Applications of the Achmatowicz Rearrangement in Natural Product Synthesis

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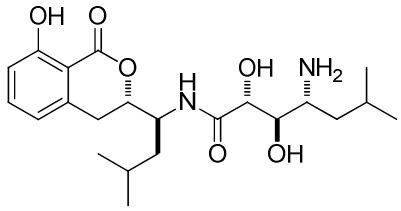
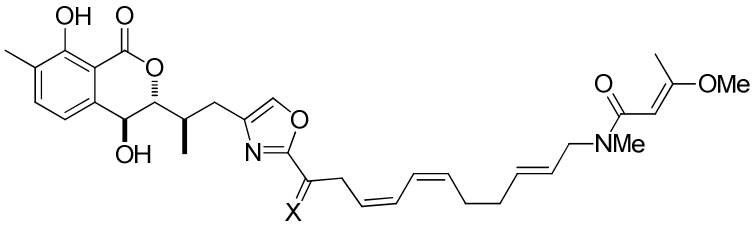
Abstract

The structurally related PM-94128 and Ajudazols A and B exhibit differing biological activities but share the isocoumarin core structure. PM-94128 belongs to a large family of compounds known as the aminodihydroisocoumarins and was isolated in 1997. It has been shown to be an inhibitor of DNA and RNA synthesis and have potent cytotoxic activity *in vivo*. The Ajudazols A and B were isolated in 2004 and have antifungal activity against several important food spoilers.



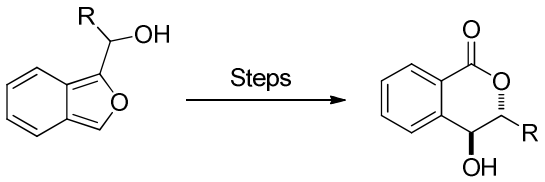
PM-94128



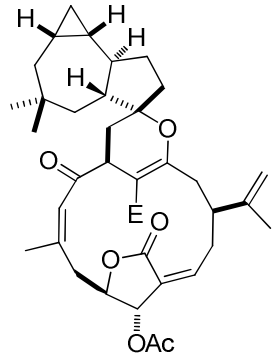
Adjudazol A X = CH_2

Adjudazol B X = H, CH_3

The work that follows details the design and development of a novel method for the generation of the isocoumarin core from isobenzofuran utilizing the Achmatowicz rearrangement of α-hydroxyisobenzofurans.

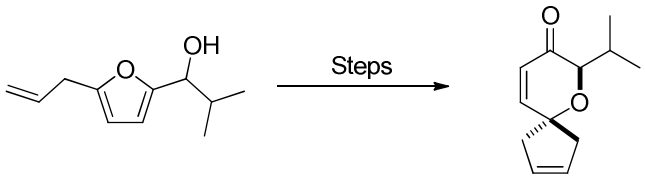


Spirocyclic pyrans such as Polymaxenolide are structurally complex molecules, containing large amounts of functionality. The biological activity of Polymaxenolide is unknown and there have been no total syntheses reported to date.



E = CO_2Et

Also reported in this thesis is the design and synthesis of a model system of Polymaxenolide, using the Achmatowicz rearrangement of α-hydroxyfurans.



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Author Declaration

This thesis represents the original work of Stephen John Hobson unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Dundee and University of Glasgow, under the supervision of Dr Rodolfo Marquez, during the period September 2005 to December 2008.

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

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Abbreviations

Ac	-	Acetate
Aju	-	Protein encoded by *aju* gene
aju	-	Gene encoding an Aju protein
B.fragilis	-	Bacillus Fragilis
bs	-	Broad singlet
B.subtilis	-	Bacilis subtilis
Bu	-	Butyl
CAN	-	Cerium Ammonium Nitrate
CI	-	Chemical Ionisation
CSA	-	Camphorsulfonic acid
d	-	Doublet
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
dd	-	Double doublet
de	-	Diastereotopic excess
DEPC	-	Diethylpyrocarbonate
DHP	-	2,3-Dihydropyran
DIAD	-	Di*iso*propyl azodicarboxylate

D*i*BAl-H	-	Di*iso*butylaluminium hydride
DMAP	-	4-Dimethylaminopyridine
DMF	-	Dimethylformamide
2,2-DMP	-	2,2-Dimethoxypropene
DMS	-	Dimethylsulfide
DMSO	-	Dimethylsulfoxide
DNA	-	Deoxyribonucleic acid
dt	-	Double triplet
E.coli	-	Escherichia coli
EDA	-	Ethylenediamine
EDCl	-	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	-	Enantiomeric excess
EI	-	Electron ionization
Et	-	Ethyl
EtOAc	-	Ethyl acetate
FAB	-	Fast atom bombardment
GI_{50}	-	Half maximal growth inhibition concentration
HIV	-	Human immunodeficiency virus
HMPA	-	Hexamethylphosphoramide
HMTA	-	Hexamethylenetetramine
HOBt	-	Hydroxybenzotriazole

HPLC	-	High-performance liquid chromatography
HRMS	-	High resonance mass spectrometry
IBX	-	2-Iodoxybenzoic acid
IC_{50}	-	Half maximal inhibition concentration
KHMDS	-	Potassium bis(trimethylsilyl)amide
LAH	-	Lithium aluminium hydride
LDA	-	Lithium di*iso*propylamide
LHMDS	-	Lithium bis(trimethylsilyl)amide
LiDBB	-	Lithium di*tert*butylbiphenyl
m	-	Multiplet
M	-	Molar
MAD	-	Methylaluminium bis(2,6-di*tert*butyl-4-methylphenoxide)
*m*CPBA	-	*meta*-Chloroperoxybenzoic acid
Me	-	Methyl
MIC	-	Minimum inhibitory concentration
mL	-	Millilitre(s)
mm	-	Millimeter(s)
mmol	-	MilliMolar
MOM	-	Methoxymethyl ether
MRSA	-	Methicillin-resistant Staphylococcus aureus
Ms	-	Methanesulfonyl

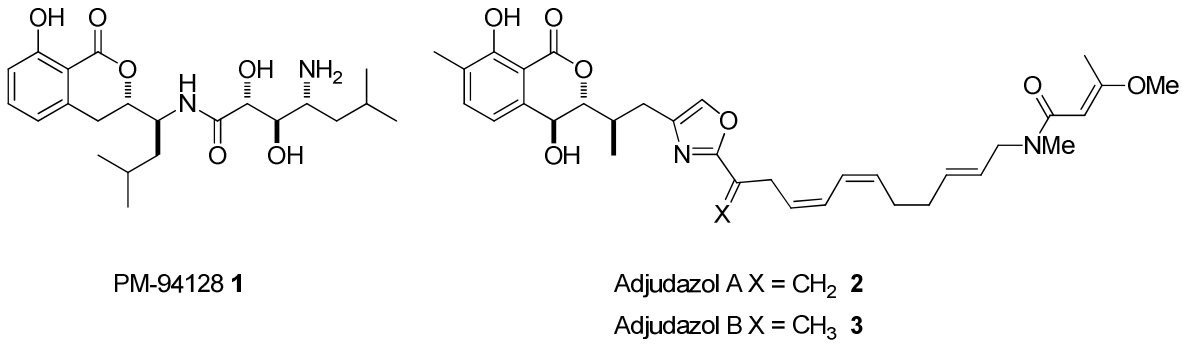
n	-	Normal
NBS	-	*N*-Bromosuccinimide
NHMDS	-	Sodium bis(trimethylsilyl)amide
NMO	-	*N*-Methylmorpholine-*N*-oxide
NMR	-	Nuclear magnetic resonance
N*O*e	-	Nuclear Overhauser effect
Ph	-	Phenyl
PHMS	-	Polyhydrogenmethylsiloxane
PMB	-	*para*-Methoxybenzyl
P*P*TS	-	Pyridinium p-toluenesulfonate
PTSA	-	*p*-Toluenesulfonic acid
*p*TsOH	-	*p*-Toluenesulfonic acid
q	-	Quartet
quint	-	Quintet
RCM	-	Ring closing metathesis
RNA	-	Ribonucleic acid
RT	-	Room temperature
s	-	Singlet
sept	-	Septet
t	-	Triplet
TBAF	-	Tetra-*n*butylammonium fluoride

TBDMSCl	-	*tert*Butyldimethylsilyl
TEA	-	Triethylamine
TEM	-	Transmission electron microscopy
tert	-	Tertiary
Tf	-	Trifluoromethanesulfonate
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofruan
TIPS	-	Tri*iso*propoxysilyl
TLC	-	Thin layer chromatography
TMEDA	-	Tetramethylethylenediamine
TMS	-	Trimethylsilyl
Tr	-	Triphenylmethane
Ts	-	4-Toluenesulfonyl

1. Introduction

1.1. Isocoumarins

The isocoumarins, to which PM-94128 **1**[1] belongs, are a large family of compounds possessing the fused phenolactone (Figure 1.1). The recently isolated Ajudazols A **2** and B **3** (discussed in section 1.2) share the isocoumarin core, although the literature names this structure an isochromanone;[2] both compounds have complex functionality in their respective linear chains and as such have attracted attention from the synthetic community due to their structural complexity and significant biological diversity within their respective families.



PM-94128 **1**

Adjudazol A X = CH_2 **2**

Adjudazol B X = CH_3 **3**

Figure 1.1. PM-94128 and the Ajudazol A & B

Three common bacterial strains have been found to produce some very interesting natural products. From *Bacillus*, *Streptomyces* and *Xenorhabdus* cell lines several isocoumarin containing natural product series have been isolated[3,4] including the Amicoumacins[5] and the Xenocoumacins.[6]

1.1.1. Bacillus isocoumarins

The *Bacillus* strain belongs to a genus of rod-shaped, non pathogenic spore forming aerobic bacteria. Identifiable as gram positive cells, they can normally be found in the soil and gastro intestinal (GI) tracts of various animals. The *Bacillus* species includes both free-living and pathogenic species (Figure 1.2).

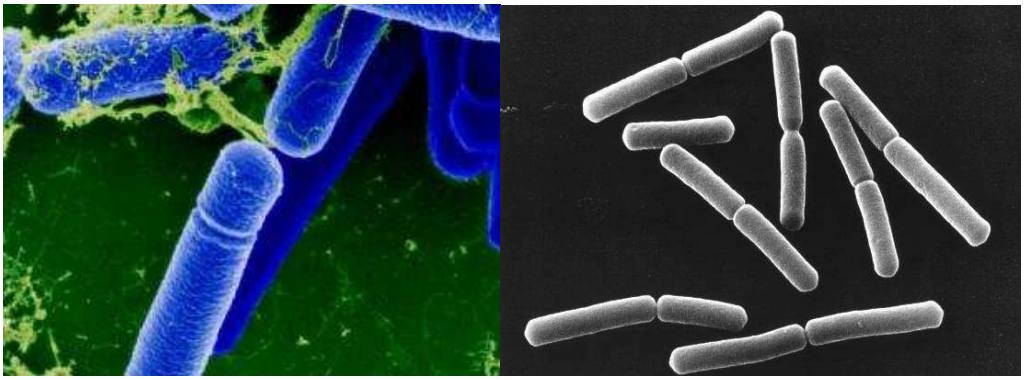


Figure 1.2. *Bacillus subtilis* cells.[7,8]

The Bacillus strain of bacteria has yielded the greatest diversity and number of isocoumarins.

In 1997 Cañedo was able to extract PM-94128 **1** from PhM-PHD-090, a strain of *Bacillus subtilis*, isolated from marine sediment.[1] The closely related Y-05460M-A **4** isocoumarin was isolated five years before from the *Bacillus sp* strain Y-05460M, while the AI-77 series of compounds was isolated from the *Bacillus pumillus* cell line (*AI-77*).[9,10] Also from a *Bacillus pumillus* strain (BN-103) was isolated the Amicoumacin series of antibiotics[5] whose biological activity has been studied the most within this isocoumarin family of compounds.[11] Interestingly *Bacillus subtilis* strains also produce one of the very first antibiotics described in this family; Kristenin[12] and the recently characterised Bacilosarcins A **5** and B **6**.[13]

Interestingly of the many Bacillus species two are considered medically significant; *Bacillus anthracis* (causing Anthrax) and *Bacillus cereus* (causing food borne illness similar to that of *Staphylococcus*).[14,15]

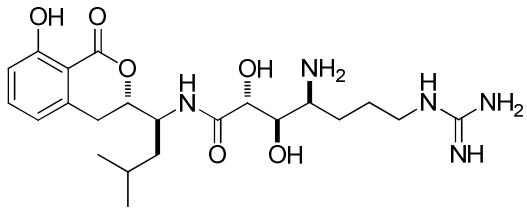
1.1.2. Streptomycetes isocoumarins

The Streptomycetes are members of the bacterial order *Actinomycetales*; these bacteria resemble fungi (they have a branching filamentous structure). *Streptomyces* species are found worldwide in soil and are important in soil ecology. It is widely accepted that their unique antibiotic production is to help the organism compete with other organisms in the relatively nutrient-depleted environment of the soil by reducing competition. By far, the most successful genus in this group is *Streptomyces* with over 500 species. Few species of *Streptomyces* are pathogenic to animals, although a few species cause plant

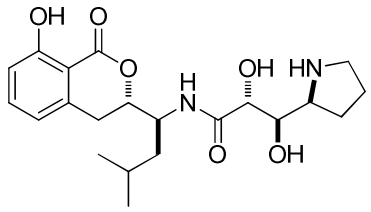
diseases.[16,17] Reticulol (to be discussed later) is produced by *Streptomyces mobaraenis*[18] and *Streptomyces rubreticulae*[19] along with many other isocoumarin type natural products.

1.1.3. Xenorhabdus isocoumarins

Xenorhabdus spp. is a Gram negative gamma *proteo*-bacterium that forms entomopathogenic symbioses with soil nematodes. The bacteria produce antibiotics, intracellular protein crystals and numerous other products, of which Xenocoumacins 1 **7** and 2 **8** are important.[20]



Xenocoumacin 1



Xenocoumacin 2

Figure 1.3. Xenocoumacin 1 and 2.

1.1.4. Bachiphelacin

One of the very first isocoumarins isolated was Bachiphelacin **9** (Figure 1.4).[21] It differs from other isocoumarins in its structure as it has an elongated linear chain and the terminal alkyl amino function does not originate from one of the 20 common amino acids.

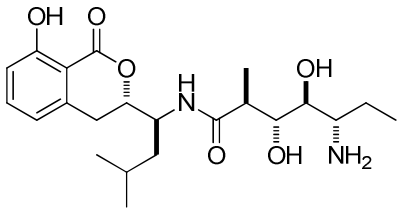


Figure 1.4. Bachiphelacin, 9.

Bachiphelacin **9** possesses both antibiotic properties and cytotoxicity against gram positive bacteria (MIC of 12 μM against *S.aureus*) and P-388 lymphatic leukaemia cells (IC_{50} 15 μM) respectively. It is another of the isocoumarins isolated from a bacillus strain (*Bacillus thiaminolyticus* IFO 3967/B-1-7). Carrasco found that that Bachiphelacin had a potent toxic effect against HeLa cells.[22] Studies of its mechanism of action led to the conclusion that this

antibiotic is an inhibitor of protein synthesis in eukaryotic cells. The antibiotic had no effect on protein synthesis in *Saccharomyces cerevisiae* or *Escherichia coli*, but inhibited the protozoan *Trypanosoma brucei*. *In vitro* protein synthesis in a rabbit reticulocyte cell-free system was blocked by Bachiphelacin. Carrasco also identified a moderate, 5 μM antiherpetic activity in his screen for potential antiherpes compounds.[23]

Bachiphelacin is active against a multi-resistant *Staphylococcus aureus* strain and a strain of *Bacillus subtilis*. It exhibits an antiviral activity against Newcastle Disease (a highly contagious disease that affects domestic poultry, cage and aviary birds and wild birds).[24,25] The likelihood of epidemics whenever a viral infection is recorded, makes this compound relevant across many sectors and interests.

1.1.5. PM-94128 and Y-05460M-A

PM-94128 **1** has been shown to be cytotoxic against several tumour cell lines in the 50 nM activity range (Table 1.1). The activity was assessed against four different tumour cell lines, P-388 (lymphoid leukaemia), A-549 (human lung carcinoma), HT-29 (human colon carcinoma) and MEL-28 (human melanoma) cell lines[1,26] using an adaptation of the method originally published by Bergeron.[27]

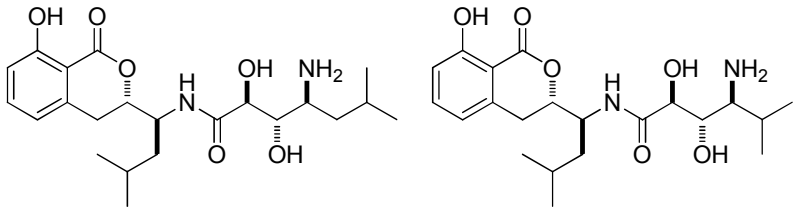


Figure 1.5. PM-94128 and Y-05460M-A.

It was also discovered that PM-94128 **1** had an inhibitory effect on DNA, RNA and protein syntheses,[1,26] determined by measuring T-thymidine, T-uracil and T-leucine incorporation from P-388 culture fluids via the method described by Tomita.[28] PM-94128 was found to have an IC_{50} of 0.1 μM in protein synthesis inhibition and an IC_{50} of 2.5 μM inhibiting DNA / RNA synthesis. The fact that these IC_{50}s, compared with those against that of the whole cell line, are much

lower than against protein synthesis, would seem to indicate the possibility of multiple targets. More research into the biological activity and mechanism of action is consequently needed.

The related and structurally similar isocoumarin Y-05460M-A **4** (Figure 1.5), has the same spectrum, although less potent cytotoxic activity than PM-94128.2[9]
Y-05460M-A was also tested against P-388 and L-1210 lymphoid leukaemia cell lines with IC_{50} values of 0.11 μM and 0.32 μM respectively.
The biological activity assessment (Table 1.1) of Y-05460M-A shows strong cytotoxicity *in vitro* but it exhibits weak antitumour activity *in vivo*.

Compound	P-388	A-549	HT-29	MEL-28
PM-94128 **1**	50 nM	47 nM	47 nM	47 nM
Y-05460M-A **4**	11 μM	-	-	-
Amicoumacin A **10**	-	1.7 μM	3.5 μM	0.35 μM

Table 1.1. Antitumour activities.

1.1.6. Amicoumacin A to C

Amicoumacin A **10**, B **11** and C **12** (Amicoumacin B is also known as AI-77-B) are structurally related to PM-94128 **1** and they represent the largest quantity of biological data for this class of compound (Figure 1.6). They exhibit antibacterial, anti-inflammatory[30,31] and antiulcer activities.[32,33] while they show potent gastoprotective and antiulcerogenic activities they have the distinct property of being non-centrally suppressive and non-anticholinerigc or histaminergic. Their significant biological activity has highlighted them as potential therapeutic leads.[34]

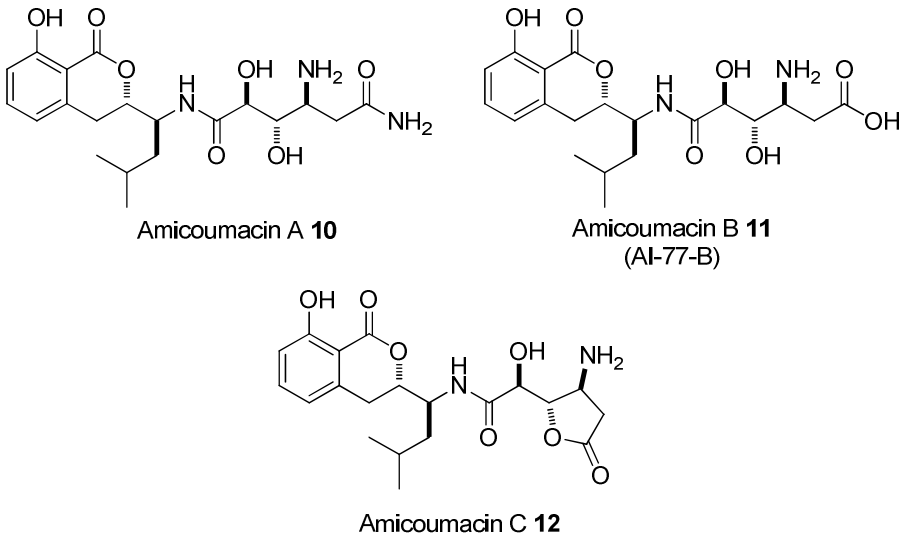


Figure 1.6. Amicoumacin A, B and C.

The antiulcerogenic activity of Amicoumacin-A was investigated using a stress induced gastric ulceration procedure.[5,35] The ulcers were treated with Amicoumacin A, a fairly substantial preventative ratio of 72% at 25 mg/kg was observed (Amicoumacin-B and C had greater protective effects at this does, 100% and 83% respectively). The control pro-kinetic agent sulfiride achieved only 34% protection at 30 mg/kg.

In 2002 the antiulcerogenic activities of the Amicoumacins were described by Pinchuk,[32] it was found that the Amicoumacins were potent antiulcerogenic compounds but the doses administered to the rats to achieve protection were 3.5 times higher than lethal doses (LD_{50} values). An examination of chronic gastritis and peptic ulcer disease causes highlighted *Helicobacter pylori* (*H. pylori*) infection. When tested against *H. pylori* Amicoumacin A exhibited potent antibacterial activity (significant activities were not observed in Amicoumacins B and C) and therefore an antiulcerogenic activity.

Amicoumacin A was tested against strains of pathogenic and non-pathogenic intestinal bacteria. *Entercoccus faecium*, *Shigella flexneri* and *Campylobacter Jejuni* were sensitive to Amicoumacin A. These results are important because these 3 bacterial species represent three common human intestinal pathogens.[36]

> "Enterococci account for approximately 110,000 urinary tract infections, 40,000 wound infections, 25,000 cases of nosocomial bacteremia and 1100 cases of endocarditis. Furthermore, the enterococci are among the most antibiotic resistant of all bacteria, with some isolates resistant to all known antibiotics"- Dr Gary Kaiser [37]

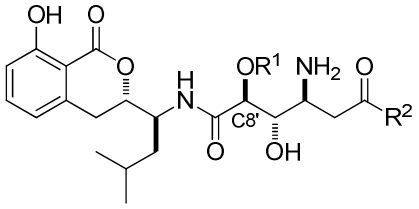
Shigella flexneri is a human intestinal pathogen, causing dysentery by invading the epithelium of the colon and is responsible, worldwide, for an estimated 165 million episodes of shigellosis and 1.5 million deaths per year. Shigellosis is not only a significant cause of infant mortality in developing nations, but maintains endemic levels of infection worldwide.[38]

C.jejuni (*Campylobacter jejuni*) is a highly prevalent food-borne pathogen that causes diarrhoeal disease in humans.[39,40]

The sensitivity *E.faecium*, *S.flexneri* and *C.jejuni* to Amicoumacin A has resulted in research into the use of Amicoumacin secreting bacteria (e.g. *B.subtilis*) as Pro-biotics.[32,41]

Amicoumacin A has also been shown to have antitumour activity against a range of human cancer cell lines, with activities ranging from 0.35 to 1.7 μM. (See Table 1.1).

Phosphorylative inactivation of antibiotics is a known process and is believed to be one of the resistance mechanisms used by bacteria.[42,43] As part of a screen for new antibiotics[44] against methicillin-resistant *Staphylococcus aureus* (MRSA), Amicoumacin A was isolated along with Amicoumacin B (AI-77-B) and two novel phosphate ester derivatives (Table 1.2), from a strain of *Bacillus pumillus* (MU313B). Phosphorlyation was observed to be exclusively at C8' and not at either C9' or phenol positions



Compound	R^1	R^2
10 (Amicoumacin A)	H	NH_2
13	H_3PO_4	NH_2
11 (Amicoumacin B)	H	OH
14	H_3PO_4	OH

Table 1.2.Phosphorylated derivatives of Amicoumacin A and B.

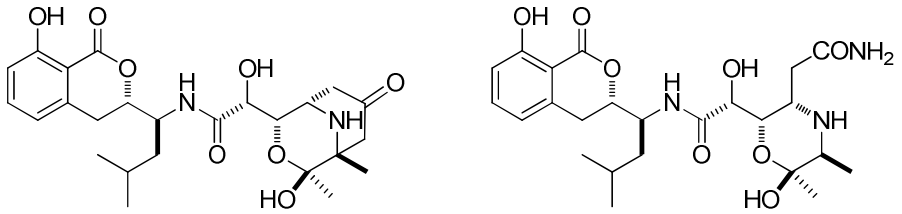
Hashimoto and co-workers analysed the fermentation broth by HPLC, monitoring the quantities of each compound.[44] Time course experiments showed that **13**

was produced as concentrations of Amicoumacin A decreased. As production of **14** increased amounts of Amicoumacin B decreased (although the scale of **11** production was less than with **10**).

To clarify the structure-activity relationship of hydroxyl and amide/acid moiety of Amicoumacins, the antibacterial activity of the four compounds were tested against *Staphylococcus aureus* (ATCC 43300) with Vancomycin as the control. Amicoumacin A **10** activity was similar to Vancomycin, while **11**, **13** and **14** showed no activity at concentrations tested. The results suggested that the C8' hydroxyl and C12' amide group of Amicoumacin A plays a critical role for antiMRSA activity.

Phosphorylation of Amicoumacins is an interesting finding, possibly in relation to self-resistance and the export of Amicoumacins from a bacterial cell.

Another possible insight into the metabolism of the isocoumarins emerged recently when Bacilosarcin A **5** and B **6** were characterized.[13] They were isolated from the *Bacillus subtilis* strain TP-B0611 and inhibit plant growth (Figure 1.7).



Bacilosarcin A Bacilosarcin B

Figure 1.7. Bacilosarcins A 5 and B 6.

Structurally the Bacilosarcins are important because they contain a 2-hydroxy morpholine (Bacilosarcin B) and 3-oxa-9-azabicyclo[3.3.1]nonan-7-one (Bacilosarcin A) substructures that are very rare in natural products.

Bacilosarcin A **5** is the more active of the two molecules and showed 82% inhibition (at 50 μM) of barnyard millet sprouts versus 98% inhibition by Amicoumacin A (Bacilosarcin B showed only very weak 7% inhibition at similar concentrations).

This finding suggests Bacilosarcin A could be a prodrug of Amicoumacin A, as the Bacilosarcins appear to represent two metabolites in the cellular processing of some aminodihydroisocoumarins (Figure 1.8).

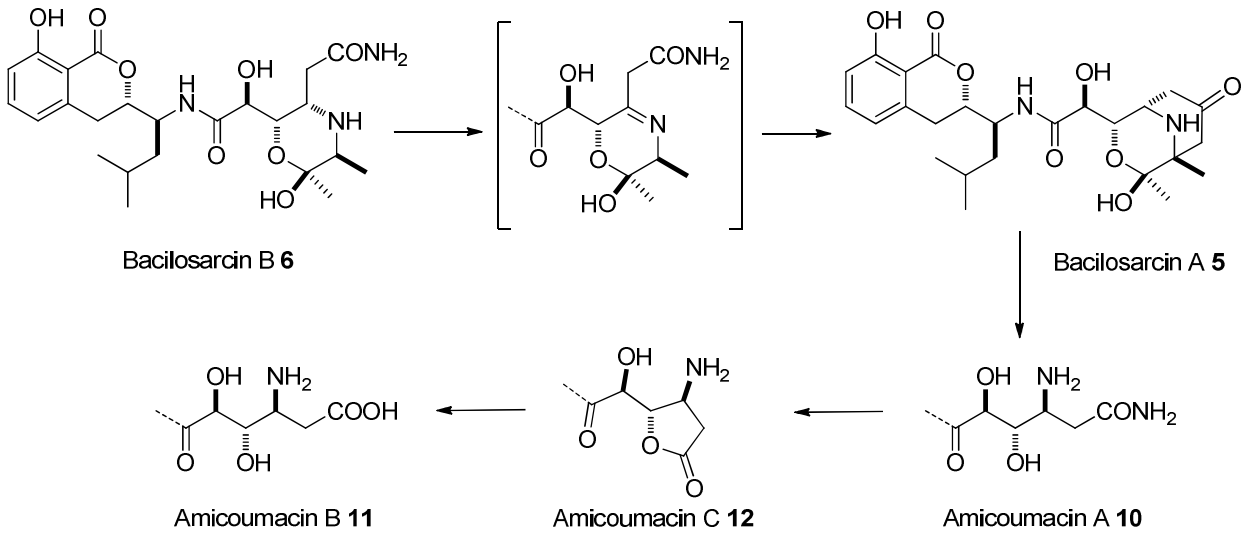


Figure 1.8. Correlations between Bacilosarcins and Amicoumacin.

1.1.7. AI-77s and Sg17-1-4

The AI-77 range of compounds (AI-77-A, B, C, D, F and G) were isolated from a soil sample that was classified as *Bacillus pumilis* AI-77 and represents the majority of synthetic research for this class of compound.[45]

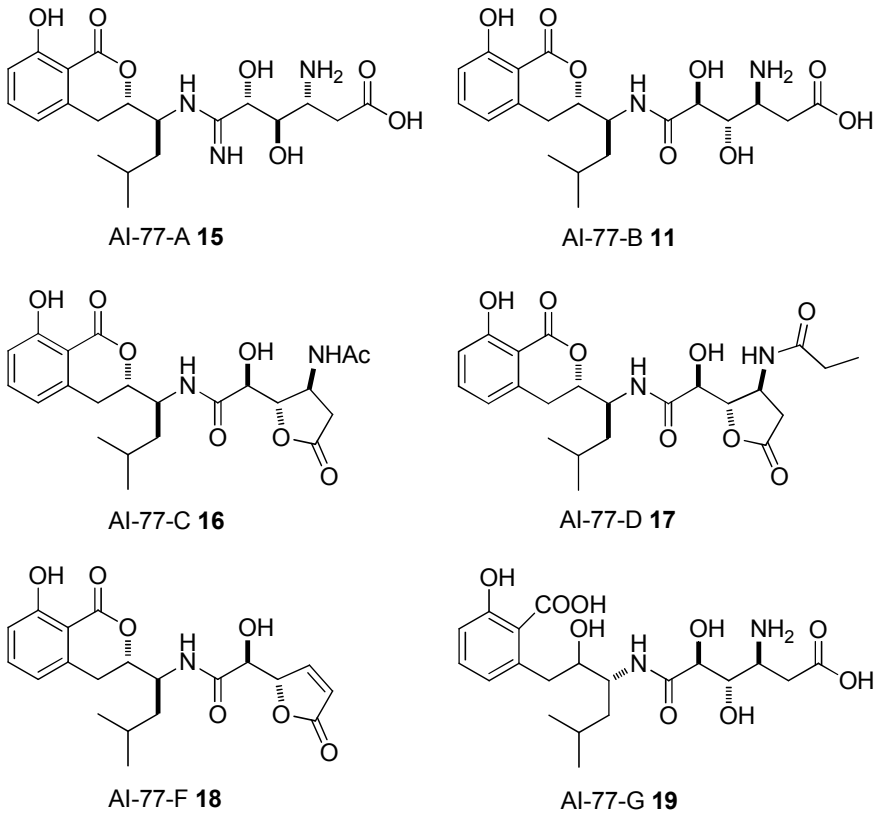


Figure 1.9. The AI-77 range of antibiotics.[46]

As a major product in the fermentation process, AI-77-B did not show any antibacterial activity and exhibited only gastro-protective activity. AI-77s C **16**, D **17**, F **18** and G **19** showed lower activities than **15**.
Pharmacological examination of the AI-77s showed antibacterial activity (7 to 236 μM) and a potent gastro-protective activity, together with an inhibitory effect paw edema in rats.[34]

A possible route for AI-77-B metabolism was hypothesized upon isolation and characterisation of Sg17-1-4 **20**.[47] There is no account for the structure of Sg17-1-4 but the distribution of compounds isolated could suggest a metabolic route as one can expect **20**to be derived from AI-77-B **11**. Cytotoxicities were measured against cervical cancer HeLa cells, Sg17-1-4 has slightly lesser potency than AI-77-B.

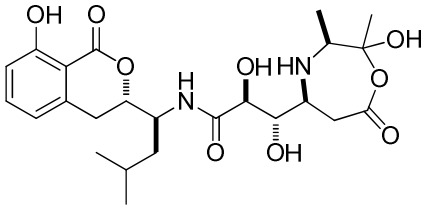
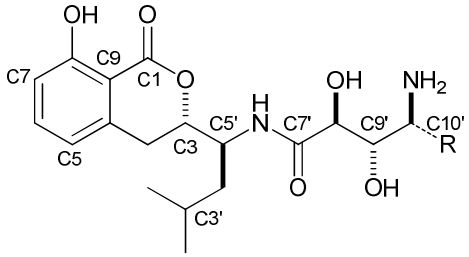


Figure 1.10. Sg17-1-4.

Structurally the aminodihydroisocoumarins are composed of a fusion of two modified L-amino acid residues. The eastern (15C) fragment is a modified leucine molecule where the β-carbon (C3 – based upon Shimojima's numbering system[48]) of the original amino acid, becomes incorporated into the isocoumarin ring system. The western C7'-C11' fragment is comprised of the second amino acids, out of all the known aminodihydroisocoumarins, 7 are derived from the 20 common amino acids (Table 1.3), the others are derivatives thereof. In all cases, the parent amino acid has been modified to include a new dihydroxy-propanoic acid moiety (connected to the α/C10' carbon). The difference in biological activities between the aminodihydroisocoumarins is due to the side chains of the parent amino acid.[49]



R group	Amino Acid	Compound
Guanidine	Arginine	Xenocoumacin **7**
Acetic acid	Aspartic acid	AI-77-B **11**
iso-Propyl	Valine	Y-05460M-A **4**
Pyrrolidine	Proline	Xenocoumacin **8**
iso-Butyl	Leucine	PM-94128 **1**
Acetamide	Asparagine	Amicoumacin A **10**

Table 1.3. Isocoumarins derived from common amino acids.

The absolute configurations, of the 5 stereocenters of AI-77-B were established through X-ray crystallography (Figure 1.11) studies by Shimojima and co-workers[9,10] in the early 1980's. The centers have all been assigned the S-configuration. Nuclear magnetic resonance and synthetic studies have been completed on PM-94128[50] and AI-77-B[9,10] and in both cases they support Shimojima's proposed configurations (Figure 1.1).

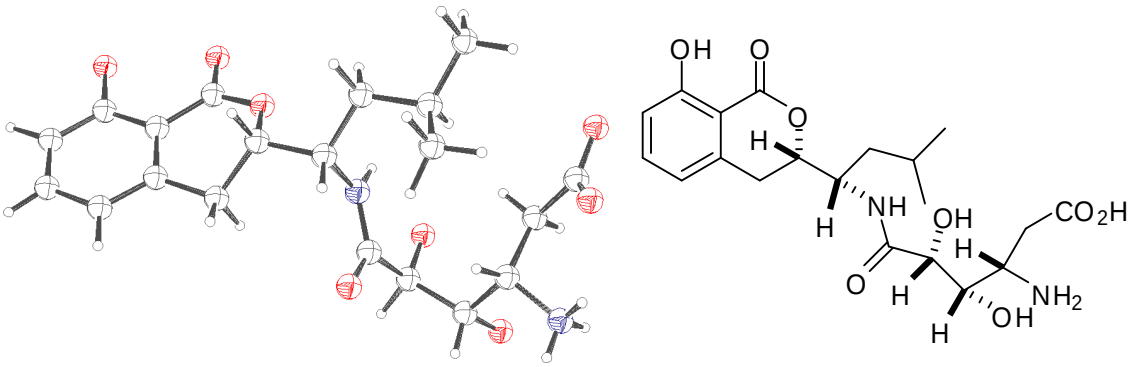
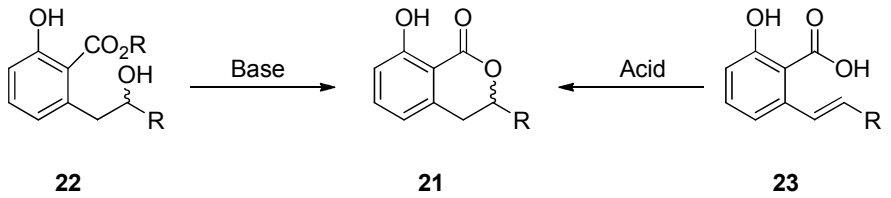


Figure 1.11 The structure of AI-77-B as solved by Shimojima and collegues.[9,10]

The dihydroisocoumarin fragment **21** is found in a variety of natural products and there have been a significant number of methods reported for their construction. The methods generally involve some form of nucleophilic attack onto an unsaturated system, whether that is a hydroxide anion attacking an

ester or amide **22**[51,53] or an acid promoted ring closure of a carboxylate onto an adjacent olefin **23**.[54-56]



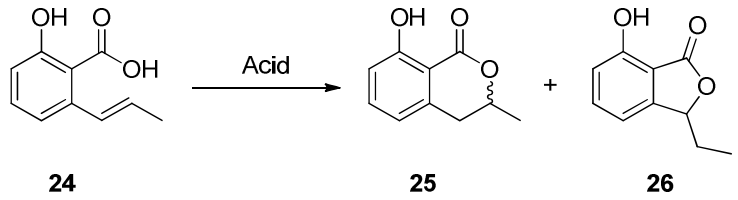
22 **21** **23**

Scheme 1.1. The most common routes used to access isochromanone cores.

There have also been reports of more unusual routes, for instance radical chemistry[57] transition metal catalysed reactions[58] and Lewis acid ring expansions.[59]

1.1.8. Shioiri's synthesis of AI-77-B

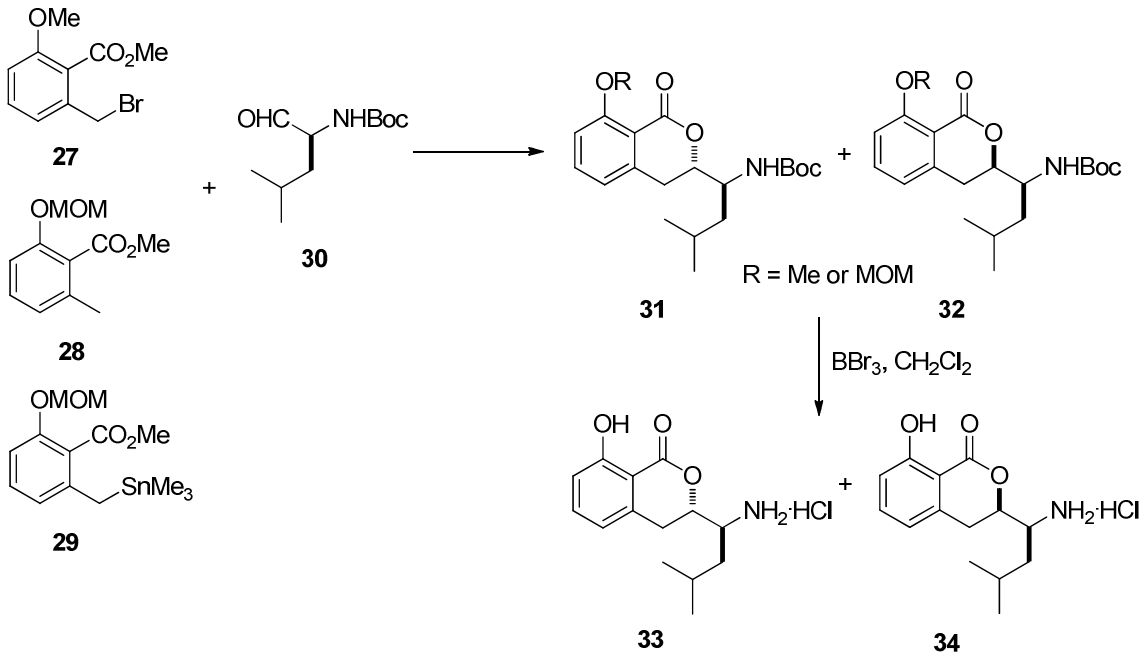
The first reported synthesis of AI-77-B was reported by Shioiri in 1989.[60] Initially Shioiri attempted the intramolecular addition of a carboxylate **24** onto an adjacent olefin under acidic conditions. This approach suffered selectivity problems between desired 6-*endo*-*trig* cyclisation product **25** and the favoured 5-*exo*-*trig* cyclisation product **26**.



24 **25** **26**

Scheme 1.2. Shioiri's initial attempts to synthesize the core of AI-77-B.

A second approach was conceived; involving a benzylic anion coupling of partners **27**–**29** to a leucine derived aldehyde **30**, thus a one step construction of the aminodihydroisocoumarins **31** and **32**, by diastereoselective addition followed by spontaneous lactonisation was achieved. A number of salicylate derived starting materials were studied along with variations in the reaction conditions (Scheme 1.3).



Scheme 1.3. General reaction scheme for aminodihydroisocoumarin formation.

A chelation controlled model was proposed for the selectivity observed in the reaction with the nucleophile attacking the carbonyl from the least hindered face (Scheme 1.3). α-Aminoaldehyde **30** is deprotonated (using an excess of base) to give an N-lithium derivative which seems to serve as an internal ligand for chelation control. When titanium tetrachloride was used as an additive, the reaction gave moderate yields, but the selectivity was reversed in favour of the *syn* aminodihydroisocoumarin **32**. The optimal conditions were found to be with LDA (2.6 eq), which gave moderate yields, but most selectivity (4:1, *anti*:*syn*).

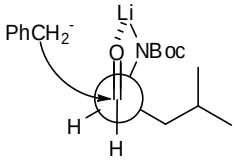
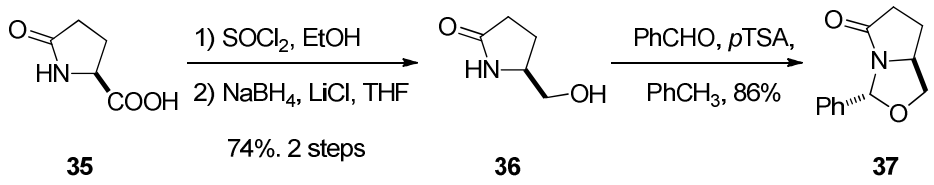


Figure 1.12. The model proposed by Shioiri et al

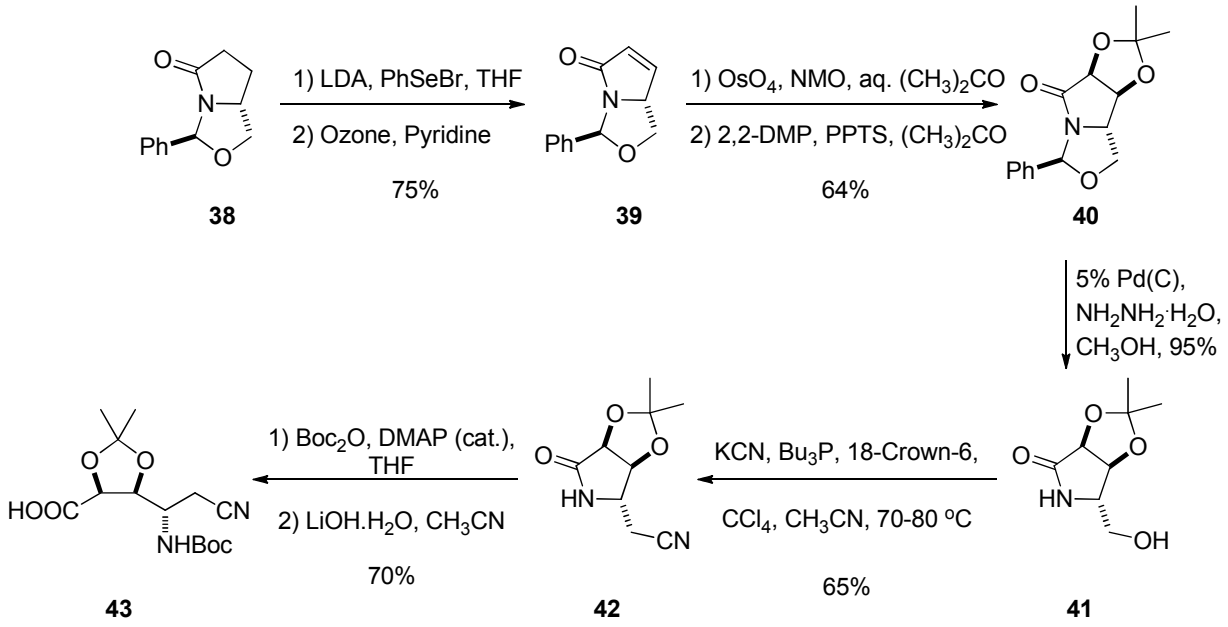
Cyclisation of the isocoumarin molecule proved to be spontaneous and all that remained in the synthesis was cleavage of the phenolic and N-protecting group, which was achieved by treatment with boron tribromide giving **33** and **34**.

Synthesis of the linear amino diol fragment began with a N-O benzylidene derivative of D-pyroglutaminol **35** as reported by Thottathil.[61]



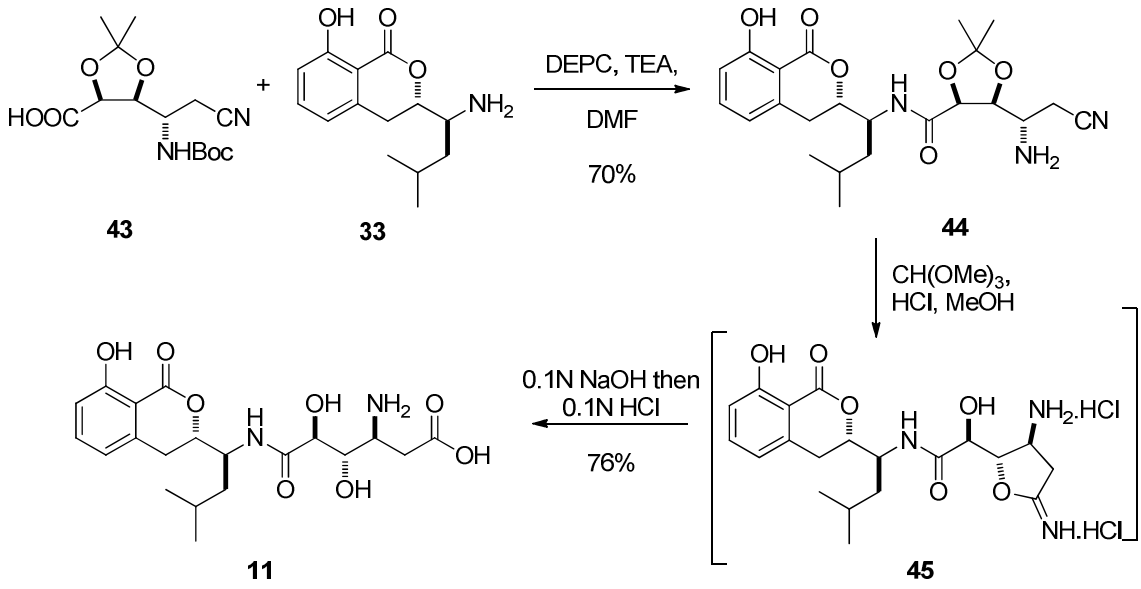
Scheme 1.4. Thottathil's synthesis of 43.

α,β-Unsaturated lactam **39** was produced, by oxidative elimination of the seleninde derived from lactam **37**. The newly installed olefin was oxidized via Upjohn conditions (OsO_4/NMO) from the less hindered convex back face with a 97% diastereotopic excess, followed by acetonide protection to yield ketal **40**. Catalytic hydrogenation using palladium and hydrazine hydrate yielded the free alcohol **41**. Conversion of the alcohol to a nitrile group was achieved according to conditions established within the Shioiri group to yield cyanide **42**. *t*Butyl carbamate protection followed by amide hydrolysis under basic conditions yielded acid **43**(Scheme 1.5).



Scheme 1.5. Shioiri's synthesis of the amino.

The synthesis of AI-77-B was completed by coupling acid **43** and amine **33** with diethyl phosphorocyanidate (DEPC) and triethylamine. A Pinner reaction (trimethylorthoformate and 5% hydrochloric acid in methanol) converted the nitrile to the requisite carboxylate functionality, which cyclised spontaneously to generate the *bis* hydrochloric acid salt **45.** Basic treatment of salt **45** with 0.1 N-lithium hydroxide followed by neutralization with 0.1 N hydrochloric acid gave the completed AI-77-B molecule **11** (Scheme 1.6).

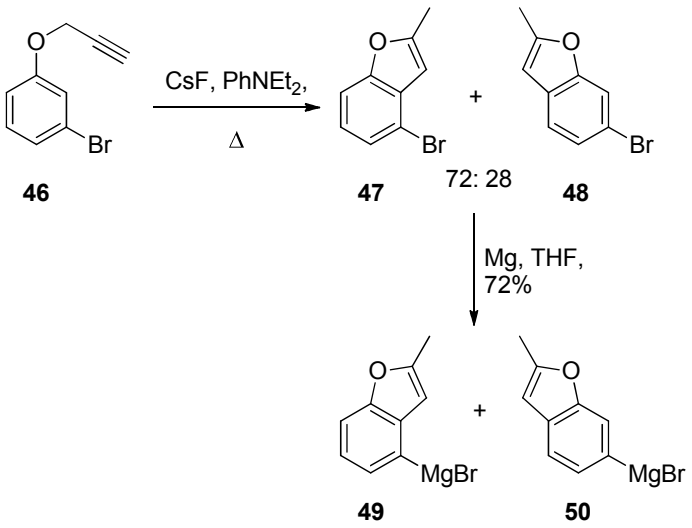


Scheme 1.6. Shioiri's synthesis of AI-77-B.

1.1.9. Kotsuki's synthesis of AI-77-B

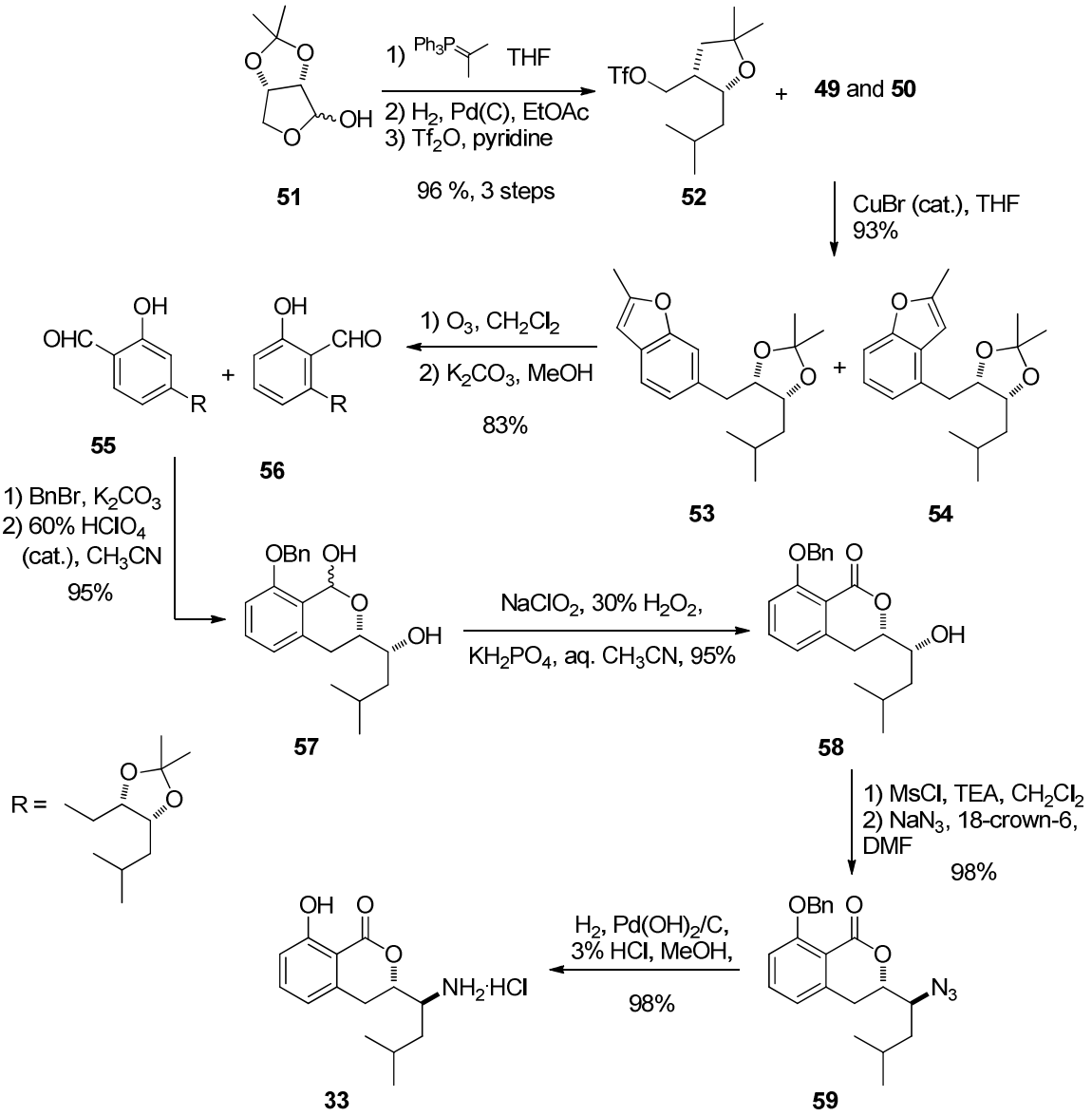
Another more recent synthesis of AI-77-B was reported by Kotsuki in 1999,[62] wherein a novel salicyclic acid synthon was generated.

To begin, *meta*-bromophenyl propargyl ether **46** was converted to benzofurans **47** and **48** via a caesium fluoride mediated rearrangement in good regioselectivity (Scheme 1.7) and the resulting bromides were converted into the corresponding Grignards **49** and **50**. It was not possible to separate regioisomers of the CsF rearrangement until generation of aldehydes **55** and **56.**



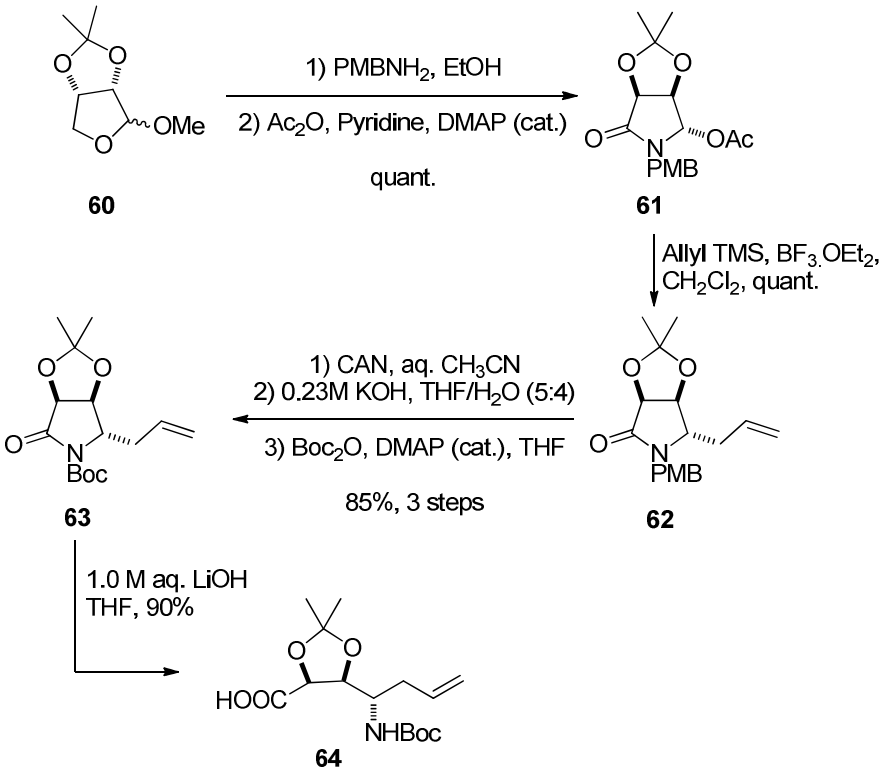
Scheme 1.7. Benzofuran generation.

The remaining carbon framework was derived from D-ribose; protected as an acetonide to generate lactol **51**. Wittig olefination of **51**, gave the olefin that was reduced by catalytic hydrogenation and the free alcohol converted to the triflate **52**. Coupling of Grignard reagents **49** and **50** to triflate **52** generated the key intermediates **53** and **54**. Ozonolysis and base hydrolysis of the resulting acetates gave salicylaldehyde aldehydes **55** and **56** that were separable by chromatography. Benzyl protection of the phenol **56** was followed by acetonide deprotection gaving hemiacetal **57**. Careful oxidation with sodium periodate and hydrogen peroxide gave lactone **58** that was transformed to **59** via mesylation of the secondary alcohol and displacement with sodium azide (Mitsunobu azidation) with S_N2 inversion of the center. Catalytic hydrogenation of azide **59** gave the amine that was converted to the hydrochloride salt **33**, by acidic work up to complete Kotsuki's synthesis (Scheme 1.8). Vallee later used this approach in his synthesis of PM-94128 **1**.[50]



Scheme 1.8. Kotsuki's synthesis of the aminodihydroisocoumarin 39.

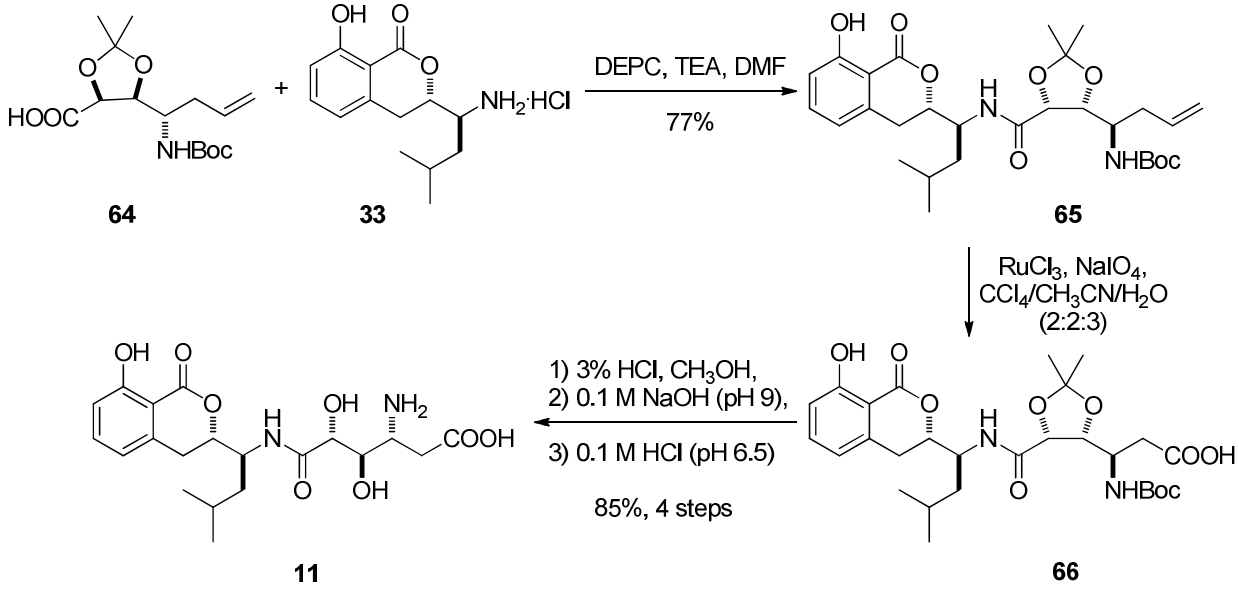
Kotsuki's synthesis of the linear section of AI-77-B began with acetal **60** (Scheme 1.9) that was treated with PMB amine acetic anhydride/pyridine/DMAP to give lactam **61**. A Sakurai type reaction of acetate **61**, Allyl TMS and $BF_3{\cdot}OEt_2$ as the Lewis acid produced **62**, the Allyl group adding from the lower face of the lactone ring. CAN oxidative removal of the PMB group was followed by reprotection of the free amine to give the N-Boc protected lactam **63**. Lithium hydroxide promoted hydrolysis of the lactam ring produced desired acid **64**.



Scheme 1.9. Kotsuki's synthesis of the acetonide coupling partner 69.

Coupling of isocoumarin **33** and acid **64** via DEPC mediated conditions proceeded in good yield to give amide **65**. Oxidative cleavage of the terminal double bond gave acid **66**. Global removal of the protecting groups was achieved by acid base acid reaction sequence yielding **11** (

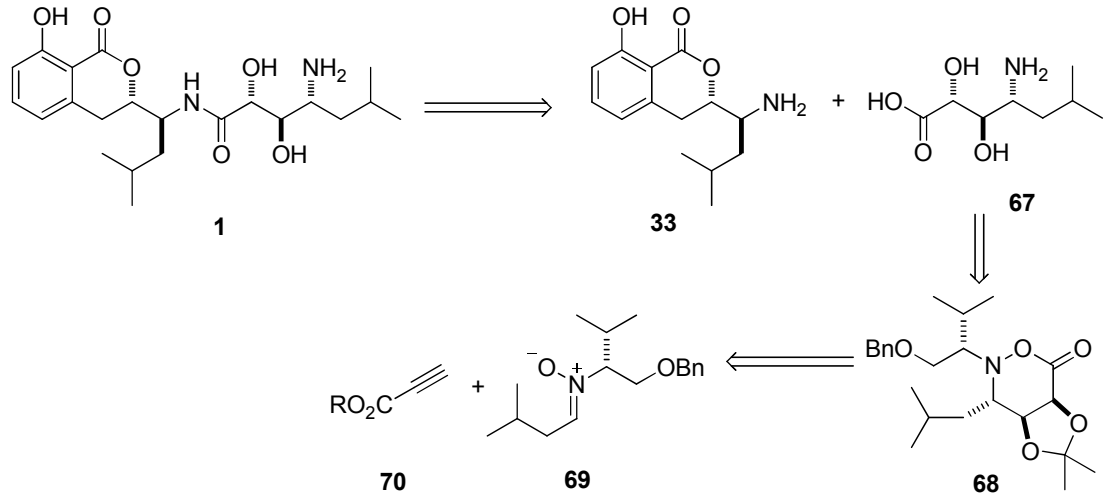
Scheme 1.10).



Scheme 1.10. Coupling of isocoumarin 33 and acid 64.

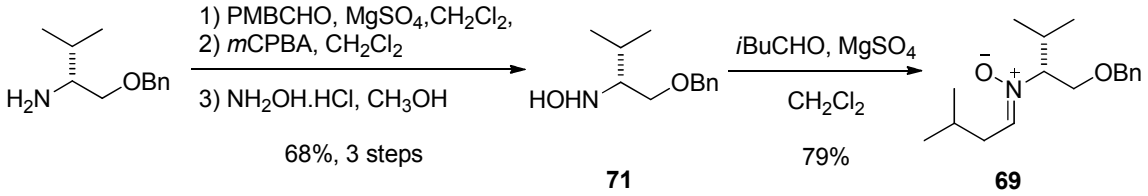
1.1.10. Vallee's sythesis of PM-94128

Vallee described the synthesis of PM-92128 (the only full synthesis reported to date), utilizing the common disconnection across the peptide bond (Scheme 1.11).[50] The dihydroisocoumarin fragment **33** was synthesized following Kotsuki's approach[62] while the dihydroxyamino acid portion **67** was targeted through diastereoselective alkylation of a chiral nitrone **69** and a 2,3-dihydro-[1,2]oxazin-6-one dihydroxylation.



Scheme 1.11. The retrosynthesis of PM-94128 designed by Vallée.

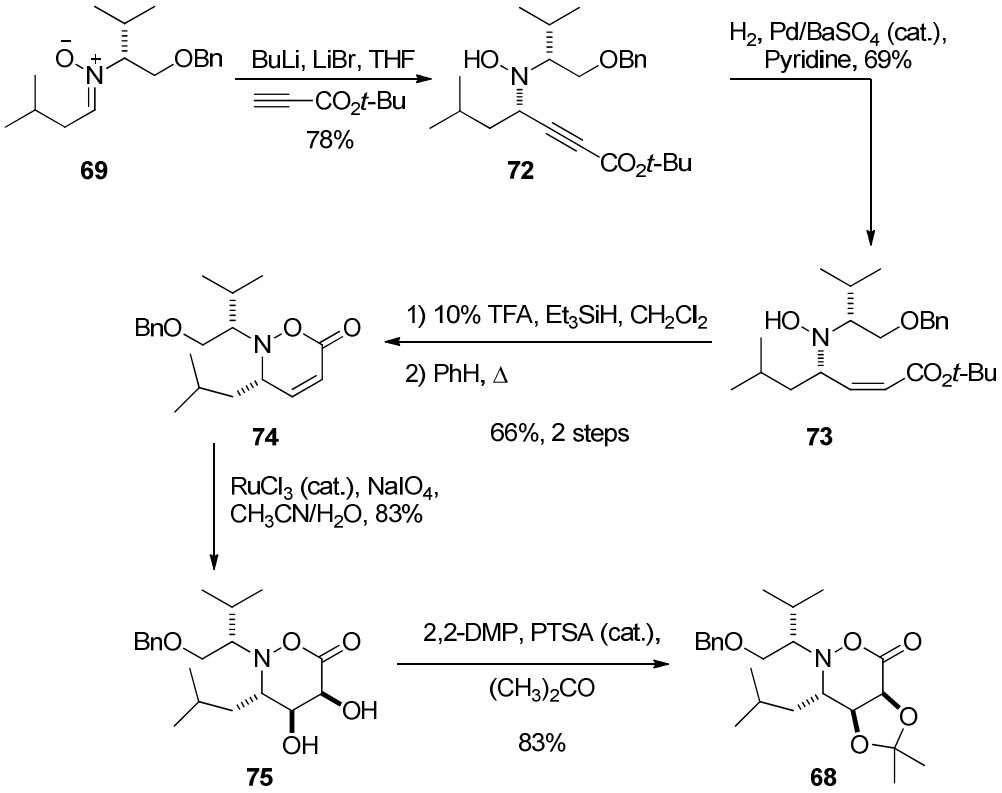
The nitrone **69**, was synthesized (Scheme 1.12) by the selective *O*-benzylation of valinol, oxidation to the hydroxylamine **71** and condensation with *iso*valeraldehyde producing the desired nitrone **69** in 49% yield.



