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Adventures in Natural Product Chemistry

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Abstract

Halichlorine, pinnaic acid and pinnarine are a novel family of marine alkaloids, characterised by their common 6-aza-spiro[4.5]decane ring system. First isolated in 1996 by Uemura et al, they have been shown to be biologically active with potential applications in the fields of inflammatory response and tumor metastasis.

This project details the attempted total synthesis of the halichlorine family, focusing on the construction of the 6-aza-spiro[4.5]decane core ring system from cyclopentanone derivatives. Synthesis of the challenging C-14 and C-13 centers was achived diastereoselectively *via* Tsuji-Trost allylations. However, attempts to deliver the C-9 spirocyclic centre were met with failure. Exploration of secondary synthetic routes were also largely unsuccessful.

Secondary projects detail the attempted *N*-allylation of sulfinimines, aza-Heck cyclisations for the synthesis of anatoxin-a analogues and Synthetic methodology for the synthesis of renewable monomers from the seed oil derived fatty acid, vernolic acid.

Acknowledgments

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Finally, to my wife Hannah and daughter Evelyn, without whom I would never have come this far, words cannot express my gratitude.

Abbreviations

BINAP	**2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene**
Boc	*tert*-butyloxycarbonyl
Cbz	Carboxybenzyl
CDI	Carbonyldiimidazole
CV	Column volume
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Bis(dibenzylideneacetone)
DBU	1,8-diazabicycloundec-7-ene
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
MNBA	2-Methyl-6-nitrobenzoic anhydride
MS	Molecular sieves
NOESY	Nuclear Overhauser effect spectroscopy
PCC	Pyridinium chlorochromate
Pyr	Pyridine
Red-Al™	Sodium bis(2-methoxyethoxy)aluminiumhydride
TBDPS	*tert*-Butyldiphenylsilyl ether
TBS	*tert*-Butyldimethylsilyl ether
TMSCl	Trimethylsilyl chloride

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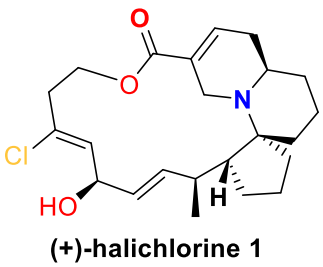
Efforts Towards the Total Synthesis of the Halichlorine Family of Marine Alkaloids

1. Introduction

1.1 Target Natural Products

1.1.1 Halichlorine – Isolation and Biological Activity

In 1996 the Uemura group isolated the novel alkaloid, halichlorine **1** (Figure 1) from the black marine sponge *halichondria okadai* Kadota, harvested from Japanese waters whilst conducting an extensive search for biologically active natural products from marine organisms.[1]



(+)-halichlorine 1

Figure 1 - Halichlorine and the marine sponge *Halichondria okadai* Kadota, image from: http://www.shimoda.tsukuba.ac.jp/~hassei/animals/okadai.html [2]

The *halichondria* family of sponges are highly notable for being a rich source of biologically active molecules, such as okadaic acid[3] (a potent phosphate 1 and 2A inhibitor) and the halichondrins[4] (a group of molecules which exhibit exquisite anticancer activity).

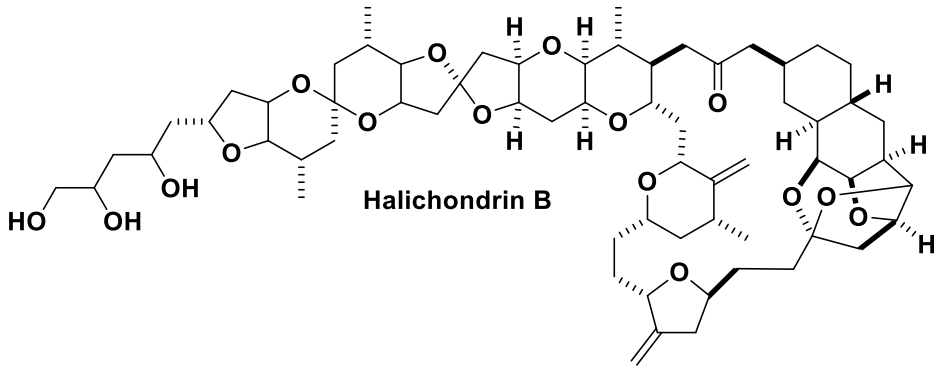
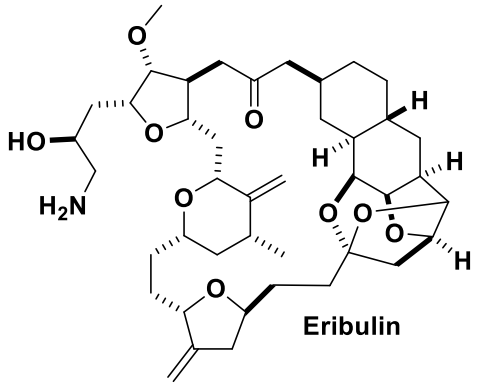


Figure 2 - Halichondrin B

Halichondrin B (Figure 2) specifically has been targeted as a pharmaceutical, leading to the development of the simplified macrocyclic analogue Eribulin (**Error! Reference source not found.**), currently on the market for the treatment of breast cancer and liposarcoma by Eisai Co. ltd.



Biological activity evaluation of halichlorine **1** has shown a selective inhibition of the induced expression of the vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} value of 7 μg mL^{-1}.[5,6] VCAM-1 is a member of the immunoglobulin superfamily of cellular adhesion molecules, which are involved in the migration of leukocytes from circulation into inflamed tissue through adhesion to the very late antigen-4 (VLA-4), as depicted in the multi stage adhesion model (Figure 3, step 3.).

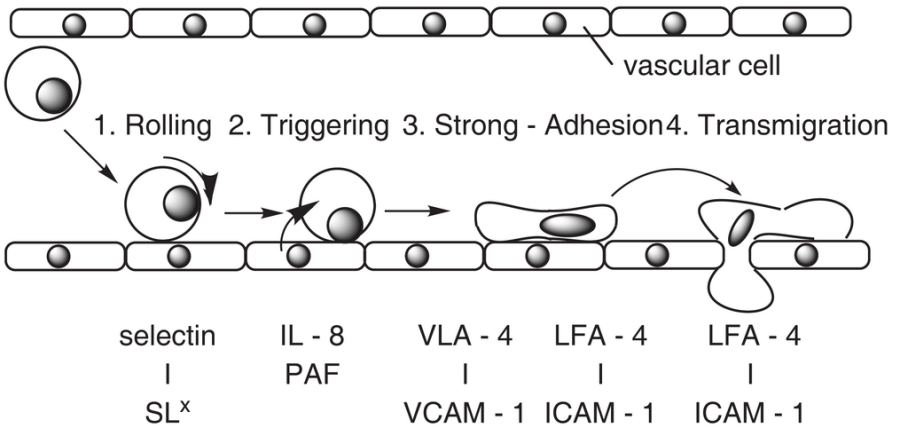


Figure 3 - Model of multi stage adhesion of leukocytes to the vascular cell wall, figure taken from: *Mar. Drugs*, 2004, **2**, 39–54[7]

The up-regulation of VCAM-1 favours the firm adhesion of leukocytes to the endothelium. Once adhered, leukocytes are then able to move through the vascular cells to reach the site of inflammation. This promotion of leukocyte adhesion through the increased expression of VCAM-1 as part of an inflammatory response has implications for the fields of tumour metastasis, angiogenesis and microtubule formation. Thus, halichlorine may be a valuable lead in the discovery and development of novel active pharmaceutical compounds for a number of inflammatory related diseases, including atherosclerosis and rheumatoid arthritis, as well as allergic reactions and metastasis.[8,9]

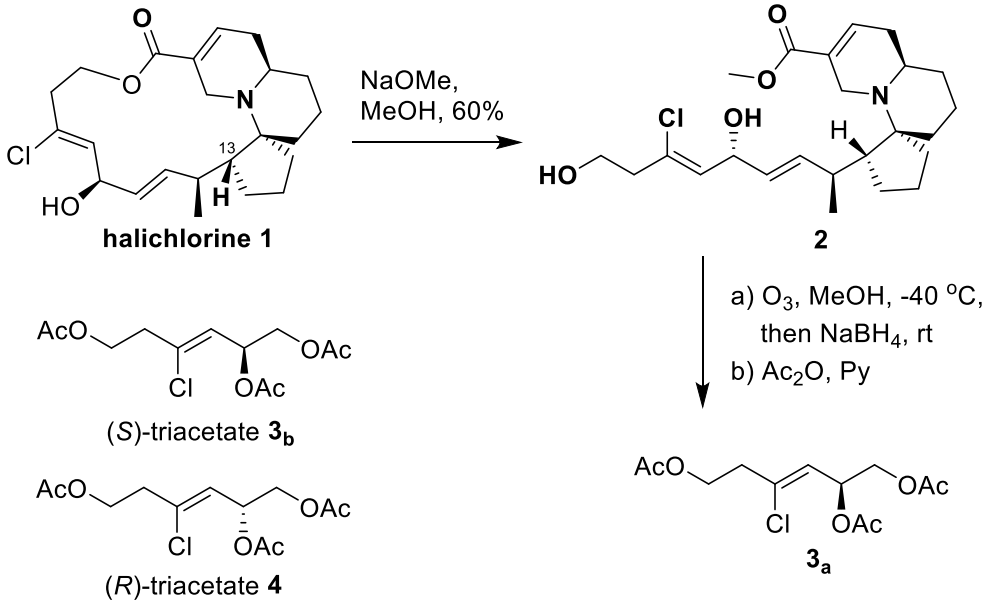
Atherosclerosis is a chronic inflammatory disease, the early stages of which involve the migration and accumulation of leukocytes on the vascular wall, mediated by VCAM-1, resulting in a thickening and hardening of arteries. Halichlorine has been shown to reduce the induced expression of VCAM-1 and monocyte

adhesion by attenuating the activation of the transcription factor NF-κB.[10] NF-κB is believed to be responsible for the atheromatous change in endothelial cells, leading to atherosclerosis. Upon stimulation by inflammatory mediators, endothelial cells transfer NF-κB from the cytosol to the cell nucleus. This results in an up-regulation of the gene expression of inflammatory molecules (VCAM-1), causing adhesion of monocytes to the vascular wall.

Halichlorine has also been shown to inhibit Ca^{2+} ion channels in vascular smooth muscle cells.[11] These cells, which make up the majority of vascular cell walls, are capable of mediating blood pressure by changing the diameter of the blood vessel. Inhibition of the L-type Ca^{2+} ion channels result in a reduction of the intercellular Ca^{2+} ion concentration, which in turn reduces the contraction of the vascular smooth muscle cells. It has therefore been proposed that halichlorine may be valuable for the development of treatments for hypertension.

1.1.2 Structural Elucidation of Halichlorine **1**

The structure and relative stereochemistry of halichlorine was determined by Uemura and co-workers through extensive NMR analysis. The absolute stereochemistry, however, remained unknown until 1998 when the Uemura group reported their investigations of the degradation of halichlorine.[12] Ring opening of halichlorine to **2** and subsequent partial oxidative degradation with ozone gave the fragment $\mathbf{3_a}$ (**Error! Reference source not found.**). Comparison of the degradation product $\mathbf{3_a}$ and the asymmetrically synthesised analogues ($\mathbf{3_b}$ and **4**), synthesised separately from tartaric acid, enabled assignment of absolute stereochemistry of the C-13 side chain by comparison.

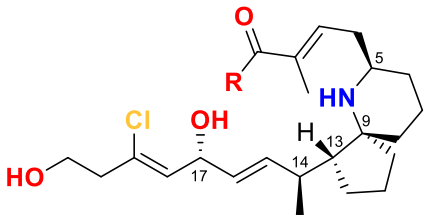


The two side chain enantiomers $\mathbf{3_a}$ and **4** were prepared from D-tartaric acid and L-tartaric acid respectively. Comparison against the retention time of the deg-

radation product **3a** *via* chiral HPLC was employed in order to assign the absolute configuration, with the enantiomer **3a** matching the degradation product **3b.** The absolute configuration of halichlorine was therefore assigned as 5*R*, 9*S*, 13*S*, 14*S*, 17*R*. This assignment was subsequently confirmed by Danishefsky's total synthesis in 2001.[13]

1.1.3 Pinnaic Acids – Isolation and Biological Activity

During the Uemura group's search for biologically active molecules from marine organisms in 1996, they also reported the isolation and structural elucidation of two novel fatty acids, pinnaic acid **5** and tauropinnaic acid **6** (Figure 4).[14] Both **5** and **6** were isolated from the Okinawan bivalve *Pinna muricata,* which is also the natural source of the pinnatoxins and pinnamine, both of which are potent Ca^{2+} ion channel activating toxins.



pinnaic acid 5 R = OH
tauropinnaic acid 6 R = $NHCH_2CH_2SO_3H$

Figure 4 -Pinnaic acids and the marine bivalve *Pinna muricate*, image from: http://liboupat2.free.fr/aquafaun/tropiq/Mollusq/pinna.html [15]

Pinnaic acid **5** and tauropinnaic acid **6** were found to be specific inhibitors of cytosolic phospholipase A_2 ($cPLA_2$) *in vitro* with an IC_{50} of 0.2 mM and 0.9 mM, respectively. The phospholipase A_2 family of lipolytic enzymes catalyse the hydrolysis of intracellular and extracellular membrane phospholipids, with the cytosolic 85-kDa phospholipase ($cPLA_2$) playing an important role in the release of arachadonic acid from the phospholipids in mammalian cells. The release of arachadonic acid is responsible for the mediation of the biosynthesis of biological messenger molecules such as prostaglandins, leukotrienes and thromboxanes, which are involved in the control of inflammatory response. Specific inhibitors of $cPLA_2$ such as pinnaic acid **5** and tauropinnaic acid **6** therefore have the potential to be valuable in the development of drugs compounds for the treatment of inflammation and other related diseases.[16–18]

The structure of pinnaic acid **5** and tauropinnaic acid **6** was elucidated by Uemura and co-workers through ^{1}H and ^{13}C NMR studies. Analysis of the n.O.e correlations and coupling constants gave the relative configurations at C-5, C-9 and C-13 as (*R*), (*S*) and (*R*) respectively, in agreement with the corresponding stereogenic centres of halichlorine. However, due to the low quantity of the pinnaic acids available through isolation (<1 mg from 10 kg of bivalve), it was not possible to assign with certainty the configurations of C-14 and C-17 at the time of isolation. Uemura, however, expressed a preference for the C-14 position as (*R*), the opposite configuration to halichlorine **1**.

The absolute stereochemistry of pinnaic acid **5** remained uncertain until the publication of the Danishefsky group's elegant enantioselective total synthesis of both natural pinnaic acid **5** as well as epi-pinnaic acid, which assigned the C-14 position as (*S*), the same as halichlorine **1**.[19,20]

1.1.4 Azaspirocyclic Core Structure of the Halichlorine Family

Although isolated from two biologically unrelated natural sources, over 1500 km apart, halichlorine **1** and pinnaic acid **5** share a unique core and structural homology, leading to their classification as a novel class of alkaloids characterised by a 6-aza-spiro[4.5]decane ring system (Figure 5). This highly functionalised ring system presents a major synthetic challenge for the chemist. Accordingly, the halichlorine family has attracted attention within the synthetic chemistry community.

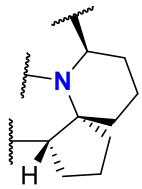
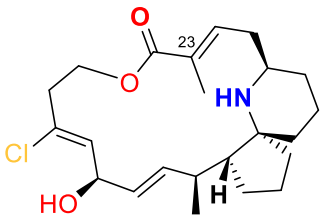


Figure 5- Azaspirocyclic core of the halichlorine family

Due to the similarities between the pinnaic acids **5**, **6** and halichlorine **1**, Uemura has proposed that these natural products may share a biogenetic relationship, possibly originating from a common symbiotic organism or dietary source. This has led to a search for possible biosynthetic intermediates between halichlorine **1** and pinnaic acid **5** from various marine organisms in order to provide evidence of the Uemura groups theory of a relationship between these two compounds.

1.1.5 Pinnarine – Isolation and Biological Activity

In 2011 the Uemura group reported the isolation and structural elucidation of a new member of the halichlorine family, pinnarine **7** (Figure 6).[21] The new alkaloid **7** was isolated from the sponge *halichondria okadai Kadota* (from which halichlorine **1** was isolated), appearing to provide evidence for the proposed biogenetic pathway between halichlorine **1** and pinnaic acid **5**.



(+)-pinnarine 7

Figure 6 – Pinnarine **7**

In the original report, only 0.5 mg of pinnarine **7** was isolated from 80 kg of sponge, along with 3.8 mg of halichlorine **1**. The structure of **7** was assigned by comparison of the ^{1}H and ^{13}C NMR spectra of halichlorine **1** and HRMS. The ^{1}H NMR spectra of **7** resembled that of halichlorine **1** except for the displacement of the C-23 methylene to a methyl group, demonstrated by ^{1}H-^{1}H COSY correlations and backed up by the mass spectrometry showing two hydrogen atoms more than halichlorine. Further NMR studies were unable to provide additional data due to the limited amount of sample. However, synthesis of pinnarine **7** was achieved from an authentic sample of pinnaic acid sodium salt **8** (Figure 7).[22] Macro-lactonisation using 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-dimethylaminopyridine (DMAP) at room temperature gave pinnarine **7** in a 74% yield. The ^{1}H, ^{13}C NMR spectra, and chromatographic behaviour

matched those of naturally isolated pinnarine, confirming the proposed structure. Furthermore, using synthetic (+)-pinnarine, the comparison of circular dichroism spectroscopic data to the natural pinnarine corresponded, indicating the same absolute configuration to halichlorine.

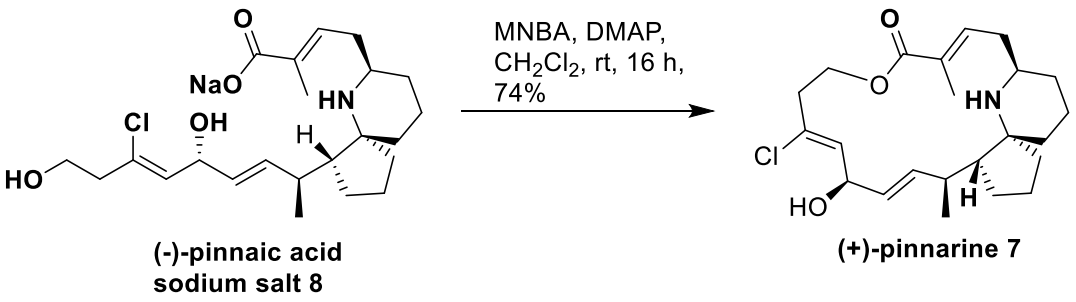


Figure 7 - Synthesis of pinnarine **7**

The conversion of pinnaic acid to pinnarine with the same absolute chemistry as halichlorine allowed Uemura to propose that the three molecules may be steps along a common biosynthetic pathway, with a novel ring closing transformation converting pinnarine to halichlorine. However, with no further related molecules to the family discovered and the biological origin remaining a mystery, the biosynthesis remains speculative.

1.2 Previous Synthetic Studies Towards Halichlorine **1**, Pinnaic Acid 5 and Pinnarine **7**

Since the isolation and structural elucidation of both halichlorine **1** and pinnaic acid **5** by Uemura and co-workers, there has been a substantial number of papers reported on their total and formal synthesis, as well as model studies of synthetic approaches to the 6-aza-spiro[4.5]decane core ring system.

In 2005 Clive and co-workers published an extensive review on the synthetic efforts to date, including their own synthesis,[23] followed in 2012 with a narrative review of the Clive group's synthetic efforts in the book series, "Strategies and Tactics in Organic Synthesis".[24]

Total syntheses of either halichlorine **1** or pinnaic acid **5** have been completed by the groups of Danishefsky,[13,19] Heathcock,[25] Uemura,[22,26,27] Zhao[28] and Clive[29] and Aoyogi[30]. Formal syntheses have been reported by Kibayashi,[31] Martin,[32] Zhao,[33] Tomioka,[34] Tu and Wang[35] and the Stockman group[36]. Finally, many model studies have been undertaken on the core ring structure of the halichlorine family and related molecules.

The following review is an overview of the first total synthesis of halichlorine **1** by Danishefsky, as well as major approaches to the construction of the azaspirocyclic core ring system of the halichlorine family, and key bond forming steps, from subsequent total syntheses. For a more comprehensive review of the synthetic history of the halichlorine family, Clive's 2005 review is recommended.[23]

1.2.1 The First total Synthesis of (+)-Halichlorine **1**, Danishefsky

The first synthetic efforts towards the core structure of halichlorine were reported by Danishefsky in 1999 (Figure 8),[37] describing an asymmetric synthesis of the C-1 – C-15 spiroquinolizidine core of halichlorine in twelve steps. Starting from Meyer's asymmetric lactam **11**,[38] made by heating γ-keto acid **9** with D-(-)-phenylglycinol **10**. Lactam **12** was then prepared *via* treatment of **11** with an excess of allyltrimethylsilane and titanium tetrachloride. Reductive debenzylation followed by *N*-Boc protection furnished the lactam **13**. The C-14 methyl group was installed *via* a stereoselective methylation from the convex face to yield **14**. Direct conversion of **14** to ring opened alcohol **16** proved unsuccessful, instead requiring hydrolysis to the enantiomerically pure acid **15** with LiOH, followed by $NaBH_4$ reduction of the mixed anhydride, furnishing alcohol **16**. The primary alcohol **16** was then protected as its TBDPS ether **17**, setting the stage for the construction of the heterocyclic spirocyclic ring system (Figure 8).

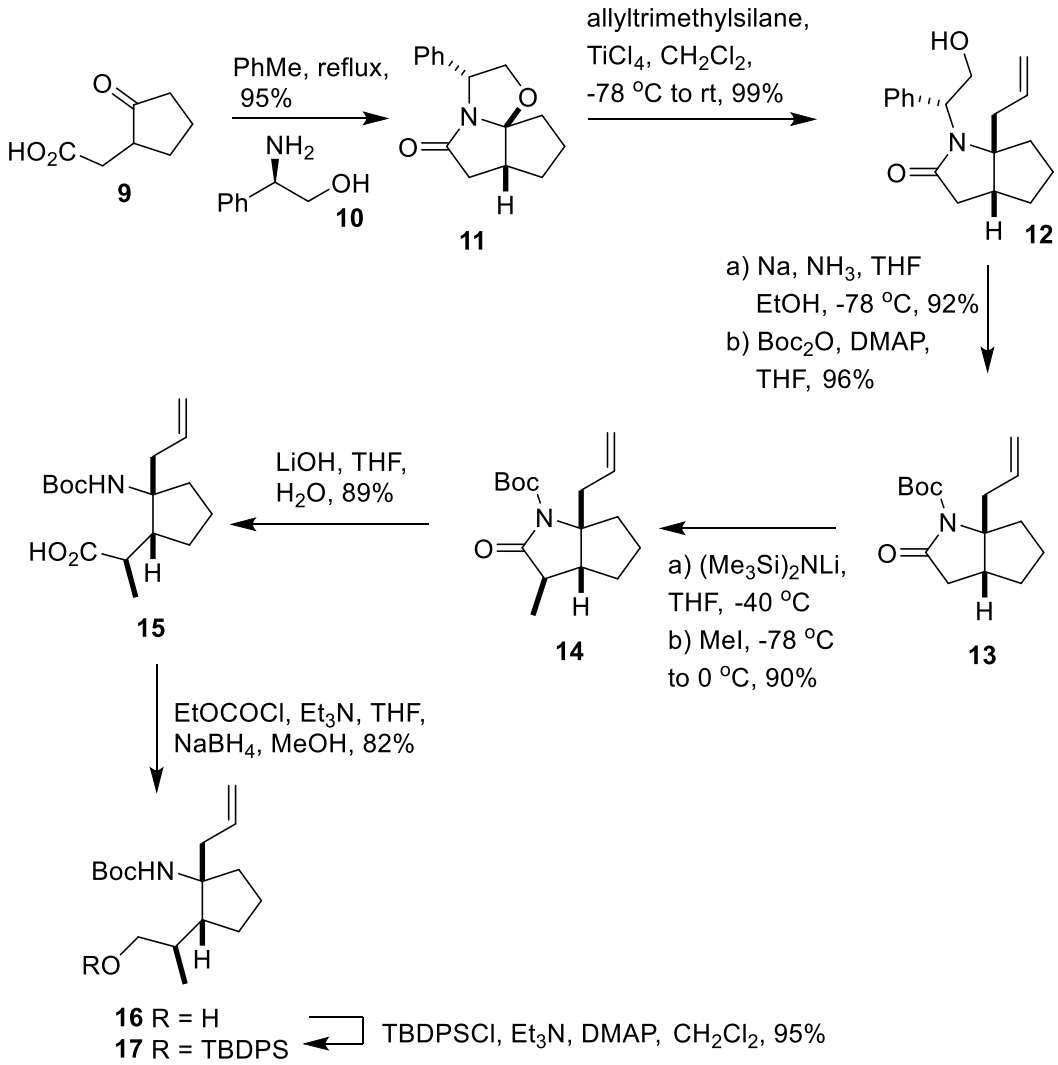
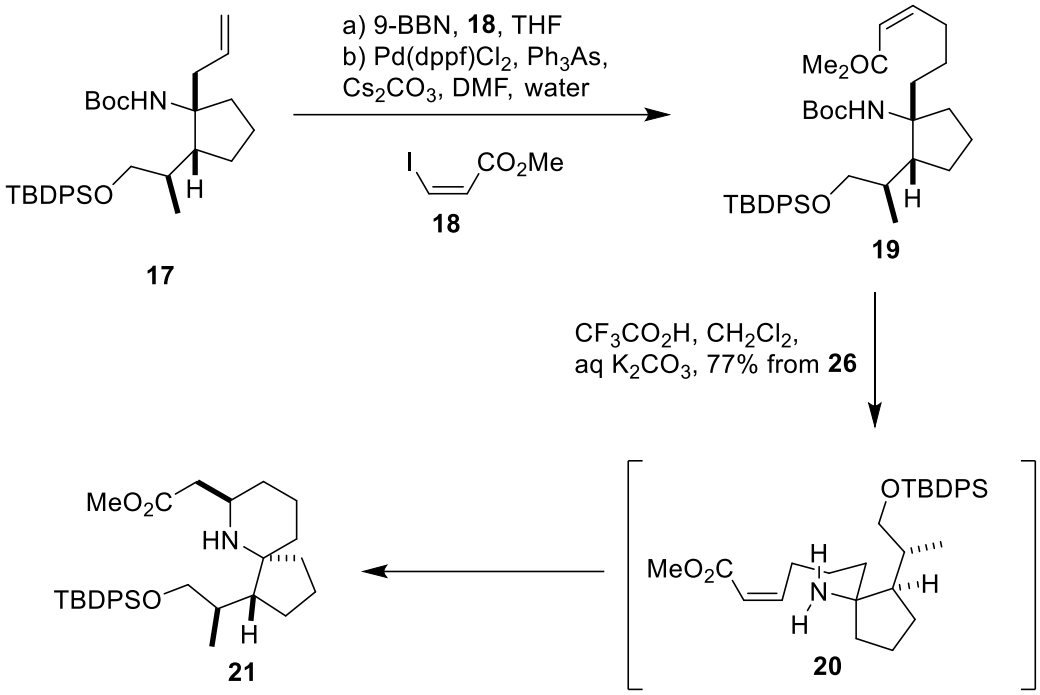


Figure 8 - Danishefsky's synthesis part 1

In order to construct the heterocyclic ring system, elongation of the allyl side chain followed by an intramolecular addition cyclisation were employed. Hydroboration of **17** followed by Suzuki-Miyaura cross-coupling with *Z*-3-iodoacrylate **18** furnished **19**. Boc deprotection of **19** with TFA and subsequent neutralisation with K_2CO_3 resulted in a spontaneous intramolecular Michael addition to afford **21** as a single isomer with a yield of 77% from **17**. The high stereochemical control was rationalised by a chair-shaped transition state **20** where the larger substituents assume pseudo-equatorial positions to give the correct stereochemistry (**Error! Reference source not found.**).



Finally, transformation of **21** to the fully functionalised spiroquinolizidine **24** was achieved firstly by a Claisen condensation of **21** with *tert*-butyl acetate to yield β-keto ester **22**. A Mannich reaction with formaldehyde then afforded the ring-closed product **23** as a mixture of diastereoisomers and tautomers. Conversion of the β-keto ester **23** to the corresponding α,β-unsaturated ester **24** was achieved using Ganem's protocol using ($Cp_2Zr(H)Cl$).[39] Selective deprotection of **24** was achieved *via* two routes to give the primary alcohol **25** or amino acid **26**, using HF-pyridine or under acidic conditions respectively (Figure 9).

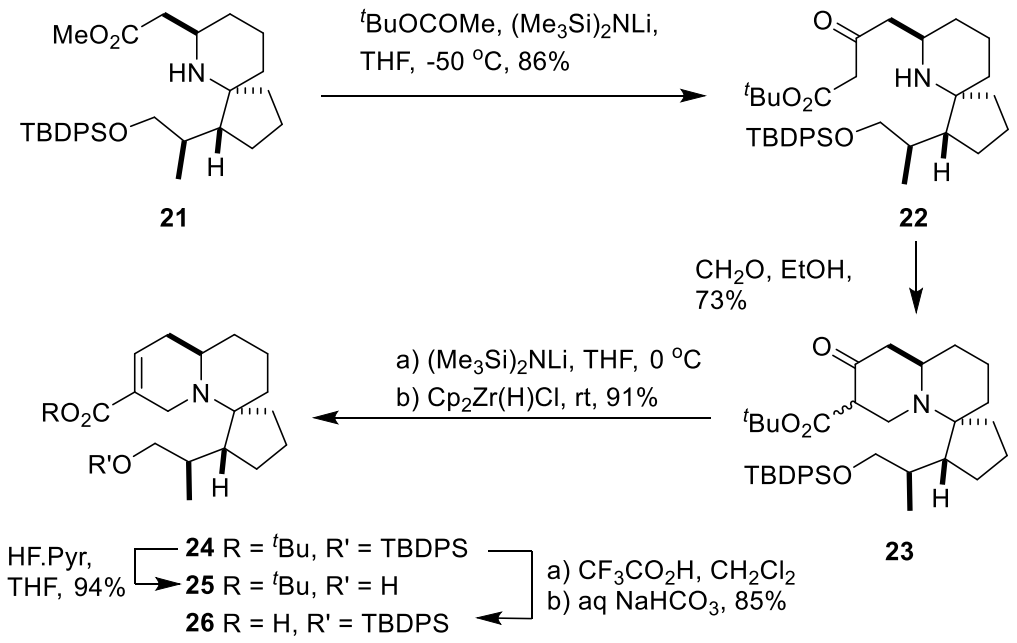


Figure 9 - Danishefsky's synthesis part 3

Soon after publication of their synthesis of the halichlorine spiroquinolizidine core **26**, Danishefsky published the completion of their total synthesis of (+)-halichlorine **1** from **25** (Figure 10).[13] Oxidation of the deprotected alcohol **25** to the aldehyde **25** proved challenging, with tetra-*n*-propyl ammonium perruthenate (TPAP) and excess *N*-methylmorpholine *N*-oxide (NMO) in acetonitrile proving successful without purification due to the epimerisation of **27** during silica gel chromatography. Attempts to conduct Horner-Wadsworth-Emmons olefination on **27** was met with failure or complete racemisation of the C-14 position. However, conversion of **27** to the alkyne **28** using the Gilbert reagent was achieved with only traces of epimerisation (<5%) at the C-14 position observed.[40] Hydrozirconation of **28** and subsequent metal exchange with zinc afforded **29**, which underwent coupling with **30** in the presence of Soai's amino alcohol **31**.[41,42] The product **32** was afforded as a 4:1 mixture of the desired C-17(*R*) diastereomer and its *S* epimer. TBDMS protection of both the alcohol and

carboxylic acid and selective deprotection of the carboxylic acid with ammonium fluoride gave **33**. Macrocyclisation under Keck's conditions followed by separation of the C-17 epimers gave **34**.[43] Finally desilylation with HF.pyridine released (+)-halichlorine **1**, completing the first total synthesis of halichlorine in a total of 21 linear steps.

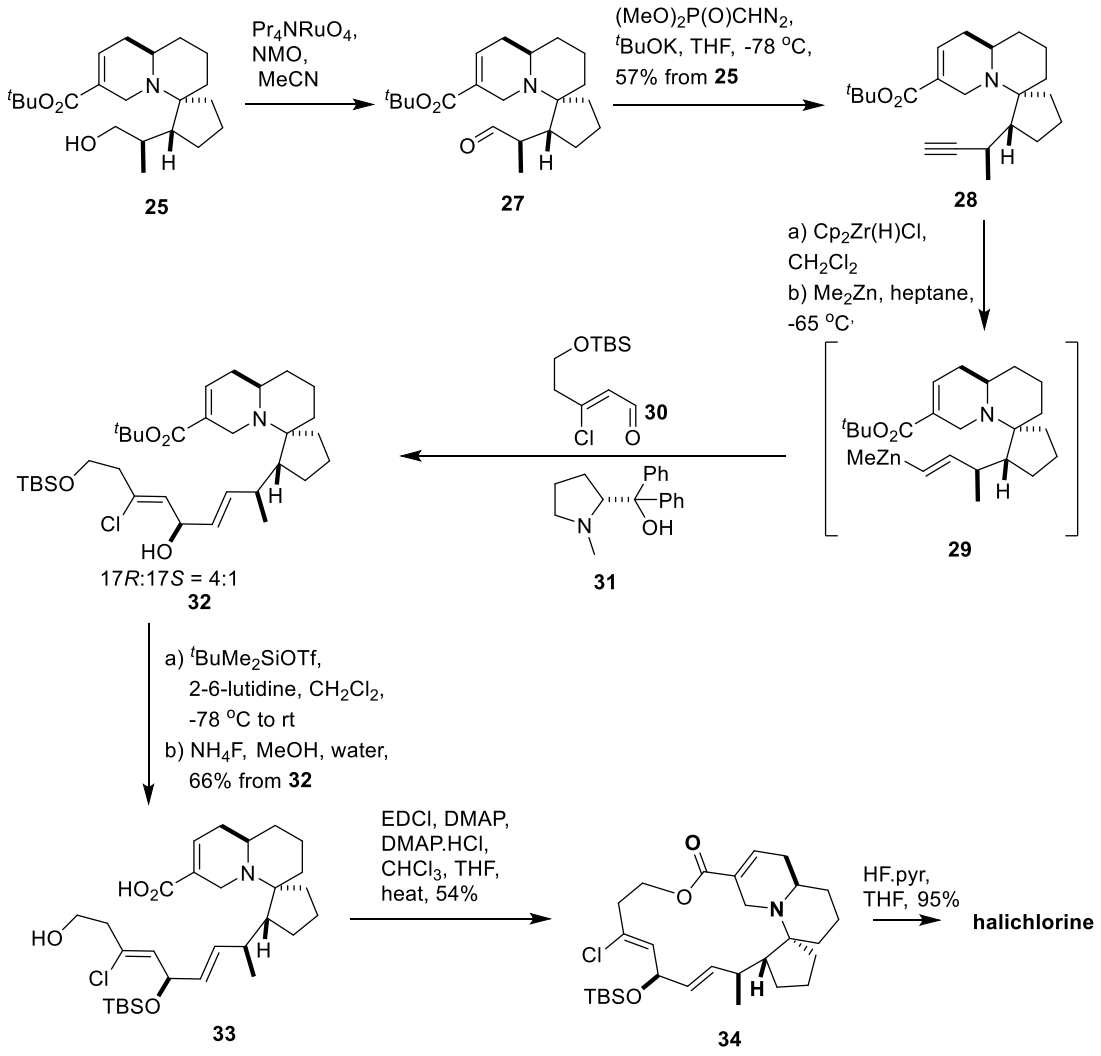


Figure 10 - Danishefsky's synthesis part 4

Close comparisons of the spectroscopic data, mass spectrometry and chromatographic profiles of synthetic halichlorine **1** with the naturally isolated product

were in agreement, confirming Uemura's previously reported absolute stereochemistry.[1]

With the synthesis of halichlorine under their belt, the Danishefsky group focused their attention on pinnaic acid. With the C-14 and C-17 stereocenters remaining unassigned in the natural product, a synthetic route which allowed access to all four potential isomers was desired in order to determine the absolute stereochemistry of pinnaic acid. In 2001 Danishefsky published his preliminary investigations into such a synthesis of pinnaic acid, building on the experience and intermediates gained from the total synthesis of halichlorine.[19,20] Compound **17**, from the total synthesis of halichlorine, was taken forward with the C-14 methyl group set corresponding with natural halichlorine. Hydroboration of **17** with 9-BBN followed by palladium catalysed cross-coupling with the vinyl iodide **35** gave **36**. Boc deprotection then treatment with DBU resulted in a stereoselective cyclisation to **37** with the *E*-geometry, analogous to the intramolecular Michael addition employed for the synthesis of halichlorine. Desilylation to the unprotected alcohol followed by oxidation to the corresponding aldehyde was unsuccessful. However, after considerable experimentation protecting the secondary amine with a trifluoroacetyl group gave **38** allowing for desilylation with HF to **39** allowed for oxidation to the aldehyde **40** (Figure 11).

