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Flexible Synthesis of Spirocyclic Pyrans and Piperidines

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Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

School of Chemistry

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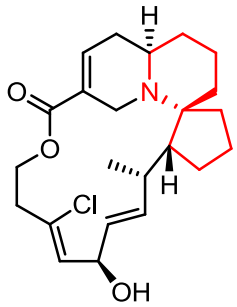
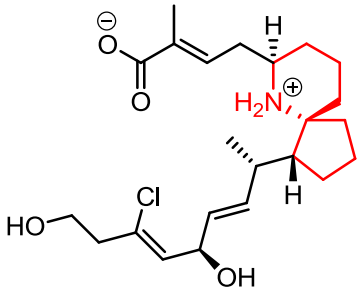
Abstract

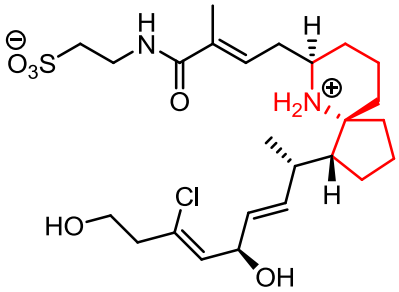
Spirocyclic piperidines and spirocyclic pyrans are prevalent throughout nature, often appearing in natural products which exhibit exciting biological activities. Notable examples of spirocyclic piperidine-containing biologically active natural products are halichlorine, pinnaic acid and tauropinnaic acid.



Halichlorine



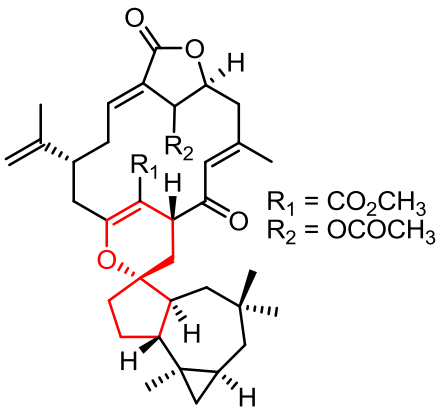
Pinnaic acid



Tauropinnaic acid

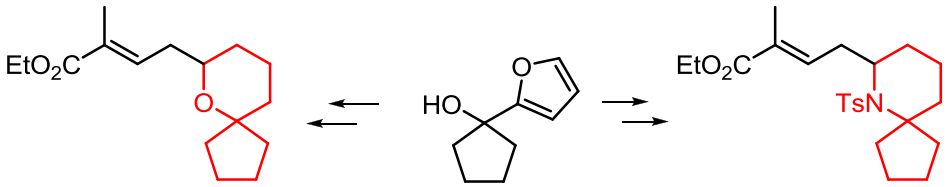
Despite their structural similarity, halichlorine and the pinnaic acids were isolated from separate organisms; halichlorine was isolated from extracts of the marine sponge *Halichondria okadai* while both pinnaic acid and tauropinnaic acid were isolated from the Okinawan bivalve mollusc *Pinna muricata*.

The complex hybrid molecule polymaxenolide contains a representative spirocyclic pyran core. The biological profile of polymaxenolide is not yet known, however its hybrid origins have rendered it a target of significant interest.

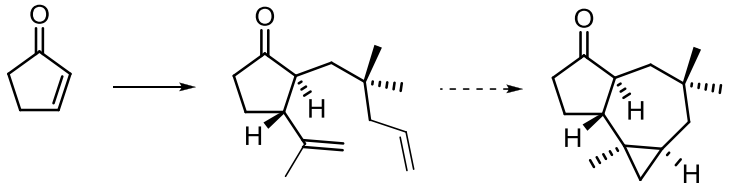


Polymaxenolide

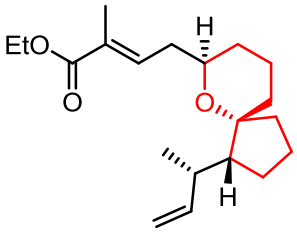
The work described herein details the development of a methodology capable of accessing both spirocyclic pyran and spirocyclic piperidine core structures from a common cyclic tertiary furfuryl alcohol intermediate. The key spirocycle forming step involves the oxidative rearrangement of cyclic tertiary furfuryl alcohols and amines for the synthesis of spirocyclic pyrans and piperidines, respectively.



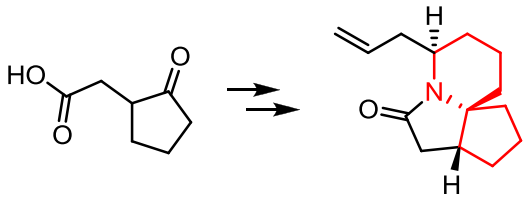
Efforts towards the synthesis of a complex, africanane-derived Southern fragment, with the intention of applying this methodology towards the synthesis of polymaxenolide are reported.



This methodology has been further elaborated to complete an asymmetric synthesis of the upper framework of an oxa-analogue of pinnaic acid.



The potential for a spectator protecting group free synthesis of pinnaic acid was also explored and the synthesis of an advanced intermediate is also reported.



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Finally, to Elisa: Thank you from the bottom of my heart for always being supportive, always caring and always giving me strength. For all of this, and much, much more, I thank you.

Author Declaration

This thesis represents the original work of Frank D. Ferrari unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow, under the supervision of Dr. Rodolfo Marquez, during the period October 2008 to September 2012.

Portions of the work described herein have been published elsewhere as listed below.

Ferrari, F. D.; Ledgard, A. J.; Marquez, R. *Tetrahedron* **2011**, *67*, 4988.

Abbreviations

4Å-MS	4 Ångström molecular sieves
4-MP	4-Methoxyphenol
9-BBN	9-Borabicyclo(3.3.1)nonane
Ac	Acetate
acac	Acetylacetone
Akt (Protein kinase B)	Serine/threonine-specific protein kinase
AIBN	Azobis*iso*butyronitrile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	Broad singlet
Bu	Butyl
Bz	Benzoyl
CAN	Cerium Ammonium Nitrate
CBS	Corey-Bakshi-Shibata
Cbz	Carboxybenzyl
CI	Chemical Ionisation
cod	Cyclooctadienyl
Cp	Cyclopentadienyl
cPLA2	Cytosolic phospholipase A2
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet
Da	Dalton
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBB	Di-*tert*-butylbiphenylide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone

DEAD	Diethyl azodicarboxylate
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Di-*iso*-butylaluminium hydride
DIPEA	Di-*iso*-propylethyl amine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dt	Doublet of triplet
EDCi	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	Enantiomeric excess
EI	Electron ionisation
ESI	Electrospray ionisation
Et	Ethyl
FAB	Fast atom bombardment
FOD	1,1,1,2,2,3,3-Heptafluoro-7,7-dimethyl-4,6-octanedionate
HBTU	*O*-Benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyl-uronium-hexafluorophosphate
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
i	*iso*
IC_{50}	Half maximal inhibition concentration
Imid.	Imidazole
IR	Infrared
km	kilometre

L.A.	Lewis acid
LDA	Lithium di*iso*propylamide
m	Multiplet
M	Molar
MAPK	Mitogen-activated protein kinase
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MEM	Methoxyethoxyl
Mes	Mesityl
MHC	Major histocompatability complex
mL	Millilitre(s)
mm	Millimetre(s)
mM	Millimolar
mmol	Millimole
MOM	Methoxymethyl
Ms	Methanesulfonyl
MU	Mass units
MW	Microwave
N	Normal
Napth	Naphthalide
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
nM	Nanomolar
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
n*O*e	Nuclear Overhauser effect
PCC	Pyridinium chlorochromate
Ph	Phenyl
PI3K	Phosphoinositol 3-kinase
PMB	*para*-Methoxybenzyl
PMBA	*para*-Methoxybenzaldehyde
PMP	*para*-Methoxyphenyl
PPE	Polyphosphate ester

PPTS	Pyridinium p-toluenesulfonate
Pr	Propyl
Pyr	Pyridine
q	Quartet
Red Al	Sodium bis(2-methoxyethoxy)aluminium hydride
Red Alp	Sodium bis(2-methoxyethoxy)(pyrrolidin-1-yl)aluminium hydride[78]
RCM	Ring-closing metathesis
RT	Room temperature
s	Singlet
t	Triplet
t	*tert*
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
tert	Tertiary
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid/trifluoroacetyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
THP-1	Human acute monocytic leukaemia cell line
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
TREAT-HF	Triethylamine trihydrofluoride
Ts	*p*-Toluenesulfonyl
*p*TsOH	*p*-Toluenesulfonic acid
VCAM-1	Vascular cell adhesion molecule-1

1. Introduction

Marine Natural Products

Some of the most fascinating and intricate chemical structures elucidated have their origins in marine ecosystems.[1] Marine life remains an environment not nearly understood, a source of speculation and mystery. Yet, while this domain consistently bestows profound discovery and illumination, curiosity is often rewarded with further provocation.

The number of documented species inhabiting the oceans is ~215,000. Taking into account all possible metabolic processes and, accordingly, the number of possible metabolites in each metabolic process, the extent of structural diversity contained within *documented* marine life is staggering.[2]

Unidentified marine life must also be taken into account. It is said that 10% of marine life in European oceans remains unidentified. This figure rises to 38% for the oceans around South Africa. In Antarctica up to 58% of species are unknown, 70% in Japan, the Mediterranean deep-sea 75% and Australia an incredible 80%.[3]

As a result, the most precise estimation possible of the number of species present in the oceans lies at approximately 2.2 million.[4]

Already, from those organisms that are known, the abundance of natural products that have been isolated have often perplexed and stimulated organic chemists, while frequently finding huge interest in the biological community through exhibiting therapeutic potential.[5] Examples of structures which cater to the desires of both groups are the pinnaic acids and halichlorine.

Halichlorine and the Pinnaic Acids

Isolation and Characterisation

Halichlorine

An extensive project for unearthing biologically active species produced by marine organisms was undertaken in the coastal waters of Japan. From the extraction of a stock of the black marine sponge *Halichondria okadai* Kadota, the compound halichlorine **1** was discovered in 1996, and was found to exhibit inhibitory activity towards the induction of vascular cell adhesion molecule-1 (VCAM-1).[6] Despite a somewhat low recovery of halichlorine **1** (200 kg afforded a mere 70.8 mg of halichlorine, corresponding to an isolation yield of 3.5×10^{-7}%) extensive structural assignments were made using 1D and 2D NMR and IR spectroscopy, mass spectrometry and partial degradation reactions to establish the absolute configuration of halichlorine **1** as that shown (**Figure 1**).

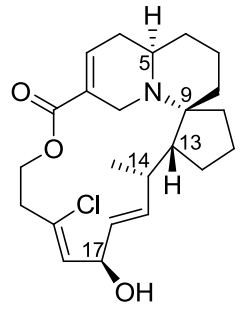

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Figure 1. Halichlorine

The Pinnaic Acids

Also revealed through this comprehensive venture were two novel polyketides containing structurally similar 6-azaspiro[4.5]decane cores; pinnaic acid **2** and tauropinnaic acid **3** (**Figure 2**). These related molecules were isolated, also in 1996, from 10 kg of the Okinawan bivalve mollusc *Pinna muricata* in quantities of 1

mg and 4 mg respectively, and were found to inhibit cytosolic 85 kDa phospholipase A2 (cPLA2).[7] In a similar fashion, 1D and 2D NMR spectroscopy and mass spectrometry assisted the elucidation of their structures. The absolute configuration at C14 and C17 was not fully established, however, as partial degradation experiments were not possible on the small quantities isolated.

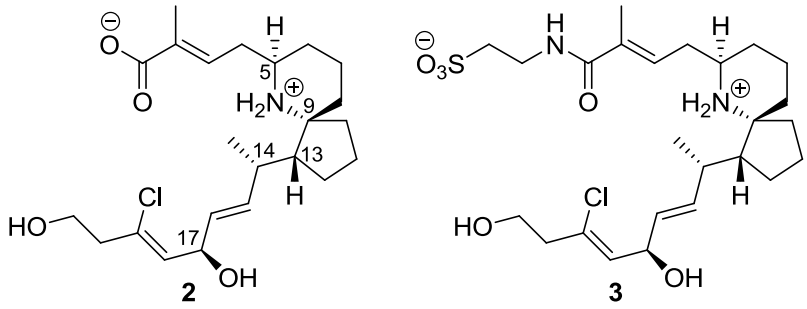

Figure 2. The pinnaic acids: pinnaic acid **2** and tauropinnaic acid **3**.

Biological Activity

VCAM-1 Inhibition

Acute inflammation occurs when neutrophils adhere to the vascular endothelium. Subsequent neutrophil migration into the surrounding tissues results in damage to that tissue. This sequence of events is mediated by specific adhesion molecules such as VCAM-1.[8] Inhibition of VCAM-1 has been shown to induce anti-inflammatory effects and as such, therapeutic agents acting at this site show potential for the treatment of cardiovascular disorders such as angina, coronary artery disease and atherosclerosis.[9] Halichlorine **1** was found to inhibit VCAM-1 with an IC_{50} of 7 μg/mL. A recent study investigated the effects of halichlorine **1** on vascular contractility and the result was the disclosure of L-type Ca^{2+} channel inhibitory activity in vascular smooth muscle cells.[10] Such vasodilatory activity is often exhibited by antihypertensive agents.[11]

In addition, VCAM-1 facilitates the adhesion of cancerous cells to the endothelium and as such, is a verified target in an effort to prevent metastasis.[12] Comprehensive biological studies have found that many factors in breast cancer

propagation and eventual metastasis are directly linked to VCAM-1 expression. VCAM-1 was found to mediate the binding of tumour-associated macrophages to cancerous cells, while enhancing the seeding of breast tumours and simultaneously protecting those breast cancer cells from apoptosis in the lung through the induction of survival signals when engaged by integrins (**Figure 3**).[13]

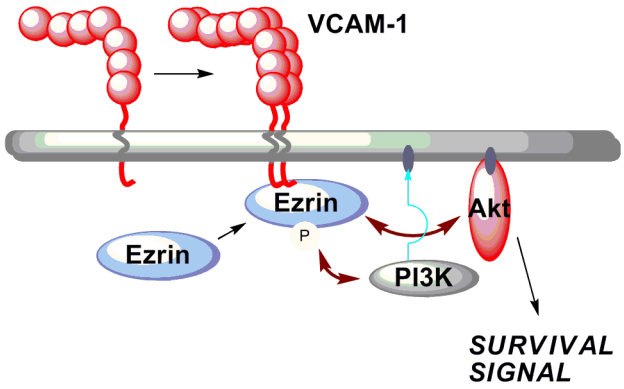

Figure 3. VCAM-1 triggers the survival signal through phosphorylation of Ezrin, a cytoplasmic linker and known docking site for phosphoinositol 3-kinases (PI3K), and subsequent binding to serine/threonine kinase Akt, also an identified target for the inhibition of cell proliferation.[13]

Further corroboration of the implication of VCAM-1 over-expression in the survival of cancerous tissue is provided by the fact that tumour death was observed in cells lacking VCAM-1 expression (**Figure 4**).[14]

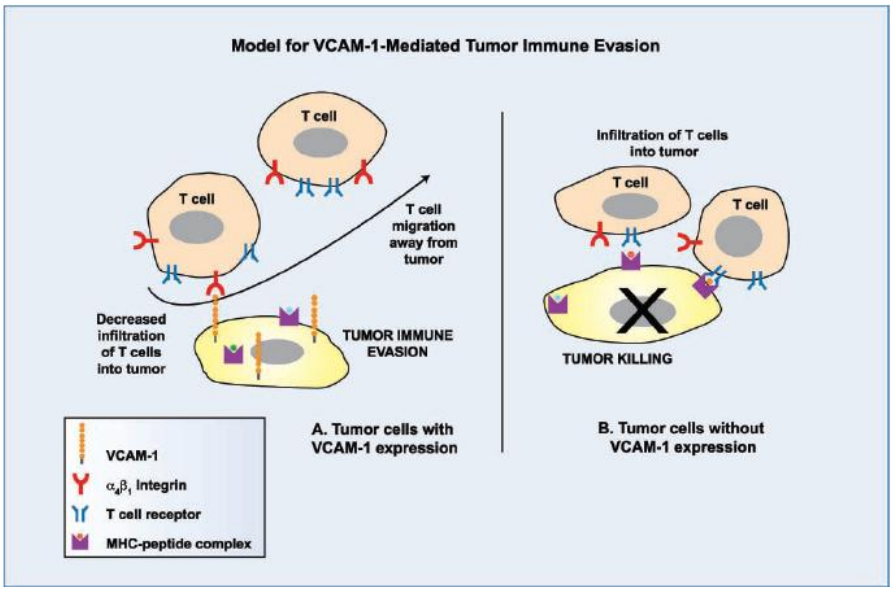

Figure 4. Those cells not expressing VCAM-1 were unable to evade the immune response.[14]

cPLA2 Inhibition

cPLA2 is pivotal in the release of arachidonic acid, which in turn is involved in the biosynthesis of crucial mediators of the inflammatory response and cell proliferation pathway.[15] Arachidonic acid is further metabolised to form both prostaglandins and leukotrienes. Prostaglandins, among other functions, trigger constriction and dilatation of vascular smooth muscle and leukotrienes are involved in asthmatic, allergic and inflammatory reactions.[16,17] Further metabolic modifications generate thromboxanes which are vasoconstrictors and platelet aggregation promoters.[18] As such, it appears that each metabolic destiny of arachidonic acid contributes to the inflammatory response as a whole, therefore compounds capable of specifically inhibiting cPLA2 activity are potential anti-inflammatory agents (**Figure 5**). The spirocyclic piperidines pinnaic acid **2** and tauropinnaic acid **3** have each displayed inhibitory activity against cPLA2 (200 nM and 90 nM respectively).[6]

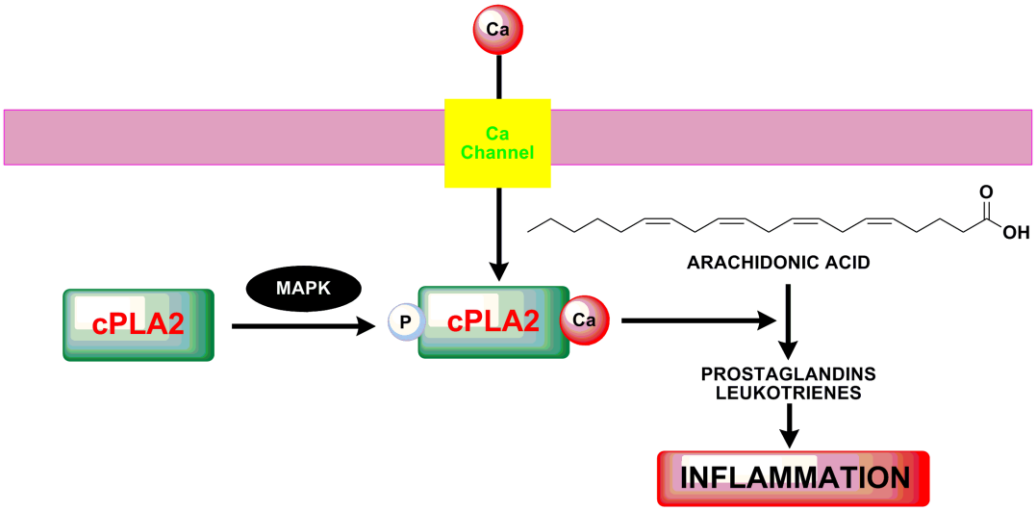

Figure 5. The role of cytosolic phospholipase A2 in the activation of inflammation.[19]

Structural Relationships and Origins

Despite being isolated from completely distinct organisms, 1500 km apart, halichlorine **1** and the pinnaic acids **2** and **3** possess remarkably similar attributes. This leads to the supposition that these compounds are the product of metabolic

pathways present in a common symbiotic organism or food source, and that they may be biosynthetically related.[1a]

Pinnarine

The recent characterisation of pinnarine **4** (**Figure 6**), also isolated from *Halichondria okadai*, seems to enforce the hypothesis of common biosynthesis as its structure represents the macrolactonisation of pinnaic acid **2**.[20] Indeed, Prof. Uemura and co-workers demonstrated this transformation from pinnaic acid **2** to pinnarine **4** through synthetic manipulation. No biological activity for pinnarine **4** has been so far reported.

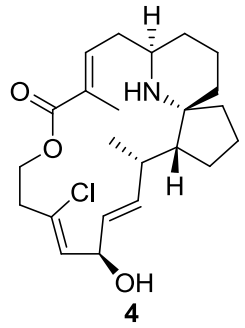

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Figure 6. Pinnarine **4**.

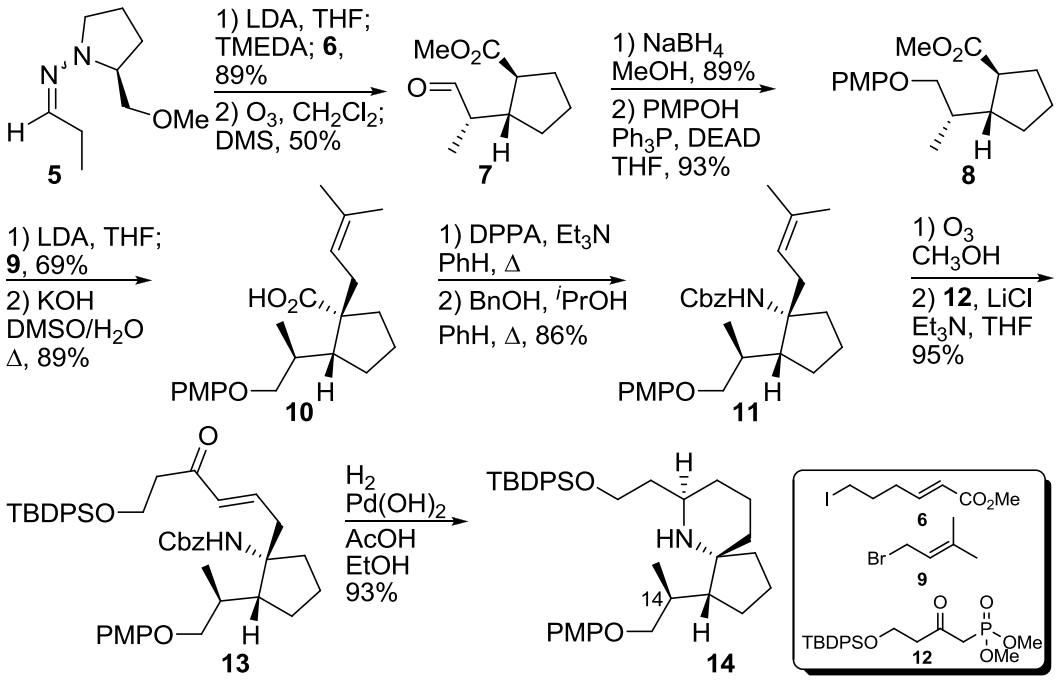
Interest from the Synthetic Community

Given their attractive, yet challenging structures in addition to their potential therapeutic value, it is not surprising that halichlorine **1** and the pinnaic acids **2** and **3** have received significant attention from the synthetic community. From the time of their discovery some 16 years ago, the volume of work dedicated to their synthesis is astounding, yet they continue to present attractive synthetic targets, maintaining significant interest.[21]

Previous Approaches

The Arimoto-Uemura Synthesis of a Complex Spirocyclic Piperidine (1999)

The first efforts towards accessing these fascinating spirocyclic alkaloids were described, rather fittingly, by those who were responsible for their discovery.[22] Uemura and Arimoto reported their strategy for accessing the functionalized spirocyclic core structure of halichlorine and pinnaic acid as progressing through the stereoselective Michael addition of the lithiate of hydrazone **5** to conjugated ester **6**, stereochemically controlled by the nature of the Enders' hydrazone (**Scheme 1**).[23] *In situ* intramolecular cyclisation and hydrazone cleavage afforded aldehyde **7**, which was subsequently reduced and protected as the PMP-ether **8**. Alkylation with prenyl bromide **9**, followed by saponification of the ester gave carboxylic acid **10**. A subsequent Curtius rearrangement generated the corresponding isocyanate which after treatment with benzyl alcohol gave the cyclic tertiary Cbz-amide **11**. Ozonolysis followed by Horner-Wadsworth-Emmons olefination with phosphonate **12** afforded enone **13**. An elegant, four-stage transformation was then induced. Simultaneously, the olefin was hydrogenated, the Cbz-protection removed, the corresponding imine was formed and was then reduced to complete the first approach towards the fully functionalized spirocyclic core **14**.



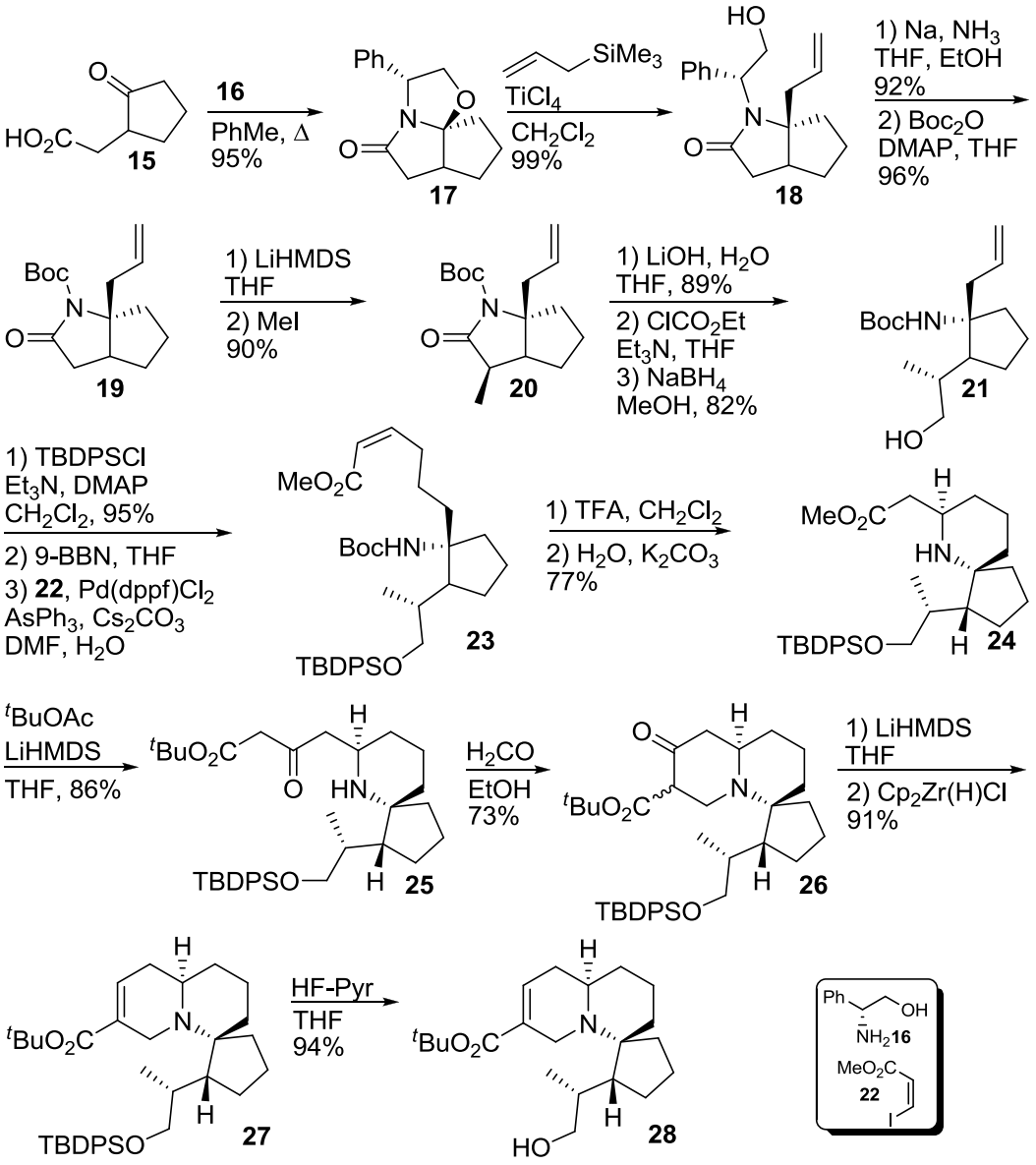
Scheme 1. The Arimoto-Uemura approach to the functionalised spirocyclic core **14**.

At the time of publication, the stereochemistry at C-14 had not been confirmed and as such, this stereocentre possessed what is now known to be the opposite orientation. Nevertheless, this first report of the synthetic endeavours towards pinnaic acid was to prove very influential, highlighting an exceptionally elegant and efficient method to generate the spirocyclic piperidine core.

Danishefsky's Synthesis of a Halichlorine Intermediate (1999)

Shortly following the disclosure of the Arimoto-Uemura methodology, Danishefsky and co-workers described their initial approach towards the spirocyclic piperidine alkaloids (**Scheme 2**).[24] Meyers' lactam **17**[25] was obtained *via* amide coupling of aminophenyl ethanol **16** and 2-(2-oxocyclopentyl)acetic acid **15**. Sakurai allylation followed and subsequent *N*-group cleavage and amide reprotection gave Boc-protected amide **19**.[26] Facially selective methylation afforded lactam **20** which was subsequently hydrolysed. Activation of the resulting acid, followed by reduction, afforded the corresponding primary alcohol **21**.[27] Silyl protection of the

primary alcohol ensued, followed by hydroboration of the terminal double bond, and a subsequent Suzuki cross-coupling with vinyl iodide **22**.[28] Upon removal of the Boc protection, the corresponding cyclic tertiary amine underwent an intramolecular Michael addition, resulting in the spirocyclic piperidine core **24**. A two carbon chain extension of spirocycle **24** was achieved *via* a crossed Claisen condensation and a subsequent Mannich reaction effected ring closure to generate tricyclic spirocycle **26**. Deoxygenation *via* the formation of a hydrozirconium enolate followed by silyl group removal afforded the tricyclic piperidine core of halichlorine **28** (**Scheme 1**).[29]

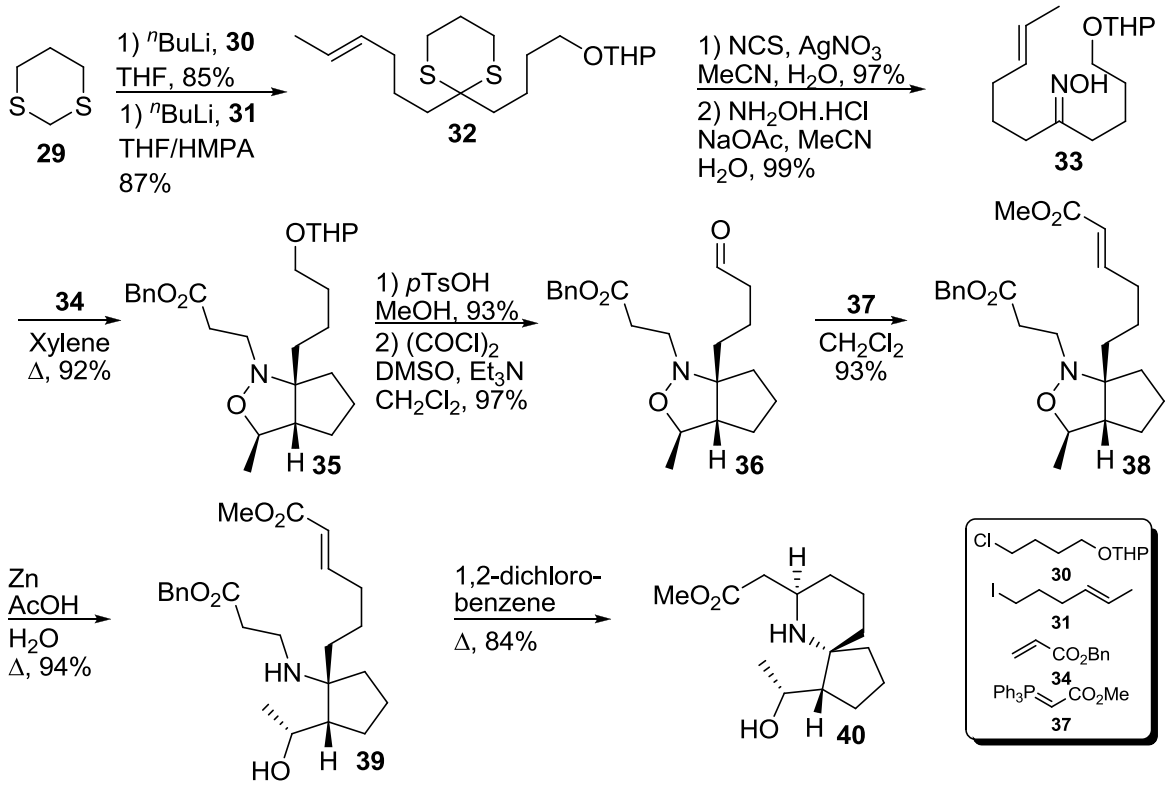


Scheme 2. The Danishefsky group synthesis of advanced halichlorine intermediate **28**

The Danishefsky approach was the first to undertake the synthesis of the halichlorine tricycle. Although various succeeding methods for the synthesis of the third ring of halichlorine were reported, many subsequent synthetic efforts towards halichlorine have adopted the use of a similar intramolecular Michael addition to generate the spirocyclic core.

Zhao's Synthesis of Spirocyclic Piperidines (1999)

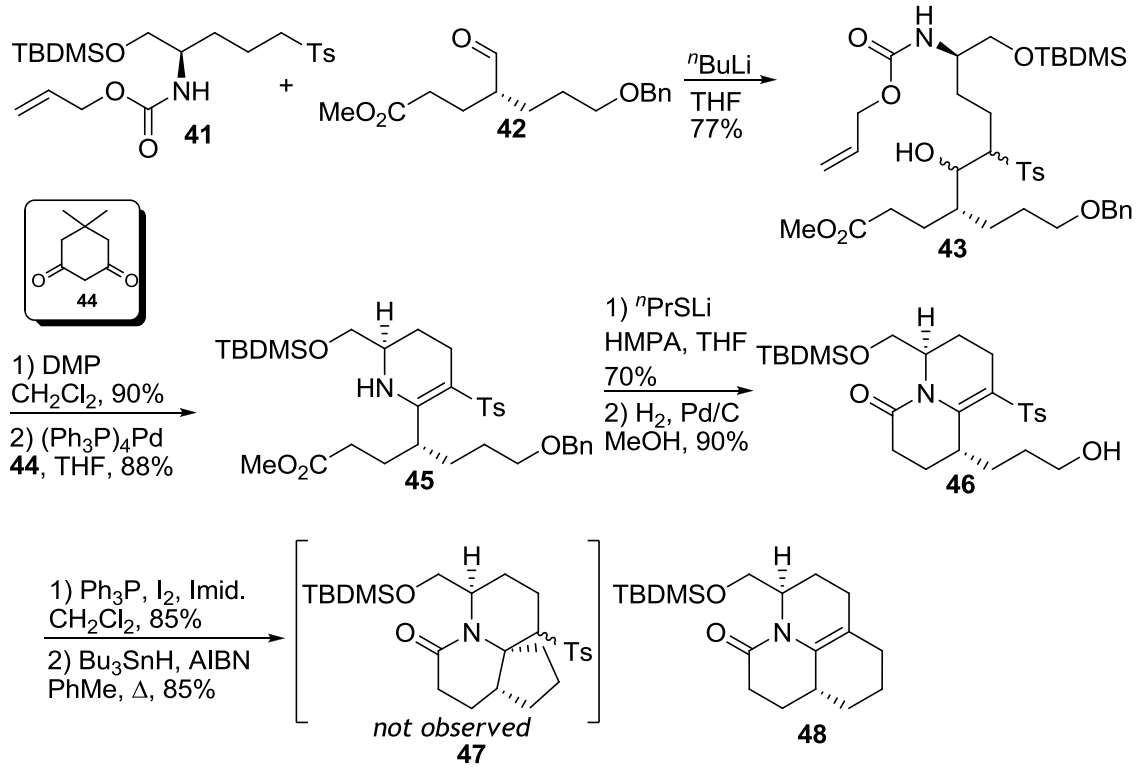
One such strategy which utilised an analogous intramolecular Michael addition as the key spirocyclisation step was reported in 1999 by Zhao and co-workers (**Scheme 3**).[30] Their approach began with the differential double-alkylation of dithiane **29** to incorporate the protected primary alcohol **30**, and olefin-containing **31** chains, giving rise to substituted dithiane **32**. Thioketal cleavage followed by treatment with hydroxylamine afforded the corresponding oxime **33**. Upon heating with benzyl acrylate **34** a [3+2]-cycloaddition was triggered between the corresponding *in situ* formed nitrone and the olefin of the alkyl chain to generate, as a single product, bicyclic adduct **35**.[31] Deprotection followed by oxidation, and subsequent Wittig olefination afforded enoate **38**. Cleavage of the N-O bond followed to afford cyclic tertiary amine **39**. Heating effected the simultaneous intramolecular Michael addition, and liberation of benzyl acrylate, generating the spirocyclic piperidine **40**. The synthesis of the analogous spirocyclic piperidine, possessing the opposite stereochemistry at the pseudo C-14 position, was also described utilising the corresponding *Z*-olefin of alkyl iodide **31**.



Scheme 3. Zhao's synthesis of the spirocyclic core **40**.

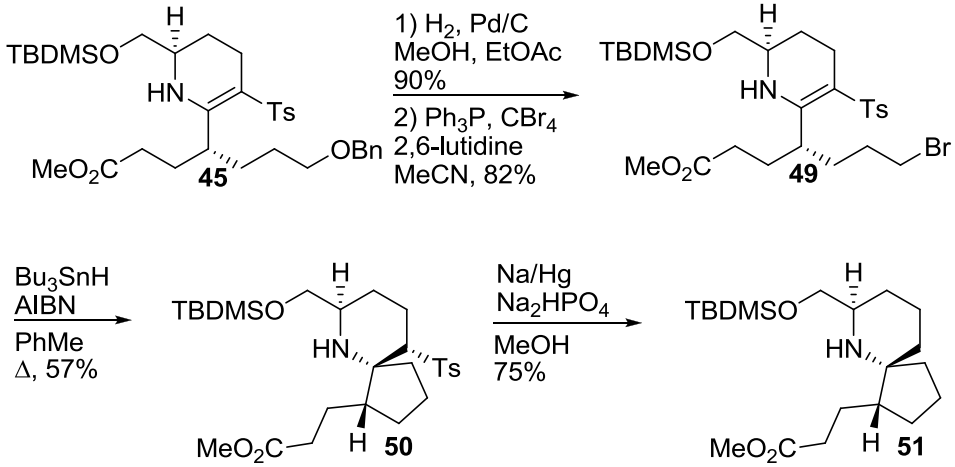
Clive's Route Towards the Halichlorine and Pinnaic Acid Cores (1999)

In the first of many in-depth and imaginative contributions towards the synthesis of these alkaloids, Clive and co-workers attempted to utilise a radical cyclisation for the synthesis of the halichlorine tricyclic core (**Scheme 4**).[32] Coupling of glutamic acid derived allylcarbamate **41**[33] with aldehyde **42**[34] afforded diastereomeric alcohols **43**. Oxidation was followed by removal of the allyloxycarbonyl protection, resulting in imine formation and tautomerisation to the corresponding cyclic enamine **45**. Lactamisation followed by benzyl group removal then afforded primary alcohol **46**.[35] Conversion of alcohol **46** to the corresponding iodide then enabled the exploration of the key radical cyclisation step. In contrast to the expected outcome, a 6-*endo*-cyclisation occurred, generating tricycle **48**, rather than the desired 5-*exo*-cyclisation product **47.**



Scheme 4. Clive's first generation radical cyclisation.

Fortunately, the desired spirocyclisation was found to occur when carried out on an earlier substrate. Debenzylation of **45** afforded the primary alcohol which was converted to the corresponding bromide **49**. At this juncture, the radical cyclisation conditions were found to give the desired 5-*exo* ring closure, generating spirocyclic piperidine **50**. Subsequent desulfonylation afforded the core structure of pinnaic acid **51** (**Scheme 5**).[36]

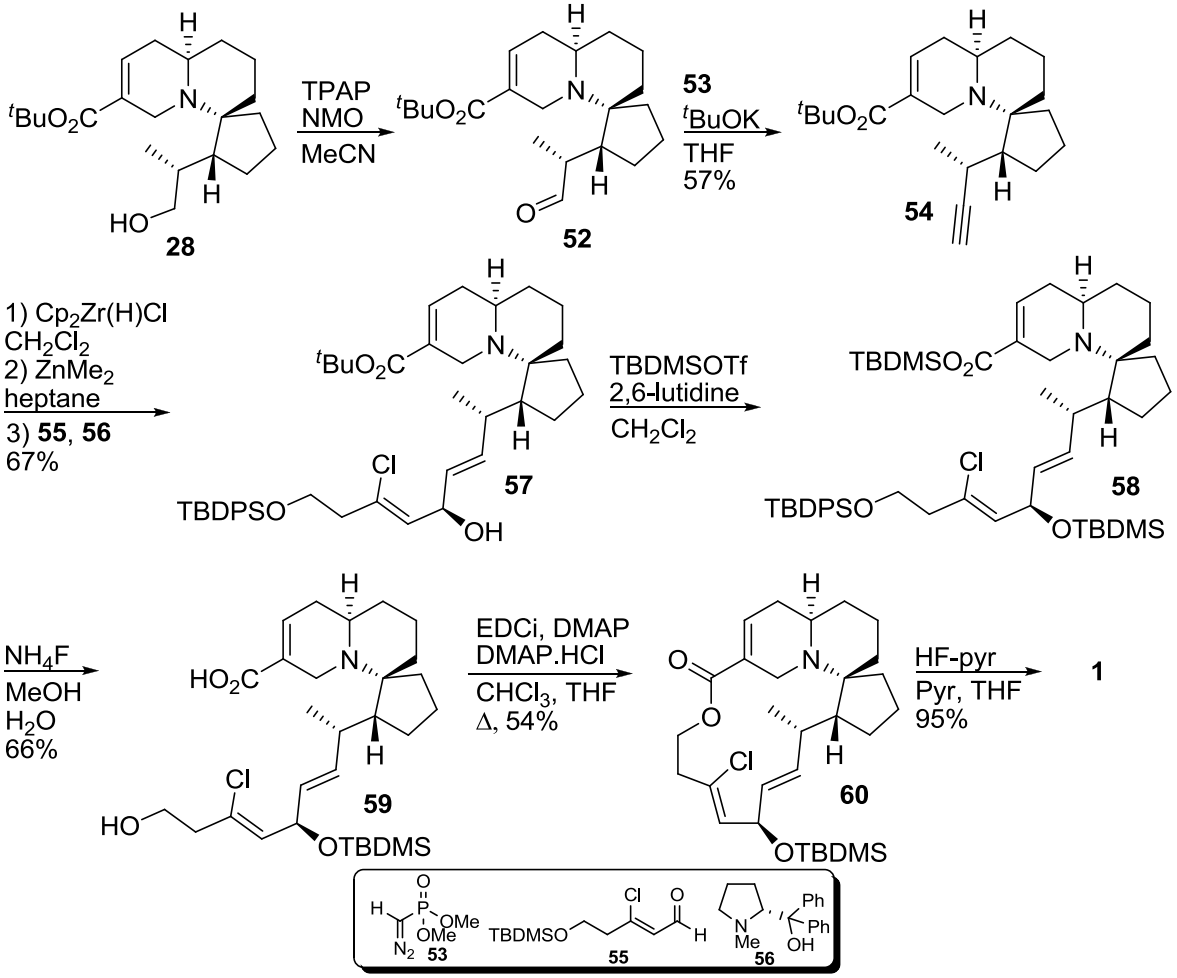


Scheme 5. Clive's revised radical cyclisation.

This report represents the initial efforts of what would become a truly vast contribution from the Clive group towards the synthesis of halichlorine and pinnaic acid. In the following years, several different and creative approaches would be disclosed.

Danishefsky's Asymmetric Total Synthesis of Halichlorine (1999)

The first total synthesis of halichlorine **1** was completed by Danishefsky and co-workers (**Scheme 6**).[37] Following on from their previously reported tricyclic intermediate **28** (**Scheme 2**), primary alcohol oxidation was found only to be achievable using Ley oxidation conditions without epimerisation of the C-14 stereocentre.[38] Subsequent Seyferth-Gilbert homologation[39] afforded alkyne **54**, which upon hydrozirconation and zinc exchange, followed by addition to aldehyde **55**, gave a 4:1 mixture of diastereoisomers in favour of the desired allylic alcohol **57**.[40,41] The ratio was achieved through the use of Soai's chiral amino alcohol **56**.[42] The mixture of diastereoisomers was carried on without separation to undergo ester hydrolysis and simultaneous silyl protection.[43] Subsequent silyl group removal at the carboxyl and primary alcohols afforded seco-acid **59**.[44]
Keck macrolactonisation[45] proceeded to give 14-TBDMS-halichlorine **60**, which upon a final deprotection completed the first total synthesis of halichlorine **1** in 2% overall yield over 30 steps.



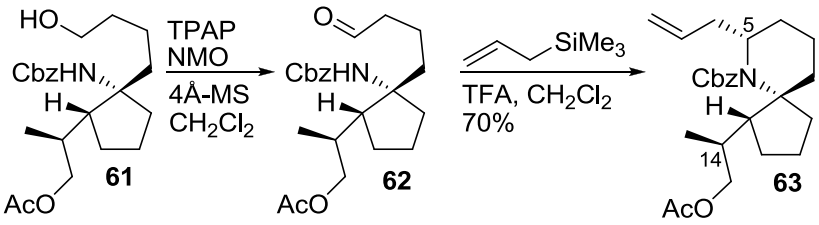
Scheme 6. The first synthesis of halichlorine **1**.

Surprisingly, despite its success, this remains the only route that has utilised a directed vinyl zinc addition to introduce the lower side-chain unit **55**.

Forsyth's Synthesis of Spirocyclic Piperidines (1999)

A matter of days after the submission of the first total synthesis of halichlorine, Forsyth submitted his strategy for the synthesis of spirocyclic piperidines (**Scheme 7**).[46] Forsyth's route detailed the application of a methodology developed through the use of simple starting cyclic tertiary amides as a model system, to a more elaborate amine **61**, the synthesis of which was not disclosed. Oxidation of the

primary alcohol **61** to give aldehyde **62**, followed by *in situ* imine formation and simultaneous allylation afforded substituted spirocyclic piperidine **63** as a single diastereoisomer, albeit possessing the opposite stereochemistry at C-5. Due to the ambiguity at the time, it also displayed opposite C-14 orientation to that of the natural substrate.

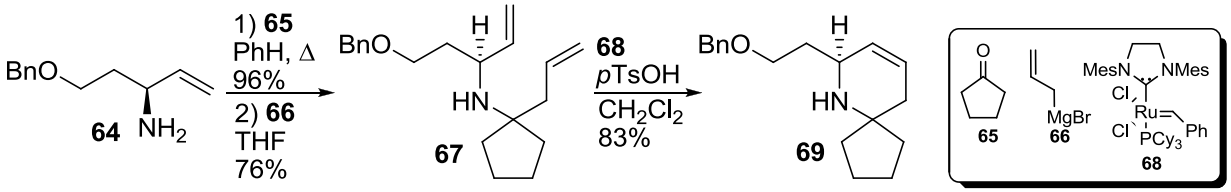


Scheme 7. The Forsyth approach to spirocyclic piperidines.

Further elaboration was described through the oxidation and Wittig olefination of the terminal olefin, however, precise conditions and yields were not reported.

Wright's Synthesis of Spirocyclic Piperidines (2000)

Wright described a concise approach to the synthesis of unsubstituted spirocyclic piperidines involving the formation of an allyl imine, and subsequent allylation of the imine carbon to give a *bis*-olefinic species **64** (**Scheme 8**). Ring-closing metathesis then afforded the desired spirocyclic piperidine **69**. [47]



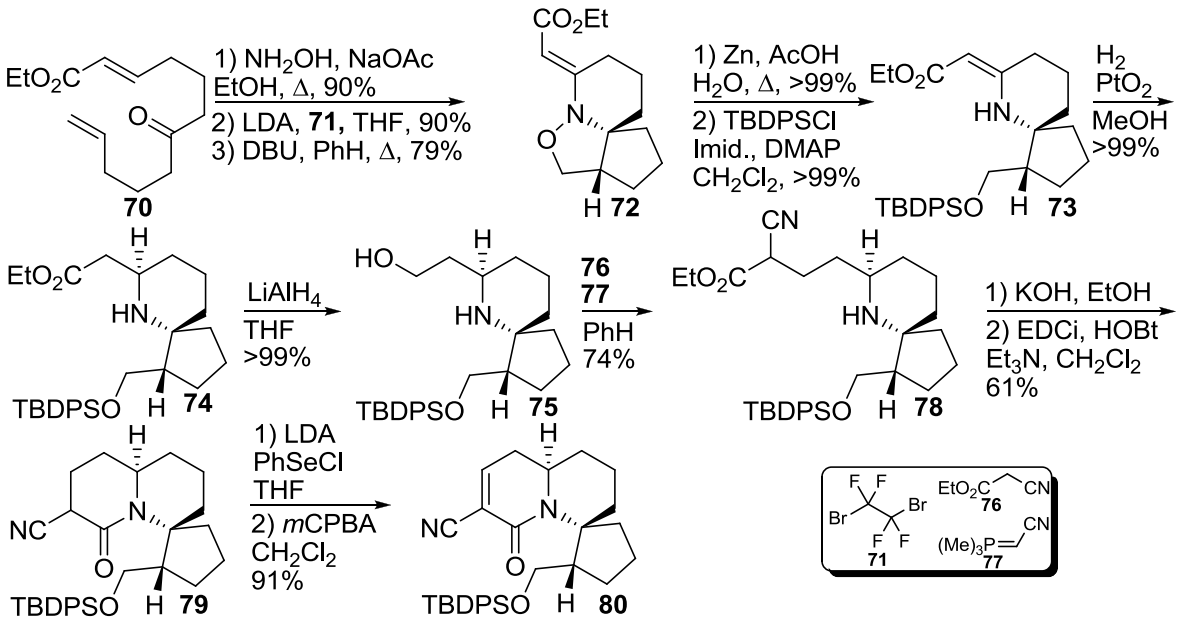
Scheme 8. Wright's ring-closing metathesis method for forming spirocyclic piperidines.

Of particular note in this strategy is the application of *p*TsOH during the ring-closing metathesis step. In the absence of this additive, cyclisation proceeded with poor yields, likely owing to the deleterious effect naked nitrogen atoms can have on

ruthenium catalysts. The inclusion of *p*TsOH rendered the now protonated species amenable to metathesis reactions, without the need for *N*-protection.

The Itoh-Shishido Approach to the Synthesis of Halichlorine (2000)

Shishido's approach towards the synthesis of azatricyclic piperidines related to halichlorine centred on a tandem intramolecular Michael addition/[3+2]-cycloaddition[31] of the corresponding oxime of ketone **70** (**Scheme 9**).[48] While some earlier reports hinged on intramolecular Michael addition protocols as the key transformation, and others described a nitrone [3+2]-cycloaddition, this work represents the first strategy for the synthesis of the spirocyclic alkaloids through the exploitation of both processes in tandem. Cleavage of the N-O bond with concomitant double-bond isomerisation yielded the free alcohol which was protected to give silyl ether **73**. Olefin hydrogenation proceeded from the desired face, and subsequent ester reduction afforded primary alcohol **75**. A Tsunoda-Mitsunobu coupling gave rise to ester **78**, which was hydrolysed and subsequently lactamised affording tricyclic piperidine **79**.[49, 50] Selenoxide elimination afforded the corresponding halichlorine core **80**.



Scheme 9. The Itoh-Shishido route to the halichlorine core **80**.

The collaborative efforts of Shishido and Itoh also established a number of initial biological activities through the evaluation of their spirocyclic piperidine intermediates against THP-1 cell lines (**Figure 7**).[51]

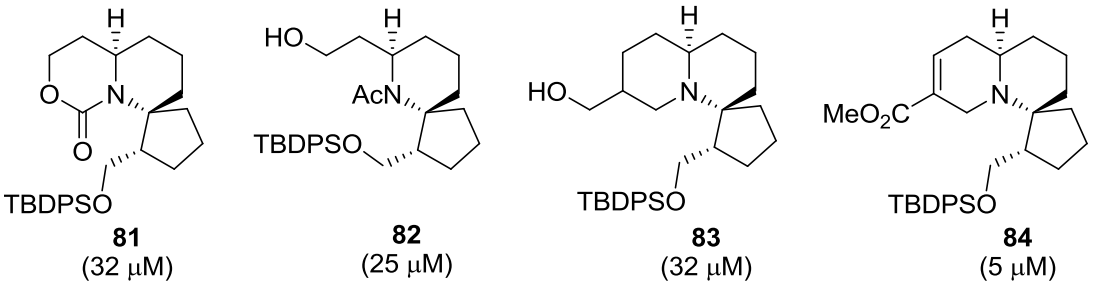


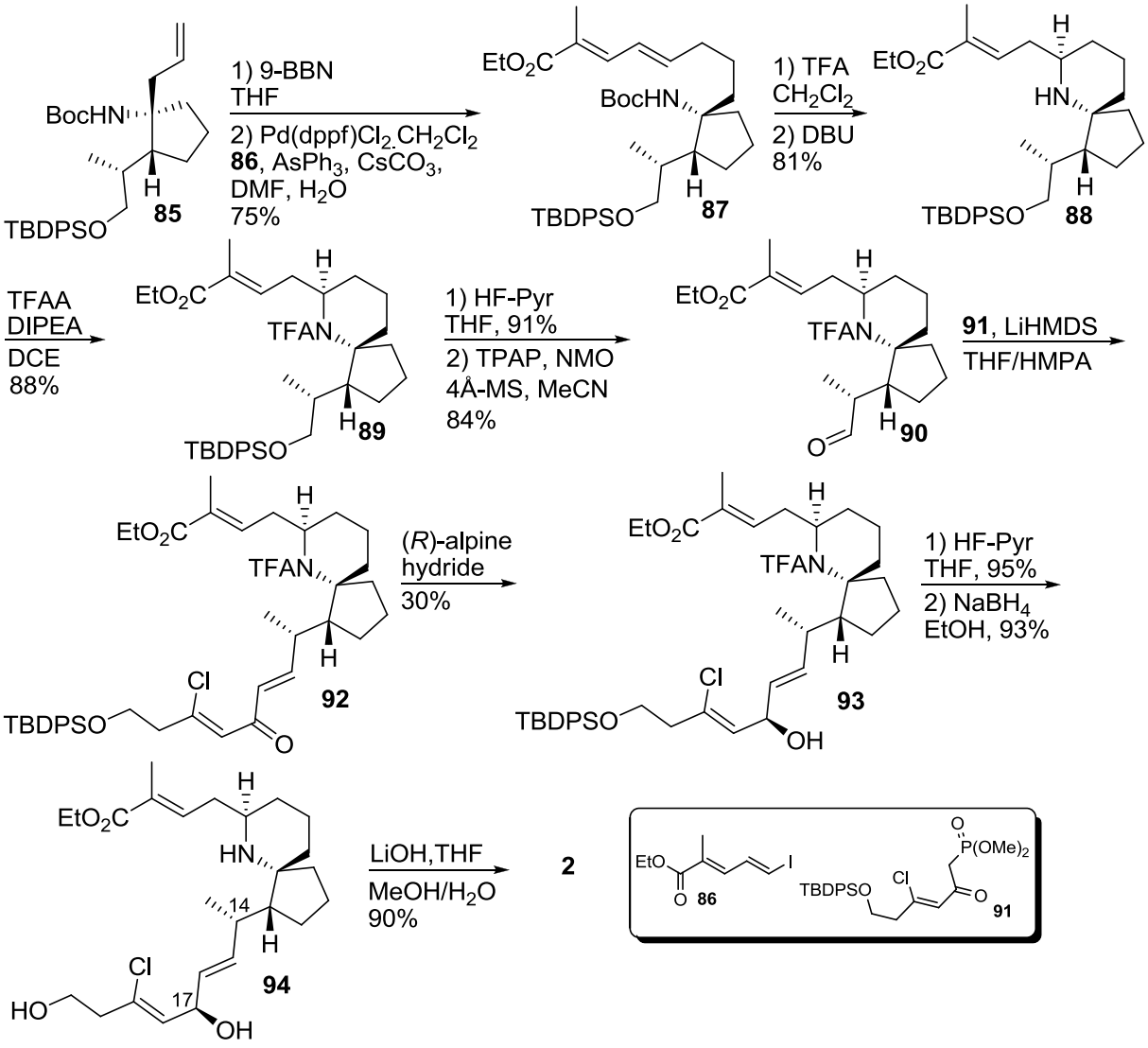
Figure 7. Those intermediates found to display activity. The numbers in parentheses refer to the recorded IC_{50} values against THP-1 cell lines.

Danishefsky's Asymmetric Total Synthesis of Pinnaic Acid (2001)

Despite the plethora of distinct approaches to the spirocyclic cores reported in the preceding years, none had emerged detailing the complete synthesis of pinnaic acid, until Danishefsky described the first total synthesis of pinnaic acid **2** in 2001 (**Scheme 10**).[52] Danishefsky's synthesis applied certain aspects of his halichlorine synthesis, and was tailored to suit the generation of the open chain spirocyclic piperidine.

As with their halichlorine strategy, Danishefsky and co-workers began their synthesis of pinnaic acid **2** starting from Meyer's lactam **17** (**Scheme 2**) followed by conversion to the protected amino alcohol **85**. Subsequent hydroboration followed by Suzuki cross-coupling using alkyl iodide **86**, afforded ethyl dienoate **87**.[53] Amine deprotection followed by 1,6-Michael-type addition afforded piperidine **88**, the key spirocyclic core of pinnaic acid. Trifluoroacetate protection of the amine followed by silyl removal and oxidation of the resulting alcohol afforded aldehyde **90**. Aldehyde **90** was then coupled with phosphonate **91** to obtain dienone **92**.[41] Stereoselective reduction[54] afforded allylic alcohol **93** which upon global

deprotection and hydrolysis completed the first synthesis of pinnaic acid **2** over 21 steps and in 3% overall yield.

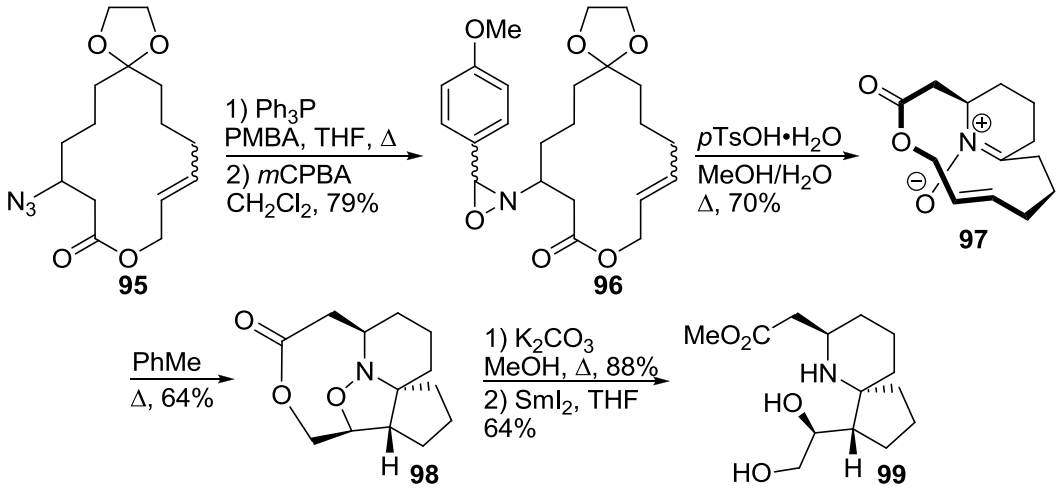


Scheme 10. The first asymmetric total synthesis of pinnaic acid **2**.

