1 and **H**-3 in structure (*rac*)-**37** indicates that (*rac*)-**37** adopts the conformation shown in Figure 2.7.2. In this case, the amide is axial and the nitrile containing side chain is equatorial. The same analysis for (*rac*)-**315** indicates the expected conformation depicted in Figure 2.7.2.



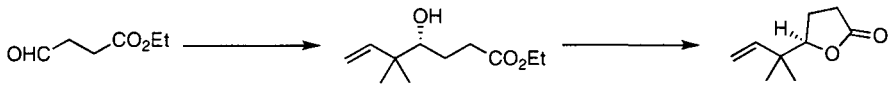
(*rac*)-**37** (*rac*)-**315**

*Figure 2.7.2: Conformational analysis and coupling constants for (rac)-**37** and (rac)-**315** in CD_3OD (**37**) or $CDCl_3$ (**315**).*

Chapter 3 Results - Asymmetric Synthesis of Fragment 37

3.1 Asymmetric *iso*prenylation of **296**

To transform the racemic route reported in Chapter 2 into an asymmetric synthesis required formation of (*R*)-**295** and (*R*)-**294**. The subsequent steps in the synthetic route are diastereoselective transformations, controlled by internal steric factors and kinetics. Therefore, attention turned to the formation of (*R*)-**295** by asymmetric *iso*prenylation (Scheme 3.1.1).

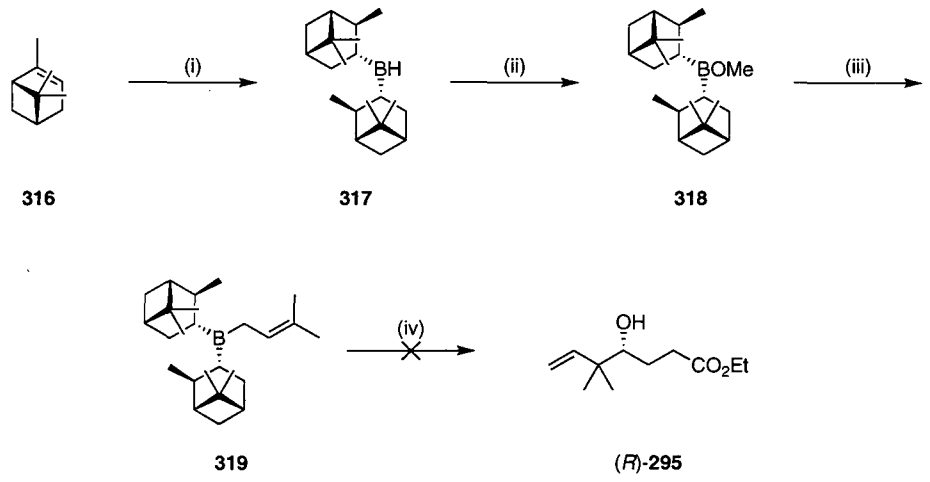


296 (*R*)-**295** (*R*)-**294**

*Scheme 3.1.1: Planned conversion to asymmetric route using (R)-**294**.*

Several methods exist to add an allyl group asymmetrically to an aldehyde, but relatively few methods have been reported for addition of the *iso*prenyl group. The most widely reported is Brown's borane-based chemistry, using α-pinene as a chiral auxiliary.[59] In principle, the allyl and prenyl methods are analogous and should be interchangeable.

Many related borane-based reagents have been prepared by the reaction of a Grignard reagent with a boronate, such as **318**.[82,83] Attempts to replicate this approach, using prenyl magnesiumchloride to form borane **319** failed. (Scheme 3.1.2). The susceptibility of prenyl halides to give a Wurtz coupling upon Grignard formation was the probable cause of this disappointment.[84]

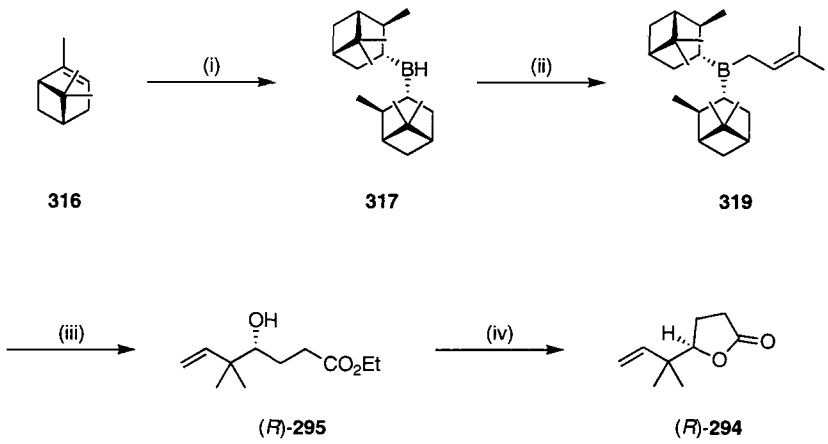


*Scheme 3.1.2: Attempted preparation and reaction of **319**.*

Reagents and Conditions: (i) $BH_3.SMe_2$, THF, RT, 16 h. (ii) MeOH, Et_2O, 0 °C, 2 h. (iii) Prenylmagnesium chloride, Et_2O, –78 °C to RT, 20 min. (iv) **296**, Et_2O, –78 °C to RT, 16 h.

As Scheme 3.1.2 shows, hydroboration on the least hindered face of α-pinene provides borane **317**. Methanolysis and subsequent treatment with the corresponding Grignard should afford reagent **319**, which can be reacted directly with an aldehyde.

The formation of **319** directly from **317** has been accomplished by addition of 3-methyl-1,2-butadiene (**320**).[59] This route has the advantage of rapid preparation and leaves the reaction mixture free from magnesium salts, which can slow the reaction of **319** with an aldehyde.[85] The preparation and reaction of **319** is shown in Scheme 3.1.3.



*Scheme 3.1.3: Successful synthesis and reaction of reagent **319**.*

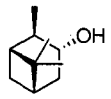
Reagents and Conditions: (i) $BH_3.SMe_2$, THF, RT, 16 h. (ii) 3-methyl-1,2-butadiene (**320**), THF, 0 °C, 16 h. (iii) **296**, THF, –78 °C to RT, 16 h. (iv) TFA (cat.), CH_2Cl_2, reflux, 38 – 61% overall, 84% *e.e.*

Hydroboration of the allene takes place on the less hindered terminus and rapidly forms prenylborane **319**. Upon addition of aldehyde **296** reaction proved rapid, and following isolation of unstable alcohol (*R*)-**295**, it was cyclised to (*R*)-**294** by treatment with catalytic TFA in refluxing CH_2Cl_2. When the NMR spectrum of (*R*)-**294** was recorded in the presence of chiral shift reagent $Yb(tfc)_3$, ^1H NMR integration of the methyl signals indicated an *e.e.* of 84%, consistent with the related literature examples of the reaction.[59,83]

The reaction has some drawbacks. The most common work up protocol involves addition of basic hydrogen peroxide and heating the reaction mixture at reflux for 1 hour. In this case, saponification of the lactone results from such treatment. The reaction mixture was acidified following work up but low yields sometimes resulted. The reaction was also particularly sensitive to moisture and air, such that the use of Schlenk apparatus and argon was necessary and the glassware had to be rigorously dried.

One other complication, due to the nature of the reagent, is that two equivalents of α-pinene alcohol **321** are produced as by products of the hydrogen peroxide oxidation. Purification by chromatography was complicated by the presence of **321**. It was found that two silica gel columns, eluting the first with an ethyl acetate / petrol

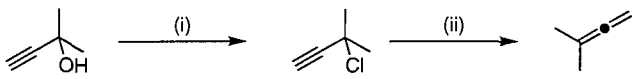
solvent system and the second with an ether / dichloromethane solvent system were required to effect the removal of **321** from lactone (*R*)-**294**.



321

*Figure 3.1.1: Alcohol by product to be removed following reaction of aldehyde **296** with borane **319**.*

Allene **320** is volatile and expensive so it proved necessary to prepare this starting material by combining protocols from literature reported methods.[86,87] Alcohol **322**, commercially available in large quantity, was converted into chloride **323** by treatment with calcium chloride in hydrochloric acid. Upon addition of **323** to a refluxing mixture of zinc-copper couple and ethanol, allene **320** was distilled from the reaction mixture in 44% yield (Scheme 3.1.4).

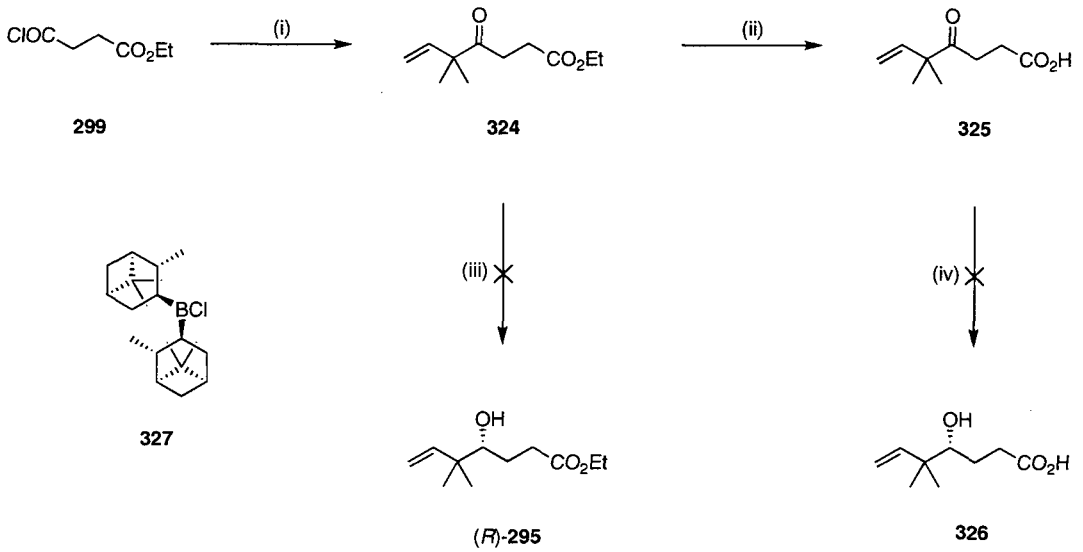


322 **323** **320**

*Scheme 3.1.4: Synthesis of allene **320**.*

Reagents and Conditions: (i) $CaCl_2$, hydroquinone (cat.), HCl (conc., aq.), 0 °C to RT, 4 h, 42%. (ii) Zn-Cu couple, EtOH, 65 °C to 80 °C, distil product away, 44%.

An alternative route to alcohol (*R*)-**295**, based on the asymmetric reduction of ketone **324** or keto-acid **325** was also examined.[88,89] Ketone **324** was prepared by reaction of acid chloride **299** with zinc dust and prenyl chloride to give **324** in 48% yield after chromatography. Saponification of **324** proceeded in 95% yield to afford **325**. Asymmetric reduction of both **324** and **325** failed to produce even a trace of product (Scheme 3.1.5).



*Scheme 3.1.5: Preparation and attempted asymmetric reductions of ketones **324 / 325**.*

Reagents and Conditions: (i) Zn dust, prenyl chloride, Et_2O, sonication, RT, 30 min, 48%. (ii) LiOH, THF, H_2O, 72 h, 95%. (iii) **327**, Et_2O, RT, 11 days.[88] (iv) **319**, THF, reflux, 4 h.[88,89]

3.2 Hydroxylation of (*R*)-**294** to **309**

With the development of an efficient route to (*R*)-**294**, it was clear that further optimisation of the lactone α-hydroxylation protocol was necessary for the synthetic route to be acceptable and to avoid loss of precious material. With yields averaging 40%, further studies were conducted to try to gain an improvement. The previous protocol is shown in Scheme 3.2.1.

(*R*)-**294** **309**

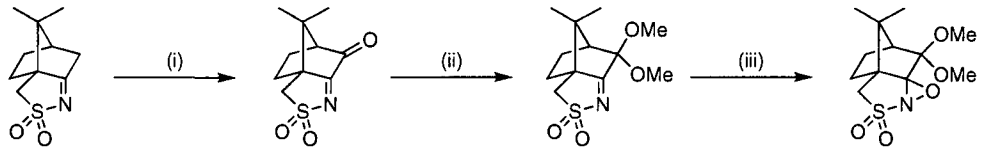
*Scheme 3.2.1: Hydroxylation of lactone (R)-**294**.*

Reagents and Conditions: (i) LiTMP, THF, –78 °C to 0 °C, 1 h. (ii) **305**, THF, –78 °C, 15 min, 40%, *d.r.* 3:1 (typical values).

The role of reaction temperature was investigated and it was found that addition of oxaziridine **305** at –20 °C improved the diastereoselectivity to 8:1 (*anti*:*syn*).[80] Yields for reactions conducted at this temperature ranged from 26% to 46%, further

indicating the unreliability of the reaction. Quenching the reaction at –78 °C with HCl and quickly concentrating the reaction mixture led to a yield of 37%.

Several modified forms of oxaziridine **305** have been reported, in particular the dimethylacetal oxaziridine **330** prepared from (–)-**313** in three steps (Scheme 3.2.2).[90] When a solution of (+)-**330** was added to the enolate of **294** (as Schemes 2.4.5 and 3.2.1) at –78 °C, the result was improved diastereoselectivity (*d.r.* 9:1 *anti*:*syn*), but the yield remained low (23 – 25%). The acetal can coordinate to the metal in the enolate and improve diastereomeric ratios but it appears to have no positive effect on the yield.



313 **328** **329** **330**

*Scheme 3.2.2: Synthesis of modified oxaziridine **330**.*

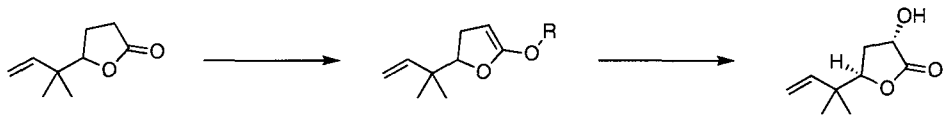
Reagents and Conditions: (i) SeO_2, AcOH, reflux, 21 h, 86%. (ii) $(MeO)_3CH$, H_2SO_4, Amberlyst-15 resin, MeOH, reflux, 16 h, 55%. (iii) *m*CPBA, K_2CO_3, CH_2Cl_2, RT, 74 h, 69%.

Though these modifications led to significant improvement in diastereoselectivity, the low yields and failure to account for the full mass balance of the reaction led to the conclusion that destruction of lactone **294** or **309** was occurring either in the reaction or during work up and purification. When **309** was subjected to extended contact with silica gel, there was no significant loss of product.

It is possible that the lactone may be opened to the hydroxy-acid during work up or purification, though it did not proved possible to confirm hydrolysis in this case. The lengthy synthesis of oxaziridines **305** (4 steps) and **330** (6 steps) was also approaching that of the planned route to fragment **37** and proved very time consuming. These reasons, together with the fact that an excess of hydroxylation reagent was required, prompted investigation of alternative methods to achieve the α-hydroxylation of (*R*)-**294**.

3.3 Hydroxylation *via* oxidation of a ketene acetal

Oxidation of a ketene acetal presented itself as a possible solution to the problem. Initial attempts to prepare and isolate silyl ketene acetals **331** and **332** were unsuccessful, indicating the sensitive nature of these intermediates. Formation of these acetals *in situ* followed by reaction with *m*CPBA afforded the desired lactone (*rac*)-**309** in 2% yield, with no appreciable diastereoselectivity (Scheme 3.3.1). The use of DMDO, also formed *in situ*, was more successful.



294 **331 R = TBDMS** **332 R = TMS** (*rac*)-**309**

*Scheme 3.3.1: Formation of (rac)-**309** via a ketene acetal.*

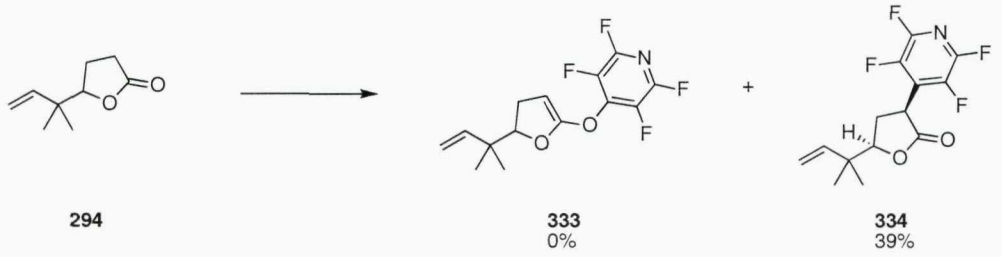
Reagents and Conditions: 1. (i) LiTMP, THF, –78 °C to 0 °C, 1 h. (ii) TBDMS-Cl, –78 °C to 0 °C, 2 h. (iii) *m*CPBA, CH_2Cl_2, RT, 16 h, 2%, mixture of diastereoisomers.

2. (i) LiTMP, THF, –78 °C, 2 h. (ii) TMS-Cl, –78 °C to RT, 2 h. (iii) Oxone, $NaHCO_3$, acetone, H_2O, –78 °C to 0 °C, 2 h, 14% (*rac*)-**309** + 65% **294**.

When **332** was exposed to DMDO, epoxidation proceeded smoothly giving lactone (*rac*)-**309** in 14% yield together with 65% recovered starting material. Addition of anhydrous DMDO to **332** afforded starting material. Attempts to use the more bulky TBDPS group in place of TMS or use of $Me_3O^+BF_4^-$ to trap the enolate as a methyl enol ether were also unsuccessful, affording starting material.

Pentafluoropyridine has been reported to form stable enol ethers from lithium enolates.[91] Application of this methodology to **294** was the next logical step towards increasing the stability of the ketene acetal to air, water and the oxidation reaction. **294** was deprotonated with LiTMP at –78 °C and pentafluoropyridine was added to the enolate (Scheme 3.3.2). This resulted in the formation of a single product in 39% yield together with recovered starting material (10%). NMR was unable to completely confirm the structure of the product, as the resonances at δ_H 4.31 and δ_C 38.1 ppm did not indicate the alkene proton / carbon present in *O*-alkylated product

333. X-ray crystallography identified the product as the C-alkylated product **334**, with *syn* stereochemistry (Figure 3.3.1).



*Scheme 3.3.2: Failure to synthesise **333**, reaction resulted in **334**.*

Reagents and Conditions: (i) LiTMP, THF, –78 °C, 1 h. (ii) Pentafluoropyridine, –78 °C to RT, 2 h, 39%.

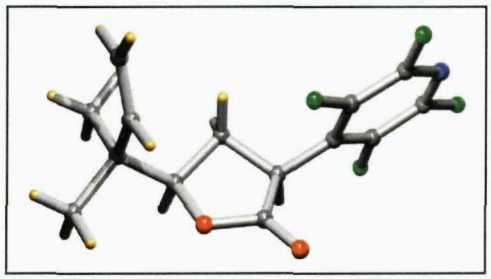


*Figure 3.3.1: X-ray crystal structure of **334**.*

3.4 Replacement of the α-hydroxylation reaction

After extensive experimentation on the α-hydroxylation of lactone **294** had failed to provide a good increase in yield, investigation into an alternative synthetic route began. Retrosynthetic analysis indicated that lactone **309** could be easily obtained from a diol similar to **335** by cyclisation under acidic conditions. A suitable synthetic equivalent for diol **335** was diol **336**, derived from (*S*)-malic acid (**38**) (Figure 3.4.1).

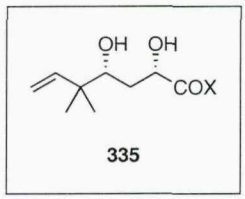
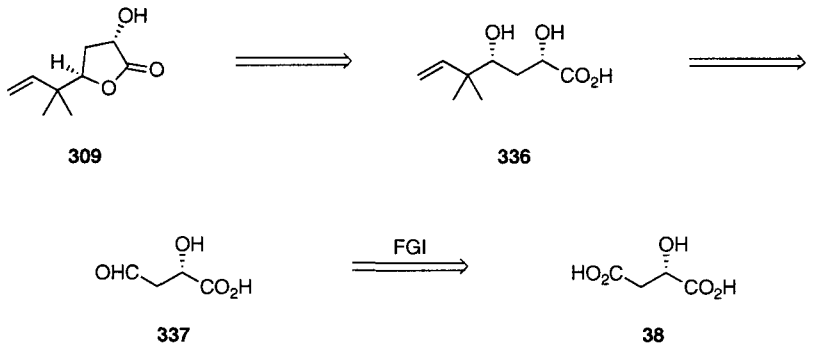
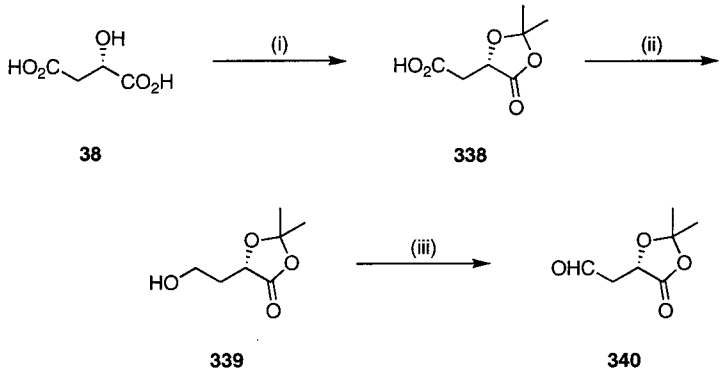


Figure 3.4.1: Target diol, X = any suitable leaving group.



*Scheme 3.4.1: Retrosynthetic analysis of lactone **309** to (S)-malic acid (**38**).*

(*S*)-Malic acid (**38**) has been used as a starting point for the synthesis of aldehyde **340**.[92,93] Initial experimentation was encouraging, but quickly proved unreliable. Protection of **38** as the acetonide was trivial but reduction of the resultant carboxylic acid and re-oxidation to the aldehyde proved more challenging (Scheme 3.4.1).



*Scheme 3.4.1: Protection, reduction and oxidation of (S)-malic acid (**38**).*

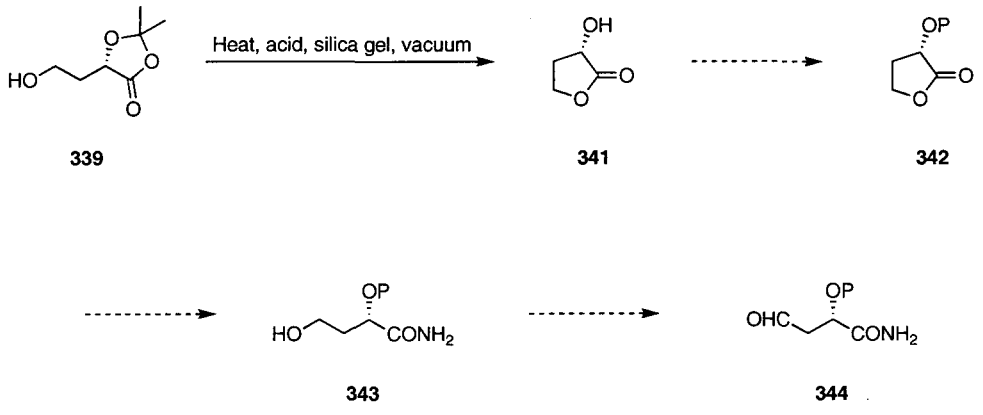
Reagents and Conditions: (i) 2,2-dimethoxypropane, *p*-TsOH (1%), acetone, RT, 16 h, 70 – 100%. (ii) $BH_3.SMe_2$, THF, 0 °C, 16 h, 69%. (iii) Swern oxidation, 33%.

Aldehyde **340** was only isolated in a useful quantity once using the conditions in Scheme 3.4.1, despite many attempts to repeat the reaction. The sequence proved highly capricious when the intermediates were not purified. In particular when acid **338** was not crystallised prior to use, the reduction proved highly unreliable and often results in many by products. Similarly, it was necessary to subject alcohol **339** to silica gel chromatography to remove inorganic residues remaining from reduction or

the Swern oxidation yielded many sulfur-containing by products and only a trace of aldehyde **340**.

When pure alcohol **339** was treated with Dess-Martin periodinane,[94] aldehyde **340** was isolated in 55% yield over two steps. Though a pleasing result, this procedure is far from ideal as the cost of the reagent is prohibitive for the large-scale preparation required for an early step in the synthesis.

It was quickly discovered that alcohol **339** was exceptionally unstable, readily undergoing cyclisation to lactone **341** with loss of acetone (Scheme 3.4.2). Heat, acid or prolonged contact with silica gel all induce this cyclisation, as did concentration of a solution of **339** under vacuum. Unfortunately, attempts to make use of **341** as an intermediate by protection of the alcohol, opening of the lactone and oxidation of the resulting alcohol were unsuccessful, add unnecessary steps to the synthetic route and were quickly abandoned.



*Scheme 3.4.2: Degradation of alcohol **339** and unsuccessful use of resultant lactone **341**. P = Suitable alcohol protecting group.*

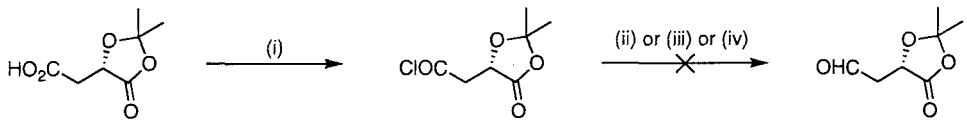
Returning to the reduction of **338** to **339**, refinement of the experimental protocol demonstrated that by very careful concentration of the reaction mixture from acetone and subsequent filtration through silica gel, it was possible to isolate **339** with minimal degradation, but not free of solvent. Attempts to improve the oxidation of **339** to **340** proved futile, despite a great many reagents and conditions being tried. Treatment of **339** with both PCC[95] and TPAP / NMO[96] was unsuccessful, but sulfur

trioxide-pyridine complex in DMSO was successful alone[97] (22%), and in conjunction with one equivalent of pyridine (46%) added to remove any residual H_2SO_4 formed by the reaction of SO_3 with atmospheric moisture.[98] Finally, a large number of reactions based on a catalytic quantity (1 mol%) of TEMPO and a stoichiometric re-oxidant were tested, all without much success (Table 3.4.1).

Entry	Catalyst	Oxidant	Solvent	Conditions	Result
1	4-hydroxy TEMPO	NaOCl [99-101]	CH_2Cl_2	KBr, 0 °C, 1 h, then RT, 112 h	No desired product
2	4-hydroxy TEMPO	I_2 [102]	CH_2Cl_2 / H_2O	$NaHCO_3$, RT, 16 h	No desired product
3	4-hydroxy TEMPO	I_2 [102]	$PhCH_3$ / H_2O	$NaHCO_3$, RT, 16 h	Trace of aldehyde
4	4-hydroxy TEMPO	Oxone [103]	CH_2Cl_2	TBAB, RT, 112 h	No desired product
5	4-hydroxy TEMPO	Oxone [103]	$PhCH_3$	TBAB, RT, 112 h	No desired product
6	4-hydroxy TEMPO	NaOCl [99-101]	CH_2Cl_2	KBr, $NaHCO_3$	Trace of aldehyde
7	TEMPO	NaOCl [99-101]	CH_2Cl_2	KBr, $NaHCO_3$	Trace of aldehyde

Table 3.4.1: Summary of TEMPO oxidations.

In an effort to develop a synthesis that didn't rely on alcohol **339**, attempts were made to convert acid **338** into acid chloride **345** and effect its reduction but the reactions were unsuccessful (Scheme 3.4.3).



338 **345** **340**

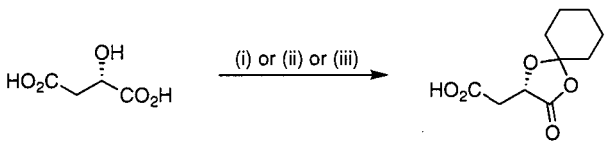
*Scheme 3.4.3: Attempted use of acid chloride **345** in the conversion of **338** into **340**.*

Reagents and Conditions: (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C to RT, 16 h. (ii) Et_3SiH, Pd / C, neat, RT, 4 h.[67,68] (iii) Bu_3SnH, $PdCl_2$ (5 mol%), PPh_3 (20 mol%), $PhCH_3$, RT, 30 min.[104] (iv) H_2, Pd / $BaSO_4$ (3 mol%), $PhCH_3$, RT, 24 h.

It was clear that careful control of the temperature and pH would be required to ensure success of these reactions so the dimethyl protecting group was switched for a

cyclohexyl group, with the increased steric bulk and boiling point providing an increase in stability.

Literature methods to install a cyclohexyl group rely on addition of the Lewis acid $BF_3.OEt_2$ to induce addition to cyclohexanone.[105] This method did not prove satisfactory, with a protected product of poor quality resulting. Attempts to use the dimethyl acetal of cyclohexanone resulted in the dimethyl ester of (*S*)-malic acid. Use of Eaton's reagent as solvent also failed. Use of cyclohexanone as solvent, with *p*-TsOH (1 mol%) proved successful in modest yield (59%), affording a pure product with no purification (Scheme 3.4.4).



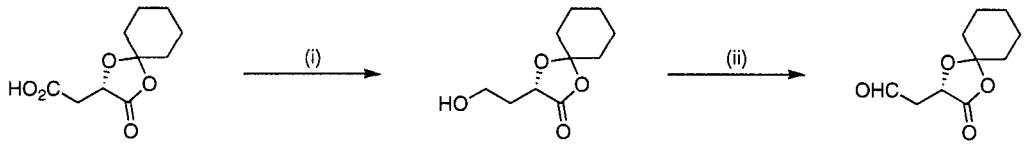
38 **346**

Scheme 3.4.4: Protection of (S)-malic acid.

Reagents and Conditions: (i) Cyclohexanone, *p*-TsOH, neat, RT, 30 h, 59%. (ii) Cyclohexanone, PPTS, $PhCH_3$, Dean and Stark, reflux, 16 h, 92%. (iii) Cyclohexanone, $BF_3.OEt_2$, Et_2O, 0 °C to RT, 16 h, 90% (impure).

Upon scale up, it became apparent that use of cyclohexanone as solvent was impractical. The amount of water produced in the reaction caused it to stall and then reverse, with heating and removal of water under vacuum failing to solve the problem. Initial experiments with standard acetal protection (toluene, reflux) resulted in a charring of the starting material but when PPTS and a Dean and Stark trap were used, the reaction was successful, clean and high yielding (92%).

Reduction of **346** with borane proceeded smoothly in excellent yield. Gratifyingly, the alcohol product **347** was tolerant of the reaction conditions, concentration under vacuum and chromatography on silica gel. The alcohol was in the first instance oxidised using sulfur trioxide-pyridine complex in DMSO and dichloromethane.[97] Addition of an equivalent of pyridine increased the yield from 27% to 44% (Scheme 3.4.5).[98]

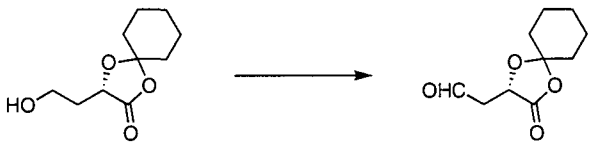


346 347 348

*Scheme 3.4.5: Reduction and oxidation of **346**.*

Reagents and Conditions: (i) $BH_3.SMe_2$, THF, 0 °C to RT, 24 h, 91 – 100%. (ii) SO_3.py, $^iPr_2NEt$, pyridine, DMSO, CH_2Cl_2, RT, 44%.

Returning to the TEMPO-based oxidation, and with selection of the correct stoichiometric re-oxidant, it proved possible to effect the oxidation of **347** to **348** quickly and cleanly. Using TEMPO or 4-hydroxy-TEMPO (1 mol%) and trichloro*iso*cyanuric acid (TCCA) as a chlorine source afforded aldehyde **348** in 81% yield after chromatography (Scheme 3.4.6).[106] Addition of sodium acetate proved necessary as the HCl generated in the reaction appeared to cause it to stall.[107] Major advantages of this reaction were speed (typically 10 – 30 minute reaction time), the lack of by products, high yield and ease of scale up. Additionally, the reaction waste did not contain any heavy metals or toxic products, simplifying disposal.



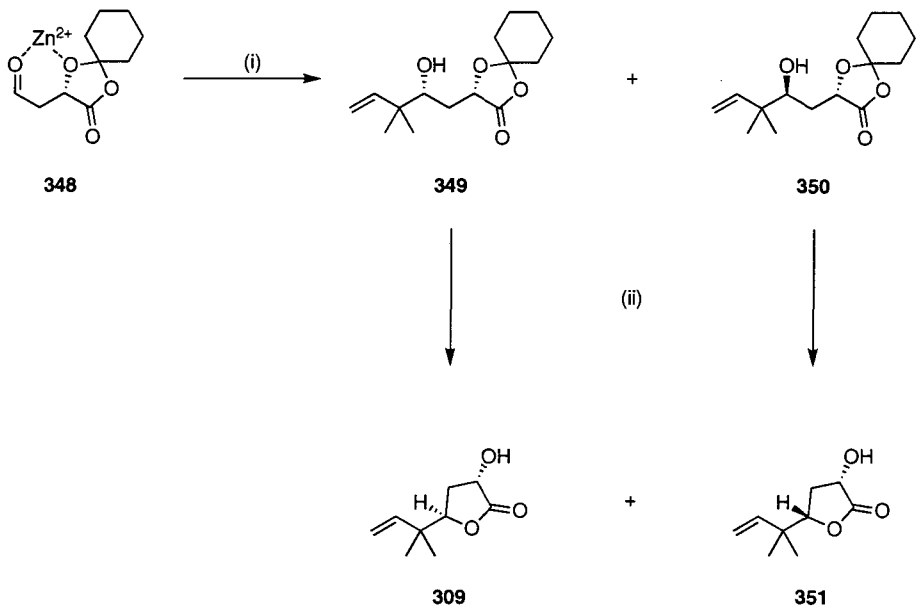
347 348

*Scheme 3.4.6: Improved procedure for oxidation of **347** to **348**.*

Reagents and Conditions: 4-hydroxy TEMPO (1 mol%), TCCA, NaOAc, CH_2Cl_2, 0 °C, 2 h, 54 – 81%.

3.5 Asymmetric *iso*prenylation of aldehyde **348**

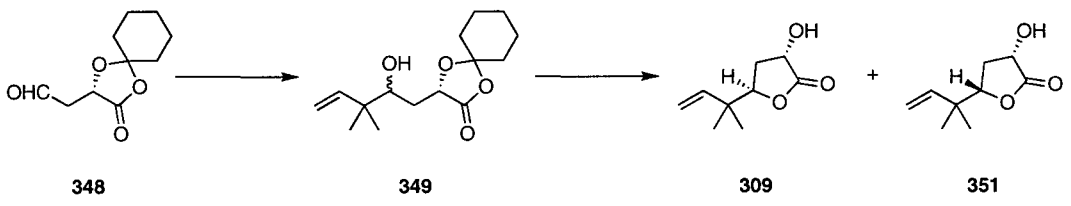
Various methods to introduce the *iso*prenyl group were employed to ensure maximum yield of the desired lactone **309**. Treatment of aldehyde **348** with prenyl bromide and zinc dust, followed by cyclisation of intermediates **349** and **350** with TFA resulted in a mixture of diastereoisomers **309** and **351** (1:1 ratio) (Scheme 3.5.1).



*Scheme 3.5.1: Isoprenylation of aldehyde **348** using zinc-based prenyl bromide addition.*
Reagents and Conditions: (i) Zn dust, prenyl bromide, NH_4Cl, THF, H_2O, RT, 2 h. (ii) TFA (cat.), CH_2Cl_2, reflux, 2 h, 55 – 80% (2 steps).

Use of a Grignard reagent was unproductive due to the tendency of the reagent to homocouple during formation. Upon successful formation of a small amount of prenylmagnesium chloride, the reagent showed little selectivity not only between the diastereoisomers formed but also between the two carbonyls in the starting material.

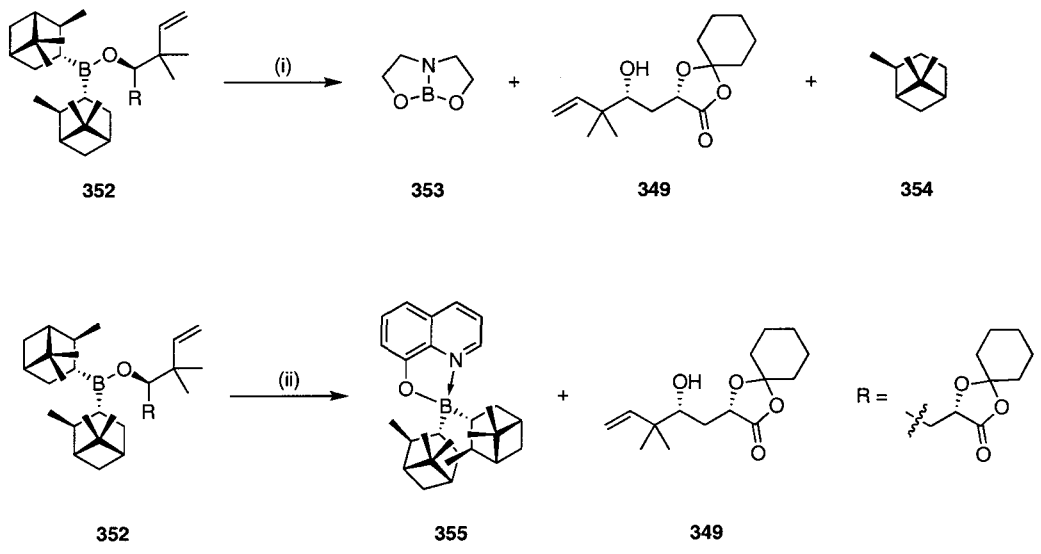
The best diastereoselectivities were obtained using the chiral borane methodology, as previously used in Scheme 3.1.3. When applied to aldehyde **348**, the desired lactone **309** was given in 39% yield with a *d.r.* of 6:1 (Scheme 3.5.2).[59] It appeared that cyclisation of **349** to **309** had occurred in the reaction or upon work up.



*Scheme 3.5.2: Asymmetric isoprenylation of aldehyde **348**.*
Reagents and Conditions: **319**, THF, –78 °C to RT, 16 h, 39%, *d.r 6:1.*

Upon repetition of the reaction, **349** was treated with catalytic TFA and heated in dichloromethane to encourage cyclisation to lactone **309**. Chromatography of **349** often resulted in cyclisation or removal of the protecting group, so advancing the crude material to lactone **309** prevented loss during purification. The presence of inorganic boron residues in the crude product severely retarded the speed of cyclisation under acidic conditions. Use of TFA and *p*-TsOH both resulted in an extremely slow reaction, sometimes taking as long as seven days (compared to one to two hours). Use of a higher boiling solvent (chloroform) did not improve reaction times. An aqueous work up to remove the problem causing inorganics was necessary, as sometimes the stalled reaction could not be completed.

The quench procedure for this reaction continued to make use of basic hydrogen peroxide, which was not ideal conditions for the delicate lactone **309**. Alternate work up procedures are known and a number of these were examined. Simple protonolysis with acetic acid or TFA and a simple quench with methanol failed to give improvement. Agents which complex to boron compounds and either form insoluble or very apolar complexes have been reported (Scheme 3.5.3).



352 **353** **349** **354**

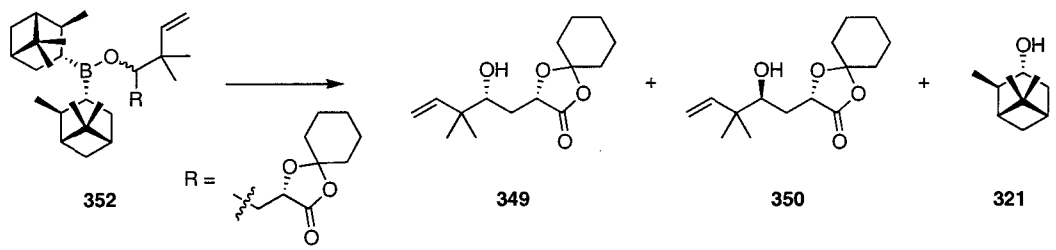
352 **355** **349**

Scheme 3.5.3: Complexation method for work up of organoborane reactions.
Reagents and Conditions: (i) Diethanolamine, RT, 2 h. (ii) 8-hydroxyquinoline, MeOH, RT, 16 h.

Addition of diethanolamine to the reaction mixture is reported to promote formation of the insoluble complex **353**, which can be removed by filtration.[108] This should

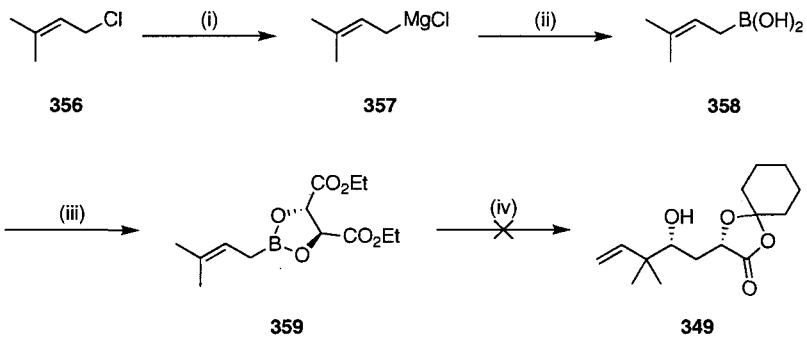
simplify isolation of alcohol **349**, the desired product. When this work up was applied to **352**, the desired product **349** was isolated in 20% yield and still required purification by chromatography. Addition of a solution of 8-hydroxyquinoline to **352** was also examined as this is reported to give a fluorescent yellow, air-stable, highly apolar complex **355**.[109,110] In this case, **355** formed but did not crystallise from the reaction mixture and so could not be removed by filtration. It was not possible to remove **355** by silica gel chromatography, as every fraction became contaminated with a yellow impurity. Attempts to partition the reaction mixture between methanol and petrol were also unsuccessful.

A milder method for the oxidation of organoboranes at room temperature has been described by Kabalka,[111] involving the addition of solid sodium perborate to the reaction mixture (Scheme 3.5.4). The procedure proved highly effective, consistently providing lactone **309** in 50 – 60% yield after TFA cyclisation.



Scheme 3.5.4: Mild oxidative work up using sodium perborate.
Reagents and Conditions: $NaBO_3.4H_2O$, RT, 24 h, 60% (2 steps), *d.r.* 6:1.

The use of other chiral *iso*prenylating agents was also explored, such as the boron tartrate complex **359**. These reagents are prepared from an alkylborate, an organolithium or Grignard reagent and a tartrate (Scheme 3.5.5).[112,113]

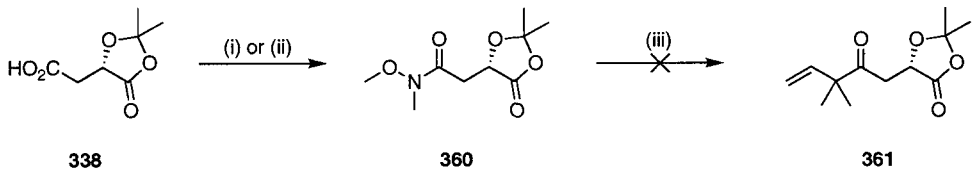


*Scheme 3.5.5: Attempted reaction of borane **359** with aldehyde **348**.*

Reagents and Conditions: (i) Mg, THF, 0 °C, 1 h. (ii) $B(OMe)_3$, THF, –78 °C to RT, 16 h, HCl work up. (iii) Diethyl tartrate, $MgSO_4$, Et_2O, RT, 16 h. (iv) **348**, THF, –78 °C, 6 h.

Difficulties associated with the preparation of prenylmagnesium chloride, made the preparation of **358** and **359** difficult to effect.[84,114,115] Following Grignard formation, freshly distilled trimethylborate was added. Boronic acid **358** was detected by NMR but as it is reported to be unstable when dry, its isolation was not attempted.[112] Addition of aldehyde **348** did in one case afford a small amount of **349** but the result was not reproducible. The reaction of an organolithium with tributylborate was also tried, without success.