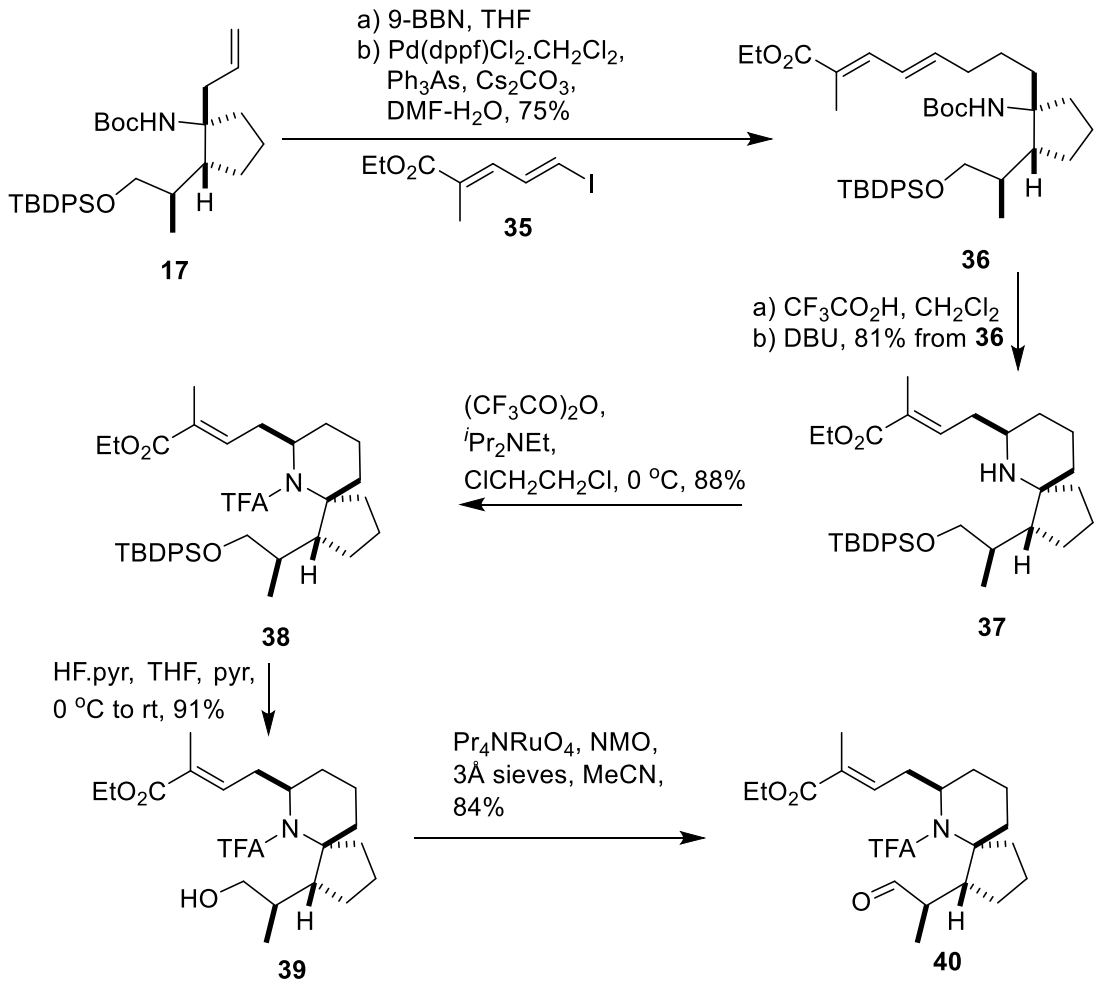
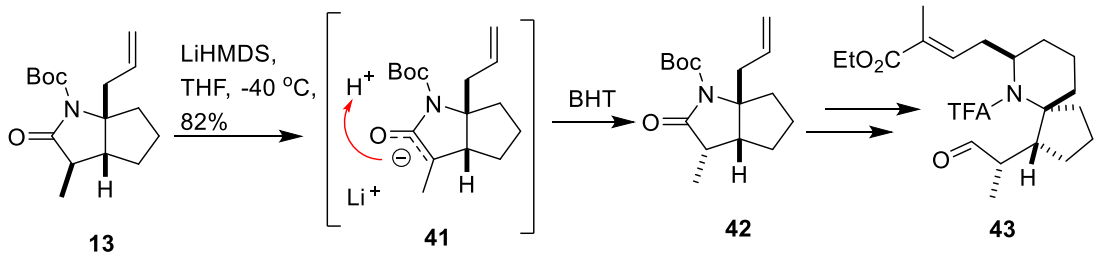


Figure 11 - Danishefsky's synthesis part 5

Synthesis of the *S* C-14 epimer of **40**, **43** was then achieved through inversion of the C-14 methyl group of lactam **13**. Deprotonation of **13** and kinetic quenching with 2,6-di-*t*ert-butyl-4-methylphenol afforded the inverted product **42**. Conversion to the C-14 epimer **43** was achieved *via* the previously described route (Figure 12).



13 41 42 43

Figure 12 - Danishefsky's synthesis part 6

Synthesis of the two C-14 epimer intermediates then allowed for completion of the synthesis of pinnaic acid as well as its three other unnatural C-14/C-17 epimers. Firstly, synthesis of natural pinnaic acid was achieved in five steps from **40.** Condensation of the known Weinreb phosphonate **44**[44] with the C-14(*R*) isomer **40** proved problematic, with the reaction not reaching completion and separation of the product **45** from the starting material **40** proving difficult (Figure 13). The crude mixture was therefore reduced with either (*R*)- or (*S*)-alpine hydride to give **46** in ca. 30% yield over two steps after separation. Both the silyl ether and nitrogen were deprotected to give **47** using HF.pyr, which was subsequently TFA deprotected to **48** and hydrolysed to pinnaic acid **5**. **5** was later found to be the natural pinnaic acid, however substantially more synthetic work was required to make this assignment with the C-17 alcohol groups absolute stereochemistry unknown.

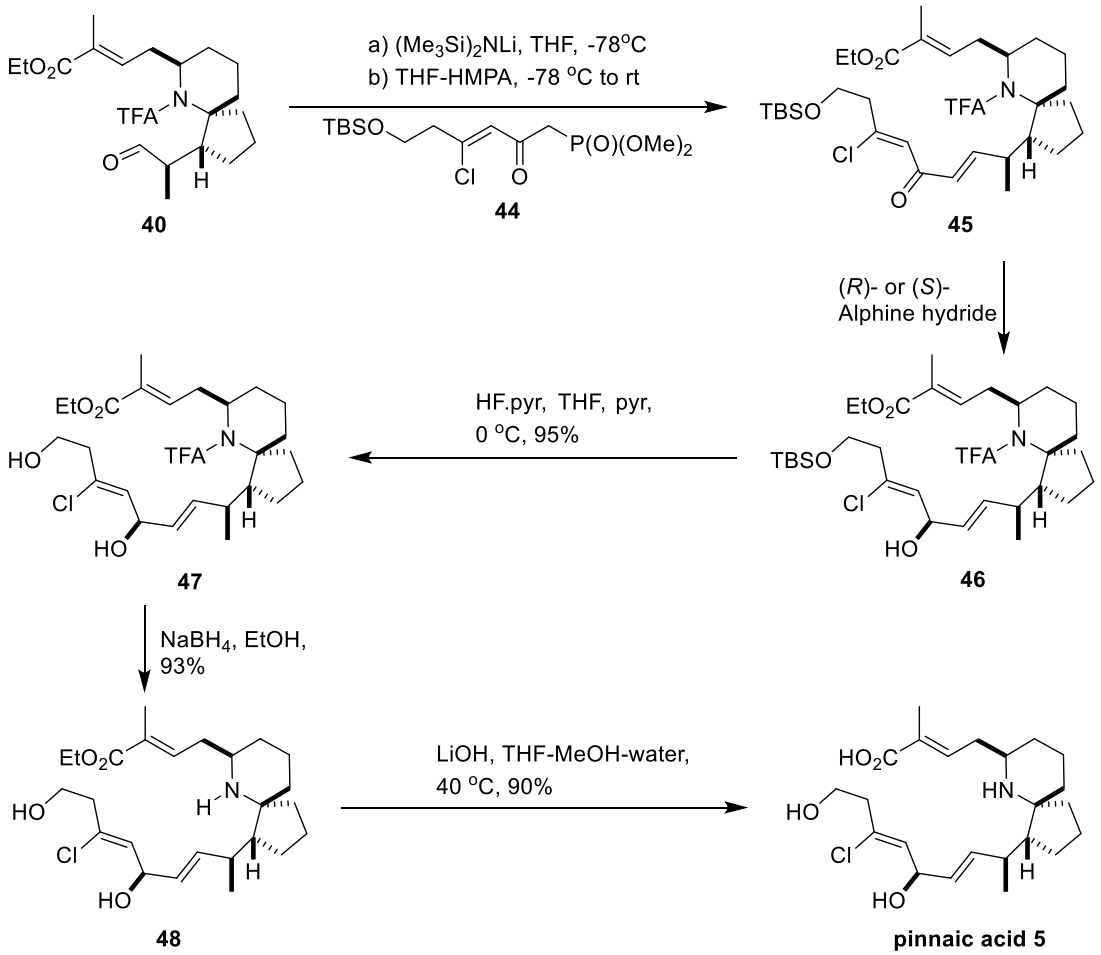


Figure 13 - Danishefsky's synthesis part 7

The assignment of absolute stereochemistry was aided by the synthesis of the opposite C-17 isomer. Luche reduction of **44** with $NaBH_4$ gave the opposite C-17 intermediate epimer **49** which was converted to C-17-epi-pinnaic acid with the opposite C-17 geometry to pinnaic acid **5**, *via* the same synthetic steps as with the natural pinnaic acid (Figure 14).

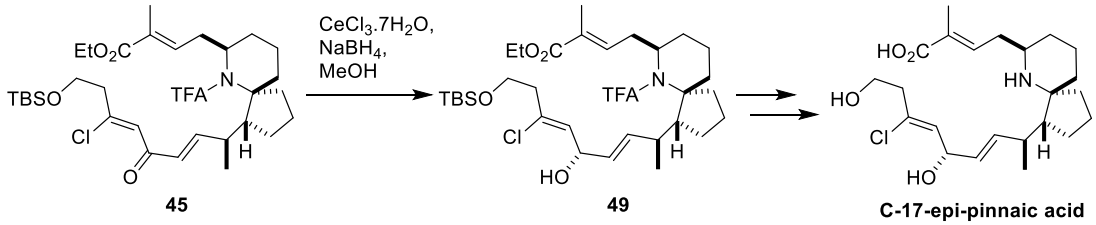


Figure 14 - Danishefsky's synthesis part 8

Preparation of the remaining two C-14(*R*) isomers was achieved once again by condensation of C-14 intermediate epimer **43** with **44** to give a mixture of product **50** and starting material **43**. Reduction of the mixture gave a separable mixture of the C-17 isomers **51a** and **51b** with a ratio of (1.7:1). Taken forward individually, **51a** and **51b** gave the corresponding C-14-epi-pinnaic acid and C-14-C-17-epi-pinnaic acid respectively, by the previously described method (Figure 15).

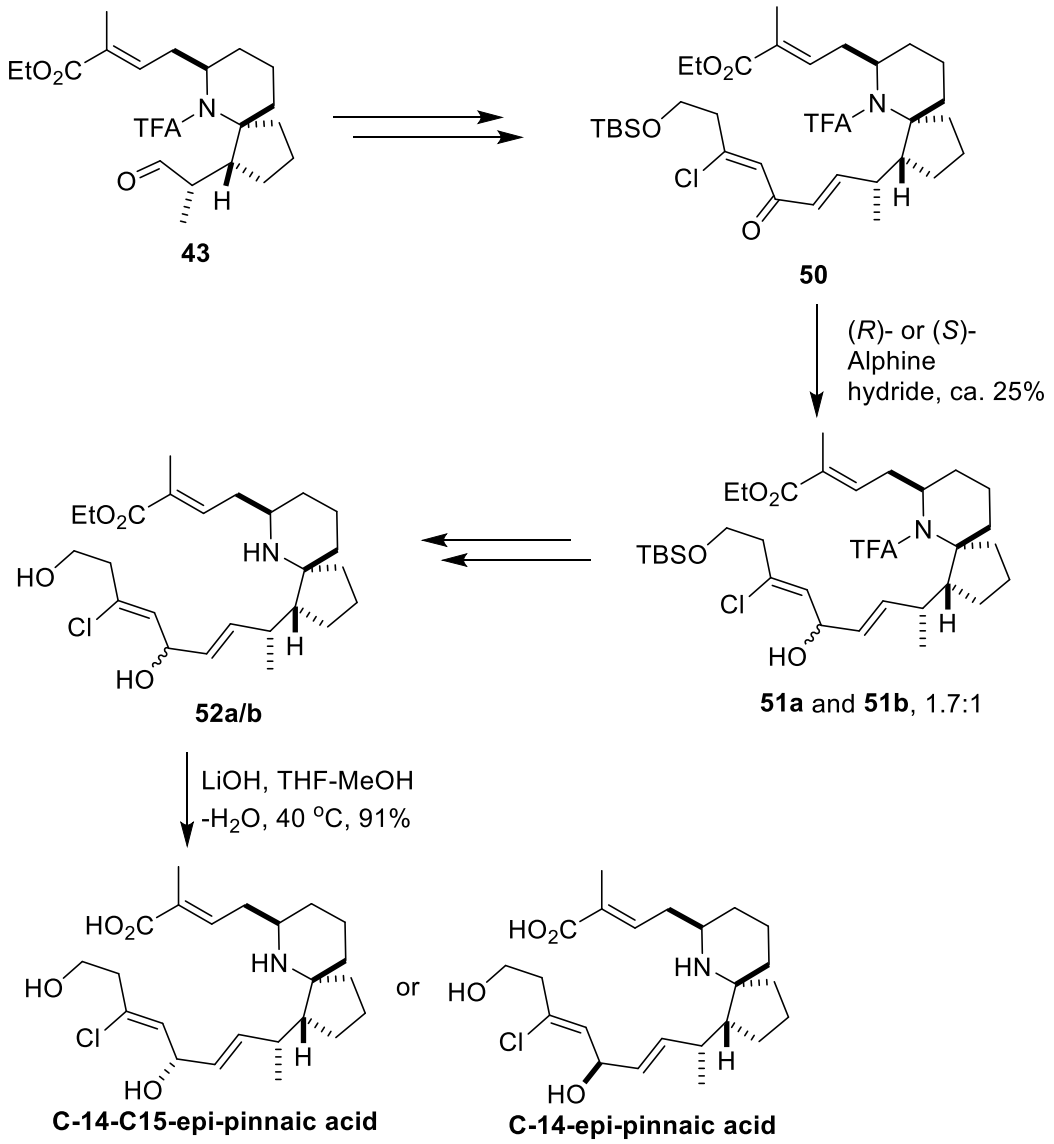


Figure 15 - Danishefsky's synthesis part 9

Synthesis of all four of the potential epimers of natural pinnaic acid that were in question enabled a definitive assignment of the stereochemistry of pinnaic acid to be made. The ^{1}H NMR analysis indicated **5** to be the natural pinnaic acid in comparison with its epimers. With the C-14 position now assigned as *S,* degradation of the synthetic material was undertaken *via* ozonolysis and reduction

to **5**, which corresponded exactly with the degradation product previously prepared by the Uemura group, with a configuration of *R* at the C-17 position. Thus, natural pinnaic acid was assigned as C-14(*S*) and C-17(*R*) (Figure 16).

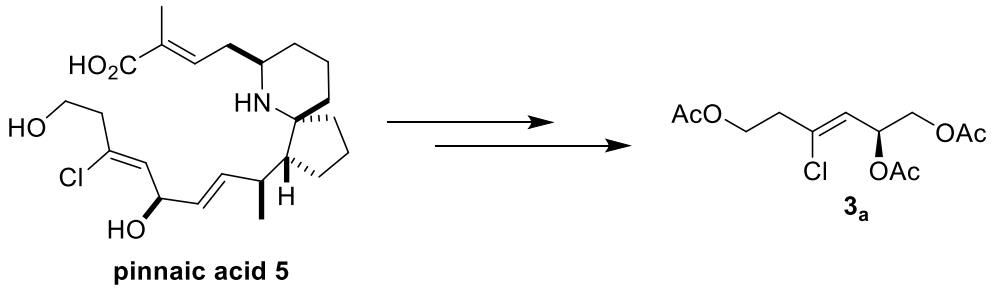


Figure 16 - Danishefsky's synthesis part 10

Danishefsky's synthesis represents a real tour de force of synthesis, with many of the approaches deployed remaining a mainstay in the works of others in subsequent synthesis. In particular, the intramolecular Michael addition approach to the formation of the spirocyclic ring junction elegantly delivers the desired stereochemistry and has been subsequently deployed by many other attempts at the synthesis of halichlorine, demonstrating its synthetic effectiveness.

1.2.2. Heathcock's total Synthesis of (±)-Halichlorine

Reporting in 2004, the Heathcock laboratory was the next to publish a total synthesis of both halichlorine and the pinnaic acid as racemates (Figure 17).[25] Utilising a largely linear synthesis route to construct the core ring system of the

halichlorine family, Heathcock was then able to use the common late stage intermediate compound **59**, to successfully synthesis halichlorine and pinnaic acid.

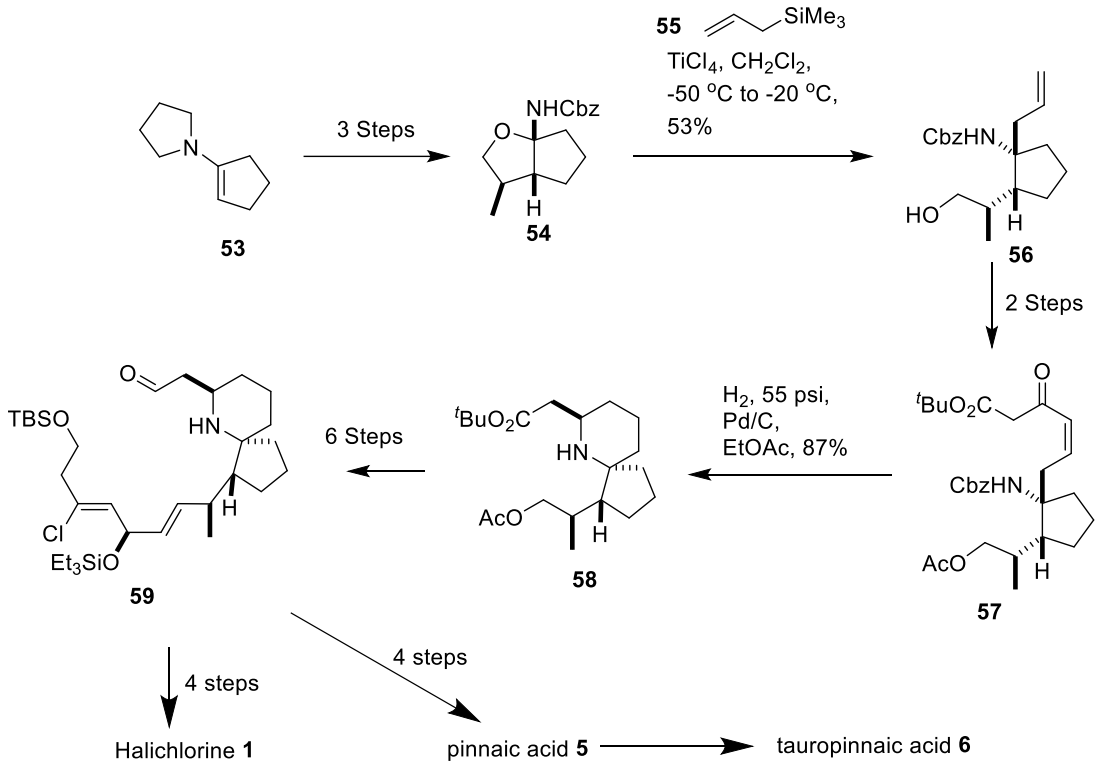


Figure 17 - Heathcock's total synthesis of halichlorine

Acylammonium ion precursor **54** was prepared according to an already published procedure with a C-14 epimer ratio of 6:1 from 1-cyclopentenylpyrrolidine **53** in 3 steps.[45] Treatment of **54** with $TiCl_4$ then allyltrimethylsilane **55** gave **56**, setting the geometry at the spirocyclic carbon. **56** was converted to the (*E*)-enone **57** *via* acetylation of **56** and subsequent olefin cross metathesis, ready for ring closing of the spirocycle. Cbz deprotection and hydrogenation of the double bond with palladium on charcoal resulted in a spontaneous cyclisation to **58**

as a single isomer, a step highly analogous to the cyclisation deployed in Danishefsky's synthesis. Synthesis of **58** completes construction of the core spirocyclic ring system and C-14 methyl position of halichlorine.

A further 6 steps converted the spirocyclic intermediate **58** into the late stage intermediate **59** which was successfully utilised in the synthesis of halichlorine (in a further 4 steps), Pinnaic acid (4 steps), and tauropinnaic acid (5 steps).

With the successful synthesis of racemic (±)-halichlorine, which was found to be crystalline, the first X-ray crystal structure of halichlorine was obtained. The crystallography data confirmed a *cis* ring fusion as was previously predicted by Danishefsky.[46] This, along with the synthesis of both pinnaic acids and halichlorine from the same late stage intermediate, further confirmed the relative stereochemistry configurations of the natural products.

1.2.3. Uemura's total Synthesis of Pinnaic Acid and Halichlorine

Since the Uemura group's original isolation of halichlorine and pinnaic acid in 1996 they have maintained a consistent presence amongst groups working on the synthetic chemistry of halichlorine and its related compounds. To date the Uemura group has published a model synthesis of the spirocyclic core of pinnaic acid in 1999,[47] a total synthesis of (±)-pinnaic acid (based on their previous model synthesis),[26] synthesis of the tricyclic core of halichlorine,[48] an asymmet-

ric total synthesis of pinnaic acid,[22] and finally an enantioselective total synthesis of both halichlorine and pinnaic acid in 2014.[27] The Uemura lab has contributed a substantial portion of the work on the synthetic efforts towards the halichlorine family.

Uemura's first efforts centred around the synthesis of the azabicyclic core of pinnaic acid **66** (Figure 18), with erroneous stereochemistry at the C-14 position (as the natural product had yet to be clearly defined). Starting from the SAMP hydrazone **60**, lithiation and then reaction with the Michael acceptor **61** gave the product **62** as a single isomer after removal of the auxiliary by ozonolysis. Setting the stereochemistry of the C-14 position (erroneously), as well as preparing the cyclopentane portion of the spirocyclic ring system. Protection of the aldehyde **62** as a *p*-methoxyphenyl ether gave **63** over 2 steps. Alkylation of **63** was achieved with complete facial selectivity using prenyl bromine to yield **64**, setting the geometry of the spirocyclic carbon. In a further 5 steps the ester was converted to Cbz protected amine *via* hydrolysis then a Curtius rearrangement, and the pendent chain installed in the previous step was extended and functionalised, furnishing **65**. Catalytic hydrogenation of **65** gave the spirocyclic intermediate **66** in an excellent 93% yield, in a ring closing step once again analogous to those employed by Danishefsky and Heathcock. This completed the model synthesis of the pinnaic acid core.

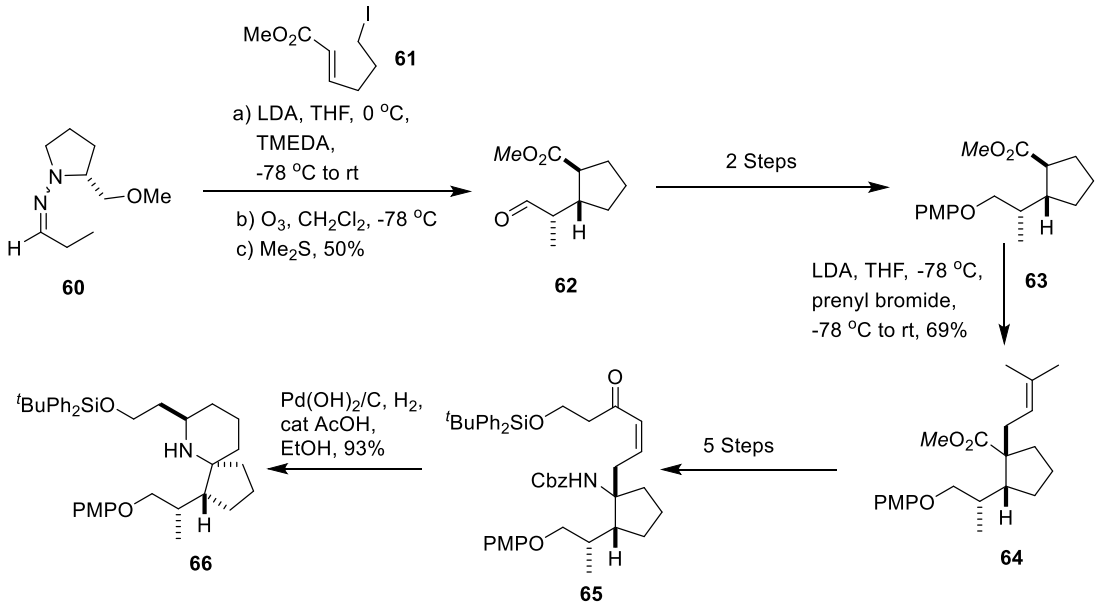


Figure 18 - Uemura's synthesis part 1

In 2003 the Uemura group published their completion of synthetic efforts towards (±)-pinnaic acid **5**,[26] working from the azabicyclic core system **67** synthesised in largely the same method as their previously reported core **66**, but now using the correct C-14 geometry for natural halichlorine as reported by Danishefsky (Figure 19).[13] In a further 6 steps Uemura was able to convert **67** to the intermediate **68**, the racemate of intermediate **49**, synthesised during Danishefsky successful synthesis of pinnaic acid **5**, completing the formal synthesis of (±)-pinnaic acid.

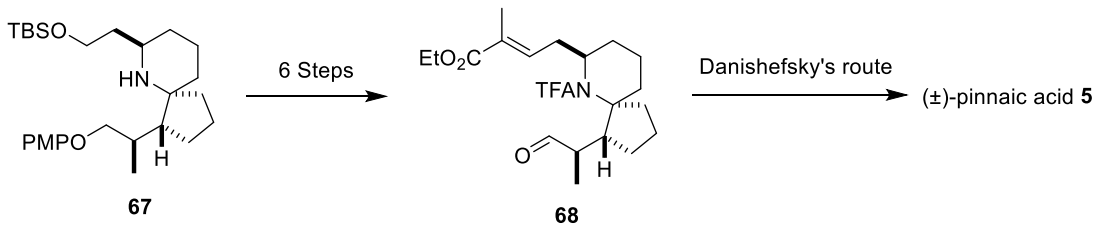


Figure 19 - Uemura's synthesis part 2

As well as their work towards the total synthesis of (±)-pinnaic acid, the Uemura group simultaneously published preliminary work on the core structure of halichlorine.[48] Building upon their synthesis of (±)-pinnaic acid, the starting point was the previously synthesised racemic intermediate **69**,[26] which was converted **70** in 2 steps *via* ozonolysis and subsequent Horner-Wadsworth-Emmons olefination to extend the pendent chain and then reduction to form the bicyclic intermediate **70**, as seen in the previous synthetic approaches. However it is notable that a catalyst loading of 50 mol% was required to afford the cyclised product (Figure 20). Preparation of the intermediate **71** ready for closing of the 3rd ring of halichlorine's core was completed in 4 steps. Grubbs II catalysis effectively furnished the fully cyclised intermediate **72** which was then cleaved in 2 steps to the target aldehyde **73,** finishing the synthesis of the halichlorine core ring system.

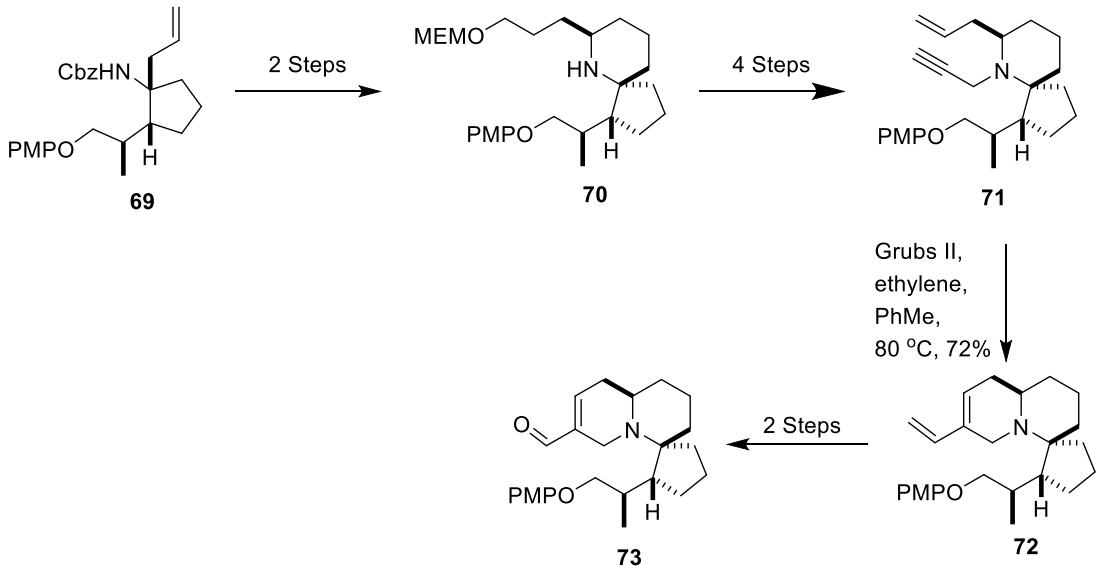


Figure 20 - Uemura's synthesis part 3

In 2007 the Uemura group published a complete asymmetric total synthesis of pinnaic acid using a new cross metathesis approach for both the upper and lower side-chains and using (*R*)-(+)-pulegone **74** as a chiral starting material, setting the C-14 methyl position from the start (Figure 21).[22] The functionalised cyclopentanone **75**, (previously prepared in 5 steps from (*R*)-(+)-pulegone), was converted *via* [3+2] cyclisation to the *anti* product **77** with a high degree of stereoselectivity. Condensation of the bulky hydroxylamine *o*-mesitykenesulfonylhydroxylamine (MSH) (**78**) with the ketone **77** and subsequent Beckmann rearrangement gave the bicyclic lactam **79**, with the correct geometry for the formation of the spirocyclic carbon centre. Conversion of **79** to **80** was achieved in 2 steps *via* the hydrazine. Cbz protection of the lactam and subsequent ring opening with $LiBH_4$ gave the enantiomerically pure alcohol **81**. Extension of the upper pendant side chain was achieved in 4 steps *via* a Horner-Wadsworth-Emmons olefination to afford the (*E*)-enone **82**.

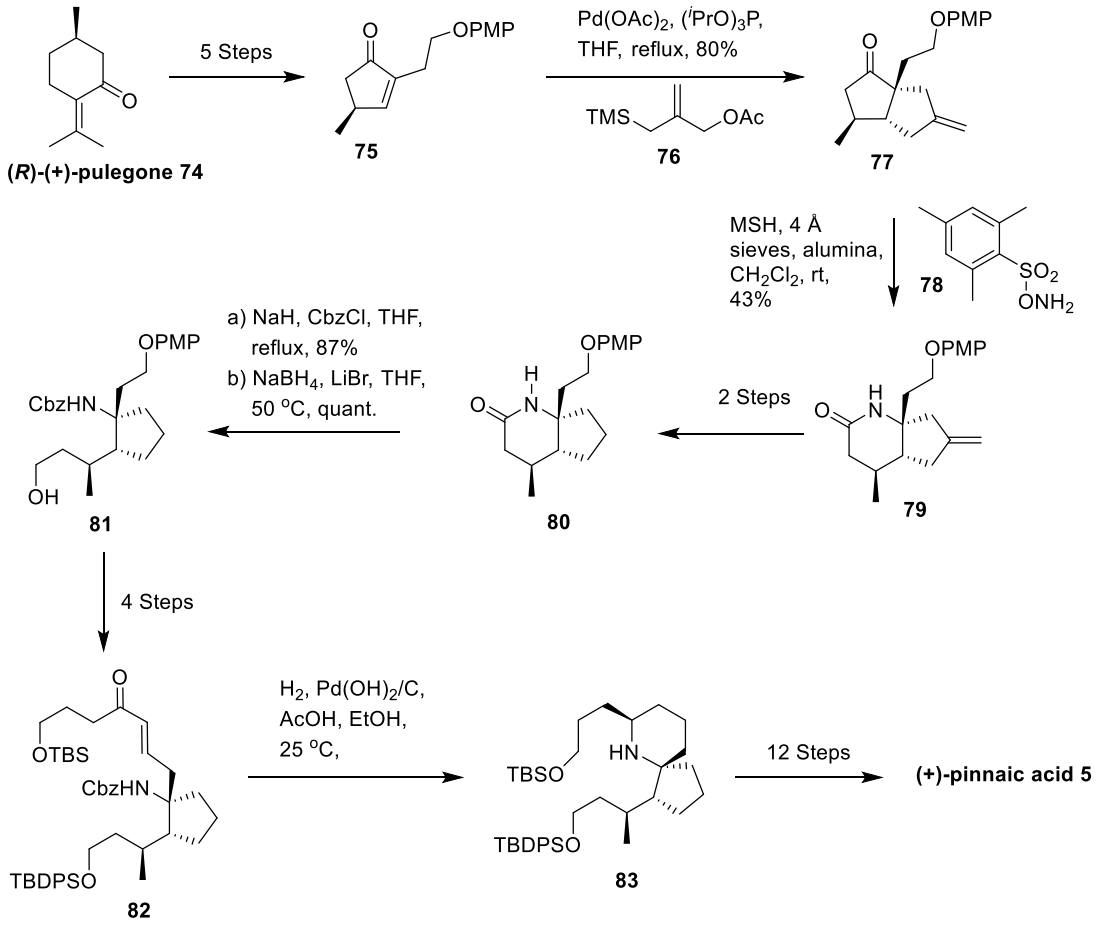


Figure 21 - Uemura's synthesis part 4

Tandem hydrogenation/cyclisation was employed as in previous syntheses, effectively delivering the piperidine ring system **83**, completing the synthesis of the core ring system of pinnaic acid. Completion of the synthesis of pinnaic acid **5** was completed in a further 12 steps to extend the upper pendant chain *via* Grubbs-Hoveyda II catalyst, and Grubbs II catalyst to extend the lower pendant sidechain. (+)-Pinnaic acid was isolated in a total of 26 steps, with an overall yield of 0.8%.