Scheme 1.12. Generation of nitrone 74.

Addition of *t*butyl lithium propiolate to nitrone **69** was achieved successfully to give hydroxylamine **72** as a single product. Selective reduction of the alkyne unit using Lindlar's conditions gave the corresponding *Z*-olefin **73**. Hydroxylamine protection was necessary at this point to avoid nitrone formation; this was achieved by ester saponification followed by cyclisation-dehydration by reluxing in toluene. Dihydroxylation of the *Z*-olefin was accomplished using Shing's

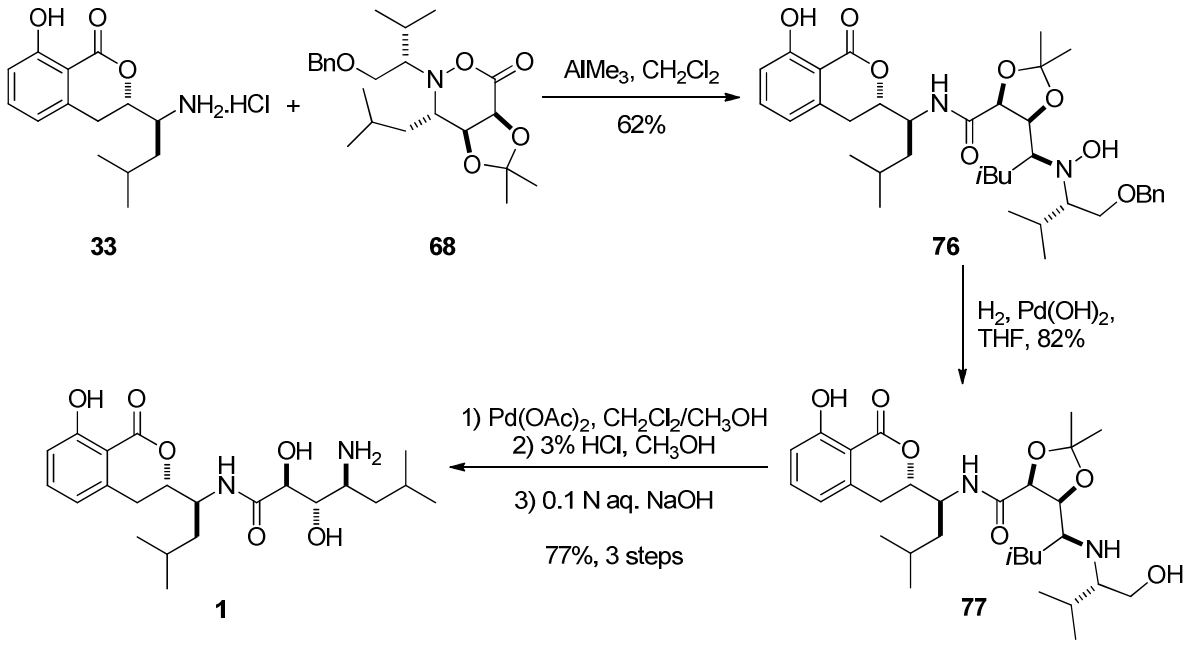
dihydroxylation protocol, giving *syn* diol **75**.[63] Protection of the diol **75** with acidic dimethoxypropane produced the coupling partner **69.**



Scheme 1.13. Synthesis of coupling partner 68.

Coupling of oxazinone **68** with dihydroisocoumarin **33** was performed in the presence of trimethylaluminium (3.5 eq). Attempts to couple (and open) the oxazinone with only 1.5 equivalents of **33** and sodium-2-ethyl-hexanoate resulted in poor yields.

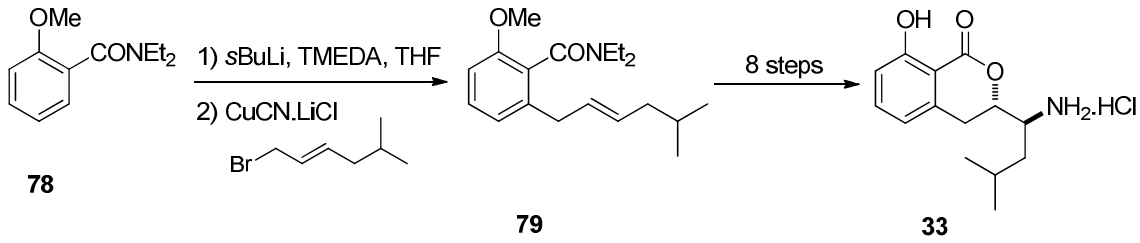
Removal of the chiral auxilliary involved concomitant hydrogenolysis of the *O*-benzyl and N-O bonds, to be followed by oxidative amino alcohol cleavage using palladium(II) acetate giving free amine. Acetyl group deprotection was achieved by 3% HCl in methanol to give PM-94128 **1**.



Scheme 1.14. Coupling of aminodihydroisocoumarin 33 and 68.

1.1.11. Other notable syntheses

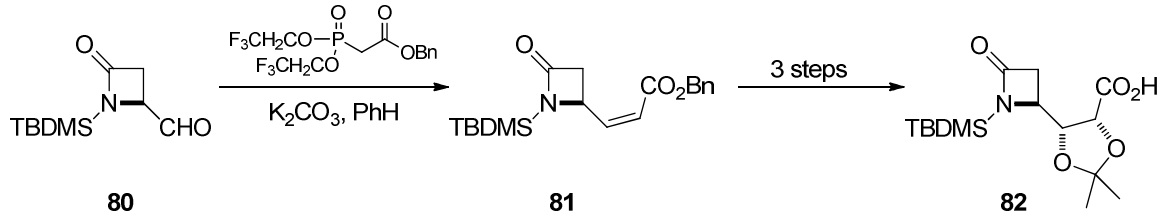
Superchi,[64] presented his synthesis of the aminodihydroisocoumarin moiety of AI-77-B, using a metallation/alkylation sequence followed by dihydroxylation/ring forming reactions.



Scheme 1.15. Superchi's approach to aminodihydroisocoumarin 39.

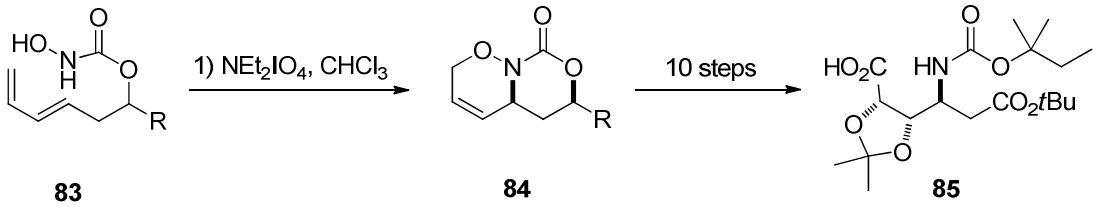
Thomas, Russell and Davies and Durgnat and Vogel all recorded novel syntheses of the eastern fragment of AI-77-B while using Shioiri's procedure[60] or a modification thereof (benzylic anion addition to leucine derived aldehyde) to generate isocoumarin coupling partner **33**.

Thomas's approach to lactam **82** was via olefination of lactam-aldehyde **80** derived from L-aspartic acid then *syn*-dihydroxylation of 4-alkenylazetidinone **87**, that was modified further to give **82**.[65]



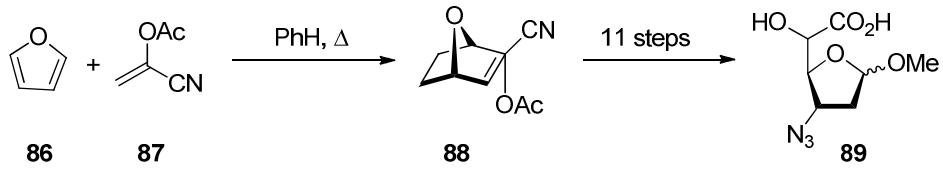
Scheme 1.16. Thomas's approach to lactam 82.

Russell and Davies[66,67] were able to utilize their intramolecular acylnitroso Diels-Alder methodology (taking advantage of Shea's[68] work on Type II Diels-Alder chemistry and Craigs[69] studies into the asymmetric Diels-Alder chemistry) to synthesize acid **91**.



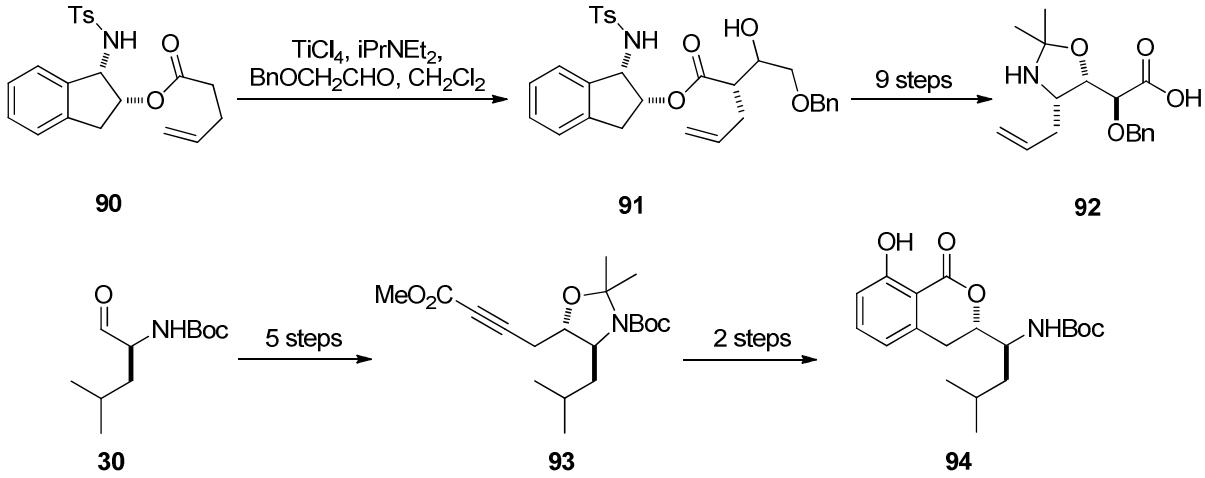
Scheme 1.17. Synthesis of acid 85.

Durgnat and Vogel[70] designed their synthesis around a Diels-Alder approach between furan **86** and cyanovinyl acetate **87**, the bridged ether **88** was modified to give the desired acid coupling partner **89**.



Scheme 1.18. Synthesis of furanoside 89

Ghosh, Bischoff and Cappiello[71] used a titanium enolate mediated *syn*-aldol reaction of **90**, Curtius rearrangement and Dondoni aldehyde homologation to generate the acid coupling partner **92** via ester **91**. While aminodihydroisocoumarin **100** was synthesized from **94** through alkylation and protection giving **93** that underwent Diels-Alder/Retro Diels-Alder reaction sequence.



Scheme 1.19. Synthesis of oxazolidine 92 and aminodihydroisocoumarin 94.

Ward and Proctor have also reported several syntheses of aminodihydroisocoumarin family members. Bachiphelacins **9** amino diol fragment was synthesized via dihydroxylation of chiral allylsilane **95**.[72]

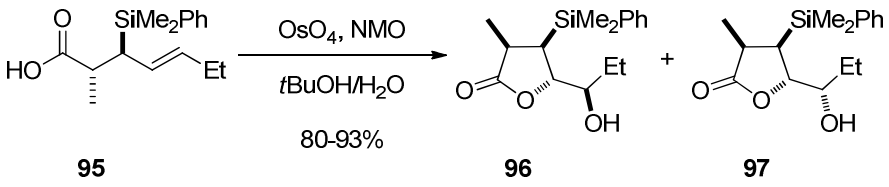


Figure 1.13. Upjohn dihydroxylation of acid 101.

Ward and Proctor were also able to synthesize AI-77-B **11** and Amicoumacin C **12**, using aspartic acid that could be diprotected as the benzyl ester **98** then converted to the Cβ-aldehyde **99**, then olefinated with Horner-Wadsworth-Emmons conditions giving **100**, that was then dihydroxylated.

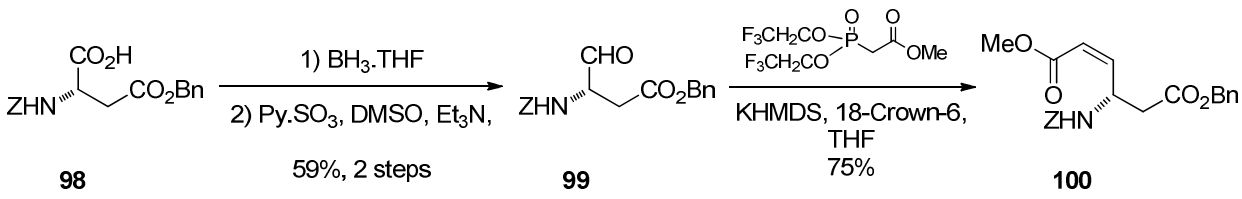


Figure 1.14. Synthesis of olefin 100.

Our interest in the aminodihydroisocoumarins led us to the discovery of the isochromanones and the Ajudazols. The isocoumarins are structurally related to the isochromanones, they both have benzoic lactone structures with an *alpha* stereocenter. Biologically they have very different activities, making them very intersting targets within the Marquez research group.

1.2. Isochromanones

1.2.1. Ajudazol A and B

Ajudazol A and B were discovered in 2004, during a screening of myxobacteria for new biologically active compounds.[2,73]

The myxobacteria group of organisms was first described by Roland Thaxter in 1892. Myxobacteria are found in most environments; however their main habitats are temperate topsoil and rotting vegetation. Physiologically they exhibit several features that have made them the subject of significant scientific interest.[74]

As prokaryotes, Myxobacteria show a unique cooperative social behaviour,[74] based on a complex communication system that allows colonies a swarming motility (they can move by gliding or creeping on surfaces) which enables them to coordinate in a predatory manner against other microbes

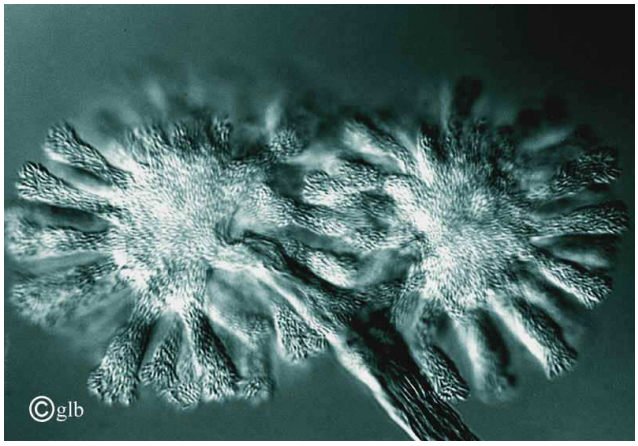


Figure 1.15. Bacterial rods during gliding process.[75]

To complement their predatory activity, the bacteria produce lytic *exo*-enzymes against their prey. The lysis products of 'prey' bacteria and fungi are sufficient to sustain the Myxobacterias growth etc. Under starvation conditions, Myxobacteria undergo a form of multicellular development where they are able to assemble fruiting bodies and more complex structures. Within these bodies resistant cell types (myxospores) are produced.[76] Myxospores are resistant to desiccation giving the organism a dormant stage to its life cycle. Myxobacteria also secrete an array of biologically active metabolites including antibiotics and antitumour agents.

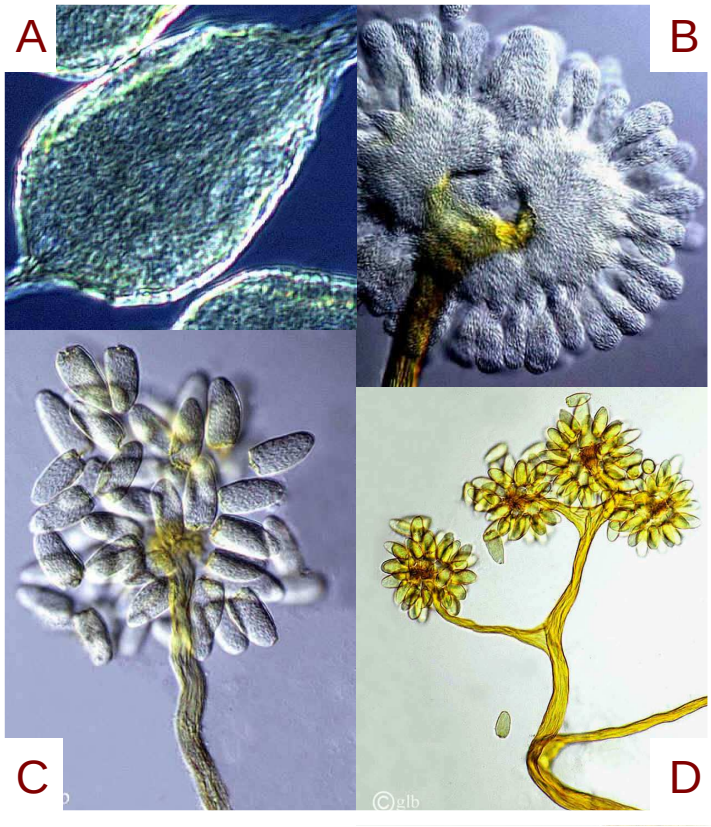


Figure 1.16 Spore body of myxobacterium; B, C and D – Stages in the development of the 'fruitbody' of the myxobacterium Chondromyces crocatus.[75]

The species *Chondromyces crocatus* has been particularly prolific at exhibiting high antifungal and cytotoxic effects. The activities have been ascribed to the large number of secondary metabolites produced by the species. Of these secondary metabolites, Adjudazols A **2** and B **3** were observed as well as Crocacin A to D and Chondramides A to D. The crocacins are a family of N-acyl dipeptides, known to block electron flow in the third complex of the cytochrome bc_1 segment of the eukaryotic respiratory chain, while the chondramides are new depsipeptides structurally related to jasplakinolide,[77,78] which is highly cytostatic against mammalian cell lines.[79,80]

The discovery of the Ajudazols came surreptitiously from further purification of crude extracts, also leading to the further discovery of the chondrochlorens, a new ß-amino styrene.[2]

The antimicrobial activity of the Ajudazols has been partially assessed; Ajudazol B incompletely inhibited growth of several important fungi including *Botrytis cinerea*, *Ustilago maydis*. It has also displayed weak activity against several Gram-positive bacteria. Ajudazol A showed only minor activity against a few

fungi and Gram-positive bacteria.

The Ajudazols antifungal activity is significant because fungi like *Botrytis cinerea* are a ubiquitous fungal pathogen causing gray rot. *Botrytis cinerea* affects a large number of economically important agricultural and horticultural crops. It opportunistically infects wounds or senescing tissue and also invades young tissues, causing necrosis.[81] While *Ustilago maydis* (corn smut) infects maize (*Zea mays*) and teosinte (*Euchlena mexicana*) and can ruin whole harvests depending on level of infection.

Studies, to investigate the mechanism of action and influence of the Ajudazols on the mitochondrial respiratory energy metabolism were conducted in 2004. Nicotinamide adenine dinucleotide (NADH) oxidation in sub mitochondrial particles (SMPs) (as determined by UV/VIS spectrophotometry) was inhibited by 50% at a concentration of 22 nM (Ajudazol A) and 18 nM (Ajudazol B), respectively.[73]

Faced with this potent activity the site of inhibition within the electron transport chain was investigated. The results indicated that the site of inhibition of Ajudazols is on the substrate side of cytochrome *b*. Cytochromes can be reduced either by NADH via complex I (NADH: *ubiquinone oxidoreductase*) or by succinate. To determine whether the Ajudazols interfere with complex I, complex II, or with both, the effect on reduction kinetics of cytochrome *b* using either NADH or succinate as the substrate was investigated. Ajudazol A and B inhibited the reduction of cytochrome *b* only when NADH was the electron donor. The investigations on the mechanism of action of the Ajudazols suggest that the Ajudazols block the electron flow in SMPs specifically at the site of complex I. The observation is supported by further investigations which demonstrated that the new compounds block the electron flow in SMPs specifically at the NADH: *ubiquinone-oxidoreductase* complex 1 site.

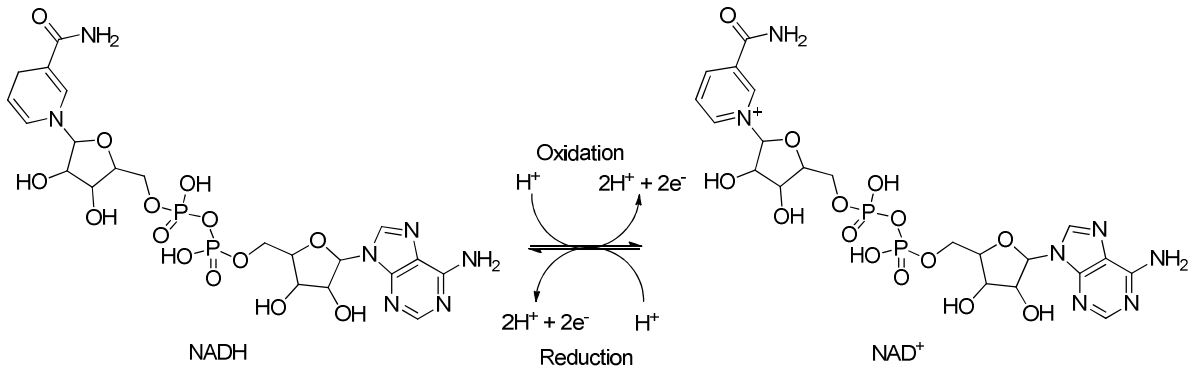


Figure 1.17. The NADH oxidation/reduction cycle.

The Ajudazols A and B consist of an isochromanone (C1-C9) fragment and a C10-C29 fragment (Figure 1.18). The isochromanone fragment possesses C_8 hydroxyl and C9 alkyl groups, while the C10-C29 contains a *Z*-diene (C17-C20) and an *E*-olefin (C23-C24) which is linked to an (*E*)-3-methoxy-N-methylbut-2-enamide. This enamide is shared among other compounds isolated from *Chondromyces* bacteria (for example the Crocacins). Another feature of the Ajudazol framework is the (S)-*sec*propyl oxazole fragment that connects the isochromanone and the linear 18C tail portion.

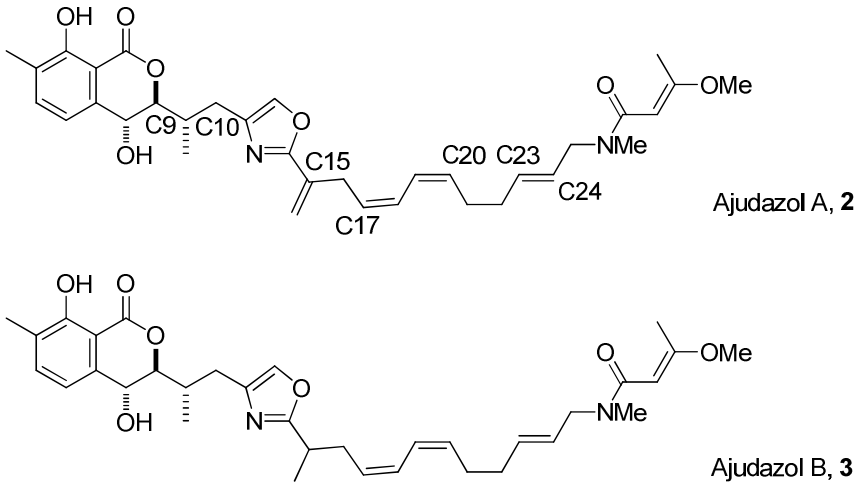


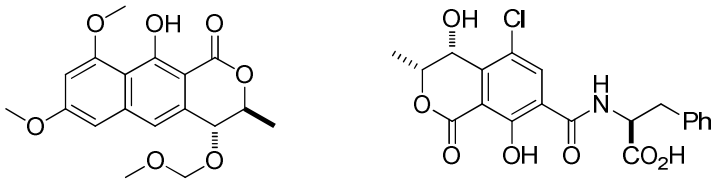
Figure 1.18. Ajudazols A 2 and B 3

The sole difference between the Ajudazols is the C15 carbon. In Ajudazol B it is a methyl group (unassigned conformation) rather than an *exo*-methylene olefin (as with Ajudazol A).

The stereochemistry of the Ajudazols has been assigned by extensive NMR studies although no crystallographic data has been reported.[82] The C9 carbon center has been assigned the *S*-configuration, as has the C10 carbon, while the

C8 hydroxyl center has the *R*-conformation. The C15 carbon of Ajudazol B has not been assigned.

The isochromanone functionality is one of only a few examples of the more common isocoumarin core **21**, bearing C8 hydroxyl functionality. The literature contains only four other natural products containing C8 hydroxyl isochromanones, with only two possessing an alkyl group in the C4 position.[83]



Bioxanthracene ES-242s **101** 4(R)-Hydroxychratoxin A **102**

Figure 1.19. Examples of isochromanone natural products, bearing C_4 oxygens.

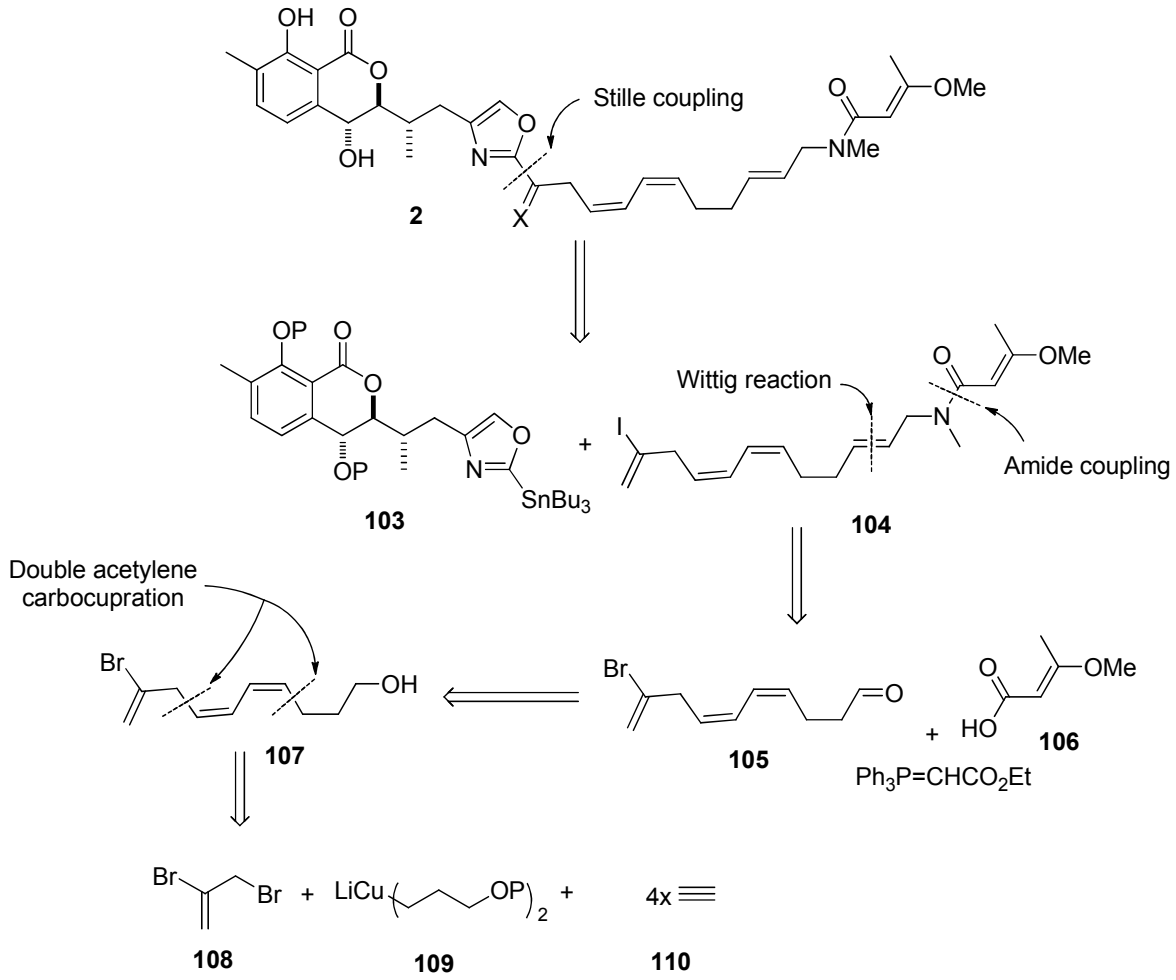
Other than the C8 hydroxyl and C9 functionality the isochromanones and isocoumarins differ only in ring stereochemistry. The aminodihydroisocoumarins are *R* configured while the Ajudazols have *S*-configuration.

To date there have been only two reported approaches towards the synthesis of the Ajudazols. Both of these are concerned with the synthesis of the C9/C15-C29 eastern fragment of the molecule. There have been no publications detailing the synthesis of the isochromanone bicycle.

1.2.2. Taylor's synthesis of the C15-C29 fragment, 104

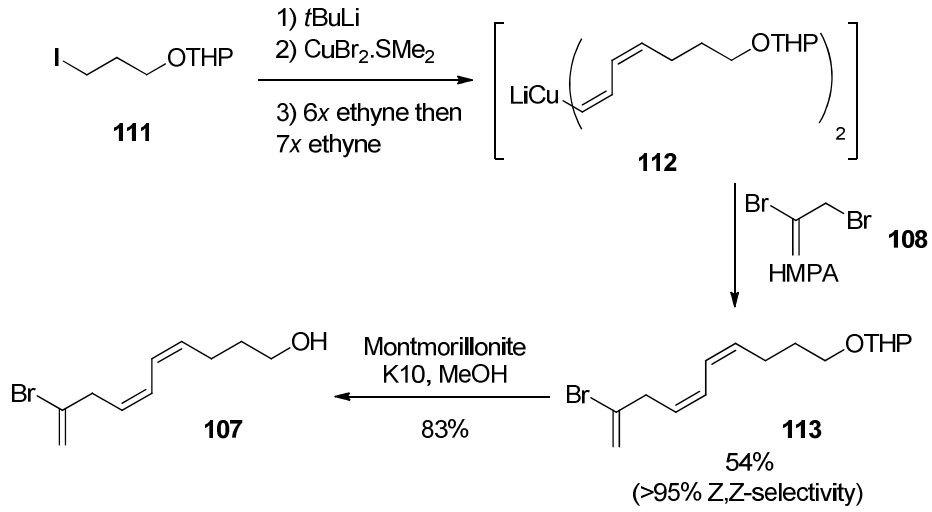
As part of his efforts towards the synthesis of Ajudazol A **2**, Taylor presented the one-pot double acetylene carbo-cupration of a functionalised alkyl cuprate **109**, that was trapped with 2,3-dibromopropene **110**.[84]

Taylor's retrosynthesis (Scheme 1.20) is based on the key Stille disconnection of 2-stannyl-oxazole **103** and vinyl halide **104**. Halide **104** was thought to come from the amide coupling of the amine derived from the Wittig olefination of aldehyde **105** and 3-methoxybutenoic acid **106**. The aldehyde **105** could come from alcohol **107**, which in turn could be generated through the key double acetylene carbo-cupration reaction and subsequent trapping with halide **108**.



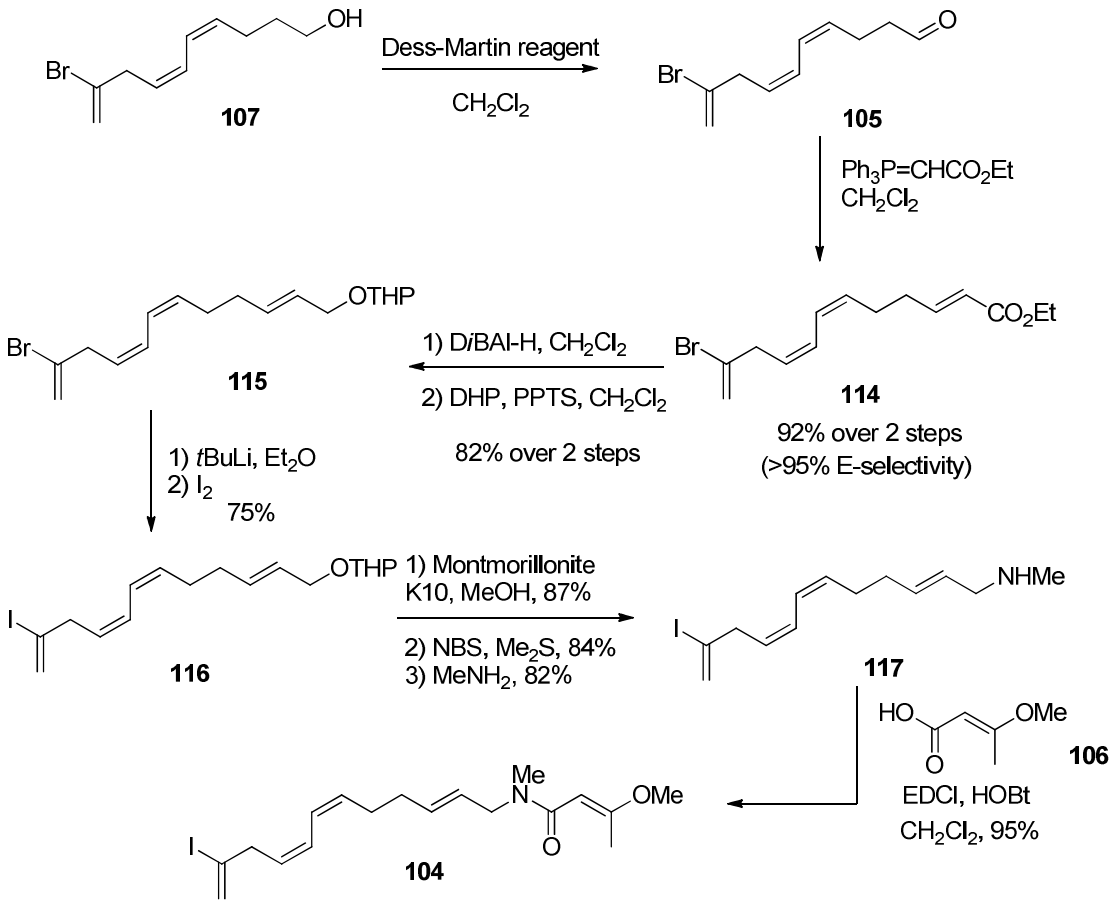
Scheme 1.20. Taylor's retrosynthesis of the Ajudazol A molecule.

The forward synthesis began with the metal-halogen exchange of iodide **111**, followed by *trans*-metallation to generate dialkyl-cuprate. Reaction of cuprate with acetylene **110** generated the *Z,Z*-dienyl intermediate **112** which was trapped with 2,3-dibromopropene **108**, to give triene **113**. THP ether cleavage gave alcohol **107** (Scheme 1.21).



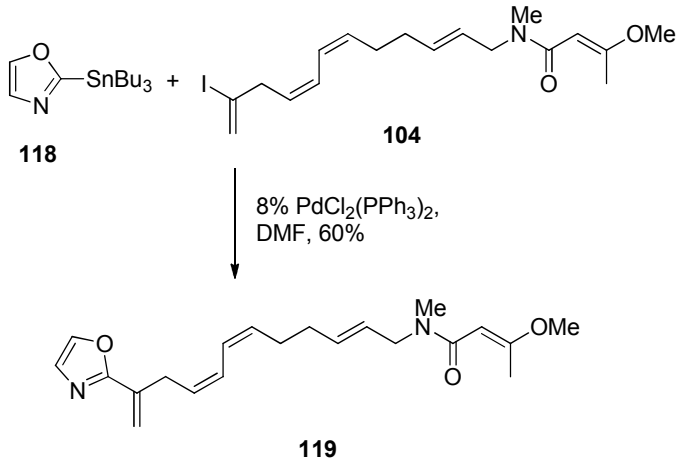
Scheme 1.21. The first stages of the synthesis

Oxidation of **107** and Wittig olefination of the resulting aldehyde **105** produced the tetrene **114**, which was reduced and the allylic alcohol masked as the THP ether **115**. Conversion of the bromide functionality to an iodide was achieved via a metal-halogen exchange process with *t*BuLi and the resulting alkyl-lithium quenched with molecular iodine to give vinyl-iodide **116**. Cleavage of the THP group was followed by free alcohol conversion to the corresponding secondary amine **117** via the bromide intermediate. Coupling of amine **117** and acid **106** completed the synthesis of Taylor's C15-C29 **104** fragment of Ajudazol (Scheme 1.22).



Scheme 1.22. The final reactions of the sequence

The suitability of the vinyl iodide towards the planned Stille coupling reaction was examined see Scheme 1.23. Reacting vinyl iodide **104** with 2-oxazole stannane **118** produced in 60% yield the desired compound **119**. $Pd(PPh_3)_4$ and $PdCl_2(MeCN)_2$ were also tested for this coupling, but the best results were obtained using $PdCl_2(PPh_3)_2$.

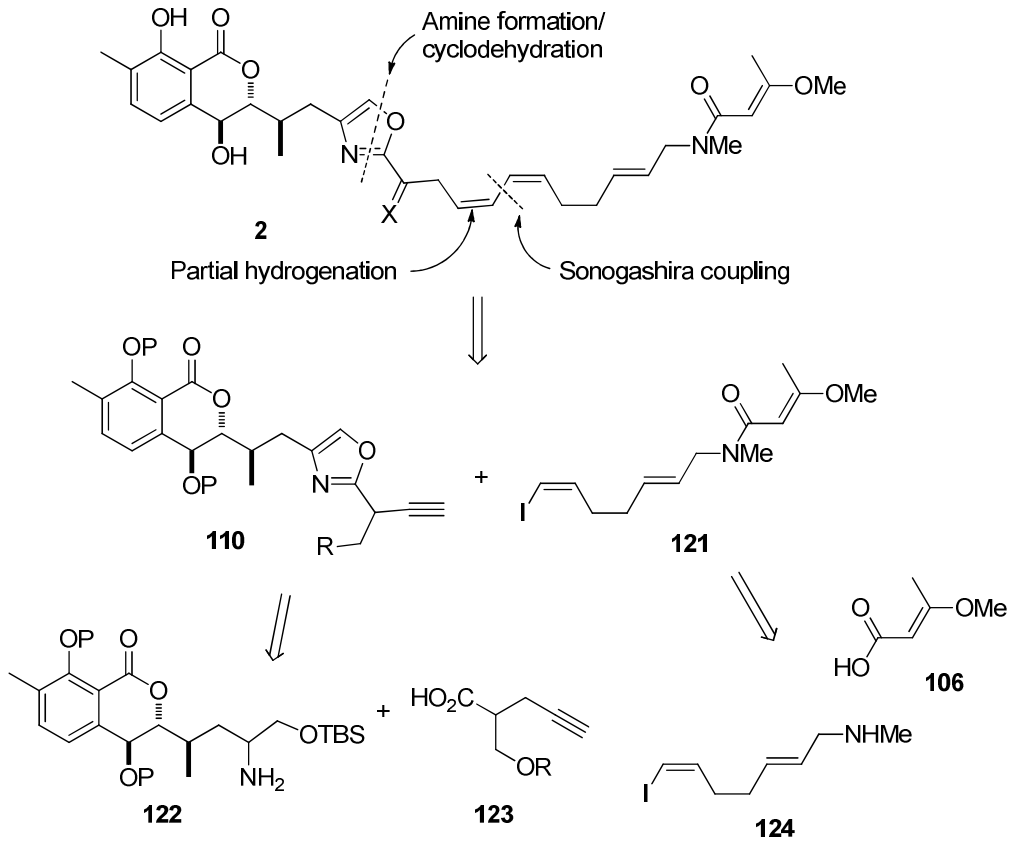


Scheme 1.23. Stille reaction tests between vinyl iodide and oxazole 119

1.2.3. Rizzacasa's synthesis of the C9-C29 fragment 121

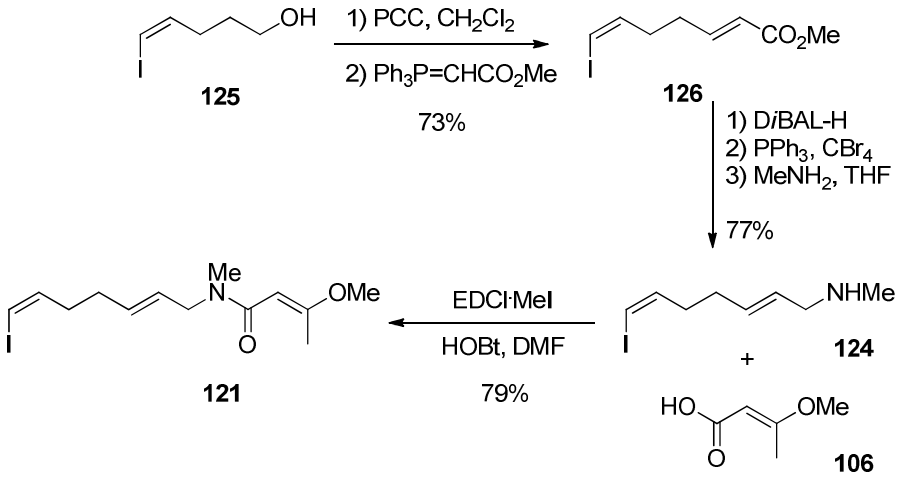
More recently, Rizzacasa reported his convergent approach to the synthesis of the C9-C29 portion of the Ajudazols. Rizzacasa's approach relies on a cyclodehydration/Sonogashira coupling/alkyne hydrogenation reaction sequence.[85]

Retrosynthetically the C18-C19 bond was introduced by Sonogashira cross coupling reaction between alkyne **120** and vinyl iodide **121**. The alkyne could be seen to come from acid **123** followed by oxazole formation using a variant of the Wipf protocol.[86,87] Vinyl iodide **124** is thought to come from coupling of allylic amine **124** and acid **106**. (Scheme 1.24)



Scheme 1.24. The retrosynthesis designed by Rizzacasa.

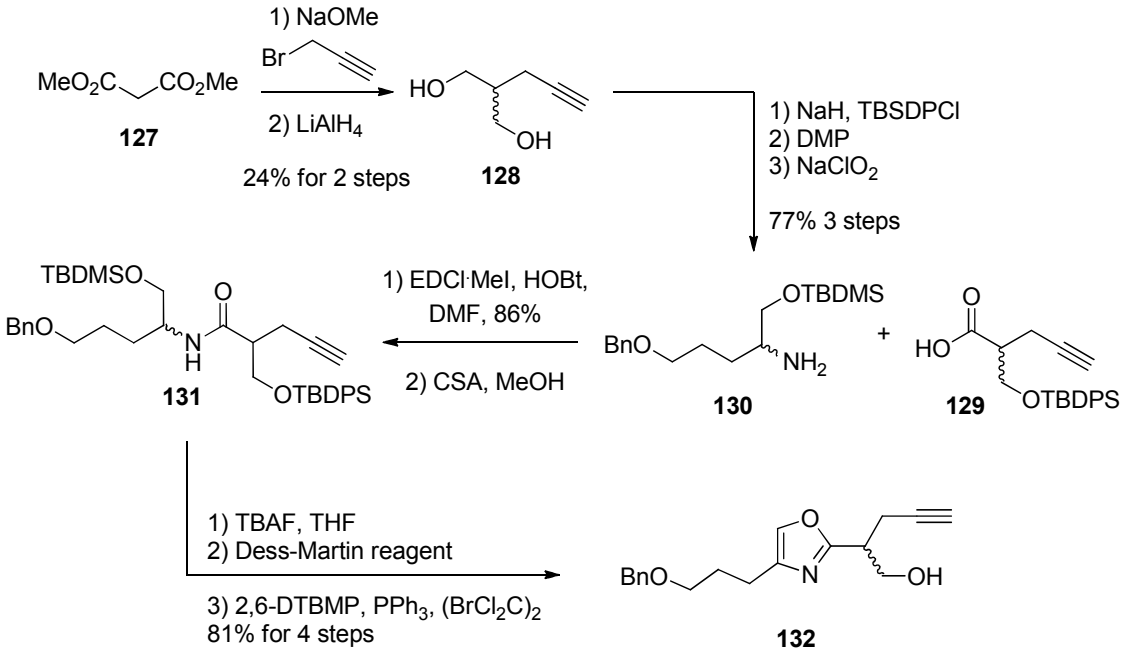
Rizzacasa's synthesis of the C9-C29 segment began with the oxidation and olefination of known alcohol **125**, giving diene **126**. The ester was reduced to the allylic alcohol then converted to the bromide and displaced with methylamine to give secondary amine **124**. Peptide coupling between acid **106** and amine **124** produced desired vinyl iodide **121** (Scheme 1.25).



Scheme 1.25. Synthesis of the common coupling partner

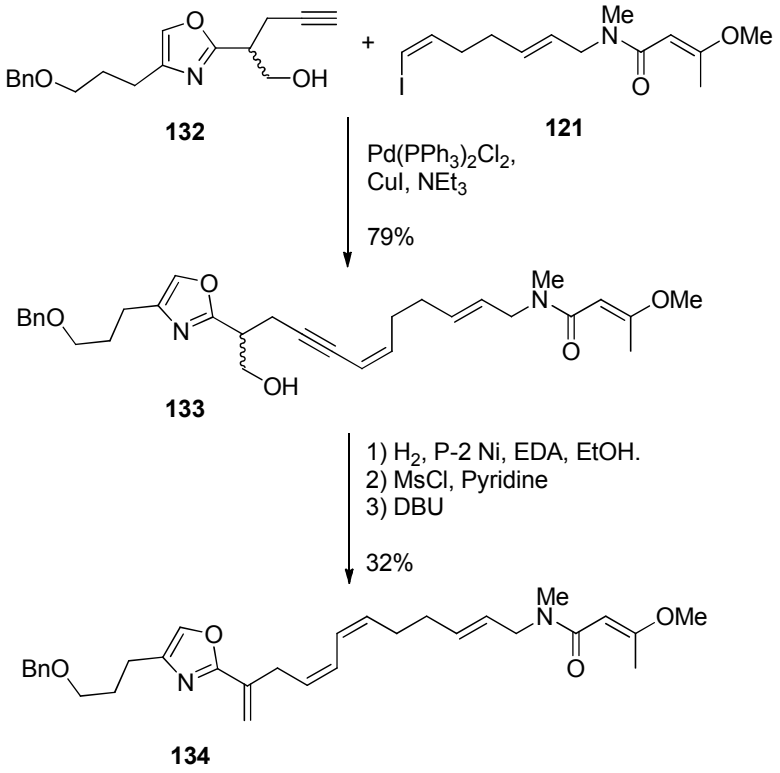
The oxazole fragment **132** was synthesized from dimethyl malonate **127**, which was alkylated and then reduced to yield diol **128**. Mono-protection and oxidation produced the acid **129**. Coupling of the acid with known racemic amine **130**

afforded amide **131.** Selective silyl ether deprotection of the *t*butyldimethyl silyl group allowed Dess Martin Oxidation of the resulting alcohol that could be transformed to the desired oxazole **132** (Scheme 1.26).



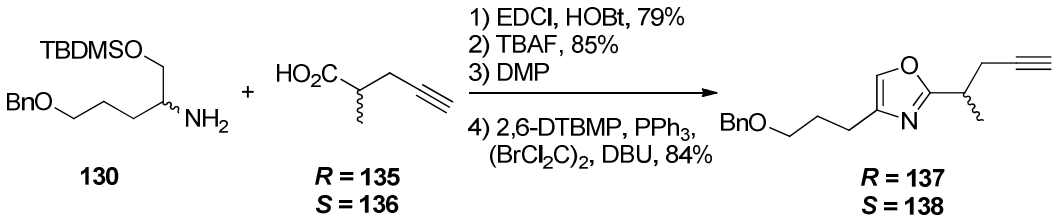
Scheme 1.26 Production of the oxazole fragment corresponding to Ajudazol A.

Coupling of alkyne **132** and vinyl iodide **121** under Sonogashira cross coupling conditions gave the desired ene-yne **133**. Partial hydrogenation of the alkyne followed by mesylation of the primary alcohol and elimination produced (Scheme 1.27), poly-ene **134** as Rizzacasa's model system for the synthesis of the Ajudazols.



Scheme 1.27. Coupling of vinyl iodide 121 and oxazole 132.

Rizzacasa then modified his synthesis of compound **132** (Scheme 1.28) in order to replicate the system present in Ajudazol B **2**. This enantioselective approach allows for either enantiomer of oxazole **137** or **138** to be synthesized, simply by selecting the appropriate acid-coupling partner **135** or **136** (Scheme 1.27).



Scheme 1.28. Synthesis of both enantiomers of Ajudazol B.

1.3. Other isocoumarin containing natural products

There are a number of isocoumarin containing compounds that are structurally simpler, but are important due to their biological profile.

Reticulol **139** was isolated from isolated from *Steptomyces rubreticulae,* a strain of soil *actinomyces called streptoverticillium*, NA-4803. Structurally, **139** is very similar to both Phytoalexin and Mellein but the compound is planar and lacks a stereocenter.

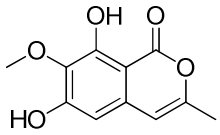
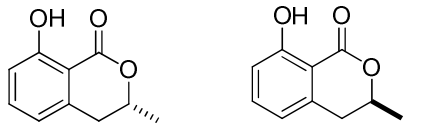


Figure 1.20. Reticulol 139

Reticulol **139**, is important because it is a cyclic 3',5'-monophosphodiesterase inhibitor. It has been shown that Topoisomerase 1 treated with 45 μM Reticulol does not replicate or transcribe DNA.[19]

(R)-(-)-Mellein **140** is widespread in nature having been isolated, *inter alia*, from many fungi and several insects in which it appears to play a pheromonal role. (S)-(+)-Mellein **141** is also a fungal metabolite, one source being the marine fungus *Helicascus kanaloanus*.



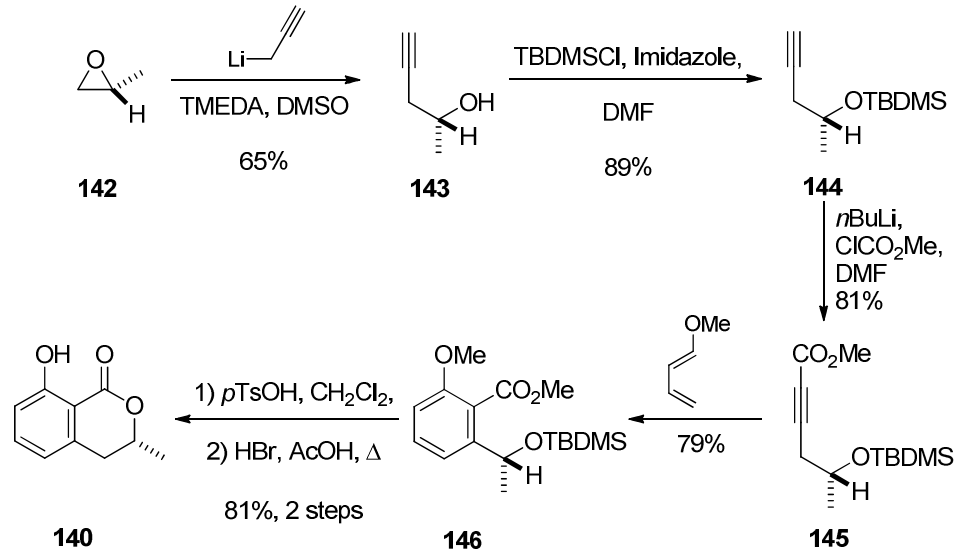
(R)-(-)-Mellein **140** (S)-(-)-Mellein **141**

Figure 1.21. Both enantiomers of Mellein.

The differing activities of aminodihydroisocoumarins from antiinflammatory to antitumour would seem to indicate a wide range of different biological targets. However compounds like AI-77-B **11** and the Xenocoumacins have not been tested for any antitumour activities. Although AI-77-B is known to be very cytotoxic when administered intraperitoneally. Combining this with observations in oncology, tumour cells have significantly increased uptake of minerals/sugars etc from their extra-cellular matrices. This could mean that others in the

aminodihydroisocoumarin family of compounds have similar cytotoxicity to PM-94128 that is as yet undiscovered.

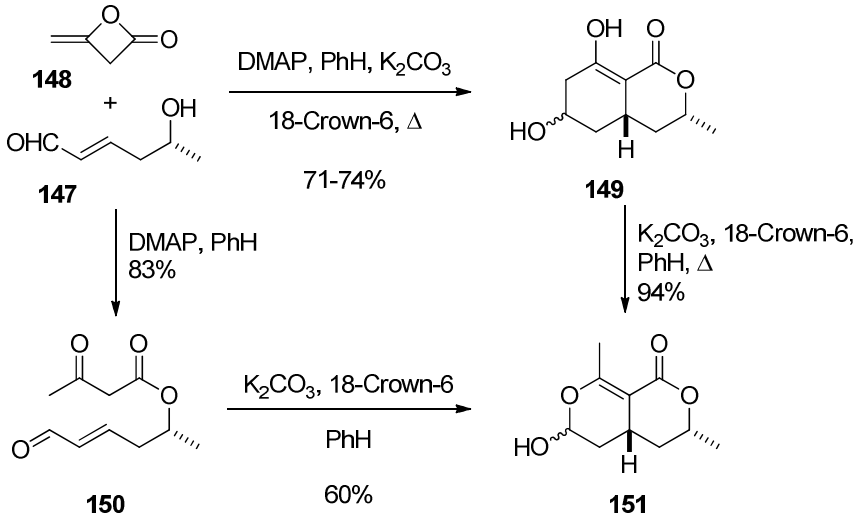
The first stereospecific synthesis of both enantiomers of Mellein was reported by Gill.[88] It began with alkylation of *R*-propylene oxide **142** using propargyl bromide derived anion that gave alcohol **143.** Silyl protection of the free alcohol was followed by alkylation of the terminal alkyne with methyl-chloroformate in 81% yield. Diels-Alder reaction between ester **145** and 1-methoxy-1,3-butadiene gave the salicylate derivate **146**, that upon treatment with toluene-sulfonic acid and hydrogen bromide gave **140**. The opposite *S*-enantiomer of Mellein **141** was synthesized from *S*-propylene oxide as per Scheme 1.29.



Scheme 1.29. Gill's synthesis of *R*-Mellein 146.

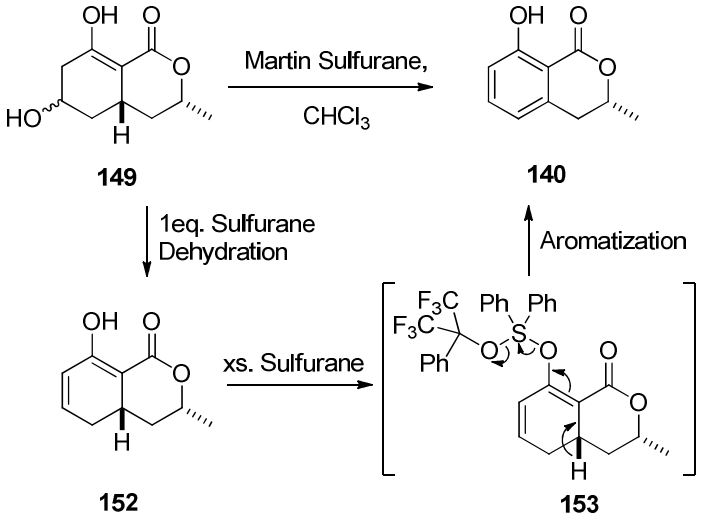
An interesting oxidative approach, to the synthesis of the 3,4-dihydroisocoumarins Mellein **140** and metabolic derivatives, was reported by Watanabe (Scheme 1.30).[89] Here the authors report a novel one-pot esterification-Michael addition-aldol reaction of a δ-hydroxy-α,β-unsaturated aldehyde **147** and a diketene **148**. The product was aromatized to give *R*-Mellein **140**.

Interestingly, the step-wise procedure was examined first in 47% overall yield while the one-pot version gave reproducible yields between 71% and 74% reproducibly.



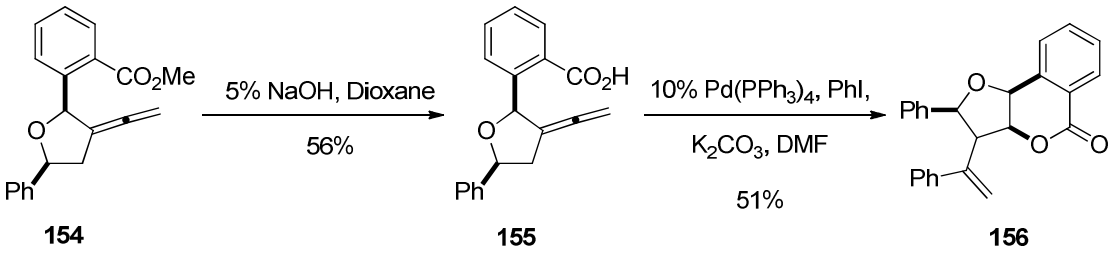
Scheme 1.30. Watanbe's synthesis.

Treatment of alcohol **149** with excess amounts of Martin Sulfurane gave *R*-Mellein **140** unexpectedly, via a two-step dehydration-aromatisation process, through intermediates **152** and **153** (Scheme 1.31).



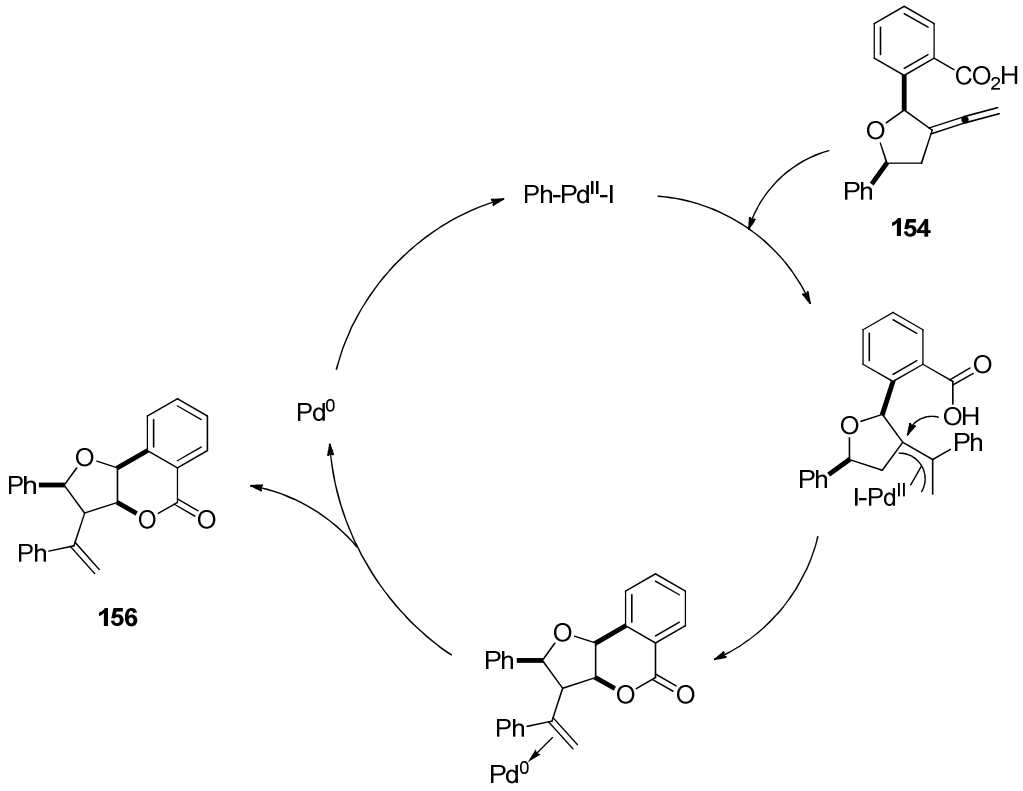
Scheme 1.31. Mechanism of aromatization by Martin Sulfurane.

Finally Cho and Choo reported their interesting synthetic approach to sterically congested cyclic lactones, through palladium-catalyzed cyclisations of allenyl tetrahydrofurans bearing a carboxylic acid (Scheme 1.32).[90]



Scheme 1.32. Synthetic route taken by Cho and Choo.

Mechanistically, an aryl-palladium halide intermediate adds to the center carbon of allene unit, resulting in the formation of a π-allylpalladium intermediate. This intermediate is attacked by the intramolecular nucleophilic carboxylate to afford the observed tricyclic product **156**, Scheme 1.33.



Scheme 1.33. Proposed mechanism of palladium-catalysed cyclisation.

1.4. Biosynthetic origin

Before the 1990s, it was speculated that the aminodihydroisocoumarins were of mixed polyketide biosynthetic origin. In 1991, McInerney proposed that the aromatic portion of the bicycle is derived from leucine and four acetate units.[6] The linear polyketide **157**, is cyclised (and aromatized as water is eliminated) by a polyketide synthase (PKS) in a type 1 iterative manner (Figure 1.22).

Bechthold's work in to this area has helped provide mechanistic evidence of PKS activities.[91]

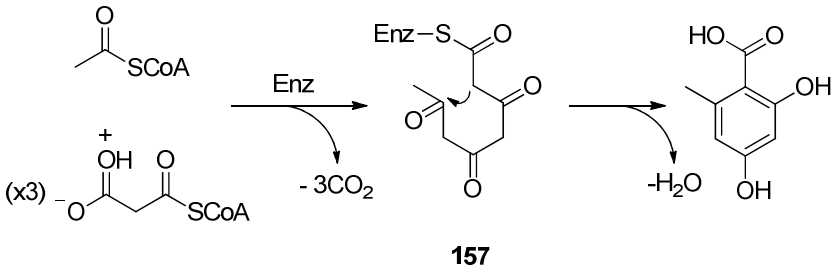


Figure 1.22. The orsellinic acid biosynthetic pathway.[92]

Isocoumarin **160**, is formed as the product of a ring closing reaction of **158,** giving **159.** De-oxygenation at C6 is followed by enantioselective reduction at the C3-C4 olefin. The free amine is then malonylated with a moeity derived from acetic acid and the requisite amino acid giving **160**. Finally oxidation at C8' takes place, presumably via water incorporation onto the linear chain. Reduction at C9' produces the final aminodihydroisocoumarin, Figure 1.23.

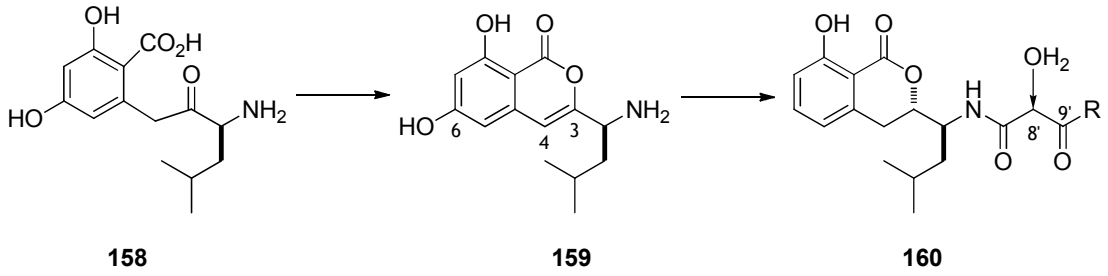


Figure 1.23. Formation of the dihydroisocoumarin system.[6]

McInerney's proposed biosynthesis was corroborated some 17 years later, when Buntin *et al*. published their work into the biosynthesis of the Ajudazols, noting that the formation of the isochromanone is one of the last transformations to occur.[93] Although the research showed a different method of combining the linear orsellinic acid and linear fragment, both papers agreed on the method of isocoumarin formation.

Buntin determined that the backbone of the Ajudazols molecule comes from a mixed system of type 1 polyketide synthase and a non-ribosomal polypeptide synthetase (NRPS) multi-enzyme.