A further approach attempted to exploit the addition of Grignard reagents to Weinreb amides to form ketones, as it may be possible to effect an asymmetric reduction of ketone **361**. The Weinreb amide **360** was synthesised in one step from acid **338**, but attempts transform **360** into keto-ester **361** were unsuccessful (Scheme 3.5.6).[116]



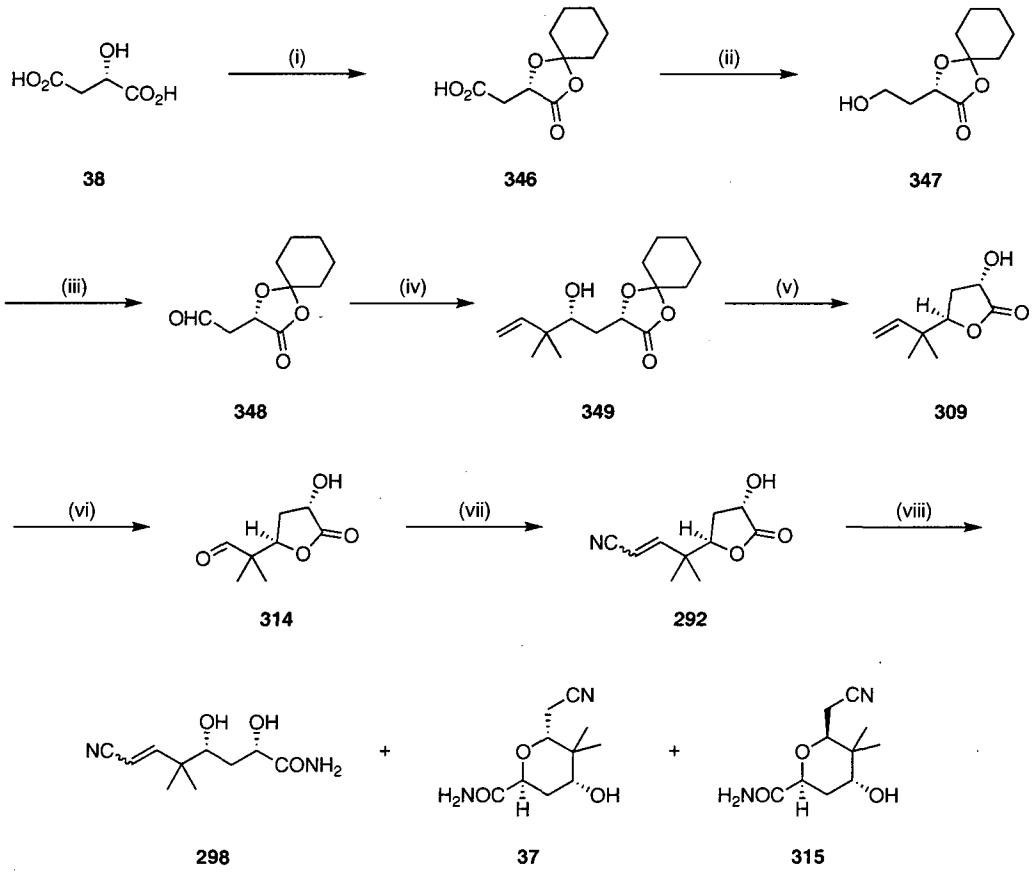
*Scheme 3.5.6: Preparation and attempted reaction of Weinreb amide **360**.*

Reagents and Conditions: (i) *O,N*-dimethylhydroxylamine.HCl, DCC, NEt_3, CH_2Cl_2, 0 °C, 1 h, 62%. (ii) (a) Oxalyl chloride, DMF (cat.), CH_2Cl_2, 0 °C to RT, 18 h. (b) *O,N*-dimethylhydroxylamine.HCl, NEt_3, 0 °C, 3 h, 49%. (iii) Prenylmagnesium chloride, THF, –78 °C to RT.

Consequently, an extensive investigation led to the conclusion that *iso*prenylation was best achieved using Brown's α-pinene borane **319**. The favoured work up procedure was that developed by Kabalka, using sodium perborate.[111]

3.6 Summary and the conversion of lactone **309** into enantiomerically pure **37**

Having secured the enantiomerically pure lactone **309**, it was advanced to the desired nitrile **292** using similar conditions to those developed in the racemic route. The ylide **362** was prepared by deprotonation of acetonitriletriphenylphosphonium bromide (**302**) with NaOH. Heating **362** with aldehyde **314** afforded **292** in 70% yield. Following isolation of nitrile **292**, the ring was expanded as previously to form the tetrahydropyran ring system. Treatment with aqueous ammonia in methanol afforded a mixture of **298**, **37** and **315**. A full summary of the synthetic route to **37** is shown in Scheme 3.6.1.



Scheme 3.6.1: Asymmetric synthesis of nitrile 37.

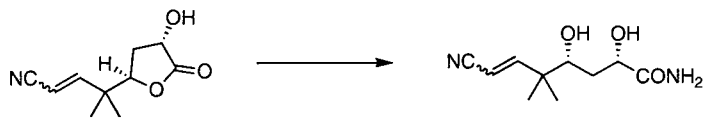
Reagents and Conditions: (i) Cyclohexanone, PPTS, $PhCH_3$, Dean and Stark, reflux, 16 h, 92%. (ii) $BH_3.SMe_2$, THF, 0 °C to RT, 24 h, quant. (iii) 4-hydroxy-TEMPO, TCCA, NaOAc, CH_2Cl_2, 0 °C, 2 h, 54 – 81%. (iv) **319**, THF, –78 °C to RT, 16 h. (v) TFA (cat.), CH_2Cl_2, reflux, 2 h, 60%, *d.r* 6:1. (2 steps). (vi) (a) O_3, CH_2Cl_2, –78 °C, 10 min. (b) PPh_3, –78 °C to RT, 1 h, 49%. (vii) Ph_3PCHCN (**362**), $PhCH_3$, reflux, 36 h, 70%, *E*:*Z* 5:1. (viii) NH_3, MeOH, H_2O, RT, 16 h, 29% **298**, 11% **37**, 13% **315**.

It was clear from preliminary work on the key cyclisation reaction in Scheme 3.6.1 that extensive experimentation would be required to optimise the reaction in favour of the desired product **37** over **315**.

Chapter 4 Results - Optimisation of Michael Addition Cyclisation Reaction and Investigation of Coupling Reactions

4.1 Investigation into the cyclisation of nitrile **298** to fragments **37** and **315**

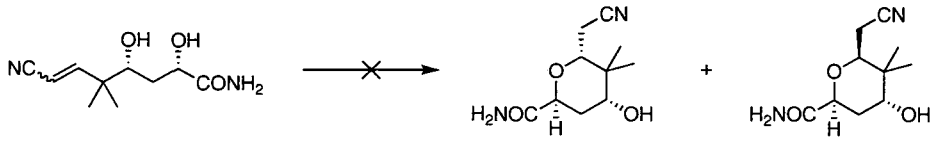
From the results obtained for the ring expansion of lactone **292** to tetrahydropyran **37**, it was clear that further investigation was needed to obtain a better diastereoselectivity than 1:2 (desired **37** : undesired **315**) for the reaction. The first step was to intercept and purify the open chain precursor **298**, formed on reaction of lactone **292** with ammonia. This was achieved in good yield using liquid ammonia in methanolic THF at –40 °C (Scheme 4.1.1).



292 **298**

*Scheme 4.1.1: Isolation of amide **298**.*
Reagents and Conditions: NH_3 (l), THF / MeOH (1:1), –40 °C, 3 h, 83%.

From **298**, a suitable base and solvent was required to induce cyclisation to fragment **37** and the unwanted diastereoisomer **315**. There are few transformations of this type reported in the literature compared to cyclisations of alcohols onto α,β-unsaturated carbonyl compounds. Scheme 4.1.2 details many of the methods examined for the conversion of diol **298** to THP **37**, each of which returned starting material.



298 37 315

*Scheme 4.1.2: Unsuccessful attempts to cyclise amide **298**.*

Reagents and Conditions:
1. ^{t}BuOK, THF, –78 °C to RT.[117]
2. KHMDS, THF, –78 °C to RT.
3. LiHMDS, THF, –78 °C to RT.
4. NH_3, THF, H_2O, 0 °C to RT.
5. THF, MeOH or H_2O, microwave irradiation.
6. NaOH, DMSO, RT.
7. Ag_2CO_3, dioxane, H_2O, RT.
8. CuCl, pyridine, CH_2Cl_2, RT.[118]

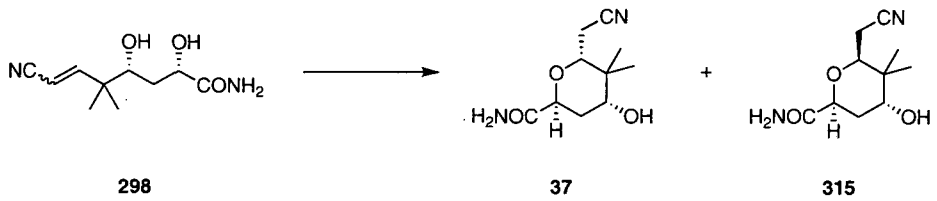
Importantly, treatment with strong bases or aqueous ammonia in THF failed to induce cyclisation, indicating a strong solvent dependency. Microwave irradiation was also unsuccessful even with solvents that develop high pressure during microwave heating, such as THF.

An alternative strategy sought to exploit the difference in p*K*a of an alcohol in water compared to DMSO. Since the p*K*a in DMSO of RO**H** is around 30, while that of OC**H**HCN is around 28, cyclisation of the alkoxide to an α,β-unsaturated nitrile should be favourable. A solution of **298** in DMSO treated with sodium hydroxide quickly darkened. However, upon workup neither fragments **37**, **315** or recovered starting material could be isolated.

The final two reactions (entries 7 and 8, Scheme 4.1.2) sought to polarise the nitrile group with a Lewis acid to make the alkene more susceptible to nucleophilic attack. Both silver(I) and copper(I)[118] salts were tried, but in both cases these returned starting material upon work up.

Exposure of **298** to TBAF in THF did induce cyclisation, but only when the solution was left to stand at 4 °C. No reaction resulted with TBAF at –78 °C and with

TBAOH in an increase in yield resulted (Scheme 4.1.3). In both cases, the reaction favoured undesired THP **315** over **37**.



298 **37** **315**

*Scheme 4.1.3: Unsuccessful attempts to cyclise diol **298**.*
Reagents and Conditions: TBAOH, MeOH, –95 °C to –78 °C to RT, 16 h, 80%, *d.r.* 1:2.2 (**37**:**315**).

Treatment with TBAOH at –95 °C failed to induce cyclisation but at higher temperatures, a mixture of diastereoisomers always resulted. With DBU in THF at room temperature the sole product of the reaction was **315**, with none of the desired product **37** isolated. A series of small scale test reactions were carried out using $CsCO_3$ as a base in various solvents. The results are summarised in Table 4.1.1.

Solvent	**Result**
THF	1:1.2 (**37**:**315**)
Methanol	1:1.2 (**37**:**315**)
Ethyl Acetate	Incomplete, 1:2.7 (**37**:**315**)
Acetonitrile	1:1.3 (**37**:**315**)
Dioxane	1:2.8 (**37**:**315**)
Acetone	Incomplete, 1:1.1 (**37**:**315**)

Table 4.1.1: Small scale reactions to investigate the effect of different solvents on cyclisation. All reactions were run at RT in air until complete by TLC.

These results indicated that better selectivities were obtained with polar solvents such as acetonitrile, methanol and acetone, though the latter reaction stalled before cyclisation was completed. The cyclisation was also faster in acetonitrile and

methanol. As none of these methods had yielded **37** as the major product, an alternative approach was explored.

4.2 Use of the Bestmann ylide to control the stereochemical course of the cyclisation reaction.

Ylide **364**, developed by Bestmann, is capable of reacting with first an alcohol and second a carbonyl to introduce an α,β-unsaturated carbonyl functionality (Scheme 4.2.1).[119,120]

363 **364** **365** **366**

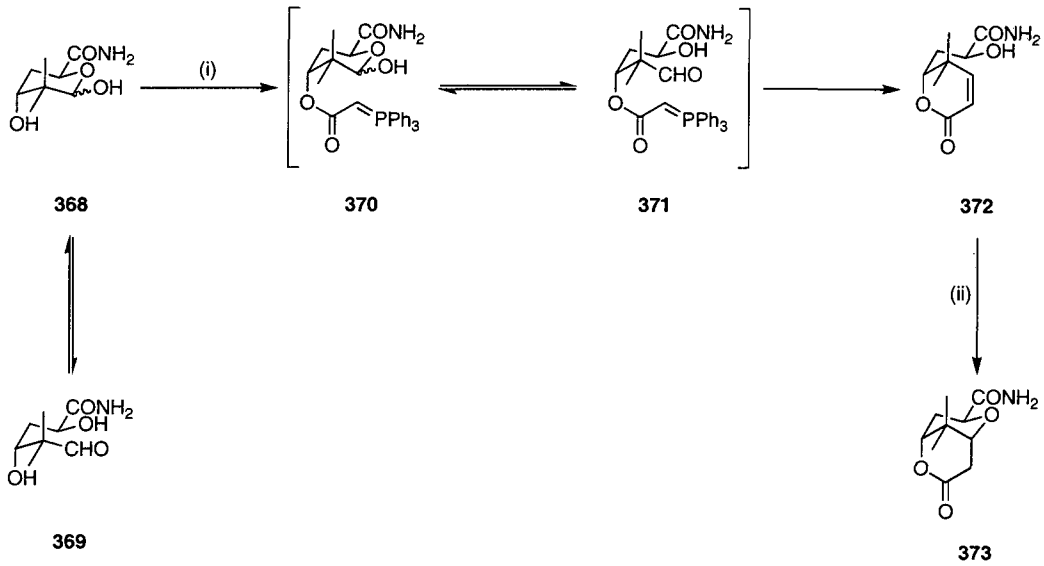
*Scheme 4.2.1: Example reaction of ylide **364**.*
Reagents and Conditions (example): NEt_3, PhH, reflux.[119]

364 can be quickly prepared from the commercial ylide **367** by treatment with LiHMDS, with the elimination of lithium ethoxide (Scheme 4.2.2).[121-123]

367 **364**

*Scheme 4.2.2: Synthesis of ylide **364**.*
Reagents and Conditions: LiHMDS, $PhCH_3$, THF, RT, 16 h, 90%.

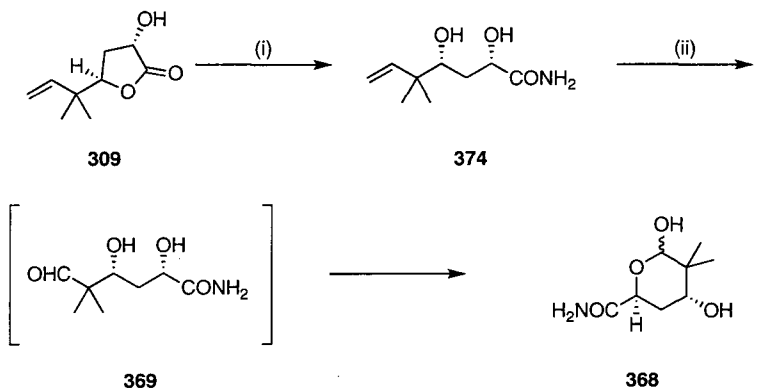
The application of **364** to the synthesis of fragment **37** would allow for cyclisation to take place only onto one face of the alkene, controlling the stereochemical outcome of the reaction (Scheme 4.2.3).



*Scheme 4.2.3: Proposed method to use Bestmann ylide **364** to control the stereochemistry of cyclisation reaction (**372** to **373**).*

Reagents and Conditions: (i) **364**, $PhCH_3$, reflux. (ii) Suitable base.

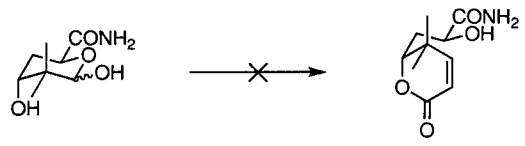
As Scheme 4.2.3 shows, addition of the alcohol of lactol **368** to ketene **364** should follow with a Wittig olefination reaction to give lactone **372**. The bicyclic ring system can only form to one face of the alkene, delivering **373** with the required stereochemistry in the resultant tetrahydropyran. This may happen spontaneously or may require treatment of **372** with a base. To attempt this chemistry first required the synthesis of the precursor lactol **368**. This was achieved by reaction of lactone **309** with ammonia to diol **374**, followed by ozonolysis of the terminal alkene (Scheme 4.2.4).



*Scheme 4.2.4: Synthesis of lactol **368**.*

Reagents and Conditions: (i) NH_3, dioxane, H_2O, RT, 16 h, 56%. (ii) (a) O_3, CH_2Cl_2, MeOH (5:1), –78 °C. (b) PPh_3, –78 °C to RT, 64%.

Lactol **368** was combined with ylide **364** and subjected to various reaction conditions. All of these failed, resulting in consumption of the starting material and production of a very polar product which did not prove possible to purify or characterise (Scheme 4.2.5).

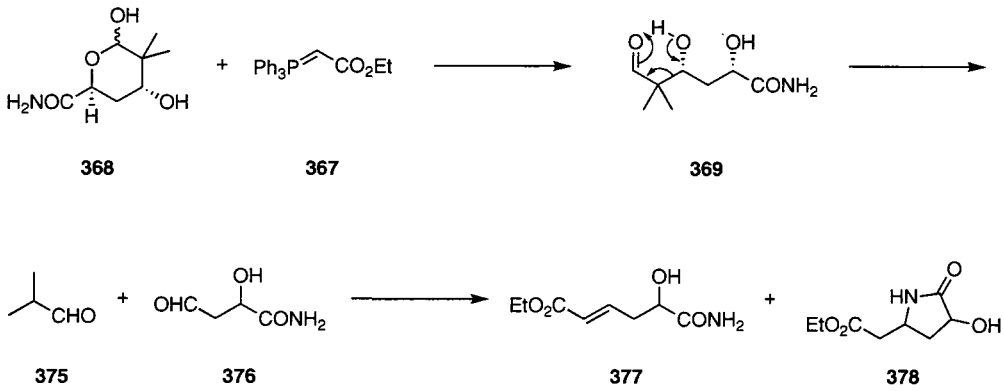


368 **372**

*Scheme 4.2.5: Attempted reaction of lactol **368** with ylide **364**.*

Reagents and Conditions: 1. **364**, $PhCH_3$, reflux.
2. **364**, NEt_3, $PhCH_3$, reflux.[119]
3. **364**, K_2CO_3, 18-crown-6, $PhCH_3$, reflux.[124]
4. **364**, microwave irradiation, THF.

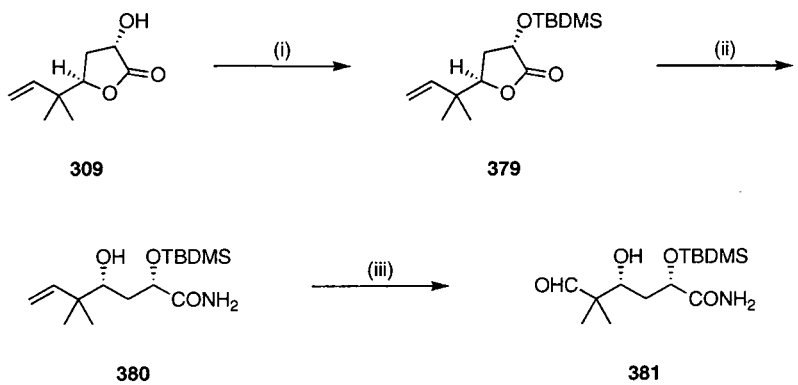
To show that lactol **368** would react with an ylide as required, it was treated with (carbethoxymethylene)triphenylphosphorane (**367**) under conditions known to promote reactions between lactols and ylides (Scheme 4.2.6).[124] No reaction resulted at room temperature, so the mixture was heated at reflux for 16 hours. This facilitated a retro-aldol reaction of **369** to **375** and **376**, and Wittig olefination of the resultant aldehyde (**376**) to produce hydroxyester **377** in low yield. No product resulting from Wittig olefination of aldehyde **375** was observed, possibly due to its low boiling point (61 – 62 °C [125]). Further products were observed (Scheme 4.2.6), though none could be isolated and characterised. One was believed to be lactam **378**, but several attempts at purifying the product failed to remove a co-polar impurity so only a tentative assignment was made.



*Scheme 4.2.6: Reaction of lactol **368** with ylide **367**.*

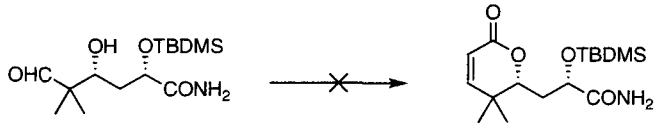
Reagents and Conditions: K_2CO_3, 18-crown-6, dioxane, RT, 36 h, then reflux, 16 h, 8%. Starting material and product are racemic.

Since reaction with the lactol was unsuccessful, a silyl protected form of **369** was prepared to facilitate reaction with ylide **364**. The synthesis of the protected aldehyde **381** is detailed in Scheme 4.2.7. Lactone **309** was protected with TBDMS chloride and the resultant lactone **379** reacted with ammonia. Ozonolysis of **380** resulted in aldehyde **381**, albeit in low yield. **381** was combined with ketene ylide **364** under various conditions (Scheme 4.2.8), but unfortunately the reaction was not successful.



*Scheme 4.2.7: Synthesis of protected aldehyde **381**.*

Reagents and Conditions: (i) TBDMS-Cl, imidazole, CH_2Cl_2, RT, 56 h, 44%. (ii) NH_3, H_2O, dioxane, RT, 40 h, 85%. (iii) (a) O_3, CH_2Cl_2, –78 °C, 5 min. (b) PPh_3, –78 °C to RT, 30 min, 11% (+39% impure).



381 382

*Scheme 4.2.8: Unsuccessful reaction of **381** with ketene ylide **364**.*

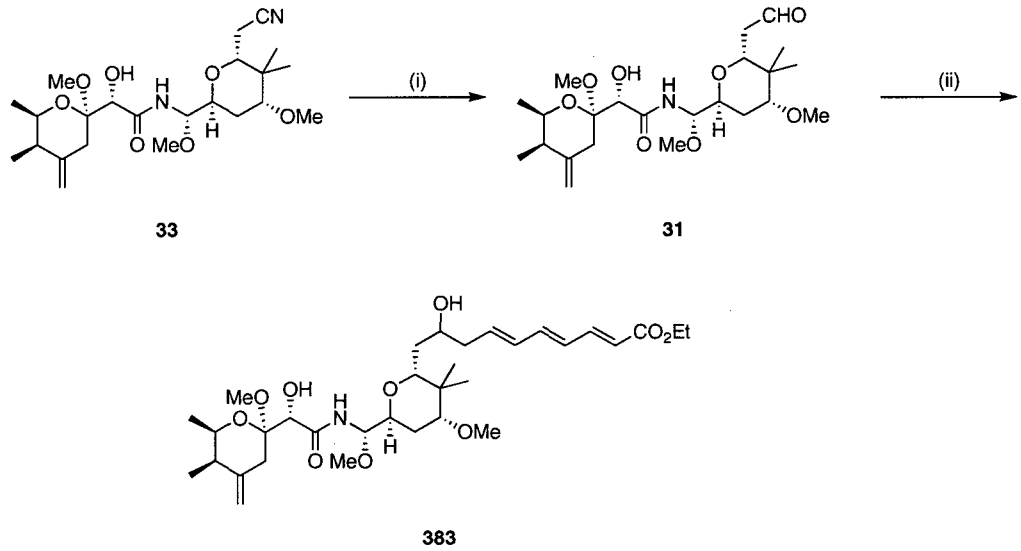
Reagents and Conditions: 1. THF, reflux.

2. *p*-TsOH, THF, reflux.[120]

With the unsuccessful application of Bestmann's ylide **364**, and the inability to achieve the required diastereomeric ratio directly from the nitrile **298**, a new approach was needed.

4.3 Substitution of the nitrile for an ester

In the original plan for this thesis, the nitrile was used as a surrogate aldehyde to enable the triene side chain to be attached (Scheme 4.3.1).



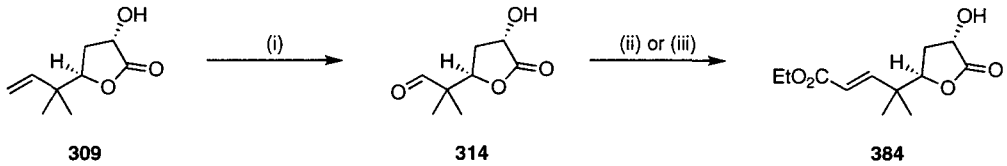
33 31 383

Scheme 4.3.1: Proposed final steps in synthesis of onnamide F.

Reagents and Conditions: (i) DIBAL-H, CH_2Cl_2. (ii) **32**, aluminium tris-(2,6-diphenylphenoxide) (**402**), LiTMP, THF, $PhCH_3$.

The nitrile had been selected as it offers a reliable route to aldehydes *via* reduction. Esters too may serve as precursors to aldehydes and it was hoped that this switch

might allow a stereoselective tetrahydropyran synthesis. Therefore, a synthesis of **384** was required. The possibility of using a Grubbs cross metathesis reaction between **309** and methyl acrylate was examined but this led to dimerisation with the starting material **309** and methyl fumarate being isolated from the reaction. The ester could be introduced *via* the two-step ozonolysis-Wittig sequence used to introduce the nitrile (Scheme 4.3.2).



309 **314** **384**

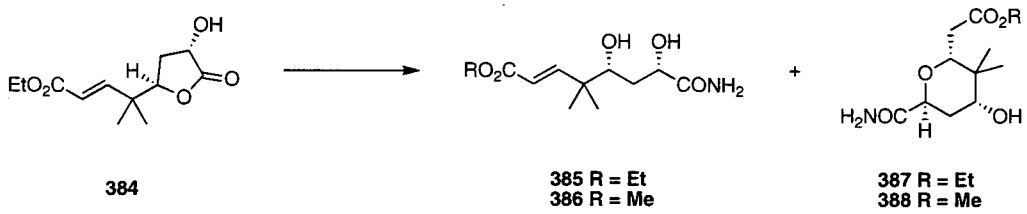
*Scheme 4.3.2: Ozonolysis and olefination of lactone **309**.*

Reagents and Conditions: (i) (a) O_3, CH_2Cl_2, –78 °C, 15 min. (b) PPh_3, –78 °C to RT, 1 h, 71%. (ii) Ph_3PCHCO_2Et (**367**), MeCN, reflux, 108 h, 72% (2 steps, **314** not isolated). (iii) Triethyl phosphonoacetate, LiCl, NEt_3, THF, RT, 36 h, 40%.

The ozonolysis of alkene **309** proved troublesome due to its low solubility in CH_2Cl_2 at low temperature. Addition of methanol promoted side reactions, leading to degraded products, which could not be recovered. Upon scale up, the best solvent was found to be ethyl acetate, with the reaction quenched with triphenylphosphine rather than dimethyl sulfide, which proved very slow (> 24 hours).

The Wittig reaction between **314** and **367** was first attempted in toluene, but the high boiling point induced degradation of all components and required a large excess of ylide to provide a low yield of α,β-unsaturated ester **384**. The use of acetonitrile at reflux allowed the transformation to be achieved in good yield as the *E* isomer. A Horner-Wadsworth-Emmons reaction between **314** and the commercially available triethyl phosphonoacetate also gave access to **384** as exclusively as the *E* isomer.[126] The yield remained low but the reaction time was greatly reduced from 108 to 36 hours.

When lactone **384** was treated with aqueous ammonia in methanol, a complex product mixture comprised of both the open-chain diols **385** and **386** and the THPs **387** and **388** resulted (Scheme 4.3.3). The methyl and ethyl esters could not be separated.



384 **385 R = Et** **386 R = Me** **387 R = Et** **388 R = Me**

*Scheme 4.3.3: Reaction of **384** with ammonia.*
Reagents and Conditions: NH_3, H_2O, MeOH, 16 h, RT.

It was found that reaction of aqueous ammonia with **384** in both acetonitrile and dioxane resulted in the isolation of diol **385** in both cases. This provided a straightforward route to **385** without the use of liquid ammonia, as detailed in Scheme 4.3.4.

384 **385**

*Scheme 4.3.4: Conversion of lactone **384** into diol **385**.*
Reagents and Conditions: NH_3, H_2O, dioxane, RT, 16 h, 62%.

With easy access to diol **385**, research began into the cyclisation reaction. There is greater literature precedent for cyclisations involving Michael type additions of alkoxides to α,β-unsaturated esters and protocols for control of the stereochemistry in the product are also well documented.

Sodium hydride has been used to effect such a cyclisation,[127,128] as has potassium *tert*-butoxide.[117,129-132] Obtaining the correct stereochemistry is frequently reported as challenging, with *syn*-2,6-disubstituted tetrahydropyrans generally easier to access. Temperature is important as the reaction is reversible.[117,129,131]

Treatment of **385** with sodium hydride in THF was unsuccessful. Use of catalytic potassium *tert*-butoxide was also unsuccessful but with a stoichiometric equivalent a very small amount of the undesired diastereoisomer **389** was isolated (Scheme

4.3.5).[117] Unfortunately, there was insufficient material for full characterisation but ^{1}H NMR suggested that the material isolated was **389**.

385 **389**

Scheme 4.3.5: Cyclisation with potassium tert-butoxide to give the undesired diastereoisomer.
Reagents and Conditions: ^{t}BuOK, THF, –78 °C, 4 h.

Attention now turned to reactions in more polar solvents. The use of DBU in DMF has been reported to achieve such cyclisation reactions at elevated temperatures and to yield the thermodynamic product.[133] Pleasingly, treatment of **385** with DBU in DMF afforded THP **387** in 60% yield with excellent stereocontrol for the desired diastereoisomer (Scheme 4.3.6). The *syn*-2,6-stereoisomer **389** was detected in the ^{1}H NMR spectrum of the crude product mixture, but could not be isolated in pure form.

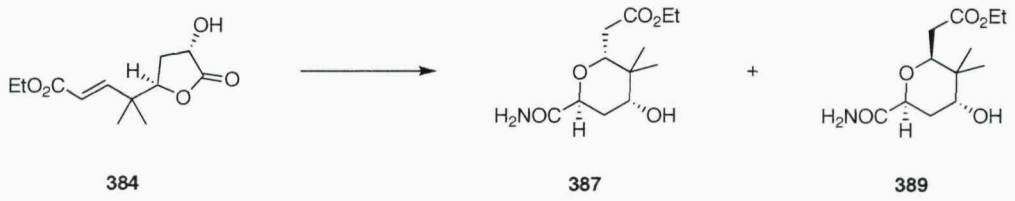
385 **387**

Scheme 4.3.6: Cyclisation to selectively obtain THP 387.
Reagents and Conditions: DBU, DMF, RT, 16 h, 60%, reaction *d.r.* 14:1 (**387**:**389**).

Treatment of **385** with sodium hydroxide in DMSO also afforded **387** in good yield (74%) after chromatography, though this procedure proved highly capricious. Notably, application of the NaOH / DMSO protocol to the related nitrile **298** resulted in degradation of the reaction components.

Since the use of DMF had provided excellent stereocontrol, it was now applied to the reaction of lactone **384** with ammonia. By treatment of **384** with ammonia in DMF

followed by addition of DBU or an extended reaction time, it was possible to convert **384** directly into THP **387** with somewhat poorer diastereoselectivity (Scheme 4.3.7).



384 **387** **389**

*Scheme 4.3.7: Conversion of **384** to THPs **387** and **389** in one reaction.*

Reagents and Conditions: 1. (i) Dilute NH_3, H_2O, DMF, RT, 72 h. (ii) DBU, DMF, RT, 6 h, 44%, *d.r.* 1.4:1 (**387**:**389**)

2. NH_3, H_2O, DMF, RT, 24 h, 9% (+16 % **385**), *d.r.* 2.2:1 (**387**:**389**).

4.4 Crystal structure and NMR experiments

The structure of THP **387** was verified by X-ray crystallography and by NMR experiments. The obtained X-ray crystal structure is shown in Figure 4.4.1, with the hydrogen-bonded structure shown in Figure 4.4.2.

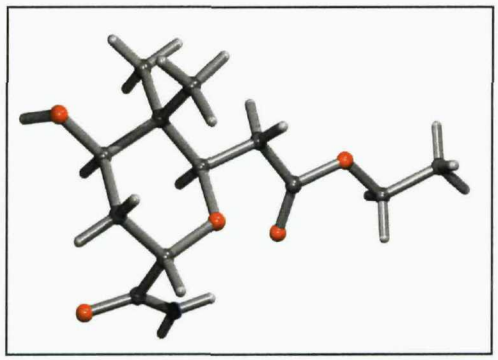


*Figure 4.4.1: X-ray crystal structure of **387**.*

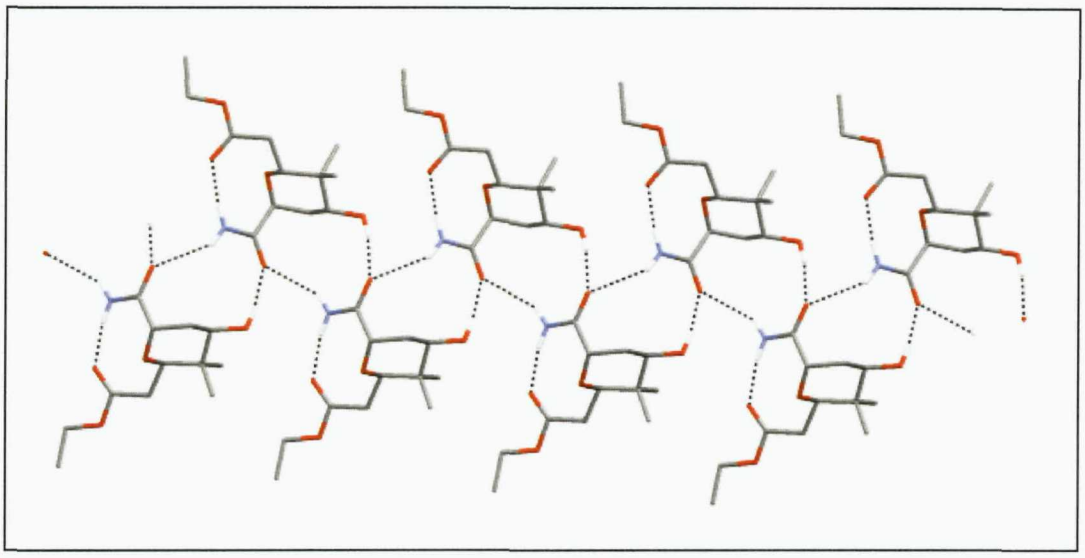


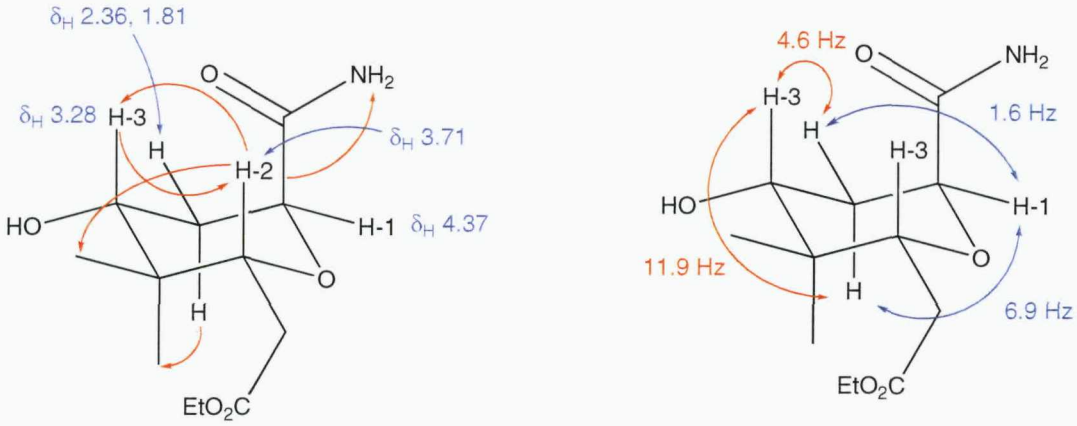
*Figure 4.4.2: Hydrogen bonding in **387**.*

The structure of **387** was also confirmed *via* n.O.e. experiments, with results confirming the structure (Table 4.4.1). As with THPs **37** and **315**, 2D NMR experiments were used to aid assignment.

Irradiation site	**δ_H / ppm**	**n.O.e. effect**
H-1	4.37	None
H-2	3.72	Enhance $\mathbf{H}_3$, methyl and N**H**
H-3	3.28	Enhance $\mathbf{H}_2$ and methyl
Ring C$\mathbf{H}_2$	2.36, 1.81	Enhance methyl

*Table 4.4.1: n.O.e. experiment results for **387**.*

There is no through-space interaction between **H**-1 and **H**-2, indicating that the structure is correct. Figure 4.4.3 shows the relevant n.O.e. interactions. Analysis of the key coupling constants also indicates the structure shown in Figure 4.4.3, with the ester equatorial and the amide axial.

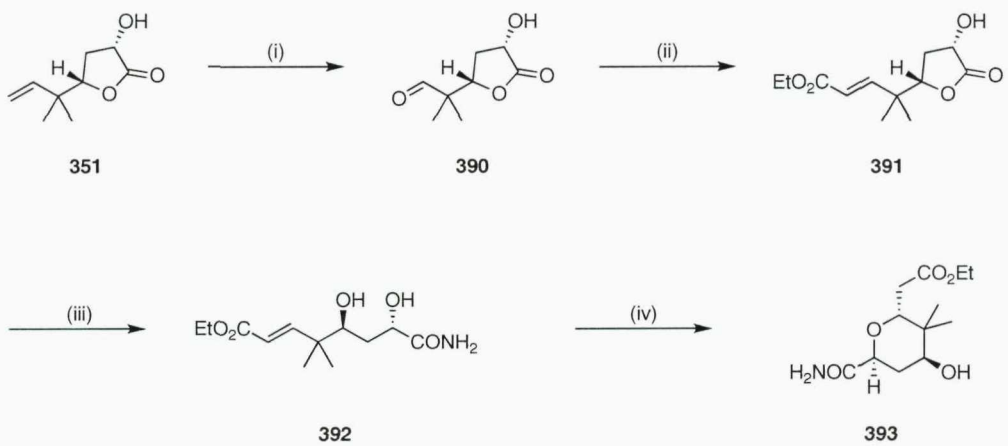


387

*Figure 4.4.3: Relevant n.O.e. interactions and chemical shifts (left) and conformational analysis and coupling constants (right) of **387**.*

4.5 Application of DBU / DMF methodology to *syn* lactone

Since cyclisation of **385** with DBU in DMF had been so successful in generating the desired THP diastereoisomer **387**, the reaction was examined with **351**, the diastereoisomer of lactone **309** (Scheme 4.5.1). Here too, the reaction proved highly diastereoselective, giving **393** in moderate yield. The structure of **393** was confirmed by X-ray crystallography (Figure 4.5.1).



*Scheme 4.5.1: Application of successful synthesis methodology to syn diastereoisomer **351**.*

Reagents and Conditions: (i) (a) O_3, EtOAc, –78 °C, 20 min. (b) Me_2S, –78 °C to RT, 16 h, then PPh_3, 1 h. (ii) Triethyl phosphonoacetate, LiCl, NEt_3, THF, RT, 16 h, 46% (2 steps). (iii) NH_3, H_2O, dioxane, RT, 20 h, 92%. (iv) DBU, DMF, RT, 24 h, 35%.

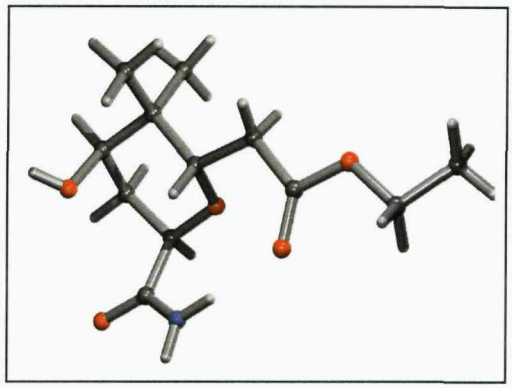
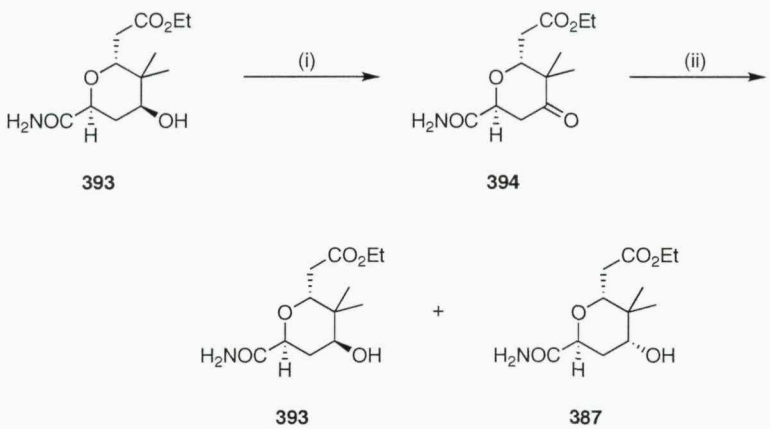


Figure 4.5.1: X-ray crystal structure of ***393***

In principle, **393** could be of use, provided the alcohol stereochemistry could be inverted.[32,34] To investigate that possibility, alcohol **393** was oxidised with Dess-Martin periodinane and then reduced with sodium borohydride (Scheme 4.5.2). Disappointingly, this produced a 1:1 mixture of **393** and **387** (by NMR). Alternative reagents such as L-selectride may prove more successful, but there was insufficient material and little need to attempt such a reduction in this case.



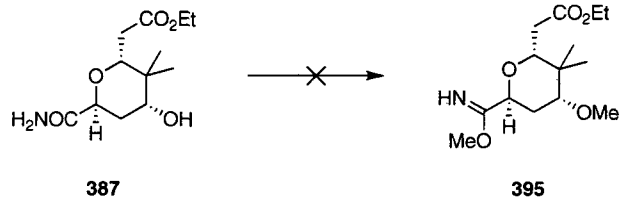
Scheme 4.5.2: Oxidation and reduction of ***393****.*

Reagents and Conditions: (i) DMP, $CHCl_3$, RT, 3 h, 73%. (ii) $NaBH_4$, EtOH, 0 °C, 2 h, *d.r.* 1:1.

4.6 Imidate formation and attempted coupling

With a short and robust route to fragment **387**, the imidate formation and the key coupling reaction with an acid chloride was examined. Initial experimentation employing published conditions proved to be unsuccessful, with imidate formation

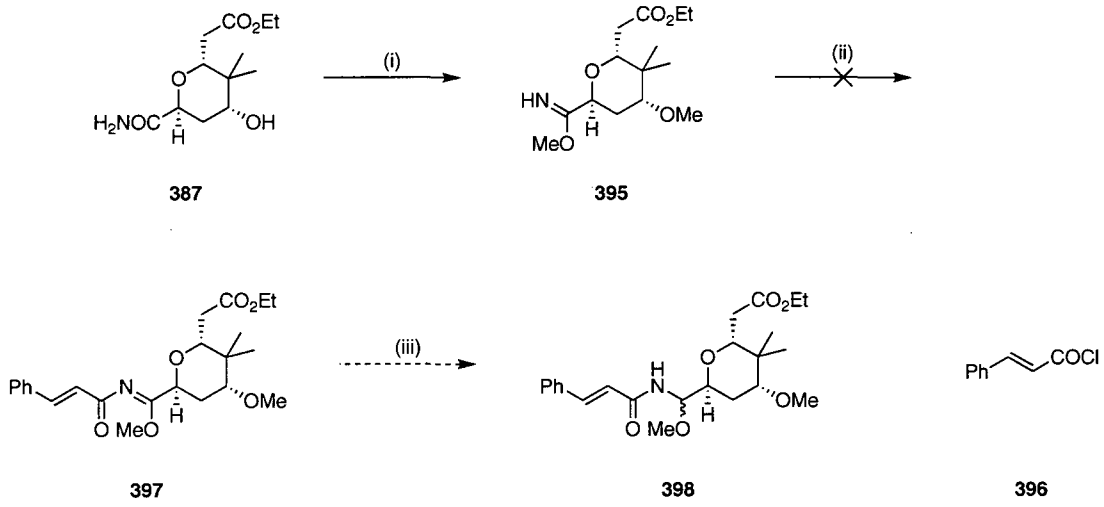
more challenging than indicated in the literature (Scheme 4.6.1).[21,25,32,54,56] Heating of the reaction mixture was required in order to encourage any reaction.



387 **395**

Scheme 4.6.1: Initial attempts at imidate formation.
Reagents and Conditions: $Me_3O^+BF_4^-$, CH_2Cl_2, RT to 40 °C, 24 h.

Imidate **395** was particularly susceptible to hydrolysis and was not amenable to aqueous work up and handling procedures described in the literature.[54,56] To avoid such handling, **395** was generated *in situ* before addition of cinnamoyl chloride **396** (Scheme 4.6.2).