This first synthesis of pinnaic acid also served to assign the correct relative stereochemistry to the tentatively assigned C-14 and unknown C-17 positions. The confirmation was achieved through the synthesis of the four epimers at C-14 and C-17 of pinnaic acid. Comparisons of the NMR spectra obtained for these analogous structures to those spectra obtained for the isolated natural pinnaic acid allowed the identification of their synthetic equivalent which most closely corresponded to the natural pinnaic acid. The absolute configuration, however, has not yet been confirmed.[20]

White's Strategy Towards Pinnaic Acid (2001)

A fine example of a wonderfully imaginative methodology towards accessing spirocyclic piperidines was reported by White in 2001 (**Scheme 11**).[55] In White's approach, macrocyclic azide **95**, accessed through ring-closing metathesis, was converted to aryl oxaziridine **96**. Treatment of **96** with *p*TsOH generated a keto-hydroxylamine which spontaneously underwent intramolecular condensation to give rise to nitrone **97**. A subsequent transannular cycloaddition then afforded the key tetracycle **98**. Methanolysis followed by reductive cleavage yielded the advanced intermediate diol **99** (**Scheme 11**).[56]



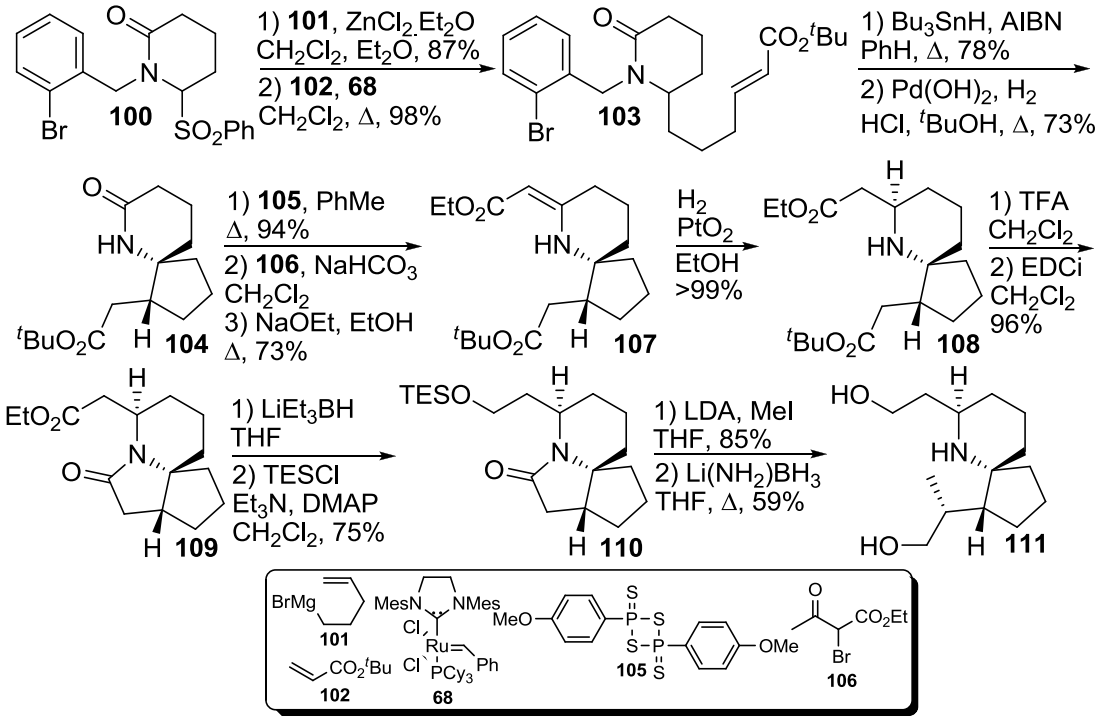
Scheme 11. The White group approach to the synthesis of spirocyclic piperidines.

Unfortunately, further functionalisation to incorporate the C-14 methyl group could not be achieved. Nonetheless, this strategy remains a highly creative method for the synthesis of spirocyclic piperidines.

Ihara's Spirocyclic Core (2003)

Ihara reported a radical translocation/cyclisation strategy towards the spirocyclic piperidine core **111** (**Scheme 12**).[57] Sulfone **100**, readily accessed from

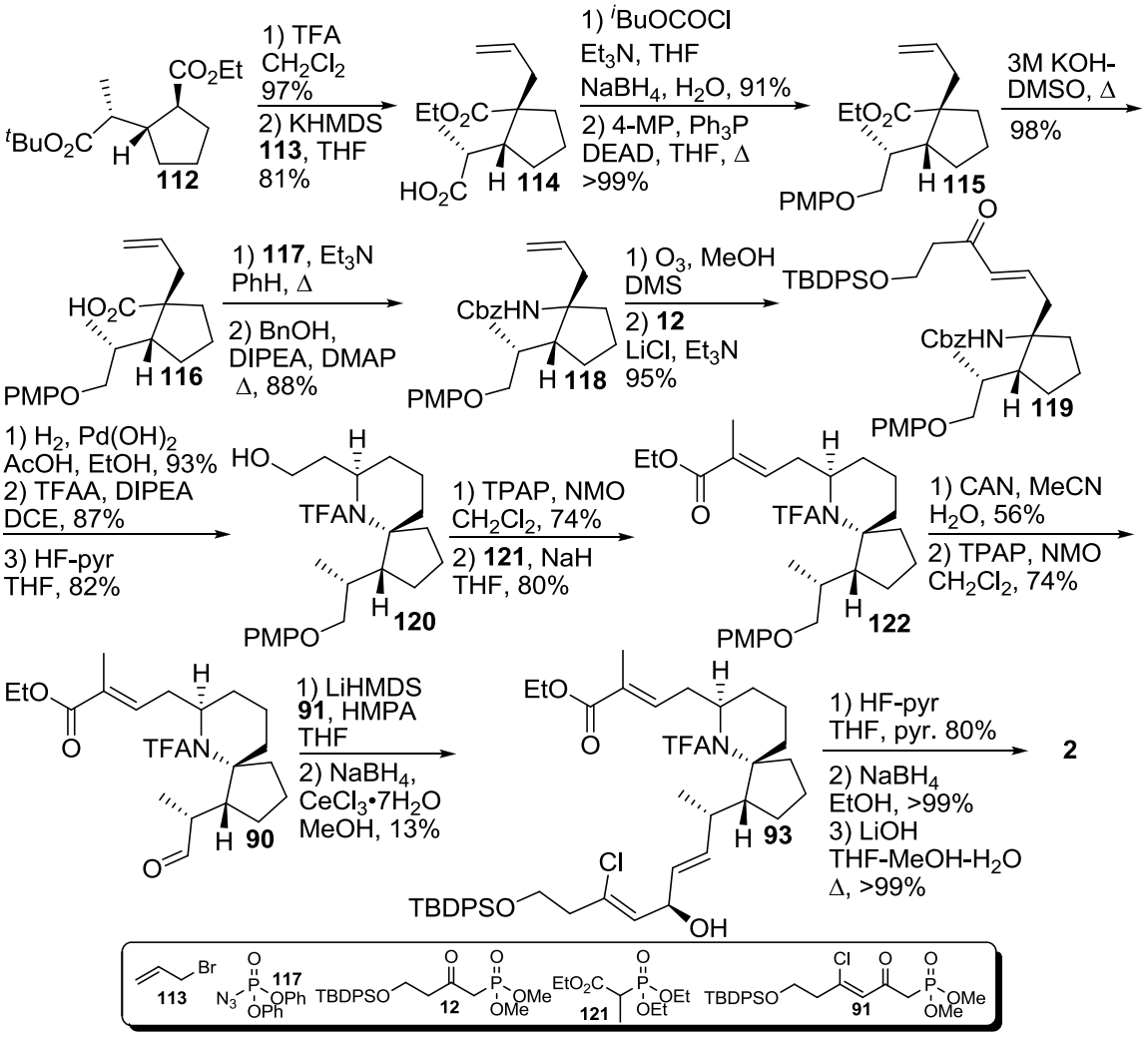
glutarimide, underwent Grignard addition and cross-metathesis to afford enoate ester **103**.[58] Generation of the aryl radical, followed by translocation gave the corresponding α-aminyl radical, which upon subsequent intramolecular cyclisation afforded spirocycle **104** as the major product. Benzyl group removal, followed by treatment with Lawesson's reagent **105** afforded the corresponding thiolactam which was subsequently coupled with ethyl 2-bromoacetoacetate **106** under Eschenmoser's conditions.[59] Deacetylation then afforded to conjugated ester **107**. Hydrogenation of olefin **107** afforded the desired diastereoisomer **108** which after ester cleavage followed by lactamisation afforded tricyclic spirocycle **109**. Ester reduction generated the primary alcohol, which was silylated to afford TES-ether **110**. Face-directed methylation and lactam ring opening with simultaneous silyl group cleavage afforded the spirocyclic core **111** (**Scheme 12**).[60]



Scheme 12. Ihara's approach to the spirocyclic core **111**.

Arimoto and Uemura's Synthesis of Pinnaic Acid (2003)

Following on from their seminal publication, Arimoto and Uemura completed their racemic synthesis of pinnaic acid **2**.[61] Their synthesis proceeded through the cyclic tertiary amine **118** which was accessed *via* the Curtius rearrangement of carboxylic acid **116**. Ozonolysis of alkene **118** followed by Horner-Wadsworth-Emmons olefination afforded enone **119** which was then subjected to the previously developed hydrogenation conditions to effect spirocycle formation. Sequential nitrogen protection followed by desilylation gave primary alcohol **120**. Oxidation of alcohol **120** followed by Horner-Wadsworth-Emmons olefination afforded enoate **122**. PMP-ether cleavage, followed by oxidation and olefination with phosphonate **91** afforded the corresponding enone which upon reduction under Luche conditions afforded allylic alcohol **93** (**Scheme 13**). Completion of the synthesis was achieved by following a deprotection sequence analogous to Danishefsky's synthesis of pinnaic acid **2**.

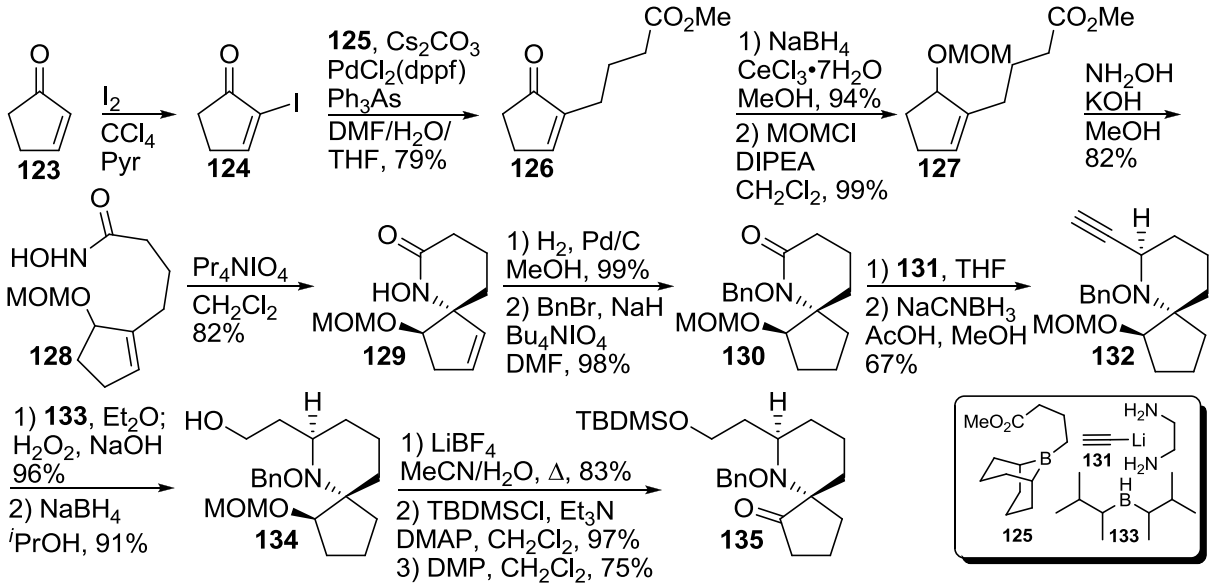


Scheme 13. The Arimoto-Uemura first generation synthesis of pinnaic acid **2**.

Kibayashi's Formal Synthesis of Pinnaic Acid and Halichlorine (2003-2004)

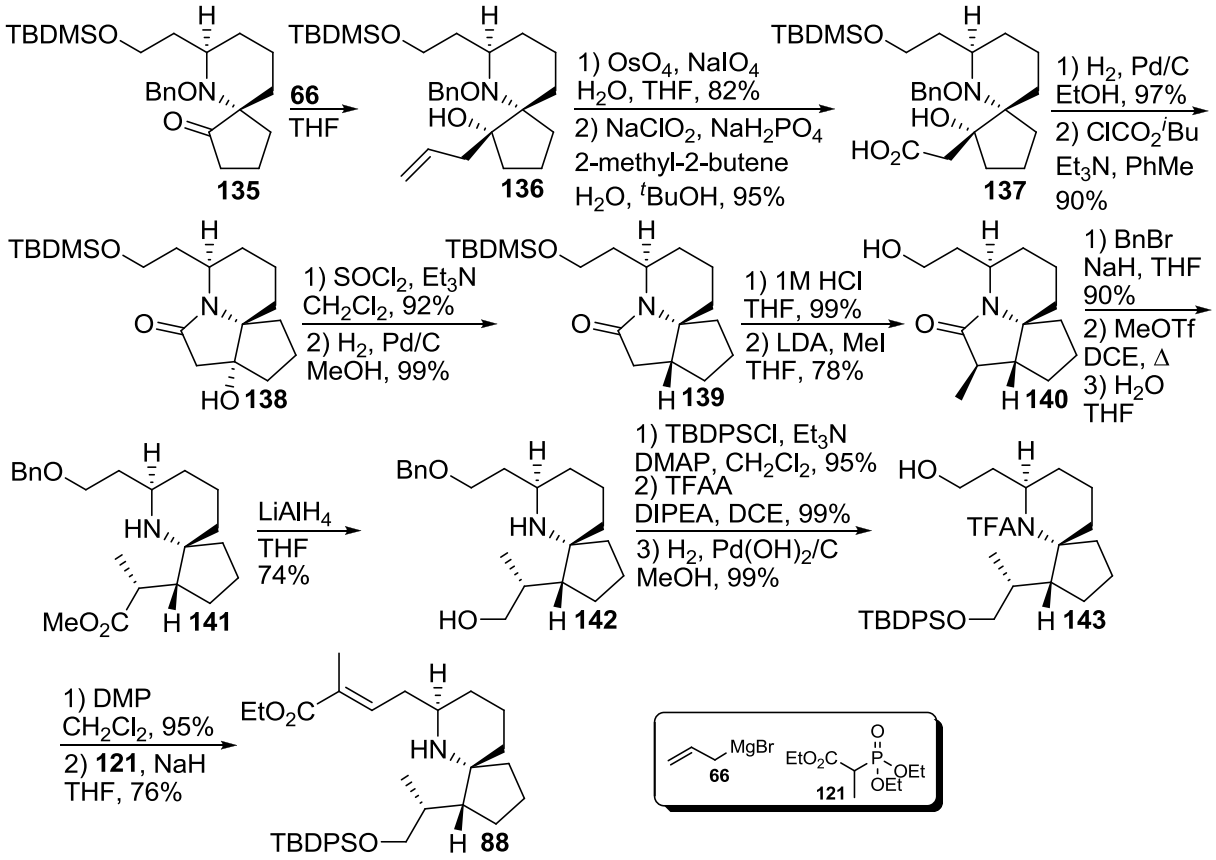
Kibayashi reported his efforts towards the synthesis of the spirocyclic cores of pinnaic acid and halichlorine, and shortly thereafter described the formal syntheses of both natural products starting from cyclopentenone **123** (**Scheme 14**).[62] Iodination of cyclopentenone **123** and subsequent Suzuki cross-coupling gave ester **126**.[63] Luche reduction followed by MOM-protection afforded cyclic allylic alcohol **127**. Treatment with hydroxylamine then yielded hydroxamic acid **128**, which was oxidised to the corresponding *N*-acylnitroso species and then cyclised to yield the spirocyclic core **129**. Hydrogenation of the cyclic olefin followed by benzylation

afforded spirocycle **130**. Subsequent alkynylation followed by reduction generated the terminal alkyne **132**, which upon hydroboration and reduction led to primary alcohol **134**. MOM deprotection, followed by selective silylation of the primary alcohol and oxidation of the remaining secondary alcohol gave spirocyclic ketone **135**.



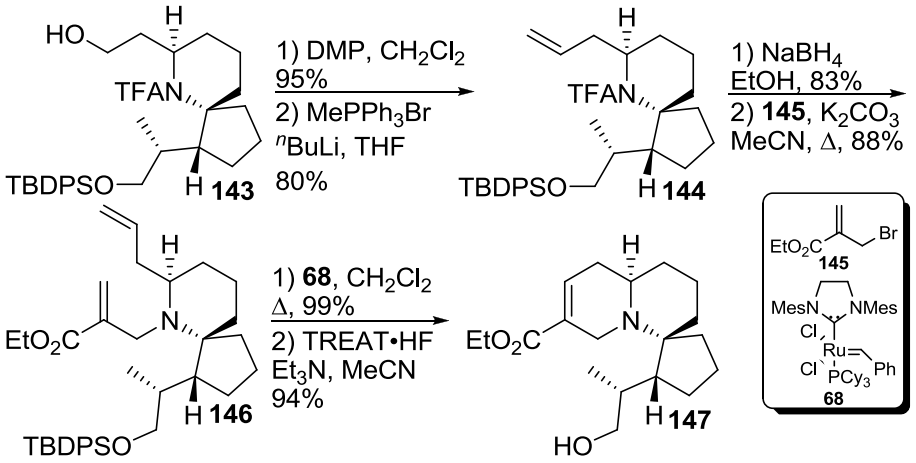
Scheme 14. The synthesis of Kibayashi's spirocyclic ketone **135**.

Allyl Grignard addition to ketone **135**, followed by dihydroxylation/periodate cleavage and Pinnick oxidation afforded carboxylic acid **137**. Hydrogenolysis and subsequent activation of the acid allowed an intramolecular amide coupling to take place, generating the tricyclic core **138**. Dehydroxylation followed by deprotection and facially directed methylation afforded primary alcohol **140**. Benzylation of the primary alcohol and subsequent lactam ring opening afforded methyl ester **141**, which was reduced to the primary alcohol **142**.[64] Silylation of alcohol **142**, followed by nitrogen protection and benzyl group removal afforded primary alcohol **143**. DMP oxidation and Wittig olefination afforded the Danishefsky intermediate **88**, completing the formal synthesis of pinnaic acid (**Scheme 15**).



Scheme 15. The Kibayashi synthesis of the Danishefsky intermediate **88**.

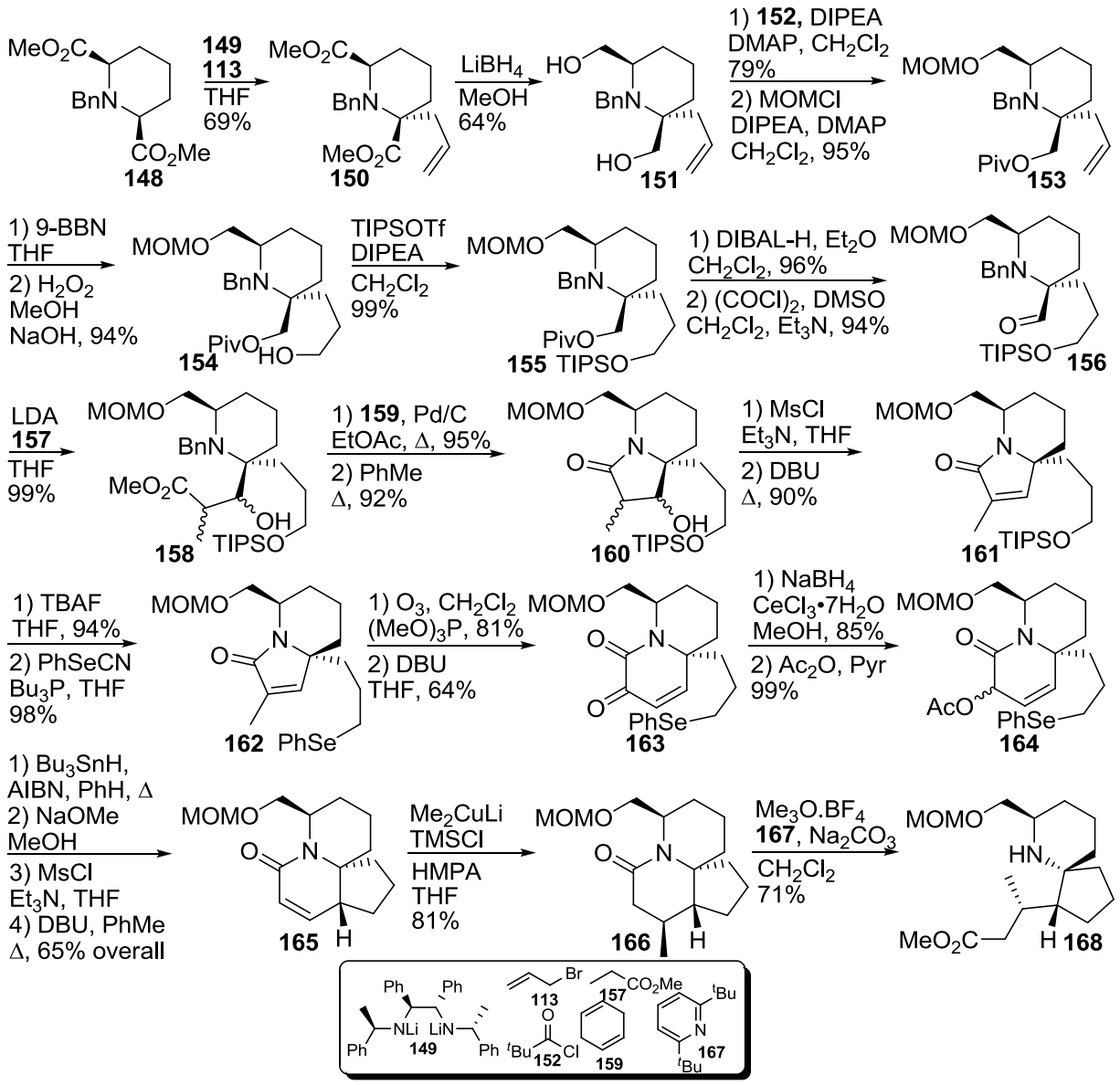
From the same primary alcohol **143**, oxidation followed by Wittig methylenation afforded allyl substituted spirocyclic piperidine **144** (**Scheme 16**). Nitrogen deprotection followed by alkylation with bromomethyl acrylate **145** afforded bis-olefin **146**, which upon ring-closing metathesis and deprotection afforded tricyclic piperidine **147**, the ethyl ester analogue of the Danishefsky intermediate **27** (**Scheme 2**).[65] Through this work, the Kibayashi group was the first to demonstrate the applicability of ring-closing metathesis for the construction of the third ring of the halichlorine core.



Scheme 16. Synthesis of the ethyl ester analogue **147** of Danishefsky's halichlorine intermediate

Clive's Alternative Route to the Spirocyclic Core (2004)

In an alternative method towards the formation of spirocyclic piperidines, Clive disclosed an improved radical cyclisation strategy (**Scheme 17**).[66] The second generation approach concerned the stereoselective allylation of piperidine **148** to afford allyl piperidine **150**, the diester functionality of which was subsequently reduced to afford diol **151**.[67, 68] Differential protection of the two primary alcohols followed by hydroboration generated primary alcohol **154**, which was protected as the TIPS-ether **155**. Pivaloyl reduction followed by oxidation of the resulting alcohol afforded aldehyde **156** which was then alkylated to give β-hydroxy ester **158**. Benzyl group removal allowed lactamisation to take place affording bicycle **160**. Hydroxyl elimination followed by desilylation and treatment with phenylselenocyanide afforded the phenylselenide **162**.[69] Ozonolysis, followed by intramolecular aldol condensation and dehydration gave enone **163**. Luche reduction and acetylation afforded a mixture of acetates **164** which, upon radical cyclisation, yielded a mixture of enone **165** and diastereomeric acetates. This mixture was deacetylated and the resultant hydroxyl groups eliminated to afford the desired tricyclic enone **165**. Facially selective methylation afforded tricyclic piperidine **166**.[70] Lactam ring opening finally afforded the halichlorine and pinnaic acid spirocyclic core structure **168**.[71]

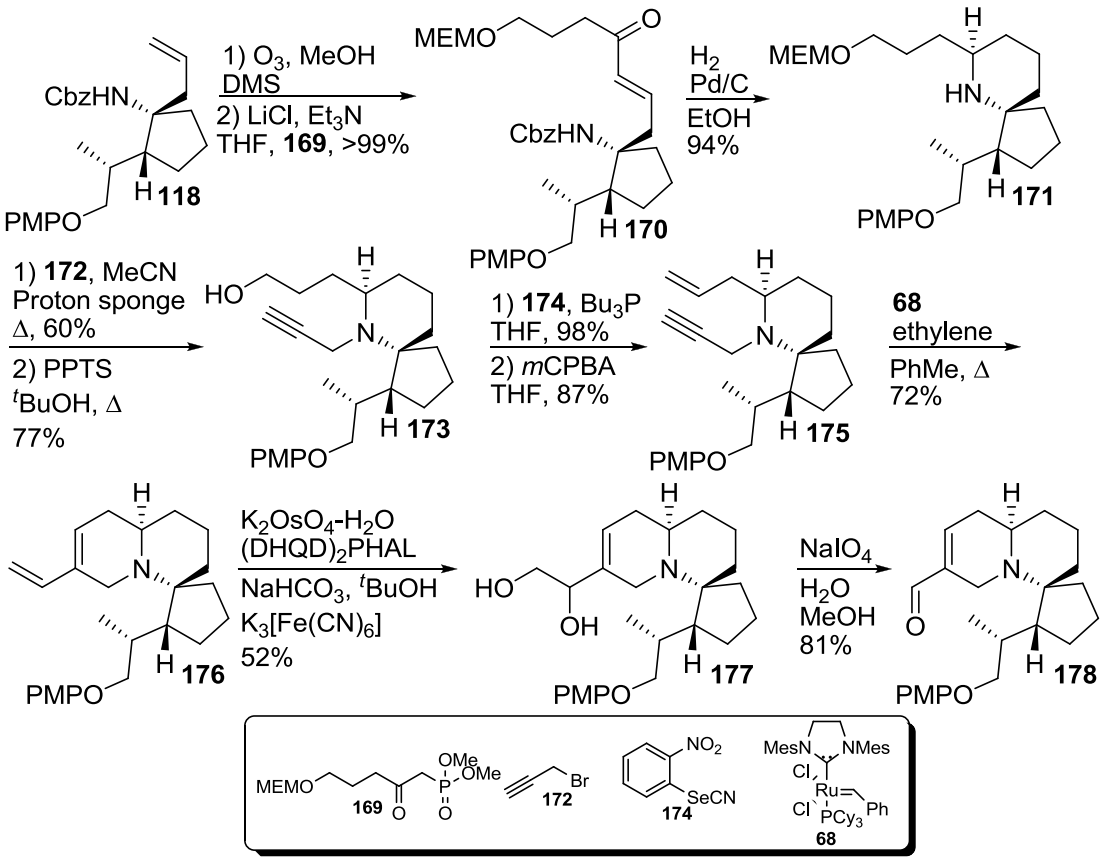


Scheme 17. Clive 2nd generation approach

The Arimoto-Uemura Strategy for the Synthesis of Halichlorine (2004)

In addition to the successful completion of their racemic synthesis of pinnaic acid, Arimoto and Uemura reported a novel approach to the tricyclic core of halichlorine.[72] From their previously reported cyclic tertiary Cbz-amide **118**, ozonolysis followed by Horner-Wadsworth-Emmons olefination afforded enone **170**. Application of their one-pot four-step hydrogenolysis induced cascade afforded

spirocyclic piperidine **171** in excellent yield. *N*-Alkylation followed by MEM-ether cleavage afforded primary alcohol **173**, which upon Grieco elimination afforded terminal olefin **175**.[69] A key ene-yne metathesis reaction then gave diene **176**, the *exo*-olefin of which was subjected to dihydroxylation conditions to give diol **177**.[73] Oxidative cleavage of diol **177** afforded the α,β-unsaturated aldehyde **178**, representing the tricyclic core of halichlorine (**Scheme 18**).



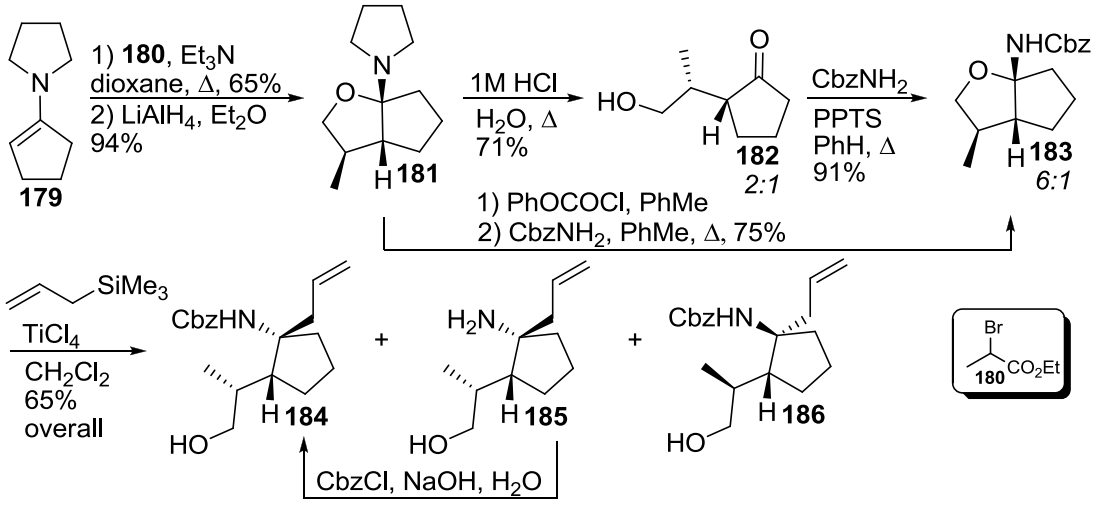
Scheme 18. The Arimoto-Uemura route to the halichlorine tricyclic core **178**.

Heathcock's Syntheses of Pinnaic Acid. Tauropinnaic Acid and Halichlorine (2004)

Long known for their elegant approaches towards polycyclic alkaloids, Heathcock and co-workers disclosed racemic syntheses of all three spirocyclic piperidine alkaloids pinnaic acid, halichlorine and tauropinnaic acid.[74]

In Heathcock's synthesis, the key bicyclic hemi-aminal **183** was accessed *via* an enamine alkylation of pyrrolidine **179** followed by a reduction and hydrolysis to give a mixture of cyclopentanones **182** in a 2:1 ratio. Cyclisation of the product mixture then afforded the desired bicyclic hemi-aminal **183**.[75] Alternatively, pyrrolidine hemi-aminal **181** was directly converted into the bicyclic Cbz-hemi-aminal **183** in a one-pot procedure.

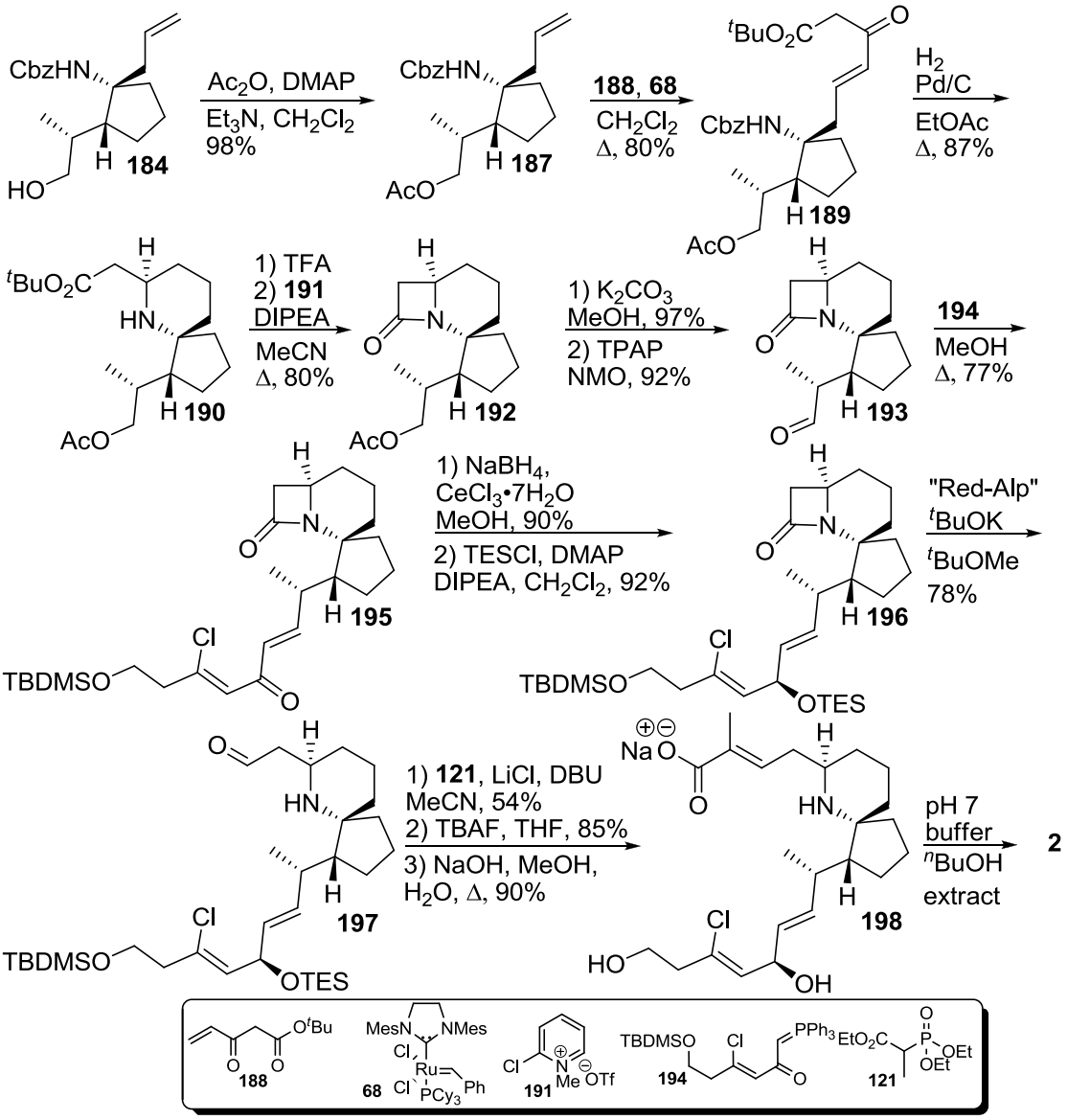
Nucleophilic addition to the hemi-aminal moiety proved troublesome and was found to be possible only when introducing an allyl group under Sakurai-type conditions. (**Scheme 19**).



Scheme 19. Synthesis of tertiary Cbz-amide **184**.

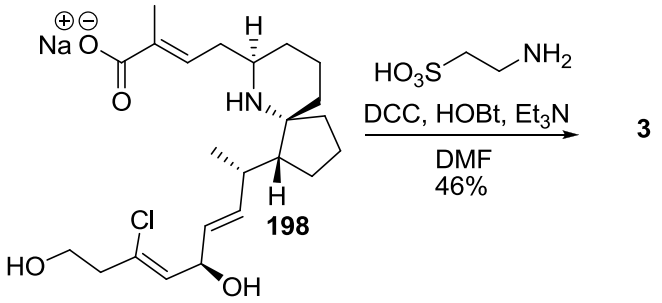
Protection of the primary alcohol **184** as the acetate **187** followed by cross-metathesis with enone **188** gave Cbz-amine **189** (**Scheme 20**).[76] Hydrogenolysis resulted in a similar tandem intramolecular Michael addition to that induced in previous syntheses to afford spirocyclic piperidine **190.** Hydrolysis of the ester followed by lactamisation gave access to the azatidinone intermediate **192.**[77] Acetate cleavage followed by oxidation afforded aldehyde **193** which subsequently underwent Wittig-olefination with phosphorane **194** to incorporate the lower side-chain. Luche reduction of enone **195** followed by silyl protection afforded the silyl ether **196.** Lactam opening using Red-Alp[78] afforded aldehyde **197**, which underwent a Masamune-Roush modified Horner-Wadsworth-Emmons olefination

followed by deprotection, hydrolysis and buffer treatment to afford pinnaic acid **2** in 20 steps and 3.0% overall yield.[79]



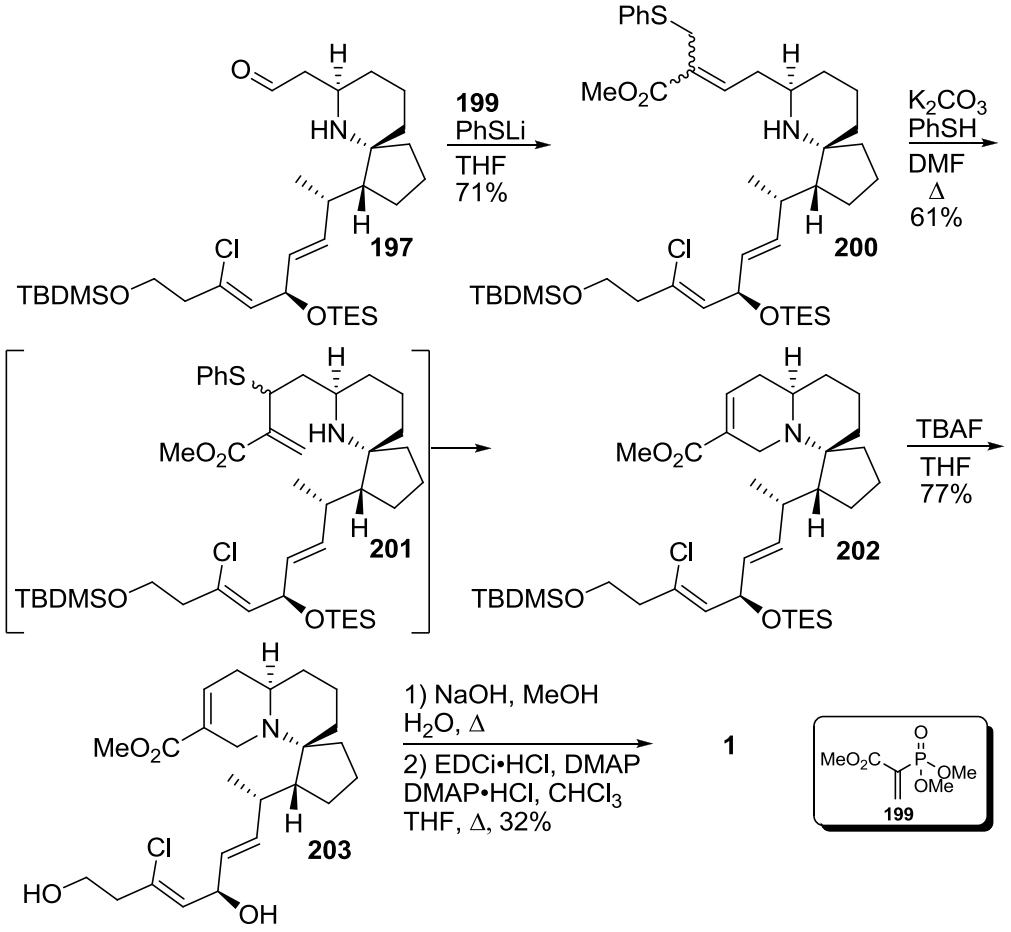
Scheme 20. Heathcock's synthesis of pinnaic acid **2**.

The Heathcock group also reported a straightforward one-step coupling of the sodium salt of pinnaic acid **198** with taurine to complete the synthesis of tauropinnaic acid **3** (**Scheme 21**).



Scheme 21 Heathcock's synthesis of tauropinnaic acid **3**.

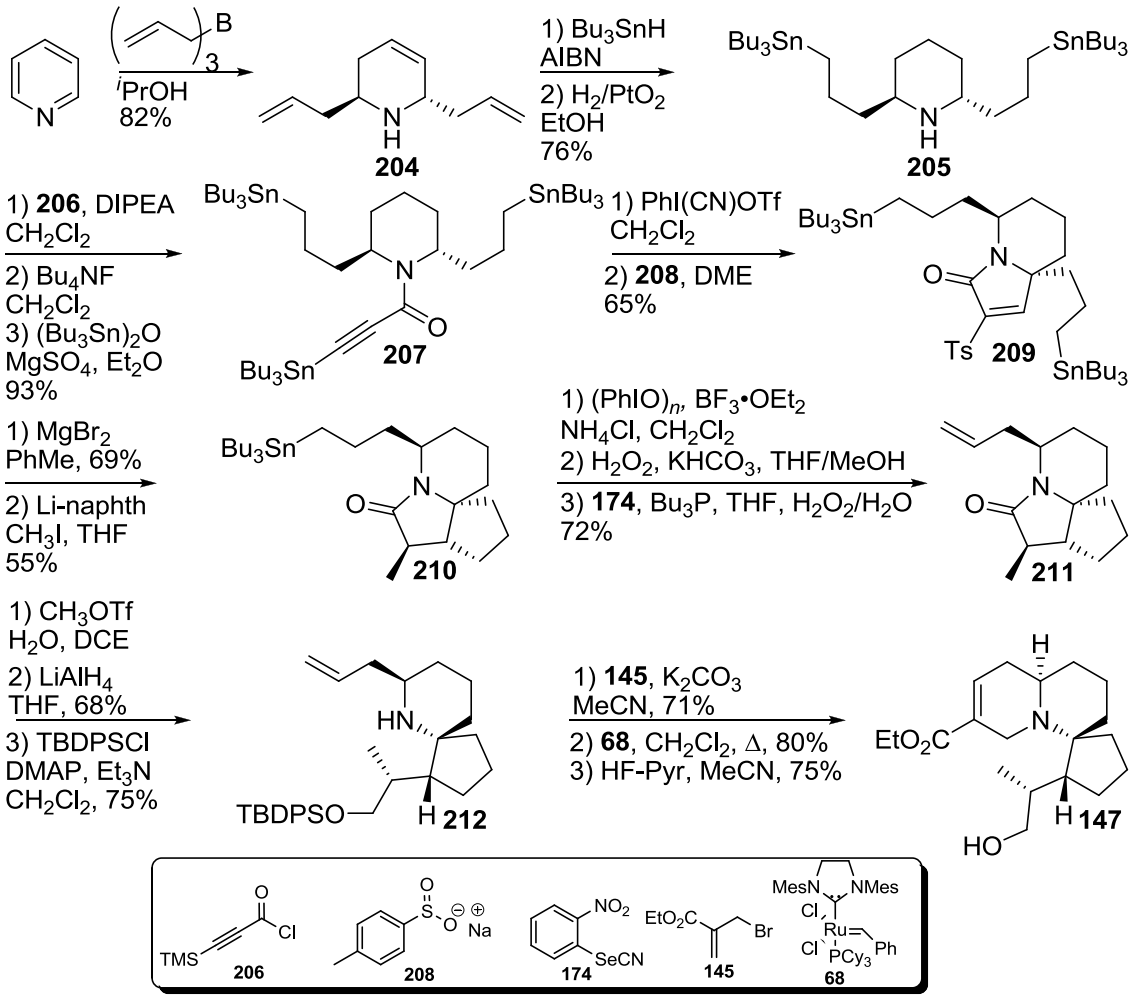
In order to access the tricyclic halichlorine, Heathcock subjected aldehyde **197** to a Horner-Wadsworth-Emmons olefination with the corresponding *in situ* formed phenylthiomethylphosphonate of phosphonoacrylate **199**.[80] Ring closure was affected through the addition/elimination of thiophenoxide and subsequent Michael addition of the amine unit to afford tricyclic piperidine **202**. Deprotection and saponification followed by Keck macrolactonisation completed the synthesis of halichlorine **1** in 21 steps and 0.8% overall yield (**Scheme 22**).[45]



Scheme 22 Heathcock's synthesis of halichlorine **1**.

Feldman's Formal Synthesis of Halichlorine (2004)

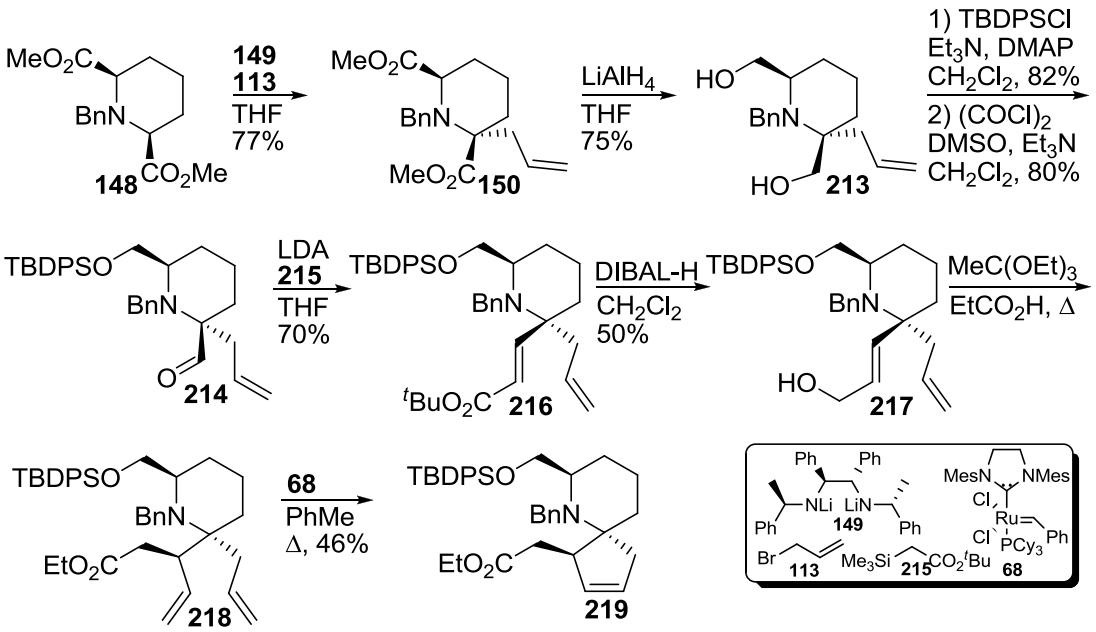
In 2004, the Feldman group reported the formal synthesis of halichlorine by synthesising the analogous ethyl ester **147** of Danishefsky's intermediate **28** (**Scheme 23**).[81] Their approach commenced with the allylation of pyridine to afford *bis*-allylated piperidine **204.**[82] Hydrostannylation of both terminal olefins, followed by hydrogenation of the *endo*-cyclic olefin afforded the bis-stannane **205.** Alkylation of amine **205** followed by stannylation of the alkyne intermediate then afforded tristannane **207.** The alkynylstannane moiety was then cyclised *via* a key alkynyliodonium salt/alkylidene-carbene cascade sequence to afford bicyclic enamide **209.**[83] Selective transmetallation with magnesium bromide then affected the closure of the third ring, completing the spirocycle, and reductive methylation of the corresponding amidosulfone intermediate afforded the desired methyl amide **210.** Conversion of the remaining primary stannane to the corresponding alcohol,[84] followed by Grieco elimination afforded the desired terminal olefin **211.**[69] Lactam reduction, followed by silylation of the free alcohol gave silyl ether **212.** Sequential *N*-alkylation, ring-closing metathesis and silyl group removal completed Feldman's formal synthesis. [62b]



Scheme 23 Feldman formal Halichlorine

Simpkins' Ring-Closing Metathesis Approach (2004)

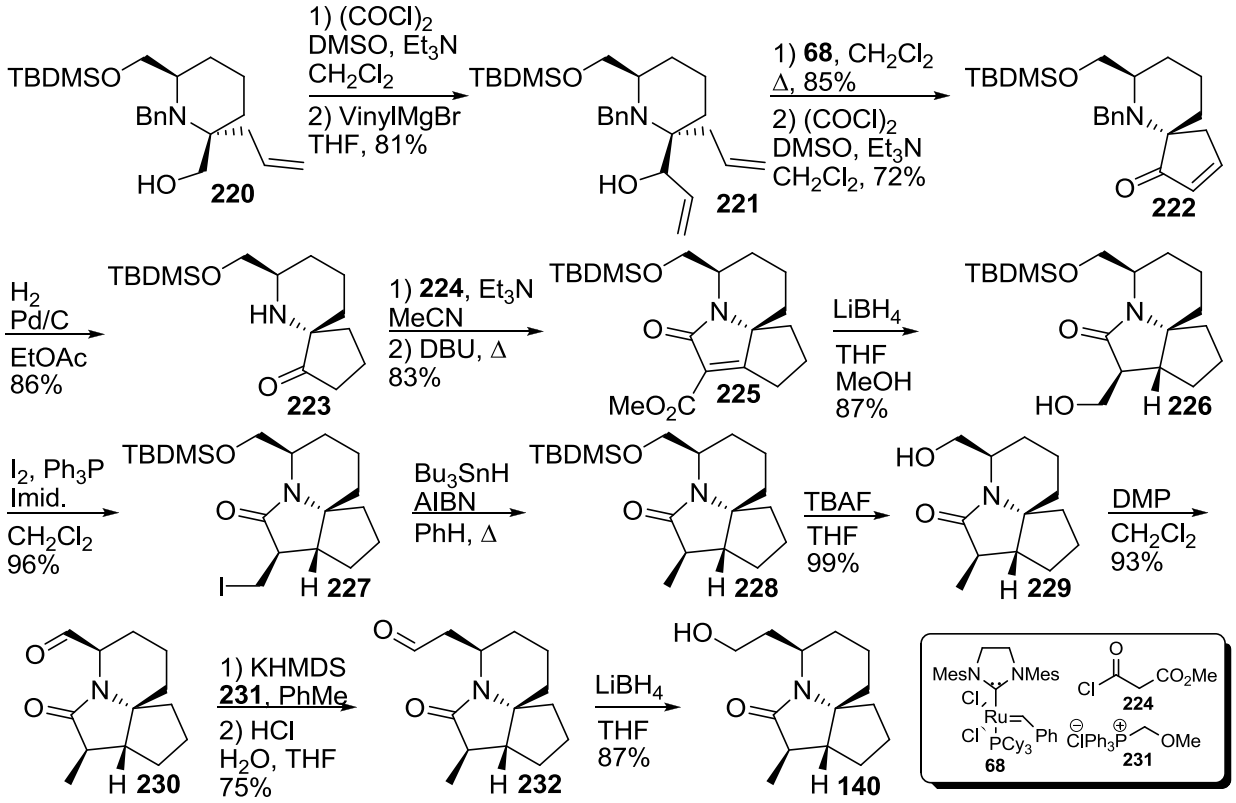
In 2004, Simpkins demonstrated the utility of ring-closing metathesis in his approach to the construction of the 5-membered spirocyclic ring (**Scheme 24**).[85] The route explored the synthesis of spirocyclic piperidines *via* the enantioselective allylation and differential functionalisation of diester **148** to eventually afford aldehyde **214**.[67a, 68b] Peterson olefination then accessed conjugated ester **216** which was subsequently reduced to generate allylic alcohol **217**.[86] A Johnson-Claisen rearrangement furnished bis-olefin **218,** which upon ring-closing metathesis led to the functionalised spirocyclic piperidine **219**.[87]



Scheme 24 Simpkins' ring-closing metathesis approach.

Clive's Ring-Closing Metathesis Approach Intersecting Kibayashi's Strategy (2005)

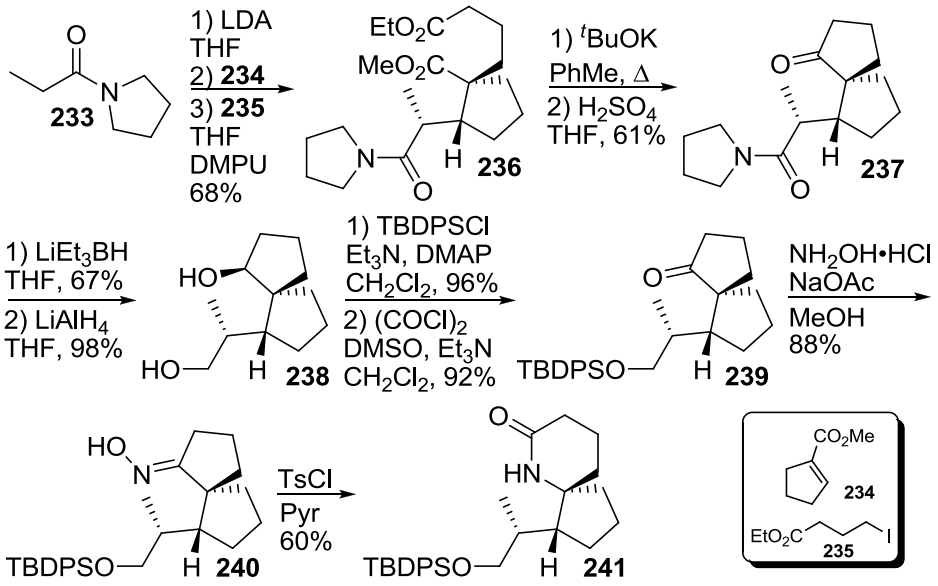
In a closely related strategy to that of Simpkins, Clive and co-workers developed a ring-closing metathesis based approach (**Scheme 25**).[88] Progressing from the Simpkins intermediate **220**, alcohol oxidation followed by Grignard addition afforded bis-olefin **221**. Ring-closing metathesis afforded the corresponding cyclic allylic alcohol, which was oxidised to enone **222**. Enone hydrogenation generated spirocyclic ketone **223**, which was then *N*-alkylated. Subsequent condensation proceeded to afford tricyclic enoate **225**, which was selectively reduced to generate the primary alcohol **226**. Alcohol **226** was converted to the corresponding iodide **227** and subsequently reduced to afford tricyclic piperidine **228**.[89] Silyl group removal followed by oxidation of the resultant primary alcohol generated aldehyde **230** which was homologated into aldehyde **232**. Final reduction of aldehyde **232** yielded primary alcohol **140**, an intermediate in Kibayashi's formal synthesis.[62b]



Scheme 25 Clive's ring-closing metathesis approach.

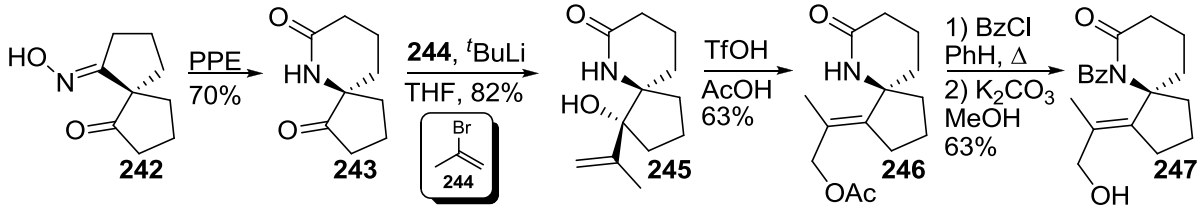
Pilli (2005) and Paquette (2005); The Beckmann Rearrangement in Spirocyclic Piperidine Synthesis

Pilli and co-workers began their synthesis of spirocyclic piperidine cores from the Heathcock diester **236.**[90, 91] Subsequent Dieckmann condensation of diester **236** followed by decarboxylation afforded bicyclic ketone **237.** Complete reduction of both ketone and amide units afforded the bicyclic diol intermediate **238** which was selectively protected and the resultant alcohol oxidised to afford bicyclic ketone **239**. Oxime formation and subsequent treatment of oxime **240** with *p*TsCl induced the key stereoselective Beckmann rearrangement to afford the spirocyclic amide **241** (**Scheme 26**).[92]



Scheme 26 Pilli's Beckmann rearrangement.