Generally, an acetyl transferase loads a dicarboxyl extender onto an acyl carrier protein (ACP) and then is condensed with a starter acyl unit, catalyzed by a

ketosynthase, the resulting ß-ketoacyl intermediate remains thioester linked to the ACP. Ketoreductase processing of the β-ketone is likely followed by dehydratase and then enoyl reductase domains to yield an alcohol, enoyl or methylene group before the chain migrates to a ketosynthase and further cycles of extension. When the polyketide length is reached, termination occurs usually accompanied by cyclisation.

Polyketide synthases, as a group, use a wide range of organic acids as starter units, extenders may be malonyl, alkyl malonyl and methoxy-malonyl. Polyketide structural diversity is a result of this wider substrate tolerance. Chirality is introduced through branched extender units and asymmetric reduction of ß-ketones to alcohol, chirality as a result increases polyketide structural diversity. Figure 1.24 and Figure 1.25 show the sequence of biochemical transformations that that result in the formation of the Ajudazols.

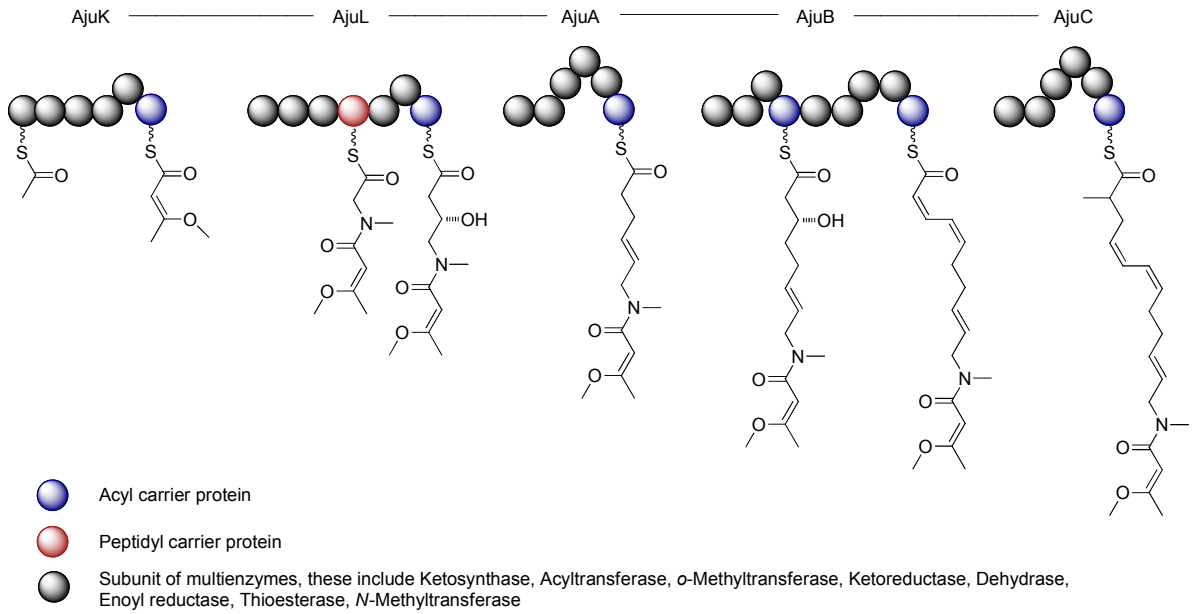


Figure 1.24. The first 8 steps of Ajudazol biosynthesis by mixed PKS-NRPS synthetase.

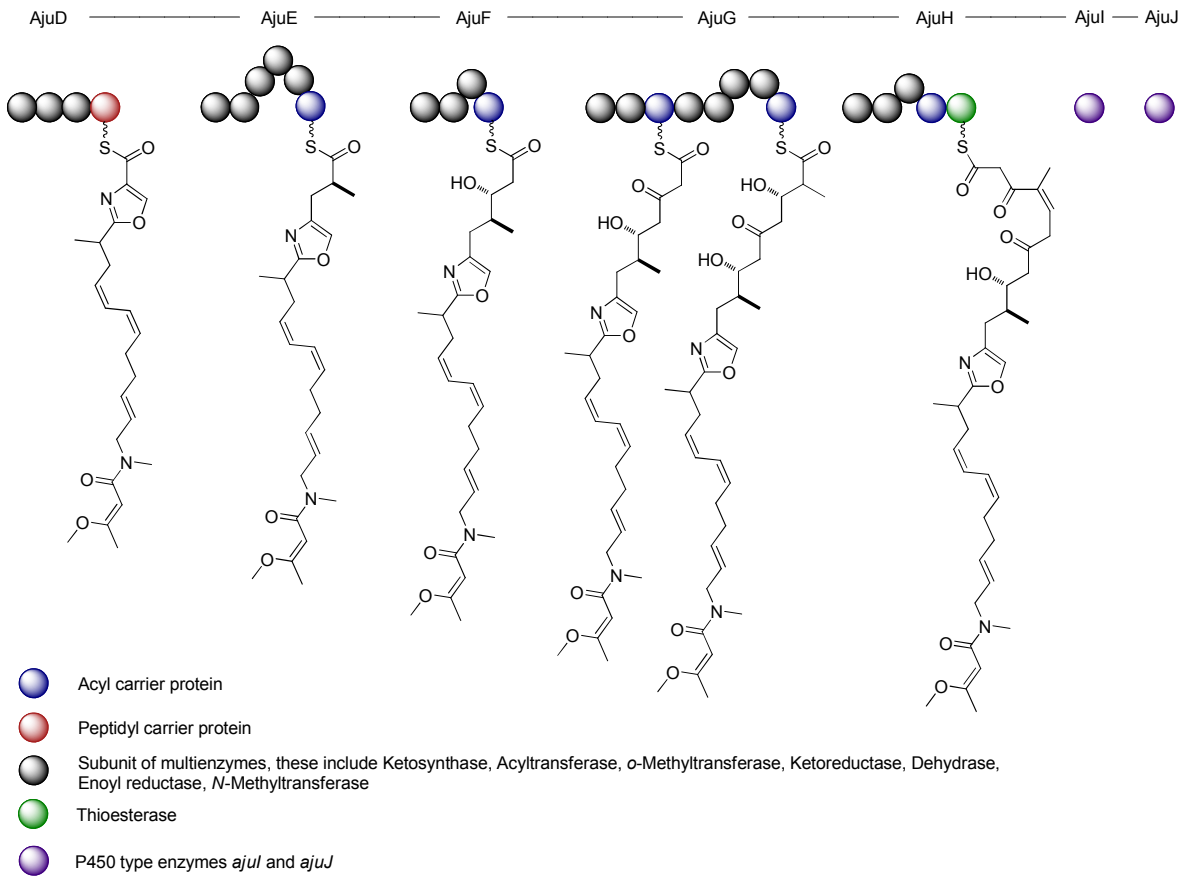


Figure 1.25. The final 8 modifications of the Ajudazol biosynthesis model.

Alcohol stereochemistry in the isochromanone ring, is determined by specific ketoreductases. Sequence analysis has shown few consistent differences between the ketoreductases types. Research to corroborate and properly examine reductase mechanisms of action is needed.

Biosynthesis of aromatic molecules in bacteria is generally achieved with type I and II PKS systems. This means that there are 2 possible mechanisms for chain release, coupled to the formation of the isochromanone functionality. Mechanism A involves the attack of the C9 hydroxyl group onto the thioester **161**, catalysed by an appropriate thioesterase. Ejection of the peptide carrier bound-thiol causes release of the 10-membered lactone **162**, where we see a C2-C9 aldol reaction followed by a ring aromatization reaction (Figure 1.26).

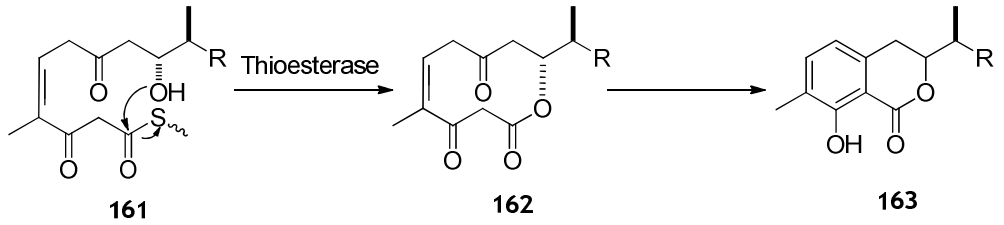


Figure 1.26. Proposed mechanism for 173 formation – Mechanism A.

Mechanism B has an intramolecular aldol/aromatisation reaction of **171** before the thioester catalyzed cleavage/lactonisation reaction of intermediate **164.** giving **165** (Figure 1.27).

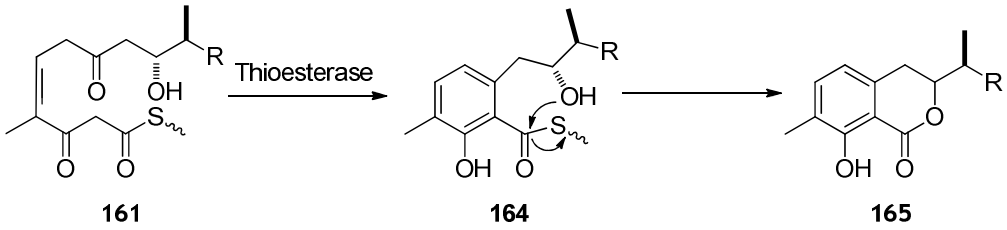


Figure 1.27. Proposed mechanism of 173 formation – Mechanism B.

There are several post PKS modifications needed to complete the synthesis of Ajudazols (C8 hydroxylation and *exo*-methylene formation). Responsible for these modifications are the enzymes AjuI and AjuJ (they have a great deal of homology to P_{450} enzymes) The product released from AjuH is likely to be deshydroxyAjudazol, **166**; which is a suitable substrate for AjuI and AjuJ. AjuI oxidizes the *exo*-methyl group and AjuJ is responsible for C8 oxidation resulting in the complete Ajudazol A molecule. In the case of Ajudazol B, **3** is modified by AjuJ only. As Ajudazol A is the major metabolite, the former reaction sequence would appear to be the preferred pathway.

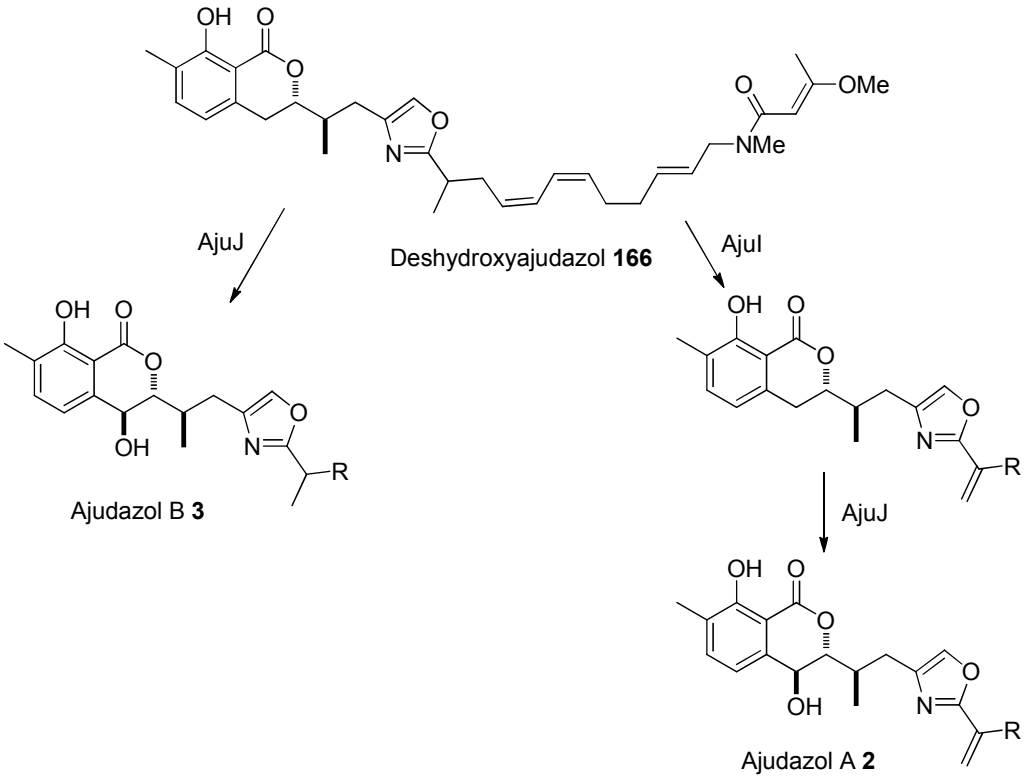


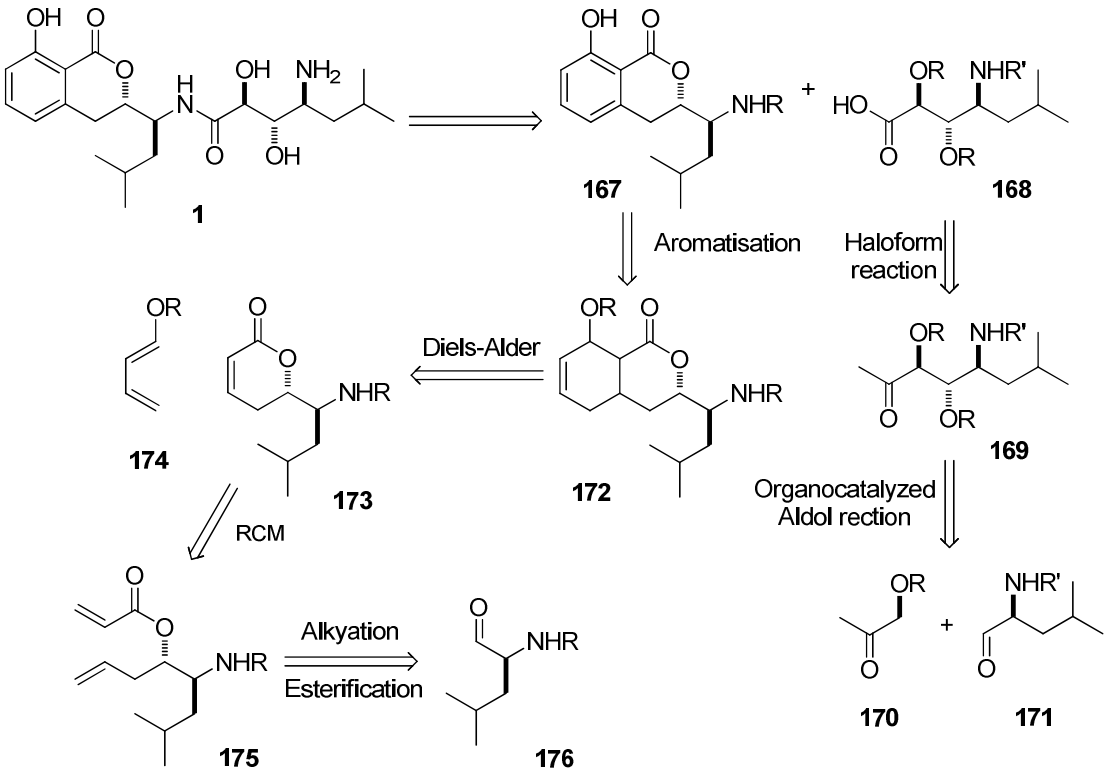
Figure 1.28. Buntin's proposed post-PKS modifications.

2. Results and discussion

2.1. Synthesis of PM-94128

We envisioned PM-94128 **1** as having come from the amide disconnection favoured by previous syntheses. The linear acid compound **168** was thought to be have arisen from the oxidation of ketone **169**, this having come from the product of a proline catalyzed aldol reaction between hydroxyacetone **170** and from N-protected leucine derived aldehyde **171**.

On the other hand aminodihydroisocoumarin bicycle **167** was thought of as originating from the aromatisation of allylic alcohol **172**. **172** could in turn be the product of the Diels-Alder reaction of diene **174** and α-pyrone **173**. α-Pyrone can come from the ring closing metathesis reaction of diene-ester **175**, which could be attained by stereoselective alkylation and esterification of N-protected leucinal **176** (Scheme 2.1).



Scheme 2.1. Our retrosynthesis of PM-94128

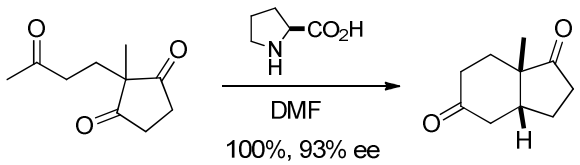
2.1.1. Proline organocatalysis

Proline and proline derivatives have found widespread use as organocatalytical reagents in synthesis.

> "Proline – a universal asymmetric catalyst?…there are various chemical reasons that contribute to prolines role in catalysis. Proline is bifunctional, with a carboxylic acid and amine portion. These two functional groups can act as both acid or base and facilitate chemical transformations in concert, similar or enzymatic catalysis "– Dr Benjamin List[94]

Proline has been reported in a large variety of reaction types ranging from asymmetric transfer hydrogenation reactions,[95-97] to Bayliss-Hillman chemistry[98] and even Diels-Alder type dimerisation reactions.[99,100] Derivatives have also found widespread use; Corey has applied the oxazaborolidine deriviative of proline both in the asymmetric reduction of ketones (Corey-Bakshi-Shibata reduction) and as an asymmetric catalyst for Diels-Alder reactions.[101,102]

Proline was described as the catalyst for the Hajos, Parrish, Wiechert and Sauer reaction, more commonly the Hajos-Parrish reaction.[103-106] The Hajos-Parrish reaction has found widespread use in the enantioselective synthesis of complex bicycles. In its original application the reaction saw proline catalysis of the conversion of trione **177** to the bicyclic dione **178** (Scheme 2.2).

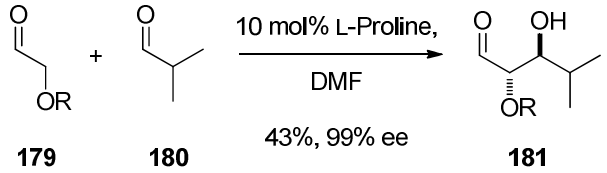


177 **178**

Scheme 2.2. Hajos-Parrish reaction of 2-methyl-2-(3-oxobutyl)cyclopentane-1,3-dione.

The Hajos-Parrish reaction is essentially an intramolecular application of the reaction that was envisioned for synthesis of the amino-diol fragment **168**.

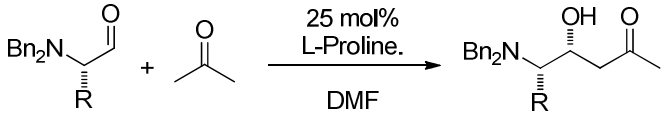
The large body of work in 'direct intermolecular aldol reactions' made us confident its application would be successful.[107-110] Macmillan (Scheme 2.3) reported the use of hydroxy carbonyl compounds **179** with aldehydes **180** in the presence of catalytic quantities of L-proline, yielding *anti*-diols **181** in good yield with excellent selectivities.[111]



179 **180** **181**

Scheme 2.3. Macmillan's method of generating *anti*-diols.

Further literature searches of proline organocatalyzed aldol reactions, highlighted the paper published by Ma, in which they detail their formal synthesis of the eastern fragment of PM-94128.[112] Their efforts were primarily concerned with reporting a method for the diastereoselective reaction of *N*,*N*-dibenzyl-α-aminoaldehydes **182** with ketones **183** catalyzed by proline (Scheme 2.5). This then was applied to the synthesis of PM-94128 **1**.



182 **183** **184**

Scheme 2.4. The reaction expanded by Ma *et al*.

Ma showed that L-proline catalyzed the direct aldol reactions of L-aminoaldehyde derived dibenzyl derivatives with a range of ketones, in moderate to excellent yields and stereoselectivites. Ma's original aim was to expand the scope of the reaction to allow for the use of functionalized aldehydes and/or ketones as well as a further demonstration of the benefits of the reaction methodology over more common approaches that use silyl ketene acetals, titanium homo-enolates and boron enolates (these materials tend to be very moisture sensitive). Initial reactions between substituted N-phenylalanine and acetone showed good yields (48 to 98%) with up to 96% d.e. at the newly formed center. N-Trityl phenylalanine was the best substrate for the reaction in terms of selectivity, while dibenzyl phenylalaninal had near quantitative conversion but selectivities were reduced to 90% d.e. Table 2.1 highlights a selection of Ma's results. Altering the stereochemistry of the proline catalyst from L to D allowed the generation of the *anti*-product. However the reaction was much less selective for the *anti*-product and the diastereotopic excess was greatly reduced to 34%.

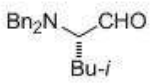
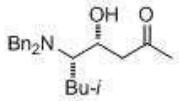
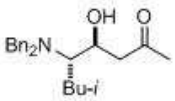
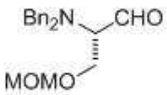
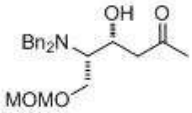
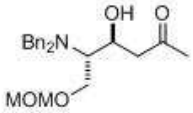
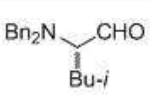
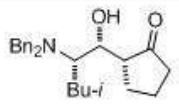
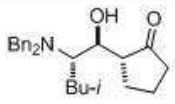
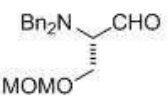
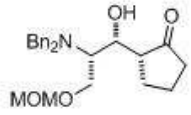
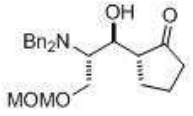
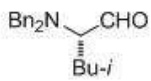
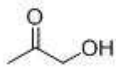
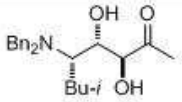
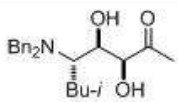
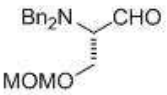
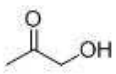
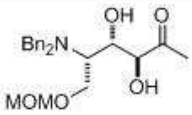
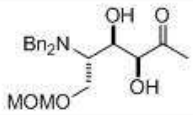
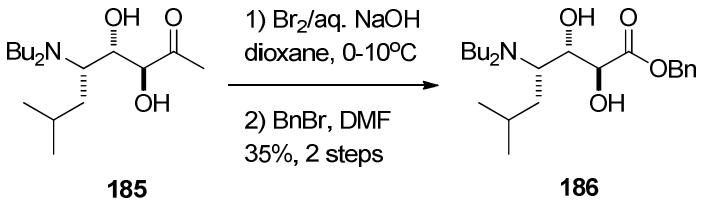
Entry	Aldehyde	Ketone	Details	Major Product		Minor Product	
1			3 days		90%		4%
2			3 days		61%		14%
3			DMSO, 1.5 days		59%		3%
4			DMSO, 1.5 days		56%		10%
5			HMPA, 1.5 days		74%		4%
6			HMPA, 1.5 days		61%		9%

Table 2.1. L-Proline catalysed direct aldol reaction of dibenzyl aldehydes and ketones.

The reaction of dibenzylleucinal and hydroxy acetone in HMPA (Entry **1**) yielded *anti*-diol (90%) and *syn*-diol (4%). *Anti*-diol **185** was noted to resemble an advanced intermediate in the synthesis of PM-94128; hence the ketone was transformed into the corresponding acid via an oxidative cleavage reaction with sodium hypobromite then esterified to complete the synthesis of the diol-ester, **186** (Scheme 2.5)



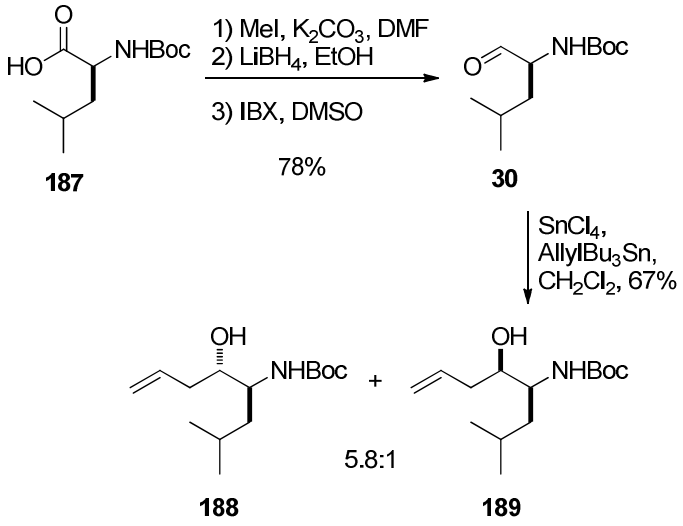
Scheme 2.5. Transformation of ketone 195 to ester 196.

It was decided that Ma's work represented an excellent approach to the synthesis of the amino-diol fragment of PM-94128, so it was decided to adopt this methodology with our bicycle synthesis.

2.1.2. Initial synthetic efforts

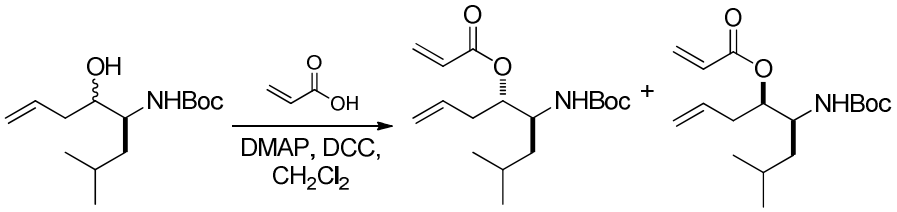
Our forward synthesis of **167** began with the esterification of Boc-N-Leucine **187**. IBX oxidation of alcohol produced aldehyde **30** in 80% yield, it had been reported in the literature that Swern oxidation conditions were too harsh and epimerisation of the α-carbon stereocenter would occur.[113] Attempts with the less basic/harsh SWERN like SO_3.pyridine conditions failed to produce aldehyde **30** (Scheme 2.6).

Alkylation of aldehyde **30** was achieved using Grignard reagent (allyl magnesium bromide), producing the homo-allylic alcohols **188** and **189** in good yield.[114] However, the alkylation was non-selective, with a ratio of 3:2 in favour of the *anti*-diastereoisomer (**188**). Improvements to the selectivity were achieved by applying Ghosh's conditions.[71] Allyl-tributyltin and tin tetrachloride in dichloromethane gave, homo allylic alcohol **188** in much larger quantities than **189** with a slight decrease in isolated yield (67%). The ratio of diatereoisomers could be improved from 5.8:1 to 10:1 in small scale experiments.



Scheme 2.6. Generation of the homo-allylic alcohols 199 and 200.

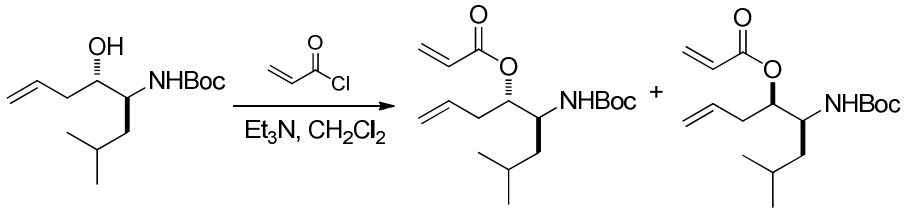
The inseparable alcohols **188** and **189** were treated with acrylic acid and dicyclohexylcarbodiimide (DCC) giving in 65% yield esters **190** and **191** that were separable by column chromatography.[115-116] The reaction however produced many side products, making purification difficult.



188 & 189 **190,** 55% **191,** 10%

Scheme 2.7. Esterification of homo allyic alcohols.

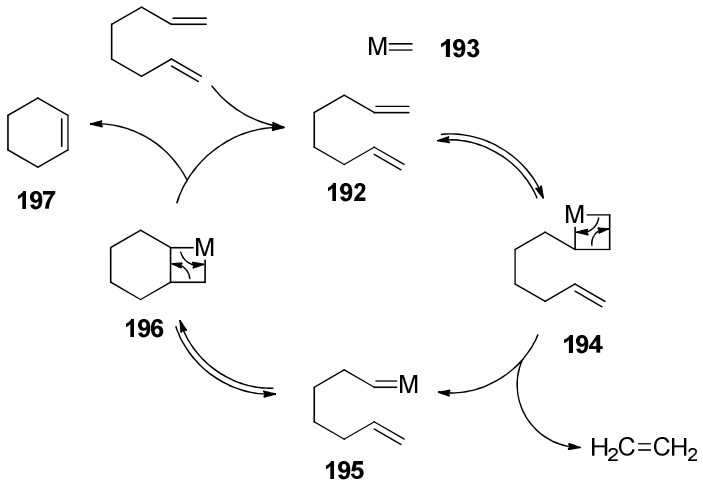
An alternative approach was found using acryloyl chloride and triethylamine that generated esters **190** and **191**, in much improved 96% yield (Scheme 2.8).[117,118] Interestingly the reaction did not proceed with pyridine as solvent and base.



188 & 189 **190**, 82% **191**, 14%

Scheme 2.8. Acid Chloride esterification.

In the 1960 and 1970s, interest in catalytic olefin metathesis reactions increased greatly. In its simplest form, the olefin metathesis reaction consists of a redistribution of alkylidene components.[119] In 1970, Chauvin and Hérisson[120] proposed the first and now widely accepted cross-metathesis mechanism (Scheme 2.9). The mechanism involves the [2+2] cycloaddition between an alkene double bond **192** and a transition metal carbene **193** forming a metallocycle intermediate **194**. The metallocyclobutane intermediate produced, can then cyclorevert reversibly to give starting material or a new metallo-carbene species **195**, which can then under go a second [2+2] cycloaddition giving intermediate **196.** This can cyclo revert to **195** or to the ring closed alkene **197**. The reaction is quicker than the uncatalyzed reaction because the activation energy is lowered through *d*-orbital interactions on the metal.



Scheme 2.9. The mechanism for the ring closing metathesis reaction.

Some 25 years later, Yves Chauvin, Robert Grubbs and Richard Schrock jointly won the Nobel prize for the development of the metathesis method in organic synthesis. The official press-release contained Figure 2.1 and is an excellent analogy of the metathesis reaction.

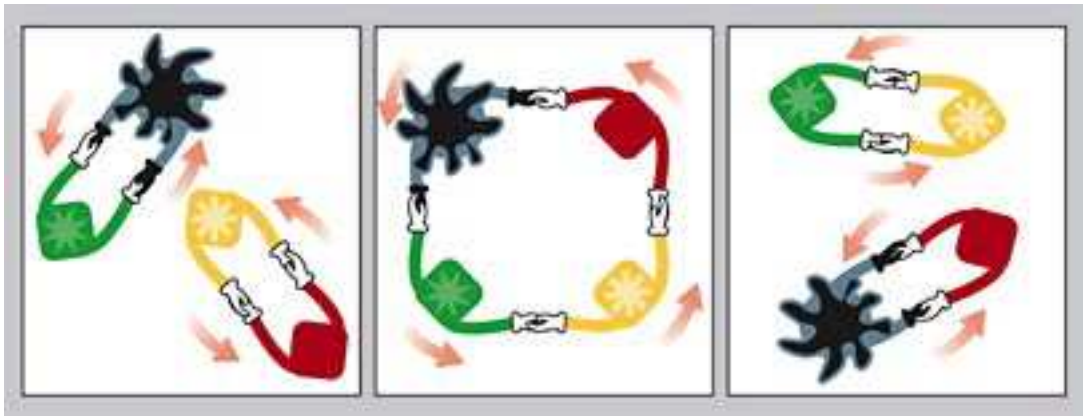
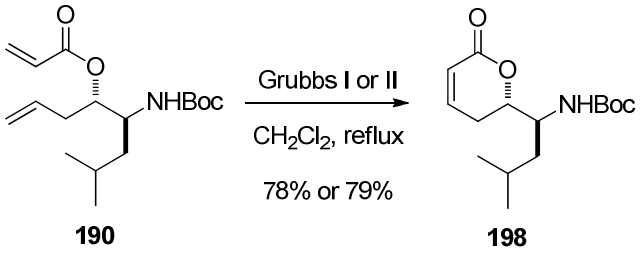


Figure 2.1. Schrock's metathesis scheme.[121]

> "Metathesis can be viewed as a dance of two molecules, with a catalyst pair (left) that includes a metal (black) joining "hands" with an alkene (yellow/red) pair. The pair then join in a circle (center) and then go off with different partners (right)". – Yves Chauvin[122]

Diene ester **190** had the correct stereochemistry so it was treated with 5 mol% Grubbs 1st generation catalyst producing α-pyrone **198** in good yield 78%.[115,117] Using Grubbs 2nd generation catalyst decreased the reaction time (48 to 36 hours) and increased the yield to 79%. The structure was determined by NMR analysis and confirmed by X-ray crystallography (Figure 2.2).



190 **198**

Scheme 2.10. Ring closing metathesis of diene-ester 190.

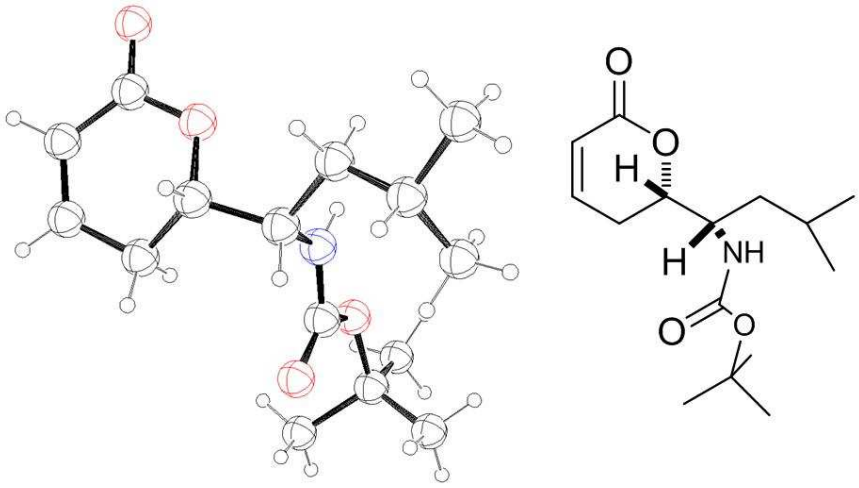
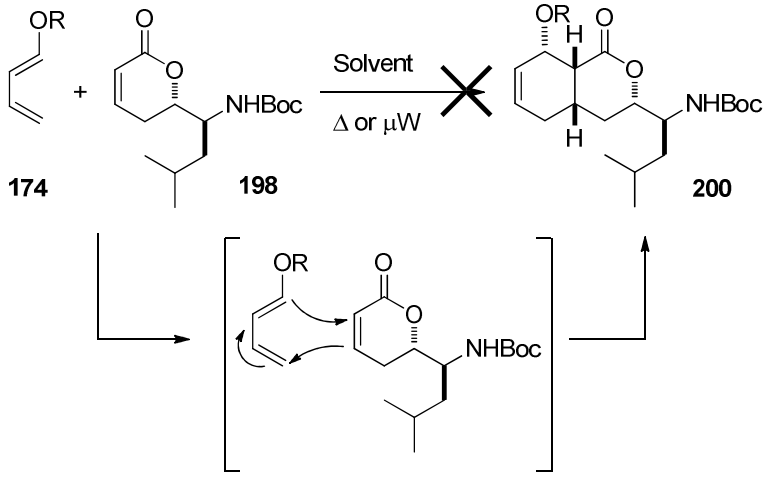


Figure 2.2. Xray structure of 198.

Ester **191** was similarly treated with Grubbs 1st generation catalyst, producing α-pyrone **199** in 75% yield.

The key step in our synthesis of the aminodihydroisocoumarin fragment **167** was the Diels-Alder reaction of α-pyrone **198** and a suitable diene **174** (Scheme 2.11). The choice of diene is key as it would allow us to set the second ring of the aminodihydroisocoumarin, but would also and provide significant scope for analogue generation.



174 **198** **200**

Scheme 2.11. The key Diels-Alder reaction of our reaction sequence.

The Diels-Alder reaction is the cycloaddition of a conjugated diene with a dienophile (alkene or alkyne usually) involving the dienes 4π electrons and the dienophiles 2π electrons. The driving force of the reaction is the formation of new σ-bonds, which are energetically more stable than the π-bonds. For the reaction to proceed, an overlap of the molecular orbitals is required. It is the HOMO (Highest Occupied Molecular Orbital) of the diene which interacts with the LUMO (Lowest Unoccupied Molecular Orbital) of the dienophile. The Diels-Alder reaction gives *endo* and *exo*-adducts that arise from the reaction transition state, where the dienophile can adopt 2 orientations. The *endo* adduct is the kinetic product and is formed by a bonding interaction between the carbonyl of the dienophile and the developing π bond of the product. Figure 2.3 shows the molecular orbitals, HOMO and LUMO of the reactants and the expected *endo* and *exo* adducts. It is expected that the *endo* adduct will be the preferred product of the reaction, however a mixture of adducts would still give the same product upon aromatization (oxidation) in subsequent transformations.[123]

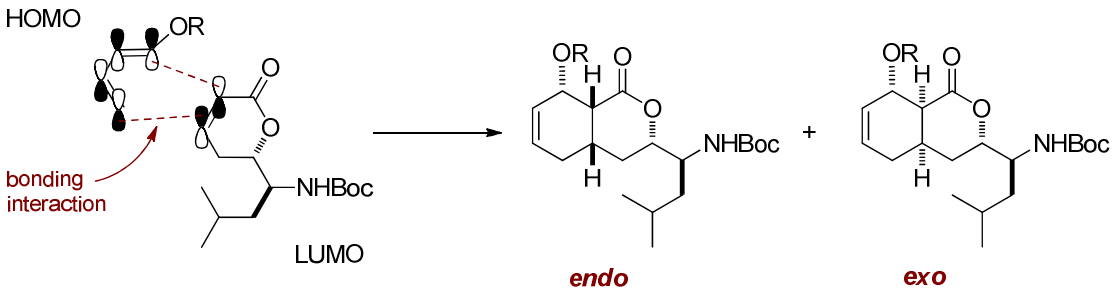
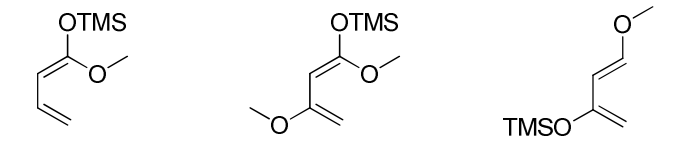


Figure 2.3. Diels-Alder reaction.

Initial experiments using 1-(trimethylsiloxy)-1,3-butadiene **201** and α-pyrone **198** were attempted using a variety of solvents and Lewis Acids The initial reactions were carried out in dichloromethane were unsuccessful, changing to higher boiling point solvents (i.e. benzene, toluene and xylenes) also failed to produce allylic alcohol **200**. Lewis acids have been reported to catalyse the Diels-Alder reaction so it was decided to investigate their effect on our system.[124-127] The use of Trimethylaluminium, aluminium trichloride and diethylaluminium chloride was explored, however in all cases, no change to the reaction outcome was observed. The use of higher pressures through sealed tubes also failed to give any of the desired products (see **Appendix 1** for reaction conditions).

It was reasoned that a possible explanation for the lack of reactivity observed was that the diene was not electron rich enough to participate in the cycloaddition reaction, i.e. the HOMO and LUMO of the diene and dienophile were not close enough in energy. Hence we turned our attention to using a more electron rich diene and elected to use diene **202**.

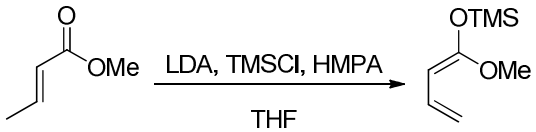
202 is a modified Brassard/Chan diene, where the C_3 methoxy group of the Brassard/Chan diene **203,** has been moved to the C_1 position. It also lacks the C_3 TMS ether of Danishefsky's diene **204** (Figure 2.4).



Modified diene **202** | Brassard/Chan diene **203** | Danishefsky diene **204**

Figure 2.4. Comparisons between commonly used dienes.

Diene **202** was made according to Molin's procedure by treating freshly distilled methyl crotonate **205** with lithium di*iso*propylamine (LDA) and trapping the resulting enolate with trimethylsilyl chloride (Scheme 2.12).[128] When the reaction was attempted using commercially available LDA and reagents straight from the bottle, no product was observed. Thus reagents had to be distilled and the LDA made fresh from *n*BuLi and *i*Pr_2NH.



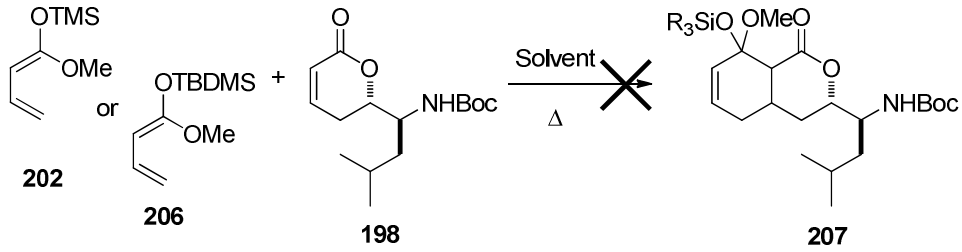
205 **202**

Scheme 2.12. Generating diene 202.

The reaction between diene **205** dienophile **198**, was attempted at relatively low temperatures (refluxing dichloromethane), but no reaction could be detected. Switching to higher boiling solvents (benzene, toluene or xylene) with and without aluminium Lewis acids failed to change the reaction outcome returning only α-pyrone and diene degradation products.

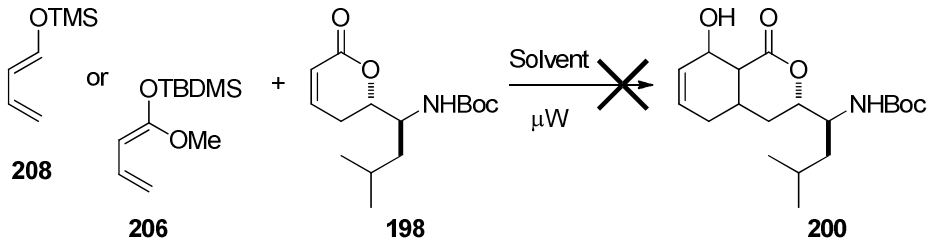
Faced with the lack of success the modified *t*butyldimethylsilyl diene **206** was synthesized. It was thought that the presence of the TBDMS group would make the diene more stable than diene **202**. This extra stability resulted in much less

degradation of the diene over the prolonged reaction times. To further combat the dienes instability problems, smaller batches of the diene were made on a regular basis so as to avoid degradation during storage (see **Appendix 2** for details of reaction conditions). Frustratingly there remained no reaction progress.



Scheme 2.13. Modifications to the Diels-Alder reaction.

Finally we turned our attention and efforts to microwave chemistry (Scheme 2.14). Various conditions were examined in which equivalents, concentrations, reaction duration and importantly temperature were varied to try and achieve a favourable reaction outcome. There was however, no successful outcome observed (see **Appendix 3** for reaction conditions).



Scheme 2.14. Attempts to synthesize 200

The use diphenyl ether as the reaction solvent gave what appeared to be a trace (by TLC analysis) of the product. Unfortunately, further exploration of the reaction using higher temperatures and various reaction times, returned only α-pyrone **198** and diene degradation (see **Appendix 3** for reaction conditions).

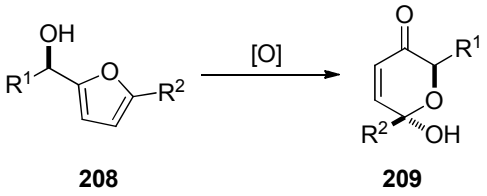
Finally the reaction was attempted without solvent increasing the concentrations further (see **Appendix 4** for reaction conditions) with no success.

Faced with the continuous lack of success during the Diels-Alder cycloadditions a new approach was developed.

2.2. An alternate approach

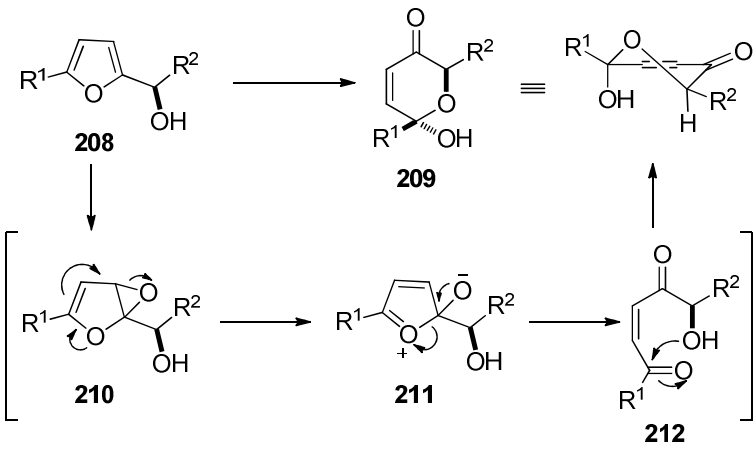
Our alternate approach was based on a modified version of the Achmatowicz rearrangement which if successful would provide access to a number of interesting targets including Ajudazol-A (a synthetic target within the Marquez group).

The Achmatowicz rearrangement was first reported in 1971. It produces α,β-unsaturated pyranones **208** from α-hydroxyfurans **209** under epoxidising conditions.[129-131]



Scheme 2.15. Conversion of hydroxy furans to pyranones.

The accepted mechanism for the rearrangement involves hydroxyl directed epoxidiation of the allylic position of furan **208** across the C2-C3 olefin (Scheme 2.16). A 6 electron movement occurs around the ring, opens epoxide **210**, to yield zwitterion **211**. Carbonyl formation causes the ring to open and generate 1,4-diketone **212**. An intramolecular nucleophilic attack of the free hydroxyl onto the adjacent ketone closes the ring and generates hemi-acetal **209**. The stereochemistry in the α-hydroxyfuran is retained in the product. As expected the α-anomer is the major product due to the anomeric effect.



Scheme 2.16. Achmatowicz rearrangement

There have been many conditions reported for the rearrangement to date, the most popular being N-bromosuccinimide/water[132-134] and vanadyl acetoacetonate/*tert*butyl hydrogen peroxide.[135-137] Other conditions that have also been reported include hydrogen peroxide,[138,139] pyridinium chlorochromate,[141] *meta*-chloroperoxybenzoic acid[141] molecular oxygen (with tetraphenylporphine[142,143] or rose bengal[144,145]). Sharpless asymmetric epoxidation conditions have also been reported introducing a resolution step as part of the rearrangement.[146-148]

The Achmatowicz rearrangement has found widespread use in organic chemistry, particularly in natural product synthesis, where it has been widely utilized to generate substituted pyrans. The rearrangement can tolerate a wide range of substrates bearing complex functionality, being utilized in the syntheses of Isoaltholactone (**A**),[149] Yessotoxin (**B**)[150] and Mycopoxidene(**C**).[151]

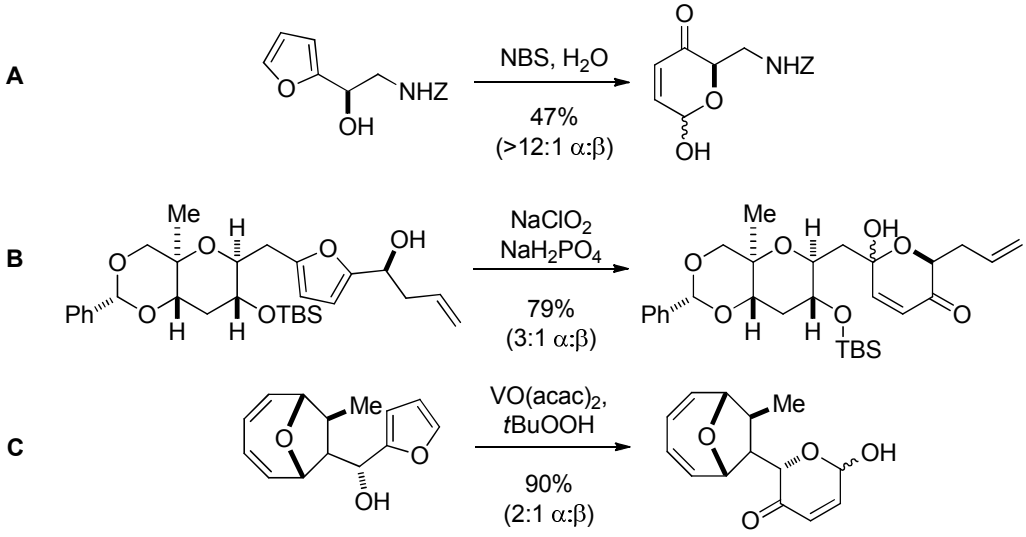
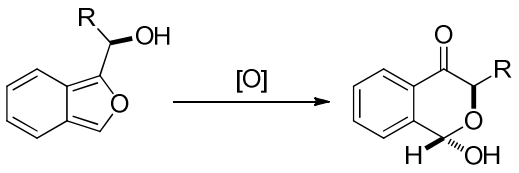


Figure 2.5. The Achmatowicz rearrangement in natural product synthesis.

While the reaction has gained widespread use in organic chemistry there is further scope for its application, there are fewer than twenty examples (based upon SciFinder® searches) where the furan has substituent's at either the C3 or C4 positions. Only three examples have been reported where both the C3 and C4 positions are substituted.

However despite the lack of literature precedence it was reasoned that an Achmatowicz rearrangement reaction of an α-hydroxy*isobenzo*furan **213** would provide bicyclic lactols **214**, which could be further functionalised, to generate

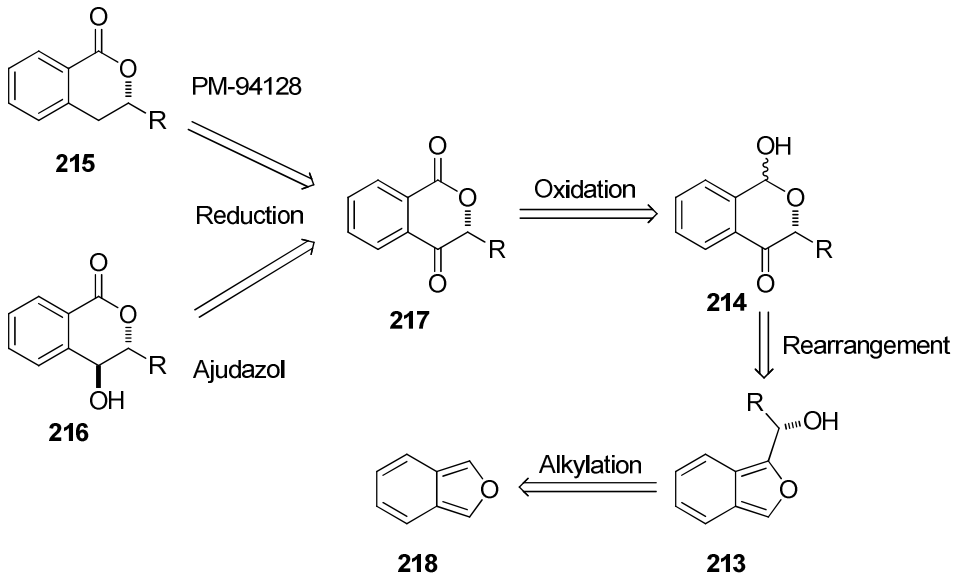
isochromanones (corresponding to the Ajudazols) and Isocoumarins (corresponding to the PM-94128 family of molecules).



213 **214**

Scheme 2.17. Our proposed application of the Achmatowicz rearrangement.

Based on this hypothesis a new model system was designed in which both the Isocoumarin (PM-94128) **215** and Isochromanone **(**Ajudazol) **216** core structures could originate from reduction of keto-lactone **217** (Scheme 2.18). Keto-lactone **217** could be obtained through the oxidation of Achmatowicz rearrangement product **214**. Lactol **214** would in turn originate from the rearrangement of α-hydroxy*iso*benzofuran **213** which could be obtained by alkylation of *iso*benzofuran **218**.



215 **216** **217** **214** **218** **213**

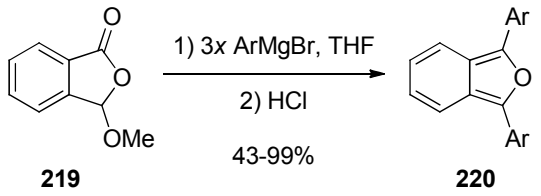
Scheme 2.18. Model synthesis design.

2.2.1. Model system synthesis

Most of the methods reported to date involve the generation of substituted *iso*benzofurans.

Bis-Grignard addition to phthalide **219** followed by treatment of the subsequent lactol with acid has been used to generate 1,3-diaryl*iso*benzofurans **220**. The

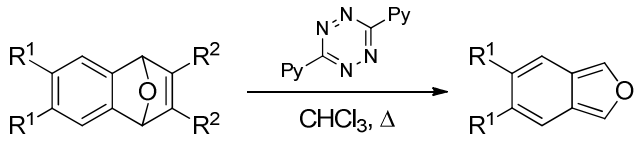
first alkylation is presumably at the anomeric position, displacing the methoxy group as a result. The second addition at the lactone gives a hemi-acetal intermediate that upon treatment with hydrochloric acid the hydroxyl is eliminated as water resulting in aromatisation.[152]



219 **220**

Scheme 2.19. Double Grignard addition generating *iso*benzofuran 227

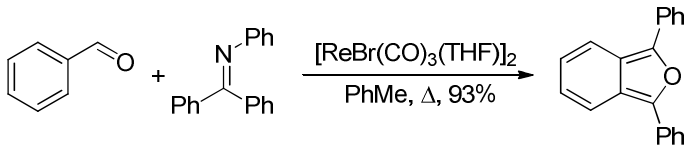
Retro Diels-Alder reactions of bridged ether type compounds **221** using pyridyl tetrazine reagents has also resulted in substituted *iso*benzofuran generation (Scheme 2.20).[153,154] **221** is synthesized from treatment of 1,2,4,5-tetrakis(trimethylsilyl)benzene with an iodonium triflate then further reaction with furan. **221** is then reacted with with 3,6-di-2-pyridyl-1,2,4,5-tetrazine in chloroform at reflux temperature generating *iso*benzofuran **222** via a retro Diels-Alder reaction pathway.[155]



221 62-82% **222**

Scheme 2.20. Cycloaddition resulting in *iso*benzofuran formation.

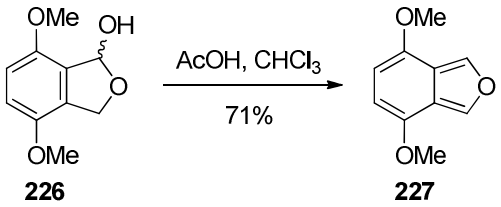
Cycloadditions between ketimines **224** and an excess of benzaldehyde **223** in the presence of a Rhenium(I) catalyst have been used successfully to generate *iso*benzofurans.[156] C-H insertion of the rhenium and nucleophilic attack onto the benzaldehyde electrophile followed by cyclisation, gives an aminal intermediate that undergoes oxidative elimination of the N-rhenium species resulting in **225** formation (Scheme 2.21).



223 **224** **225**

Scheme 2.21. Rhenium catalyzed *iso*benzofuran synthesis.

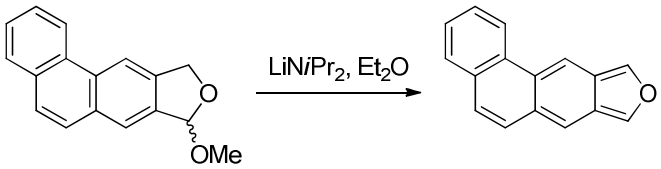
Acidic elimination methods to achieve aromatisation have also been reported. Scheme 2.22 shows Da-Ming's synthesis of *bis*-methoxy*iso*benzofuran **227** from lactol **226** which was treated with acetic acid in chloroform, resulting in the elimination of water and a proton.[157]



226 **227**

Scheme 2.22. Acidic dehydration resulting *iso*benzofuran formation.

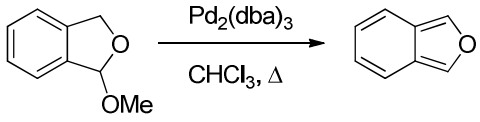
Similarly base mediated elimination methods can yield *iso*benzofuran compounds (Scheme 2.23). Treatment of methyl acetal **228** with lithium di*iso*propylamine has been used in its transformation to *iso*benzofuran **229**. Deprotonation results in elimination of the methoxide and aromatization.[158]



228 **229**

Scheme 2.23. Synthesis of aromatic polycycle 236.

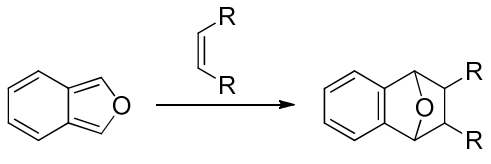
A different method for generating *iso*benzofurans from methyl acetals **230** was reported by Mikami using palladium(0) catalysis.[159] Mechanistically there is an initial oxidative insertion of the palladium into the C-O acetal bond, followed by elimination giving *iso*benzofuran **218** (Scheme 2.24).



230 **218**

Scheme 2.24.Several Pd(0) catalysts were examined in this reaction.

Despite the fact that there are a number of ways to generate *iso*benzofurans their synthetic use has largely been limited to their use as highly reactive dienes in Diels-Alder reactions (Scheme 2.25).[160-162]

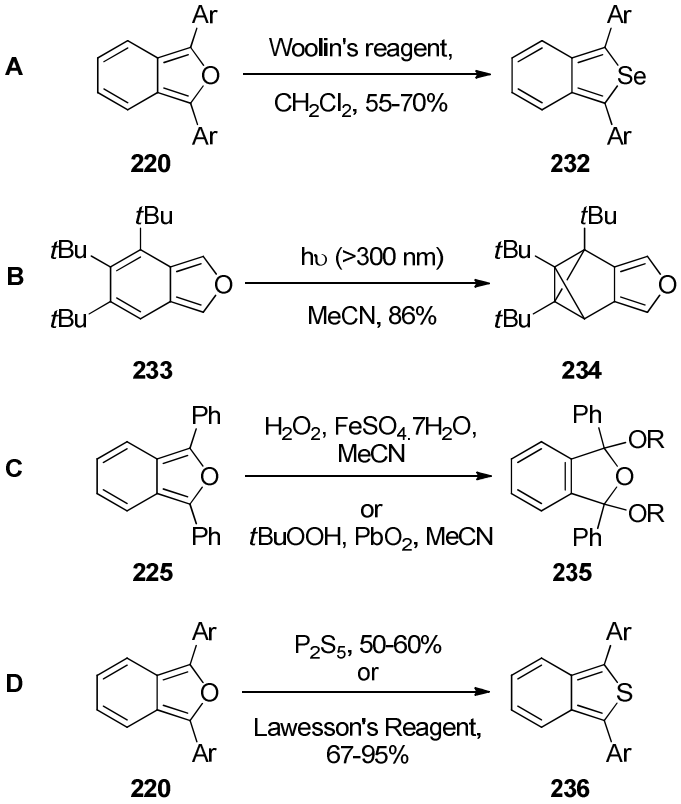


218 **231**

Scheme 2.25. Diels-Alder reaction of *iso*benzofuran 225.

But there are very few other examples of the use of these molecules, other than as reactants in Diels-Alder reactions.

Scheme 2.26. shows the limited use *iso*benzofurans have received. Mohanakrishnan conducted a study of the optical and electrochemical properties of diarylbenzo[c]selenophenes and their subsequent correlation with their structures.[163] A series of selenophenes **232** was synthesized from the corresponding *iso*benzofurans **220** in good yields using Woolin's reagent (Scheme 2.26 **A**). The photochemical reactivity of substituted *iso*benzofuran **233** was examined by Yoshida in 1992 (Scheme 2.26 **B**), whereby irradiation of *iso*benzofuran **233** gave **234** by photovalence isomerisation.[164] Carloni investigated the reactivity of *iso*benzofurans towards singlet oxygen (Scheme 2.26 **C**), evaluating **225**s suitability for biological radical detection. Oxygen and carbon centred radicals were reacted with **225** and the subsequent change in fluorescense monitored.[165] Finally aromatic *iso*benzofurans **220** have been transformed into thia-naphthalenes in three separate studies. Dufraisse utilized thia-napthalene compounds as a starting material in pyrolysis reactions with the aim of synthesizing anthracene (and derivatives).[166] In 1960 Deana and co-workers synthesized thia-napthalene derivatives from *iso*benzofurans using carbon disulfide (as Dufraisse did in 1937) with the goal of generating benzocyclobutenes from pyrolysis of **236**.[167] Swager reported in 2008 the use of thia-napthalenes (and *iso*benzofurans) as potential biological chromophores using *in vivo* near-infrared (NIR) fluorescence.[168] It was also found that **236** could be generated from **220** upon treatment with Lawesson's reagent (Scheme 2.26 **D**).

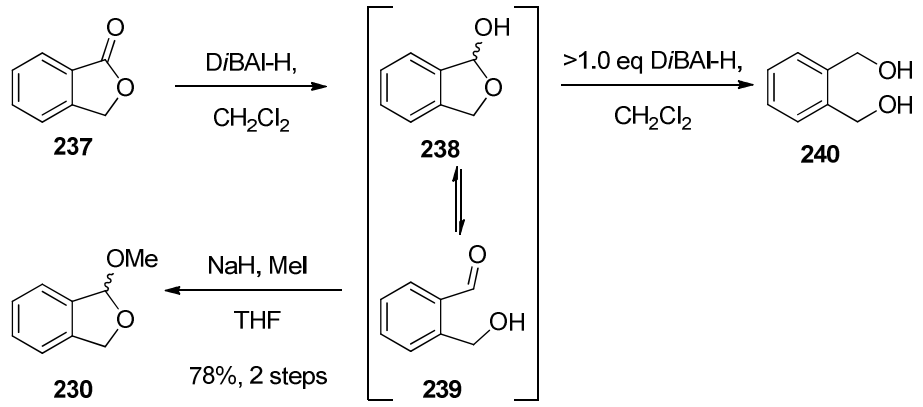


Scheme 2.26. Reported uses of *iso*benzofurans.

For our approach the procedure of Crump and Rickborn was selected,[169] wherein *iso*benzofurans are generated from acetals through the use of base. This approach was ideal for our purposes, as mechanistically it involved the likely generation of the *iso*benzofuran anion. Trapping of this anion with an appropriate aldehyde would provide the desired alcohol precursor for the rearrangement.

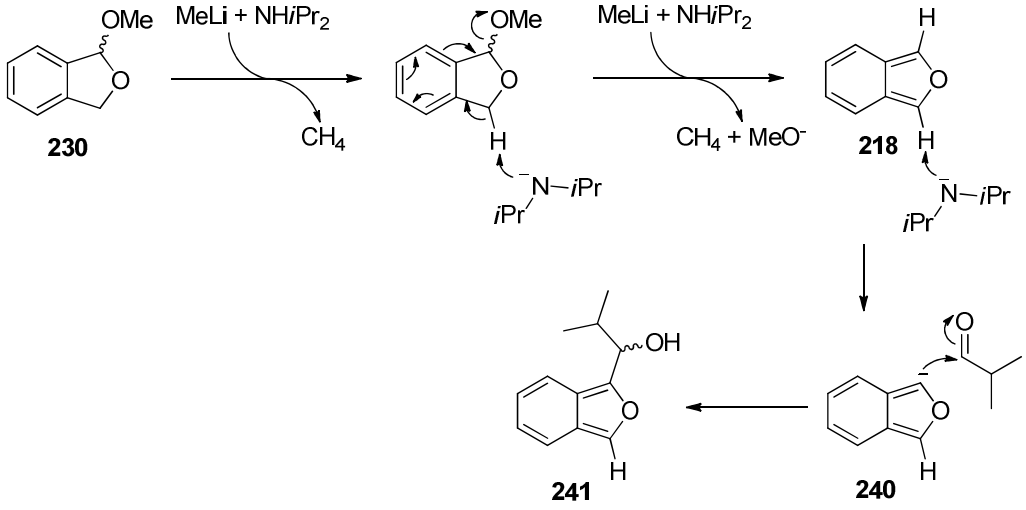
Our synthesis began with phthalide **237** which was carefully reduced to the corresponding lactol by treatment with 1 equivalent di*iso*butylaluminium hydride (Scheme 2.27). It was found that lactol **238** readily reacted with any excess of D*i*BAl-H therefore reducing the reactive benzaldehyde intermediate **239** to the known 1,2-Benzenedimethanol **240**.[170] The isolation and purification of lactol **238** proved problematic as the lactol opened readily to the aldehyde-alcohol **239**. Characterisation proved even more difficult as NMR analysis with non-hydrogen bonding deuterated solvents such as D_6-benzene failed to resolve the spectra. Hence it was decided to alkylate the lactol directly and bypass the isolation step. Treatment of the lactol **238** with 1.2 equivalents of sodium hydride and methyl iodide (filtered through basic alumina to remove traces of HI) at 0 ^{o}C gave acetal **230**. The acetal proved to be less prone to ring opening

and degradation; however it was made in small batches to avoid this problem all together.



Scheme 2.27. Reduction of phthalide to methyl acetal 247.