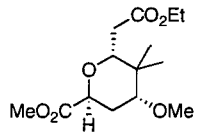


387 **395** **397** **398** **396**

Scheme 4.6.2: Attempted imidate formation and further reaction.
Reagents and Conditions: (i) $Me_3O^+BF_4^-$, CH_2Cl_2, 40 °C, 24 h. (ii) Cinnamoyl chloride (**396**), NEt_3, CH_2Cl_2, RT, 24 h. (iii) $NaBH_4$, EtOH, CH_2Cl_2, 0 °C, 1 h.

Ester **399** was isolated from one such reaction, suggesting that the formation of imidate **395** was successful. Formation of **395** in acetonitrile with added disodium hydrogenorthophosphate appeared to give **395**,[134] though this could not be conclusively proved by NMR or MS. The use of poly(vinylpyridine) has been

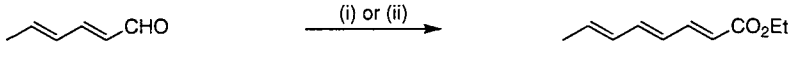
suggested as a suitable base for formation of the imidate and would be a good starting point for further investigation of the reaction.[17]



399

4.7 Synthesis of the triene side chain and attempted coupling

A synthesis of the triene side chain **32** was completed in one step, *via* a procedure reported by Ley.[65] Horner-Wadsworth-Emmons olefination of aldehyde **297** was completed by using sodium hydride,[65] and LiCl / NEt_3[126] as bases, giving the desired triene in 53% and 71% yields respectively (Scheme 4.7.1).

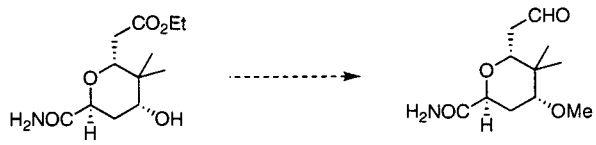


297 32

Scheme 4.7.1: Synthesis of triene 32.

Reagents and Conditions: (i) Triethyl phosphonoacetate, NaH, THF, 0 °C to RT, 20 h, 53%.
(ii) Triethyl phosphonoacetate, LiCl, NEt_3, THF, RT, 16 h, 71%

The DIBAL reduction of fragment **387** was tested and found to be successful, though purification problems prevented isolation of this material in pure form. It is possible that protection of the alcohol will be necessary to achieve reduction in high yield (Scheme 4.7.2).

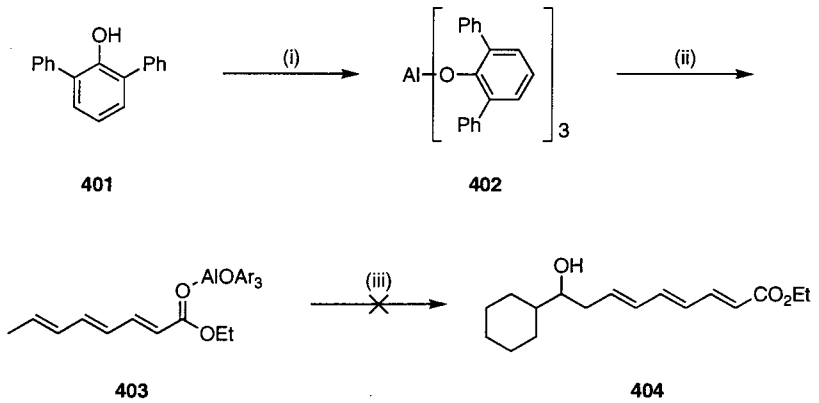


387 400

Scheme 4.7.2: Trial reduction of ester 387 to aldehyde 400.

Reagents and Conditions: DIBAL-H, CH_2Cl_2, –78 °C, 4 h, not purified.

As **400** was not isolated in a large enough quantity, the coupling reaction to attach triene **32** was tested with cyclohexanecarboxaldehyde. The aluminium complex was prepared from reaction of the related phenol with trimethylaluminium (Scheme 4.7.3).[22]



*Scheme 4.7.3: Attempted coupling of triene **32** and cyclohexanecarboxaldehyde.*
Reagents and Conditions: (i) $AlMe_3$, $PhCH_3$, RT, 45 min. (ii) **32**, cyclohexanecarboxaldehyde, THF, –78 °C, 45 min. (iii) LiTMP, THF, –78 °C to RT, 18 h.

Unfortunately, none of the desired product **404** could be isolated from the reaction after extensive chromatography and the reaction requires further experimentation to obtain a successful result.

Chapter 5 Results and Discussion - Research Towards the Related Natural Product Psymberin

5.1 Initial retrosynthetic analysis

Since the central section of the natural product psymberin (**24**) is similar to fragment **387** described above, it seemed logical to exemplify the newly developed method with a synthetic route to **24**. Following the total synthesis of **24**, the correct structure is known and has been fully published.[17]

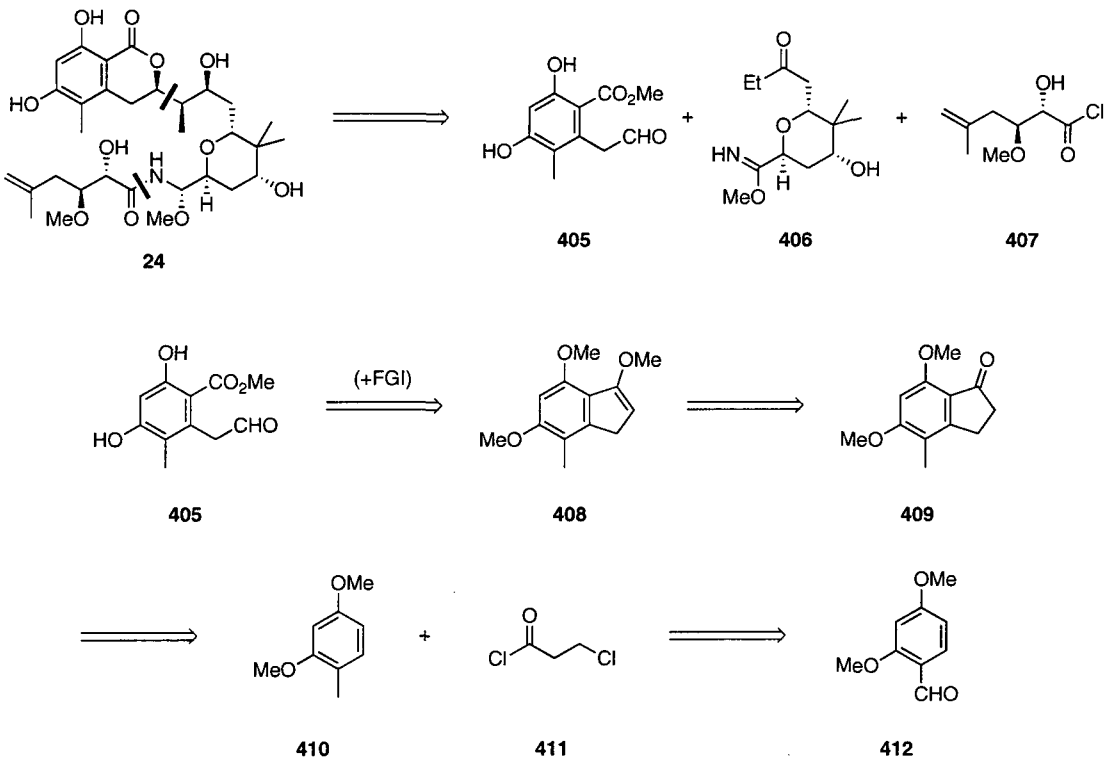


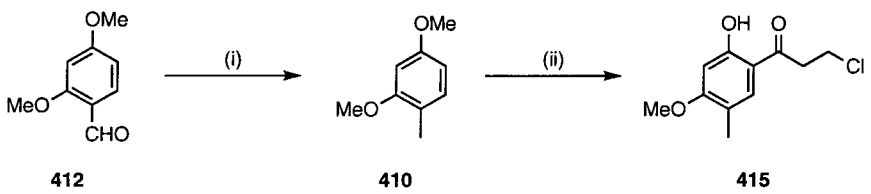
Figure 5.1.1: Retrosynthetic analysis of psymberin (24).

Retrosynthetic analysis of psymberin mirrored that described by De Brabander by initially splitting the molecule into three fragments, **405**, **406** and **407**.[17] **406** is very similar to fragment **387** and it seemed reasonable to prepare it by using the ring expansion methodology developed in the approach to onnamide F. THP **406** can be joined to **405** by an aldol reaction, with a selective reduction to convert the ketone into a chrial alcohol, as reported by De Brabander *et al.*[17]

Retrosynthetic analysis of fragment **405** is shown in Figure 5.1.1. It seemed plausible to construct **405** by ozonolysis of **408**,[135] which in turn could be prepared from indanone **409**.[136] **409** could be prepared by a Friedel-Crafts acylation-alkylation between **410** and **411**,[137,138] giving aldehyde **412** as a convenient starting point.

5.2 Friedel-Crafts synthetic route

Attempts to prepare **405** began with a catalytic hydrogenation of **412** under acidic conditions, which proceeded slowly but smoothly to give 2,4-dimethoxytoluene **410** in 62% yield.[139] The proposed Friedel-Crafts acylation-alkylation sequence between **410** and **411** proved problematic, with aluminium trichloride initiating acylation at C5 and cleavage of the C4 methyl ether (Scheme 5.2.1).[137]

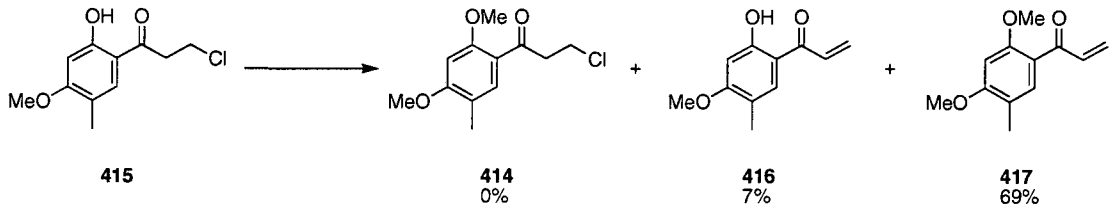


412 **410** **415**

*Scheme 5.2.1: Catalytic hydrogenation and Friedel-Crafts acylation to give **415**.*

Reagents and Conditions: (i) H_2, Pd / C, HCl, EtOH, RT, 24 h, 62%. (ii) 3-chloropropionyl chloride (**411**), $AlCl_3$, CH_2Cl_2, RT, 20 h, 69%.

The reaction was attempted in different solvents without success, it being particularly slow in non-chlorinated solvents. To prevent side reactions involving the free phenol moiety, an attempt was made to re-protect **415** using methyl iodide and a base.[140] This resulted in HCl elimination and protection of the phenol, as evidenced by the isolation of phenol **416** and ether **417** (Scheme 5.2.2).

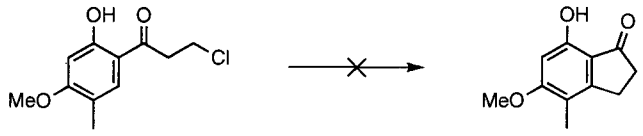


415 **414** 0% **416** 7% **417** 69%

*Scheme 5.2.2: Attempted re-protection of **415**.*

Reagents and Conditions: MeI, K_2CO_3, acetone, RT (72 h) to reflux (5 h), 7% **416**, 69% **417**.

Attempts to induce an intramolecular Friedel-Crafts alkylation of **415** under strongly acidic conditions met with failure with no reaction apparent at low temperature, while higher temperatures (approaching 100 °C) resulted in decomposition (Scheme 5.2.3).[138] This result led to the exploration of a new route to **405**, based on benzyne chemistry.



415 **418**

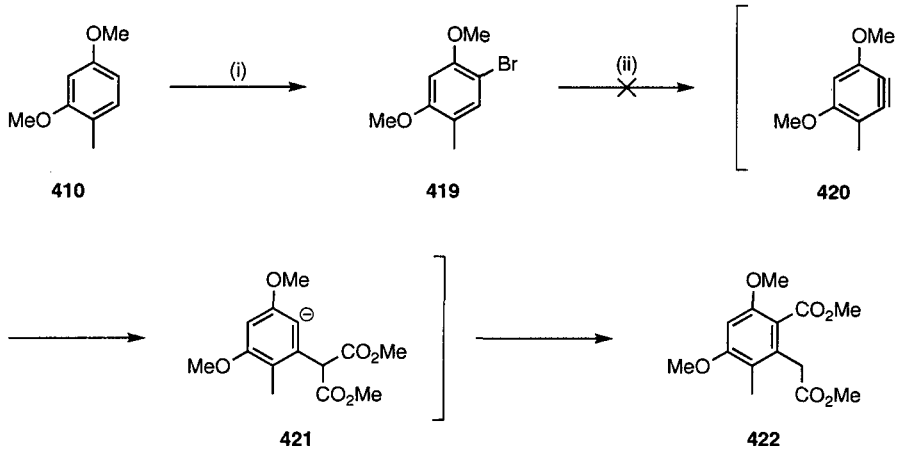
*Scheme 5.2.3: Attempted cyclisation of **415** to **418**.*

Reagents and Conditions: H_2SO_4, neat, 100 °C, 16 h or RT, 8 days.

5.3 Benzyne route to psymberin fragment

Compounds similar to **414** have been prepared using benzyne chemistry to introduce the ester functionality (Scheme 5.3.1).[141] If successful, an unsymmetrical malonate or selective reaction of the methylene ester would be used to further the synthesis.

Toluene **410** was successfully brominated at C5 to give **419** in excellent yield. Attempted formation of **420** with LDA did not proceed. As there was no dehalogenation of **419** in the reaction, it is likely that the benzyne intermediate **420** did not form. This was confirmed by treatment of **419** with LiTMP (both 1 equiv. and 2 equiv.) and quenching with deuterium chloride. NMR indicated no deuterium incorporation into the sample in either case.

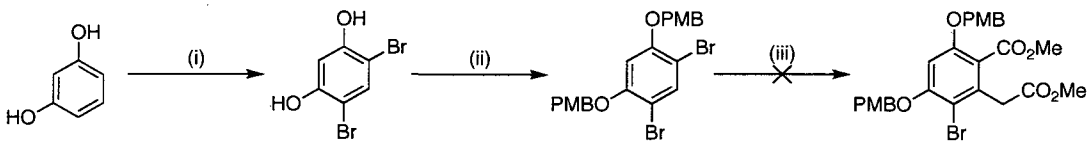


*Scheme 5.3.1: Route to diester **422** via benzyne chemistry.*

Reagents and Conditions: (i) Br_2, AcOH, RT, 2 h, 91%. (ii) LDA or LiTMP, NaH, dimethyl malonate, THF, 0 °C, 16 h.

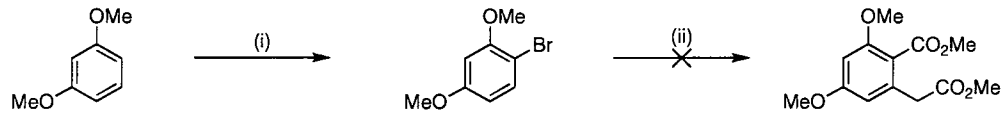
To test the possibility that the presence of the toluene methyl group in **419** was preventing the reaction from proceeding, two simple aromatic systems were synthesised to test the benzyne reaction. Protected bromide **426** offered the possibility of replacing the remaining bromide in the product **427** with a methyl group at a later stage while bromide **429** was the arene used in the literature precedent for the formation of **431** in the benzyne reaction.[141] The syntheses and attempted reactions of **426** and **429** are shown in Schemes 5.3.2 and 5.3.3 respectively.

Bromide **426** was prepared by dibromination of **423**, followed by protection of both phenols as PMB ethers. Subsequent treatment with base did not induce benzyne formation. **429** was an example used to test the methodology as it is taken directly from the literature.[141] Some dibromination of **428** occurred during the preparation of **429** but that by product was readily removed by column chromatography. More worryingly, it did not prove possible to induce the conversion of **429** to **431**, as had been described in the reference. Further research is necessary to determine a synthesis of psymberin.



423 **424** **426** **427**

Scheme 5.3.2: Bromination and protection of ***423****, followed by attempted benzyne formation.*
Reagents and Conditions: (i) Br_2, $CHCl_3$, RT, 5 h, 88%. (ii) *p*-methoxybenzyl chloride, K_2CO_3, DMF, RT, 72 h, 68%. (iii) LiTMP, dimethylmalonate, THF, 0 °C to reflux, 24 h.

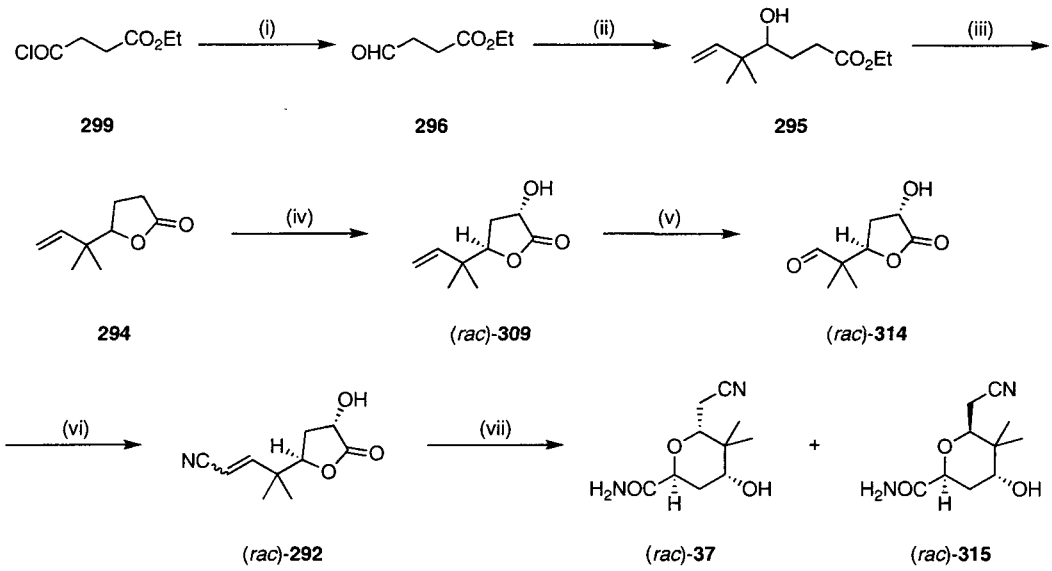


428 **429** **431**

Scheme 5.3.3: Bromination of ***428****, followed by attempted benzyne formation.*
Reagents and Conditions: (i) Br_2, AcOH, RT, 30 h, 49 %. (ii) LiTMP, dimethyl malonate, THF, 0 °C to RT, 16 h.

Conclusions

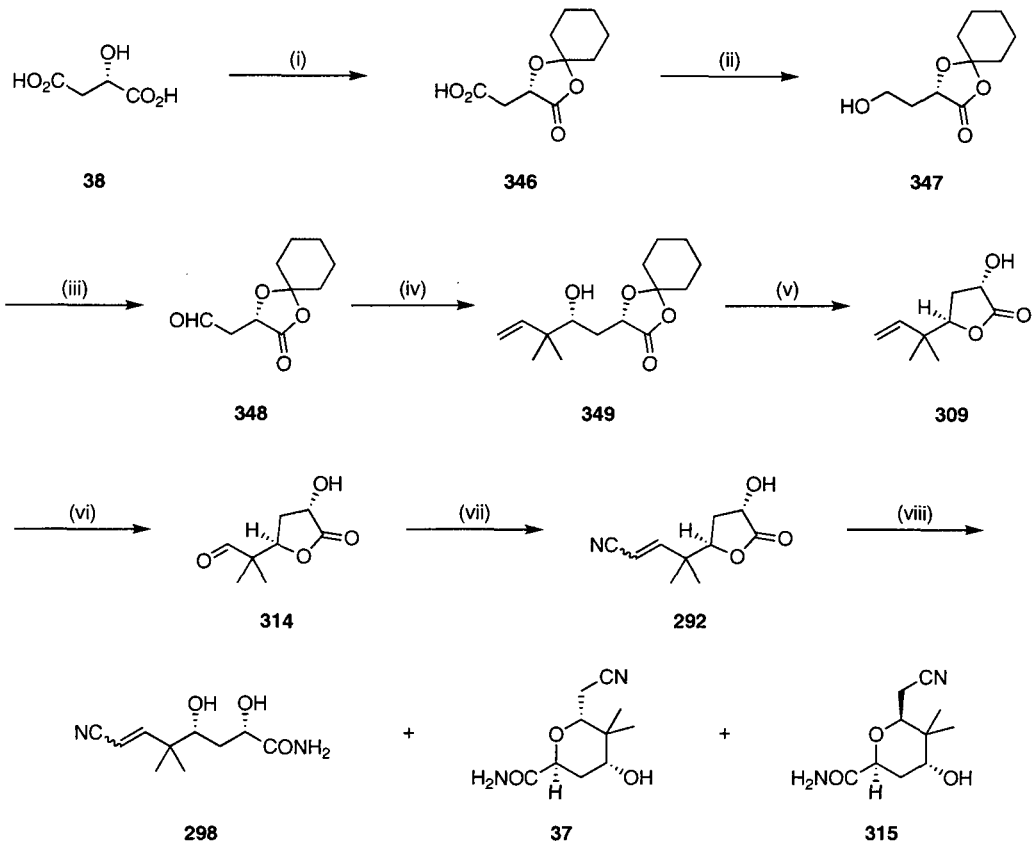
The initial route to nitrile fragment (*rac*)-**37**, *via* α-hydroxylation of a chiral lactone, provided a very concise seven step synthesis from the commercially available acid chloride **299**, albeit in low yield. A synthesis of an enantiomerically pure product should be possible *via* chiral lactone (*R*)-**294**.



Summary Scheme 1: Racemic synthesis of ***37****.*

Reagents and Conditions: (i) Et_3SiH, Pd / C, neat, 0 °C, 2 h, 72%. (ii) Zn dust, prenyl bromide (**300**), NH_4Cl, H_2O, THF, RT, 2 h, 98% (crude). (iii) TFA (cat.), CH_2Cl_2, reflux, 1 h, 88%. (iv) (a) LiTMP, THF, –78 °C, 2 h. (b) **305**, THF, –78 °C, 30 min, 40%, *d.r.* 3:1. (v) (a) O_3, CH_2Cl_2, –78 °C, 15 min. (b) PPh_3, –78 °C to RT, 1 h, 28 – 71%. (vi) ^tBuOK, $Br^-Ph_3P^+CH_2CN$, THF, 0 °C to RT, 48 h, 35%, *E*:*Z* 8:1. (vii) NH_3, dioxane, H_2O, RT, 24 h, 28%, *d.r.* 1:2.1 (**37**:**315**).

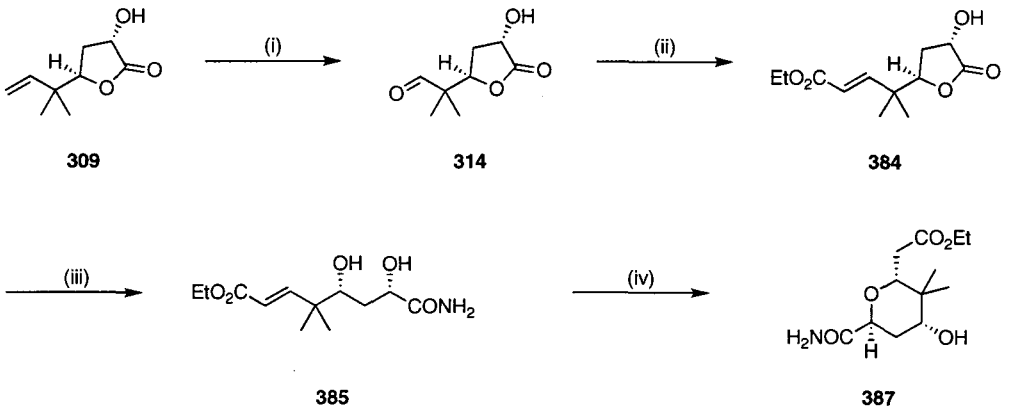
The main reason for switching to the malic acid based synthesis was the inability to improve the α-hydroxylation reaction yield. The diastereomeric ratio obtained for **294** to **309** was good (up to 9:1), but yields obtained were highly variable. The use of malic acid as a starting material removed the need to synthesise the oxaziridine reagent **305** and provided the opportunity to easily scale up the synthesis. Brown prenylboration was highly diastereoselective as expected, and the remaining steps in the synthesis were transferable from the racemic route, providing fragment **37** asymmetrically in 1.4% yield over eight steps.



Summary Scheme 2: Asymmetric synthesis of 37.

Reagents and Conditions: (i) Cyclohexanone, PPTS, $PhCH_3$, Dean and Stark, reflux, 16 h, 92%. (ii) $BH_3.SMe_2$, THF, 0 °C to RT, 24 h, quant. (iii) 4-hydroxy-TEMPO, TCCA, NaOAc, CH_2Cl_2, 0 °C, 2 h, 54 – 81%. (iv) **319**, THF, –78 °C to RT, 16 h. (v) TFA (cat.), CH_2Cl_2, reflux, 2 h, 60%, *d.r.* 6:1 (2 steps). (vi) (a) O_3, CH_2Cl_2, –78 °C, 10 min. (b) PPh_3, –78 °C to RT, 1 h, 49%. (vii) Ph_3PCHCN (**362**), $PhCH_3$, reflux, 36 h, 70%, *E*:*Z* 5:1. (viii) NH_3, MeOH, H_2O, RT, 16 h, 24%, d.r. 1:1.2 (**37**:**315**)

Replacement of the nitrile for an ester was a logical exchange, given that an aldehyde is required to complete the synthesis of onnamide F. It was possible to induce cyclisation of **385** to ester **387** with excellent diastereoselectivity, and with no obvious equibrilation of **387**. The use of ester **385** enabled the DBU / DMF reaction conditions reported in the literature to be employed.[133] Previously, these conditions were uses to provide a *syn* thermodynamic product but in this case, the desired *anti* diastereoisomer was the main product. The overall yield from malic acid to ester **387** was 9.6% in nine steps. It was possible to directly reduce the ester to an aldehyde with DIBAL, verifying that the swap from the nitrile series to the ester series was the correct choice.



Summary Scheme 3: Ester modification of fragment.

Reagents and Conditions: (i) (a) O_3, CH_2Cl_2, –78 °C, 15 min. (b) PPh_3, –78 °C to RT, 1 h. (ii) Ph_3PCHCO_2Et (**367**), MeCN, reflux, 108 h, 72% (2 steps). (iii) NH_3, H_2O, dioxane, RT, 16 h, 62%. (iv) DBU, DMF, RT, 16 h, 60%.

The triene unit of onnamide F was successfully synthesised in one step, although the aluminium-mediated coupling reaction between the triene and an aldehyde requires more research. Initial investigation into the imidate coupling step was problematic and the fact that the reaction is not trivial has been confirmed by observations in the literature.[17] The isolation of ester **399** proves that the imidate was formed but that hydrolysis was prevalent over reaction with the acid chloride.

With a short route to the central fragment of onnamide F, pederin and psymberin developed, some research was directed towards a synthesis of psymberin. Development of a route to the required aromatic system was unsuccessful, with key reactions failing. Further work would be needed to improve the synthesis and produce a high-quality route.

Overall, a very short and efficient synthetic route to the central fragment of onnamide F has been developed. Further research into the coupling reactions between imidate **395** and pederic acid fragment **36** and between aldehyde **400** and triene **32** are necessary to complete the synthesis of the natural product.

Chapter 6 Experimental Section

General Experimental

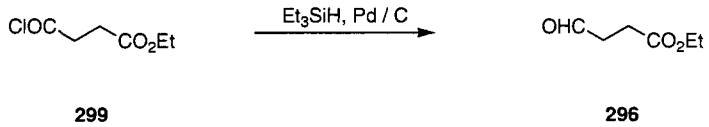
All chemicals were obtained from commercial suppliers and used without further purification unless otherwise stated. All air or moisture sensitive reactions were performed under nitrogen or argon as indicated. Dry solvents were freshly distilled where required. THF and diethyl ether were distilled from sodium / benzophenone ketyl. Dichloromethane, chloroform and acetonitrile were distilled from calcium hydride. Methanol and ethanol were distilled from magnesium turnings / iodine. Toluene was distilled from sodium.

Mass spectral data was recorded on a ThermoQuest TraceMS GC mass spectrometer with electron or chemical ionisation as the ionisation source or on a Waters ZMD electrospray mass spectrometer operating in positive or negative ion mode as indicated. NMR spectra were recorded on a Bruker AV-300 spectrometer (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) or a Bruker DPX-400 spectrometer (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C) in the solvents indicated at 300 K. Chemical shifts were referenced to residual solvent peaks ($CDCl_3$: 7.27 ppm for ^{1}H, 77.2 ppm for ^{13}C, d_6-DMSO: 2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C, CD_3OD: 3.31 ppm for ^{1}H, 49.0 ppm for ^{13}C). Multiplicities are given as s=singlet, d=doublet, t=triplet, q=quartet and br=broad signal. 2D NMR experiments were used to aid assignments where necessary. IR data was collected as a neat oil, compressed solid or $CHCl_3$ / CH_2Cl_2 solution on a Thermo Nicolet 380 FT – IR with a Smart Orbit golden gate attachment or on a Mattson Satellite FT – IR golden gate spectrometer. TLC was run on aluminium backed silica gel plates. Column chromatography was run on Fisher Scientific silica gel 60A, particle size 35–70 micron. Compound names were generated where appropriate using ACD/Labs' ACD/Name. Data for minor compounds is included where inseparable mixtures were obtained pure and where it was possible to separate minor compounds. It is omitted where it was not possible to separate minor compounds from reaction impurities.

Experimental Detail

Ethyl 4-oxobutanoate (**296**)

Known compound.



299 **296**

Chemical Formula: $C_6H_9ClO_3$
Molecular Weight: 164.59

Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130.14

Prepared by the methods reported by Citron[67] and Pham.[68] To a mixture of ethyl succinyl chloride (**299**) (2.06 g, 1.78 mL, 12.52 mmol) and Pd (5 % on C, 125 mg) was added Et_3SiH (1.74 g, 2.40 mL, 15.00 mmol) at 0 °C under nitrogen. The mixture was stirred at this temperature for 1 h and then warmed to RT for 1 h. The mixture was then diluted with CH_2Cl_2 (50 mL), filtered through a pad of Celite® and concentrated. Purification by column chromatography on silica gel eluting with 5–20% EtOAc / petrol afforded the title compound **296** as a light yellow oil (1.18 g, 9.05 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$, decomposed slightly)

δ_H ppm 9.81 (1H, s, C**H**O), 4.14 (2H, q, J = 7.1 Hz, OC**H**$_2$), 2.79 (2H, t, J = 6.3 Hz, C**H**$_2$), 2.61 (2H, t, J = 6.3 Hz, C**H**$_2$), 1.25 (3H, t, J = 7.1 Hz, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, decomposed slightly)

δ_C ppm 200.1 (**C**HO), 172.3 (**C**=O), 60.9 (O**C**H$_2$), 38.7 (**C**H$_2$), 26.8 (**C**H$_2$), 14.3 (OCH$_2$**C**H$_3$).

LRMS (EI)

m/z 102 ([M–EtH]$^+$, 42%), 85 ([M–OEt]$^+$, 100%), 74 (33%), 73 (23%), 57 (29%), 56 (31%), 55 (21%), 45 (25%).

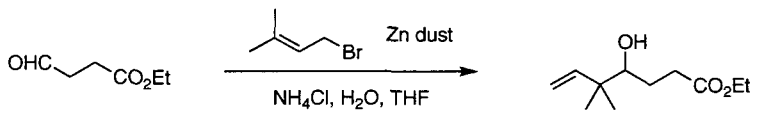
FT – IR ($CHCl_3$ film)

cm^{-1} 2980 (w), 2937 (w), 1782 (m), 1728 (s), 1416 (m).

Spectroscopic data are in agreement with the literature.[142]

Ethyl 4-hydroxy-5,5-dimethylhept-6-enoate (**295**)

New compound (unstable).



296 **295**

Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130.14

Chemical Formula: $C_{11}H_{20}O_3$
Molecular Weight: 200.27

Prepared using a method reported by Luche.[69] To a solution of aldehyde **296** (700 mg, 5.38 mmol) in THF (3.5 mL) was added zinc dust (528 mg, 8.07 mmol) and NH_4Cl (sat., aq., 13 mL). The mixture was rapidly stirred at 0 °C and prenyl bromide (1.20 g, 0.93 mL, 8.07 mmol) was added dropwise, producing an immediate exotherm and zinc began to disappear from the reaction. The mixture was stirred for 2 h at RT in air and then diluted with Et_2O (50 mL). The aqueous phase was separated and washed with Et_2O / EtOAc 1:1 mix (3 x 50 mL). The combined organic phases were washed with water (30 mL) and brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated to a light yellow oil (920 mg, 4.59 mmol, 85%). A small sample was purified by column chromatography on silica gel, eluting with 20% EtOAc / petrol. The pure sample was characterised but degraded both during purification and in the NMR solvent ($CDCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 5.83 (1H, dd, J = 17.3, 10.8 Hz, H_2C=C**H**), 5.11 (1H, dd, J = 10.8, 1.4 Hz, **H**HC=CH), 5.06 (1H, dd, J = 17.3, 1.4 Hz, H**H**C=CH), 4.14 (2H, q, J = 7.2 Hz, O**C**$H_2$$CH_3$), 3.27 (1H, ddd, J = 10.7, 5.3, 2.0 Hz, **C**HOH), 2.55–2.37 (2H, m, **C**H_2C=O), 1.86 (1H, dtd, J = 14.1, 7.5, 2.0 Hz, CHOHC**H**H), 1.57 (1H, dddd, J = 14.1, 10.7, 7.3, 6.6 Hz, CHOHCH**H**), 1.26 (3H, t, J = 7.2 Hz, OCH$_2$C**H**$_3$), 1.04 (3H, s, **C**H_3), 1.03 (3H, s, **C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 174.3 (**C**=O), 145.0 (H_2**C**=CH), 113.6 (H_2**C**=CH), 83.1 (**H**COH), 60.4 (O**C**H_2), 41.7 (**C**$(CH_3)_2$), 31.8 (**C**H_2), 26.6 (**C**H_2), 22.9 (**C**H_3), 22.2 (**C**H_3), 14.2 (**C**H_3).

Contains the correct signals but there is extensive degradation of the sample.

Degradation signals are observed at: 60.8, 33.1, 29.4, 29.1, 28.8 ppm.

LRMS (EI)

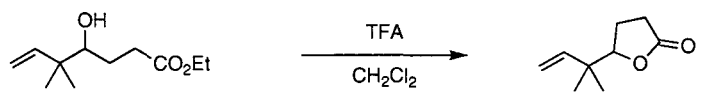
m/z 155 ([γ–butyrolactone+H]$^+$, 28%), 154 ([γ–butyrolactone]$^+$, 28%), 86 (34%), 85 ([M–C_5H_9]$^+$, 100 %), 69 ([M–γ–butyrolactone]$^+$, 55%), 67 (36%), 57 (52%), 55 (55%), 53 (39%), 43 (30%), 41 (71%).

FT – IR ($CHCl_3$ solution)

cm^{-1} 3019 (w), 2973 (w), 1766 (s) (lactone), 1730 (s).

5-(1,1-Dimethylprop-2-en-1-yl)dihydrofuran-2(3*H*)-one (**294**)

Known compound.



295 **294**

Chemical Formula: $C_{11}H_{20}O_3$
Molecular Weight: 200.27

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

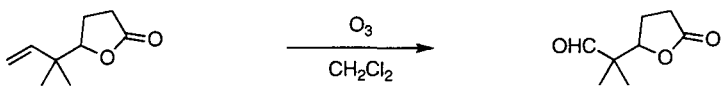
A solution of alcohol **295** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) was treated with TFA (2 drops) and heated at reflux under nitrogen for 1 h. The mixture was cooled to RT, diluted with CH_2Cl_2 (30 mL) and washed with $NaHCO_3$ (sat., aq., 20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with water (20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated to a yellow oil. The crude oil was purified by column chromatography on silica gel, eluting with 20–30% EtOAc / petrol to afford the title compound **294** as a colourless oil (68 mg, 0.44 mmol, 90%).

^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	5.79 (1H, dd, *J* = 17.4, 10.9 Hz, H_2C=C**H**), 5.11 (1H, dd, *J* = 10.9, 1.2 Hz, **H**HC=CH), 5.08 (1H, dd, *J* = 17.4, 1.2 Hz, H**H**C=CH), 4.25 (1H, dd, *J* = 8.3, 7.1 Hz, OC**H**), 2.48 (2H, m, **H_2**CC=O), 2.10 (1H, dddd, *J* = 13.0, 8.4, 7.1, 5.6 Hz, C**H**HCH_2C=O), 1.93 (1H, dddd, *J* = 13.0, 10.1, 9.4, 8.3 Hz, CH**H**CH_2C=O), 1.09 (3H, s, **CH_3**), 1.05 (3H, s, **CH_3**).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	177.3 (**C**=O), 142.0 (H_2**C**=CH), 114.6 (H_2**C**=CH), 87.0 (**O**CH), 40.2 (**C**(CH_3)$_2$), 29.1 (**C**C=O), 23.2 (**CH_2**CH_2C=O), 23.0 (**CH_3**), 22.6 (**CH_3**).
LRMS	(EI)
m/z	155 ($[M+H]^+$, 88%), 137 (52%), 109 (37%), 85 ($[M-C_5H_9]^+$, 100 %), 69 ([M–γ–butyrolactone]$^+$, 44%), 67 (36%), 57 (35%), 55 (36%), 53 (32%), 41 (45%).
HRMS	(EI)
	Found 154.0992, $[C_9H_{14}O_2]^+$ requires 154.0994 amu.
FT – IR	($CHCl_3$ solution)
cm^{-1}	2971 (m), 1769 (s), 1639 (w), 1463 (m), 1418 (m).

No data are given in literature reference.[143]

2-Methyl-2-(5-oxotetrahydrofuran-2-yl)propanal (**301**)

New compound.



294 **301**

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

Chemical Formula: $C_8H_{12}O_3$
Molecular Weight: 156.18

Ozone (1–2% in oxygen) was passed through a solution of lactone **294** (1.14 g, 7.4 mmol) in CH_2Cl_2 (50 mL) at –78 °C until a blue colour persisted (30 min). The mixture was purged with oxygen for 15 min and then PPh_3 (3.88 g, 14.8 mmol) in CH_2Cl_2 (9 mL) was added. The mixture was stirred for 1 h at –78 °C, tested for peroxides, then warmed slowly to RT and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 20–50% EtOAc / petrol to afford the title compound **301** as a light yellow oil (590 mg, 3.78 mmol, 51%).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 9.55 (1H, s, **CHO**), 4.59 (1H, dd, J = 8.9, 7.1 Hz, OC**H**), 2.57–2.51 (2H, m, C**H**$_2$C=O), 2.26 (1H, dddd, J = 13.1, 8.2, 7.1, 5.2 Hz, C**H**HCH$_2$C=O), 2.00 (1H, dddd, J = 13.1, 10.3, 9.6, 8.9 Hz, CH**H**CH$_2$C=O), 1.13 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 203.4 (**C**HO), 176.5 (**C**=O), 83.0 (OCH), 49.1 (**C**CHO), 28.6 (**C**H$_2$C=O), 23.2 (**C**H$_2$CH$_2$C=O), 18.0 (**C**H$_3$), 17.2 (**C**H$_3$).

LRMS (CI)

m/z 174 ($[M+NH_4]^+$, 100%), 157 ($[M+H]^+$, 14%).

HRMS (CI)

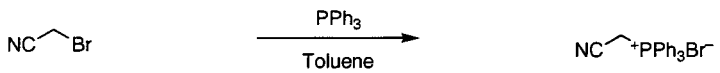
Found: 157.0860, $[C_8H_{12}O_3+H]^+$ requires 157.0865 amu.

FT – IR (Neat)

cm^{-1} 2975 (m), 2936 (w), 2880 (w), 2825 (w), 2714 (w), 1768 (s), 1721 (s).

Acetonitriletriphenylphosphonium bromide (**302**)

Known compound.



302

Chemical Formula: C_2H_2BrN
Molecular Weight: 119.95

Chemical Formula: $C_{20}H_{17}BrNP$
Molecular Weight: 382.23

A mixture of bromoacetonitrile (1.00 g, 0.58 mL, 8.34 mmol) and PPh_3 (2.23 g, 8.50 mmol) in toluene (10 mL) was heated to 50 °C under nitrogen for 16 h. The reaction was cooled to RT and the resulting white powder was collected by filtration and washed with petrol. The white solid product **302** was dried under high vacuum (2.78 g, 7.28 mmol, 87%).

^{1}H NMR (300 MHz, d_6-DMSO)

δ_H ppm 8.04–7.95 (3H, m, 3 x $\mathbf{H}_{Ar}$), 7.93–7.83 (12H, m, 12 x $\mathbf{H}_{Ar}$), 5.93 (2H, d, J = 15.9 Hz, NCC$\mathbf{H}_2$).

^{13}C NMR (75 MHz, d_6-DMSO)

δ_C ppm 136.0 (3 x p-$\mathbf{C}_{Ar}$), 133.7 (d, J = 9.9 Hz, 6 x m-$\mathbf{C}_{Ar}$), 130.5 (d, J = 13.2 Hz, 6 x o-$\mathbf{C}_{Ar}$), 116.2 (d, J = 87.9 Hz, 3 x $CH_2\mathbf{P}C$), 112.7 (d, J = 8.8 Hz, N**C**), 14.4 (d, J = 54.9 Hz, NC$\mathbf{C}H_2$).

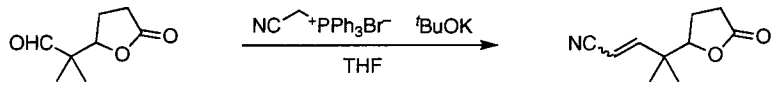
LRMS (ES^+)

m/z 302 ($[M–Br]^+$, 100%)

Spectroscopic data are in agreement with the literature.[144]

4-Methyl-4-(5-oxotetrahydrofuran-2-yl)pent-2-enenitrile (**293**)

New compound.



301

Chemical Formula: $C_8H_{12}O_3$
Molecular Weight: 156.18

293

Chemical Formula: $C_{10}H_{13}NO_2$
Molecular Weight: 179.22

A solution of acetonitriletriphenylphosphonium bromide (1.60 g, 4.19 mmol) in THF (20 mL) was cooled to 0 °C under nitrogen and ^{t}BuOK (550 mg, 4.90 mmol) was added in one portion. A faint yellow colour appeared and the mixture was stirred at 0 °C for 1 h. A solution of aldehyde **301** (540 mg, 3.46 mmol) in THF (10 mL) was added dropwise to the reaction mixture at 0 °C. The mixture was warmed to RT and stirred for 16 h. Water (3 mL) was added, resulting in dissolution of the solid that had formed. The mixture was extracted with EtOAc (2 x 30 mL) and the combined organic phases were washed with water (10 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 40–50 % EtOAc / petrol to afford the title compound **293** as a light yellow oil (595 mg, 3.32 mmol, 95 %, *E*:*Z* 6:1).

^{1}H NMR (300 MHz, $CDCl_3$) Peaks for the major *E* isomer:

δ_H ppm 6.72 (1H, d, *J* = 16.7 Hz, NCHC=C**H**), 5.39 (1H, d, *J* = 16.7 Hz, NC**H**C=CH), 4.28 (1H, dd, *J* = 9.4, 6.9 Hz, OC**H**), 2.57–2.51 (2H, m, C**H$_2$**C=O), 2.19 (1H, dddd, *J* = 13.1, 8.3, 6.9, 4.7 Hz, C**H**HCH$_2$C=O), 1.97–1.81 (1H, dddd, *J* = 13.1, 10.4, 9.6, 9.4 Hz, CH**H**CH$_2$C=O), 1.16 (3H, s, C**H$_3$**), 1.11 (3H, s, C**H$_3$**).

Peaks due to the minor *Z* isomer:

6.39 (1H, d, *J* = 12.6 Hz, NCHC=C**H**), 5.45 (1H, d, *J* = 12.6 Hz, NC**H**C=CH), 4.39 (1H, dd, *J* = 8.9, 6.8 Hz, OC**H**), 1.33 (3H, s, C**H$_3$**), 1.33 (3H, s, C**H$_3$**).