A similar synthetic approach based on a Beckmann rearrangement was simultaneously adopted by Paquette and co-workers (**Scheme 27**).[93] In Paquette's approach, oxime **242** was subjected to the Beckmann rearrangement conditions to generate spirocyclic lactam **243**.[94] Stereoselective alkylation of the ketone afforded the tertiary allylic alcohol **245**, which underwent allylic rearrangement to generate acetate **246**. Amide protection followed by deacetylation afforded spirocycle **247**.[95]

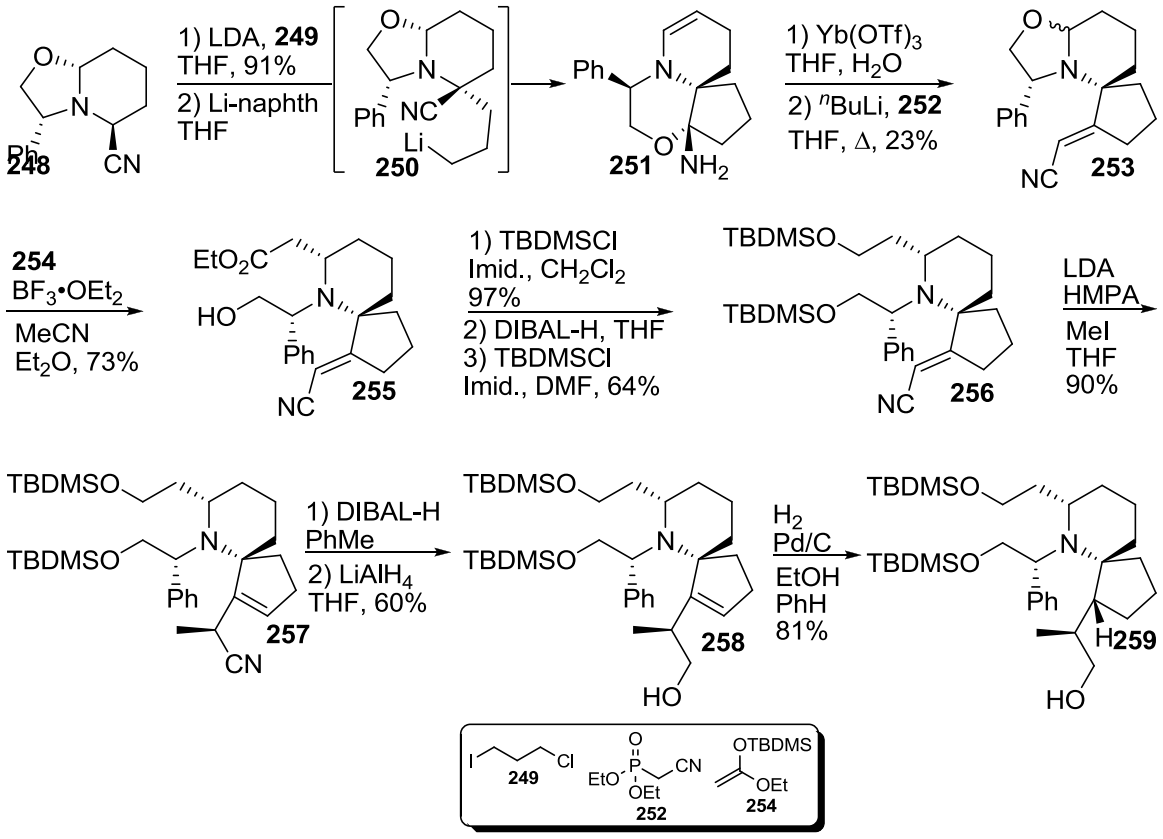


Scheme 27 Paquette's Beckmann rearrangement approach

Husson's "CN(*R*,*S*) Building Block" Method (2005)

Husson and co-workers developed a route towards the spirocyclic cores of the pinnaic acid series utilising their previously developed "CN(*R*,*S*) building block" **248** (**Scheme 28**).[96, 97] Alkylation of the bicyclic unit **248** followed by lithium-

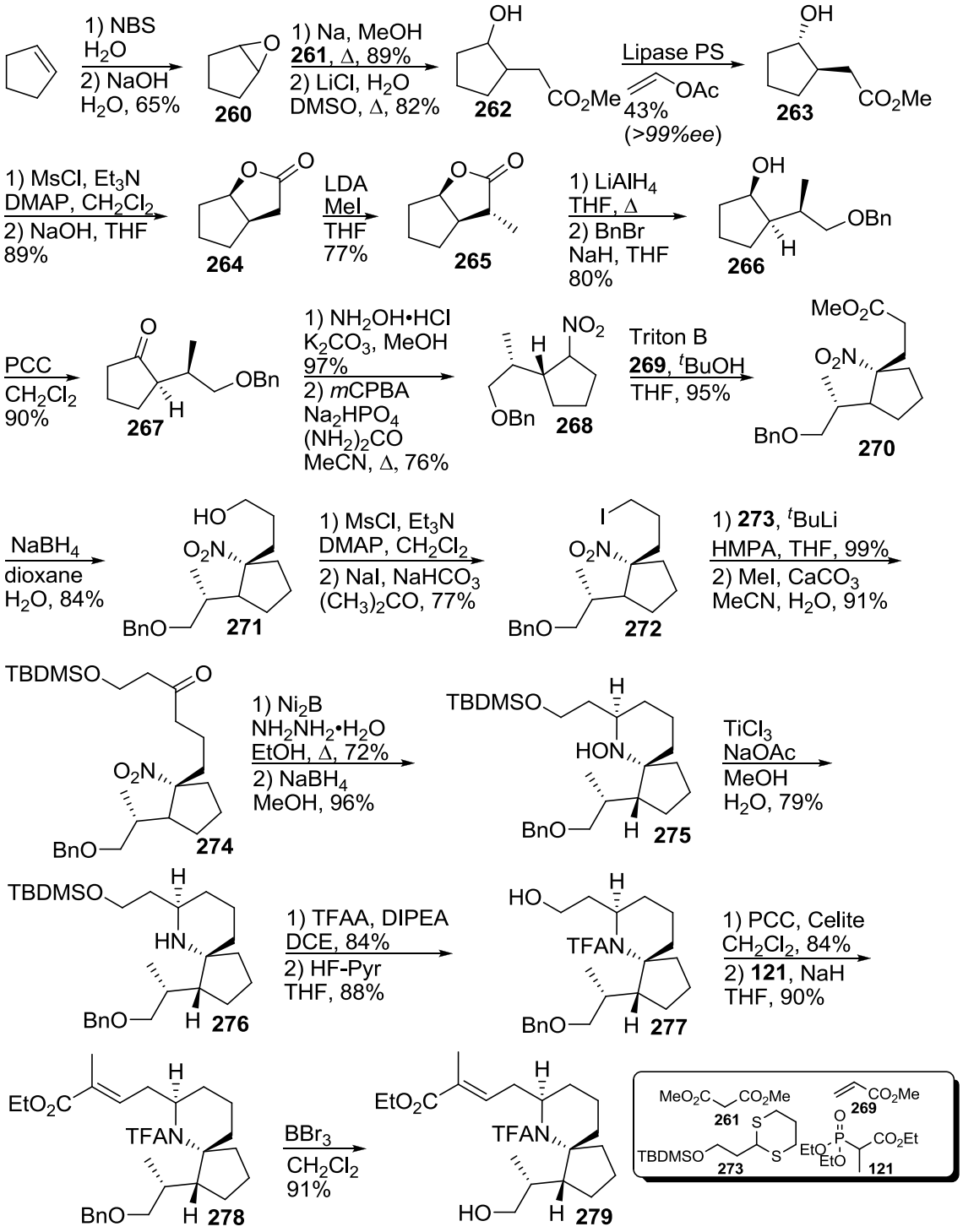
halogen exchange effected a spiroannulation process to afford the tricyclic core **251**.[98] Lewis-acid mediated hydrolysis, followed by Horner-Wadsworth-Emmons olefination afforded the unsaturated nitrile **253**.[99, 100] Silyl ketene acetal **254** addition to an *in situ* generated iminium ion, with simultaneous desilylation afforded ester **255**.[101] Alcohol protection followed by ester reduction and silylation afforded the *bis*-silylated spirocyclic piperidine **256**. Methylation resulted in the expected olefin migration giving rise to substituted cyclopentenone **257**, which after two reduction rounds was converted into primary alcohol **258**.[102] Final hydrogenation completed the approach to the spirocyclic core **259** in possession of the opposite stereochemistry at C-14 with respect to the natural analogue.



Scheme 28. Husson's use of the "CN(*R,S*) Building Block".

Zhao's Formal Synthesis of Pinnaic Acid (2005)

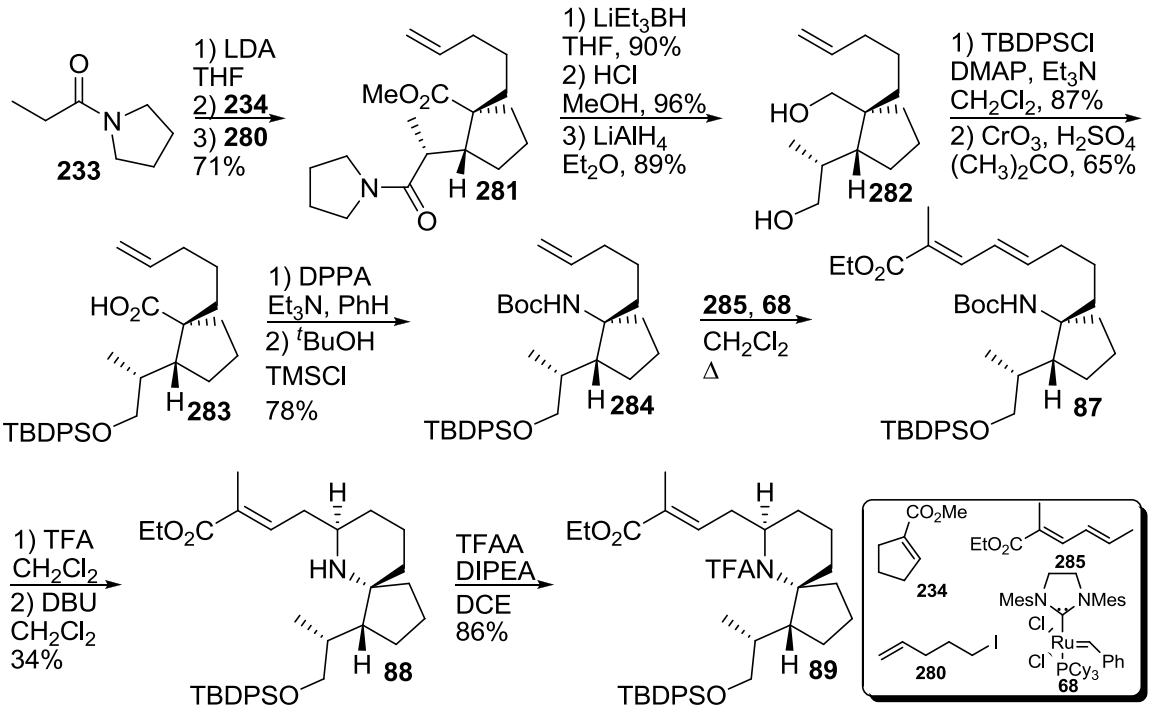
Building on their earlier work, Zhao and co-workers described a formal synthesis of pinnaic acid in 2005 (**Scheme 29**).[103] Their route began with the epoxidation of cyclopentene, to afford cyclopentanyl epoxide **260**, followed by ring opening and enzymatic resolution to obtain enantiopure cyclopentanol **263**. [104] Lactonisation and facially-directed methylation of lactone **264** generated lactone **265**. Lactone reduction followed by chemoselective benzylation accessed the benzyl protected alcohol **266.** Oxidation of the free secondary alcohol gave cyclopentanone **267** which was then converted to the nitro cyclopentane **268** *via* oxidation of an oxime intermediate. Deprotonation and Michael addition onto methyl acrylate gave ester **270** which was subsequently reduced and converted into iodide **272.**[105] The iodide was displaced by substituted dithiane **273** and the thioketal hydrolysed to generate ketone **274**.[106] Attempted reduction of the nitro group with an aim to generate the corresponding amine was expected to induce cyclic imine formation akin to the method of ring closure described by Arimoto and Uemura.[107, 61] Instead, cyclisation yielded the corresponding nitrone which was subsequently reduced to give hydroxylamine **275**.[108] Cleavage of the N-O bond followed by trifluoroacetate protection and desilylation afforded piperidine **276**.[109] Alcohol oxidation followed by olefination and debenzylation afforded the spirocyclic piperidine intermediate **279** originally described by Danishefsky as part of his total synthesis.



Scheme 29. The Zhao group formal synthesis of pinnaic acid.

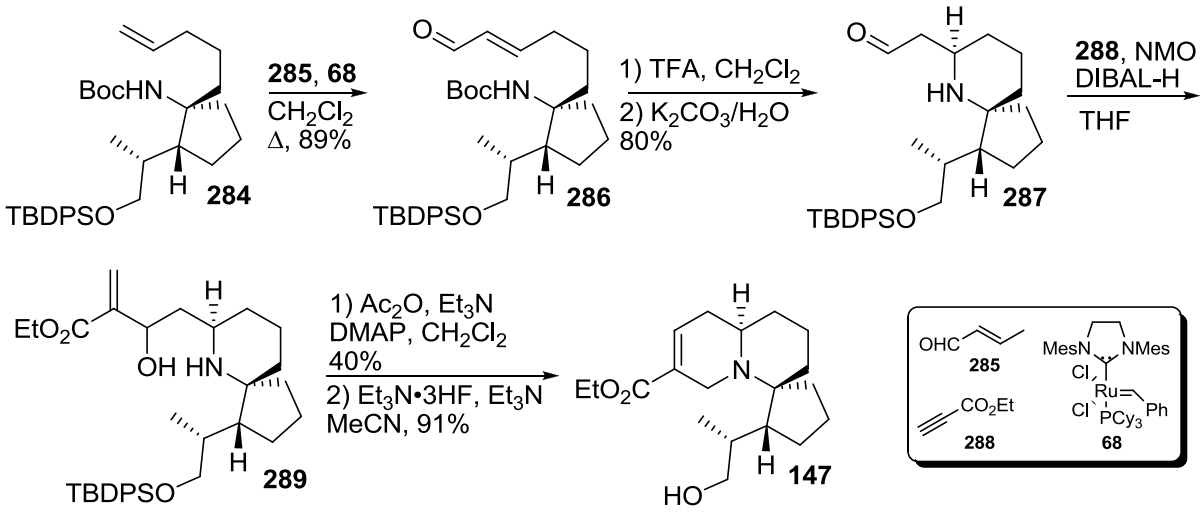
Martin's Formal Syntheses of Pinnaic Acid and Halichlorine (2005)

Martin reported the formal syntheses of both pinnaic acid and halichlorine from dihydroxycyclopentane **282.**[110] Densely functionalised cyclopentane **281** was accessed through the three-component alkylation between pyrrolidine **233**, cyclopentenecarboxylate **234** and alkyl iodide **280** first reported by Heathcock (**Scheme 26**).[111] Subsequent three-step overall reduction of the pyrrolidine and ester functionalities led to the *bis*-primary alcohol species **282**. Regiospecific protection followed by oxidation afforded the carboxylic acid **283**, which then underwent a Curtius rearrangement with subsequent protection to generate the cyclic tertiary Boc-amide **284.**[112] Cross-metathesis of alkene **284** with dienoate **285** afforded the doubly conjugated ester **87,**[113] which upon removal of the nitrogen protecting group, underwent Danishefsky's intramolecular 1,6-conjugate addition to generate spirocyclic piperidine **88**. TFA protection of the nitrogen completed the synthesis of fully protected spirocyclic piperidine **89** (**Scheme 30**).



Scheme 30 Martin's formal synthesis of pinnaic acid

Martin's formal synthesis of halichlorine began with the common advanced intermediate **284** which underwent cross-metathesis with but-2-enal **285** to afford conjugated aldehyde **286** (**Scheme 31**). Deprotection of the nitrogen induced the aza-Michael cyclisation to afford spirocyclic piperidine **287**. Completion of the halichlorine core was achieved by applying Ramachandran's vinylalumination conditions to aldehyde **287** to give allylic alcohol **289** as a mixture of diastereoisomers.[114] Subsequent acetylation of the diastereomeric mixture **289** affected a cyclisation/displacement event. Final silyl group removal completed the synthesis of the ethyl ester analogue **147** of the Danishefsky intermediate **28**.[65]

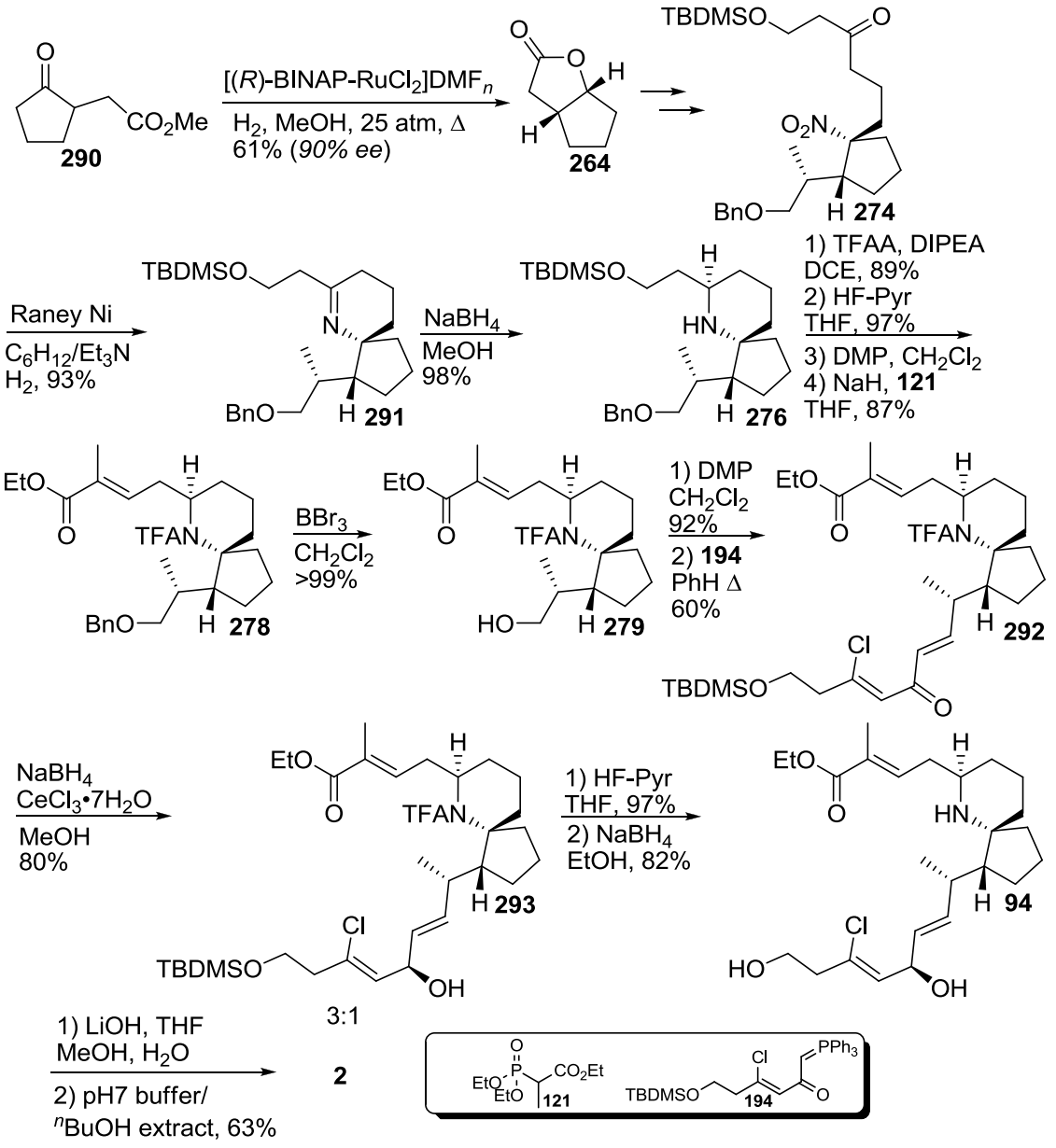


Scheme 31 Martin's formal synthesis of Halichlorine

Zhao's Enantioselective Total Synthesis of Pinnaic Acid (2007)

In 2007, Zhao and co-workers completed the enantioselective total synthesis of pinnaic acid.[115] Their initial steps in the synthesis followed the previous route, save for an optimised approach to the intermediate lactone **264**. Adoption of the previously reported approach led to the synthesis of cyclic tertiary nitro cyclopentane **274**.[116, 103] In contrast to their previous route, the Zhao group utilised Raney nickel for the reduction of the nitro group to the corresponding amine. This resulted in spontaneous formation of the cyclic imine **291**. Sodium

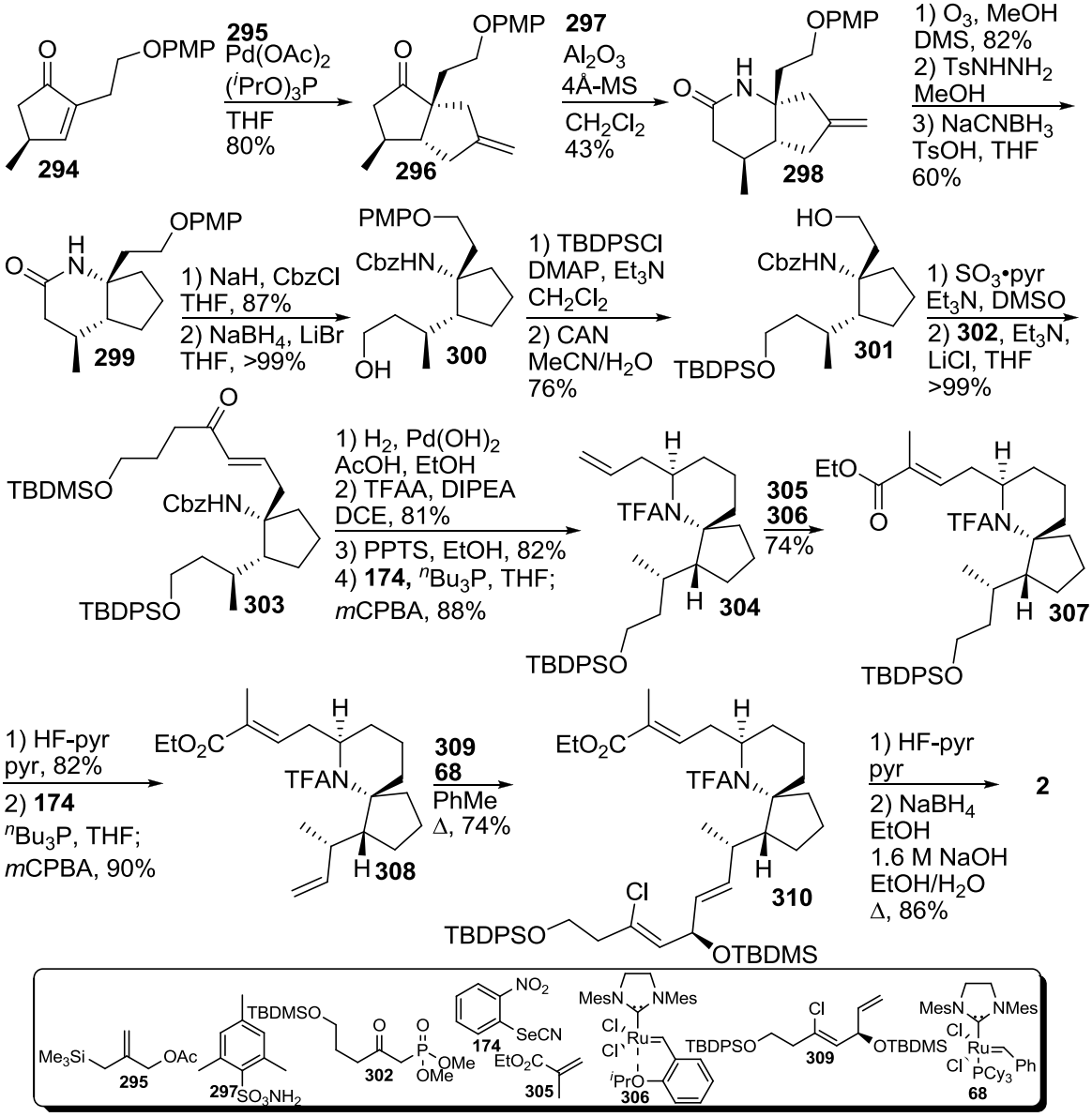
borohydride reduction then gave the desired piperidine **276** as a single diastereoisomer. In keeping with the previous strategy, side chain extension was achieved by Horner-Wadsworth-Emmons olefination with phosphonate **121**, affording unsaturated ester **278**. In Zhao's approach, the lower side chain unit was incorporated following a similar olefination strategy to that employed by the Heathcock group. Wittig olefination with phosphorane **194** gave the desired enone which upon Luche reduction afforded a separable 3:1 mixture of diastereoisomers in favour of the desired allylic alcohol **293.** Global deprotection then completed the total synthesis of pinnaic acid **2** in 3% overall yield over 27 steps (**Scheme 32**).



Scheme 32 Zhao's total synthesis of pinnaic acid

Arimoto and Uemura's Asymmetric Total Synthesis of Pinnaic Acid (2007)

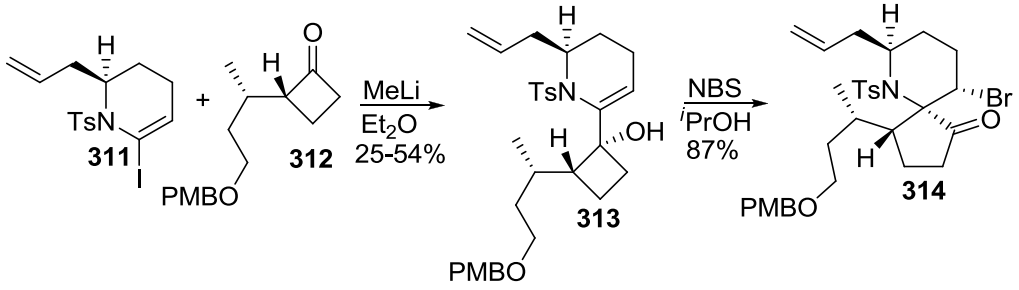
Arimoto and Uemura also reported an asymmetric total synthesis of pinnaic acid which utilised cross-metathesis reactions to incorporate both upper and lower side chains (**Scheme 33**).[117] Construction of the cyclopentenone starting block **294** was achieved in 5 steps from *(R)*-(+)-pulegone. A Pd-catalysed trimethylenemethane [3+2]-cyclisation then gave bicyclic ketone **296** which upon regioselective Beckmann rearrangement afforded lactam **298**.[118, 119] Removal of the unwanted *exo*-olefin was achieved through ozonolysis, followed by Caglioti-modified Wolff-Kishner deoxygenation[120] to afford pyridinone **299**. Amide protection followed by reductive lactam ring opening afforded alcohol **300** which was subsequently silyl-protected. Removal of the PMP-protection followed by oxidation and Horner-Wadsworth-Emmons olefination yielded enone **303**. At this point, the key tandem hydrogenation-cyclisation cascade, characteristic of the Arimoto-Uemura approach, was employed. Amine protection and selective removal of the TBDMS protecting group followed by Grieco elimination afforded the terminal olefin **304**.[121, 122] Cross-metathesis with ethyl methacrylate **305**, in the presence of Hoveyda-Grubbs second-generation catalyst **306** afforded the ethyl enoate **307.** Subsequent TBDPS removal, followed by a second Grieco elimination[122] afforded terminal olefin **308**. A final cross-metathesis with the custom allylic alcohol **309** in the presence of Grubbs 2nd generation ruthenium catalyst **68** incorporated the lower side-chain unit in a single step. Sequential deprotection and saponificaion completed the synthesis of pinnaic acid **2** in 3% yield over 26 steps.



Scheme 33 Arimoto-Uemura second generation asymmetric synthesis of pinnaic acid

Dake's Convergent Approach to Spirocyclic Piperidines (2008)

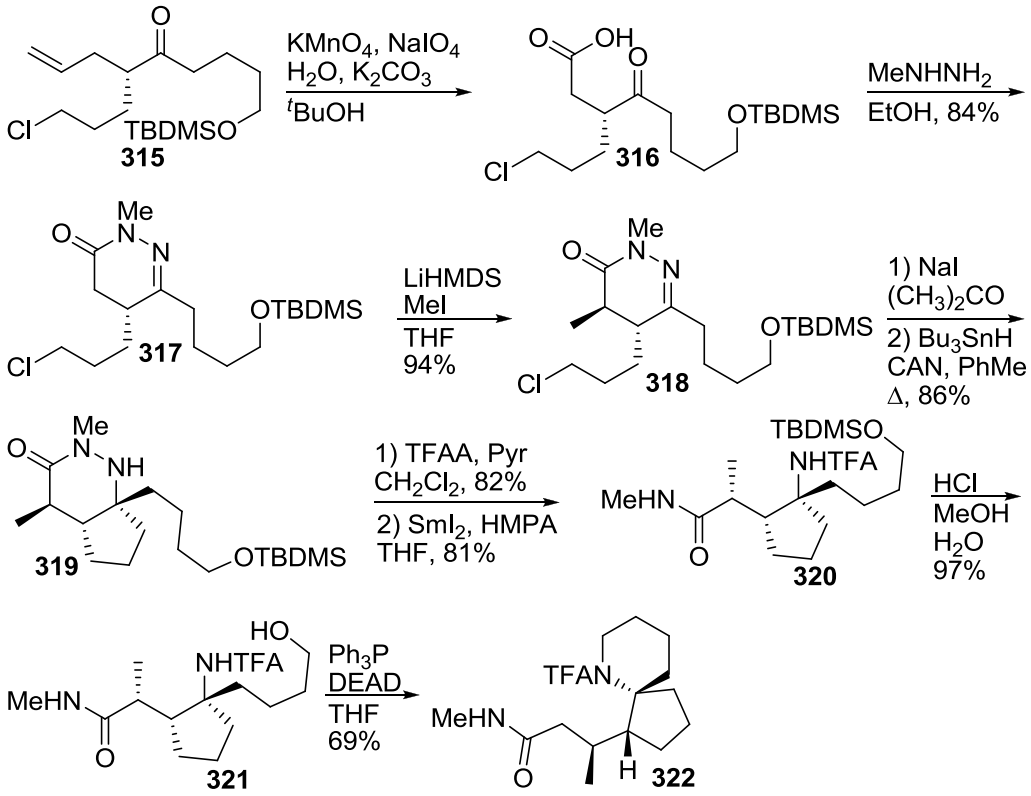
A particularly unique and extremely convergent approach to the spirocyclic core of pinnaic acid was described by Dake in 2008 (**Scheme 34**).[123] Vinyl iodide **311** was lithiated and coupled with bespoke cyclobutanone **312**. Under treatment with *N*-bromosuccinimide, sterically crowded allylic alcohol **313** smoothly underwent a semipinacol rearrangement to generate the spirocyclic core **314**.



Scheme 34 Dake's convergent, radical approach to the synthesis of spirocyclic piperidines.

Keck's Approach to the Spirocyclic Core (2008)

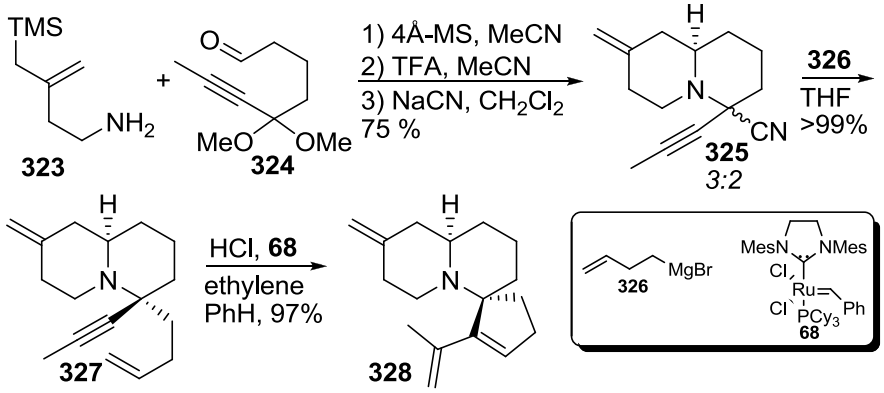
In 2008, Keck reported his efforts towards the synthesis of the pinnaic acid core structure utilising an intramolecular Mitsunobu displacement (**Scheme 35**).[124] Keck's approach begins with ketone **315**, which upon oxidative cleavage of the terminal olefin afforded the corresponding carboxylic acid **316**. Exposure of acid **316** to methyl hydrazine resulted in the formation of the *N*-methyl pyridazinone **317**.[125] Facially-selective methylation then afforded methyl pyridazinone **318**. A Finkelstein conversion allowed the formation of the corresponding iodide which underwent radical cyclisation to generate bicyclic pyridazinone **319**. Nitrogen protection followed by reductive N-N bond cleavage afforded amide **320**.[126] Selective desilylation gave rise to primary alcohol **321**, which suitably cyclised under Mitsunobu conditions to generate spirocyclic piperidine **322**. Unfortunately, while the use of the Mitsunobu reaction was successfully applied to primary alcohol **321**, its application to an equivalent homoallylic secondary alcohol was entirely unfruitful.



Scheme 35 Keck's synthesis of a spirocyclic piperidine core.

Martin's Strategy Towards the Halichlorine Core (2009)

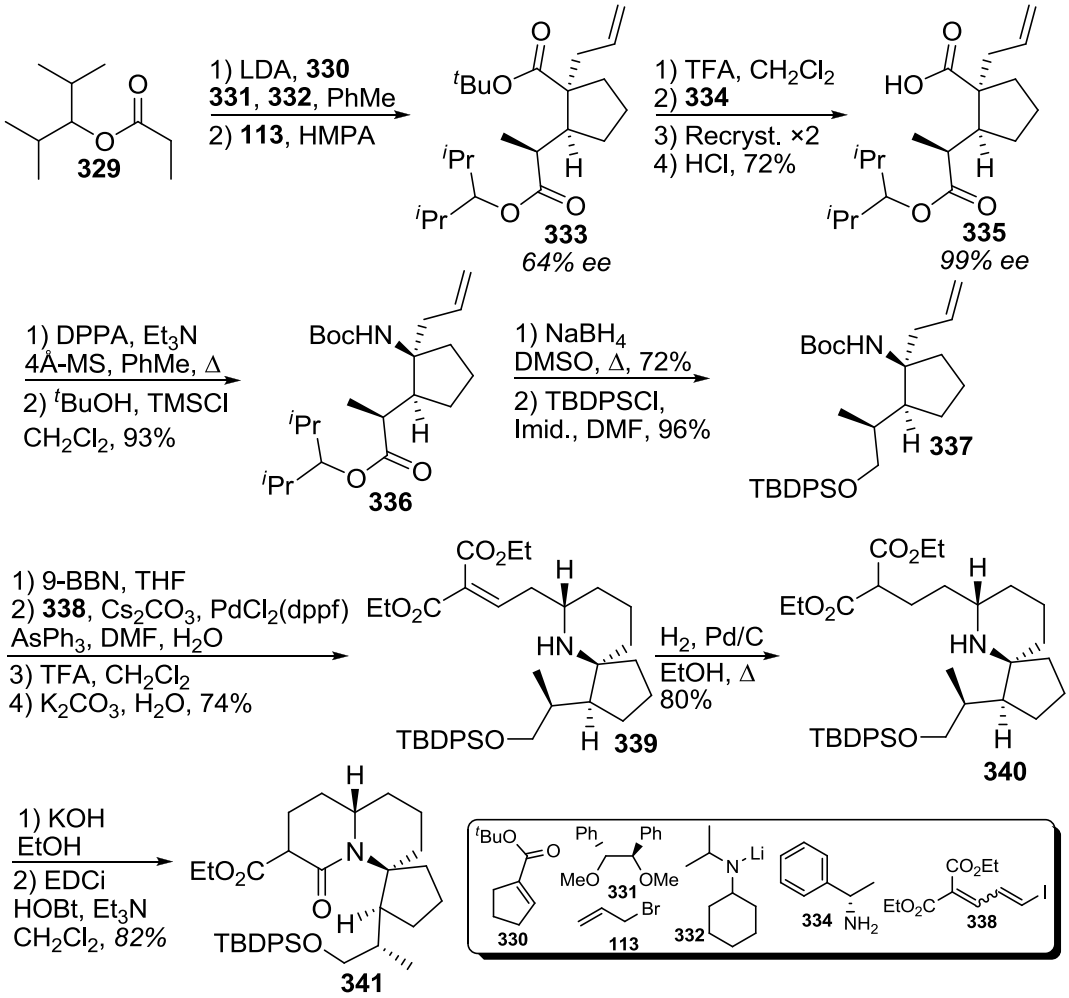
In 2009, Martin and co-workers reported a unique approach to the synthesis of the halichlorine core (**Scheme 36**).[127] In their approach, the key bicycle **325** was accessed *via* coupling of amine **323** and aldehyde **324** through imine formation followed by intramolecular allylation. Nucleophilic addition of sodium cyanide afforded the key bicycle **325**. Grignard addition to bicyclic piperidine **325** afforded terminal olefin **327**, which underwent ene-yne ring-closing metathesis to afford the tricyclic core of halichlorine **328**.



Scheme 36 Martin's ene-yne metathesis strategy for the synthesis of the halichlorine tricycle **328**.

Tomioka's Formal Synthesis of Halichlorine (2009)

In 2009 Tomioka reported a formal synthesis of halichlorine from the polyfunctionalised cyclopentane unit **333**.[128] The synthesis of cyclopentane unit **333** followed a similar three component transformation to that employed previously by Pilli (**Scheme 37**).[90] Hydrolysis of ester **333** followed by optical resolution afforded carboxylic acid **335**, which subsequently underwent Curtius rearrangement to yield cyclic tertiary amide **336.**[112, 129] Isopropyl ester reduction and protection of the resulting alcohol gave silylated alcohol **337**, the opposite enantiomer to the intermediate accessed by the Danishefsky group. Alkene hydroboration followed by Suzuki cross-coupling with iodide **338** gave the corresponding dienoate, which upon Boc deprotection underwent intramolecular 1,6-conjugate addition to yield spirocyclic piperidine **339**. Olefin hydrogenation and lactamisation then afforded the tricyclic core **341** of halichlorine.

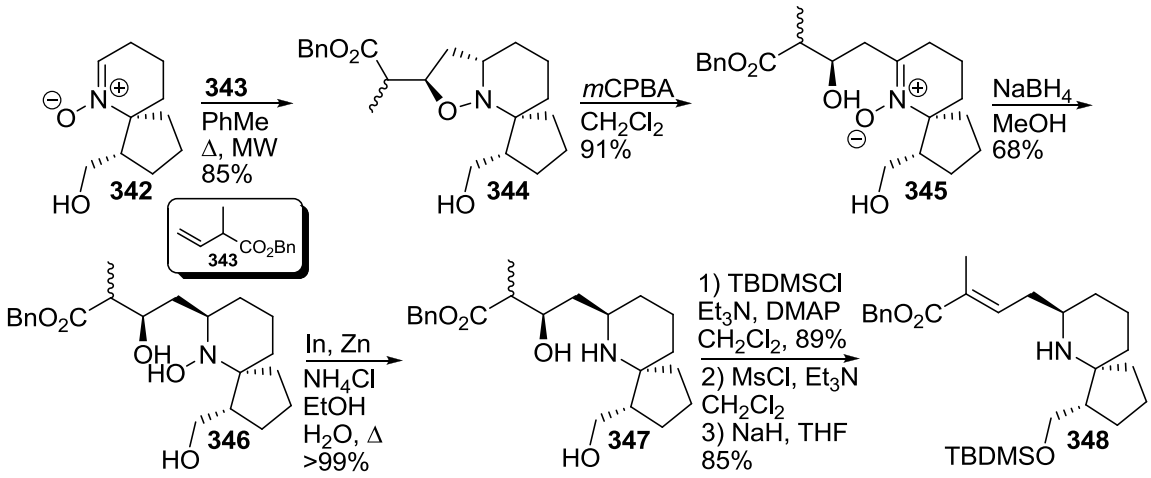


Scheme 37 The Tomioka group synthesis of the halichlorine core **341**.

Caprio's Approach to the Spirocyclic Piperidine Cores of Pinnaic Acid and Halichlorine (2009)

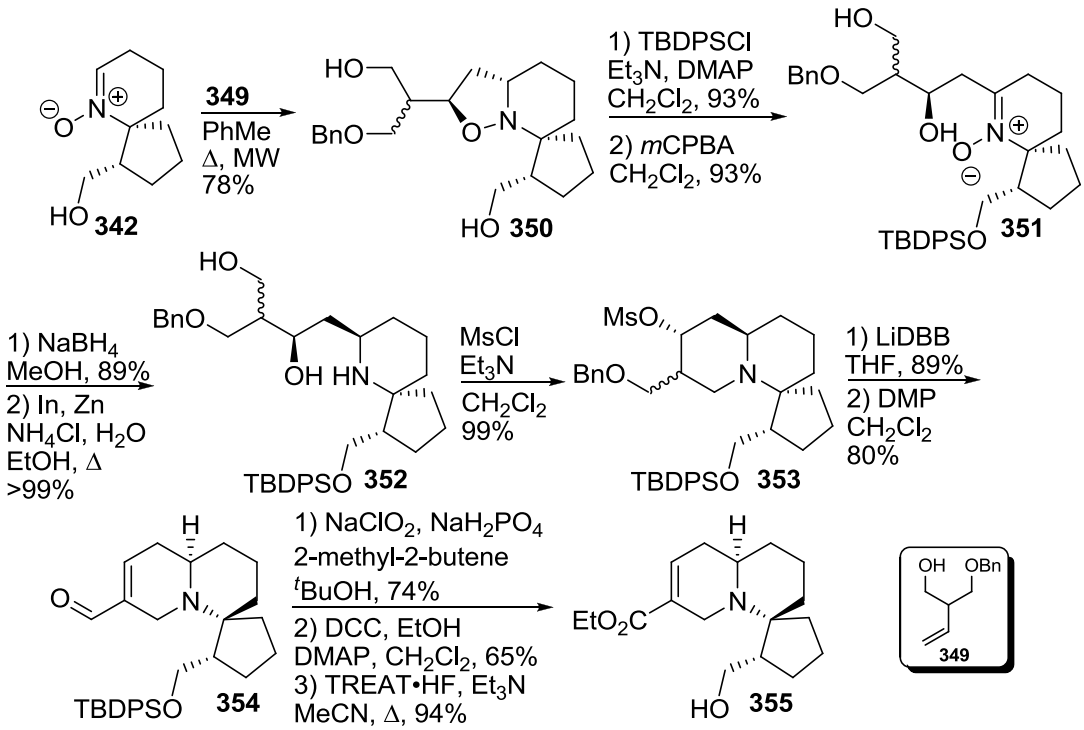
Caprio described an approach to the spirocyclic piperidine cores of pinnaic acid and halichlorine[130] which utilised nitrone **342**[131] as the reactive intermediate. Nitrone **342** underwent a 1,3-dipolar cycloaddition with terminal olefin **343** to yield isoxazolidine **344** as a 1:1 mixture of diastereoisomers.[132] Oxidative ring opening afforded substituted nitrone **345** which was subsequently reduced to the corresponding hydroxylamine **346**. Cleavage of the N-O bond afforded piperidine **347**,[133] which underwent primary alcohol protection, and elimination of the

secondary hydroxyl *via* the corresponding mesylate to afford the spirocyclic piperidine core of pinnaic acid **348** (**Scheme 38**).



Scheme 38 Caprio's approach to the pinnaic acid core **348**.

Caprio's efforts towards the halichlorine core also began with nitrone **342** which underwent a 1,3-dipolar cycloaddition to generate isoxazolidine **350**.[134] Alcohol protection followed by oxidative cleavage and N-O bond cleavage then afforded piperidine **352**. Mesylation of both primary and secondary alcohols then facilitated cyclisation, the regiospecificity arising from the formation of the more energetically favourable 6-membered ring, to generate tricycle **353**. Debenzylation followed by oxidation and mesylate elimination afforded unsaturated aldehyde **354**. Finally, Pinnick oxidation, followed by esterification and desilylation afforded the tricyclic spiropiperidine core **355** (**Scheme 39**).

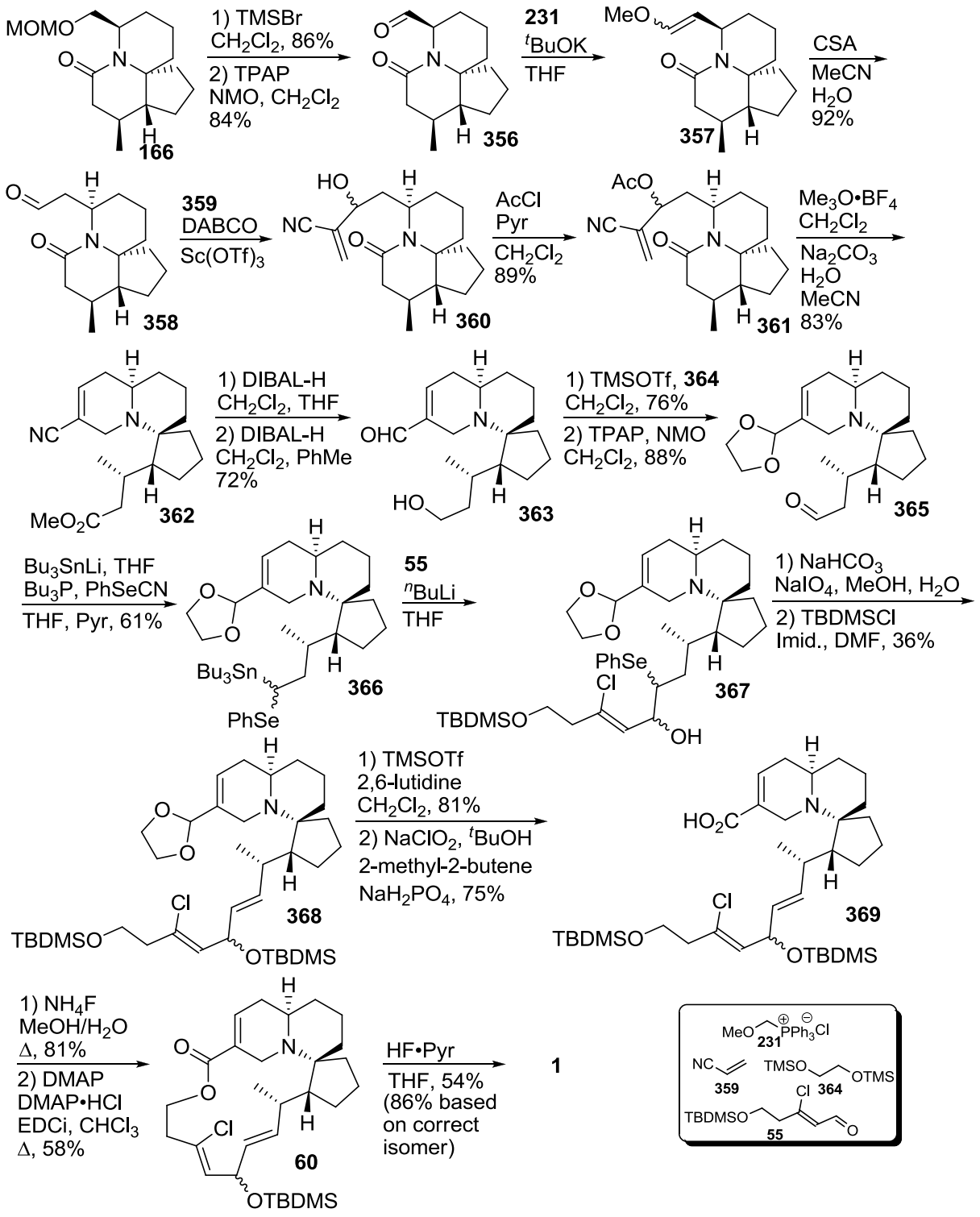


Scheme 39 Caprio's approach to the halichlorine core **355**.

Clive's Total Synthesis of Halichlorine (2009)

In 2009, Clive reported a total synthesis of halichlorine[135] which utilised the previously reported tricyclic amide **166** (**Scheme 40**). MOM ether cleavage followed by oxidation and Wittig olefination afforded the homologated aldehyde **358**.[38] Baylis-Hillman reaction of aldehyde **358** with acrylonitrile **359** followed by acetylation afforded a mixture of acetates **361**. Lactam ring opening and spontaneous intramolecular conjugate displacement afforded the tricyclic core of halichlorine **362**.[71, 136] Two sequential reductions followed by ketalisation of the resultant aldehyde **363** and oxidation of the primary alcohol afforded aldehyde **365**. Aldehyde **365** was treated with Bu_3SnLi and the resultant mixture of stannyl alcohols were immediately converted to the corresponding selenides **366**. Treatment of stannyl selenides **366** with BuLi then generated a selenium-stabilised carbanion[137] and addition to known β-chloroaldehyde **55** accessed a mixture of β-hydroxyselenides **367**. Selenoxide elimination followed by alcohol protection gave

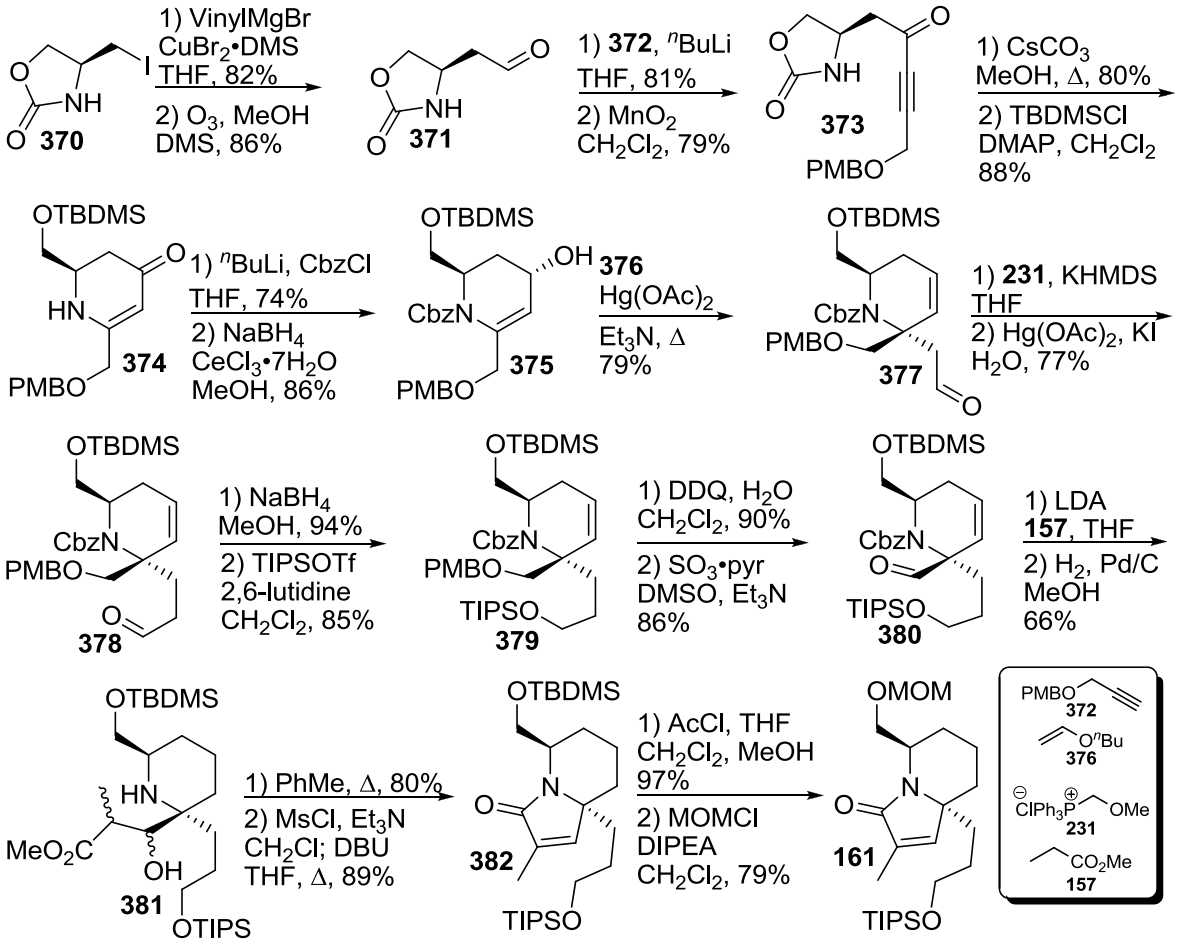
the *bis*-silyloxy intermediate **368**. Ketal hydrolysis[138] followed by oxidation of the resulting aldehyde then gave the desired carboxylic acid **369**.[139]



Scheme 40 Clive's total synthesis of halichlorine **1**.

Selective desilylation[140] of the primary alcohol, followed by Keck macrolactonisation[45] afforded known macrocyclic intermediate **60** and a final deprotection afforded halichlorine **1** as a mixture of isomers in 0.07% over 46 steps, based on the desired isomer.

At a well-developed point of this synthesis, it became apparent that the initial stereoselective allylation (**Scheme 17**) had not proceeded with the high level of enantioselectivity desired (~67% *ee*). Not content with these results, the Clive group proceeded to establish a novel, alternative route to the synthesis of an optically pure intermediate (**Scheme 41**). Clive's new approach began with serine-derived iodide **370**[141] which was converted to aldehyde **371** and then elongated into the internal alkyne **373**.[142] Alkyne **373** was then cyclised and the primary alcohol protected to afford piperidinone **374**. Cbz-protection followed by Luche reduction afforded cyclic allylic alcohol **375**. Allyl alcohol **375** was then converted into the vinyl ether and subjected to a Claisen-type rearrangement, affording aldehyde **377**.[143] Subsequent chain homologation of aldehyde **377** afforded aldehyde **378** which underwent reduction followed by protection of the resulting alcohol to afford the differentially protected triol **379**.



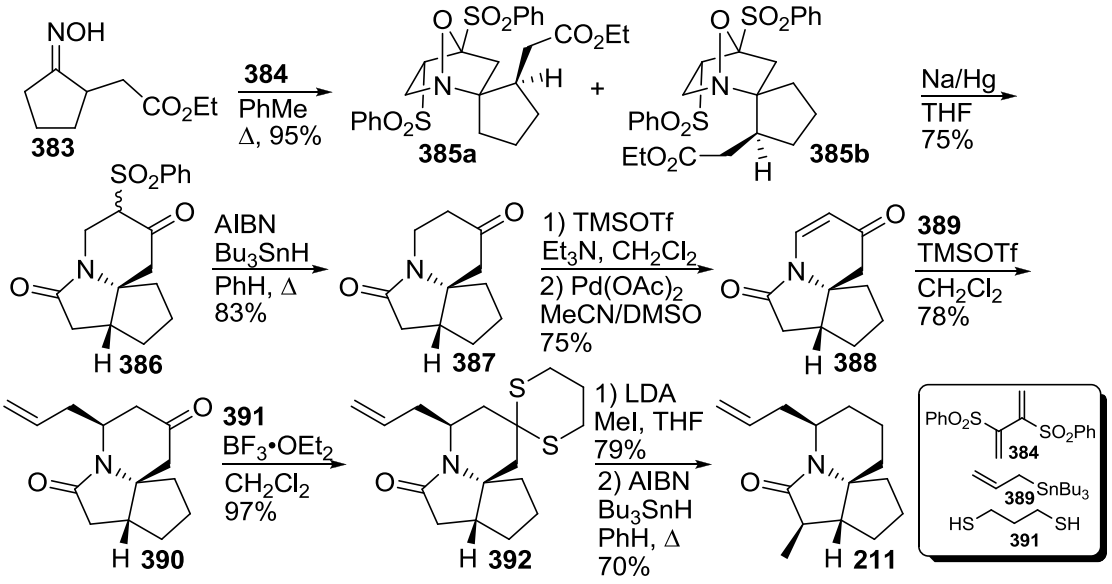
Scheme 41 Clive's novel route to chiral piperidines **161**.

Removal of the PMB group, followed by oxidation yielded aldehyde **380**. Aldehyde alkylation followed by alkene hydrogenation afforded the diastereomeric alcohols **381** possessing the fully saturated, unprotected piperidine. Lactamisation followed by hydroxyl elimination afforded the enamide **382**. Protecting group manipulation then completed the synthesis of optically pure intermediate **161**.

Padwa's Formal Synthesis of Halichlorine (2010)

Padwa reported a formal synthesis of halichlorine based on a tandem conjugate addition/dipolar cycloaddition between oxime **383** and 2,3-bis(phenylsulfonyl)-1,3-butadiene **384**. [144] The cycloaddition yielded an inconsequential mixture of diastereoisomeric spirocycles **385a** and **385b** (**Scheme 42**).[145] The mixture was

reduced with sodium amalgam to generate α-phenylsulfonyl piperidinone **386** which was reduced under radical conditions to afford tricyclic amide **387**.[146] Saegusa oxidation gave enone **388**, which then underwent conjugate addition to yield allyl piperidinone **390** as the major diastereoisomer (15:1).[147] Thioketal protection of the ketone unit, followed by diastereoselective methylation, and subsequent thioketal reduction afforded tricyclic piperidine **211**, completing the formal synthesis of pinnaic acid.

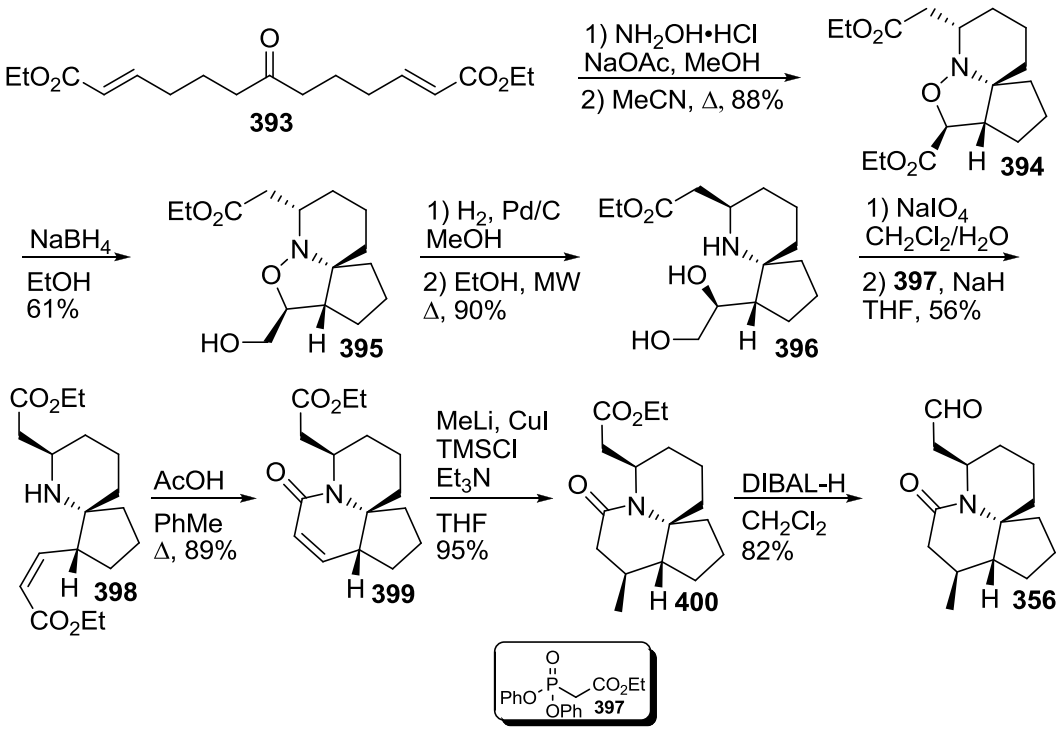


Scheme 42 The Padwa strategy for the synthesis of Feldman intermediate **211**.

Stockman's Formal Synthesis of Halichlorine (2012)

In 2012, Stockman and co-workers reported a formal synthesis of halichlorine through the utilisation of their elegant tandem cyclisation of a symmetrical ketodiester **393** as the key spirocycle forming step (**Scheme 43**).[148] In their synthesis, ketodiester **393** was accessed *via* the double addition of pentenylmagnesium bromide to ethyl formate, followed by oxidation of the resultant alcohol. Cross-metathesis with ethyl acrylate then afforded the key symmetrical ketodiester **393**.[149] Conversion of ketoester **393** into the corresponding oxime allowed a Michael addition to take place with one of the conjugated ester moieties, generating a nitrone intermediate, which then underwent [3+2]-cyclisation with the remaining conjugated ester to afford the

desired tricyclic alkoxylamine **394**. Regioselective ester reduction[150] followed by hydrogenation and epimerisation gave the 1,2-diol **396**, the ethyl ester analogue of Prof. White's terminal intermediate **99** (**Scheme 11**). Subsequent periodate cleavage and Ando olefination afforded the desired *Z*-double bond isomer **398** as the major product.[151] Acid catalysed lactamisation yielded amide **399** which upon cuprate addition gave the tricyclic piperidine **400**.[152] A final ester reduction afforded the known aldehyde **356**, intersecting Clive's synthesis of halichlorine.

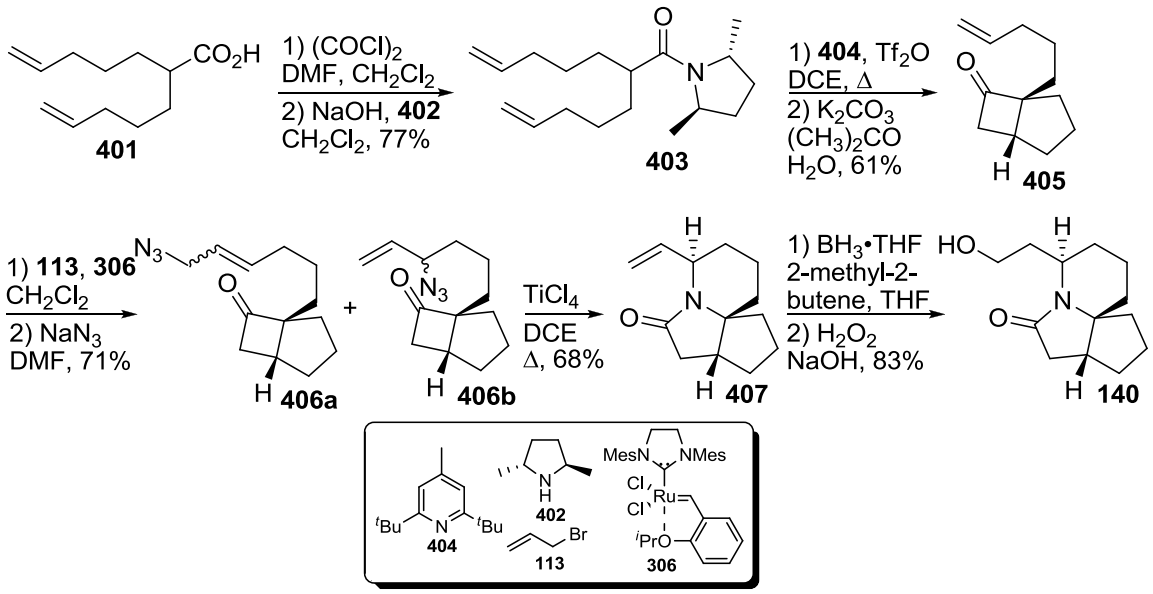


Scheme 43 Stockman's synthesis of Clive's aldehyde **356**.