In 2014 Arimoto and Uemura published the most recent enantioselective total synthesis of halichlorine in a paper based upon Uemura's previously reported 2007 work on pinnaic acid (Figure 22).[22,27] Alcohol **84** was constructed in a method largely identical to the previously reported **83,** starting from (*R)*-(+)-pulegone. 5 steps converted **84** to the intermediate **85**, which was subjected to ring closing Grubbs metathesis (as Uemura had previously employed) to afford the tricyclic compound core intermediate **86**. Finally, deprotection of the lower side chains esters and a Shiina macrolactonisation completed the synthesis of halichlorine.[49]

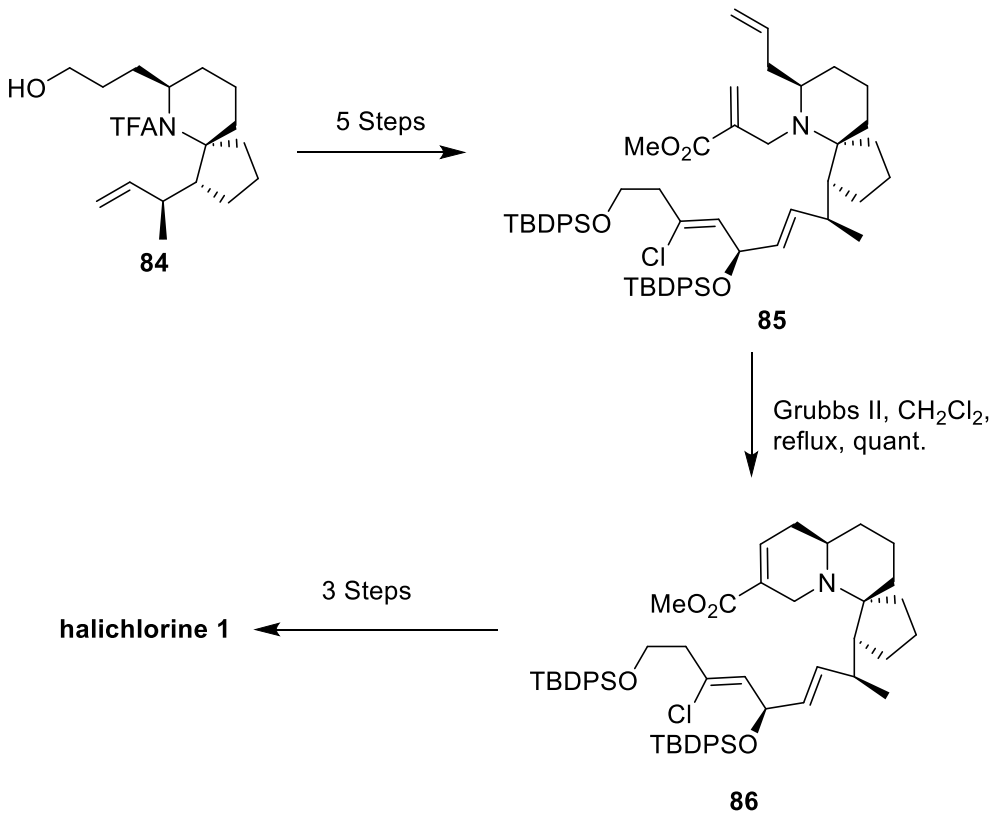


Figure 22 - Uemura's synthesis part 5

1.2.4. Zhao and Ding's Total Synthesis

In 2004, Zhao and Ding published an enantioselective approach to the cores of both halichlorine and pinnaic acid (Figure 23).[33] In 2007 they reported further progress with an enantioselective total synthesis of pinnaic acid.[28] The later synthesis differed from the first by the use of asymmetric ruthenium catalysis for the synthesis of the chiral bicyclolatone **88** from the racemic γ-keto ester **87**, rather than the previously published enzymatic route. Selective methylation of **88** from the least hindered face gave **89**, with the desired stereochemistry for the C-14 methyl group. The lactone **89** was converted to the nitrocyclopentane **90** in 5 steps. Michael addition of methyl acrylate into **90** gave **91**, with the desired geometry at the spirocyclic carbon centre. Extension of the newly installed pendant chain ready for formation of the spirocyclic ring system was achieved in 5 steps, yielding the intermediate ketone **92**.

In a variation on the cyclisation employed in previous syntheses by the likes of Danishefsky and Heathcock, Raney nickel was used to reduce the nitro group to the free amine, resulting in a spontaneous attack of the amine into the ketone to form the spirocyclic imine **93**. Selective reduction with sodium borohydride in methanol then gave the azaspirocycle **94** as a single diastereoisomer.

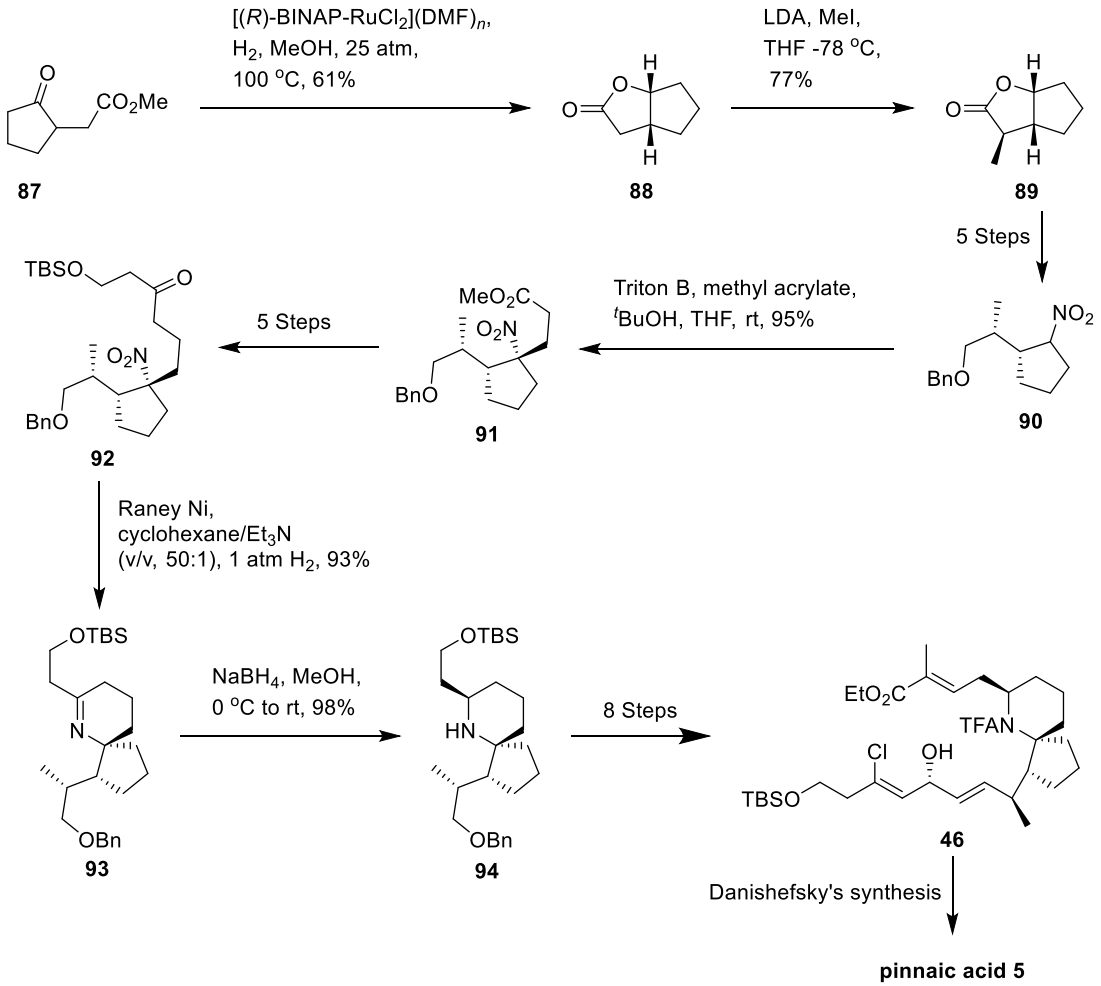


Figure 23 - Zhao and Ding's synthesis part 1

From the intermediate **94**, a further 8 steps saw the conversion to the intermediate **46**, which had been previously prepared by Danishefsky, enabling completion of the synthesis of (+)-pinnaic acid using Danishefsky's route, with a total yield of 2.3% over 27 steps.

1.2.5. Clive's Syntheses

The Clive laboratory has been active within the field of halichlorine and pinnaic acid synthesis since 1999, publishing a number of exploratory studies into relating spiro compounds,[50–53] an extensive review of the synthetic efforts towards halichlorine and pinnaic acid from the wider synthetic community,[23] a total synthesis of (±)-halichlorine,[29] and a first-hand account of the group's efforts and challenges, published in the book series 'Strategies and Tactics in Organic Synthesis'.[24]

Clive's first synthetic efforts towards pinnaic acid focused on a potential radical cyclisation to establish the geometry of the spirocyclic center.[50] The optically pure intermediate **99** was prepared from the two sub units **96** and **98** (Figure 26).

The sub unit **96** was synthesised from D-glutamic acid, which was converted into the known ester **95**. A further 5 steps of functional group interconversion and protection afforded the sulfone sub unit **96** in good yields (Figure 24).

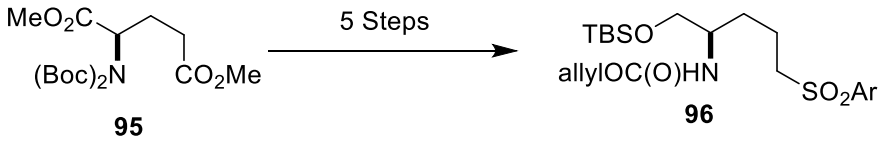


Figure 24 - Clive's synthesis part 1

The second sub unit **98** was prepared in 6 steps from **97** with the use of an asymmetric alkylation of an Evan's oxazolidinone to achieve the desired selectivity at the C-13 position (Figure 25).

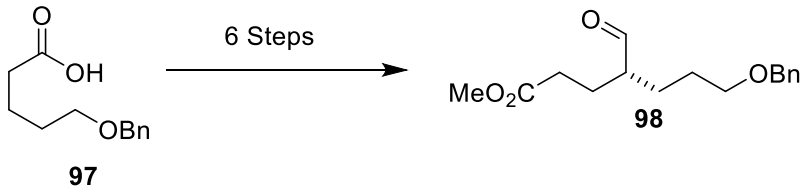


Figure 25 - Clive's synthesis part 2

Coupling of the sub units **96** and **98** was achieved by deprotonation of the sulfone **96** and reacting the resulting carbanion with **98** (Figure 26). Oxidation of **99** to the ketone, and subsequent removal of the allyl group resulted in sulfone **100**, ready for cyclisation to the spirocyclic core **101.** Conversion of **99** to the corresponding bromide allowed for a radical cyclisation using AIBN to give the spirocycle **101**. Finally, desulfonylation gave the target spirocyclic core molecule **102** completing the spirocyclic core.

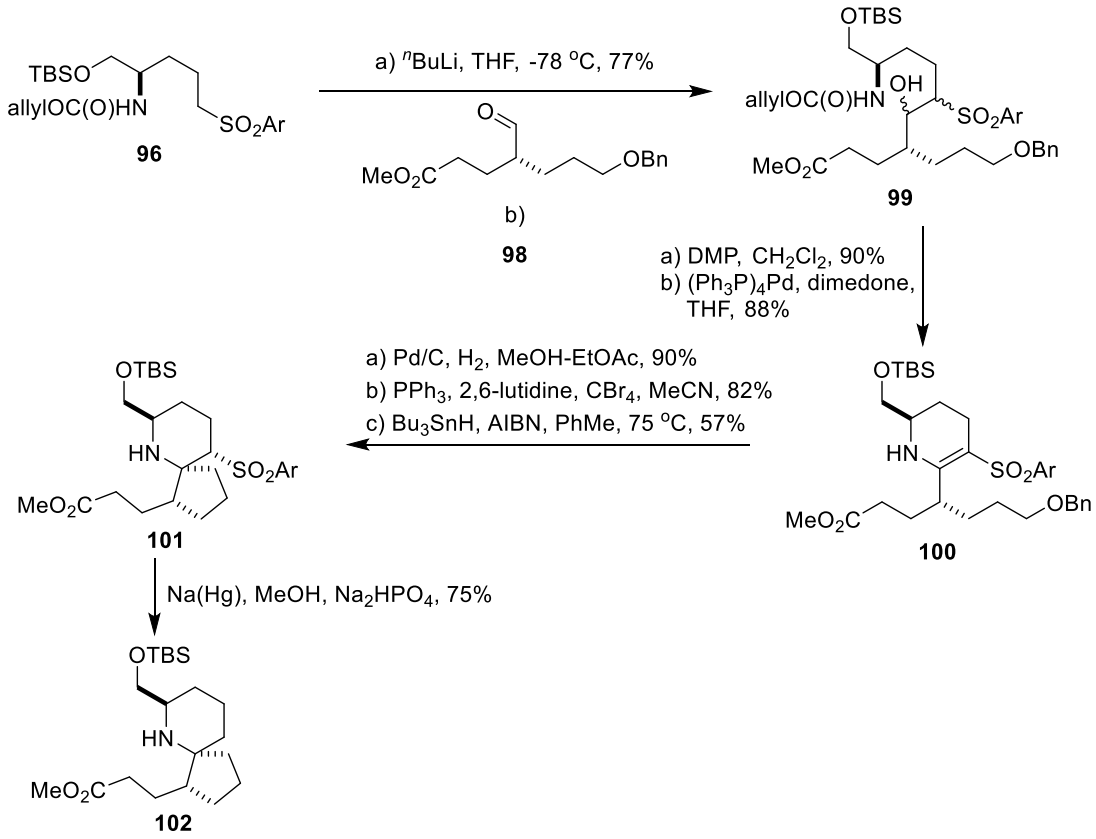


Figure 26 - Clive's synthesis part 3

In 2004 Clive reported a new approach to the spirocyclic core of halichlorine which, in 2009, lead to a total synthesis of (±)-halichlorine (Figure 27).[29,51] Starting from the symmetrically disubstituted piperidine bis-ester **103**, allylation with the chiral lithium amide base **104** afforded **105**, setting up the key geometry at the spirocyclic center (however with an ee of only 67%).

A further 7 steps were then needed to reach the aldehyde **106,** which was then constrained as the lactam **107** in a further 10 steps ready for a selective radical cyclisation, yielding the tricyclic intermediate **108**.

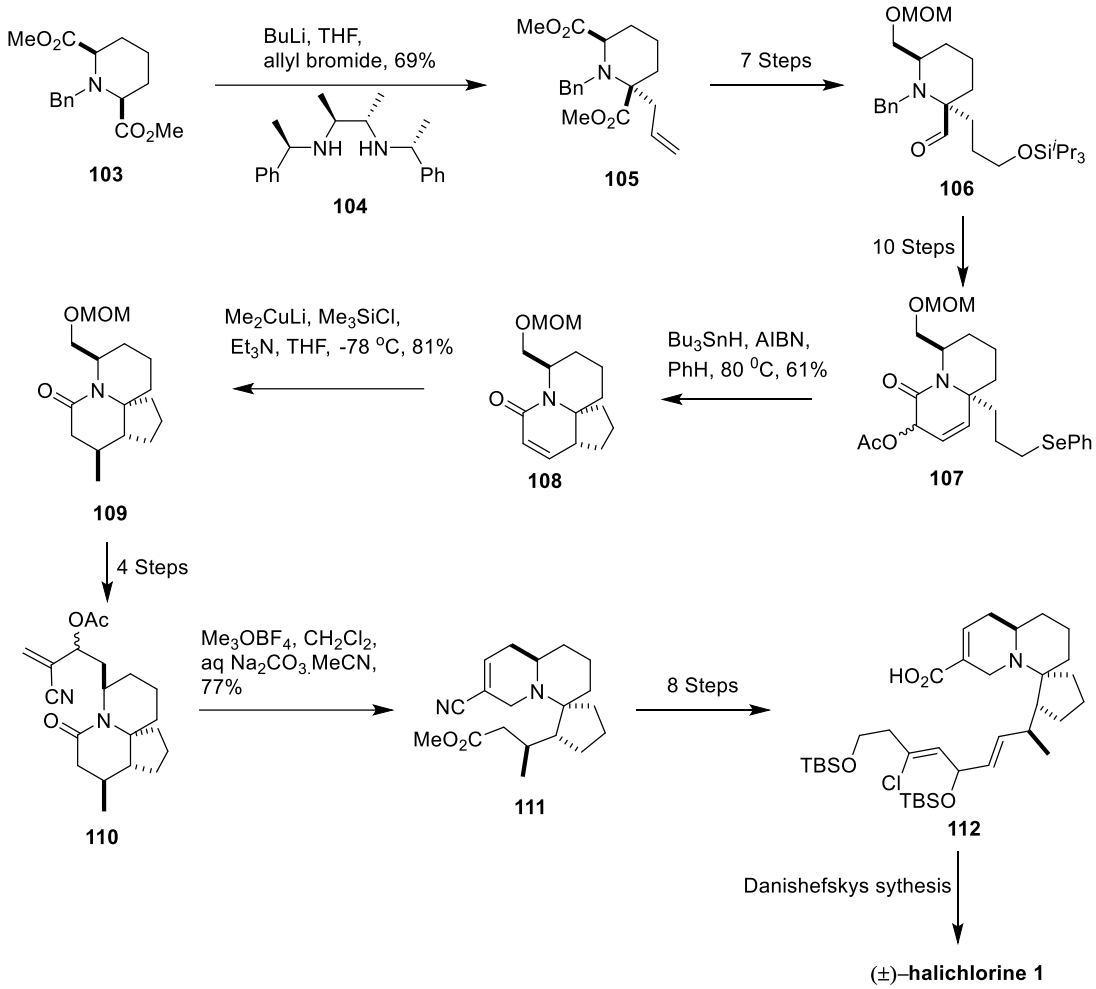


Figure 27 - Clive's synthesis part 4

The C-14 methyl group was installed by an efficient 1,4-conjugate addition with lithium dimethylcuprate to the convex side of **108** to give **109**, with all the core geometry set.

Moving towards the total synthesis of halichlorine in 2009,[29] the Clive group returned to the advanced intermediate **109**, previously reported (Figure 27).

Extension of the upper side chain was achieved in 4 steps to give **110**. Ring opening of the lactam resulted in a spontaneous intramolecular conjugate displacement to afford **111,** completing the tricyclic core of halichlorine. A further 8 steps reached the intermediate **112**, previously synthesised by Danishefsky, enabling completion of the synthesis in 3 further steps as previously reported.

1.2.6. Side Chain Synthesis

Shortly after the Uemura group reported the isolation of halichlorine and pinnaic acid, the Weinreb group published a route for the synthesis of the C-15 – C-21 chlorinated divinyl alcohol chain.[44] They proposed a subsequent introduction to the core 6-aza-spiro{4.5}decane ring system *via* a Horner-Wadswoth-Emmons olefination of an aldehyde with a functionalised unsaturated keto-phosphonate, allowing for control of the geometry at both of the olefinic sites.[54] Z-δ-Chloro-γ,δ-unsaturated-β-keto phosphinate **118** was prepared from 3-butyn-1-ol **113**, lithiation and subsequent carboxylation gave 5-hydroxy-2-pentynoic acid **114**. A selective CuCl-catalysed anti-addition of HCl across the alkyne **114**, developed by Kurtz,[55] gave the desired *Z* vinyl chloride **115**. Di-silylation of the alcohol and carboxylic acid with TBSCl and subsequent selective deprotonation of the carboxylic acid under basic conditions provided TBS ether **116**. Conversion to the *N*-methoxy-*N*-methyl Weinreb amide **117** and subsequent reaction with $BrMgCH_2P(O)(OMe)_2$ gave the final Z-δ-chloro-γ,δ-unsaturated-

β-keto phosphinate **118**. The substrate **118** was tested in a model Horner-Wadswoth-Emmons olefination with cyclohexanecarboxaldehyde **119** in the presence of DBU and LiCl. The product **120** was formed exclusively with the desired *Z,E*-geometry. Reduction of **120**, *via* the Luche method,[56] cleanly yielded the divinyl alcohol **121** (Figure 28). Since publication, Weinreb's side chain has proven to be an effective method for the installation of the C-15 – C-21 functionality and has be shown to be stable to chromatography. It has therefore found use in many of the subsequent total syntheses, formal syntheses and model studies, either directly or with minor modification.

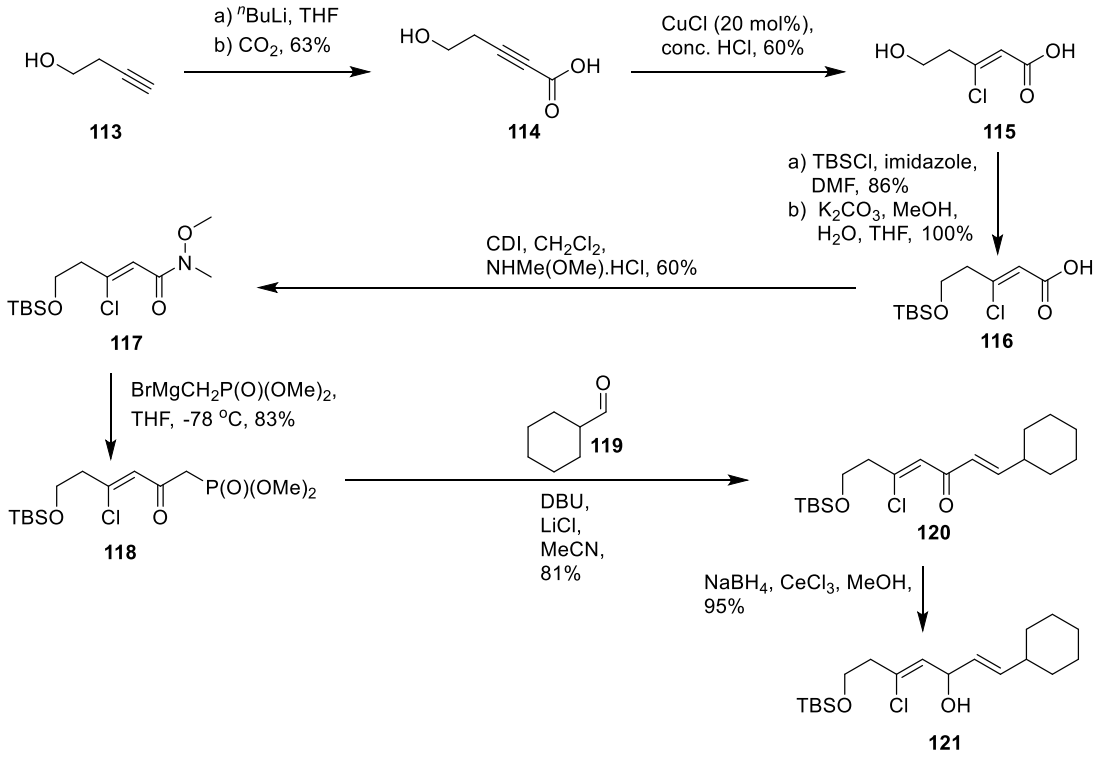


Figure 28 - Weinreb's C-15-21 side chain synthon

The Taber group published their contribution to the field with a general method for the preparation of (*Z*)-3-chloroallylic alcohols in 2002.[57] 2-Chloro-3-4-epoxy-1-butene **124** was achieved by epoxidation of 3,4-dichloroepoxide **122** with

m-CPBA and subsequent dehydrohalogenation with molten potassium hydroxide in a 64% yield over two steps. The chloroepoxide **124** underwent a conjugate addition in the presence of the organocuprate complex, generated from CuBr.Me_2S, through the addition of phenylmagnesium bromide in THF to give **125** as a mixture of 1,4-addition products with a *Z*:*E* ratio greater than 10:1 (Figure 29).

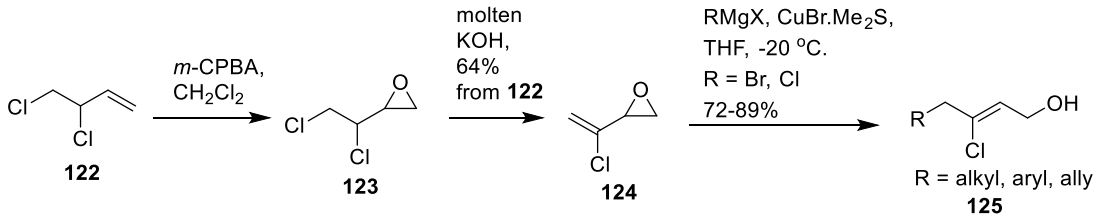


Figure 29 - Taber's Z-3-chloroallylic alcohol preparation

1.3. Studies Within the Stockman Group

Previously the Stockman group has been active within the field of synthesis of the halichlorine family of molecules, culminating in the publication of a formal synthesis in 2012, which converged with Clive's total synthesis. Efforts focused on an approach combining tandem reactions and two-directional synthesis for the rapid assembly of the azaspirocyclic halichlorine core, an approach that has been successfully applied to the synthesis of histrionicotoxin alkaloids, hippodamine, *epi*-hippodamine, homoanatoxin and anatoxin, within the group.[58–61]

In 2004 Stockman and co-workers reported the synthesis of azaspirocyclic core **136**,[62] utilising an intramolecular [3+2] nitrone-olefin cycloaddition on a symmetrical keto diester synthesised in a bi-directional manner.

Initially, intermediate **129** was synthesised in 5 steps using the group's dithiane methodology developed for histrionicotoxin.[63] However, scaling-up the procedure proved troublesome, so an alternative was investigated (Figure 30). The compound 5-Bromopentene **126** was converted to the corresponding Grignard reagent, which was then reacted with ethyl formate in a two-directional manner to give the symmetrical dienol **127**. PCC oxidation of the alcohol and protection of the resulting ketone as its ketal gave **128**. The first reported route utilised a double oxidative cleavage of the terminal olefins with ruthenium(III) chloride and sodium periodate to give the corresponding dialdehyde. Double Horner-Wadsworth-Emmons olefination with triethyl phosphonoacetate afforded the symmetrical (*E, E*)-keto diester **129** after deprotection (not shown). In 2012 the Stockman group updated the synthesis of **129**, using cross-metathesis of **128** with ethyl acrylate and Hoveyda-Grubbs II catalyst to give the product **129** in a highly efficient manner, ready for tandem cyclisation.

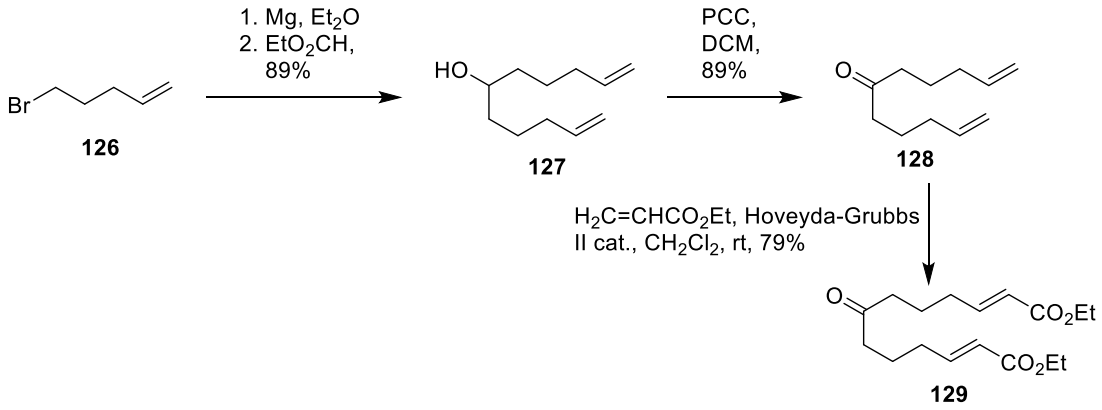


Figure 30 - Stockman's synthesis part 1

Formation of an oxime with intermediate **129** resulted in a tandem Michael addition/1,4-azaprotiocyclotransfer reaction to generate the nitrone intermediate **131** (Figure 31). Heating of the nitrone resulted in an intramolecular [3+2] nitrone alkene cycloaddition, affording the azaspirocyclic core **132** as a single diastereomer, unfortunately with the opposite desired geometry at the upper sidechain C-5 junction. Selective reduction of the ester with $NaBH_4$ gave alcohol **133** which was then ring opened at the N-O bond by palladium hydrogenolysis to give the corresponding diol **134**. Epimerisation of the C-5 position was achieved upon heating with ethanol, *via* a reversible Michael addition, yielding **135**, analogous to White's pinnaic acid intermediate.[64] Protection of the diol to the corresponding acetonide and trifluoroacetate protection of the piperidine nitrogen gave the fully protected azaspirocyclic core **136**.

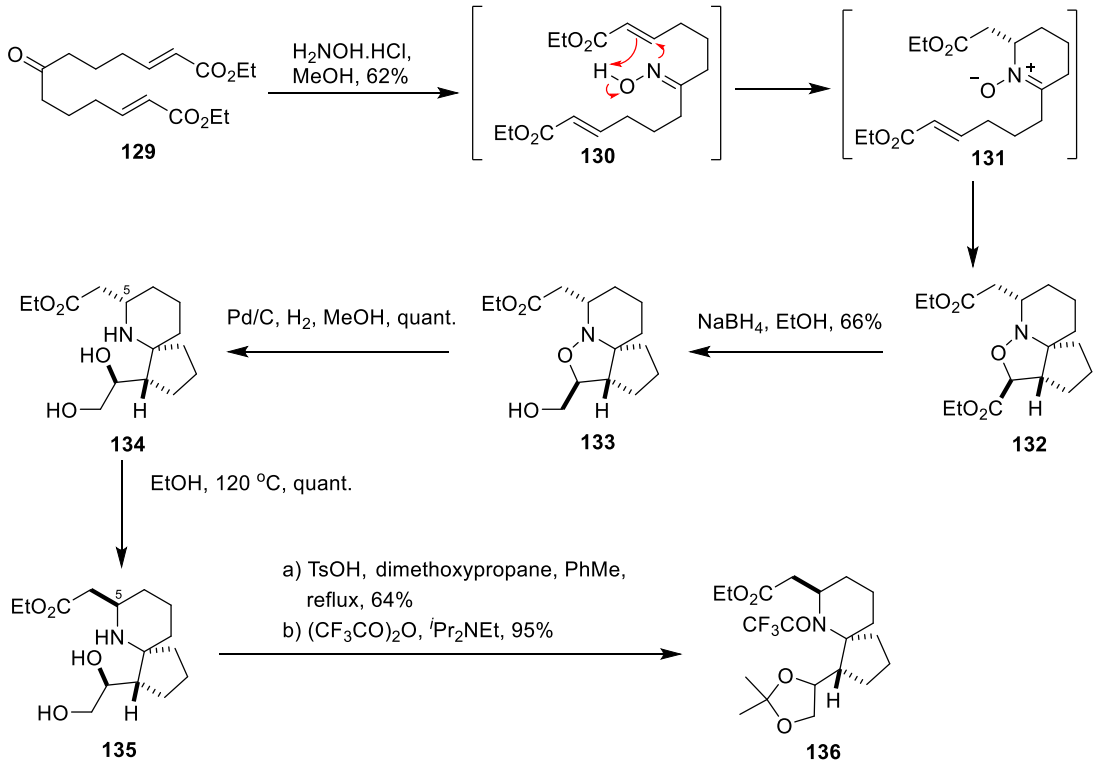


Figure 31 - Stockman's synthesis part 2

In 2012 the Stockman group reported a continuation of the work towards halichlorine and pinnaic acid **5**.[36] Reducing the number of steps to construct the symmetrical diester **129,** as previously described (Figure 30), and reporting the synthesis of **141** from the diol **135**. Compound **141** is an intermediate in Clive's total synthesis,[29] therefore constituting and formal synthesis of halichlorine (Figure **27**).

The keto-ester **129** was prepared and converted to the azaspirocyclic diol **135** *via* the previously described steps (Figure 31). Installation of the C-14 methyl group proved initially challenging, however it was achieved in a further four steps. Oxidative cleavage of diol **135** to **136** was followed by an Ando homologation to

afford the *Z*-enolate **138** (Figure 32). Heating **138** in toluene and acetic acid gave lactam **139**, which was selectively methylated using the Gilman reagent (lithium dimethylcuprate) to afford lactam **140**. The formal synthesis was completed *via* reduction of the ester with DIBAL-H to give the corresponding aldehyde **141**, as previously synthesised by Clive and co-workers in their total synthesis of halichlorine **1**.

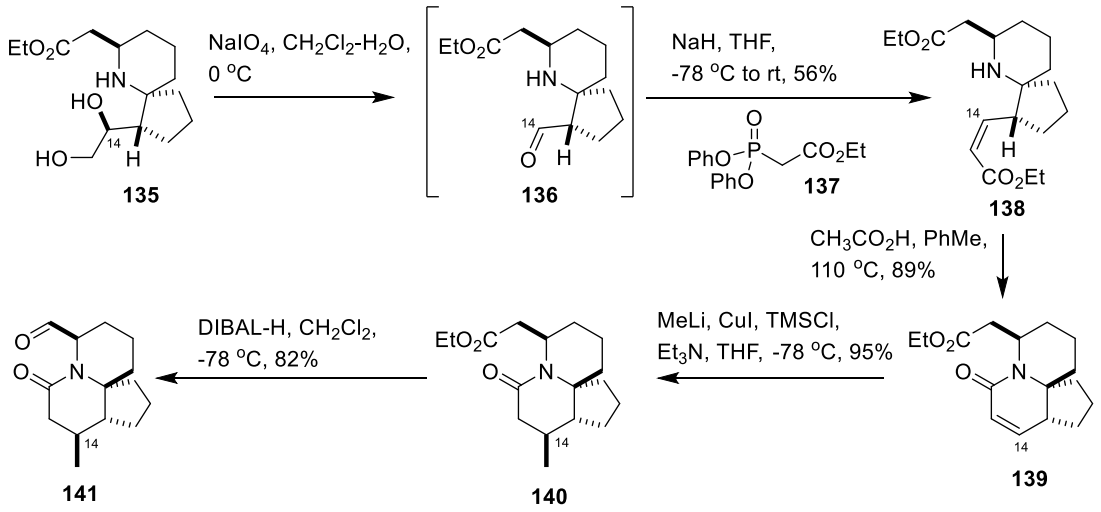


Figure 32 - Stockman's synthesis part 3

Although successful in completing a formal synthesis of halichlorine **1**, installation of the C-14 methyl group with the correct relative stereochemistry had proved to be challenging. This is presumably due to the crowded steric environment of the C-14 centre. Constraining the side chain by lactamisation, facilitated selective alkylation. However, this required multiple steps from a precursor which already possess stereochemistry at the C-14 position. Although these challenges limited the route to a formal synthesis, the highly efficient manner in which the core structure was synthesised through bidirectional reactions makes this approach an attractive addition to the literature.