^{13}C NMR (75 MHz, $CDCl_3$) Peaks for the major *E* isomer:

δ_C ppm 176.3 (**C**=O). 158.6 (**H**C=CHCN), 117.2 (**C**N), 100.3 (HC=**C**HCN), 85.3 (O**C**H), 41.4 (**C**$(CH_3)_2$), 28.9 ($\mathbf{CH_2}$C=O), 23.5 ($\mathbf{CH_2}CH_2CO$), 22.8 ($\mathbf{CH_3}$), 21.2 ($\mathbf{CH_3}$).

Peaks due to the minor *Z* isomer:

156.8 (**C**H=CHCN), 99.3 (**C**HCN), 86.1 (O**C**H), 42.0 (**C**$(CH_3)_2$), 29.0 ($\mathbf{CH_2}$C=O), 23.7 ($\mathbf{CH_2}$HCO), 21.7 ($\mathbf{CH_3}$).

LRMS (CI)

m/z 197 ($[M+NH_4]^+$, 100%).

HRMS (CI)

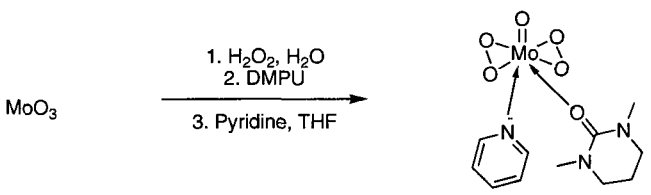
Found 180.1029, $[C_{10}H_{13}NO_2+H]^+$ requires 180.1025 amu.

FT – IR (neat)

cm^{-1} 3060 (w), 2966 (m), 2925 (w), 2880 (w), 2223 (m), 1767 (s), 1630 (m).

Oxidoperoxymolybdenum(pyridine)(DMPU), MoOPD (**303**)

Known compound.



303

Chemical Formula: MoO_3
Molecular Weight: 143.94

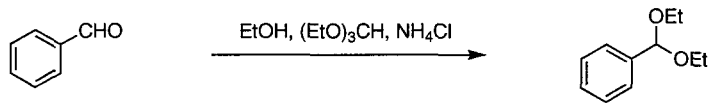
Chemical Formula: $C_{11}H_{17}MoN_3O_6$
Molecular Weight: 383.21

Prepared by a modified method to that reported by Vedejs.[64] A three-necked flask charged with MoO_3 (2.88 g, 20.0 mmol) in H_2O_2 (30%, aq., 30 mL) was warmed to 40 °C under nitrogen, with an ice bath ready to cool any exotherm. After maintaining 40 °C for 5.5 h, the reaction was cooled to RT, filtered and the filtrate cooled to 10 °C. DMPU (3 mL, 20.0 mmol) was added dropwise with stirring and the yellow precipitate was collected by filtration after 15 min. The solid was washed with cold water and dried in a vacuum desiccator overnight, affording 5.15 g, 15.99 mmol of

$MoO_5.(H_2O)(DMPU)$. The solid was suspended in THF (13 mL) and cooled to 10 °C. Pyridine (1.34 g, 1.37 mL, 16.93 mmol) was added dropwise and the resultant yellow solid was collected by filtration, washed with Et_2O (45 mL) and dried in a desiccator (5.73 g, 15.0 mmol, 88%. 75% overall).

Benzaldehyde diethylacetal (**307**)

Known compound.



306 **307**

Chemical Formula: C_7H_6O
Molecular Weight: 106.12

Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24

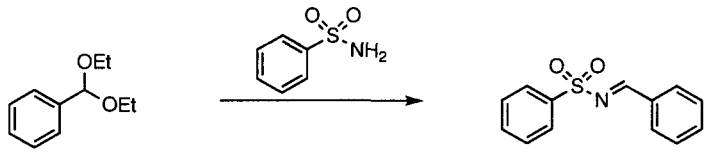
Prepared by the method reported by Zwierzak.[72] Benzaldehyde (5.1 mL, 50.0 mmol), ethanol (8.8 mL, 150 mmol), triethyl orthoformate (9.2 mL, 55.0 mmol) and ammonium chloride (134 mg, 5 mol%) were heated at reflux under nitrogen for 1.5 h. Ethanol was removed under vacuum and the residue was dissolved in CH_2Cl_2 (100 mL). The combined organic phases were washed with water (40 mL) and brine (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated to afford **307** as a light yellow oil (9.06 g, 50.3 mmol, quantitative yield), which was used immediately.

^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	7.51–7.47 (2H, m, 2 x $\mathbf{H}_{Ar}$), 7.40–7.29 (3H, m, 3 x $\mathbf{H}_{Ar}$), 5.52 (1H, s, $\mathbf{CH}(OEt)_2$), 3.61 (2H, dq, J = 9.5, 7.1 Hz, $OC\mathbf{H}_2CH_3$), 3.57 (2H, dq, J = 9.5, 7.1 Hz, $OC\mathbf{H}_2CH_3$), 1.25 (6H, t, J = 7.1 Hz, $OCH_2C\mathbf{H}_3$).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	139.3 ($\mathbf{C}_{Ar}$), 128.5 ($\mathbf{C}H_{Ar}$), 128.3 (2 x $\mathbf{C}H_{Ar}$), 126.8 (2 x $\mathbf{C}H_{Ar}$), 101.8 ($\mathbf{C}H(OEt)_2$), 61.2 (2 x OCH_2), 15.4 (2 x $OCH_2\mathbf{C}H_3$).
FT – IR	($CHCl_3$ solution)
cm^{-1}	3066 (w), 3020 (w), 2974 (m), 2881 (m), 1723 (w), 1451 (w).

Spectroscopic data are in agreement with the literature.[145]

N-Benzylidenebenzenesulfonamide (**308**)

Known compound.



307 **308**

Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24

Chemical Formula: $C_{13}H_{11}NO_2S$
Molecular Weight: 245.30

Prepared by the method reported by Davis.[73] A mixture of acetal **307** (9.06 g, 50.3 mmol) and benzenesulfonamide (7.86 g, 50.0 mmol) was heated to 170 °C, during which time ethanol was collected by distillation. The mixture became liquid and after 30 min was cooled to RT under high vacuum, causing it to solidify. CH_2Cl_2 (40 mL) was added to the flask, followed by slow addition of *n*-pentane with stirring until a solid precipitated. The white solid was collected by filtration, washed with *n*-pentane and dried in a desiccator (7.60 g, 31 mmol, 62%). A small sample was recrystallised from 20% toluene / petrol for analytical purposes.

mp 75–77 °C (toluene / petrol). (Lit. 75–76°C, solvent not given).[146]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 9.08 (1H, s, N=C**H**), 8.02 (2H, ddd (overlapped), J = 7.0, 1.5, 1.3 Hz, 2 x $\mathbf{H}_{Ar}$), 7.94 (2H, ddd (overlapped), J = 7.0, 2.0, 1.5 Hz, 2 x $\mathbf{H}_{Ar}$), 7.67–7.48 (6H, m, 6 x $\mathbf{H}_{Ar}$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 170.8 (N=**C**H), 138.5 ($\mathbf{C}_{Ar}$), 135.2 ($\mathbf{C}_{Ar}$), 133.7 ($\mathbf{C}H_{Ar}$), 132.5 ($\mathbf{C}H_{Ar}$), 131.6 (2 x $\mathbf{C}H_{Ar}$), 129.4 (4 x $\mathbf{C}H_{Ar}$), 128.2 (2 x $\mathbf{C}H_{Ar}$).

LRMS (ES^+)

m/z 300 ($[M+Na+MeOH]^+$, 100%), 268 ($[M+Na]^+$, 15%), 246 ($[M+H]^+$, 15%).

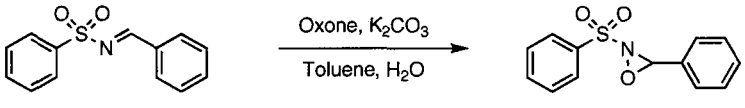
FT – IR (compressed solid)

cm^{-1} 3062 (w), 1597 (s), 1570 (s), 1446 (s).

Spectroscopic data are in agreement with the literature.[146]

2-(Phenylsulfonyl)-3-phenyloxaziridine (**304**)

Known compound.



308 **304**

Chemical Formula: $C_{13}H_{11}NO_2S$
Molecular Weight: 245.30

Chemical Formula: $C_{13}H_{11}NO_3S$
Molecular Weight: 261.30

Prepared by the method reported by Davis.[74] To sulfonimine **308** (3.76 g, 15.3 mmol) in toluene (120 mL) was added K_2CO_3 (109.3 g, 780 mmol) in water (90 mL). The mixture was rapidly stirred under nitrogen and Oxone® (47.1 g, 76.6 mmol) in water (93 mL) was added *via* a dropping funnel over 15 min. The mixture became warm and was cooled over an ice bath. A brown suspension separated from the reaction mixture and after 3 h, the aqueous phase was separated and extracted with toluene (50 mL) and $CHCl_3$ (100 mL). The combined organic phases were washed with Na_2SO_3 (10%, aq., 3 x 50 mL), which removed the suspension. The organic phase was dried over $MgSO_4$, filtered and concentrated, keeping the water bath at 23 °C. *n*-Pentane was added and the resultant white solid **304** was collected by filtration and dried under vacuum (3.03 g, 11.6 mmol, 76%).

mp 90–93 °C (decomp., *n*-pentane). (Lit 97 °C, *n*-pentane).[73]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 8.08–8.05 (2H, m, 2 x $\mathbf{H}_{Ar}$), 7.77 (1H, tt, J = 5.5, 1.1 Hz, $\mathbf{H}_{Ar}$), 7.65 (2H, tt, 8.0, 1.5 Hz, 2 x $\mathbf{H}_{Ar}$), 7.51–7.39 (5H, m, 5 x $\mathbf{H}_{Ar}$), 5.50 (1H, s, NOC**H**).

^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	135.2 (**C**H$_{Ar}$), 131.6 (**C**H$_{Ar}$), 130.6 (**C**$_{Ar}$), 129.5 (4 x **C**H$_{Ar}$), 129.3 (**C**$_{Ar}$), 128.9 (2 x **C**H$_{Ar}$), 128.4 (2 x **C**H$_{Ar}$), 76.5 (NO**C**H).

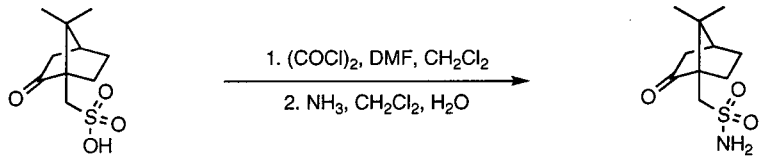
LRMS	(ES^+)
m/z	316 ([M+Na+MeOH]$^+$, 10%), 300 ([M–O+Na+MeOH]$^+$, 100%), 284 ([M+Na], 50%).

FT – IR	($CHCl_3$ film)
cm^{-1}	3095 (w), 3063 (w), 1598 (w) and 1448 (w).

Spectroscopic data are in agreement with the literature.[73]

(–)-(1*R*)-Camphorsulfonamide (**312**)

Known compound.



311 **312**

Chemical Formula: $C_{10}H_{16}O_4S$
Molecular Weight: 232.30

Chemical Formula: $C_{10}H_{17}NO_3S$
Molecular Weight: 231.31

Prepared by a modification of the method reported by Hartman.[147] (–)-(1*R*)-Camphorsulfonic acid **311** (4.65 g, 20.0 mmol) in CH_2Cl_2 (125 mL) was cooled to 0 °C under nitrogen. Oxalyl chloride (3.81 g, 2.60 mL, 30.0 mmol) was added dropwise to the stirred solution followed by the careful addition of DMF (10 drops), causing effervescence. After 48 h at RT, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with water (50 mL) and brine (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated to afford the intermediate chloride as a yellow oil. The chloride was used immediately to avoid hydrolysis.

Prepared by the method reported by Davis.[77] The crude chloride (assumed 20.0 mmol) in CH_2Cl_2 (56 mL) was added *via* a dropping funnel to stirred NH_3 (35%, aq.,

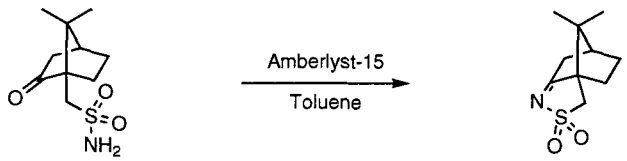
56 mL) over 30 min at 0 °C under nitrogen. The mixture was stirred at 0 °C for 2 h and at RT for 20 h. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated to afford the title compound **312** as a white solid (4.21 g, 18.2 mmol, 91% (2 steps)).

mp	134–137 °C (CH_2Cl_2). (Lit. 127–130 °C, CH_2Cl_2).[77]
^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	5.38 (2H, br s, N**H**$_2$), 3.48 (1H, d, J = 15.0 Hz, C**H**HSO$_2$), 3.13 (1H, d, J = 15.0 Hz, CH**H**SO$_2$), 2.43 (1H, ddd, J = 18.6, 4.9, 2.7 Hz, C**H**H), 2.27–1.93 (5H, m, C**H**H, CH**H**/C**H**), 1.47 (1H, m, C**H**H/C**H**), 0.94 (3H, s, C**H**$_3$), 0.88 (3H, s, C**H**$_3$).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	217.8 (**C**=O), 59.6 (**C**), 54.2 (**C**H$_2$), 49.3 (**C**), 43.3 (**C**H$_2$), 43.0 (**C**H), 27.2 (**C**H$_2$), 27.0 (**C**H$_2$), 20.1 (**C**H$_3$), 19.6 (**C**H$_3$).
LRMS	(ES^+)
m/z	254 ($[M+Na]^+$ 35%), 236 ($[M-H_2O+Na]^+$, 100%), 214 ($[M-H_2O+H]^+$, 45%).
FT – IR	(compressed solid)
cm^{-1}	2967 (w), 2893 (w), 1733 (m), 1642 (m), 1455 (w), 1416 (w).

Spectroscopic data are in agreement with the literature.[77]

(+)-Camphorsulfonimine (**313**)

Known compound.



312

Chemical Formula: $C_{10}H_{17}NO_3S$
Molecular Weight: 231.31

313

Chemical Formula: $C_{10}H_{15}NO_2S$
Molecular Weight: 213.30

Prepared by the method reported by Davis.[77] To a solution of the crude camphorsulfonamide **312** (8.44 g, 36.5 mmol) in toluene (150 mL), was added Amberlyst-15 ion exchange resin (1.25 g). The flask was connected to a Dean and Stark trap and heated at reflux under nitrogen for 6 h. The flask was allowed to cool slightly, and when the imine began to crystallise, CH_2Cl_2 (30 mL) was added. The warm solution was filtered to remove the ion exchange resin and concentrated to a pale brown solid (7.63 g, 35.8 mmol, 98%). This was recrystallised from ethanol to afford the title compound **313** as a white crystalline solid (5.99 g, 28.1 mmol, 77%).

mp 182–186 °C (ethanol). (Lit. 225–228 °C, ethanol).[77]

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 3.18 (1H, d, J = 13.2 Hz, C**H**HSO$_2$), 2.97 (1H, d, J = 13.2 Hz, CH**H**SO$_2$), 2.78 (1H, ddd, J = 19.3, 4.5, 2.0 Hz, C**H**H), 2.39 (1H, d, J = 19.3 Hz, C**H**H), 2.27 (1H, t (overlapped), J = 4.5 Hz, CH**H**/C**H**), 2.12–2.02 (2H, m, C**H**$_2$/C**H**), 1.79 (1H, t, J = 9.5 Hz, C**H**H/C**H**), 1.48 (1H, t, J = 8.5 Hz, CH**H**/C**H**), 1.08 (3H, s, C**H**$_3$), 0.86 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 195.6 (**C**=N), 64.6 (**C**), 49.6 (**C**H$_2$), 48.1 (**C**), 44.7 (**C**H), 36.0 (**C**H$_2$), 28.5 (**C**H$_2$), 26.7 (**C**H$_2$), 19.6 (**C**H$_3$), 19.1 (**C**H$_3$).

LRMS (ES^+)

m/z 449 ($[2M+Na]^+$, 20%), 268 ($[M+Na+MeOH]^+$, 15%), 236 ($[M+Na]^+$, 100%).

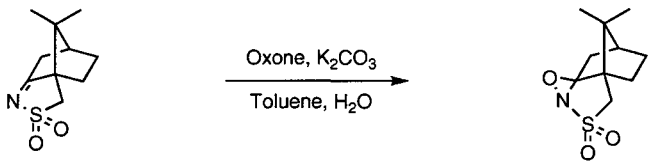
FT – IR (Compressed solid)

cm^{-1} 3002 (w), 2964 (m), 2891 (m), 1637 (s), 1454 (m), 1414 (m).

Spectroscopic data are in agreement with the literature.[77]

(–)-(2*S*, 8a*R*)-Camphorsulfonyl oxaziridine (**305**)

Known compound.



313

Chemical Formula: $C_{10}H_{15}NO_2S$
Molecular Weight: 213.30

(–)-**305**

Chemical Formula: $C_{10}H_{15}NO_3S$
Molecular Weight: 229.30

Prepared by the method reported by Davis.[77] A solution of camphorsulfonimine **313** (2.00 g, 9.38 mmol) in toluene (30 mL) was added to a solution of K_2CO_3 (23.0 g, 166 mmol) in distilled water (30 mL). The mixture was stirred rapidly at 0 °C under nitrogen and Oxone® (28.8 g, 46.9 mmol) in water (30 mL) was added dropwise over 30 min (foaming occurred). The reaction was stirred for 16 h and then treated with further Oxone® until complete by TLC, adding K_2CO_3 as necessary to maintain pH 9. CH_2Cl_2 (80 mL) and water (50 mL) were added and the phases were separated into an aqueous phase and an organic / precipitate phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and then the combined organic phases with precipitate were washed with Na_2SO_3 (sat., aq., 2 x 40 mL), dried over $MgSO_4$, filtered and concentrated to a white solid. This solid was recrystallised from *iso*propanol to afford the title compound **305** as a white solid (1.62 g, 7.06 mmol, 75 %).

$[\alpha]_D^{26}$ –36.1 (c = 0.502, l = 2, $CHCl_3$). (Lit –43.6 °, c = 2.16, $CHCl_3$).[77]

mp 169–172 °C (*iso*propanol). (Lit. 165–167 °C, *iso*propanol).[77]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 3.28 (1H, d, *J* = 14.0 Hz, SO_2CHH), 3.10 (1H, d, *J* = 14.0 Hz, SO_2CHH), 2.63 (1H, ddd, *J* = 15.5, 4.4, 2.6 Hz, **CH**H), 2.14–1.90 (4H, m, CH_2/**CH**), 1.77 (1H, d, *J* = 15.5 Hz, **CH**H/**CH**), 1.53 (1H, m, CH**H**/**CH**), 1.18 (3H, s, CH_3), 1.04 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 98.8 (**C**O), 54.1 (**C**), 48.4 (**C** and CH_2 overlapped), 45.9 (**C**H), 33.7 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 20.6 (CH_3), 19.5 (CH_3).

LRMS (ES^+)

m/z 284 ($[M+Na+MeOH]^+$, 20%), 252 ($[M+Na]^+$, 100%).

FT – IR (compressed solid)

cm^{-1} 2999 (m), 2983 (m), 2958 (m), 2893 (w).

Spectroscopic data are in agreement with the literature.[77]

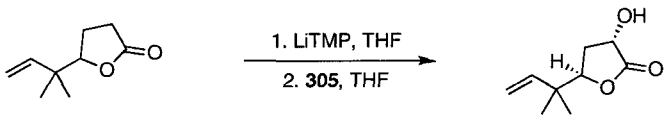
(+)-**305** has been prepared by the same method and NMR data are in agreement with both that reported above and the literature.[77]

$[\alpha]_D^{26}$ +47.4 (*c* = 0.635, *l* = 2, $CHCl_3$). (Lit +44.6 °, *c* = 2.19, $CHCl_3$).[77]

rel-(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**)

Method A: Hydroxylation at –78 °C

New compound.



294

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

309

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

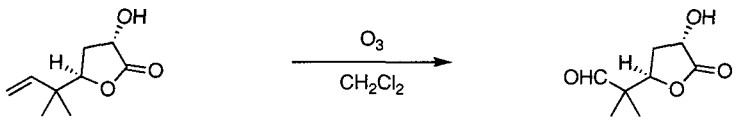
Prepared by the general methods for hydroxylation reactions reported by Davis,[77,78,148] White,[79] and Cardillo.[80] 2,2,6,6-Tetramethylpiperidine (737 mg, 0.88 mL, 5.23

mmol) in THF (5 mL) was cooled to 0 °C under argon. *n*-Butyllithium (1.7M in hexanes, 3.10 mL, 5.23 mmol) was added dropwise and the resultant yellow solution stirred for 30 min at 0 °C before cooling to –78 °C. A solution of lactone **294** (620 mg 4.02 mmol) in THF (6 mL) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2 h, during which time a yellow colour appeared. A solution of oxaziridine **305** (1.20 g, 5.23 mmol) in THF (14 mL) was added dropwise over 15 min and the solution maintained at –78 °C for a further 30 min. NH_4Cl (sat., aq., 15 mL) was added and after 15 min, the mixture was warmed to RT and extracted with EtOAc (3 x 40 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 20–30% EtOAc / petrol to afford the title compound **309** as a colourless oil (272 mg, 1.60 mmol, 40%, reaction overall *d.r.* 3:1 *anti*:*syn*).

^{1}H NMR	(400 MHz, $CDCl_3$)
δ_H ppm	5.75 (1H, dd, *J* = 17.5, 11.0, H_2C=C**H**), 5.15 (1H, dd, *J* = 11.0, 1.1 Hz, **H**HC=CH), 5.11 (1H, dd, *J* = 17.5, 1.1 Hz, H**H**C=CH), 4.41 (1H, dd, *J* = 8.8, 6.4 Hz, OC**H**), 4.40 (1H, dd, *J* = 8.3, 4.9 Hz, OC**H**), 3.23 (1H, br s, O**H**), 2.33 (1H, ddd, *J* = 14.2, 8.8, 4.9 C**H**HCOH), 2.17 (1H, ddd, *J* = 14.2, 8.3, 6.4 Hz, CH**H**COH), 1.10 (3H, s, C**H**$_3$), 1.07 (3H, s, C**H**$_3$).
^{13}C NMR	(100 MHz, $CDCl_3$)
δ_C ppm	177.8 (**C**=O), 141.6 (H_2**C**=CH), 115.4 (H_2**C**=CH), 85.5 (**C**HOC=O), 67.9 (**C**OH), 40.4 (**C**(CH_3)$_2$), 31.6 (**C**H$_2$), 23.0 (**C**H$_3$), 22.97 (**C**H$_3$).
LRMS	(CI)
m/z	188 ([M+NH_4]$^+$, 100%), 171 ([M+H]$^+$, 22%), 125 (20%).
HRMS	(EI)
	Found 170.0937, [$C_9H_{14}O_3$]$^+$ requires 170.0943 amu.
FT – IR	($CHCl_3$ film)
cm^{-1}	3424 (br), 3081 (w), 2970 (m), 2929 (w), 2872 (w), 1767 (s), 1634 (m).

rel-2-[(2*R*,4*S*)-4-Hydroxy-5-oxotetrahydrofuran-2-yl]-2-methylpropanal (**314**)

New compound.



309 **314**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Ozone (1–2% in oxygen) was passed through a solution of lactone **309** (660 mg, 3.88 mmol) in CH_2Cl_2 (40 mL) at –78 °C until a blue colour persisted (15 min). The reaction was purged with oxygen for 20 min and then PPh_3 (2.04 g, 7.76 mmol) in CH_2Cl_2 (3 mL) was added. After 1 h, the mixture was tested for peroxides, warmed to RT, washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 1–8% MeOH / $CHCl_3$ to afford the title compound **314** as a colourless oil (1.10 mmol, 190 mg, 28%). When the reaction was conducted in EtOAc and quenched with Me_2S and PPh_3, the yield was 71%.

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 9.54 (1H, s, C**H**O), 4.78 (1H, dd, *J* = 7.7, 6.2 Hz, OC**H**), 4.50 (1H, dd, *J* = 7.8, 5.8 Hz, OC**H**), 2.35 (1H, ddd, *J* = 14.2, 7.8, 6.2 Hz, C**H**H), 2.32 (1H, ddd, *J* = 14.2, 7.7, 5.8 Hz, CH**H**), 1.15 (6H, s, 2 x C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 203.0 (**C**HO), 176.7 (**C**=O), 81.5 (**C**HOC=O), 67.7 (**C**HOH), 49.3 (**C**(CH$_3$)$_2$), 31.5 (**C**H$_2$), 18.3 (**C**H$_3$), 17.9 (**C**H$_3$).

LRMS (CI)

m/z 190 ([M+NH$_4$]$^+$, 100%), 72 (57%), 58 (65%), 44 (68%).

HRMS (EI)

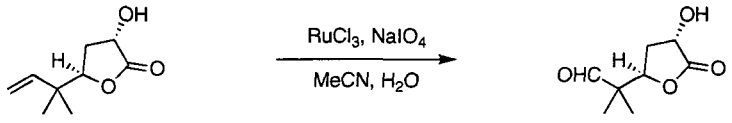
Found 172.0736, [$C_8H_{12}O_4$]$^+$ requires 172.0733 amu.

FT – IR (CH_2Cl_2)

cm^{-1} 3400 (br m), 3056 (w), 2981 (m), 2933 (m), 2872 (w), 1763 (s), 1721 (s).

rel-2-[(2*R*,4*S*)-4-Hydroxy-5-oxotetrahydrofuran-2-yl]-2-methylpropanal (**314**)

New compound.



309 **314**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

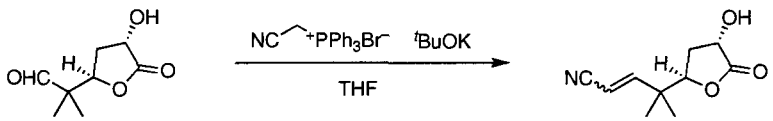
Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Prepared using a method reported by Yang.[149] A solution of lactone **309** (260 mg, 1.53 mmol) in acetonitrile (10 mL) was stirred at room temperature and treated with $RuCl_3$ (13 mg, 3.5 mol%) in distilled water (2 mL). To the black solution was added $NaIO_4$ (687 mg, 3.26 mmol) portionwise. The reaction was stirred for 3 h at RT and then treated with further $NaIO_4$ (2 eq, 490 mg, 2.33 mmol). After 1.5 h $Na_2S_3O_3$ (sat., aq., 5 mL) was added and the reaction mixture extracted with EtOAc (2 x 30 mL) and CH_2Cl_2 (2 x 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel, eluting with 30–45% EtOAc / petrol to afford the title compound **314** as a colourless oil (134 mg, 0.79 mmol, 51%).

Spectroscopic data are in agreement with that reported above.

rel-4-[(2*R*,4*S*)-4-Hydroxy-5-oxotetrahydrofuran-2-yl]-4-methylpent-2-enenitrile (**292**)

New compound.



314 **292**

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

Acetonitriletriphenylphosphonium bromide **302** (3.18 g, 8.32 mmol) in THF (25 mL) was cooled to 0 °C under nitrogen and treated with ^{t}BuOK (1.09 g, 9.74 mmol). The mixture was stirred at 0 °C for 45 min resulting in a yellow colour. Aldehyde **314** (599 mg, 3.48 mmol) in THF (25 mL) was added dropwise over 5 min. After 48 h at RT, HCl (2 M, aq.) was added to pH 1 and the mixture extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue (2.59 g) was purified by column chromatography on silica gel, eluting with 30% EtOAc / Et_2O to afford the title compound **292** as a light yellow oil (236 mg, 1.21 mmol, 35%, *E*:*Z* 8:1).

^{1}H NMR (300 MHz, $CDCl_3$) Peaks for the major *E* isomer:

δ_H ppm 6.68 (1H, d, *J* = 16.6 Hz, NCHC=C**H**), 5.42 (1H, d, *J* = 16.6 Hz, NC**H**C=CH), 4.50 (1H, t, *J* = 7.0 Hz, OC**H**), 4.41 (1H, dd, *J* = 7.5, 5.3 Hz, OC**H**), 2.30–2.14 (2H, m, C**H**$_2$), 1.16 (3H, s, C**H**$_3$), 1.11 (3H, s, C**H**$_3$).

Peaks due to the minor *Z* isomer:

6.33 (1H, d, *J* = 12.4 Hz, NCC**H**), 5.47 (1H, d, *J* = 12.4 Hz, NCCHC**H**).

^{13}C NMR (75 MHz, $CDCl_3$) Peaks for the major *E* isomer:

δ_C ppm 176.5 (**C**=O), 158.1 (NCHC=**C**H), 117.1 (**C**N), 100.8 (NCH**C**=CH), 84.0 (**C**OC=O), 67.8 (**C**HOH), 41.5 (**C**(CH$_3$)$_2$), 31.8 (**C**H$_2$), 22.7 (**C**H$_3$), 21.4 (**C**H$_3$).

Peaks due to the minor *Z* isomer:

156.3 (NCHC=**C**H), 99.7 (NCH**C**=CH), 84.7 (**C**OC=O), 23.3 (**C**H_3), 21.9 (**C**H_3).

LRMS (ES^+)

m/z 250 ([M+Na+MeOH]$^+$, 27%), 218 ([M+Na]$^+$, 100%).

HRMS (ES^+)

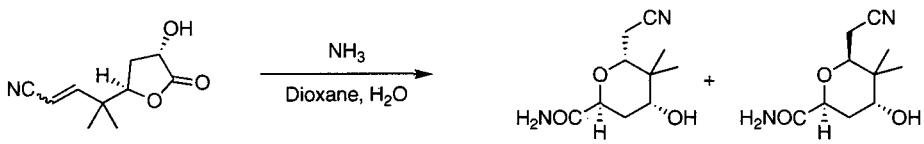
Found 218.0788, [$C_{10}H_{13}NO_3$+Na]$^+$ requires 218.0787 amu.

FT – IR (CH_2Cl_2)

cm^{-1} 3426 (br), 3056 (w), 2972 (m), 2925 (m), 2864 (w), 2224 (m), 1770 (s), 1630 (m).

rel-(2*S*,4*R*,6*R*)-6-(Cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**37**) and *rel*-(2*S*,4*R*,6*S*)-6-(cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**315**)

New compound.



292 **37** **315**

Ratio: 1:2

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Lactone **292** (0.11 mmol, 20 mg) was treated with concentrated aqueous ammonia (35%) (1 mL) and 1,4-dioxane (0.5 mL). The mixture was stirred at RT for 24 h and then concentrated. The residue was azeotroped with $CHCl_3$ (5 x 2 mL) and purified on silica, eluting with 40% EtOAc / petrol to afford **37** as a white solid (2.1 mg, 10 μmol, 9%) and **315** as a white solid (4.5 mg, 21 μmol, 19%).

Data for **37**

mp 142–146 °C (methanol).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 4.46 (1H, dd, *J* = 5.9, 4.2 Hz, C**H**CONH$_2$), 3.56 (1H, dd, *J* = 9.2, 4.2 Hz, C**H**CH$_2$CN), 3.43 (1H, dd, *J* = 9.8, 4.2 Hz, C**H**OH), 2.86 (1H, dd, *J* = 17.1, 9.2 Hz, C**H**HCN), 2.79 (1H, dd, *J* = 17.1, 4.2 Hz, CH**H**CN), 2.25 (1H, dt, *J* = 13.5, 4.2 Hz, C**H**H), 1.83 (1H, ddd, *J* = 13.5, 9.8, 5.9 Hz, CH**H**), 0.97 (3H, s, C**H**$_3$), 0.91 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 176.4 (**C**=O), 120.4 (**C**N), 78.5 (O**C**HCH$_2$CN), 73.2 (O**C**HCONH$_2$), 72.5 (**C**HOH), 39.2 (**C**(CH$_3$)$_2$), 30.8 (**C**H$_2$), 23.8 (**C**H$_3$), 19.6 (**C**H$_2$CN), 14.6 (**C**H$_3$).

LRMS (ES^+)

m/z 235 ($[M+Na]^+$, 100%).

HRMS (ES^+)

Found 235.1056, $[C_{10}H_{16}N_2O_3+Na]^+$ requires 235.1053 amu.

FT – IR ($CHCl_3$)

cm^{-1} 3467 (br), 3346 (br), 2974 (m), 2919 (m), 2880 (w), 2844 (w), 1677 (s), 1592 (m).

Data for **315**

mp 142–144 °C (methanol).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 6.57 (1H, br s, N**H**$_2$), 5.52 (1H, br s, N**H**$_2$), 4.43 (1H, dd, *J* = 12.5, 3.1 Hz, C**H**CONH$_2$), 4.08, (1H, dd, *J* = 9.3, 3.9 Hz, C**H**CH$_2$CN), 3.69 (1H, t, *J* = 2.7 Hz, C**H**OH), 2.55 (1H, dd, *J* = 16.8, 3.9 Hz, C**H**HCN), 2.48 (1H, dd, *J* = 16.8, 9.3 Hz, CH**H**CN), 2.11 (1H, app. dt, *J* = 14.6, 3.1 Hz, C**H**$_2$ equatorial), 2.05 (1H, br s, O**H**), 1.95 (1H, ddd, *J* = 16.8, 12.5, 2.7 Hz, C**H**$_2$ axial), 0.99 (3H, s, C**H**$_3$), 0.96 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 174.2 (**C**=O), 118.2 (**C**N), 75.1 (**C**HCH$_2$CN), 73.4 (**C**OH), 72.6 (**C**HC=O), 37.0 (**C**(CH$_3$)$_2$), 32.7 (**C**H$_2$COH), 22.6 (**C**H$_3$), 19.5 (**C**H$_2$CN), 19.1 (**C**H$_3$).

LRMS (ES^+)

m/z 235 ($[M+Na]^+$, 100%).

HRMS (ES^+)

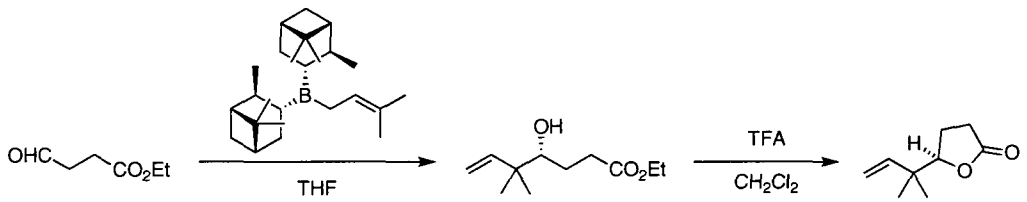
Found 235.1055, $[C_{10}H_{16}N_2O_3+Na]^+$ requires 235.1053 amu.

FT – IR ($CHCl_3$)

cm^{-1} 3465 (br), 3350 (br), 2958 (m), 2923 (m), 2864 (m), 2840 (m), 1674 (s), 1590 (m).

(5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)dihydrofuran-2(3*H*)-one ((*R*)-**294**))

Racemate is known, single enantiomer is new.



296

Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130.14

(*R*)-**295**

Chemical Formula: $C_{11}H_{20}O_3$
Molecular Weight: 200.27

(*R*)-**294**

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

Prepared using methods reported by Brown.[59,82,83] Glassware was dried at 150 °C overnight, cooled in a desiccator and vacuum-refilled with argon before use. A solution of (1*R*)-(+)-α-pinene (1.96 g, 2.31 mL, 14.4 mmol) in THF (1.8 mL) under argon was rapidly stirred over a water bath at 25 °C. $BH_3.SMe_2$ (0.57 mL, 10 M, 5.70 mmol) was added dropwise and upon complete addition, the stirrer was adjusted to the slowest setting and the mixture was stirred for 16 h. A white precipitate separated from the reaction and THF, dimethyl sulfide and some α-pinene were removed under high vacuum. Argon was returned to the flask, THF (3 mL) was added and the mixture was cooled to –5 °C. 3-Methyl-1,2-butadiene (1.5 M solution in THF, 4 mL,

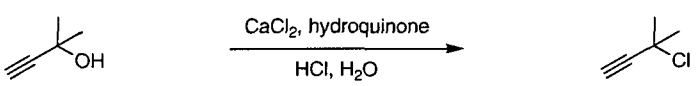
6.00 mmol) was added dropwise and the reaction was stirred at 0 °C for 6 h, warmed to RT and stirred for 16 h, during which time the white precipitate dissolved. The reaction mixture was cooled to –78 °C and a solution of aldehyde **296** (750 mg, 5.76 mmol) in THF (12 mL) was added slowly. The mixture was warmed to RT over 3 h and stirred at this temperature for 16 h. The reaction was then treated with NaOH (3 M, aq., 10 mL) and H_2O_2 (30%, aq., 5 mL) (exotherm), and heated at reflux for 2 h, after which time the mixture was cooled to RT and acidified with HCl (2 M, aq.). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic phases were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated to a yellow oil. The crude material was dissolved in CH_2Cl_2 (75 mL), treated with TFA (10 drops), heated at reflux under nitrogen for 1 h then cooled to RT. The reaction mixture was washed with $NaHCO_3$ (sat., aq., 20 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phases were washed with water (20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified twice by chromatography on silica gel. The first column was eluted with 15–30% EtOAc / petrol and the second with 1% Et_2O / CH_2Cl_2 to afford the title compound (*R*)-**294** as a colourless oil (547 mg, 3.55 mmol, 61% over two steps, 84% *e.e.*).

$[\alpha]_D^{23}$ +2.0 ($c = 0.79$, $l = 2$, $CHCl_3$).

Spectroscopic data are in agreement with that reported above.

3-Chloro-3-methylbut-1-yne (**323**)

Known compound.



322 **323**

Chemical Formula: C_5H_8O
Molecular Weight: 84.12

Chemical Formula: C_5H_7Cl
Molecular Weight: 102.56

Prepared by the method reported by Chengebroyen.[86] To a mixture of 2-methyl-3-butyn-2-ol (**322**) (42.06 g, 48.4 mL, 500 mmol) and HCl (36%, aq., 180 mL) at 0 °C was added hydroquinone (339 mg, 3.08 mmol). The mixture was stirred at 0 °C for

10 min and then $CaCl_2$ (55.49 g, 500 mol) was added portion-wise over 1 h. Upon complete addition, the mixture was warmed to RT and stirred for 3 h. The organic phase was separated, dried over Na_2CO_3 and filtered. The crude residue was purified by distillation at atmospheric pressure, to afford the title compound **323** as a light oil (21.76 g, 0.21 mol, 42%, b.p. 71–80 °C).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 2.55 (1H, s, **CH**), 1.80 (6H, s, 2 x **CH_3**).

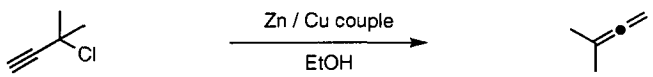
^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 86.8 (HC≡**C**), 72.1 (**CH**), 57.1 (**C**($(CH_3)_2$)Cl), 34.8 (2 x **CH_3**).

Spectroscopic data are in agreement with the literature.[86]

3-Methyl-1,2-butadiene (**320**)

Known compound.



323 **320**

Chemical Formula: C_5H_7Cl
Molecular Weight: 102.56

Chemical Formula: C_5H_8
Molecular Weight: 68.12

Prepared by the method reported by Chengebroyen.[86] Zn-Cu couple prepared *via* the method described by Swain.[87] Zinc dust (46.86 g, 717 mmol) and deionised water (144 mL) were degassed with argon with stirring for 30 min. $CuSO_4.5H_2O$ (5.55 g, 22.2 mmol) was added and degassing / stirring was continued for a further 30 min. The black solid was collected by filtration under a blanket of argon, washed with deionised water (250 mL) and acetone (250 mL) and dried in a desiccator. The solid was then suspended in ethanol (150 mL), the mixture was warmed to 65 °C and 3-chloro-3-methylbut-1-yne (**323**) (21.00 g, 205 mmol) was added slowly and cautiously. Upon complete addition, the reaction was heated to 80 °C and the product distilled through a Vigruex column. The distillate was collected at b.p. 40–56 °C, 60–61 °C and 70–74 °C. The third fraction contained only ethanol, the remaining fractions were combined and washed repeatedly with water to remove ethanol and

then dried over $MgSO_4$ to afford the title compound **320** as a colourless liquid (6.21 g, 91.2 mmol, 44%).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 4.53 (2H, septet, J = 3.2 Hz, $\mathbf{CH_2}$), 1.69 (6H, t, J = 3.2 Hz, 2 x $\mathbf{CH_3}$).

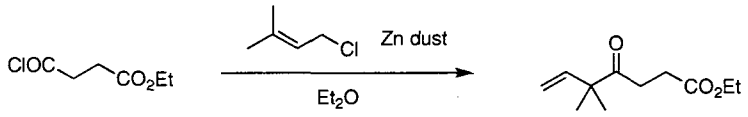
^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 206.9 (H_2C=**C**), 94.2 (**C**$(CH_3)_2$), 72.7 (**C**H_2), 20.3 (2 x **C**H_3).

The compound proved to volatile for MS and IR. Spectroscopic data are in agreement with the literature.[86]

Ethyl 5,5-dimethyl-4-oxohept-6-enoate (**324**)

Known compound.



299

Chemical Formula: $C_6H_9ClO_3$
Molecular Weight: 164.59

324

Chemical Formula: $C_{11}H_{18}O_3$
Molecular Weight: 198.26

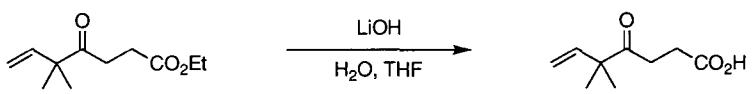
Prepared by the general method reported by Ranu.[150] Prenyl chloride (0.62 mL, 575 mg, 5.50 mmol) was added to a suspension of zinc dust (523 mg, 8.00 mmol) in Et_2O (20 mL) under argon at RT and the mixture was stirred for 30 min. Ethyl succinyl chloride **299** (0.713 mL, 823 mg, 5.00 mmol) was added and the mixture was placed in an ultrasound water bath for 30 min. Water (2 mL) was added and the mixture was extracted with Et_2O (2 x 30 mL). The combined organic phases were washed with water (20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by column chromatography on silica gel, eluting with 5% EtOAc / petrol to afford the title compound **324** as a colourless oil (477 mg, 2.47 mmol, 48%).

^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	5.95 (1H, dd, J = 17.5, 10.5 Hz, H_2C=C**H**), 5.17 (1H, dd, J = 10.5, 0.9 Hz, **H**HC=CH), 5.17 (1H, dd, J = 17.5, 0.9 Hz, H**H**C=CH), 4.12 (2H, q, J = 7.2 Hz, O**C**$H_2$$CH_3$), 2.79 (2H, t, J = 6.6 Hz, **C**H_2), 2.53 (2H, t, J = 6.6 Hz, **C**H_2), 1.26 (6H, s, 2 x **C**H_3), 1.25 (3H, t, J = 7.2 Hz, OCH_2**C**H_3).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	211.5 (C=O), 173.0 (**C**O_2Et), 142.6 (H_2**C**=CH), 114.5 (H_2**C**=CH), 60.7 (OCH_2CH_3), 50.7 (**C**$(CH_3)_2$), 32.6 (**C**H_2), 28.4 (**C**H_2), 23.8 (2 x **C**H_3), 14.4 (OCH_2**C**H_3).
LRMS	(CI)
m/z	129 ($[M–C_5H_9]^+$, 40%), 101 ($[M–C_2H_9CO]^+$, 100%).
FT – IR	(neat)
cm^{-1}	2977 (m), 2931 (m), 2874 (w), 1736 (s), 1712 (s), 1635 (w), 1467 (w), 1414 (w).

Spectroscopic data are in agreement with the literature.[151]

5,5-Dimethyl-4-oxohept-6-enoic acid (**325**)

New compound.



324 **325**

Chemical Formula: $C_{11}H_{18}O_3$
Molecular Weight: 198.26

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

To a solution of keto-ester **324** (290 mg, 1.46 mmol) in THF (11 mL) was added LiOH (307 mg, 7.32 mmol) in water (4 mL). The reaction mixture was stirred at RT for 72 h and then acidified with HCl (2 M, aq.). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by

column chromatography on silica gel, eluting with CH_2Cl_2:MeOH:AcOH (97:2:1) to afford the title compound **325** as a light coloured oil (236 mg, 1.39 mmol, 95%).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 9.56 (1H, br s, CO_2**H**), 5.94 (1H, dd, J = 17.6, 10.5 Hz, HHC=C**H**), 5.17 (1H, dd, J = 10.5 0.9 Hz, **H**HC=CH), 5.17 (1H, dd, J = 17.6, 0.9 Hz, H**H**C=CH), 2.80 (2H, t, J = 6.6 Hz, **C**H_2), 2.58 (2H, t, J = 6.6 Hz, **C**H_2), 1.25 (6H, s, 2 x **C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 211.5 (**C**=O), 178.7 (**C**O_2H), 142.5 (H_2**C**=CH), 114.7 (H_2**C**=CH), 50.6 (**C**$(CH_3)_2$), 32.4 (**C**H_2), 28.4 (**C**H_2), 23.8 (2 x **C**H_3).