Aubé's Formal Synthesis of Halichlorine (2012)

In the most recent contribution to date based on the synthesis of pinnaic acid-related spirocyclic piperidines, Aubé reported his formal synthesis based on accessing the Kibayashi group intermediate **140** (**Scheme 44**).[153] In the Aubé group approach, the carboxylic acid **401**[154] was coupled with chiral pyrrolidine **402** to afford *bis*-olefinic amide **403**. A [2+2]-cycloaddition with subsequent imine hydrolysis led to the [3.2.0] bicycle **405**.[155] Olefin metathesis with allyl bromide

113, followed by azide displacement afforded a mixture of allylic azides **406a** and **406b**.[156] Treatment of the amide mixture with $TiCl_4$ promoted a key Schmidt reaction, upon which a separable 10:1 mixture of diastereoisomers in favour of the desired spirocycle **407** was obtained. A final hydroboration afforded Kibayashi's previously reported intermediate alcohol **140**.

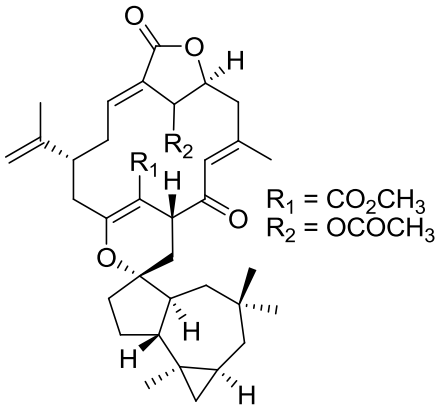


Scheme 44. Aubé's synthesis of the Kibayashi alcohol **140**.

In conclusion, the hugely diverse range of efforts that have been disclosed detailing the pursuit of these synthetically demanding natural products is a credit to their complex and fascinating structures. The strategies employed have been highly imaginative and elegant, both extending the scope of existing transformations and also describing the development of novel processes to overcome the challenges contained within these structures. Although a number of the strategies employed have not, for different reasons, ventured as far as the total syntheses, or indeed formal syntheses, the contribution of these works must not be considered with any less importance. Each approach described was born from ingenuity, invention or inspiration, and only through equal consideration of all previous efforts can the ultimate goal of the development of efficient syntheses, capable of furnishing significant quantities of these bioactive natural products, be achieved so that the scientific community can better understand their biological role.

Polymaxenolide

While spirocyclic piperidine-containing natural products like those extensively described have been the subject of numerous synthetic endeavours and biological evaluation, polymaxenolide **408 (Figure 8)**, a representative spirocyclic pyran-containing natural product, has never before been synthesised, nor is its biological profile known.



408

Figure 8. Polymaxenolide **408**.

Polymaxenolide **408** was isolated from the hybrid soft coral *Sinularia maxima x Sinularia polydactyla* in 2004 by Kamel and co-workers. [157] While polymaxenolide **408** has not exhibited any known biological activity, its hybrid origins have rendered it a target of interest; a significant proportion (18%) of terrestrial metabolites so far isolated from hybrid species have exhibited biological activity entirely distinct from that encountered in their associated parent species. [158]

2. Results and Discussion

Spirocyclic Pyrans and Piperidines

The similar structural features present in the spirocyclic cores of halichlorine **1** pinnaic acid **2**, tauropinnaic acid **3** and polymaxenolide **408** suggested that it might be possible to approach the spirocyclic piperidine and spirocyclic pyran cores with the concept of a divergent synthesis in mind. Hence, it was postulated that the syntheses of both spirocyclic cores might, in fact, be achievable from a common synthetic intermediate (**Figure 9**).

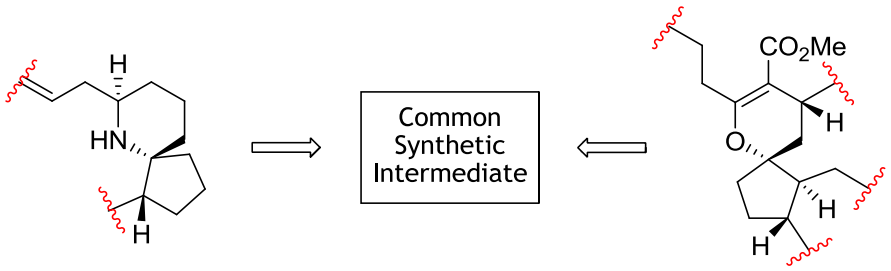


Figure 9. Entry to spirocyclic pyran and piperidine cores may be possible from a common synthetic precursor.

Previous Methodology

The use of 2,5-disubstituted furan rings **412** to generate pyran units via the Achmatowicz rearrangement was previously explored for the synthesis of spirocyclic pyrans (**Figure 10**).[159] In the original approach, it was envisioned that ring-closing metathesis of a pyran **410** bearing two terminal olefins, connected to the same quaternary carbon, would furnish the desired spirocyclic structures **409**. The *bis*-olefinated pyran **410** could potentially result from the Sakurai allylation of lactol **411**, the product of oxidative rearrangement of furfuryl alcohol **412**.

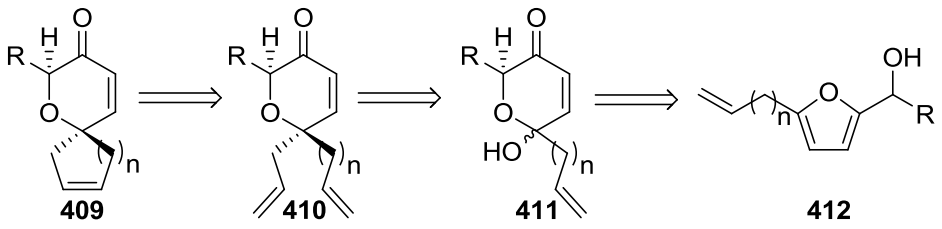


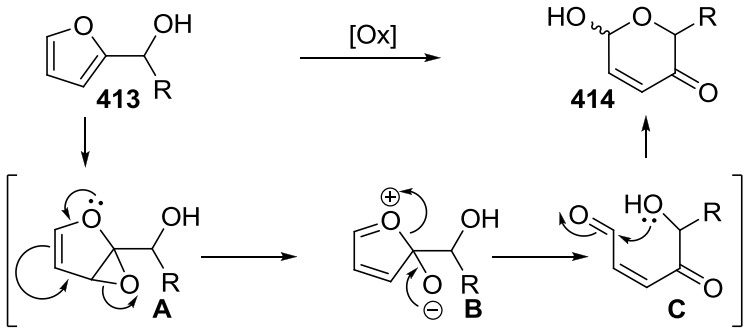
Figure 10. Retrosynthetic analysis of the first generation route to spirocyclic pyrans

The Achmatowicz Oxidative Rearrangement

Mechanism

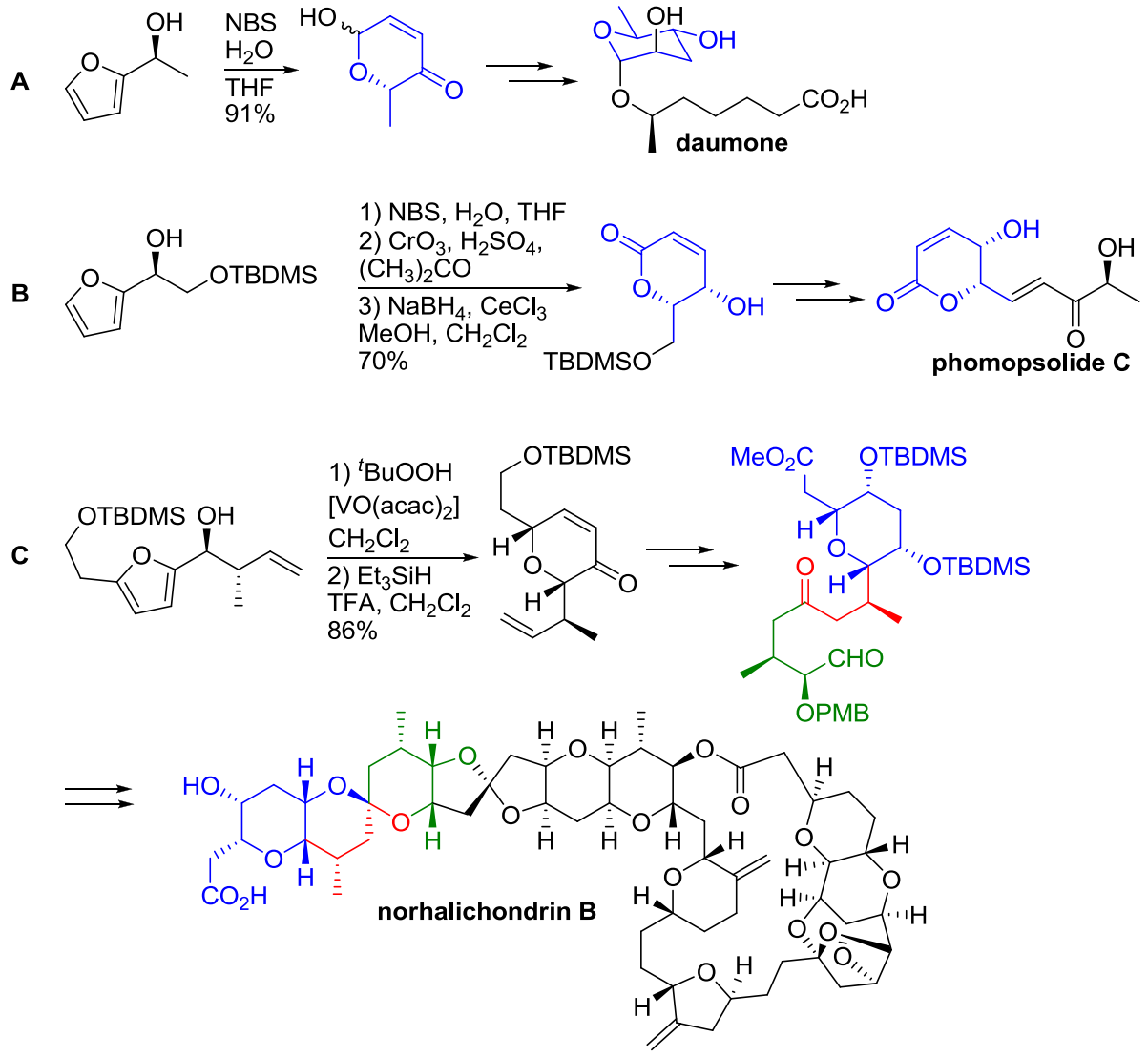
The rearrangement of furfuryl alcohols **413** to give hydroxypyranones **414** under oxidative conditions is commonly referred to as the Achmatowicz oxidative rearrangement, after its founder Osman Achmatowicz Jr.[160] The rearrangement was originally induced by the treatment of furfuryl alcohols with bromine, however, a variety of milder conditions have since found widespread employment including *N*-bromosuccinimide in water.[161] Most commonly, however, the oxidative rearrangement is affected by the use of epoxidising agents, for example *m*CPBA and $VO(acac)_2/{}^tBuOOH$.[162] Sharpless asymmetric epoxidations are conventionally used in cases where either resolution or enantiomeric induction is desired.[163]

The rearrangement itself presumably proceeds *via* the formation of epoxide **A**, directed by the presence of the hydroxyl group α- to the furyl ring, which subsequently induces ring decomposition *via* zwitterionic intermediate **B** (**Scheme 45**). As a result, 1,4-dicarbonyl species **C** is generated, which then undergoes ring-closure to form the hemi-acetal product **414**.



Scheme 45. The mechanism of the Achmatowicz oxidative rearrangement

This versatile rearrangement has found widespread application in organic chemistry and, in particular, natural product synthesis (**Scheme 46**). Examples range from the synthesis of saccharide analogues such as daumone (**A**),[164] through unsaturated lactone derivative phomopsolide C (**B**),[165] to more complex macrostructures, for example, norhalichondrin B (**C**).[166]



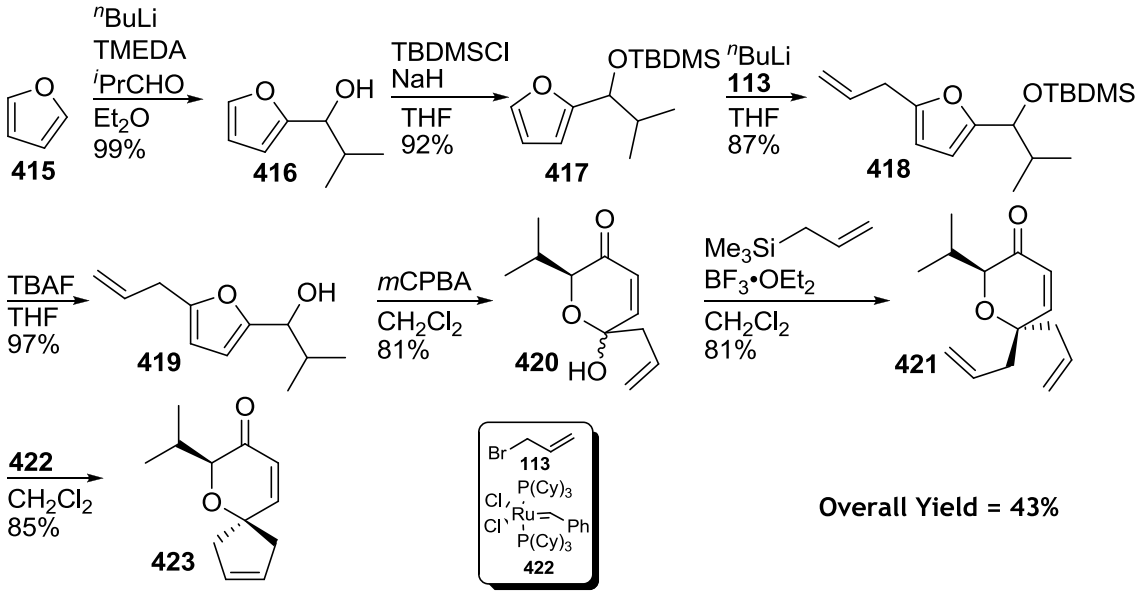
Scheme 46. Applications of the Achmatowicz oxidative rearrangement in total synthesis.

The plentiful instances of this reaction in the literature rightly illustrate its standing as a powerful tool in organic chemistry. Its use as a comprehensive method for the assembly of spirocyclic structures however, has so far been mostly limited to the synthesis of spiroketals.[167]

First Generation Spirocyclic Pyran Syntheses

Utilising the first generation methodology developed within the group, a selection of spirocyclic pyran structures was prepared starting from furan **415**.[159] The

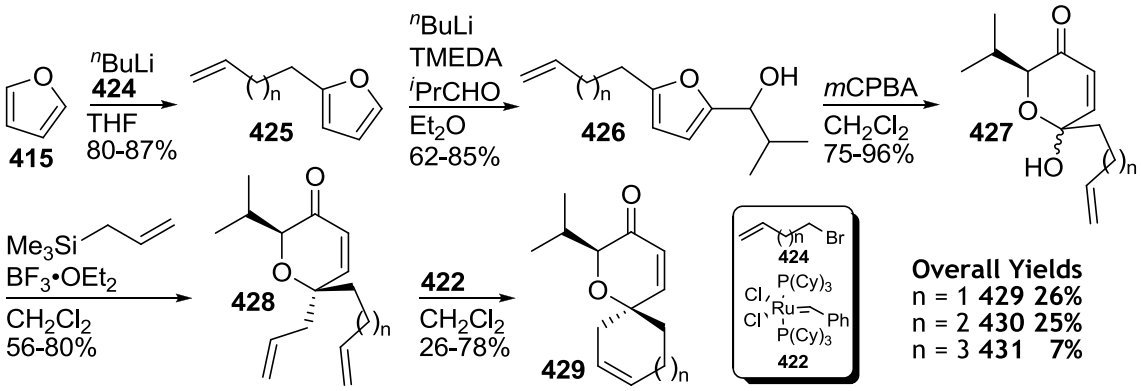
synthesis of the oxaspiro[5.4]decenone **423** began with the addition of lithiofuran to isobutyraldehyde to afford furfuryl alcohol **416** which was subsequently protected as silyl ether **417**. A second lithiation and trapping with allyl bromide **113** allowed access to 2,5-disubstituted furan **418**. Deprotection of the furfuryl alcohol **418** followed by exposure to oxidative conditions effected the Achmatowicz rearrangement to generate hemi-acetal **420**. Lewis acid mediated Sakurai-type allylation followed by ring-closing metathesis then afforded the desired spirocyclic product **423** in 43% overall yield over the 7 step sequence (**Scheme 47**).



Scheme 47. The first generation synthesis of [5.4]-spirocyclic pyran **423**,

The synthesis of the subsequent spiro[5.5], [5.6] and [5.7] ring systems followed a slightly different route. In this case the alkylation stages were reversed, such that the terminal alkenyl substituent was introduced before furyl lithiation and addition to isobutyraldehyde. This more concise route was not applicable for the synthesis of the [5.4] ring system **423** due to the risk of competing allylic deprotonation in place of furyl lithiation. This new approach avoided the need for hydroxyl protecting group manipulation. Thus, in the case of the [5.5] ring system, the desired spirocyclic dihydropyranone product **429** was accessed in 26% yield over 5 steps from furan. Similarly, the [5.6] spirocyclic pyranone **430** was accessed in 5 steps in 25% overall yield. For the larger ring systems, however, the ring closing

metathesis step proved troublesome, and the synthesis of oxaspiro[5.7]tridecenone **431** proceeded in 7% overall yield (**Scheme 48**).



Scheme 48. Application of the methodology to larger spirocyclic pyrans

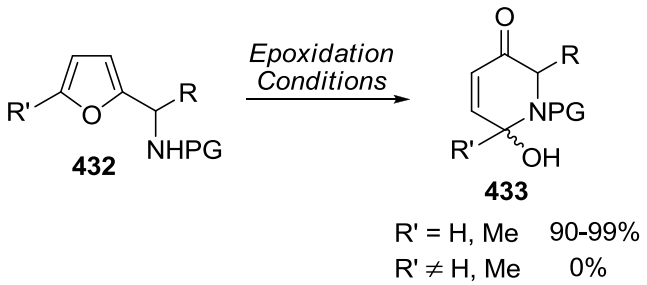
This early strategy demonstrated the selectivity of the oxidative rearrangement, affording the desired lactols in the presence of various functionalities, including olefins, without detrimental effect. In addition, the Lewis-acid promoted allylation afforded single diastereoisomers, with the addition being dictated by the orientation of the isopropyl substituent.

Despite the poor yield observed for the larger ring-closing metathesis, this strategy provided access to spirocyclic pyrans in relatively few steps from commercially available starting materials. The true viability of this strategy for the divergent approach to spirocyclic cores would, however, be determined based on its transferability to the synthesis of analogous spirocyclic piperidines.

Application to Spirocyclic Piperidines

It was believed that 5-substituted furfuryl amines **432** would behave similarly to their oxa-counterparts, however, in an extension of the first generation methodology, the oxidative rearrangement of the furfuryl amine precursors proved to be temperamental; its success was highly influenced by the nature of the C5 furan substituent.[159b] While most groups were tolerated α- to the furfuryl amine, those compounds in possession of a substituent larger than a methyl at the C5 position of the furan ring failed to undergo the oxidative rearrangement and, as a

result, did not afford any of the desired hemi-aminals **433** (**Scheme 49**). The precise reasons for the difference in behaviour between the oxa- and aza-systems are not fully understood.



Scheme 49. Furfuryl amines possessing C5-substituent larger than Me did not undergo oxidative rearrangement

A New Strategy for the Synthesis of Spirocycles

Faced with an unreliable approach to the synthesis of the hemi-aminal intermediate **433**, a new strategy for the synthesis of the spirocyclic amine cores was required. In the devised second generation approach, spirocyclic pyranones **434** and spirocyclic piperidinones **435** were envisioned as having originated from the oxidative rearrangement of cyclic tertiary furfuryl alcohols **436** and cyclic tertiary amines **437** respectively (**Figure 12**). If successful, this approach would potentially provide a concise route to the desired spirocyclic pyrans and piperidines.

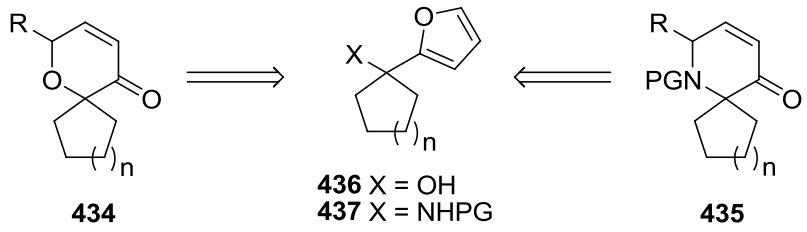
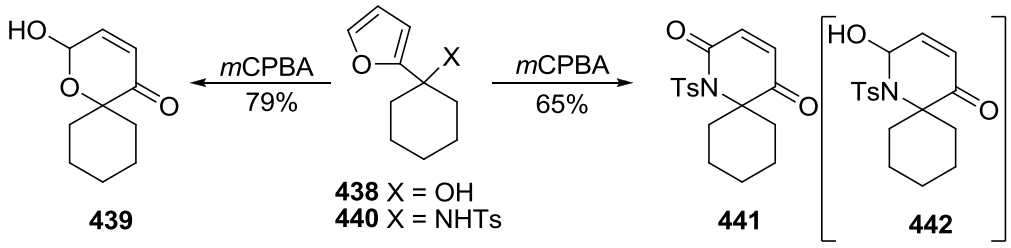


Figure 12. Retrosynthetic analysis of second generation approach to spirocyclic pyrans and piperidines.

This methodology was strongly inspired by a solitary example of the synthesis of spirocycles found in the work of Couladouros.[168] It was reported that

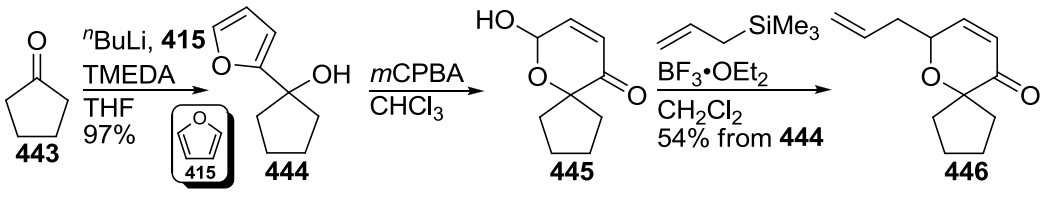
cyclohexylfuryl carbinol **438** underwent oxidative rearrangement to generate the corresponding spirocyclic hydroxypyranone **439**. The analogous tosyl-amide **440**, however, unexpectedly afforded the spirolactam unit **441** as the sole product in place of the anticipated hydroxypyridinone **442** (**Scheme 50**).



Scheme 50. Couladouros' example of the oxidative rearrangement methodology

Initial Model Systems

The initial model studies began with cyclopentanone **443** which, upon lithiofuran addition, afforded the known furfuryl alcohol **444** in reasonable (40%) yield.[169] It was found that by using an excess (5 eq.) of the lithiated furan the cyclic tertiary furfuryl alcohol **444** could be obtained in near-quantitative yield. As expected, treatment of the furfuryl carbinol **444** with *m*CPBA effected an oxidative rearrangement to yield lactol **445**. Unfortunately, the lactol intermediate **445** was found to decompose upon contact with silica gel, and as such the crude was taken forward without purification to the following transformation. Boron trifluoride promoted Sakurai-type allylation of lactol **445** with allyltrimethylsilane afforded the functionalised [5.4] spirocyclic pyran **446** unit in moderate yield over the three step sequence (**Scheme 51**).[170]



Scheme 51. The synthesis of a functionalised spirocyclic pyran unit **446**.

Scope of the Methodology

In order to ascertain its flexibility, the methodology was applied to the synthesis of the corresponding [5.3] **449**, [5.5] **450**, [5.6] **453** and [5.7] **456** spirocyclic dihydropyranones (**Table 1**).

The results obtained were satisfactory with the exception of the attempted formation of the highly strained [5.3] spirocyclic dihydropyranone **449**. While all remaining ring systems were obtained as the major product over the entire sequence, this system afforded a complex mixture from which the desired allyl spirocyclic dihydropyranone **449** was isolated in very low yield.[171]

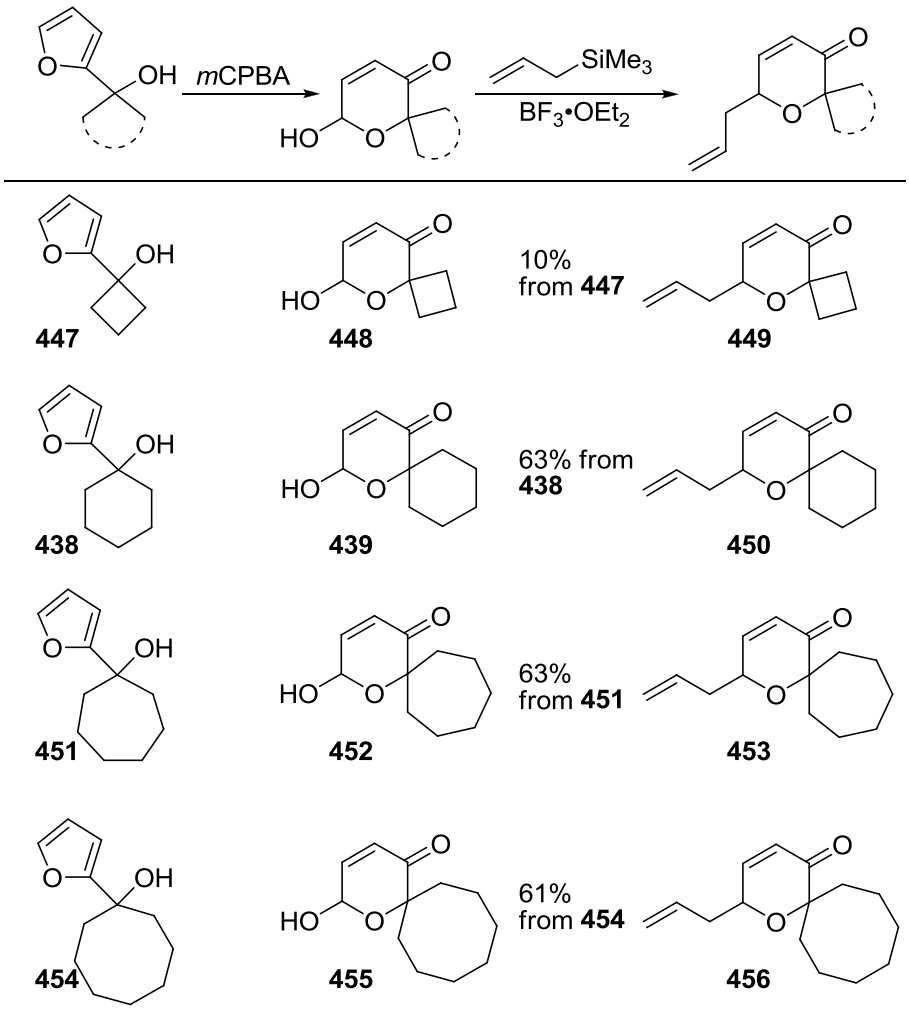


Table 1. The application of the second generation approach to the synthesis of spirocyclic pyrans.

Despite the difficulty in generating the [5.3] ring system **449**, this revised strategy compared favourably with the previous methodology. This new approach allowed improved access into spirocyclic ring systems, particularly for the generation of larger ring systems.

Having achieved the desired spirocyclic pyran core **446**, subsequent modification of the functionality within the pyran unit was explored in order to access the desired fully saturated spirocyclic units.

Synthesis of a Spirocyclic Pyran Core of Polymaxenolide

Pyran Functionalisation

As part of the initial studies the 5-membered spirocycle **446** was subjected to a variety of reduction conditions in an effort to entirely reduce the enone unit.

Enone reduction was thought of as potentially proceeding via one of two routes: A) sequential ketone reduction followed by elimination; or B) conjugate reduction followed by deoxygenation of the remaining ketone moiety (**Figure 13**).

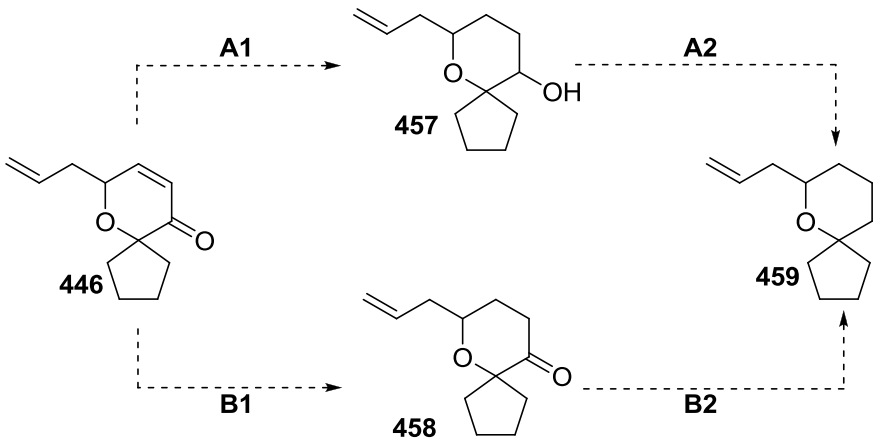
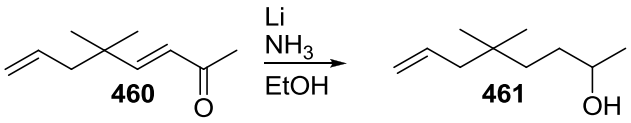


Figure 13. The possible pathways for enone reduction.

Birch Reduction

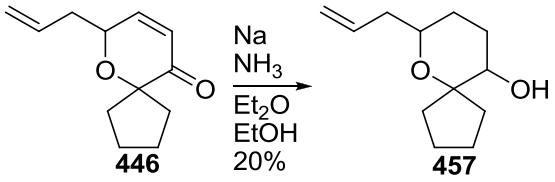
The sequential reduction strategy rested on the use of a Birch reduction. Such reductions have been shown to reduce enones to aliphatic alcohols in a single step. A closely related precedent which suggested that a Birch reduction would be ideal

for the reduction of the spirocyclic dihydropyranone system involved the reduction of enone **460** to aliphatic alcohol **461** without detrimental effect on the terminal olefin (**Scheme 52**).[172]



Scheme 52. Example of the Birch reduction in synthesis.

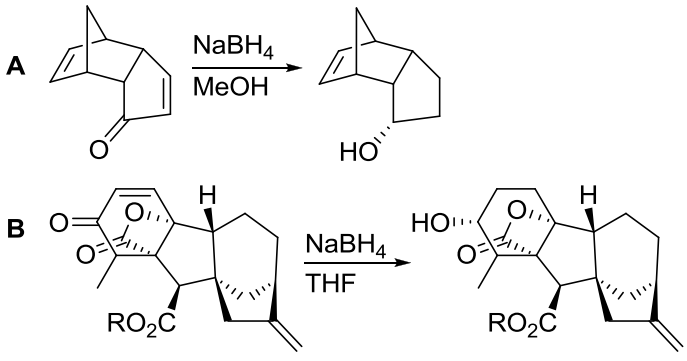
Dihydropyranone **446** was then subjected to Birch reduction conditions (**Scheme 53**). Unfortunately, although the desired alcohol **457** was generated in a single step the poor yield made the transformation unviable in a total synthesis context.



Scheme 53. Birch reduction of enone **446**.

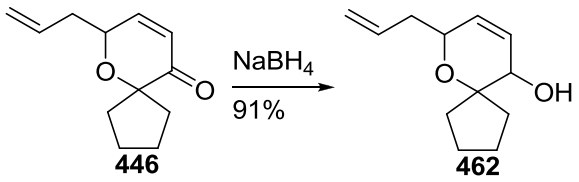
Sodium Borohydride Reduction

There is ample literature precedence for enones undergoing conjugate hydride addition followed by a subsequent 1,2-addition to afford the corresponding aliphatic alcohol when treated with excess sodium borohydride (**Scheme 54, A** and **B**).[173]



Scheme 54. One-pot 1,4- and 1,2-reduction of enones by $NaBH_4$.

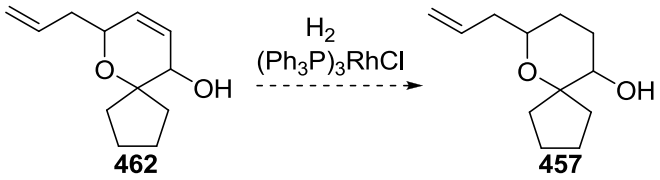
It was envisioned that this reduction strategy, when applied to the spirocyclic dihydropyranone system, would afford alcohol **457** in improved yields compared to the initial Birch reduction conditions. Unfortunately, sodium borohydride treatment of enone **446** resulted in selective 1,2-reduction in excellent yield to afford allylic alcohol **462** as a single diastereoisomer, the relative stereochemistry of which was not unambiguously assigned (**Scheme 55**). Despite repeated attempts under a variety of modified conditions, no 1,4-reduction was detected.



Scheme 55. Treatment of enone **446** with $NaBH_4$ resulted in exclusive 1,2-reduction.

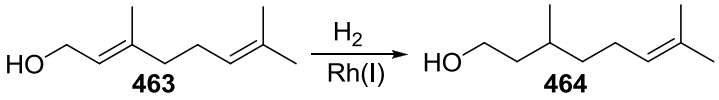
Wilkinson's Directed Hydrogenation

Possessing significant quantities of the allylic alcohol **462** as a result of the $NaBH_4$ reduction attempts, it was surmised that hydroxyl directed hydrogenation using Wilkinson's rhodium catalyst may afford the desired cyclic alcohol product **457** (**Scheme 56**). Once the aliphatic alcohol is obtained, the final deoxygenation conditions could be investigated.



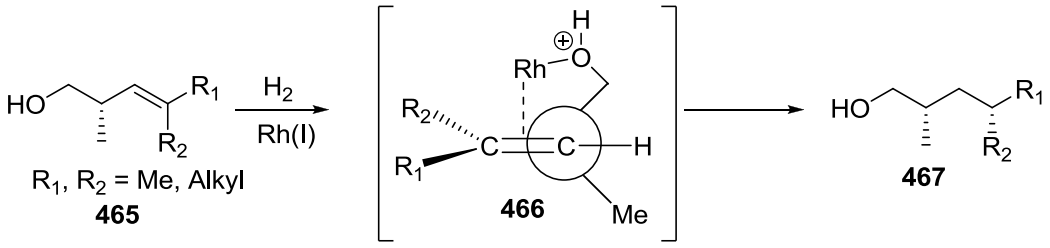
Scheme 56. The proposed hydroxyl-directed hydrogenation of allylic alcohol **462**.

Wilkinson's catalyst ($(Ph_3P)_3RhCl$) has been utilised to achieve regioselective hydrogenations whereby allylic and homoallylic alcohols direct hydrogenation to occur at their proximal site in the presence of additional double bonds (**Scheme 57**).[174]



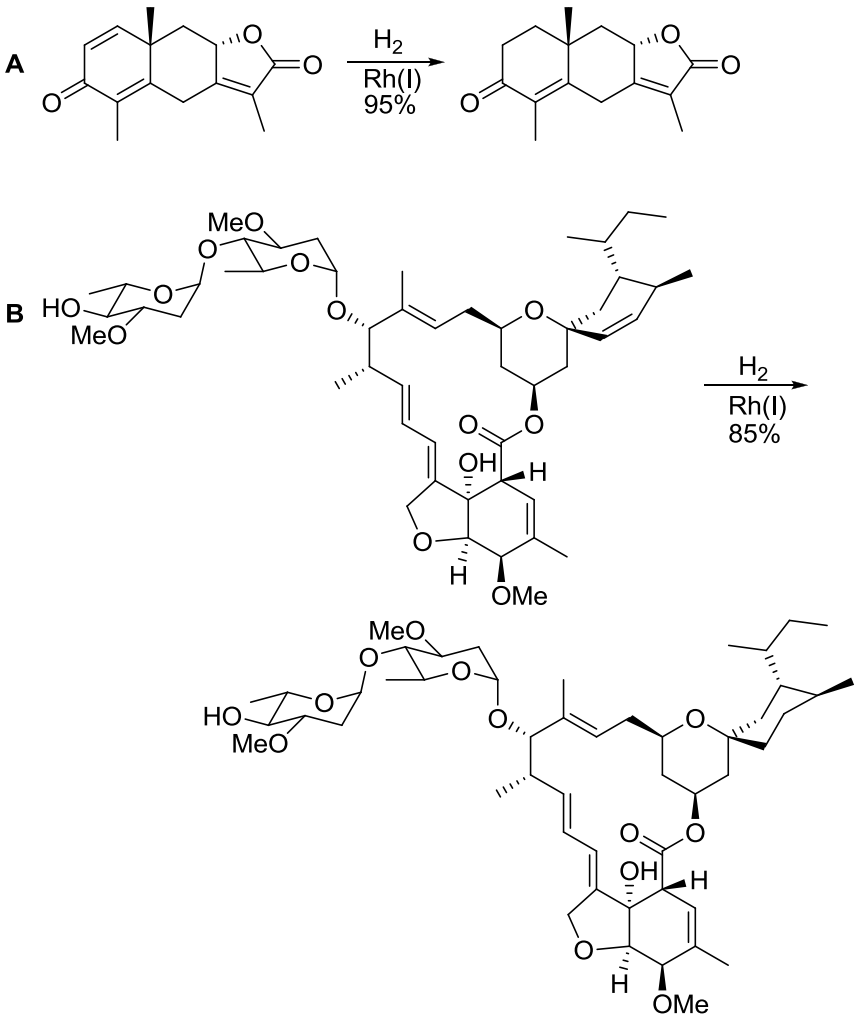
Scheme 57. Hydroxyl-directed hydrogenation with Wilkinson's catalyst.

Chirality present at the site of the alcohol can also be exploited to induce stereoselectivity to the newly hydrogenated site. Hydrogenation, facilitated by the coordination **466** between the catalyst and the hydroxyl unit, was found to occur stereoselectively, directed by allylic 1,3-strain (**Scheme 58**).[175]



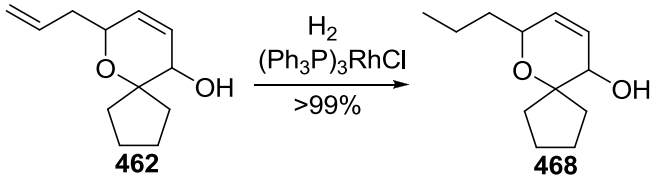
Scheme 58. Exploiting chirality with Wilkinson's catalyst.

Wilkinson's catalyst has also been shown to be selective in a different way whereby the catalyst has been used to facilitate the selective hydrogenation of the less substituted double bonds in polyunsaturated species (**A**,**B Scheme 59**).[176]



Scheme 59. Wilkinson's selective hydrogenation in total synthesis.

Unfortunately, when the hydrogenation of spirocyclic dihydropyranol **462** was explored, the bias towards less substituted olefins was found to trump the hydroxyl-directed selectivity. As a result, the terminal olefin was the only double bond to be hydrogenated in quantitative yield (**Scheme 60**).



Scheme 60. Hydrogenation resulted in selective removal of the terminal olefin.

Hence, it was deemed necessary to investigate and develop an alternative synthetic pathway in which conjugate reduction of the enone could be followed by a ketone deoxygenation sequence.

Stryker's Copper Hydride Hexamer

Conjugate reductions using copper hydride sources have been shown to be very effective in a variety of substrates.[177] Furthermore, Stryker has also described that the desired 1,4-reduction can take place in the presence of additional olefin functionality (**Table 2**).[178]

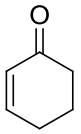
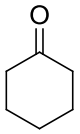
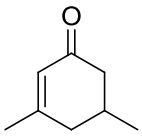
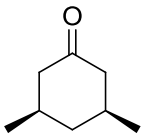
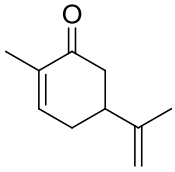
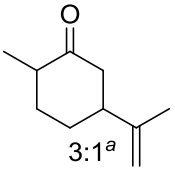
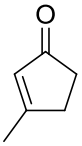
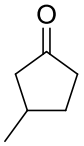
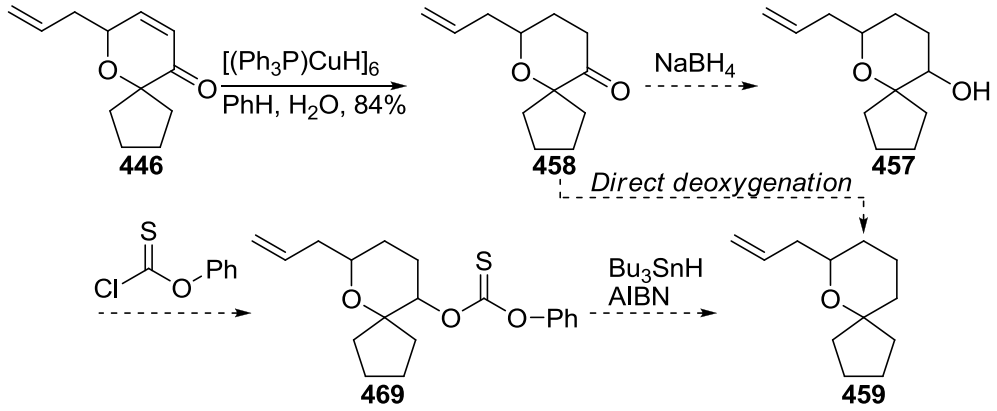
Substrate	Product	Substrate	Product
			 >100:1
	 3:1[a]		

Table 2. Examples of Stryker's conjugate reduction.

a - Stereochemistry not unambiguously assigned

Gratifyingly, conjugate hydride addition using Stryker's reagent (triphenylphosphine copper hydride hexamer) was highly successful, affording the desired spirocyclic pyranone **458** in good yield. Having achieved the desired conjugate reduction, two options became apparent to achieve the desired deoxygenation. In the first option, reduction of the ketone unit would deliver alcohol **457** which could then potentially be removed *via* the corresponding xanthate **469** under Barton-McCombie conditions.[179] Alternatively, the direct reduction of the carbonyl was also considered (**Scheme 61**).



Scheme 61. Stryker's reduction of enone **446.**

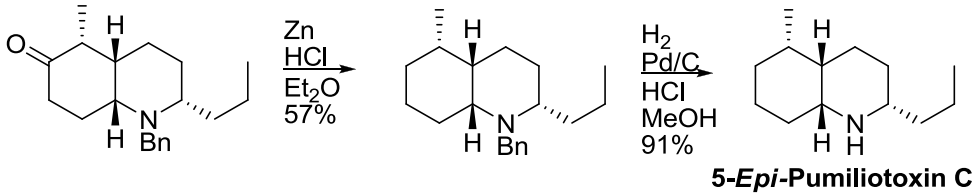
The increased number of steps associated with the Barton-McCombie strategy prompted efforts to be focussed on a possible one-step carbonyl reduction. For such reasons, a direct deoxygenation was investigated whereby complete removal of the carbonyl unit might be achieved in a single operation.

Deoxygenation

The two most common 'named-reaction' deoxygenations which will entirely reduce a carbonyl compound to the corresponding methylene unit are the Clemmensen reduction[180] and the Wolff-Kishner reduction.[181]

Clemmensen Reduction

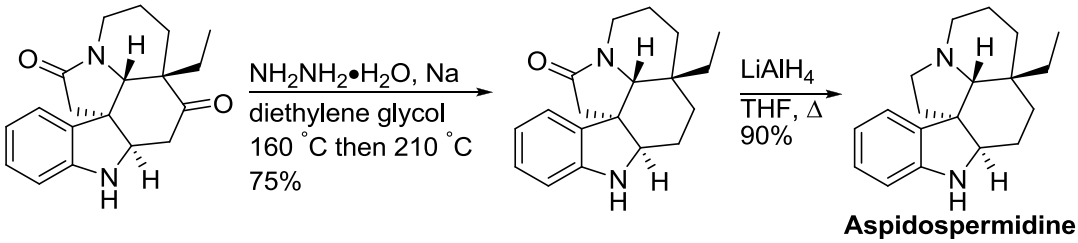
The reduction of carbonyl compounds to their corresponding alkanes in the presence of zinc and concentrated acid is known as the Clemmensen reduction. Such conditions are relatively harsh, and as a result, various modifications have been developed whereby the same original concept can be carried out in a milder environment. These modified procedures have assisted this method of deoxygenation to become popular in natural product synthesis. An example of its use is found in Kibayashi's synthesis of 5-*epi*-pumiliotoxin C (**Scheme 62**).[182]



Scheme 62. Clemmensen reduction in Kibayashi's route to 5-*epi*-pumiliotocin C.

Wolff-Kishner Reduction

While Clemmensen reduction has the benefit of being carried out in a single step, the Wolff-Kishner reduction usually proceeds *via* the initial formation of the equivalent hydrazone intermediate. Subsequent reduction of the hydrazone, driven by the deprotonation and elimination of N_2, affords the desired, fully reduced methylene unit. The Wolff-Kishner reduction has found common use in natural product synthesis including, for example, Marino's synthesis of aspidospermidine (**Scheme 63**).[183]



Scheme 63. Wolff-Kishner deoxygenation in the synthesis of apidospermidine.

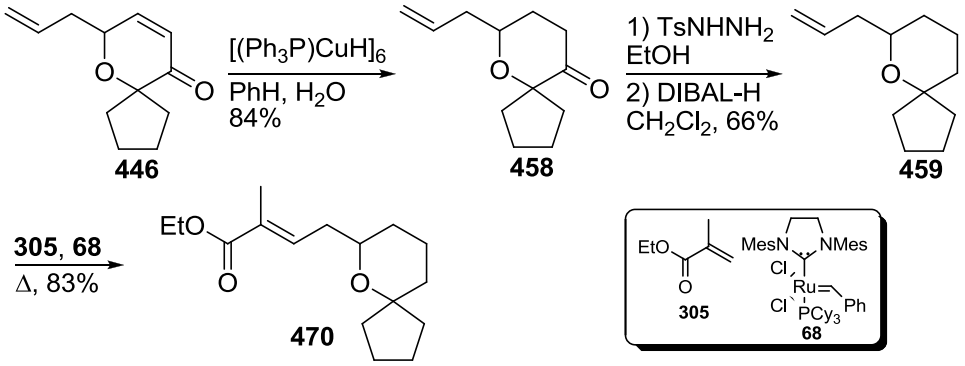
Both deoxygenation reactions are carried out using fairly harsh, yet opposing conditions. The Clemmensen reduction uses strongly acidic conditions, often at high temperatures. Although recent modifications have enabled the reaction to be carried out at lower temperatures, there is still the necessity for an acidic environment. The Wolff-Kishner reduction, on the other hand, requires strongly basic conditions and high temperatures. A milder variant of this two-step process is the Caglioti-modified Wolff-Kishner reduction.[184]

The Caglioti-modified Wolff-Kishner reduction exploits tosyl-hydrazide in place of hydrazine to generate a tosyl-hydrazone intermediate. This intermediate can then be reduced using a variety of mild reducing agents.

This latter method for deoxygenation was deemed to carry the least risk of unwanted side-reactions and as such was applied to the spirocyclic pyran system.

Completing the Core

Following Padwa's conditions for Caglioti-Wolff-Kishner deoxygenation,[185] pyranone **458** was converted to the corresponding tosyl-hydrazone by treatment with tosyl-hydrazide in ethanol. Subsequent DIBAL-H reduction of the crude tosyl-hydrazone afforded the oxa-spirocyclic pyran **459** in good yield. Further elaboration of the spirocyclic core was realised in the cross-metathesis of fully saturated pyran **459** with ethyl methacrylate **305** in the presence of Grubbs 2nd generation catalyst **68**. This afforded the trisubstituted conjugated ethyl ester **470** as a single double bond isomer, completing the synthesis of the oxa-pinnaic acid core (**Scheme 64**).[171]



Scheme 64. Completing the spirocyclic pyran core **470**.

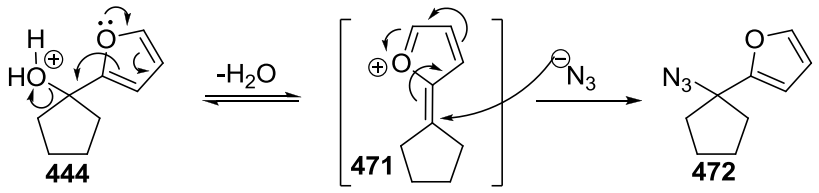
The next task was to investigate whether this methodology could be transferable to the synthesis of a spirocyclic piperidine counterpart, which would display those same functionalities present in halichlorine and the pinnaic acids.

Application to the Synthesis of Spirocyclic Piperidines

From the Common Synthetic Precursor

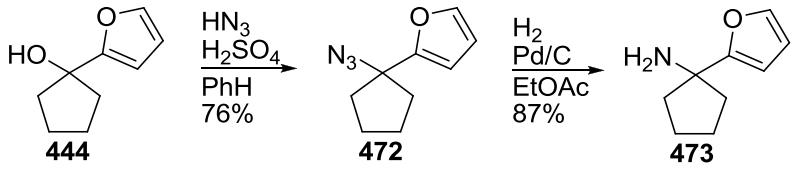
In order to tailor the recently developed methodology to the synthesis of spirocyclic piperidines, it became necessary to access a cyclic tertiary furfuryl amine precursor.

Pleasantly, treatment of furfuryl alcohol **444** under Couladouros' conditions effectively converted it to the corresponding amine *via* the formation, and subsequent reduction, of cyclic tertiary furfuryl azide **472**.[168] Mechanistically, the reaction requires treatment with hydrazoic acid in the presence of sulphuric acid which suggests that elimination of water first affords the planar furanium intermediate **471** (**Scheme 65**). Subsequent addition of the nucleophilic azide then leads to the formation of the desired cyclic tertiary furfuryl azide **472**.



Scheme 65. Proposed mechanism of cyclic tertiary furfuryl azide formation.

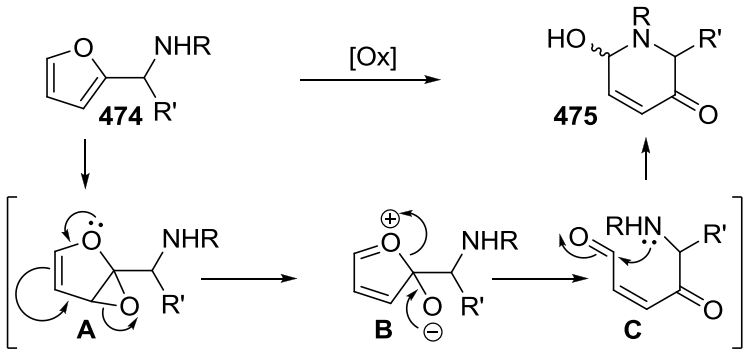
Hydrogenation over Pd/C generated the cyclic tertiary amine **473** cleanly, paving the way for the oxidative rearrangement conditions to be applied (**Scheme 66**).



Scheme 66. Conversion of the tertiary furfuryl alcohol **444** to the corresponding amine **473**.

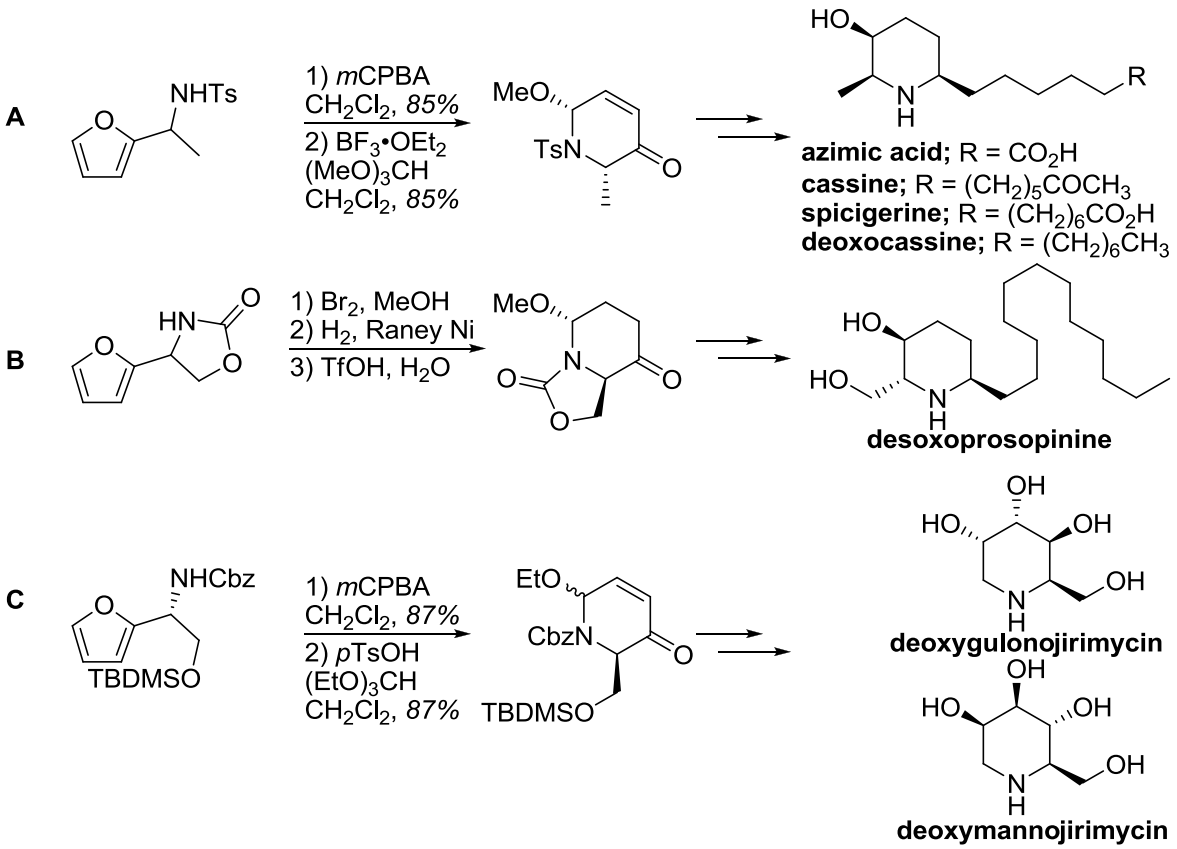
The Aza-Achmatowicz Oxidative Rearrangement in Synthesis

The equivalent oxidative rearrangement of furfuryl amines to that previously utilised is often referred to as the aza-Achmatowicz oxidative rearrangement, a term coined by Ciufolini who was first to explore its use.[186] The mechanism proceeds in the same fashion as the traditional oxa-counterpart, forming the pyridinone product **475** (**Scheme 67**).



Scheme 67. The aza-Achmatowicz oxidative rearrangement mechanism.

The rearrangement of furfuryl amines has, similarly, found widespread application in organic synthesis with its use being described in Padwa's syntheses of members of the *Cassia* and *Prosopis* family (**A**),[185] Ciufolini's synthesis of desoxoprosopinine (**B**)[187] among many other examples from his group and the synthesis of aza-sugars as reported by O'Doherty (**C**) (**Scheme 68**).[188]

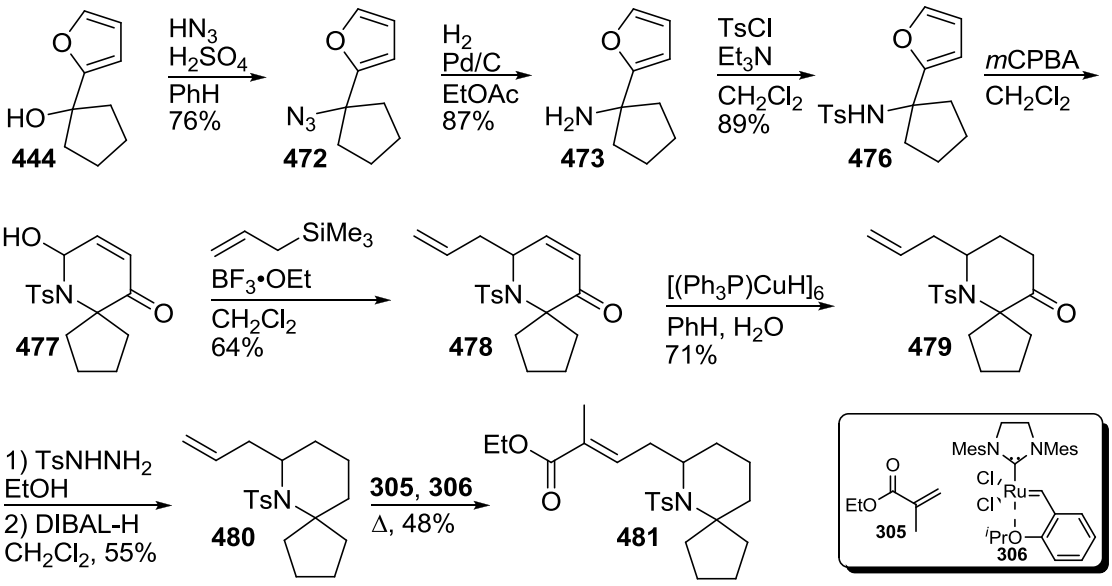


Scheme 68. The aza-Achmatowicz oxidative rearrangement in synthesis.

Synthesis of the Spirocyclic Piperidine Core of Pinnaic Acid

Unfortunately, exposing the free amine **473** to the oxidative rearrangement conditions afforded no discernable product. Indeed, the majority of examples of the aza-Achmatowicz oxidative rearrangement being utilised involve tosyl-protected amine precursors.[185] Many carbamate- and amide-protected furfuryl amines have also been shown to tolerate the oxidative rearrangement conditions, however, the subsequent allylation step involves the use of a Lewis-acid, which could potentially cause undesired protecting group removal.[186-188] Hence, tosyl-protection of the newly formed tertiary amine **473** was deemed the safer route. Treatment of tosyl-amide **476** with *m*CPBA proceeded to afford the desired hemi-aminal crude **477**, which was immediately subjected to Sakurai-type allylation conditions to afford dihydropiperidinone **478**.[170]

As was in the case of the corresponding spirocyclic pyran, selective 1,4-reduction was achieved using Stryker's reagent to afford piperidone **479**.[178] Piperidone deoxygenation under Caglioti-Wolff-Kishner conditions then produced the desired spirocyclic piperidine **480**.[185] Finally, cross-metathesis in the presence of Grubbs 2nd generation catalyst **68** afforded 33% yield of enoate ester **481**. Optimisation of the cross-metathesis using Hoveyda-Grubbs 2nd generation catalyst **306** improved the efficiency of the cross-coupling and afforded the spirocyclic piperidine core **481** of pinnaic acid in 48% yield as a single *E*-isomer (**Scheme 69**).[171]



Scheme 69. Synthesis of the pinnaic acid spirocyclic piperidine core **481**.