1.4. Summary of Synthetic Efforts

Since their isolation by Uemura in 1996 and 2011 respectively, the halichlorine family have had a considerable quantity of work published on approaches to their synthesis. Clive's summary of synthetic work towards these natural products reviews the field as it stood in 2005,[23] covering the total syntheses reviewed herein along with the studies of Kibayashi,[30,31,65,66] Feldman,[67] White,[64] Shishido and Itoh,[68,69] Zhao and Lee,[70,71] Wright,[72] Ihara,[73] Keck,[74] Simpkins,[75] Forsyth,[76] Dake,[77] and finally Pilli.[78] In more recent times other formal synthesis and model studies have also been published by Martin,[32] Capiro,[79] Tomioka,[34] Dowden,[80] Padwa,[81] and Tu and Wang.[35] A total synthesis has also been published by Aoyagi.[30]

2. Results and Discussion

2.1 Retrosynthetic Analysis for the Synthesis of Pinnarine 7

The retrosynthetic analysis of pinnarine **7** begins with a disconnection of the lactone to give pinnaic acid **5** (Figure 33). This forward step has already been conducted with synthetic pinnaic acid by Uemura.[21] Further disconnection of the C-15 – C-21 side chain could give the late stage intermediate **143**. The intermediate **143** is designed to undergo cross metathesis with functionalised vinyl chloride side chains such as **142**. The synthesis of side chain **142** has been previously developed by Weinreb,[44] Uemura,[27] and within the Stockman group, with the potential to set the C-17 alcohol geometry before or after homologation. Detachment of the α, β-unsaturated ester chain could give **144**, a forward step achievable using a Wittig olefination. The late-stage highly functionalised bicyclic intermediate **144** would be the branch point in the synthesis from which pinnaic acid **5**, pinnarine **7** and halichlorine **1** may be accessed. Removal of the aldehyde and nitrogen protecting groups should allow access to **144** from the intermediate **145** *via* an aza-Michael addition. The stereochemistry of the spirocentre will be set by a selective addition into ketimine **146**, which may be synthesised *via* a condensation of amines and ketone **147**. Finally disconnection of the allyl side chain of ketone **147** gives cyclopentanone **148**.

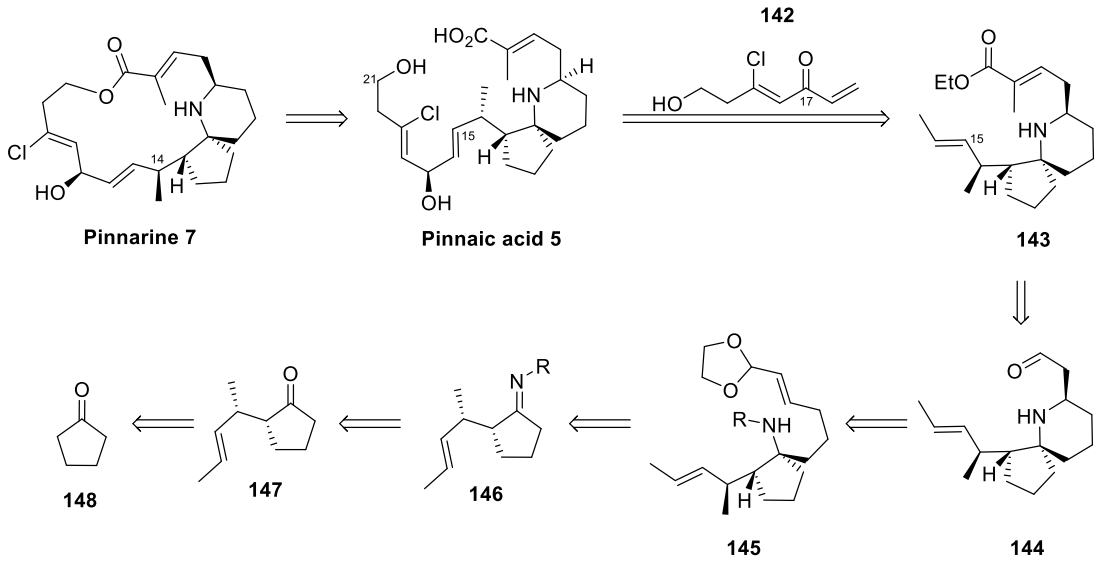


Figure 33 - Retrosynthetic analysis

The aim of this synthetic approach is to provide an expedient route to the target natural products. Firstly, the focus is on the installation of the C-14 methyl group in the correct orientation from as early in the synthesis as possible. This has previously been a major challenge in prior Stockman group syntheses. Secondly, the focus is on the construction of the spirocyclic ring junction, to pave the way for ring closing and upper/lower side chain synthesis.

2.2 Previous Work in the Stockman Group on the Synthesis of Intermediate **146**

Previously within the Stockman group, efforts have been made towards the synthesis of the ketimine intermediate **157** *via* Buchwald-Hartwig coupling and subsequent [3,3] sigmatropic rearrangement (Figure 34).

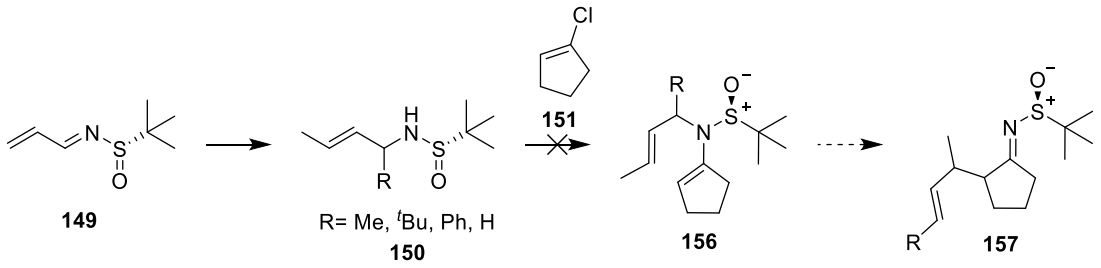


Figure 34 - Previous attempts at the synthesis of **156** via Buchwald-Hartwig coupling reactions

However, attempts at coupling allyl amines **150** with 1-chlorocyclopentene **151** were unsuccessful, leading to a new approach being considered. Condensation of amines onto the functionalised cyclopentanone **160** allowed access to the intermediate **146**. Using the diastereoselective Claisen rearrangement reported by Mikami, between 1-methoxycyclopent-1-ene **158** and pent-3-ene-2-ol **159**, **160** was synthesised.[82] However, the reported diastereoselectivity was not observed, giving the product **160** as a mixture of diastereomers (Figure 35).

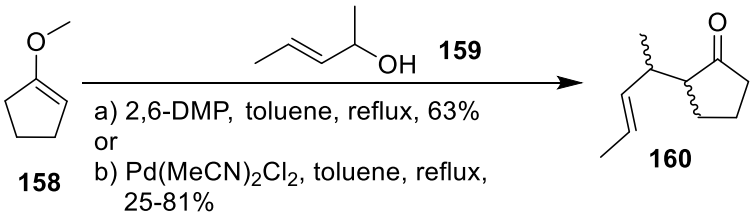


Figure 35 - Synthesis of **160**

Diastereoisomers **160** were subjected to a condensation reaction with 2-methyl-2-propanesulfinamide **161** to give the sulfinimine **162** in poor yields (Figure 36).

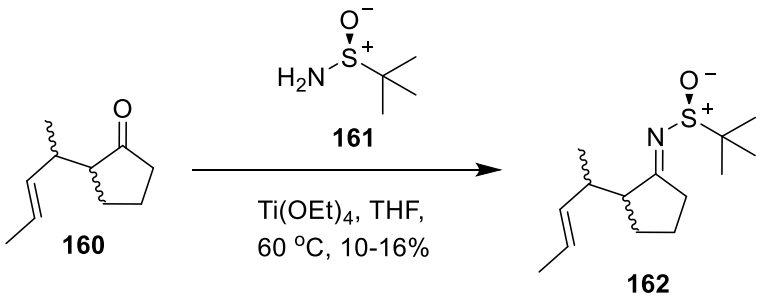


Figure 36 - Development of **160**

These preliminary results represent a brief attempt at developing this route for the synthesis of the halichondrins. The work detailed here is the elaboration of these previous attempts, aiming to explore to a greater depth the retrosynthetic pathway detailed in Figure 33.

2.3 Synthetic Efforts Towards the Synthesis of the Halichlorine Family

2.3.1 Work Towards the Diastereoselective Synthesis of **160**

The first phase of this project was the development of a diastereoselective and potentially enantioselective synthesis of the imine **146** (Figure 33). The two previous attempts using a Buchwald-Hartwig coupling and subsequent [3,3]-sigmatropic rearrangement or *via* Mikami's Claisen rearrangement were either unsuccessful or delivered no diastereoselectivityrespectively.[82] A new approach was considered making use of the Tsuji-Trost type allylations of sulfinimines developed within the Stockman Group.

α-Allylation of sulfinimines has been achieved in high yields with excellent *d.r.* using achiral phosphine ligands in a Tsuji-Trost type reaction on range of chiral sulfinimines using allyl carbonate (Figure 37). Although there is comprehensive precedent for simple unsubstituted allyl electrophiles, Tsuji-Trost reactions performed with substituted allyl electrophiles are less common. In particular, substituents in the homoallylic position, so as to form two new stereocenters upon allylation, have only been reported by the group of Braun, who published a diastereoselective and enantioselective allylation of a cyclohexanone enolate using disubstituted, racemic, allylic substrates.[83–86]

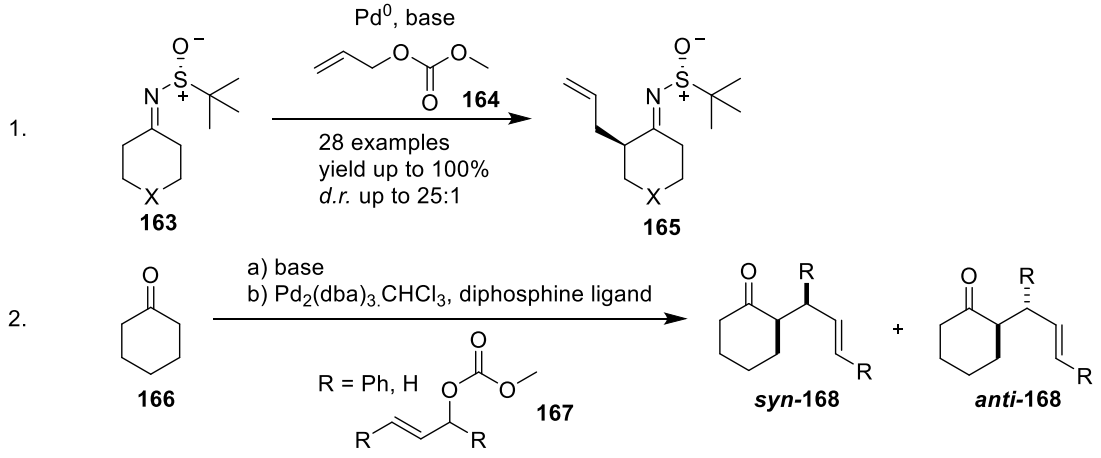


Figure 37 -Tsuji-Trost allylation of sulfinimines, 2. Braun's diastereoselective Tsuji-Trost allylation

Braun's synthesis of **168** showed the potential of using disubstituted ally carbonates as electrophiles in Tsuji-Trost type allylations. We therefore envisioned a chiral sulfinimine directed Tsuji-Trost allylation with disubstituted ally carbonates in order to deliver the highly functionalised substrate **162** (Figure 36).

Synthesis of sulfinimine **169** was achieved using the Ellman groups methodology in good yields (Scheme 11).[87,88] Expedient purification was required through a short silica column followed by careful storage (excluding water and air), to limit hydrolysis of **169**. The disubstituted allyl carbonate (*E*)-methyl pent-3-en-2-yl carbonate **167** was afforded by refluxing dimethyl carbonate **170** with neat 3-penten-2-ol **159** in the presence of catalytic potassium carbonate.

A Tsuji-Trost allylation between sulfinimine **169** and (*E*)-methyl pent-3-en-2-yl carbonate **167** was conducted in the presence of tetrakis(tri-phenylphosphine)palladium(0) in conjunction with Hunigs base. When the reaction was heated to 65 °C and with rigorous exclusion of air and moisture, a 7% yield of **162** was achieved. However, under all attempted conditions, rapid catalyst degradation was observed which accounted for the poor yield (Figure 38).

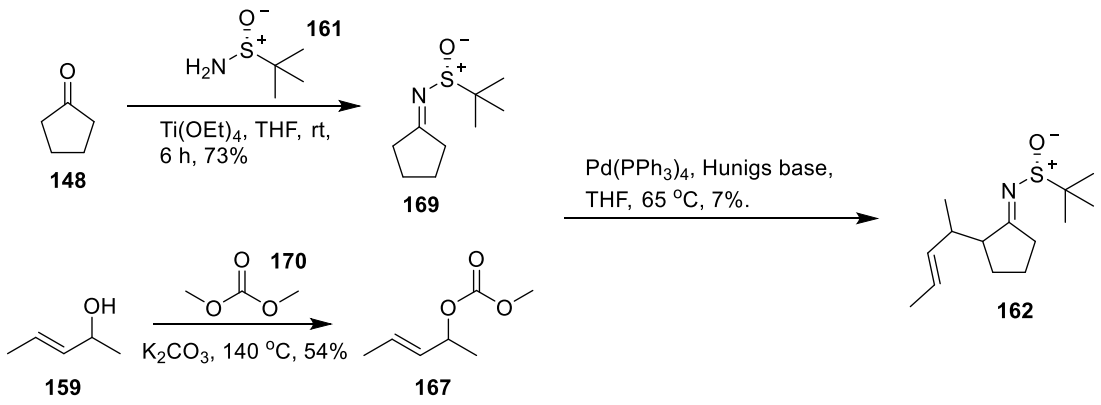


Figure 38 - Sulfinimine directed allylation

The difficulty of using (*E*)-methyl pent-3-en-2-yl carbonate **167** for Tsuji-Trost allylations was evident. The palladium allyl species formed upon allylation of

the metal centre is a poor electrophile compared to the more reactive unsubstituted allyl palladium species previously demonstrated. The reduction in reactivity is due to the increased electron density from the methyl groups, donated into the allyl system, along with the increased steric hindrance of the methyl groups over hydrogens.

A revised approach using the Tsuji-Trost allylation, as described by Braun and co-workers (Figure 37), with a cyclopentanone enolate was developed (Figure 39).[83–86] Diastereoselective allylation of cyclopentanone **148** would enable access to diastereomerically pure **160**, which has previously proved challenging using the method of Mikami (Figure 35). This would set the stage for further exploration of methods to construct the spirocyclic C-9 centre.

Synthesis of the allylated cyclopentanone **160** *via* the method described by Braun proved to be a great challenge. Initial attempts proved unsuccessful, returning only cyclopentanone aldol condensation product (not shown). Adjusting the equivalents of base and rate of addition, as well as rigorous purification and drying of the starting materials, gave the product **160** in low yields (17%), over long reaction times (168 h), with no diastereoselectivity observed. Reaction monitoring proved difficult due to overlapping of products and reagents by TLC analysis (this also impacted the purification and isolation of the product **160**). No detectable ion peak for the product **160** was observed by mass spectrometry. The most effective method of reaction monitoring was aliquot sampling by ^{1}H

NMR of the reaction mixture. This limited the scale to which the reaction could be monitored, preventing small scale testing. Optimisation was clearly needed in order to make the synthesis of **160** viable.

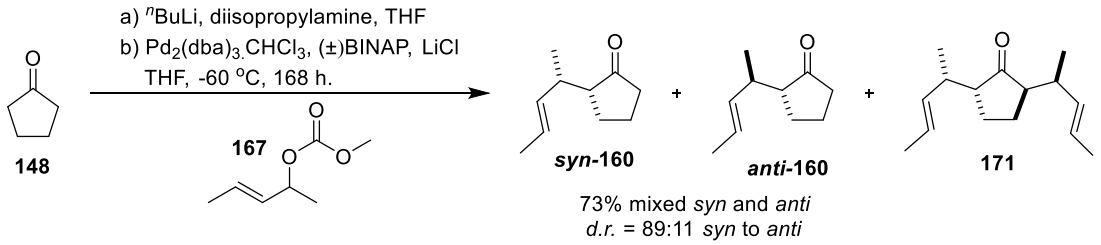


Figure 39 - Allylation of cyclopentanone **148**

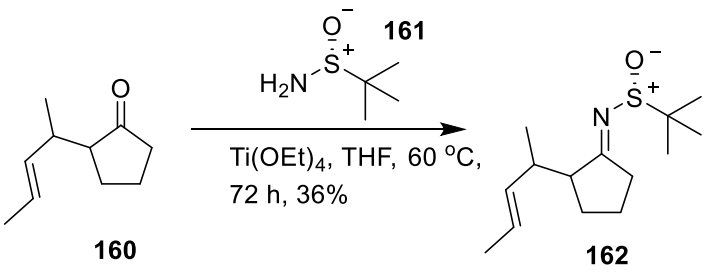
Diastereoselectivity was found to be inversely dependent upon the temperature, with low temperature giving higher diastereoselectivity at the cost of reaction rate. The best diastereoselectivity (89:11, *syn*:*anti*) was achieved at -60 °C and below, with the reaction times extending as the reaction temperature dropped (Scheme 12). Comparison to literature data revealed the major diastereomer to be the *syn* product **160** as desired.[82] Catalyst loading appeared to have little effect on the *d.r.* with higher loading giving marginally faster reaction times. Reactions carried out on a 5 mmol scale allowed for effective reaction monitoring by ^{1}H NMR. Sampling the reaction mixture with 0.2 mL aliquots daily proved effective. However, this revealed the consumption of the desired product **160** by the formation of the undesired doubly allylated byproduct **171**. The synthesis of the byproduct **171** results in a "sweet-spot" approach to assessing the reaction endpoint being required, where consumption of the starting material to form **160** must be weighed against the consumption of the product in order to select the end point of the reaction with the highest yield. Early termination of the

reaction was preferable as the unreacted carbonate **167** may be recovered for further reactions.

The final challenge in the synthesis of **160** was the isolation of the product from the crude reaction mixture. Chromatographic methods proved ineffective due to co-elution of the product **160** with both the starting material **167** and by-product **171**. Distillation of the product was effective for the isolation of **160** but only on larger scales. All distillations carried out on small scale crude reaction mixtures produced poor yields. No method employed for the isolation of **160** has been able to separate the two diastereomers from one another.

Although this transformation represents a significant synthetic challenge practically, as described, the reaction was optimised to give good yields and acceptable *d.r.* on a 5 mmol scale.

With **160** in hand, efforts were undertaken to improve the poor conversion of **160** into the corresponding sulfinimine **162**, previously reported (10-16%) (Figure 36). A yield of 36% was achieved when heating to 60 °C in THF (Table 1, Entry 3). However, increasing the temperature or the addition of desiccants resulted in degradation of the starting material and product, delivering poor yields (Table 1, Entries 4, 5).



Entry	160 (equiv.)	161 (equiv.)	$Ti(OEt)_4$ (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield	Notes
1	1	1.1	2	THF	rt	24	-	N/A
2	1	1.1	2	THF	60 °C	24	Trace	N/A
3	1.3	1	2.6	THF	60 °C	72	36%	N/A
4	1.3	1	2.6	THF	Reflux	24	trace	4 Å ms
5	1.3	1	2.6	Toluene	Reflux	24	trace	4 Å ms

Table 1 - Synthesis of **162**

2.3.2 Large Scale Synthesis of Starting Materials and Reagents

A major challenge for the continuation of synthetic efforts towards the total synthesis of the halichondrins has been the ongoing synthesis of a constant supply of starting materials and intermediates. With small scale synthesis of intermediates preventing effective development at the "head" of the synthesis from being conducted. The main "bottle neck" has been the Tsuji-Trost allylation of cyclopentanone **148** to give **160**, which has previously only been conducted at

small (10 mmol) scale. This small scale has previously severely limited the progress of the synthesis, preventing effective exploration of imine intermediates **146**. Scaling up of the synthesis of **160,** as well as the synthesis of carbonate **167** and its precursors **159,** was therefore of key importance for the ongoing total synthesis.

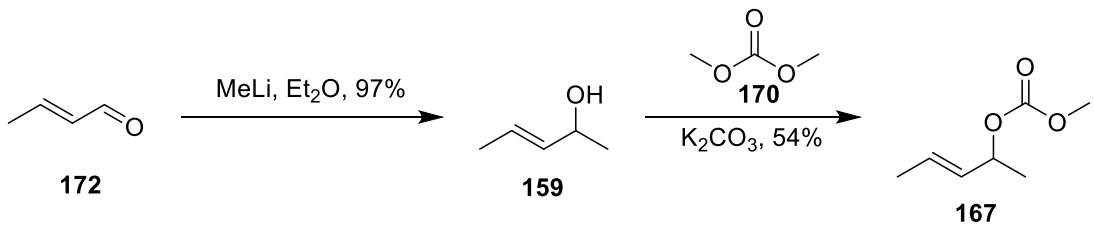
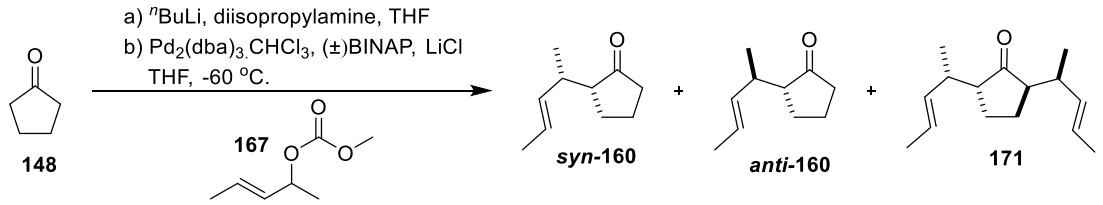


Figure 40 - Large scale synthesis of carbonate **167**

Alcohol **159** was synthesised from crotonaldehyde **172** *via* treatment with methyl lithium in almost quantitative yields on a 10 g scale (Figure 40). The alcohol **160** had previously been purchased for small scale reactions, but on a larger scale would have been prohibitively expensive. The alcohol **160** was therefore synthesised using readily available reagents, allowing for large scale synthesis of carbonate **167**, in yields comparable to those observed on a smaller scale.

With a larger scale synthesis of the carbonate **167** in hand, scaling up of the synthesis of **160** was explored (Table 2). The previous largest scale for the synthesis of **160** was starting from 10 mmol (841 mg) of cyclopentanone **148** (Table 2, entry 1).



Entry	Scale (mmol)	Time (hours)	Yield of 160	Yield of 171	*d.r.* of 160 (*syn*:*anti*)	Catalyst loading (mol %)
1	10	168[a]	65%	10%	89:11	5
2	25	168[a]	62%	12%	89:11	5
3	52	96[b]	49%	22%	86:14	1
4	66	96[b]	45%	27%	89:11	1
5	138	72[b]	51%	5%	89:11	0.75

a- reaction ended at maximum ratio of product **160** over **167** and **171**. b- full consumption of **167** observed.

Table 2 - Scale up of the synthesis of **160**

Increasing the scale of the Tsuji-Trost synthesis of **160** from 10 to 25 mmol had little effect on the reaction, with comparable yields achieved in similar reaction times (Table 2, entry 2). The ratio of the products **160** and **171**, was found to be highly dependent upon the reaction length. The yield of the desired product is hampered by either significant quantities of unreacted carbonate **167**, or conversion to the di-allylated side product **171**. The yields in Table 2 represent the maximum yield of **160** achieved upon termination of the reaction at the point deemed to be the most suitable compromise end point. The reaction time of 7 days for the small-scale (10-25 mmol) reactions was the best compromise as an end point for the reactions. Increasing the reaction scale to approximately 50

mmol, however, dramatically reduced the time taken for the full consumption of the carbonate **167** (Table 2, entries 3,4), with full consumption of **167** observed after 4 days. Catalyst loading was also reduced from 5 to 1 mol %, with no effect to the diastereomeric ratio.

Finally, further increasing the scale to 138 mmol of ketone gave the best results yet (Table 2, entry 5). At a lower catalyst loading of only 0.75 mol %, a reduction in reaction time to 72 hours was observed. Purification of the reaction mixture gave a yield of 51% of the desired product with an excellent d.r. of 89:11. The undesired by-product **171** was recovered with a yield of 5%, along with a mixed fraction of the product/by-product equating to a further 30% of the mass balance for the reaction.

Although this represents an effective scale up of the Tsuji-Trost reaction for the synthesis of **160**, enabling progress at the head of the synthesis to be made, the reaction conditions and reaction lengths, along with the complexity of the synthesis, remain partly restrictive on the rate of development.

2.4 Development at the Head of the Total Synthesis

With the synthesis of the functionalised cyclopentanone **160** on a small scale giving good yields and diastereoselectivity, work was begun on the synthesis of ketimine intermediates **146** from the functionalised cyclopentanone **160** (Figure

41). The synthesis of several ketimine analogues **150** has subsequently enabled the exploration of selective alkylations for the synthesis of amines with the general structure **173**.

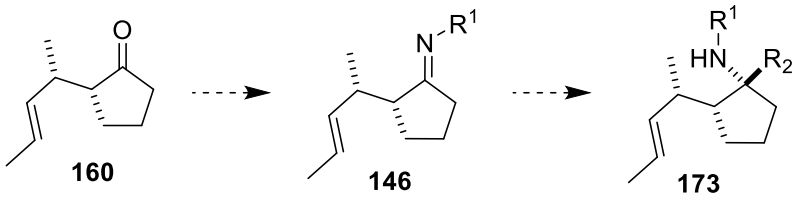
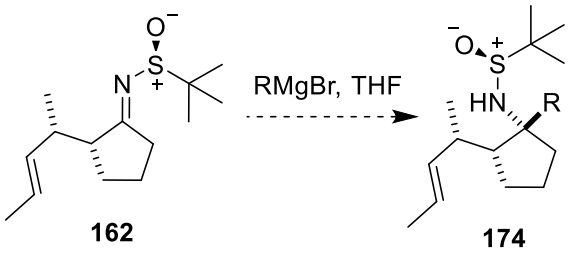


Figure 41 - Proposed route for the synthesis of ketimine intermediates **146** and their alkylation

2.4.1 – Exploration of the Alkylation of the Sulfinimine **162**

Using the sulfinimine **162**, synthesised using the methods previously described (Table 1), primary attempts at alkylation were undertaken. The sulfinimines developed by Ellman and co-workers are well established and highly versatile chiral auxiliaries for alkylation of imines.[88] It was therefore proposed that conversion of **160** to the chiral sulfinimine **162** would enable stereoselective alkylation to be conducted.

Initial investigations into alkylation were conducted using Grignard reagents as nucleophiles, which are well documented for the alkylation of sulfinimines (Table 3).[88]



162 174

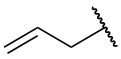
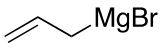
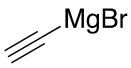
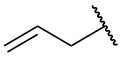
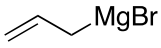
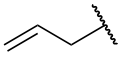
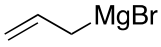
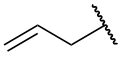
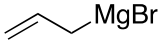
Entry	R=	Grignard reagent	Equiv. of Grignard	Lewis acid	Temperature	Yield (%)
1	Me	MeMgBr	1.1	-	0 °C to rt	0
2	Et	EtMgBr	1.1	-	0 °C to rt	0
3	^{n}Bu	^{n}BuMgBr	1.1	-	0 °C to rt	0
4			1.1	-	0 °C to rt	0
5			1.1	-	0 °C to rt	0
6	Me	MeMgBr	5	-	0 °C to rt	0
7	Me	MeMgBr	10	-	0 °C to rt	0
8	Me	MeMgBr	5	-	Reflux	0
9			5	-	0 °C to rt	0
10			10	-	0 °C to rt	0
11			5	-	Reflux	0
12	Me	MeMgBr	5	$Yb(OTf)_3$	0 °C to rt	0
13	Me	MeMgBr	5	$BF_3.OEt_2$	0 °C to rt	0

Table 3 - Attempted Grignard additions to **162**

Simplified Grignard reagents were selected for initial test rather than the "ideal" Grignard reagent (Figure 42). The selection of simplified nucleophiles was made in order to allow for rapid testing of a range of nucleophiles in order to gain a

greater understanding of the transformation. Methyl, ethyl and ^{n}butyl Grignard reagents were primarily tested along with allyl and ethynyl Grignard reagents (Table 3, entries 1-5).

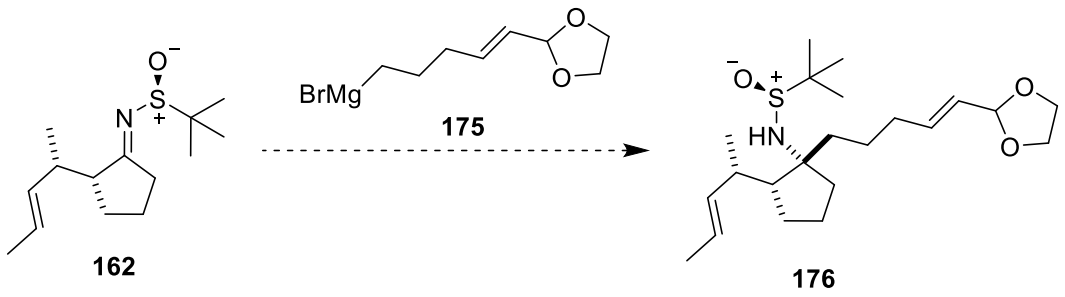


Figure 42 - "Ideal" Grignard reaction for the synthesis of the intermediate **176**

Allyl Grignard was selected for two key reasons. Firstly, the addition of an allyl group would allow for further functionalisation. This would potentially enable progress towards intermediates suitable to undergo the aza-Michael addition described in the retro synthesis (Figure 33, **144** to **145**). Secondly, allyl Grignard reagents react *via* the carbon γ to the metal, reducing the impact of steric hindrance on the reagent, and potentially allowing addition into a highly sterically crowded environment. Ethynyl Grignard was also selected due to the low steric profile of the alkyne Grignard reagent.

None of the five tested Grignard reagents gave any of the desired addition products **174** (Table 3, entries 1-5), with only traces of the product detected by mass spectrometry. Further tests were conducted using both the methyl and allyl Grignard reagents. Increasing the stoichiometry of the Grignard reagents resulted in no change to the reaction outcome, returning only starting material

(Table 3, entries 6,7,9,10)). Increasing the temperature to reflux in THF also had no impact on the reaction outcome (Table 3, entries 6,11). Finally, methylations were attempted using methyl Grignard reagent in conjunction with a Lewis acid. Ytterbium triflate and boron trifluoride diethyl etherate were both employed, however in both cases no reaction was returned, as with previous attempts.

With none of the attempted Grignard's showing any addition, there are clearly factors impeding the transformations progress. The basicity of Grignard reagents is one factor that may have impeded the addition reactions. Deprotonation of an acidic proton alpha to the imine, by the highly basic Grignard reagent would result in formation of the enamine **177** or **178**, preventing nucleophilic attack (Figure 43). Quenching of the reaction would reprotonate the enamine, returning the starting material **162**. Although the sulfinimine **162** was able to be recovered from the reaction mixture, hydrolysis of the imine back to the ketone **160** was also observed in the workup preventing efficient recycling of starting material for further exploration.

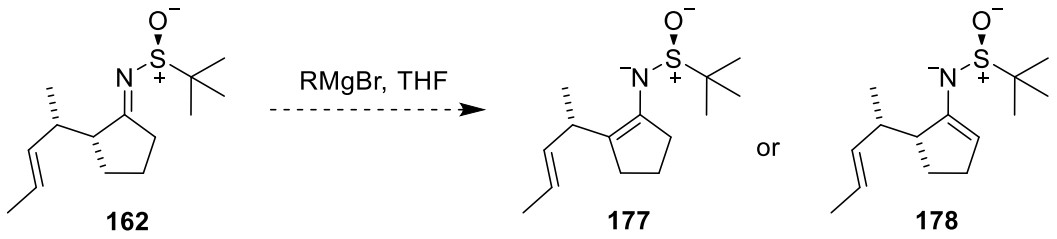
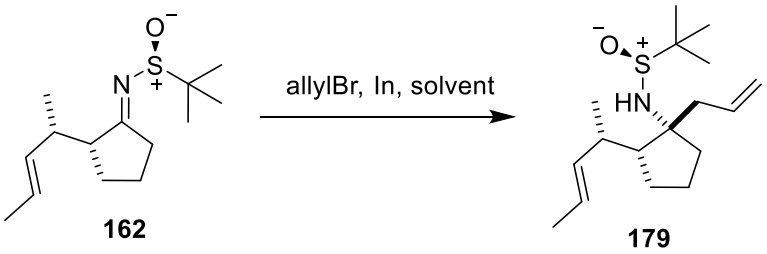


Figure 43 - Deactivation of **162** via deprotonation with base

To combat this, nucleophiles with a lower basicity than Grignard reagents were considered. Barbier reagents, which use indium over magnesium have been

shown in the literature to be effective reagents for the alkylation of sulfinimines.[89] It was therefore proposed that lower basicity of indium Barbier reagents may enable their addition into **162**, avoiding the deprotonation pathway (Table 4). A second factor for the selection of indium Barbier reagents is the potential to conduct the alkylations *via* a radical mechanism, by selecting an appropriate solvent system to promote free radical formation.[90,91] A radical addition would be beneficial due to the comparatively low steric bulk of radical reagents, which may help to enable the addition into the sterically hindered centre.