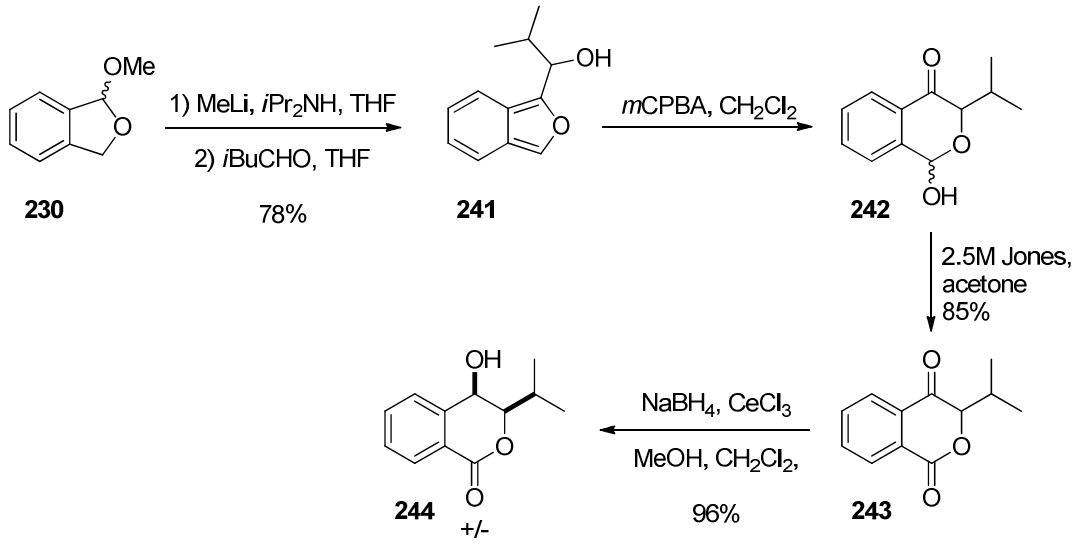
α-Hydroxy*iso*benzofuran **249** was generated in one-pot from methyl acetal **230** by treatment with di*iso*propylamine and methyl lithium in tetrahydrofuran by modification of the protocol described by Crump and Rickborn.[169] It is believed that during the reaction an *in situ* catalytic quantity of LDA is generated which deprotonates methyl acetal **230**. The subsequent movement of electrons (an aromatisation process) causes elimination of the methoxy group which leaves presumably as a methoxide ion. Deprotonation of the newly generated *iso*benzofuran molecule **218** gives anion **240** which upon trapping with *iso*butryaldehyde furnished the desired α-hydroxy*iso*benzofuran **241**. Crump and Rickborn quenched anion **240** with D_2O and detected deuterium incorporation.



Scheme 2.28. Synthesis of *iso*benzofuran alcohol 241.

Attempts to isolate *iso*benzofuranyl alcohol **241** (via silica gel and neutral alumina chromatography) resulted in complete degradation of the highly

reactive intermediate. Thus it was decided to react the crude alcohol **241**, under Achmatowicz rearrangement conditions (*meta*-chloroperoxybenzoic acid in dichloromethane at 0 °C) to avoid these purification issues. Thus lactol **242** was generated; although, the lactol also proved to be too unstable to withstand purification. It was decided to oxidize the crude lactol **242** using Jones reagent gave keto-lactone compound **243**. Unfortunately purification by flash column chromatography degraded **243** readily. Exchanging the solid phase for neutral alumina greatly reduced decomposition, however the molecule could not be obtained in high enough purity. At this point it was decided to reduce the ketolactone **243** to the more stable isochromanone **244** under Luche conditions.[171] A facially selective (regioselective) reduction of the ketone was observed, to generate the *syn* diastereoisomer (Scheme 2.29).



Scheme 2.29. Model system synthesis.

The structure of **244** was assigned by NMR studies and later corroborated by X-ray studies of the crystalline solid.

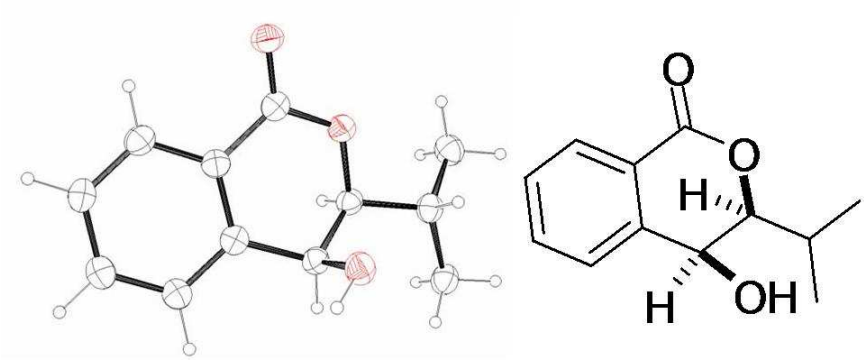
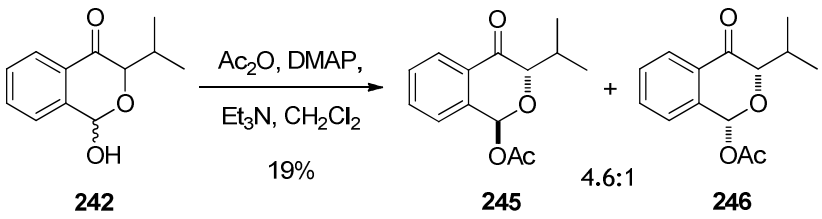


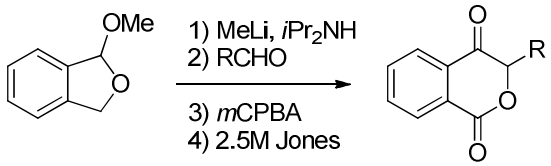
Figure 2.6. The structure of 244 as solved by X-ray analysis.

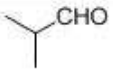
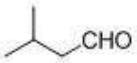
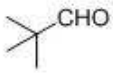
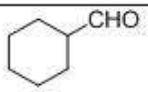
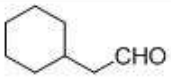
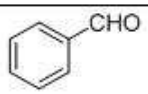
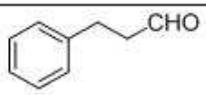
To assess the anomeric ratio of products from the Achmatowicz rearrangement, the unstable lactol **242** was resynthesized and protected immediately as the acetate (Scheme 2.30). A 4.6:1 ratio of anomers was observed in the crude reaction mixture, with the α product the predominant anomer. This is consistent with other examples of the rearrangement in organic synthesis. [149-151]



Scheme 2.30. Acetylation of lactol 250.

To expand and explore the scope of the rearrangement the reaction sequence was carried out using a number of structurally diverse aldehydes as substrates (Table 2.2).



Aldehyde	Keto-lactone	Yield*
	**243**	85%
	**247**	94%
	**248**	84%
	**249**	82%
	**250**	72%
	**251**	83%
	**252**	57%
	**253**	67%
	**254**	67%
	**255**	93%

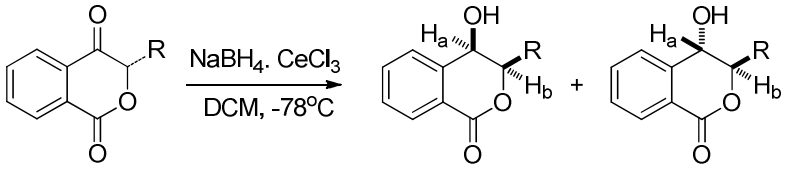
*Crude Yield

Table 2.2. Table of aldehydes used in our reaction sequence.

Keto-lactones **243, 247** to **255** were synthesized as per the 4 step reaction series described in Scheme 2.29 in good to excellent yields.

Isochromanones **252** to **264**-**272** were then transformed from the corresponding lactones using the established Luche conditions, see Table 2.3. In all cases the expected chemo-selectivity was observed (ketone reduction).

Analysis of the isochromanone *syn*:*anti* ratios showed that sterically hindered tertiary carbons and quaternary carbons provided complete selectivity, with the *syn* product being the preferred diastereoisomer. Linear, unbranched carbon chains were less selective, with no selectivity observed in the methyl example **264** (Entry **2**) in the R position while an increase in selectivity was observed as the alkyl chain increased in length (Entries **3** and **4**)



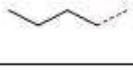
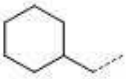
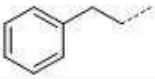
Entry	R group	Compound	Yield	*syn* / *anti*
1		**244**	96%	100 / 0
2		**256**	90%	50 / 50
3		**257**	71%	60 / 40
4		**258**	56%	90 / 10
5		**259**	80%	75 / 25
6		**260**	77%	100 / 0
7		**261**	82%	100 / 0
8		**262**	58%	50 / 50
9		**263**	48%	100 / 0
10		**264**	90%	50 / 50

Table 2.3. Isochromanones 244, 256-264.

The syn:*anti* relationships of the isochromanones were determined with ^{1}H NMR analysis. Wherein a small coupling of less than 2.5 was observed for *syn* compounds, while a larger coupling was observed for anti compounds (J_{ab} *syn* ≤ 2.5 Hz; J_{ab} *anti* ≥ 6.0 Hz).

X-ray crystal structures were successfully obtained for the *syn*-ethyl phenyl **264** and cyclohexyl isochromanones **261**. **264** was separable from the *anti* diastereoisomer by crystallisation (diethyl ether: petroleum spirits). The crystal structures obtained corroborated the success of the isobenzofuran rearrangement as well as confirmed the *syn*-relationship between the C8 and C9 stereocenters.

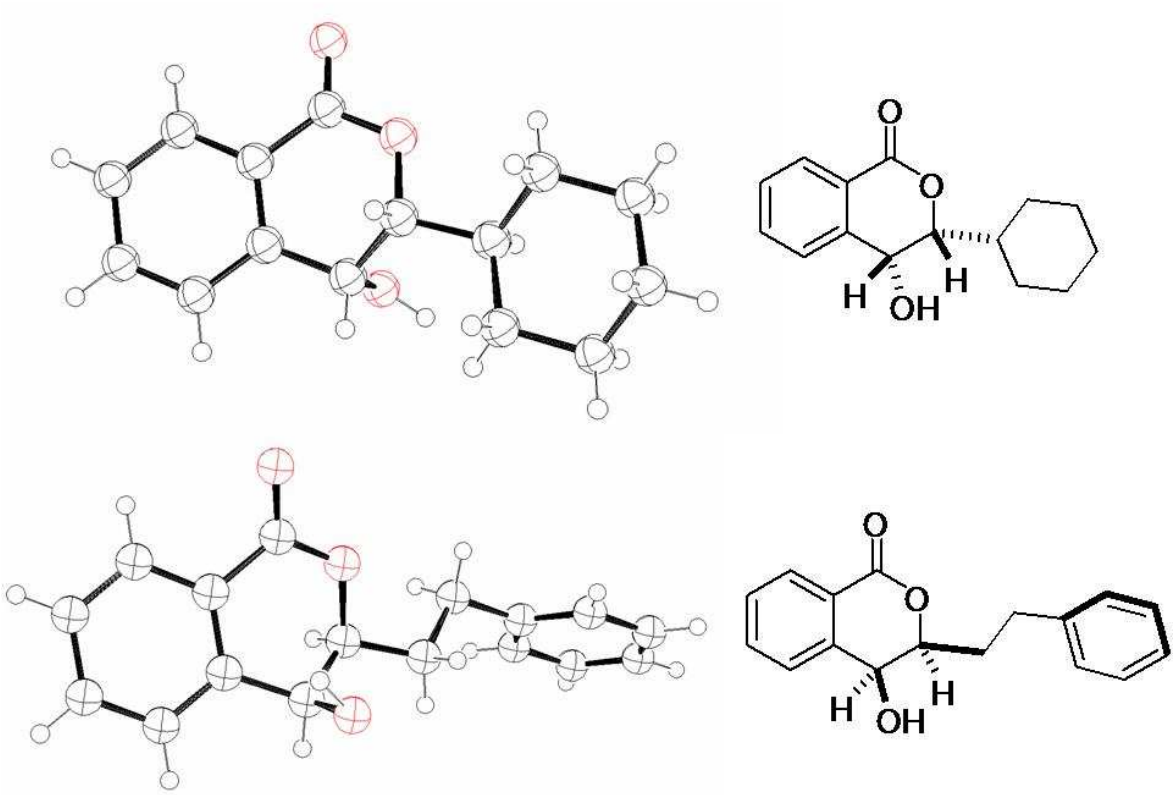
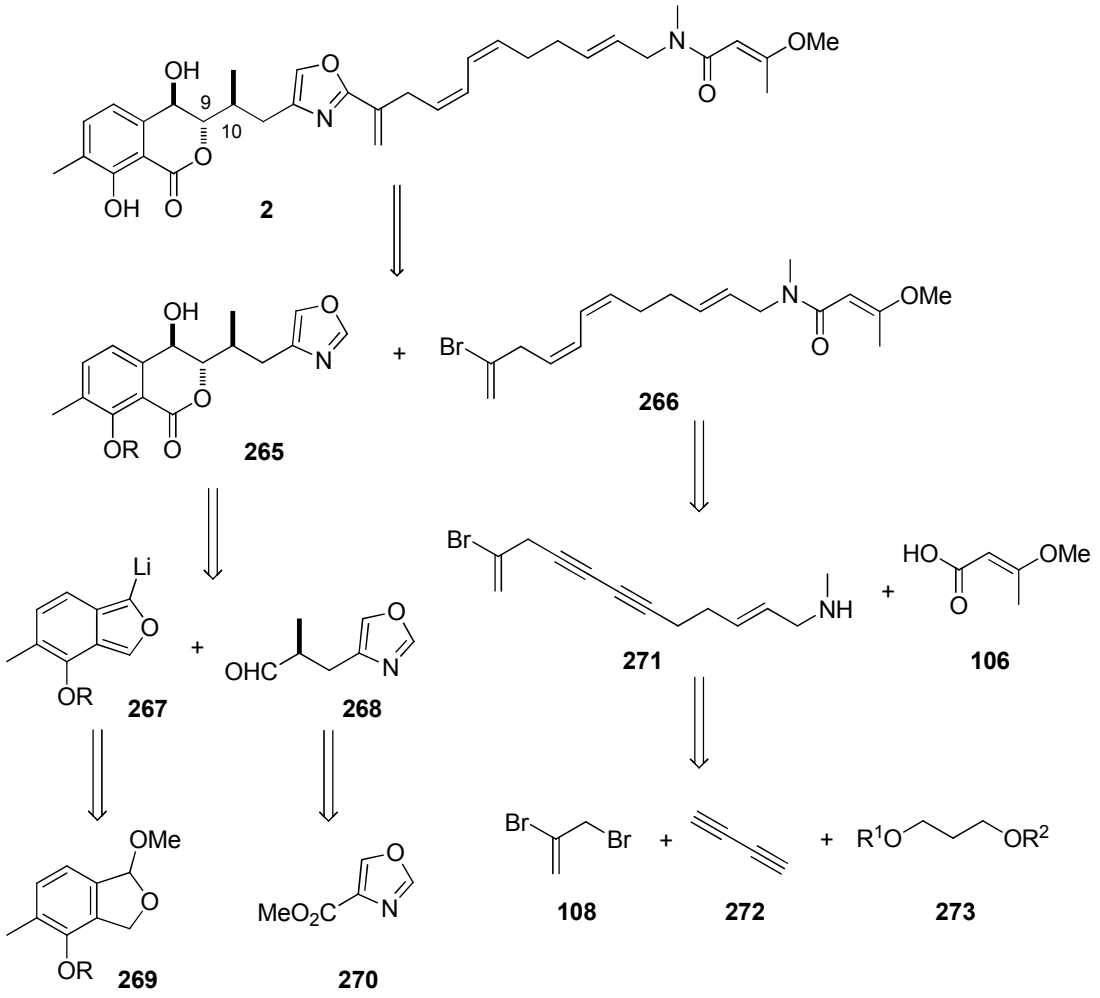


Figure 2.7. The structures of 261 and 264 as solved by X-ray analysis.

The results were encouraging, in that a large amount of functionality was tolerated in the Achmatowicz rearrangement and subsequent transformations. Indeed phenyl and cyclohexyl groups, that would create steric tension at the newly formed stereocenter, were tolerated. We therefore began to look at synthetic applications of our methodology.

2.2.2. Studies towards the synthesis of Ajudazol A

Retrosynthetically, we envisioned Ajudazol A **2** as originating from the palladium promoted coupling of bromide **266** and oxazole **265**.

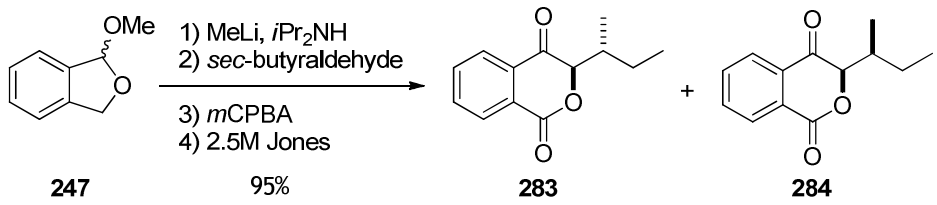


Scheme 2.31. Retrosynthesis of the Ajudazols

The oxazole substituted isochroman-1-one unit **265** was thought of as being obtained through the coupling of the isoxybenzofuran anion **267** and aldehyde **268** followed by treatment of the resulting alcohol under our recently developed rearrangement conditions. The *iso*benzofuran anion **267** could be accessed from the methyl acetal **269**, while the oxazole aldehyde **268** could originate from ester **270**. Bromide **266** on the other hand could be formed by the condensation of amine **271** and methoxybutenoic acid **106**. *Bis*-alkyne **271** could in turn originate from the double acetlyation of butadiyne unit **272** (Scheme 2.31).

In order to assess the effect of the aldehyde C10 stereocenter on the stereochemical outcome of the *iso*benzofuran alkylation and rearrangement sequence a further model system was designed. 2-(±)-Methylbutyraldehyde (*sec*butyaldehyde) was chosen as the model as it represents the first 3 carbons of the Ajudazols aliphatic fragment.

2-Methylbutyraldehyde was condensed with *iso*benzofuran anion **240** and then oxidised using our developed protocols to yield the consequent keto-lactones **274** and **275** that were obtained in a 1.6:1 ratio of diastereoisomers with the *anti* compound (**274**) the preferred conformation (Scheme 2.32).



Scheme 2.32. Formation of diastereoisomers, 283 and 284.

The selectivity of the reaction can be explained using the Felkin-Ahn model for addition to carbonyls.[172] The model predicts the 2 lowest energy non-eclipsed conformations that the aldehyde can adopt. In both conformations the carbonyl is orientated perpendicular to R_{large} (in this case the ethyl group). Given that the nucleophile (the *iso*benzofuran anion **240**) will attack the aldehyde carbonyl along the Burgi-Dunitz angle of ~107°. The favoured conformation for the aldehyde has the carbonyl orientated between R_{large} (ethyl group) and R_{medium} (methyl group) such that the nucleophile (Nu^-) will 'pass' the hydrogen (conformation **A**) rather than the methyl (conformation **B**) (Figure 2.8). Conformation **A** is the preferred conformation and the predicted product of this model will come via this orientation.

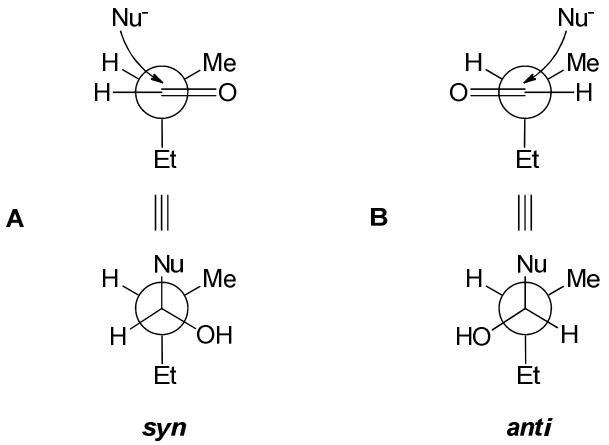
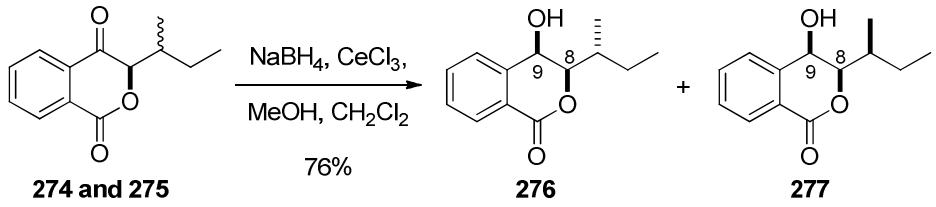


Figure 2.8. Felkin-Ahn conformations for the addition of the *iso*benzofuran anion.

When either enantiomer of 2-methylbutyraldehyde adopts conformation **A** the product of the addition reaction has the *syn* relationship. This opposite is true when the aldehyde adopts conformation **B**, the result with either enantiomer is the *anti*-product.

It is hypothesized the *anti*-product is present because the substituents R_{small} and R_{medium} (hydrogen and methyl respectively) are not sufficiently size differentiated for there to be full steric control over the addition.

When **274** and **275** where reacted under our established Luche reduction conditions 2 products were obtained, this is consistent with the facially selective reduction observed before. The relative stereochemistry of these products was determined by NMR analysis of coupling between C8 and C9 hydrogens. As before couplings of ≤ 2.5 Hz were observed in both **276** and **277** indicating a *syn* relationship between these groups.



Scheme 2.33. Synthesis of 276 and 277.

This relationship was later confirmed by X-ray crystallographic analysis of the *syn:anti* compound **276** (Figure 2.9) as **276** was separable from **277** by recrystallisation (diethyl ether: petroleum ether).

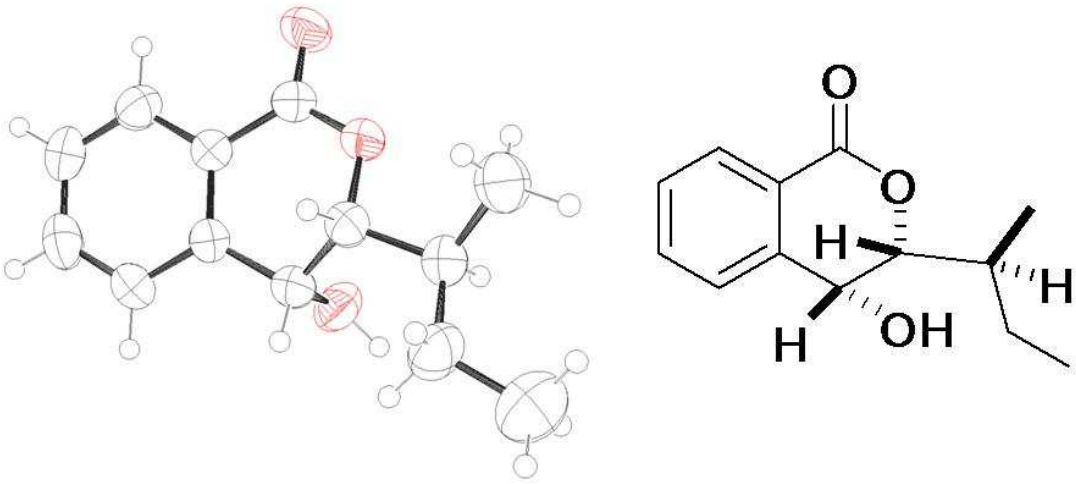
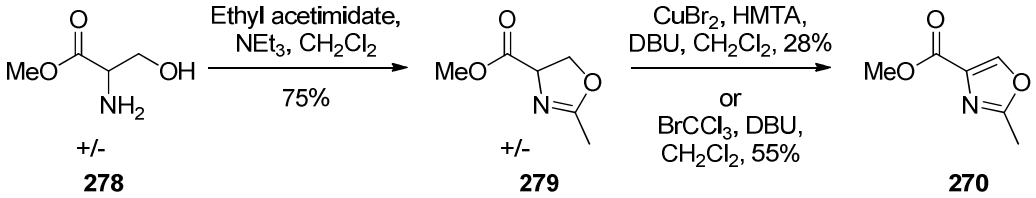


Figure 2.9. The structure of 276.

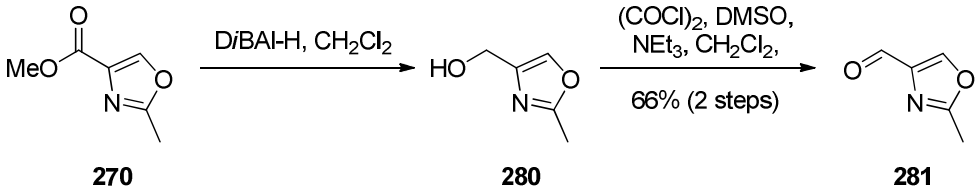
With the desired *syn:anti* compound in hand we were confident that this methodology could be applied to the synthesis of the Ajudazols as stereocenter inversion is a well-documented transformation (see section 2.2.3).

Synthesis of the oxazole coupling partner began with D,L-Serine methyl ester **278** which was converted to oxazoline **279** by cycloaddition reaction in moderate yield according to Leahy's protocol.[173] Unfortunately aromatisation of the oxazoline using Leahy's method (copper(II) bromide, hexamethyl tetraamine and 1,8-Diazabicyclo[5.4.0]undec-7-ene) gave poor conversion (up to 28% yield). The low yield is most likely due to the difficult work-up caused by the copper salt by-products of the reaction. The work-up involved treatment of the reaction mixture with aqueous ammonium salts that resulted in dark blue aqueous and organic phases that were very close in colour and therefore difficult to separate. Nicolaou's conditions[174] bromotrichloromethane and 1,8-Diazabicyclo[5.4.0]undec-7-ene, increased the yield to 55% and made the reaction considerably easier to work up and purify.



Scheme 2.34. Synthesis of oxazole 270

Oxazole-ester **270** was then reduced with di*iso*butylaluminium hydride to the corresponding alcohol in good yield. Interestingly lithium aluminium hydride proved to be too strong/harsh a reagent as reduction of the oxazole heterocycle was observed along with the desired alcohol **280**. Oxidation of the primary alcohol gave aldehyde **281** in good yield, both IBX and Swern oxidation conditions produced the same quantities of the desired aldehyde (Scheme 2.35).

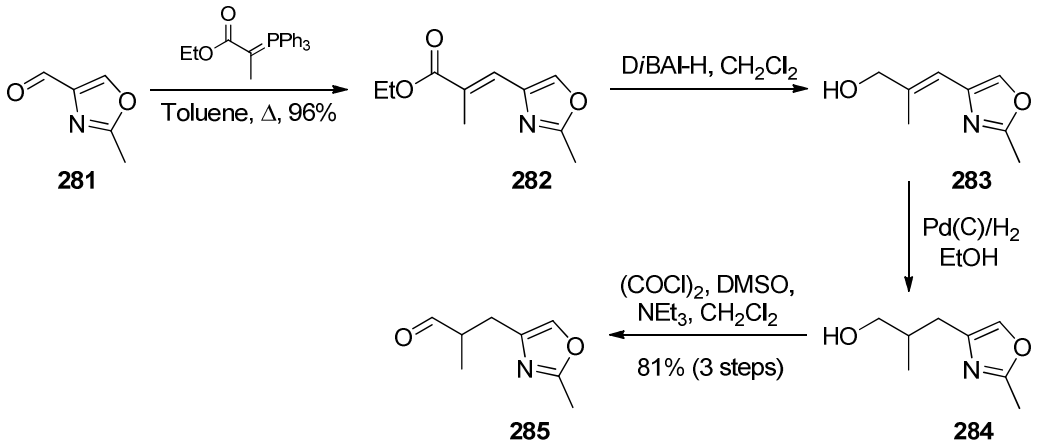


Scheme 2.35. Oxidation to aldehyde 281.

Wittig olefination reaction of aldehyde **281** gave ester **282**, interestingly it required higher temperatures (vigorously refluxing toluene at 120 ^{o}C) to proceed. The use of dichloromethane and benzene gave no reaction product whatsoever. This is not surprising considering the hindered natured of the phosphonate used.

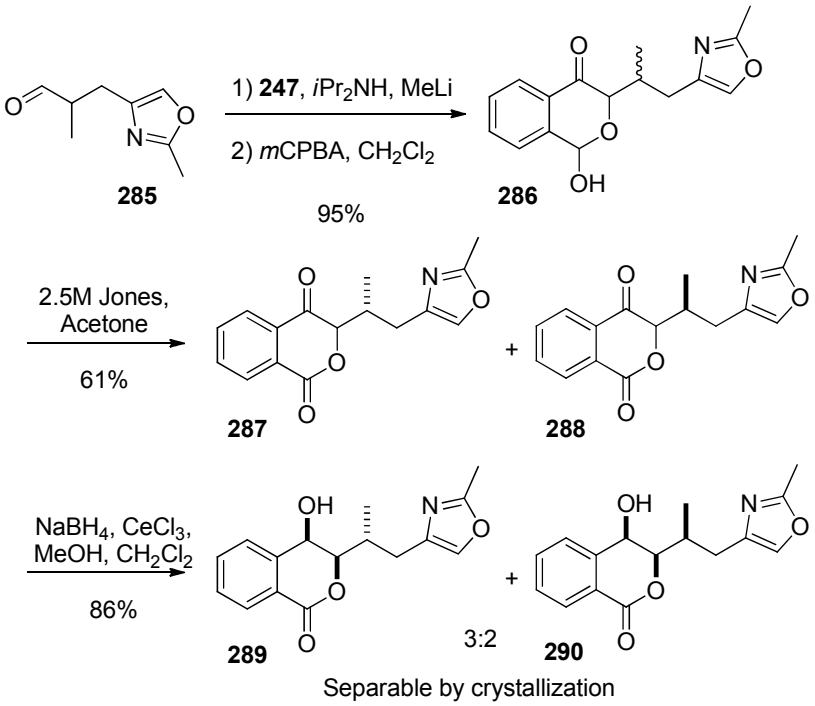
[1,2] Reduction of the ester yielded allylic alcohol **283** that was further reduced with palladium on carbon to give racemic alcohol **284**. Simultaneous [1,2] and [1,4] reduction of the α,β unsaturated ethyl ester **282** was attempted using lithium aluminium hydride, unfortunately gave mixtures of allylic hydroxyl **283**, saturated alcohol **284** and what appeared to oxazole reduction side products (reduction in a [1,6] fashion).

Finally oxidation of alcohol **284** under Swern conditions yielded the desired aliphatic aldehyde **285**. Oxidation of the alcohol using IBX gave the aldehyde in similar yields. Ease of purification and safety concerns during scale up made the Swern oxidation the preferred procedure.



Scheme 2.36. Synthesis of aldehyde 285.

Coupling of aldehyde **285** with *iso*benzofuran anion **240**, as per our procedure, gave a lactol **286** that were oxidised immediately to the corresponding lactones **287** and **288**. Reduction of the lactones under Luche conditions gave the **289** (*syn*:*anti*) and **290** (*syn*:*syn*) diastereoisomers in 3:2 ratio respectively.



Scheme 2.37. Synthesis of the Ajudazol model system.

As with previous examples complete *syn* selectivity during the reduction was observed. The structure and stereochemistries were corroborated by X-ray analysis of the major diastereoisomer **289**, which could be selectively crystallized.

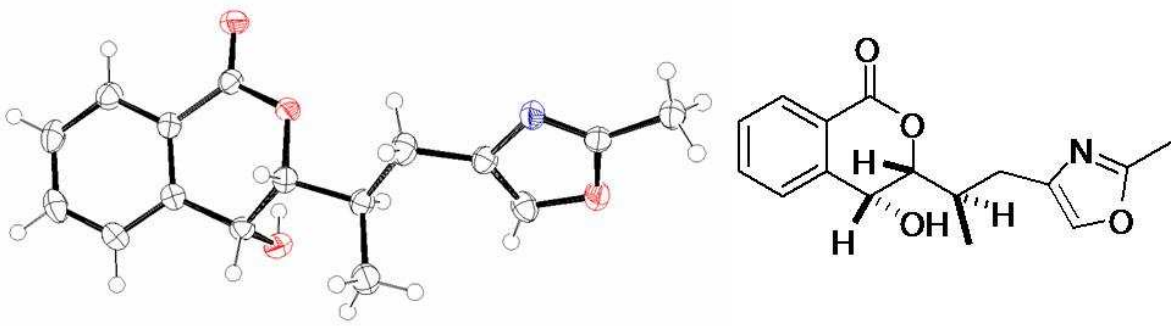
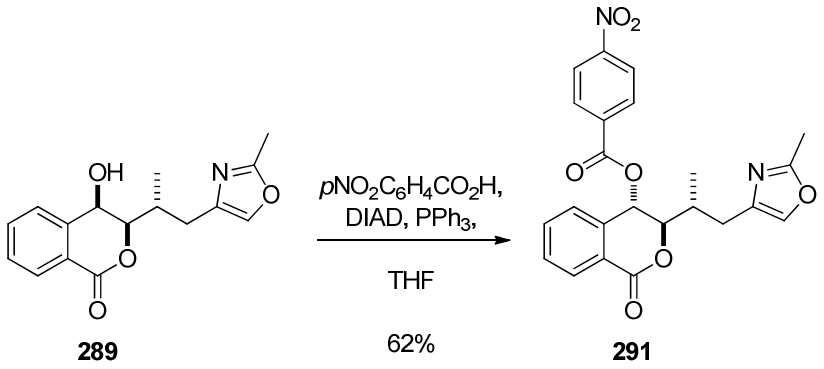


Figure 2.10. Crystal structure of Ajudazol model system.

2.2.3. Mitsunobu inversion

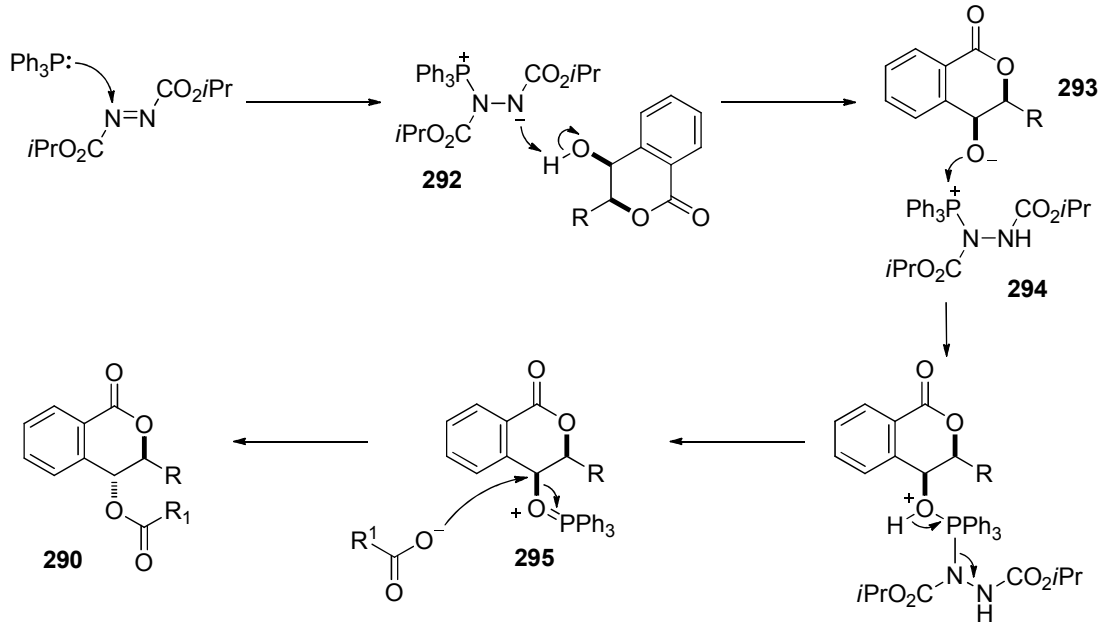
The Ajudazol isochromanone ring system has the *anti*:*anti* relationship between groups. To examine the feasibility of inverting the hydroxyl group, **289** was treated with 4-nitrobenzoic, di*iso*propylazadicarboxylate and triphenyl phosphine as per Mitsunobu conditions. The reaction successfully produced the benzoate ester **291** matching the stereochemistry present in the western section of the Ajudazols.[175-177]

When diethylazadicarboxylate (DEAD) was used as the acid activation agent, none of the benzoate product was observed. 4-Nitrobenzoic acid was used as the nucleophile in the hope that the nitro-benzoate **291** might have been induced to crystallize.



Scheme 2.38. Mitsunobu inversion of alcohol 299.

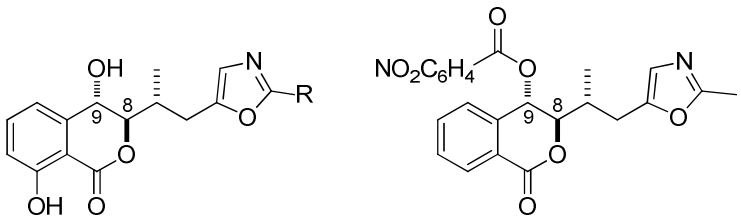
The Mitsunobu reaction works by phosphorous addition to the weak N=N π bond of di*iso*propylazodicarboxylate giving an anion **292** that is basic enough to remove the alcohol proton. The alkoxide intermediate **293** can then attack the phosphonium cation **294**, displacing the amine. The final step is displacement of the phosporous oxonium **295** by the nucleophile (4-nitrobenzoic acid) in an Sn2 manner giving ester **291**.



Scheme 2.39. Mitsunobu mechanism

Removal of the nitro benzoate group was not attempted at this point as there was insufficient material to conduct the experiment.

Having successfully generated nitro-benzoate **290**, it was possible to compare its NMR against that of Ajudazol A **2**. The analysis showed that **290** had almost identical coupling constants (± 0.1 Hz) to that observed in **2** and therefore the correct stereochemistry.

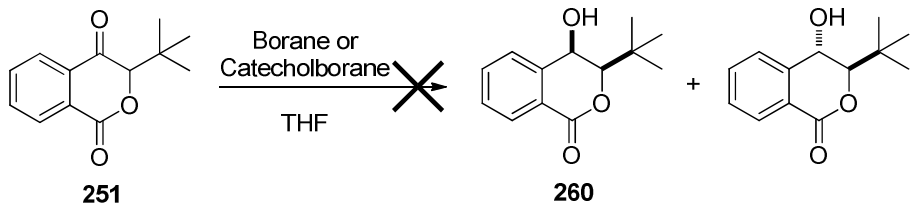


2 **290**

	Ajudazol A **2**		*p* -NO_2 ester **290**	
Atom	δ =	J_{ab} =	δ =	J_{ab} =
C_8	4.8	6.5	6.4	6.4
C_9	4.4	6.7	4.6	6.8

Table 2.4. C8-C9 proton couplings in 2 and 290.

Having successfully achieved the synthesis of the Ajudazol model system it was decided to investigate whether reduction of the C8 ketone could be achieved where the *anti* product was favoured rather than the *syn* reduction products observed so far. Keto-lactone **251** was selected as a test substrate as it had previously given only one *syn*-product. Unfortunately treatment of **251** with borane (as tetrahydrofuran and dimethyl sulfide complexes) gave only degradation products with none of the starting material or desired isochromanone products recovered. Catecholborane was unreactive with this substrate (Scheme 2.40).



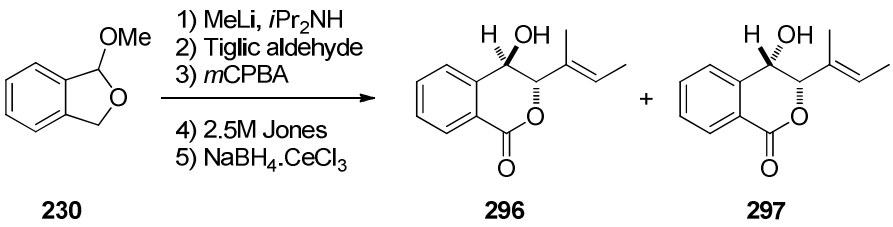
251 **260**

Scheme 2.40. Attempted borane reduction of keto-lactone 251.

2.2.4. An unexpected product

As part of our aldehyde screening (Table 2.2 andTable 2.3), tiglic aldehyde was chosen to test our methodology. Tiglic aldehyde is a potentially very useful substrate but also potentially dangerous from a side reaction point of view

(Scheme 2.41). Utilizing tiglic aldehyde as per our conditions gave 1 product in 8% yield. The product observed, was believed to be **296** and **297**. However, on closer examination of the NMR data it was noticed that there were no signals corresponding to an olefin in the ^{13}C NMR spectra. There where however, 4 signals between 42 and 57 ppm, which based on other similar compounds, no signals in this region were expected.



230 **296** **297**

Scheme 2.41. The expected products using tiglic aldehyde.

Mass spectrometry of the product showed a peak at 301 m/z in both FAB and CI modes, while infrared spectroscopy showed no absorptions corresponding to a hydroxyl group. There was an absorption in the IR spectra at 820 cm^{-1} which could potentially be attributed to an epoxide. Crystallization of the unknown product allowed the use of X-ray analysis that revealed a very different and unexpected bridged-tetracycle **298** (Figure 2.11).

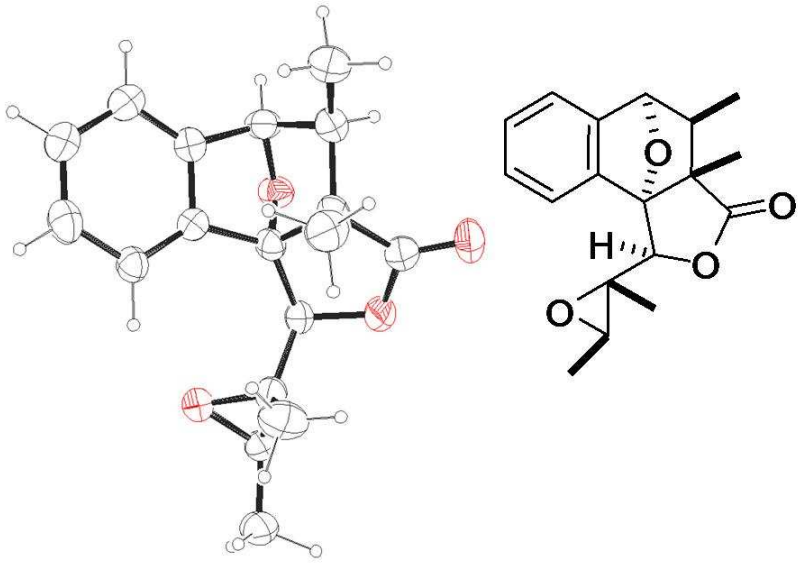
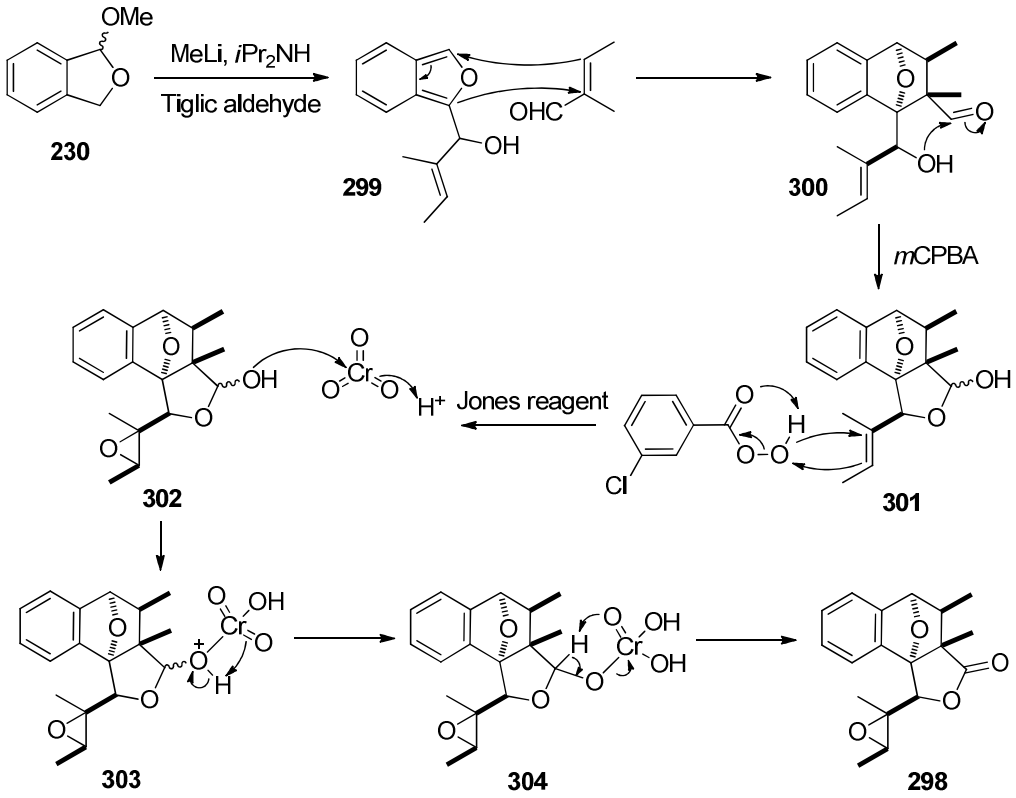


Figure 2.11. The unexpected product.

Mechanistically we believe that the *iso*benzofuran anion **240** was formed and coupled with tiglic aldehyde as expected. At this point the *iso*benzofuran **299** undergoes a Diels-Alder reaction with the excess tiglic aldehyde present, giving

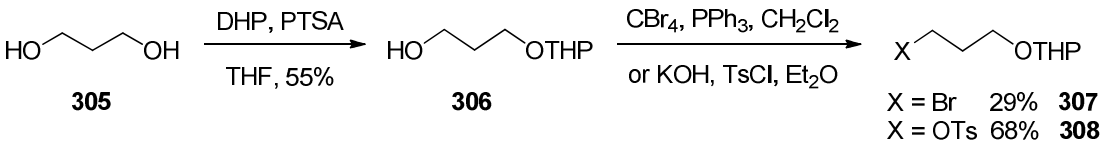
the *endo*-product **300** solely; this then lactonizes to give **301**. Treatment with *m*CPBA then epoxidizes the dimethyl-double bond giving **302**, finally Jones reagent oxidises the lactol to give the observed lactone-epoxide **298** via the oxygen cation **303** and the chromate diol **304** intermediates.



Scheme 2.42. Proposed mechanism for the generation of bridged ether 298.

2.2.5. Studies towards the Ajudazol A C15-C29 fragment.

Our synthesis began with propane-1,3-diol **305** which was mono-protected as the THP ether **306** under mildly acidic conditions[84] in acceptable 55% yield. The alcohol functionality was then to either a bromide **307**[178](via an Appel reaction in 29% yield), or to the corresponding tosylate **308**[179] (68% yield), Scheme 2.43.

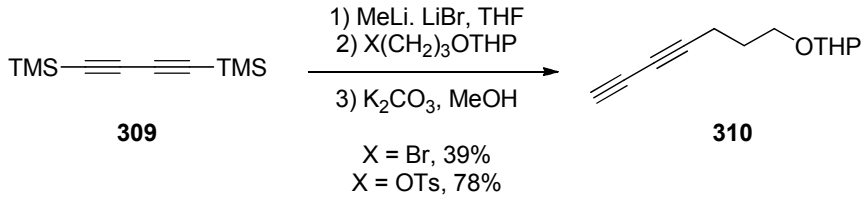


Scheme 2.43. Synthesis of coupling partners 307 and 308.

Treatment of TMS butadiyne **309** with methyllithium lithium bromide complex gave the mono-desilylated anion that was treated with bromide **307**, then potassium carbonate to give the mono-alkylated alkyne **310**. Using bromide **307**

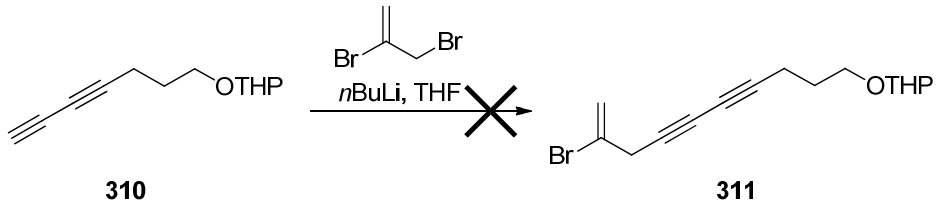
as coupling partner proved highly problematic, as during the reaction an insoluble black material was formed that made extractions/filtration difficult. It was also discovered that a dihalide containing impurity was present in the bromide coupling partner, resulting in poor 38% yield when compared to Fiandanese's[180] or Hennies[181] procedure that obtained 56% yield of **310**.

Changing the leaving group to a tosylate resulted in a much more efficient reaction as yields were improved to 78% and did not result in the formation of the problematic side products (Scheme 2.44).



Scheme 2.44. Synthesis of the Ajudazol side chain.

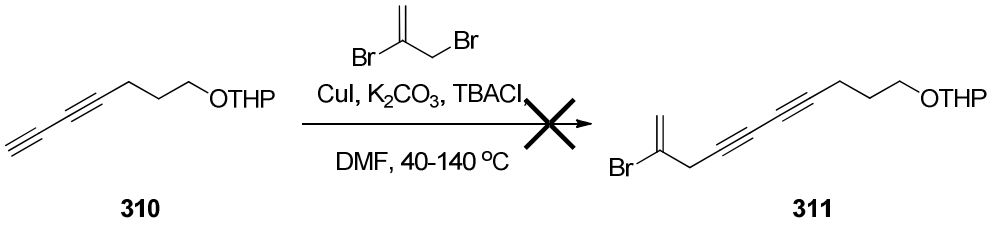
Unfortunately attempts to further alkylate the terminal alkyne have been unsuccessful. Initially the alkyne **314** was treated with *n*butyl lithium then 2,3-dibromopropene, the conditions were altered to include larger quantities of base and longer deprotonation times, with no success, returning only unreacted starting material.



Scheme 2.45.Alkylation attempts of 310

Upon examination of the literature, Tuyét's copper catalysed allylic substitution of terminal alkynes was found.[182] Tuyét reports that treatment of various terminal alkynes with a variety of allylic halides in the presence of copper(I) salts, tetrabutylammonium chloride and potassium carbonate gave allyl substituted acetynic compounds; thus alkyne **310** was applied to Tuyét's conditions. Unfortunately none of the desired bromo-compound **311** was obtained, so the temperature of the reaction was increased incrementally to much higher temperatures (up to 140 ^{o}C), with no change (Scheme 2.46). Due to

time constraints there has been no time to further investigate this alkyne allylation step.



Scheme 2.46.Tuyét's alkylation conditions.

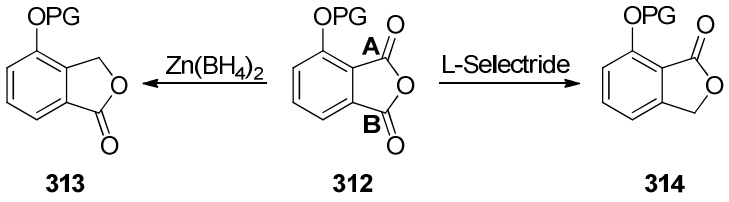
2.3. Future work

Despite the success in having shown that *iso*benzofurans are reactive intermediates with significant potential, there are still a number of issues that still need to be addressed.

2.3.1. Introduction of the C8 hydroxyl

The first obstacle to overcome will be the introduction of the hydroxyl functionality; this can be achieved by several means.

Treatment of phthalic anhydride **312** with zinc borohydride according to Kayser's procedure,[183] results in complete reduction at the A position, Scheme 2.47. The selectivity observed is due to chelation of the zinc borohydride between the carbonyl and methyl ether group. The opposite selectivity can be achieved using L-selectride, which because of steric hindrance cannot reduce the A position carbonyl, resulting in the formation of **314**. This method would be particularly useful because it allows the generation of both phthalides **313** and **314**.

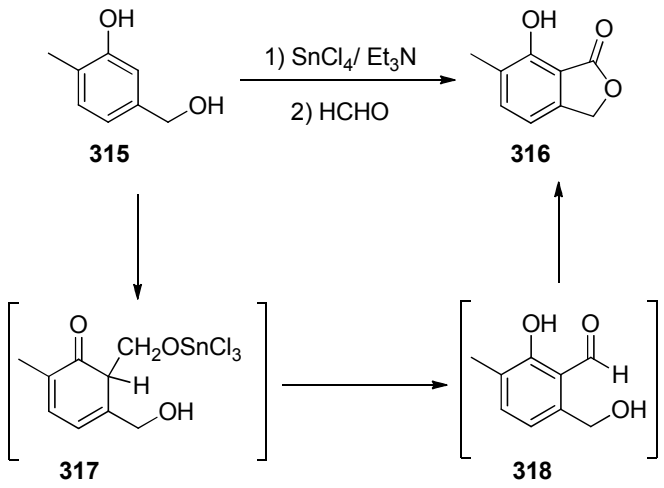


Scheme 2.47. Introduction of the hydroxyl.

The choice of protecting group is also important here, a sterically large protecting group is likely to block that face of the anhydride, preventing

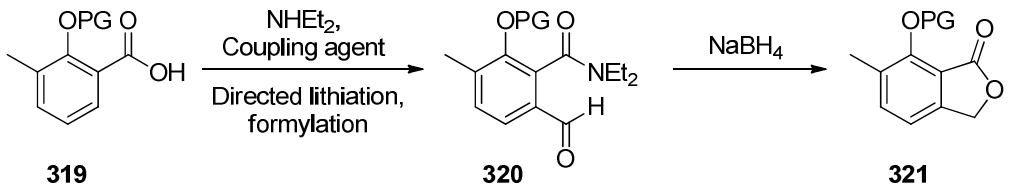
reduction of the anhydride **312** at the A position. It is also likely that reduction of the lactone **314** to the desired lactol would be impeded by the protecting group. We believe a large protecting group is needed for alkylation regioselectivity (see 2.3.2), should problems be encountered perhaps a protecting group exchange sequence could be required.

Hydroxy phthalide **316** can also be obtained from the formylation of diol **315** upon treatment with tin tetrachloride, triethylamine and formaldehyde. The reaction proceeds by reaction of diol **315** with tin to give the phenoxide salt that gives intermediate **317** upon treatment with formaldehyde. Enolisation to the corresponding phenol is followed by oxidation with a second molecule of formaldehyde giving intermediate **318** which undergoes lactonisation and a third oxidation step to give phthalide **316** (Scheme 2.48).[184]



Scheme 2.48. Synthesis of phthalide 316.

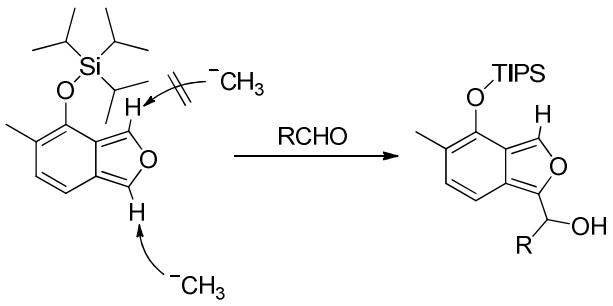
Protected salycilate **319** can be functionalised to obtain phthalide **321**. Conversion of the acid functionality to the corresponding amide using diethyl amine and thionyl chloride would then give the substrate for a formylation reaction. Reduction of the aldehyde group in **320** by sodium borohydride would allow lactonisation to occur, giving phthalide **321**.[185]



Scheme 2.49.Vilsmeier reaction of salicylate 319.

2.3.2. Alkylation regioselectivity

During the aromatization of acetal **230**, the second deprotonation can occur on either face of the *iso*benzofuran molecule. When the *iso*benzofuran is desymmetrized (i.e. incorporating the C8 hydroxyl functionality), deprotonation at the *iso*benzofuran C3 position is preferred. It is hoped that a sterically bulky protecting group on the hydroxyl would enhance the regiochemistry by blocking the C1 hydrogen from the methyl anion leaving the C3 proton unhindered. A trityl (Tr) or tri*iso*propylsilyl (TIPS) ether group should provide the necessary steric bulk required for selectivity. Using a trityl group would have the added bonus of not requiring a deprotection step as the Jones oxidation conditions would be acidic enough to facilitate cleavage of the group.

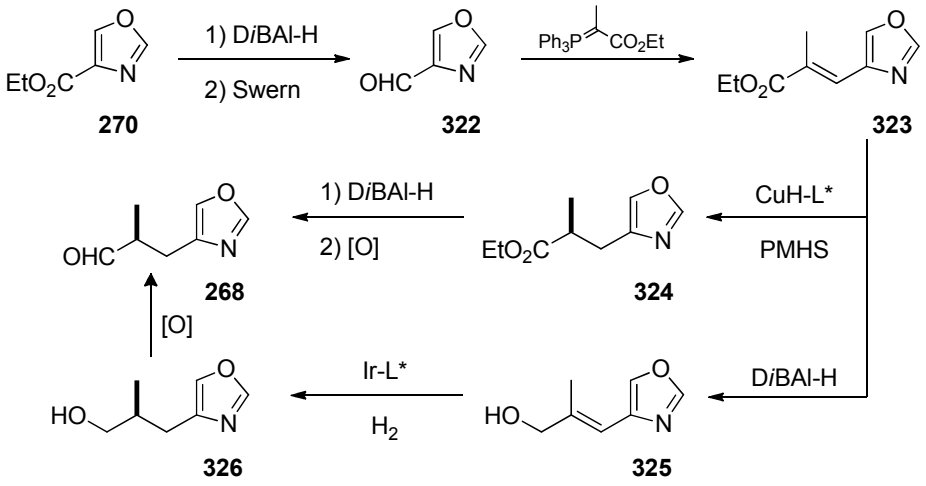


Scheme 2.50. Regioselective contol of alkylation.

2.3.3. Enantiopure Aldehyde

Having addressed the region chemistry of *iso*benzofuran alkylation, enantiopure aldehyde **268** will be incorporated into our synthesis as per Scheme 2.29. Aldehyde **268** will be synthesized by one of two means from α,β unsaturated ester **323**, depending on where in the sequence the chirality need be introduced. Treatment of **323** with Stryker's reagent (chiral cuprate reagent), should give optically pure ester **324**,[186] that could be further reduced to the corresponding alcohol then oxidised to give aldehyde **268**.

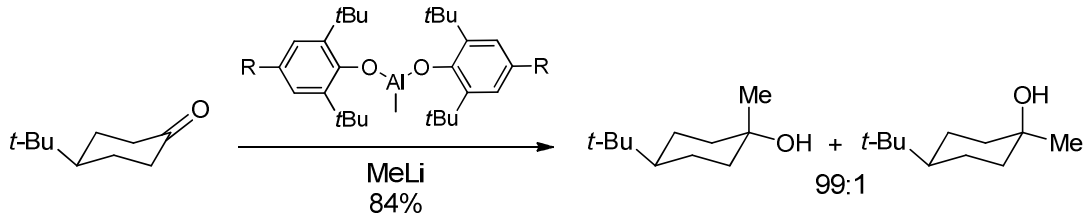
Treatment of **323** with D*i*BAl-H should give allylic alcohol **325**. Hydroxyl directed reduction of the olefin through an iridium (Crabtree like) catalyst should also provide the chiral alcohol that could then be oxidised,[187] giving **268**.



Scheme 2.51. The approach to the desired chiral aldehyde.

2.3.4. Completion of the C1-C14 fragment

Having already demonstrated that *iso*benzofuran addition to an aldehyde is selective, giving the *anti*-configuration between C9 and C10, it is anticipated that aldehyde **268** (optically pure with the *S* configuration) will enhance these results. Should there be a need, Yamamoto's MAD (MethylAluminium bis(2,6-Di-*tert*butyl-4-methylphenoxide) chemistry should provide the necessary enhancement to selectivity (Scheme 2.52).[188] The sterically hindered MAD Lewis acid has been shown to favour *anti*-Felkin Ahn control. Applied to our system it will enhance the selectivity already observed.

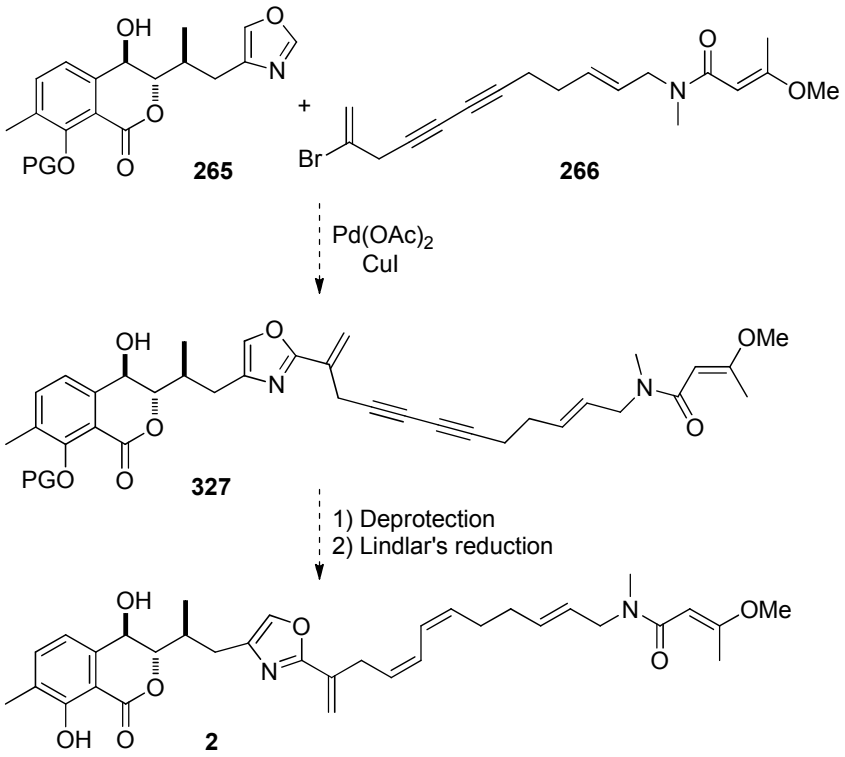


Scheme 2.52. Yamamoto's MAD additive.

2.3.5. Further work

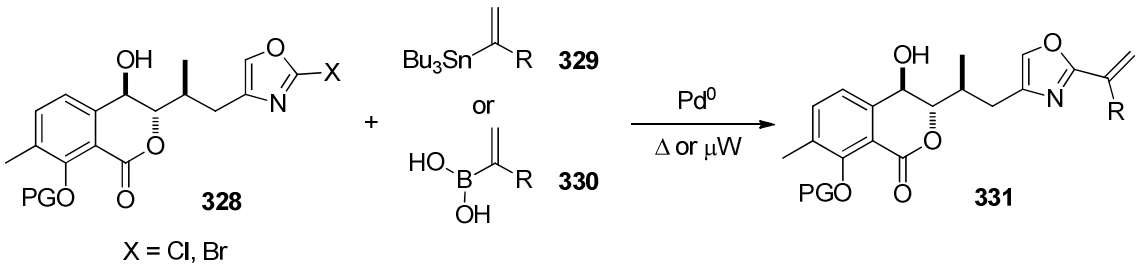
The final steps in the total synthesis of Ajudazol A would begin with the palladium mediated coupling between the vinyl bromide bearing C1-C14 'eastern fragment' **266** and oxazole containing C15-C29 'western unit' **265**. Although there is no previous precedence for this type of coupling, we believe that Bellina's conditions for the coupling of unfunctionalised oxazoles and aryl iodides could be successfully extrapolated into our system to produce diyne **327**.[189] Removal of the protecting group would then generate phenol, which

upon a double selective *syn*-hydrogenation would complete our synthesis of Ajudazol A **2**.[190]



Scheme 2.53. Completion of Ajudazol A

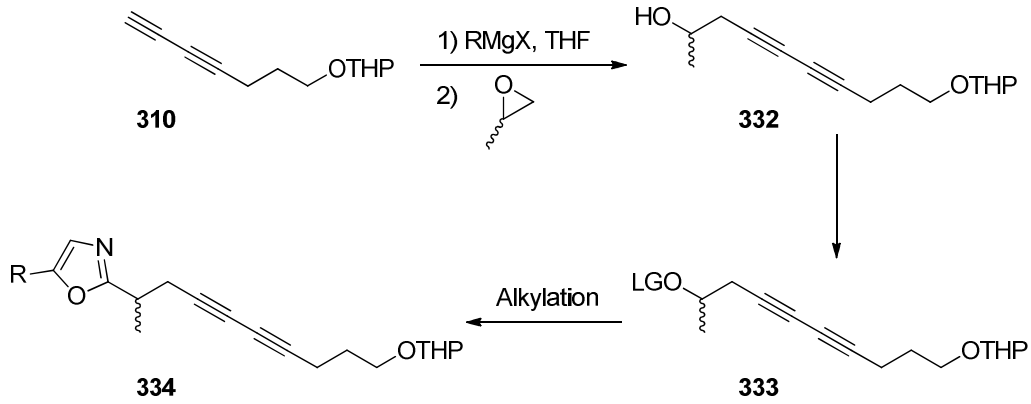
There is the very real possibility that the proposed palladium coupling between vinyl bromide **266** and oxazole **265** might fail. Should this be the case, several alternative approaches have been conceived. Reverting to a more traditional Stille coupling either between vinyl stannane **329** and a 2-chloro oxazole unit **328** is feasible. This would require a switch in starting material from the simple oxazole ester **270** to the C2-chloro substituted analogue.[191,192] Similarly we could revert to a Suzuki coupling between C2 halogen substituted oxazole **328** and boronic acid **330** using Greaney's microwave conditions (Scheme 2.54).[193]



Scheme 2.54. An alternate approach that could be utilized.