The synthesis of the spirocyclic piperidine core of pinnaic acid **481** illustrates the transferability of this methodology between oxa- and aza-systems.

In possession of a flexible synthesis of spirocyclic pyrans and piperidines, more elaborate structures were sought to test the applicability of the methodology.

Complex Natural Product Synthesis

The ultimate goal from the development of this methodology was its applicability to the syntheses of complex natural products. In the case of spirocyclic pyrans, polymaxenolide **408** was the primary target while the bioactive marine alkaloids halichlorine **1**, pinnaic acid **2** and tauropinnaic acid **3** were the spirocyclic piperidine-containing targets.

Towards Polymaxenolide

Proposed Biosynthetic Pathway

A potential biosynthetic pathway leading to polymaxenolide **408** has been proposed.[157a] As polymaxenolide **408** is a hybrid metabolite, it could be thought of as originating from the coupling of the known cembranoid skeleton **A**, and naturally occurring 9α,15-epoxyafricanene **482** (**Figure 14**). Enol addition to the epoxide followed by hemi-acetal formation, and finally elimination would give rise to the spirocyclic hybrid metabolite.

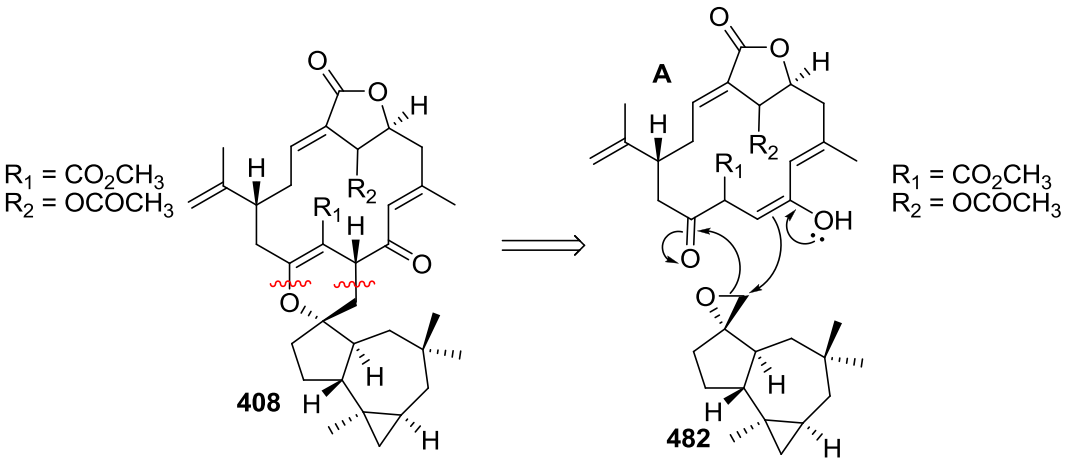
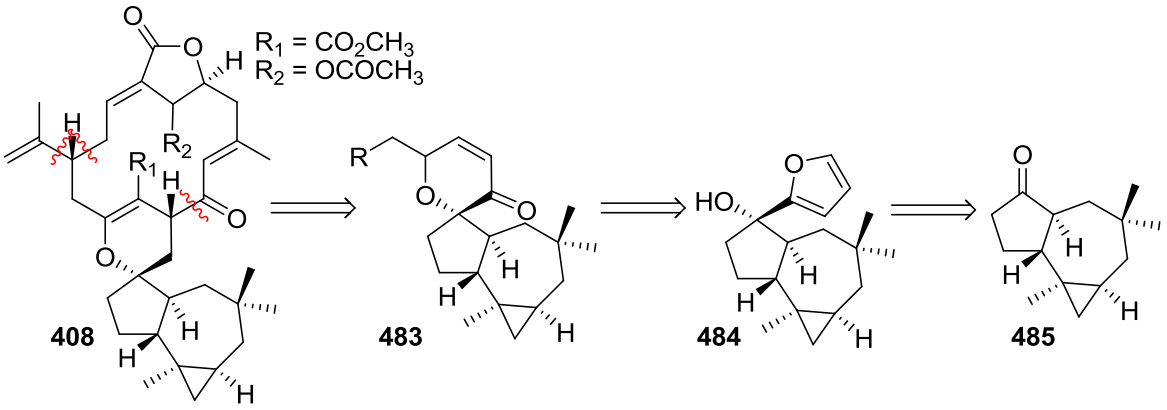


Figure 14. The proposed biosynthetic entry to polymaxenolide **408**.

Retrosynthetic Analysis

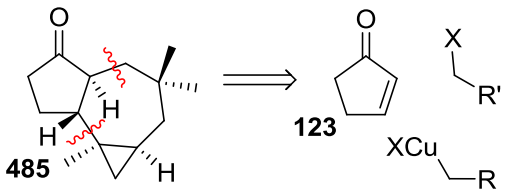
Despite the likelihood of the two species reacting in nature in the described fashion to deliver polymaxenolide, the spirocyclic core of the hybrid metabolite was of particular synthetic interest.

Retrosynthetically, polymaxenolide was envisioned as originating from the oxidative rearrangement of tricyclic tertiary furfuryl alcohol **484** (**Scheme 70**). The Achmatowicz oxidative rearrangement product appeared to be perfectly suited for further manipulation through a Lewis-acid mediated alkylation to afford functionalised spirocyclic dihydropyranone **483**. The enone functionality could then potentially be remodelled to incorporate the Northern, cembranoid fragment.



Scheme 70. Retrosynthetic analysis for the synthesis of polymaxenolide **408.**

Ketone **485**, in turn, was thought of as having originated through a one-pot, three-component, conjugate addition/alkylation reaction would incorporate useful functionality with the desired *anti*-relationship at the ring junction (**Scheme 71**).



Scheme 71. The proposed retrosynthesis of key tricyclic ketone **485.**

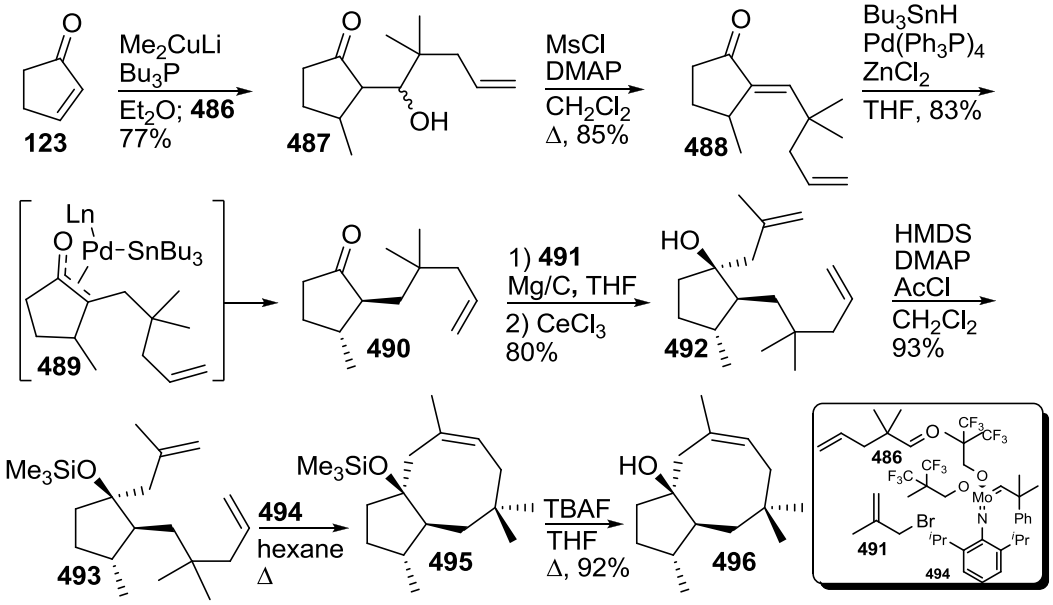
Towards the Synthesis of the Africanane Core

In order to incorporate the previously developed spirocyclic pyran methodology for the synthesis of polymaxenolide **408**, the construction of the more complex, tricyclic ketone **485** was undertaken. The proposed route was supported by the efforts of both Vanderwal and Fürstner who had independently developed similar reaction sequences to successfully generate α,β-difunctionalised cyclopentanones.

Fürstner's Synthesis of Dactylol

Fürstner's synthesis of dactylol contained a three-component-one-pot conjugate addition/trapping approach in which methyl cuprate was introduced to cyclopentenone **123**, followed by trapping of the resultant enolate with the neo-pentyl aldehyde **486**.[189] A subsequent elimination was effected by treatment with MsCl in the presence of DMAP.

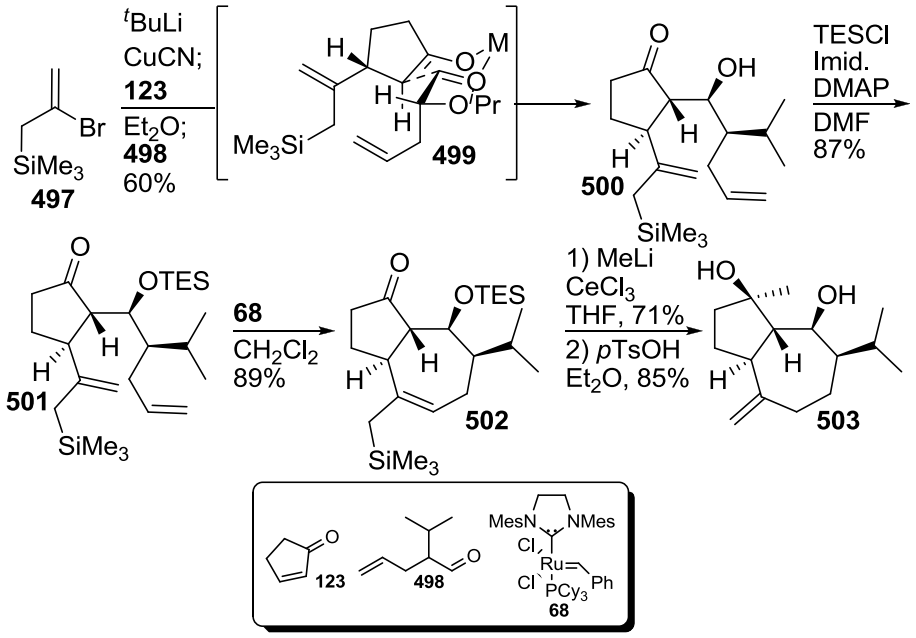
Enone reduction then gave, exclusively, the *anti*-product **490** using a palladium catalysed tributyltin hydride addition. In order to complete the synthesis of dactylol, Fürstner used a Grignard addition to introduce a methylallyl substituent which gave rise to a 1.2:1.0 mixture of alcohol products **492**. After separation, each diastereoisomer was treated independently however only that which led to the desired target molecule is shown. Alcohol protection was found to be necessary in order for the Schrock molybdenum carbene catalysed ring-closing metathesis to take place. Final deprotection afforded dactylol **496** in 92% yield (**Scheme 72**).



Scheme 72. Fürstner's synthesis of dactylol **496.**

Vanderwal's Synthesis of Teucladiol

Vanderwal utilised a similar initial transformation for his synthesis of teucladiol whereby a substituted isopropenyl cuprate was added in a 1,4-fashion to cyclopentenone **123.**[190] Subsequent trapping of the enolate with aldehyde **498** afforded the *anti*-aldol product **500**; the orientation of the hydroxyl group is dictated through Felkin-Anh control. Subsequent alcohol protection was carried out, followed by ring-closing metathesis in the presence of Grubbs 2nd generation catalyst **68** provided the bicyclic ketone **502**. Final alkylation and desilylation with simultaneous protodesilylation completed Vanderwal's concise approach to teucladiol **503** (**Scheme 73**).



Scheme 73. Vanderwal's synthesis of teucladiol **503.**

Efforts Towards the Synthesis of Africanane-Derived Natural Products

Buoyed by the precedence for conjugate addition/trapping, followed by medium-sized ring-closing metathesis to generate similar cyclic structures, it was postulated that application of this type of chemistry could lead to the synthesis of a variety of africanane-derived natural products (**Figure 15**) through simple alterations in a number of steps.[191]

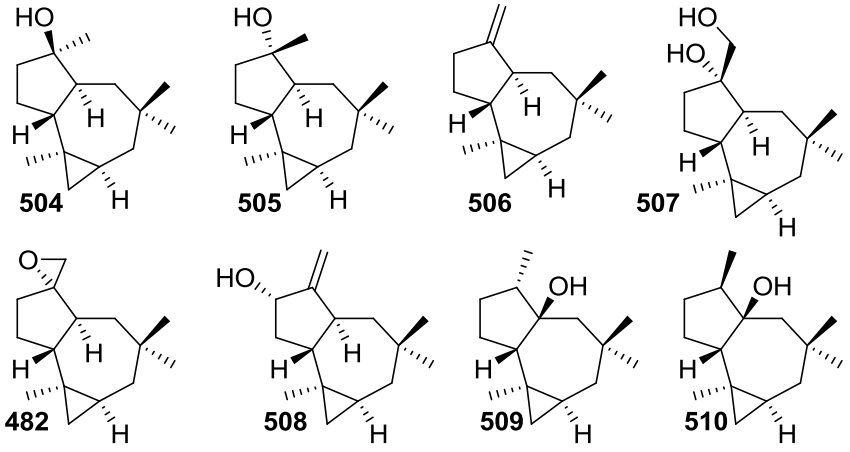
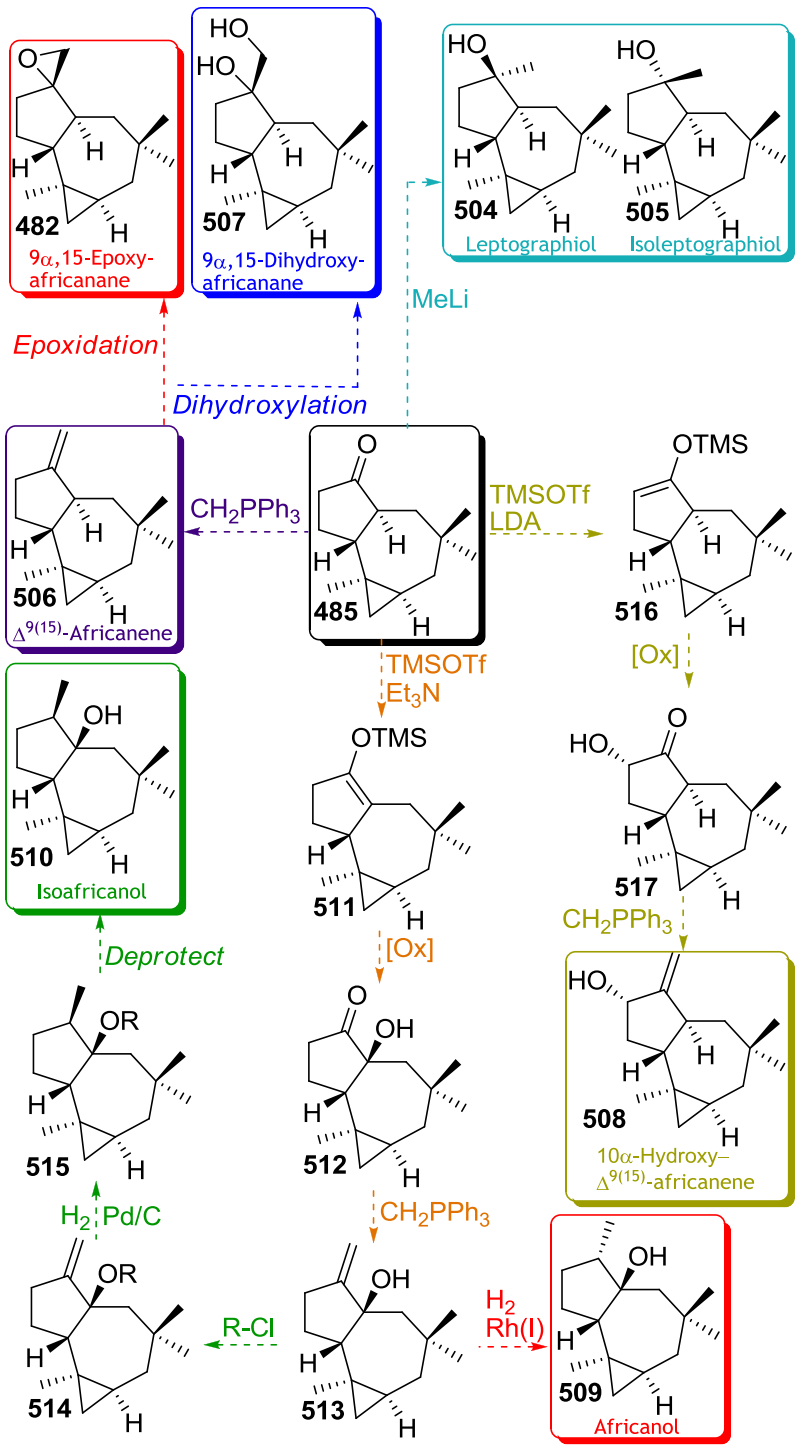


Figure 15. Africanane-derived natural products.

It was anticipated that up to eight africanane natural products could be accessed from key tricyclic ketone **485** (**Scheme 74**). For instance, nucleophilic addition of methyllithium to ketone **485** could potentially lead to both leptographiol **504** and isoleptographiol **505**. Methylenation of ketone **485** would lead to the *exo*-cyclic methylene derivative $\Delta^{9(15)}$-africanene **506**. Subsequent epoxidation of the *exo*-cyclic methylenated tricycle **506** could then lead to the postulated biosynthetic precursor to polymaxenolide, 9α,15-epoxyafricanane **482**. Similarly dihydroxylation of the *exo*-cyclic methylene unit could be envisioned to afford 9α,15-dihydroxyafricanane **507**.

Africanol **509** itself could be accessed *via* an initial Rubottom-type oxidation to afford the α-hydroxy ketone **512**. Subsequent methylenation, followed by Wilkinson's hydroxyl-directed hydrogenation of the *exo*-cyclic double bond should afford the desired natural product **509**. Alternatively, it may be possible to induce hydrogenation to occur from the opposite face if the tertiary alcohol is protected with a bulky substituent to afford protected alcohol **514**. This could potentially allow the generation of isoafricanol **510**.

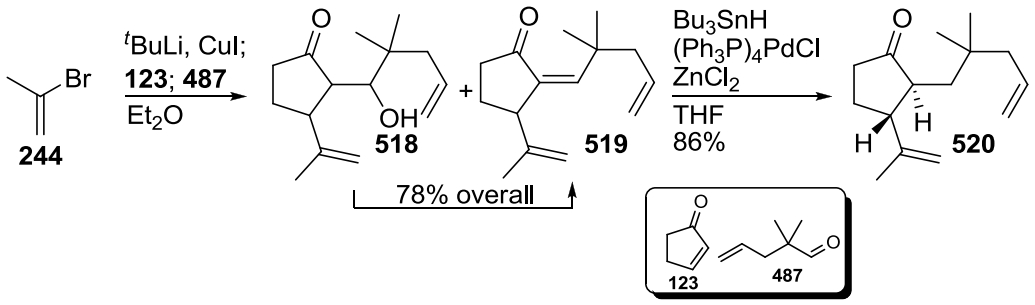
Finally, it may be possible to influence the Rubottom oxidation to take place with the opposite regiochemistry using TMS-enolate **516**, to afford the less substituted α-hydroxy ketone **517**. Final methylenation would complete the synthesis of 10α-hydroxy-$\Delta^{9(15)}$-africanene **508** (**Scheme 74**).



Scheme 74. Proposed access to a variety of Africanane-derived natural products from key tricyclic ketone **485.**

Towards the Synthesis of the Tricyclic Ketone

The synthesis of the key tricyclic ketone **485** began with cyclopentenone **123** which was treated with the *in situ* formed isopropenyl cuprate under Snyder's conditions.[192] The resulting enolate was trapped by the neo-pentyl aldehyde **487** used by Fürstner in his synthesis of dactylol.[189] Interestingly, the addition yielded a mixture, not of diastereoisomers, but of the expected β-hydroxyketone product **518** and elimination product **519**. The original intention was to eliminate the β-hydroxyl moiety using Fürstner's elimination protocol, followed by a facially selective palladium catalysed reduction. A pleasant observation, however, was that simply allowing the reaction mixture to stir for an extended period at room temperature formed the elimination product **519** cleanly. The result of this was a one-pot conjugate addition/alkylation/elimination reaction which accessed enone **519** in 78% overall yield, affording the reduction precursor in a single operation. Subsequent palladium catalysed tributyltin hydride reduction proceeded smoothly to regio- and stereoselectively reduce the enone, affording bis-olefin **520** (**Scheme 75**).



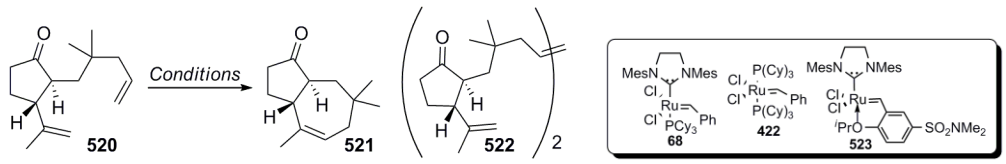
Scheme 75. Synthesis of the ring-closing metathesis precursor **520.**

Surprisingly, the ring-closing metathesis step proved to be problematic with initial attempts resulting in, largely, recovered starting material **520** with traces of dimerisation product **522** (**Table 3**). Subjecting *bis*-olefin **520** to conditions identical to those reported in Vanderwal's synthesis of teucladiol, resulted only in traces of dimer **522** (entry 1).[190] Simultaneous application of Taber's conditions, reported in his synthesis of africanol, afforded no reaction after 1h, and trace dimerisation product **522** after longer reaction time (entries 2 and 3).[193] A slight

increase in catalyst concentration also failed to yield satisfactory results (entry 4),[194] while increased substrate concentration merely induced increased dimerisation (entry 5). The use of conditions described for the ring-closing metathesis of structurally divergent [4.6]-bicyclic compounds also failed to give the desired cyclisation product **521**, instead affording traces of dimerisation adduct **522** as the only product (entry 6).[195] Increasing the reaction temperature and substrate concentration by applying Romo's conditions described in his synthesis of oomphadiol induced greater dimerisation (entry 7).[196] Dilution reduced the quantity of dimer **522** formed, however, similarly afforded no detectable amounts of ring-closed product **521** (entry 8). Adopting Paquette's conditions using Grubbs 1st generation catalyst **422** afforded similar results over prolonged reaction times (entry 9), with increased concentrations leading to increased dimerisation (entry 10).[197] Lewis-acids have been shown to prevent catalyst degradation, however, in this case, the use of Lewis-acids resulted in no reaction being observed (entry 11).[198] Disappointingly, the use of the recently developed Zhan 1B catalyst **523** led to increased dimerisation (entry 12).[199]

Conversely, Lei's conditions for a similar ring-closing metathesis with Grubbs 2nd generation catalyst **68**, required the reaction taking place under an inert atmosphere for 1h, then stirred open to the air overnight presumably to purposefully, yet gradually induce catalyst degradation in an effort to suppress its reactivity. Unfortunately, such conditions were found to be equally unsuccessful (entry 13).[200]

Particularly surprising was the lack of success granted when the reaction was carried out in 4.5 mM dilution with 5% Grubbs 2nd generation ruthenium catalyst **68** (entry 14). During the course of these investigations, a report emerged from the Nakata group in which they describe their strategy towards the same tricyclic ketone **485** utilising precisely the approach described herein.[201] In Nakata's report, ring-closing metathesis using 5% catalyst **68** at a dilution of 4.5 mM was successful, albeit in lower yield (53%) than was perhaps expected, demonstrating the difficulties in encouraging *bis*-olefin **520** to form the bicyclic ketone **521**.

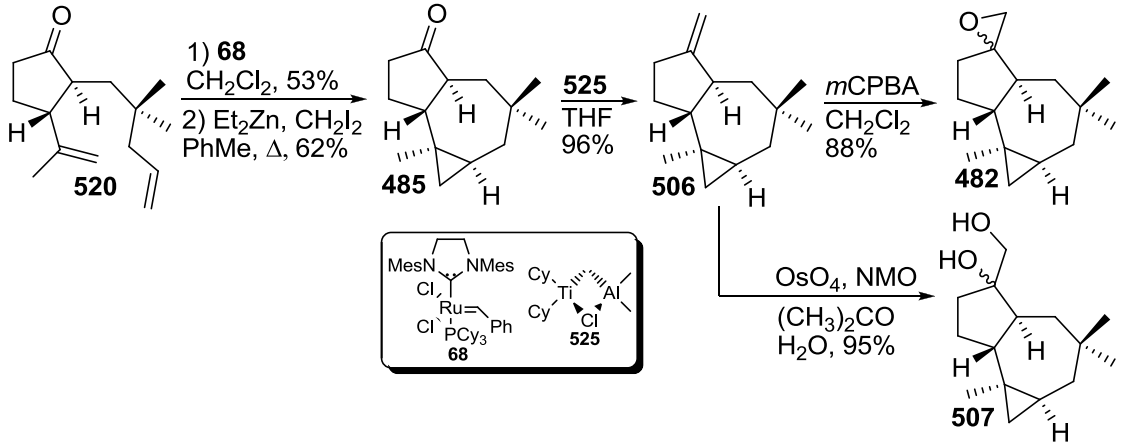


Entry	Catalyst	Conc.	Conditions	Products
1	5% + 2.5% **68**	15mM	CH_2Cl_2, Δ, 2.5h + 4h	**520**, trace **522**
2	2% **68**	5mM	CH_2Cl_2, Δ,1h	**520**
3	2% **68**	5mM	CH_2Cl_2, Δ,18h	**520,** trace **522**
4	5% **68**	5mM	CH_2Cl_2, Δ, 18h	**520,** trace **522**
5	5% **68**	15mM	CH_2Cl_2, Δ, 18h	35% **522**
6	10% **68**	5mM	CH_2Cl_2, Δ, 2h	**520,** trace **522**
7	3% **68**	25mM	PhMe, Δ, 3h	40% **522**
8	3% **68**	5mM	PhMe, Δ, 3h	25% **522**
9	30% **422**	3mM	CH_2Cl_2, Δ,36h	**520,** trace **522**
10	30% **422**	5mM	CH_2Cl_2, Δ, 72h	18% **522**
11	30% **422**	5mM	CH_2Cl_2, Δ, 18h[a]	**520**
12	5% **523**	5mM	CH_2Cl_2, Δ, 18h	45% **522**
13	1% **68**	5mM	CH_2Cl_2, Δ, 1h[b]	**520**
14	5% **68**	4.5mM	CH_2Cl_2, Δ, 1.5h	30% **522**

a - +1.5 eq. $Ti(O^iPr)_3$ *b* - then 18h open to air

Table 3. Conditions attempted for ring-closing metathesis of *bis*-olefin **520.**

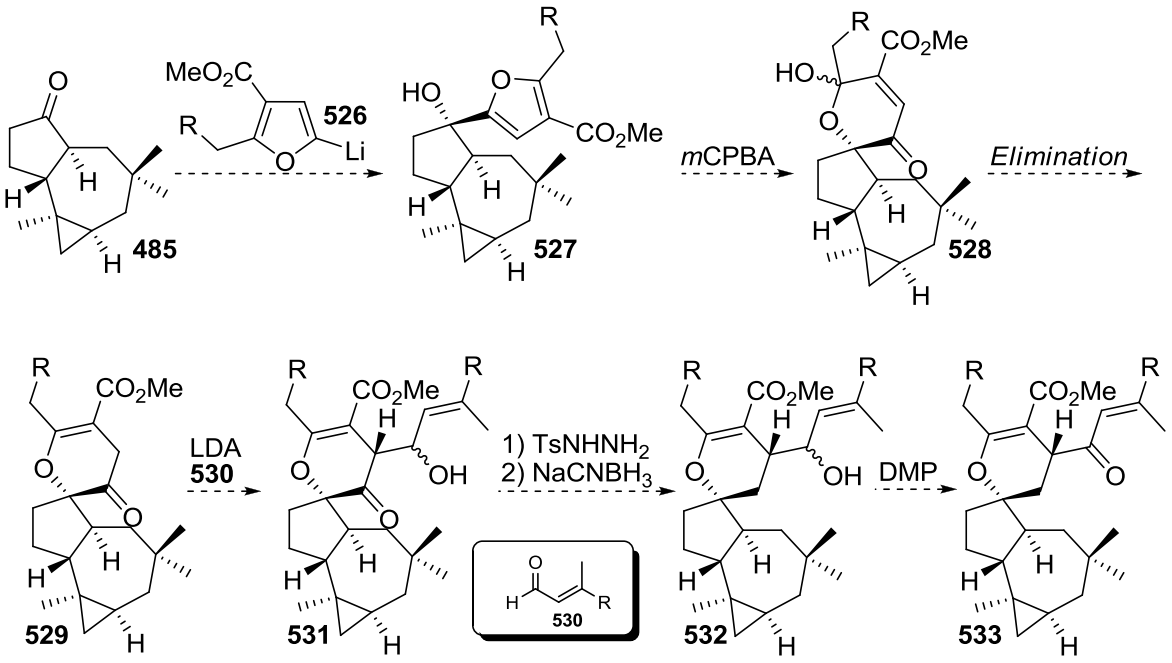
Subsequent Simmons-Smith reaction proved successful in affording the desired cyclopropane **524** (**Scheme 76**). As anticipated (**Scheme 74**), methyllithium addition was reported to provide a separable mixture of the leptographiols **504** and **505,** while methylenation using the Tebbe reagent **525** smoothly generated $\Delta^{9(15)}$-africanene **506**. Subsequent epoxidation, or dihydroxylation, afforded 9α,15-epoxyafricanane **482** and 9α,15-dihydroxy-africanane **507**, respectively.[201]



Scheme 76. Nakata's synthesis of tricyclic ketone **485** and subsequent entry to 9α,15-epoxyafricanane **482** and 9α,15-dihydroxy-africanane **507.**

Future Work

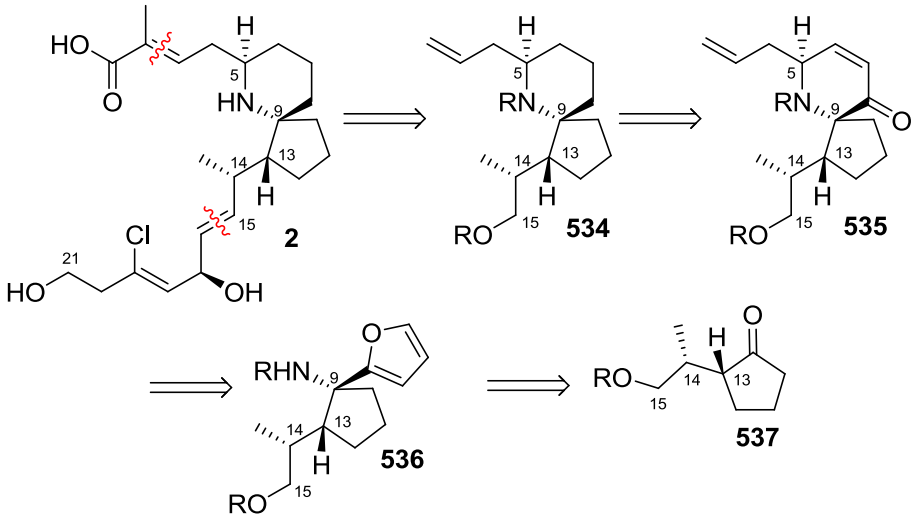
In order to progress the synthesis of polymaxenolide, following the completion of the synthesis of tricyclic ketone **485**, a disubstituted furan **526** should be introduced to afford cyclic tertiary furfuryl alcohol **527**. Subsequent Achmatowicz oxidative rearrangement should afford the tertiary hemi-acetal product **528**, upon which elimination could provide the driving force required to achieve alkene isomerisation, leading to the tetrasubstituted olefin **529.** This isomerisation event should expose the position α-to the ketone for deprotonation and alkylation. A subsequent deoxygenation followed by oxidation should afford the fully substituted Southern section of polymaxenolide **533** (**Scheme 77**).



Scheme 77. Proposed entry to an advanced intermediate **533** in the synthesis of polymaxenolide.

Spirocyclic Piperidines

The synthesis of the halichlorine and pinnaic acid family of alkaloids was envisioned as proceeding through the oxidative rearrangement of furfuryl amine **536** which, in turn, was thought of as originating from cyclopentanone **537** bearing a functionalisable side-chain at the α-position. This substituent should then be capable of functionalisation so as to eventually incorporate the entire C15-C21 subunit (**Scheme 78**).



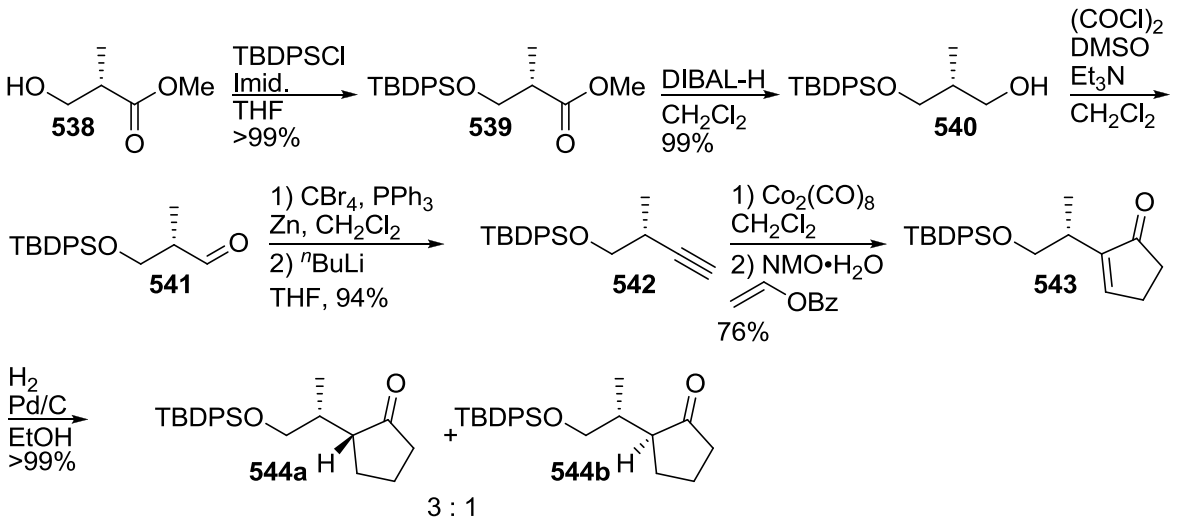
Scheme 78. Retrosynthetic analysis for the synthesis of pinnaic acid **2**.

The insertion of the C-14 stereocentre proved a challenge in a number of approaches to halichlorine and the pinnaic acids[55] and as such, it was decided to incorporate this troublesome stereocentre at the outset.

Synthesis of the Parent Ketone

The synthesis of the key functionalised cyclopentanone **544a** began with commercially available chiral Roche ester **538** which was protected as the corresponding TBDPS-ether **539**. The ester unit was then converted to aldehyde **541** *via* a sequential DIBAL-H reduction and subsequent Swern oxidation. Corey-Fuchs homologation afforded the terminal alkyne **542** in excellent yield over the

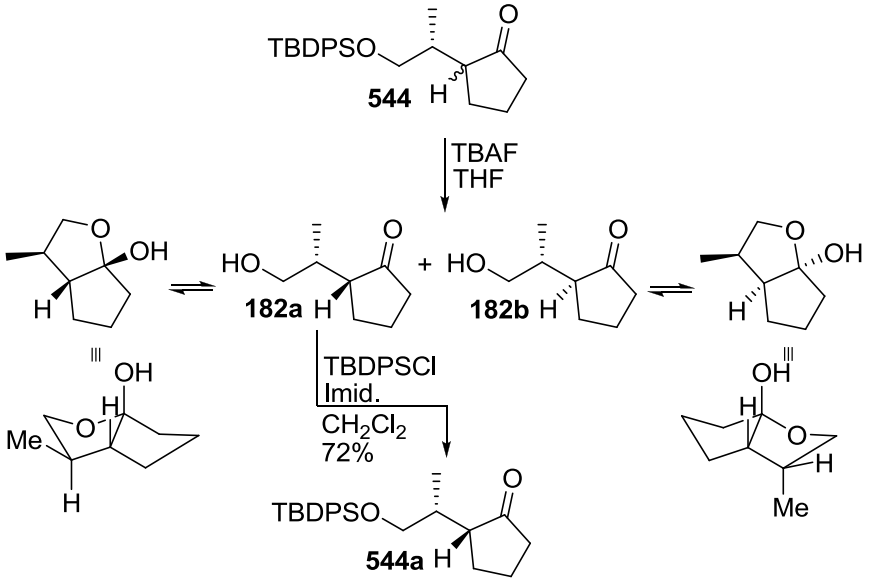
four-step process.[202] Alkyne **542** was subjected to an intermolecular Pauson-Khand cycloaddition to generate the substituted cyclopentenone **543**.[203] Hydrogenation of enone **543** afforded the diastereomeric cyclopentanones **544a** and **544b** in a 3:1 ratio (**Scheme 79**).



Scheme 79. Synthesis of key cyclopentanone **544a**.

The diastereomers could be separated by chiral HPLC or, alternatively, removal of the TBDPS protecting group afforded the corresponding known primary alcohols **182a** and **182b** which were separable by column chromatography.[74] In Heathcock's case, each diastereoisomer was characterised as a mixture of the mono-cyclic ketoalcohol and bicyclic hemiacetal forms. The ratio in which the bicyclic acetal was present in each diastereoisomeric mixture was indicative of the relative stereochemistry present in the molecule. For example, diastereoisomer **182a** was present as a 1.2:1.0 mixture in favour of the ketoalcohol, however, diastereoisomer **182b** was present as a 10:1 mixture in favour of the ketoalcohol form. This difference in ratio could be attributed to the orientation of the methyl group when in the bicyclic form. The bicyclic acetal form of diastereoisomer **182a** orientates this methyl group in an equatorial position while the equivalent methyl group in the bicyclic acetal form of diastereoisomer **182b** is orientated in the unfavourable axial position. From the hydrogenation of cyclopentenone **543** and subsequent deprotection, the major diastereoisomer was identified as **182a** by comparison of the NMR spectra obtained with that published by Heathcock and

Christie. Alcohol **182a** could then be reprotected without incident to afford diastereomerically pure cyclopentanone **544a** (**Scheme 80**).



Scheme 80. Separation of the diastereoisomers **544** by deprotection and flash column chromatography.

While reduction of the enone had afforded the desired ketone **544a** as the major product, the possibility of an increased diastereomeric ratio was explored (**Table 4**). Based on the initial reduction results, a large variety of non-chiral conditions were investigated in an effort to direct reduction from the desired face. It was hypothesised that the use of a sterically hindered catalyst could enhance the facial bias.

Hydrogenations

Initial hydrogenation attempts using Pd/C and $Pd(OH)_2$ afforded similar results (entries 1 and 2). Use of poisoned catalysts (Lindlar's catalyst), however, resulted in a reduction in facial selectivity (entry 3). Homogeneous catalysts (Wilkinson's rhodium catalyst and Crabtree's iridium catalyst) gave no reaction (entries 4 and 5). The results with Crabtree's catalyst are surprising given its common use in hydrogenating tri-substituted double bonds.[204]

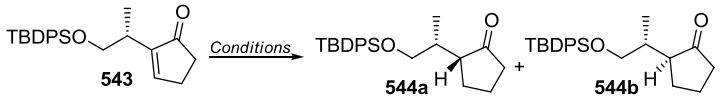
Transfer Hydrogenations

An alternative method was to increase the size of the hydrogen donor. Ammonium formate was used in a series of transfer hydrogenation reactions. Carrying out the reduction at room temperature afforded a 2.5:1 ratio in favour of the desired product (entry 6), however, this ratio could be improved to 2.9:1 by lowering the reaction temperature. Reducing the temperature to −78 °C, however, suppressed the reaction completely. After much experimentation, it was determined that the optimal ratio could be obtained when the reaction was carried out between 0 °C and −78 °C (entries 8 and 9). Conversely, warming the reaction to 50 °C showed a decline in the selectivity to 1.9:1 in favour of the desired product (entry 7).

Conjugate Hydride Addition

Conjugate hydride additions carried out by Stryker's reagent were also investigated whereby the variance was the proton source used to quench the enolate intermediate. It was hypothesised that using a bulkier proton source might influence the facial selectivity for protonation. With this in mind, a number of quenching methods were used including (i) quenching by exposing the reaction to air, (ii) quenching by the addition of water, (iii) quenching by the addition of methanol and (iv) quenching by the addition of *t*-butanol.

It was believed that quenching with air would afford the lowest ratio, increasing through to quenching with *t*-butanol. Surprisingly, the reverse selectivity was observed. Quenching with air afforded a 3:1 ratio in favour of the desired product (entry 10). Quenching with water resulted in a 2.7:1 ratio (entry 11). This ratio decreased to 2.1:1 when quenching with methanol (entry 12) and finally, to 1:1 when *t*-butanol was used (entry 13).



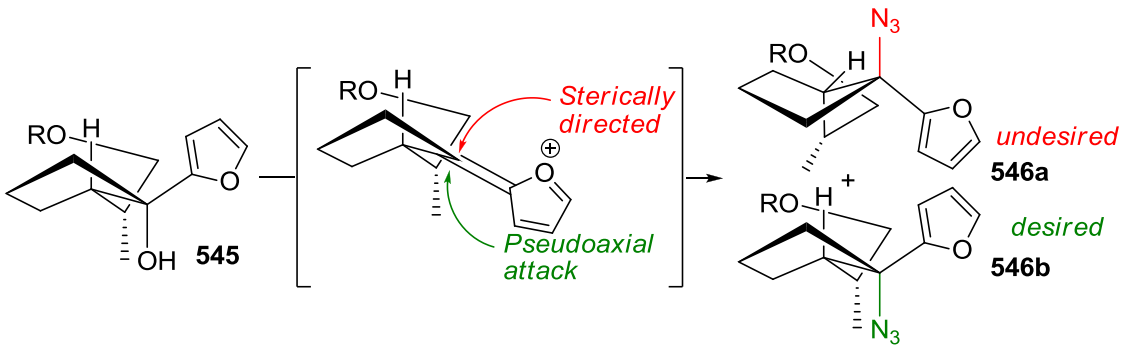
Entry	Conditions	Yield	**a : b**
1	H_2, Pd/C	97%	3.0:1.0
2	H_2, $Pd(OH)_2$	>99%	3.0:1.0
3	H_2, $Pd/BaSO_4$	88%	2.2:1.0
4	H_2, $(Ph_3P)_3RhCl$	-	-
5	H_2, $[(py)(PCy_3Ir(cod)][PF_6]$	-	-
6	HCO_2NH_4, Pd/C	89%	2.5:1.0
7	HCO_2NH_4, Pd/C (50 °C)	86%	1.9:1.0
8	HCO_2NH_4, Pd/C (−21 °C)	87%	2.9:1.0
9	HCO_2NH_4, Pd/C (−78 → 0 °C)	88%	2.9:1.0
10	$[(Ph_3P)CuH]_6$/Air	82%	3.0:1.0
11	$[(Ph_3P)CuH]_6/H_2O$	N.D.	2.7:1.0
12	$[(Ph_3P)CuH]_6$/MeOH	N.D.	2.1:1.0
13	$[(Ph_3P)CuH]_6/^t$BuOH	80%	1.0:1.0

Table 4. Reduction conditions employed for the reduction of cyclopentenone **543**.

The maximal ratio obtained was 3:1 in favour of the desired product which, without the use of complex chiral reducing agents, was deemed acceptable.

Towards the Synthesis of the Furfuryl Amine

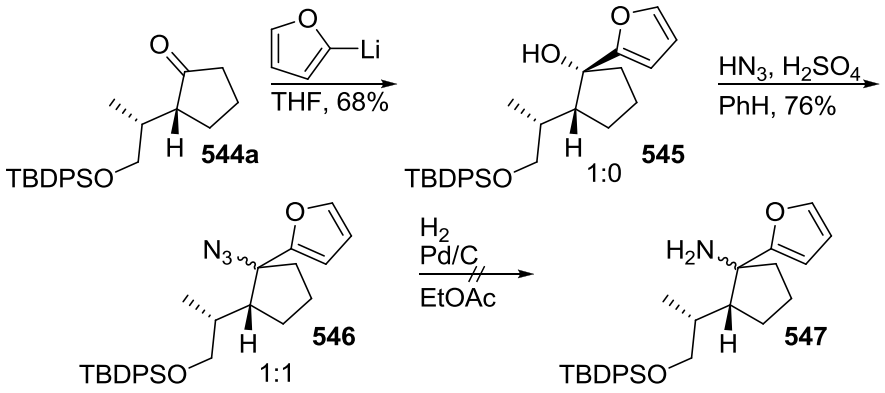
With the functionalised cyclopentanone **544a** in hand, the key furfuryl addition was attempted. Lithiofuran addition occurred with complete selectivity to generate a single addition product **545**, together with ~14% unreacted starting ketone **544a** in an inseparable mixture. It is believed that the facial selectivity of the addition was dictated by the recently installed α-stereocentre. Unfortunately, treatment of carbinol **545** with hydrazoic acid in the presence of sulphuric acid afforded a 1:1 mixture of azides **546a** and **546b**. Should steric bulk be the only directing factor involved during conversion to the azide **546**, the sole product expected would be the undesired diastereoisomer **546a**, i.e. the isomer displaying the nitrogen on the opposite face from that of pinnaic acid. Taking this result into consideration, it was postulated that a certain degree of pseudoaxial attack was also occurring to generate desired azide **546b** (**Scheme 81**).



Scheme 81. Competing lithiofuran addition leading to azides **546a** and **546b**.

It was reasoned that tailoring the reaction conditions may favour formation of the desired diastereoisomer **546b**.

The initial, most straightforward variable to be considered was reaction temperature. Parallel reactions were simultaneously carried out at room temperature and −78 °C as opposed to the regular 0 °C employed in an effort to ascertain the thermal effect on this transformation. Disappointingly, the ratio was not affected by the change in temperature, however, the reaction yield did exhibit a marked enhancement at lower temperatures. In the interests of testing the applicability of the oxidative rearrangement in a complex system, the 1:1 mixture of azides **546** was carried forward to the reduction step with the intention of separating at a later stage, if possible. Surprisingly, this crowded system resisted hydrogenation and returned only unreacted azide mixture **546** (**Scheme 82**).



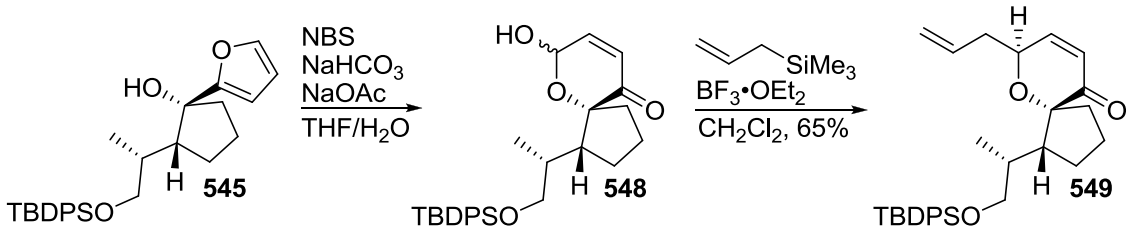
Scheme 82. Attempted conversion of tertiary alcohol **545** into tertiary amine **547**.

This result, coupled with the disappointing 1:1 ratio of azides obtained forced the decision to abandon azide formation and reduction as a strategy for the synthesis of pinnaic acid. Alternative tertiary amine formation strategies were sought.

Towards an Oxa-Analogue of Pinnaic Acid

Synthesis of a Complex Spirocyclic Pyran

In the meantime, exploiting the excellent selectivity obtained in the lithiofuran addition step, it was decided to seize the opportunity to develop the first synthesis of an oxa-analogue of pinnaic acid. It was postulated that substituting the spirocyclic piperidine core with an analogous spirocyclic pyran unit might clarify the biological role of the piperidine and, therefore, after biological testing, allow for a set of structure-activity relationships to be developed. Achmatowicz rearrangement of carbinol **545** was smoothly executed using NBS/H_2O as these conditions were found to affect the oxidative rearrangement in much shorter reaction times.[205] The previous use of *m*CPBA implemented a reaction which was complete in four hours, whereas the newly employed conditions achieved complete conversion to the corresponding lactol **548** in only ten minutes.
Subsequent Sakurai-type allylation afforded the desired allyl spirocyclic dihydropyranone **549,** as a single diastereoisomer (**Scheme 83**).



Scheme 83. Synthesis of allyl spirocyclic dihydropyranone **549**.

NOESY analysis identified a correlation between the proton in the pseudo-C-5 anomeric position and the methyl group at the pseudo-C-14 position (**Figure 16**, **A**,

green), while none was observed between the same C5 proton and the protons at either the pseudo-C13 or C-14 stereocentres (**Figure 16**, **A**, cyan). Basic molecular modelling suggested that, while such a correlation between C-5 and the C-14 methyl group may also arise in the undesired diastereoisomer, additional correlations between the C-5 proton and the C-13 and C-14 protons would also be expected (**Figure 16**, **B**). As a result, it was tentatively considered that the incumbent allyl group adopted the desired conformation.

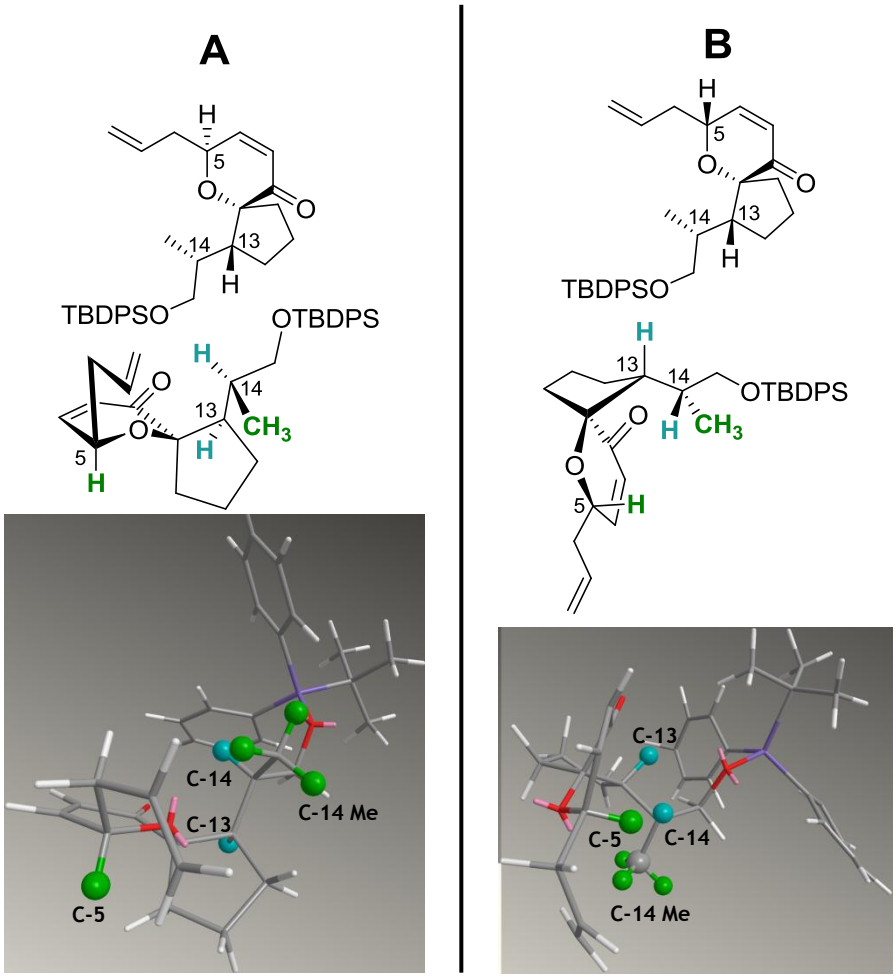
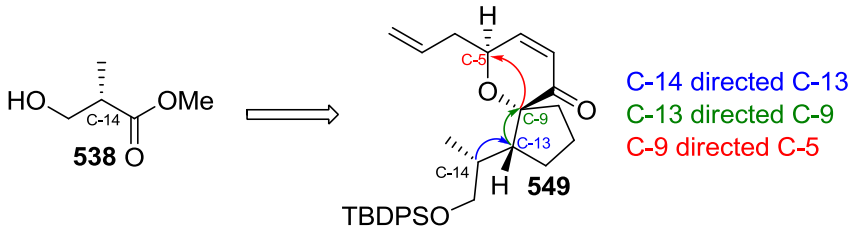


Figure 16. Proposed 3D representations of the possible diastereoisomers. NOESY correlations were observed between between C-5 and C-14 methyl substituent (green) while none were observed with C-13 and C-14 proton (cyan).

The Directing Effect of a Single Stereocentre

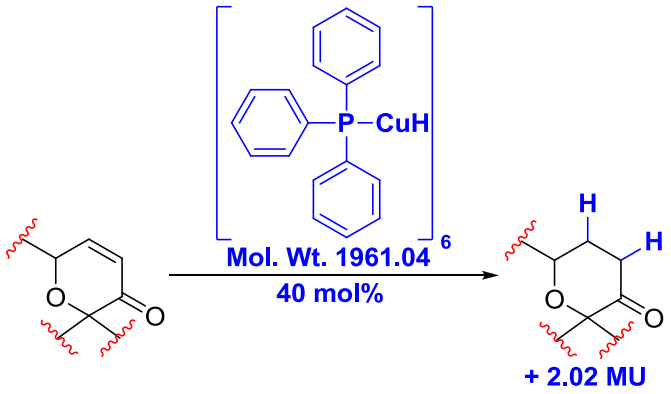
Allylspirocyclic pyran **549** represents the core structure of oxa-pinnaic acid in which four of the five stereocentres of the target appear to have been induced by the single stereocentre present in the Roche ester **538** starting material. The facial bias shown during hydrogenation of cyclopentenone **543** arose as a direct result of the orientation of the methyl at C-14. This C-13 stereocentre then directed, exclusively, lithiofuran addition, inserting the correct stereochemistry at C-9, which was retained through oxidative rearrangement. Finally, the ring conformation, dictated by stereocentre C-9, then directed allylation to occur from one, desired face inserting the C-5 stereocentre (**Scheme 84**).



Scheme 84. The directing effect of pseudo C-14.

Enone Reduction, Caglioti Deoxygenation and Cross-Metathesis

Another change to the methodology applied in the model system concerns the conjugate reduction step. Stryker's reagent was previously used, to good effect, however, employing this reagent in 40 mol% to essentially deliver one hydride to the system, with quenching of the resultant enolate responsible for the incorporation of the α-proton, given its molecular weight exceeds 1960 mass units, was considered to be very atom inefficient (**Scheme 85**).



Scheme 85. Atom inefficient conjugate reduction.

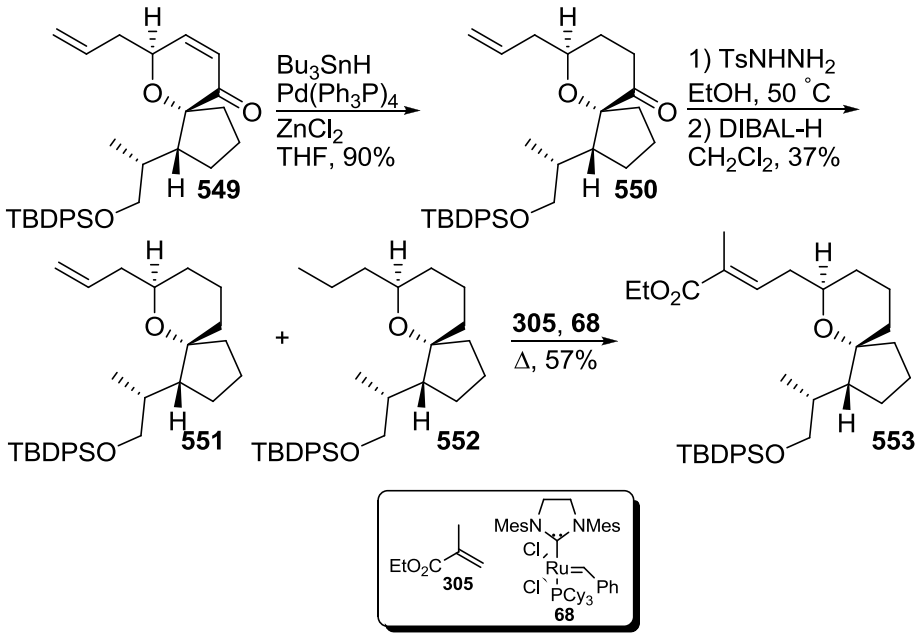
For such reasons, the use of a palladium catalysed tributyltin hydride reduction was investigated.[189] Certainly, tributyltin hydride is toxic, and tin impurities can be troublesome to remove from a reaction mixture, however, the previous reduction of the enone with Stryker's reagent would take place overnight in deoxygenated benzene, which is also toxic.

The palladium catalysed reduction was complete within one hour, and work-up followed by chromatography was straightforward. The time reduction, coupled with the newly applied *N*-bromosuccinimide-mediated oxidative rearrangement gave rise to an overall procedure whereby the Achmatowicz oxidative rearrangement, Sakurai-type allylation and palladium catalysed tributyltin hydride reduction were performed, and purified to afford spirocyclic pyranone **550**, comfortably in a single day.

The previously utilised Caglioti-modified Wolff-Kishner reduction conditions were ineffectual on this complex, rendering it necessary to heat the reaction vessel to 50 °C in order to achieve a reasonable rate of reaction.[117] As a consequence, it is believed that the tosyl-hydrazide dissociated to form diimide, which then proceeded to carry out undesired hydrogenation of the terminal double bond. This resulted in, after treatment of the *in situ* formed hydrazone with DIBAL-H, an inseparable mixture of desired allyl spirocyclic pyran **551**, and propyl spirocyclic pyran **552** in a 1:1 ratio.

The pyran mixture was subjected to cross-metathesis using Grubbs 2nd generation ruthenium catalyst **68** in an excess of ethyl methacrylate **305**. As expected, the

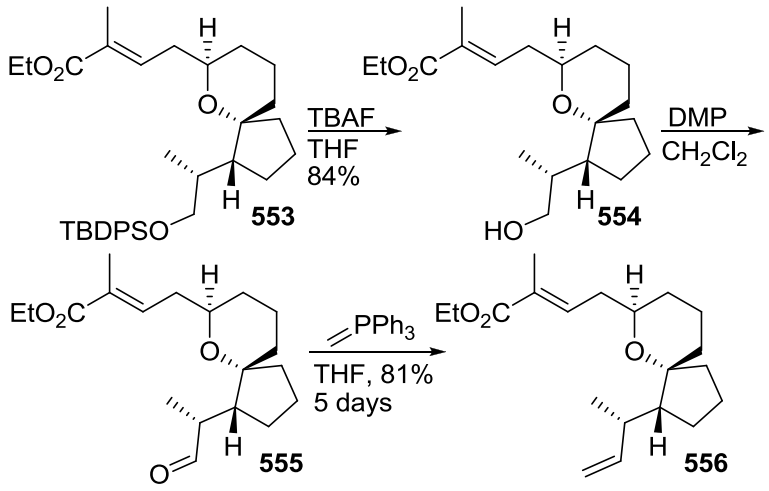
terminal olefin reacted in the presence of the fully reduced spirocycle without incident to afford enoate **553** (**Scheme 86**).