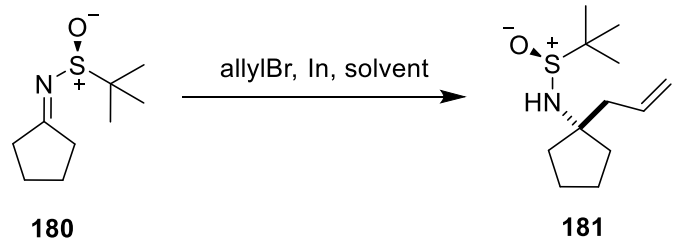


Entry	Equiv. allyl bromide	Equiv. indium	Solvent	Temperature	Yield
1	1.1	1.25	THF	rt	0
2	1.1	1.25	H_2O, MeOH, 50:50	rt	0
3	2	2.5	H_2O, MeOH, 50:50	60 °C	0
4	1.1	1.25	H_2O, CH_2Cl_2, 50:50	rt	0
5	2	2.5	H_2O, CH_2Cl_2, 50:50	60 °C	0
6	2	2.5	H_2O	rt	0

Table 4 - Indium Barbier reactions

Allylations using indium and allyl bromide in THF as a solvent system are reported to give a two-electron reaction mechanism (as with Grignard reagents). When addition attempts were conducted in THF however, no reaction was observed (Table 4, entry 1). Changing to a biphasic water/organic solvent system enables indium Barbier reactions to progress via a free radical reaction mechanism. Both water/methanol and water/dichloromethane solvent systems were tested, however they both resulted in no reaction being observed (Table 4, entries 2,4). Increasing the stoichiometry of the allyl bromide and indium, as well as raising the reaction temperature also had no effect on the reaction with no progress observed once again (Table 4, entries 3,5). Finally, conducting the reaction in a solely water based solvent system also gave no reaction (Table 4, entry 6).

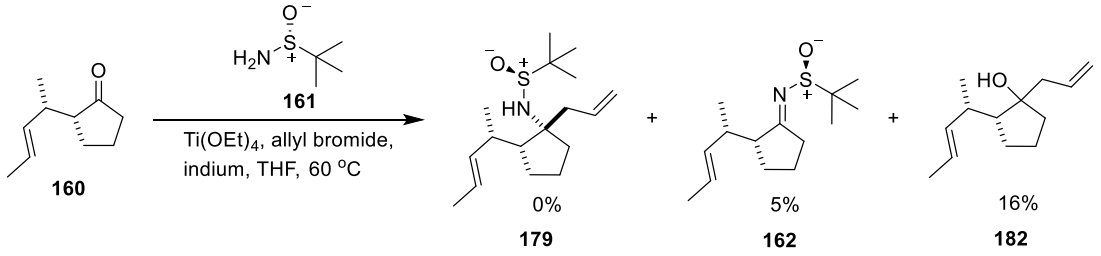
Reactions on the unsubstituted sulfinimine **180** were conducted as a model system. The desired product **181** was observed in all cases under the conditions reported in Table 4, apart from the water only solvent system, which gave no reaction (Figure 44). Although this result proves the effectiveness of the indium Barbier additions into sulfinimines, it also indicates the deficiency of using simplified imines as a model for **162**, as they poorly represent its reactivity.



180 **181**

Figure 44 - Indium addition model system

A second approach to the alkylation of **162** using indium was to conduct the condensation of **161** with the ketone **160** and subsequent alkylation with the indium reagent in a "one pot" synthesis. In situ formation of the sulfinimine **162** under Lewis acidic conditions would then allow for alkylation of the activated imine to give the product **179** (Figure 45), as described by the methodology of Bosque and co-workers.[92]



160 **179** **162** **182**

Figure 45 - Sulfinimine condensation Barbier reaction

Attempts to conduct the one pot condensation/alkylation however were not successful. Formation of the sulfinimine intermediate **162**, along with the alcohol **182** (from the addition of the allyl indium reagent to the ketone **164** before condensation of the amine **161** could occur) was observed, however no alkylation of the imine to give **179**.

The failure of these addition attempts clearly indicates the challenges posed by the substrate **162**. The congested steric environment, paired with the potential sensitivity to base, are likely the reason that alkylation attempts were unsuccessful. None of the tested Grignard or Barbier reactions delivered the desired product **173**.

Attempts at allylation of the sulfinimine **162** with allyl pinacol borane and allyl trimethylsilane as nucleophiles were examined (Figure 46). Treatment of **162** with allyl-Bpin in the presence of copper(I) chloride was unsuccessful, with no addition observed. The Sakurai reaction,[93] utilising allyl trimethylsilane and the Lewis acid titanium tetrachloride was also unsuccessful with no reaction observed.

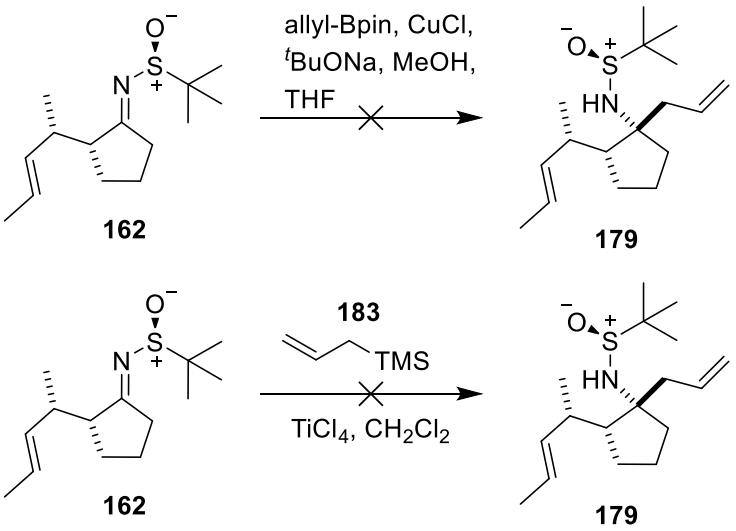


Figure 46 - Silane and borane addition attempts

With nucleophilic additions into the sulfinimine **162** proving ineffective, alternative approaches were considered. Using the formal [2+2] annulation method-

ology developed by Silvani, it was proposed that the reaction of the cyclic sulfinimine **162** with allenoates may give the spirocyclic azetidine **185** (Figure 47).[94] Unfortunately, however, no reaction was observed.

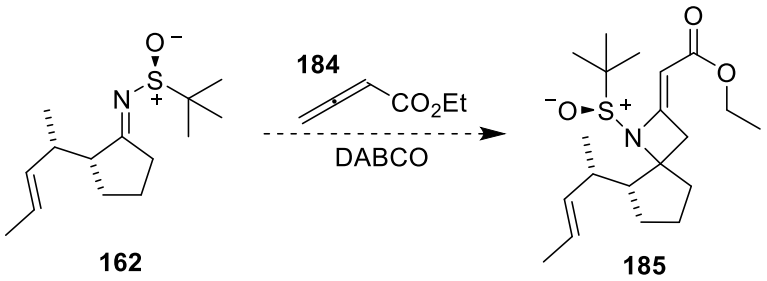


Figure 47 - Attempted azetidination via Silvani's formal [2+2] annulation methodology

As a final effort to add a nucleophile to the sulfinimine **162,** it was decided to attempt to reduce the sulfinimine **162** to the corresponding amine **186** (Figure 48). A hydride represents the smallest possible nucleophile, therefore a failure to reduce the imine **162** with a hydride would indicate that the imine is simply too sterically hindered for any nucleophilic attack to occur. The sulfinimine **162** was subjected to treatment with LAH in THF, however only traces of the reduced imine were observed by mass spectrometry and the amine **186** could not be isolated. This result concluded the efforts to use the sulfinimine **162**, which has been shown to be almost entirely unsusceptible to nucleophilic additions.

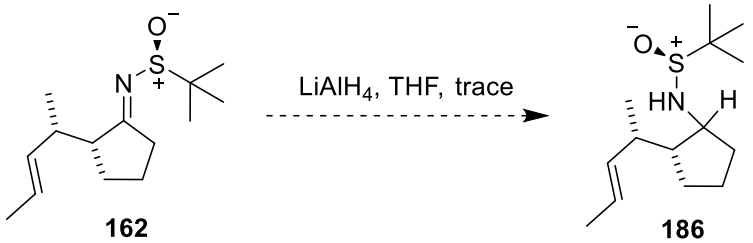


Figure 48 - Attempted reduction of **162**

Nucleophilic additions into ketones on five membered ring systems are known to be challenging, with the ring sterically hindering the attack of the nucleophile

into the electrophile. Ketimines are poor electrophiles in comparison to ketones, therefore it may be theorised that the poor electrophilicity of the bulky sulfinimine **162** is due to a combination of the large ᵗbutyl group and the side chain adjacent to the ketimine, creating a highly congested steric environment around the electrophile and the lower reactivity of the electrophile itself (Figure 49).

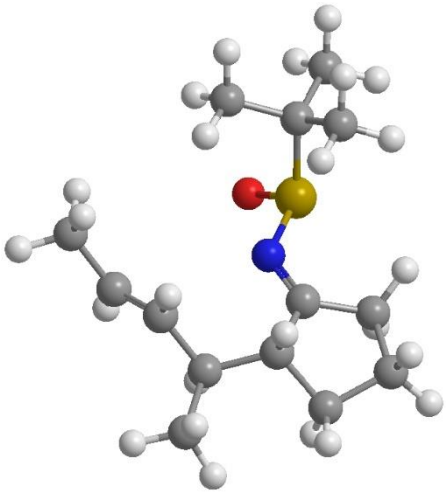


Figure 49 – MM2 energy minimised 3D representation of **162** illustrating the steric environment of the electrophile

2.4.2 – Development of Other Ketimines

The bulk of synthetic efforts were directed towards the sulfinimine **162**, which failed to yield any of the desired addition products under a wide range of conditions. As such the scope of ketimines was broadened, aiming for higher ketimine reactivity and/or reduced steric bulk, facilitating investigation into a range of other potentially viable nucleophilic additions into the ketimines.

The oxime **188** was synthesised from the diastereomerically enriched ketone **160,** with the aim of testing the viability of *N*-phosphinoylimines for the formation of the C-5 quaternary centre (Figure 50).[95] Addition of allyl Grignard to the *N*-phosphinoylimine **189, previously** formed in situ from **188,** gave a complex reaction mixture with traces of the desired product **190**. However, isolation of the trace product from the reaction mixture was unsuccessful.

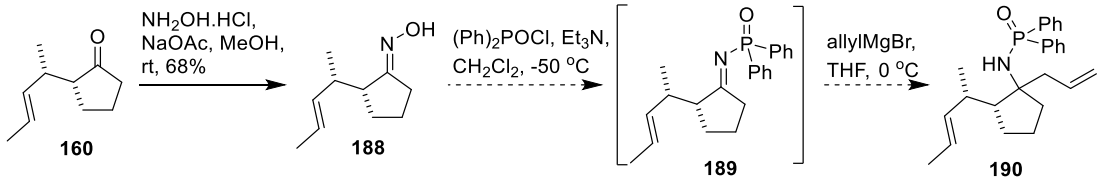


Figure 50 - Alkylation of N-phosphinoylimine **189** formed in situ

Attempts have also been made to synthesis the *N*-Boc protected imine **194** (Figure 51), which would potentially help to activate the imine to nucleophilic attack due to the electron withdrawing properties of the Boc group.[96] Installation of the *N*-Boc imine *via* the α-amido sulfone **193** however was unsuccessful, with no reaction observed.[97]

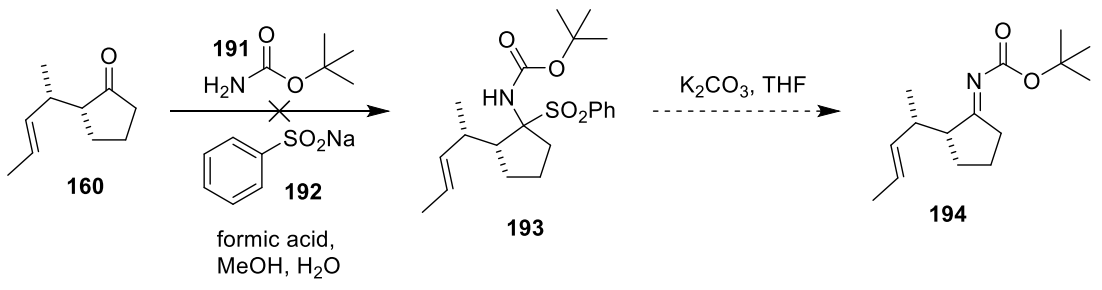


Figure 51 - attempted synthesis of the Boc protected imine **194**

Nitrone formation can be an effective method of activating an imine for nucleophilic addition, due to their electron withdrawing nature.[98] Alternatively the

use of a nitrone-olefin [3+2] cycloaddition on the nitrone **196** may allow for a different approach to the synthesis of the C-9 spirocyclic centre (Figure 52). The condensation reaction between *N*-methylhydroxylamine hydrochloride **195** and **160** however was unsuccessful, preventing further exploration of nucleophilic additions to nitrones or cycloadditions.

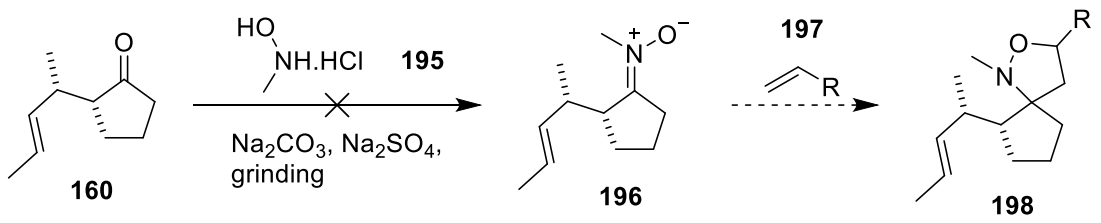


Figure 52 - Attempted condensation of N-methylhydroxylamine hydrochloride with **160**, for alkylation or nitrone-olefin (3+2) cycloadditions

This concluded efforts to synthesis spirocyclic core precursor molecules **173** *via* addition into ketimine intermediates.

2.5 1,4-Conjugate Addition Approach

With the synthesis of intermediates with the general core structure of **173** proving unsuccessful, an alternative approach was sought for the synthesis of the spirocyclic centre **144**. 1,4-conjugate addition of a nucleophile into the enoate **199** would give the intermediate **200**. Deprotonation and subsequent reaction with an appropriate electrophile would give intermediate **201**. Demethylation of the ester would then allow for a Curtius rearrangement to give the desired intermediate amine **203,** analogues to Uemura's synthesis (Figure 18).

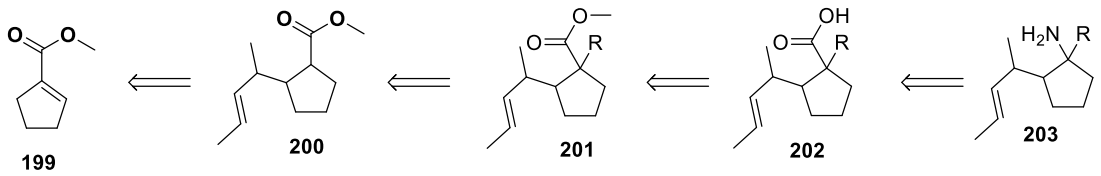
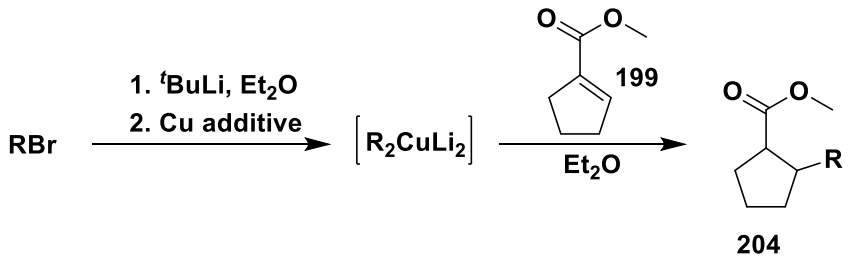


Figure 53 -Revised retrosynthesis for 1,4-conjugate addition

Attempts were made at 1-4 conjugate additions into the methyl carboxylate **199** using both the desired nucleophile R^1Br and a simpler analogue *i*-PrBr, using a range of different copper additives and conditions to form lithium cuperate nucleophiles (Table 5). However, 1,4-conjugate addition to give **204** was not observed in all cases, with only the 1,2-addition product isolated from the reaction.



Entry	R	Cu additive	Solvent	Temperature	Yield (%)	notes
1	R^1	CuCN	THF	-78 oC	0	1,2-addition
2	R^1	CuCN	THF	-78 to -40 oC	0	1,2-addition
3	R^1	CuCN	Et2O	-78 to -40 oC	0	1,2-addition
4	R^1	CuBr	Et2O	-78 to -40 oC	0	1,2-addition
5	R^1	CuCl	Et2O	-78 to -40 oC	0	1,2-addition
6	iPr	CuCN	THF	-78 oC	0	1,2-addition
7	iPr	CuCN	THF	-78 to -40 oC	0	1,2-addition
8	iPr	CuCN	Et2O	-78 to -40 oC	0	1,2-addition
9	iPr	CuCN	Et2O	-78 to -40 oC	0	1,2-addition

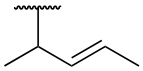
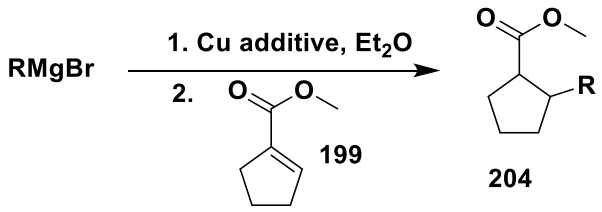


Table 5 - Attempted lithium cuprate 1,4-additions

Moving on, a range of copper catalysed Grignard additions were attempted (Table 6). However identical results were achieved to the lithium cuprate reactions with only 1,2-additions observed.



Entry	R	Cu additive	Solvent	Temperature	Yield (%)	notes
1	^{i}Pr	CuBr	Et_2O	-78 to -40 °C	0	1,2-addition
2	^{i}Pr	CuBr.Me_2S	Et_2O	-78 to -40 °C	0	1,2-addition
3	^{i}Pr	CuCl	Et_2O	-78 to -40 °C	0	1,2-addition
4	R^1	CuCl	Et_2O	-78 to -40 °C	0	1,2-addition
5	R^1	CuBr	Et_2O	-78 to -40 °C	0	1,2-addition
6	R^1	CuBr.Me_2S	Et_2O	-78 to -40 °C	0	1,2-addition
7	allyl	CuBr	Et_2O	-78 to -40 °C	0	1,2-addition
8	allyl	CuCl	Et_2O	-78 to -40 °C	0	1,2-addition
9	allyl	CuI	Et_2O	-78 to -40 °C	0	1,2-addition
10	allyl	CuBr	Et_2O	0 °C	0	1,2-addition
11	allyl	CuCl	Et_2O	0 °C	0	1,2-addition

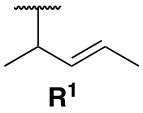


Table 6 - Attempted copper catalysed Grignard 1,4-additions

With 1,4-conjugate additions proving unsuccessful, as well as the original Tsuji-Trost route also ending in failure, an attempt was made to make a crossover of the two approaches (Figure 54). Conversion of the previously synthesised ketone intermediate **159** to the corresponding nitrile **205** followed by hydrolysis to the corresponding carboxylic acid **206** would allow for access to the desired intermediate **200**, as was the goal of the 1,4-conjugate addition route.

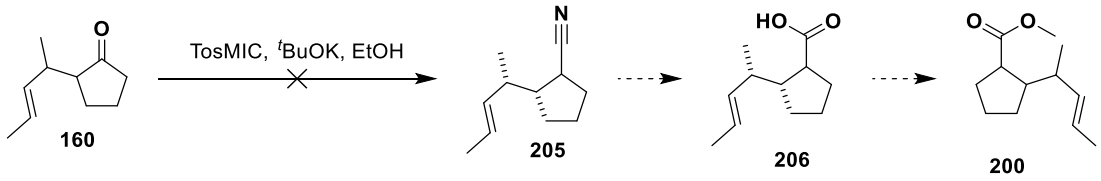


Figure 54 - Crossover synthesis

Unfortunately, synthesis of the nitrile **205** from the ketone **160** also proved unsuccessful, bringing an end to the synthetic efforts towards the halichlorine family using our proposed retro synthesis analyses.

2.6 C-15 Side Chain Synthesis

2.6.1 Synthetic Efforts Towards the Synthesis of the C-15 – C-21 Vinyl Chloride Side Chain

As is clearly indicated by the previous total syntheses of halichlorine **1** and the pinnaic acids **5** and **6**, having access to a range of potential C-15 – C-21 sidechain coupling partners is important for the late stage development of any synthesis of the halichlorine family of molecules.

Synthesis of potential C-15 side chains for use in the later stages of the total synthesis was therefore undertaken, with the aim to synthesise molecules of the general structure of **142** (Figure 33). With several synthetic approaches to the side chain already developed, it was decided to begin synthesis of Weinreb's phosphonate sidechain **118**.

Weinreb's phosphonate **118** has been a mainstay in the synthesis of halichlorine **1** and pinnaic acid **5**, for approaches utilising Wittig olefination reactions and can be adapted for approaches utilising cross metathesis.

Carboxylation of 3-butyn-1-ol **113** *via* deprotonation with ^{n}BuLi and subsequent reaction with carbon dioxide (dry ice) gave the carboxylic acid **114** (Figure 55). Stereoselective addition of HCl across the alkyne gave the chlorinated product **115** in good yields (72-86%) with a *Z*:*E* isomer ratio between 76:24 and 80:20. TBS protection of the alcohol and carboxylic acid moieties allowed separation of the exclusively *Z* product **207**, with a yield of 75% after purification.

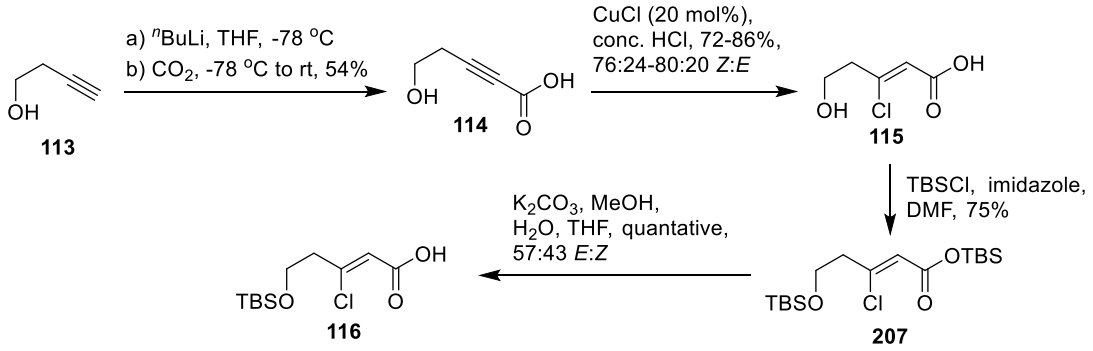


Figure 55 - Synthesis of Weinreb's side chain

Selective deprotection of the carboxylic acid under basic conditions yielded **116**. However, scrambling of the double bond geometry was observed, with a *Z*:*E* isomer ratio of 43:57, not observed in the literature. An alternative route was therefore sought for sidechain synthesis. Using a route previously developed by the Stockman group, the C-15 sidechain **301** was synthesised in 4 steps from the alcohol **113** (Figure 56).

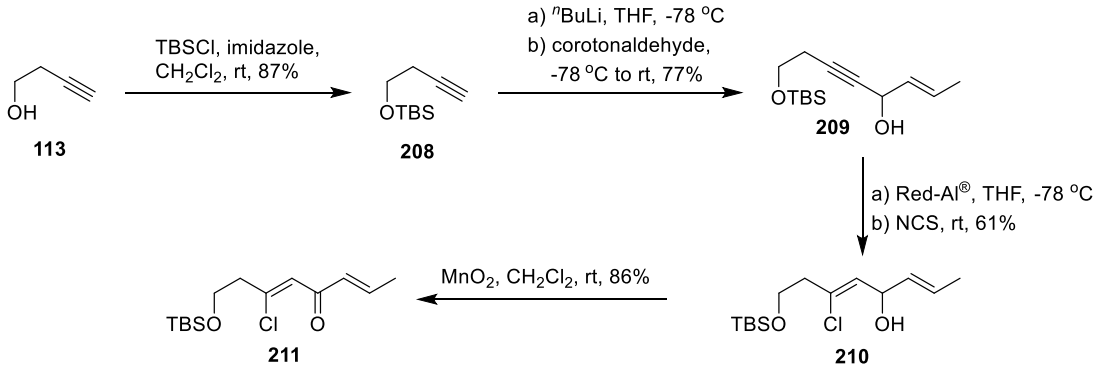


Figure 56 - Synthesis of the Stockman side chain

TBS protection of 3-butyn-1-ol **113** yielded the protected alcohol **208** in 87% yields. Lithiation with ^{n}BuLi and subsequent addition to crotonaldehyde afforded **209** with a yield of approximately 77%.

Reduction of the alkyne **209** and *in situ* chlorine addition gave the hydroxy vinyl chloride **210** in good yield with the correct stereochemistry of the vinyl bond. Oxidation of **210** with MnO_2 to **211** however proved variable, with the result found to be highly dependent upon the batch of manganese oxide used. However, synthesis of **211** from **210** was achieved in yields up to 86%, completing the synthesis of the C-15 side chain ready for cross metathesis coupling with potential halichlorine and pinnaic acid core analogues.

Previously within the Stockman group, the side chain **211** has been successfully coupled with the simplified pinnaic acid core analogue **212,** demonstrating the viability of a cross metathesis approach for the late stage addition of the C-15 side chain to pinnaic acid like cores (Figure 57).

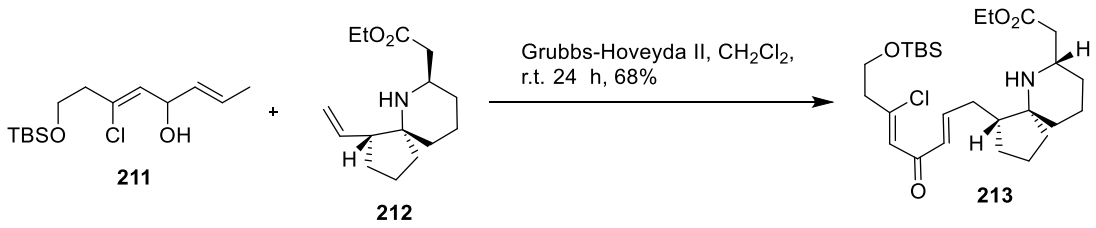


Figure 57 - previous model study for the attachment of the C-15 side chain *via* cross metathesis.

2.7 *N*-allylation of Sulfinimines

Recently, *N*-allylation of sulfinimines was reported by Yang (Figure 58), a previous member of the Stockman group. Under the same conditions previously explored for the Tsuji-Trost allylation of sulfinimines (Figure 38), allylation of the nitrogen position of the sulfinimine was reported, rather than the formerly explored allylation of the ketimine carbon position.[99]

Using the base DBU, *N*-allylation of the sulfinimine **215** (formed from the condensation of alpha tetralone **214** and 2-methyl-2-propanesulfinamide **160**) was reportedly observed in modest yield, to give **217**, along with the *C*-allylated product **216**.

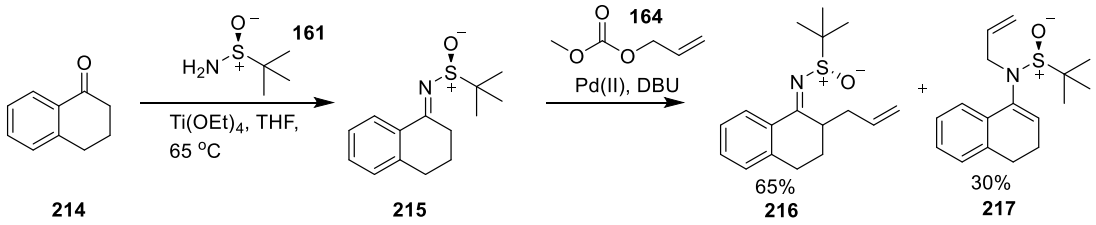


Figure 58 - Yang's *N*-allylation

N-allylation of sulfinimines would potentially provide an alternative route for the synthesis of compounds **156** (Figure 59), which when previously attempted *via* a Buchwald-Hartwig coupling approach, was unsuccessful (Figure 34). Opening up the potential to explore the previously theorised [3,3] sigmatropic rearrangement of **156** and subsequent development towards the halichlorine **1** core.

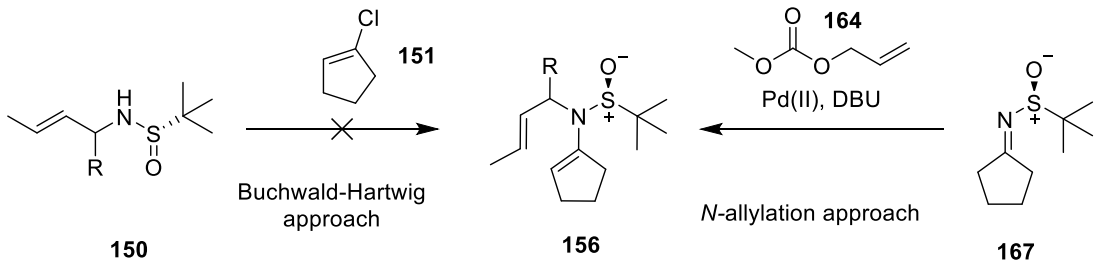
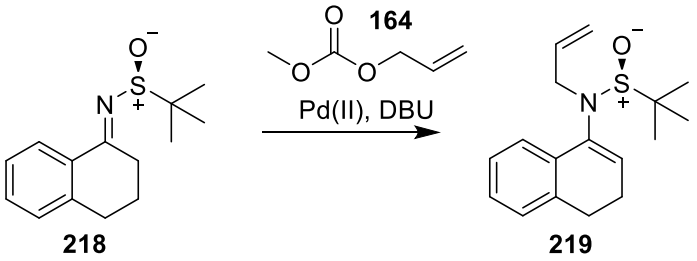


Figure 59 - Alternative route to **156**

Reproduction of the reported *N*-allylation observed under Yang's optimal conditions, however, was unsuccessful (Table 7, entry 1). Using a range of other bases, which had been previously used in Yang's paper, for *N*-allylation, again gave only the *C*-allylated product (Table 7, entries 2,3). Repetition of the reactions conducted at a lower temperature also resulted in none on the desired product **219** (Table 7, entries 4,5,6). Doping the reaction mixture with Pd(II) as well as not using anhydrous conditions also failed to yield **219** (Table 7, entries 7,8). Finally, proton sponge and BEMP were tested as bases, but these also proved unsuccessful (Table 7, entries 9,10).



Entry	Base	Temp (°C)	Yield of 219 (%)	Notes
1	DBU	Reflux	0	
2	Et_3N	Reflux	0	
3	DIPEA	Reflux	0	
4	DBU	40	0	
5	Et_3N	40	0	
6	DIPEA	40	0	
7	DBU	40	0	Non-dry solvent / glassware
8	DBU	40	0	Doped with $Pd(OAc)_2$ (10mg)
9	Proton sponge	40	0	
10	BEMP	40	0	

Table 7 - Attempted *N*-allylation of **218**

Unable to reproduce the originally reported result, this line of investigation was ended. Since the conclusion of this work, the group of Lu has published on the rearrangement of *N*-methylated *N*-*tert*-butanesulfinyl enamines **221** (Figure 60).[100] *N*-Methylation was achived *via* treatment with KHMDS and MeOTF, leading to an Aza-Mislow-Evans rearrangement to the ketone product **222**. This rearrangement may explain the failure to isolate the *N*-allylation product **219.**

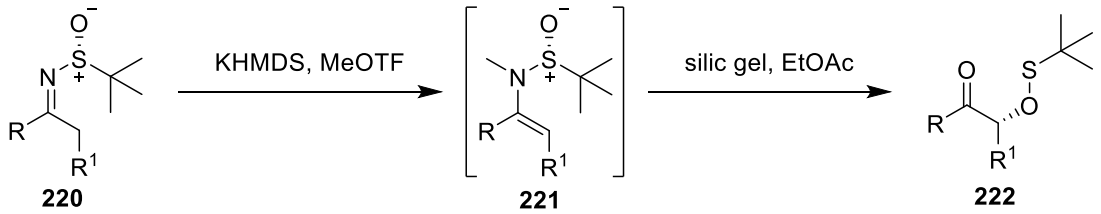


Figure 60 - rearrangement of *N*-methylated *N*-*tert*-butanesulfinyl enamines

2.8 Conclusions

Efforts towards the total synthesis of halichlorine **1** and its related family of molecules, the pinnaic acids **5/6** and pinnarine **7,** have proven unsuccessful to date, with efforts stalling at the construction of the C-9 spirocyclic center of the core structure. Efforts to circumvent the synthetic challenges posed by the intermediate ketimine's **159** lack of reactivity *via* alternative synthetic methodologies and pathways have also been met with impasses, preventing further exploration of the proposed synthetic route derived from the initial retro synthetic analysis for the synthesis (Figure 33).

Diastereoselective synthesis of the functionalised cyclopentanone **145** has been successful, with optimisation for large scale synthesis effectively completed enabling further exploration of derivative molecules to be conducted (Table 2).

Synthesis of potential C-14 side chains suitable for olefin metathesis with late stage azaspirocyclic core molecules during the closing stages of the total synthesis has been completed with the side chain molecule **211** (Figure 56).

Investigation of the *N*-allylation of sulfinimines previously reported by Yang has been abandoned after repetition of the literature was unsuccessful in delivering the reported *N*-allylation (Figure 58), preventing further exploration of the methodology. Recent developments in the field indicate the rearrangement of *N*-allylated sulfinimine may be responsible for the failure to isolate the desired product.

2.9 Future Work

With all attempts to date unsuccessful at delivering the synthesis of the C-9 quaternary spirocyclic centre from a range of ketimines **146**, the viability of the synthetic route through such ketimines is in question. However, continuation of the exploration of the ketone intermediate **160** and other ketimines **146,** in order to deliver the C-9 centre, is possible.

Nucleophilic addition into the ketone **160** to give **223**, and conversion of the resulting alcohol to tosyl or mesyl sulfonate ester leaving group may then allow for nucleophilic substitution to give the amine **225**, delivering C-9 quaternary centre (Figure 61).

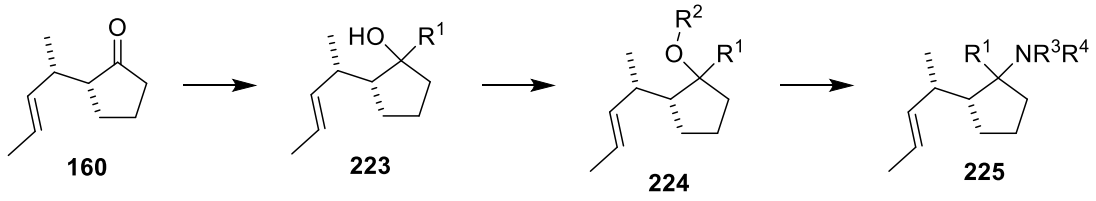


Figure 61 - possible development of the ketone intermediate **160**

A promising route for the development of the oxime intermediate **188** is the recent work of Kürti,[101] who demonstrated an acid-catalysed aryl boronic allylation of oximes (Figure 62). Notably Kürti's methodology derived successful allylation of highly hindered and bulky oximes, as well as oximes on small 4 and 5 membered rings. Conceivably this methodology may therefore deliver the allylation of **188** to deliver the C-9 quaternary centre.