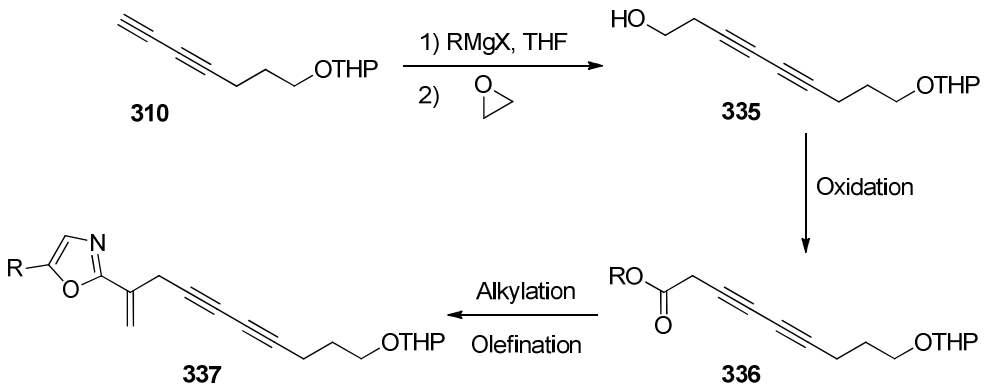
Ajudazol B **3** will be synthesized in a different manor. The two natural products **2** and **3** differ in only one aspect, **3** has a CH methyl at the C15 position while

Ajudazol A **2** has an *exo*-methylene group. To account for the difference, terminal alkyne **310** can be alkylated with *R* or *S*-propylene oxide, that would give secondary alcohol **332.** Conversion of alcohol **332** to a suitable leaving group would allow it to be coupled with a suitable oxazole coupling partner. The reason for using *R* or *S* enantiomers of propylene oxide is due to the fact that Ajudazol B was not assigned C15 stereochemistry upon *iso*lation and characterisation.[2] Utilizing both enantiomers will allow us to both confirm the configuration of the natural product, by comparison of physical data (optical rotations etc) and simultaneously synthesize an anologue.



Scheme 2.55. Proposed synthesis of Ajudazol B.

Ajudazol A could be similarly synthesized should it be required. Alkylation of terminal alkyne **310** with ethylene oxide would give primary alcohol **335** that could be oxidised to the corresponding ester. Alkylation of ester **336** with a suitable oxazole derived nucleophile would give a ketone intermediate that could be olefinated under Petassis or Tebbe conditions to yield the desired *exo*-olefin functionality in **337** (Scheme 2.56).

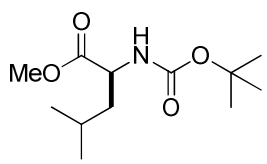


Scheme 2.56. Modified approach to Ajudazol A.

3. Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether and dichloromethane (DCM) were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40°C using a Buchi Rotavapor. IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (vmax) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were respectively recorded at 400MHz and 100MHz using a Bruker DPX Avance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dm = double multiplet, dd = double doublet, dt = double triplet) and (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15000 full widths at half height. Where a 100% peak was not observed in Low resolution mass spectra the highest peak was taken to be 100%. Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 μm) as the stationary phase. TLC was performed on aluminium sheets precoated with silica (Merck Silica Gel 60 F254). The plates were visualised by the quenching of UV fluorescence (λmax 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

Methyl-(*S*)-2-(*tert*butoxycarbonylamino)-4-methylpentanoate.[113]



A solution of (*S*)-2-(*tert*butoxycarbonylamino)-4-methylpentanoic acid **197** (15.0 g, 60.2 mmol) in anhydrous dimethylformamide (150 mL), was treated

sequentially with potassium hydrogen carbonate (13.3 g, 132 mmol) and methyl iodide (previously alumina filtered) (5.99 mL, 96.1 mmol), reaction mixture was stirred completion by TLC analysis and quenched with water (50 mL). The mixture was extracted with ethyl acetate (2x 50 mL) the organic layer was washed with saturated sodium chloride (50 mL). Combined organic layers were dried over sodium sulfate and concentrated *in vacuo*, to yield 15.8 g (99%) of the desired ester as a clear oil, further purification was not necessary. .

^{1}H ($CDCl_3$, 400 MHz) δ: 4.90 (1H, d, *J* = 8.2, CH*NH*), 4.25-4.24 (1H, m, *CH*NH), 3.66 (3H, s, OCH_3), 1.65-1.39 (3H, m, CH_2CH), 1.37 (9H, s, $C(CH_3)_3$), 0.87 (6H, m, $CH(CH_3)_2$).

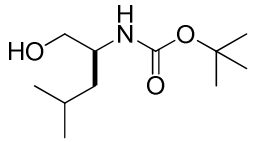
^{13}C ($CDCl_3$, 100 MHz) δ: 172.2 (*C*O), 154.9 (NH*C*O), 81.7 ($C(CH_3)_3$),54.6 (OCH_3), 52.8 (*C*HNH), 43.2 ($CHCH_2CH$), 29.5 ($C(CH_3)_3$), 26.4 ($CH(CH_3)_2$), 23.5 ($CH(CH_3)_2$), 21.6 ($CH(CH_3)_2$).

m/z [CI^+ (+ve), *iso*butane] 246.2 $[M+H]^+$ (100%), HRMS found 246.1704, $C_{12}H_{24}NO_4$ requires 246.1705 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}: 2916, 1749, 1682.

$[a]_D^{27}$ = -54.8 ($CHCl_3$, c = 1.1), Lit. [113] $[a]_D^{20}$ = -11.6 ($CHCl_3$)

_tert_Butyl-(*S*)-1-hydroxy-4-methylpentan-2-yl-carbamate.[113]



A solution of (*S*)-methyl-2-(*tert*butoxycarbonylamino)-4-methylpentanoate (15.8 g, 60.0 mmol) in anhydrous tetrahydrofuran (150 mL) was treated with anhydrous lithium chloride (5.09 g, 120 mmol), sodium borohydride (4.54 g, 120 mmol) and the mixture was stirred for 20 minutes. Ethanol (200 mL) was added slowly and the resulting opaque white solution was stirred for 12 hours. The reaction mixture was cooled to 0 °C, then acidified to pH 4 with 10% aqueous citric acid (45 mL) and concentrated *in vacuo*. The residue was dissolved in diethyl ether (100 mL) and washed with water (3x 50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, to give crude residue which was purified by flash column chromatography (silica gel, elution with 25% ethyl acetate in petroleum spirit) to yield 12.6 g (96% yield) of the desired alcohol as a clear oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 4.49 (1H, bs, CH*NH*), 3.70-3.58 (2H, m, CH_2OH), 3.47-3.42

(1H, m, *CH*NH), 2.42 (1H, bs, OH), 1.62-1.56 (1H, m, *CH*(CH_3)$_2$), 1.38 (9H, s, C(*CH*$_3$)$_3$), 1.25-1.18 (2H, m, *CH*$_2$CH), 0.86 (6H, m, CH(*CH*$_3$)$_2$).

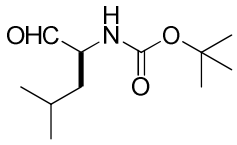
^{13}C ($CDCl_3$, 100 MHz) δ: 156.9 (NH*C*O), 79.8 (*C*(CH_3)$_3$), 66.9 (*C*H$_2$OH), 51.2 (*C*HNH), 40.6 (CH*C*H$_2$CH), 28.6 (C(*C*H$_3$)$_3$), 24.9 (*C*H(CH_3)$_2$), 23.3 (CH(*C*H$_3$)$_2$), 22.5(CH(*C*H$_3$)$_2$).

m/z [CI$^+$ (+ve), *iso*butane] 218.2 [M+H]$^+$ (100%), HRMS found 218.1754, $C_{11}H_{24}NO_3$ requires 218.1756 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}: 3455, 2978, 1675.

$[a]_D^{26}$ = -53.60 ($CHCl_3$, c = 1.0), Lit. [72] $[a]_D$ = -27.9 (MeOH, c = 2.1)

_tert_Butyl-(S)-4-methyl-1-oxopentan-2-yl-carbamate, 30.[71]

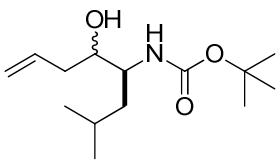


A solution of Boc-N-leucinol (12.6 g, 58.0 mmol) in DMSO (150 mL) was treated with a solution of IBX (19.5 g, 69.6 mmol) in DMSO (140 mL). The reaction was stirred at 40 °C for 16 hours until completion by TLC. The reaction was quenched with water (100 mL) and diethyl ether (50 mL) was added, the organic layer was washed with water (3x 75 mL) and the organic extracts combined and dried over sodium sulfate. The solution was concentrated *in vacuo* to give 10.4 g aldehyde **197** (83% yield) a colourless, viscous oil, further purification was not required.

^{1}H ($CDCl_3$, 400 MHz) δ: 9.52 (1H, s, CHO), 4.88 (1H, bs, CH*NH*), 4.22-4.15 (1H, m, *CH*NH), 1.70-1.45 (2H, m, *CH*$_2$CH), 1.38 (9H, s, C(*CH*$_3$)$_3$), 1.18 (1H, m, *CH*(CH_3)$_2$), 0.88 (6H, m, CH(*CH*$_3$)$_2$).

^{13}C ($CDCl_3$, 100 MHz) δ: 199.6 (*C*HO), 162.4 (NH*C*O), 81.2 (*C*(CH_3)$_3$), 53.6 (*C*HNH), 39.4 (CH*C*H$_2$CH), 28.7 (C(*C*H$_3$)$_3$), 24.9 (*C*H(CH_3)$_2$), 23.6 (CH(*C*H$_3$)$_2$), 21.6 (CH(*C*H$_3$)$_2$).

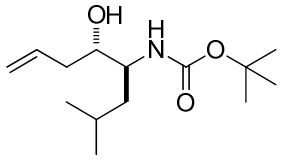
_tert_Butyl-5-hydroxy-2-methyloct-7-en-4-ylcarbamate,188 and 189.[71]



To a stirred solution of Boc-N-Leucinal **30** (10.4 g, 48.3 mmol) in dichloromethane (240 mL) at -78 °C, was added tin chloride (96.6 mL, 96.6

mmol, 1 M in dichloromethane) and the resulting solution stirred for 10 minutes. The reaction was treated with allyl tributyltin (22.5 g, 72.5 mmol) and stirred for 3 hours, then allowed to attain room temperature and stirred for a further 7 hours. The reaction was quenched with ammonium chloride solution (50 mL) and diluted with dichloromethane (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting grey residue was dissolved in anhydrous methanol (65 mL) and treated with sodium borohydride (1.83 g, 48.3 mmol) and stirred for 5 minutes. The grey suspension formed was treated with saturated sodium carbonate (50 mL) and diethyl ether (100 mL) and extracted into diethyl ether. Organic extracts were combined and washed with water (2x 50 mL) and brine (50 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo* Purification by flash column chromatography (silica gel, elution with 20% diethyl ether in petroleum spirits) gave 8.32 g (67% yield) of homo-allylic alcohols **188** and **189** as a clear oil and as an 7:1 mixture of *anti:syn* diastereoisomers.

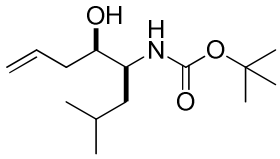
_tert_Butyl-(4*S*,5*S*)-5-hydroxy-2-methyloct-7-en-4-ylcarbamate, 188.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.89-5.79 (1H, m, CH_2*CH*CH_2), 5.17-5.13 (2H, m, *CH*$_2$$CHCH_2$), 4.64 (1H, d, *J* = 9.0 Hz, *NH*), 3.66-3.63 (1H, m, *CH*NH), 3.60-3.57 (1H, m, *CH*OH), 2.33-2.29 (2H, m, CH*CH*$_2$$CH$), 2.01 (1H, d, *J* = 2.9 Hz, *OH*), 1.69-1.59 (2H, m, CH*CH*$_2$$CH$), 1.44 (9H, s, $C(CH_3)_3$), 1.36-1.25 (1H, m, *CH*$(CH_3)_2$), 0.86 (6H, m, $CH(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.2 (NH*C*O), 134.6 (CH_2*C*HCH_2), 118.4 (*C*H_2CH), 79.2 (*C*$(CH_3)_3$), 72.8 (CH_2*C*HOH), 52.0 (CH*C*HNH), 41.9 (CH*C*H_2CH), 39.2 (*C*H_2CHNH), 28.6 (C(*C*$H_3)_3$), 24.8 (*C*$H(CH_3)_2$), 23.2 (CH(*C*$H_3)_2$), 22.2 (CH(*C*$H_3)_2$).

_tert_Butyl-(4_S_,5_R_)-5-hydroxy-2-methyloct-7-en-4-ylcarbamate, 189.



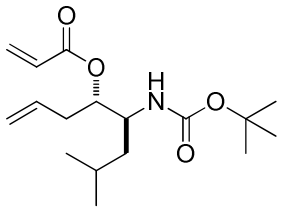
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.89-5.79 (1H, m, CH_2***C**H*CH_2), 5.17-5.13 (2H, m, ***C**H*$_2$$CHCH_2$), 4.64 (1H, d, *J* = 9.0 Hz, ***N**H*), 3.66-3.63 (1H, m, ***C**H*NH), 3.60-3.57 (1H, m, ***C**H*OH), 2.33-2.29 (2H, m, CH***C**H*$_2$$CH$), 2.01 (1H, d, *J* = 2.9 Hz, ***O**H*), 1.69-1.59 (2H, m, CH***C**H*$_2$$CH$), 1.44 (9H, s, C(***C**H*$_3$)$_3$), 1.36-1.25 (1H, m, ***C**H*$(CH_3)_2$), 0.79 (6H, m, CH(***C**H*$_3$)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.2 (NH***C**O*), 135.0 (CH_2***C**H*CH_2), 117.9 (***C**H*$_2$CH), 78.8 (***C**H*$_3$)$_3$), 73.9 (CH_2***C**H*OH), 53.2 (CH***C**H*NH), 38.5 (CH***C**H*$_2$CH), 37.2 (***C**H*$_2$CHNH), 28.5 (C(***C**H*$_3$)$_3$), 23.7 (***C**H*$(CH_3)_2$), 22.7 (CH(***C**H*$_3$)$_2$), 20.5 (CH(***C**H*$_3$)$_2$).

m/z [CI^+ (+ve), ***iso***butane] 258.3 $[M+H]^+$ (100%), HRMS found 258.2071, $C_{14}H_{28}NO_3$ requires 258.2069 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}: 3438, 2957, 1687, 1170.

(4_S_,5_S_)-5-(_tert_Butoxycarbonylamino)-7-methyloct-1-en-4-yl acrylate, 190.



Homoallylic alcohols **188** and **189** (5.34 g, 20.7 mmol) were dissolved in dichloromethane (104 mL) and cooled to 0 °C. Acryloyl chloride (2.95 mL, 36.3 mmol) and triethylamine (10.1 mL, 72.6 mmol) were added sequentially and the reaction was stirred for 10 hours. Once complete by TLC analysis the solution was neutralised using 1 M hydrochloric acid solution. The organic phase was separated then washed sequentially with water (2x 30 mL) and brine (30 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, elution with 10 % diethyl ether in petroleum spirits) gave **190** 5.30 g (82% yield) and **191** 883 mg (14% yield) as a clear oil .

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.45 (1H, d, *J* = 17.3 Hz, COCH***C**H*$_2$), 6.15 (1H, dd, *J* = 16.0, 8.1 Hz, CO***C**H*CH_2), 5.88 (1H, d, *J* = 10.4 Hz, COCH***C**H*$_2$), 5.83-5.75 (1H, m, CH_2CH***C**H*$_2$), 5.16-5.04 (2H, m, CH_2CH***C**H*$_2$), 5.03-5.00 (1H, m, ***C**H*OC), 4.51 (1H, d,

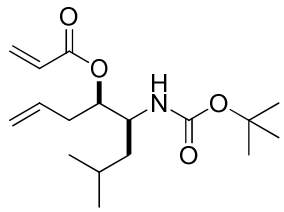
J = 10.0 Hz, *NH*), 3.96-3.91 (1H, m, *CH*NH), 2.42-2.40 (2H, m, C(O)*CH*$_2$CH), 1.71-1.63 (1H, m, *CH*(CH$_3$)$_2$), 1.47 (9H, s, C(*CH*$_3$)$_3$), 1.31-1.24 (2H, m, *CH*$_2$CH(CH$_3$)$_2$), 0.94 (3H, m, CH(*CH*$_3$)$_2$), 0.92 (3H, m, CH(*CH*$_3$)$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz) δ: 165.6 (CH*C*O), 155.6 (NH*C*O), 133.1 (CH$_2$*C*H), 131.2 (*C*H$_2$CH), 128.1 (CH$_2$*C*H), 118.4 (*C*H$_2$CH), 79.3 (CH$_2$*C*H), 75.4 (*C*(CH$_3$)$_3$), 50.3 (CH*C*HNH), 42.0 (*C*H$_2$CH), 36.3 (CH*C*H$_2$CH), 28.3 (C(*C*H$_3$)$_3$), 24.7 (*C*H(CH$_3$)$_2$), 23.1 (CH(*C*H$_3$)$_2$), 22.1 (CH(*C*H$_3$)$_2$).

m/*z* [CI$^+$ (+ve), *iso*butane] 312.2 [M+H]$^+$ (100%). HRMS found 312.2176, C$_{17}$H$_{30}$NO$_4$ requires 312.2175 [M+H]$^+$.

$[a]_D^{25}$ = -1.9 (CHCl$_3$, c = 1.0)

(4*S*,5*R*)-5-(*tert*Butoxycarbonylamino)-7-methyloct-1-en-4-yl acrylate, 191.



^{1}H NMR (CDCl$_3$, 400 MHz) δ: 6.33 (1H, dd, *J* = 17.3 , 1.1 Hz, COCH*CH*$_2$), 6.15 (1H, dd, *J* = 17.3, 10.4 Hz, CO*CH*CH$_2$), 5.88 (1H, d, *J* = 12.0 Hz, COCH*CH*$_2$), 5.78-5.65 (1H, m, CH$_2$CH*CH*$_2$), 5.05-4.98 (2H, m, CH$_2$CH*CH*$_2$), 4.94 (1H, d, *J* = 8.0 Hz, *CH*OC), 4.36 (1H, d, *J* = 10.0 Hz, *NH*), 3.87-3.80 (1H, m, *CH*NH), 2.37-2.25 (2H, m, C(O)*CH*$_2$CH), 1.63-1.57 (1H, m, *CH*(CH$_3$)$_2$), 1.36 (9H, s, C(*CH*$_3$)$_3$), 1.24-1.19 (2H, m, *CH*$_2$CH(CH$_3$)$_2$), 0.86 (3H, m, CH(*CH*$_3$)$_2$), 0.84 (3H, m, CH(*CH*$_3$)$_2$).

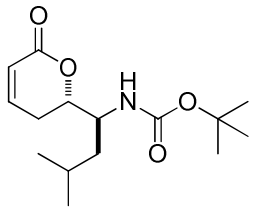
^{13}C NMR (CDCl$_3$, 100 MHz) δ: 165.4 (CH*C*O), 155.8 (NH*C*O), 133.1 (CH$_2$*C*H), 131.3 (*C*H$_2$CH), 128.2 (CH$_2$*C*H), 118.4 (*C*H$_2$CH), 80.1 (CH$_2$*C*H), 75.1 (*C*(CH$_3$)$_3$), 51.3 (CH*C*HNH), 42.2 (*C*H$_2$CH), 36.1 (CH*C*H$_2$CH), 28.4 (C(*C*H$_3$)$_3$), 24.4 (*C*H(CH$_3$)$_2$), 23.2 (CH(*C*H$_3$)$_2$), 21.8 (CH(*C*H$_3$)$_2$).

m/*z* [CI$^+$ (+ve), *iso*butane] 312.2 [M+H]$^+$ (100%), HRMS found 312.2178, C$_{17}$H$_{30}$NO$_4$ requires 312.2175 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}: 3367, 3079, 2959, 1689, 1639, 1169.

$[\alpha]_D^{25}$ = -4.3 (CHCl$_3$, c = 1.0)

***tert*Butyl-(*S*)-3-methyl-1-((*S*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-butylcarbamate, 198.**



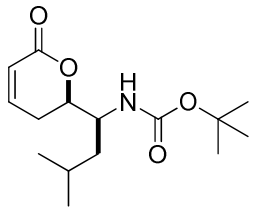
Diene **190** (3.76 g, 12.1 mmol) was dissolved in dichloromethane (120 mL), to this was added Grubbs second generation catalyst 5 mol% (518 mg, 0.61 mmol), heated to reflux and stirred for 48 hours. Once complete the black solution was concentrated *in vacuo* and suspended in diethyl ether (100 mL) then filtered through florisil. The filtrate was concentrated *in vacuo* and purification by flash column chromatography (elution with 20% diethyl ether and petroleum spirits) gave 2.67 g (78%) of α-pyrone **198** as a crystalline solid (m.p. 55-57 ^{o}C)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.91 (1H, ddd, *J* = 9.6, 6.4, 2.1 Hz, COCH*CH*), 5.99 (1H, dd, *J* = 9.8, 2.4 Hz, CO*CH*CH), 4.59 (1H, d ,*J* = 9.9 Hz, *NH*), 4.42 (1H, dd, *J* = 12.8, 1.5 Hz, CH_2*CH*CH), 3.87-3.81 (1H, m, *CH*NH), 2.56-2.48 (1H, m, CHCH*CH_2*), 2.27 (1H, ddd, *J* = 18.6, 5.6, 3.9 Hz, CHCH*CH_2*), 1.73-1.62 (2H, m, *CH_2*CH(CH_3)$_2$), 1.43 (9H, s, C(*CH_3*)$_3$), 1.39-1.35 (1H, m, *CH*(CH_3)$_2$), 0.92 (3H, d, *J* = 6.3 Hz, CH(*CH_3*)$_2$), 0.92 (6H, d, *J* = 6.3 Hz, CH(*CH_3*)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.1 (CH*C*O), 155.8 (NH*C*O), 145.9 (*C*HCHCO), 120.8 (CH*C*HCO), 79.9 (CHCH$_2$*C*H), 79.6 (*C*(CH_3)$_3$), 50.4 (CH*C*HNH), 41.1 (CHCH*C*H$_2$), 28.3 (*C*H$_2$CH(CH_3)$_2$), 26.9 (C(*C*H$_3$)$_3$), 24.8 (*C*H(CH_3)$_2$), 23.0 (CH(*C*H$_3$)$_2$), 22.0 (CH(*C*H$_3$)$_2$).

$[a]_D^{25}$ = -5.7 ($CHCl_3$, c = 1.0)

***tert*Butyl-(S)-3-methyl-1-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-butylcarbamate, 199.**



Diene **191** (869 mg, 2.79 mmol) was dissolved in dichloromethane (28 mL), to this was added Grubbs second generation catalyst 5 mol% (118 mg, 0.14 mmol), heated to reflux and stirred for 44 hours. Once complete the black solution was

concentrated *in vacuo* and suspended in diethyl ether (20 mL) then filtered through florisil. The filtrate was concentrated *in vacuo* and purification by flash column chromatography (elution with 20% diethyl ether and petroleum spirits) gave 593 mg (75 %) of α-pyrone **199** as a crystalline solid (m.p.103-104 °C).

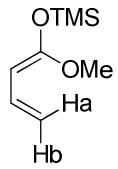
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.92 (1H, m, COCH*CH*), 6.03 (1H, dt, *J* = 9.6, 1.8 Hz, CO*CH*CH), 4.72 (1H, d ,*J* = 8.3 Hz, *NH*), 4.44 (1H, d, *J* = 11.6 Hz, CH_2*CH*CH), 3.86-3.79 (1H, m, *CH*NH), 2.51-2.35 (2H, m, CHCH*CH*$_2$), 1.76-1.69, 1H, m, *CH*(CH_3)$_2$), 1.50-1.44 (2H, m, *CH*$_2$CH(CH_3)$_2$), 1.45 (9H, s, C(*CH*$_3$)$_3$), 0.96 (3H, d, *J* = 6.7 Hz, CH(*CH*$_3$)$_2$), 0.94 (3H, d, *J* = 6.5 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.1 (CH*C*O), 155.5 (NH*C*O), 145.2 (COCH*C*H), 121.2 (CO*C*HCH), 80.6 (CHCH$_2$*C*H), 79.7 (*C*(CH_3)$_3$), 50.9 (CH*C*HNH), 38.1 (CHCH*C*H$_2$), 28.4 (CH_2*C*H(CH_3)$_2$), 26.4 (C(*C*H$_3$)$_3$), 24.6 (*C*H(CH_3)$_2$), 23.7 (CH(*C*H$_3$)$_2$), 21.4 (CH(*C*H$_3$)$_2$). *m/z* [CI$^+$ (+ve), *iso*butane] 284.4 [M+H]$^+$ (100%), HRMS found 284.1865, $C_{15}H_{26}NO_4$ requires 284.1862 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}: 3447, 2958, 1686, 1167.

$[a]_D^{26}$ = -3.9 ($CHCl_3$, c = 1.0)

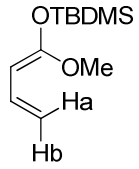
(*E*)-(1-Methoxybuta-1,3-dienyloxy)trimethylsilane, 202.[128]



A solution of freshly distilled di*iso*propylamine (3.07 mL, 21.9 mmol) in anhydrous tetrahydrofuran (50 mL) at 0 °C was treated with *n*BuLi (14.0 mL, 21.9 mmol, 1.56 M in hexanes) and stirred for 15 minutes. The reaction was cooled to -78 °C and stirred for 30 minutes; hexamethyl phosphoramide (4.29 mL, 23.9 mmol) followed by methyl crotonate **205** (2.11 mL, 19.9 mmol) were added and the reaction was stirred for a further 40 minutes. A solution of trimethylsilyl chloride (4.09 mL, 31.9 mmol) in anhydrous tetrahydrofuran (20 mL) was then added slowly and the resulting yellow solution was allowed to attain room temperature over 1 hour. Cold pentane (50 mL) was added, followed by water (30 mL) and the organic phase was separated then washed with water (3x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The brown residue was purified by short pass vacuum distillation (88 °C at 32 mm Hg) giving 4.61 g silyl enolate **202** in 67% yield.

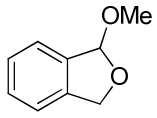
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.42 (1H, sext, *J* = 7.6 Hz, CH*CH*CH_2), 4.78 (1H, d, *J* = 17.2 Hz, *CH*$CHCH_2$), 4.54 (1H, d, *J* = 10.4 Hz, *Ha*), 4.43 (1H, d, *J* = 10.3 Hz, *Hb*), 3.5 (3H, s, OCH_3), 0.17 (9H, s, (Si(CH_3)$_3$).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.7 (*C*OCH_3), 132.2 (CH*C*HCH_2), 106.8 ($CHCHCH_2$), 80.4 (*C*$HCHCH_2$), 54.5 (OCH_3), 0.4 (Si(CH_3)$_3$).

(*E*)-*tert*butyl(1-methoxybuta-1,3-dienyloxy)dimethylsilane, 206.



A solution of freshly distilled di*iso*propylamine (3.07 mL, 21.9 mmol) in anhydrous tetrahydrofuran (50 mL) at 0 °C was treated with *n*BuLi (14.0 mL, 21.9 mmol, 1.56 M in hexanes) and stirred for 15 minutes. The reaction was cooled to -78 °C and stirred for 30 minutes; hexamethyl phosphoramide (4.29 mL, 23.9 mmol) followed by methyl crotonate **205** (2.11 mL, 19.9 mmol) were added and the reaction was stirred for a further 40 minutes; hexamethyl phosphoramide (4.29 mL, 23.9 mmol) then methyl crotonate (2.11 mL, 19.9 mmol) were added and the reaction stirred for a further 30 minutes. A solution of dimethyl-*tert*butylsilyl chloride (3.61 g, 23.9 mmol) in anhydrous tetrahydrofuran (13 mL) was then added slowly and the resulting yellow solution allowed to attain room temperature over 1 hour. Cold pentane (50 mL) was added, followed by water (30 mL) and the organic phase was separated then washed with water (3x 20 mL). The brown residue was purified by short pass vacuum distillation (96 °C at 28 mm Hg) giving 2.27 g silyl enolate **206** in 53% yield.
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.35 (1H, sext, *J* = 7.6 Hz, CH*CH*CH_2), 4.67 (1H, dd, *J* = 17.2, 0.9 Hz, *CH*$CHCH_2$), 4.42 (1H, dd, *J* = 10.4, 0.9 Hz, *Ha*), 4.30 (1H, d, *J* = 10.4 Hz, *Hb*), 3.39 (3H, s, OCH_3), 0.77 (9H, s, SiC(*C*H_3)$_3$), 0.00 (6H, s, Si(*C*H_3)$_2$).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.6 (*C*OCH_3), 135.3 (CH*C*HCH_2), 107.6 ($CHCHCH_2$), 80.2 (*C*$HCHCH_2$), 57.3 (OCH_3), 24.9 (C(*C*H_3)$_3$), 19.3 (*C*(CH_3)$_3$), -1.9 (Si(*C*H_3)$_2$).

1-Methoxy-1,3-dihydro-*iso*benzofuran, 230.[159]



To a -78 °C solution of phthalide **237** (10.0 g, 74.7 mmol) in anhydrous dichloromethane (370 mL) was added slowly di*iso*butylaluminium hydride (78.4 mL, 78.4 mmol, 1 M in hexanes) and stirred until completion by TLC analysis (4 h). The reaction was warmed to 0 °C, diluted with diethyl ether (200 mL) and quenched by the successive addition of water (3.1 mL), 15% aq sodium hydroxide (3.1 mL) and water (7.8 mL). The resultant slurry was stirred for 30 minutes, sodium sulfate was added and the resulting slurry stirred for a further 30 minutes. The solids were removed by filtration and the solution evaporated under vacuum.

The crude residue was dissolved in anhydrous tetrahydrofuran (170 mL) and was cannulated to a solution of sodium hydride (3.75 g, 93.4 mmol) in tetrahydrofuran (200 mL) at 0 °C and stirred for an hour. Methyl iodide (filtered through basic alumina previously) was added (23.3 mL, 375 mmol) to reaction mixture and stirred for a further 4 hours. Once complete according to TLC analysis, water (50 mL) was added to quench and diluted with diethyl ether (100 mL). Combined organic extracts were washed with water (2x 50 mL), brine (50 mL) and dried over sodium sulfate. Purification by flash column chromatography (20% elution with diethyl ether and petroleum spirits) gave 8.83 g (78%) of methyl acetal **230** as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.26 (4H, m, Ar-*H*), 6.19 (1H, d, *J* = 2.2 Hz, *CH*), 5.22 (1H, d, *J* = 12.8 Hz, CH_2O), 5.08 (1H, d, *J* = 12.8 Hz, CH_2O), 3.44 (3H, s, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.9 (Ar-*C*), 137.3 (Ar-*C*), 129.2 (Ar-*C*), 127.7 (Ar-*C*), 122.9 (Ar-*C*), 121.0 (Ar-*C*), 107.6 (*C*H), 72.2 (CH_2), 54.3 (OCH_3).

m/*z* [CI^+ (+ve), *iso*butane] 151.1 $[M+H]^+$ (100%). HRMS found 151.0756, $C_9H_{11}O_2$ requires 151.0760 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}: 3049, 2859, 1615, 1192.

General procedure for the preparation of lactones 243, 247 to 255.

A 0 °C solution of methyl acetal **230** in anhydrous tetrahydrofuran at was treated with di*iso*propylamine and stirred for 10 minutes. Methyl lithium solution (1.6 M

in diethyl ether) was added slowly and the reaction stirred for 30 minutes. The reaction mixture was cooled to -78 ^{o}C and the freshly distilled aldehyde was added. The resulting solution was then stirred for a further 2 hours at -78 ^{o}C before being quenched with water at 0 ^{o}C. The mixture was extracted with diethyl ether and the combined organic extracts were then washed with water, saturated sodium chloride solution and dried over sodium sulfate. Solvent removal under reduced pressure then afforded the desired α-hydroxy *iso*benzofuran intermediate which was used in the next step without further purification.

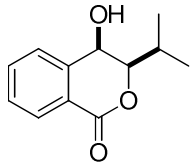
The crude α-hydroxy *iso*benzofuran unit was then dissolved in anhydrous dichloromethane and cooled to 0 ^{o}C. The solution was then treated with 3-chloroperoxybenzoic acid and the resulting mixture stirred at 0 ^{o}C until completion. The reaction was quenched with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude residual lactol was taken on crude without the need of further purification. The newly prepared lactol was dissolved in acetone and treated with freshly made 2.5 M Jones reagent. The resulting red/brown solution was then stirred for 2 hours or until complete consumption of starting material (as by TLC analysis on alumina plates). The reaction was quenched with water and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed sequentially with water (3*x*), saturated sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude keto-lactones obtained could then be taken on crude to the next step.

General procedure for the reduction of lactones to isochroman-1-ones (244, 256-264).

The freshly obtained crude lactones (**243, 247 to 255**) were dissolved in anhydrous dichloromethane and cooled to -78 ^{o}C. The mixture was treated with a solution of cerium (III) chloride in anhydrous methanol (0.4 M in methanol, 2 equivalents) and the resulting suspension was stirred for 10 minutes followed by addition of 1.5 equivalents sodium borohydride and stirred until completion as indicated by TLC analysis. The reaction solution was warmed to room temperature, diluted with dichloromethane and quenched with 10% aqueous

citric acid solution (10 mL). The biphasic mixture was stirred for 20 minutes and the aqueous phase was extracted into dichloromethane and washed sequentially with water (2*x*) and brine. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude residues were purified by flash column chromatography (silica gel).

4-Hydroxy-3-*iso*propylisochroman-1-one, 244.



Keto-lactone **243** was prepared using the general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.01 g, 6.73 mmol) in tetrahydrofuran (34 mL) and di*iso*propylamine (189 µL, 1.35 mmol); methyl lithium (9.25 mL, 14.8 mmol); *iso*butyraldehyde (733 µL, 8.08 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.81 g, 8.08 mmol); in dichloromethane (34 mL). Oxidation was achieved on a solution of crude lactol (1.31 g, 6.36 mmol); in acetone (32 mL) using 2.5 M Jones (5.08 mL, 12.7 mmol) to afford 1.16 g of the desired keto-lactone **243** (85%) without further purification.

Isochroman-1-one, **244** was prepared using the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone 18 (200 mg, 0.98 mmol) in dichloromethane (5 mL) and using cerium(III) chloride (4.90 mL, 1.96 mmol, 0.4 M in methanol) and sodium borohydride (56 mg, 1.47 mmol). Purification by flash column chromatography (silica gel, diethyl ether in dichloromethane in petroleum spirits 30:20:70) afforded 194 mg of the desired isochromanone **244** (96%) as a clear oil and as a sole *syn* diastereoisomer.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.11 (1H, dd, *J* = 8.0, 0.8 Hz, Ar-*H*), 7.65 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.51 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.45 (1H, dm, *J* = 7.6 Hz, Ar-*H*), 4.74 (1H, dd, *J* = 7.6, 1.6 Hz, *CH*OH), 3.99 (1H, dd, *J* = 9.6, 1.6 Hz, CH*CH*), 2.39-2.30 (1H, m, *CH*(CH_3)$_2$), 2.18 (1H, d, *J* = 7.2 Hz, OH), 1.19 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$), 1.09 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

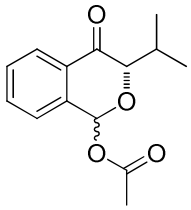
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.1 (*C*O_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.4 (Ar-*C*), 129.9 (Ar-*C*), 128.1 (Ar-*C*), 124.3 (Ar-*C*), 86.6 (*C*HOH), 65.2 (CH*C*H), 28.7

(*C*H(CH$_3$)$_2$), 19.4 (CH(*C*H$_3$)$_2$), 18.2 (CH(*C*H$_3$)$_2$).

m/*z*: [CI$^+$ *Iso*butane]: 207 [M+H]$^+$ (100%), 189 [M+H-H$_2$O]$^+$ (35%). HRMS found 207.1018 $C_{12}H_{15}O_3$ requires 207.1022 [M+H]$^+$.

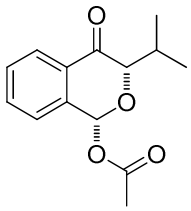
υ_{max} (neat)/cm^{-1}; 3446, 2852, 1699, 1558, 1267.

3-*Iso*propyl-1-oxoisochroman-4-yl acetate, 245 and 246.



Lactol **242** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.07 g, 7.10 mmol) in tetrahydrofuran (35 mL) and di*iso*propylamine (199 µL, 1.42 mmol); methyl lithium (9.7 mL, 15.6 mmol); *iso*butyraldehyde (773 µL, 8.52 mmol). The rearrangement was performed using 3-chloroperoxybenzoic acid (1.91 g, 8.52 mmol); in dichloromethane (35 mL). A portion of the previously crude lactols (279 mg, 1.36 mmol) were dissolved in anhydrous dichloromethane (7 mL) and cooled to 0 ^{o}C. The 0 ^{o}C solution was treated with triethylamine (284 µL, 2.03 mmol) and *N, N'*-dimethylaminopyridine (17 mg, 136 µmmol) and stirred for 30 minutes. Acetic anhydride (192 µL, 2.03 mmol) was then added to the reaction and the resulting mixture stirred until completion by as indicated by TLC analysis (2 h). The reaction was quenched with saturated sodium carbonate (5 mL) and diluted with dichloromethane (5 mL). The organic phase was washed with water (2 x 5 mL) and brine (5 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (silica gel, 20% diethyl ether in petroleum spirits) gave 65 mg (19%) of the desired acetates **245** and **246** as a 4.6:1 (α:β) mixture of anomers.

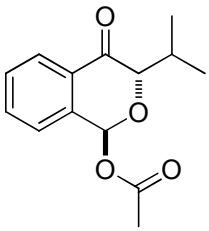
Acetic acid (1*R*,3*R*)-3-*iso*propyl-4-oxo-isochroman-1-yl ester, 246.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02 (1H, dd, *J* = 8.0, 1.6 Hz, Ar-*H*), 7.63 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.53 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.40 (1H, d, *J* = 6.8 Hz, Ar-*H*), 7.13 (1H, s, *CH*OAc), 4.54 (1H, d, *J* = 2.8 Hz, CO*CH*), 2.61-2.52 (1H, m, (*CH*(CH_3)$_2$), 2.09 (3H, s, CO*CH$_3$*), 1.08 (3H, d, *J* = 6.8 Hz, (CH(*CH$_3$*)$_2$)), 0.88 (3H, d, *J* = 6.8 Hz, (CH(*CH$_3$*)$_2$)).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.1 (*C*O), 169.6 (*C*OCH_3), 137.9 (Ar-*C*), 134.4 (Ar-*C*), 129.9 (Ar-*C*), 129.4 (Ar-*C*), 126.3 (Ar-*C*), 126.1 (Ar-*C*), 90.5 (*C*HOCO), 79.8 (*C*HO), 30.2 (*C*H(CH_3)$_2$), 21.1 (CO*C*H_3), 19.1 (CH(*C*H_3)$_2$), 16.1 (CH(*C*H_3)$_2$).

Acetic acid (1*S*,3*R*)-3-*iso*propyl-4-oxo-isochroman-1-yl ester, 245.



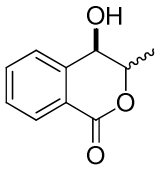
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01 (1H, m, Ar-*H*), 7.64 (1H, td, *J* = 7.6, 1.6 Hz, Ar-*H*), 7.52 (1H, m, Ar-*H*), 7.35 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.04 (1H, s, *CH*OAc), 4.14 (1H, d, *J* = 5.2 Hz, CO*CH*), 2.51-2.48 (1H, m, (*CH*(CH_3)$_2$), 2.24 (3H, s, CO*CH$_3$*), 1.05 (3H, d, *J* = 7.2 Hz, (CH(*CH$_3$*)$_2$)), 0.99 (3H, d, *J* = 6.8 Hz, (CH(*CH$_3$*)$_2$)).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 198.2 (*C*O), 169.6 (*C*OCH_3), 139.1 (Ar-*C*), 134.4 (Ar-*C*), 129.9 (Ar-*C*), 129.5 (Ar-*C*), 126.5 (Ar-*C*), 124.8 (Ar-*C*), 90.2 (*C*HOCO), 84.8 (*C*HO), 29.6 (*C*H(CH_3)$_2$), 21.2 (CO*C*H_3), 19.0 (CH(*C*H_3)$_2$), 17.6 (CH(*C*H_3)$_2$).

m/z [CI^+ (+ve), *iso*butane] 189 $[M+H\text{-}OAc]^+$ (100%).

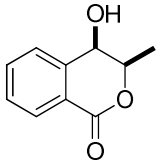
υ_{max} (neat)/cm^{-1}; 3442, 2925, 1699, 1558, 1287.

4-Hydroxy-3-methylisochroman-1-one, 256.



Keto-lactone **247** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.03 g, 6.92 mmol) in tetrahydrofuran (35 mL) and di*iso*propylamine (194 µL, 1.38 mmol); methyl lithium (9.5 mL, 15.2 mmol) and acetaldehyde (1.02 g, 8.28 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.86 g, 8.30 mmol); in dichloromethane (35 mL). Oxidation was achieved on a solution of crude lactol (1.20 g, 6.74 mmol); in acetone (34 mL) using 2.5 M Jones (5.39 mL, 13.5 mmol) to generate 1.16 g of the desired keto-lactone **247** (94%) without further purification. Isochromanone, **256** was prepared using the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **247** (1.16 g, 6.58 mmol) in dichloromethane (33 mL) and using cerium(III) chloride (32.9 mL, 13.16 mmol, 0.4 M in methanol) and sodium borohydride (373 mg, 9.87 mmol). Purification was achieved by flash column chromatography (silica gel, 20 % ethyl acetate in petroleum spirits) to afford 1.05 g of isochromanone **256** (90%) as a clear oil and as 1:1 mixture of diastereoisomers.

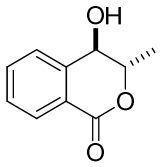
4-Hydroxy-(3*R*,4*R*)-3-methyl-isochroman-1-one, 256*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, dd, *J* = 7.8, 1.2 Hz, Ar-*H*), 7.59 (1H, td, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.47 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.42 (1H, dd, *J* = 7.4, 1.2 Hz, Ar-*H*), 4.64-4.59 (1H, m, *CH*OH), 4.54 (1H, dd, *J* = 7.2, 1.9 Hz, CH*CH*), 1.99 (1H, d, *J* = 7.3 Hz, OH), 1.51 (3H, d, *J* = 6.6 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 164.4 (CO_2CH), 141.3 (Ar-*C*), 134.4 (Ar-*C*), 130.3 (Ar-*C*), 128.9 (Ar-*C*), 125.2 (Ar-*C*), 123.6 (Ar-*C*), 79.1 (*C*HOH), 69.5 (CH*C*H), 18.1 (CH*C*H_3).

4-Hydroxy-(3*R*,4*S*)-3-methyl-isochroman-1-one, 256*anti*.

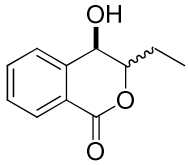


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01 (1H, dd, *J* = 7.8 Hz, Ar-*H*), 7.60 (1H, td, *J* = 7.4, 1.2 Hz, Ar-*H*), 7.54 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.44-7.39 (1H, m, Ar-*H*), 4.63 (1H, t, 7.6 Hz, *CH*OH), 4.49-4.43 (1H, m, CH*CH*), 2.48 (1H, d, *J* = 7.3 Hz, OH), 1.57 (3H, d, *J* = 6.8 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 164.9 (*C*O_2CH), 141.3 (Ar-*C*), 134.5 (Ar-*C*), 130.3 (Ar-*C*), 128.9 (Ar-*C*), 125.3 (Ar-*C*), 123.6 (Ar-*C*), 79.2 (*C*HOH), 67.5 (CH*C*H), 18.1(CH*C*H_3).

υ_{max} (neat)/cm^{-1}; 3440, 2849, 1652, 1286.

3-Ethyl-4-hydroxyisochroman-1-one, 257.

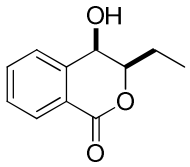


Keto-lactone **248** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.00 g, 6.66 mmol) in tetrahydrofuran (35 mL) and di*iso*propylamine (137 µL, 1.33 mmol); methyl lithium (9.2 mL, 14.66 mmol) and propionaldehyde (577 µL, 8.00 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.79 g, 8.00 mmol); in dichloromethane (35 mL). Oxidation was achieved on a solution of crude lactol (1.12 g, 5.83 mmol); in acetone (29 mL) using 2.5 M Jones (4.66 mL, 11.7 mmol) to generate 1.08 g of the desired keto-lactone **248** (84%) without further purification.

Isochroman-1-one, **257** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **248** (1.08 g, 5.66 mmol) in dichloromethane (28 mL) and using cerium(III) chloride (28.3 mL, 11.3 mmol, 0.4 M in methanol) and sodium borohydride (321 mg, 8.49 mmol).

Purification by flash column chromatography (silica gel, 30 % ethyl acetate in petroleum spirits) afforded 771 mg of isochromanone **257** (71%) as a non-separable mixture of diastereoisomers in a 60:40 ratio (*syn:anti*).

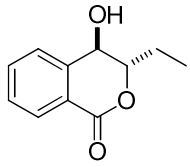
3-Ethyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 257*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.11-8.09 (1H, m, Ar-*H*), 7.64 (1H, td, *J* = 7.5, 1.3 Hz, Ar-*H*), 7.52 (1H, dt, *J* = 7.6, 1.3 Hz, Ar-*H*), 7.47 (1H, dm, Ar-*H*), 4.65 (1H, d, *J* = 1.0 Hz, *CH*OH), 4.39-1.35 (1H, m, CH*CH*), 2.22 (1H, bs, OH), 2.09-1.99 (1H, m, CH_2), 1.98-1.89 (1H, m, CH_2), 1.12 (3H, t, *J* = 7.5 Hz, CH_2CH_3).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 165.0 (CO_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.4 (Ar-*C*), 129.9 (Ar-*C*), 127.9 (Ar-*C*), 124.4 (Ar-*C*), 82.6 (*C*HOH), 66.2 (CH*C*H), 23.5 (CH_2CH_3), 9.7 (CH_2CH_3).

3-Ethyl-(3*R*,4*S*)-4-hydroxy-isochroman-1-one, 257*anti*.



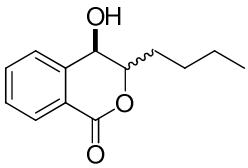
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.63-7.58 (1H, m, Ar-*H*), 7.52-7.45 (1H, m, Ar-*H*), 7.41 (1H, m, Ar-*H*), 5.38 (1H, d, *J* = 5.2 Hz, *CH*OH), 4.39-4.35 (1H, m, CH*CH*), 2.22 (1H, bs, OH), 2.09-1.99 (1H, m, CH_2), 1.98-1.88 (1H, m, CH_2), 1.05 (3H, t, *J* = 7.4 Hz, CH_2CH_3).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 165.0 (CO_2CH), 140.3 (Ar-*C*), 134.0 (Ar-*C*), 129.4 (Ar-*C*), 125.8 (Ar-*C*), 123.2 (Ar-*C*), 122.4 (Ar-*C*), 82.6 (*C*HOH), 74.2 (CH*C*H), 25.6 (CH_2CH_3), 9.9 (CH_2CH_3).

m/z [CI^+ (+ve), *iso*butane] 193 $[M+H]^+$ (100%), HRMS found 193.0863, $C_{12}H_{13}O_3$ requires 193.0865 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3433, 2975, 1697, 1607, 1275.

3-Butyl-4-hydroxyisochroman-1-one, 258.



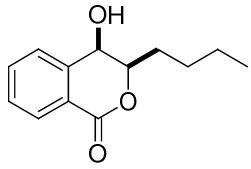
Keto-lactone **249** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (930 mg, 6.18 mmol) in

tetrahydrofuran (31 mL) and di*iso*propylamine (173 µL, 1.24 mmol); methyl lithium (8.5 mL, 13.6 mmol) and valeraldehyde (788 µL, 7.41 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.66 g, 7.41 mmol); in dichloromethane (31 mL). Oxidation was achieved on a solution of crude lactol (1.31 g, 6.82 mmol); in acetone (34 mL) using 2.5 M Jones (5.46 mL, 13.6 mmol) to generate the 1.10 g of the desired keto-lactone **249** (82%) without further purification.

Isochroman-1-one, **258** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **249** (973 mg, 5.12 mmol) in dichloromethane (26 mL) and using cerium(III) chloride (25.6 mL, 10.2 mmol, 0.4 M in methanol) and sodium borohydride (290 mg, 7.68 mmol).

Purification by flash column chromatography (silica gel, 40 % diethyl ether in petroleum spirits) yielded 630 mg of isochromanone **258** (56%) as a yellow solid and as a 9:1 mixture of diastereoisomers (*syn:anti*).

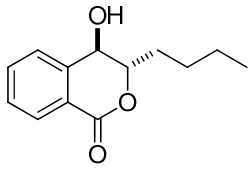
3-Butyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 258*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06 (1H, dt, *J* = 7.8, 1.8 Hz, Ar-*H*), 7.58 (1H, td, *J* = 7.5, 1.4 Hz, Ar-*H*), 7.46 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.40 (1H, dd, *J* = 7.5, 0.5 Hz, Ar-*H*), 4.57 (1H, d, *J* = 1.8 Hz, *CH*OH), 4.42-4.38 (1H, m, CH*CH*), 2.03 (1H, bs, OH), 1.99-1.91 (1H, m, $CH_2CH_2CH_2CH_3$), 1.86-1.76 (1H, m, $CH_2CH_2CH_2CH_3$), 1.56-1.49 (1H, m, $CH_2CH_2CH_2CH_3$), 1.43-1.32 (3H, m, $CH_2CH_2CH_2CH_3$), 0.98 (3H, t, *J* = 7.2 Hz, $CH_2CH_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 164.9 (CO_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.5 (Ar-*C*), 129.9 (Ar-*C*), 127.9 (Ar-*C*), 124.2 (Ar-*C*), 81.2 (*C*HOH), 66.6 (CH*C*H), 30.1 ($CH_2CH_2CH_2CH_3$), 27.2 ($CH_2CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_2CH_3$).

3-Butyl-(3*R*,4*S*)-4-hydroxy-isochroman-1-one, 258*anti*.



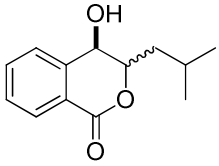
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02 (1H, dd, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.58 (1H, td, *J* = 7.5, 1.4 Hz, Ar-*H*), 7.46 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.40 (1H, dd, *J* = 7.5, 0.5 Hz, Ar-*H*), 4.67 (1H, d, *J* = 7.5 Hz, *CH*OH), 4.37-4.32 (1H, m, CH*CH*), 2.03 (1H, bs, OH), 1.99-1.91 (1H, m, $CH_2CH_2CH_2CH_3$), 1.86-1.76 (1H, m, $CH_2CH_2CH_2CH_3$), 1.70-1.62 (1H, m, $CH_2CH_2CH_2CH_3$), 1.66-1.58 (3H, m, $CH_2CH_2CH_2CH_3$), 0.85 (3H, t, *J* = 7.2 Hz, $CH_2CH_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 164.9 (CO_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.5 (Ar-*C*), 129.9 (Ar-*C*), 127.9 (Ar-*C*), 124.2 (Ar-*C*), 82.9 (*C*HOH), 68.1 (CH*C*H), 31.9 ($CH_2CH_2CH_2CH_3$), 27.0 ($CH_2CH_2CH_2CH_3$), 22.7 ($CH_2CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_2CH_3$).

m/z: [CI$^+$ *Iso*butane]: 221.1 [M+H]$^+$ (100%), HRMS found 221.1180 $C_{13}H_{17}O_3$ requires 221.1178 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}; 3420, 2972, 1685, 1279.

4-Hydroxy-3-*iso*butylisochroman-1-one, 259.



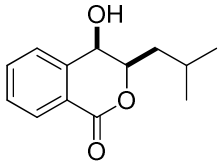
Keto-lactone **250** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.01 g, 6.71 mmol) in tetrahydrofuran (33 mL) and di*iso*propylamine (188 µL, 1.34 mmol); methyl lithium (9.2 mL, 14.8 mmol) and *iso*valeraldehyde (863 µL, 8.05 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.80 g, 8.05 mmol); in dichloromethane (33 mL). Oxidation was achieved on a solution of crude lactol (1.42 g, 6.45 mmol); in acetone (33 mL) using 2.5 M Jones (5.16 mL, 12.9 mmol) to generate 1.06 g of the desired keto-lactone **250** (72%) without further purification.

Isochroman-1-one, **259** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **250** (1.06 g, 4.88 mmol) in dichloromethane (26 mL) and using

cerium(III) chloride (24.4 mL, 9.75 mmol, 0.4 M in methanol) and sodium borohydride (277 mg, 7.31 mmol).

Purification by flash column chromatography (silica gel, 40% diethyl ether in petroleum spirits) gave 848 mg of isochromanone **259** (80%) as a clear oil and as a 75:25 mixture of diastereoisomers (*syn*:*anti*).

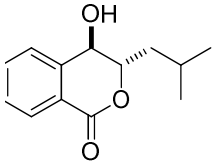
4-Hydroxy-(3*R*,4*R*)-3-*iso*butyl-isochroman-1-one, 259*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (1H, d, *J* = 7.4 Hz, Ar-*H*), 7.58 (1H, dt, *J* = 7.3, 1.1 Hz, Ar-*H*), 7.44-7.40 (2H, m, Ar-*H*), 4.55 (1H, d, *J* = 1.8 Hz, *CH*OH), 4.49 (1H, ddd, *J* = 8.6, 4.6, 1.9 Hz, CH*CH*), 3.54 (1H, bs, OH), 1.94-1.88 (2H, m, CH_2CH), 1.60-1.52 (1H, m, *CH*(CH_3)$_2$), 0.93 (6H, t, *m*, CH*(CH$_3$)$_2$*).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 165.2 (CO_2CH), 141.4 (Ar-*C*), 134.3 (Ar-*C*), 130.3 (Ar-*C*), 128.8 (Ar-*C*), 128.8 (Ar-*C*), 125.8 (Ar-*C*), 81.3 (*C*HOH), 66.9 (CH*C*H), 39.1 (CH_2CH), 23.9 (*C*H(CH_3)$_2$), 23.1 (CH(*CH$_3$*)$_2$), 21.5 (CH(*CH$_3$*)$_2$).

4-Hydroxy-(3*R*,4*S*)-3-*iso*butyl-isochroman-1-one, 259*anti*.



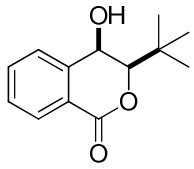
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.81-7.78 (1H, m, Ar-*H*), 7.58 (1H, td, *J* = 7.3, 1.1 Hz, Ar-*H*), 7.44-7.40 (2H, m, Ar-*H*), 4.49 (1H, d, *J* = 7.3 Hz, *CH*OH), 4.47 (1H, dd, *J* = 13.3, 7.2 Hz, CH*CH*), 3.54 (1H, bs, OH), 1.85-1.79 (2H, m, CH_2CH), 1.60-1.52 (1H, m, *CH*(CH_3)$_2$), 0.90-0.84 (1H, m, CH_2CH), 0.93 (6H, m, CH(*CH$_3$*)$_2$).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 165.3 (CO_2CH), 140.4 (Ar-*C*), 134.3 (Ar-*C*), 130.1 (Ar-*C*), 129.7 (Ar-*C*), 124.1 (Ar-*C*), 123.7 (Ar-*C*), 79.6 (CH*C*H), 68.3 (*C*HOH), 41.0 (CH_2CH) 24.1 (*C*H(CH_3)$_2$), 23.1 (CH(*CH$_3$*)$_2$), 22.2 (CH(*CH$_3$*)$_2$).

m/*z* [CI^+ (+ve), *iso*butane] 221 $[M+H]^+$ (100%), HRMS found 221.1176, $C_{13}H_{17}O_3$ requires 221.1178 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3442, 2925, 1699, 1558, 1287.

3-*tert*Butyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 260.



Keto-lactone **251** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.09 g, 7.24 mmol) in tetrahydrofuran (36 mL) and di*iso*propylamine (203 µL, 1.45 mmol); methyl lithium (9.9 mL, 15.9 mmol) and trimethylacetaldehyde (940 µL, 8.68 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.95 g, 8.68 mmol); in dichloromethane (36 mL). Oxidation was achieved on a solution of crude lactol (1.32 g, 6.00 mmol) in acetone (30 mL) using 2.5 M Jones (4.79 mL, 11.9 mmol) to give 1.31 g (83%) of the unstable keto-lactone **251** after filtration through a short plug of silica gel. The keto-lactone was used immediately.

Isochroman-1-one, **260** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **251** (220 mg, 1.01 mmol) in dichloromethane (5 mL) and using cerium(III) chloride (5.05 mL, 2.02 mmol, 0.4 M in methanol) and sodium borohydride (172 mg, 4.55 mmol).

Purification by flash column chromatography (silica gel, 20% diethyl ether in 10% dichloromethane in petroleum spirits) yielded 171 mg of isochromanone **260** (77%) as a clear oil and as a single *syn* diastereoisomer.

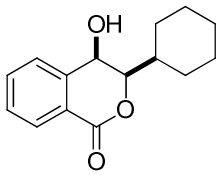
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.10 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.65 (1H, dt, *J* = 7.2, 1.2 Hz, Ar-*H*), 7.52 (1H, dt, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.45 (1H, d, *J* = 7.6 Hz, Ar-*H*), 4.87 (1H, d, *J* = 1.2 Hz, *CH*OH), 4.06 (1H, d, *J* = 1.6 Hz, CH*CH*), 1.93 (1H, bs, OH), 1.21 (9H, s, C(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.6 (*C*O_2CH), 141.0 (Ar-*C*), 134.4 (Ar-*C*), 130.4 (Ar-*C*), 129.8 (Ar-*C*), 127.5 (Ar-*C*), 124.1 (Ar-*C*), 87.2 (*C*HOH), 66.4 (CH*C*H), 34.6 (*C*(CH_3)$_3$), 26.6 (C(*C*H_3)$_3$)

m/z [CI$^+$ (+ve), *iso*butane] 221.3 [M]$^+$ (100%), HRMS found 221.1176, $C_{13}H_{16}NO_3$ requires 221.1178 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}; 3424, 2960, 1700, 1606, 1282.

3-Cyclohexyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 261.



Keto-lactone **252** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.00 g, 6.66 mmol) in tetrahydrofuran (34 mL) and di*iso*propylamine (187 µL, 1.33 mmol); methyl lithium (9.2 mL, 14.8 mmol) and cyclohexanecarboxaldehyde (1.01 mL, 8.07 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.81 g, 8.07 mmol); in dichloromethane (34 mL). Oxidation was achieved on a solution of crude lactol (1.52 g, 6.18 mmol) in acetone (31 mL) using 2.5 M Jones (4.94 mL, 12.4 mmol) to give 927 mg (57%) of the unstable keto-lactone **252** after filtration through a short plug of silica gel. The keto-lactone was used immediately.

Isochroman-1-one, **261** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **252** (410 mg, 1.68mmol) in dichloromethane (8 mL) and using cerium(III) chloride (8.40 mL, 3.36 mmol, 0.4 M in methanol) and sodium borohydride (95 mg, 2.52 mmol).

Purification by flash column chromatography (silica gel, 30% ethyl acetate in petroleum spirits) afforded 339 mg of isochromanone **261** (82%) as a white crystalline solid and as a sole *syn* diastereoisomer (mp. 163 ^{o}C - 166 ^{o}C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (1H, dt, *J* = 7.7, 0.7 Hz, Ar-*H*), 7.64 (1H, td, *J* = 7.5, 1.4 Hz, Ar-*H*), 7.52 (1H, dt, *J* = 7.6, 1.3 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 7.4, 1.2 Hz, Ar-*H*), 4.69 (1H, d, *J* = 5.3 Hz, *CH*OH), 4.09 (1H, dd, *J* = 9.8, 1.7 Hz, CH*CH*), 2.33 (1H, dm, CycHex-*H*), 2.09-2.03 (1H, m, CycHex-*H*), 1.99-1.94 (1H, dm, CycHex-*H*), 1.84-1.78 (1H, m, CycHex-*H*), 1.75-1.71 (1H, m, CycHex-*H*), 1.59 (1H, bs, OH), 1.45-1.15 (4H, m, CycHex-*H*), 1.13-0.99 (2H, m, CycHex-*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.0 (*C*O_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.5 (Ar-*C*), 129.9 (Ar-*C*), 128.1 (Ar-*C*), 124.5 (Ar-*C*), 85.4 (*C*HOH), 64.8 (CH*C*H), 37.9 (CycHex-*H*), 29.5 (CycHex-*H*), 28.1 (CycHex-*H*), 26.3 (CycHex-*H*), 25.7 (CycHex-*H*), 25.5 (CycHex-*H*).

m/z [CI^+ (+ve), *iso*butane] 247 $[M+H]^+$ (100%), HRMS found 247.1335, $C_{15}H_{19}O_3$

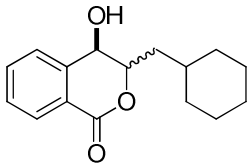
requires 247.1335 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3442, 2925, 1699, 1558, 1287.

Cyclohexylacetaldehyde.

Anhydrous dichloromethane (80 mL) was treated with oxalyl chloride solution (23.4 mL, 46.8 mmol, 2 M in dichloromethane) at -78 ^oC. Dimethylsulfoxide (6.6 mL, 93.6 mmol) was then added to the reaction and the resulting mixture stirred for 1 hour. The reaction was then treated with through the slow addition of a solution of cyclohexyl ethanol (3.26 mL, 23.4 mmol) in anhydrous dichloromethane (40 mL). The reaction was stirred for 1 hour at -78 ^oC, warmed to room temperature and then treated with triethylamine (26.1 mL, 187.2 mmol). The reaction was stirred for a further 1 hour before being quenched at 0^oC through the addition of 1 M hydrochloric acid (20 mL). The resulting biphasic mixture was stirred for 20 minutes and extracted with dichloromethane (50 mL). The combined organic extracts were washed with sat. aq. sodium bicarbonate (20 mL), water (2x 30 mL), brine (30 mL), dried over sodium bicarbonate and concentrated *in vacuo*. The crude residue 2.89 g (98%) was taken on without further purification.

3-(Cyclohexylmethyl)-4-hydroxyisochroman-1-one, 262.



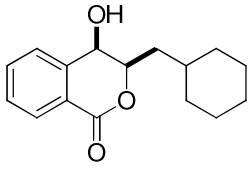
Keto-lactone **253** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.01 g, 6.71 mmol) in tetrahydrofuran (34 mL) and di*iso*propylamine (188 µL, 1.34 mmol); methyl lithium (9.23 mL, 14.8 mmol) and cyclohexyl-acetaldehyde (1.02 g, 8.06 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.81 g, 8.06 mmol); in dichloromethane (34 mL). Oxidation was achieved on a solution of crude lactol (1.52 g, 6.18 mmol) in acetone (30 mL) using 2.5 M Jones (4.86 mL, 12.15 mmol) to generate 1.16 g of the desired keto-lactone **253** (67%) without further purification.

Isochroman-1-one, **262** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **253** (1.06 g, 4.11 mmol) in dichloromethane (20 mL) and using

cerium(III) chloride (20.5 mL, 8.21 mmol, 0.4 M in methanol) and sodium borohydride (233 mg, 6.17 mmol).

Purification was achieved by flash column chromatography (silica gel, 30 % ethyl acetate in petroleum spirits) to afford 615 mg of isochroman-1-one, **262** (58%) as a clear oil and as a 1:1 mixture of diastereoisomers.

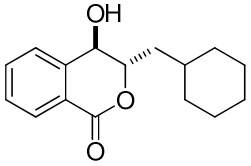
3-Cyclohexylmethyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 262*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.64-7.60 (1H, m, Ar-*H*), 7.51-7.48 (1H, m, Ar-*H*), 7.41 (1H, m, Ar-*H*), 5.31 (1H, d, *J* = 3.6 Hz, *CH*OH), 4.56-4.52 (1H, m, CH*CH*), 2.00 (1H, bs, OH), 1.77-1.53 (8H, m, Alkyl-*H*), 1.23-1.08 (5H, m, Alkyl-*H*).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.5 (*C*O_2CH), 146.9 (Ar-*C*), 134.2 (Ar-*C*), 134.1 (Ar-*C*), 129.5 (Ar-*C*), 125.9 (Ar-*C*), 124.2 (Ar-*C*), 83.7 (*C*HOH), 70.4 (CH*C*H), 39.7 (Alkyl-*C*), 34.3 (Alkyl-*C*), 33.8 (Alkyl-*C*), 32.9 (Alkyl-*C*), 26.5 (Alkyl-*C*), 26.3 (Alkyl-*C*), 26.0 (Alkyl-*C*).