Scheme 86. Synthesis of the oxa-pinnaic acid core **553**.

Incorporating the Lower Side-Chain Unit

Oxa-pinnaic acid core **553** was desilylated to afford the corresponding primary alcohol **554**. Careful oxidation with Dess-Martin periodinane afforded aldehyde **555**. The oxidation of similar aza-analogues accessed as intermediates in total syntheses of pinnaic acid and halichlorine, were found to pose problems, particularly with regard to epimerisation.[37] Fortunately, through the use of Dess-Martin periodinane, no epimerisation was observed, affording aldehyde **555** as a single product. Wittig olefination of aldehyde **555** then afforded the terminal olefin **556** in good yield over both steps (**Scheme 87**).

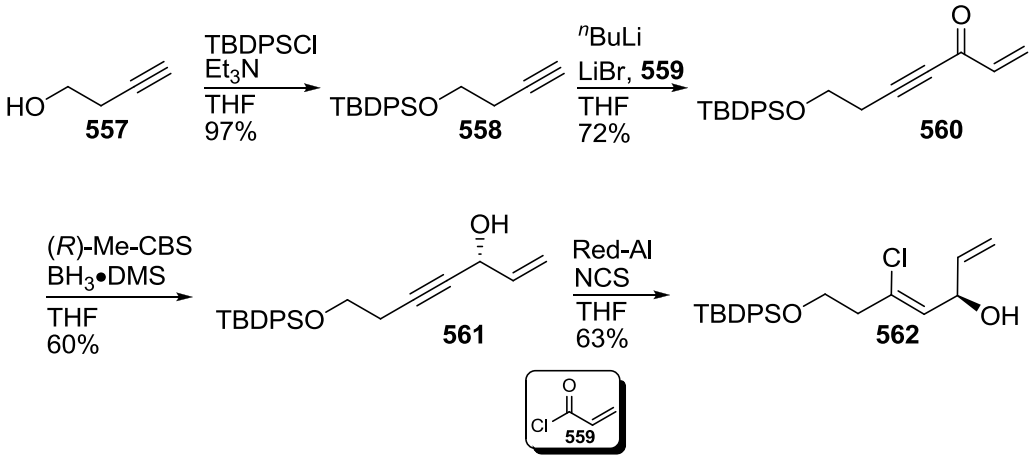


Scheme 87. Conversion of the primary alcohol to the terminal olefin **556.**

The necessity for a long reaction time during the olefination step came as no surprise considering that olefination conditions described during the synthesis of aza-analogues were reported to require in excess of 48 h reaction time.[52, 61, 74]

The C15-C21 Side Chain

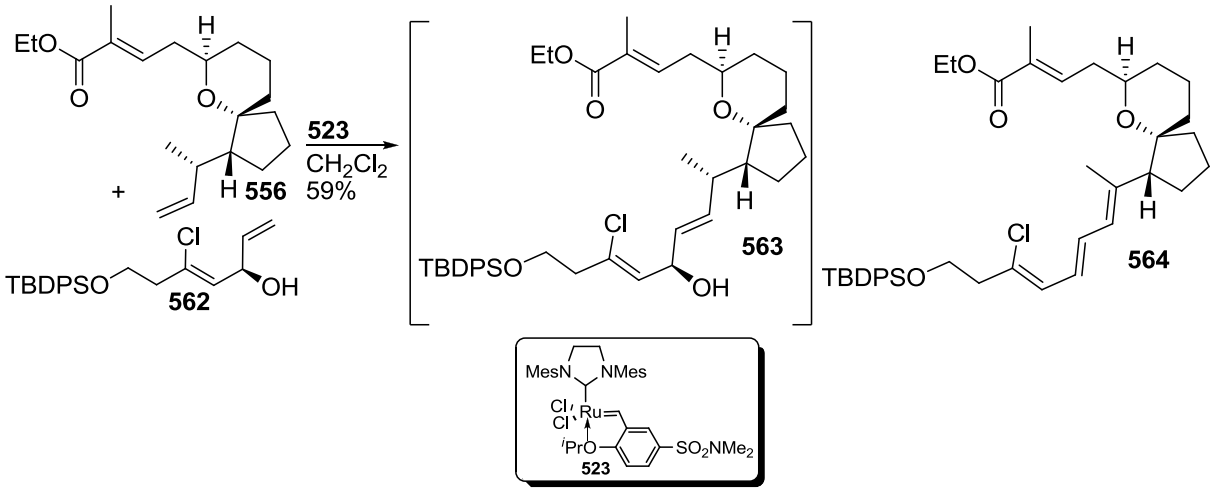
The synthesis of the side chain unit **562** was achieved following a similar route to that reported by Uemura.[117] The only exception was that the alkyne addition was carried out on acryloyl chloride **559** instead of acrolein (**Scheme 88**). This subtle modification afforded enone **560** directly, without the need for an additional oxidation step. Reagent controlled reduction followed by chlorohydride addition across the alkyne unit afforded the desired cross-metathesis coupling partner **562**. While Uemura and Arimoto performed their cross-metathesis on the TBDMS-protected substrate, it was decided to attempt the cross-metathesis on the free secondary alcohol **562**. Recent reports by Hoveyda have indicated that the presence of an unprotected allylic alcohol was beneficial for maximising reaction rate and *E*-selectivity.[206]



Scheme 88. Synthesis of the C15-C21 side-chain unit **562**.

Cross-Metathesis Between the Upper and Lower Fragments

Having completed the synthesis of the chloroalkene unit **562** the key cross-metathesis reaction with alkene **556** was attempted using the Zhan 1B catalyst **523**.[199] Unfortunately, an unexpected, concomitant elimination was found to occur affording, in place of the desired oxa-pinnaic acid framework **563**, the corresponding triene **564** (**Scheme 89**).



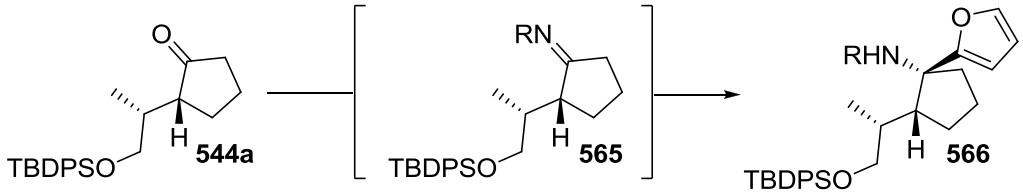
Scheme 89. Cross-metathesis afforded the unexpected triene **564**.

Towards Pinnaic Acid

Incorporating the Nitrogen

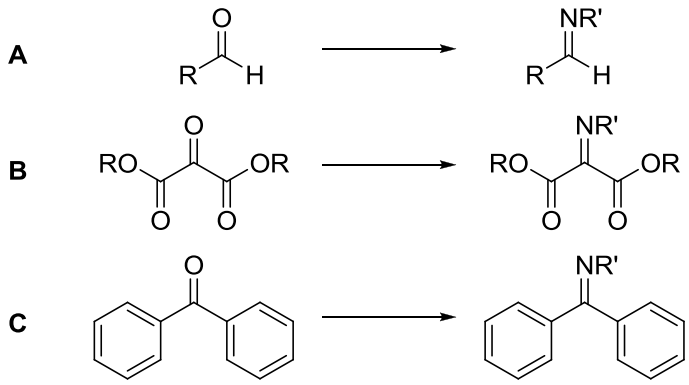
During the synthesis of the spirocyclic pyran and spirocyclic piperidine model systems, it was observed that oxidative rearrangement and subsequent functionalisation used to generate the spirocyclic pyran core **470** was transferable to the synthesis of a direct aza-equivalent **481**. This led to the hypothesis that, should the synthesis of an equivalent cyclic tertiary amine **566** be achieved, the route to the pinnaic acid series could progress by directly transferring the chemistry which successfully led to the synthesis of the oxa-pinnaic acid cross-metathesis precursor **556**.

Given that lithiofuran addition to cyclopentanone **544a** afforded the desired tertiary alcohol **545** as a single product, it was, therefore, postulated that a similar, facially selective result might arise from the reaction between lithiofuran and an analogous ketimine **565** (**Scheme 90**).



Scheme 90. Postulated lithiofuran addition to an analogous ketimine **565**.

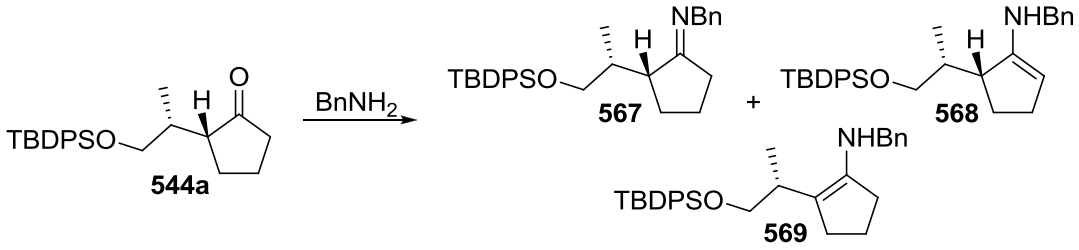
Examples of aldimine formation are plentiful in the literature; less so in the case of ketimine formation.[207] Naturally, aldehydes are more reactive than ketones, and as such, imines of this type can be easily generated. Examples of ketimine formation tend to involve substrates in which there no acidic protons in the α-position (**Scheme 91, A, B** and **C**).[208] Nevertheless, it was decided to investigate simple imine formation using benzyl amine as the nitrogen source in the first instance.



Scheme 91. Examples of ketimine formation are usually limited to those without α-protons.

Benzyl Imine Formation

The coupling between substituted cyclopentanone **544a** and benzyl amine, under Dean-Stark conditions afforded the desired imine **567**, together with the two enamine isomers **568** and **569** in a 1:1:1 ratio (**Scheme 92**).



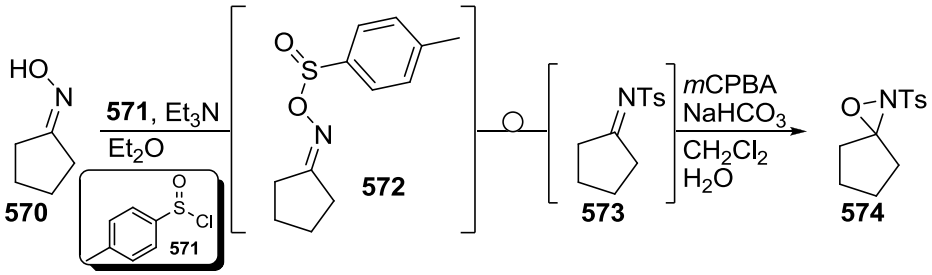
Scheme 92. Attempted benzyl-imine formation.

This result suggested that the use of electron rich nitrogen sources would likely result in enamine formation and as such would lead to the destruction of the recently installed α-stereocentre. For such reasons, it was decided to investigate the formation of an imine in which the electrons are tied up in a conjugated system. It was proposed that, should such an intermediate be accessible, the double-bond would be less likely to isomerise, and therefore, less likely to destroy the stereocentre. This brings with it separate issues however, as reducing the reactivity of the amine component would make imine formation even more difficult.

Forming a Tosylimine

As part of the investigations into the formation of a suitable imine, the possible formation of a tosyl-imine was explored. It was desirable to afford an eventual tosyl-protected cyclic tertiary furfuryl amine **578** as this group was known to withstand the proposed synthetic sequence.

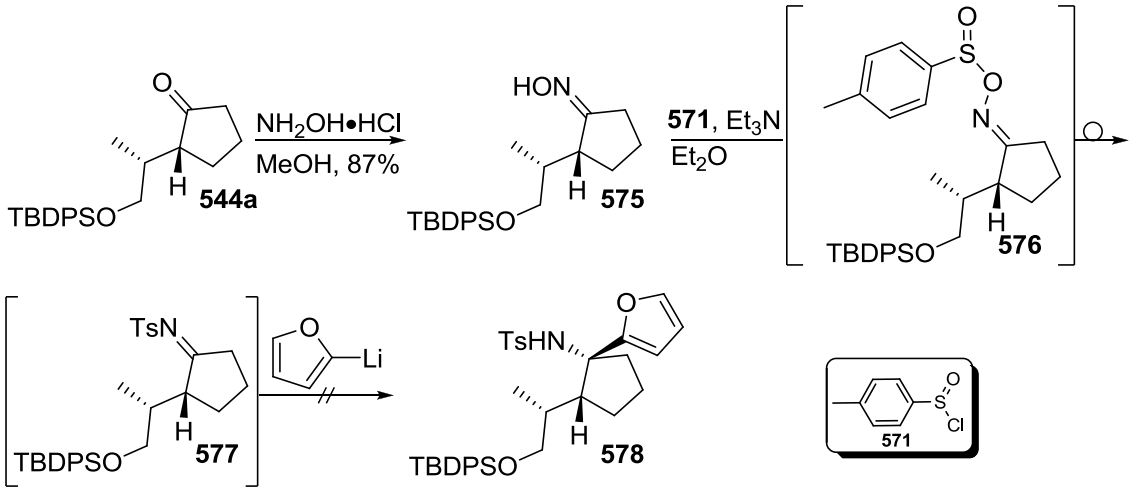
The generation of a tosyl ketimine in the traditional fashion using tosyl-amide has been documented as unfeasible.[209] The reason cited is that the nitrogen source exhibits too poor nucleophilicity to undergo addition to the carbonyl unit and to subsequently eliminate water. There are, however, alternative methods to access the same tosyl-imine intermediate. Treatment of an oxime **570** with toluene sulfinyl chloride **571** was reported to generate the tolyl-sulfinyloxime intermediate **572**, which spontaneously rearranged to the corresponding tosyl-imine **573**.[210] Such sulfinyl chlorides are notoriously unstable, as are the tosyl-imine intermediates themselves, therefore, the resultant tosyl-imine **573** was directly oxidised to the corresponding oxaziridine **574** (**Scheme 93**).



Scheme 93. Reported rearrangement of sulfinyloxime **572** to sulfinylimine **573**.

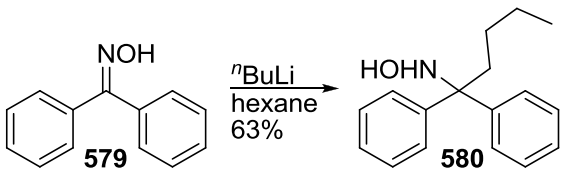
Ketone **544a** was converted to the corresponding oxime **575** in good yield. The oxime **575** was treated with toluene sulfinyl chloride **571**, at 0 °C, followed by stirring at ambient temperature in an effort to effect the reported rearrangement (**Scheme 94**). Lithiofuran was then added to the putatively formed imine **577**. Unfortunately, formation of the desired product **578** was never observed. In an effort minimise any issues related to the inherent instability of the reagents and intermediates, the sulfinyl chloride **571** was generated *in situ*, and oxime **575** was added. The solution was allowed to warm up to room temperature and treated

with lithiofuran. At no point were any of the unstable intermediates ever isolated, and every effort was taken to, as far as it possible without the use of a glove-box, maintain a completely dry atmosphere. Despite such precautions, no imine **577** was ever detected using this approach and as such no tertiary furfuryl amine **578** was formed, instead a complex mixture of indiscernible degradation products was observed.



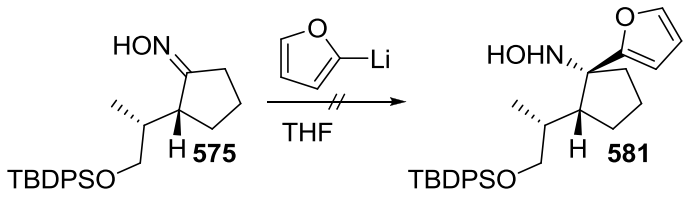
Scheme 94. Attempted synthesis of tosyl-protected cyclic tertiary furfuryl amine **578**.

Alternatively, alkyllithium addition to oximes has been reported, although the reaction appears to be somewhat substrate dependent.[211] While the reported *n*-butyllithium addition to benzophenone-derived oxime **579** afforded the desired product **580** in 63% yield (**Scheme 95**), the corresponding methyllithium addition afforded no reaction. Similarly, the chemical nature of the oxime exhibits an effect on the success of the addition. For example, in contrast to the earlier result, an acetone-derived ketoxime underwent *n*-butyllithium addition in 17% yield, while aldoxime derivatives such as *p*-anisaldehyde oxime and cinnamaldehyde oxime afforded the expected products in 40% and 55% yield respectively.



Scheme 95. Alkyllithium addition to oximes has been reported.

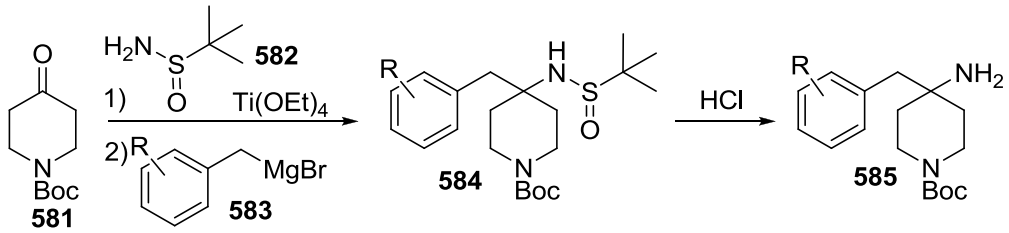
Unfortunately, the attempted addition of 5 eq. lithiofuran to oxime **575** was entirely unsuccessful, returning only unreacted oxime starting material (**Scheme 96**).



Scheme 96. Attempted lithiofuran addition to oxime **575**.

Alternative Entry to a Tosyl-Imine

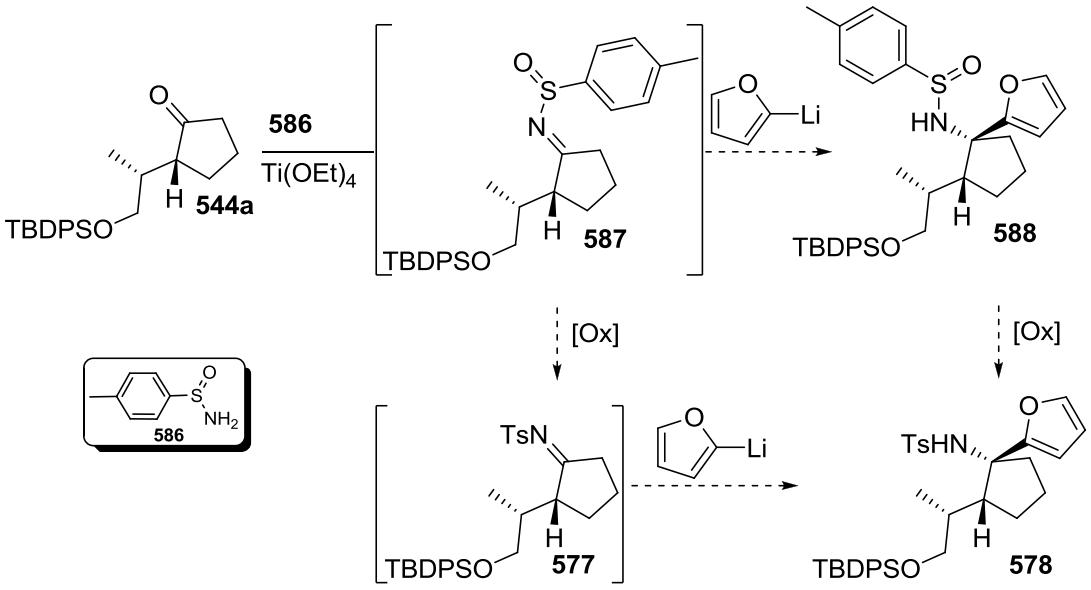
It has been reported that carbon nucleophiles successfully add to sulfinyl imines, to give tertiary amines after acidic work-up.[212] Of specific relevance was the success reported upon formation of the cyclic sulfinylamine **584**. Grignard addition to the imine carbon followed by subsequent sulfinyl cleavage afforded a variety of substituted benzyl aminopiperidines **585** (**Scheme 97**).



Scheme 97. Collins synthesis of substituted benzyl aminopiperidines **585**.

The oxidation of sulfinamides to sulfonamides in the presence of *m*CPBA has also been reported.[213] Hence, two distinct routes could potentially lead to the same desired tosyl-protected cyclic tertiary furfuryl amine **578** based on this methodology; one route would concern oxidation of the sulfinyl imine **587** to the corresponding sulfonyl imine **577** prior to lithiofuran addition (**Scheme 98**). Alternatively, addition could be carried out prior to oxidation. Given the instability observed during the previous investigations, it was deemed that the route with the best potential for success relied on addition to the sulfinylimine **587**. In the

interests of eventually accessing the desired tosyl-protected cyclic tertiary amine, the Ellman *t*-butane sulfinamide was replaced with toluene sulfinamide **586**.[213]

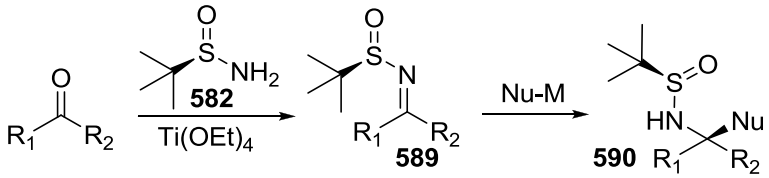


Scheme 98. The potential routes to tosyl-protected cyclic tertiary furfuryl amine **578**.

Unfortunately, the initial reaction proved unsuccessful. It was postulated that the toluene sulfinylimine **587** generation was likely to be responsible for the observed failure. Indeed, toluene sulfinylamide **586**, while commercially available, is reasonably expensive and is known to be, in itself, unstable. For such reasons, the sulfinylamide **586** was formed *in situ* and therefore its quality could not be determined prior to the reaction attempt.

Ellman Chiral Sulfinylimine Formation

It was then decided to investigate alternative sulfinylimine forming conditions. Of particular interest was the Ellman procedure in which he described the use of *t*-butane sulfinamines **582** as nitrogen sources for the formation of imines **589** (**Scheme 99**).[214] Chiral sulfinyl amines **582** were also reported as a way to direct the incumbent nucleophile with good stereocontrol.



Scheme 99. Ellman sulfinylimine **589** generation and subsequent addition.

Sulfinyl imine **589** formation was reported to proceed without incident, with a wide variety of substrates. Furthermore, a number of nucleophiles have also been successfully added to these sulfinylimines. The examples in which furanyllithium species were successfully added to a series of sulfinyl ketimines **589** were specifically relevant. In each case the addition proceeded to give tertiary furfuryl sulfinylamines **591** in good to excellent yield, and with very good diastereoselectivity (**Table 5**).[214]

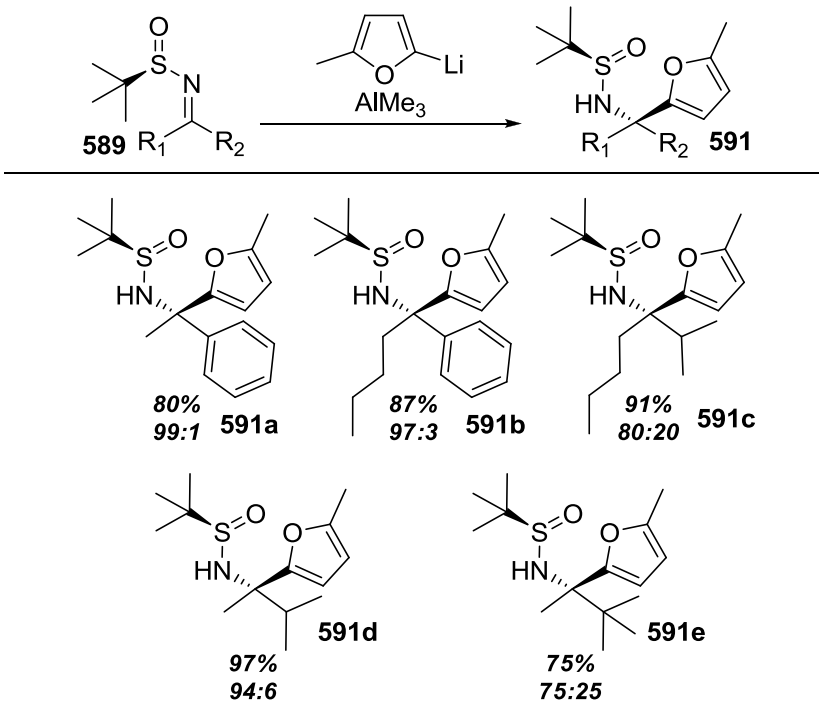
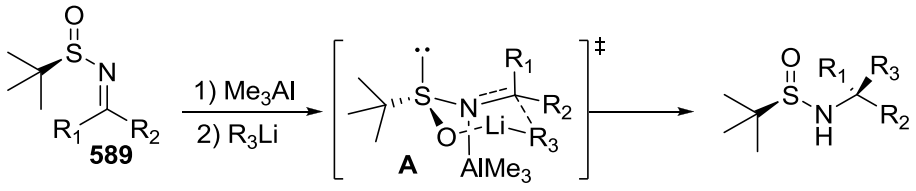


Table 5. Examples of Ellman's tertiary furfuryl sulfinylamine **591** formation.

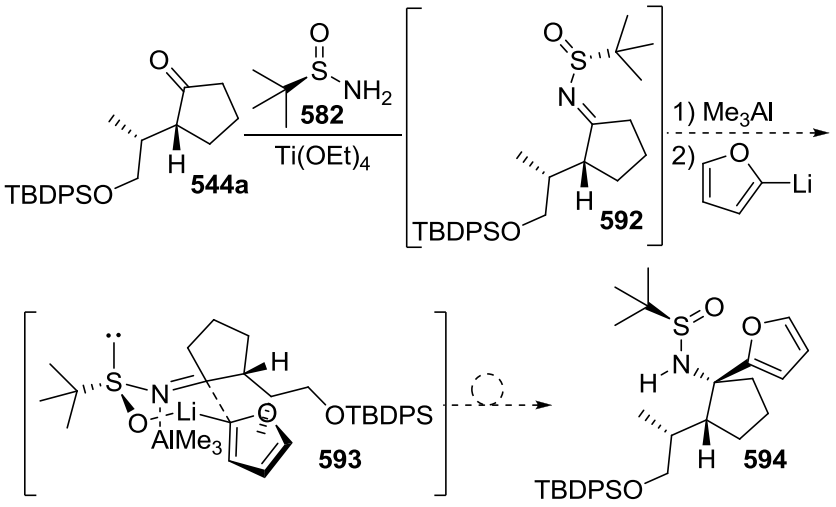
In addition, Ellman has reported that the use of $AlMe_3$ can also enhance the selectivity of addition.[214] Mechanistically, it is proposed that coordination between the imine nitrogen and aluminium occurs, while a second interaction between lithium and the sulfinyl oxygen also takes place, to generate a chair-like

transition state **A** (**Scheme 100**). The nucleophile, therefore, is encouraged to approach from the same face as the sulfinyl oxygen, resulting in an enhanced selectivity. Experimentally, Ellman reported that it is necessary to expose the imine **589** to $AlMe_3$ prior to inclusion of the lithiofuran. In fact, mixing the lithiofuran with the Lewis acid prior to introduction of the imine species did not afford the same results. This observation further supports the hypothesis that the reaction proceeds *via* a chair-like transition state where the nitrogen is coordinated with the aluminium.



Scheme 100. Ellman's proposed transition state **A**.

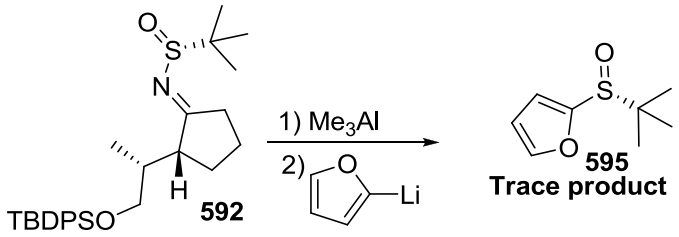
Ketone **544a** was treated with commercially available *t*-butanesulfinyl amine **582** in the presence of $Ti(OEt)_4$. Imine **592** formation occurred smoothly, and subsequent lithiofuran addition was attempted after prior exposure of the imine **592** to $AlMe_3$ in the first instance (**Scheme 101**).



Scheme 101. Attempted lithiofuran addition to sulfinylimine **592**.

The reaction was sluggish, affording, largely, unreacted starting material, with a trace of a species displaying characteristic furyl signals based on ^1H NMR analysis.

Further investigation of these products led to the realisation that the lithiofuran was not adding to the desired imine carbon. Instead, the only product **595**, isolated in trace amounts, possessing furyl signals was the product of lithiofuran abstraction of the sulfinyl moiety (**Scheme 102**).

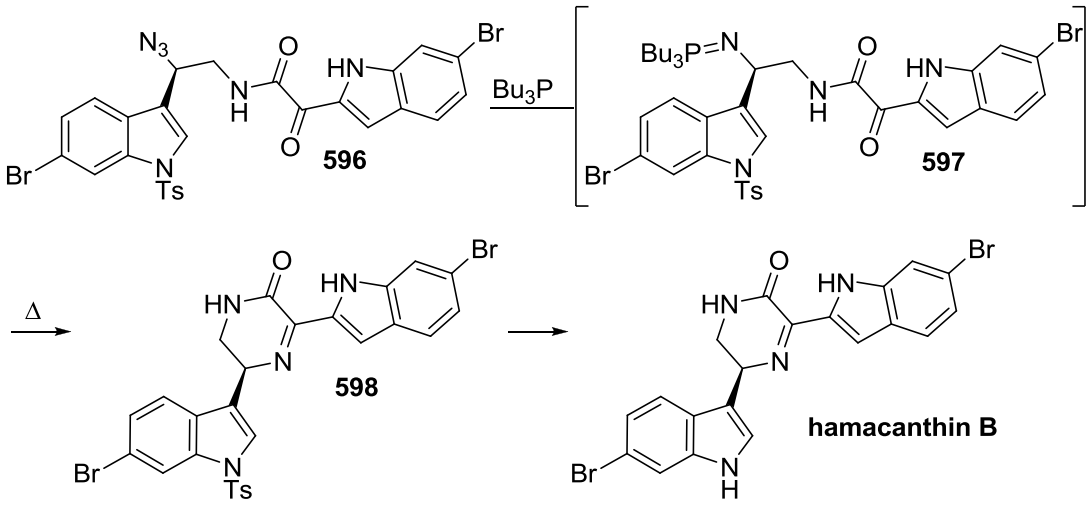


Scheme 102. Formation of undesired by-product **595**.

In depth mechanistic studies were not performed due to time constraints, and this route was, for the time being, abandoned in favour of other alternatives.

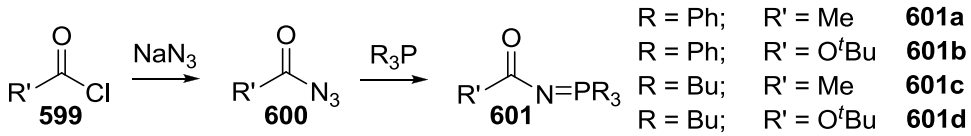
The Aza-Wittig Strategy

The aza-Wittig reaction has found utility in natural product synthesis, being exploited during Wang's synthesis of hamacanthin B, for example (**Scheme 103**).[215] In this case, an intramolecular aza-Wittig reaction was induced to assemble the central dihydropyrazinone ring. The key aza-Wittig olefination was achieved *via* the formation of the iminophosphorane intermediate **597**, accessed by exposing azide **596** to tributylphosphine. Subsequent intramolecular condensation completed the aza-Wittig coupling.



Scheme 103. The aza-Wittig reaction in Wang's synthesis of hamacanthin B.

A number of iminophosphoranes **601** were synthesised according to literature procedures (**Scheme 104**).[216] These included acetamide derived iminotriphenyl- and tributylphosphoranes **601a** and **601b**, and *t*-butyl-carbamate derived iminotriphenyl- and tributylphosphoranes **601c** and **601d**. These iminophosphoranes **601** were generated in a straightforward manner by treatment of the corresponding alkyl chlorides **599** with sodium azide to generate the corresponding acyl or carbamoyl azides **600**. Subsequent exposure to triphenylphosphine afforded the desired iminophosphoranes.

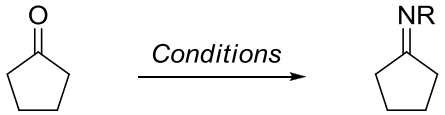


Scheme 104. General synthesis of iminophosphoranes **601**.

The rationale behind the choice of iminophosphoranes concerned the documented differences in reactivity and also the utility of their potential products.[217] For example, the carbamate derivatives **601b** should be more nucleophilic than the corresponding amide **601a**, however, the incorporation of an amide is preferable given its increased stability to some of the stronger, Lewis acidic conditions which the proposed product would subsequently be exposed to. Tributylphosphine-derived iminophosphoranes **601c** and **601d** are reportedly more reactive than their

triphenylphosphine counterparts **601a** and **601b**, and this modification was postulated as a possible way to circumvent the reduced reactivity of acetamide by combining it with a more reactive phosphine component.

Unfortunately, in the case of cyclopentanone, no combination of amide and phosphine resulted in any product formation. Prolonged reaction times and elevated temperatures either with conventional or microwave heating also resulted in no reaction (**Table 6**).



Ylid	THF	PhH	Yield
601a[a]	65 °C, 12 h	90 °C, 12 h	-
	MW, 150 °C, 12 h	MW, 150 °C, 12 h	-
601b	65 °C, 12 h	90 °C, 12 h	-
	MW, 150 °C, 12 h	MW, 150 °C, 12 h	-
601c	65 °C, 12 h	90 °C, 12 h	-
	MW, 150 °C, 12 h	MW, 150 °C, 12 h	-
601d[b]	65 °C, 12 h	90 °C, 12 h	-
	MW, 150 °C, 12 h	MW, 150 °C, 12 h	-

a no reaction observed in THF after 10 days at 65 °C; *b* no reaction observed in *m*-xylenes at 125 °C after 12 h or after 12 h at 250 °C with MW irradiation.

Table 6. Aza-Wittig reaction conditions employed.

While the aza-Wittig reaction initially appeared to be a promising method for nitrogen incorporation, examples of intermolecular aza-Wittig reactions with cyclic ketones are limited.

It is believed that the lack of reactivity is likely due to a large steric barrier which must be overcome. The formation of the desired oxaphosphetidine transition state **A** (**Figure 17**) potentially demands too high an energy input in order to proceed.

The failure to generate any product on the simple cyclic ketone, led to the postulate that attaining the transition state in the more sterically encumbered cyclopentanone was unlikely.

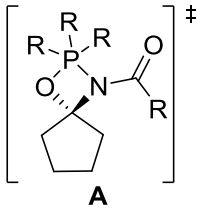
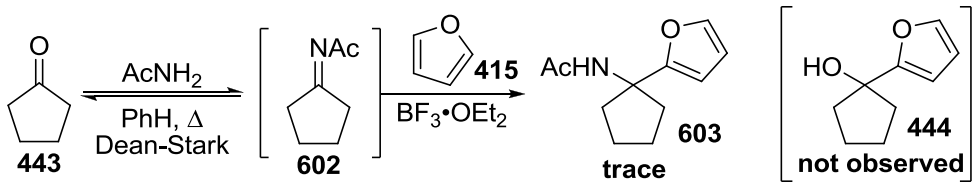


Figure 17. Proposed sterically hindered oxaphosphetidine transition state **A**.

Forming an Acetamide Imine

In tandem, the formation of an acetamide derived imine **602** was investigated. It was envisioned that the imine **602** could be formed by treatment of cyclopentanone **443** with acetamide in refluxing benzene, in the presence of a catalytic amount of PPTS, under Dean-Stark conditions (**Scheme 105**).[74] Addition of furan **415** followed by boron trifluoride-diethyl etherate was expected to yield the tertiary furfuryl amine **603** *via* imine activation.[218] It was postulated that the natural reactivity of furan **415** might facilitate its addition to the imine carbon, without necessity for lithiation. Unfortunately, only traces of the desired cyclic tertiary furfuryl acetamide **603** were detected by analysis of the crude ^{1}H NMR. Interestingly, there was no evidence of cyclic tertiary furfuryl alcohol **444** formation. This suggested that allowing the natural reactivity of the furyl ring to gently carry out the reaction, rather than forcing the addition with a stronger nucleophile, led to the selective furan addition to the *in situ* formed imine **602** in the presence of the corresponding ketone **443**.

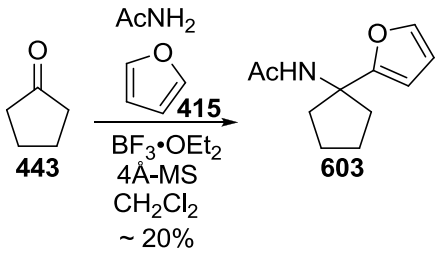


Scheme 105. Attempted formation of cyclic tertiary furfuryl acetamide **603**.

In an effort to confirm this hypothesis, cyclopentanone **443**, furan **415** and acetamide were stirred together in the presence of molecular sieves to aid in the removal of water. A catalytic amount of boron trifluoride-diethyl etherate was

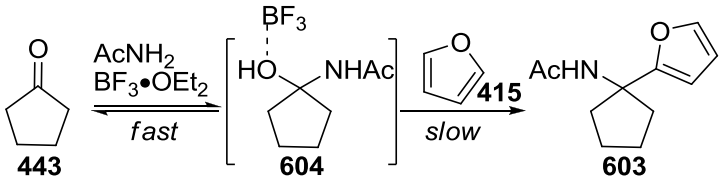
added at room temperature, and the reaction was allowed to stir overnight (**Scheme 106**).

The desired product **603** was obtained in low yield after purification but, most importantly, there was no trace of the cyclic tertiary furfuryl alcohol **444**. This result supported the hypothesis that it was possible to preferentially form the cyclic tertiary furfuryl acetamide **603** over the corresponding cyclic tertiary furfuryl alcohol **444**.



Scheme 106. One-pot synthesis of cyclic tertiary furfuryl acetamide **603**.

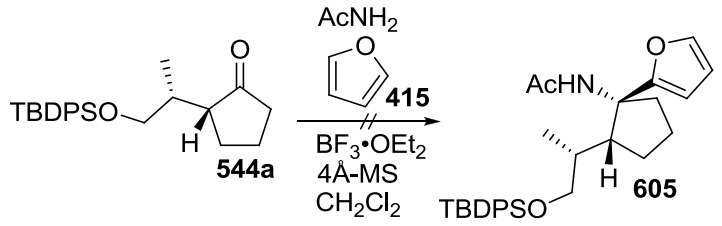
The reasons given for the inability to form tosyl-ketimines are based on the poor nucleophilicity of tosyl-amide.[213] As a result, it seems contradictory that acetamide should be capable of forming the corresponding imine as acetamide is a source of *less* nucleophilic nitrogen than tosyl-amide. It was, therefore, hypothesised that a different mechanism must have taken place in order to afford the small quantities of cyclic tertiary furfuryl acetamide **603** observed: one which does not involve the formation of an imine species **602**. It is postulated that reversible formation of the hemi-aminal intermediate **604** takes place, which could rapidly hydrolyse back to the starting ketone **443**. Slow furan **415** addition would provide an alternative reaction pathway for hemi-aminal **604** to irreversibly generate the observed furfuryl acetamide product **603** (**Scheme 107**). This equilibrium would be consistent to that described by Hiemstra in his comprehensive overview of *N*-acyl iminium chemistry.[219]



Scheme 107. Proposed hemi-aminal intermediate in the synthesis of cyclic tertiary furfuryl acetamide **603**.

In practice, confirmation of this hypothesis is provided by Heathcock's synthesis of pinnaic acid (**Scheme 19**).[74] The bicyclic hemi-aminal intermediate **183** can be considered as an alkylated representation of the hemi-aminal intermediate **604**, its stability enhanced by the alkoxide component which renders issues of hydrolysis back to a starting ketone inconsequential.

It was proposed, then, that allowing longer reaction times might afford improved yields of the desired tertiary acetamide **603**. Before optimisation was carried out, however, the methodology was applied to the substituted ketone **544a** in order to assess the suitability of this transformation for the generation of the elaborated cyclic tertiary furfuryl acetamide **605** (**Scheme 108**). Unfortunately, in the case of this more hindered system, no trace of product was observed during 48 h of reaction time.

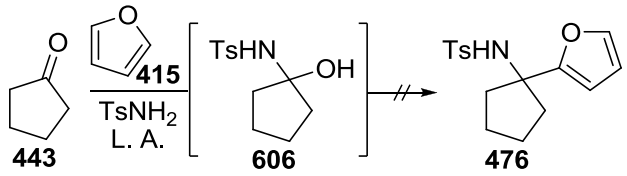


Scheme 108. Attempted synthesis of the more elaborate cyclic tertiary furfuryl acetamide **605**.

Attempts for One-pot Tosyl Amide Synthesis

Given the potential for the addition of furan to hemi-aminal units to generate tertiary furfuryl amines, the synthesis of tosyl-substituted hemi-aminals was investigated. It was proposed that, as tosyl-amide is more nucleophilic than acetamide, a tosyl-hemi-aminal might be more readily formed than the acetamide

counterpart. Displacement of the hydroxyl component with furan could then lead to the formation of the desired cyclic tertiary tosyl-protected furfuryl amide product **476**. A variety of acid catalysts ($BF_3.OEt_2$, *p*TsOH, PPTS, $Ti(O^iPr)_3$, $Yb(OTf)_3$, $Eu(FOD)_3$, HCl) were screened, along with variations in solvent (CH_2Cl_2, Et_2O, THF, PhMe) and drying agent ($MgSO_4$, 4Å-MS). Unfortunately, no combination resulted in product formation after 24h at room temperature (**Scheme 109**). Eventually, formation of the more stable substituted ethyl hemi-aminal was also attempted by carrying out the reaction in EtOH, however, this, too, afforded no reaction.



Scheme 109. Attempted one-pot synthesis of tosyl-protected furfuryl amine **476** *via* hemi-aminal intermediate **606**.

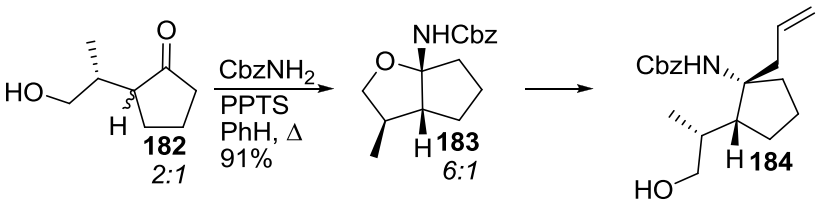
An Alternative Approach to the Cyclic Tertiary Furfuryl Amine

Addition to a Hemi-aminal

An alternative strategy for nitrogen incorporation was investigated whereby a bicyclic hemi-aminal underwent Lewis acid-catalysed nucleophilic addition. This approach was heavily inspired by Heathcock's synthesis of pinnaic acid.[74] In his approach, Heathcock's bicycle hemi-aminal **183** was formed by treating alcohol **182** with benzylcarbamate in the presence of pyridinium *p*-toluenesulfonate (**Scheme 110**). The resultant bicyclic hemi-aminal **183** was then coupled with allyltrimethylsilane in the presence of titanium tetrachloride. Heathcock reports that addition of more elaborate nucleophiles was attempted to no avail, however, the identity of the nucleophiles was not reported.

One of the most noteworthy observations was the fact that while the starting material was present as a 2:1 ratio of diastereoisomers **182**, a 6:1 ratio of

diastereoisomers in favour of the desired product **183** was obtained from the reaction. This demonstrated the tendency for the C13-stereocentre to epimerise towards the desired product. In fact, when a diastereoisomerically pure sample of **182** was used in the reaction the same diastereoisomeric ratio was afforded upon bicyclic hemi-aminal formation, illustrating that separation of alcohols **182** was not necessary.

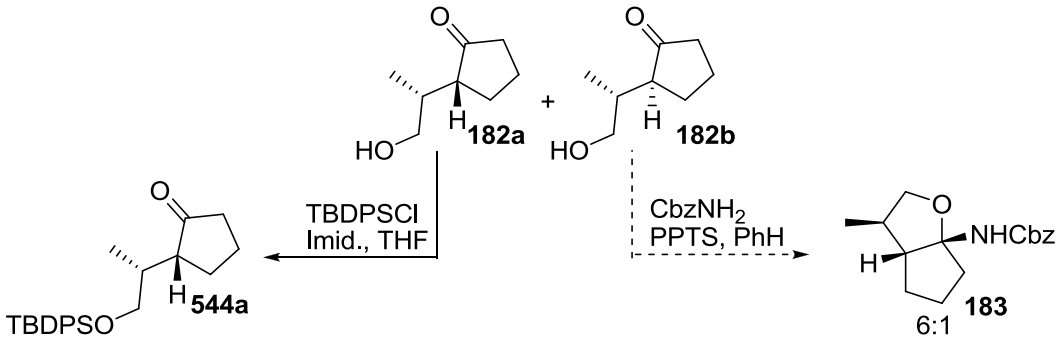


Scheme 110. Heathcock's bicyclic hemi-aminal **183** from diastereoisomeric alcohols **182**.

These observations led to the consideration of an alternative approach to a cyclic tertiary furfuryl amine intermediate.

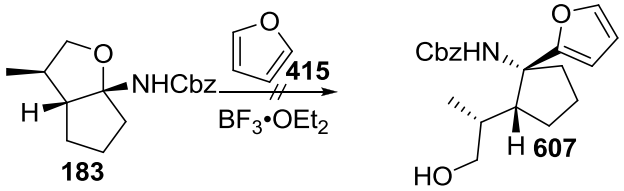
During the synthesis of the key substituted cyclopentanone **544a**, the separation of a 3:1 diastereoisomeric mixture of alcohols **182a** and **182b** was described, followed by reprotection of the desired isomer **182a** to afford silylated alcohol **544a** (**Scheme 111**).

The observations made by Heathcock highlighted the potential for using the undesired isomer **182b** to investigate bicyclic hemi-aminal formation.



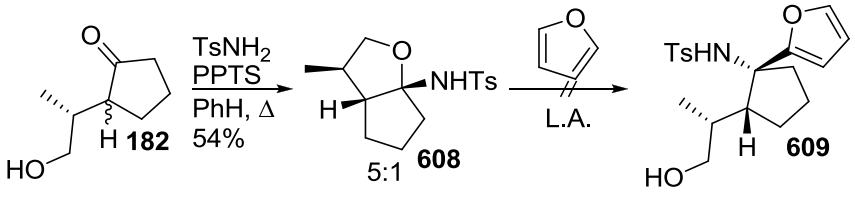
Scheme 111. The potential for undesired diastereoisomer **182b** to be used for the synthesis of bicyclic hemi-aminal **183.**

The bicyclic hemi-aminal **183** was synthesised according to Heathcock's procedure and the incorporation of a furan nucleophile in the presence of boron trifluoride-diethyl etherate, was attempted (**Scheme 112**). Unfortunately, all attempts resulted in a complex mixture of products, none of which were identifiable as the desired tertiary furfuryl amine, likely due to the lability of the Cbz group. Heathcock also reported a significant portion *N*-deprotected product, which was subsequently reprotected. It was conceivable that the use of the more rigorous conditions (i.e. BF_3) resulted in a considerable degree of Cbz removal prior to furan addition.



Scheme 112. Attempted furyl addition to Heathcock hemi-aminal **183**.

In an attempt to minimise the potential deprotection taking place, the use of a more stable protecting group was considered. It was, therefore, anticipated that using the more nucleophilic tosyl-amide would not have a detrimental effect on the formation of the bicyclic hemi-aminal, but would result in a more stable substrate upon which the furan addition could be attempted. Indeed, formation of the corresponding bicyclic hemi-aminal **608** was successful, however, all attempts to incorporate the furan were unsuccessful (**Scheme 113**).



Scheme 113. Attempted furyl addition to tosyl-protected hemi-aminal **608**.

The only identifiable by-product obtained was tosyl-amide; a result which suggested that the recently introduced protected nitrogen was eliminating preferentially to the ether component. In addition, no furyl signals were detected by ^{1}H NMR

spectroscopy, indicating that the elimination of tosyl-amide was occurring independently of the addition of the furyl nucleophile.

Summary of Efforts Towards a Cyclic Tertiary Amine

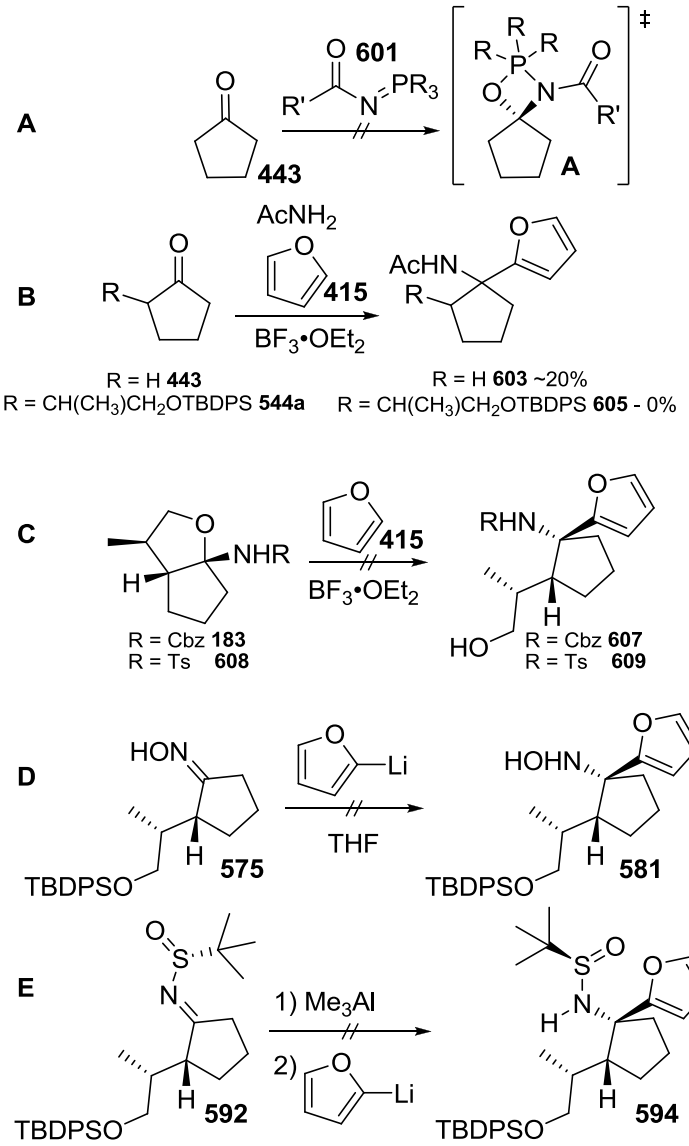
The failure of the aza-Wittig strategy was most likely due to steric hindrance. As a result, a substituted amide together with a bulky phosphine group proved too hindered to allow formation of a four-membered oxaphosphetidine **A** with a cyclic ketone **443** (**Scheme 114**, **A**).

Formation of a cyclic tertiary furfuryl acetamide **603** was achieved, albeit in low yield, on a simple cyclopentanone **443** model system, however, application of these same conditions to the more elaborate substituted cyclopentanone **544a** failed to afford even trace amounts of the desired cyclic tertiary furfuryl amide **605** (**Scheme 114**, **B**).

All attempts to open the bicyclic hemi-aminals **183** with furan also proved fruitless. Changing the protecting group to afford hemi-aminal **608** also proved futile as no addition product **607** or **609** was afforded (**Scheme 114**, **C**).

Coupling these observations with the failure to add lithiofuran to either the oxime **575**, or the Ellman sulfinylimine **592** (**Scheme 114**, **D** and **E**), while relatively similar systems have been shown to undergo this type of reaction successfully, tentatively led to the conclusion that in the case of substituted cyclopentanone **544a**, the environment was simply too sterically hindered to allow the incorporation of a furan ring together with any kind of substituted amine.

This argument is perhaps further supported by the presence of ~14% residual starting material when lithiofuran was added to the equivalent ketone **544a**. Substituting the carbonyl oxygen with any kind of substituted nitrogen created a more sterically hindered environment, and as such turned an incomplete reaction into no reaction at all.



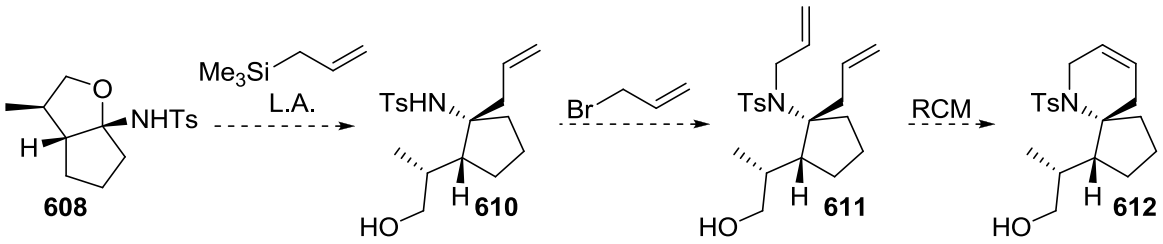
Scheme 114.Summary of efforts towards a cyclic tertiary furfuryl amine.

Faced with such compelling evidence, the addition of furan to an imine species, with the intention of further functionalisation towards pinnaic acid, halichlorine and tauropinnaic acid was abandoned in favour of an alternative strategy.

Alternative Strategies Investigated

Heathcock reported that an allyl group could be successfully introduced to the Cbz-protected hemi-aminal **183**.[74] It was postulated that if an allyl chain could be introduced to the corresponding tosylated hemi-aminal **608** in the same fashion,

subsequent allylation of the nitrogen would afford bis-olefinated intermediate **611.** Ring-closing metathesis could then lead to the desired spirocyclic piperidine **612** (**Scheme 115**)**.** Further elaboration may be achieved by means of oxidation to the corresponding imine followed by a Sakurai-type allylation.



Scheme 115. Postulated ring-closing metathesis approach from bicyclic hemi-aminal **608**.

Unfortunately, as was the case when furan was used as the nucleophile, treatment of tosyl-hemi-aminal **608** with allyltrimethylsilane under Lewis acid mediated conditions resulted in none of the desired product **610**. ^{1}H NMR analysis simply indicated the presence of tosyl-amide suggesting that elimination had taken place.

Potential for a Protecting-Group Free Synthesis

In tandem with the described efforts towards pinnaic acid, the potential for a protecting group free approach was being pursued. For each of the described pathways towards pinnaic acid, there are two sites of protection: the nitrogen and the primary alcohol. It was proposed that the necessity for protecting groups would be removed if these two units were tethered by means of a cyclic amide (**Figure 18**).

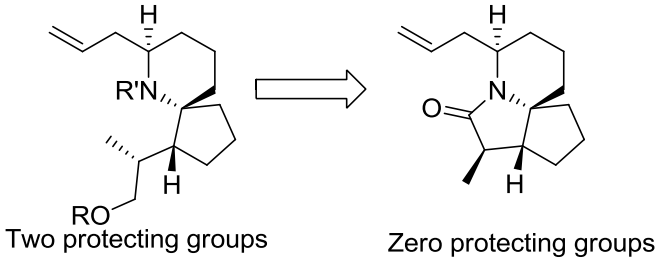
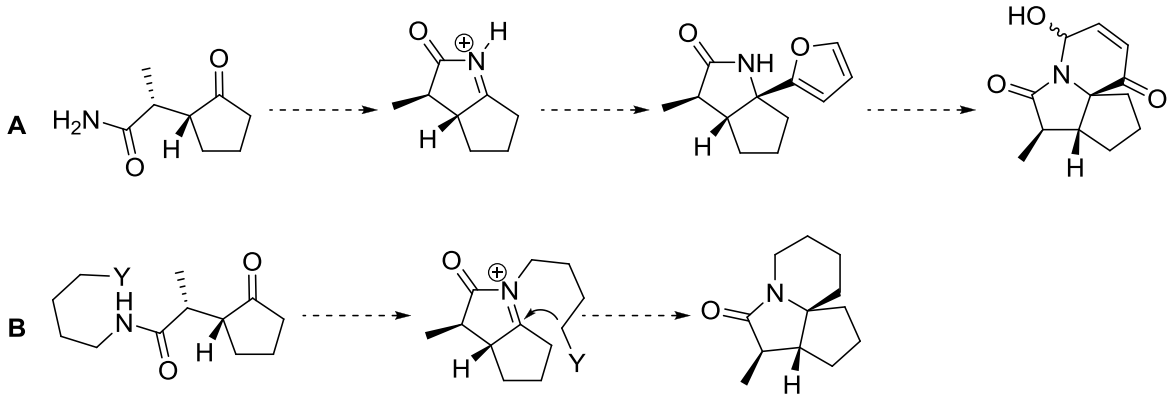


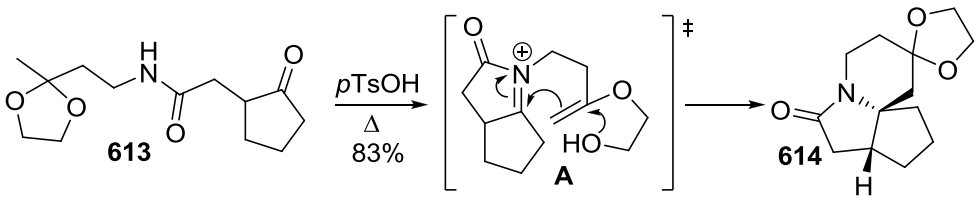
Figure 18.The potential for a protecting-group free synthesis.

Furthermore, the previously developed strategy hinging on the aza-Achmatowicz rearrangement could still be applied provided a furyl substituent could be introduced (**Scheme 116**, **A**).[171] Alternatively, it could also be possible to assemble the third ring by way of inducing an intramolecular cyclisation to occur from a suitable substituent present on the nitrogen (**Scheme 116**, **B**).



Scheme 116. Two potential routes for protecting-group free synthesis.

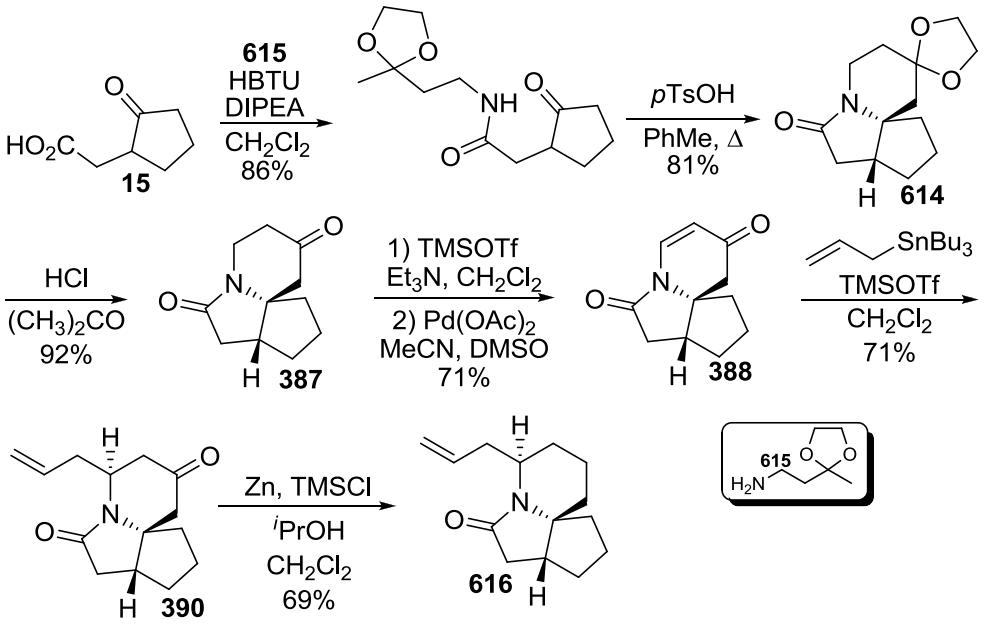
During his first generation synthesis of methyl homodaphniphyllate, Heathcock formed a very similar three-ring spirocyclic piperidine **614** to that which would be desired for the synthesis of pinnaic acid.[220] Heathcock achieved the elegant cyclisation of amide **613** through formation of the *N*-acyliminium species **A** (**Scheme 117**). Closure of the spirocycle, possible only by participation of the acetal unit, afforded, in a single pot, the desired tricyclic spirocycle **614** in very good yield. This rearrangement would not have taken place in the absence of the acetal unit and as such, this structure does not constitute a spectator protecting group, rather it is an essential functionality for the formation of the desired product.