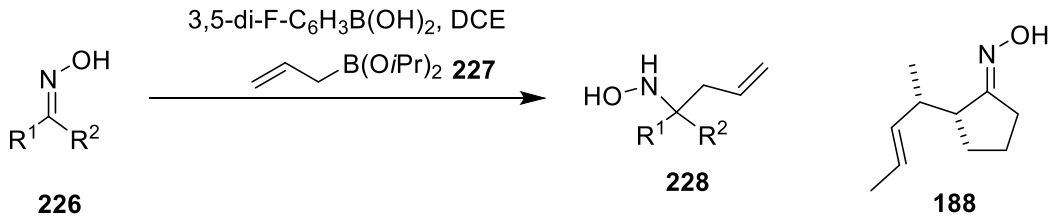


Figure 62 - allylation of **188**

Exploration of other synthetic routes for the synthesis of halichlorine, avoiding the ketimine intermediate **146** remains the most attractive route for the continuation of studies into the total synthesis of the halichlorine family, owing to the impasses described above.

The previous formal synthesis of halichlorine conducted within the Stockman group (Figure 30, Figure 31, Figure 32), utilising a bidirectional approach and tandem reactions, was limited by two key synthetic transformations. Firstly, the epimerisation of the C-5 centre, and secondly the installation of the challenging C-14 methyl group with the correct stereochemistry.

Recently within the Stockman group, the epimerisation of the C-5 centre has been achieved at an earlier stage of the synthetic pathway, converting **229** to its C-5 epimer **230** (Figure 63).

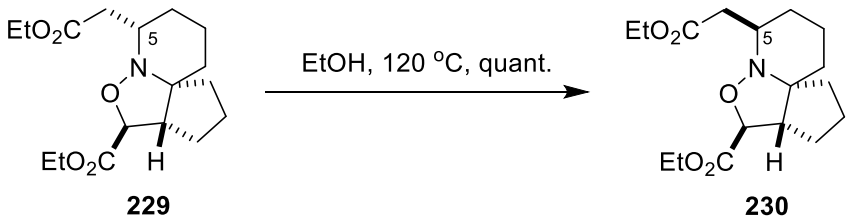


Figure 63 - Epimerisation of the C-5 centre

The epimerisation of the C-5 centre at this stage in the synthesis opens up the possibility for the exploration of new routes for the synthesis of the halichlorine family as well as new approaches for the instillation of the C-14 methyl group (Figure 64).

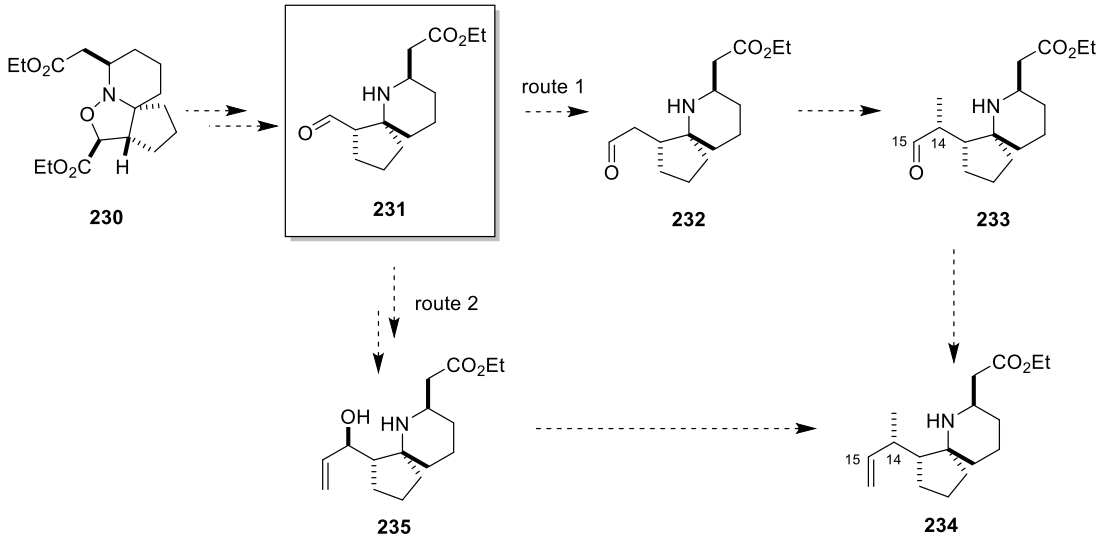


Figure 64 - Potential route for the installation of the C-14 methyl from **230**

After epimerisation of the C-5 position, conversion to the intermediate **231**, using a previously developed methodology, would allow for exploration of the installation of the C-14 methyl group *via* a number of alternative routes. This includes alpha methylation to give **233**, or alternatively, selective alkylation then a S_N2 inversion of the C-14 centre to give the product **234**. These two examples are demonstrative of the range of possibilities this new approach to the halichondrins core offers.

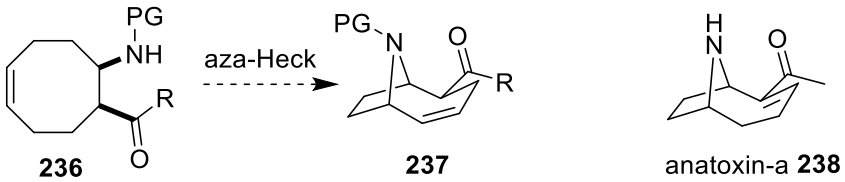
The side chain **211,** suitable for coupling *via* cross metathesis, has been completed, however having access to a range of other side chain analogues will be

beneficial to the ongoing efforts for the synthesis of the halichondrins. Completion of the Wittig side chain **120**, along with the development of other variations of the C-14 side chain, will facilitate rapid late stage development of the total synthesis. Therefore, they remain a central goal for any ongoing efforts towards the total synthesis of the halichlorine family.

Aza-Heck Cyclisations for the Synthesis of Anatoxin-a Analogues

3. Synthesis of Anatoxin-a Analogues

Recently within the Stockman group, synthetic methodology has been in development for the use of aza-Heck cyclisation reactions for the synthesis of bicyclic alkaloids. These bicyclic alkaloids have an analogous structure to anatoxin-a **238** (also known as "very fast death factor"), a highly potent nicotinic acetylcholine receptor agonist, found naturally in cyanobacteria (Figure 65).



236 **237** anatoxin-a **238**

Figure 65 - Aza-Heck reaction and anatoxin-a **238**

Synthesis of the aza-Heck precursor **242** was developed from **239** (Figure 66). Addition of chlorosulfonyl isocyanate **240** gave the β-lactam **241** in fair yields, which was ring opened to give the aza-Heck precursor **242** (Figure 66). Catalyst screening and optimisation was conducted by other members of the group for the aza-Heck cyclisation, identifying $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMF as the optimal conditions for the aza-Heck cyclisation reaction.

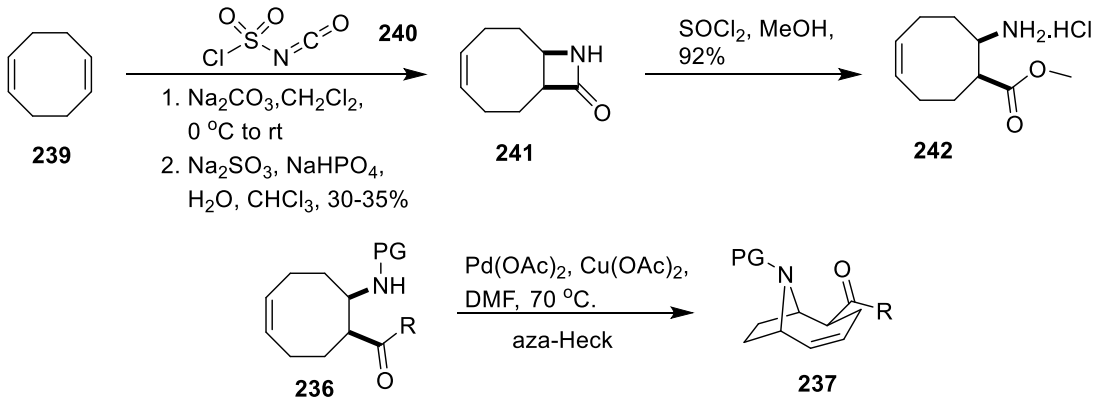


Figure 66 - Synthesis of precursors and aza-Heck conditions

Due to the potential for compounds with a close structural relationship to anatoxin-a **238** to exhibit acute toxicity when unprotected (without a nitrogen protecting group), a well understood protection group strategy is critical for the safe development of this methodology, and will ensure compatibility with a wide range of secondary synthetic transformations.

Synthesis of precursors **236** with a range of protecting groups was conducted in conjunction with several other researchers in order to rapidly asses a range of protecting groups. Boc and Cbz protections were completed and cyclised under the previously developed conditions (Figure 67).

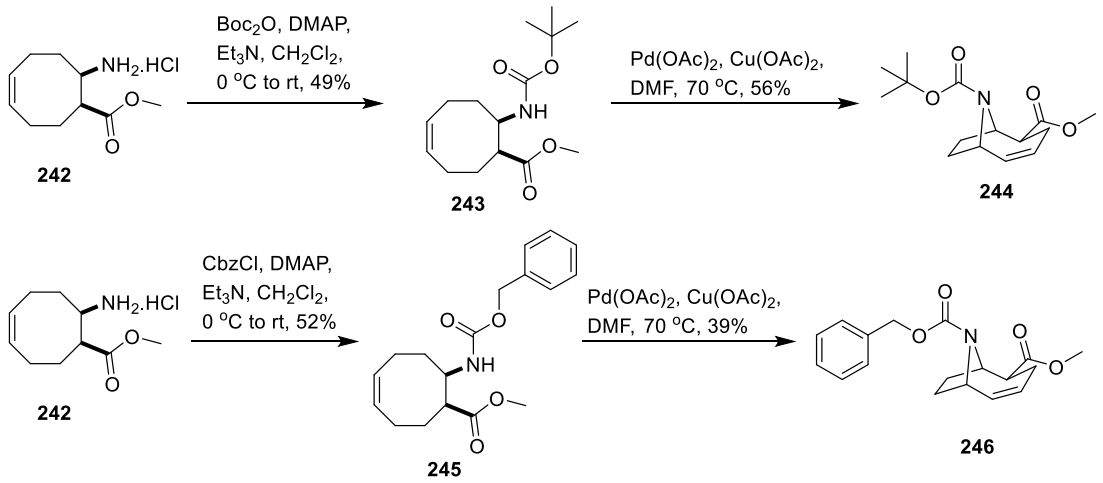


Figure 67 - Protections and aza-Heck cyclisations

Both Boc and Cbz protecting groups were installed in fair yields to give **243** and **245** respectively. Cyclisation of the Boc protected **243** was conducted with fair yields. Notably, under the reaction conditions for the cyclisation of the Boc protected precursor **243**, traces of the deprotected amine were observed by mass spectrometry in the reaction mixture. The crude reaction mixture was therefore subjected to a re-protection during the workup. Neutralizing the acetic acid present in the reaction mixture with triethylamine, before treatment with Boc_2O and DMAP, gave the fully protected product **244**, with no trace of the unprotected amine detected. NMR analysis of the bicyclic product **244** however was impeded by the rotameric nature of the product, with all peaks appearing as broad multiplets, apart from the methyl and *tert*-butyl groups. Cyclisation of the Cbz protected **245** to the bicyclic product **246** produced poor yields however, with no deprotection observed. The product **246** was also shown to be rotameric at room temperature when analysed by NMR. Coalescence of the split peaks was observed at 80 °C, and resulted in a sharp, well resolved spectra.

A range of other protection groups for **237**, along with further transformations of the cyclised products, have been investigated by other members of the group.

Monomers from Vernolic Acid

4. Introduction

4.1 Vernolic Acid as a Source of Renewable Monomers

In recent times seed oils have become an important source of renewable bio feed stocks and have found many uses in the chemical industries, such as within the adhesives, coatings, solvent and polymer industries, to name but a few.[102] Functionally diverse and able to be harvested from high yielding crops, seed oils represent an attractive feedstock for industrial application, as well as a potential "green" alternative to more traditional non-renewable petrochemicals, especially for the synthesis of renewable polymers.[103–105]

This project focuses on the use of Vernonia seed oil extracted from Vernonia seeds as the bio feed stock for the synthesis of monomers. *Vernonia galamensis* (also known as ironweed) is a plant common to eastern Africa and is the highest yielding source of Vernonia oil (Figure 68), with an oil content of up to 42% by mass.[106] Hydrolysis of the Vernonia oil triglycerides yields the epoxy fatty acid called vernolic acid **247**, with a yield of up to 80% by mass, representing an exceptionally high yield.[107] The high yield of vernolic acid is due to the singular makeup of the triglycerides **248**, which consist of only three vernolic acid units

and one glycerol unit. This makeup is unusual compared to other common seed oils where the triglycerides can consist of up to three different fatty acids, such as in soybean and linseed oils.

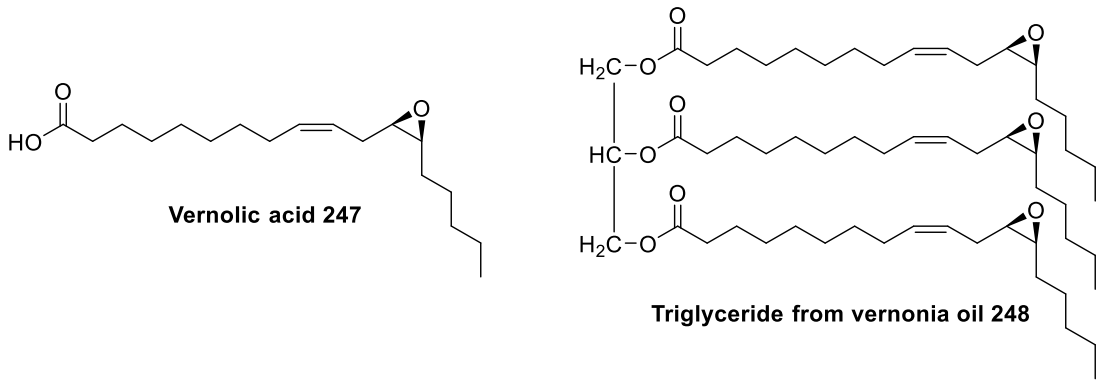


Figure 68 - Vernolic acid **247** and the triglyceride from vernonia oil

The second key factor for the selection of Vernonia oil as a feed stock along with the yield of vernolic acid is the chemical functionality offered by vernolic acid **247**. With a carboxylic acid, alkene and epoxide functionality, a wide variety of synthetic chemistry can be conducted into the different functionalities, which may lead to a range of monomers being developed from a single source. Currently, products already exist on the market using Vernonia oil in its triglyceride form as a crosslinking epoxide polymerization monomer, used for surface coatings and finishes.

This project aims to provide a total approach to polymer synthesis, starting at the crop feedstock (*Vernonia galamensis*) through isolation of vernolic acid **247**, chemical modification for monomer synthesis and finally polymerisation of

monomers. In doing so, a "green" route will be developed from start to finish, which will deliver high value, functional polymers from a renewable feedstock.[2]

The project is divided into three focus areas. Firstly, the extraction of the Vernonia seeds to yield Vernonia oil (as well as the uses for the seed "cake" waste) and the hydrolysis of the triglycerides to yield vernolic acid **247**.

For the extraction of Vernonia oil a key advancement has been the use of super critical CO_2, as opposed to the traditional mechanical or solvent based oil extraction methods which are lower yielding and leave a waste seed cake with lower utility. Extraction of Vernonia oil from the seeds by super critical CO_2 yielded 32% by mass, with an extraction efficiency of 80%. The extraction of the Vernonia oil *via* super critical CO_2 also leaves a "clean" seed cake, which may be suitable for use as animal feed. GC analysis of the extracted oil gave a vernolic acid content of 79-80%, compared to 66% *via* extraction with *n*-hexane.

The second focus area is the synthetic processing of vernolic acid **247** into viable monomers for use in polymerisation reactions. The work contained herein is the development of the synthetic strategy for monomer synthesis from vernolic acid. Aiming to synthesis monomers for use in polyesterification polymerisations, the monomers must have a diacid, diol or a combination of a carboxylic acid and an alcohol functionality to be viable for polymerisation.

Along with synthesising monomers with desirable functionality, we aim to achieve monomer synthesis in a minimum number of concise, high yielding steps with minimal to no purification. In doing so, we aim to reduce the waste and environmental impact of the monomer synthesis.

The final focus area is the polymerisation, testing and application of polymers synthesised from vernolic acid derived monomers. With a range of monomers developed from vernolic acid **247**, we aim to employ catalytic, enzymatic or supercritical polymerisation techniques to create a range of potentially functional polymers, completing our approach to the utilisation of Vernonia oil for the synthesis of sustainable polymers.

5. Results and Discussion

5.1 Synthesis of the Monomer **249**

At the onset of this project preliminary testing had been conducted on the synthesis of the hydroxy dienoic acid monomer **249** from vernolic acid **247** (Figure 69). Base mediate opening of the epoxide, using LDA, should furnish the monomer **249**, however poor conversion, a large excess of reagents used and a crude product mixture requiring complex purification was observed. It was apparent that optimisation would be vital to the potential of using **249** as a monomer.

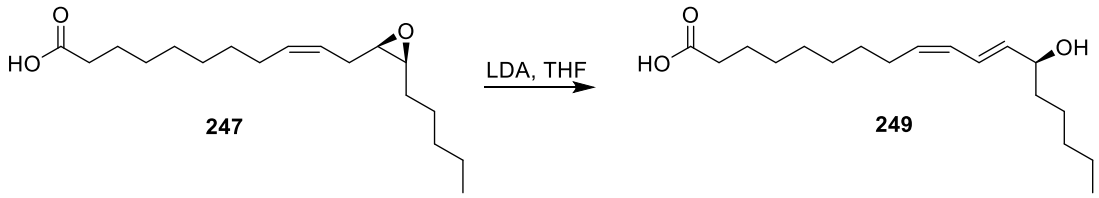


Figure 69 - synthesis of monomer **249**

The initial method provided from the preliminary testing had used a large excess (6 equivalents) of commercially purchased LDA at a high dilution, which when repeated gave the same poor results as had been previously observed, with incomplete consumption of the vernolic acid **247** and a low yield (Table 8). Adjusting the concentration from 0.02 molar to 0.1 gave the same results as before, with a concentration of 1 molar resulting in a mixture too viscous to properly stir and a completely intractable mixture of products by NMR.

Substituting commercially purchased LDA, which had proven highly variable in molarity and quality, for freshly prepared LDA was the obvious next step. LDA was prepared in situ from ^{n}BuLi and diisopropylamine, resulting in a large improvement in conversion, with no vernolic acid **247** present in the reaction mixture after 1 h. With complete conversion observed, the equivalents of LDA were reduced to 3, and the reaction scale increased to 5 g of vernolic acid, with no drop in conversion and yield. Concentration was increased once again, giving identical results. Isolation of **247** was achieved in quantitative yields, with no further purification required, after modification of the workup procedure to include an acid wash, removing any traces of diisopropyl amine from the product.

Finally reducing the LDA equivalents to 2.2 saw a small drop in conversion, with traces of vernolic acid **247** present in the crude mixture. However, the crude product was deemed pure enough for polymerisation.

With quantitative yields achieved, no purification needed, and minimal excesses of reagents used, all of the synthesis goals for this monomer were achieved and the product and method passed on for polymerisation testing.

Entry	Concentration M	LDA equivalents	Conversion %	Yield %	Scale mmol	notes
1	0.02	6[a]	Ca~70	-[c]	0.337	Using commercial purchased LDA
2	0.1	6[a]	Ca~75	-[c]	0.337	Using commercial purchased LDA
3	1	6[a]	-[b]	-[c]	0.337	Using commercial purchased LDA
4	0.1	6	100	84[d]	0.337	
5	0.1	3	100	89[d]	0.337	
6	0.1	3	100	99[d]	16.887	
7	0.2	3	100	99[d]	16.887	
8	0.2	2.2	Ca~99	98[d]	16.887	

a- Theoretical equivalents added based on the volume of LDA added and the reported molarity of the commercially purchased reagent. b- conversion not measured due to intractable NMR data. c- product not isolated from crude mixture. d- yield of product with no further purification required.

Table 8 -synthesis of **249**

5.2 Synthesis of the Monomer **250**

With the base mediated opening of the epoxide successful, the second monomer selected for synthesis was the dihydroxy enoic acid product **250**, via acid mediated epoxide opening (Figure 70).

Refluxing vernolic acid in acetic acid, followed by the addition of potassium hydroxide in methanol, afforded the ring opened product **250**. After a challenging recrystallised at low temperature due to the "butter like" qualities of the products, the pure product was afforded with a total yield of 85% in two crops (66%, 19%). This completed the synthesis work on this monomer, which was now suitable for polymerisation testing.

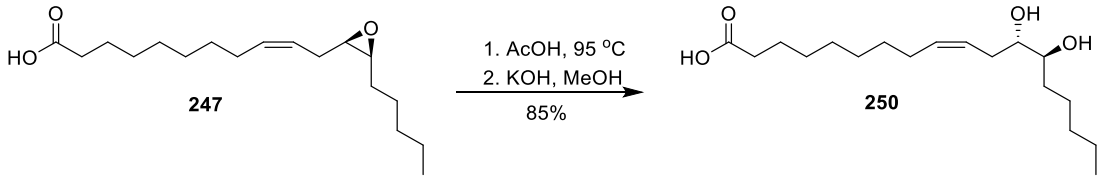


Figure 70 - synthesis of monomer **250**

5.3 Synthesis of Other Single Step Monomers

With the synthesis of two monomers completed in a single step from vernolic acid **247**, the synthesis of other monomers in a single step from vernolic acid **247** were explored, specifically the global reduction of vernolic acid **247** to the triol **251** with $LiAlH_4$ (Figure 71). However, attempts at the reduction resulted in complex mixtures of products, with varying levels of reduction, which were unsuitable and undesirable for use as monomers.

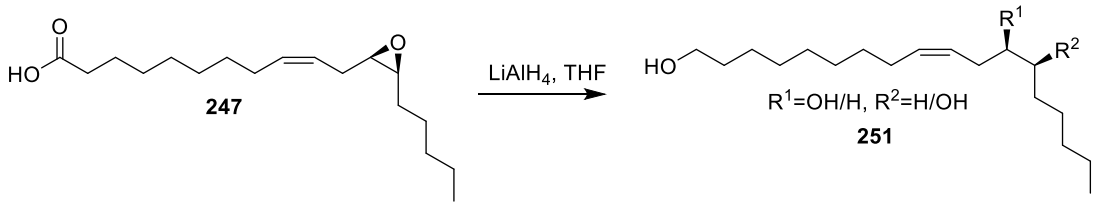


Figure 71 - $LiAlH_4$ reduction of **247**

In the same vain, the monomer products **249** and **250** were also submitted to $LiAlH_4$ reductions, which gave similar results of complex mixtures to the reduction of vernolic acid. These monomers were therefore not explored further.

5.4 Synthesis of the Monomer Intermediate Aldehyde 252

With single step synthesis of monomers explored from vernolic acid **247**, multi-step preparations were examined, focusing on using the epoxide cleaved aldehyde product **252** as an intermediate for the synthesis of a variety of monomers.

Cleaving the epoxide of vernolic acid **247** with periodic acid and subsequent isomerisation into conjugation gives the alpha-beta-unsaturated aldehyde product **252**, known also as traumatin, a plant hormone (Figure 72).[108] The enone **252** may then be subjected to a range of oxidisations or reductions to give a number of different diacid and diol monomers.

Cleavage of the epoxide was achieved using periodic acid, although, isolation proved challenging. When using ^{t}BuOH and water as solvent for the reaction,

the ^{t}BuOH proved impossible to remove without degrading the product. Changing to THF and water for the solvent system allowed for isolation of the product in yields of 64% after purification via rapid column chromatography. However, the product proved to be highly unstable, degrading to an unrecoverable mixture when columned slowly over silica, as well as at room temperature in solution or concentrate. Immediate usage for subsequent steps proved to be best practice.

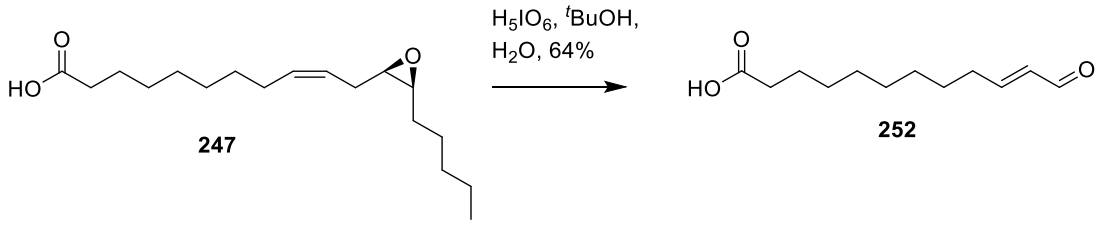


Figure 72 - synthesis of aldehyde **252**

5.5 Synthesis of Monomers from the Intermediate Aldehyde **252**

Synthesis of the diol **253** was successfully conducted *via* the reduction of aldehyde **252** with $LiAlH_4$ to give the monomer **253** as well as the over reduced fully saturated monomer **254** in a 2:1 ratio of the desired saturated monomer to the unsaturated. Although separation of the two products proved to be unfeasible, the mixture could still be effectively used as a monomer, completing the work on this product.

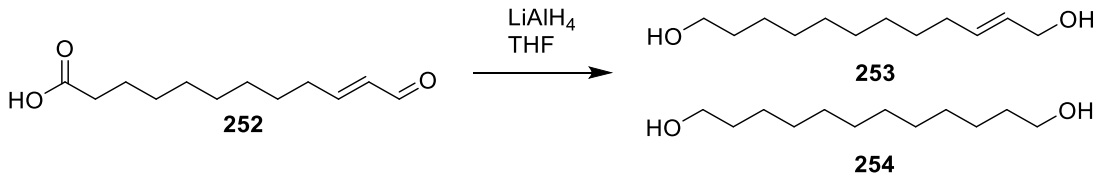
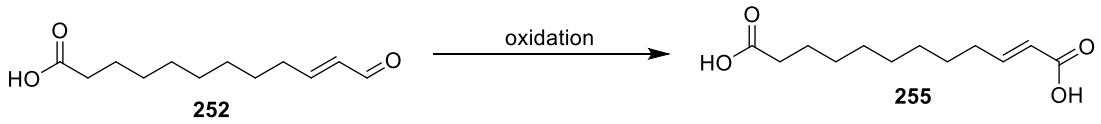


Figure 73 - diol monomers

5.5.1 Oxidation of the Aldehyde 239 to the Diacid Monomer 242

Attempts to oxidise the aldehyde **252** to the diacid monomer **255** were conducted using a range of different oxidation conditions (Table 9). The instability aldehyde intermediate **252** however proved to be challenging to overcome, with all the attempted protocols resulting in complete degradation of the reaction mixture.



Entry	Oxidation	Reagents	Result
1	Pinnick	$NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, H_2O	Degradation
2	Pinnick	$NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, MeCN, H_2O	Degradation
3	Jones	CrO_3/H_4SO_4, Acetone	Degradation, trace by ms
4		$(PhSe)_2$, H_2O_2, H_2O	Degradation, trace by ms
5		H_5IO_6, PCC, MeCN	Degradation
6		Oxone, DMF	Degradation
7		$KMnO_4$, Na_2HPO_4, H_2O	Degradation
8	Tollens	$AgNO_3$, KOH, EtOH, H_2O	Degradation

Table 9 - oxidation screen for **255**

Further attempts to telescope the synthesis of the aldehyde **252** and the oxidation or reduction to corresponding monomers were attempted in order to try

and avoid the isolation and degradation of the aldehyde **252**. However, both methods resulted in an intractable mixture of degradation products (Figure 74).

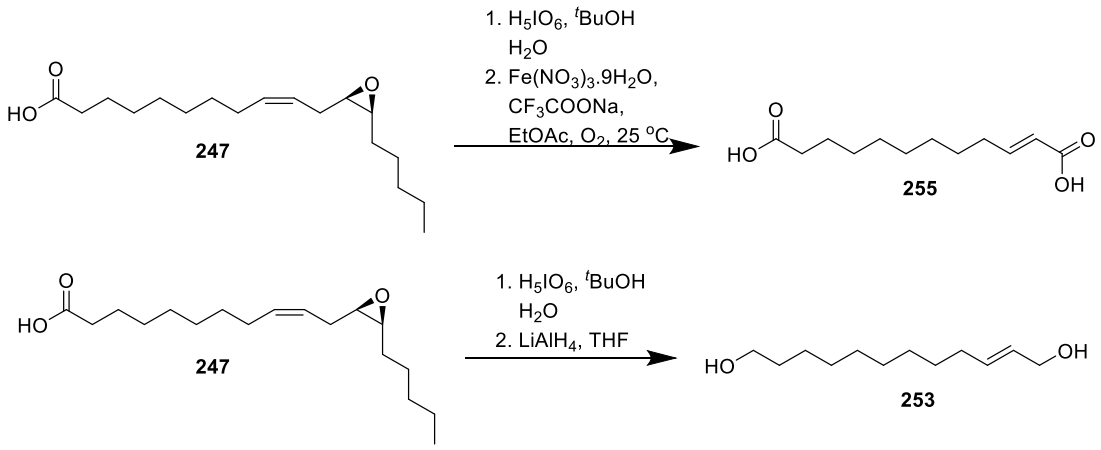


Figure 74 - one step monomer syntheses

Finally, attempts to selectively reduce the aldehyde **252** to the corresponding hydroxy acid **256** using a Luche reduction were also unsuccessful, due to degradation of the aldehyde **252** (Figure 75).

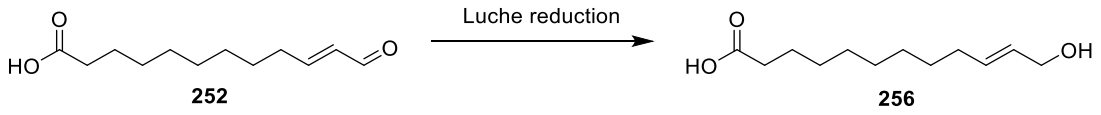


Figure 75 - Luche reduction of **252**

5.6 Conclusions and Future Work

The hydroxy dienoic acid **249** and the diol **250** have been synthesised on a large scale in quantitative and good yields respectively with either no or minimum purification needed after isolation. Exploration of homopolymerisation reactions utilising **249** and **250** are being undertaken, as well as material property testing.

Synthesis of the aldehyde **252** has been completed successfully, however the product has proven to be highly unstable, limiting its viability. Degradation of starting materials and reaction mixtures has hampered the synthesis of monomers from the aldehyde **252** by oxidation or reduction.

Nevertheless, the reduced monomer **253** was successfully synthesised as a mixture with the full reduced byproduct **254**. This mixture is also undergoing polymerisation testing.

Oxidation of the aldehyde **252** to the diacid **255** has proven elusive, with the unstable nature of the aldehyde **252** hampering progress.

In total, several viable monomers have been synthesised and optimised, although a number of challenges have hampered attempts to develop a wider range of monomers, such as the instability of intermediates and products. Notably, the “butter like” properties of vernolic acid **247** and its products also proved to be practically challenging.

Currently, work is ongoing on the synthesis and characterisation of the material properties of the monomers reported herein, along with attempts to resolve the synthesis of monomers from the aldehyde **252** and to develop other novel monomers from vernolic acid **247**.

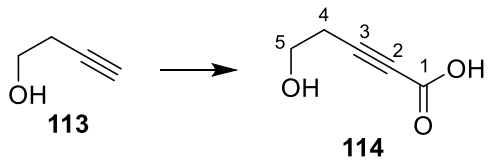
6. Experimental

All reagents were purchased from commercial sources and used without additional purification unless stated otherwise. Cyclopentanone, cyclohexanone and diisopropyl amine were freshly distilled under argon onto 4 Å molecular sieves. LiCl was oven dried prior to use. Tetrahydrofuran was freshly distilled under an atmosphere of argon, from the sodium anion of benzophenone. All other anhydrous solvents were purchased or obtained from in house solvent purification towers. All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen or argon, unless stated otherwise. Brine is a saturated aqueous solution of sodium chloride. Solvent evaporation was performed using a rotary evaporator under reduced pressure.

Thin layer chromatography was performed on Merck silica gel 60 F254 or Fluka alumina plates and visualised by UV lamp, aqueous alkaline potassium permanganate or ethanolic acidic vanillin. Column chromatography was performed on silica gel Fluka 60 or Merck aluminium oxide 90. ^{1}H and ^{13}C NMR spectral data were recorded using a Bruker DPX300, Bruker DPX400, Bruker AV400, Bruker AV(III)400 and Bruker AV(III)400HD spectrometers. Chemical shifts are quoted in ppm with either chloroform (^{1}H-NMR - 7.26 ppm) or deuterated chloroform (^{13}C-NMR – 77.0 ppm) as reference, unless stated otherwise. Coupling constant values *J* are given in Hertz. Infrared spectral data were recorded using

a Perkin-Elmer 1600 FTIR spectrometer. Mass spectra data were recorded using a Bruker MicroTOF (ESI) spectrometer. Optical rotations were measured at ambient temperature (23 °C) in $CHCl_3$ solutions with a polarimeter using a 1 mL capacity cell with 1 cm path length.

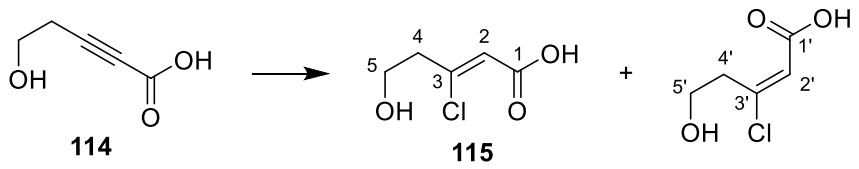
5-Hydroxypent-2-ynoic acid (114) [44]



To 3-butyn-1-ol (4.00 g, 57.1 mmol) in tetrahydrofuran (100 mL) at -78 °C in a schlenk flask fitted with a dropping funnel, ^{n}BuLi (1.95 M in hexanes, 58.5 mL, 114 mmol) was added dropwise over 1 hour, under an atmosphere of N_2. Carbon dioxide was bubbled through the resulting slurry for 1 hour, before tipping the reaction mixture onto a bed of dry ice. After warming to room temperature, 6 M HCl (20 mL) was added to dissolve the white solid. The resulting solution was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvent was then removed under reduced pressure to give the crude product as a yellow oil. Cooling to –20 °C gave the product as white needles. Careful decanting of the supernatant fluid, and trituration of the crystalline product with CH_2Cl_2 (6 × 10 mL), gave 5-hydroxypent-2-ynoic acid **59** as a fine white powder (3.55 g, 31.1 mmol, 55%); **IR** $\boldsymbol{\nu_{max}}$ ($CHCl_3$)/cm^{-1} 3243 (O-H), 2239 (C≡C), 1641 (C=O); **^{1}H NMR** (400 MHz, Methanol-d_4) δ 3.70 (2H, t, J = 6.5 Hz, H-5), 2.56 (2H, t, J = 6.5 Hz, H-4); **^{13}C NMR** (101 MHz, Methanol-d_4) δ 156.0 (C-1), 87.5 (C-3), 75.1 (C-2), 60.6 (C-5), 23.4 (C-4).