3-Cyclohexylmethyl-(3*R*,4*S*)-4-hydroxy-isochroman-1-one, 262*anti*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06 (1H, dt, *J* = 8.0, 1.6 Hz), 7.58 (1H, dt, *J* = 7.2, 1.2 Hz), 7.46 (1H, dt, *J* = 7.6, 1.2 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 4.56-4.52 (1H, m), 4.05 (1H, bs), 2.00 (1H, bs), 1.77-1.53 (8H, m, CycHex), 1.23-1.08 (5H, m, CycHex).

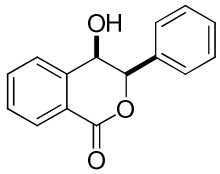
^{13}C NMR ($CDCl_3$, 400 MHz) δ: 165.0 (*C*O_2CH), 140.3 (Ar-*C*), 134.4 (Ar-*C*), 130.5 (Ar-*C*), 129.9 (Ar-*C*), 127.8 (Ar-*C*), 123.0 (Ar-*C*), 84.0 (*C*HOH), 67.2 (CH*C*H), 37.9 (Alkyl-*C*), 33.9 (Alkyl-*C*), 33.1 (Alkyl-*C*), 32.5 (Alkyl-*C*), 32.3 (Alkyl-*C*), 26.4 (Alkyl-*C*), 26.2 (Alkyl-*C*).

m/z [CI^+ (+ve), *iso*butane] 261 $[M+H]^+$ (100%), HRMS found 261.1490, $C_{15}H_{19}O_3$

requires 261.1491 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3446, 2925, 1637, 1286.

4-Hydroxy-(3*R*,4*R*)-3-phenyl-isochroman-1-one, 263.



Keto-lactone **254** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.02 g, 6.82 mmol) in tetrahydrofuran (34 mL) and di*iso*propylamine (191 µL, 1.36 mmol); methyl lithium (9.4 mL, 15.0 mmol) and benzaldehyde (827 µL, 8.18 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.83 g, 8.18 mmol); in dichloromethane (34 mL). Oxidation was achieved on a solution of crude lactol (1.61 g, 6.69 mmol) in acetone (33 mL) using 2.5 M Jones (5.35 mL, 13.4 mmol) to give 1.04 g (64%) of the unstable keto-lactone **254** after filtration through a short plug of silica gel. The keto-lactone was used immediately.

Isochroman-1-one, **263** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **254** (1.05 g, 4.40 mmol) in dichloromethane (22 mL) and using cerium(III) chloride (22.0 mL, 8.80 mmol, 0.4 M in methanol) and sodium borohydride (249 mg, 6.60 mmol).

Purification was achieved by flash column chromatography (silica gel, 20% ethyl acetate in petroleum spirits) to afford 507 mg of isochroman-1-one, **263** (48%) as a yellow solid (m.p. 60.5-63.7 ^oC) and as a single *syn* diastereoisomer.

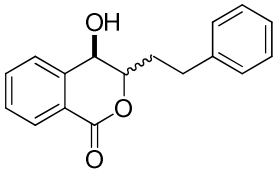
^1H NMR ($CDCl_3$, 400 MHz) δ: 8.05 (1H, dd, *J* = 8.0, 1.2 Hz, Ar-*H*), 7.57 (1H, td, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.56-7.51 (2H, m, Ar-*H*), 7.48-7.35 (5H, m, Ar-*H*), 5.50 (1H, d, *J* = 1.6 Hz, *CH*OH), 4.72 (1H, d, *J* = 1.9 Hz, CH*CH*), 2.55 (1H, bs, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.9 (*C*O_2CH), 139.4 (Ar-*C*), 135.2 (Ar-*C*), 134.5 (Ar-*C*), 130.5 (Ar-*C*), 130.0 (Ar-*C*), 128.8 (Ar-*C*), 128.7 (Ar-*C*), 128.2 (Ar-*C*), 126.6 (Ar-*C*), 124.0 (Ar-*C*), 81.8 (*C*HOH), 68.2 (CH*C*H).

m/z [CI^+ (+ve), *iso*butane] 241.3 $[M+H]^+$ (100%), HRMS found 241.0866, $C_{15}H_{13}O_3$ requires 241.0865 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3430, 3064, 2919, 1708, 1605, 1284.

4-Hydroxy-3-phenethylisochroman-1-one, 264.

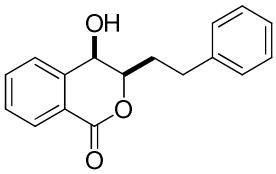


Keto-lactone **255** was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.03 g, 6.84 mmol) in tetrahydrofuran (34 mL) and di*iso*propylamine (192 µL, 1.37 mmol); methyl lithium (9.38 mL, 15.0 mmol); 3-phenylpropanal (1.08 mL, 8.21 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.84 g, 8.21 mmol); in dichloromethane (34 mL). Oxidation was achieved on a solution of crude lactol (1.85 g, 6.53 mmol) in acetone (33 mL) using 2.5 M Jones (5.22 mL, 13.1 mmol) to give 1.69 g (93%) of the unstable keto-lactone **255** after filtration through a short plug of silica gel. The keto-lactone was used immediately.

Isochroman-1-one, **264** was prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactone **255** (248 mg, 0.93 mmol) in dichloromethane (5 mL) and using cerium(III) chloride (4.65 mL, 1.86 mmol, 0.4 M in methanol) and sodium borohydride (53 mg, 1.40 mmol).

Purification of the crude residue by flash column chromatography (silica gel, 20% ethyl acetate in petroleum spirits) gave 225 mg of isochromanone **264** as a white solid in 90% yield and as a 1:1 mixture of diastereoisomers that could be separated by recrystallisation (diethyl ether: petroleum spirits).

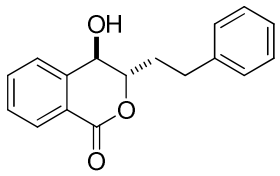
4-Hydroxy-(3*R*,4*R*)-3-phenethyl-isochroman-1-one, 264*syn*.



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06 (1H, dd, *J* = 7.6, 1.2 Hz, Ar-*H*), 7.60-7.55 (1H, m, Ar-*H*), 7.50-7.36 (2H, m, Ar-*H*), 7.24-7.11 (5H, m, Ar-*H*), 4.53 (1H, bs, *CH*OH), 4.35 (1H, ddd, *J* = 9.1, 4.7, 1.9 Hz, CH*CH*), 2.94-2.91 (1H, m, CH_2CH_2Ph), 2.81-2.76 (1H, m, CH_2CH_2Ph), 2.20-2.14 (1H, m, CH_2CH_2Ph), 2.12-1.95 (1H, m, CH_2CH_2Ph), 1.92 (1H, bs, OH).

^{13}C NMR ($CDCl_3$, 400 MHz) δ: 164.8 (*C*O_2CH), 141.5 (Ar-*C*), 140.8 (Ar-*C*), 134.4 (Ar-*C*), 130.5 (Ar-*C*), 129.9 (Ar-*C*), 128.6 (Ar-*C*), 128.5 (Ar-*C*), 127.8 (Ar-*C*), 126.2 (Ar-*C*), 125.2 (Ar-*C*), 79.8 (*C*HOH), 68.1 (CH*C*H), 31.9 (CH_2*C*H_2Ph), 31.0 (*C*$H_2$$CH_2$Ph).

4-Hydroxy-(3*R*,4*S*)-3-phenethyl-isochroman-1-one, 264*anti*.



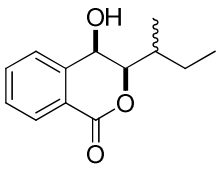
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03 (1H, dd, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.60-7.55 (1H, m, Ar-*H*), 7.50-7.36 (2H, m, Ar-*H*), 7.24-7.11 (5H, m, Ar-*H*), 4.68 (1H, t, *J* = 6.8 Hz, *CH*OH), 4.32-4.27 (1H, ddd, *J* = 9.2, 8.1, 3.1 Hz, CHCH), 2.94-2.91 (1H, m, CH_2*C*H_2Ph), 2.81-2.76 (1H, m, CH_2*C*H_2Ph), 2.20-2.14 (1H, m, *C*$H_2$$CH_2$Ph), 2.12-1.95 (1H, m, *C*$H_2$$CH_2$Ph), 1.92 (1H, bs, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.3 (*C*O_2CH), 140.8 (Ar-*C*), 140.1 (Ar-*C*), 134.4 (Ar-*C*), 130.3 (Ar-*C*), 128.9 (Ar-*C*), 128.6 (Ar-*C*), 128.5 (Ar-*C*), 127.8 (Ar-*C*), 126.2 (Ar-*C*), 125.2 (Ar-*C*), 81.7 (*C*HOH), 66.9 (CH*C*H), 33.6 (CH_2*C*H_2Ph), 30.9 (*C*$H_2$$CH_2$Ph).

m/z [CI$^+$ (+ve), *iso*butane] 269.1 $[M+H]^+$ (100%), HRMS found 269.1180, $C_{17}H_{17}O_3$ requires 269.1178 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3445, 2924, 1698, 1576, 1282..

3-*sec*Butyl-4-hydroxyisochroman-1-one, 276 and 277.

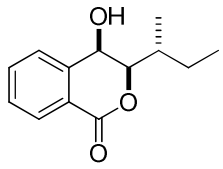


Keto-lactones **274** and **275** were prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.00 g, 6.69 mmol) in tetrahydrofuran (33 mL) and di*iso*propylamine (187 µL, 1.34 mmol); methyl lithium (9.19 mL, 14.7 mmol) and (+/-) 2-methylbutanal (859 µL, 8.03 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.79 g, 8.03 mmol); in dichloromethane (33 mL). Oxidation was achieved on a solution of crude lactol (1.32 g, 6.00 mmol); in acetone (35 mL) using 2.5 M Jones (4.79 mL, 11.9 mmol) to yield 1.39 g of the

desired keto-lactones **274** and **275** (95%) as a 1.6:1.0 mixture of *anti*:*syn* diastereoisomers without further purification. Isochroman-1-ones **276 (*syn*,*anti*)** and **277** (***syn*,*syn***) were prepared using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of keto-lactones **274** and **275** (1.39 g, 6.41 mmol) in dichloromethane (26 mL) and using cerium(III) chloride (32.1 mL, 12.8 mmol, 0.4 M in methanol) and sodium borohydride (363 mg, 9.62 mmol).

Purification was achieved by flash column chromatography (silica gel, 30% ethyl acetate in petroleum spirits) to afford 1.07 g of isochromanones **276** and **277** (76%) as a yellow solid and as a 1.6:1.0 mixture of diastereoisomers (*syn*,*anti*:*syn*,*syn*) that were separable by recrystallisation from diethyl ether: petroleum spirits.

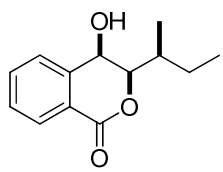
3-(*R*)-*sec*Butyl-(3*R*,4*R*)-4-hydroxy-isochroman-1-one, 276 (*syn*,*anti*).



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.65-7.61 (1H, m, Ar-*H*), 7.65-7.61 (1H, m, Ar-*H*), 7.46 (1H, d, *J* = 7.5 Hz, Ar-*H*), 4.79 (1H, d, *J* = 1.3 Hz, *CH*OH), 4.11 (1H, dd, *J* = 2.0, 1.8 Hz, CH*CH*), 2.37 (1H, bs, OH), 2.21-2.13 (1H, m, *CH*CH_3), 1.80-1.70 (1H, m, *CH*$_2$$CH_3$), 1.37-1.24 (1H, m, *CH*$_2$$CH_3$), 1.16 (3H, d, *J* = 6.6 Hz), 0.98 (3H, t, *J* = 7.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.3 (*C*O_2CH), 140.1 (Ar-*C*), 134.4 (Ar-*C*), 130.3 (Ar-*C*), 129.9 (Ar-*C*), 128.1 (Ar-*C*), 124.3 (Ar-*C*), 85.4 (*C*HOH), 65.2 (CH*C*H), 34.6 (*C*HCH_2), 24.8 (CH*C*H_2), 14.9 (*C*HCH_3), 10.7 (CH_2*C*H_3).

3-(*R*)-*sec*Butyl-(3*S*,4*S*)-4-hydroxy-isochroman-1-one, 277 (*syn*,*syn*).



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.88 (1H, d, *J* = 8.2 Hz, Ar-*H*), 7.71-7.67 (1H, m, Ar-*H*), 7.65-7.61 (1H, m, Ar-*H*), 7.46 (1H, d, *J* = 7.5 Hz, Ar-*H*), 4.74 (1H, d, *J* = 1.3 Hz, *CH*OH), 4.09 (1H, dd, *J* = 2.5, 1.8 Hz, CH*CH*), 2.37 (1H, bs, OH), 2.21-2.13 (1H, m, *CH*CH_3), 1.98-1.90 (1H, m, *CH*$_2$$CH_3$), 1.37-1.24 (1H, m, *CH*$_2$$CH_3$), 1.07

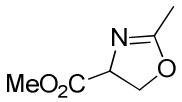
(3H, d, *J* = 6.8 Hz), 0.95 (3H, t, *J* = 7.5 Hz,).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.2 (*C*O_2CH), 140.1 (Ar-*C*), 134.4 (Ar-*C*), 130.3 (Ar-*C*), 129.9 (Ar-*C*), 128.1 (Ar-*C*), 124.3 (Ar-*C*), 84.6 (*C*HOH), 65.2 (CH*C*H), 34.5 (*C*HCH_2), 24.8 (CH*C*H_2), 14.2 (*C*HCH_3), 10.4 (CH_2*C*H_3).

m/z [CI^+ (+ve), *iso*butane] 221 $[M+H]^+$ (100%), HRMS found 221.1179, $C_{13}H_{17}O_3$ requires 221.1179 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3426, 2967, 1696, 1285.

2-Methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester, 279.[173]



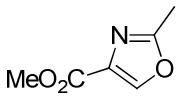
A solution of DL-serine methyl ester **278** (2.00 g, 16.8 mmol) and ethyl acetimidate (2.08 g, 16.8 mmol) in dichloromethane (65 mL) was treated with triethylamine (4.90 mL, 35.2 mmol) (3x 1.63 mL) over 30 minutes. The resulting cloudy solution was then stirred at room temperature until completion by TLC analysis (18 h). The crude reaction was filtered through celite and washed with diethyl ether (3x 100 mL). The organic layer was concentrated *in vacuo* and the crude residue purified by short path distillation (151 ^oC) to give 1.76 g (75%) of 2-methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester **279** as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.71-4.67 (1H, m, CO*CH*), 4.45 (1H, dd, *J* = 8.6, 8.0 Hz, CH*CH*$_2$), 4.37 (1H, dd, *J* = 10.6, 8.8 Hz, CH*CH*$_2$), 3.76 (3H, s, O*CH*$_3$), 1.99 (3H, d, *J* = 1.2 Hz, C*CH*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.7 (*C*O_2CH_3), 167.8 (N*C*CH_3), 69.4 (CO*C*HN), 51.7 (OCH_3), 36.4 (CH_2*C*H_2), 26.5 (*C*H_2CH_2), 13.8 (NC*C*H_3).

υ_{max} (neat)/cm^{-1}; 2955, 1743, 1669, 1438.

2-Methyl-oxazole-4-carboxylic acid methyl ester, 270.[173,174]



Procedure A.

To a suspension of copper (II) bromide (6.86 g, 30.7 mmol) and hexamethylene tetraamine (4.30 g, 30.7 mmol) in anhydrous dichloromethane (65 mL) was added a solution of 2-methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester **279** (1.75 g, 12.29 mmol) in dichloromethane (20 mL). The resulting solution was

stirred at room temperature for 30 minutes to give a brown suspension that was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (4.59 mL, 30.7 mmol) and stirred for 2 hours. The reaction was concentrated *in vacuo* and the crude residue was diluted with ethyl acetate (200 mL). The solution was treated by the slow addition of an ammonium chloride: ammonium hydroxide mixture (1:1) (200 mL). The organic phase was separated and washed again with the ammonium chloride: ammonium hydroxide solution (2x 100 mL), water (50 mL) and brine (50 mL) sequentially. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude residue was purified by flash column chromatography (silica gel, 50% diethyl ether in petroleum ether) to yield 502 mg (28%) of known oxazole **270** as a white solid.

Procedure B.

A 0 ^{o}C solution of 2-methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester **279** (11.5 g, 80.3 mmol) in dichloromethane (250 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (23.9 mL, 160 mmol) and stirred for 10 min. Trichlorobromomethane (8.68 mL, 88 mmol), was then added to the reaction mixture and the resulting solution stirred at 0 ^{o}C for 1 hour. The mixture was then warmed to room temperature and stirred until completion as indicated by TLC analysis (9 h). The solvent was evaporated under reduced pressure and crude residue was purified by flash column chromatography (silica gel, 50% diethyl ether in petroleum ether) to give 6.49 g (55%) of oxazole **270** as a white solid.

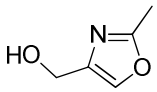
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, s, Ar-*H*), 3.84 (3H, s, (Ar-*H*), 2.45 (3H, s, Ar-*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.4 (*C*O_2CH_3), 161.7 (Ar-*C*), 143.8 (Ar-*C*), 120.2 (Ar-*C*), 52.2 (CO_2*C*H_3), 13.9 (Ar-*C*H_3).

m/z [EI^{+}] 141.07 [M]$^{+}$ (76%), 110.04 [M-CH_3O]$^{+}$ (100%). HRMS found 141.0423, $C_6H_7NO_3$ requires 141.0426 [M]$^{+}$.

υ_{max} (neat)/cm^{-1}; 2923, 1734, 1639, 1440.

(2-Methyloxazol-4-yl)methanol, 280.[173]



To a -78 °C solution of 2-methyl-oxazole-4-carboxylic acid methyl ester **270** (5.44 g, 38.5 mmol) in dichloromethane (200 mL) was added di*iso*butylaluminium hydride (78.9 mL, 78.9 mmol, 1.0 M in dichloromethane) and stirred for 3 hours. The reaction mixture was warmed up to 0 °C then diluted with diethyl ether (100 mL) and treated with the sequential addition of water (3.2 mL), 15% aq sodium hydroxide (3.2 mL) and water (6.3 mL). The resulting suspension was stirred at 0 °C for 30 minutes and then treated with sodium sulfate. The mixture was warmed to room temperature and then stirred for a further 30 minutes. The solids were filtered off and the solvent evaporated *in vacuo*. The crude residue obtained was purified by flash column chromatography (silica gel, 60% ethyl acetate in petroleum spirits) to yield 3.51 g (82%) of 2-methyl-oxazole-4-methanol **280** as a clear oil.

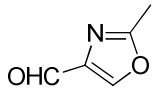
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41 (1H, s, Ar-*H*), 4.8 (2H, s, *C*H_2OH), 3.66 (1H, bs, OH), 2.38 (3H, s, Ar-*C*H_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 162.2 (Ar-*C*), 140.2 (Ar-*C*), 134.8 (Ar-*C*), 56.1 (*C*H_2OH), 13.8 (Ar-*C*H_3).

m/z [CI^+ (+ve) *iso*butane] 114.15 $[M+H]^+$ (100%), 96.14 $[M+H\text{-}H_2O)]^+$ (16%). HRMS found 114.0556, $C_5H_8NO_2$ requires 114.0556 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 3387, 2933, 1648, 1443.

2-Methyl-oxazole-4-carbaldehyde, 281.[173]



A -78 °C solution of oxalyl chloride (0.73 mL, 1.46 mmol) in anhydrous dichloromethane (5 mL) was treated with dimethylsulfoxide (0.21 mL, 2.92 mmol) and stirred for 30 minutes. A solution of 2-methyl-oxazole-4-methanol **280** (110 mg, 1.46 mmol) in dichloromethane (5 mL) was then cannulated slowly into the reaction mixture and the reaction stirred for 1 hour at -78 °C. Triethylamine (0.61 mL, 4.38 mmol) was then added to the reaction, which was allowed to warm to room temperature and stirring continued for a further 2 hours. The reaction was diluted with dichloromethane (5 mL) and quenched

by the addition of 2 M HCl (5 mL). The resulting biphasic mixture was extracted into dichloromethane (5 mL) and the combined organic phases were washed with saturated aqueous sodium sulfate (10 mL), water (2 *x* 10 mL), brine (10 mL) and dried over sodium bicarbonate. Solvent removal *in vacuo* followed by purification of the crude residue by flash column chromatography (silica gel, 30% ethyl acetate in petroleum spirits) yielded 87 mg (81%) of aldehyde **281** as a brown solid (m.p. 65-69 ^{o}C).

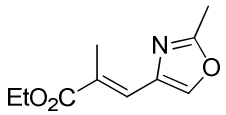
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.90 (1H, s, *CHO*), 8.16 (1H, s, Ar-*H*), 2.54 (3H, s, Ar-*CH_3*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 183.8 (*C*HO), 163.1 (Ar-*C*), 144.5 (Ar-*C*), 140.9 (Ar-*C*), 13.8 (Ar-*C*H_3).

m/z [EI^{+}(+ve)] 111.06 [M]$^{+}$ (100%). HRMS found 111.0318, $C_8H_{11}NO_2$ requires 111.0320 [M]$^{+}$.

υ_{max} (neat)/cm^{-1}; 2983, 1690, 1647, 1444, 1107.

2-Methyl-(*E*)-3-(2-methyl-oxazol-4yl)-acrylic acid ethyl ester, 282.



To a refluxing solution of 2-methyl-oxazole-4-carbaldehyde, **281** (2.31 g, 24 mmol) in toluene (100 mL) was added (carbethoxyethylidene) triphenylphosphorane (17.25 g, 47.6 mmol) in three portions over 30 min. The resulting reaction mixture was refluxed for 3 hours before it was cooled down to room temperature and the solvent evaporated under reduced pressure. The crude residue was then loaded directly onto silica and purified by flash column chromatography (silica gel, 20% ethyl acetate in petroleum spirits) to give 3.15 g (96%) of the desired olefin **282** as a yellow oil and as a single *E* isomer.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (1H, s, Ar-*H*), 7.43 (1H, d, *J* = 0.7 Hz, C*H*CCH_3), 4.24 (2H, q, *J* = 7.1 Hz, *CH_2*CH_3), 2.48 (3H, s, Ar-*CH_3*), 2.20 (3H, d, *J* = 1.2 Hz, C*CH_3*), 1.32 (3H, t, *J* = 7.1 Hz, *CH_2*CH_3).

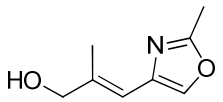
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3 (*C*O_2CH_2), 161.5 (Ar-*C*), 138.9 (Ar-*C*), 137.6 (Ar-*C*), 128.8 (*C*CH_3), 127.3 (*CH*CCH_3), 60.9 (*C*H_2CH_3), 14.5 (Ar-*C*H_3), 14.3 (C*C*H_3), 13.9 (CH_2*C*H_3).

m/z [Cl^{+} (+ve), isobutane] 196.25 [M]$^{+}$ (100%). HRMS found 196.0976, $C_{10}H_{14}NO_3$

requires 196.0974 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}; 2983, 1690, 1647, 1444, 1107

2-Methyl-(*E*)-3-(2-methyl-oxazol-4-yl)-prop-2-en-1-ol, 283.



(*E*)-2-Methyl-3-(2-methyl-oxazol-4yl)-acrylic acid ethyl ester **282** (2.74 g, 14.4 mmol) was dissolved in anhydrous dichloromethane (75 mL) and cooled to -78 °C. The solution was treated with diisobutylaluminium hydride (30.9 mL, 1.0 M soln. in dichloromethane, 30.9 mmol) and stirred at -78 °C for 2 hours. The reaction mixture was warmed up to 0 °C and diluted with diethyl ether (75 mL) before being quenched by the sequential addition of water (1.1 mL), 15% aq sodium hydroxide (1.1 mL) and water (2.7 mL). The resulting cloudy suspension was stirred for 30 minutes, treated with sodium sulfate and then stirred for a further 30 minutes. The resulting suspension was filtered through celite and washed with diethyl ether (3x 50 mL). The combined organic phases were concentrated *in vacuo* and the residual clear oil was purified by flash column chromatography (silica gel, 30% ethyl acetate in petroleum spirits) to yield 2.10 g (98%) of the desired (*E*)-2-methyl-3-(2-methyl-oxazol-4-yl)-prop-2-en-1-ol **283** as a colourless oil.

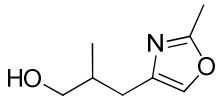
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (1H, s, Ar-*H*), 6.29 (1H, s, *CH*CCH_3), 4.17 (2H, s, *CH_2*OH), 2.46 (3H, s, Ar-*CH_3*), 1.98 (3H, s, C*CH_3*), 1.89 (H, bs, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.9 (Ar-*C*), 139.6 (*C*CH_3), 137.7 (CH*C*CH_3), 135.3 (Ar-*C*), 114.2 (*CH*CCH_3), 68.3 (CH_2OH), 16.1 (Ar-*C*), 13.8 (C*CH_3*).

m/z [EI^+(+ve)] 153.13 $[M]^+$ (100%), 135.12 $[M-H_2O]^+$(90%). HRMS found 153.0793, $C_8H_{11}NO_2$ requires 153.0790 $[M]^+$.

υ_{max} (neat)/cm^{-1}; 3607, 1642, 1442.

2-Methyl-3-(2-methyl-oxazol-4-yl)-propan-1-ol, 284.



Procedure A

A solution of (*E*)-2-methyl-3-(2-methyl-oxazol-4-yl)-prop-2-en-1-ol **283** (142 mg, 0.93 mmol) in methanol (30 mL) was placed in an H-Cube flow hydrogenator over

10% palladium on carbon catalyst, at 40 bar and 35 °C. The reaction was cycled for 3 hours before the hydrogenation was stopped and the solvent evaporated under reduced pressure to yield 140 mg (97%) of the desired 2-methyl-3-(2-methyl-oxazol-4-yl)-propan-1-ol **284** as a colourless oil, which could be used without the need of further purification.

Procedure B

A solution of (*E*)-2-methyl-3-(2-methyl-oxazol-4-yl)-prop-2-en-1-ol **283** (2.05 g, 13.39 mmol) in absolute ethanol (130 mL) was charged with palladium on carbon (10% Pd on activated carbon, 134 mg). The reaction was then placed under a hydrogen atmosphere and stirred until completion as indicated by TLC analysis (2 h). The suspension was filtered through celite and the filtrate concentrated under vacuum. The crude residue was purified via flash column chromatography (silica gel, elution gradient 50% to 70% diethyl ether in petroleum spirits) to give 1.99 g (96%) of the desired 2-methyl-3-(2-Methyl-oxazol-4-yl)-propan-1-ol **284** as a colourless oil.

Procedure C

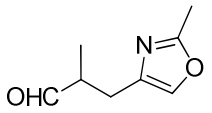
A solution of (*E*)-2-methyl-3-(2-methyl-oxazol-4-yl)-prop-2-en-1-ol **283** (8.93 g, 45.7 mmol) in tetrahydrofuran (280 mL) was cooled to 0 °C and treated with lithium aluminium hydride (18.3 mL, 64 mmol, 3.5 M in tetrahydrofuran) and stirred for 4 hours. The reaction mixture was diluted with diethyl ether (75 mL) before being quenched by the sequential addition of water (2.4 mL), 15% aq sodium hydroxide (3.0 mL) and water (7.3 mL). The resulting cloudy suspension was stirred for 30 minutes, treated with sodium sulfate and then stirred for a further 30 minutes. The resulting suspension was filtered through celite and washed with diethyl ether (3 *x* 50 mL). The combined organic phases were concentrated under vacuo and the residual clear oil was purified by flash column chromatography (silica gel, 30% ethyl acetate in petroleum spirits) to yield 3.63 g (50%) of the desired alcohol 2-methyl-3-(2-Methyl-oxazol-4-yl)-propan-1-ol **284** as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32 (1H, t, *J* = 0.9 Hz, Ar-*H*), 3.59 (1H, dd, *J* = 11.2, 4.9 Hz, *CH*$_2$OH), 3.48 (1H, dd, *J* = 11.7, 6.8 Hz, *CH*$_2$OH), 2.64 (1H, bs, OH), 2.54 (2H, dd, *J* = 6.3, 0.9 Hz, CH*CH*$_2$), 2.46 (3H, s, Ar-*H*), 2.07-1.99 (1H, m, *CH*CH_3), 0.95 (3H, d, *J* = 6.8 Hz, Ar-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.4 (Ar-*C*), 138.4 (Ar-*C*), 134.6 (Ar-*C*), 67.3 (*C*H_2OH), 35.1 (CH_2*C*H), 29.9 (CH*C*H_2), 16.7 (CH*C*H_3), 13.9 (C-*C*H_3). *m/z* [EI^+(+ve)] 155.15 $[M]^+$ (100%), 138.15 $[M\text{-}OH]^+$ (16%). HRMS found 155.0943, $C_8H_{13}NO_2$ requires 155.0946 $[M]^+$.

υ_{max} (neat)/cm^{-1}; 2992, 1638, 1461.

2-Methyl-3-(2-methyl-oxazol-4-yl)-propionaldehyde, 285



Procedure A

A -78 °C solution of oxalyl chloride (17.07 mL, 34.14 mmol) in anhydrous dichloromethane (50 mL) was treated with dimethylsulfoxide (5.27 mL, 68.1 mmol) and stirred for 30 minutes. A solution of 2-methyl-3-(2-methyl-oxazol-4-yl)-propan-1-ol **284** (3.53 g, 22.7 mmol) in dichloromethane (50 mL) was then cannulated slowly into the reaction mixture and the reaction stirred for 1 hour at -78 °C. Triethylamine (14.2 mL, 102.15 mmol) was then added to the reaction and stirring was continued at room temperature for a further 2 hours. The reaction was diluted with dichloromethane (50 mL) and quenched by the addition of 2 M hydrochloric acid solution (50 mL). The resulting biphasic mixture was extracted with dichloromethane (50 mL) and the combined organic phases were washed with saturated aqueous sodium bicarbonate (50 mL), water (2x 50 mL), brine (50 mL) and dried over sodium sulfate. The solvents were removed under educed pressure and the crude residue was purified via flash column chromatography (silica gel, elution 50% diethyl ether in petroleum spirits) to give 1.82 g (52%) of the desired aldehyde **285** as a colourless oil.

Procedure B

A stirred solution of iodoxybenzoic acid (542 mg, 1.94 mmol) in dimethylsulfoxide (5 mL) was treated with a solution of 2-methyl-3-(2-methyl-oxazol-4-yl)-propan-1-ol **284** (201 mg, 1.29 mmol) in dimethylsulfoxide (2 mL) and stirred until completion (3 hours) by TLC analysis. The reaction was diluted with diethyl ether (10 mL) and quenched by the addition of water (5 mL) and extracted into diethyl ether. The combined organic extracts were washed sequentially with water (3 x 10 mL), saturated aqueous sodium bicarbonate

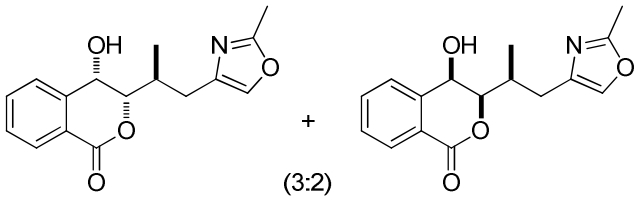
solution (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate and the solvents were removed under reduced pressure. The crude residue obtained was purified via flash column chromatography (silica gel, elution with 50% diethyl ether in petroleum spirits) to give 169 mg (85%) of aldehyde **285** as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.72 (1H, d, *J* = 1.3 Hz, *CHO*), 7.29 (1H, t, *J* = 0.9 Hz, Ar-*H*), 2.90 (1H, ddd, *J* = 14.7, 6.5, 1.0 Hz, CH*CH*$_2$), 2.82-2.73 (1H, m, CHO*CH*), 2.52 (1H, ddd, *J* = 14.7, 7.0, 0.9 Hz, CH*CH*$_2$), 2.41 (3H, s, Ar-*CH*$_3$), 1.12 (3H, d, *J* = 7.1 Hz, CH*CH*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.1 (*C*HO), 161.5 (Ar-*C*), 137.6 (Ar-*C*), 134.7 (Ar-*C*), 45.4 (*C*HCH$_3$), 27.0 (CH_2), 13.9 (Ar-*C*H$_3$), 13.3 (CH*CH*$_3$).

υ_{max} (neat)/cm^{-1}, 2975, 2934, 1719, 1652, 930.

4-Hydroxy-3-((*S*)-1-(2-methyloxazol-4-yl)propan-2-yl)isochroman-1-ones, 289 and 290.

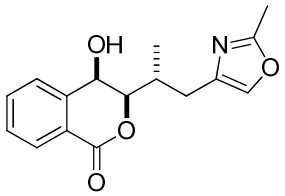


Keto-lactones **287** and **288** were prepared using the general procedure for the preparation of lactones, starting from a solution of acetal **230** (1.36 g, 9.04 mmol) in tetrahydrofuran (45 mL) and di*iso*propylamine (254 µL, 1.81 mmol); methyl lithium (12.4 mL, 19.9 mmol); 2-methyl-3-(2-methyl-oxazol-4-yl)-propionaldehyde, **285** (1.8 g, 11.8 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (2.43 g, 10.9 mmol); in dichloromethane (45 mL). Oxidation was achieved on a solution of crude lactol (2.46 g, 8.28 mmol); in acetone (41 mL) using 2.5 M Jones (6.62 mL, 16.6 mmol) to generate 1.57 g of the desired keto-lactone intermediates **287 (*anti*)** and **288 (*syn*)** (61%) in a 3:2 ratio of diastereoisomers.

Isochroman-1-ones, **289** and **290** were prepared using the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from a solution of the keto-lactones **287** and **288** (1.46 g, 5.08 mmol) in dichloromethane (25 mL) and using cerium(III) chloride (25.4 mL, 10.2 mmol, 0.4 M in methanol) and sodium borohydride (288 mg, 10.2 mmol). Purification was achieved by flash column chromatography (silica gel, 50% ethyl acetate in petroleum spirits) to afford 1.26

g (86%) of the desired isochromanones **289** and **290** as a 3:2 (*syn,anti*:*syn,syn*) mixture of diastereoisomers from which the *(syn,anti)* diastereoisomer could be crystallized out (diethyl ether: petroleum spirits). *It must be noted that extended exposure to silica gel resulted in extensive compound decomposition.*

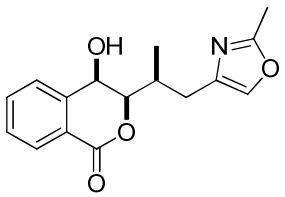
(3*S*,4*S*)-4-Hydroxy-3-[(*S*)-1-methyl-2-(2-methyl-oxazol-4-yl)-ethyl]-isochroman-1-one, 289 (*syn*,*anti*).



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.10 (1H, dd, *J* = 7.3 Hz, Ar-*H*), 7.64 (1H, dt, *J* = 7.5, 1.2 Hz, Ar-*H*), 7.51 (1H, dt, *J* = 7.7, 1.3 Hz, Ar-*H*), 7.48 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.31 (1H, s, Ar-*H*), 4.77 (1H, s, *CH*OH), 4.20 (1H, dd, *J* = 8.9, 1.4 Hz, CH*CH*), 3.83 (1H, bs, OH), 3.16 (1H, dd, *J* = 14.4, 2.9, CH*CH$_2$*), 2.64-2.28 (1H, m, *CH*CH$_3$), 2.48 (1H, dd, *J* = 14.4, 8.7 Hz, CH*CH$_2$*), 2.24 (3H, s, Ar-*CH$_3$*), 1.09 (3H, d, *J* = 6.8 Hz, CH*CH$_3$*).

^{13}C ($CDCl_3$, 100 MHz) δ: 164.8 (*C*O$_2$CH), 161.3 (Ar-*C*), 140.4 (Ar-*C*), 138.4 (Ar-*C*), 134.9 (Ar-*C*), 134.2 (Ar-*C*), 130.4 (Ar-*C*), 129.8 (Ar-*C*), 128.0 (Ar-*C*), 124.5 (Ar-*C*), 84.3 (*C*HOH), 65.5 (CH*C*H), 33.4 (CH*C*H$_2$), 28.2 (*C*HCH$_3$), 15.5 (CH*C*H$_3$), 13.7 (Ar-*C*H$_3$).

(3*R*,4*R*)-4-Hydroxy-3-[(*S*)-1-methyl-2-(2-methyl-oxazol-4-yl)-ethyl]-isochroman-1-one, 290 (*syn*,*syn*).



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.64-7.59 (1H, m, Ar-*H*), 7.50-7.46 (2H, m, Ar-*H*), 7.29 (1H, s, Ar-*H*), 4.98 (1H, m, *CH*OH), 4.13 (1H, dd, *J* = 9.3, 1.2 Hz, CH*CH*), 2.71 (1H, dd, *J* = 14.5, 4.3 Hz, CH*CH$_2$*), 2.56-2.51 (1H, m, *CH*CH$_3$), 2.46 (1H, dd, *J* = 14.4, 7.1 Hz, CH*CH$_2$*), 2.21 (3H, s, Ar-*CH$_3$*), 1.16 (3H, d, *J* = 6.6 Hz, CH*CH$_3$*).

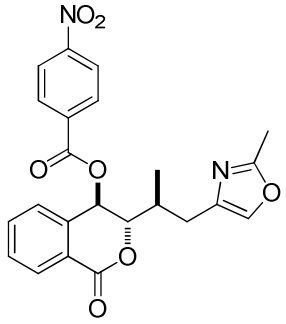
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.1 (*C*O$_2$CH), 161.9 (Ar-*C*), 140.6 (Ar-*C*), 137.7 (Ar-*C*), 134.8 (Ar-*C*), 134.5 (Ar-*C*), 130.1 (Ar-*C*), 129.4 (Ar-*C*), 128.0 (Ar-*C*), 124.6

(Ar-*C*), 84.9 (*C*HOH), 64.6 (CH*C*H), 32.9 (CH*C*H_2), 28.4 (*C*HCH$_3$), 15.4 (CH*C*H$_3$), 13.6 (Ar-*C*H$_3$).

m/*z* [CI$^+$ (+ve), *iso*butane] 288 [M+H]$^+$ (100%). HRMS found 288.1238, $C_{16}H_{18}O_4N$ requires 288.1236 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}; 3423, 2930, 1707, 1605, 1460, 1277, 911.

(3*S*,4*R*)-3-((*S*)-1-(2-methyloxazol-4-yl)propan-2-yl)-1-oxoisochroman-4-yl-4-nitrobenzoate, 290.



A solution of isochroman-1-one **289** in tetrahydrofuran (2 mL) was treated with triphenylphosphine (82 mg, 0.31 mmol) and 4-nitrobenzoic acid (52 mg, 0.31 mmol) and stirred for 10 minutes at room temperature. The resulting solution was treated dropwise with di*iso*propylazodicarboxylate (61 µL, 0.31 mmol) and stirred for a further 12 hours. The solvent were evaporated under reduced pressure and the crude residue purified by flash column chromatography (silica gel, 20% to 60% ethyl acetate in petroleum spirits) to give 53 mg of 4-nitrobenzyl ester **290** (62%) as a clear oil.

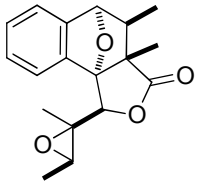
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.24 (2H, d, *J* = 8.8 Hz, Ar-*H*), 8.17 (2H, d, *J* = 9.2 Hz, Ar-*H*), 8.11 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.57 (1H, dt, *J* = 9.6, 2.0 Hz, Ar-*H*), 7.48 (1H, m, Ar-*H*), 7.30 (1H, d, J = 8.0 Hz, Ar-*H*), 7.28 (1H, s, Ar-*H*), 6.41 (1H, d, *J* = 6.4 Hz, *CH*OCO), 4.61 (1H, dd, *J* = 6.8, 4.8 Hz, CH*CH*), 2.67 (1H, dd, *J* = 14.8, 7.2 Hz, CH*C*H_2),2.32 (1H, m, CH*C*H_3), 2.25-2.19 (1H, m, CH*C*H_2), 2.12 (3H, s, Ar-*C*H_3), 0.97 (3H, d, *J* = 6.8 Hz, CH*C*H_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.9 (*C*O_2CH), 163.6 (Ph*C*O_2), 161.7 (Ar-*C*), 150.9 (Ar-*C*), 137.5 (Ar-*C*), 136.3 (Ar-*C*), 135.2 (Ar-*C*), 134.4 (Ar-*C*), 134.3 (Ar-*C*), 131.2 (Ar-*C*), 130.6 (Ar-*C*), 129.9 (Ar-*C*), 126.7 (Ar-*C*), 124.5 (Ar-*C*), 123.8 (Ar-*C*), 82.4 (*C*HOH), 68.1 (CH*C*H), 33.6 (CH*C*H_2), 29.7 (*C*HCH$_3$), 14.4 (CH*C*H$_3$), 13.9 (Ar-*C*H$_3$).

m/*z* [CI$^+$ (+ve), *iso*butane] 437 [M+H]$^+$ (100%). HRMS found 437.1346, $C_{23}H_{21}O_7N_2$ requires 437.1349 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}; 2981, 1726, 1607, 1530, 1266.

4-Ethyl-1-(3-hydroxy-2-methyl-oxiranyl)-3a-propyl-5,9b oxa-3a,4,5,9b-tetrahydro-1*H*-naphtho[1,2-*c*]furan-3-one, 298.



298 was prepared using general procedure for the preparation of lactones, starting from a solution of acetal **230** (876 mg, 5.83 mmol) in tetrahydrofuran (30 mL) and di*iso*propylamine (164 µL, 1.17 mmol); methyl lithium (8.01 mL, 12.8 mmol); tiglic aldehyde (676 µL, 6.99 mmol). The oxidative rearrangement was performed using 3-chloroperoxybenzoic acid (1.57 g, 6.99 mmol); in dichloromethane (30 mL). Oxidation was achieved on a solution of crude lactol (1.28 g, 5.89 mmol); in acetone (30 mL) using 2.5 M Jones (4.71 mL, 11.8 mmol). The crude residues were reacted using general the general procedure for the reduction of lactones to iso-chroman-1-ones, starting from **298** (1.10 g, 5.06 mmol) in dichloromethane (25 mL) and using cerium(III) chloride (25.3 mL, 10.1 mmol, 0.2 M in methanol) and sodium borohydride (287 mg, 7.59 mmol). Purification of the crude residue by flash column chromatography (silica gel, 20% ethyl acetate in petroleum spirits) gave 152 mg of **298** as a yellow solid (m.p. 87-94 ^{o}C) in 8% yield.

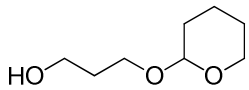
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (1H, m, Ar-*H*), 7.31-7.27 (3H, m, Ar-*H*), 5.14 (1H, d, *J* = 4.6 Hz, Ar*CH*CH), 4.54 (1H, s, *CH*OCO), 3.16 (1H, q, *J* = 5.5 Hz, CH*CH*CH_3), 2.91 (1H, oct, *J* = 3.8 Hz, CH_3*CH*C), 1.59 (3H, s, C*CH_3*), 1.45 (3H, d, *J* = 5.4 Hz, *CH_3*CH), 0.74 (3H, s, epoxide*CH_3*), 0.69 (3H, d, *J* = 7.3 Hz, CHCH*CH_3*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (*C*O2C), 142.9 (Ar-*C*), 139.1 (Ar-*C*), 127.3 (Ar-*C*), 127.2 (Ar-*C*), 122.4 (Ar-*C*), 121.8 (Ar-*C*), 97.5 (C*C*O), 85.8 (Ar*C*O), 82.1 (Ar*C*O), 59.5 (CH*C*CH_3), 57.5 (CH_3*C*HO), 52.5 (O*C*CH), 42.1 (CH*C*HCH$_3$), 16.5 (OC*C*H$_3$), 14.6 (*C*H$_3$CH), 13.7 (COC*C*H$_3$), 11.7 (CH*C*H$_3$).

m/z [CI$^+$ (+ve), (*iso*butane)] 301.3 [M+H]$^+$ (100%), [FAB$^+$ (NOBA)] 301.3 [M+H]$^+$ (100%).

ν_{max} (film)/ cm^{-1}: 2913, 1747, 1571, 1109, 1059.

3-(tetrahydro-2H-pyran-2-yloxy)propan-1-ol, 306.[179]



To a stirred solution of 1,3-propane diol **305** (5.01 g, 65.7 mmol) in tetrahydrofuran (165 mL) at 0 °C was added *para*-toluene sulfonic acid (2.53 g, 13.1 mmol) and stirred for 10 minutes. The resulting opaque solution was treated with dihydropyran (6.1 mL, 67.0 mmol) in 3 portions over 30 minutes. The solution was stirred for 12 hours and then quenched with saturated aqueous sodium hydrogen carbonate solution (10 mL). Diethyl ether (50 mL) was added and the biphasic mixture stirred for 30 minutes. The organic layer was extracted and washed with water (2x 40 mL), dried over saturated sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, elution with 60% diethyl ether in petroleum spirit) yielded 5.82 g (55%) THP ether **306** as a clear oil.

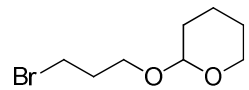
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.58 (1H, bs, O*CH*O), 3.94-3.76 (4H, m, HO*CH*$_2$ & CHO*CH*$_2$), 3.60-3.48 (2H, m, CH_2CH_2CH), 2.77 (1H, bs, OH), 1.87-1.69 (4H, m, *Alkyl-H*), 1.57-1.52 (4H, m, *Alkyl-H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 99.1 (O*C*HO), 66.1 (CH_2CH_2O), 62.6 ($CHOCH_2$), 61.3 ($HOCH_2$), 32.1 ($HOCH_2CH_2$), 30.6 ($CHCH_2CH_2$), 25.3 (CH_2CH_2CHO), 19.7 ($CHCH_2CH_2$).

m/z [CI$^+$ (+ve), *iso*butane] 161.3 $[M+H]^+$ (100%). HRMS found 161.1175, $C_8H_{17}NO_3$ requires 161.1178 $[M+H]^+$.

υ_{max} (neat)/cm^{-1}: 3433, 2943, 1137, 1074

2-(3-bromopropoxy)tetrahydro-2H-pyran, 307.



A solution of 3-(tetrahydro-2H-pyran-2-yloxy)propan-1-ol, **306**.82 g, 36.4 mmol) in dichloromethane (360 mL) was treated with carbon tetrabromide (36.2 g, 109.2 mmol) and triphenylphosphine (28.6 g, 109.2 mmol) and stirred for 3 hours. Once complete by TLC analysis, the solvent was evaporated under reduced pressure and the solids formed were adsorbed directly onto silica. Purification by flash column chromatography (silica gel, 40-50 % dichloromethane in petroleum spirits) gave 2.40 g (29%) of alkylbromide **307**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.61 (1H, t, *J* = Hz, O*CH*O), 3.90-3.84 (2H, m,

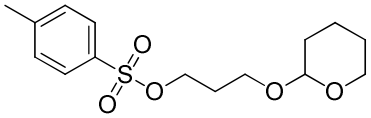
CHO*CH*$_2$), 3.56-3.49 (4H, m, Br*CH*$_2$CH$_2$ & CH$_2$*CH*$_2$O), 2.14 (2H, quint, *J* = 6.2 Hz, CH$_2$*CH*$_2$CH$_2$), 1.83-1.79 (1H, m, CH*CH*$_2$CH$_2$), 1.74-1.69 (1H, m CH*CH*$_2$CH$_2$), 1.59-1.52 (4H, m, *Alkyl-H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 98.9 (O*C*HO), 64.9 (CH$_2$*C*H$_2$O), 62.2 (CHO*C*H$_2$), 32.9 (Br*C*H$_2$), 30.7 (BrCH$_2$*C*H$_2$), 30.6 (CH*C*H$_2$CH$_2$), 25.4 (*C*H$_2$CH$_2$CHO), 19.5 (CHCH$_2$*C*H$_2$).

m/z [CI$^+$ (+ve), *iso*butane] 223.3 [M+H]$^+$ (100%).

υ_{max} (neat)/cm^{-1}: 2861, 1381, 1126, 1201

Toluene-4-sulfonic acid 3-(tetrahydro-pyran-2-yloxy)-propyl ester, 308.[179]



To a stirred solution of 3-(tetrahydro-2H-pyran-2-yloxy)propan-1-ol, **306** (998 mg, 6.23 mmol) in diethyl ether (31 mL) 0 °C was added tosyl chloride (1.3 g, 6.5 mmol) and stirred for 10 minutes. Freshly powdered potassium hydroxide (699 mg, 12.5 mmol) was added in 3 portions over 30 minutes, then stirred for 12 hours. Water (10 mL) and diethyl ether (10 mL) were added to quench and the organic layer separated washed with water (2x 20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (elution with 30% diethyl ether in petroleum spirit) yielded **308** as a clear oil (1.34 g) in 68% yield.

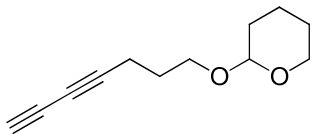
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79 (2H, d, *J* = 8.3 Hz, Ar-*H*), 7.33 (2H, dd, *J* = 8.5, 0.4 Hz, Ar-*H*), 4.46-4.44 (1H, m, O*CH*O), 4.20-4.11 (2H, m, SO*CH*$_2$CH$_2$), 3.78-3.71 (2H, m, CH$_2$CH$_2$*CH*$_2$), 3.48-3.35 (2H, m, O*CH*$_2$CH$_2$), 2.44 (3H, s, Ar-*CH*$_3$), 1.95-1.88 (2H, m, CH*C*H$_2$CH$_2$), 1.63-1.42 (6H, m, *Alkyl-H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.7 (Ar-*C*), 133.2 (Ar-*C*), 129.8 (2x Ar-*C*), 127.9 (2x Ar-*C*), 98.9 (O*C*HO), 67.7 (SO*C*H$_2$CH$_2$), 62.8 (CHO*C*H$_2$), 62.2 (CH$_2$*C*H$_2$O), 30.5 (CH*C*H$_2$CH$_2$), 29.3 (CH$_2$*C*H$_2$CH$_2$), 25.4 (OCH$_2$*C*H$_2$), 21.6 (*C*H$_3$), 19.4(CHCH$_2$*C*H$_2$).

m/z [CI$^+$ (+ve), *iso*butane] 231.3 [M+H-THP]$^+$ (100%), 315.5 [M+H]$^+$ (36%). HRMS found 315.1263, $C_{15}H_{23}O_5S$ requires 315.1266 [M+H]$^+$.

υ_{max} (neat)/cm^{-1}: 2943, 1597, 1359, 1176, 943.

2-Hepta-4,6-diynyloxy-tetrahydro-pyran, 310.[180]



To a stirred solution of 1,4-bis(trimethylsilyl)butadiyne **309** (1 eq) in anhydrous tetrahydrofuran (0.2 M) at room temperature was added methyl lithium lithium bromide (1.1 eq). The reaction was stirred at room temperature for 5 hours, then cooled to -78 ^{o}C at which point hexamethylphosphoramide (2 eq) was addedTHP ether (1.0 eq) was added slowly over 20 minutes. The reaction was stirred for 8 hours and allowed to attain room temperature over that period. Once complete by TLC analysis saturated aqueous ammonium chloride solution (20 mL) and diethyl ether (20 mL) were added. The organic layer was separated. The black residue obtained was dissolved in methanol (0.2 M) and potassium carbonate (1.2 eq) was added. The reaction was stirred for 12 hours then diluted with diethyl ether (20 mL) and water (20 mL). The organic layer was separated then washed with water (2*x* 20 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (elution with 2-5% diethyl ether in petroleum spirit) yielded **310** as a clear oil.

Using bromide 307

1,4-bis(trimethylsilyl)butadiyne (1.75 g, 9.01 mmol), methyl lithium lithium bromide (6.6 mL, 9.91 mmol, 1.5 M in diethyl ether), tetrahydrofuran (45 mL), hexamethylphosphoramide (3.14 mL, 18.0 mmol), 2-(3-bromopropoxy)tetrahydro-2H-pyran 311 (2.00 g, 9.01 mmol, 1M in tetrahydrofuran) then methanol (45 mL), potassium carbonate (1.49 g, 10.8 mmol) giving 650 mg of **310** as a clear oil in 38% yield.

Using Tosylate 308

1,4-bis(trimethylsilyl)butadiyne (787 mg, 4.06 mmol), methyl lithium lithium bromide (2.98 mL, 4.74 mmol, 1.5 M in diethyl ether), tetrahydrofuran (20 mL), hexamethylphosphoramide (1.41 mL, 8.12 mmol), toluene-4-sulfonic acid 3-(tetrahydro-pyran-2-yloxy)-propyl ester (1.28 g, 4.06 mmol, 1M in tetrahydrofuran) then methanol (20 mL), potassium carbonate (673 mg, 4.87 mmol) giving 611 mg of **310** as a clear oil in 78% yield**.**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.58 (1H, d, *J* = 4.1 Hz, O*CH*O), 3.87-3.77 (2H, m, CHO*CH*$_2$), 3.52-3.42 (2H, m, CH_2*CH*$_2$O), 2.39 (2H, t, *J* = 7.0 Hz, CC*CH*$_2$), 1.95 (1H, s, CC*CH*), 1.85-1.77 (3H, m, CCH_2*CH*$_2$ & CH*CH*$_2$$CH_2$), 1.73-1.67 (1H, m, CH*CH*$_2$$CH_2$), 1.57-1.50 (4H, m, Alkyl-*H*).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 98.8 (O*C*HO), 77.8 (C*C*CH_2), 68.4 (*C*CCH_2), 65.6 (HC*C*), 64.9 (H*C*C), 64.6 (CH_2CH_2*C*H_2), 62.2 (CHO*C*H_2), 30.6 (CH*C*H_2CH_2), 28.3 (CH_2*C*H_2CH_2), 25.5 (OCH_2*C*H_2), 19.5 ($CHCH_2$*C*H_2), 16.0 (CC*C*H_2)

m/*z* [Cl^+ (+ve), *iso*butane] 193.3 $[M+H]^+$ (100%). HRMS found 193.1228, $C_{12}H_{17}O_2$ requires 193.1229 $[M+H]^+$.

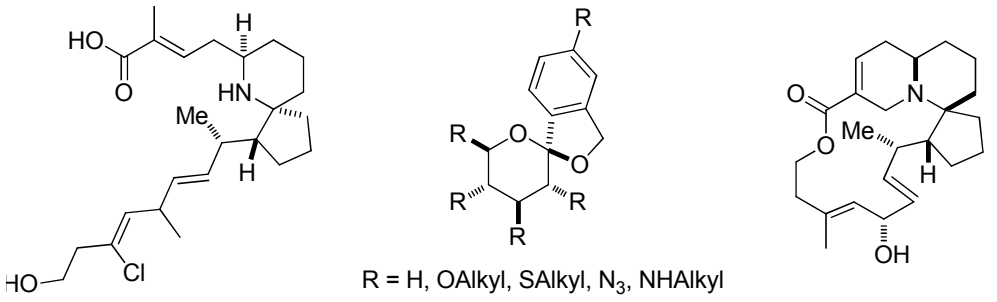
υ_{max} (neat)/cm^{-1}: 2947, 1581, 1182

Spirocyclic Pyrans: Towards Polymaxenolide

4. Introduction

4.1. Spirocyclic pyrans

Spirocyclic pyrans and piperidines have been reported in a number of highly active natural products and synthetic/semisynthetic derivatives, such as Polymaxenolide, pinnaic acid **335** and a number of spirocyclic saccharides and nucleosides **336**.[195-197]



335 **336** **337**

Figure 4.1. Pinnaic acid 335, spirocyclic glycosides 336, Halichlorine 337.

Polymaxenolide is particularly interesting because of its structural complexity that incorporates a novel fusion between uncommon terpene building blocks.

4.2. Isolation and characterization

Corals constitute a significant proportion of the tropical reef biomass. One of the most abundant soft corals is of the genus *Sinularia*, which tends to form large mono-specific carpets of up to 10 m^2. Soft corals are a group of cnidarians, organisms possessing a cnidocyte, a type of venomous cell that allows the organism a method of catching prey and the ability to defend themselves against predators. Soft corals are known to produce classes of complex secondary metabolites such as sesquiterpenes and diterpenes with a wide variety of carbon skeletons and a range of biological activities.[198,199]

Figure 4.2. *Sinularia maxima* (left)[200] and *Sinularia polydactyla* (right).[201]

Studies on *Sinularia* species secondary metabolites highlighted the ichthyotoxicity of the aqueous extracts of some 160 soft corals from all known coral families.[202] The ichthyotoxicity for the *Sinularia* genus was 63% (the average across all sampled was 60%), however the *Sinularia* species were disproprotionately represented in the most toxic group of extracts (50% of the *Sinularia* genus were amongst the most toxic, all fish treated with these metabolites were dead within 45 min).[199]

Of the secondary metabolites characterised from the *Sinularia* species, Polydactins A **338** and B **339** have been highlighted due to there biological activities and relatively small size. Isolated from *Sinularia polydacylya* (Ehreberg), taken from the South China Sea, the polydactins have moderate to weak cytotoxic activity against KB and MCF cell lines. Polydactin A showed the stronger activity against both carcinoma cell lines (58 and 63 nM respectively) while Polydactin B was much less active against the same targets (16 and 21 μM respectively).[203]

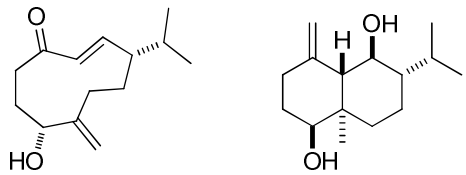
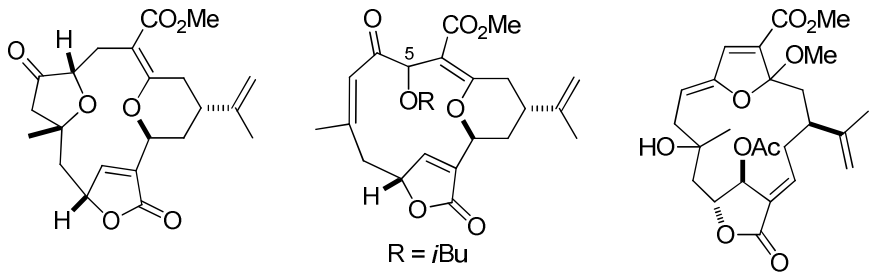


Figure 4.3. Polydactins A 338 and B 339.

A further study of the isolation and charcterisation of *S.maxima* and *S.polydactyla* secondary metabolites by Kamel identified several new cembranoid diterpenes (Figure 4.4).[204] The cytotoxicities of compounds **340** to **342** were assessed against a variety of carcinomas, **342** strongly inhibited the growth of ovarian, breast, pancreatic, colon and cervical cancer cell lines, with

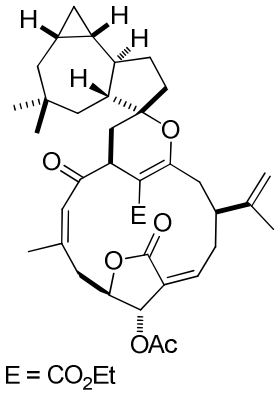
GI_{50} (concentration of drug required to inhibit the growth of cells by 50% relative to untreated cells) values between 39 nM and 0.58 μM.



340 **341** **342**

Figure 4.4. Cytotoxic diterpenes

Polymaxenolide **343** (Figure 4.5) was similarly isolated from soft corals *Sinularia maxima* and *Sinularia polydactyla* in 2004 by Kamel and co-workers.[205] The molecule is important because it is composed of a rare fusion between uncommon terpene building blocks. The biological properties/activities of Polymaxenolide have not yet been reported.



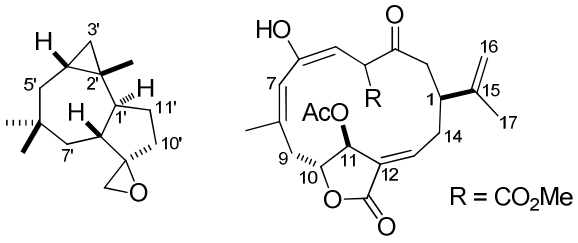
343

Figure 4.5. Polymaxenolide

4.3. Biosynthesis

Complex sesquiterpenes and diterpenes are frequently encountered in the extracts of soft corals of the genus *Sinularia*.[199]

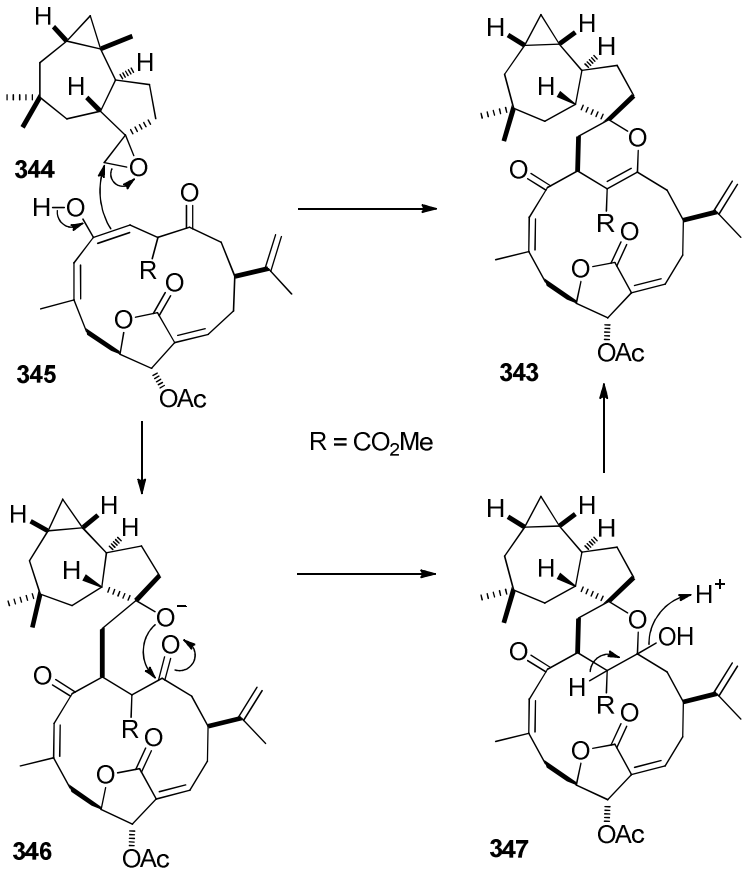
It is believed Polymaxenolide is a product of hybridisation between 2 terpenes, the product of a mixed biosynthetic pathway. It is composed of both cembrane-type terpene **344** and an africanane-sesquiterpene **345** skeleton, joined through a distinct C,C bond linkage. The structural assembly, is the first recorded between these two naturally occurring terpenes.



344 **345**

Figure 4.6. Africanane-sesquiterpene and cembrane diterpene.

Kamel[205] postulated a 'probable biogenetic route' to Polymaxenolide **343**, in which the C5 enolate of **345** attacks the *exo*-cyclic epoxide methylene carbon of **344**. Nucleophilic attack of the tertiary alkoxide **346** onto the ketone results in hemi-acetal formation. Elimination of the hydroxyl results in formation of the internal *E*-olefin and completes the biosynthesis of Polymaxenolide **343**.



344 **345** **343** **346** **347**

Scheme 4.1. The mechanism of formation of Polymaxenolide. R = CO_2Me.

Harborne and Turner[206] hypothesised that the novel hybrid framework of Polymaxenolide (and others) can occur via three different mechanisms

1) Interference with normal biosynthetic pathways resulting in a build-up of intermediates.

2) Elaboration of pathways leading to combinations of basic parent skeletons and

others derived from a second parent

3) Regulation or disruption (at a genetic level) following hybridization causing shifts in where the compound is produced

4.4. Structural features

Polymaxenolide **343** presents a highly complex architecture, showcasing 2 internal *Z*-olefins (*tri* substituted, C7-C8 and C12-C13) as well as *syn* (C2'-C4') and *anti* (C1'-C8') ring junctions. There is also complex cyclic functionality, 6 different ring structures are present including a 14C macrocycle, cyclopropa[*e*]azulene ring system and an interesting [5.4] spirocyclic pyran core that links Polymaxenloides two terpene components (Figure 4.7[207]).