Scheme 117.Heathcock's synthesis of tricyclic core **614**.

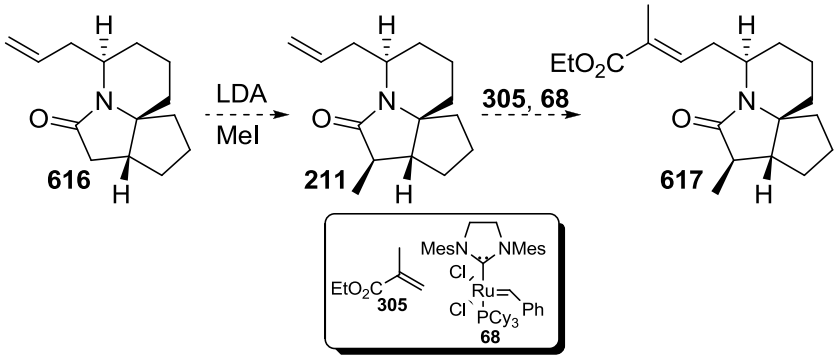
Tricyclic Spirocycle Formation

In order to test the feasibility of this chemistry for the synthesis of pinnaic acid, the same species **614** was synthesised and carried forth *via* acetal hydrolysis which exposed ketone **387** (**Scheme 118**). Padwa reported that Saegusa-type oxidation followed by allylation afforded tricyclic piperidine **390** as a 15:1 mixture of diastereoisomers, however, in this instance a single product was obtained.[144] Arimoto recently described a convenient method for deoxygenation using zinc dust and chloro(trimethyl)silane.[221] Pleasantly, application of Arimoto's conditions on the tricyclic piperidine substrate **390** resulted in complete deoxygenation without detrimental effect to either the amide functionality, or the terminal olefin to afford the fully saturated tricyclic piperidine unit **616**.



Scheme 118. Synthesis of novel tricyclic core **616**.

At this point, a subsequent methylation should occur with facial selectivity to afford the Feldman intermediate **211** (**Scheme 119**).[81] Cross-metathesis with ethyl methacrylate would then afford an advanced intermediate towards pinnaic acid without the use of spectator protecting groups. Unfortunately, these latter steps were not performed due to time constraints.

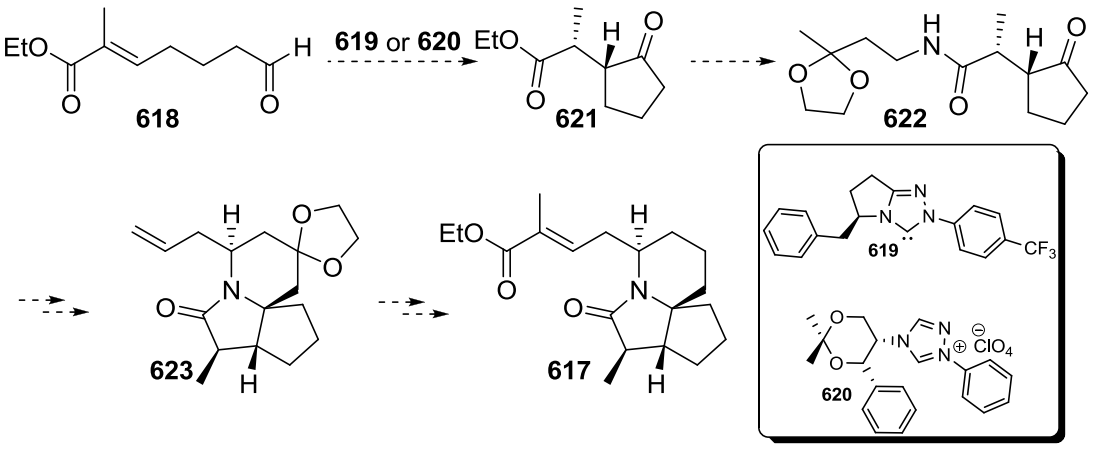


Scheme 119. Proposed elaboration to fully functionalised pinnaic acid core **617**.

Future Work

Enantioselective Protecting Group Free Total Synthesis of Pinnaic Acid

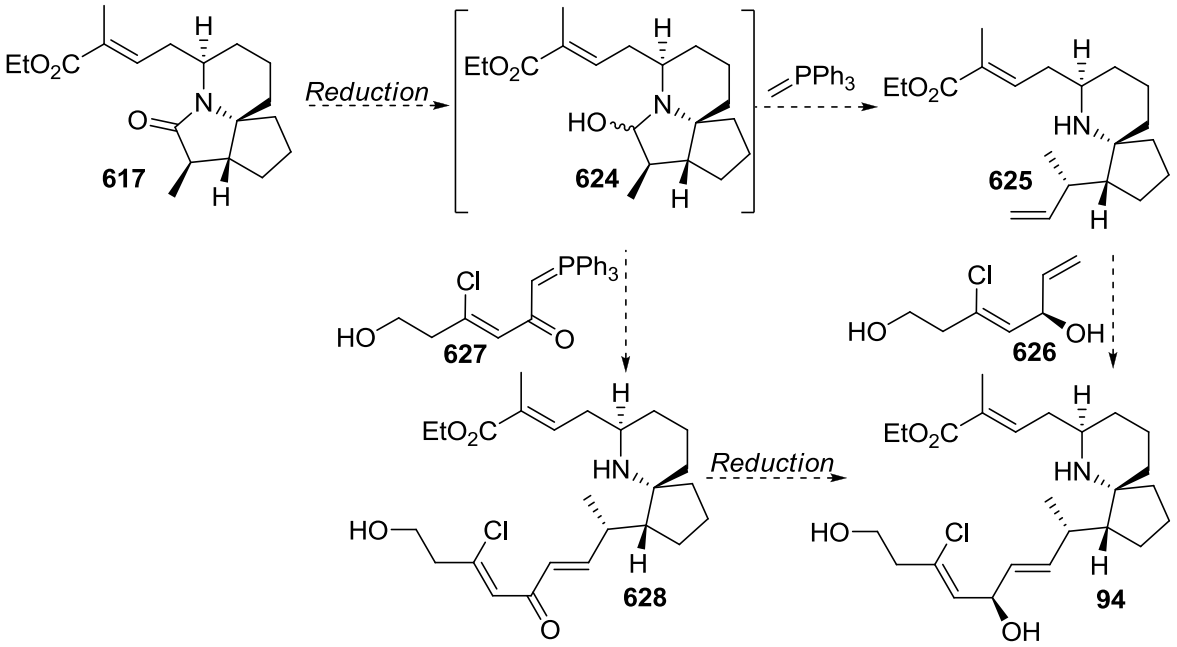
Future work on the development of an enantioselective synthesis of pinnaic acid which benefits from the use of no spectator protecting groups should focus on the formation of an enantiopure substituted cyclopentanone which possesses the key amide functionality. This could potentially be achieved by the use of an enantioselective intramolecular Stetter reaction, catalysed by either Rovis' catalyst **619**,[222] or Enders' catalyst **620** (**Scheme 120**).[223] This type of reaction has been shown to effectively generate enantioenriched cyclopentanones by using an easy to access chiral catalyst. The previous chemistry should then be applicable, with the exception of the now redundant methylation step.



Scheme 120. Proposed enantioselective synthesis of intermediate **617**.

Practically, completion of the synthesis could be realised by the partial reduction of lactam **617** to the hemi-aminal **624** which could, in the open chain form, undergo a Wittig reaction to form the corresponding terminal olefin **625**. Olefin **625** could then undergo a subsequent cross-metathesis with lower side-chain unit **626**. Alternatively, the entire lower side chain could be incorporated *via* Wittig reaction with phosphorane **627**. Luche reduction would lead to the same allylic alcohol

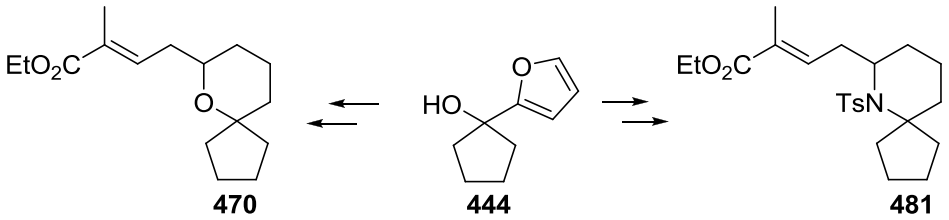
intermediate **94** (**Scheme 121**). Final ester hydrolysis would then complete the synthesis of pinnaic acid **2**.



Scheme 121. Completing the synthesis of pinnaic acid.

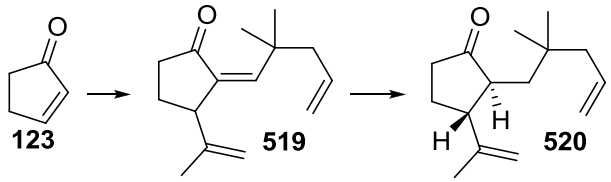
Summary

To conclude, a divergent approach to the synthesis of spirocyclic pyran **470** and spirocyclic piperidine **481** cores has been developed through the Achmatowicz and aza-Achmatowicz oxidative rearrangements, respectively. Each core was accessed *via* common cyclic tertiary furfuryl alcohol **444** (**Scheme 122**).[171]



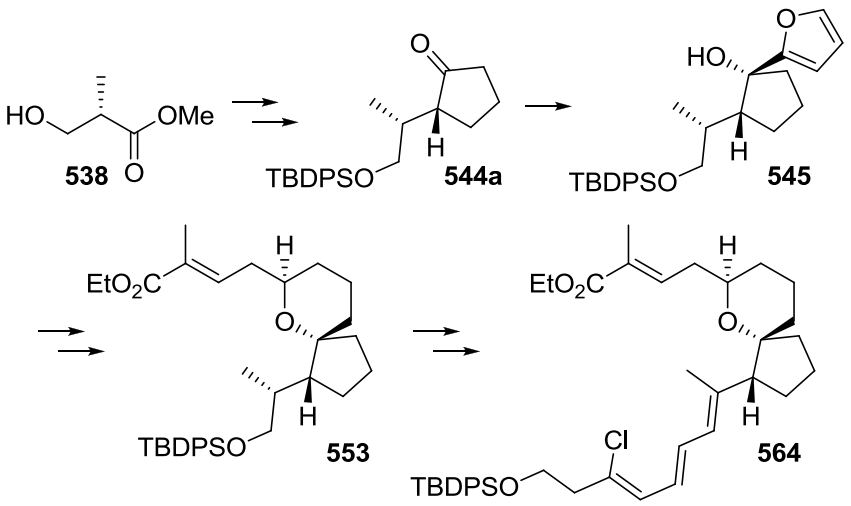
Scheme 122. Synthesis of pyran core **470** and piperidine core **481** from common synthetic intermediate **444**.

The partial synthesis of a more elaborate parent structure has been undertaken for the application of the developed methodology to the synthesis of polymaxenolide **408**. Early results have afforded *bis*-olefinic species **520** (**Scheme 123**).



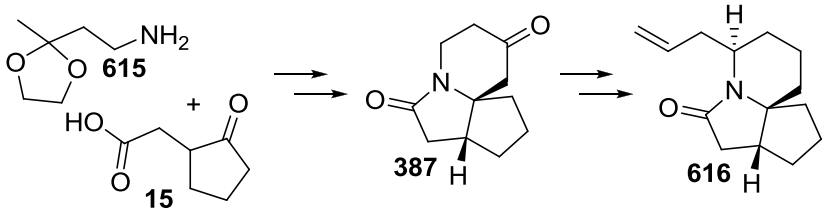
Scheme 123. Early work towards applying the developed methodology for the synthesis of polymaxenolide.

The developed methodology was successfully applied to the synthesis of a triene derivative of an oxa-pinnaic acid analogue **564**, representing the entire carbon framework of a pyran analogue of pinnaic acid **2** (**Scheme 124**). While the final cross-metathesis resulted in elimination, this approach utilised the solitary stereocentre present in the Roche ester starting material **538** to direct the orientation of each additional stereocentre present in advanced intermediate **553**.



Scheme 124. The synthesis of the oxa-pinnaic acid triene **564.**

A novel route to an advanced intermediate **616** related to pinnaic acid has been completed without the use of spectator protecting groups (**Scheme 125**). This route was heavily inspired by the cyclisation reported by Heathcock.[220]



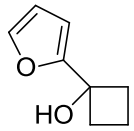
Scheme 125. Synthesis of advanced pinnaic acid precursor **616** without the use of spectator protecting groups.

3. Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether and dichloromethane were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Büchi Rotavapor. IR spectra were recorded neat using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm-1). Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded using a Bruker DPX Avance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dm = doublet of multiplet, dd = doublet of doublet, dt = doublet of triplet) and (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray (ESI), fast atom bombardment (FAB), electron impact (EI) and chemical ionisation (CI) mass spectrometer operating at a resolution of 15000 full widths at half height. Where a 100% peak was not observed in low resolution mass spectra the highest peak was taken to be 100%. Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 mm) as the stationary phase.

TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254). The plates were visualised by the quenching of UV fluorescence (λmax 254 nm) and/or by staining with either anisaldehyde or potassium permanganate followed by heating.

1-(Furan-2-yl)cyclobutanol 447

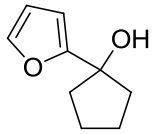


Furan **415** (465 mg, 6.83 mmol) was added to a stirred solution of *n*-butyllithium (2.7 mL, 2.5 M in hexanes) and *N,N,N',N'*-tetramethylethylenediamine (794 mg, 6.83 mmol) in tetrahydrofuran (10 mL) at −78 °C under argon. The resultant solution was stirred at −78 °C under argon for 1 hour. Cyclobutanone (96 mg, 1.37 mmol) was added and the solution was stirred at −78 °C under argon for a further 1 hour.

The reaction was quenched with ice-cold saturated aqueous ammonium chloride (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 9:1 → petroleum ether-diethyl ether 5:1) of the crude residue afforded 1-(furan-2-yl)cyclobutanol **447** (188 mg, 1.36 mmol, >99%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.38 (1H, dd, *J* = 1.7, 0.5 Hz), 6.33 (1H, dd, *J* = 3.2, 1.7 Hz), 6.28 (1H, dd, *J* = 3.2, 0.5 Hz), 2.55 (1H, brs), 2.53-2.46 (2H, m), 1.90-1.81 (2H, m), 1.70-1.58 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 158.1, 142.1, 110.0, 104.9, 72.2, 35.6, 12.1; IR (neat) ν_{max} = 3352 (OH), 2989 (C—H), 2947 (C—H), 1504 (Furan C=C), 1080 (C—O), 1006 (Furan) cm^{-1}; HRMS (CI) observed $[M\text{-}OH]^+$ 121.0650, calculated for C_8H_9O 121.0653.

1-(Furan-2-yl)cyclopentanol 444[169]



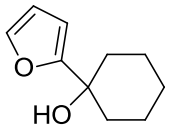
Cyclopentanone **443** (1.90 g, 22.61 mmol) was added to a stirred suspension of magnesium sulphate (13.61 g, 113.05 mmol) in tetrahydrofuran (140 mL) under argon. The resulting mixture was then allowed to stir at room temperature for 2 hours before being cooled to −78 °C.

In a separate flask, furan **415** (7.70 g, 113.05 mmol) was added to a −78 °C solution of *n*-butyllithium (2.5M in hexanes, 45 mL, 113.05 mmol) and *N,N,N',N'*-tetramethylethylenediamine (13.14 g, 113.05 mmol) in tetrahydrofuran (100 mL) under argon. The resulting solution was stirred at −78 °C for 1h, and was then transferred dropwise *via* cannula into the flask containing the cyclopentanone - magnesium sulphate mixture in tetrahydrofuran at −78 °C.

The reaction was then allowed to warm to room temperature overnight before being quenched by the addition of ice water (100 mL) and extracted with diethyl ether (3 x 75 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (100 mL), dried over sodium sulfate and concentrated under vacuum. Purification of the crude residue by flash column chromatography (silica gel, isocratic elution petroleum ether-diethyl ether 9:1) of the crude residue afforded 1-(furan-2-yl)cyclopentanol **444** (3.33 g, 21.86 mmol, 97%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.32 (1H, dd, *J* = 1.8, 0.8 Hz), 6.28 (1H, dd, *J* = 3.2, 1.8 Hz), 6.18 (1H, dd, *J* = 3.2, 0.8 Hz), 2.23 (1H, brs), 2.06-2.00 (2H, m), 1.88-1.95 (4H, m), 1.74-1.70 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 159.4, 141.5, 110.0, 104.1, 79.5, 39.6, 23.6; IR (neat) ν_{max} = 3342 (OH), 2966, 2874, 1504 (Furan C=C), 1074 (C—O), 1001 (Furan) cm^{-1}; HRMS (EI) observed M^+ 152.0834, calculated for $C_9H_{12}O_2$ 152.0837.

1-(Furan-2-yl)cyclohexanol 438[168]

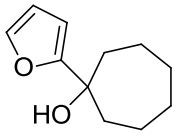


Furan **415** (328 mg, 4.83 mmol) was added to a stirred solution of *n*-butyllithium (1.9 mL, 2.5 M in hexanes) and *N,N,N',N'*-tetramethylethylenediamine (561 mg, 4.83 mmol) in tetrahydrofuran (10 mL) at −78 °C under argon. The resultant solution was stirred at −78 °C under argon for 1 hour. Cyclohexanone (95 mg, 0.97 mmol) was added and the solution was stirred at −78 °C under argon for a further 1 hour.

The reaction was quenched with ice-cold saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). Combined organics were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 9:1 → petroleum ether-diethyl ether 5:1) of the crude residue afforded 1-(furan-2-yl)cyclohexanol **438** (154 mg, 0.93 mmol, 96%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.34-7.32 (1H, m), 6.30 (1H, dd, J = 3.2, 1.8 Hz), 6.19 (1H, d, J = 3.2 Hz), 2.02-1.92 (3H, m), 1.87-1.78 (2H, m), 1.77-1.66 (2H, m), 1.57-1.26 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 160.0, 141.3, 110.0, 104.4, 70.0, 36.5, 25.5, 22.2; IR (neat) ν_{max} = 3407 (OH), 2935, 2859, 1501 (Furan C=C), 1342 (C—OH), 1057 (C—O), 1008 (Furan)cm^{-1}; HRMS (CI) observed $[M\text{-}OH]^+$ 149.0963, calculated for $C_{10}H_{13}O$ 149.0966.

1-(Furan-2-yl)cycloheptanol 451

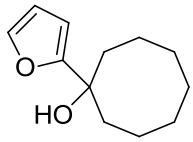


Furan **415** (289 mg, 4.24mmol) was added to a stirred solution of *n*-butyllithium (1.7 mL, 2.5 M in hexanes) and *N,N,N',N'*-tetramethylethylenediamine (493 mg, 4.24 mmol) in tetrahydrofuran (10 mL) at −78 °C under argon. The resultant solution was stirred at −78 °C under argon for 1 hour. Cycloheptanone (145 mg, 1.29 mmol) was added and the solution was stirred at −78 °C under argon for a further 1 hour.

The reaction was quenched with ice-cold saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 9:1 → 5:1 petroleum ether-diethyl ether 5:1) of the crude residue afforded 1-(furan-2-yl)cycloheptanol **451** (231 mg, 1.28 mmol, 99%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.35 (1H, appd, *J* = 1.7 Hz), 6.30 (1H, dd, *J* = 3.2, 1.7 Hz), 6.19 (1H, brd, *J* = 3.2 Hz), 2.14 (2H, ddd, *J* = 14.4, 9.6, 1.3 Hz), 1.97 (2H, ddd, *J* = 14.4, 9.0, 1.3 Hz), 1.91 (1H, brs), 1.77-1.41 (8H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 160.8, 141.5, 109.9, 104.1, 74.1, 40.1, 29.4, 22.1; IR (neat) ν_{max} = 3460 (OH), 2924, 2859, 1504 (Furan C=C), 1084 (C—O), 1014 (Furan) cm^{-1}; HRMS (CI) observed $[M\text{-}OH]^+$ 163.1119, calculated for $C_{11}H_{15}O$ 163.1123.

1-(Furan-2-yl)cyclooctanol 454

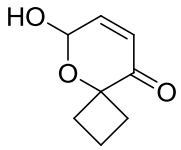


Furan **415** (465 mg, 6.55 mmol) was added to a stirred solution of *n*-butyllithium (2.6 mL, 2.5 M in hexanes) and *N,N,N',N'*-tetramethylethylenediamine (761 mg, 6.55 mmol) in tetrahydrofuran (10 mL) at −78 °C under argon. The resultant solution was stirred at −78 °C under argon for 1 hour. Cyclooctanone (165 mg, 1.31 mmol) was added and the solution was stirred at −78 °C under argon for a further 1 hour.

The reaction was quenched with ice-cold saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 9:1 → petroleum ether-diethyl ether 5:1) of the crude residue afforded 1-(furan-2-yl)cyclooctanol **454** (248 mg, 1.28 mmol, 98%) as a colourless oil.

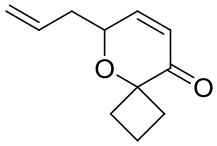
^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 7.35 (1H, dd, *J* = 1.8, 0.7 Hz), 6.30 (1H, dd, *J* = 3.2, 1.8 Hz), 6.20 (1H, dd, *J* = 3.2, 0.7 Hz), 2.14-2.01 (4H, m), 1.88 (1H, brs), 1.75-1.59 (5H, m), 1.55-1.41 (5H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 159.9, 141.5, 109.9, 104.8, 73.8, 34.8, 28.1, 24.6, 21.9; IR (neat) ν_{max} = 3398 (OH), 2924, 2854, 1504 (Furan C=C), 1087 (C—O), 1018 (Furan) cm^{-1}; HMRS (CI) observed $[M\text{-}OH]^+$ 177.1274, calculated for $C_{12}H_{17}O$ 177.1279.

6-Hydroxy-5-oxaspiro[3.5]non-7-en-9-one 448



1-(Furan-2-yl)cyclobutanol **447** (189 mg, 1.37 mmol) was dissolved in chloroform (7 mL) and cooled to 0 °C under argon. 3-Chloroperbenzoic acid (354 mg, 2.05 mmol) was added portionwise. The resultant solution was stirred at 0 °C for 30 minutes, then for 3 hours at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with chloroform (3 × 10 mL). Combined organics were washed with brine (10 mL), then dried over sodium sulfate, filtered and concentrated to afford 6-hydroxy-5-oxaspiro[3.5]non-7-en-9-one **448** as a colourless oil, which was carried forward without further purification.

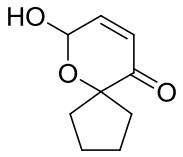
6-Allyl-5-oxaspiro[3.5]non-7-en-9-one 449



6-Hydroxy-5-oxaspiro[3.5]non-7-en-9-one **448** was dissolved in anhydrous dichloromethane (3 mL) and cooled to 0 °C under argon. Allyltrimethylsilane (469 mg, 4.10 mmol) was added, followed by boron trifluoride-diethyl etherate (194 mg, 1.37 mmol) dropwise. The resultant solution was stirred at 0 °C under argon for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted with diethyl ether (3 × 5 mL). Combined organics were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane-diethyl ether 9:1) of the crude residue afforded 6-allyl-5-oxaspiro[3.5]non-7-en-9-one **449** (24 mg, 0.13 mmol, 10% over two steps) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.85 (1H, dd, *J* = 10.2, 1.5 Hz), 6.00 (1H, dd, *J* = 10.2, 2.4 Hz), 5.86 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz), 5.21-5.19 (1H, m), 5.18-5.14 (1H, m), 4.43 (1H, tt, *J* = 6.6, 1.9 Hz), 2.74-2.65 (1H, m), 2.53-2.44 (1H, m), 2.40 (1H, dd, *J* = 14.2, 7.1 Hz), 2.37-2.28 (1H, m), 2.13-2.01 (2H, m), 1.93-1.79 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 197.0, 149.6, 133.0, 125.1, 118.3, 80.8, 69.0, 39.0, 30.0, 29.9, 12.6; IR (neat) ν_{max} = 3078 ($CH_2CH{=}CH_2$), 2953, 2848, 1687 (C=C—C=O), 1642 ($CH_2CH{=}CH_2$), 1072 (C—O),996 ($C{=}CH_2$), 959, 916 ($C{=}CH_2$), 746 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 179.1067, calculated for $C_{11}H_{15}O_2$ 179.1072.

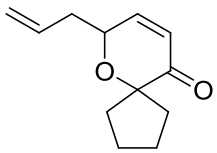
7-Hydroxy-6-oxaspiro[4.5]dec-8-en-10-one 445



A 0 °C solution of 1-(furan-2-yl)cyclopentanol **444** (811 mg, 5.33 mmol) in chloroform (30 mL) under argon was treated with the portion-wise addition of *m*-chloroperoxybenzoic acid (≤77%, 1.79 g, 7.99 mmol). The rate of addition was such that the temperature of the reaction was not allowed to exceed 10 °C throughout the process. Once the addition was complete, the reaction was stirred at 0 °C for 30 min, then for 3 hours at room temperature.

The reaction was diluted with chloroform (25 mL) and washed with 20% potassium iodide (25 mL). The aqueous phase was then extracted with chloroform (3 × 25 mL). The combined organic extracts were washed successively with 30% sodium thiosulfate (25 mL), saturated aqueous sodium hydrogen carbonate (25 mL), water (25 mL) and brine (25 mL). The organic phases was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield 7-hydroxy-6-oxaspiro[4.5]dec-8-en-10-one **445** as a colourless oil which was taken on to the next step without further purification.

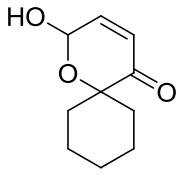
7-Allyl-6-oxaspiro[4.5]dec-8-en-10-one 446



7-Hydroxy-6-oxaspiro[4.5]dec-8-en-10-one **445** was dissolved in dichloromethane (15 mL) and allyltrimethylsilane (939 mg, 8.22 mmol) was added. The resultant solution was cooled to −78 °C and boron trifluoride-diethyl etherate (583 mg, 4.11 mmol) was added. The reaction mixture was stirred at −78 °C until for 1 hour and was then diluted with dichloromethane (15 mL), and quenched by the slow addition of saturated aqueous ammonium chloride (25 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate (25 mL), brine (25 mL), dried over sodium sulfate, filtered and concentrated under vacuum. Flash column chromatography (silica gel, isocratic elution petroleum ether-diethyl ether 9:1) of the crude residue afforded the 7-allyl-6-oxaspiro[4.5]dec-8-en-10-one **446** (556 mg, 2.89 mmol, 54% over two steps) as a colourless oil.

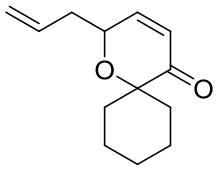
^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.85 (1H, ddd, J = 10.3, 1.5, 0.4 Hz), 6.02 (1H, dd, J = 10.3, 2.4 Hz), 5.83 (1H, ddt, J = 17.3, 10.3, 6.8 Hz), 5.17-5.15 (1H, m), 5.14-5.09 (1H, m), 4.41 (1H, tt, J = 6.8, 2.0 Hz), 2.49-2.40 (1H, m), 2.40-2.30 (2H, m), 2.14-2.06 (1H, m), 1.82-1.62 (5H, m), 1.53-1.44 (1H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C: 198.0, 148.7, 132.3, 125.1, 117.1, 88.3, 67.8, 38.2, 35.0, 31.8, 23.9, 23.3; IR (neat) ν_{max} = 3080 ($CH_2CH{=}CH_2$), 2956, 2932, 2872, 1685 (C=C—C=O), 1643 ($CH_2CH{=}CH_2$), 1073 (C—O), 996 ($C{=}CH_2$), 955, 917 ($C{=}CH_2$), 748 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 193.1228, calculated for $C_{12}H_{17}O_2$ 193.1229.

2-Hydroxy-1-oxaspiro[5.5]undec-3-en-5-one 439[168]



1-(Furan-2-yl)cyclohexanol **438** (154 mg, 0.93 mmol) was dissolved in chloroform (7 mL) and cooled to 0 °C under argon. 3-Chloroperbenzoic acid (311 mg, 1.39 mmol) was added portionwise. The resultant solution was stirred at 0 °C for 30 minutes, then for 3 hours at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with chloroform (3 × 10 mL). Combined organics were washed with brine, then dried over sodium sulfate, filtered and concentrated to afford 2-hydroxy-1-oxaspiro[5.5]undec-3-en-5-one **439** as a colourless oil, which was carried forward without further purification.

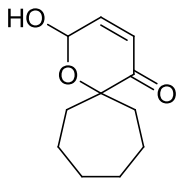
2-Allyl-1-oxaspiro[5.5]undec-3-en-5-one 450



2-Hydroxy-1-oxaspiro[5.5]un-7-en-9-one **439** was dissolved in anhydrous dichloromethane (2 mL) and cooled to 0 °C under argon. Allyltrimethylsilane (317 mg, 2.78 mmol) was added, followed by boron trifluoride-diethyl etherate (131 mg, 0.93 mmol) dropwise. The resultant solution was stirred at 0 °C under argon for 30 minutes. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted with diethyl ether (3 × 5 mL). Combined organics were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane-diethyl ether 9:1) afforded 2-allyl-1-oxaspiro[5.5]undec-3-en-5-one **450** (120 mg, 0.58 mmol, 63% over two steps) as a colourless oil.

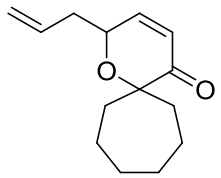
^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.84 (1H, dd, *J* = 10.3, 1.4 Hz), 5.97 (1H, dd, *J* = 10.3, 2.4 Hz), 5.91 (1H, dddd, *J* = 17.0, 13.9, 7.4, 6.4 Hz), 5.22-5.10 (2H, m), 4.38 (1H, tt, *J* = 6.7, 1.9 Hz), 2.52-2.35 (2H, m), 2.05-1.88 (2H, m), 1.72-1.44 (6H, m), 1.34-1.20 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 199.6, 149.5, 133.6, 125.3, 118.0, 79.1, 67.5, 39.3, 31.7, 28.4, 25.4, 21.5, 20.6; IR (neat) ν_{max} = 3076 ($CH_2CH{=}CH_2$), 2930, 2855, 1683 (C=C—C=O), 1642 ($CH_2CH{=}CH_2$), 1084 (C—O), 989 ($C{=}CH_2$), 944, 914 ($C{=}CH_2$), 776 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 207.1389, calculated for $C_{13}H_{19}O_2$ 207.1385.

2-Hydroxy-1-oxaspiro[5.6]dodec-3-en-5-one 452



1-(Furan-2-yl)cycloheptanol **451** (231 mg, 1.28 mmol) was dissolved in chloroform (10 mL) and cooled to 0 °C under argon. 3-Chloroperbenzoic acid (355 mg, 2.06 mmol) was added portionwise. The resultant solution was stirred at 0 °C for 30 minutes, then for 3 hours at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with chloroform (3 × 10 mL). Combined organics were washed with brine (10 mL), then dried over sodium sulfate, filtered and concentrated to afford 2-hydroxy-1-oxaspiro[5.6]dodec-3-en-5-one **452** as a colourless oil, which was carried forward without further purification.

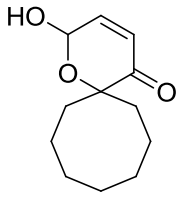
2-Allyl-1-oxaspiro[5.6]dodec-3-en-5-one 453



2-Hydroxy-1-oxaspiro[5.6]dodec-3-en-5-one **452** was dissolved in anhydrous dichloromethane (2 mL) and cooled to 0 °C under argon. Allyltrimethylsilane (439 mg, 3.85 mmol) was added, followed by boron trifluoride-diethyl etherate (182 mg, 1.28 mmol) dropwise. The resultant solution was stirred at 0 °C under argon for 30 minutes. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane-diethyl ether 9:1) afforded 2-allyl-1-oxaspiro[5.6]dodec-3-en-5-one **453** (178 mg, 0.81 mmol, 63% over two steps) as a colourless oil.

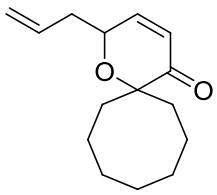
^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.83 (1H, dd, *J* = 10.3, 1.4 Hz), 5.94 (1H, dd, *J* = 10.3, 2.4 Hz), 5.88 (1H, ddt, *J* = 17.2, 10.3, 6.9 Hz), 5.20-5.10 (2H, m), 4.39 (1H, tt, *J* = 6.9, 1.8 Hz), 2.51-2.42 (1H, m), 2.42-2.33 (1H, m), 2.19-2.10 (1H, m), 2.04-1.94 (1H, m), 1.74-1.48 (10H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 200.2, 149.4, 133.5, 125.0, 118.0, 82.5, 67.8, 39.3, 36.4, 31.7, 29.3, 29.1, 22.1, 21.7; IR (neat) ν_{max} = 3078 ($CH_2CH=CH_2$), 2924, 2857, 2702, 1683 (C=C—C=O), 1642 ($CH_2CH=CH_2$), 1064 (C—O), 986 ($C=CH_2$), 957, 916 ($C=CH_2$), 782 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 221.1544, calculated for $C_{14}H_{21}O_2$ 221.1542.

2-Hydroxy-1-oxaspiro[5.7]dodec-3-en-5-one 455



1-(Furan-2-yl)cyclooctanol **454** (248 mg, 1.28 mmol) was dissolved in chloroform (10 mL) and cooled to 0 °C under argon. 3-Chloroperbenzoic acid (429 mg, 1.92 mmol) was added portionwise. The resultant solution was stirred at 0 °C for 30 minutes, then for 3 hours at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with chloroform (3 × 10 mL). The combined organic layers were washed with brine (10 mL), then dried over sodium sulfate, filtered and concentrated to afford 2-hydroxy-1-oxaspiro[5.7]dodec-3-en-5-one **455** as a colourless oil, which was carried forward without further purification.

2-Allyl-1-oxaspiro[5.7]dodec-3-en-5-one 456

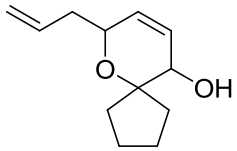


2-Hydroxy-1-oxaspiro[5.7]dodec-3-en-5-one **455** was dissolved in anhydrous dichloromethane (3 mL) and cooled to 0 °C under argon. Allyltrimethylsilane (438 mg, 3.83 mmol) was added, followed by boron trifluoride-diethyl etherate (181 mg, 1.28 mmol) dropwise. The resultant solution was stirred at 0 °C under argon for 30 minutes. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted with diethyl ether (3 × 5 mL). Combined organics were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane-diethyl ether 9:1) afforded 2-allyl-1-

oxaspiro[5.7]dodec-3-en-5-one **456** (182 mg, 0.78 mmol, 61% over two steps) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.82 (1H, dd, *J* = 10.3, 1.4 Hz), 5.94 (1H, dd, *J* = 10.3, 2.4 Hz), 5.88 (1H, dddd, *J* = 17.0, 13.8, 7.3, 6.5 Hz), 5.19-5.11 (2H, m), 4.37 (1H, tt, *J* = 6.5, 1.8 Hz), 2.50-2.42 (1H, m), 2.41-2.33 (1H, m), 2.16-2.09 (1H, m), 1.97-1.89 (1H, m), 1.82-1.45 (12H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 200.1, 149.3, 133.5, 124.9, 117.9, 81.4, 67.8, 39.3, 32.2, 31.6, 28.5, 27.3, 22.6, 20.8, 20.7; IR (neat) ν_{max} = 3077 ($CH_2CH{=}CH_2$), 2967, 2922, 2850, 1683 (C=C—C=O), 1642 ($CH_2CH{=}CH_2$), 1060 (C—O), 992 ($C{=}CH_2$), 915 ($C{=}CH_2$), 781 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 235.1701, calculated for $C_{15}H_{23}O_2$ 235.1698.

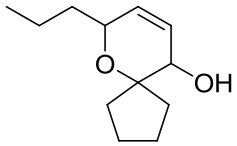
7-Allyl-6-oxaspiro[4.5]dec-8-en-10-ol 462



Sodium borohydride (24 mg, 0.63 mmol) was dissolved in methanol (0.7 mL) and cooled to 0 °C under argon. 7-Allyl-6-oxaspiro[4.5]dec-8-en-10-one **446** (100 mg, 0.52 mmol) in methanol (0.3 mL) was added dropwise and the resultant solution was allowed to stir at 0 °C for 30 mins and then at room temperature for a further 12 hours. The reaction mixture was quenched by the slow addition of 6M HCl (1 mL) and was stirred for 15 mins. The resultant mixture was diluted with water (2 mL) and extracted diethyl ether (2 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford 7-allyl-6-oxaspiro[4.5]dec-8-en-10-ol **462** (91 mg, 0.47 mmol, 83%) as a colourless oil which was not purified further.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 5.82 (1H, dddd, *J* = 16.8, 10.2, 7.2, 6.6 Hz), 5.71 (2H, m), 5.11-5.00 (2H, m), 4.17 (1H, brs), 4.11 (1H, m) 2.34-2.18 (2H, m), 1.91-1.79 (2H, m), 1.77-1.56 (7H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 134.4, 130.2, 129.5, 117.1, 85.9, 69.5, 68.1, 39.8, 37.1, 27.3, 24.8, 23.9.

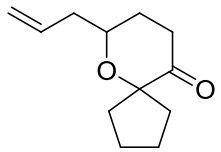
7-Propyl-6-oxaspiro[4.5]dec-8-en-10-ol 468



7-Allyl-6-oxaspiro[4.5]dec-8-en-10-ol **462** (144 mg, 0.74 mmol) was dissolved in benzene (29 mL) under an atmosphere of hydrogen and tris(triphenylphosphine)rhodium chloride (14.5 mg, 0.02 mmol) was added. The resultant suspension was allowed to stir at room temperature for 12 hours. The reaction mixture was then concentrated and azeotroped twice with toluene to remove any residual benzene. The brown residue was then taken up in diethyl ether and filtered through Florisil before being concentrated to afford 7-propyl-6-oxaspiro[4.5]dec-8-en-10-ol **468** (145 mg, 0.74 mmol, quant.)

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 5.70-5.61 (2H, qt, J = 10.3, 1.8 Hz), 4.15 (1H, br s), 4.02 (1H, m), 1.95-1.94 (1H, m), 1.89-1.82 (1H, m), 1.77-1.53 (7H, m), 1.46-1.36 (4H, m), 0.90 (3H, t, J = 7.4 Hz).

7-Allyl-6-oxaspiro[4.5]decan-10-one 458

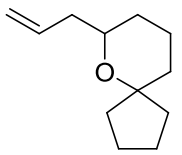


A solution of 7-allyl-6-oxaspiro[4.5]dec-8-en-10-one **446** (488 mg, 2.54 mmol) in a deoxygenated benzene : water mixture (70 mL : 141 µL) was transferred *via* cannula to a flask containing (triphenylphosphine)copper hydride hexamer (1.0 g, 0.51 mmol) under argon. The resultant red/brown suspension was stirred at room temperature overnight before being opened to the air, and being allowed to stir for 30 minutes. The suspension was filtered through Celite®, concentrated under vacuum, and azeotroped with toluene to remove any residual benzene. Flash column chromatography (silica gel, elution gradient hexane → hexane-ethyl acetate

19:1) of the crude residue afforded 7-allyl-6-oxaspiro[4.5]decan-10-one **458** (476 mg, 2.45 mmol, 96%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 5.73-5.55 (1H, m), 5.05-4.99 (2H, m), 3.79-3.71 (1H, m), 2.51 (1H, dm, *J* = 16.1 Hz), 2.41 (1H, dm, *J* = 16.1 Hz), 2.34-2.25 (1H, m), 2.22-2.13 (2H, m), 2.01-1.91 (2H, m), 1.88-1.76 (1H, m), 1.74-1.55 (6H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 212.3, 134.6, 117.0, 91.6, 70.4, 40.2, 36.7, 36.0, 35.1, 30.5, 24.9, 24.4; IR (neat) ν_{max} = 3077 ($CH_2CH=CH_2$), 2955, 2870, 2858, 1714 (C=O), 1642 ($CH_2CH=CH_2$), 1078 (C—O), 995 ($C=CH_2$), 971, 914 ($C=CH_2$), cm^{-1}; HRMS (CI) observed $[M+H]^+$ 195.1387, calculated for $C_{12}H_{19}O_2$ 195.1385.

7-Allyl-6-oxaspiro[4.5]decane 459

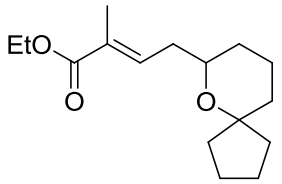


A room temperature solution of 7-allyl-6-oxaspiro[4.5]decan-10-one **458** (109 mg, 0.56 mmol) in absolute ethanol (6 mL) under argon was treated with tosyl-hydrazide (110 mg, 0.59 mmol), and the resultant solution was stirred for 18.5 hours. The reaction mixture was concentrated under vacuum and the residue was dissolved in anhydrous dichloromethane (5.4 mL) and cooled to 0 °C. DIBAL-H (1M in hexanes, 2 mL, 2.0 mmol) was then added over 15 min and the resultant yellow solution was allowed to warm up to room temperature over 1.5 hours. The mixture was diluted with dichloromethane (10 mL), and quenched by the slow addition of 3M sodium hydroxide (15 mL). The organic layer, was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated under vacuum. Flash column chromatography of the crude residue (silica gel, isocratic elution petroleum ether) afforded 7-allyl-6-oxaspiro[4.5]decane **459** (71 mg, 0.39 mmol, 70%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 5.52 (1H, dddd, *J* = 17.3, 10.2, 7.5, 6.4 Hz), 5.04 (1H, dm, *J* = 17.2 Hz), 4.99 (1H, dm, *J* = 10.2 Hz), 3.44 (1H, dtd, *J* = 11.1, 6.4, 2.1 Hz),

2.24 (1H, dtt, *J* = 14.2, 6.5, 1.5 Hz), 2.10 (1H, dm, *J* = 14.2 Hz), 1.92-1.84 (1H, m), 1.76-1.62 (4H, m), 1.61-1.39 (9H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 135.7, 116.1, 83.9, 71.4, 41.6, 41.4, 35.0, 32.7, 31.4, 24.4, 23.3, 21.4; IR (neat) ν_{max} = 3074 ($CH_2CH{=}CH_2$), 2956, 2932, 2863, 2847, 1641 ($CH_2CH{=}CH_2$), 1084 (C—O), 997 ($C{=}CH_2$), 911 ($C{=}CH_2$) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 181.1590, calculated for $C_{12}H_{21}O$ 181.1592.

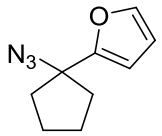
(*E*)-Ethyl 2-methyl-4-(6-oxaspiro[4.5]decan-7-yl)but-2-enoate 470



A mixture of 7-allyl-6-oxaspiro[4.5]decane **459** (100 mg, 0.56 mmol), Grubbs 2nd generation catalyst (13.3 mg, 17 µmol) and ethyl methacrylate (1.4 mL, 11.2 mmol) was heated to reflux overnight. The reaction mixture was then concentrated under vacuum and the crude residue was purified by flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) to yield (*E*)-ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate **470** (123 mg, 0.46 mmol, 83%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ_H: 6.76 (1H, t, *J* = 6.9 Hz), 4.25 (2H, q, *J* = 6.9 Hz), 3.53-3.41 (1H, m), 2.34-2.18 (2H, m), 1.91-1.83 (1H, m), 1.80 (3H, brs), 1.75-1.62 (4H, m), 1.60-1.35 (9H, m), 1.26 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 168.2, 138.8, 128.9, 84.1, 70.8, 60.4, 41.5, 36.2, 34.8, 32.6, 31.6, 24.3, 23.2, 21.3, 14.3, 12.7; IR (neat) ν_{max} = 2955, 2931, 2867, 2848, 1708 (O=COEt), 1650 ($C{=}C{-}CO_2Et$), 1082 (C—O) 991 (*trans* $C{=}C{-}CO_2Et$), 803 ($R_2C{=}CHR$) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 267.1957, calculated for $C_{16}H_{27}O_3$ requires 267.1960.

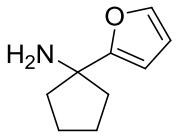
2-(1-Azidocyclopentyl)furan 472



Ice-cold hydrazoic acid was generated *in situ* in four batches as follows: luke warm water (4.25 mL) was added to sodium azide (4.25 g, 65.44 mmol) and the resultant suspension was stirred for 15 minutes. Benzene (25 mL) was added and the biphasic suspension was cooled to 0 °C. Concentrated H_2SO_4 (2.63 mL) was added dropwise and the mixture was allowed to stir at 0 °C for 20 minutes. The organic phase was carefully syringed into a dry flask at 0 °C and 1-(furan-2-yl)cyclopentanol **444** (600 mg, 3.94 mmol) was added followed by H_2SO_4 (132 µl). The resulting solution was stirred for 5 minutes at 0 °C before being quenched with ice-cold ammonium hydroxide solution. The four quenched batches were combined in a separatory funnel and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with saturated aqueous ammonium chloride (20 mL), dried over sodium sulfate and concentrated. Flash column chromatography (silica gel, isocratic elution hexane) of the crude residue afforded 2-(1-azidocyclopentyl)furan **472** (2.11 g, 11.91 mmol, 76%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.39 (1H, dd, J = 1.8, 0.8 Hz), 6.34 (1H, dd, J = 3.2, 1.8 Hz), 6.28 (1H, dd, J = 3.2, 0.8 Hz), 2.14-2.03 (4H, m), 1.93-1.73 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 155.4, 142.4, 110.1, 106.1, 70.5, 36.6, 23.3; IR (neat) ν_{max} = 2962, 2875, 2092 (N_3), 1500 (Furan C=C) 1074 (C—N), 1014 (Furan) cm^{-1}; HRMS (EI) observed M^+ 177.0906, calculated for $C_9H_{11}N_3O$ 177.0902.

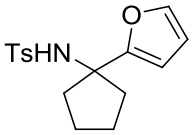
1-(Furan-2-yl)cyclopentanamine 473



2-(1-Azidocyclopentyl)furan **472** (2.0 g, 11.29 mmol) was dissolved in ethyl acetate (16 mL) and Pd/C 10% (200 mg) was added. A balloon filled with H_2 was applied to this stirred solution. Repeated bubbling of H_2 through the Pd catalyst, or loading, was performed at 10 min intervals for a total of 1 hour. At such times, the reaction mixture was filtered through a Celite® pad and concentrated to afford 1-(furan-2-yl)cyclopentanamine **473** (1.66 g, 10.98 mmol, 97%) as a colourless oil which was used without further purification.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.31 (1H, dd, J = 1.8, 0.8 Hz), 6.27 (1H, dd, J = 3.2, 1.8 Hz), 6.08 (1H, dd, J = 3.2, 0.8 Hz), 2.08-2.00 (2H, m), 1.92-1.83 (2H, m), 1.77-1.70 (6H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 162.3, 141.1, 109.9, 102.8, 60.5, 40.1, 24.0; IR (neat) ν_{max} = 2956, 2924, 2870, 2854, 1458 (C=C), 1074 (C—N), 1014 (Furan), 800 (NH) cm^{-1}; HRMS (EI) observed M^+ 151.0991, $C_9H_{13}NO$ requires 151.0997.

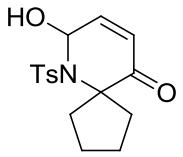
N-(1-Furan-2-yl)cyclopentyl-4-toluenesulfonamide 476



1-(Furan-2-yl)cyclopentanamine **473** (1.66 g, 10.98 mmol) was dissolved in dichloromethane (25 mL) and triethylamine (1.93 mL, 13.72 mmol) was added to the solution under argon. The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride (2.62 g, 13.72 mmol) was added. The solution was allowed to warm to room temperature and was stirred overnight under argon. The reaction mixture was then diluted with dichloromethane (15 mL) and washed sequentially with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL). The

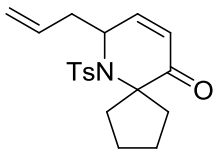
organic layers were combined, dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane-ethyl acetate 4:1) of the crude residue afforded *N*-(1-furan-2-yl)cyclopentyl-4-toluenesulfonamide **476** (2.29 g, 7.51 mmol, 68%) as a white solid (m.p. 149 °C). ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.47 (2H, d, *J* = 8.3 Hz), 7.10 (2H, d, *J* = 8.3 Hz), 6.91 (1H, appdd, *J* = 1.8, 0.7 Hz), 6.00 (1H, dd, *J* = 3.2, 1.8 Hz) 5.98 (1H, dd, 3.2, 0.7 Hz), 5.18 (1H, bs), 2.35 (3H, s), 2.23-2.17 (2H, m), 2.10-2.03 (2H, m), 1.82-1.76 (2H, m), 1.62-1.58 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 155.0, 142.4, 141.6, 138.4, 129.2, 127.1, 109.7, 106.8, 64.2, 38.1, 22.4, 21.4; IR (neat) ν_{max} = 3254 (NH), 2972, 2953, 2918, 2875, 1599 (NH), 1460 (Furan C=C), 1315 (Ts), 1153 (Ts), 1096 (C—N), 1004 (Furan) cm^{-1}; HRMS (EI) observed M^+ 305.1085, calculated for $C_{16}H_{19}NO_3S$ 305.1086.

7-Hydroxy-6-tosyl-6-azaspiro[4.5]dec-8-en-10-one 477



N-(1-Furan-2-yl)cyclopentyl-4-toluenesulphonamide **476** (427 mg, 1.40 mmol) was dissolved in chloroform (7 mL) and *m*-chloroperoxybenzoic acid (≤77%, 470 mg, 2.10 mmol) was added portion-wise at 0 °C under an argon atmosphere. The temperature was not allowed to exceed 10 °C during the addition. Once addition was complete, the reaction was allowed to warm to room temperature and stirred for 3 hours. After such time, the solution was diluted with chloroform and washed with 20% potassium iodide (10 mL), 30% sodium thiosulfate (10 mL), sodium hydrogen carbonate (10 mL), water (10 mL) and brine (10 mL) sequentially. The organic layer was dried over sodium sulfate, filtered and concentrated to afford crude 7-hydroxy-6-tosyl-6-azaspiro[4.5]dec-8-en-10-one **477** as a yellow foam which was taken forward without further purification.

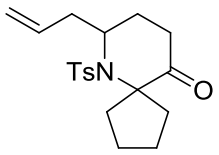
7-Allyl-6-tosyl-azaspiro[4.5]dec-8-en-10-one 478



7-Hydroxy-6-tosyl-6-azaspiro[4.5]dec-8-en-10-one **477** (449 mg, 1.40 mmol) was dissolved in dichloromethane (7 mL) and allyltrimethylsilane (319 mg, 2.79 mmol) was added and the solution was cooled to −78 °C under an inert atmosphere. Boron trifluoride diethyl etherate (198 mg, 1.40 mmol) was added and the solution was allowed to stir under an argon atmosphere at −78 °C for 45 minutes. After such time, the reaction mixture was diluted with Dichloromethane (10 mL) and washed with cold saturated aqueous ammonium chloride (2 × 10 mL). The organic phase was then dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 9:1 → petroleum ether-diethyl ether 3:1) of the crude residue afforded 7-allyl-6-tosyl-azaspiro[4.5]dec-8-en-10-one **478** (311mg, 0.90 mmol, 64% over two steps) as a white solid (m.p. 89-90 °C).

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.56 (2H, d, *J* = 8.3 Hz), 7.21 (2H, d, *J* = 8.3 Hz), 6.85 (1H, dd, *J* = 10.2, 4.6 Hz), 6.00-5.91 (1H, m), 5.88 (1H, dd, *J* = 10.2, 1.8 Hz), 5.22-5.20 (1H, m), 5.19-5.16 (1H, m), 5.11-5.04 (1H, m), 2.82 (1H, dtt, *J* = 13.4, 6.4, 1.3 Hz), 2.60 (1H, dtm, *J* = 13.4, 8.1 Hz), 2.37 (3H, s), 2.13-2.02 (3H, m), 1.80-1.71 (3H, m), 1.44-1.32 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 196.4, 146.2, 143.6, 139.0, 133.9, 129.8, 126.8, 124.8, 118.9, 73.1, 57.3, 42.5, 41.5, 32.2, 23.9, 22.6, 21.6; IR (neat) ν_{max} = 3069 ($CH_2CH{=}CH_2$), 2957, 2874, 1642 (C=C—C=O), 1598 ($CH_2CH{=}CH_2$), 1329 (Ts), 1166 (Ts), 1089 (C—N), 1000 ($C{=}CH_2$), 911 ($C{=}CH_2$), 816 (*cis* C=C) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 346.1476, calculated for $C_{19}H_{24}NO_3S$ 346.1477.

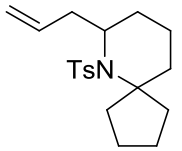
7-Allyl-6-azaspiro[4.5]decan-10-one 479



7-Allyl-6-azaspiro[4.5]dec-8-en-10-one **478** (300 mg, 1.89 mmol) was dissolved in a deoxygenated solution of benzene (100 mL) and water (0.2 mL) under argon. The resulting solution was then transferred *via* cannula to a flask containing (triphenylphosphine)copper hydride hexamer (1 g, 0.51 mmol) under argon. The resultant red/brown suspension was stirred at room temperature for 18 hours. The reaction mixture was opened to the air and was allowed to stir for 1 hour before being filtered through a pad of Celite® and concentrated. Flash column chromatography (silica gel, elution gradient hexane → hexane-ethyl acetate 9:1) of the crude residue afforded 7-allyl-6-azaspiro[4.5]decan-10-one **479** (258 mg, 0.74 mmol, 85%) as a white solid (m.p. 88-90 °C).

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.74 (2H, d, *J* = 8.2 Hz), 7.29 (2H, d, *J* = 8.2 Hz), 5.69-5.57 (1H, m), 5.06-5.04 (1H, m), 5.03-5.00 (1H, m), 4.05 (1H, ddt, *J* = 10.7, 6.3, 4.6 Hz), 2.66 (1H, dt, *J* = 15.7, 7.4 Hz), 2.50 (1H, ddd, *J* = 16.9, 9.3, 6.8 Hz), 2.42 (3H, s), 2.41-2.30 (3H, m), 2.20-2.03 (3H, m), 1.98-1.88 (1H, m), 1.86-1.76 (3H, m), 1.74-1.64 (1H, m), 1.57-1.45 (1H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 209.5, 143.4, 139.2, 139.1, 134.2, 129.8, 129.7, 127.2, 118.2, 76.5, 53.9, 39.4, 38.2, 36.6, 31.9, 25.5, 24.5, 24.1, 21.6; IR (neat) ν_{max} = 3070 ($CH_2CH{=}CH_2$), 2955, 2877, 1712 (C=O), 1597 ($CH_2CH{=}CH_2$), 1311 (Ts), 1149 (Ts), 1095 (C—N), 1003 ($C{=}CH_2$), 964, 902 ($C{=}CH_2$) cm^{-1}; HRMS (CI) observed $[M+H]^+$ 348.1632, calculated for $C_{19}H_{26}NO_3S$ 348.1633.

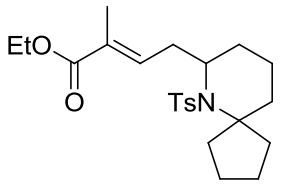
7-Allyl-6-azaspiro[4.5]decane 480



Tosyl-hydrazide (315 mg, 1.69 mmol) was added to 7-allyl-6-azaspiro[4.5]decan-10-one **479** (535 mg, 1.54 mmol) in absolute ethanol (15 mL) at room temperature under argon. The resultant solution was allowed to stir at room temperature overnight. The solvent was evaporated and the tosyl-hydrazone was dissolved in dry dichloromethane (20 mL) then cooled to 0 °C. DIBAL-H (5.4 mL, 1M in hexanes) was added dropwise over a period of 45 minutes. The resultant solution was allowed to stir at 0 °C for 2 hours. At such times, the reaction mixture was diluted with dichloromethane (20 mL) and quenched by the dropwise addition of 15% sodium hydroxide solution (15 mL). Dilution with water (10 mL) allowed the formation of a biphasic solution which was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 17:3 → diethyl ether) of the crude residue afforded 7-allyl-6-azaspiro[4.5]decane **480** (281 mg, 0.84 mmol, 55%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.65 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 8.2 Hz), 5.87-5.71 (1H, m), 5.12-5.05 (2H, m), 4.32-4.22 (1H, m), 3.52-3.40 (1H, m), 2.66-2.50 (2H, m), 2.43-2.34 (1H, m), 2.40 (3H, s), 2.16-1.42 (8H, m); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 142.7, 142.5, 142.4, 129.7, 129.6, 126.6, 126.4, 117.6, 69.2, 55.1, 40.7, 40.0, 38.5, 36.5, 36.1, 23.4, 23.2, 21.5, 20.3; IR (neat) ν_{max} = 3070 ($CH_2CH{=}CH_2$), 2947, 2877, 1597 ($CH_2CH{=}CH_2$), 1311 (Ts), 1149 (Ts), 1095 (C—N), 1003 ($C{=}CH_2$), 964, 902 ($C{=}CH_2$) cm^{-1}; HRMS (CI) observed $[M + H_2O - H]^+$ 350.1788, calculated for $C_{19}H_{28}NO_3S$ 348.1790.

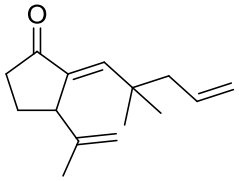
(*E*)-Ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate 481



To a solution of 7-allyl-6-azaspiro[4.5]decane **480** (25 mg, 0.075 mmol) in neat ethyl methacrylate (187 µl, 1.50 mmol) was added Hoveyda-Grubbs 2nd generation ruthenium catalyst (5 mg, 0.008 mmol). The resulting mixture was heated to reflux overnight. The reaction mixture was concentrated. Flash column chromatography (silica gel, elution gradient hexane-ethyl acetate 4:1 → hexane-ethyl acetate 1:1) of the crude residue afforded ethyl 2-methyl-4-(6-azaspiro[4.5]decan-7-yl)but-2-enoate **481** (15 mg, 0.036 mmol, 48%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.65 (2H, d, *J* = 8.4 Hz), 7.25 (2H, d, *J* = 8.1 Hz), 6.70 (1H, t, *J* = 6.8 Hz), 4.37-4.29 (1H, m), 4.18 (2H, q, *J* = 7.0 Hz), 3.55-3.44 (1H, m), 2.88-2.59 (2H, m), 2.41 (3H, s), 2.43-2.34 (2H, m), 2.26-1.94 (4H, m), 1.89 (3H, brs), 1.86-1.41 (7H, m) 1.29 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ_C 168.1, 142.6, 138.5, 138.4, 130.1, 130.0, 129.8, 129.7, 125.9, 72.9, 60.7, 56.3, 38.8, 36.9, 35.1, 34.5, 34.0, 25.9, 25.2, 23.1, 21.5, 14.4, 12.9; IR (neat) ν_{max} = 2947, 2870, 1705 (O=COEt), 1653 (C=C—CO_2Et), 1373 (Ts), 1149 (Ts), 1095 (C—N), 972 (*trans* C=C—CO_2Et), 810 (R_2C=CHR) cm^{-1}; HRMS (FAB) observed [M + H_2O − H]$^+$ 436.2155, calculated for $C_{23}H_{34}NO_5S$ 436.2158.