LRMS (ES$^-$)

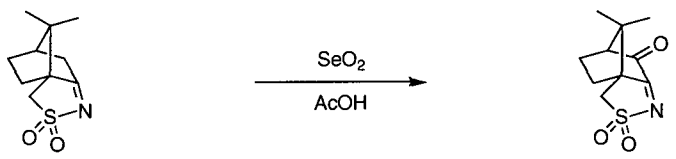
m/z 169 ([M–H]$^-$, 100%).

FT – IR (neat)

cm^{-1} 3089 (w), 2974 (m), 2932 (m), 2868 (w), 2656 (br w), 1704 (s), 1635 (m), 1467 (w), 1413 (m), 1401 (m).

3-Oxocamphorsulfonyl imine (**328**)

Known compound.



313 **328**

Chemical Formula: $C_{10}H_{15}NO_2S$
Molecular Weight: 213.30

Chemical Formula: $C_{10}H_{13}NO_3S$
Molecular Weight: 227.28

Prepared by the method reported by Davis.[90] To a solution of **313** (1.56 g, 7.31 mmol) in acetic acid (50 mL) was added selenium dioxide (1.09 g, 9.82 mmol). The mixture was heated at reflux under nitrogen for 16 h before further SeO_2 (405 mg, 3.65 mmol) was added. The mixture was heated at reflux for a further 5 h, cooled to RT and filtered through Celite® to remove precipitated selenium. The filtrate was

diluted with CH_2Cl_2 (50 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated to a yellow solid (1.44 g, 6.34 mmol, 86%).

mp 188–192 °C (CH_2Cl_2). (Lit. 190–191 °C, solvent not given).[152]

^{1}H NMR (300 MHz, $CDCl_3$) Also shows some starting material.

δ_H ppm 3.45 (1H, d, J = 13.4 Hz, C**H**HSO$_2$), 3.21 (1H, d, J = 13.4 Hz, CH**H**SO$_2$), 2.78 (1H, d, J = 4.9 Hz, C**H**C=O), 2.41–2.15 (2H, m, C**H**$_2$), 2.09–1.75 (2H, m, C**H**$_2$), 1.17 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 197.8 (**C**=O), 181.5 (**C**=N), 62.9 (**C**), 59.3 (**C**H), 50.3 (**C**H$_2$), 44.8 (**C**), 28.3 (**C**H$_2$), 22.5 (**C**H$_2$), 20.4 (**C**H$_3$), 18.7 (**C**H$_3$).

LRMS (ES^+)

m/z 250 ($[M+Na]^+$, 39%), 282 ($[M+Na+MeOH]^+$, 100%), 477 ($[2M+Na]^+$, 25%).

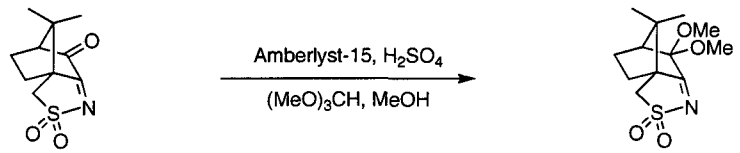
FT – IR (compressed solid)

cm^{-1} 3004 (w), 2953 (w), 2922 (w), 2853 (w), 1759 (s), 1653 (w), 1454 (w), 1414 (w).

Spectroscopic data are in agreement with the literature.[152]

3,3-Dimethoxycamphorsulfonyl imine (**329**)

Known compound.



328

Chemical Formula: $C_{10}H_{13}NO_3S$
Molecular Weight: 227.28

329

Chemical Formula: $C_{12}H_{19}NO_4S$
Molecular Weight: 273.35

Prepared by the method reported by Davis.[90] A mixture of **328** (1.42 g, 6.25 mmol), trimethyl orthoformate (10 mL), H_2SO_4 (98%, 0.5 mL), Amberlyst-15 ion-exchange resin (300 mg) and methanol (20 mL) was heated at reflux under nitrogen for 16 h then cooled to RT and filtered. H_2O (5 mL) was added, the aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude solid was recrystallised from ethanol to afford the title compound **329** as an off-white solid (938 mg, 3.43 mmol, 55%).

mp 178–181 °C (ethanol). (Lit 186–187 °C, ethanol).[90]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 3.47 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.15 (1H, d, J = 13.4 Hz, $CHHSO_2$), 2.99 (1H, d, J = 13.4 Hz, $CHHSO_2$), 2.34 (1H, d, J = 2.2 Hz, CH), 2.05–1.80 (4H, m, 2 x CH_2), 1.10 (3H, s, CH_3), 1.01 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 188.8 (C=N), 103.3 ($C(OMe)_2$), 64.5 (C), 52.4 (CH), 50.8 (CH_3), 50.6 (CH_3), 49.2 (CH_2), 46.3 (C), 29.6 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 20.8 (CH_2).

LRMS (ES^+)

m/z 274 ($[M+H]^+$, 27%), 291 ($[M+NH_4]^+$, 30%), 337 ($[M+Na+MeCN]^+$, 100%), 569 ($[2M+Na]^+$, 40%).

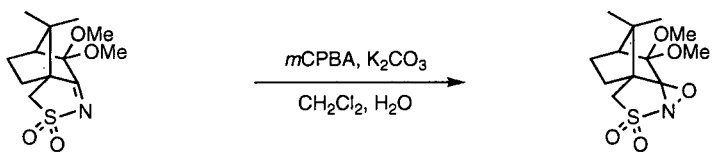
FT – IR (compressed solid)

cm^{-1} 3005 (w), 2956 (w), 1656 (w).

Spectroscopic data are in agreement with the literature.[90]

(+)-[(Dimethoxycamphoryl)sulfonyl]oxaziridine (**330**)

Known compound.



329

Chemical Formula: $C_{12}H_{19}NO_4S$
Molecular Weight: 273.35

330

Chemical Formula: $C_{12}H_{19}NO_5S$
Molecular Weight: 289.35

Prepared by the method reported by Davis.[90] **329** (921 mg, 3.37 mmol) in CH_2Cl_2 (40 mL) was added to K_2CO_3 (sat., aq., 40 mL). *m*CPBA (8.71 mg, 5.05 mmol) was added and the reaction was stirred for 50 h at RT. Further *m*CPBA (470 mg, 2.72 mmol) was added and the reaction stirred for 24 h at RT. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were washed with $Na_2S_2O_3$ (sat., aq., 15 mL) and water (15 mL), dried over $MgSO_4$, filtered and concentrated to a white solid (674 mg, 2.33 mmol, 69%).

mp 192–198 °C (CH_2Cl_2). (Lit. 189 °C (decomp.)).[90]

$[\alpha]_D^{28}$ +71.4 (c = 0.8, l = 2, $CHCl_3$). (Lit. +91.3 °, c = 3.39, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 3.30 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.25 (1H, d, J = 13.9 Hz, $CHHSO_2$), 3.08 (1H, d, J = 13.9 Hz, $CHHSO_2$), 2.28 (1H, d, J = 4.0 Hz, CH), 1.96–1.75 (4H, m, 2 x CH_2), 1.33 (3H, s, CH_3), 1.06 (3H, s, CH_3).

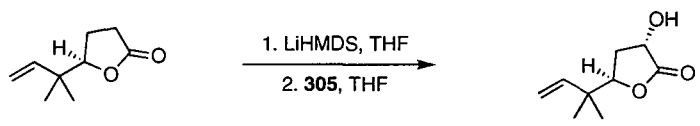
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	103.0 (**C**$(OMe)_2$), 97.8 (**C**ON), 54.8 (**C**), 53.1 (**C**H), 51.1 (**C**H_3), 50.8 (**C**H_3), 47.6 (**C**H_2), 45.3 (**C**), 28.3 (**C**H_2), 21.8 (**C**H_3), 20.7 (**C**H_3), 20.7 (**C**H_2).

LRMS	(ES^+)
m/z	312 ($[M+Na]^+$, 37%), 344 ($[M+Na+MeOH]^+$, 100%), 601 ($[2M+Na]^+$, 18%).

FT – IR	(compressed solid)
cm^{-1}	3002 (w), 2945 (w), 2839 (w).

Spectroscopic data are in agreement with the literature.[90]

rel-(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**)
Method B: –20 °C / HCl quench hydroxylation



294

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

309

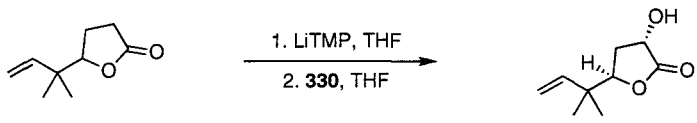
Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

To a solution of HMDS (137 mg, 0.18 mL, 0.85 mmol) in THF (2 mL) at 0 °C under nitrogen was added *n*-butyllithium (2.25 M in hexanes, 0.38 mL, 0.85 mmol) dropwise. After 45 min at 0 °C, the faint yellow solution was cooled to –78 °C and treated with a solution of lactone **294** (100 mg, 0.65 mmol) in THF (2 mL). The mixture was stirred for 15 min at –78 °C and then warmed to 0 °C for 1.5 h before it was cooled to –20 °C and treated with a solution of oxaziridine **305** (195 mg, 0.85 mmol) in THF (2.5 mL). After 1.5 h, HCl (2 M, aq., 1 mL) was added and the reaction mixture was concentrated. The crude product was purified by column chromatography on silica gel, eluting with 2–10% Et_2O / CH_2Cl_2 to afford the title compound **309** as a colourless oil (51 mg, 0.30 mmol, 46%, overall *d.r.* 8:1 *anti*:*syn*).

Spectroscopic data are in agreement with that reported above.

rel-(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**)

Method C: Hydroxylation with oxaziridine **330**



294

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

309

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

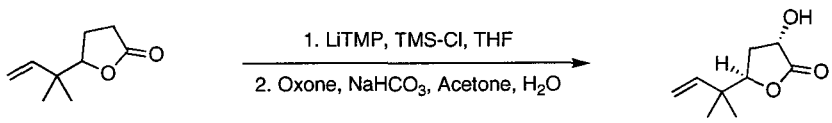
The procedure was repeated with LiTMP as the base and oxaziridine **330** was added at –78 °C. The reaction afforded **309** as a colourless oil (25 mg, 0.15 mmol, 23%, *d.r.* 9:1).

Spectroscopic data are in agreement with that reported above.

rel-(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**)

Method D: *Via* ketene acetal **332**

New compound.



294

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

309

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

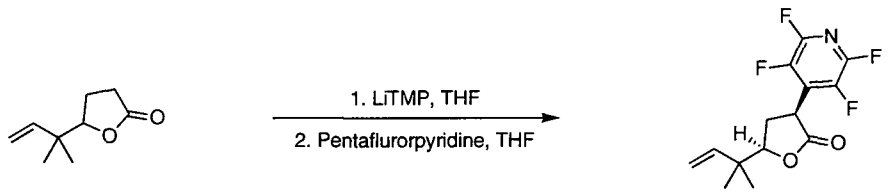
To a solution of 2,2,6,6-tetramethylpiperidine (119 mg, 140 µL, 0.84 mmol) in THF (3 mL) at 0 °C under nitrogen was added *n*-butyllithium (2.22 M in hexanes, 0.38 mL, 0.84 mmol) dropwise. After 30 min at 0 °C, the faint yellow solution was cooled to –78 °C and treated with a solution of lactone **294** (100 mg, 0.65 mmol) in THF (2 mL). The mixture was stirred for 2 h at –78 °C, TMS-Cl (91 mg, 110 µL, 0.84 mmol) was added, and the mixture warmed to RT for 2 h and then re-cooled to –78 °C. To a mixture of water (0.7 mL), Oxone® (800 mg, 1.3 mmol) and $NaHCO_3$ (546 mg, 6.5 mmol) was added acetone (3 mL) and the mixture was cooled to –78 °C. The cooled ketene acetal solution was transferred into the DMDO solution dropwise and the mixture stirred for 2 h. The reaction was warmed to RT and quenched by addition of $Na_2S_2O_3$ (sat., aq., 2 mL). The phases were separated and the aqueous phase

extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 10–20% EtOAc / petrol to afford first starting material **294** (66 mg, 0.43 mmol, 65%) and then the title compound **309** as a colourless oil (16 mg, 90 μmol, 14%, *d.r.* 3:1).

Spectroscopic data are in agreement with that reported above.

rel-(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-(2,3,5,6-tetrafluoropyridin-4-yl)dihydrofuran-2(3*H*)-one (**334**)

New compound.



294

Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

334

Chemical Formula: $C_{14}H_{13}F_4NO_2$
Molecular Weight: 303.25

To a solution of 2,2,6,6-tetramethylpiperidine (110 μL, 0.65 mmol) in THF (2 mL) at 0 °C under nitrogen was added *n*-butyllithium (2.2 M in hexanes, 0.29 mL, 0.65 mmol) dropwise. The mixture was stirred for 60 min at 0 °C, cooled to –78 °C, and treated with a solution of lactone **294** (77 mg, 0.5 mmol) in THF (2 mL). The mixture was stirred for 1 h at –78 °C and then pentafluoropyridine (70 μL, 0.65 mmol) was added. The mixture was stirred for 20 min at –78 °C, warmed to RT and stirred for 2 h. $NaHCO_3$ (sat., aq., 5 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 5–10% EtOAc / petrol to afford the title compound **334** as an oil which solidified to a clear solid (59 mg, 0.20 mmol, 39%). The solid was crystallised from CH_2Cl_2 / hexane for X-ray crystallography.

mp 74–79 °C (CH_2Cl_2 / hexane).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 5.86 (1H, dd, J = 17.6, 10.9 Hz, H_2C=C**H**), 5.19 (1H, dd, J = 10.9, 1.0 Hz, **H**HC=CH), 5.13 (1H, dd, J = 17.6, 1.0 Hz, H**H**C=CH), 4.40 (1H, dd, J = 10.8, 5.7 Hz, OC**H**), 4.31 (1H, dd, J = 12.7, 9.3 Hz, OC**H**), 2.55 (1H, ddd, J = 12.7, 9.3, 5.7 Hz, C**H**H), 2.26 (1H, app. q, J = 12.7 Hz, CH**H**), 1.19 (3H, s, C**H**$_3$), 1.13 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 172.6 (**C**=O), 145.3 (m, **C**$_{Ar}$), 141.3 (H_2C=**C**H), 142.1 (m, **C**$_{Ar}$), 139.1 (m, **C**$_{Ar}$), 138.7 (m, **C**$_{Ar}$), 129.9 (m, **C**$_{Ar}$), 115.2 (H_2**C**=CH), 85.9 (O**C**H), 39.9 (**C**$(CH_3)_2$), 38.1 (**C**HC=O), 31.0 (**C**H_2), 22.8 (**C**H_3), 22.3 (**C**H_3).

LRMS (ES^+)

m/z 326 ($[M+Na]^+$, 40%), 358 ($[M+Na+MeOH]^+$, 100%), ($[2M+Na]^+$, 30%).

HRMS (ES^+)

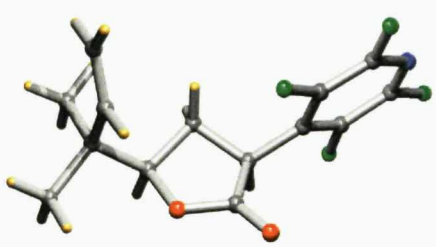
Found 326.0778, $[C_{14}H_{13}F_4NO_2+Na]^+$ requires 326.0775 amu.

FT – IR (compressed solid)

cm^{-1} 2966 (w), 2925 (w), 2872 (w), 1770 (s), 1650 (m), 1456 (s).

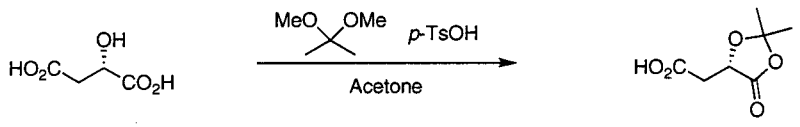
CHN Found C 54.87%, H 4.42%, N 4.33%. Calculated C 55.45%, H 4.32%, N 4.62%.

X-ray crystallography



[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic acid (**338**)

Known compound.



38 **338**

Chemical Formula: $C_4H_6O_5$
Molecular Weight: 134.09

Chemical Formula: $C_7H_{10}O_5$
Molecular Weight: 174.15

Prepared by the method reported by Denmark.[93] To a solution of (*S*)-malic acid (**38**) (5.00 g, 37.3 mmol) in acetone (50 mL) was added 2,2-dimethoxypropane (15.52 g, 18.3 mL, 149 mmol) and *para*-toluenesulfonic acid monohydrate (71 mg, 1 mol%). The mixture was stirred for 16 h at RT and then water (25 mL) containing $NaHCO_3$ (31 mg, 1 mol%) was added. The mixture was extracted with CH_2Cl_2 (5 x 25 mL) and the combined organic phases washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated to a white solid. Et_2O (40 mL) was added to dissolve the solid followed by addition of *n*-hexane (60 mL). A white solid crystallised upon hexane addition and the mixture was concentrated to 50% volume and allowed to stand for 30 min. The white crystalline solid **338** was collected by filtration and dried under vacuum (4.52 g, 26.2 mmol, 70%).

$[\alpha]_D^{26}$ +19.1 (c = 0.5, l = 2, MeOH). (Lit. +20.2 ° (c not reported)).[153]

mp 92–97 °C (hexane). Lit. 110–112 °C (EtOAc / petrol).[153]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 11.00 (1H, br s, CO_2**H**), 4.72 (1H, dd, J = 6.4, 3.9 Hz, O**CH**), 3.00 (1H, dd, J = 17.4, 3.9 Hz, **CH**H), 2.85 (1H, dd, J = 17.2, 6.4 Hz, CH**H**) 1.62 (3H, s, **C**H_3), 1.57 (3H, s, **C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 175.3 (**C**=O), 172.0 (**C**=O), 111.6 (O**C**O), 70.6 (O**C**H), 36.2 (**C**H_2), 26.9 (**C**H_3), 26.0 (**C**H_3).

LRMS (ES$^-$)

m/z 173 ([M–H]$^-$, 100%).

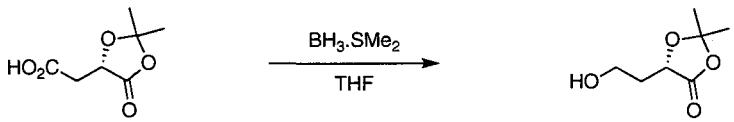
FT – IR (compressed solid)

cm^{-1} 3256 (br), 1755 (s), 1731 (s), 1694 (s), 1401 (m).

Spectroscopic data are in agreement with the literature.[93]

(5*S*)-5-(2-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-one (**339**)

Known compound.



338 **339**

Chemical Formula: $C_7H_{10}O_5$
Molecular Weight: 174.15

Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.17

Prepared by the method reported by Burton.[92] A solution of **338** (871 mg, 5.00 mmol) in THF (15 mL) was cooled to 0 °C under nitrogen and treated with $BH_3.SMe_2$ (0.55 mL, 10 M solution, 5.50 mmol) dropwise over 5 min. The mixture was warmed to RT and stirred for 16 h. Further $BH_3.SMe_2$ (100 μL, 10 M solution, 1.00 mmol) was added and the mixture stirred for a further 2 h. MeOH (5 mL) was added slowly at 0 °C to destroy excess borane. The mixture was warmed to RT and the solvent removed under reduced pressure. The crude product was rapidly purified by column chromatography on silica gel, eluting with acetone. NMR indicated the product **339**, together with some acetone. In this instance the product was immediately advanced to the DMP oxidation reaction.

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 4.56 (1H, dd, *J* = 7.1, 4.9 Hz, OC**H**), 3.90–3.76 (2H, m, **CH$_2$**OH), 2.20–2.09 (2H, m, **CH**H and **OH** overlapped), 2.00 (1H, m, CH**H**), 1.62 (3H, s, **CH$_3$**), 1.56 (3H, s, **CH$_3$**).

^{13}C NMR (75 MHz, $CDCl_3$)

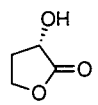
δ_C ppm 173.7 (**C**=O), 111.1 (**O**CO), 72.2 (**O**CH), 58.9 (**C**H_2OH), 34.3 (**C**H_2), 27.3 (**C**H_3), 25.8 (**C**H_3).

FT – IR ($CHCl_3$ solution)

cm^{-1} 3418 (br m), 2939 (m), 2865 (w), 1790 (s), 1451 (w).

Spectroscopic data are in agreement with the literature.[154] The compound degraded in the mass spectrometer and did not provide an adequate spectrum.

Compound **339** degraded on standing to (3*S*)-3-hydroxydihydrofuran-2(3*H*)-one (**341**) Known compound.



341

Chemical Formula: $C_4H_6O_3$
Molecular Weight: 102.09

$[\alpha]_D^{28}$ –52.6 (c = 0.45, l = 2, $CHCl_3$). (Lit. –69.7 °, c = 0.93, $CHCl_3$).[155]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 4.53 (1H, dd, J = 10.2, 8.3 Hz, OC**H**), 4.42 (1H, td, J = 8.9, 2.1 Hz, OC**H**), 4.22 (1H, ddd, J = 10.4, 9.2, 6.1 Hz, OC**H**), 3.92 (1H, br s, O**H**), 2.59 (1H, dddd (overlapped), J = 12.6, 8.3, 6.1, 2.1 Hz, C**H**H), 2.27 (1H, dddd (overlapped), J = 12.6, 10.4, 10.2, 8.9 Hz, CH**H**).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 178.2 (**C**=O), 67.4 (**O**CH), 65.2 (**C**H_2), 30.8 (**C**H_2).

LRMS (CI)

m/z 103 ($[M+H]^+$, 90%), 58 (100%), 55 (38%), 45 (20%), 42 (47%).

FT – IR (neat)

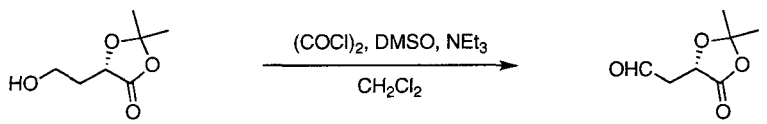
cm^{-1} 3407 (br), 2991 (w), 2917 (w), 1763 (s), 1638 (w), 1454 (w).

Spectroscopic data are in agreement with the literature.[155]

[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetaldehyde (**340**)

Method A: Swern Oxidation

Known compound.



339

Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.17

340

Chemical Formula: $C_7H_{10}O_4$
Molecular Weight: 158.15

Prepared using the method reported by Swern[156] and modified by Harrowven.[157] To a solution of oxalyl chloride (349 mg, 0.24 mL, 2.75 mmol) in CH_2Cl_2 (5 mL) at –78 °C under nitrogen was added a solution of DMSO (430 mg, 0.39 mL, 5.50 mmol) in CH_2Cl_2 (1 mL) dropwise over 10 min. After 10 min a solution of **339** (200 mg, 1.25 mmol) in CH_2Cl_2 (1 mL) was added over 5 min. After 1 h stirring at –78 °C, NEt_3 (632 mg, 0.87 mL, 6.25 mmol) was added slowly and the mixture warmed to RT. Water (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with 40% EtOAc / petrol to afford the title compound **340** as a colourless oil (66 mg, 0.42 mmol, 33%).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 9.76 (1H, s, C**H**O), 4.78 (1H, dd, J = 6.9, 3.5 Hz, OC**H**), 3.10 (1H, ddd, J = 18.3, 3.5, 0.8 Hz, C**H**H), 2.90 (1H, ddd, J = 18.3, 6.9, 1.0 Hz, CH**H**), 1.62 (3H, s, C**H**$_3$), 1.57 (3H, s, C**H**$_3$).

^{13}C NMR	(100 MHz, $CDCl_3$)
δ_C ppm	196.9 (**C**HO), 172.4 (**C**=O), 111.5 (O**C**O), 68.9 (O**C**H), 44.9 (**C**H_2), 27.0 (**C**H_3), 25.8 (**C**H_3).

LRMS	(CI)
m/z	159 ([M+H]$^+$, 20%), 85 (40%), 59 (55%).

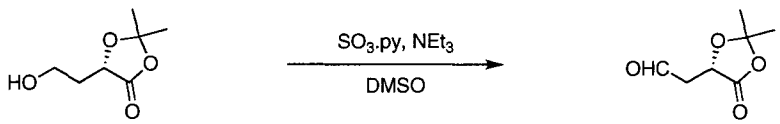
FT – IR	($CHCl_3$ solution)
cm^{-1}	2928 (s), 2865 (m), 1792 (s), 1727 (s), 1451 (m).

Spectroscopic data are in agreement with the literature.[95]

[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetaldehyde (**340**)

Method B: SO_3.py oxidation

Known compound.



339

Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.17

340

Chemical Formula: $C_7H_{10}O_4$
Molecular Weight: 158.15

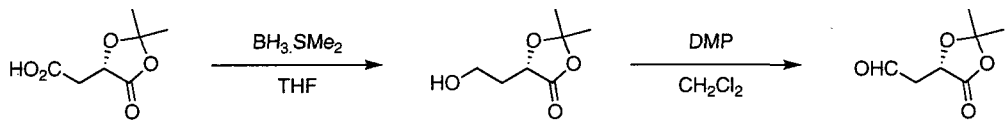
Prepared using the method reported by Liu.[97] To a solution of alcohol **339** (200 mg, 1.25 mmol) in NEt_3 (506 mg, 0.70 mL, 5 mmol) and DMSO (0.5 mL) at 10 °C under nitrogen was added a solution of SO_3.py complex (398 mg, 2.50 mmol) in DMSO (1.5 mL). The mixture was stirred for 1 h at RT before treatment with further SO_3.py (199 mg, 1.25 mmol). After a further 16 h at RT, water (2 mL) was added and the reaction mixture was diluted with EtOAc (15 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated to a brown oil. The crude residue was purified by column chromatography, eluting with 40–50% EtOAc / pentane to afford the title compound **340** as a colourless oil (54 mg, 0.34 mmol, 27%).

Spectroscopic data are in agreement with that reported above.

[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetaldehyde (**340**)

Method C: Dess-Martin Periodinane oxidation

Known compound.



338 **339** **340**

Chemical Formula: $C_7H_{10}O_5$
Molecular Weight: 174.15

Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.17

Chemical Formula: $C_7H_{10}O_4$
Molecular Weight: 158.15

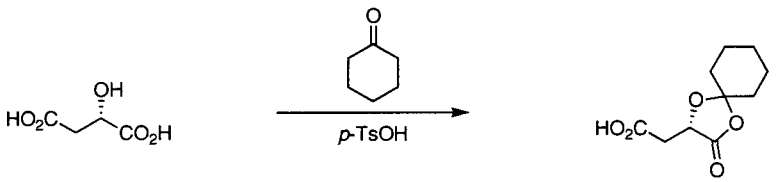
Prepared using the procedure reported by Martin.[94] To a solution of Dess-Martin periodinane (2.12 g, 5 mmol) and $NaHCO_3$ (2.10 g, 25 mmol) in CH_2Cl_2 (5 mL) was added the crude product resulting from the reduction of **338** (0.871 g, 5 mmol) to **339** in CH_2Cl_2 (10 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 1 h at 0 °C and then further DMP (424 mg, 1 mmol) and $NaHCO_3$ (420 mg, 5 mmol) were added. The reaction was warmed to RT and maintained at this temperature for 2 h. $Na_2S_2O_3$ (sat., aq., 10 mL) was added and the mixture was stirred at RT for 10 min then extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with $Na_2S_2O_3$ (sat., aq., 5 mL), water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel, eluting with 20–50% EtOAc / petrol to afford the title compound **340** as a colourless oil (434 mg, 2.74 mmol, 55% over 2 steps).

Spectroscopic data are in agreement with that reported above.

[(2*S*)-3-Oxo-1,4-dioxaspiro[4.5]dec-2-yl]acetic acid (**346**)

Method A: Neat, RT

Known compound.



38

Chemical Formula: $C_4H_6O_5$
Molecular Weight: 134.09

346

Chemical Formula: $C_{10}H_{14}O_5$
Molecular Weight: 214.22

(*S*)-Malic acid **38** (20.00 g, 149.2 mmol) in cyclohexanone (43.90 g, 46.4 mL, 447.3 mmol) was treated with *para*-toluensulfonic acid monohydrate (284 mg, 1 mol%) and the slurry was stirred at RT for 30 h. CH_2Cl_2 (50 mL) and water (25 mL) containing $NaHCO_3$ (126 mg, 1 mol%) were added and the phases separated. The aqueous phase was washed with CH_2Cl_2 (2 x 15 mL) and the combined organic phases then washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated to a brown oil. *n*-Heptane (200 mL) was added and the mixture allowed to stand for 17 h. The resulting solid precipitate was collected by filtration, washed with *n*-heptane (50 mL) and dried under vacuum to afford the title compound **346** as a light brown solid (18.96 g, 88.53 mmol, 59%).

mp 100–106 °C (*n*-heptane). (Lit. 104–105 °C, solvent not given).[158]

$[\alpha]_D^{26}$ +11.3 (c = 0.5, l = 2, $CHCl_3$). Lit +7.18 ° (c = 1, $CHCl_3$).[159]

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 10.81 (1H, br s, COO**H**), 4.72 (1H, dd, J = 6.5, 4.0 Hz, OC**H**), 3.00 (1H, dd, J = 17.3, 4.0 Hz, C**H**H), 2.85 (1H, dd, J = 17.3, 6.5 Hz, CH**H**), 1.90–1.79 (2H, m, 2 x cyclohexyl-**H**), 1.78–1.57 (6H, m, 6 x cyclohexyl-**H**), 1.54–1.34 (2H, m, 2 x cyclohexyl-**H**).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 175.2 (**C**=O), 172.0 (**C**=O), 112.2 (O**C**O), 70.0 (O**C**H), 36.2 (**C**H_2), 35.3 (**C**H_2), 24.3 (**C**H_2), 22.9 (**C**H_2).

LRMS (ES$^-$)

m/z 213 ([M–H]$^-$, 100%), 449 ([2M–2H+Na]$^-$, 20%).

FT – IR (compressed solid)

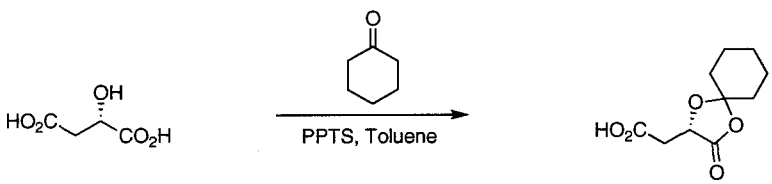
cm^{-1} 3187 (br), 2950 (w), 2921 (w), 2860 (w), 1786 (s), 1729 (s), 1698 (s).

Spectroscopic data are in agreement with the literature.[159]

[(2*S*)-3-Oxo-1,4-dioxaspiro[4.5]dec-2-yl]acetic acid (**346**)

Method B: Dean and Stark

Known compound.



38

Chemical Formula: $C_4H_6O_5$
Molecular Weight: 134.09

346

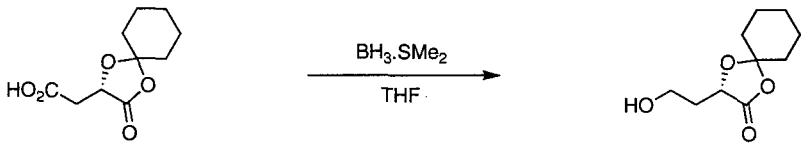
Chemical Formula: $C_{10}H_{14}O_5$
Molecular Weight: 214.22

(*S*)-Malic acid **38** (40.00 g, 298.3 mmol), cyclohexanone (73.00 g, 78.0 mL, 743.8 mmol) and pyridinium-*para*-toluene sulfonate (740 mg, 1 mol%) in toluene (250 mL) was heated at reflux under a Dean and Stark trap for 16 h. The mixture was cooled to RT, concentrated and petrol (250 mL) was added. Upon stirring, a solid precipitate formed and was collected by filtration, washed with petrol and dried under high vacuum to afford the title compound **346** as a white solid (58.62 g, 273.6 mmol, 92%).

Spectroscopic data are in agreement with that reported above.

(3*S*)-3-(2-Hydroxyethyl)-1,4-dioxaspiro[4.5]decan-2-one (**347**)

Known compound.



346 **347**

Chemical Formula: $C_{10}H_{14}O_5$
Molecular Weight: 214.22

Chemical Formula: $C_{10}H_{16}O_4$
Molecular Weight: 200.23

Prepared using the method reported by Burton.[92] To a solution of stirred solution of acid **346** (1.00 g, 4.67 mmol) in THF (15 mL) at 0 °C under nitrogen was added $BH_3.SMe_2$ (0.70 mL, 10 M, 7.00 mmol) dropwise, resulting in hydrogen gas evolution. After 30 min at 0 °C and 20 h at RT, the mixture was re-cooled to 0 °C and methanol (4 mL) was added slowly, resulting in further H_2 evolution. The reaction mixture was warmed to RT, stirred for 30 min then concentrated. Purification by rapid column chromatography on silica gel eluting with Et_2O, afforded the title compound **347** as a colourless oil (850 mg, 4.24 mmol, 91%.).

$[\alpha]_D^{26}$ –3.0 (c = 0.525, l = 2, $CHCl_3$). Lit not published.

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 4.57 (1H, dd, J = 6.8, 5.2 Hz, OC**H**), 3.85 (2H, m, C**H**$_2$OH), 2.16 (1H, dddd (overlapped), J = 14.6, 7.0, 5.2, 5.2 Hz, C**H**H), 2.02 (1H, dddd, J = 14.6, 6.8, 6.6, 4.7 Hz, CH**H**), 1.94–1.59 (8H, m, 8 x cyclohexyl-**H**), 1.57–1.35 (2H, m, 2 x cyclohexyl-**H**).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 173.8 (**C**=O), 112.1 (O**C**O), 72.3 (O**C**H), 59.4 (**C**H$_2$OH), 37.1 (**C**H$_2$), 35.8 (**C**H$_2$), 34.8 (**C**H$_2$), 24.8 (**C**H$_2$), 23.4 (**C**H$_2$).

LRMS (ES$^+$)

m/z 201 ([M+H]$^+$, 50%), 223 ([M+Na]$^+$, 50%).

HRMS (ES^+)

Found 423.1985, $[C_{20}H_{32}O_8+Na]^+$ (2M+Na) requires 423.1989 amu.

FT – IR (neat)

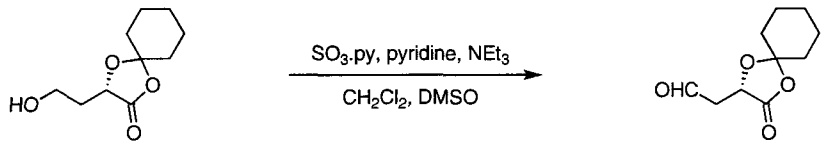
cm^{-1} 3427 (br w), 2937 (m), 2864 (w), 1782 (s), 1451 (m).

Spectroscopic data has not been published due to compound stability.

[(2*S*)-3-Oxo-1,4-dioxaspiro[4.5]dec-2-yl]acetaldehyde (**348**)

Method A: SO_3.py oxidation with pyridine

Known compound.



347 **348**

Chemical Formula: $C_{10}H_{16}O_4$
Molecular Weight: 200.23

Chemical Formula: $C_{10}H_{14}O_4$
Molecular Weight: 198.22

Procedure based on the method reported by Chen.[98] To a solution of alcohol **347** (768 mg, 3.84 mmol) and NEt_3 (1.36 g, 1.9 mL, 13.44 mmol) in CH_2Cl_2 (5 mL) was added a pre-mixed solution of SO_3.py complex (1.22 g, 7.67 mmol) and pyridine (607 mg, 0.62 mL, 7.67 mmol) in DMSO (2 mL) at RT under nitrogen. After 1 h, further SO_3.py (0.61 g, 3.84 mmol), pyridine (304 mg, 0.31 mL, 3.84 mmol) and NEt_3 (680 mg, 0.95 mL, 6.72 mmol) were added and the mixture stirred for a further 20 min. CH_2Cl_2 (15 mL) was added, followed by H_2O (3 mL) and the phases were immediately separated. The aqueous phase was washed with CH_2Cl_2 (2 x 15 mL) and the combined organic phases were washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated to a brown oil. This crude oil was purified by column chromatography on silica gel, eluting with 15% EtOAc / heptane to afford the title compound **348** as a light yellow oil (320 mg, 1.61 mmol, 44%).

$[\alpha]_D^{26}$ +1.1 ($c = 0.51$, $l = 2$, $CHCl_3$). Lit + 2.5 ° ($c = 0.7$, $CHCl_3$).[159]

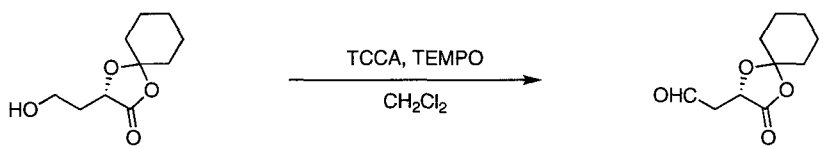
^{1}H NMR	(400 MHz, $CDCl_3$)
δ_H ppm	9.78 (1H, t, J = 1.0 Hz, **CH**O), 4.80 (1H, dd, J = 7.0, 3.7 Hz, O**CH**), 3.08 (1H, ddd, J = 18.2, 3.7, 1.0 Hz, **CH**H), 2.91 (1H, ddd, J = 18.2, 7.0, 1.0 Hz, CH**H**), 1.94–1.84 (2H, m, 2 x cyclohexyl-**H**), 1.82–1.60 (6H, m, 6 x cyclohexyl-**H**), 1.55–1.40 (2H, m, 2 x cyclohexyl-**H**).
^{13}C NMR	(100 MHz, $CDCl_3$)
δ_C ppm	196.8 (**C**HO), 172.3 (**C**=O), 112.3 (O**C**O), 68.4 (O**C**H), 44.9 (**C**H_2), 36.2 (**C**H_2), 35.2 (**C**H_2), 24.4 (**C**H_2) and 23.0 (**C**H_2).
LRMS	(ES^+)
m/z	221 ($[M+Na]^+$, 50%), 253 ($[M+Na+MeOH]^+$, 63%).
FT – IR	(neat)
cm^{-1}	2937 (m), 1865 (m), 1791 (s), 1727 (s), 1451 (m).

Spectroscopic data are in agreement with the literature.[159]

[(2*S*)-3-Oxo-1,4-dioxaspiro[4.5]dec-2-yl]acetaldehyde (**348**)

Method B: TEMPO / TCCA oxidation

Known compound.



347

Chemical Formula: $C_{10}H_{16}O_4$
Molecular Weight: 200.23

348

Chemical Formula: $C_{10}H_{14}O_4$
Molecular Weight: 198.22

Prepared by the general methods of De Luca [106] and Jenny.[107] To a solution of alcohol **347** (3.40 g, 16.98 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added TEMPO (27 mg, 1 mol%) and trichloro*iso*cyanuric acid (3.95 g, 16.98 mmol). The reaction was stirred for 2 h at 0 °C and then warmed to RT and filtered through Celite®. The filtrate was diluted with CH_2Cl_2 (50 mL), washed with Na_2CO_3 (sat., aq., 20 mL), HCl (0.1 M, aq., 2 x 20 mL) and brine (2 x 15 mL), dried over $MgSO_4$, filtered and

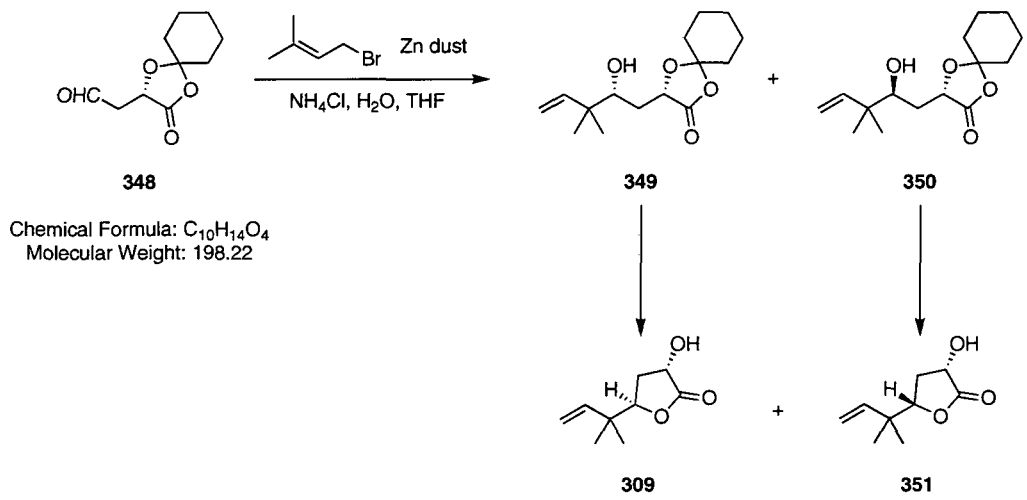
concentrated to a colourless oil (2.74 g, 13.82 mmol, 81%). Repetition on a 10 g scale with NaOAc added at the start of the reaction (3 equiv. based on TCCA) and the use of 4-hydroxy-TEMPO gave a 54% yield of **348** after chromatography on silica gel.

Spectroscopic data are in agreement with that reported above.

(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**) and (3*S*,5*S*)-5-(1,1-dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**351**)

Method A: Zinc / prenyl chloride

New compound.



Chemical Formula: $C_{10}H_{14}O_4$
Molecular Weight: 198.22

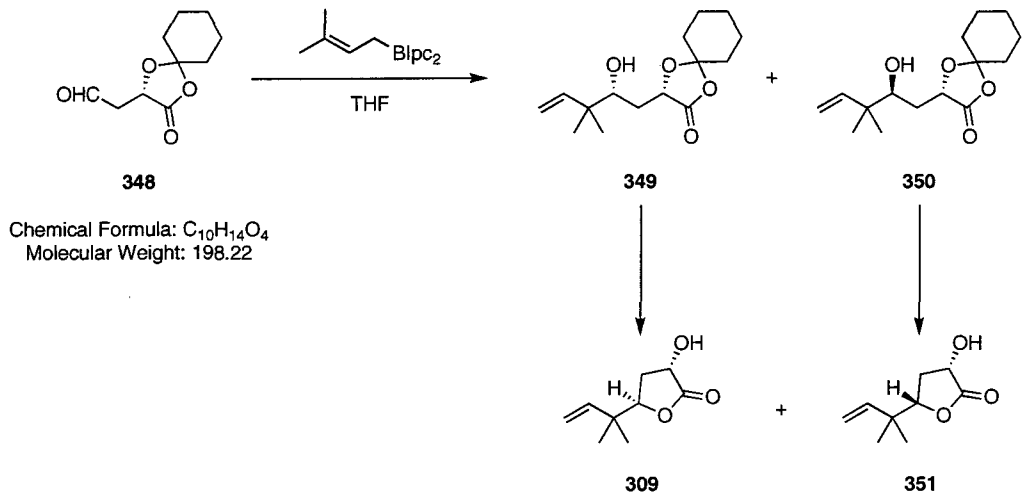
Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Procedure based on the method reported by Luche.[69] To a solution of aldehyde **348** (233 mg, 1.18 mmol) in THF (3 mL) at 10 °C was added zinc dust (100 mg, 1.53 mmol), NH_4Cl (sat., aq., 7 mL) and prenyl bromide (228 mg, 180 µL, 1.53 mmol). The reaction was stirred at RT for 2 h and then the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was rapidly purified by column chromatography on silica gel, eluting with 30% EtOAc / heptane to afford the title compounds **309** and **351** as a 1:1 mixture of diastereoisomers.

Spectroscopic data are in agreement with that reported above.