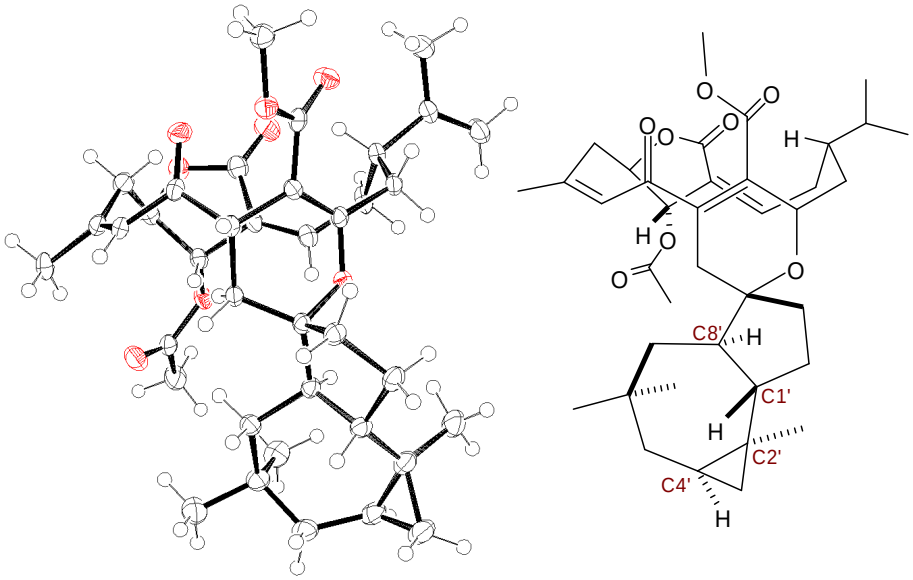


Figure 4.7. X-ray crystallographic structure of Polymaxenolide .

Rather than orientate as Figure 4.5 suggests, the macrocycle sits out of the plane, creating a hollow space in the center of the molecule (Figure 4.8). The africanane terpene component is almost planar, lying in a perpendicular fashion to the cembrane diterpene.

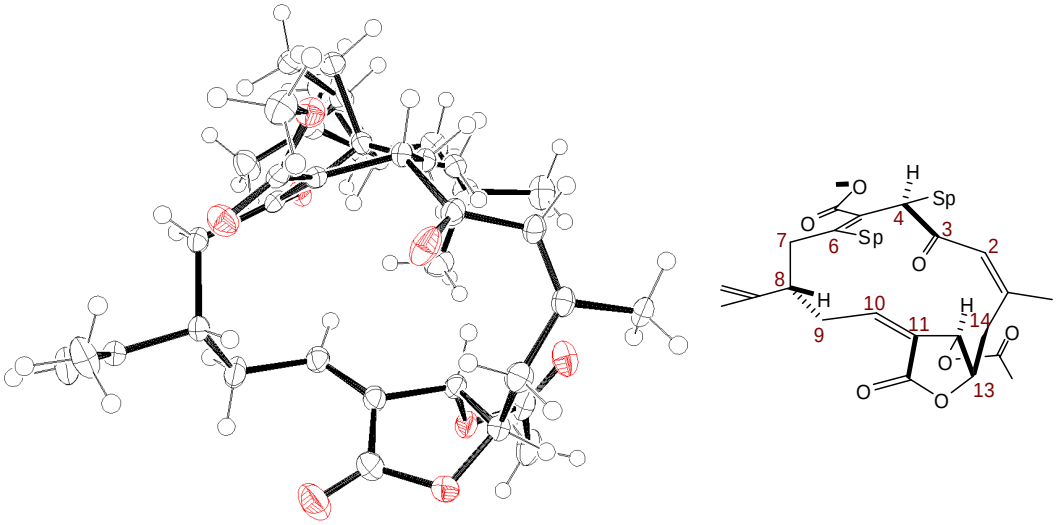


Figure 4.8. Polymaxenolide . Sp = spirocycle

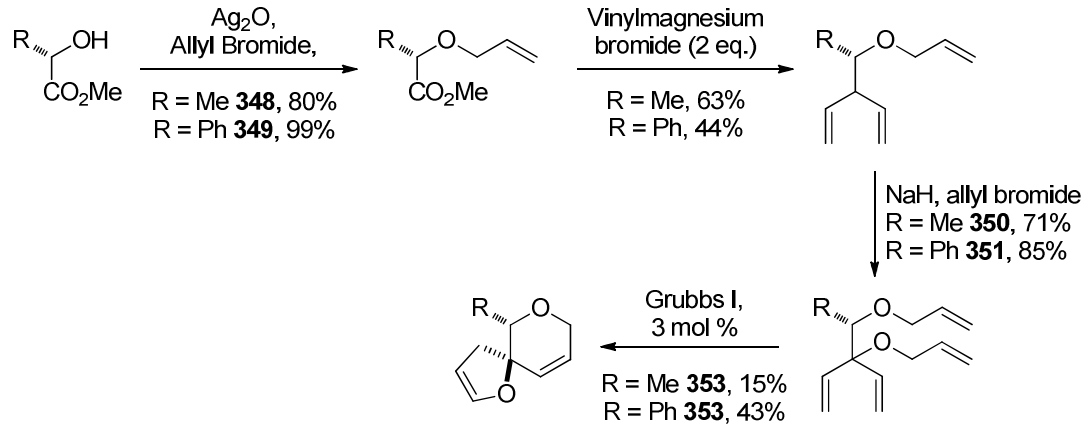
4.5. Spirocyclic pyrans

There have been many different approaches to the synthesis of spirocyclic piperidines, including radical cyclisations,[208] nitrone dipolar cycloadditions,[209] amine spiroannulations,[210-212] intramolecular Diels Alder,[213] *tertiary*-amine effect based approach[214] and Michael additions.[215,216] There are far fewer examples for the preparation of functionalized spirocyclic pyrans and none to date detailing the synthesis of Polymaxenolide .

The approaches to the synthesis of spirocyclic pyrans are more limited in scope and suitability.

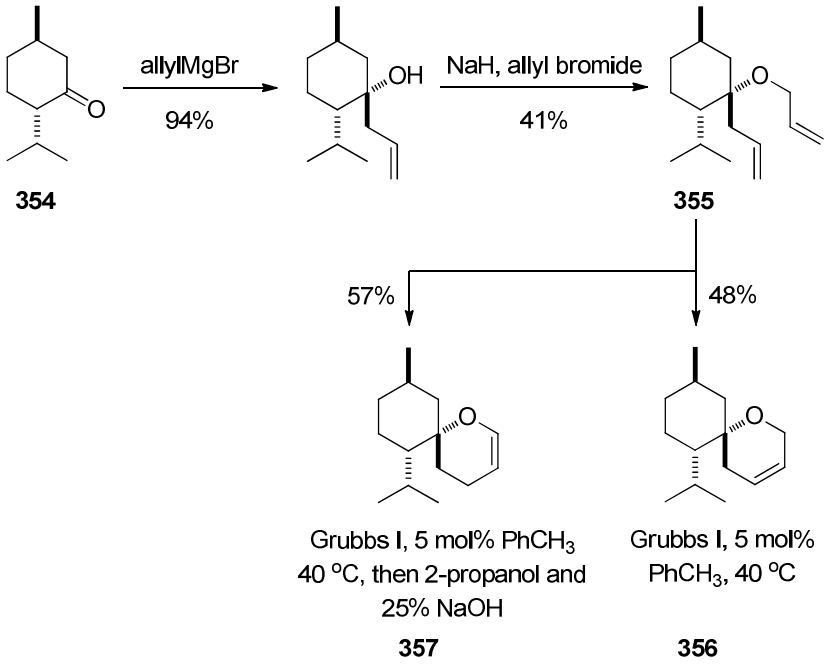
4.5.1. Ring closing metathesis

Olefin metathesis of quaternary alkene ether compounds is a common synthetic route in spirocycle generation. Schmidt has been able to show that spirocyclic pyrans can be generated from tetrene ethers.[217] In Schmidt's approach α-hydroxy carboxylic acid esters **348** and **349** were transformed into the corresponding tetrenes **350** and **351** (Scheme 4.2). Ring closing metathesis of the polyenes, gave as single diastereoisomers the spirocyclic pyrans **353** and **354** in poor to acceptable yields.



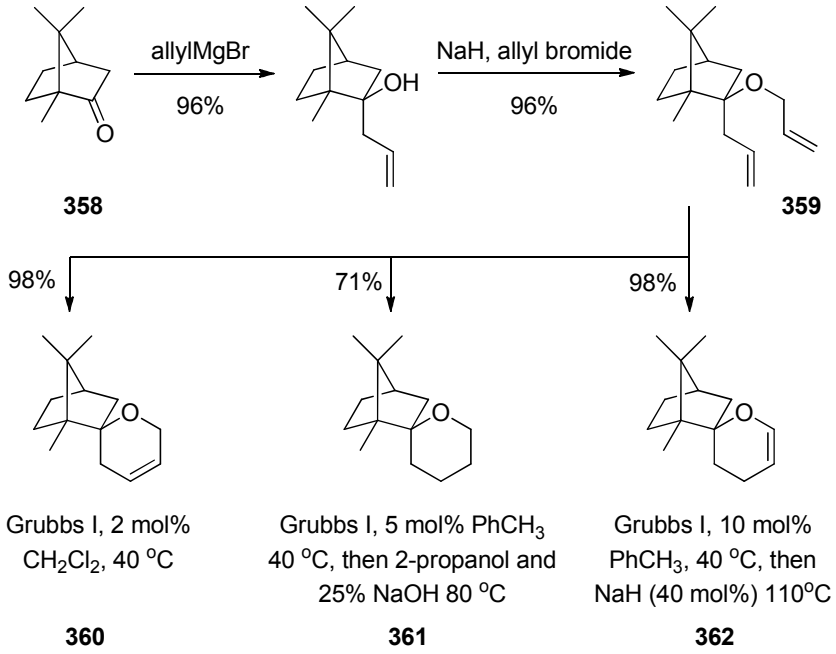
Scheme 4.2. Schmidt's' spirocycle methodology.

Schmidt also reported the synthesis of Menthone **354** and Camphor **358** derived spirocycles.[218] The RCM precursors were made in two steps from the corresponding ketone that was alkylated and converted to the requisite ether. Metathesis reaction of **355** gave spirocycle **356,** interestingly a modification of the reaction conditions allowed for the generation of olefin isomerisation/reduction product **357** (Scheme 4.4 and Scheme 4.3).



Scheme 4.3. Synthesis of Menthone derived spirocycles 357 and 356.

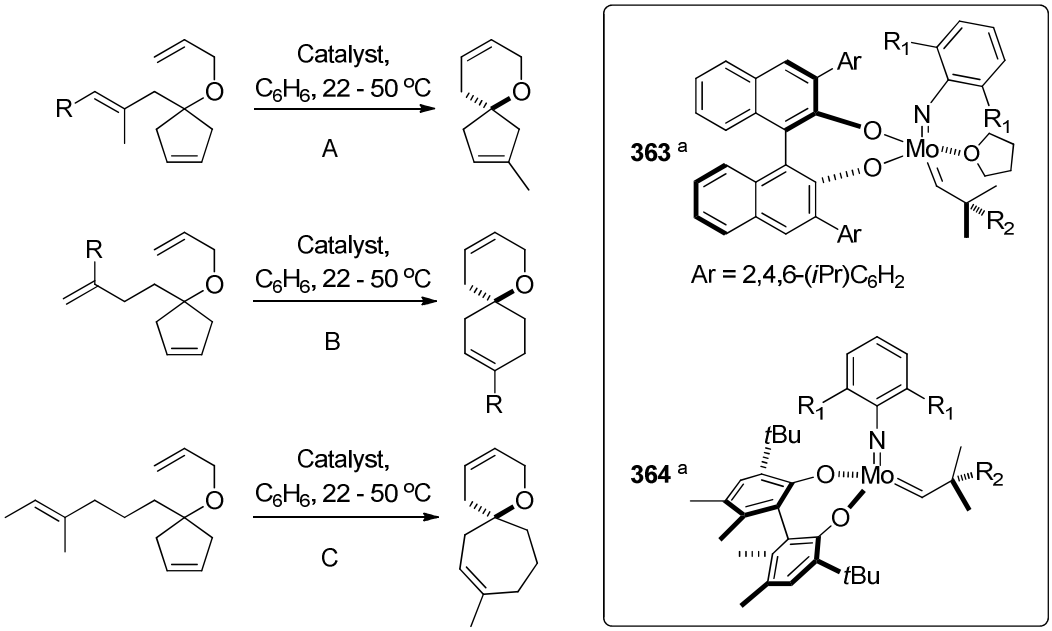
Similarly Camphor **357** derived diene **359** could be treated with Grubbs first generation catalyst to give spirocycle **360**. Modifications to the reaction conditions resulted in isomerisation of the double bond giving **361** and **362**.



Scheme 4.4. Synthesis of Camphor derived spirocycles 360, 361 and 362.

Further enhancements to the ring closing metathesis reactions selectivities were observed by Shrock and Hoyveda.[219] They achieved excellent yields and enantioselectivities of conversion using Molybdenum centered catalysts instead of Grubbs ruthenium based equivalent.

Hoyveda details the *in situ* generation of 5 molybdenum catalysts and their olefin metathesis applications using THF as solvent and additive. Five catalysts were tested against different achiral cyclopentenyl ethers, generating spirocyclic pyrans via a ring opening/ring closing reaction sequence. (Table 4.1) shows results of Hoyveda's catalyst screen against 5 different substrates, the results show reasonable levels of enantioselectivity (62 to 88% ee) combined with good to excellent yields.



Reaction	R	Catalyst	Catalyst loading	Yield	e.e.
A	H	***R* - 363a**	5 mol %	45%	88%
A	Me	***R* - 363b**	9 mol %	75%	80%
B	Me	***R* - 363c**	9 mol %	80%	83%
B	TMS	***S* - 364a**	5 mol %	70%	85%
C	-	***S* - 364b**	5 mol %	90%	62%

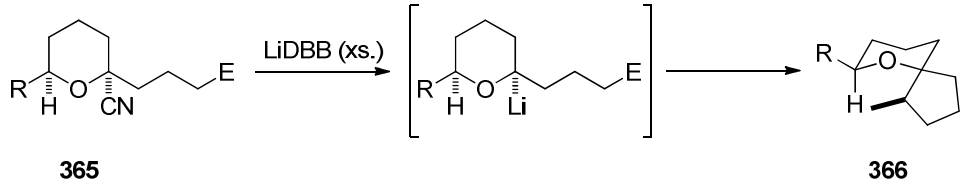
[a] **363a** R_1 = *i* Pr, R_2 = Ph; **364b** R_1 = Cl, R_2 = Me; **363c** R_1 = *i* Pr, R_2 = Ph

[b] **364a** R_1 = *Cl* , R_2 = Me; **364b** R1 = Me, R2 = Ph

Table 4.1. The results of Hoyveda's catalyst screen

4.5.2. Spiroannulation

Alkyllithium cyclisations onto alkenes or other electrophiles have been well documented.[220,221] Rychnovsky has shown that alkyllithium spirocyclisations, can be performed on a wide selection of electrophile functionality.[222,223] However this process is rarely applied to complex natural product targets

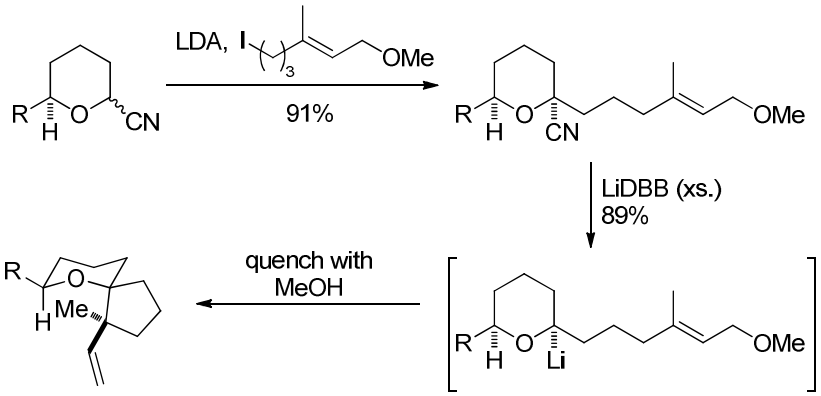


365 **366**

Scheme 4.5. Treatment of the nitrile with excess lithium *tert*butylbiphenyl causes reduction of the nitrile.

Alkenes, alkynes, nitriles, halides, phosphonates and epoxides have all been validated against Rychnovsky's method. It was also shown that more complex

electrophiles such as allylic ethers are suitable to the reaction sequence (Scheme 4.6).

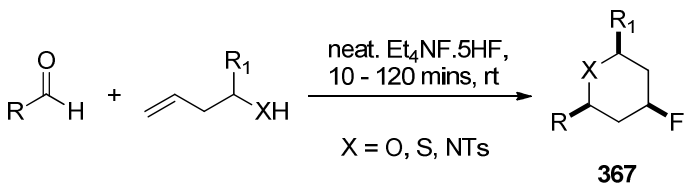


Scheme 4.6. Rychnovsky's method.

4.5.3. Prins cyclisations

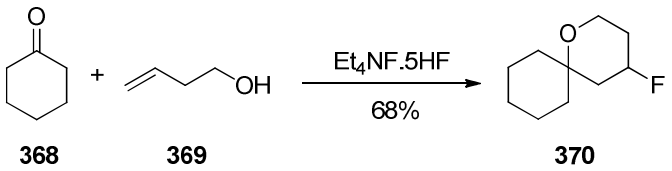
The Prins reaction of homoallylic alcohols (nucleophiles) and aldehydes producing functionalised tetrahydropyrans is one of the most widely documented methods.[224-228] Lewis acids are utilized in the reaction by coordinating to the carbonyl oxygen, promoting nucleophilic attack at the electrophilic carbon. In 2008 several examples of Prins cyclisations were reported, making use of different Lewis acid catalysts to achieve the desired THP structures.

Fuchigami[229] was able to show tetraethylammonium fluoride.hydrogen fluoride ($Et_4NF.5HF$) can participate in a Prins cyclisation reaction producing fluorinated tertrahydropyrans **367** showcasing *syn* stereochemistry between substituents. Fuchigami showed that it was possible to exchange but-3-en-1-ol for the equivalent thiol and amine (and mono-tosylate derivative), to produce fluorinated thiacycles and piperidines (selectivity was reduced with sulfur and amine derivative as *syn* and *anti* fluoro compounds were observed).



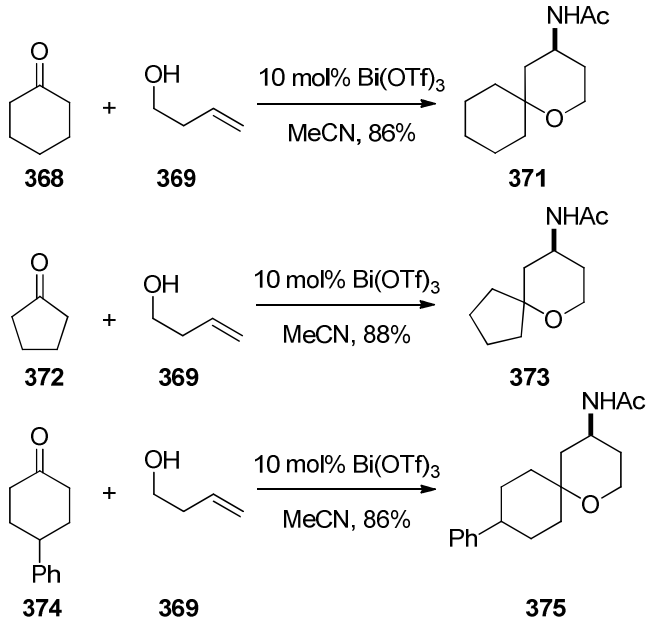
Scheme 4.7. Fuchigami's approach.

Fuchigami was also able to show that cyclic ketones could be used to generate spirocyclic pyrans under Prins conditions. Hence, treatment of cyclohexanone **368** with homoallylic alcohol **369** and tetraethylammonium fluoride.hydrgoen fluoride generated fluorinated spirocycle tetrahydropyran **370** (Scheme 4.8).



Scheme 4.8. Synthesis of spirocycle 370.

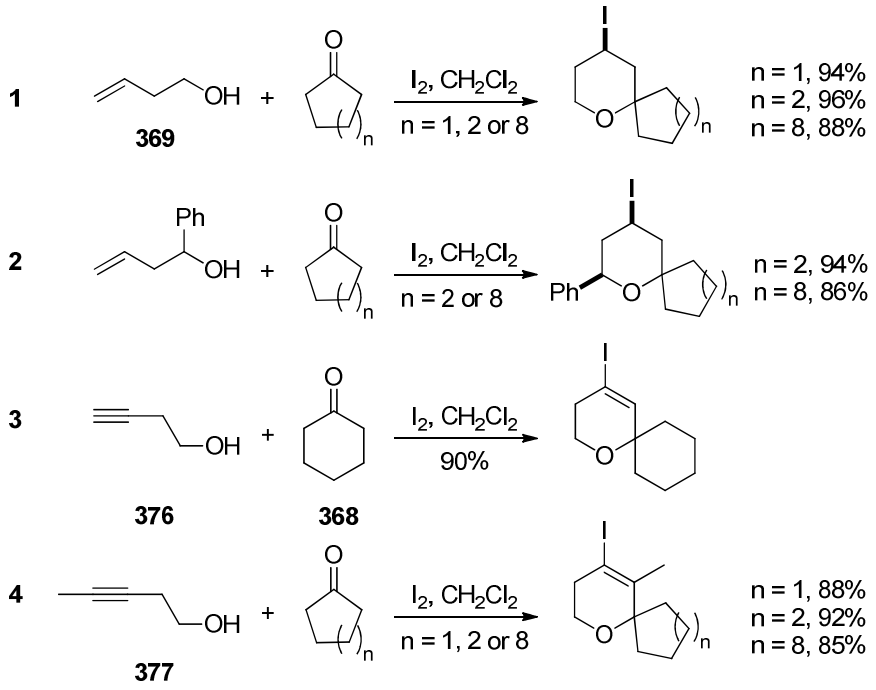
As part of a Prins-Ritter sequence Yadav showed that 4 aminotetrahydropyrans can be generated using Bismuth triflate as Lewis acid catalyst.[230]
Several aldehydes were utilized in the sequence from isopropyl and cyclohexyl to cinnamyl and naphalene. Three cyclic ketones **368**, **372** and **374** were transformed into the corresponding spirocyclic pyrans by the same method (Scheme 4.9). Yadav also altered the nitrile nucleophile, exchanging acetonitrile for benzonitrile, phenylacetonitrile or trimethylacetonitrile to introduce further functionality to the pyran core.



Scheme 4.9. Prins cyclisations of cyclic ketones.

Yadav was able to generate 4-iodotetrahydropyrans using molecular iodine as Lewis acid and nucleophile in the reaction.[231] Using this modified set of reaction conditions 4 series of spirocycles were generated based upon the starting alcohol. The use of alkynes **384** and **385** (series 3 and 4) was significant as it

allowed for the introduction of further functionality into the spirocycle structure.



Scheme 4.10. Series two gave *syn* diastereoisomers exclusively.

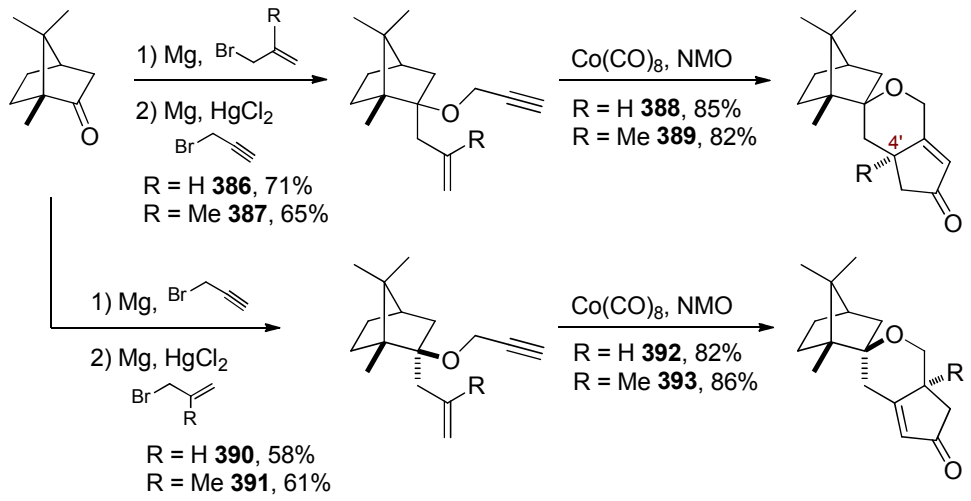
Attempts to identify other iodide sources, such as LiI, tBu_4NI and NaI failed to produce the desired transformation. Cerium trichloride/lithium iodide were later reported by Yadav as a novel reagent system for the synthesis of 4-iodotetrahydropyrans.[232] It was found that under the same conditions cyclic ketones gave higher yields when compared to the acyclic ketones.[233]

4.5.4. Pauson Khand

The Pauson Khand reaction has been utilized as a key step in the synthesis of many natural products; including Brefeldin A,[234] Incarvilline[235] and Kainic acid.[236] Due to poor enantioselectivities of cyclisations there was a need for chiral auxilliaries, leading to the use of Menthol,[237,238] *trans*-2-phenylcyclohexanol[237,238] and Camphor derived alcohols.[239-241]

Tanyeli[242] used Camphor derived alkyl ethers as a PKR precursor in the synthesis of spirocyclic cyclopentapyrans. Camphor **358** was treated with allyl magnesium bromide, then converted to the corresponding ether **378** upon treatment with propargyl bromide. Pauson Khand reaction of the alkyne-olefin gave the spirocycle **380**. Tanyeli was then able to introduce a methyl group at the 4'

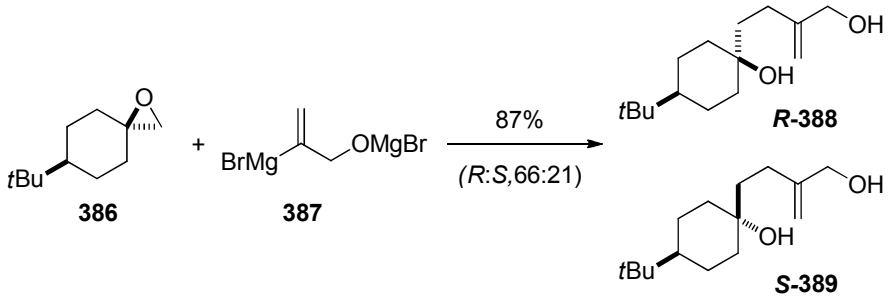
carbon of **379**, by exchanging the allyl group for 2-methylpropene in the first Grignard addition step and generating spirocycle **381** as before. It was found the products regioselectivity could be reversed by alternating the reaction sequence, initially alkylating with a propargyl group then forming the corresponding ether with allylic bromide. Pauson Khand reaction of the ene-ynes **382** and **383** gave spirocycles **384** and **385** in good yields.



Scheme 4.11. PKR of propargylic ethers.

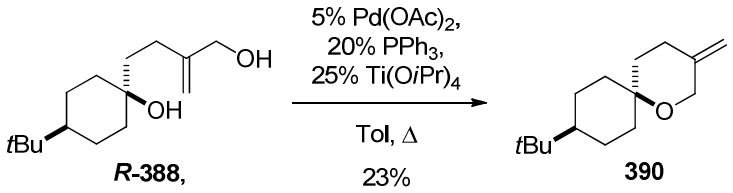
4.5.5. Other methods

Another interesting example of spirocycle generation was reported by Harrity in 2008, during the synthesis of Rhopaloic acid.[243] The synthesis was based on the key cyclisation of diols *R*-**396** and *S*-**396** (Scheme 4.13), which could be synthesized from organo metallic addition of Grignard **395** to epoxide **394**.



Scheme 4.12. Organomagnesium 387 addition to epoxide 386.

The catalytic palladium/titanium cyclodehydration of diol ***R*-388** gave spirocycle **390** in acceptable yields. The titanium was shown to be a key participant in the reaction facilitating alcohol addition to the Pd π-allyl complex, via a soft titanium alkoxide.

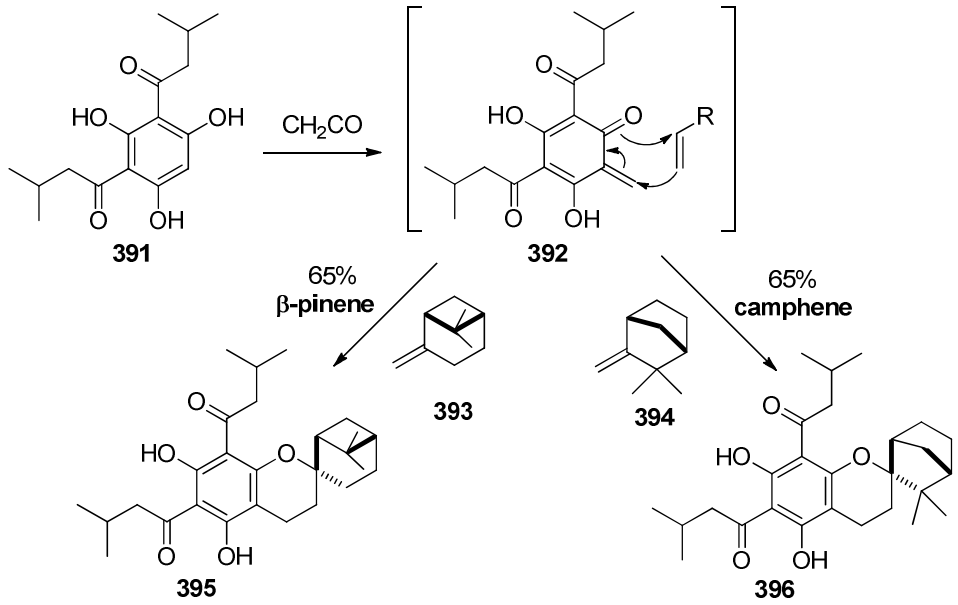


Scheme 4.13. Spirocyclodehydration reactions of allylic alcohols.

Interestingly the reaction yields were improved when the primary alcohol was converted to the acetate, 23% to 67% for the formation of **390**. The reason stated for such a large increase in the reaction yields, is that the acetate stops the competing dimerisation reaction.

Finally an example of spirocycle generation by a Diels Alder approach was reported by Singh in 2008.[244] Singh took *O*-qunione methides derived from oxidation of phloroglucinol derivatives Jenseone or Grandinol and reacted them with terpene derived dienophiles.

The biomimetic 3 component reaction involves the Knoevenagel condensation of formaldehyde and 2,4-diisovaleryl phloroglucinol followed by [4+2] cycloaddition between the resulting diene and dienophiles β-pinene **393** or camphene **394** to yield complex spirocycles **395** and **396**



Scheme 4.14. Synthesis of the *S*-Euglobal derived spirocycles.

5. Results and discussion

5.1. Spirocyclic natural products

As part of our studies towards the synthesis of spirocycle containing natural products (i.e. Polymaxenolide **343**, Figure 5.1) we have been interested in developing an easy and efficient method of generating functionalised spirocyclic compounds which would complement other methods available to date.

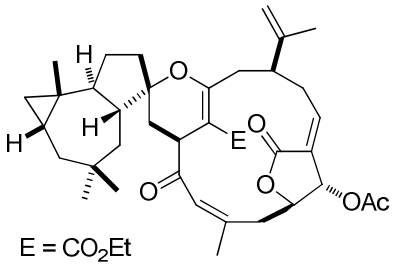
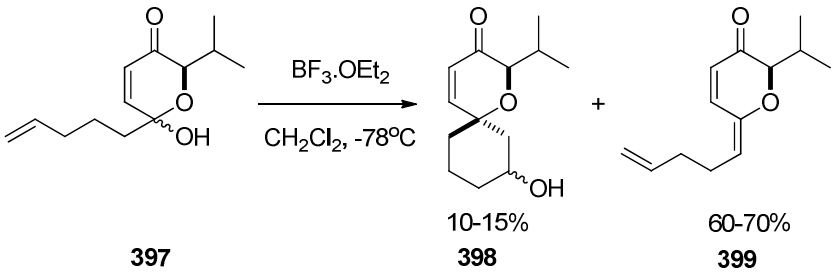


Figure 5.1.Polymaxenolide .

5.1.1.Initial findings

Previous efforts within the Marquez lab to generate spirocycle **398**,[245] were centered on a Prins type cyclisation of an olefin onto a pyran derived oxonium ion (Scheme 5.1).

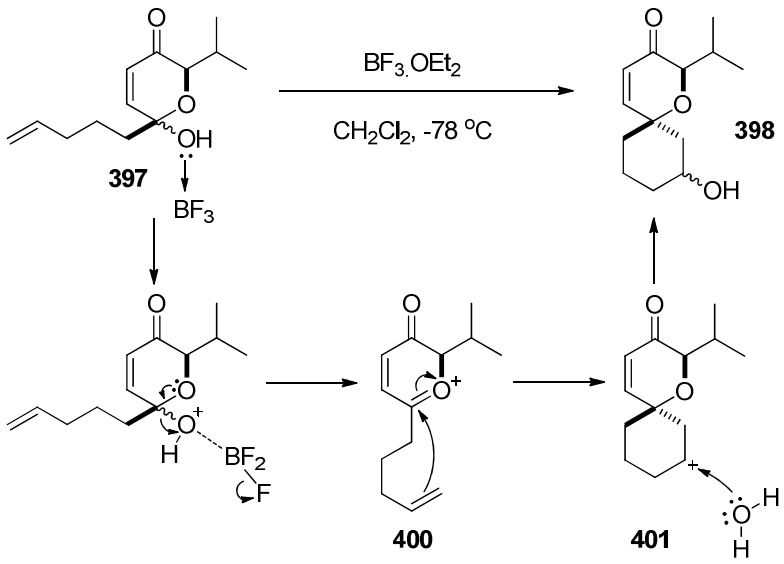


Scheme 5.1. Efforts to generate spirocycle 406.

Treatment of lactol **397** (see Scheme 5.4 for synthesis) with boron trifluoride diethyl etherate gave 2 products, generated the desired spirocyclic alcohol **398** and *exo*-olefin **399**.

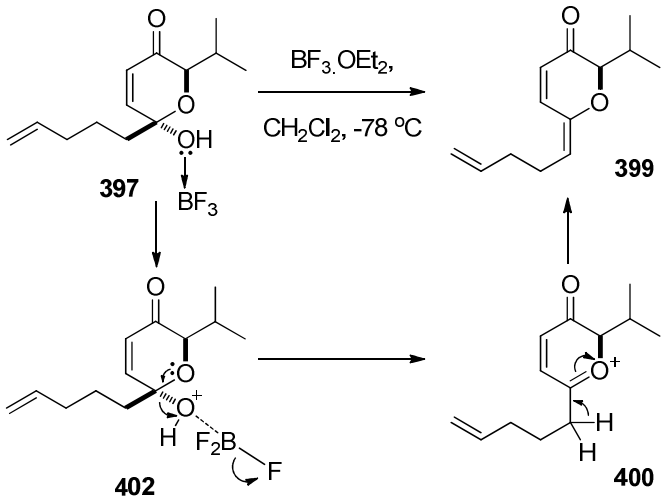
Mechanistically, spirocycle **399** originates from the nucleophilic attack of the terminal olefin in intermediate **400** onto the oxonium (Scheme 5.2), via the

Prins cyclisation pathway, overall an intramolecular 6-*exo*-*trig* cyclisation is observed. The resulting cation is quenched by the addition of water.



Scheme 5.2. Mechanism of formation of 406.

The formation of the *exo*-olefin molecule **408** is believed to be the result of a quicker competing reaction pathway (Scheme 5.3). Intermediate **402** forms as expected but instead of the internal cyclisation event, deprotonation (elimination of a proton) alpha to the oxonium ion is observed, resulting in the *exo*-olefin functionality. The overall effect is simply dehydration/elimination.



Scheme 5.3. Synthesis of *exo*-cycle 399.

In light of the inability to favour the cyclisation pathway (Scheme 5.2) over deprotonation (Scheme 5.3) a new route to spirocycle **398** was devised to incorporate an allylation/RCM reaction sequence.

5.1.2. Retrosynthesis

In our new approach, bicycle **403** could be obtained through the ring closing metathesis reaction of **404**, the product of the Sakurai reaction of lactol **405** with allyl trimethylsilane. The lactol **405** could originate from the oxidative rearrangement of α-hydroxyfuran **406** that could be produced by a double deprotonation/alkylation sequence of furan **86**.

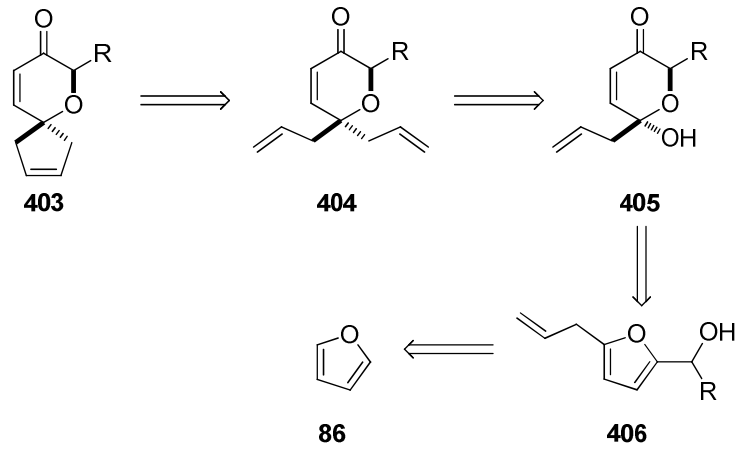
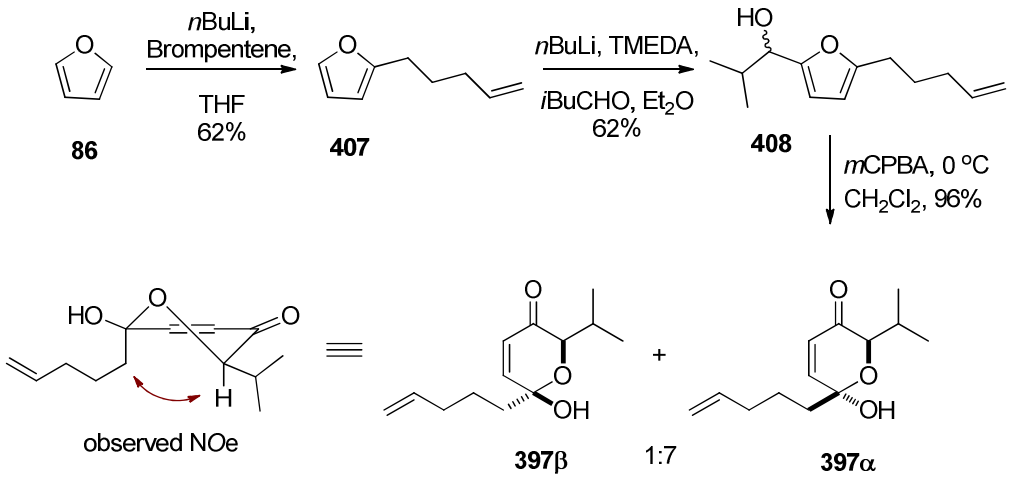


Figure 5.2. Retrosynthesis of the spirocyclic core of Polymaxenolide .

5.1.3. Synthesizing lactol, 397.

The investigation began with furan **86** which was deprotonated with *n*butyl lithium and alkylated with 5-bromopentene, giving known alkenyl furan **407**[246] in good yield. A second deprotonation, followed by trapping with *iso*butryaldehyde (chosen to introduce some steric bulk at the C2 position of the eventual pyranone) gave racemic alcohol **408** in 62%. Oxidative transformation using the Achmatowicz rearrangement,[129-131] of furfuryl alcohol **408** afforded lactol **397** (Scheme 5.4) in good 96% yield. The stereochemistry at the anomeric center was assigned by N*O*e studies of **397α** and **397β**. Correlations where observed between the CH_2 of the axial alkyl group and the hydrogen at the C2 position in the β anomer, these hydrogen interactions were not observed between the axial alkyl and C2-H in the α conformer.



Scheme 5.4. Conversion of furan 86 to lactol 397.

As expected the α-anomer was favoured over the β-anomer, in a reproducible ratio of 7:1. This result is consistent with the anomeric effect whereby electron withdrawing groups occupy the axial (α) position. In the α anomer, there is a favourable alignment of orbitals which allows back donation of electrons from the ring oxygen into the σ* orbital of the C-OH bond, the β-anomer does not have this favourable overlap.

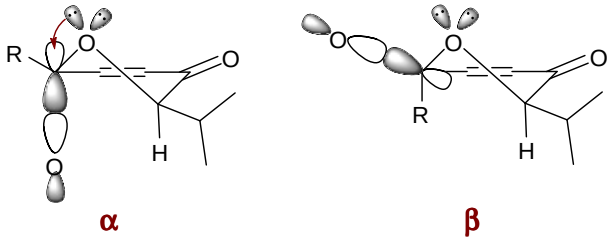
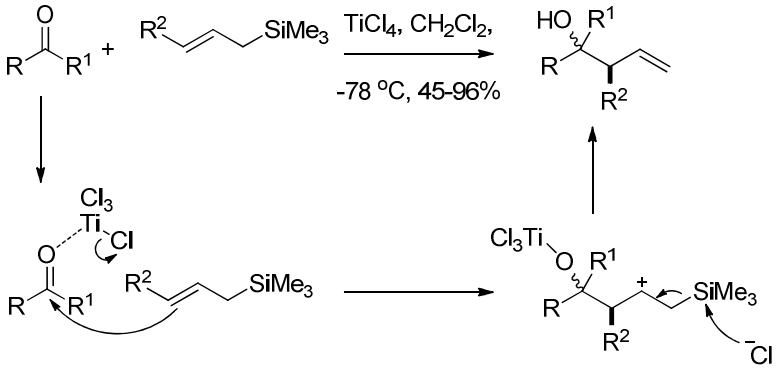


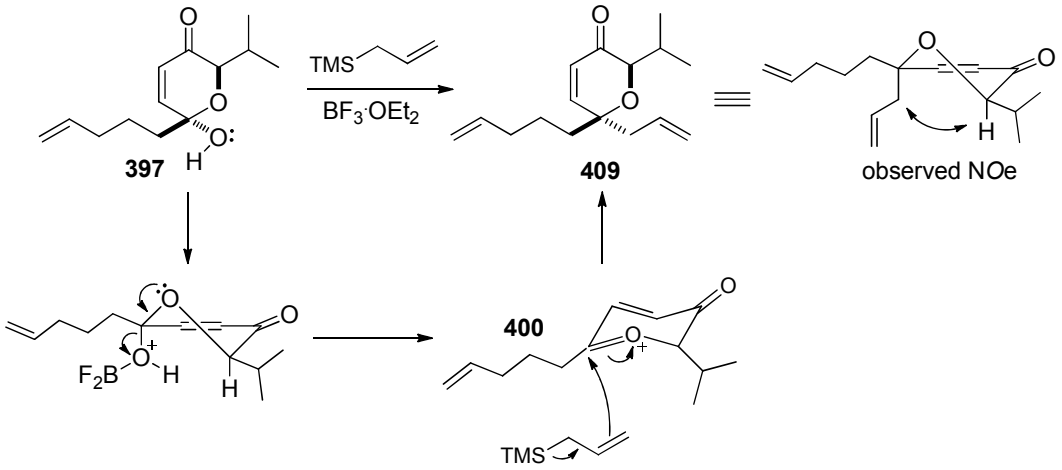
Figure 5.3. α and β anomers of 397

Sakurai reported in 1976 that allylsilanes react with a wide variety of aldehyde and ketones in the presence of stoichiometric amounts of titanium tetrachloride (later expanded to incorporate a plethora of Lewis acids) to form homo-allylic alcohols (Scheme 5.5).[247,248] Over time this transformation has been found to be highly regioselective, can be used with common electrophiles (aldehydes, ketones acetals and ketals)[249] and several catalytic protocols have been developed using TMSOTf,[250] $Cp_2Ti(OTf)_2$[251] and Ph_3CClO_4.[252] Mechanistically, the reaction proceeds by Lewis acid activation of the carbonyl group, which upon nucleophilic attack of the terminal olefin results in formation of a carbon-carbon bond and a silyl-stabilized β-carbocation, subsequent loss of the TMS group then regenerates the terminal olefin.



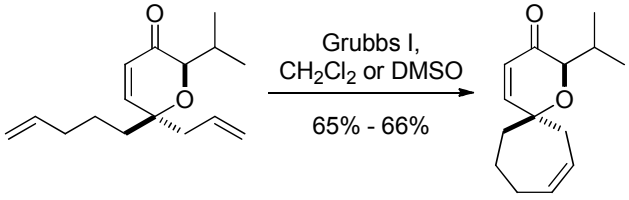
Scheme 5.5. Formation of homo-allylic alcohol.

Treatment the lactol **397** with allyl trimethyl silane in the presence of boron trifluoride diethyl etherate gave the diene compound **409**. Interestingly the allyl group occupies the α-position exclusively (Scheme 5.6). This was again determined by N*O*e studies of the crude and purified residues. The allylation is consistent with Woerpel's model[253] for the addition of nucleophiles to pyran derived oxonium ions. Wherein, axial attack of the incoming nucleophile is favoured over the corresponding equatorial addition.



Scheme 5.6. Allylation of oxonium 407.

Diene **409** was then treated with Grubbs 1st generation catalyst to give the desired spirocycle **410** in 65% yield. Interestingly there was very little difference in yields when either dichloromethane or dimethylsulfoxide where employed as solvent. The only difference was the efficiency of the reaction as the DMSO reaction gave an increased amount of side products; it did however give a slight increase in yield (66%).

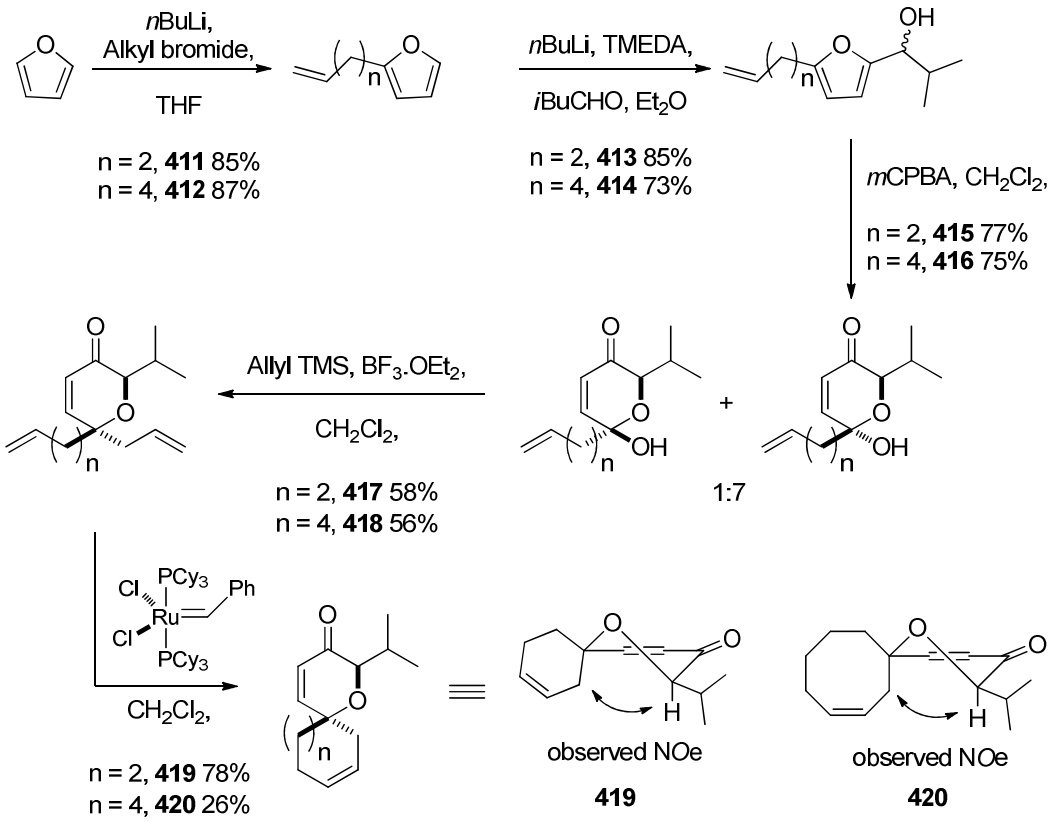


409 **410**

Scheme 5.7. Synthesis of spirocycle 410.

5.1.4. Other ring systems

Having synthesized spirocycle **410**, the method was expanded to incorporate different sized ring systems. Spirocycle **419** was synthesized using 4-bromobut-1-ene to alkylate furan while spirocycle **420** was produced from alkylation of furan with 5-bromohex-1-ene. The reaction sequence was repeated as per the synthesis of **410**.



419 **420**

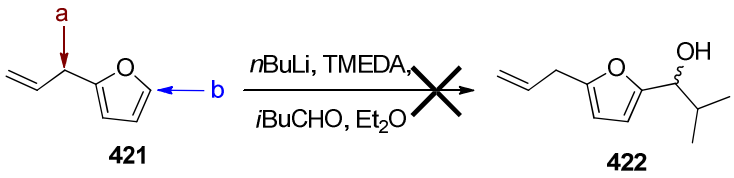
Scheme 5.8. Synthesis of spirocycles 419 and 420.

5.1.5. Synthesis of the [4.5] spirocycle

When the reaction sequence was directed to the generation of the 5-membered ring **429**, a significant problem was encountered. Alkylation of allyl-furan **421** using the established procedure failed to give the desired furfuryl alcohol **422**. It

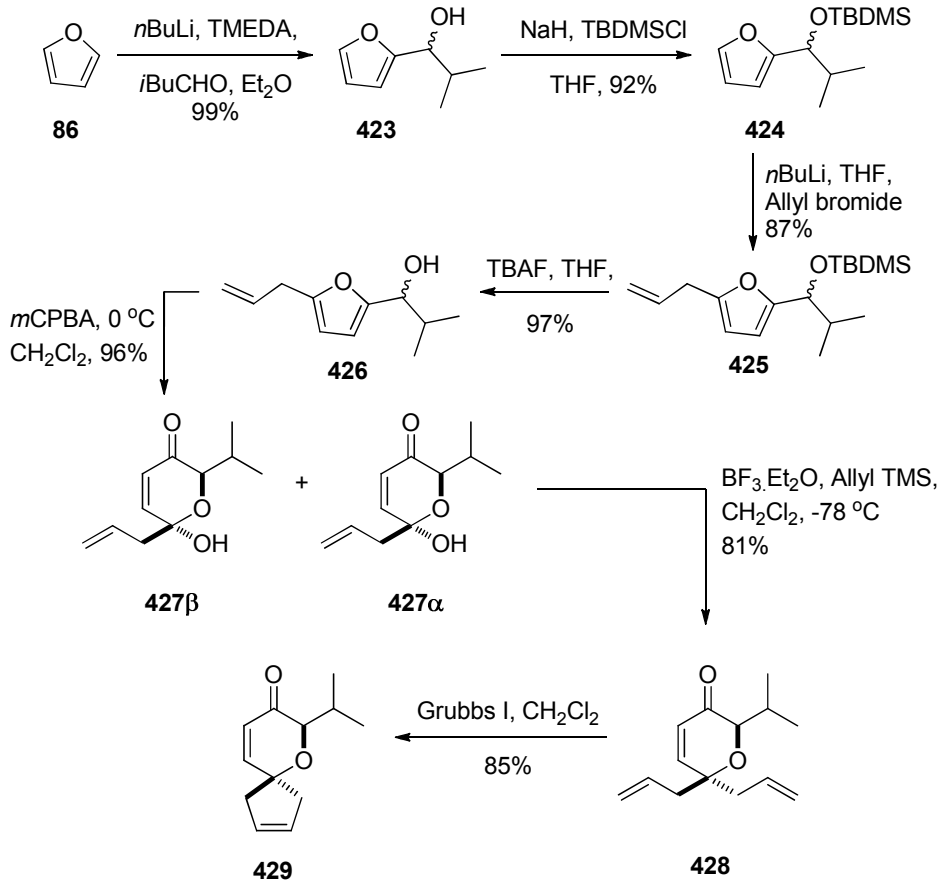
was concluded that the acidity of the allylic protons (Scheme 5.9) was too closely matched to that for the furan C5 proton (*position b*), which resulted in non-selective deprotonation and alkylation products.

Joule and Mills[254] give the pKa for furan C2/C5 protons to be 35 while Clayden *et al.*[123] give the pKa of propene at approximately 43. Clearly exchanging a hydrogen for a furan will increase the acidity of the these protons, providing some explanation to **421**s unexpected reactivity.



Scheme 5.9. Attempts to alkylate allyl furan 429.

A modified synthetic route was devised in which the alkylation order was reversed. Hence the furan anion was trapped with *iso*butryaldehyde as per West's[255] conditions giving secondary alcohol **423** that was protected as a *tert*butyldimethylsilyl ether **424**, that could be C5 alkylated with allyl bromide, to give **425**. Cleavage of the silyl ether with TBAF gave the secondary alcohol **426**. Treatment of **426** with *m*CPBA according to our established rearrangement conditions gave lactol anomers **427** and **428** selectively (7.8:1 ratio of α to β). Allylation of the lactol mixture was followed by ring closing metathesis reaction, giving spirocycle **429** in 85% yield.



Scheme 5.10. Modified route for the synthesis of the spirocycle 429.

Spirocycle **429** was generated in 43% overall yield from furan **86** in 7 steps, while spirocycles **410**, **419** and **420** were generated in 26%, 19% and 7% yield respectively. The lower yields are due to the decreased yields observed in the ring closing metathesis reactions of **409**, **419** and **420**. This observation is likely due to the increased number of conformations available to longer chain alkyl groups, making ring closing metathesis less likely therefore increasing the probability of cross metathesis products.

The synthesis has been shown to be an efficient method for generating spirocyclic pyrans and has demonstrated complete control of the quaternary carbon stereochemistry. Harris,[256] Tadano[257] and others have shown that an enantiopure alcohol can be subjected to Achmatowicz rearrangement conditions without detriment to the enantiomeric excess at that position. Their observations combined with our method, that features exclusive allyation in the α-position, allow us complete stereoselectivity over the reaction sequence.

5.1.6. Optimisation of the cyclisation protocol

It was found that the catalyst 'life' could be increased dramatically, particularly in the longer reactions by darkening the reaction vessel. When the reaction vessel was completely covered in aluminium foil the rate at which the ruthenium catalyst was degraded was reduced. In the case of spiro compound **420** completion could not be achieved without the foil covering.

Further optimisations were attempted by modifying the heating process and the nature of the RCM catalyst. Using microwave heating instead of reflux conditions gave only a marginal 1% in reaction yield of spirocycle **419** (Entry **2**, Table 5.1)

Using Grubbs 2nd generation catalyst under both reflux and microwave conditions gave increased yields of spirocycle **419**. Reflux conditions gave an enhanced yield of 80% (an increase of +2%) while microwave conditions gave an improvement of 7% to 85% isolated yield (Entries **3** and **4**, Table 5.1).

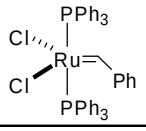
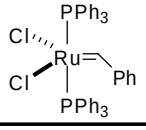
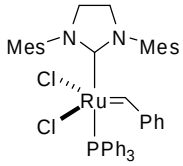
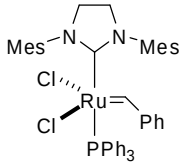
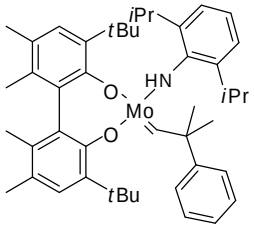
Entry	Catalyst	Conditions	Yield
1		Reflux (40 °C), 4 hours	78%
2		Microwave, 100 °C for 4 minutes	79%
3		Reflux (40 °C), 4 hours	80%
4		Microwave, 100 °C for 4 minutes	85%
5		Microwave, 100 °C for 4 minutes	No Reaction

Table 5.1. Summarising the catalyst screen.

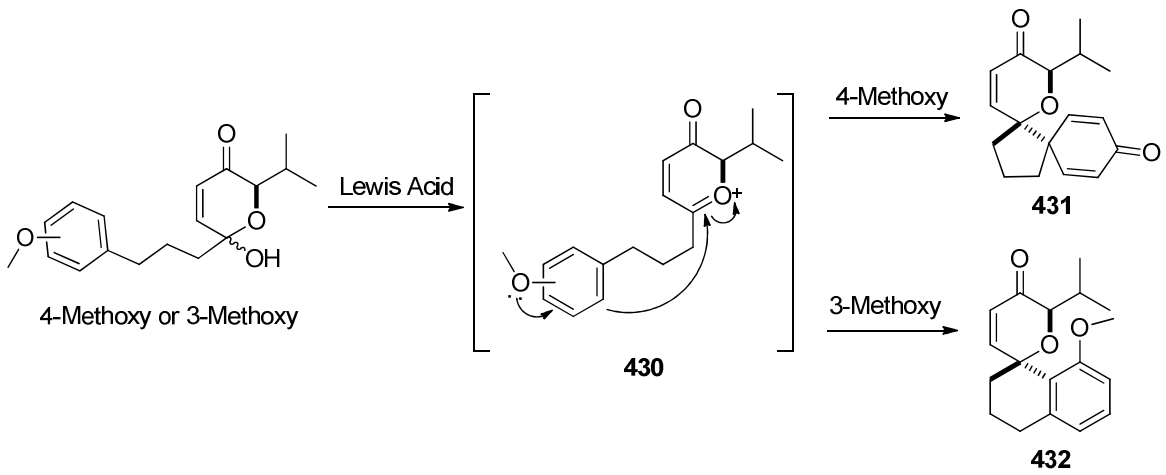
When the more reactive molybdenum based Schrock catalyst was used no cyclisation product was obtained, instead it produced what appeared to be traces of homodimer.

Catalyst loadings and alternate solvents were not examined during the optimisation process.

5.2. Methoxy directed cyclisations

Having successfully developed an efficient approach to the synthesis of spirocyclic pyrans, we turned our attention to the generation of other more complicated spirocyclic systems. We were particularly keen to explore the use of electron rich aromatic phenyl rings as nucleophiles during the cyclisation step. A successful cyclisation using aromatic substituents would provide ready access to a new class of spirocyclic compounds depending on the aromatic rings substitution pattern (Scheme 5.11).

Synthetically it was expected that incorporating an electron rich phenyl ring would sufficiently increase electron availability and allow the aromatic nucleophile to react with the oxonium intermediate **430**, in the process suppressing the dehydration competition reaction.

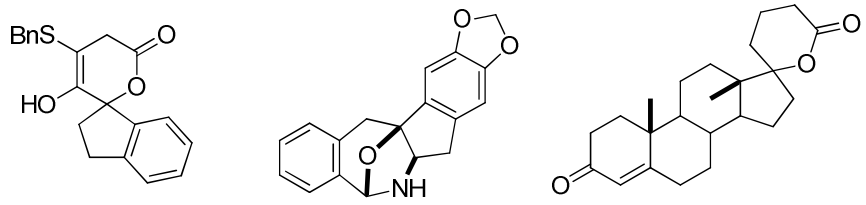


Scheme 5.11. Generation of functionalised spirocycles 431 and 432.

It is believed that the methoxy group will influence the cyclisation reaction, directing formation of the new ring. In the 4-methoxy example it is believed a *bis*-spirocyclic compound **431** will be produced as a result of the electron donating nature of the methoxy ether (*ortho*, *para* direction). While the 3-

methoxy substituted compound will produce a spiro-fused ring system **432** (2 other products could theoretically be produced by this route but it is believed that their production will be minimal due to their ring size and conformations).

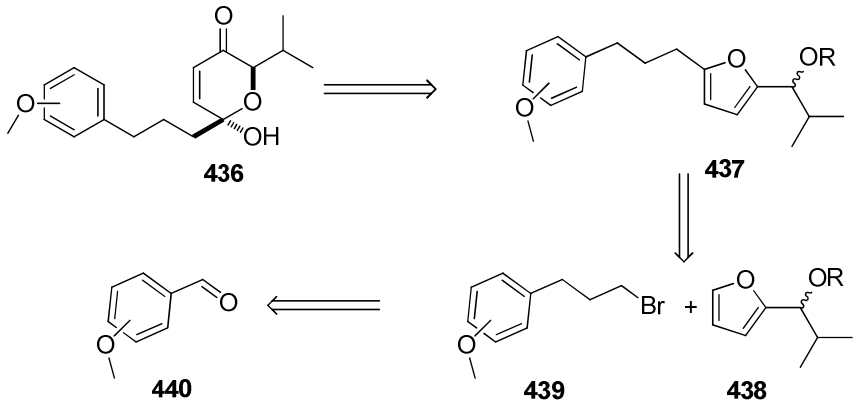
These new spirocycles bear some resemblance to several important and interesting classes of compound. 5,6-Dihydropyrone derivatives (**433**) have been identified as non-peptide HIV protease inhibitors and *anti*-viral agents.[258] Ribasine **434**,[259] and derivatives have complex skeletal frameworks and finally spirocyclic steroid ethers **435** have been shown to exhibit *anti*-estrogenics properties (Scheme 5.12).[260]



433 **434** **435**

Scheme 5.12. Spirocycles 437, 438 and 439

We envisioned the cyclisation precursors **436** to be generated from the oxidative rearrangement of furfuryl alcohol **437**. **437** could in turn be generated from the alkylation of protected furyl alcohol **438** with bromide **439** that could be thought of as having come from anisaldehyde **440**.

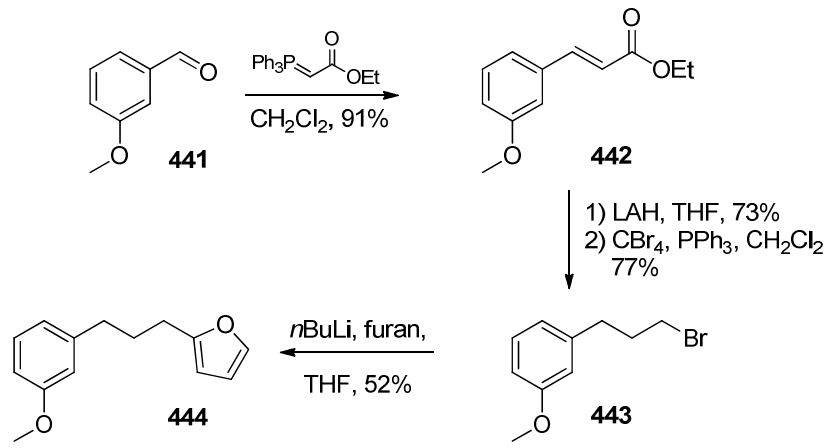


Scheme 5.13. Generating lactol 436

5.2.1. First synthetic route

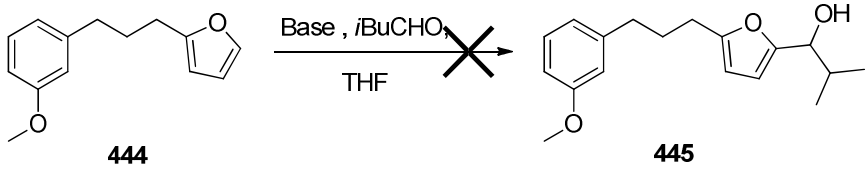
Bromide **443**[261] was synthesized from 3-methoxy benzaldehyde, that was transformed to the known α,β-unsaturated ester **442**[262] by Wittig olefination conditions (carbethoxymethylidene triphenylphosphorane in refluxing

dichloromethane) as the E-olefin exclusively. This reaction was optimised using microwave heating that gave slightly reduced yields but greatly reduced reaction times, 8 to 10 minutes instead of 5+ hours. Lithium aluminium hydride reduction of the ester to the saturated alcohol was achieved in good yield.[263] The alcohol was converted to the desired bromide **443** using Appel halogenation conditions. Furan was treated with *n*butyl lithium and the anion was quenched with bromide **443** to give compound **444** in 52% yield (Scheme 5.14).



Scheme 5.14 Synthesis of 444.

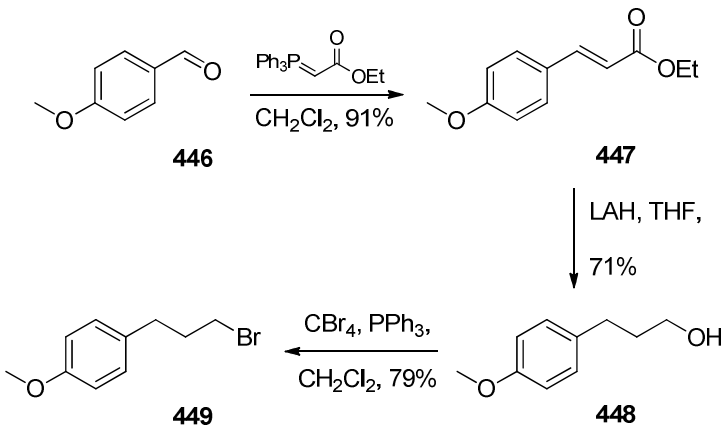
Alkyl furan **444** was then treated with a second equivalent of *n*butyl lithium and the anion quenched with *iso*butryaldehyde. However the desired α-hydroxyfuran compound **445** was not produced. Further attempts to couple **444** with *iso*butyraldehyde proved unsuccessful, the base was changed to lithium di*iso*propylamine (both commercially available and generated *in situ* from *n*BuLi and *i*Pr_2NH), unfortunately failing to generate any of the desired carbinol **445**.