(*E*)-2-(2,2-Dimethylpent-4-enylidene)-3-(prop-1-en-2-yl)cyclopentanone 519



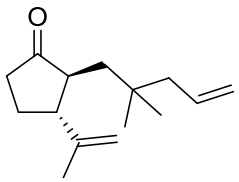
Bromopropene **244** (1.47 g, 12.18 mmol) was dissolved in diethyl ether (150 mL) under argon and cooled to −78 °C. *t*-Butyllithium (12.8 mL, 1.9 M in hexanes) was added dropwise and the resultant solution was stirred at −78 °C for 30 minutes. Copper iodide (1.16 g, 6.09 mmol) was added in one portion and the reaction flask was removed from the cooling bath and stirred at room temperature for precisely 3 minutes. During this time the suspension steadily grew darker towards black. The reaction mixture was recooled to −78 °C and cyclopentenone (500 mg, 6.09 mmol) was added. The resultant brown suspension was stirred at −78 °C for 2 hours. 2,2-Dimethylpentenal (683 mg, 6.09 mmol) was added and the reaction mixture was stirred, warming gradually to room temperature for 12 hours.

The reaction was quenched with saturated aqueous Ammonium chloride (75 mL) and extracted with diethyl ether (3 × 75 mL).

The combined organic layers were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 4:1) of the residue afforded (*E*)-2-(2,2-dimethylpent-4-enylidene)-3-(prop-1-en-2-yl)cyclopentanone **519** (1.03 g, 4.74 mmol, 78%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.55 (1H, t, *J* = 2.6 Hz), 5.76-5.66 (1H, m), 5.05-5.00 (2H, m), 4.79-4.73 (2H, m), 3.01 (1H, ddd, *J* = 16.3, 7.3, 2.1 Hz), 2.77-2.69 (1H, m), 2.55-2.43 (2H, m), 2.23 (1H, dd, *J* = 17.6, 10.0 Hz), 2.17 (2H, brd, *J* = 7.4 Hz), 1.76 (3H, s), 1.13 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 206.7, 146.5, 144.7, 134.6, 134.5, 117.7, 110.0, 47.1, 42.5, 40.3, 36.6, 33.0, 27.1, 27.0, 20.7; IR (neat) ν_{max} 3077 ($CH_2CH{=}CH_2$), 2964, 2916, 2874, 1722 (C=C—C=O), 1641 ($CH{=}CH_2$), 1412 ($C{=}CH_2$), 1364 ($C(CH_3)_2$), 1152 ($C(CH_3)_2$), 995 ($CH{=}CH_2$), 889 ($R_2C{=}CH_2$) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 219.1745, calculated for $C_{15}H_{23}O$ 219.1749.

2-(2,2-Dimethylpent-4-enyl)-3-(prop-1-en-2-yl)cyclopentanone 520



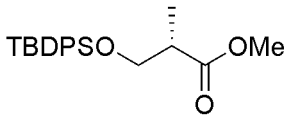
2-(2,2-Dimethylpent-4-enylidene)-3-(prop-1-en-2-yl)cyclopentanone **519** (500 mg, 2.29 mmol) was dissolved in tetrahydrofuran (5 mL) and zinc chloride (468 mg, 3.44 mmol) was added followed by palladium tetrakis(triphenylphosphorane) (5.5 mg, 4.6 μmmol). Tributyltin hydride (800 mg, 2.75 mmol) was added dropwise and the resultant yellow solution was stirred for 1 hour at ambient temperature under argon.

The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with saturated aqueous potassium fluoride (3 × 10 mL), then dried over sodium sulfate, filtered and concentrated.

Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) of the crude residue afforded 2-(2,2-dimethylpent-4-enyl)-3-(prop-1-en-2-yl)cyclopentanone **520** (424 mg, 1.92 mmol, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.82 (1H, ddt, *J* = 17.6, 10.2, 7.4 Hz), 5.04-4.97 (2H, m), 4.79 (1H, dd, *J* = 2.5, 1.4 Hz), 4.77-4.76 (1H, m), 2.68 (1H, ddd, *J* = 18.4, 12.3, 6.5 Hz), 2.52-2.44 (2H, m), 2.17-2.11 (1H, m), 2.03 (1H, dd, *J* = 18.5, 12.3 Hz), 1.98-1.93 (3H, m), 1.77 (3H, s), 1.40 (1H, dd, *J* = 14.3, 7.5 Hz), 1.10 (1H, dd, *J* = 14.2, 9.1 Hz), 0.89 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 219.9, 146.3, 135.4, 117.3, 109.8, 47.8, 47.2, 42.7, 42.3, 41.8, 38.2, 33.3, 27.4, 27.2, 20.9; IR (neat) ν_{max} 3077 ($CH_2CH{=}CH_2$), 2957, 2920, 2870, 1742 (C=O), 1645 ($CH{=}CH_2$), 1409 ($C{=}CH_2$), 1150 ($C(CH_3)_2$), 995 ($CH{=}CH_2$), 912 ($CH{=}CH_2$), 889 ($R_2C{=}CH_2$) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 221.1908, calculate for $C_{15}H_{25}O$ 221.1905.

(*S*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate 539

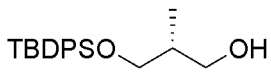


(S)-Methyl 3-hydroxy-2-methylpropanoate **538** (2.14 g, 18.13 mmol) and imidazole (5.48 g, 19.95 mmol) were dissolved in dichloromethane (24 mL) and cooled to 0 °C under argon. TBDPSCl (1.48 g, 21.76 mmol) was added dropwise and the resultant solution was stirred, warming to room temperature overnight.

The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-ethyl acetate 9:1) of the crude residue afforded (*S*)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate **539** (6.45 g, 18.09 mmol, >99%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 (4H, d, *J* = 7.1 Hz), 7.43-7.37 (6H, m), 3.83 (1H, dd, *J* = 9.7 Hz, 8.0 Hz), 3.72 (1H, dd, *J* = 9.3 Hz, 6.2 Hz), 3.69 (3H, s), 2.76-2.68 (1H, m), 1.15 (3H, d, *J* = 7.1 Hz), 1.03 (9H, s); $[a]_D^{22}$ + 6.8 (*c* 1.0, $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 175.5, 135.7, 135.7, 133.7, 133.6, 129.8, 127.8, 66.0, 51.7, 42.5, 26.8, 19.4, 13.6; IR (neat): ν_{max} 2953, 2931, 2858, 1740 (O=COMe), 1471 (CH_2O), 1197 ($C(CH_3)_3$), 1105 (Si—O), 1026 (OMe) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 357.1891, calculated for $C_{21}H_{29}O_3Si$ 357.1886.

(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol 540



(*S*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate **539** (7.80 g, 21.88 mmol) was dissolved in dichloromethane (90 mL) under argon and cooled to 0 °C.

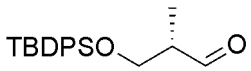
DIBAL-H (48.1 mmol, 48.1 mL, 1M in hexanes) was added dropwise. The resultant solution was stirred warming to room temperature under argon for 1 hour.

A saturated aqueous solution of Rochelle's salt (150 mL) was added for quenching and the resultant biphasic solution was stirred vigorously until the organic phase became clear.

The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient hexane → hexane-ethyl acetate 9:1) of the crude residue afforded (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **540** (7.19 g, 21.88 mmol, 99%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.67 (4H, d, *J* = 7.0 Hz), 7.45-7.38 (6H, m), 3.73 (1H, dd, *J* = 10.1, 4.4 Hz), 3.68 (2H, t, *J* = 5.7 Hz), 3.59 (1H, dd, *J* = 9.8, 7.9 Hz), 2.55 (1H, t, *J* = 5.7 Hz), 2.04-1.96 (1H, m), 1.06 (9H, s), 0.83 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 135.7, 135.7, 133.3, 133.2, 129.9, 127.9, 69.0, 67.9, 37.4, 27.0, 19.3, 13.3; $[a]_D^{25}$ + 4.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3369 (OH), 2958, 2929, 2856, 1471 (CH_2O), 1188 ($C(CH_3)_3$), 1111 (Si—O), cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 329.1934, calculated for $C_{20}H_{29}O_2Si$ 329.1937.

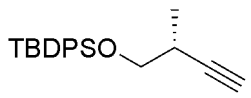
(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanal 541



Oxalyl chloride (6.00g, 47.24 mmol) was dissolved in dichloromethane (320 mL) and cooled to −78 °C under argon. Dimethylsulfoxide (7.38 g, 94.48 mmol) in dichloromethane (10 mL) was slowly added and the resultant solution was stirred at −78 °C for 30 minutes. A solution of (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **540** (7.76 g, 23.62 mmol) in dichloromethane (45 mL) was added dropwise and the resultant solution was stirred at −78 °C for 1 hour. At such time, triethylamine (19.12 g, 188.97 mmol) was added dropwise and the reaction mixture was stirred, venting through bleach, at −78 °C for 15 minutes,

then warmed gradually towards room temperature over 45 minutes. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (500 mL) and the biphasic solution was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with brine, then dried over sodium sulfate, filtered and concentrated to afford (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal **541** as a colourless oil which was used without further purification.

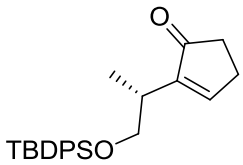
(*R*)-*tert*-Butyl(2-methylbut-3-ynyloxy)diphenylsilane 542[202]



Triphenylphosphine (18.59 g, 70.86 mmol) and zinc dust (4.63 g, 70.86 mmol) were suspended in dichloromethane (40 mL) under argon and cooled to 0 °C. Tetrabromomethane (23.50 g, 70.86 mmol) in dichloromethane (15 mL) was added dropwise and the resultant mixture was stirred at 0 °C under argon for 1.5 hours.
Crude (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **541** (ca. 23.62 mmol) in dichloromethane (20 mL) was added dropwise at 0 °C and the suspension was stirred warming to room temperature overnight.
The reaction mixture was poured into hexane (150 mL) and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* at room temperature then dissolved in anhydrous tetrahydrofuran (50 mL). The resultant solution was cooled to −78 °C under argon. *n*-Butyllithium (24 mL, 2.5 M in hexanes) was added dropwise and the solution was stirred at −78 °C under argon for 1.5 hours.
The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (40 mL) and extracted with diethyl ether (3 x 45 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution hexane) of the crude residue afforded (*R*)-*tert*-butyl(2-methylbut-3-ynyloxy)diphenylsilane **542** (7.15 g, 22.17 mmol, 94% over two steps).
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.69 (4H, appdt, *J* = 7.7, 1.3 Hz), 7.46-7.37 (6H, m), 3.75 (1H, dd, *J* = 9.7, 5.8 Hz), 3.55 (1H, dd, *J* = 9.4, 7.6 Hz), 2.72-2.63 (1H, m),

2.04 (1H, d, *J* = 2.4 Hz), 1.25 (3H, d, *J* = 6.8 Hz), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 135.8, 135.7, 133.7, 129.8, 127.8, 86.7, 69.2, 67.6, 28.9, 26.9, 19.4, 17.5; $[a]_D^{22}$+ 2.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3308 (CCH), 2959, 2932, 2859, 1362 (CCH), 1188 ($C(CH_3)_3$), 1111 (Si—O), 937 (CCH) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 323.1830, calculated for $C_{21}H_{27}OSi$ 323.1831.

(*R*)-2-(1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)cyclopent-2-enone 543

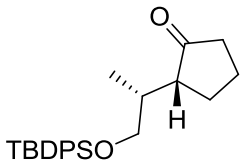


$Co_2(CO)_8$ (1.06 g, 3.10 mmol) was dissolved in dichloromethane (25 mL) at room temperature under argon with vigorous stirring. A solution of (*R*)-*tert*-butyl(2-methylbut-3-ynyloxy)diphenylsilane **542** (1.00 g, 3.10 mmol) in dichloromethane (10 mL) was added dropwise and the resultant dark red solution was stirred at room temperature under argon for 2 hours. The reaction mixture was then filtered through a pad of silica using dichloromethane as the eluent. The filtrate was concentrated and passed through a second pad of silica using 10% diethyl ether in petroleum ether as the eluent. The resulting filtrate was concentrated, taken up in vinyl benzoate (20 mL) and warmed gently to 27 °C under argon. A solution of $NMO.H_2O$ (2.56 g, 18.91 mmol) in dichloromethane (35 mL) was added over the course of 1 hour. The resultant dark solution was stirred at 27 °C under argon overnight. The reaction mixture was filtered through a pad of silica using diethyl ether as the eluent and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) of the crude residue afforded (*R*)-2-(1-(*tert*-butyldiphenylsilyloxy) propan-2-yl) cyclopent-2-enone **543** (846 mg, 2.36 mmol, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.63-7.60 (4H, m), 7.43-7.33 (7H, m), 3.72 (1H, dd, *J* = 9.7, 5.3 Hz), 3.61 (1H, dd, *J* = 9.7, 6.0 Hz), 2.83-2.77 (1H, m), 2.54-2.50 (2H, m), 2.36-2.33 (2H, m), 1.16 (3H, d, *J* = 7.21 Hz), 1.16 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$)

δ_C: 209.5, 158.0, 148.3, 135.7, 133.9, 129.7, 127.7, 66.8, 34.9, 32.7, 27.0, 26.7, 19.5, 16.1; $[a]_D^{22}$ + 1.6 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3071, 2959, 2930, 2859, 1701 (C=C—C=O), 1630 (C=C—C=O), 1200 ($C(CH_3)_3$), 1111 (Si—O), 990 (RC=C—C=O), 926 (C=C—C=O), 824 ($R_2C=CH_2$), 700 (*cis* C=C) cm^{-1}. HRMS: (CI) observed $[M+H]^+$ 379.2092, calculated for $C_{24}H_{31}O_2Si$ 379.2093.

(*R*)-2-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)cyclopentanone 544a

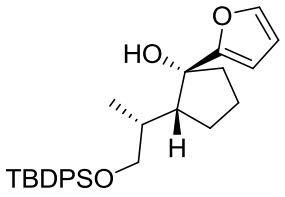


(*R*)-2-(1-(*tert*-Butyldiphenylsilyloxy) propan-2-yl) cyclopent-2-enone **543** (1.42 g, 3.75 mmol) was dissolved in absolute ethanol (20 mL) at room temperature and palladium 5% on charcoal (390 mg) was added. An atmosphere of hydrogen was generated and the resultant suspension was stirred at room temperature under hydrogen for 2 hours. The reaction mixture was passed through Celite® and concentrated before being dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C under argon. Tetrabutylammonium fluoride solution (7.50 mmol, 7.50 mL, 1M in tetrahydrofuran) was added dropwise and the resultant solution was stirred warming to room temperature under argon overnight. The reaction was quenched with water and the aqueous phase was extracted with ethyl acetate (2 x 10 mL), followed by diethyl ether (2 x 10 mL) and finally twice with dichloromethane (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Careful flash column chromatography of the crude residue (silica gel, isocratic elution diethyl ether-hexane 3:1) afforded the desired diastereoisomer (*R*)-2-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)cyclopentanone **182a** (387 mg, 2.72 mmol, 72%)[74] which was dissolved in dichloromethane (15 mL) and cooled to 0 °C under argon. Imidazole (222 mg, 3.26 mmol) was added, followed by TBDPSCl (822 mg, 2.99 mmol) dropwise. The resultant cloudy solution was stirred, warming to room temperature, under argon overnight. The

reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated to afford (*R*)-2-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)cyclopentanone **544a** (1.04 g, 2.72 mmol, >99%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.68-7.64 (4H, m), 7.43-7.36 (6H, m), 3.60 (1H, dd, *J* = 9.9, 5.5 Hz), 3.46 (1H, dd, *J* = 9.9, 8.1 Hz), 2.48-2.29 (3H, m), 2.06-1.89 (3H, m), 1.75-1.59 (2H, m), 1.04 (9H, s), 0.72 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 221.8, 135.7, 134.9, 129.8, 127.8, 67.4, 50.8, 39.2, 34.7, 27.0, 24.0, 20.9, 19.4, 12.3; $[a]_D^{22}$ + 26.8 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3073, 2961, 2859, 1732 (C=O), 1155 ($C(CH_3)_3$), 1111 (Si—O), cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 381.2247, calculated for $C_{24}H_{33}O_2Si$ 381.2250.

(*1R,2R*)-2-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-1-(furan-2-yl)-cyclopentanol 545



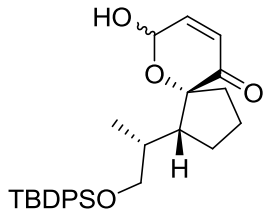
Furan **415** (613 mg, 9.00 mmol) was added to a stirred solution of *n*-butyllithium (9.00 mmol, 3.6 mL, 2.5 M in hexanes) and *N,N,N',N'*-tetramethylethylenediamine (1.05 g, 9.00 mmol) in tetrahydrofuran (40 mL) at −78 °C under argon, and stirring was continued for 1 hour. (*R*)-2-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl) cyclopentanone **544a** (685 mg, 1.80 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to −78 °C under argon. The lithiofuran solution was added to the solution of ketone and stirring was continued under argon, warming to room temperature overnight.

The reaction as quenched with saturated aqueous ammonium chloride and extracted with diethyl ether (3 × 50 mL). Combined organic extracts were dried

over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) afforded (*1R,2R*)-2-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-1-(furan-2-yl)cyclopentanol **545** (638 mg, 1.42 mmol) as an inseparable mixture (>6:1) of desired furfuryl alcohol and unreacted ketone.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.63-7.60 (2H, m), 7.53-7.50 (2H, m), 7.45-7.33 (6H, m), 7.29 (1H, dd, *J* = 1.8, 0.9 Hz), 6.29 (1H, dd, *J* = 3.2, 1.8 Hz), 6.19 (1H, dd, *J* = 3.2, 0.9 Hz), 3.82 (1H, d, *J* = 1.2 Hz), 3.32 (1H, dd, *J* = 10.5, 7.0 Hz), 3.27 (1H, dd, *J* = 10.5, 4.2 Hz), 2.26-2.20 (1H, m), 2.11-2.01 (1H, m), 1.99-1.84 (4H, m), 1.74-1.61 (2H, m), 1.01 (9H, s), 0.84 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 160.4, 140.9, 135.8, 133.3, 129.8, 127.8, 110.4, 104.4, 80.4, 68.3, 52.2, 42.8, 37.2, 29.9, 26.8, 22.1, 19.2, 17.0.

(*1R,5R*)-1-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-7-hydroxy-6-oxaspiro[4.5]dec-8-en-10-one 548

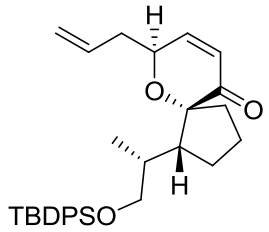


(*1R,2R*)-2-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-1-(furan-2-yl)cyclopentanol **545** (400 mg, 0.89 mmol) was taken up in a mixture of tetrahydrofuran (4.5 mL) and water (1.2 mL) and cooled to 0 °C. Sodium hydrogen carbonate (150 mg, 1.78 mmol) and sodium acetate (73 mg, 0.89 mmol) were added, followed by *N*-bromosuccinimide (175 mg, 0.98 mmol) in one portion. Stirring was continued for 10 minutes.

The reaction was quenched with saturated aqueous sodium thiosulfate (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (10 mL), then dried over sodium sulfate, filtered and concentrated to afford (*1R,5R*)-1-((*R*)-1-(*tert*-

butyldiphenylsilyloxy)propan-2-yl)-7-hydroxy-6-oxaspiro[4.5]dec-8-en-10-one **548** as a colourless oil which was used without further purification.

(*1R,5R,7S*)-7-Allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-6-oxaspiro[4.5]dec-8-en-10-one 549



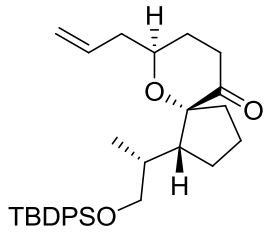
Crude (*1R,5R*)-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)prop-an-2-yl)-7-hydroxy-6-oxaspiro[4.5]dec-8-en-10-one **548** was dissolved in dichloromethane (15 mL) and cooled to 0 °C under argon. Allyltrimethylsilane (204 mg, 1.78 mmol) was added followed by boron trifluoride-diethyl etherate (127 mg, 0.89 mmol) dropwise. The resultant solution was stirred at 0 °C for 30 minutes.

The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 19:1) of the crude residue afforded (*1R,5R,7S*)-7-allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy) propan-2-yl)-6-oxaspiro[4.5]dec-8-en-10-one **549** (285 mg, 0.58 mmol, 65% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.62-7.59 (4H, m), 7.41-7.32 (6H, m), 6.60 (1H, dd, *J* = 10.5, 2.9 Hz), 5.84-5.75 (1H, m), 5.80 (1H, dd, *J* = 10.5, 2.0 Hz), 5.14-5.10 (2H, m), 4.26 (1H, ddd, *J* = 9.7, 7.2, 2.5 Hz), 3.47 (1H, dd, *J* = 9.7, 4.9 Hz), 3.20 (1H, dd, *J* = 9.5, 8.7 Hz), 2.48-2.42 (1H, m), 2.35-2.29 (1H, m), 2.28-2.23 (1H, m) 1.99-1.90 (2H, m), 1.88-1.82 (2H, m), 1.79-1.71 (1H, m), 1.65-1.50 (2H, m), 1.02 (9H, s), 1.01 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 198.8, 149.2, 135.8, 135.7, 134.3, 134.2, 133.8, 129.6, 129.5, 127.7, 127.6, 124.9, 118.1, 89.2, 71.3, 68.3, 50.6, 41.4, 40.9, 36.6, 28.6, 27.0, 22.9, 19.4, 15.8; $[a]_D^{22}$ −64.0 (*c* 0.1, $CHCl_3$) IR (neat): ν_{max}

3071 ($CH_2CH=CH_2$), 2959, 2857, 1678 (C=C—C=O), 1641 ($CH_2CH=CH_2$), 1186 ($C(CH_3)_3$), 1109 (Si—O), 1088 (C—O), 997 ($C=CH_2$), 937, 920 ($C=CH_2$), 698 (*cis* C=C) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 489.2824, calculated for $C_{31}H_{41}O_3Si$ 489.2825.

(*1R,5R,7R*)-7-Allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-6-oxaspiro[4.5]decan-10-one 550



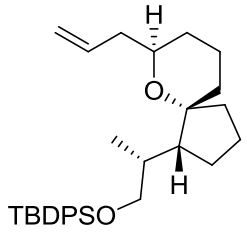
(*1R,5R,7S*)-7-allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-6-oxaspiro-[4.5]dec-8-en-10-one **549** (270 mg, 0.55 mmol) was dissolved in tetrahydrofuran (3 mL) at room temperature under argon. Zinc chloride (113 mg, 0.83 mmol) and palladium tetrakis(triphenylphosphorane) (1.3 mg, 0.001 mmol) were added followed by tributyltin hydride (193 mg, 0.66 mmol) dropwise. The resultant yellow solution was stirred at room temperature for 1 hour.

The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 19:1) of the crude residue afforded (*1R,5R,7R*)-7-allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)-propan-2-yl)-6-oxaspiro[4.5]decan-10-one **550** (244 mg, 0.50 mmol, 90%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.66-7.62 (4H, m), 7.42-7.35 (6H, m), 5.84-5.76 (1H, m), 5.11-5.05 (2H, m), 3.64-3.60 (1H, m), 3.34 (1H, dd, *J* = 9.6, 5.4 Hz), 3.23 (1H, dd, *J* = 9.6, 8.0 Hz), 2.37-2.26 (3H, m), 2.21-2.15 (1H, m), 2.06-1.94 (2H, m), 1.87-1.49 (7H, m), 1.39-1.29 (1H, m), 1.05 (9H, s), 0.99 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 213.8, 135.8, 135.7, 134.7, 134.2, 129.6, 127.7, 117.2, 91.0, 72.8, 68.6, 48.5, 41.7, 41.0, 35.6, 28.2, 27.6, 27.0, 22.5, 19.4, 15.2; $[a]_D^{22}$ +24.0 (*c* 0.1,

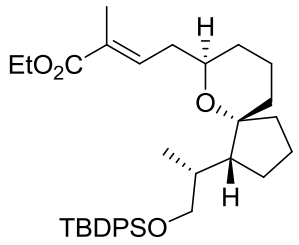
$CHCl_3$); IR (neat): ν_{max} 3071 ($CH_2CH{=}CH_2$), 2859, 2930, 2857, 1715 (C=O), 1643 ($CH_2CH{=}CH_2$), 1186 ($C(CH_3)_3$), 1105 (Si—O), 1086 (C—O), 1007, 997 ($C{=}CH_2$), 941, 914 ($C{=}CH_2$) cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 491.2985, calculated for $C_{31}H_{43}O_3Si$ 491.2981.

((*R*)-2-((*1R,5S,7R*)-7-allyl-6-oxaspiro[4.5]decan-1-yl)propoxy)(*tert*-butyl)diphenylsilane 551



(*1R,5R,7R*)-7-allyl-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)prop-an-2-yl)-6-oxaspiro-[4.5]decan-10-one **550** (120 mg, 0.24mmol) was dissolved in absolute ethanol (1.5 mL) under argon and cooled to 0 °C. Tosyl-hydrazide (91 mg, 0.49mmol) was added in one portion and the resultant solution was heated to 50 °C overnight. The reaction mixture was concentrated and dissolved in dry dichloromethane (2.5 mL) and cooled to 0 °C. DIBAL (0.86 mmol, 0.86 mL, 1M in hexanes) was added dropwise over 1 hour and the resultant solution was stirred for 2 hours at 0 °C. The reaction was quenched with saturated aqueous Rochelle's salt (5 mL) and the biphasic mixture was stirred until the organic phase became clear (~1.5 h). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, then dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 19:1) of the crude residue afforded ((*R*)-2-((*1R,5S,7R*)-7-allyl-6-oxaspiro[4.5]decan-1-yl)propoxy)(*tert*-butyl)diphenylsilane **551** (70 mg, 1:1 mixture desired product 0.088 mmol, 37%) as a colourless oil which was carried forward without further purification.

(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-6-oxa-spiro[4.5]decan-7-yl)-2-methylbut-2-enoate 553

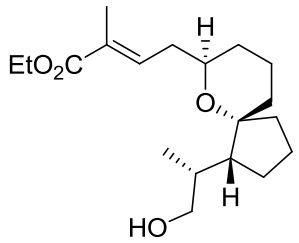


To a deoxygenated solution of ((*R*)-2-((*1R,5S,7R*)-7-allyl-6-oxaspiro[4.5]decan-1-yl)propoxy)(*tert*-butyl)diphenylsilane **551** in ethyl methacrylate was added Grubbs 2nd generation ruthenium catalyst. The resultant green solution was heated to 125 °C overnight.

Excess ethyl methacrylate was removed *in vacuo* and flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) of the resultant crude residue afforded (*E*)-ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-6-oxaspiro[4.5]-decan-7-yl)-2-methylbut-2-enoate **553** (28 mg, 0.050 mmol, 57%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.66-7.64 (4H, m), 7.42-7.35 (6H, m), 6.90-6.87 (1H, m), 4.19-4.13 (2H, m), 3.62-3.57 (1H, m), 3.45 (1H, dd, *J* = 9.5, 5.4 Hz), 3.37 (1H, appt, *J* = 9.5 Hz), 2.49 (1H, br s), 2.37-2.25 (2H, m), 2.08-2.01 (1H, m), 1.91-1.83 (1H, m), 1.85 (3H, s), 1.71-1.49 (8H, m), 1.32-1.17 (3H, m), 1.23 (3H, t, *J* = 7.4 Hz), 1.05 (9H, s), 0.81 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 168.2, 138.7, 135.7, 134.1, 129.7, 128.9, 127.8, 84.5, 72.2, 68.5, 60.5, 40.6, 39.5, 36.3, 36.0, 33.5, 31.4, 27.0, 23.0, 20.4, 20.0, 19.3, 14.4, 12.8, 12.7; $[a]_D^{22}$ +24.0 (*c* 0.1, $CHCl_3$); IR (neat): ν_{max} 3071, 2957, 2932, 2859, 2359, 2330, 1735, 1709 (O=COEt), 1628 (C=C—CO_2Et), 1209 (C(CH_3)$_3$), 1111 (Si—O), 1082 (C—O), 992 (*trans* C=C—CO_2Et) 804 (R_2C=CHR)cm^{-1}; HRMS (CI/ISO) observed $[M+H]^+$ 563.3551, calculated for $C_{35}H_{51}O_4Si$ 563.3557.

(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-hydroxypropan-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate 554

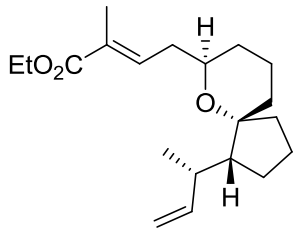


(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-(*tert*-butyldiphenylsilyloxy) propan-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate **553** (25 mg, 0.044 mmol) was dissolved in tetrahydrofuran (1 mL) under argon and cooled to 0 °C. Tetrabutylammonium fluoride solution (0.088 mmol, 88 µl, 1M in tetrahydrofuran) was added slowly. The resultant solution was stirred warming to room temperature over 12 hours.

The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 × 5 mL), diethyl ether (2 × 5 mL) and chloroform (2 × 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-diethyl ether 5:1 → petroleum ether-diethyl ether 1:1) of the crude residue afforded (*E*)-ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-hydroxypropan-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate **554** (12 mg, 0.037 mmol, 84%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.86-6.83 (1H, m), 4.17 (2H, q, *J* = 7.1 Hz), 3.60-3.55 (1H, m), 3.39-3.43 (2H, m), 2.40-2.32 (1H, m), 2.31-2.25 (1H, m), 2.20-2.18 (1H, m), 1.99-1.85 (3H, m), 1.83 (3H, d, *J* = 0.9 Hz), 1.73-1.46 (9H, m), 1.35-1.19 (2H, m), 1.29 (3H, t, *J* = 7.1 Hz), 0.90 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 168.4, 138.7, 129.2, 84.5, 72.8, 68.2, 60.6, 41.3, 40.6, 36.2, 35.9, 34.5, 31.2, 23.9, 20.2, 20.1, 14.5, 13.2, 12.7; $[a]_D^{22}$ +48.0 (*c* 0.05, $CHCl_3$); IR (neat) ν_{max} 3374 (OH), 2938, 2863, 1708 (O=COEt), 1653 (C=C—CO_2Et), 1060 (C—O) cm^{-1}; HRMS: (EI) observed $[M]^+$ 324.2306, calculated for $C_{19}H_{32}O_4$ 324.2301.

(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*S*)-but-3-en-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate 556

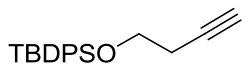


(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*R*)-1-hydroxypropan-2-yl)-6-oxa-spiro[4.5]decan-7-yl)-2-methylbut-2-enoate **554** (10 mg, 0.031 mmol) was dissolved in dichloromethane (1 mL) under argon at room temperature. Dess-Martin periodinane (20 mg, 0.046 mmol) was added and the resultant solution was stirred at room temperature under argon for 5 hours. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated to afford (*E*)-ethyl 2-methyl-4-((*1R,5S,7R*)-1-((*R*)-1-oxopropan-2-yl)-6-oxaspiro[4.5]decan-7-yl)but-2-enoate **555** as a colourless oil which was used without further purification.

Methyltriphenylphosphonium bromide (16 mg, 0.046 mmol) was taken up in tetrahydrofuran (0.5 mL) and cooled to 0 °C under argon. *n*-Butyllithium (0.046 mmol, 18 µl, 2.5 M in hexanes) was added dropwise and the resultant suspension was stirred for 1 hour. Crude (*E*)-ethyl 2-methyl-4-((*1R,5S,7R*)-1-((*R*)-1-oxopropan-2-yl)-6-oxaspiro-[4.5]de-can-7-yl)but-2-enoate **555** was dissolved in tetrahydrofuran (0.5 mL) and cooled to −78 °C. The ylid containing solution was added dropwise to the stirred solution of aldehyde and solution was stirred, warming to room temperature under argon, for 12 hours. A further 1.5 equiv. ylid was added and the reaction mixture was stirred for a further 24 hours. As the reaction had still not gone to completion, 3 equiv ylid was added with stirring at room temperature for 6 h, followed by heating to reflux for 12 hours. Another 3 equiv. ylid was added, followed by heating to reflux for 48 hours was required to obtain complete conversion of the starting material. The reaction mixture was concentrated *in vacuo* and flash column chromatography (silica gel, elution gradient petroleum

ether → petroleum ether-diethyl ether 9:1 → petroleum ether-diethyl ether 17:3) of the crude residue afforded (*E*)-ethyl 4-((*1R,5S,7R*)-1-((*S*)-but-3-en-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate **556** (8 mg, 0.025 mmol, 81% over two steps) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.89-6.85 (1H, m), 5.84-5.77 (1H, m), 4.96-4.91 (2H, m), 4.18 (2H, q, *J* = 7.3 Hz), 3.58-3.53 (1H, m), 2.51-2.48 (1H, m), 2.38-2.25 (2H, m), 2.10-2.08 (1H, m), 1.97-1.90 (1H, m), 1.83 (3H, d, *J* = 0.9 Hz), 1.73-1.54 (8H, m), 1.32-1.26 (3H, m), 1.28 (3H, t, *J* = 7.3 Hz), 1.02 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 168.3, 145.5, 138.7, 129.9, 112.1, 84.6, 72.9, 68.3, 60.5, 44.1, 40.9, 36.3, 35.9, 31.3, 24.2, 20.4, 20.0, 15.1, 14.5, 12.7; $[a]_D^{22}$ +16.0 (*c* 0.05, $CHCl_3$); IR (neat) ν_{max} 2924, 2857, 1711 (O=COEt), 1068 (C—O), 996 (C=CH_2), 910 (C=CH_2) cm^{-1}; HRMS: (EI) observed [M]$^+$ 320.2355, calculated for $C_{20}H_{32}O_3$ 320.2351.

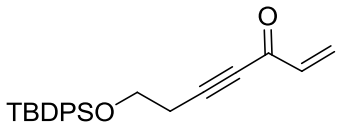
But-3-ynyloxy)(*tert*-butyl)diphenylsilane 558[117]



Butyn-1-ol **557** (556 mg, 7.93 mmol) was dissolved in dichloromethane (9 mL) and DMAP (97 mg, 0.79 mmol) was added. The resultant solution was cooled to 0 °C and Et_3N (1.55 mL, 11.10 mmol) was added followed by TBDPSCl (1.96 g, 7.13 mmol). The resultant solution was then stirred, warming to room temperature, for 12 hours. The crude reaction mixture was filtered through a pad of silica, using dichloromethane as the eluent, and concentrated to afford (but-3-ynyloxy)(*tert*-butyl)diphenylsilane **558** (2.08 g, 6.74 mmol, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.74-7.72 (4H, m), 7.48-7.41 (6H, m), 3.84 (2H, t, *J* = 7.1 Hz), 2.50 (2H, dt, *J* = 7.1, 2.6 Hz), 1.99 (1H, t, *J* = 2.6 Hz), 1.11 (9H, s).

7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-4-yn-3-one 560[117]



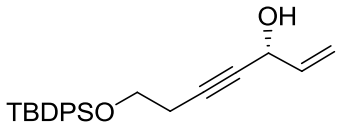
(But-3-ynyloxy)(*tert*-butyl)diphenylsilane **558** (500 mg, 1.62 mmol) was dissolved in tetrahydrofuran (3.3 mL) and cooled to −78 °C. *n*-Butyllithium (1.6 M in hexane, 1.92 mmol) was added dropwise and the resultant solution was stirred for 20 min at −78 °C, the allowed to warm to room temperature. LiBr (71 mg, 0.81 mmol) was added and the suspension was stirred at room temperature for a further 20 min before being cooled to −78 °C. Acryloyl chloride **559** (186 mg, 2.06 mmol) in tetrahydrofuran (0.5 mL) was added dropwise over 1 hour. The reaction mixture was then stirred at −78 °C for 1 hour.

The reaction was quenched at −78 °C with saturated aqueous Ammonium chloride (10 mL) and diethyl ether (10 mL) was added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated.

Flash column chromatography (silica gel, elution gradient petroleum ether → petroleum ether-diethyl ether 9:1) of the crude residue afforded 7-(*tert*-butyldiphenylsilyloxy)hept-1-en-4-yn-3-one **560** (429 mg, 1.18 mmol, 73%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.69-7.67 (4H, m), 7.47-7.37 (6H, m), 6.55 (1H, dd, J = 17.1, 1.0 Hz), 6.38 (1H, dd, J = 17.4, 10.2 Hz), 6.13 (1H, dd, J = 10.2, 1.0 Hz), 3.85 (2H, t, J = 6.6 Hz), 2.66 (2H, t, J = 6.6 Hz), 1.07 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 197.1, 138.1, 136.0, 135.7, 133.7, 133.4, 130.0, 127.9, 92.7, 79.5, 61.6, 26.9, 23.4, 19.3.

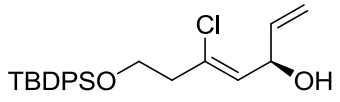
(*R*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-4-yn-3-ol 561[117]



(*R*)-Methyl-CBS (371 mg, 1.34 mmol) was dissolved in tetrahydrofuran (6 mL) and BH_3-THF (1.1 mL, 1.10 mmol) was added. The resultant solution was stirred at room temperature for 30 min before being cooled to −40 °C. 7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-4-yn-3-one **560** (661 mg, 1.83 mmol) in tetrahydrofuran (5 mL) was added dropwise over 20 minutes. The resultant mixture was stirred at −40 °C for 1.5 hours. The reaction mixture was quenched by the addition of methanol (5 mL) and concentrated. Flash column chromatography (silica gel, elution gradient hexane → hexane-ethyl acetate 19:1) of the crude residue afforded (*R*)-7-(*tert*-butyldiphenylsilyloxy)hept-1-en-4-yn-3-ol **561** (397 mg, 1.09 mmol, 60%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.69-7.67 (4H, m), 7.43-7.37 (6H, m), 5.94 (1H, ddd, *J* = 17.0, 10.1, 5.4 Hz), 5.42 (1H, td, *J* = 17.0, 1.3 Hz), 5.18 (1H, td, *J* = 10.1, 1.3 Hz), 4.85-4.80 (1H, m), 3.78 (2H, t, *J* = 7.0 Hz), 2.51 (2H, dt, *J* = 7.0, 2.0 Hz), 1.74 (1H, d, *J* = 6.3 Hz), 1.05 (9H, s).

7-(*tert*-Butyldiphenylsilyloxy)-5-chlorohepta-1,4-dien-3-ol 562[117]



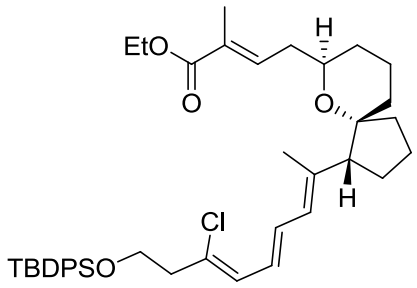
(*R*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-4-yn-3-ol **561** (100 mg, 0.27 mmol) was dissolved in diethyl ether (6 mL) and cooled to −78 °C. Red-Al (≥ 65% wt. in toluene, 132 µl, 0.44 mmol) was added dropwise and the reaction mixture was stirred, warming to room temperature for 12 hours. The reaction mixture was cooled to −78 °C and *N*-chlorosuccinimide (48 mg, 0.36 mmol) was added. The

resultant solution was protected from light and stirred, warming to room temperature, for a further 12 hours.

The reaction was quenched with methanol (2 mL) and concentrated. Flash column chromatography (silica gel, isocratic elution benzene-acetone 100:1) of the crude residue afforded (*R*,*Z*)-7-(*tert*-butyldiphenylsilyloxy)-5-chlorohepta-1,4-dien-3-ol **562** (69 mg, 0.17 mmol, 64%) as a colourless oil.

1H NMR: 7.67-7.64 (4H, m), 7.43-7.37 (6H, m), 5.88 (1H, ddd, *J* = 17.1, 10.4, 5.7 Hz), 5.62 (1H, d, *J* = 7.9 Hz), 5.34 (1H, d, *J* = 17.2 Hz), 5.15 (1H, d, *J* = 10.4 Hz), 5.11-5.08 (1H, m), 3.85 (1H, dd, *J* = 11.9, 5.9 Hz), 2.61-2.50 (2H, m), 1.67 (1H, dd, *J* = 14.7, 3.5 Hz), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 138.0, 135.7, 133.8, 129.8, 128.8, 127.8, 115.4, 70.5, 61.0, 42.8, 27.0, 19.4.

(*E*)-Ethyl 4-((*1R,5S,7R*)-1-((*2S,3E,5R,6Z*)-9-(*tert*-butyldiphenylsilyloxy)-7-chloro-5-hydroxynona-3,6-dien-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate 563

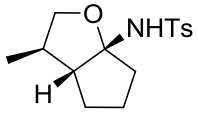


(*E*)-Ethyl-4-((*1R,5S,7R*)-1-((*S*)-but-3-en-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate **577** (7 mg, 0.022 mmol) and Zhan 1B catalyst **523** (5 mg, 0.007 mmol) were dissolved in freeze-thaw degassed dichloromethane (0.5 mL) in a 0.5 – 2 mL microwave vial under argon. (*R,Z*)-7-(*tert*-Butyldiphenylsilyloxy)-5-chlorohepta-1,4-dien-3-ol **562** (23 mg, 0.057 mmol) in freeze-thaw degassed dichloromethane (0.25 mL) was added and the resultant green solution was stirred at 40 °C for 24 hours. At such times, a further portion of Zhan 1B catalyst **523** (5 mg, 0.007 mmol) in freeze-thaw degassed dichloromethane (0.5 mL) was added. The brown solution was stirred at 40 °C for a further 24 hours. The reaction mixture was concentrated and flash column chromatography (silica gel, elution

gradient petroleum ether → petroleum ether-diethyl ether 37:3) of the crude residue afforded (*E*)-ethyl 4-((*1R,5S,7R*)-1-((*2S,3E,5R,6Z*)-9-(*tert*-butyldiphenylsilyloxy)-7-chloro-5-hydroxynona-3,6-dien-2-yl)-6-oxaspiro[4.5]decan-7-yl)-2-methylbut-2-enoate **563** (9 mg, 0.013 mmol, 61%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.66-7.63 (4H, m), 7.42-7.36 (6H, m), 6.70 (1H, tq, *J* = 7.4, 1.3 Hz), 6.48 (1H, dd, *J* = 14.9, 10.8 Hz), 6.40 (1H, dd, *J* = 15.1, 9.9 Hz), 6.17 (1H, d, *J* = 9.9 Hz), 6.02 (1H, d, *J* = 10.8 Hz), 4.20-4.15 (2H, m), 3.85 (2H, t, *J* = 6.5 Hz), 3.67-3.62 (1H, m), 2.74 (1H, dd, *J* = 7.0, 4.0 Hz), 2.65-2.57 (2H, m), 2.21-1.89 (7H, m), 1.88 (3H, s), 1.72-1.63 (9H, m), 1.28 (3H, t, *J* = 7.1 Hz), 1.03 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 170.7, 142.9, 139.2, 139.1, 135.7, 134.9, 132.1, 130.6, 129.8, 129.7, 127.9, 127.8, 127.6, 77.7, 72.0, 61.6, 60.4, 53.3, 43.2, 42.4, 38.9, 36.7, 36.3, 31.4, 30.5, 29.9, 26.7, 20.3, 15.0, 14.6, 12.7; $[a]_D^{27}$ −2.7 (*c* 0.15, CH_3CN); IR (neat) ν_{max} 2957, 2928, 2901, 2855, 1713 (O=COEt), 1263 (*cis* RCH=CHR), 1113 (Si—O), 1084 (C—O), 997 (*trans* C=C—CO_2Et), 966 (C=C), 824 (R_2C=CHR), 741 (CCl), 702 (RC=CR) cm^{-1}; HRMS: (ESI) observed $[M+H]^+$ 675.3605, calculated for $C_{41}H_{56}ClO_4Si$ 675.3631.

4-Methyl-*N*-((3*R*,3a*R*,6a*R*)-3-methylhexahydro-2H-cyclopenta[*b*]furan-6a-yl)benzenesulfonamide 608



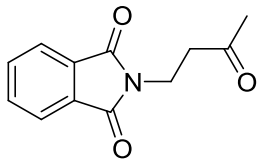
A mixture of alcohols **182** (215 mg, 1.51 mmol) was dissolved in benzene (1 mL) and *p*$TsNH_2$ (388 mg, 2.27 mmol) was added followed by PPTS (38 mg, 0.15 mmol). The reaction mixture was then heated to reflux with Dean-Stark assisted removal of water for 2 hours.

The solution was cooled to room temperature and ethyl acetate (5 mL) was added followed by saturated aqueous sodium hydrogen carbonate (5 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum

ether → petroleum ether-ethyl acetate 9:1) of the crude residue afforded a 5:1 ratio of diastereoisomers in favour of 4-methyl-*N*-((3*R*,3a*R*,6a*R*)-3-methylhexahydro-2H-cyclopenta[*b*]furan-6a-yl)benzenesulfon-amide **608** (242 mg, 0.82 mmol, 54%) as a thick colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.80 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.7 Hz), 5.35 (1H, brs), 3.67 (1H, dd, *J* = 8.6, 7.3 Hz), 2.97 (1H, dd, *J* = 10.6, 8.9 Hz), 2.42 (3H, s), 2.21 (1H, t, *J* = 7.5 Hz), 1.91-1.57 (6H, m), 1.45 (1H, ddd, *J* = 12.2, 5.8, 1.2 Hz), 0.94 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 143.2, 129.5, 127.4, 127.3, 104.9, 73.8, 58.7, 42.6, 40.2, 31.1, 24.7, 21.7, 15.8; IR (neat) ν_{max} 3273, 3023, 2960, 2869, 1726, 1600, 1326, 1306, 1154, 1094, 1045, 1018, 946, 930, 896, 878, 813, 750, 664 cm^{-1}; HRMS: (CI) observed $[M+H]^+$ 296.1315, calculated for $C_{15}H_{22}NO_3S$ 296.1320.

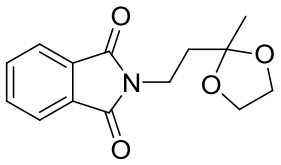
4-Phthalimidobutan-2-one[224]



Phthalimide (18.0 g, 122.34 mmol) was dissolved in ethyl acetate (70 mL) and methyl vinyl ketone (10 mL, 123.27 mmol) was added followed by benzyltrimethylammonium hydroxide (3 mL, 19.57 mmol). The reaction mixture was heated to reflux for 1 h, before being concentrated to afford 4-phthalimidobutan-2-one (24.1 g, 110.95 mmol, 91%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.83 (2H, dd, *J* = 5.5, 3.0 Hz), 7.71 (2H, dd, *J* = 5.4, 3.1 Hz), 3.97-3.93 (2H, m), 2.87 (2H, t, *J* = 7.4 Hz), 2.18 (3H, s).

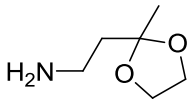
2-Methyl-2-(2-phthalimidoethyl)-1,3-dioxolane[225]



4-Phthalimidobutan-2-one (10 g, 46.04 mmol) was dissolved in benzene (60 mL) and ethylene glycol (7.26 mL, 130.2 mmol) was added followed by *p*TsOH (4.1 g, 23.8 mmol). The reaction mixture was then heated to reflux for 48 hours with Dean-Stark assisted removal of water. The reaction mixture was poured into ice-water and extracted with toluene (3 x 30 mL). The combined organic phase was washed sequentially with saturated aqueous sodium hydrogen carbonate, water and brine before being dried over sodium sulfate, filtered and concentrated to afford 2-methyl-2-(2-phthalimidoethyl)-1,3-dioxolane (8.66 g, 33.15 mmol, 72%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.83 (2H, dd, J = 5.5, 3.1 Hz), 7.70 (2H, dd, J = 5.4, 3.0 Hz), 3.95-3.92 (4H, m), 3.85-3.79 (2H, m), 2.09-2.05 (2H, m), 1.38 (3H, s).

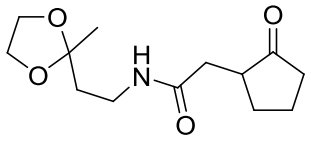
2-(2-Methyl-1,3-dioxolan-2-yl)ethylamine 615[225]



2-Methyl-2-(2-phthalimidoethyl)-1,3-dioxolane (2 g, 7.65 mmol) was dissolved in methanol (20 mL) and hydrazine hydrate (400 mg, 8.00 mmol) was added. The reaction mixture was heated to reflux for 15 h, and then concentrated. The resultant residue was cooled to 0 °C while 20% aqueous sodium hydroxide (5 mL) was added dropwise. The resultant solution was stirred for 30 min before being extracted with $CHCl_3$ (3 x 15 mL). The combined organic phase was washed with water, dried over sodium sulfate, filtered and concentrated to afford 2-(2-methyl-1,3-dioxolan-2-yl)ethylamine **615** (813 mg, 6.20 mmol, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.86-3.82 (4H, m), 2.72 (2H, t, *J* = 7.0 Hz), 1.73 (2H, t, *J* = 7.0 Hz), 1.22 (3H, s).

N-(2-(2-Methyl-1,3-dioxolan-2-yl)ethyl)-2-(2-oxocyclopentyl)acetamide 613[220]

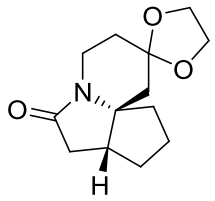


2-(2-Oxocyclopentyl)acetic acid **15** (500 mg, 3.52 mmol) was dissolved in dry dichloromethane (15 mL) and HBTU (1.60 g, 4.22 mmol) was added. 2-(2-Methyl-1,3-dioxolan-2-yl)ethylamine **615** (554 mg, 4.22 mmol) was then added, followed by DIPEA (1.53 mL, 8.79 mmol). The resultant cloudy suspension was allowed to stir, gradually becoming clearer, at room temperature for 16 hours.

The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine, then dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-ethyl acetate 3:1 → petroleum ether-ethyl acetate 1:1) of the crude residue afforded *N*-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-2-(2-oxocyclopentyl)acetamide **613** (772 mg, 3.02 mmol, 86%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.35 (1H, brs), 3.94 (4H, d, *J* = 2.2 Hz), 3.33 (2H, q, *J* = 6.0 Hz), 2.77 (2H, s), 2.54 (1H, dd, *J* = 14.9, 5.1 Hz), 2.47-2.42 (1H, m), 2.35-2.09 (4H, m), 1.94-1.42 (2H, m), 1.29 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 220.6, 170.3, 108.8, 64.5, 46.0, 37.6, 37.3, 36.9, 36.5, 29.6, 23.7, 20.7.

Hexahydro-1H-spiro[cyclopenta[*i*]indolizine-2,2'-[1,3]dioxolan]-6(7H)-one 614[220]

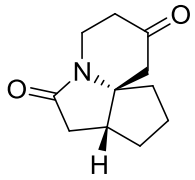


N-(2-(2-Methyl-1,3-dioxolan-2-yl)ethyl)-2-(2-oxocyclopentyl)acetamide **613** (500 mg, 1.96 mmol) was dissolved in toluene (10 mL) and *p*TsOH (20 mg, 0.16 mmol) was added. The resultant solution was heated to reflux with Dean-Stark removal of water for 18 hours.

The reaction mixture was concentrated, then taken up in dichloromethane (10 mL) and washed with saturated aqueous sodium hydrogen carbonate (2 × 15 mL). The organic phase was then washed successively with water and brine. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-ethyl acetate 3:1 → petroleum ether-ethyl acetate 1:1) of the crude residue afforded hexahydro-1H-spiro[cyclopenta[*i*]indolizine-2,2'-[1,3]dioxolan]-6(7H)-one **614** (376 mg, 1.58 mmol, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.08 (1H, dd, *J* = 13.5, 5.1, 1.7 Hz), 3.96 (4H, dd, *J* = 15.2, 5.2 Hz), 2.79 (1H, dd, *J* = 13.5, 2.4 Hz), 2.64 (1H, dd, *J* = 17.8, 10.6 Hz), 2.27-2.19 (1H, m), 2.04 (1H, dd, *J* = 17.8, 3.2 Hz), 1.98-1.93 (1H, m), 1.79-1.35 (9H, m).

Hexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione 387[144]

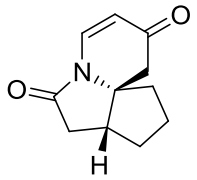


Hexahydro-1H-spiro[cyclopenta[*i*]indolizine-2,2'-[1,3]di-oxolan]-6(7H)-one **614** (200 mg, 0.84 mmol) was dissolved in acetone (4 mL) at room temperature and

concentrated HCl (1 mL) was added. The resultant solution was stirred for 12 hours. The reaction mixture concentrated then treated with water and carefully made basic with solid K_2CO_3. The aqueous mixture was then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-ethyl acetate 3:1 → petroleum ether-ethyl acetate 5:2) of the crude residue afforded hexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **387** (148 mg, 0.77 mmol, 92%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.44 (1H, ddd, *J* = 13.5, 7.6, 1.9 Hz), 2.91 (1H, tdd, *J* = 11.7, 4.8, 1.2 Hz), 2.78 (1H, dd, *J* = 17.9, 10.3 Hz), 2.53 (1H, d, *J* = 13.2 Hz), 2.41-2.30 (4H, m), 2.21 (1H, ddd, *J* = 17.9, 3.4, 1.4 Hz), 2.02-1.93 (1H, m), 1.76-1.69 (1H, m), 1.66-1.60 (2H, m), 1.53-1.40 (2H, m).

7a,8,9,10-Tetrahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione 388[144]



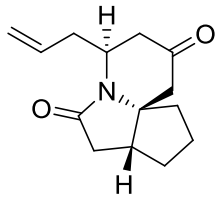
Hexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **387** (100 mg, 0.52 mmol) was dissolved in dichloromethane (5 mL) at room temperature and triethylamine (173 µL, 1.24 mmol) was added followed by TMSOTf (112 µL, 0.62 mmol). The resultant solution was stirred at room temperature for 12 hours. The reaction mixture was quenched by the addition of saturated aqueous sodium hydrogen carbonate (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine, then dried over sodium sulfate, filtered and concentrated. The crude residue was then dissolved in a mixture of MeCN (1.5 mL) and DMSO (0.5 mL). $Pd(OAc)_2$ (139 mg, 0.62 mmol) was added and the resultant black suspension was stirred at room temperature for 36 hours.

The crude suspension was filtered through Celite® and washed with ethyl acetate. The filtrate was concentrated then dissolved in ethyl acetate (10 mL) and washed

with water. The organic phase was washed with brine, and then dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution petroleum ether-ethyl acetate 1:1) of the crude residue afforded 7a,8,9,10-tetrahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **388** (70 mg, 0.37 mmol, 71%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.63 (1H, dd, *J* = 7.8, 0.7 Hz), 5.45 (1H, dd, *J* = 7.8, 0.7 Hz), 2.90 (1H, dd, *J* = 18.7, 10.7 Hz), 2.73 (1H, d, *J* = 15.7 Hz), 2.58-2.53 (1H, m), 2.48 (1H, dd, *J* = 15.6, 0.9 Hz), 2.25 (1H, dd, *J* = 18.7, 6.7 Hz), 1.96-1.61 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 193.7, 171.4, 137.5, 110.0, 71.5, 48.6, 41.2, 38.1, 36.9, 32.6, 24.2.

4-Allylhexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione 390[144]

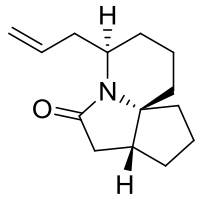


7a,8,9,10-tetrahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **388** (70 mg, 0.37 mmol) was dissolved in dichloromethane (2 mL) and cooled to 0 °C under argon. Allyltributyltin (133 mg, 0.40 mmol) was added, followed by TMSOTf (73 µL, 0.40 mmol). The resultant solution was allowed to stir at 0 °C for 1 h, and then was warmed to room temperature and stirred for a further 15 minutes. 6 M HCl (5 mL) was added to the mixture and the resultant biphasic solution was stirred for 30 minutes. The phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, elution gradient petroleum ether-ethyl acetate 3:1 → petroleum ether-ethyl acetate 5:2) of the crude residue afforded 4-allylhexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **390** (61 mg, 0.26 mmol, 71%) as a colourless oil.

^{1}H NMR 5.75-5.67 (1H, m), 5.11-5.07 (2H, m), 4.70-4.64 (1H, m), 2.74 (1H, ddd, *J* = 17.7, 10.4, 1.3 Hz), 2.57 (1H, dd, *J* = 14.7, 7.8 Hz), 2.45 (2H, brs), 2.44-2.38 (2H,

m), 2.35-2.23 (3H, m), 2.08-2.02 (1H, m), 1.83-1.71 (3H, m), 1.62-1.56 (1H, m), 1.43-1.36 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 206.9, 174.1, 134.1, 118.6, 72.5, 53.2, 49.0, 43.3, 43.1, 39.5, 39.2, 37.4, 34.1, 25.8.

4-Allyloctahydrocyclopenta[*i*]indolizin-6(7H)-one 616



4-Allylhexahydrocyclopenta[*i*]indolizine-2,6(1H,7H)-dione **390** (50 mg, 0.21 mmol) was dissolved in a mixture of dichloromethane (7.5 mL) and isopropanol (22.5 mL). Zinc dust (1.37 g, 21.0 mmol) was added, followed by chloro(trimethyl)silane (2.67 mL, 21.0 mmol). The resultant suspension was stirred at room temperature for 3 hours. The reaction mixture was quenched by the addition of sodium hydrogen carbonate (2.10 g, 25.0 mmol) and the suspension was stirred for 10 min before being filtered and the filtrate concentrated. The residue was dissolved in $CHCl_3$ (10 mL) and washed with saturated aqueous ammonium chloride (15 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. Flash column chromatography (silica gel, isocratic elution dichloromethane-ethyl acetate 9:1) of the crude residue afforded 4-allyloctahydrocyclopenta[*i*]indolizin-6(7H)-one **616** (32 mg, 0.15 mmol, 69%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.75 (1H, tdd, J = 17.1, 10.2, 6.9 Hz), 5.06-5.01 (2H, m), 4.36 (1H, q, J = 7.2 Hz), 2.61 (1H, dd, J = 17.1, 10.3 Hz), 2.40-2.26 (2H, m), 2.20-2.14 (1H, m), 2.10 (1H, dd, J = 17.2, 5.8 Hz), 1.96-1.89 (1H, m), 1.82-1.30 (11H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 173.6, 135.9, 117.1, 70.7, 47.9, 43.6, 38.4, 38.1, 37.9, 37.3, 33.5, 27.3, 25.7, 17.3.

4. References

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