(3*S*,5*R*)-5-(1,1-Dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**309**) and (3*S*,5*S*)-5-(1,1-dimethylprop-2-en-1-yl)-3-hydroxydihydrofuran-2(3*H*)-one (**351**)

Method B: Chiral borane method



Prepared using the methods reported by Brown.[59,82,83] To a stirred solution of (1*R*)-(+)-α-pinene (392 mg, 0.46 mL, 2.88 mmol) in THF (0.5 mL) at 20 °C under argon was added $BH_3.SMe_2$ (120 μL, 10 M, 1.20 mmol) dropwise. A white solid separated after 30 min and stirring was continued for 3 h. The reaction mixture was cooled to 0 °C, 3-methyl-1,2-butadiene **320** (82 mg, 120 μL, 1.20 mmol) was added dropwise and the mixture was stirred for a further 5 h at RT then cooled to –78 °C. A pre-cooled (–78 °C) solution of aldehyde **348** (198 mg, 1.00 mmol) in THF (2 mL) was added and the reaction mixture was allowed to warm to RT over 6 h. After a further 10 h, the mixture was re-cooled to 0 °C and NaOH (3 M, aq., 2 mL) and H_2O_2 (30%, aq., 1 mL) were added. The mixture was maintained at 0 °C for 30 min, heated at reflux for 30 min, then cooled to RT and extracted with EtOAc (15 mL). The aqueous phase was acidified with HCl (2 M, aq.) to pH 1–2 and re-extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with $Na_2S_2O_3$ (sat., aq., 5 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 20% EtOAc / heptane to afford first the title compound **309** as a colourless oil (67 mg, 0.39 mmol, 39%) followed by **351** as a white solid (12 mg, 70 μmol, 7%). Use of $NaBO_3.4H_2O$ added to the mixture at RT for 18 h in place of H_2O_2 / NaOH led to a yield of 60%.

$[\alpha]_D^{26}$ +8.6 (c = 0.5, l = 2, $CHCl_3$).

Spectroscopic data are in agreement with that reported above.

Data for **351**:

mp 65–67 °C (EtOAc).

$[\alpha]_D^{28}$ –38.7 (c = 0.3, l = 2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 5.81 (1H, dd, J = 17.4, 10.9 Hz, H_2C=C**H**), 5.15 (1H, dd, J = 10.9, 1.2 Hz, **H**HC=CH), 5.11 (1H, dd, J = 17.4, 1.2 Hz, H**H**C=CH), 4.53 (1H, dd, J = 11.1, 8.6 Hz, OC**H**), 4.15 (1H, dd, J = 11.1, 5.2 Hz, OC**H**), 3.18 (1H, br s, O**H**), 2.50 (1H, ddd, J = 12.5, 8.6, 5.2 Hz, C**H**H), 1.96 (1H, dt, J = 12.5, 11.1 Hz, CH**H**), 1.12 (3H, s, C**H**$_3$), 1.08 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 177.5 (**C**=O), 141.8 (H_2**C**=CH), 114.9 (H_2**C**=CH), 83.2 (**C**OC=O), 68.9 (**C**HOH), 39.7 (**C**(CH_3)$_2$), 32.7 (**C**H$_2$), 23.0 (**C**H$_3$), 22.4 (**C**H$_3$).

LRMS (CI)

m/z 171 ($[M+H]^+$, 20%), 155 ($[M+H–CH_4]^+$, 10%), 125 ($[M–CO_2]^+$, 25%), 95 (25%), 82 (65%), 69 ($[C_5H_9]^+$ 55%), 55 (35%), 41 (100%).

HRMS (EI)

Found 155.0711, $[C_8H_{11}O_3]^+$ (M+H–CH_4) requires 155.0708 amu.

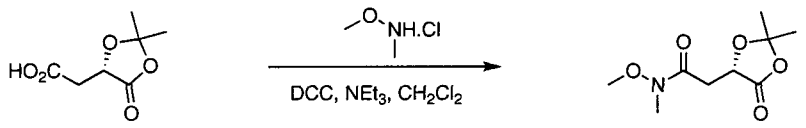
FT – IR (compressed solid)

cm^{-1} 3391 (br m), 2972 (m), 2930 (w), 2869 (w), 1749 (s), 1642 (w), 1460 (w), 1419 (w).

2-[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]-*N*-methoxy-*N*-methylacetamide (**360**)

Method A: DCC

New compound.



338

Chemical Formula: $C_7H_{10}O_5$
Molecular Weight: 174.15

360

Chemical Formula: $C_9H_{15}NO_5$
Molecular Weight: 217.22

Prepared using the method reported by Wulff.[160] A solution of carboxylic acid **338** (2.00 g 11.48 mmol), *O*,*N*-dimethylhydroxylamine HCl (1.23 g, 12.63 mmol) and NEt_3 (1.28 g, 1.76 mL, 12.63 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. DCC (2.60 g, 12.63 mmol) was added in one portion. After 30 min, the reaction mixture was warmed to RT, maintained at that temperature for 30 min, then filtered. The filtrate was concentrated and purified by column chromatography on silica gel, eluting with 20–50 % EtOAc / pentane to afford the title compound **360** as a thick oil (1.54 g 7.10 mmol, 62%).

$[\alpha]_D^{29}$ +0.9 (c = 0.45, l = 2, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 4.85 (1H, dd, J = 7.4, 3.3 Hz, OC**H**), 3.74 (3H, s, OC**H**$_3$), 3.21 (3H, s, NC**H**$_3$), 3.05 (1H, dd, J = 17.2, 3.3 Hz, C**H**H) 2.94 (1H, dd, J = 17.2, 7.4 Hz, CH**H**), 1.63 (3H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 174.0 (**C**=O), 172.8 (**C**=O), 110.4 (**C**(CH$_3$)), 78.4 (OCH), 61.1 (OCH$_3$), 35.2 (CH$_2$), 32.1 (NCH$_3$), 27.4 (CH$_3$), 26.0 (CH$_3$).

LRMS (ES$^+$)

m/z 160 ([M–acetone+H]$^+$, 100%), 218 ([M+H]$^+$, 40%).

HRMS (ES$^+$)

Found 240.0842, $[C_9H_{15}NO_5+Na]^+$ requires 240.0842 amu.

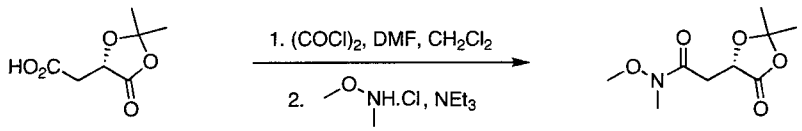
FT – IR (neat)

cm^{-1} 2990 (w), 2942 (w), 1789 (s), 1662 (s).

2-[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]-*N*-methoxy-*N*-methylacetamide (**360**)

Method B: Acid chloride

New compound.



338

Chemical Formula: $C_7H_{10}O_5$
Molecular Weight: 174.15

360

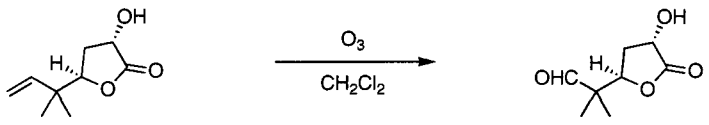
Chemical Formula: $C_9H_{15}NO_5$
Molecular Weight: 217.22

To a solution of acid **338** (174 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added oxalyl chloride (165 mg, 110 µL, 1.30 mmol) and DMF (3 drops), causing effervescence. The reaction was stirred at 0 °C for 20 min and then at RT for 18 h. *O*,*N*-dimethylhydroxylamine HCl (117 mg, 1.20 mmol) was added, the mixture was cooled to 0 °C and NEt_3 (506 mg, 0.69 mL, 5.00 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h and then at RT for 2 h before being quenched by addition of water (20 mL) and EtOAc (50 mL). The phases were separated, the aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were washed with water (10 mL) and brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was subjected to column chromatography, eluting with 20–40% EtOAc / pentane to afford the title compound **360** as a thick yellow oil (107 mg, 0.49 mmol, 49%).

Spectroscopic data are in agreement with that reported above.

2-[(2*R*,4*S*)-4-Hydroxy-5-oxotetrahydrofuran-2-yl]-2-methylpropanal (**314**)

New compound.



309 **314**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

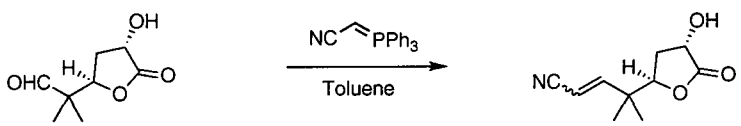
Aldehyde **314** (enantiomerically pure) was prepared as reported above. Column chromatography on silica gel, eluting with Et_2O afforded the title compound **314** as a colourless oil (318 mg, 1.85 mmol, 49%).

$[\alpha]_D^{28}$ –81.1 ($c = 0.27$, $l = 2$, $CHCl_3$).

Spectroscopic data are in agreement with that reported above.

4-[(2*R*,4*S*)-4-hydroxy-5-oxotetrahydrofuran-2-yl]-4-methylpent-2-enenitrile (**292**)

New compound.



314 **292**

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

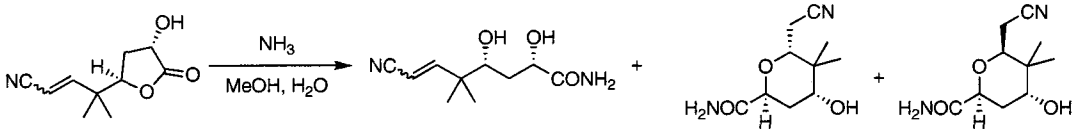
A mixture of **314** (97 mg, 0.56 mmol) and Ph_3PCHCN (187 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) was heated to 40 °C for 16 h. No reaction had occurred so the mixture was concentrated and the solvent replaced with toluene (10 mL). Further ylide (187 mg, 0.62 mmol) was added and the mixture heated to 85 °C for 16 h then cooled to RT. Further ylide (187 mg, 0.62 mmol) was added and the mixture heated at reflux for 20 h and then cooled and concentrated. Purification by column chromatography on silica gel, eluting with Et_2O afforded the title compound **292** as a thick oil and as an inseparable mixture of diastereoisomers (76 mg, 0.39 mmol, 70%, *E*:*Z* 5:1).

$[\alpha]_D^{28}$ –36.9 (c = 0.415, l = 2, MeOH). Value recorded for inseparable mixture of *E* and *Z* isomers.

Spectroscopic data are in agreement with that reported above.

(2*S*,4*R*,6*R*)-6-(Cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**37**) and (2*S*,4*R*,6*S*)-6-(cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**315**)

New compounds.



292 **298** **37** **315**

Ratio 1:1.2

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

A solution of lactone **292** (*E*/*Z* mixture, 72 mg, 0.37 mmol) in methanol (2 mL) was treated with ammonia (28%, aq., 1 mL). The mixture was stirred for 16 h at RT and then concentrated onto silica gel and purified by column chromatography, eluting with EtOAc to afford first **37** as a white solid (8.4 mg, 40 μmol, 11%), followed by **315** as a white solid (10.5 mg, 49 μmol, 13%) and finally **298** as a white solid (23 mg, 0.108 mmol, 29%).

Data for **37** (desired diastereoisomer)

$[\alpha]_D^{29}$ +81.1 (c = 0.19, l = 2, MeOH).

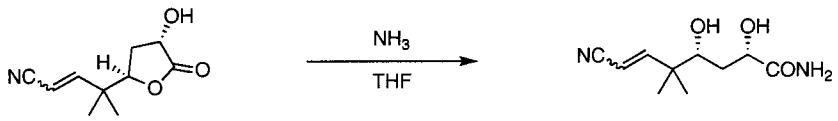
Data for **315** (undesired diastereoisomer)

$[\alpha]_D^{29}$ –140.0 (c = 0.15, l = 2, MeOH).

Spectroscopic data are in agreement with that reported above for racemic compound.

rel-(2*S*,4*R*)-7-Cyano-2,4-dihydroxy-5,5-dimethylhept-6-enamide (**298**)

New compound.



292 **298**

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Ammonia (2 mL) was condensed at –78 °C under nitrogen. A solution of **292** (*E*/*Z* mixture, 62 mg, 0.32 mmol) in THF (2 mL) was added to the ammonia and the reaction was stirred for 19 h at –78 °C. The reaction proved to be very slow and so was warmed to –40 °C for 4 h and then to RT and then concentrated under reduced pressure to a white solid (65 mg, 0.31 mmol, 97%). Only the E isomer was isolated after chromatography, although crude NMR indicated *E*:*Z* 6:1.

mp 31 – 34 °C (EtOAc).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 6.86 (1H, d, *J* = 16.8 Hz, NCHC=C**H**), 5.51 (1H, d, *J* = 16.8 Hz, NC**H**C=CH), 4.15 (1H, dd, *J* = 7.6, 5.3 Hz, H_2NCOC**H**OH), 3.69 (1H, dd, *J* = 10.4, 1.8 Hz, $C(CH_3)_2$C**H**OH), 1.92 (1H, ddd, *J* = 14.0, 5.3, 1.8 Hz, C**H**H), 1.59 (1H, ddd, *J* = 14.0, 10.4, 7.6 Hz, CH**H**), 1.07 (3H, s, $C\mathbf{H}_3$), 1.06 (3H, s, $C\mathbf{H}_3$).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 179.9 (**C**=O), 163.7 (NCHC=**C**H), 118.9 (**C**N), 99.1 (NCH**C**=CH), 77.1 (**C**HOH), 72.3 (**C**HOH), 44.1 ($\mathbf{C}(CH_3)_2$), 37.5 ($\mathbf{C}H_2$), 22.6 ($\mathbf{C}H_3$), 22.5 ($\mathbf{C}H_3$).

LRMS (ES^+)

m/z 235 ($[M+Na]^+$, 100%).

HRMS (ES^+)

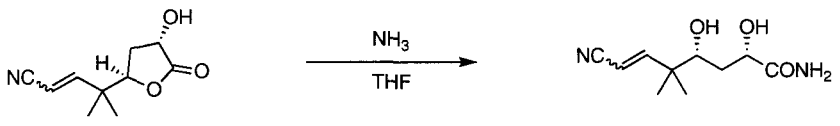
Found: 235.1055, $[C_{10}H_{16}N_2O_3+Na]^+$ requires 235.2053 amu.

FT – IR (CH_2Cl_2 solution)

cm^{-1} 3354 (br), 2968 (m), 2917 (m), 2840 (w), 2214 (m), 1670 (s), 1628 (m), 1580 (m).

(2*S*,4*R*)-7-Cyano-2,4-dihydroxy-5,5-dimethylhept-6-enamide (**298**)

New compound.



292 **298**

Chemical Formula: $C_{10}H_{13}NO_3$
Molecular Weight: 195.22

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Compound **298** (enantiomerically pure) was prepared as reported above. Column chromatography eluting with EtOAc to 5% MeOH in EtOAc afforded **298** as a white solid (179 mg, 0.84 mmol, 83%).

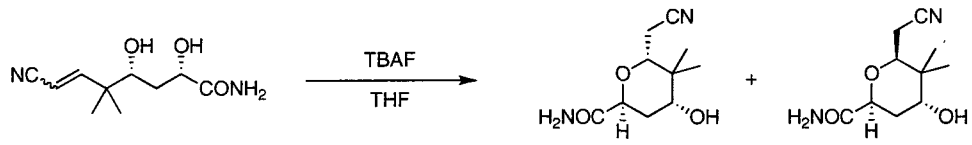
$[\alpha]_D^{28}$ –8.3 (c = 0.2, l = 2, MeOH). Value recorded for inseparable mixture of *E* and *Z* isomers.

Spectroscopic data are in agreement with that reported above.

rel-(2*S*,4*R*,6*R*)-6-(Cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**37**) and *rel*-(2*S*,4*R*,6*S*)-6-(cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**315**)

Method A: TBAF

New compounds.



298 **37** **315**

Ratio 1:2.8

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

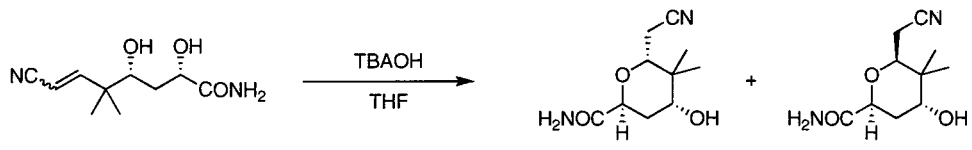
To a solution of nitrile **298** (*E*/*Z* mixture, 15 mg, 71 μmol) in THF (0.75 mL) at –78 °C under nitrogen was added tetra-*n*-butylammonium fluoride (1 M in THF, 70 μL, 70 μmol). The reaction was stirred at –78 °C for 2 h, warmed to –40 °C over 2 h and then to –18 °C over 2 h. TLC indicated that no reaction took place at these temperatures so the mixture was allowed to stand at 4 °C for 3 weeks, during which time 2 products formed. Silica gel was added to the reaction mixture and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with EtOAc afforded first **37** (1.8 mg, 8.5 μmol, 12%), followed by **315** (4.9 mg, 23 μmol, 33%) as white solids.

Spectroscopic data are in agreement with that reported above.

rel-(2*S*,4*R*,6*R*)-6-(Cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**37**) and *rel*-(2*S*,4*R*,6*S*)-6-(cyanomethyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**315**)

Method B: TBAOH

New compounds.



298 **37** **315**

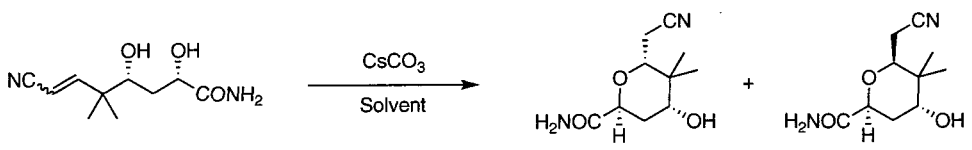
Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

To a solution of nitrile **298** (*E*/*Z* mixture, 14 mg, 66 μmol) in methanol (0.5 mL) at –95 °C under nitrogen was added tetra-*n*-butylammonium hydroxide (1.54 M in methanol, 43 μL, 66 μmol). The mixture was stirred at –95 °C for 4 h, warmed to –78 °C for 3 h and then to RT overnight (18 h). Silica gel was added and the solvent removed under reduced pressure. Purification by column chromatography on silica gel, eluting from 50% EtOAc / petrol to EtOAc afforded first **37** (3.2 mg, 15 μmol, 23%), followed by **315** (7.8 mg, 37 μmol, 56%) as white solids.

Spectroscopic data are in agreement with that reported above.

Small scale cyclisation experiments (**37**) and (**315**)



298 **37** **315**

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

Chemical Formula: $C_{10}H_{16}N_2O_3$
Molecular Weight: 212.25

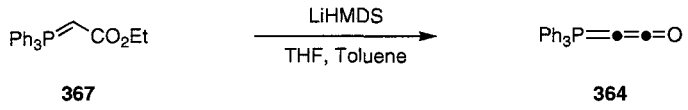
The following procedure is representative. A solution of nitrile **298** (*E*/*Z* mixture, 5 mg, 24 μmol) and Cs_2CO_3 (31 mg, 94 μmol) in the appropriate solvent (1 mL) was

stirred at RT for 48 h and then concentrated, dissolved in $CDCl_3$, filtered and analysed by ^1H NMR to determine ratios of **37**:**315**.

Spectroscopic data are in agreement with that reported above.

(Triphenylphosphoranylidene)-ketene (**364**)

Known compound.



367 **364**

Chemical Formula: $C_{22}H_{21}O_2P$
Molecular Weight: 348.37

Chemical Formula: $C_{20}H_{15}OP$
Molecular Weight: 302.31

Prepared by methods reported by Bestmann.[121,123] A solution of HMDS (3.8 mL, 18.0 mmol) in THF (25 mL) was cooled to 0 °C under nitrogen and treated with *n*-butyllithium (1.8 M in hexanes, 10.0 mL, 18.0 mmol) dropwise. The mixture was stirred at 0 °C for 1 h during which time a second flask containing carbethoxymethylene triphenylphosphorane **367** (5.23 g, 15.0 mmol) in toluene (25 mL) was cooled to 0 °C under nitrogen. The prepared base was transferred slowly into the flask containing the phosphorane, the mixture was warmed to RT and stirred overnight. The reaction mixture was filtered through a plug of basic alumina to remove lithium ethoxide and the filtrate was concentrated to afford the title compound **364** as a light brown solid (4.08 g, 13.5 mmol, 90%).

mp 81–84 °C (CH_2Cl_2). (Lit 171–172 °C, diglyme).[123]

^1H NMR (300 MHz, $CDCl_3$)

δ_H ppm 7.68 (5H, m, 5 x $\mathbf{H}_{Ar}$), 7.60–7.58 (4H, m, 4 x $\mathbf{H}_{Ar}$) 7.53–7.44 (6H, m, 6 x $\mathbf{H}_{Ar}$).
(Also indicates some Ph_3P=O).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 132.5 (d, J = 12.3 Hz, $\mathbf{C}H_{Ar}$), 132.3 (d, J = 9.9 Hz, **C**=O), 131.4 (d, J = 11.0 Hz, $\mathbf{C}H_{Ar}$), 130.5 (d, J = 104.0 Hz, $\mathbf{C}_{Ar}$), 129.0 (d, J = 12.1 Hz, $\mathbf{C}H_{Ar}$). **C**=C=O is off scale for this NMR (–10.5 ppm).[161]

^{31}P NMR (121 MHz, $CDCl_3$)

δ_P ppm 6.07 (Ph_3**P**=C=C=O). Also shows 29.6 (Ph_3P=O).

LRMS (ES^+)

m/z 335 ($[M+H+MeOH]^+$, 100%).

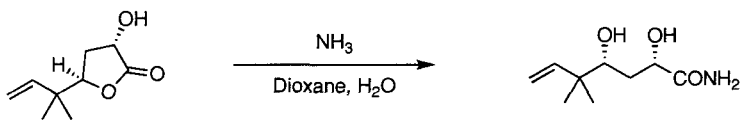
FT – IR (Neat)

cm^{-1} 2942 (w), 2091 (s), 1483 (w), 1435 (m).

Spectroscopic data are in agreement with the literature.[123]

rel-(2*S*,4*R*)-2,4-Dihydroxy-5,5-dimethylhept-6-enamide (**374**)

New compound.



309 **374**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_9H_{17}NO_3$
Molecular Weight: 187.24

A solution of lactone **309** (30 mg, 0.18 mmol) in 1,4-dioxane (1 mL) was treated with ammonia (35%, aq., 1 mL) and stirred at RT overnight. The mixture was concentrated and adsorbed onto silica. Purification by column chromatography on silica gel, eluting from 0–1% MeOH / EtOAc afforded the title compound **374** as a white solid (19 mg, 100 μmol, 56%).

mp 85–87 °C (methanol).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 5.87 (1H, dd, J = 17.8, 10.7 Hz, H_2C=C**H**), 5.04–4.97 (1H, dd, J = 17.8, 1.4 Hz, **H**HC=CH) 5.02–4.99 (1H, dd, J = 10.7, 1.4 Hz, H**H**C=CH), 4.14 (1H, dd, J = 8.0, 5.0 Hz, H_2NCOC**H**OH), 3.60 (1H, dd, J = 10.6, 1.9 Hz, $C(CH_3)_2$C**H**OH), 1.97 (1H, ddd, J = 14.3, 5.0, 1.9 Hz, C**H**H), 1.54 (1H, ddd, J = 14.3, 10.6, 8.0 Hz, CH**H**), 1.00 (6H, s, 2 x CH_3).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 180.0 (**C**=O), 146.4 (H_2**C**=CH), 112.8 (H_2**C**=CH), 78.5 (**C**HOH), 73.0 (**C**HOH), 42.5 (**C**$(CH_3)_2$), 37.3 (CH_2), 24.1 (CH_3), 22.4 (CH_3).

LRMS (ES^+)

m/z 210 ($[M+Na]^+$, 100%), 397 ([2M+Na], 20%).

HRMS (ES^+)

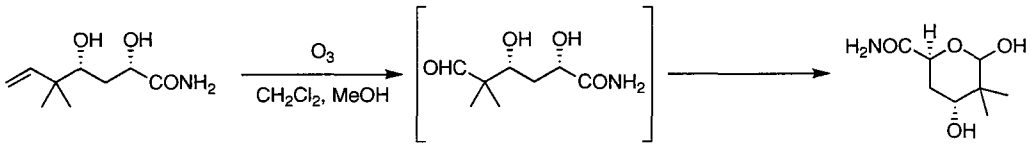
Found 210.1100, $[C_9H_{17}NO_3+Na]^+$ requires 210.1101 amu.

FT – IR (compressed solid)

cm^{-1} 3440 (br m), 3402 (br m), 3327 (br m), 3259 (br m), 3220 (br m), 2966 (m), 2932 (w), 2865 (w), 1679 (m), 1655 (s), 1589 (m), 1466 (w), 1413 (m).

rel-(2*S*,4*R*)-4,6-Dihydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxamide (**368**)

New compound.



374

Chemical Formula: $C_9H_{17}NO_3$
Molecular Weight: 187.24

368

Chemical Formula: $C_8H_{15}NO_4$
Molecular Weight: 189.21

Ozone (1–2% in oxygen) was passed through a solution of hydroxy amide **374** (100 mg, 0.53 mmol) in CH_2Cl_2 (30 mL) and methanol (5 mL) at –78 °C until a blue colour

persisted. The mixture was purged with oxygen for 20 min then a solution of PPh_3 (290 mg, 1.10 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was warmed to RT, tested for peroxides then concentrated. The crude residue was purified by column chromatography on silica gel, eluting from 0–1% MeOH / EtOAc to afford the title compound **368** as a white solid (64 mg, 0.34 mmol, 64%) as an inseparable 2:1 mixture of diastereoisomers.

mp 141–142 °C (methanol).

^{1}H NMR (400 MHz, CD_3OD) Peaks for the major diastereoisomer:

δ_H ppm 4.88 (1H, s, OC**H**OH), 4.34 (1H, dd, *J* = 8.3, 7.4 Hz, C**H**CONH$_2$), 3.64 (1H, br t, *J* = 2.5 Hz, C**H**OH), 1.89 (1H, d, *J* = 2.9 Hz C**H**H), 1.87 (1H, t, *J* = 2.3 Hz, CH**H**), 1.01 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$).

Peaks due to the minor diastereoisomer:
4.74 (1H, s, OC**H**OH), 4.57 (1H, dd, *J* = 10.8, 4.3 Hz, C**H**CONH$_2$), 2.08–1.95 (2H, m, C**H**$_2$), 1.09 (3H, s, C**H**$_3$), 0.93 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, CD_3OD) Peaks for the major diastereoisomer:

δ_C ppm 177.7 (**C**=O), 98.5 (**C**HOH), 74.8 (**C**HOH), 72.5 (**C**HCONH$_2$), 39.7 (**C**(CH$_3$)$_2$), 33.9 (**C**H$_2$), 22.1 (**C**H$_3$), 18.3 (**C**H$_3$).

Peaks due to the minor diastereoisomer:
178.0 (**C**=O), 100.9 (**C**HOH), 73.8 (**C**HOH), 65.6 (**C**HCONH$_2$), 38.1 (**C**(CH$_3$)$_2$), 33.0 (**C**H$_2$), 24.3 (**C**H$_3$), 21.4 (**C**H$_3$),

LRMS (ES^+)

m/z 212 ($[M+Na]^+$, 100%), 401 ($[2M+Na]^+$, 27%)

HRMS (ES^+)

Found 212.0890, $[C_8H_{15}NO_4+Na]^+$ requires 212.0893 amu.

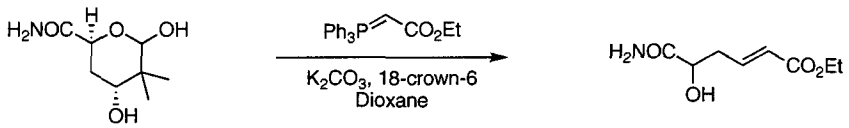
FT – IR (CH_2Cl_2 solution)

cm^{-1} 3470 (w), 3395 (br w), 3330 (br w), 3259 (br w), 3201 (br w), 2953 (w), 2930 (w), 2896 (w), 2873 (w), 1693 (s), 1659 (s), 1594 (m), 1481 (m), 1454 (m).

CHN Found C 50.73%, H 8.30%, N 7.32%. Calculated C 50.78%, H 7.99%, N 7.40%.

Ethyl (2*E*)-6-amino-5-hydroxy-6-oxohex-2-enoate (**377**)

New compound.



368 **377**

Chemical Formula: $C_8H_{15}NO_4$
Molecular Weight: 189.21

Chemical Formula: $C_8H_{13}NO_4$
Molecular Weight: 187.19

A mixture of **368** (90 mg, 0.48 mmol), K_2CO_3 (79 mg, 0.57 mmol), ylide **367** (199 mg, 0.57 mmol) and 18-crown-6 (26 mg, 20 mol%) in 1,4-dioxane (5 mL) was heated at reflux for 16 h under nitrogen. The mixture was cooled to RT, concentrated and purified by column chromatography on silica gel, eluting from 0–5% MeOH / EtOAc. The product was re-purified in the same manner, eluting with 0–5% MeOH / $CHCl_3$ to afford **377** as a white solid (7 mg, 0.037 mmol, 8%).

mp 43 – 45 ° C (methanol).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 6.96 (1H, dt, J = 15.6, 7.4 Hz, $H_2CC\mathbf{H}$=C), 6.52 (1H, br s, N**H**H), 5.98 (1H, dt, J = 15.6, 1.4 Hz, **CH**CO_2Et), 5.59 (1H, br s, NH**H**), 4.29 (1H, dd (overlapped), J = 4.3, 3.9 Hz, **CH**OH), 4.27 (2H, q, J = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 2.88 (1H, br d, J = 4.3 Hz, O**H**), 2.81 (1H, dddd, J = 14.8, 7.4, 3.9, 1.4 Hz, CH**H**), 2.59 (1H, dtd, J = 14.8, 7.4, 1.4 Hz, C**H**H), 1.30 (3H, t, J = 7.2 Hz, $OCH_2C\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 174.9 (**C**ONH_2), 166.3 (**C**O_2Et), 143.2 (**HC**=$CHCO_2Et$), 125.4 (HC=**C**HCO_2Et), 70.8 (**C**HOH), 60.7 (OCH_2CH_3), 37.6 (**C**H_2), 14.4 (OCH_2CH_3).

LRMS (ES^+)

m/z 210 ($[M+Na]^+$, 100%).

HRMS (ES^+)

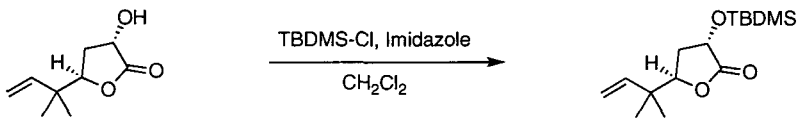
Found 210.0738, $[C_8H_{13}NO_4+Na]^+$ requires 210.0737 amu.

FT – IR (neat)

cm^{-1} 3425 (br m), 3337 (br m), 2982 (w), 2852 (w), 1658 (br s), 1584 (m), 1446 (w).

rel-(3*S*,5*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(1,1-dimethylprop-2-en-1-yl)dihydrofuran-2(3*H*)-one (**379**)

New compound.



309 **379**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_{15}H_{28}O_3Si$
Molecular Weight: 284.47

Hydroxylactone **309** (112 mg, 0.66 mmol) in CH_2Cl_2 (3 mL) was added to a solution of imidazole (89 mg, 1.32 mmol) and TBDMS-Cl (129 mg, 0.86 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 56 h at RT under nitrogen and then concentrated. Purification by column chromatography on silica gel eluting with 5% EtOAc / petrol afforded the title compound **379** as a colourless oil (82 mg, 0.29 mmol, 44%).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 5.79 (1H, dd, J = 17.4, 10.8 Hz, H_2C=C**H**), 5.12 (1H, dd, J = 10.8, 1.1 Hz, **H**HC=CH), 5.10 (1H, dd, J = 17.4, 1.1 Hz, H**H**C=CH), 4.40 (1H, t, J = 7.0 Hz, OC**H**), 4.31 (1H, dd, J = 7.0, 4.2 Hz, OC**H**), 2.14 (1H, app. td, J = 13.6, 7.0 Hz, C**H**H), 2.04 (1H, ddd, J = 13.6, 7.0, 4.2 Hz, CH**H**), 1.09 (3H, s, C**H**$_3$), 1.06 (3H, s, C**H**$_3$), 0.91 (9H, s, C(C**H**$_3$)$_3$), 0.15 (6H, s, 2 x SiC**H**$_3$).

^{13}C NMR ($CDCl_3$)

δ_C ppm 175.8 (**C**=O), 142.0 (H_2C=**C**H), 114.9 (H_2**C**=CH), 85.1 (O**C**H), 69.2 (SiO**C**H), 40.1 (**C**(CH$_3$)$_2$), 33.8 (**C**H$_2$), 25.9 (C(**C**H$_3$)$_3$), 23.2 (**C**H$_3$), 22.8 (**C**H$_3$), 18.4 (**C**(CH$_3$)$_3$), –4.6 (Si**C**H$_3$), –5.1 (Si**C**H$_3$).

LRMS (ES$^+$)

m/z 307 ([M+Na]$^+$, 100%), 591 ([2M+Na]$^+$, 35%).

HRMS (ES$^+$)

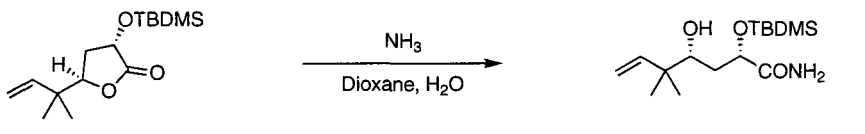
Found 307.1704, [$C_{15}H_{28}O_3Si$+Na]$^+$ requires 307.1700 amu.

FT – IR ($CHCl_3$ solution)

cm^{-1} 2954 (m), 2930 (m), 2857 (m), 1784 (s), 1472 (m), 1417 (w).

rel-(2*S*,4*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylhept-6-enamide (**380**)

New compound.



379 **380**

Chemical Formula: $C_{15}H_{28}O_3Si$
Molecular Weight: 284.47

Chemical Formula: $C_{15}H_{31}NO_3Si$
Molecular Weight: 301.50

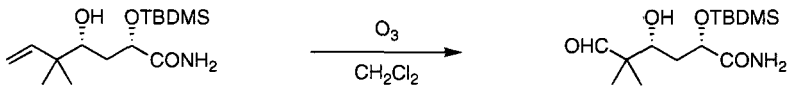
To a solution of **379** (78 mg, 0.27 mmol) in 1,4-dioxane (6 mL) was added ammonia (35%, aq., 6 mL). The mixture was stirred at RT under nitrogen for 40 h and then nitrogen was bubbled through to remove some of the ammonia. The mixture was

concentrated to a white solid and purified by column chromatography on silica gel, eluting first with Et_2O and then with EtOAc to afford the title compound **380** as an oily solid (69 mg, 0.23 mmol, 85%).

^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	6.55 (1H, br s, N**H**H), 5.85 (1H, br s, NH**H**), 5.83 (1H, dd, *J* = 17.4, 10.9 Hz, H_2C=C**H**), 5.04 (1H, dd, *J* = 10.9, 1.3 Hz, **H**HC=CH), 5.01 (1H, dd, *J* = 17.4, 1.3 Hz, H**H**C=CH), 4.30 (1H, t, *J* = 5.9 Hz, OC**H**), 3.60 (1H, br q, *J* = 5.9 Hz, C**H**OH), 2.40 (1H, br d, *J* = 5.1 Hz, O**H**), 1.84 (2H, app. t, *J* = 5.9 Hz, C$\mathbf{H}_2$), 1.02 (3H, s, C$\mathbf{H}_3$), 1.01 (3H, s, C$\mathbf{H}_3$), 0.94 (9H, s, C(C$\mathbf{H}_3$)$_3$), 0.13 (3H, s, SiC$\mathbf{H}_3$), 0.12 (3H, s, SiC$\mathbf{H}_3$).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	177.5 (**C**=O), 145.2 (H_2C=**C**H), 113.1 (H_2**C**=CH), 74.5 (**O**CH), 72.1 (**O**CH), 41.4 (**C**(CH$_3$)$_2$), 37.7 (**C**H$_2$), 25.9 (C(**C**H$_3$)$_3$), 23.3 (**C**H$_3$), 22.5 (**C**H$_3$), 18.2 (**C**(CH$_3$)$_3$), –4.7 (Si**C**H$_3$), –5.1 (Si**C**H$_3$).
LRMS	(ES^+)
m/z	302 ($[M+H]^+$, 100%), 324 ($[M+Na]^+$, 50%), 603 ($[2M+H]^+$, 15%), 625 ($[2M+Na]^+$, 75%).
HRMS	(ES^+)
	Found 324.1961, $[C_{15}H_{31}NO_3Si+Na]^+$ requires 324.1965 amu.
FT – IR	($CHCl_3$ solution)
cm^{-1}	3478 (w), 3305 (br), 2956 (m), 2930 (m), 2858 (m), 1678 (s), 1583 (w), 1471 (m), 1414 (m).

rel-(2*S*,4*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethyl-6-oxohexanamide (**381**)

New compound.



380 **381**

Chemical Formula: $C_{15}H_{31}NO_3Si$
Molecular Weight: 301.50

Chemical Formula: $C_{14}H_{29}NO_4Si$
Molecular Weight: 303.47

Ozone (1–2% in oxygen) was passed through a solution of amide **380** (200 mg, 0.86 mmol) in CH_2Cl_2 (50 mL) at –78 °C until a blue colour persisted (5 min). The mixture was purged with oxygen for 20 min and then PPh_3 (452 mg, 1.73 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at –78 °C for 30 min and then warmed to RT, tested for peroxides and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 20% Et_2O / EtOAc to afford the title compound **381** as a white solid (28 mg, 0.09 mmol, 11% pure and 101 mg, 0.33 mmol, 39% impure).

mp 95–98 °C (methanol).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 9.57 (1H, s, C**H**O), 6.58 (1H, br s, N**H**H), 5.97 (1H, br s, NH**H**), 4.34 (1H, dd, *J* = 7.5, 5.1 Hz, OC**H**), 4.03 (1H, ddd, *J* = 10.9, 4.8, 2.0 Hz, C**H**OH), 3.10 (1H, d, *J* = 4.8 Hz, O**H**), 1.95 (1H, ddd, *J* = 14.0, 10.9, 5.1 Hz, C**H**H), 1.75 (1H, ddd, *J* = 14.0, 7.5, 2.0 Hz, CH**H**), 1.08 (3H, s, C**H**$_3$), 1.03 (3H, s, C**H**$_3$), 0.94 (9H, s, C(C**H**$_3$)$_3$), 0.14 (3H, s, SiC**H**$_3$), 0.13 (3H, s, SiC**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 206.2 (**C**HO), 177.2 (**C**ONH$_2$), 71.6 (O**C**H), 71.5 (O**C**H), 50.3 (**C**(CH$_3$)$_2$), 37.4 (**C**H$_2$), 25.9 (C(**C**H$_3$)$_3$), 18.9 (**C**H$_3$), 18.1 (**C**(CH$_3$)$_3$), 16.8 (**C**H$_3$), –4.7 (Si**C**H$_3$), –5.1 (Si**C**H$_3$).

LRMS (ES^+)

m/z 326 ($[M+Na]^+$, 70%), 358 ($[M+Na+MeOH]^+$, 100%), 661 ($[2M+Na+MeOH]^+$, 50%), 693 ($[2M+Na+2MeOH]^+$, 80%).

HRMS (ES^+)

Found 326.1749, $[C_{14}H_{29}NO_4Si+Na]^+$ requires 326.1758 amu.

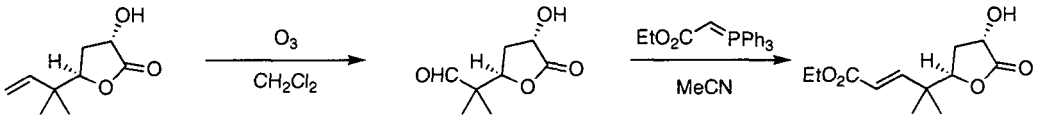
FT – IR (compressed solid)

cm^{-1} 3495 (w), 3372 (m), 3270 (m), 2106 (m), 2971 (m), 2922 (w), 2873 (w), 1660 (s), 1602 (m), 1503 (w), 1481 (w), 1463 (w), 1443 (w), 1413 (w).

Ethyl (2*E*)-4-[(2*R*,4*S*)-4-hydroxy-5-oxotetrahydrofuran-2-yl]-4-methylpent-2-enoate (**384**)

Method A: Wittig olefination

New compound.



309 **314** **384**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

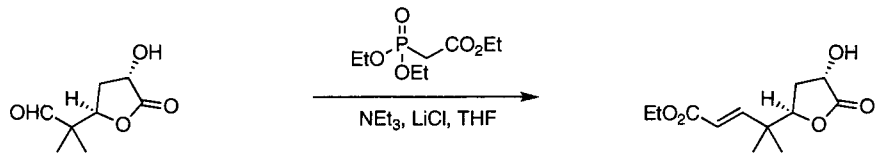
Ozone (1–2% in oxygen) was passed through a solution of lactone **309** (400 mg, 2.36 mmol) in CH_2Cl_2 (50 mL) at –78 °C until a blue colour persisted (15 min). The mixture was purged with oxygen for 20 min and then PPh_3 (1.24 g, 4.71 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred for 1 h at –78 °C, tested for peroxides then warmed to RT and concentrated. NMR confirmed the presence of an aldehyde so the crude product was dissolved in acetonitrile (25 mL) and ylide **367** (871 mg, 2.5 mmol) was added. The mixture was heated at reflux under argon for 48 h and then further ylide (617 mg, 0.75 equiv, 1.77 mmol) was added. After 40 h at reflux, further ylide (411 mg, 0.5 equiv, 1.18 mmol) was added and the reaction heated at reflux for a further 20 h. Upon cooling to RT, the mixture was concentrated and purified by column chromatography on silica gel, eluting with Et_2O to afford the title compound **384** as a colourless oil (410 mg, 1.69 mmol, 72%, (2 steps)).

$[\alpha]_D^{26}$	–26.0 (c = 0.15, l = 2, MeOH).
^{1}H NMR	(400 MHz, $CDCl_3$)
δ_H ppm	6.86 (1H, d, J = 16.0 Hz, $EtO_2CHC=C\mathbf{H}$), 5.87 (1H, d, J = 16.0 Hz, $EtO_2C\mathbf{H}C=CH$), 4.49 (1H, dd, J = 7.9, 5.8 Hz, O**CH**), 4.40 (1H, ddd, J = 8.3, 6.0, 2.8 Hz, **CH**OH), 4.20 (2H, q, J = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 3.09 (1H, d, J = 2.8 Hz, O**H**), 2.28 (1H, ddd, J = 14.0, 8.3, 5.8 Hz, C**H**H), 2.21 (1H, ddd, J = 14.0, 7.9, 6.0 Hz, CH**H**), 1.30 (3H, t, J = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 1.15 (3H, s, $C\mathbf{H}_3$), 1.13 (3H, s, $C\mathbf{H}_3$).
^{13}C NMR	(100 MHz, $CDCl_3$)
δ_C ppm	176.9 (**C**=O), 166.5 ($\mathbf{C}O_2Et$), 150.9 ($EtO_2CHC=\mathbf{C}H$), 121.8 ($EtO_2CH\mathbf{C}=CH$), 84.4 (O**C**H), 67.8 (**C**HOH), 60.8 ($O\mathbf{C}H_2CH_3$), 40.5 ($\mathbf{C}(CH_3)_2$), 31.7 ($\mathbf{C}H_2$), 22.7 (2 x $\mathbf{C}H_3$), 14.4 ($OCH_2\mathbf{C}H_3$).
LRMS	(ES^+)
m/z	265 ($[M+Na]^+$, 100%), 507 ($[2M+Na]^+$, 50%).
HRMS	(ES^+)
	Found 265.1047, $[C_{12}H_{18}O_5+Na]^+$ requires 265.1046 amu.
FT – IR	(neat)
cm^{-1}	3446 (br m), 2975 (m), 1771 (s), 1713 (s), 1650 (s), 1468 (m).

Ethyl (2*E*)-4-[(2*R*,4*S*)-4-hydroxy-5-oxotetrahydrofuran-2-yl]-4-methylpent-2-enoate (**384**)

Method B: Horner-Wadsworth-Emmons olefination

New compound.



314 **384**

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

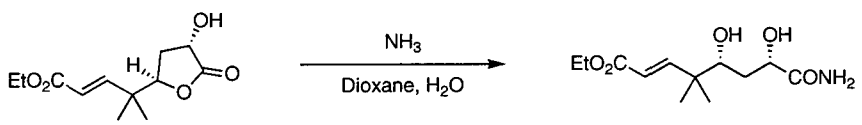
Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

Procedure based on the method reported by Rathke.[126] To triethyl phosphonoacetate (1.03 g, 0.91 mL, 4.60 mmol) in THF (10 mL) was added LiCl (244 mg, 5.75 mmol) and NEt_3 (582 mg, 0.80 mL, 5.75 mmol). The mixture was stirred at RT under argon and a solution of **314** (660 mg, 3.83 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at RT for 36 h and then quenched with HCl (2 M, aq., 10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic phases washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 60% EtOAc / petrol to afford the title compound **384** as a colourless oil (370 mg, 1.53 mmol, 40%).