Prepared in accordance with the literature. These data match the literature.[44]

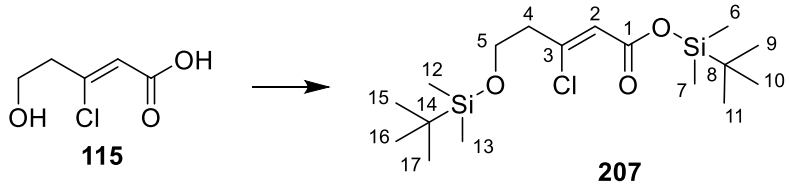
(*Z*/*E*)-3-Chloro-5-hydroxypent-2-enoic acid (115)[44]



To a solution of 5-hydroxypent-2-ynoic acid **114** (1.00 g, 8.77 mmol) in conc HCl (4 mL), CuCl (174 mg, 1.75 mmol) was added in one portion. The resulting dark green solution was stirred at room temperature for 24 hours. The reaction was quenched with water (10 mL) and the product extracted with CH_2Cl_2 (5 × 10 mL), EtOAc (5 × 10 mL). The organics were combined, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give 3-chloro-5-hydroxypent-2-enoic acid **115** as a yellow oil (1.01 g, 80:20 *Z*:*E,* 6.71 mmol, 76%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3500-2700 (O-H), 1703 (C=O); ***Z* isomer** (major); **^{1}H NMR** (400 MHz, Acetone-d_6) δ 6.21 (1H, t, *J* = 0.8 Hz, H-2), 3.83 (2H, t, *J* = 6.1 Hz, H-5), 2.68 (2H, td, *J* = 6.1, 0.8 Hz, H-4); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 164.1 (C-1), 146.8 (C-3), 118 (C-2), 58.7 (C-5), 44.1 (C-4); ***E* isomer** (minor); **^{1}H NMR** (400 MHz, Acetone-d_6) δ 6.26 (1H, t, *J* = 0.8 Hz, H-2'), 4.39 (2H, t, *J* = 6.1 Hz, H-5'), 2.88 (2H, td, *J* = 6.1, 0.8 Hz, H-4'); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 162.9 (C-1'), 145.3 (C-3'), 118.8 (C-2'), 60.5 (C-5'), 39.8 (C-4').

Prepared in accordance with the literature. These data match the literature.[44]

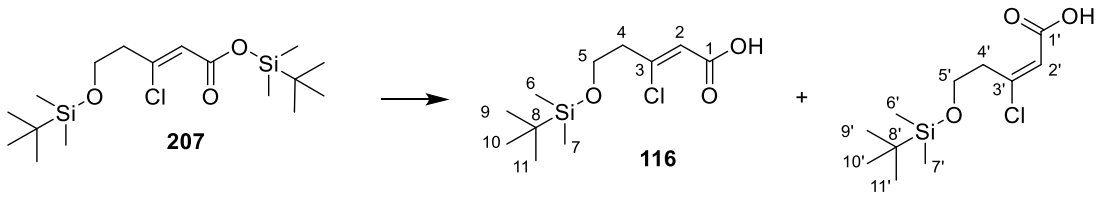
***Tert*-butyldimethylsilyl (*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-3-chloro-pent-2-enoate (207)**[44]



To a solution of (*Z*)-3-chloro-5-hydroxypent-2-enoic acid **115** (80:20 *Z:E*) (194 mg, 1.28 mmol) in DMF (1.5 mL), imidazole (351 mg, 5.17 mmol) was added followed by TBSCl (390 mg, 2.59 mmol). The reaction was stirred at room temperature for 24 hours. The reaction was quenched with water (10 mL) and the product extracted with hexanes (3 × 10 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the *tert*-butyldimethylsilyl (*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-3-chloro-pent-2-enoate **207** as a colourless oil and a single isomer (361 mg, 0.952 mmol, 75%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 1703 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.07 (1H, s, H-2), 3.84 (2H, t, *J* = 6.2 Hz, H-5), 2.61 (2H, t, *J* = 6.2 Hz, H-4), 0.94 (9H, s, H-9,10,11), 0.87 (9H, s, H-15,16,17), 0.30 (6H, s, H-6,7), 0.05 (6H, s, H-12,13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (C-1), 146.8 (C-3), 120.1 (C-2), 56.0 (C-5), 44.7 (C-4), 26.0 (C-15,16,17), 25.7 (C-9,10,11), 18.4 (C-14), 17.8 (C-8), -4.6 (C-6,7), -5.3 (C-12,13).

Prepared in accordance with the literature. These data match the literature.[44]

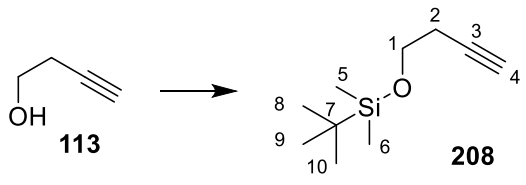
(*Z*)-5-((*Tert*-butyldimethylsilyl)oxy)-3-chloropent-2-enoic acid (116)[44]



To a solution of *tert*-butyldimethylsilyl (*Z*)-5-((*tert*-butyldimethylsilyl)oxy)-3-chloropent-2-enoate **207** (676 mg, 1.79 mmol) in THF-MeOH (4.46 mL: 23.4 mL), 1M aqueous K_2CO_3 (544 mg, 3.93 mmol) was added. The mixture was stirred for 1 hour, quenched with brine (15 mL) and cooled to 0 °C. The mixture was acidified with aqueous $KHSO_4$ (1 M) and extracted into ether. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield (*Z*/*E*)-5-((*tert*-butyldimethylsilyl)oxy)-3-chloropent-2-enoic acid **116** as a colourless oil (471 mg, 57:43, *E:Z,* 1.78 mmol, 100%); IR ν_{max} ($CHCl_3$)/cm^{-1} 3300-2500 (O-H), 1732 (C=O); ***Z* isomer**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (1H, br. s, H-2), 3.91 (2H, t, *J* = 6.0 Hz, H-5), 2.69 (2H, td, *J* = 6.0, 0.9 Hz, H-4), 0.87 (9H, s, H-9,10,11), 0.04 (6H, s, H-6,7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.69 (C-1), 148.65 (C-3), 118.33 (C-2), 59.40 (C-5), 44.40 (C-4), 25.94 (C-9,10,11), 18.36 (C-8), -5.32 (C-6,7); ***E* isomer**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.10 (1H, br. s, H-2'), 3.85 (2H, t, *J* = 6.0 Hz, H-5'), 2.64 (2H, td, *J* = 6.0, 0.8 Hz, H-4'), 0.90 (9H, s, H-9',10',11'), 0.09 (6H, s, H-6',7'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.94 (C-1'), 149.51 (C-3'), 117.80 (C-2'), 59.96 (C-5'), 44.93 (C-4'), 25.74 (C-9',10',11'), 18.09 (C-8'), -3.54 (C-6',7'); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{11}H_{21}{}^{35}ClNaO_3Si^+$ 287.0846, found 287.0834.

Prepared in accordance with the literature. These data match the literature.[44]

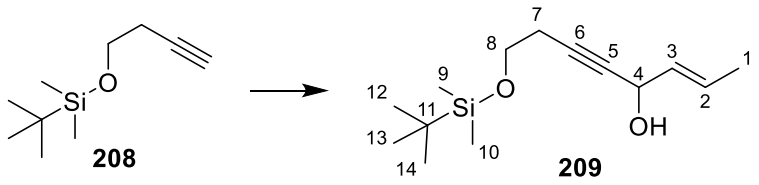
(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (208)



To a solution of 3-butyn-1-ol (5.00 g, 71.3 mmol) in CH_2Cl_2 (40 mL), imidazole (10.9 g, 157 mmol) was added in one portion and the resulting mixture stirred for 1 hour. TBSCl (11.8 g, 78.5 mmol) was added in one portion using a water bath to cool the reaction mixture. The mixture was stirred for 16 hours. The reaction was quenched with a saturated solution of ammonium chloride and extracted into the organic phase with CH_2Cl_2 (4 × 20 mL). The combined organics were dried over anhydrous $NaSO_4$, filtered and the solvent was removed under reduced pressure to give (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane **208** as a colourless oil (11.4 g, 61.8 mmol, 87%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3308 (C≡C-H), 2120 (C≡C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.71 (2H, t, *J* = 7.1 Hz, H-1), 2.40 – 2.32 (2H, m, H-2), 1.92 (1H, t, *J* = 2.1 Hz, H-4), 0.87 (9H, s, H-8,9,10), 0.05 (6H, s, H-5,6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 81.5 (C-3), 69.4 (C-4), 61.8 (C-1), 26.0 (C-8,9,10), 22.9 (C-2), 18.4 (C-7), -5.2 (C-5,6).

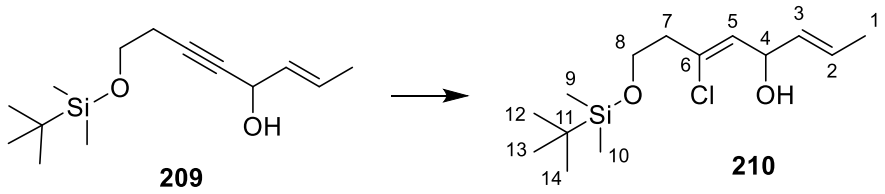
These data match the literature.[109]

(*E*)-8-((*Tert*-butyldimethylsilyl)oxy)oct-2-en-5-yn-4-ol (209)



To a solution of (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane **208** (10.0 g, 54.3 mmol) in tetrahydrofuran (120 mL) at -78 °C, ^{n}BuLi (2.14 M in hexanes, 25.3 mL, 54.3 mmol) was added dropwise to give a pale yellow solution. The resulting solution was stirred for 30 minutes then crotonaldehyde (3.81 g, 54.3 mmol) was added and the solution was allowed to warm to room temperature over 1 hour. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted into the organic phase with ether (4 × 50 mL). The combined organics were dried over anhydrous $NaSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as a yellow oil (16.4 g), Purification of a 2.50 g aliquot by flash column chromatography gave (*E*)-8-((*tert*-butyldimethylsilyl)oxy)oct-2-en-5-yn-4-ol **209** as a yellow oil (1.61 g, 6.33 mmol, 77%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3597 (O-H), ca. 2250 (C≡C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.92 – 5.78 (1H, dq, *J* = 15.1, 6.5 Hz, H-2), 5.59 (1H, dd, *J* = 15.1, 6.2 Hz, H-3), 4.78 (1H, apt. br. s, H-4), 3.71 (2H, td, *J* = 7.1, 1.1 Hz, H-8), 2.44 (2H, tdd, *J* = 7.1, 1.6, 1.1 Hz, H-7), 1.71 (3H, d, *J* = 6.5 Hz, H-1), 0.88 (9H, s, H-12,13,14), 0.06 (6H, s, H-9,10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.8 (C-3), 128.5 (C-2), 83.6(C-6), 80.9 (C-5), 63.2 (C-4), 61.9 (C-8), 26.0 (C12,13,14), 23.3 (C-7), 18.4 (C-11), 17.5 (C-1), -5.2 (C-9,10); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{14}H_{26}NaO_2Si^+$ 277.1600, found 277.1595.

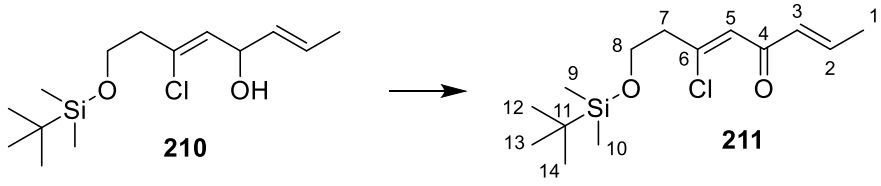
(2*E*,5*Z*)-8-((*Tert*-butyldimethylsilyl)oxy)-6-chloroocta-2,5-dien-4-ol (210)



To a solution of (*E*)-8-((tert-butyldimethylsilyl)oxy)oct-2-en-5-yn-4-ol **209** (5.00 g, 19.7 mmol) in THF (80 mL) under N_2, sodium bis(2-methoxyethoxy)aluminum hydride solution (60 wt. % in toluene, 7.95 g, 39.34 mmol) was added over 30 minutes. The resulting solution was stirred at room temperature for 18 hours. *N*-chlorosuccinimide (13.13 g, 98.4 mmol) in THF (250 mL) was added to the reaction mixture at –78 °C and the resulting solution allowed to warm to room temperature over 24 hours. The resulting black solution was quenched with H_2O (7 mL) added dropwise, followed by a 5% aq. Solution of NaOH (7 mL). The biphasic solution was stirred for 1 hour then separated and the organic phase washed with water (2 × 7 mL), brine (7 mL), and then dried over anhydrous $MgSO_4$. The solvent was then removed under reduced pressure to give the crude product as a yellow oil (6.34 g, 111%). Purification by flash column chromatography yielded (2*E*,5*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-6-chloroocta-2,5-dien-4-ol **210** as a yellow oil (3.47 g, 21.8 mmol, 61%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3341 (O-H), 1102 (C-O), 774 (C-Cl); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78 – 5.64 (1H, m, H-2), 5.57 (1H, dd, *J* = 7.9, 0.9 Hz, H-5), 5.47 (1H, ddq, *J* = 15.3, 6.7, 1.6 Hz, H-3), 4.97 (1H, t, *J* = 7.3 Hz, H-4), 3.82 – 3.68 (2H, m, H-8), 2.57 – 2.39 (2H, m, H-7), 1.66 (3H, ddd, *J* = 6.5, 1.7, 0.9 Hz, H-1), 0.85 (9H, s, H-12,13,14), 0.01 (6H, d, *J* = 2.4 Hz, H-9,10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.7 (C-

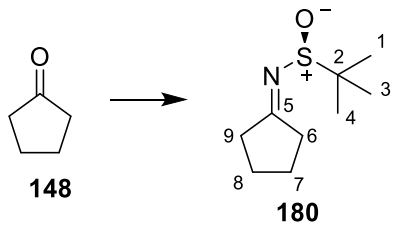
6), 131.2 (C-3), 129.3 (C-5), 127.3 (C-2), 70.2 (C-4), 60.3 (C-8), 43.0 (C-7), 25.9 (C-12,13,14), 18.3 (C-11), 17.8 (C-1), -5.4 (C-9,10); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{14}H_{27}{}^{35}ClNaO_2Si^+$ 313.1367, found 313.1361.

(2*E*,5*Z*)-8-((*Tert*-butyldimethylsilyl)oxy)-6-chloroocta-2,5-dien-4-one (211)



To a solution of (2*E*,5*Z*)-8-((*tert*-butyldimethylsilyl)oxy)-6-chloroocta-2,5-dien-4-ol **210** (50 mg, 0.172 mmol) in dichloromethane (20 mL), finely ground manganese dioxide (299 mg, 3.44 mmol) was added in one portion and the resulting slurry stirred at reflux for 48 hours. The reaction mixture was filtered through a bed of Celite®, dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure to yield (2*E*,5*Z*)-8-((*ter*t-butyldimethylsilyl)oxy)-6-chloroocta-2,5-dien-4-one **211** as a yellow oil (43 mg, 0.149 mmol, 86%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.90 (1H, dq, *J* = 15.7, 6.9 Hz, H-2), 6.43 (1H, d, *J* = 0.8 Hz, H-5), 6.25 (1H, dq, *J* = 15.7, 1.6 Hz, H-3), 3.86 (2H, t, *J* = 6.0 Hz, H-8), 2.62 (2H, td, *J* = 6.0, 0.8 Hz, H7), 1.92 (3H, dd, *J* = 6.9, 1.7 Hz, H-1), 0.88 (9H, s, H-12,13,14), 0.06 (6H, s, H-9,10); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.0 (C-4), 144.6 (C-3), 142.8 (C-6), 132.6 (C-2), 124.8 (C-5), 60.0 (C-8), 44.6 (C-7), 26.9 (C-12,13,14), 18.5 (C-1), 18.4 (C-11), -5.3 (C-9,10); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{14}H_{25}{}^{35}ClNaO_2Si^+$ 311.1210, found 311.1203.

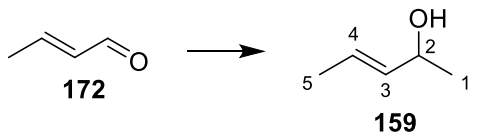
(*S*)-*N*-Cyclopentylidene-2-methylpropane-2-sulfinamide (180)



To a solution of $Ti(OEt)_4$ (5.40 g, 23 mmol) in tetrahydrofuran (120 mL) at 0 °C, cyclopentanone (1.00 g, 11.9 mmol) was added and the resulting solution stirred for 15 minutes. (*S*)-(-)-2-Methyl-2-propanesulfinamide (11.1 g, 9.14 mmol) in tetrahydrofuran (5 mL) was then added and the reaction stirred for 6 hours. The reaction was quenched with brine, filtered through a plug of Celite®, the aqueous phase was extracted with EtOAc (3 × 50 mL), the combined organics were dried over anhydrous $MgSO_4$ and filtered. The solvent was then removed under reduced pressure to give the crude product as a yellow oil (2.10 g). The product was purified by flash column chromatography, eluting with 20% EtOAc in petroleum ether to give (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide **180** as a yellow oil (1.26 g, 6.73 mmol, 73%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 1631 (C=O), 1059 (S-O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.97 – 2.43 (2H, m, H-6), 2.49 (2H, ap.t, *J* = 7.3 Hz, H-9), 1.96 – 1.69 (4H, m, H-8,9), 1.21 (9H, s, H-1,3,4); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.9 (C-5), 56.4 (C-2), 38.9 (C-9), 33.9 (C-6), 25.7 (C-8), 23.7 (C-7), 22.3 (C-1,3,4); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_9H_{18}NNaOS^+$ 210.0929, found 210.0924.

These data match the literature.[110]

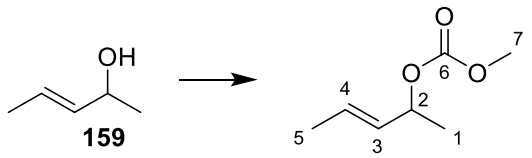
(*E*)-Pent-3-en-2-ol (159)



A 3-necked RBF (500 mL) fitted with dropping funnel and condenser was charged with a solution of crotonaldehyde (10.0 g, 143 mmol) and dry diethyl ether (140 mL) under N_2. The flask was cooled to –78 °C. To the stirred solution, MeLi (1.44 M in diethyl ether, 119 mL, 171 mmol,) was added *via* the dropping funnel over a period of 90 minutes. The flask was allowed to warm to room temperature over a period of 2 hours. Upon completion, the solution was cooled to 0 °C and quenched with a saturated aq. solution of NH_4Cl (60 mL) added dropwise over 1 hour. The product was extracted into diethylether (4 × 100 mL), the combined organics dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield the crude product as a yellow oil (12.5 g, 101%). The product was purified by distillation to yield (*E*)-pent-3-en-2-ol **159** as a colourless oil (11.9 g, 138 mmol, 97%); **b.p.** (1 atm) 120-121 °C; **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3341 (O-H), 1675 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.64 (1H, dqd, *J* = 15.3, 6.3, 0.8 Hz, H-4), 5.53 (1H, ddq, *J* = 15.3, 6.7, 1.5 Hz, H-3), 4.39 – 4.16 (1H, ap. p, H-2), 1.68 (3H, ddd, *J* = 6.3, 1.4, 0.8 Hz, H-5), 1.24 (3H, d, *J* = 6.3 Hz, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6 (C-3), 125.9 (C-4), 69.1 (C-2), 23.5 (C-1), 17.7 (C-5).

These data match the literature.[111]

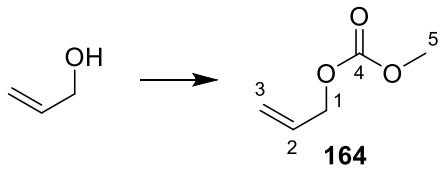
(*E*)-Methyl pent-3-en-2-yl carbonate (167)



To a mixture of 3-penten-2-ol (5.00 g, 0.058 mol) and dimethyl carbonate (15.7 g, 0.0174 mol) potassium carbonate (120 mg, 0.87 mmol) was added in one portion. The resulting suspension was refluxed for 96 hours. The reaction was quenched with water and extracted with Et_2O (4 × 50 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as a yellow oil (11.0 g). Purification by distillation gave (*E*)-methyl pent-3-en-2-yl carbonate **167** as a colourless oil (4.51 g, 31.3 mmol, 54%); **b.p.** (1 atm) 162-163 °C **; IR ν_{max}** ($CHCl_3$)/cm^{-1} 1742 (C=O), 1276 (O-C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 (1H, dq, *J* = 15.3, 6.5 Hz, H-4), 5.51 – 5.39 (1H, m, 3-H), 5.10 (1H, m, H-2), 3.71 (3H, s, H-7), 1.66 (3H, dd, *J* = 6.5, 1.6 Hz, H-5), 1.29 (3H, s, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.2 (C-6), 130.3 (C-3), 129.1 (C-4), 75.5 (C-2), 54.5 (C-7), 20.4 (C-1), 17.7 (C-5).

These data match the literature.[112]

Allyl methyl carbonate (164)



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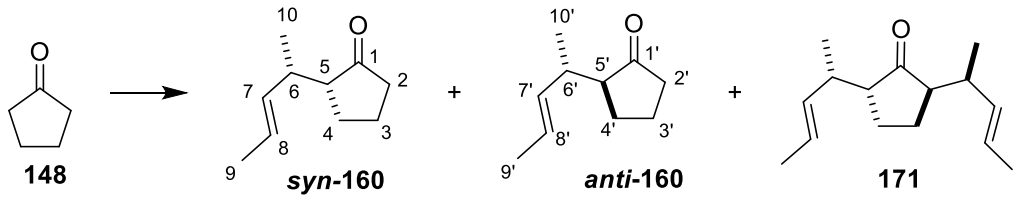
To a solution of allyl alcohol (10.0 g, 0.172 mol) and dimethyl carbonate (46.6 g, 0.517 mol) potassium carbonate (120 mg, 0.86 mmol) was added in one portion. The resulting suspension was refluxed for 48 hours. The reaction was quenched with water and extracted with Et_2O (4 × 100 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as a yellow oil which was immediately purified by distillation to give allyl methyl carbonate **164** as a colourless oil (14.9 g, 128 mmol, 75%); **b.p** (1 atm) 128-130 °C; **^{1}H NMR** (400 MHz $CDCl_3$) δ 5.90 (1H, ddtd, *J* = 17.0, 10.4, 5.8, 0.7 Hz, H-2), 5.41 – 5.10 (2H, m, H-3), 4.60 (2H, dq, *J* = 5.7, 1.1 Hz, H-1), 3.88 – 3.68 (3H, m, H-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (C-4), 131.7 (C-2), 118.9 (C-3), 68.5 (C-1), 54.8 (C-8).

These data match the literature.[113]

(*E*)-2-(Pent-3-en-2-yl)cyclopentan-1-one (160) [82,114]

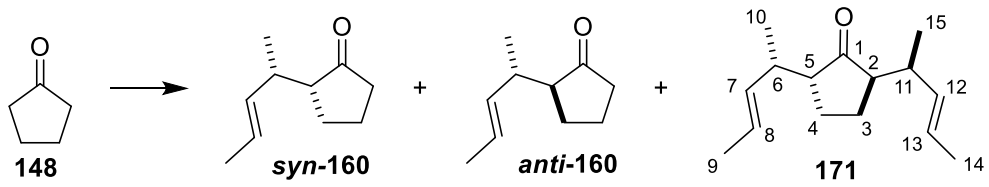


A 500 mL jacketed glass reactor was dried and purged with N_2. The reactor was charged with $Pd(dba)_3.CHCl_3$ (537 mg, 0.519 mmol), rac-BINAP (1.29 g, 2.07 mmol), and LiCl (15.8 g, 2.4 mmol), then purged with N_2 for 1 hour. The vessel was heated to 25 °C and tetrahydrofuran (140 mL) added and the resulting yellow/brown solution stirred for 30 minutes. (*E*)-methyl pent-3-en-2-yl carbonate **167** (20 g, 139 mmol) in tetrahydrofuran (10 mL) was added and the resulting yellow solution was stirred at 25 °C for 30 minutes. The jacketed reactor was then cooled to -80 °C. To a separate dry 3 necked round bottom flask purged with N_2, containing a solution diisopropylamine (23.3 mL, 166 mmol,) in tetrahydrofuran (140 mL) at –78 °C, ^{n}BuLi (2.34 M in tetrahydrofuran, 65 mL, 153 mmol,) was added dropwise over 30 minutes. The reaction mixture was warmed to 0 °C for 30 minutes, then cooled back to -78 °C. Cyclopentanone (11.7 g, 139 mmol,) was added dropwise over 30 minutes and the solution warmed to 0 °C for 30 minutes. The flask was cooled to –78 °C. The cyclopentanone enolate was then transferred by cannula dropwise into the jacketed reactor vessel. The resulting dark orange solution was then stirred for 72 hours at -80 °C. The reaction was monitored *via* NMR aliquot sampling, for consumption of the carbonate **167**. The reaction mixture was warmed to 5 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (150 mL) and extracted with CH_2Cl_2 (3 ×

150 mL). The combined organics were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude (*E*)-2-(pent-3-en-2-yl)cyclopentan-1-one **160** as a yellow oil (25.3 g, 119%). (*E*)-2-(Pent-3-en-2-yl)cyclopentan-1-one **160** was purified by vacuum distillation (10.8 g, 89:11, *syn:anti,* 70.8 mmol, 51%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 1729 (C=O); ***Syn*-product**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 – 5.32 (2H, m, H-7,8), 2.69 – 2.57 (1H, m, H-6), 2.30 – 2.19 (1H, m, H-2_a), 2.15 – 2.07 (1H, m, H-5), 2.05 – 1.97 (1H, m, H-3_a), 1.98 – 1.91 (2H, m, H-4_a, H-2_b), 1.78 – 1.63 (2H, m, H-4_b, H-3_b), 1.61 (3H, d, *J* = 5.6 Hz, H-9), 0.88 (3H, d, *J* = 6.9 Hz, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.7 (C-1), 134.8 (C-7), 124.2 (C-8), 54.1 (C-5), 39.3 (C-2), 35.8 (C-6), 24.9 (C-3), 20.8 (C-4), 18.0 (C-9), 16.1 (C-10); ***Anti*-product**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 – 5.32 (1H, m, H-8'), 5.22 (1H, ddq, *J* = 15.1, 7.4, 1.4 Hz, H-7'), 2.69 – 2.57 (1H, m, H-6'), 2.30 – 2.19 (1H, m, H-$2'_a$), 2.05 – 1.97 (2H, m, 12-H, H-$3'_a$), 1.98 – 1.91 (2H, m, H-$4'_a$,$2'_b$), 1.78 – 1.63 (2H, m, H-$4'_b$,$3'_b$), 1.59 (3H, d, *J* = 6.5 Hz, H-9'), 1.03 (3H, d, *J* = 6.9 Hz, H-10'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.7 (C-1'), 132.9 (C-7'), 125.5 (C-8'), 54.5 (C-5'), 39.2 (C-2'), 36.0 (C-6'), 25.2 (C-3'), 20.8 (C-4'), 18.8 (C-10'), 18.0 (C-9').

The *syn* and *anti* products were assigned as such against the literature,[82] and their relative ratios measured from the ^{1}H NMR peaks corresponding to the C-10/C10' methyl groups.

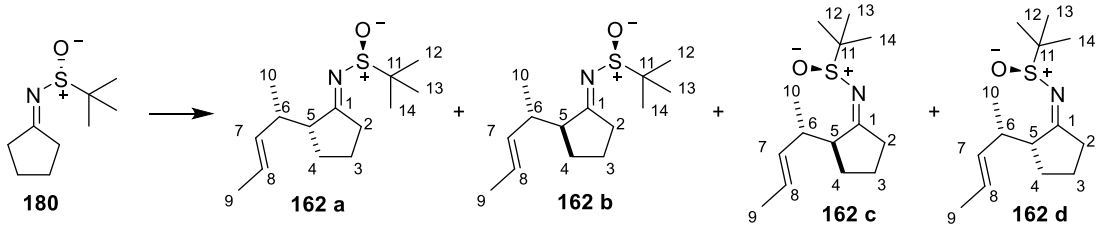
2,5-Di((*E*)-pent-3-en-2-yl)cyclopentan-1-one (171)



IR ν_{max} ($CHCl_3$)/cm^{-1} 1727 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.49 – 5.31 (4H, m, H-7,8,12,13), 2.74 – 2.62 (2H, m, H-6,11), 2.08 – 1.95 (2H, m, H-2,5), 1.98 – 1.87 (2H, m, H-3_a,4_a), 1.63 (6H, dd, *J* = 4.8, 1.0 Hz, H-9,14), 1.58 – 1.47 (2H, m, H-3_b,4_b), 0.88 (6H, d, *J* = 6.9 Hz, H-10,15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.4 (C-1), 134.9 (C-7,12), 124.1 (C-8,13), 55.7 (C-2,5), 35.6 (C-6,11), 22.4 (C-3,4), 18.0 (C-9,14), 16.1 (C-10,15); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{15}H_{24}NaOS^+$ 243.1725, found 243.1715.

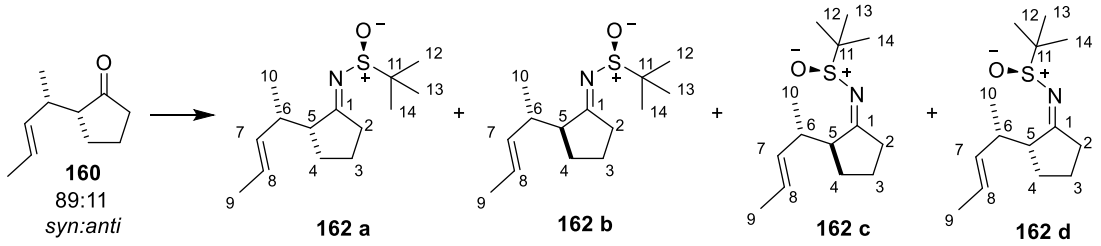
(*S*)-2-Methyl-*N*-((*E*)-2-((*E*)-pent-3-en-2-yl)cyclopentylidene)propane-2-sulfinamide (162)

Method A



To a solution of (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide **180** (50.0 mg, 0.267 mmol) in tetrahydrofuran (10 mL), Hunigs base (69.0 mg, 0.534 mmol,) was added. The reaction mixture was stirred for 30 mins at rt. (*E*)-methyl pent-3-en-2-yl carbonate **167** (66 mg, 0.454 mmol) was added in tetrahydrofuran (10 mL) followed by $Pd(PPh_3)_4$ (15.6 mg, 0.0133 mmol) in one portion. The reaction was heated to 65 °C and stirred for 96 hours. The solvent was removed under reduced pressure to give a crude mixture of the product and starting material. Purification by flash column chromatography gave (2-methyl-*N*-((*E*)-2-((*E*)-pent-3-en-2-yl)cyclopentylidene)propane-2-sulfinamide **162** as two fractions. Each fraction contained a mixture of two inseparable diastereoisomers (combined 5.0 mg, 0.0196 mmol, 7%). Individual assignment of major/minor products from each fraction to the individual products **162 a/b/c/d** was not possible.

Method B



To a solution of $Ti(OEt)_4$ (300 mg, 1.31 mmol) in tetrahydrofuran (3 mL) at 0 °C, (*E*)-2-(pent-3-en-2-yl)cyclopentan-1-one **160** (100 mg, 0.656 mmol) was added and the resulting solution stirred for 15 minutes. (*S*)-(-)-2-Methyl-2-propanesulfinamide (61.0 mg, 0.507 mmol) in tetrahydrofuran (5 mL) was added and the reaction stirred for 96 hours at 65 °C. The reaction was quenched with brine, filtered through a plug of Celite® and the aqueous phase was extracted with (4 x EtOAc). The combined organics were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a yellow oil (262 mg, 1.03 mmol, 156%). (2-methyl-*N*-((*E*)-2-((*E*)-pent-3-en-2-yl)cyclopentylidene)propane-2-sulfinamide **162** was purified by flash column chromatography, eluting with a gradient of 3-20% EtOAc in petroleum ether to give the product as two fractions. Each fraction contained a mixture of two inseparable diastereoisomers (fraction 1: $\mathbf{R_f}$ 0.225 (20 % EtOAc in petroleum ether), 44.0 mg, 0.172 mmol, 26%, fraction 2: $\mathbf{R_f}$ 0.175 (20 % EtOAc in petroleum ether), 17.0 mg, 0.0666 mmol, 10%); **IR** $\boldsymbol{\nu_{max}}$ ($CHCl_3$)/cm^{-1} 1639 (C=N), 1077 (S-O);

Fraction 1 (major) ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.51 – 5.23 (2H, m, H-7,8), 2.87 – 2.77 (1H, m, H-2_a), 2.75 – 2.65 (1H, m, H-6), 2.69 – 2.58 (1H, m, H-2_b),),

2.48 – 2.37 (1H, m, H-5), 1.96 – 1.87 (1H, m, H-3_a), 1.87 – 1.78 (1H, m, H-4_a), 1.62 (3H, d, *J* = 4.9 Hz, H-9), 1.59 – 1.45 (2H, m, H-4_b, H-3_b), 1.25 (9H, s, H-12,13,14), 1.09 (3H, d, *J* = 7.0 Hz, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.7 (5-C), 133.0 (14-C), 125.45 (16-C), 56.9 (9-C), 55.4 (1-C), 37.3 (13-C), 35.1 (4-C), 25.5 (2-C), 23.4 (3-C), 22.6 (10-C, 11-C, 12-C), 19.1 (15-C), 18.2 (C-17), 15.9 (15-C).

Fraction 1 (minor) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 – 5.23 (2H, m, H-7,8), 2.87 – 2.77 (1H, m, H-2_a), 2.75 – 2.65 (1H, m, H-6), 2.69 – 2.58 (1H, m, H-2_b), 2.57 – 2.46 (1H, m, H-5), 2.48 – 2.37 (1H, m, H-5), 1.92 (1H, dddt, *J* = 10.1, 7.7, 4.3, 2.4 Hz, H-3a), 1.87 – 1.78 (1H, m, H-4 $_a$), 1.64 (3H, d, *J* = 4.9 Hz, H-9), 1.25 (9H, s, H-12,13,14) 0.94 (3H, d, *J* = 6.9 Hz, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (C-1), 135.4 (C-7), 124.1 (C-8), 56.9 (C-11), 54.9 (C-5), 37.2 (C-6), 35.4 (C-2) 25.2 (C-4), 23.5 (C-3), 22.6 (C-12,13,14), 18.2 (C-9), 15.9 (C-10). **HRMS** (ESI^+) m/z $[M]^+$ calcd. for $C_{14}H_{26}NOS^+$ 256.1720, found 256.1730.

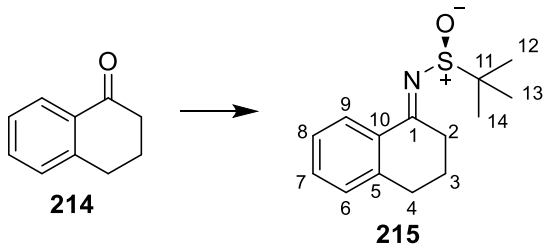
Fraction 2 (major) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.34 (2H, m, H-7,8), 3.19 – 3.04 (1H, m, H-2_a), 2.86 – 2.71 (1H, m, H-6), 2.62 – 2.43 (1H, m, H-5), 2.34 – 2.14 (1H, m, H-2_b), 1.96 – 1.81 (2H, m, H-4_a,3_a), 1.74 – 1.64 (1H, m, H-3_b), 1.61 (3H, d, *J* = 6.2 Hz, H-9), 1.58 – 1.43 (1H, m, H-4_b), 1.24 (9H, s, H-12,13,14), 1.08 (3H, d, *J* = 7.0 Hz, H-10)**; ^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.2 (C-1), 132.9 (C-7), 125.7 (C-8), 56.3 (C-11), 55.1 (C-5), 37.1 (C-6), 34.7 (C-2), 25.4 (C-4), 23.2 (C-3), 22.2 (C-12,13,14), 19.3 (C-10), 18.2 (C-9).