Spectroscopic data are in agreement with that reported above.

Ethyl (2*E*,5*R*,7*S*)-8-amino-5,7-dihydroxy-4,4-dimethyl-8-oxooct-2-enoate (**385**)

New compound.



384 **385**

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of **384** (40 mg, 170 μmol) in 1,4-dioxane (10 mL) was added ammonia (28%, aq., 1 mL). The reaction mixture was stirred at RT in air for 2 h and then

concentrated. Purification by column chromatography on silica gel, eluting with 1–2% methanol / EtOAc afforded the title compound **385** as a thick colourless oil (27 mg, 100 μmol, 62%).

$[\alpha]_D^{28}$ +4.0 (c = 0.315, l = 2, MeOH).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 7.03 (1H, d, J = 16.1 Hz, $EtO_2CHC=CH$), 5.81 (1H, d, J = 16.1 Hz, $EtO_2CHC=CH$), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.15 (1H, dd, J = 7.8, 5.0 Hz, CHOH), 3.70 (1H, dd, J = 10.6, 2.0 Hz, CHOH), 1.93 (1H, ddd, J = 14.2, 5.0, 2.0 Hz, CHH), 1.55 (1H, ddd, J = 14.2, 10.6, 7.8 Hz, CHH), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.08 (3H, s, CH_3), 1.07 (3H, s, CH_3).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 180.0 ($CONH_2$), 168.6 (CO_2Et), 156.9 ($EtO_2CHC=CH$), 120.5 ($EtO_2CHC=CH$), 77.8 (CHOH), 72.7 (CHOH), 61.6 (OCH_2CH_3), 42.9 ($C(CH_3)_2$), 37.7 (CH_2), 23.6 (CH_3), 22.9 (CH_3), 14.7 (OCH_2CH_3).

LRMS (ES^+)

m/z 282 ($[M+Na]^+$, 100%), 541 ($[2M+Na]^+$, 25%).

HRMS (ES^+)

Found 282.1310, $[C_{12}H_{21}NO_5+Na]^+$ requires 282.1312 amu.

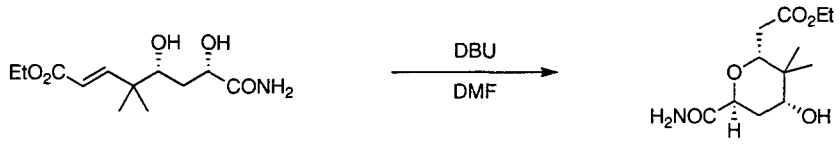
FT – IR (neat)

cm^{-1} 3338 (br m), 2971 (m), 1655 (s), 1650 (s), 1466 (m), 1420 (m).

Ethyl [(2*R*,4*R*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**387**)

Method A: DBU / DMF

New compound.



385 **387**

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of **385** (50 mg, 0.19 mmol) in DMF (2 mL) was added DBU (0.05 mL, 0.38 mmol). The reaction was stirred at RT for 16 h and then quenched by addition of HCl (2 M, aq., 5 mL). The mixture was extracted with EtOAc (4 x 10 mL) and the combined organic phases washed with water (4 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue indicated a reaction d.r. of 14:1 and was purified by column chromatography on silica gel, eluting with EtOAc to afford the title compound **387** as an enantiomerically pure white solid (30 mg, 120 μmol, 60%). A sample was crystallised from CH_2Cl_2 / petrol for X-ray crystallography.

mp 147–151 °C (CH_2Cl_2 / petrol).

$[\alpha]_D^{26}$ +93.2 (c = 0.28, l = 2, MeOH).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 4.37 (1H, dd, J = 6.9, 1.6 Hz, $H_2NCOC\mathbf{H}$), 4.18 (1H, q, J = 7.2 Hz, $OC\mathbf{H}HCH_3$) 4.16 (1H, q, J = 7.2 Hz, $OCH\mathbf{H}CH_3$), 3.71 (1H, dd, J = 10.7, 2.1 Hz, $EtO_2CCH_2C\mathbf{H}$), 3.28 (1H, dd, J = 11.9, 4.6 Hz, $C\mathbf{H}OH$), 2.64 (1H, dd, J = 17.2, 2.1 Hz, $C\mathbf{H}HCO_2Et$), 2.51 (1H, dd, J = 17.2, 10.7 Hz, $CH\mathbf{H}CO_2Et$), 2.36 (1H, ddd, J = 13.2, 4.6, 1.6 Hz, $C\mathbf{H}H$), 1.81 (1H, ddd, J = 13.2, 11.9, 6.9 Hz, $CH\mathbf{H}$), 1.27 (3H, t, J = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 0.91 (3H, s, $C\mathbf{H}_3$), 0.88 (3H, s, $C\mathbf{H}_3$).

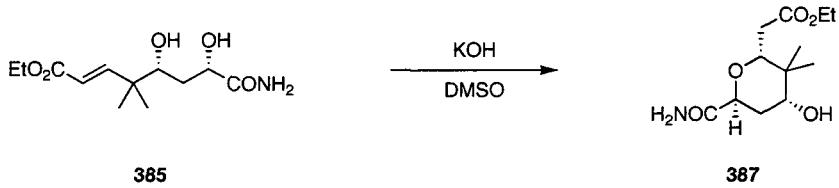
^{13}C NMR	(100 MHz, CD_3OD)
δ_C ppm	176.7 (**C**=O), 174.8 (**C**=O), 77.8 (**C**HCH$_2$CO$_2$Et), 74.7 (**C**HCONH$_2$), 72.6 (**C**HOH), 62.0 (O**C**H$_2$CH$_3$), 38.9 (**C**(CH$_3$)$_2$), 35.4 (**C**H$_2$CO$_2$Et), 30.3 (**C**H$_2$), 22.9 (**C**H$_3$), 14.5 (OCH$_2$**C**H$_3$), 12.7 (**C**H$_3$).
LRMS	(ES^+)
m/z	282 ([M+Na]$^+$, 100%), 541 ([2M+Na]$^+$, 20%).
HRMS	(ES^+)
	Found 282.1315, [$C_{12}H_{21}NO_5$+Na]$^+$ requires 282.1312 amu.
FT – IR	(compressed solid)
cm^{-1}	3453 (br w), 3405 (br w), 3332 (br w), 3304 (br w), 2994 (w), 2978 (w), 2966 (w), 2957 (w), 2877 (w), 1730 (s), 1674 (s), 1650 (m), 1594 (m), 1473 (w), 1439 (w), 1401 (m).
CHN	Found C 55.32%, H 8.19%, N 5.12%. Calculated C 55.58%, H 8.16%, N 5.40%.

X-ray crystallography

Ethyl [(2*R*,4*R*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**387**)

Method B: KOH / DMSO

New compound.



385

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

387

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

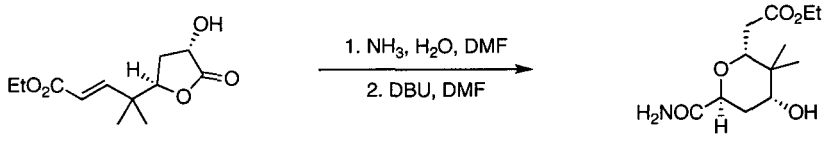
Ester **385** (10 mg, 39 μmol) and KOH (50 mg, 0.88 mmol) were dissolved in d_6-DMSO (0.75 mL) and the reaction monitored by NMR (complete within 10 min). The reaction mixture was adsorbed onto silica gel and purified by column chromatography, eluting with EtOAc to afford the title compound **387** as a white solid (7.4 mg, 29 μmol, 74%).

Spectroscopic data are in agreement with that reported above.

Ethyl [(2*R*,4*R*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**387**)

Method C: Direct from **384**, NH_3 and DBU.

New compound.



384

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

387

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of **384** (15 mg, 77 μmol) in DMF (1 mL) was added NH_3 (28%, aq., 100 μL) and the mixture was stirred at RT for 72 h. DBU (35 mg, 30 μL, 0.23 mmol) was added and the mixture stirred for 6 h at RT. The reaction mixture was poured into water (3 mL) and diluted with EtOAc (10 mL). The phases were separated and the

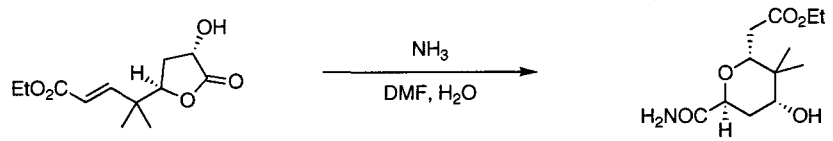
organic phase washed with water (3 x 1 mL) and brine (2 x 1 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with EtOAc to afford the title compound **387** as a thin white film (7 mg, 27 μmol, 44%).

Spectroscopic data are in agreement with that reported above.

Ethyl [(2*R*,4*R*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**387**)

Method C: Direct from **384**, NH_3.

New compound.



384 **387**

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

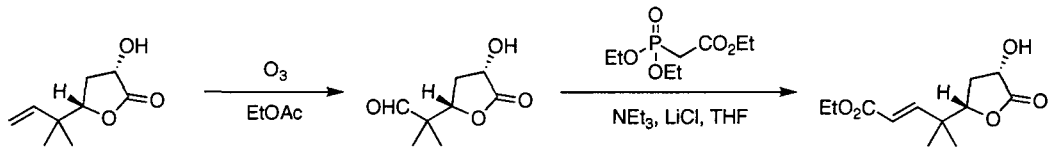
Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of **384** (25 mg, 0.10 mmol) in DMF (1 mL) was added NH_3 (28%, aq., 1 mL). The mixture was stirred at RT for 24 h and then concentrated. Purification by column chromatography on silica gel, eluting with EtOAc afforded first desired THP **387** (2.3 mg, 8.8 μmol, 9%), followed by diol **385** (4.1 mg, 16 μmol, 16%).

Spectroscopic data are in agreement with that reported above.

2-[(2*S*,4*S*)-4-Hydroxy-5-oxotetrahydrofuran-2-yl]-2-methylpropanal (**390**) and ethyl (2*E*)-4-[(2*S*,4*S*)-4-hydroxy-5-oxotetrahydrofuran-2-yl]-4-methylpent-2-enoate (**391**)

New compounds.



351 **390** **391**

Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

Chemical Formula: $C_8H_{12}O_4$
Molecular Weight: 172.18

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

Ozone (1–2% in oxygen) was passed through a solution of **351** (800 mg, 4.70 mmol) in EtOAc (50 mL) at –78 °C until a blue colour persisted (20 min). The mixture was purged with oxygen for 20 min and then dimethyl sulfide (876 mg, 1.00 mL, 14.10 mmol) was added and the mixture warmed to RT. The mixture was stirred at RT for 16 h and then PPh_3 (1.85 g, 7.05 mmol) was added. After 1 h, the reaction mixture was washed with water (2 x 15 mL) and brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. It did not prove possible to remove triphenylphosphine oxide from the product by silica gel chromatography so the contaminated product **390** was immediately advanced to the Horner-Wadsworth-Emmons reaction. Procedure based on the method reported by Rathke.[126] To a solution of triethyl phosphonoacetate (1.26 g, 1.10 mL, 5.64 mmol) in THF (5 mL) was added LiCl (299 mg, 7.05 mmol) and NEt_3 (0.98 mL, 7.05 mmol). The reaction mixture was stirred at RT under argon and **390** (assumed 4.7 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 16 h at RT and then quenched by addition of HCl (2 M, aq., 10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water (10 mL) and brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with Et_2O to afford the title compound **391** as a light yellow oil (520 mg, 2.15 mmol, 46% (2 steps)).

$[\alpha]_D^{26}$ +8.3 (c = 0.26, l = 2, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 6.92 (1H, d, J = 16.1 Hz, EtO_2CHC=C**H**), 5.88 (1H, d, J = 16.1 Hz, EtO_2C**H**C=CH), 4.54 (1H, dd, J = 11.1, 8.5 Hz, OC**H**), 4.20 (2H, q, J = 7.2 Hz, O**C**H_2CH_3), 4.20 (1H, dd, J = 11.1, 5.3 Hz, OC**H**), 2.75 (1H, br s, O**H**), 2.54 (1H, ddd, J = 12.6, 8.5, 5.3 Hz, C**H**H), 1.94 (1H, dt, J = 12.6, 11.1 Hz, CH**H**), 1.30 (3H, t, J = 7.2 Hz, OCH_2C**H**$_3$), 1.17 (3H, s, C**H**$_3$), 1.15 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 177.0 (C=O), 166.6 (**C**O_2Et), 151.2 (EtO_2CHC=**C**H), 121.6 (EtO_2**C**HC=CH), 82.1 (O**C**H), 68.8 (**C**HOH), 60.8 (O**C**H_2CH_3), 39.8 (**C**$(CH_3)_2$), 32.7 (**C**H_2), 22.7 (**C**H_3), 22.1 (**C**H_3), 14.4 (OCH_2**C**H_3).

LRMS (ES^+)

m/z 265 ($[M+Na]^+$, 100%), 507 ($[2M+Na]^+$, 30%).

HRMS (ES^+)

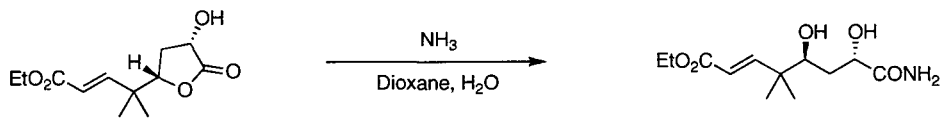
Found 265.1046, $[C_{12}H_{18}O_5+Na]^+$ requires 265.1046 amu.

FT – IR (neat)

cm^{-1} 3434 (br w), 2976 (w), 2941 (w), 2907 (w), 2881 (w), 1778 (s), 1712 (s), 1651 (m), 1467 (w).

Ethyl (2*E*,5*S*,7*S*)-8-amino-5,7-dihydroxy-4,4-dimethyl-8-oxooct-2-enoate (**392**)

New compound.



391 **392**

Chemical Formula: $C_{12}H_{18}O_5$
Molecular Weight: 242.27

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of **391** (493 mg, 2.04 mmol) in 1,4-dioxane (40 mL) was added NH_3 (28%, aq., 4 mL). The mixture was stirred at RT for 20 h then concentrated.

Purification by column chromatography on silica gel, eluting with 1–3% MeOH / EtOAc afforded the title compound **392** as a white solid (485 mg, 1.87 mmol, 92%).

mp 39–42 °C (methanol).

$[\alpha]_D^{28}$ –34.5 (c = 0.32, l = 2, MeOH).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 7.03 (1H, d, J = 16.1 Hz, $EtO_2CHC{=}C\mathbf{H}$), 5.81 (1H, d, J = 16.1 Hz, $EtO_2C\mathbf{H}C{=}CH$), 4.20 (1H, dd, J = 9.5, 3.0 Hz, C**H**OH), 4.17 (2H, q, J = 7.2 Hz, $OC\mathbf{H}_2CH_3$), 3.63 (1H, dd, J = 10.9, 1.9 Hz, C**H**OH), 1.73 (1H, ddd, J = 14.0, 10.9, 3.0 Hz, C**H**H), 1.62 (1H, ddd, J = 14.0, 9.5, 1.9 Hz, CH**H**), 1.28 (3H, t, J = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 1.08 (3H, s, $C\mathbf{H}_3$), 1.07 (3H, s, $C\mathbf{H}_3$).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 181.1 (**C**ONH_2), 168.7 (**C**O_2Et), 157.2 ($EtO_2CHC{=}\mathbf{C}H$), 120.3 ($EtO_2C\mathbf{H}C{=}CH$), 75.3 (**C**HOH), 70.4 (**C**HOH), 61.6 ($O\mathbf{C}H_2CH_3$), 42.8 ($\mathbf{C}(CH_3)_2$), 38.1 ($\mathbf{C}H_2$), 23.8 ($\mathbf{C}H_3$), 22.9 ($\mathbf{C}H_3$), 14.7 ($OCH_2\mathbf{C}H_3$).

LRMS (ES^+)

m/z 282 ($[M+Na]^+$, 15%), 541 ($[2M+Na]^+$, 100%).

HRMS (ES^+)

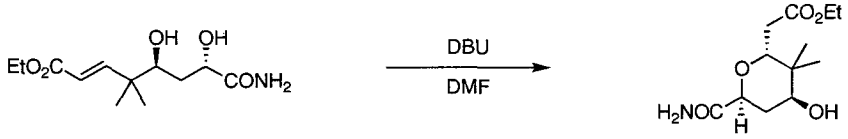
Found 282.1314, $[C_{12}H_{21}NO_5+Na]^+$ requires 282.1312 amu.

FT – IR (compressed solid)

cm^{-1} 3339 (br s), 2964 (m), 2929 (m), 2903 (w), 2877 (w), 1716 (s), 1683 (s), 1650 (s), 1576 (m), 1466 (m), 1448 (m), 1422 (m).

Ethyl [(2*R*,4*S*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**393**)

New compound.



392 **393**

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

A solution of **392** (100 mg, 0.39 mmol) in DMF (2 mL) was treated with DBU (148 mg, 150 μL, 0.98 mmol) and stirred at RT for 24 h. HCl (2 M, aq., 1 mL) was added and the mixture extracted with EtOAc (4 x 10 mL). The combined organic phases were washed with water (2 x 5 mL) and brine (2 x 5 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography on silica gel, eluting with 80% EtOAc / petrol afforded the title compound **393** as an enantiomerically pure white solid (35 mg, 0.137 mmol, 35%).

mp 120–123 °C (EtOAc).

$[\alpha]_D^{26}$ +55.5 (c = 0.345, l = 2, MeOH).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 4.31 (1H, dd, J = 8.3, 5.5 Hz, C**H**CH_2CO_2Et), 4.11–4.22 (3H, m, O**C**H_2CH_3, **CH**$CONH_2$), 3.53 (1H, t, J = 4.3 Hz, **CH**OH), 2.54 (2H, m, **C**H_2CO_2Et), 2.07–2.17 (2H, m, **C**H_2), 1.26 (3H, t, J = 7.1 Hz, OCH_2**C**H_3), 0.94 (6H, s, 2 x **C**H_3).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 178.3 (**C**=O), 174.7 (**C**=O), 74.6 (**C**HCH_2CO_2Et), 72.8 (**C**HOH), 72.3 (**C**$HCONH_2$), 62.1 (O**C**H_2CH_3), 37.4 (**C**$(CH_3)_2$), 35.3 (**C**H_2CO_2Et), 31.0 (**C**H_2), 22.7 (**C**H_3), 20.6 (**C**H_3), 14.6 (OCH_2**C**H_3).

LRMS (ES^+)

m/z 260 ($[M+H]^+$, 25%), 282 ($[M+Na]^+$, 100%), 541 ($[2M+Na]^+$, 20%).

HRMS (ES^+)

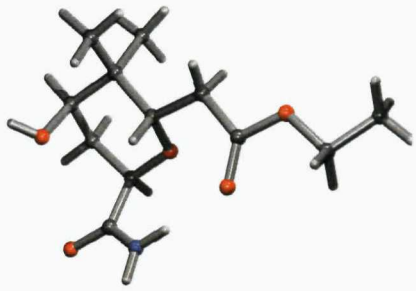
Found 282.1313, $[C_{12}H_{21}NO_5+Na]^+$ requires 282.1312 amu.

FT – IR (compressed solid)

cm^{-1} 3420 (m), 3294 (br m), 2990 (w), 2962 (w), 2942 (w), 2911 (w), 2877 (w), 1727 (s), 1670 (s), 1651 (m), 1595 (m), 1401 (m).

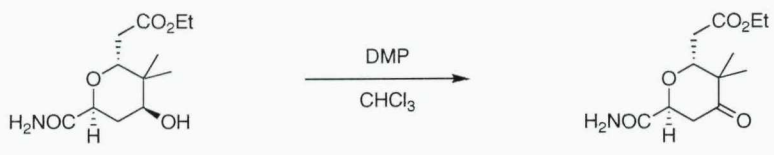
CHN Found C 55.25%, H 8.23%, N 5.19%. Calculated C 55.58%, H 8.16%, N 5.40%.

X-ray crystallography



Ethyl [(2*R*,6*S*)-6-carbamoyl-3,3-dimethyl-4-oxotetrahydro-2*H*-pyran-2-yl] acetate (**394**)

New compound.



393 **394**

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

Chemical Formula: $C_{12}H_{19}NO_5$
Molecular Weight: 257.28

To a solution of **393** (70 mg, 0.27 mmol) in $CHCl_3$ (3 mL) was added Dess-Martin periodinane (149 mg, 0.35 mmol) at RT under argon. After 2 h, further DMP (23 mg, 54 μmol) was added and after a further 1 h, the reaction mixture was filtered through

Celite®, concentrated and purified by column chromatography on silica gel twice, first eluting with 80% EtOAc / petrol and second with 50% EtOAc / petrol to afford the title compound as a colourless oil (51 mg, 0.199 mmol, 73%).

$[\alpha]_D^{28}$ +49.1 (c = 0.218, l = 2, MeOH).

^{1}H NMR (400 MHz, CD_3OD)

δ_H ppm 4.62 (1H, dd, J = 7.4, 6.4 Hz, C**H**$CONH_2$), 4.29 (1H, dd, J = 9.1, 4.0 Hz, C**H**CH_2CO_2Et), 4.26–4.12 (2H, m, O**C**H_2CH_3), 2.94 (1H, dd, J = 15.4, 6.4 Hz, C**H**H), 2.83 (1H, dd, J = 15.4, 7.4 Hz, CH**H**), 2.67 (1H, dd, J = 16.7, 4.0 Hz, C**H**HCO_2Et), 2.61 (1H, dd, J = 16.7, 9.1 Hz, CH**H**CO_2Et), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.10 (3H, s, CH_3), 1.06 (3H, s, CH_3).

^{13}C NMR (100 MHz, CD_3OD)

δ_C ppm 211.6 (CH_2**C**=OC), 175.8 (**C**=O), 173.8 (**C**=O), 78.1 (**C**HCH_2CO_2Et), 74.2 (**C**$HCONH_2$), 62.2 (OCH_2CH_3), 49.5 (**C**$(CH_3)_2$) 38.7 (**C**H_2C=OC), 35.6 (**C**H_2CO_2Et), 20.9 (**C**H_3), 19.0 (**C**H_3), 14.5 (OCH_2**C**H_3).

LRMS (ES^+)

m/z 258 ($[M+H]^+$, 40%), 280 ($[M+Na]^+$, 100%), 537 ($[2M+Na]^+$, 20%).

HRMS (ES^+)

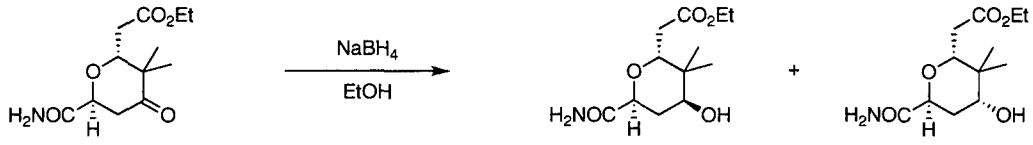
Found 280.1157, $[C_{12}H_{19}NO_5+Na]^+$ requires 280.1155 amu.

FT – IR (neat)

cm^{-1} 3390 (br w), 3187 (br w), 2979 (w), 2933 (w), 2881 (w), 1715 (s), 1685 (s), 1601 (w), 1468 (w).

Ethyl [(2*R*,4*R*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**387**) and ethyl [(2*R*,4*S*,6*S*)-6-carbamoyl-4-hydroxy-3,3-dimethyltetrahydro-2*H*-pyran-2-yl]acetate (**393**)

New compounds.



394 **393** **387**

Ratio 1:1

Chemical Formula: $C_{12}H_{19}NO_5$
Molecular Weight: 257.28

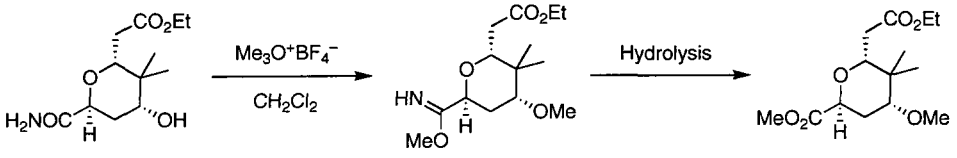
Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

To a solution of ketone **394** (48 mg, 0.19 mmol) in EtOH (5 mL) was added $NaBH_4$ (14 mg, 0.37 mmol) at 0 °C under argon. After 2 h, HCl (2 M, aq., 2 mL) was added and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated. NMR indicated a 1:1 ratio of desired (**387**) : undesired (**393**) product.

Spectroscopic data are in agreement with that reported above for this compound mixture.

Methyl (2*S*,4*R*,6*R*)-6-(2-ethoxy-2-oxoethyl)-4-methoxy-5,5-dimethyltetrahydro-2*H*-pyran-2-carboxylate (**399**)

New compound.



387 **395** **399**

Chemical Formula: $C_{12}H_{21}NO_5$
Molecular Weight: 259.30

Chemical Formula: $C_{14}H_{25}NO_5$
Molecular Weight: 287.35

Chemical Formula: $C_{14}H_{24}O_6$
Molecular Weight: 288.34

To a solution of fragment **387** (33 mg, 0.11 mmol) in CH_2Cl_2 was added trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol). The mixture was heated at 40 °C under argon for 24 h and then concentrated. The crude residue was re-

dissolved in dry CH_2Cl_2 (3 mL) and then NEt_3 (111 mg, 0.15 mL, 1.10 mmol) and cinnamoyl chloride (37 mg, 0.22 mmol) were added. The mixture was stirred at RT under argon for 24 h and then cooled to 0 °C. A suspension of $NaBH_4$ (42 mg, 1.1 mmol) in EtOH (2 mL) was added and the mixture stirred for 1 h at 0 °C. HCl (2 M, aq., 3 mL) was added and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography on silica gel, eluting with 20% EtOAc / petrol afforded the ester **399** as a thin colourless film (3 mg, 10 μmol, 9%). It appeared that the imidate **395** had hydrolysed to methyl ester **399** during the reaction or work-up.

$[\alpha]_D^{26}$ +43.2 (c = 0.125, l = 2, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 4.55 (1H, dd, J = 6.4, 2.9 Hz, C**H**CO_2Me), 4.25–4.11 (2H, m, O**C**H_2CH$_3$), 3.86 (1H, dd, J = 8.4, 4.4 Hz, C**H**CH_2CO_2Et), 3.79 (3H, s, O**C**H_3), 3.37 (3H, s, O**C**H_3), 2.98 (1H, dd, J = 10.7, 4.2 Hz, C**H**OMe), 2.54–2.42 (2H, m, **C**H_2CO_2Et), 2.32 (1H, ddd, J = 13.3, 4.2, 2.9 Hz, C**H**H), 1.80 (1H, ddd, J = 13.3, 10.7, 6.4 Hz, CH**H**), 1.28 (3H, t, J = 7.2 Hz, OCH$_2$C**H**$_3$), 0.96 (3H, s, C**H**$_3$), 0.88 (3H, s, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 172.4 (**C**=O), 172.0 (**C**=O), 81.5 (O**C**H), 78.3 (O**C**H), 72.1 (O**C**H), 60.8 (O**C**H_2CH$_3$), 57.6 (O**C**H_3), 52.2 (O**C**H_3), 38.4 (**C**$(CH_3)_2$), 35.8 (**C**H_2), 27.0 (**C**H_2), 23.2 (**C**H_3), 14.4 (**C**H_3), 14.1 (OCH$_2$**C**H$_3$).

LRMS (ES^+)

m/z 311 ($[M+Na]^+$, 100%), 600 ($[2M+Na]^+$, 60%).

HRMS (ES^+)

Found 311.1459, $[C_{14}H_{24}O_6+Na]^+$ requires 311.1465 amu.

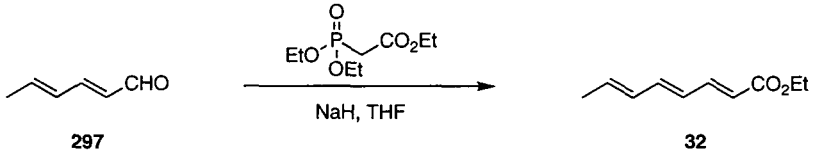
FT – IR (CH_2Cl_2 solution)

cm^{-1} 2962 (w), 2824 (w), 1732 (s), 1655 (w), 1651 (w), 1601 (w), 1519 (w), 1460 (w), 1435 (w).

Ethyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (**32**)

Method A: NaH

Known compound.



297 **32**

Chemical Formula: C_6H_8O
Molecular Weight: 96.13

Chemical Formula: $C_{10}H_{14}O_2$
Molecular Weight: 166.22

Prepared by the method reported by Ley.[65] To a stirred suspension of sodium hydride (60% in mineral oil, 462 mg, 11.54 mmol) in THF (20 mL) at 0 °C under argon was added triethyl phosphonoacetate (2.56 g, 2.3 mL 11.44 mmol). The mixture was stirred for 30 min at this temperature and then 2,4-hexadienal **297** (1.00 g, 1.2 mL, 10.40 mmol) (the commercial aldehyde is supplied as a mixture of isomers) was added dropwise. A thick gel formed and the mixture was stirred for 20 h at RT and then poured into NH_4Cl (sat., aq., 40 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases washed with water (30 mL) and brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 2–5% Et_2O / petrol to afford the title compound **32** as a light yellow solid (914 mg, 5.50 mmol, 53%). The compound contains a mixture of *cis* and *trans* products, *d.r.* 6:1. All data is for (*E*,*E*,*E*) isomer.

mp 33–36 °C (Et_2O / petrol). (Lit 30 °C, solvent not given).[65]

^{1}H NMR (300 MHz, $CDCl_3$) Data for the major (*E,E,E*) isomer only.

δ_H ppm 7.29 (1H, dd, *J* = 15.3, 11.3 Hz, =C**H**), 6.52 (1H, dd, *J* = 14.9, 10.5 Hz, =C**H**), 6.20–6.12 (2H, m, 2 x =C**H**), 5.98–5.81 (2H, m, 2 x =C**H**), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 1.83 (3H, d, *J* = 6.4 Hz, CH_3), 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) Data for the major (*E,E,E*) isomer only.

δ_C ppm 167.4 (**C**=O), 145.0 (=C**H**), 141.2 (=C**H**), 135.2 (=C**H**), 131.4 (=C**H**), 127.8 (=C**H**), 120.2 (=C**H**), 60.4 (OCH_2CH_3), 18.7 ($HC=CHCH_3$), 14.5 (OCH_2CH_3).

LRMS (ES^+)

m/z 167 ($[M+H]^+$, 37%), 189 ($[M+Na]^+$, 88%), 221 ($[M+Na+MeOH]^+$, 100%), 355 ($[2M+Na]^+$, 10%).

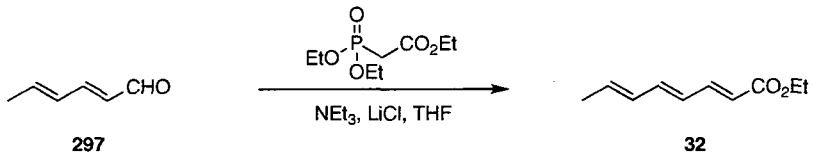
FT – IR (compressed solid)

cm^{-1} 3016 (w), 2991 (w), 2944 (w), 2906 (w), 1703 (s), 1615 (s), 1587 (m), 1476 (w), 1446 (w).

Spectroscopic data are in agreement with the literature.[65]

Ethyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (**32**)

Method A: LiCl / NEt_3



297 **32**

Chemical Formula: C_6H_8O
Molecular Weight: 96.13

Chemical Formula: $C_{10}H_{14}O_2$
Molecular Weight: 166.22

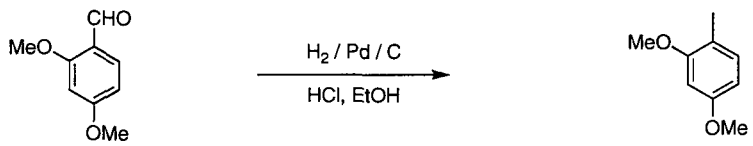
Procedure based on the method reported by Rathke.[126] NEt_3 (2.74 g, 3.8 mL, 27.04 mmol) was added to a mixture of triethyl phosphonoacetate (5.60 g, 5.0 mL, 24.97 mmol) and LiCl (1.15 g, 27.04 mmol) in THF (50 mL) at RT under argon. The mixture was then treated with 2,4-hexadienal **297** (2.00 g, 2.3 mL, 20.80 mmol) and stirred for 16 h at RT. The reaction mixture was poured into HCl (2 M, aq., 20 mL)

and the phases separated. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic phases washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 2–5% Et_2O / petrol to afford the title compound **32** as a light yellow solid (2.45 g, 14.7 mmol, 71%, *d.r.* 6:1).

Spectroscopic data are in agreement with that reported above.

2,4-Dimethoxytoluene (**410**)

Known compound.



412 **410**

Chemical Formula: $C_9H_{10}O_3$
Molecular Weight: 166.17

Chemical Formula: $C_9H_{12}O_2$
Molecular Weight: 152.19

Prepared by the method reported by De Paulis.[139] To a solution of 2,4-dimethoxybenzaldehyde **412** (500 mg, 3.01 mmol) in ethanol (10 mL) and HCl (36%, aq., 0.5 mL) was added Pd (5% on C, 60 mg) under H_2 (1 atm). After 24 h, the reaction was filtered through Celite® and the filtrate was concentrated The crude residue was purified by column chromatography on silica gel, eluting with 10% EtOAc / petrol to afford the title compound **410** as a colourless oil (283 mg, 1.86 mmol, 62%).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 7.05 (1H, dd, J = 8.1, 0.5 Hz, $\mathbf{H}_{Ar}$), 6.46 (1H, d, J = 2.5 Hz, $\mathbf{H}_{Ar}$), 6.42 (1H, dd, J = 8.1, 2.5 Hz, $\mathbf{H}_{Ar}$), 3.83 (3H, s, $OC\mathbf{H}_3$), 3.81 (3H, s, $OC\mathbf{H}_3$), 2.17 (3H, s, $ArC\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 159.2 ($\mathbf{C}_{Ar}$), 158.7 ($\mathbf{C}_{Ar}$), 130.7 ($\mathbf{C}H_{Ar}$), 119.0 ($\mathbf{C}_{Ar}$), 103.9 ($\mathbf{C}H_{Ar}$), 98.5 ($\mathbf{C}H_{Ar}$), 55.6 ($OC\mathbf{H}_3$), 55.4 ($OC\mathbf{H}_3$), 15.6 ($ArC\mathbf{H}_3$).

LRMS (EI)

m/z 152 ([M]$^+$, 100%), 137 ([M-(CH_3)]$^+$, 32%), 121 (35%), 107 (12%), 91 (10%), 77 ([Ph]$^+$, 20%).

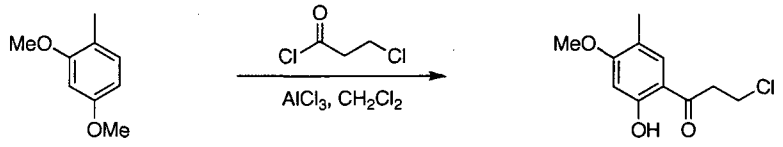
FT – IR (neat)

cm^{-1} 2943 (w), 2920 (w), 2879 (w), 2844 (w), 1599 (m), 1576 (m), 1499 (m), 1468 (m), 1453 (m), 1430 (m).

Spectroscopic data are in agreement with the literature.[162]

3-Chloro-1-(2-hydroxy-4-methoxy-5-methylphenyl)propan-1-one (**415**)

New compound.



410

Chemical Formula: $C_9H_{12}O_2$
Molecular Weight: 152.19

415

Chemical Formula: $C_{11}H_{13}ClO_3$
Molecular Weight: 228.67

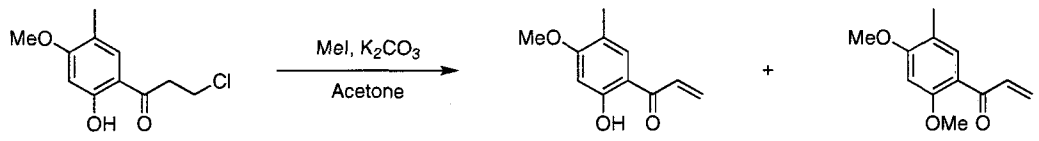
Prepared using the method reported by Abraham.[137] To a solution of toluene **410** (2.00 g, 13.14 mmol) and 3-chloropropionyl chloride (1.84 g, 1.40 mL, 14.46 mmol) in CH_2Cl_2 (100 mL) was added $AlCl_3$ (3.50 g, 26.28 mmol) and the reaction was stirred at RT for 17 h. The reaction was quenched by addition of water (25 mL) at 0 °C and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic phases were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 5–20% Et_2O / petrol to afford first starting material **410** (212 mg, 1.39 mmol, 11%) followed by the title compound **415** as a yellow solid (1.86 g, 8.19 mmol, 62%).

mp 113–117 °C (CH_2Cl_2).

^{1}H NMR	(400 MHz, $CDCl_3$)
δ_H ppm	12.47 (1H, s, O**H**), 7.42 (1H, s, $\mathbf{H}_{Ar}$), 6.40 (1H, s, $\mathbf{H}_{Ar}$), 3.92 (2H, t, J = 6.8 Hz, $\mathbf{CH}_2$), 3.87 (3H, s, OCH_3), 3.40 (2H, t, J = 6.8 Hz, $\mathbf{CH}_2$), 2.15 (3H, s, $ArCH_3$).
^{13}C NMR	(100 MHz, $CDCl_3$)
δ_C ppm	200.4 (**C**=O), 165.0 ($\mathbf{C}_{Ar}$), 164.3 ($\mathbf{C}_{Ar}$), 130.9 ($\mathbf{CH}_{Ar}$), 118.9 ($\mathbf{C}_{Ar}$), 112.7 ($\mathbf{C}_{Ar}$), 99.2 ($\mathbf{CH}_{Ar}$), 55.9 (OCH_3), 40.6 ($\mathbf{CH}_2$), 38.8 ($\mathbf{CH}_2$), 15.8 ($ArCH_3$).
LRMS	(EI)
m/z	192 ($[M–HCl+H]^+$, 65%), 191 ($[M–HCl]^+$, 100%), 165 [M–$CH_2CH_2Cl]^+$, 60%), 55 (20%).
HRMS	(EI)
	Found 228.0561, $[C_{11}H_{13}O_3{}^{35}Cl]^+$ requires 228.0553 amu.
FT – IR	(compressed solid)
cm^{-1}	2975 (m), 2947 (m), 2924 (m), 1622 (s), 1579 (m), 1495 (m), 1464 (m), 1446 (m), 1417 (m).
CHN	Found C 57.83%, H 5.68%. Calculated C 57.78%, H 5.59%.

1-(2-Hydroxy-4-methoxy-5-methylphenyl)prop-2-en-1-one (**416**) and
1-(2,4-dimethoxy-5-methylphenyl)prop-2-en-1-one (**417**)

New compounds.



415 **416** **417**

Chemical Formula: $C_{11}H_{13}ClO_3$
Molecular Weight: 228.67

Chemical Formula: $C_{11}H_{12}O_3$
Molecular Weight: 192.21

Chemical Formula: $C_{12}H_{14}O_3$
Molecular Weight: 206.24

Procedure based on the method reported by Lee.[140] To a solution of **415** (200 mg, 0.87 mmol) in acetone (5 mL) was added K_2CO_3 (180 mg, 1.31 mmol) and MeI (149 mg, 70 μL, 1.05 mmol). The mixture was stirred at RT for 20 h under argon and then further MeI (149 mg, 70 μL, 1.05 mmol) and K_2CO_3 (180 mg, 1.31 mmol) were added. The reaction was heated at reflux for 5 h, cooled to RT and stirred at this temperature for 72 h. Water (5 mL) was added, followed by EtOAc (10 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 20% Et_2O / petrol to afford first phenol **416** as a bright yellow solid (12 mg, 61 μmol, 7%) and then ether **417** as a light yellow solid (124 mg, 0.60 mmol, 69%).

Data for **416**:

mp 94–99 °C (Et_2O / petrol).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 13.11 (1H, s, O**H**), 7.52 (1H, s, $\mathbf{H}_{Ar}$), 7.27 (1H, dd, J = 16.9, 10.6 Hz, **H**C=CH_2), 6.52 (1H, dd, J = 16.9, 1.8 Hz, HC=C**H**H), 6.43 (1H, s, $\mathbf{H}_{Ar}$), 5.90 (1H, dd, J = 10.6, 1.8 Hz, HC=CH**H**), 3.88 (3H, s, O$\mathbf{CH}_3$), 2.15 (3H, s, Ar$\mathbf{CH}_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 192.4 (**C**=O), 165.6 (**C**$_{Ar}$), 165.0 (**C**$_{Ar}$), 131.2 (**HC**=CH_2), 131.1 (**CH**$_{Ar}$), 129.6 (HC=**C**H_2), 118.4 (**C**$_{Ar}$), 112.8 (**C**$_{Ar}$), 99.3 (**CH**$_{Ar}$), 55.9 (OCH_3), 15.8 (Ar**C**H_3).

LRMS (EI)

m/z 192 ($[M]^+$, 66%), 191 ($[M-H]^+$, 100%), 165 ($[M-CHCH_2]^+$, 65%), 55 (20%)

HRMS (EI)

Found 192.0789, $[C_{11}H_{12}O_3]^+$ requires 192.0786 amu.

FT – IR (compressed solid)

cm^{-1} 2963 (w), 2928 (w), 2849 (w), 1633 (m), 1576 (s), 1496 (m), 1467 (m), 1441 (m).

Data for **417**:

mp 62–65 °C (Et_2O / petrol).

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 7.55 (1H, s, **H**$_{Ar}$), 7.17 (1H, dd, J = 17.2, 10.3 Hz, **H**C=CH_2), 6.42 (1H, s, **H**$_{Ar}$), 6.32 (1 H, dd, J = 17.2, 2.0 Hz, HC=C**H**H), 5.69 (1H, dd, J = 10.3, 2.0 Hz, HC=CH**H**), 3.90 (6H, s, 2 x O**C**H_3), 2.16 (3H, s, Ar**C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 190.8 (**C**=O), 162.4 (**C**$_{Ar}$), 159.5 (**C**$_{Ar}$), 137.0 (**HC**=CH_2), 133.1 (**CH**$_{Ar}$), 126.8 (HC=**C**H_2), 120.1 (**C**$_{Ar}$), 119.2 (**C**$_{Ar}$), 94.7 (**CH**$_{Ar}$), 56.0 (OCH_3), 55.7 (O**C**H_3), 15.3 (Ar**C**H_3).

LRMS (ES^+)

m/z 229 ($[M+Na]^+$, 87%), 270 ($[M+Na+MeCN]^+$, 100%), 435 ($[2M+Na]^+$, 90%).

HRMS (EI)

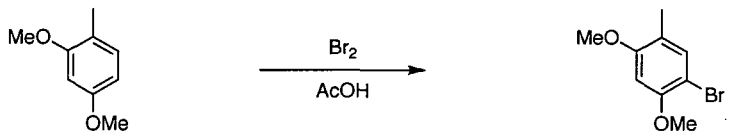
Found 206.0939, $[C_{12}H_{14}O_3]^+$ requires 206.0943 amu.

FT – IR (compressed solid)

cm^{-1} 2993 (w), 2980 (w), 2951 (w), 2921 (w), 2839 (w), 1646 (m), 1612 (m), 1590 (m), 1568 (m), 1514 (w), 1495 (w), 1455 (w), 1435 (m), 1416 (m).

3-Bromo-4,6-dimethoxytoluene (**419**)

Known compound.



410 **419**

Chemical Formula: $C_9H_{12}O_2$
Molecular Weight: 152.19

Chemical Formula: $C_9H_{11}BrO_2$
Molecular Weight: 231.09

To a solution of **410** (1.00 g, 6.57 mmol) in acetic acid (30 mL) was added bromine (1.16 g, 0.37 mL, 7.23 mmol) at RT under argon. After 24 h, $Na_2S_2O_3$ (sat., aq., 10 mL) was added and the mixture was diluted with Et_2O (50 mL) and water (15 mL). The phases were separated and the aqueous phase extracted with Et_2O (2 x 15 mL). The combined organic phases were washed with water (10 mL) and brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 10% Et_2O / petrol to afford the title compound **419** as a white solid (1.38 g, 5.97 mmol, 91%).

mp 89–95 °C (Et_2O / petrol). (Lit 89–91 °C, hexane).[163]

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 7.27 (1H, s, $\mathbf{H}_{Ar}$), 6.48 (1H, s, $\mathbf{H}_{Ar}$), 3.90 (3H, s, $OC\mathbf{H}_3$), 3.84 (3H, s, $OC\mathbf{H}_3$), 2.13 (3H, s, $ArC\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 158.0 ($\mathbf{C}_{Ar}$), 154.8 ($\mathbf{C}_{Ar}$), 134.2 ($\mathbf{C}H_{Ar}$), 120.4 ($\mathbf{C}_{Ar}$), 101.3 ($\mathbf{C}_{Ar}$), 96.7 ($\mathbf{C}H_{Ar}$), 56.7 ($O\mathbf{C}H_3$), 55.8 ($O\mathbf{C}H_3$), 15.3 ($Ar\mathbf{C}H_3$).

LRMS (EI)

m/z 232 ([M]$^+$, ^{81}Br, 100%), 230 ([M]$^+$, ^{79}Br, 95%), 217 ([M–CH_3]$^+$, ^{81}Br, 33%), 215 ([M–CH_3]$^+$, ^{79}Br, 31%), 189 (32%), 187 (32%), 151 ([M–Br]$^+$, 37%), 121 (23%), 108 (33%), 77 ([Ph]$^+$, 39%), 65 (27%).

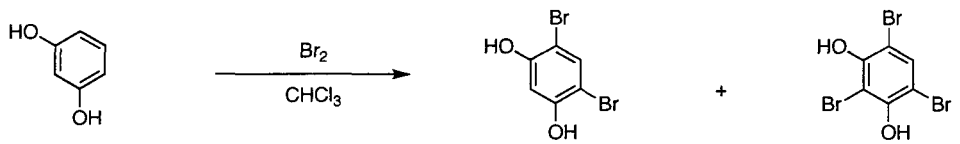
FT – IR (compressed solid)

cm^{-1} 2963 (w), 2919 (w), 2877 (w), 2847 (w), 1599 (m), 1576 (m), 1498 (m), 1466 (m), 1454 (m), 1430 (m).

Spectroscopic data are in agreement with the literature.[163]

4,6-Dibromobenzene-1,3-diol (**424**) and 2,4,6-tribromobenzene-1,3-diol (**425**)

Known compound.



423 **424** **425**

Chemical Formula: $C_6H_6O_2$
Molecular Weight: 110.11

Chemical Formula: $C_6H_4Br_2O_2$
Molecular Weight: 267.90

Chemical Formula: $C_6H_3Br_3O_2$
Molecular Weight: 346.80

Prepared by the method reported by Nolte.[164] To a solution of **423** (1.00 g, 9.08 mmol) in chloroform (50 mL) was added bromine (2.88 g, 0.93 mL, 18.0 mmol) at RT under argon. After 5 h, Na_2SO_3 (sat., aq., 25 mL) was added and the phases were separated. The aqueous phase was extracted with $CHCl_3$ (2 x 25 mL) and the combined organic phases were washed with water (15 mL) and brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 3–10% MeOH / $CHCl_3$ to afford first some tribrominated product **425** (48 mg, 0.14 mmol, 2%) as a light brown solid, followed by the title compound **424** as a white solid (2.15 g, 8.01 mmol, 88%).

Data for **424**:

mp	105–107 °C ($CHCl_3$). (Lit 112 °C, water).[165]
^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	7.54 (1H, s, $\mathbf{H}_{Ar}$), 6.75 (1H, s, $\mathbf{H}_{Ar}$), 5.50 (2H, br s, 2 x **OH**)
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	153.2 (2 x $\mathbf{C}_{Ar}$), 133.5 ($\mathbf{C}H_{Ar}$), 103.8 ($\mathbf{C}H_{Ar}$), 101.5 (2 x $\mathbf{C}_{Ar}$).
LRMS	(ES^-)
m/z	265 ($[M–H]^-$, 2 x ^{79}Br, 50%), 267 ($[M–H]^-$, 1 x ^{79}Br, 1 x ^{81}Br, 100%), 269 ($[M–H]^-$, 2 x ^{81}Br, 50%).
FT – IR	(compressed solid)
cm^{-1}	3491 (br m), 3446 (br m), 3380 (br m), 1576 (m), 1493 (m), 1463 (s), 1439 (m), 1410 (m).

Spectroscopic data are in agreement with the literature.[166]

Data for **425**:

mp	113–117 °C ($CHCl_3$). (Lit 111 °C, $CHCl_3$).[167]
^{1}H NMR	(300 MHz, $CDCl_3$)
δ_H ppm	7.60 (1H, s, $\mathbf{H}_{Ar}$), 5.93 (2H, s, **OH**).
^{13}C NMR	(75 MHz, $CDCl_3$)
δ_C ppm	149.9 (2 x $\mathbf{C}_{Ar}$), 133.2 ($\mathbf{C}H_{Ar}$), 100.6 (2 x $\mathbf{C}_{Ar}$), 98.5 ($\mathbf{C}_{Ar}$).
LRMS	(ES^-)
m/z	343 ($[M–H]^-$, 3 x ^{79}Br, 33%), 345 ($[M–H]^-$, 2 x ^{79}Br, 1 x ^{81}Br, 100%), 347 ($[M–H]^-$, 1 x ^{79}Br, 2 x ^{81}Br, 100%), 349 ($[M–H]^-$, 3 x ^{81}Br, 30%).

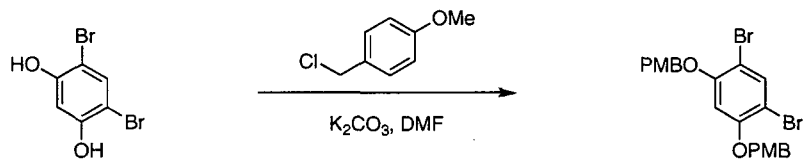
FT – IR (compressed solid)

cm^{-1} 3465 (s), 3073 (m), 2960 (w), 2917 (w), 2847 (w), 1574 (m), 1455 (s), 1425 (s).

Spectroscopic data are in agreement with the literature.[168]

1,5-Dibromo-2,4-bis[(4-methoxybenzyl)oxy]benzene (**426**)

New compound.



424 **426**

Chemical Formula: $C_6H_4Br_2O_2$
Molecular Weight: 267.90

Chemical Formula: $C_{22}H_{20}Br_2O_4$
Molecular Weight: 508.20

Procedure based on the method reported by Defauw.[169] To a solution of **424** (200 mg, 0.75 mmol) in DMF (4 mL) was added K_2CO_3 (248 mg, 1.80 mmol) and KI (299 mg, 1.80 mmol). The mixture was stirred at RT and *para*-methoxybenzyl chloride (0.24 mL, 1.80 mmol) was added. After 72 h, water (10 mL) and Et_2O (50 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography on silica gel, eluting with 10% Et_2O / petrol to afford the title compound **426** as a white solid (258 mg, 0.51 mmol, 68%).

mp 130–132 °C (Et_2O / petrol).

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 7.68 (1H, s, $\mathbf{H}_{Ar}$), 7.33 (4H, d, J = 8.8 Hz, 4 x $\mathbf{H}_{Ar}$), 6.92 (4H, dt, J = 8.8, 2.0 Hz, 4 x $\mathbf{H}_{Ar}$), 6.56 (1H, s, $\mathbf{H}_{Ar}$), 5.01 (4H, s, 2 x $\mathbf{CH}_2$), 3.83 (6H, s, 2 x $\mathbf{OCH}_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 159.7 (2 x $\mathbf{C}_{Ar}$), 155.2 (2 x $\mathbf{C}_{Ar}$), 136.1 ($\mathbf{C}H_{Ar}$), 129.0 (4 x $\mathbf{C}H_{Ar}$), 128.2 (2 x $\mathbf{C}_{Ar}$), 114.3 (4 x $\mathbf{C}H_{Ar}$), 104.2 (2 x $\mathbf{C}_{Ar}$), 102.5 ($\mathbf{C}H_{Ar}$), 71.7 (2 x $\mathbf{C}H_2$), 55.7 (2 x OCH_3).

LRMS (ES^+)

m/z 1043 ([2M+Na]$^+$, 4 x ^{81}Br, 15%), 1041 ([2M+Na]$^+$, 1 x ^{79}Br, 3 x ^{81}Br, 40%), 1039 ([2M+Na]$^+$, 2 x ^{79}Br, 2 x ^{81}Br, 53%), 1037 ([2M+Na]$^+$, 3 x ^{79}Br, 1 x ^{81}Br, 38%), 1035 ([2M+Na]$^+$, 4 x ^{79}Br, 10%), 533 ([M+Na]$^+$, 2 x ^{81}Br, 40%), 531 ([M+Na]$^+$, 1 x ^{79}Br, 1 x ^{81}Br, 80%), 529 ([M+Na]$^+$, 2 x ^{79}Br, 37%).

HRMS (ES^+)

Found 528.9623, $[C_{22}H_{20}Br_2O_4+Na]^+$ requires 528.9621 amu.

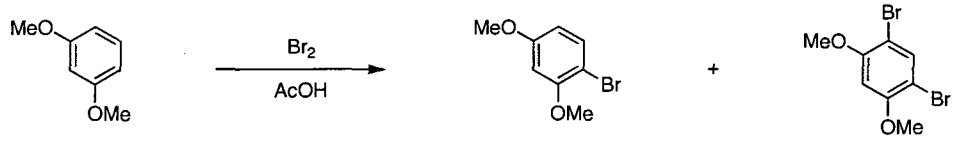
FT – IR (compressed solid)

cm^{-1} 3005 (w) 2957 (w), 2931 (w), 2881 (w), 2863 (w), 1614 (m), 1577 (m), 1567 (m), 1516 (s), 1487 (m), 1461 (m), 1443 (m), 1422 (w).

CHN Found C 52.32%, H 3.98%. Calculated C 52.00%, H 3.97%.

1-Bromo-2,4-dimethoxybenzene (**429**) and 1,3-dibromo-4,6-dimethoxybenzene (**430**)

Known compound.



428 **429** **430**

Chemical Formula: $C_8H_{10}O_2$
Molecular Weight: 138.16

Chemical Formula: $C_8H_9BrO_2$
Molecular Weight: 217.06

Chemical Formula: $C_8H_8Br_2O_2$
Molecular Weight: 295.96

To a solution of 1,3-dimethoxybenzene **428** (1.00 g, 7.24 mmol) in AcOH (10 mL) was added bromine (1.27 g, 0.41 mL, 7.96 mmol). After 30 h, Na_2SO_3 (sat., aq., 10 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic phases washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$,

filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 20% Et_2O / petrol to afford an inseparable mixture of the title compound **429** and 1-bromo-2,6-dimethoxybenzene (10% approx. by NMR) as a colourless oil (838 mg, 3.86 mmol, 49%) followed by dibrominated material **430** as a white solid (545 mg, 1.84 mmol, 25%).

Data for **429**:

^{1}H NMR (300 MHz, $CDCl_3$)

δ_H ppm 7.41 (1H, d, J = 8.7 Hz, $\mathbf{H}_{Ar}$), 6.50 (1H, d, J = 2.7 Hz, $\mathbf{H}_{Ar}$), 6.41 (1H, dd, J = 8.7, 2.7 Hz, $\mathbf{H}_{Ar}$), 3.88 (3H, s, $OC\mathbf{H}_3$), 3.80 (3H, s, $OC\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$)

δ_C ppm 160.4 ($\mathbf{C}_{Ar}$), 156.7 ($\mathbf{C}_{Ar}$), 133.3 ($\mathbf{C}H_{Ar}$), 106.1 ($\mathbf{C}H_{Ar}$), 102.6 ($\mathbf{C}_{Ar}$), 100.1 ($\mathbf{C}H_{Ar}$), 55.3 ($OC\mathbf{H}_3$), 55.7 ($OC\mathbf{H}_3$).

LRMS (EI)

m/z 218 ($[M]^+$, ^{81}Br, 97%), 216 ($[M]^+$, ^{79}Br, 100%), 203 ($[M-CH_3]^+$, ^{81}Br, 12%), 201 ($[M-CH_3]^+$, ^{79}Br, 13%), 175 (38%), 173 (38%), 107 (25%), 79 ($[Ph+H]^+$, 30%), 63 (67%).

FT – IR (neat)

cm^{-1} 3003 (w), 2955 (w), 2940 (w), 2835 (w), 1580 (s), 1487 (s), 1454 (s), 1435 (s), 1409 (m).

Spectroscopic data are in agreement with the literature.[166]

Data for **430**:

mp 115–117 °C (petrol). (Lit 141–143 °C).[170]

^{1}H NMR (400 MHz, $CDCl_3$)

δ_H ppm 7.66 (1H, s, $\mathbf{H}_{Ar}$), 6.49 (1H, s, $\mathbf{H}_{Ar}$), 3.91 (6H, s, 2 x $OC\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$)

δ_C ppm 156.4 (2 x $\mathbf{C}_{Ar}$), 136.1 ($\mathbf{C}H_{Ar}$), 102.7 (2 x $\mathbf{C}_{Ar}$), 97.7 ($\mathbf{C}H_{Ar}$), 56.7 (2 x OCH_3).

LRMS (EI)

m/z 298 ($[M]^+$, 2 x ^{81}Br, 50%), 296 ($[M]^+$, 1 x ^{81}Br, 1 x ^{79}Br 100%), 294 ($[M]^+$, 2 x ^{79}Br, 53%), 255 (20%), 253 (40%), 251 (20%), 143 (22%), 141 (20%), 131 (22%), 129 (22%).

FT – IR (compressed solid)

cm^{-1} 3028 (w), 3013 (w), 2982 (w), 2947 (w), 2847 (w), 1581 (s), 1488 (s), 1464 (s), 1455 (s), 1432 (s).

Spectroscopic data are in agreement with the literature.[166]

Appendix – X-ray Crystallography Data

Data for **334**

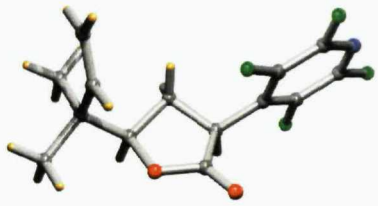


Table 1. Crystal data and structure refinement details.

Identification code	**2006sot0588 (WB/4598/35B)**
Empirical formula	$C_{14}H_{13}F_4NO_2$
Formula weight	303.25
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.7841(2) Å
	b = 10.9820(2) Å β = 112.6810(10)°
	c = 11.3662(2) Å
Volume	1357.18(4) Å^3
Z	4
Density (calculated)	1.484 Mg / m^3
Absorption coefficient	0.135 mm^{-1}
$F(000)$	624
Crystal	Block; Colourless
Crystal size	0.3 × 0.2 × 0.2 mm^3
θ range for data collection	3.60 – 27.48°
Index ranges	$-15 \le h \le 15$, $-14 \le k \le 14$, $-14 \le l \le 14$
Reflections collected	17858
Independent reflections	3100 [R_{int} = 0.0343]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9605 and 0.9505
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3100 / 0 / 193
Goodness-of-fit on F^2	0.971
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0381, $wR2$ = 0.1023
R indices (all data)	$R1$ = 0.0553, $wR2$ = 0.1138
Extinction coefficient	0.015(3)
Largest diff. peak and hole	0.313 and –0.219 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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.*
F2	1962(1)	5205(1)	853(1)	31(1)	1
F1	28(1)	6124(1)	1263(1)	29(1)	1
F3	2829(1)	7373(1)	5335(1)	29(1)	1
F4	4630(1)	6389(1)	4744(1)	36(1)	1
O2	−255(1)	8811(1)	1839(1)	29(1)	1
O1	−1671(1)	8129(1)	2531(1)	24(1)	1
N1	3293(1)	5800(1)	2800(1)	25(1)	1
C10	1343(1)	6808(1)	3317(1)	21(1)	1
C14	3474(1)	6337(1)	3888(1)	25(1)	1
C11	1170(1)	6229(1)	2176(1)	23(1)	1
C9	−527(1)	8172(1)	2550(1)	23(1)	1
C12	2550(1)	6846(1)	4189(1)	22(1)	1
C13	2157(1)	5752(1)	1968(1)	23(1)	1
C6	−1750(1)	7247(1)	3476(1)	22(1)	1
C7	−617(1)	6448(1)	3773(1)	24(1)	1
C5	−4014(1)	7568(1)	2748(1)	31(1)	1
C8	306(1)	7345(1)	3601(1)	22(1)	1
C3	−3002(1)	6611(1)	2933(1)	25(1)	1
C4	−3016(1)	5670(1)	3925(1)	31(1)	1
C2	−3211(1)	6043(1)	1657(1)	34(1)	1
C1	−3429(2)	4892(2)	1328(2)	51(1)	1

Table 3. Bond lengths [Å] and angles [°].

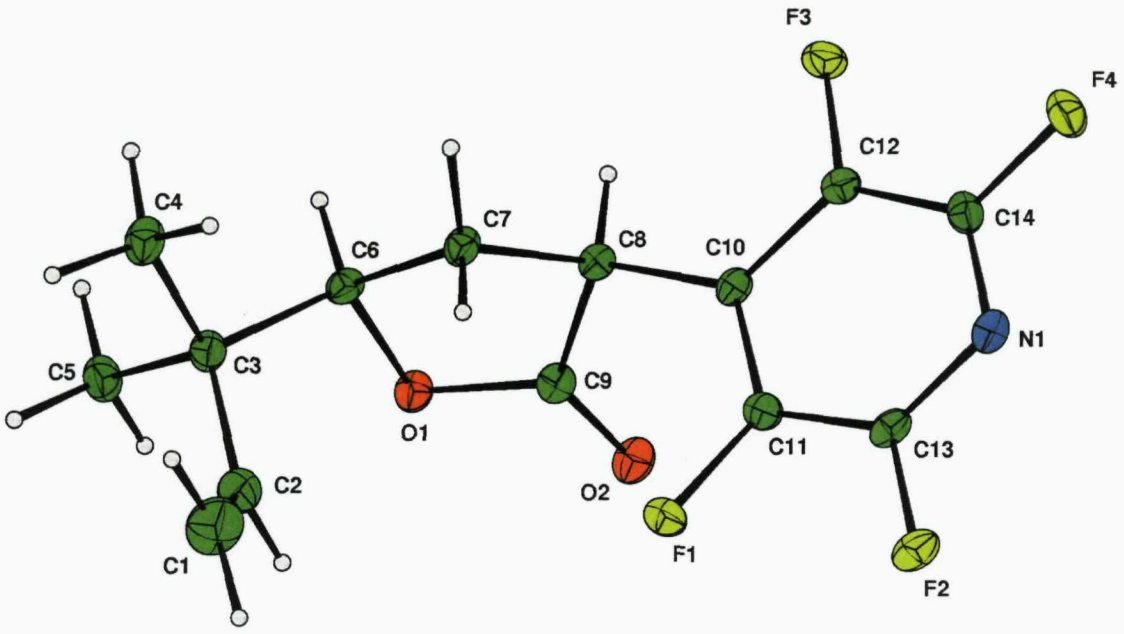
F2–C13	1.3400(15)	C10–C8	1.5004(17)
F1–C11	1.3504(15)	C14–C12	1.3799(18)
F3–C12	1.3458(14)	C11–C13	1.3767(19)
F4–C14	1.3353(15)	C9–C8	1.5202(17)
O2–C9	1.2033(15)	C6–C7	1.5237(18)
O1–C9	1.3405(15)	C6–C3	1.5303(18)
O1–C6	1.4757(15)	C7–C8	1.5347(18)
N1–C13	1.3092(17)	C5–C3	1.5420(19)
N1–C14	1.3105(17)	C3–C2	1.510(2)
C10–C12	1.3858(17)	C3–C4	1.5343(19)
C10–C11	1.3862(18)	C2–C1	1.314(2)
C9–O1–C6	110.92(9)	N1–C13–F2	117.12(11)
C13–N1–C14	116.67(11)	N1–C13–C11	123.86(12)
C12–C10–C11	115.03(11)	F2–C13–C11	119.02(12)
C12–C10–C8	122.05(11)	O1–C6–C7	104.08(9)
C11–C10–C8	122.92(11)	O1–C6–C3	109.15(10)
N1–C14–F4	117.12(11)	C7–C6–C3	116.89(11)
N1–C14–C12	123.98(12)	C6–C7–C8	101.83(10)
F4–C14–C12	118.90(12)	C10–C8–C9	113.45(10)
F1–C11–C13	119.50(11)	C10–C8–C7	116.78(11)
F1–C11–C10	120.13(11)	C9–C8–C7	102.08(10)
C13–C11–C10	120.37(12)	C2–C3–C6	110.55(11)
O2–C9–O1	122.43(12)	C2–C3–C4	112.55(12)
O2–C9–C8	128.15(12)	C6–C3–C4	107.05(11)
O1–C9–C8	109.38(10)	C2–C3–C5	108.62(12)
F3–C12–C14	119.52(11)	C6–C3–C5	108.55(11)
F3–C12–C10	120.39(11)	C4–C3–C5	109.44(11)
C14–C12–C10	120.08(12)	C1–C2–C3	127.72(16)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F2	42(1)	30(1)	27(1)	−7(1)	20(1)	−3(1)
F1	25(1)	35(1)	24(1)	−4(1)	6(1)	−2(1)
F3	29(1)	33(1)	22(1)	−6(1)	7(1)	0(1)
F4	21(1)	48(1)	37(1)	−4(1)	7(1)	2(1)
O2	34(1)	23(1)	34(1)	6(1)	18(1)	0(1)
O1	25(1)	22(1)	28(1)	7(1)	12(1)	3(1)
N1	27(1)	23(1)	30(1)	1(1)	16(1)	0(1)
C10	24(1)	18(1)	23(1)	1(1)	12(1)	−1(1)
C14	21(1)	26(1)	29(1)	1(1)	9(1)	−2(1)
C11	24(1)	22(1)	23(1)	2(1)	7(1)	−4(1)
C9	26(1)	19(1)	25(1)	−2(1)	12(1)	−1(1)
C12	27(1)	20(1)	21(1)	−1(1)	10(1)	−3(1)
C13	32(1)	19(1)	23(1)	−1(1)	16(1)	−3(1)
C6	25(1)	23(1)	21(1)	3(1)	11(1)	2(1)
C7	23(1)	26(1)	25(1)	6(1)	13(1)	4(1)
C5	23(1)	34(1)	35(1)	4(1)	11(1)	3(1)
C8	23(1)	24(1)	21(1)	−1(1)	10(1)	0(1)
C3	22(1)	26(1)	27(1)	3(1)	11(1)	0(1)
C4	30(1)	31(1)	38(1)	9(1)	18(1)	1(1)
C2	32(1)	41(1)	31(1)	−5(1)	13(1)	−7(1)
C1	58(1)	48(1)	51(1)	−20(1)	28(1)	−10(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H6	−1678	7697	4266	27	1
H7A	−784	5757	3169	29	1
H7B	−320	6129	4655	29	1
H5A	−3977	8194	2149	46	1
H5B	−3886	7947	3570	46	1
H5C	−4821	7172	2408	46	1
H8	669	7839	4399	27	1
H4A	−3829	5289	3643	47	1
H4B	−2833	6075	4746	47	1
H4C	−2393	5044	4020	47	1
H2	−3182	6581	1014	41	1
H1A	−3468	4311	1930	61	1
H1B	−3546	4642	489	61	1



Thermal ellipsoids drawn at the 35% probability level

Data for **387**

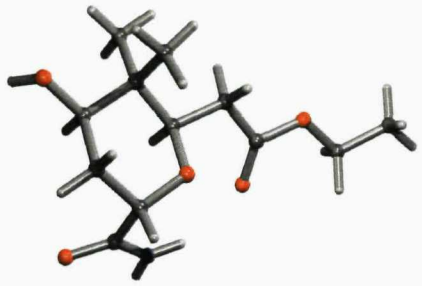


Table 1. Crystal data and structure refinement details.

Identification code	**2007sot0567 (WB/4776/98B/2)**
Empirical formula	$C_{12}H_{21}NO_5$
Formula weight	259.30
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.63070(10) Å
	b = 8.66190(10) Å
	c = 19.9310(3) Å
Volume	1317.37(3) Å^3
Z	4
Density (calculated)	1.307 Mg / m^3
Absorption coefficient	0.101 mm^{-1}
F(000)	560
Crystal	Block; Colourless
Crystal size	0.6 × 0.4 × 0.3 mm^3
θ range for data collection	3.12 – 27.48°
Index ranges	$-9 \le h \le 9$, $-9 \le k \le 11$, $-25 \le l \le 25$
Reflections collected	15098
Independent reflections	1747 [R_{int} = 0.0442]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9703 and 0.9318
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1747 / 0 / 168
Goodness-of-fit on F^2	1.021
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0312, $wR2$ = 0.0763
R indices (all data)	$R1$ = 0.0363, $wR2$ = 0.0794
Extinction coefficient	0.030(3)
Largest diff. peak and hole	0.183 and –0.178 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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	4417(2)	274(2)	1813(1)	18(1)	1
C2	3929(2)	1063(2)	1148(1)	16(1)	1
C3	4275(2)	2793(2)	1160(1)	17(1)	1
C4	2898(2)	3630(2)	1569(1)	16(1)	1
C5	1035(2)	3268(2)	1317(1)	15(1)	1
C6	859(2)	1491(2)	1349(1)	15(1)	1
C7	−292(2)	4029(2)	1791(1)	21(1)	1
C8	773(2)	3877(2)	598(1)	19(1)	1
C9	−886(2)	896(2)	1093(1)	18(1)	1
C10	−1142(2)	−819(2)	1177(1)	16(1)	1
C11	−3029(2)	−2895(2)	864(1)	22(1)	1
C12	−4420(3)	−3148(2)	341(1)	28(1)	1
N1	3569(2)	−1030(2)	1954(1)	20(1)	1
O1	5621(2)	813(2)	2161(1)	24(1)	1
O2	3230(2)	5256(1)	1552(1)	23(1)	1
O3	2170(1)	726(1)	946(1)	16(1)	1
O4	−233(2)	−1689(2)	1499(1)	23(1)	1
O5	−2579(2)	−1261(1)	840(1)	20(1)	1

Table 3. Bond lengths [Å] and angles [°].

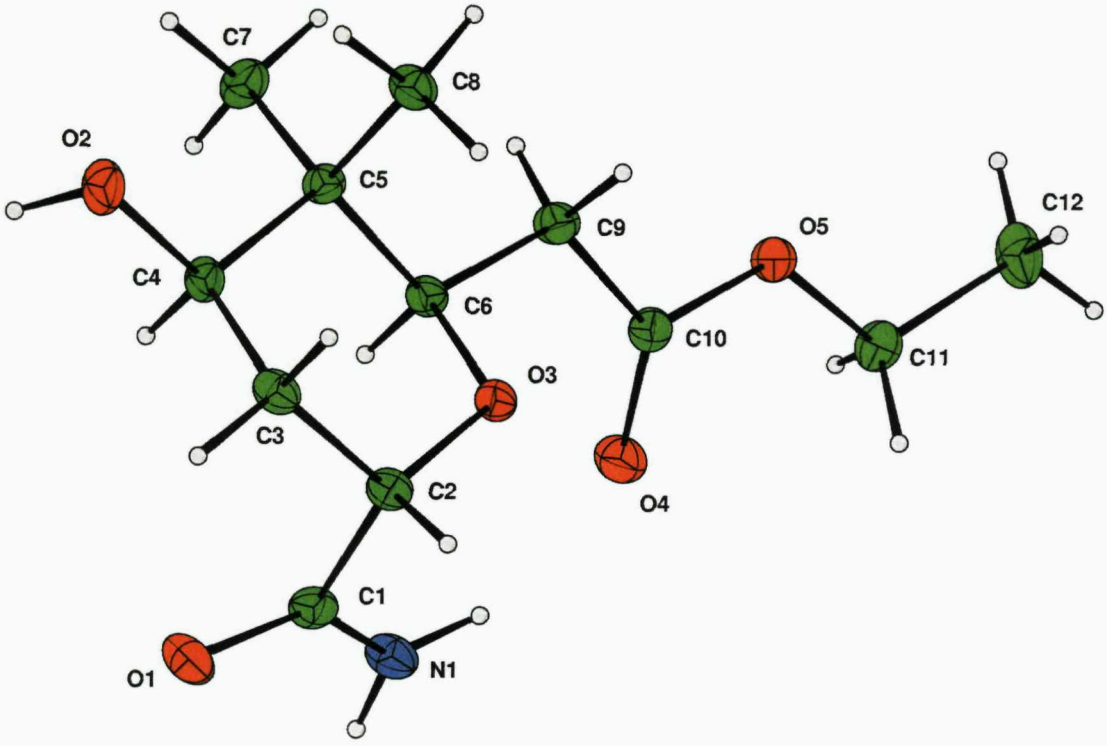
C1–O1	1.243(2)	C5–C8	1.540(2)
C1–N1	1.332(2)	C5–C6	1.547(2)
C1–C2	1.535(2)	C6–O3	1.4430(19)
C2–O3	1.4312(19)	C6–C9	1.516(2)
C2–C3	1.522(2)	C9–C10	1.508(2)
C3–C4	1.515(2)	C10–O4	1.209(2)
C4–O2	1.431(2)	C10–O5	1.341(2)
C4–C5	1.541(2)	C11–O5	1.457(2)
C5–C7	1.533(2)	C11–C12	1.503(3)
O1–C1–N1	123.98(16)	C7–C5–C6	110.20(14)
O1–C1–C2	119.63(16)	C4–C5–C6	105.60(13)
N1–C1–C2	116.24(15)	C8–C5–C6	111.60(14)
O3–C2–C3	111.57(14)	O3–C6–C9	105.43(12)
O3–C2–C1	112.29(14)	O3–C6–C5	111.96(14)
C3–C2–C1	112.54(14)	C9–C6–C5	113.59(14)
C4–C3–C2	111.03(14)	C10–C9–C6	114.28(14)
O2–C4–C3	109.59(14)	O4–C10–O5	123.86(16)
O2–C4–C5	110.84(14)	O4–C10–C9	126.75(16)
C3–C4–C5	111.51(13)	O5–C10–C9	109.39(14)
C7–C5–C4	108.68(13)	O5–C11–C12	106.63(15)
C7–C5–C8	109.93(14)	C2–O3–C6	113.60(12)
C4–C5–C8	110.73(14)	C10–O5–C11	117.02(14)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

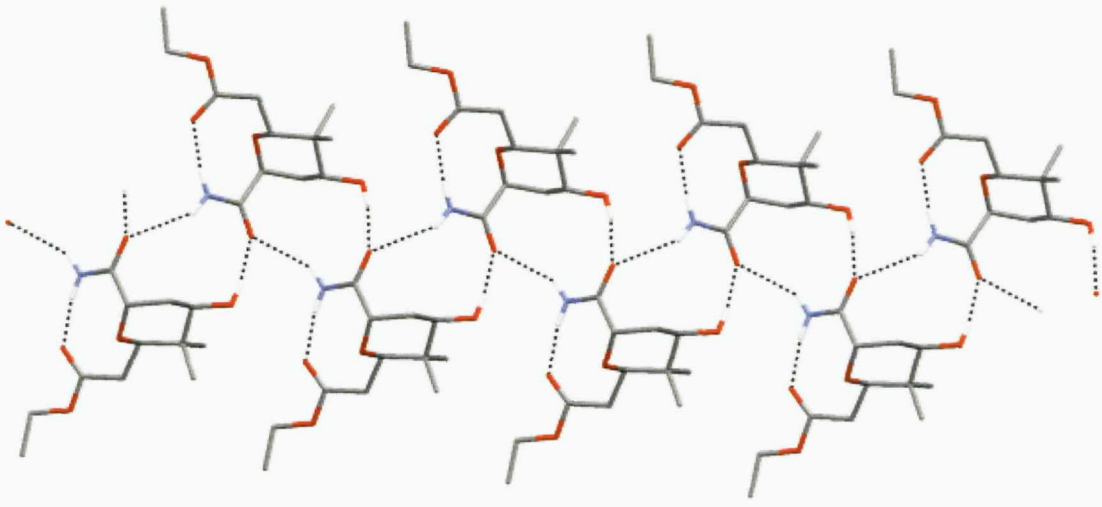
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(1)	19(1)	20(1)	−1(1)	1(1)	3(1)
C2	13(1)	19(1)	18(1)	1(1)	0(1)	0(1)
C3	14(1)	19(1)	19(1)	3(1)	−2(1)	−2(1)
C4	20(1)	13(1)	16(1)	0(1)	−3(1)	−3(1)
C5	15(1)	13(1)	16(1)	1(1)	0(1)	0(1)
C6	13(1)	17(1)	15(1)	−1(1)	0(1)	1(1)
C7	20(1)	19(1)	23(1)	−4(1)	3(1)	2(1)
C8	19(1)	19(1)	19(1)	3(1)	−4(1)	−1(1)
C9	14(1)	15(1)	24(1)	0(1)	−2(1)	−1(1)
C10	14(1)	17(1)	17(1)	−2(1)	1(1)	0(1)
C11	23(1)	15(1)	28(1)	0(1)	−3(1)	−4(1)
C12	33(1)	24(1)	28(1)	0(1)	−7(1)	−12(1)
N1	19(1)	21(1)	21(1)	6(1)	−3(1)	−1(1)
O1	21(1)	27(1)	24(1)	4(1)	−8(1)	−2(1)
O2	29(1)	16(1)	24(1)	−1(1)	−6(1)	−6(1)
O3	13(1)	18(1)	17(1)	−3(1)	−1(1)	1(1)
O4	23(1)	20(1)	27(1)	4(1)	−6(1)	−1(1)
O5	17(1)	15(1)	27(1)	−1(1)	−4(1)	−2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	4715	617	797	19	1
H3A	5447	2990	1355	21	1
H3B	4271	3196	695	21	1
H4	2992	3274	2045	20	1
H6	1004	1156	1826	18	1
H7A	−1482	3849	1623	31	1
H7B	−66	5142	1812	31	1
H7C	−174	3582	2240	31	1
H8A	−470	3815	478	28	1
H8B	1461	3249	284	28	1
H8C	1163	4953	573	28	1
H9A	−1839	1440	1333	22	1
H9B	−991	1156	611	22	1
H11A	−3475	−3176	1314	26	1
H11B	−1986	−3536	765	26	1
H12A	−5455	−2529	452	43	1
H12B	−4742	−4243	330	43	1
H12C	−3972	−2837	−99	43	1
H1A	3852	−1566	2313	24	1
H1B	2726	−1357	1688	24	1
H2A	3618	5544	1926	34	1



Thermal ellipsoids drawn at the 50% probability level



Hydrogen bonded chain

Data for **393**

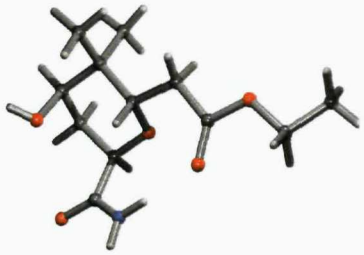


Table 1. Crystal data and structure refinement details.

Identification code	**2008sot0224 (WB/4915/82B)**
Empirical formula	$C_{12}H_{21}NO_5$
Formula weight	259.30
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.7344(2) Å
	b = 8.6509(2) Å
	c = 20.0938(4) Å
Volume	1344.47(5) Å^3
Z	4
Density (calculated)	1.281 Mg / m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	560
Crystal	Slab; Colourless
Crystal size	0.35 × 0.18 × 0.04 mm^3
θ range for data collection	3.11 – 27.48°
Index ranges	$-10 \le h \le 10, -11 \le k \le 11, -24 \le l \le 25$
Reflections collected	16494
Independent reflections	1777 [R_{int} = 0.0700]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9960 and 0.9561
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1777 / 0 / 168
Goodness-of-fit on F^2	1.159
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0407, $wR2$ = 0.1005
R indices (all data)	$R1$ = 0.0564, $wR2$ = 0.1081
Extinction coefficient	0.030(5)
Largest diff. peak and hole	0.217 and –0.207 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. Absolute structure not determined

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	–4352(4)	8195(3)	435(1)	36(1)	1
C2	–2826(3)	7939(3)	884(1)	30(1)	1
C3	–922(3)	5860(3)	1138(1)	23(1)	1
C4	–681(3)	4145(2)	1047(1)	23(1)	1
C5	1017(3)	3545(2)	1317(1)	20(1)	1
C6	4062(3)	3950(3)	1116(1)	23(1)	1
C7	4626(3)	4808(3)	1743(1)	24(1)	1
C8	4400(3)	2215(3)	1137(1)	24(1)	1
C9	3024(3)	1384(3)	1543(1)	24(1)	1
C10	1179(3)	1764(3)	1298(1)	21(1)	1
C11	926(3)	1131(3)	589(1)	26(1)	1
C12	–133(3)	1020(3)	1773(1)	29(1)	1
N1	3662(2)	6008(2)	1930(1)	27(1)	1
O1	–2349(2)	6315(2)	814(1)	26(1)	1
O2	–8(2)	6717(2)	1453(1)	28(1)	1
O3	2326(2)	4287(2)	918(1)	21(1)	1
O4	6012(2)	4447(2)	2014(1)	30(1)	1
O5	3220(2)	1871(2)	2219(1)	30(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.503(3)	C6–C8	1.525(3)
C2–O1	1.459(3)	C6–C7	1.527(3)
C3–O2	1.205(3)	C7–O4	1.242(3)
C3–O1	1.340(3)	C7–N1	1.332(3)
C3–C4	1.507(3)	C8–C9	1.521(3)
C4–C5	1.512(3)	C9–O5	1.430(3)
C5–O3	1.442(3)	C9–C10	1.546(3)
C5–C10	1.546(3)	C10–C12	1.535(3)
C6–O3	1.430(3)	C10–C11	1.539(3)
O1–C2–C1	106.40(19)	N1–C7–C6	116.8(2)
O2–C3–O1	123.9(2)	C9–C8–C6	111.14(18)
O2–C3–C4	126.6(2)	O5–C9–C8	107.20(18)
O1–C3–C4	109.42(19)	O5–C9–C10	109.77(18)
C3–C4–C5	113.71(19)	C8–C9–C10	111.97(18)
O3–C5–C4	104.95(16)	C12–C10–C11	110.03(19)
O3–C5–C10	111.94(17)	C12–C10–C9	108.84(18)
C4–C5–C10	113.78(18)	C11–C10–C9	109.67(18)
O3–C6–C8	111.71(17)	C12–C10–C5	110.45(18)
O3–C6–C7	113.46(18)	C11–C10–C5	111.55(18)
C8–C6–C7	114.0(2)	C9–C10–C5	106.21(17)
O4–C7–N1	123.8(2)	C3–O1–C2	116.34(18)
O4–C7–C6	119.1(2)	C6–O3–C5	114.47(16)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	43(2)	26(1)	39(1)	−1(1)	−8(1)	12(1)
C2	34(1)	17(1)	40(2)	−2(1)	−3(1)	3(1)
C3	20(1)	25(1)	25(1)	3(1)	3(1)	−1(1)
C4	20(1)	21(1)	28(1)	0(1)	−1(1)	0(1)
C5	19(1)	20(1)	21(1)	1(1)	2(1)	−2(1)
C6	19(1)	26(1)	23(1)	−3(1)	0(1)	−1(1)
C7	20(1)	27(1)	26(1)	−2(1)	2(1)	−2(1)
C8	22(1)	23(1)	28(1)	−4(1)	−3(1)	4(1)
C9	29(1)	20(1)	24(1)	−3(1)	−6(1)	3(1)
C10	24(1)	19(1)	21(1)	−2(1)	−2(1)	1(1)
C11	27(1)	24(1)	27(1)	−3(1)	−2(1)	2(1)
C12	29(1)	26(1)	32(1)	4(1)	0(1)	−5(1)
N1	24(1)	29(1)	27(1)	−8(1)	−5(1)	2(1)
O1	24(1)	18(1)	38(1)	1(1)	−7(1)	2(1)
O2	27(1)	26(1)	32(1)	−6(1)	−5(1)	0(1)
O3	18(1)	23(1)	22(1)	2(1)	−1(1)	−1(1)
O4	23(1)	36(1)	31(1)	−8(1)	−6(1)	3(1)
O5	38(1)	29(1)	24(1)	1(1)	−7(1)	3(1)

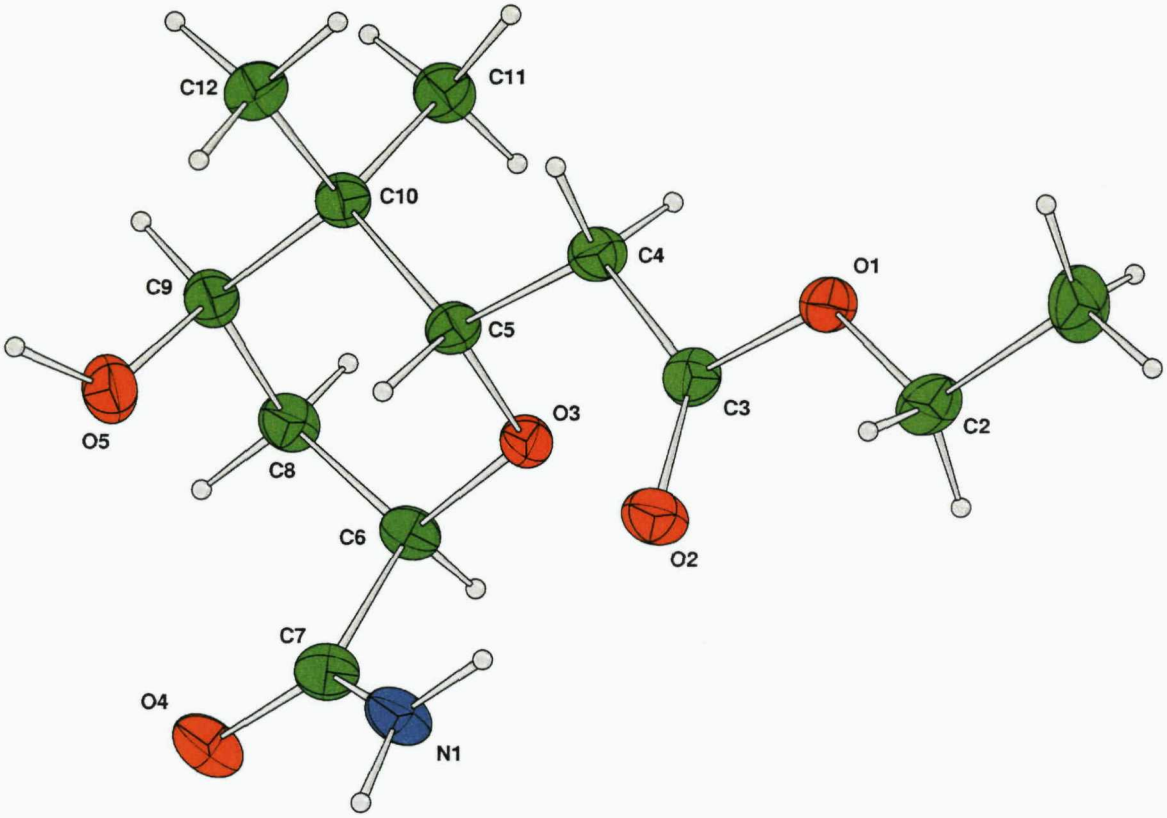
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	–4042	7911	–22	54	1
H1B	–4688	9287	449	54	1
H1C	–5322	7555	585	54	1
H2A	–1851	8614	751	36	1
H2B	–3136	8173	1351	36	1
H4A	–750	3899	567	28	1
H4B	–1640	3598	1273	28	1
H5	1145	3899	1788	24	1
H6	4812	4358	750	27	1
H8A	4408	1799	678	29	1
H8B	5551	2021	1336	29	1
H9	3218	243	1514	29	1
H11A	1330	58	570	39	1
H11B	1591	1759	274	39	1
H11C	–302	1171	471	39	1
H12A	–1306	1188	1603	43	1
H12B	–25	1490	2215	43	1
H12C	94	–92	1804	43	1
H1D	3999	6598	2262	32	1
H1E	2689	6212	1720	32	1
H5A	3271	1092	2468	45	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N1–H1D···O5^{i}	0.88	2.40	3.049(2)	130.6
N1–H1E···O2	0.88	2.20	3.058(2)	165.5
O5–H5A···O4^{ii}	0.84	1.85	2.670(2)	165.2
O5–H5A···N1^{ii}	0.84	2.66	3.049(2)	109.5

Symmetry transformations used to generate equivalent atoms:
(i) –x+1,y+1/2,–z+1/2 (ii) –x+1,y–1/2,–z+1/2



Thermal ellipsoids drawn at the 50% probability level

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