Fraction 2 (minor) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.34 (1H, m, H-8), 5.34 – 5.22 (1H, m, H-7), 3.19 – 3.04 (1H, m, H-2_a), 2.86 – 2.71 (1H, m, H-6), 2.62 – 2.43 (1H, m, H-5), 2.34 – 2.14 (1H, m, H-2_b), 1.96 – 1.81 (2H, m, H-4_a,3_a), 1.74 –

1.64 (1H, m, H-3$_b$), 1.61 (3H, d, *J* = 6.2 Hz, H-9), 1.58 – 1.43 (1H, m, H-4$_b$), 1.25 (9H, s, H-12,13,14), 0.93 (3H, t, *J* = 6.9 Hz, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.7 (C-1), 135.3 (C-7), 124.2 (C-8), 56.3 (C-11), 55.1 (C-5), 36.8 (C-6), 34.6 (C-2), 25.3 (C-4), 23.2 (C-3), 22.6 (C-12,13,14), 18.2 (C-9), 16.1 (C-10). **HRMS** (ESI$^+$) m/z $[M]^+$ calcd. for $C_{14}H_{26}NOS^+$ 256.1720, found 256.1730.

Individual assignment of major/minor products from each fraction to the individual products **162 a/b/c/d** was not possible.

(*R*,*E*)-*N*-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-2-methylpropane-2-sulfinamide (215)

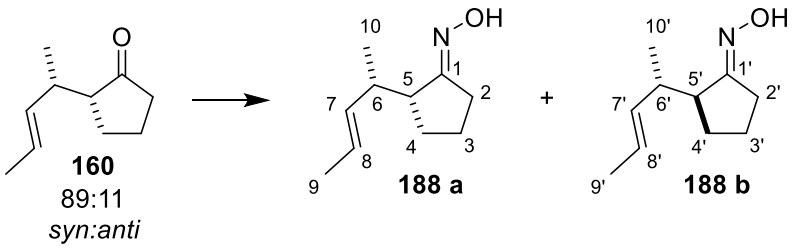


To a solution of alpha tetralone (5.00 g, 34.2 mmol) in THF (30 mL), $Ti(OEt)_4$ (15.6 g, 68.4 mmol) in THF (15 mL) was added and the resulting solution stirred at room temperature for 15 minutes. (S)-2-methylpropane-2-sulfinamide (3.18 g, 26.3 mmol) was added in one portion and the resulting solution heated to reflux for 73 hours. The reaction was quenched with brine (50 mL) and the resulting slurry filtered through a plug of Celite®. The product was extracted into diethylether (4 × 50 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield the product as a yellow oil (7.43

g, 131%). Purification by flash column chromatography gave (*R*,*E*)-*N*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-2-methylpropane-2-sulfinamide 215 as a yellow oil (4.86 g, 19.5 mmol, 86%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 1642 (C=N) 1063 (S-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 – 8.11 (1H, m, H-9), 7.37 (1H, tt, *J* = 7.4, 1.2 Hz, H-7), 7.29 – 7.19 (1H, m, H-8), 7.17 (1H, ddt, *J* = 7.7, 1.6, 0.8 Hz, H-6), 3.34 – 2.96 (2H, m, H-2), 2.91 – 2.71 (2H, m, H-4), 2.11 – 1.91 (2H, m, H-3), 1.31 (9H, d, *J* = 0.8 Hz, H-12,13,14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.1 (C-1), 142.3 (C-5), 133.2 (C-10), 132.1 (C-7), 129.0 (C-6), 127.1 (C-9) 126.6 (C-8), 57.3 (C-11), 32.5 (C-2), 29.6 (C-4), 22.8 (C-3), 22.6 (C-12,13,14).

Prepared in accordance with the literature. These data match the literature.[99]

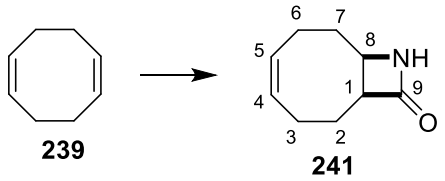
(*R*,*E*)-2-((*S*,*E*)-Pent-3-en-2-yl)cyclopentan-1-one oxime (188)



To a solution of (*E*)-2-(pent-3-en-2-yl)cyclopentan-1-one **160** (1.00 g, 6.57 mmol,) in methanol (7 mL), hydroxylamine hydrochloride (1.14 g, 16.4 mmol,) and sodium acetate (1.616 g, 19.7 mmol) were added in one portion. The resulting mixture was stirred at room temperature for 20 hours. The product was extracted into ethylacetate (4 × 20 mL) and the combined organics washed with brine (20 mL) then dried over anhydrous $MgSO_4$ and filtered. The solvent was

removed under reduced pressure to yield the crude product as a yellow oil (959 mg, 87%). Purification by flash column chromatography gave (*R*,*E*)-2-((*S*,*E*)-pent-3-en-2-yl)cyclopentan-1-one oxime **188** as a yellow oil (747 mg, 4.47 mmol, 68%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3285 (O-H), 1709 (C=N), 1372 (N-O); ***syn*-product**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (1H, s, O-H), 5.50 – 5.28 (2H, m, H7,8)), 2.70 – 2.60 (1H, m, H-2_a), 2.54 (2H, dtt, *J* = 9.2, 4.9, 1.9 Hz, H-5,6), 2.36 – 2.21 (1H, m, H-2_b), 1.90 – 1.72 (2H, m, H-3_a,4_a), 1.65 (3H, dd, *J* = 4.7, 0.8 Hz, H-9), 1.61 – 1.42 (2H, m, H-3_b,4_b), 0.96 (3H, d, *J* = 6.7 Hz, H-10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9 (C-1), 135.5 (C-7), 124.2 (C-8), 48.4 (C-5), 37.9 (C-6), 28.1 (C-2), 27.5 (C-4), 22.7 (C-3), 18.1 (C-9), 16.5 (C-10); ***anti*-product**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (1H, s, O-H'), 5.50 – 5.28 (2H, m, H7',8')), 2.70 – 2.60 (1H, m, H-2_a'), 2.54 (2H, dtt, *J* = 9.2, 4.9, 1.9 Hz, H-5',6'), 2.36 – 2.21 (1H, m, H-2_b'), 1.90 – 1.72 (2H, m, H-3_a',4_a'), 1.65 (3H, dd, *J* = 4.7, 0.8 Hz, H-9'), 1.61 – 1.42 (2H, m, H-3_b',4_b'), 1.06 (d, *J* = 6.6 Hz, H-10'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2 (C-1'), 133.8 (C-7'), 125.1 (C-8'), 48.7 (C-5'), 37.8 (C-6'), 27.8 (C-2'), 27.78 (C-4'), 22.4 (C-3'), 19.0 (C-9'), 18.2 (C-10'); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{10}H_{17}NNaO^+$ 190.1208; found 190.1194.

(1*S*,8*R*,*Z*)-9-Azabicyclo[6.2.0]dec-4-en-10-one (241)



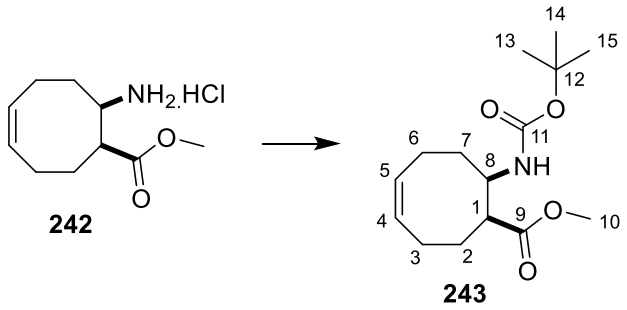
239 **241**

To a solution of 1,5-cyclooctadiene (20 g, 184.9 mmol), anhydrous sodium carbonate (2,94 g, 27.7 mmol) in dichloromethane (10 mL) in a 250 mL? round-bottom flask with condenser, cooled to 0 °C under argon, chlorosulfonyl isocyanate (26.1 g, 184.9 mmol) was added dropwise over 30 min. After stirring at 0 °C for 2 hours, the reaction mixture was allowed to warm to room temperature overnight in a large water bath. Caution must be taken to ensure adequate cooling and condensing, due to the vigorously exothermic nature of this reaction. The resultant thick brown liquid was diluted with dichloromethane (20 mL) and added dropwise to a 2-L conical flask containing a vigorously stirred, two phase mixture of, Na_2SO_3 (37 g) and Na_2HPO_4 (44 g) in water (300 mL), and chloroform (150 mL). The organic layer was separated and the aqueous phase extracted with chloroform (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, and the solvent removed under reduced pressure to yield the crude product as a yellow solid. Purification by flash column chromatography (2% $CHCl_3$: MeOH) gave the corresponding beta lactam (1S,8R,Z)-9-azabicyclo[6.2.0]dec-4-en-10-one **241** as a white solid (8.38 g, 55.4 mmol, 30%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3207 (N-H) 1731 (C=O), 1679 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (1H, s, N-H), 5.76 – 5.63 (2H, m, H-4,5), 3.89 – 3.77 (1H, m, H-8), 3.30 (1H, dtd, *J* = 11.9, 5.1, 1.7 Hz, H-1), 2.49 – 2.32 (2H, m, H-3,6), 2.05 (5H, dddd, *J* = 13.9,

9.8, 7.3, 5.1 Hz, H-2,3,6,7), 2.00 – 1.86 (1H, m, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4 (C-9), 131.2, 130.4, 54.2 (C-1), 53.5 (C-8), 30.9 (C-7), 24.5, 24.0, 22.8; **HRMS** (ESI^+) *m*/z $[M+Na]^+$ calcd. for $C_9H_{13}NNaO^+$ 174.095; found 174.0892.

These data match the literature.[115]

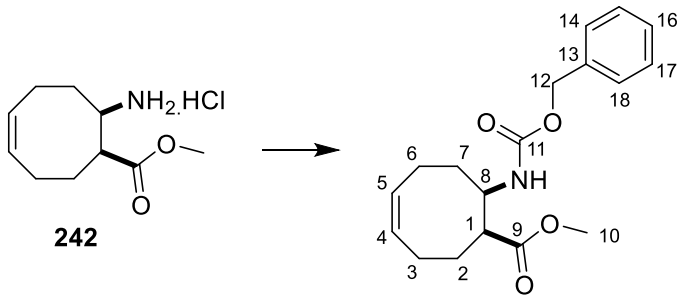
Methyl (1*S*,8*R*,*Z*)-8-((*tert*-butoxycarbonyl)amino)cyclooct-4-ene-1-carboxylate (243)



To a solution of methyl (*Z*)-8-aminocyclooct-4-ene-1-carboxylate hydrochloride **242** (200 mg, 0.913 mmol) in dichloromethane (20 mL), DMAP (10.5 mg, 0.0913 mmol) was added and the resulting solution stirred for 10 minutes. Triethylamine (101 mg, 1.10 mmol) was added dropwise followed by di-*tert*-butyl dicarbonate (225 mg, 1.10 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at rt for 48 hours. Silica (1 g) was added to the reaction mixture and the solvent was removed under reduced pressure to yield the crude product on silica. The crude product was purified by flash column chromatography to give methyl (*Z*)-8-((*tert*-butoxycarbonyl)amino)cyclooct-4-ene-1-carboxylate **243** as a yellow oil (120 mg, 0.424 mmol, 46%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.71 – 5.53 (2H, m, H-4,5), 5.08 – 4.96 (1H, m, N-H), 4.19 – 4.01 (1H, m, H-8), 3.67 (3H, s, H-10), 2.87 – 2.77 (1H, m, H-1), 2.50 – 2.38 (1H, m, H-3), 2.31 – 2.19 (1H, m, H-6), 2.09 (2H, tdd, *J* = 17.1, 7.2, 3.0 Hz, H-2,3), 2.01 – 1.90 (1H, m, H-6), 1.90 – 1.79 (1H, m, H-7), 1.79 – 1.66 (2H, m, H-2,7), 1.39 (9H, s, H-13,14,15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.70 (C-9), 155.0 (C-11), 130.4 (C-4), 129.3 (C-5), 79.2 (C-12), 51.6 (C-10), 50.2 (C-8), 48.0 (C-1), 32.9 (C-7), 28.5 (C-13,14,15), 27.3 (C-2), 24.5

(C-3), 23.4 (C-6); **HRMS** (ESI$^+$) *m*/z [M+Na]$^+$ calcd. for $C_{15}H_{25}NNaO_4^+$ 106.1681; found 306.1686.

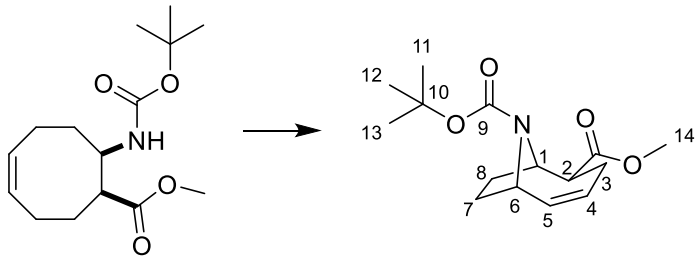
Methyl (1*S*,8*R*,*Z*)-8-(((benzyloxy)carbonyl)amino)cyclooct-4-ene-1-carboxylate (245)



To a solution of methyl (*Z*)-8-aminocyclooct-4-ene-1-carboxylate hydrochloride **242** (200 mg, 0.913 mmol) in dichloromethane (20 mL), DMAP (10.5 mg, 0.0913 mmol) was added and the resulting solution stirred for 10 minutes. Triethylamine (101 mg, 1.10 mmol) was added dropwise followed by benzyl chloroformate (176 mg, 1.10 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 48 hours. Silica (1 g) was added to the reaction mixture, the solvent was removed under reduced pressure to yield the crude product on silica. The crude product was purified by flash column chromatography to give methyl (1*S*,8*R*,*Z*)-8-(((benzyloxy)carbonyl)amino)cyclooct-4-ene-1-carboxylate **245** as a yellow oil (142 mg, 0.448 mmol, 49%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3341 (N-H), 1714 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (5H, m, H-14,15,16,17,18), 5.75 – 5.59 (2H, m, H-4,5), 5.32 (1H, d, J = 9.4 Hz, N-

H), 5.13 – 5.01 (2H, m, H-12), 4.24 (1H, tdd, J = 9.5, 5.3, 1.8 Hz, H-8), 3.69 (3H, s, H-10), 2.90 – 2.82 (1H, m, H-1), 2.46 (1H, tdd, J = 10.8, 9.5, 7.4, 4.6 Hz, H-3), 2.34 – 2.22 (1H, m, H-6), 2.20 – 2.04 (2H, m, H-2,3), 2.04 – 1.95 (1H, m, H-6), 1.90 (1H, dddd, J = 13.9, 10.1, 5.9, 4.2 Hz, H-7), 1.78 (2H, dtt, J = 18.4, 8.0, 3.2 Hz, H-2,7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6 (C-9), 155.4 (C-11), 136.6 (C-13), 130.4, 129.3 (C-16), 128.5, 128.2, 128.1, 66.7 (C-12), 51.6 (C-10), 50.8 (C-8), 47.7 (C-1), 33.0 (C-7), 27.2 (C-2), 24.4 (C-3), 23.2 (C-6); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{18}H_{23}NNaO_4^+$ 340.1525; found 340.1522.

9-(*Tert*-butyl) 2-methyl (1*R*,2*S*,6*S*)-9-azabicyclo[4.2.1]non-4-ene-2,9-dicarboxylate (244)

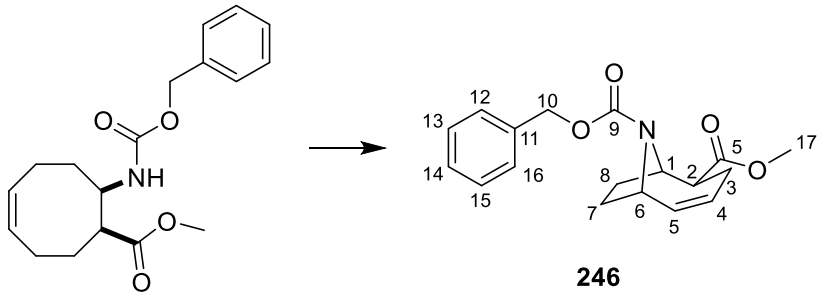


243 **244**

A suspension of methyl (*Z*)-8-((*tert*-butoxycarbonyl)amino)cyclooct-4-ene-1-carboxylate **243** (68 mg, 0.240 mmol), $Pd(OAc)_2$ (2.7 mg, 5 mol%), $Cu(OAc)_2$ (96 mg, 0.528 mmol) in DMF (1 mL) was stirred at 70 °C for 12 hours. After completion, the reaction mixture was diluted with diethyl ether (5 mL) and washed with H_2O (5 mL). The aqueous was washed with diethyl ether (3 x 5 mL) and the combined organics washed with brine (10 mL). The organic layer was

dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography gave the corresponding bridged aza-bicyclic compound, 9-(tert-butyl) 2-methyl (1*R*,2*S*,6*S*)-9-azabicyclo[4.2.1]non-4-ene-2,9-dicarboxylate **244** (36 mg, 0.128 mmol, 53%); **IR** ν_{max} ($CHCl_3$)/cm^{-1} 1735 (C=O), 1161 (C-O), 1108 (C-O); **HRMS** (ESI^+) m/z $[M+Na]^+$ calcd. for $C_{15}H_{23}NNaO_4^+$ 304.1525; found 304.1519.

9-Benzyl 2-methyl (1*R*,2*S*,6*S*)-9-azabicyclo[4.2.1]non-4-ene-2,9-dicarboxylate (246)

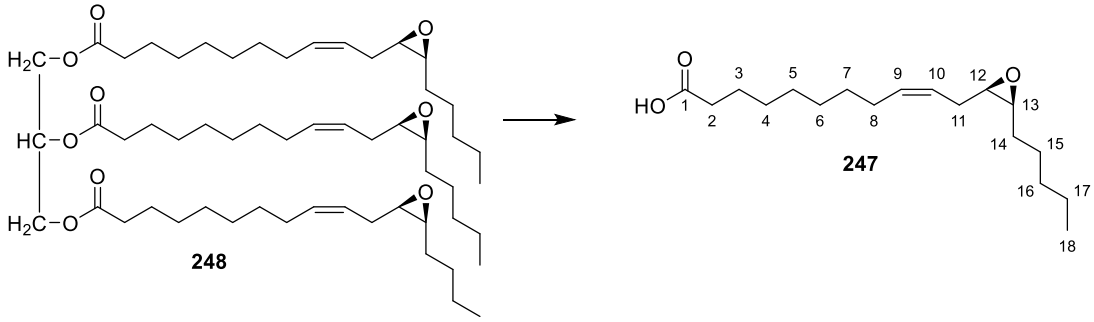


245 **246**

A suspension of methyl (*Z*)-8-(((benzyloxy)carbonyl)amino)cyclooct-4-ene-1-carboxylate **245** (65 mg,0.205 mmol), Pd(OAc)2 (2.3 mg, 5 mol%), Cu(OAc)2 (82 mg, 0.451 mmol) in DMF (1 mL) was stirred at 70 ^oC for 12 hours. After completion, the reaction mixture was diluted with diethyl ether (5 mL) and washed with water (5 mL). The aqueous was washed with diethyl ether (3 x 5 mL) and the combined organics washed with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to

yield the crude product. Purification by flash column chromatography gave the corresponding bridged aza-bicyclic compound 9-benzyl 2-methyl (1*R*,2*S*,6*S*)-9-azabicyclo[4.2.1]non-4-ene-2,9-dicarboxylate **246** (25 mg, 0.079 mmol, 39%); **^{1}H NMR** (400 MHz, DMSO-d_6, 80 °C) δ 7.40 – 7.25 (5H, m, H-12,13,14,15,16), 5.66 (1H, ddd, *J* = 11.1, 4.4, 2.1 Hz, H-5), 5.60 (1H, ddd, *J* = 11.2, 7.5, 4.0 Hz, H-4), 5.19 – 4.91 (2H, m, H-17), 4.66-4.58 (2H, m, H-1,6), 3.52 (3H, br.s, H-17), 2.79 (1H, ddd, *J* = 10.3, 4.8, 3.0 Hz, H-2), 2.38 – 2.24 (2H, m, H-7), 2.23 (1H, ddd, *J* = 16.1, 7.5, 4.8 Hz, H-3a), 2.01 – 1.88 (1H, m, H-8a), 1.88 – 1.79 (1H, m, H-3b), 1.70 – 1.59 (1H, m, H-8b); **^{13}C NMR** (101 MHz, DMSO-d_6, 80 °C) δ 172.7 (C-5), 152.8 (C-9), 136.6 (C-11), 132.5 (C-5), 127.8 (C-12,16 or 13,15), 127.2 (C- 12,16 or 13,15), 127.0 (C-14), 125.2 (C-4), 65.6 (C-10), 57.0 (C-1), 55.9 (C-6), 51.6 (C-2), 50.9 (C-17), 31.5 (C-3), 29.2 (C-9), 24.3 (C-7); **HRMS** (ESI^{+}) m/z [M+Na]$^{+}$ calcd. for $C_{18}H_{21}NNaO_4^{+}$ 338.1368; found 338.1368.

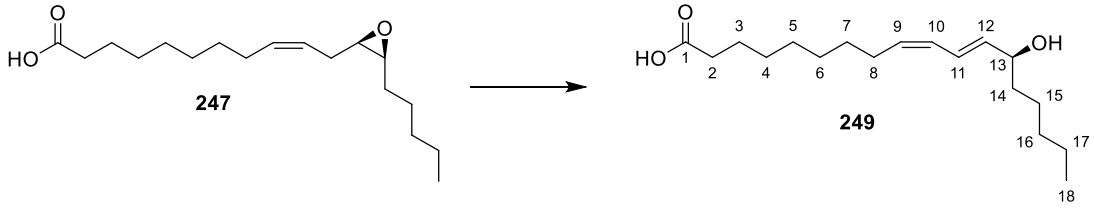
Vernolic acid ((*Z*)-11-((2*R*,3*S*)-3-Pentyloxiran-2-yl)undec-9-enoic acid) (247)



To a refluxing solution of NaOH (20 g) in MeOH (200 ml), Vernonia extract oil **248** (20 g) was added and refluxed for 40 minutes. The solution was then poured into beaker containing ice (400 g) and water (100 ml). The mixture was filtered, and all solids returned to the beaker. Ice (400 g) and water (100 ml) were added again before acidifying the mixture to a pH of 3 with acetic acid (*ca* 16 ml). The solids were filtered off whilst cold and washed with hexane (400 ml). The solid filtrate was then dissolved in water (200 ml) and hexane (200 ml), before extracting into hexane (3 x 200 ml). The organics were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure, yielding the crude product as a yellow, low melting solid (16.2 g, 84%). The product was re-crystallised by dissolving in hexane (80 ml) and cooling over dry ice, filtering through a dry ice chilled Büchner funnel and paper, rinsing with hexane (10 mL, -78 °C) to give the product (*Z*)-11-((2*R*,3*S*)-3-pentyloxiran-2-yl)undec-9-enoic acid **247** as a yellow, low melting solid (14.6 g, 49.2 mmol, 76%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3000-2500 (O-H), 1708 (C=O), 1055 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.58 – 5.46 (1H, m, H-9), 5.47 – 5.35 (1H, m, H-10), 2.93 (2H, dq, *J* = 7.4, 4.1 Hz, H-12,13), 2.42 – 2.32 (1H, m, H-11), 2.34 (2H, t, *J* = 7.5 Hz, H-2), 2.19

(1H, dt, *J* = 14.9, 6.1 Hz, H-13), 2.04 (2H, q, *J* = 7.0 Hz, H-8), 1.63 (2H, p, *J* = 7.4 Hz, H-3), 1.58 – 1.41 (2H, m, H-15), 1.39 – 1.23 (14H, m, H-4, 5, 6, 7, 15,16,17), 0.97 – 0.85 (3H, m, H-18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.5 (c-1), 132.7 (C-9), 124.1 (C-10), 57.4 (C-12 or 13), 56.8 (C-12 or 13), 34.1 (C-2), 31.9, 29.6, 29.3, 29.2, 29.1, 27.9, 27.5, 26.4, 26.4, 24.8 (C-3), 22.7, 14.2 (C-18). **HRMS** (ESI+) m/z [M+Na]+ calcd. for C18H32NaO3+ 319.2249; found 319.2244.

(*S*,9Z,11*E*)-13-Hydroxyoctadeca-9,11-dienoic acid (249)

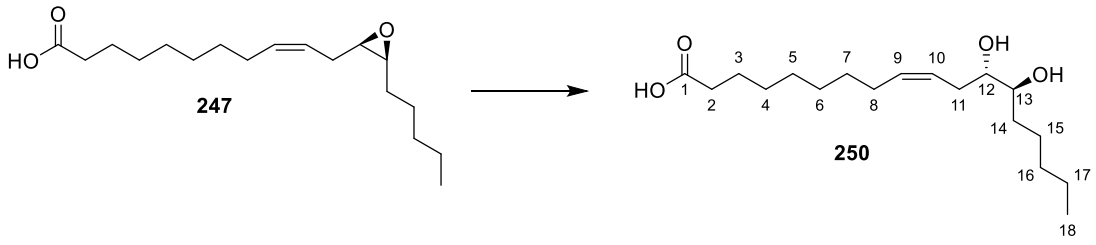


To a solution of diisopropyl amine (4.10 g, 5.68 mL, 40.53 mmol) in dry THF (20 ml) cooled to -78 °C, ^{n}Buli (2.2 M, 16.9 mL, 37.15 mmol) was added dropwise *via* a dropping funnel, rinsing with THF (5 ml). The reaction mixture was warmed to 0 °C for 30 minutes. Vernolic acid **247** (5.00 g, 16.89 mmol) in THF (150 ml) was added dropwise over 1 hour, rinsing the dropping funnel with THF (10 ml). The reaction mixture was stirred for 1 hour. Upon completion, the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl, added dropwise at 0 °C. The organics were separated and the aqueous washed with dichloromethane (3 x 50 ml). The combined organics were washed with 2 M HCl (50 ml) and dried over anhydrous $MgSO_4$, filtered and the solvent removed

under reduced pressure, yielding the product (*S*,9*Z*,11*E*)-13-hydroxyoctadeca-9,11-dienoic acid **249** as a yellow, low melting solid (4.94 g, 16.67 mmol, 99%); **IR ν_{max}** ($CHCl_3$)/cm^{-1} 3500-3000 (O-H), 3000-2500 (O-H), 1707 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.48 (1H, ddd, *J* = 15.2, 11.1, 1.2 Hz, H-11), 5.97 (1H, tt, *J* = 11.0, 1.1 Hz, H-10), 5.66 (1H, dd, *J* = 15.2, 6.8 Hz, H-12), 5.43 (1H, dt, *J* = 10.8, 7.6 Hz, H-9), 4.17 (1H, q, *J* = 6.1 Hz, H-13), 2.33 (2H, t, *J* = 7.4 Hz, H-2), 2.17 (2H, dddt, *J* = 9.8, 7.4, 4.1, 2.4 Hz, H-8), 1.62 (2H, p, *J* = 7.4 Hz, H-3), 1.53 (2H, dddd, *J* = 15.7, 13.2, 7.7, 3.7 Hz, H-14), 1.42 – 1.34 (2H, m, H-7), 1.34 – 1.24 (12H, m, H-4,5,6,15,16,17), 0.92 – 0.84 (3H, m, H-18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.5 (C-1), 135.8 (C-12), 132.9 (C-9), 128.0 (C-10), 126.0 (C-11), 73.1 (C-13), 37.4 (C-14), 34.1 (C-2), 31.9, 29.5, 29.0, 29.0, 29.0, 27.7 (C-8), 25.2 (C-7), 24.8 (C-3), 22.7, 14.2 (C-18); **HRMS** (ESI^+) *m*/z $[M+Na]^+$ calcd. for $C_{18}H_{32}NaO_3^+$ 319.2249; found 319.2244.

These data match the literature.[116]

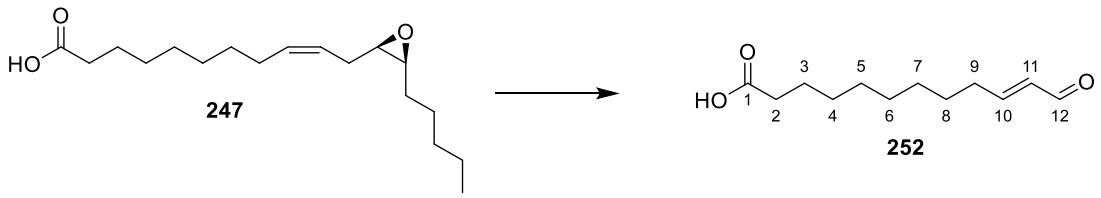
(12*S*,13*S*,*Z*)-12,13-Dihydroxyoctadec-9-enoic acid (250)



Vernolic acid **247** (2.12 g, 7.42 mmol) was dissolved in glacial acetic acid (50 ml) and heated to 95 °C for 24 hours. The glacial acetic acid was removed under

vacuum and the residues taken up in a mixture of methanol (80 ml) and KOH (4.17 g, 74.23 mmol) in water (20 ml), then stirred for 1 hour. Aqueous HCl (2 M) was added until a pH of 4 was achieved. The product was extracted with diethyl ether (4 x 25 ml), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product as an orange oil (2.52 g, 8.01 mmol, 108%). The product was dissolved in a 20% EtOAc solution in petroleum ether and precipitated by cooling to -78 °C. The product was filtered at -78 ° C and rinsed with petroleum ether (3 x 25 ml) at -78 °C, to yield the pure product (12S,13S,Z)-12,13-dihydroxyoctadec-9-enoic acid **250** as a white solid (1.54g, 4.90 mmol, 66%); **IR** ν_{max} ($CHCl_3$)/cm^{-1} 3355 (O-H), 1707 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 – 5.53 (1H, m, H-9), 5.42 (1H, dtt, *J* = 10.9, 8.2, 1.5 Hz, H-10), 3.48 (2H, ddt, *J* = 5.8, 4.1, 2.9 Hz, H-12,13)), 2.34 (2H, t, *J* = 7.3 Hz, H-2), 2.32 – 2.24 (2H, m, H-11), 2.10 – 2.00 (2H, m, H-8), 1.64 (2H, q, *J* = 7.2 Hz, H-3), 1.53 – 1.45 (2H, m, H-14), 1.41 – 1.24 (14H, m, H-4,5,6,7,15,16,17), 0.92 – 0.85 (3H, m, H-18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.0 (C-1), 133.8 (C-9), 124.9 (C-10), 74.1 (C-12 or 13), 74.0 (C-12 or 13), 33.9, 32.0, 31.9, 29.4, 29.0, 28.9, 27.4 (C-8), 25.5 (C-14), 24.8 (C-3), 22.8, 14.2 (C-18); **HRMS** (ESI^+) *m*/z $[M+Na]^+$ calcd. for $C_{18}H_{34}NaO_4^+$ 337.2355; found 337.2345.

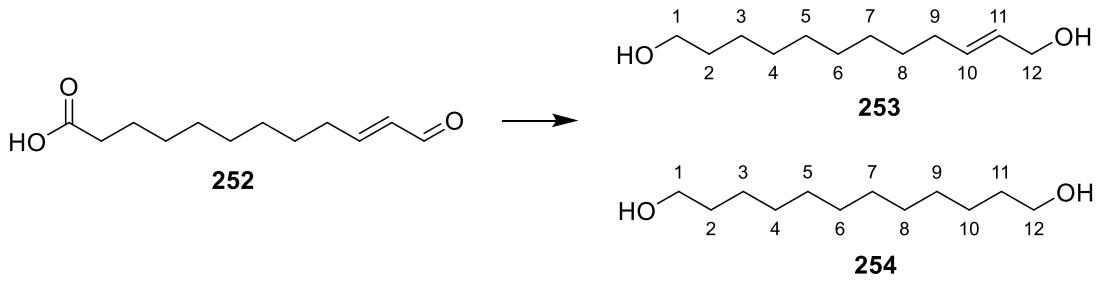
(*E*)-12-Oxododec-10-enoic acid (252)



To a solution of Vernolic acid **247** (2.00 g, 6.75 mmol) dissolved in THF (20 ml) and H_2O (20 ml), H_5IO_6 (3.07 g, 13.49 mmol) was added in one portion and stirred for 72 hours. Upon completion, the product was extracted into diethyl ether (3 x 20 ml) and the combined organics rinsed with brine (20 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product as a yellow oil. Purification *via* silica chromatography gave the product (*E*)-12-oxododec-10-enoic acid **252** as a yellow oil. (920 mg, 4.33 mmol, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.45 (1H, d, *J* = 7.92 Hz, H-12), 6.83 (1H, dt, *J* = 15.6, 6.8 Hz, 1H), 6.09 (1H, ddt, *J* = 15.6, 7.9, 1.5, 1H), 2.25-2.33 (m), 1.52-1.65 (m), 1.41-1.52 (m), 1.2-1.36 (m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.53 (12), 179.71 (1), 159.35 (10), 132.95 (11), 34.11, 34.07, 32.74, 28.98, 28.93, 28.90, 27.76, 26.94, 24.63.

The product **247** is highly unstable, degrading rapidly at temperatures elevated above room temperature. Removal of solvent under vacuum was conducted with a room temperature water bath. Purification *via* silica chromatography was conducted rapidly to avoid degradation on the column. Storage of **247** under nitrogen in a freezer allowed for medium term storage, however the product was best consumed "fresh".

(*E*)-Dodec-2-ene-1,12-diol (253)



To a solution of the aldehyde **252** (0.01 g, 0.471 mmol) in Et_2O (5 mL) at 0 °C, $LiAlH_4$ (0.0573 g, 1.51 mmol) was added in a suspension of Et_2O (5 mL) over 15 minutes. The reaction was quenched with a saturated aqueous solution of Rochelle's salts, stirred for one hour and extracted into dichloromethane (3 x 5 mL). The organics were combined and dried over $NaSO_4$ and the solvent removed under reduced pressure to give the product (*E*)-dodec-2-ene-1,12-diol **253** as a colourless oil (84 mg, 0.419 mmol, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70 – 5.50 (2H, m, H-10,11), 4.06 – 3.99 (2H, m, H-12), 3.57 (2H, t, *J* = 6.7 Hz, H-1), 1.94 – 2.03 (2H, m, H-9), 1.58 – 1.45 (2H, m, H-2), 1.38 – 1.17 (12H, m, H-3,4,5,6,7,8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.26 (C-10), 128.99 (C-11), 63.65 (C-12), 62.88 (C-1), 32.74 (C-9), 32.21, 29.42, 29.38, 29.12, 29.06, 25.75.

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