Scheme 5.15. The attempted synthesis of alcohol 445.

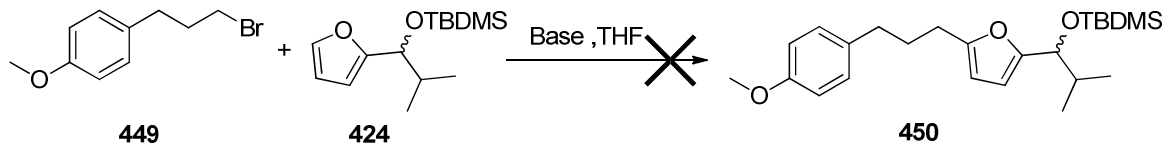
The 4-methoxy bromide **446** was synthesized in parallel to **443** and this was used as coupling partner to previously synthesized TBDMS ether **424,** in an effort to circumvent the problems encountered in Scheme 5.14**.** Thus 4-methoxy benzaldehyde was olefinated under Wittig conditions to generate the known α,β unsaturated ester **447**[264] in good yield. Conversion of the ester to the bromide **449**[266] was conducted as per the 3-methoxy series via known alcohol **448**[265]

bromide The yields of conversion were consistent across both series, interestingly the overall yield of the 3 step transformations was 51% in both cases.



Scheme 5.16.

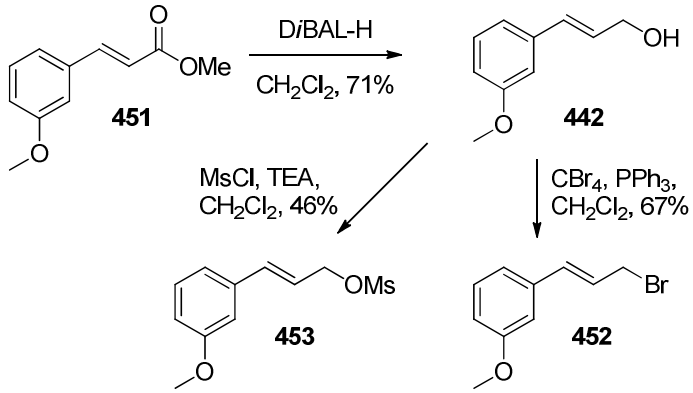
Treatment of bromide **449** with *n*butyl lithium then with furan coupling partner did not produce any of the desired aromatic bicycle **450**.



Scheme 5.17. Attempted synthesis of 450.

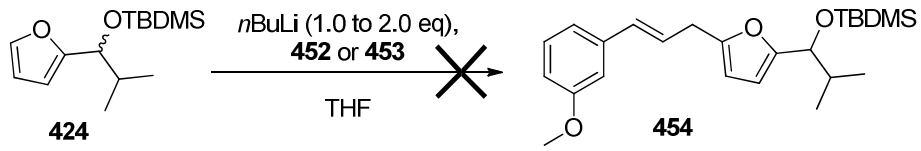
A number of different reaction conditions were explored, including different equivalents of bromide, different temperatures, different bases as well as the use of molecular sieves and *tert*butylammonium iodide (TBAI) as a phase transfer catalyst. Unfortunately all combinations of reagents and additives failed to alter the unsuccessful outcome of the reaction.

In an attempt to improve the chances of a successful coupling, it was decided to switch bromide **449** for the more reactive allylic bromide **453.**[267]
452 was synthesized from **442**[268] by 1,2 reduction of the ester functionality using a modification of Malony's procedure (di*iso*butylaluminium hydride in dichloromethane instead of toluene).[269] The allylic alcohol **442** was then transformed to allylic bromide **452** via Appel reaction.[177] To increase the chances of a successful coupling reaction, **442** was also converted into the allylic mesylate **453** in acceptable yield.[270]



Scheme 5.18. Synthesising allylic mesylate 453 and bromide 452.

Unfortunately attempts to couple TBDMS protected furan **424** and allylic bromide **452**, proved to be unsuccessful, the number of equivalents of *n*butyl lithium where altered returning unreacted starting materials in each case. Exchanging allylic mesylate **453** for the bromide also failed to produce any of the desired coupled material.

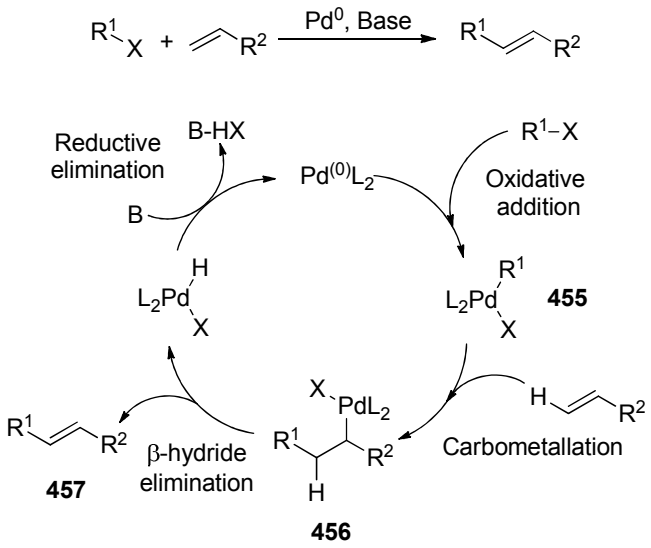


Scheme 5.19. Attempts to synthesize 454.

5.2.2. Palladium cross coupling reactions

Faced with this complete lack of success it was decided to resort to the use of transition metal catalyzed cross coupling reactions reported in the literature.

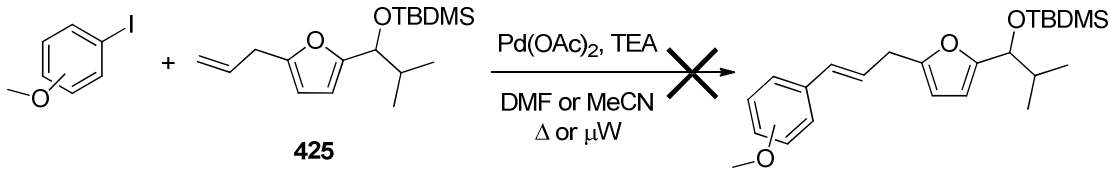
The first reaction explored was the Heck reaction, as it is known to be an accommodating reaction that can handle electron rich, deficient or neutral alkenes. A limitation of the reaction is that the halide or triflate cannot contain β-hydrogens bound to an sp^3 carbon, due to competing β-hydride elimination, that could result. However there have been several protocols designed to circumvent this issue.[271]



Scheme 5.20. Heck reaction of alkene.

The mechanism of the Heck reaction is not fully understood and appears to alter subtly according to the specific reaction.[272-273] What is known is that the first step of the catalytic cycle is an oxidative addition of the aryl halide to the $Pd^{(0)}$ catalyst affording σ-arylpalladium(II) complex **455**. The second step is a nucleophilic attack (*syn*-addition) on the *trans*-$ArPdXL_2$ **456**, then a β-hydride elimination giving the coupled product **457**.[274]

Our initial coupling attempts were between previously synthesized allyl furan **425** and 3 and 4-iodoanisole were treated with palladium acetate catalyst ($Pd(OAc)_2$) under both reflux and microwave conditions.[275,276]



Scheme 5.21. Heck reaction of 425.

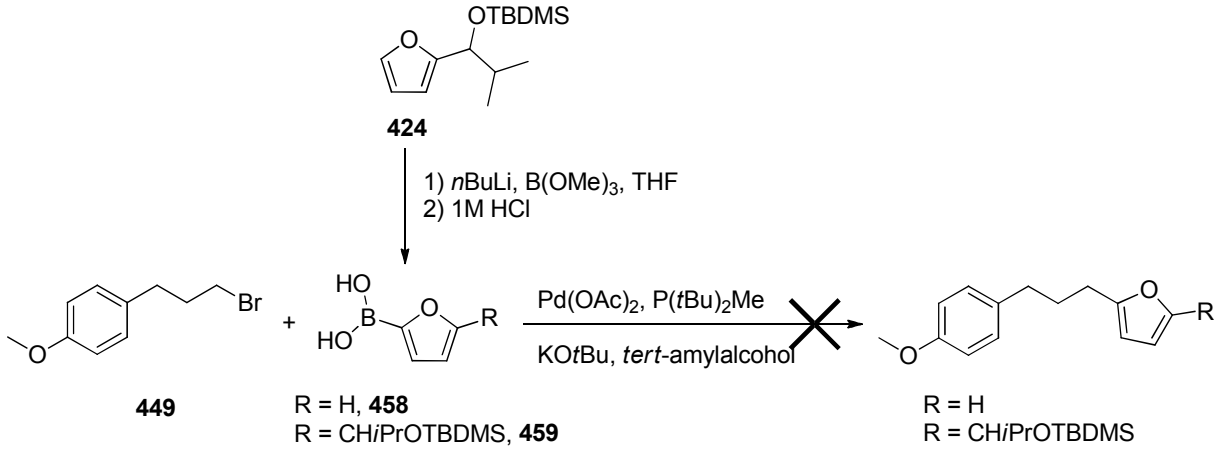
The reflux reactions seemed sluggish with little reactivity between reactants, whereas the microwave conditions were much more productive, seemingly producing desired olefin straight away. However attempts to purify the reaction product by flash column chromatography proved unsuccessful, as the compounds were inseparable from the either of the starting materials. This made confirmation of the reaction success impossible by ^1H NMR spectroscopy. Treating the crude compounds with TBAF did not change this as alkyl TBDMS ether **425** was also deprotected. Purification by derivatisation though reduction

of the olefin under either standard conditions (Pd/C, H_2) or with the H-Cube also gave significant degradation of the starting mixture.
Undeterred by this, a different approach was formulated.

Careful searches of the literature highlighted a new variant of the traditional Suzuki reaction, using 'unactivated' alkyl bromides with aryl boronic acids.

> "In summary, we have described the first palladium or nickel catalyzed method for coupling a diverse set of boronic acids and unactivated alkyl electrophiles (bromides) that possess β-hydrogens."
> – Gregory Fu[276]

The coupling of aryl bromide **449** and either commercially available furan-2-ylboronic acid **458** or synthesized TBDMS protected furanyl boronic acid **459** was attempted following Fu's protocol. Unfortunately none of the desired product was obtained.

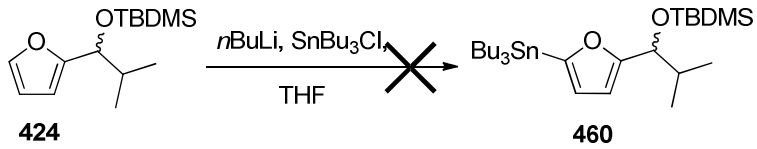


Scheme 5.22. Suzuki reaction of bromide 449 and boronic acids.

With the inability to generate either of the furan bicycles, other coupling reactions were considered.

At this point we considered the Stille coupling as a feasible alternative to the Suzuki coupling because the stannane is more nucleophilic than its corresponding boronic acid counterpart (despite the inherent toxicity of tin and tin containing compounds).[277-278]

The synthesis of stannane **460** began with furan **424**, which was treated with *n*BuLi and tributyltin chloride (Scheme 5.23).[279] Regrettably the stannane was not formed, under these conditions as indicated by ^{1}H NMR analysis.

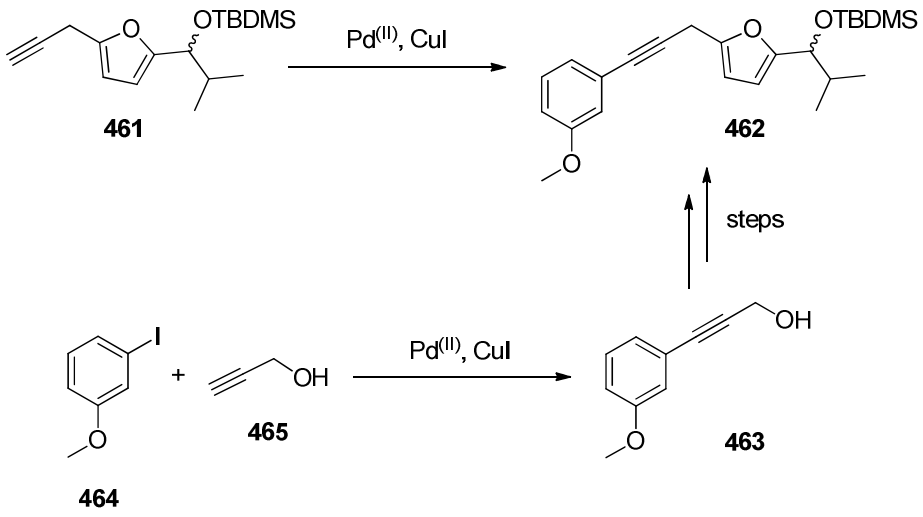


424 **460**

Scheme 5.23. Generating stannane 461.

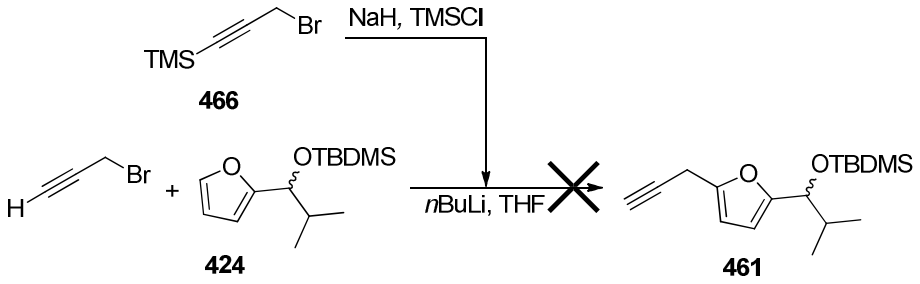
In an attempt to discover the reason for this failure, TBDMS ether **424** was deprotonated with *n*BuLi and alkylated with allyl bromide in excellent yield (71%). This suggested that the reason for the problem lay with the tributyltin chloride and not the deprotonation step. We reasoned that the problem was likely to be the presence of water in the Bu_3SnCl, which therefore quenched the furfuryl. However despite obtaining a new source of tributyltin chloride, the reaction was still unsuccessful.

The last obvious choice of palladium coupling reaction was the Sonogashira coupling. Two possible synthetic routes were considered using this cross coupling method. In the first instance alkylation of silyl furan **424** with propargyl bromide would give coupling partner **461** which could then be reacted with iodoanisole (3- or 4-) to give the desired bicycle **462**. The alternative coupling approach, reaction of propargyl alcohol and iodoanisole would give known alkynol **463.**[279] The alcohol functionality could be transformed to a suitable leaving group (halide/alkyl sulfone) and displaced with a suitable anion (Scheme 5.24).



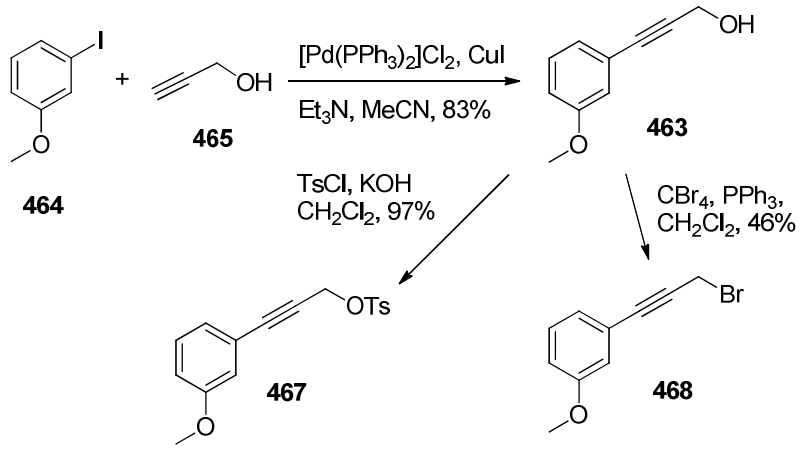
Scheme 5.24. Proposed Sonogashira routes to 462

Initially, the first route was employed but a problem was encountered almost immediately. Attempts to synthesize TMS-bromide[280] **466** that could be used in place of propargyl bromide failed. This is not surprising when you considering the alkyne proton acidity, pKa 28.7,[281] it is likely that the furan anion will undergo protonation, before the anion can displace the bromide in the desired coupling reaction.



Scheme 5.25. Attempts to alkylate 424.

The second route began with Sonogashira cross coupling reaction between 3-iodoanisole **464** and propargyl alcohol **465** to give alcohol **463** in good yield. Transformation of the alcohol functionality to the corresponding tosylate **467** or bromide **468** was achieved in 97% and 46% yield respectively.

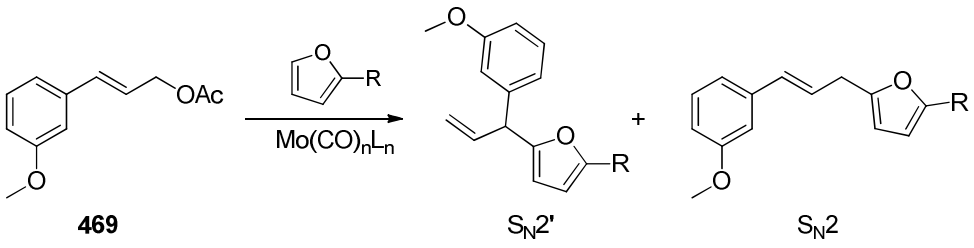


Scheme 5.26. Generating alkyne coupling partners 467 and 468

Unfortunately deprotonation of **424** with *n*BuLi and treatment with bromide **467** failed to produce any of the desired bicycle **462**. Different bases (LDA, LHMDS, KHMDS, NHMDS, KH and NaH) were employed in the reaction with either bromide **468** or tosylate **467** as the alkylating agent, unfortunately all combinations failed to produce **462**.

5.2.3. Molybdenum catalyzed allylic substitution

At this point, we became aware of a method for molybdenum catalyzed coupling of electron rich aromatics (and heteroaromatics).[282] Malkov and Kocovsky have shown that molybdenum (poly carbonyl)$_n$ complexes catalyses the reaction of allylic acetates and aromatic compounds. To that end, known acetate **469**[283] was synthesized from allylic alcohol **442** in the presence of acetic anhydride in 86% yield. However on closer inspection, the published method suggested that it would be unsuitable for our purposes; because with the substrates chosen the reaction suffers from a lack of regioselectivity. The S$_N$2 pathway is still the preferred reaction, however the reaction mixture would contain a significant quantity of the S$_N$2' reaction product as well as low overall yields (~45%).

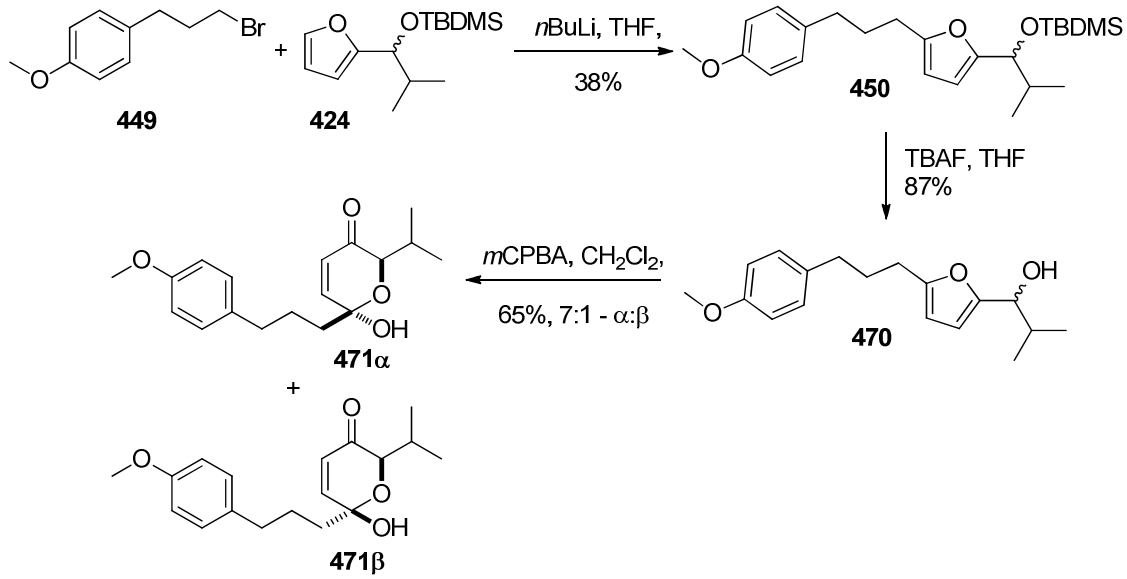


Scheme 5.27. Substitution of the allylic acetate with furan.

Due to the low regioselectivity and product yields, it was decided not to pursue this protocol.

5.2.4. Original route

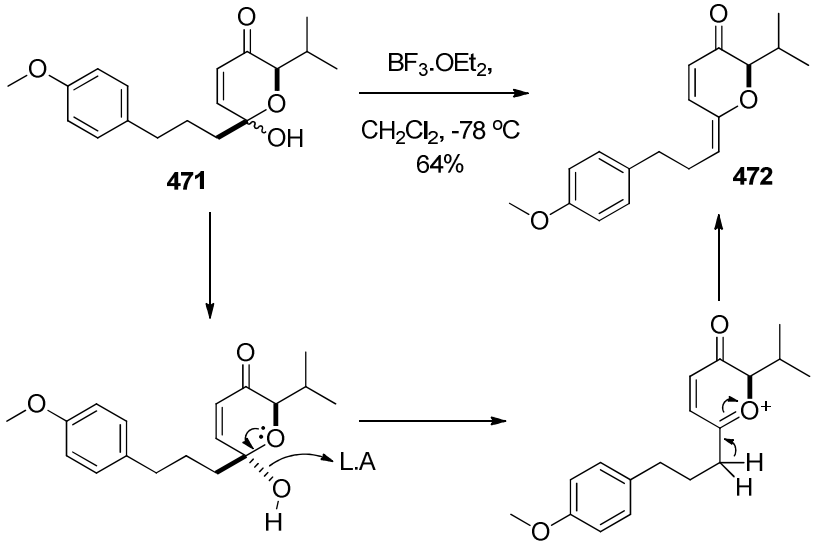
The results thus far were disheartening and abandoning the project was seriously considered. However one final coupling reaction was attempted using the same conditions as before. Surprisingly, coupling product **450** was produced in 38% yield, as a mixture of bromide and product. Fluoride cleavage of the silicon protecting group gave secondary alcohol **470** and allowed the product to be separated from remaining bromide **449**. Transformation of the alcohol **470** to the corresponding lactol **471** using our rearrangement conditions proceeded in high yield and with selectivity comparable to those obtained in the previous project.



Scheme 5.28. Synthesis of lactol 471.

5.2.5. Cyclisation vs dehydration

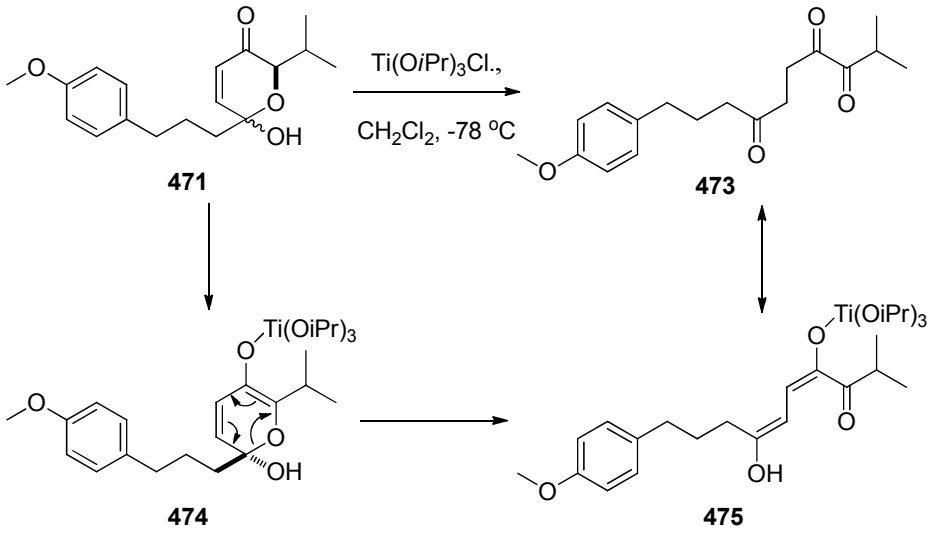
When lactol **471** was treated with boron trifluoride diethyl etherate to facilitate the nucleophilic attack of the benzene olefin onto the oxonium cation, only the dehydrated *exo*-olefin **472** was recovered. The observation is consistent with a very slow nucleophilic addition, so slow in fact that deprotonation α to the carbon atom of the oxonium ion proceeds rather than the cyclisation (Scheme 5.29).



Scheme 5.29. Formation of the dehydration product.

When the Lewis Acid was exchanged for silicon tetrachloride and ethyl aluminium chloride, the *exo*-olefin **472** was obtained exclusively. With tin tetrachloride as the Lewis acid, a small amount of **472** was obtained with larger quantities of degradation products in the reaction mixture.

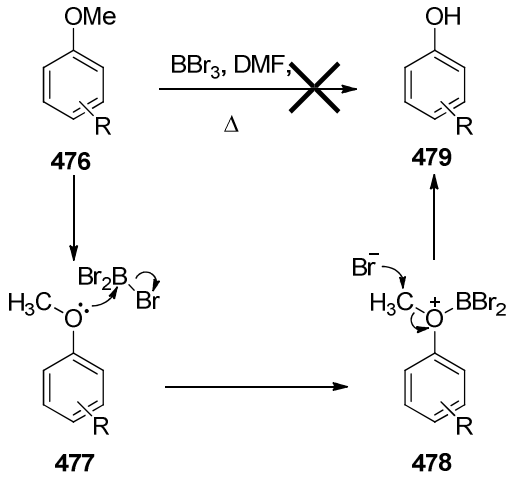
When tri*iso*propoxytitanium(IV) chloride was used an unexpected product **473** was formed. It is believed that the titanium species causes ring opening of lactol, giving the intermediate **474**, through enolisation of the ketone. Electron movement opens the ring, giving keto-diene **475**, that tautomerizes to the 1,2,5 diketone species **473**.



Scheme 5.30. Proposed synthesis of the 1,2,5 triketone system.

It did not appear as though the slow nucleophilic attack vs the quick dehydration could be influenced by alternative Lewis acids. It was decided that increasing

electron availability for the cyclisation, utilizing a phenolic hydroxyl instead of the phenolic methyl ether would provide the desired spirocyclic material. Thus, we decided to try boron tribromide as the Lewis acid to achieve the demethylation and cyclisation reactions simultaneously. Boron tribromide is widely accepted as a standard reagent for the cleavage of phenolic methyl ethers,[284,285] although a range of softer reaction conditions have been reported.[286,287] Mechanistically it is believed that the reaction proceeds by donation of the ether oxygens lone pair into the empty boron orbital **477**, a bromide anion is ejected as a result. Nucleophilic attack of the bromide onto the methyl carbon and electron movement onto the oxygen gives an oxygen-boron bond **478** that is cleaved upon acidic workup to give phenol **479** (Scheme 5.31).

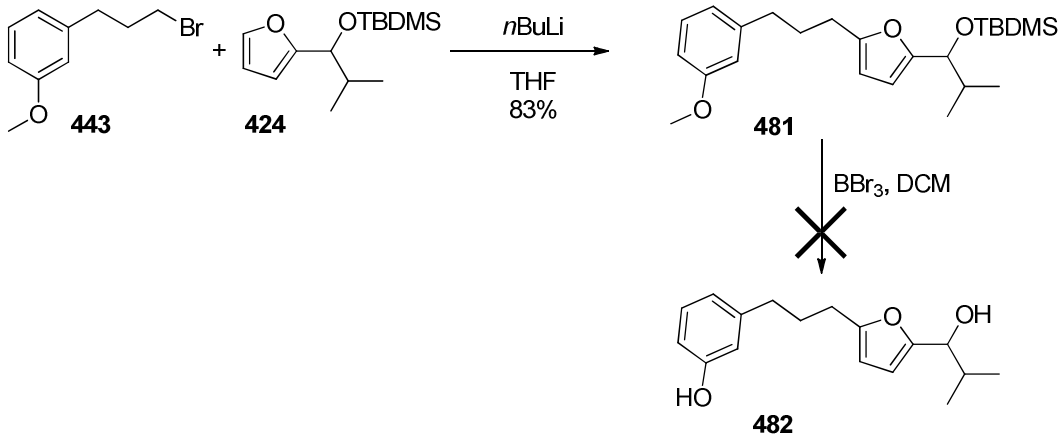


Scheme 5.31. The mechanism of BBr_3 cleavage of phenolic methyl ethers.

However treatment of lactols **471** with boron tribromide in dichloromethane gave only the *exo*-cycle **472**. It was hoped that the methyl ether would be cleaved before oxonium formation thus avoiding the troublesome dehydration reaction. Unfortunately, this appears not to be the case as only *exo*-cyclic triene **472** was formed with no deprotected phenol observed. It appears that oxonium formation is a very quick process quicker than the cleavage of methyl ethers.

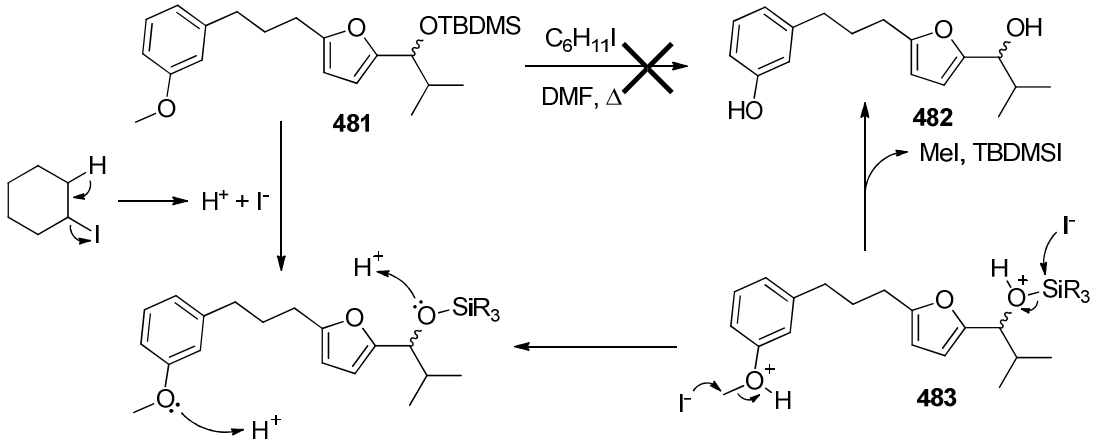
With the end of laboratory work fast approaching one final attempt to form these complex spirocycles was attempted. The synthetic route was as before with one extra step included (phenolic methyl ether cleavage). Bicycle **480** was generated from freshly distilled silyl ether **424** and bromide **443**, as previously described although the yield was greatly improved (83%). When boron tribromide was added to a solution of furanyl alcohol **480**, cleavage of both silyl and methyl

ether were anticipated, as there exist evidence of silyl ether cleavage with Lewis acids.[288-291] Unfortunately all that was achieved was extensive degradation of the starting materials.



Scheme 5.32. Attempts to synthesize diol 481

Searching the literature, milder conditions were found utilizing cyclohexyl iodide.[292] Cyclohexyl iodide undergoes thermal decomposition wherein an iodide anion is eliminated as hydrogen iodide. Protonation of the oxygens give the dication intermediate **483**. Attack of the iodide onto the carbon and silicon groups causes methyl iodide and *tert*butyldimethylsilyl iodide to be ejected from intermediate **483** giving diol **482**

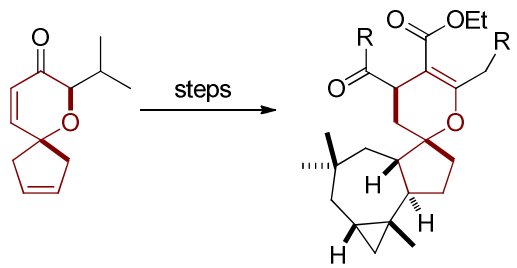


Scheme 5.33. Demethylation and desilylation of 481.

5.3. Future Work

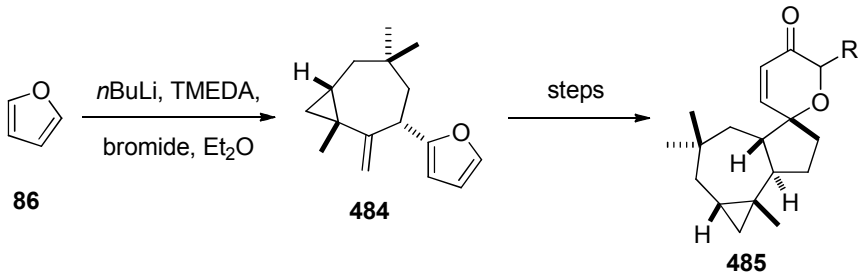
5.3.1. Spirocyclic products

With a method in place for the generation of spirocycles **410**, **419**, **420** and **429** it is intended to apply it to the synthesis of spirocyclic natural products. Of particular interest is the complex natural product Polymaxenolide .



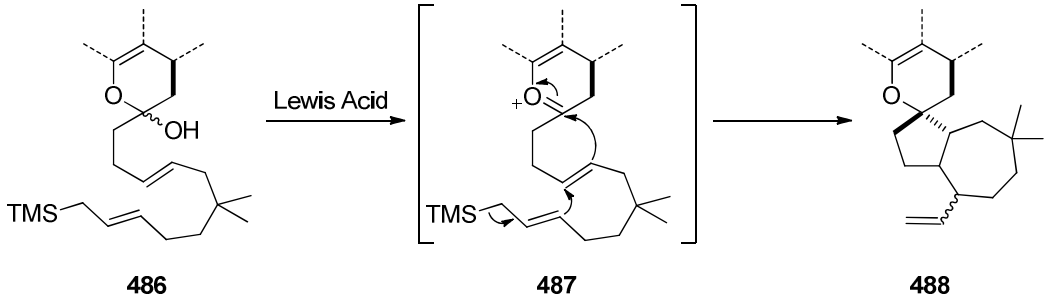
Scheme 5.34. Spirocycle 433 and Polymaxenolide 6.

The introduction of the cycloheptane fused ring system could be problematic, initially it was expected that isomerisation of the C2-C3 olefin could be achieved using Wilkinsons catalyst.[293] The new olefin could participate in a cycloaddition reaction building the carbon framework further. Another approach that is being considered is the use of a functionalised allylic bromide to alkylate furan **86** in the initial stages of the synthesis (Scheme 5.35) to produce **484** that could then be carried forward. Tadano,[294] and Oishi[295] have already demonstrated the flexibility/tolerance of the Achmatowicz rearrangement, accepting large functionality around the furan ring system.



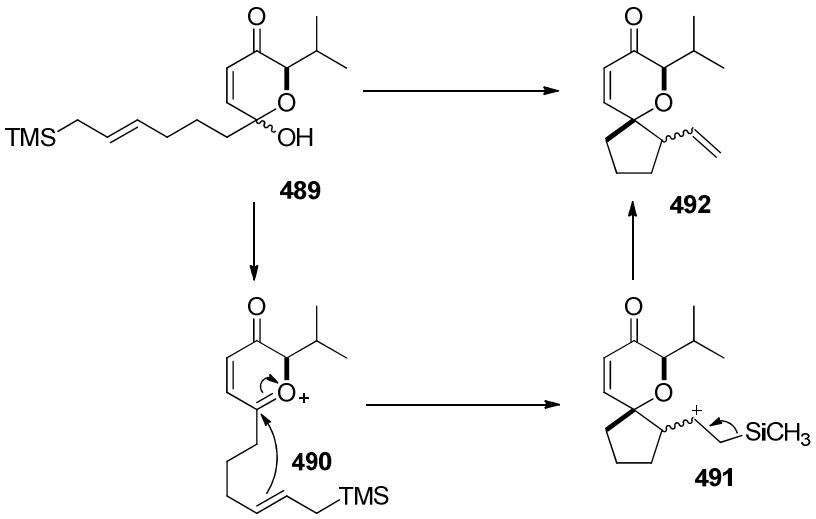
Scheme 5.35. Incorporation of the fused ring systems into the methodology.

Finally, a route that is being examined is centered on a modified Sakurai type reaction. It is envisioned that treatment of olefin **486** with Lewis acid will induce a cyclisation cascade via intermediate **487**, setting the 5 and 7 membered rings in one reaction leaving an *exo*-cyclic vinyl group **488** that could be further functionalised.



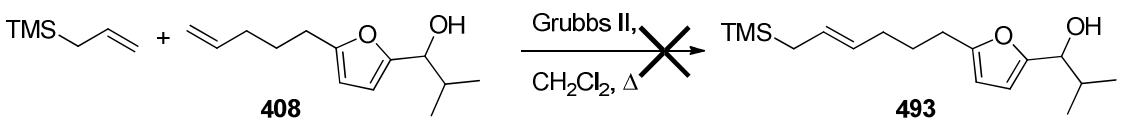
Scheme 5.36. Sakurai cascade.

To investigate the feasibility of this approach a model system has been designed, it is envisaged that treatment of olefin **489** with Lewis acid will cause oxonium formation **490** and subsequent nucleophilic attack of the olefin. The loss of the terminal TMS group from intermediate **491** regenerates the olefin giving the spirocycle **492**.



Scheme 5.37. Intramolecular Sakurai reaction

Initial experiments attempting to introduce the allylic TMS group have been unsuccessful. Cross metathesis reactions between allyl TMS and alkene furan **415** using Gouverneur's method,[296] Grubbs 2nd generation catalyst, have not provided any of the desired product **493**. It is believed that the metathesis product is unstable to silica gel and extensive product degradation has been observed.

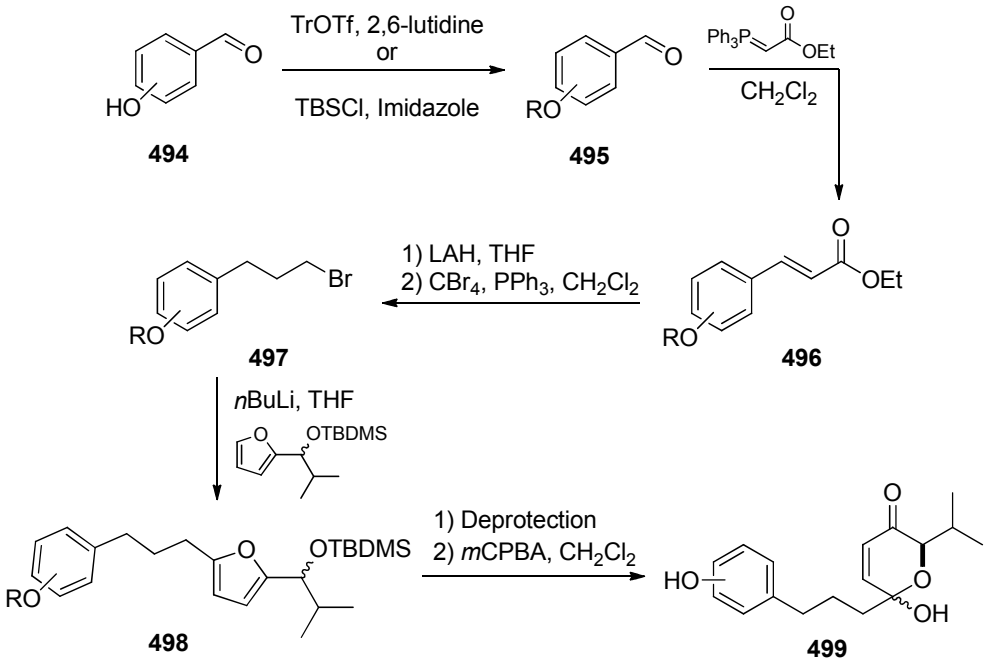


Scheme 5.38. Cross metathesis of alkene 408.[296]

In either eventuality much more research and experimentation is required to take the methodology described further towards the synthesis of Polymaxenolide.

5.3.2. Methoxy directed cyclisations

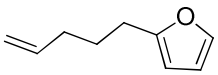
Having successfully synthesized the lactol core **491**, increasing the electron availability of the phenyl ring is the first priority for this project. The synthesis of lactol **499** must be altered slightly, in that an appropriate orthogonal protecting group must be introduced masking the phenolic alcohol. Thus aldehyde **495** will be synthesized from 3-/4-hydroxy benzaldehyde **494**, upon treatment with trityl chloride (TrCl)[297] or trialkylsilyl chloride (SiR_3Cl).[298] **495** will then be olefinated, reduced and converted to the bromide as per the previously established protocols (Scheme 5.14). Coupling reaction between freshly distilled bromide **497** and silyl ether **424** will give the bicycle **498**, cleavage of the protecting group will give the rearrangement precursor that could be converted to lactol **499**. Treatment of the lactols **499** with a Lewis acid should provide the desired spirocyclic compounds.



Scheme 5.39. Future work.

6. Experimental

2-Pent-4-enyl furan, 407.[246]



A solution of furan **86** (1.69 mL, 24.9 mmol) in anhydrous THF (125 mL) at 0 °C was treated with *n*BuLi (10.5 mL, 26.2 mmol, 2.5 M in hexanes) and the resulting mixture allowed to warm up to room temperature. The solution was stirred for 24 hours, at which point 5-bromopent-1-ene (3.09 mL, 26.2 mmol) was added slowly. The resulting reaction mixture was then stirred at room temperature for a further 24 hours. The reaction was then poured onto ice and the resulting mixture diluted with diethyl ether (100 mL). The resulting brown liquid was then stirred for 20 minutes after which it was extracted with diethyl ether (2x 30 mL). The combined organic extracts were washed with water (2x 20 mL), brine (20 mL) and then dried over sodium sulfate. Following concentration *in vacuo*, the residue was purified by short path distillation giving 2.11 g of alkene **407** (62% yield) as clear oil.

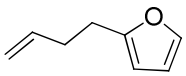
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (1H, d, *J* = 1.0 z, Ar-*H*), 6.32 (1H, d, *J* = 1.8 Hz, Ar-*H*), 6.03 (1H, d, *J* = 2.6 Hz, Ar-*H*), 5.92-5.82 (1H, m, CH_2CHCH_2), 5.10-5.02 (2H, m, CH_2CHCH_2), 2.69 (2H, t, *J* = 7.6 Hz, $CH_2CH_2CH_2$), 2.16 (2H, q, *J* = 7.2 Hz, $CH_2CH_2CH_2$), 2.69 (2H, t, *J* = 7.6 Hz, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (Ar-*C*), 140.8 (Ar-*C*), 138.2 (CH_2CHCH_2), 114.9 (CH_2CHCH_2), 110.0 (Ar-*C*), 104.8 (Ar-*C*), 33.2 ($CH_2CH_2CH_2$), 27.3 ($CH_2CH_2CH_2$), 27.2 ($CH_2CH_2CH_2$).

m/*z* [EI$^+$(+ve)] 136.1 $[M]^+$ (100%).

ν_{max} (neat)/cm^{-1}. 2092, 1642, 799.

2-But-3-enyl furan, 411.



A solution of furan **86** (1.49 mL, 22.0 mmol) in anhydrous THF (100 mL) at 0 °C was treated with *n*BuLi (8.84 mL, 22.1 mmol, 2.5 M in hexanes) and the resulting mixture allowed to warm up to room temperature. The solution was stirred for 24 hours, at which point 4-bromobut-1-ene (2.24 mL, 22.1 mmol) was added slowly. The resulting reaction mixture was then stirred at room temperature for

a further 24 hours. The reaction was then poured onto ice and the resulting mixture diluted with diethyl ether (100 mL). The resulting brown liquid was then stirred for 20 minutes and was then extracted with diethyl ether (2x 30 mL). The combined organic extracts were washed with water (2x 20 mL), brine (20 mL) and then dried over sodium sulfate. Following concentration *in vacuo*, the residue was purified by short path distillation, giving 2.28 g of alkene **411** in 85% yield as clear oil.

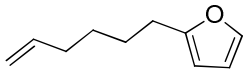
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (1H, dd, J = 1.8, 0.8 Hz, Ar-*H*), 6.21 (1H, dd, J = 3.1, 1.9 Hz, Ar-*H*), 5.93 (1H, dd, J = 3.2, 0.9 Hz, Ar-*H*), 5.82-5.74 (1H, m, CH_2CH), 5.02-4.91 (2H, m, CH_2CH), 2.65 (2H, t, J = 9.1 Hz, $CHCH_2CH_2$), 2.36-2.31 (2H, m, $CHCH_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.4 (Ar-*C*), 137.5 (CH_2CH), 117.4 (CH_2CHCH_2), 115.2 (Ar-*C*), 110.0 (Ar-*C*), 104.9 (Ar-*C*), 32.1 ($CHCH_2CH_2$), 27.5 ($CHCH_2CH_2$).

m/z [EI$^+$(+ve)] 122.1 [M]$^+$ (100%).

ν_{max} (neat)/cm^{-1}. 3080, 2959, 1641, 1009, 729.

2-Hex-5-enyl furan, 412.



A solution of furan **86** (0.99 mL, 14.6 mmol) in anhydrous THF (74 mL) at 0 °C was treated with *n*BuLi (5.84 mL, 14.6 mmol, 2.5 M in hexanes) and the resulting mixture allowed to warm up to room temperature. The solution was stirred for 24 hours, at which point 6-bromohex-1-ene (1.88 mL, 14.6 mmol) was added slowly. The resulting mixture was then stirred at room temperature for a further 24 hours. The reaction was then poured onto ice and the resulting mixture diluted with diethyl ether (100 mL). The resulting brown liquid was stirred for 20 minutes after which it was extracted with diethyl ether (2x 20 mL). The combined organic extracts were washed with water (2x 20 mL), brine (20 mL) and then dried over sodium sulfate. Following concentration *in vacuo*, the residue was purified by short path distillation. Giving 1.89 g (87% yield) of alkene **412**, as clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (1H, dd, J = 1.8, 0.8 Hz, Ar-*H*), 6.19 (1H, dd, J = 3.1, 1.9 Hz, Ar-*H*), 5.89 (1H, dd, J = 3.1, 0.8 Hz, Ar-*H*), 5.77-5.68 (1H, m, CH_2CHCH_2), 4.95-4.86 (2H, m, CH_2CH), 2.55 (2H, t, J = 7.6 Hz, CH_2CH_2Ar), 2.00-1.98 (2H, m, $CHCH_2$), 1.61-1.55 (2H, m, CH_2CH_2Ar), 1.36 (2H, quint, J = 7.3 Hz,

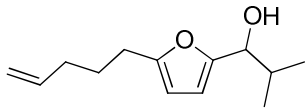
$CHCH_2\mathit{CH_2}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5 (Ar-*C*), 154.8 (Ar-*C*), 138.8 ($CH_2\mathit{C}H$), 114.4 ($\mathit{C}H_2CH$), 104.8 (Ar-*C*), 104.2 (Ar-*C*), 33.5 ($CH_2\mathit{C}H_2Ar$), 28.4 ($CH_2CH\mathit{C}H_2$), 27.5 ($CH_2CH_2\mathit{C}H_2$), 26.4 ($CH_2\mathit{C}H_2CH_2$).

m/*z* [EI^+(+ve)] 150.1 $[M]^+$ (100%).

ν_{max} (neat)/cm^{-1}.2976, 2932, 2858, 1640, 1606, 910, 781.

2-Methyl-1-(5-pent-4-enylfuran-2-yl)-propan-1-ol, 408.



To a solution of alkenyl furan **407** (2.12 g, 15.1 mmol) and TMEDA (2.49 g, 16.6 mmol) in anhydrous diethyl ether (76 mL) at 0 °C was added slowly *n*BuLi (6.4 mL, 15.9 mmol). The resulting solution was allowed to warm to room temperature over a period of 3 hours; at this point, it was cooled to −78 °C and treated with *iso*butyraldehyde (1.51 mL, 16.6 mmol). The reaction was then stirred for 30 minutes at −78 °C, after which it was allowed to warm up to 0 °C and stirred for 2 hours. Saturated aqueous ammonium chloride solution (10 mL) was added before being extracted with cold diethyl ether (2x 20 mL). The combined organic phases were washed with water (2x 15 ml), brine (15 ml), dried over sodium sulfate and concentrated *in vacuo*. The crude residue obtained was then purified by flash column chromatography (silica gel, 10% diethyl ether in petroleum spirit) to give 1.95 g (62% yield) **408** as a clear oil.

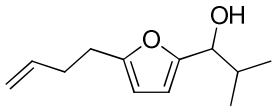
^1H NMR (500 MHz, $CDCl_3$): δ 6.06 (1H, d, *J* = 3.0 Hz, Ar-*H*), 5.87 (1H, d, *J* = 3.0 Hz, Ar-*H*), 5.77 (1H, m, $CH_2C\mathit{H}CH_2$), 4.99 (1H, dq, *J* = 17.1, 1.6 Hz, $\mathit{CH_2}CHCH_2$), 4.94 (1H, d, *J* = 10.2 Hz, $\mathit{CH_2}CHCH_2$), 4.24 (1H, d, *J* = 7.2 Hz, C*H*(OH)), 2.57 (2H, t, *J* = 7.5 Hz, $C\mathit{H_2}Ar$), 2.15 (1H, bs, OH), 2.09–2.00 (3H, m, $CH_2CHC\mathit{H_2}$ and $C\mathit{H}(CH_3)_2$), 1.69 (2H, q, *J* = 7.5 Hz, $CH_2\mathit{CH_2}CH_2$), 0.98 (3H, d, *J* = 6.8 Hz, $CH(\mathit{CH_3})_2$), 0.81 (3H, d, *J* = 6.7 Hz, $CH(\mathit{CH_3})_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3 (Ar-*C*), 154.3 (Ar-*C*), 138.2 ($CH_2\mathit{C}H$), 114.9 (CH_2CH), 107.0 (Ar-*C*), 105.2 (Ar-*C*), 73.5 (*C*H(OH)), 33.2 ($\mathit{C}H_2Ar$), 33.1 ($CH_2CH_2\mathit{C}H_2$), 27.3 ($CH_2\mathit{C}H_2CH_2$), 27.2 ($\mathit{C}H(CH_3)_2$), 18.8 ($CH(C\mathit{H_3})_2$), 18.4 ($CH(C\mathit{H_3})_2$).

m/*z* [EI^+(+ve)] 191.1 $[M\text{-}OH]^+$ (100%), HRMS found 231.1312, $C_{12}H_{20}NaO_2$ requires 231.1360 (M^++Na).

ν_{max} (neat)/cm^{-1}. 3438, 2960, 2932, 2871, 1640, 1384, 907.

2-Methyl-1-(5-But-3-enylfuran-2-yl)-propan-1-ol, 413.



To a solution of alkenyl furan **411** (784 mg, 6.42 mmol) and TMEDA (960 μL, 6.42 mmol) in anhydrous diethyl ether (32 mL) at 0 °C was added slowly *n*BuLi (2.56 mL, 6.42 mmol, 2.5 M in hexanes). The resulting solution was allowed to warm to room temperature over a period of 3 hours; at this point, it was cooled to −78 °C and treated with *iso*butyraldehyde (639 μL, 6.42 mmol). The reaction was then stirred for 30 minutes at −78 °C, after which it was allowed to warm up to 0 °C and stirred for 2 hours. Saturated aqueous ammonium chloride solution (10 mL) was added before being extracted with cold diethyl ether (2x 20 mL). The combined organic phases were washed with water (2x 15 ml), brine (15 ml), dried over sodium sulfate and concentrated *in vacuo*. The crude residue obtained was then purified by flash column chromatography (silica gel, 10% diethyl ether in petroleum spirit) to give 1.06 g (85% yield) **413** as a clear oil.

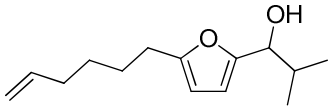
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (1H, d, J = 3.0 Hz, Ar-*H*), 5.85 (1H, d, J = 2.2 Hz, Ar-*H*), 5.79 (1H, m, CH_2CHCH_2), 4.97 (1H, dq, J = 15.4, 1.7 Hz, CH_2CHCH_2), 4.91 (1H, d, J = 10.2 Hz, CH_2CHCH_2), 4.21 (1H, dd, J = 7.0, 3.3 Hz, *CH*OH), 2.62 (2H, t, J = 7.6 Hz, ArCH_2CH_2), 2.34–2.28 (2H, m, CH_2CHCH_2), 2.01 (1H, sept, J = 6.9 Hz, $CH(CH_3)_2$), 1.83 (1H, d, J = 2.8 Hz, OH), 0.94 (3H, d, J = 6.7 Hz, $CH(CH_3)_2$), 0.77 (3H, d, J = 6.7 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9 (Ar-*C*), 154.3 (Ar-*C*), 137.5 ($CHCH_2CH_2$), 115.3 (CH_2CHCH_2), 107.1 (Ar-*C*), 105.4 (Ar-*C*), 73.6 (*C*HOH), 33.3 ($CH(CH_3)_2$), 32.1 ($CHCH_2CH_2$), 27.6 ($CHCH_2CH_2$), 18.8 ($CH(CH_3)_2$), 18.4 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 177.1 [M$^+$] (100%).

ν_{max} (neat)/cm^{-1}. 3601, 2960, 2926, 1468, 1014.

2-Methyl-1-(5-Hex-5-enylfuran-2-yl)propan-1-ol, 414.



To a solution of alkenyl furan **412** (1.39 g, 9.31 mmol) and TMEDA (1.39 mL, 9.31 mmol) in anhydrous diethyl ether (46 mL) at 0 °C was added slowly *n*BuLi (3.72 mL, 9.31 mmol, 2.5 M in hexanes). The resulting solution was allowed to warm to room temperature over a period of 3 hours; at this point, it was cooled to −78

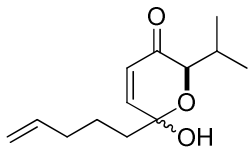
°C and treated with *iso*butyraldehyde (840 μL, 9.31 mmol). The reaction was then stirred for 30 minutes at −78 °C, after which it was allowed to warm up to 0 °C and stirred for 2 hours. Saturated aqueous ammonium chloride solution (10 mL) was added before being extracted with cold diethyl ether (2x 20 mL). The combined organic phases were washed with water (2x 15 ml), brine (15 ml), dried over sodium sulfate and concentrated *in vacuo*. The crude residue obtained was then purified by flash column chromatography (silica gel, 10% diethyl ether in petroleum spirit) to give 1.55 g **414** as a clear oil in 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (1H, d, J = 3.1 Hz, Ar-*H*), 5.87 (1H, d, J = 3.0 Hz, Ar-*H*), 5.77 (1H, m, CH_2CHCH_2), 4.97 (1H, dq, J = 17.1, 1.9 Hz, CH_2CHCH_2), 4.92 (1H, dq, J = 10.1, 0.9 Hz, CH_2CHCH_2), 4.25 (1H, d, J = 6.8 Hz, *CH*OH), 2.57 (2H, t, J = 7.5 Hz, $ArCH_2CH_2$), 2.09–1.96 (4H, m, CH_2CHCH_2, $CH(CH_3)_2$, OH), 1.61 (2H, q, J = 7.6 Hz, CH_2CH_2), 1.41 (2H, quint, J = 7.8 Hz, CH_2CH_2), 0.99 (3H, d, J = 6.7 Hz, $CH(CH_3)_2$), 0.82 (3H, d, J = 6.8 Hz, $CH(CH_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9 (Ar-*C*), 154.5 (Ar-*C*), 138.9 (CH_2CH), 114.7 (CH^2CH), 107.3 (Ar-*C*), 105.4 (Ar-*C*), 77.8 (*C*HOH), 33.7 (CH_2Ar), 33.5 (CH_2CHCH_2), 28.6 ($CH(CH_3)_2$), 28.1 (CH_2CH_2), 27.7 (CH_2CH_2), 19.1 ($CH(CH_3)_2$), 18.7 $CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 205.1 [M-OH]$^+$ (100%), HRMS found 245.1489, $C_{14}H_{22}NaO_2$ requires 245.1517 [M + Na]$^+$.

ν_{max} (neat)/cm^{-1}. 3437, 2959, 2931, 1462, 1011, 910.

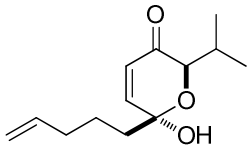
6-Hydroxy-2-*iso*propyl-6-pent-4-enyl-6H-pyran-3-one, **397.**



A 0 °C solution of furfuryl alcohol **408** (1.40 g, 6.74 mmol) in dichloromethane (34 mL) was treated with *meta*-chloroperoxybenzoic acid (1.67 g, 7.41 mmol) and the resulting opaque solution was stirred at 0 °C for 1 hour. The mixture was allowed to warm up to room temperature and the reaction was stirred for a further 2 hours. The reaction was cooled to 0 °C and quenched by the slow addition of saturated aqueous sodium bicarbonate (10 mL). The resulting emulsion was allowed to separate and was then extracted with dichloromethane (3x 15 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The solution was

concentrated *in vacuo* and the residue obtained purified by flash column chromatography (silica gel, 30% diethyl ether in petroleum spirits) to give 1.44 g (96% yield) of lactol **397** as a mixture of anomers (α:β, 8:1).

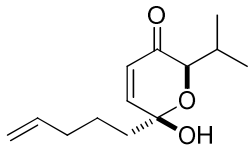
Major anomer 397α.



^{1}H NMR (500 MHz, $CDCl_3$): *δ* 6.76 (1H, d, *J* = 10.2 Hz, C*H*CHCO), 6.02 (1H, d, *J* = 10.2 Hz, CHC*H*CO), 5.75 (1H, m, CH_2CHCH_2), 5.03–4.93 (2H, m, CH_2CHCH_2), 4.32 (1H, d, *J* = 2.7 Hz, CO*CH*(O)CH), 2.89 (1H, bs, OH), 2.42 (1H, m, CH_2CHCH_2), 2.05 (2H, m, CH_2CHCH_2 and $CH(CH_3)_2$), 1.84–1.79 (2H, m, $CH_2C(O)OH$), 1.56 (1H, m, $CH_2CH_2CH_2$), 1.47 (1H, m, $CH_2CH_2CH_2$), 1.00 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 0.82 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): *δ* 197.0 (CHCH*C*O), 147.5 (*C*HCHCO), 138.1 ($CHCHCH_2$), 127.9 (CH*C*HCO), 119.5 (CH_2CHCH_2), 93.9 (*C*(O)OH), 78.2 (CO*C*H(O)CH), 41.1 (CH_2CHCH_2), 33.0 ($CH_2C(O)OH$), 28.7 ($CH(CH_3)_2$), 22.8 ($CH_2CH_2CH_2$), 19.0 ($CH(CH_3)_2$), 16.9 ($CH(CH_3)_2$).

Minor anomer 397β.



^{1}H NMR (500 MHz, $CDCl_3$): *δ* 6.86 (1H, d, *J* = 9.9 Hz, *CH*CHCO), 5.91 (1H, dd, *J* = 9.9, 0.4 Hz, CH*CH*CO), 5.77 (1H, m, CH_2CHCH_2), 5.05–4.93 (2H, m, CH_2CHCH_2), 4.19 (1H, d, *J* = 4.8 Hz, CO*CH*(O)CH), 2.35 (2H, q, *J* = 7.4 Hz, CH_2CHCH_2), 2.24-2.13 (3H, m, $CH(CH_3)_2$ and $CH_2C(O)OH$), 1.75 (1H, m, $CH_2CH_2CH_2$), 1.25 (1H, m, $CH_2CH_2CH_2$), 0.99 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 0.91 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$).

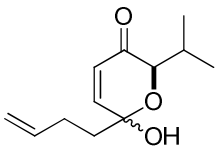
^{13}C NMR (125 MHz, $CDCl_3$): *δ* 195.2 (CHCH*C*O), 147.1 (*C*HCHCO), 141.9 (CH_2CHCH_2), 137.8 (CHC*H*CO), 121.9 (CH_2CHCH_2), 85.6 (*C*(O)OH), 78.2 (CO*C*H(O)CH), 33.5 (CH_2CHCH_2), 32.8 ($CH_2C(O)OH$), 31.8 ($CH(CH_3)_2$), 24.8 ($CH_2CH_2CH_2$), 18.9 ($CH(CH_3)_2$), 16.1 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 207.1 $[M–OH]^+$ (100%), HRMS found 247.1305, $C_{13}H_{20}NaO_3$

requires 247.1310 $[M+Na]^+$.

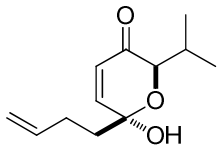
ν_{max}(film)/cm^{-1}: 3400, 2966, 2930, 1676, 1382, 908.

6-Hydroxy-2-*iso*propyl-6-but-3-enyl-6H-pyran-3-one, 415.



A 0 °C solution of furfuryl alcohol **413** (1.71 g, 8.82 mmol) in dichloromethane (44 mL) was treated with *meta*-chloroperoxybenzoic acid (2.17 g, 9.70 mmol) and the resulting opaque solution was stirred at 0 °C for 1 hour. The mixture was allowed to warm up to room temperature and the reaction stirred for a further 3 hours. The reaction was cooled to 0 °C and quenched by slow addition of saturated aqueous sodium bicarbonate (15 mL). The resulting emulsion was allowed to separate and was then extracted with dichloromethane (3x 15 mL). The combined organic extracts were washed with water (15 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo and the residue obtained purified by flash column chromatography (silica gel, 20% diethyl ether in petroleum spirits) to give 1.47 g (81% yield)of lactols **415** as a mixture of anomers (α:β, 7.8:1).

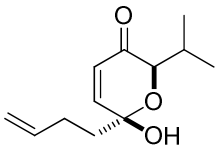
Major anomer 415α



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (1H, d, *J* = 10.2 Hz, *CH*CHCO), 6.05 (1H, d, *J* = 10.2 Hz, CH*CH*CO), 5.90 (1H, m, CH_2CHCH_2), 5.11 (1H, d, *J* = 17.2 Hz, CH_2CHCH_2), 5.04 (1H, d, *J* = 10.2 Hz, CH_2CHCH_2), 4.37 (1H, d, *J* = 2.7 Hz, COCH(O)CH), 3.05 (1H, bs, OH), 2.47 (1H, m, $CH(CH_3)_2$), 2.34 (1H, m, CH_2CHCH_2), 2.19 (1H, m, CH_2CHCH_2), 1.97 (2H, m, CH_2CH_2), 1.06 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 0.87 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.2 (CHCHCO), 147.2 (CHCHCO), 135.4 (CH_2CHCH_2), 122.3 (CHCHCO), 116.9 (CH_2CHCH_2), 115.6 (C(O)OH), 85.4 (COCH(O)CH), 31.8 (CH_2CHCH_2), 30.9 ($CH(CH_3)_2$), 29.7 (CH_2CH_2), 18.9 ($CH(CH_3)_2$), 16.9 ($CH(CH_3)_2$).

Minor anomer 415β



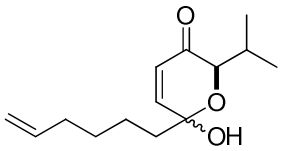
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (1H, d, J = 10.3 Hz, *CH*CHCO), 6.07 (1H, d, J = 10.2 Hz, CH*CH*CO), 5.89 (1H, m, CH_2CHCH_2), 5.09 (1H, d, J = 16.9 Hz, CH_2CHCH_2), 5.02 (1H, d, J = 10.1 Hz, CH_2CHCH_2), 3.95 (1H, d, J = 4.1 Hz, COCH(O)CH), 2.44 (1H, m, $CH(CH_3)_2$), 2.37 (1H, m, CH_2CHCH_2), 2.23 (1H, m, CH_2CHCH_2), 1.94 (2H, m, CH_2CH_2), 1.05 (3H, d, J = 6.9 Hz, $CH(CH_3)_2$), 0.95 (3H, d, J = 6.7 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2 (*C*O), 146.8 (*C*HCH), 135.9 (CH_2CH), 123.4 (*C*HCO), 116.1 (CH_2CH), 93.5 (OCOH), 89.1 (COCH), 45.2 ($CHCH_2CH_2$), 29.0 ($CH(CH_3)_2$), 21.4 ($CHCH_2CH_2$), 18.7 ($CH(CH_3)_2$), 18.6 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 193.1 [M−OH]$^+$ (85%), HRMS found 233.1148, $C_{12}H_{18}NaO_3$ requires 233.1153 [M+Na]$^+$.

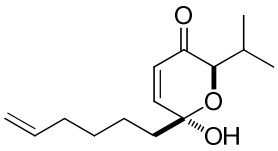
ν_{max} (film)/cm^{-1}: 3432, 2967, 2932, 1686, 1041, 910.

6-Hydroxy-2-*iso*propyl-6-Hex-5-enyl-6H-pyran-3-one, 416.



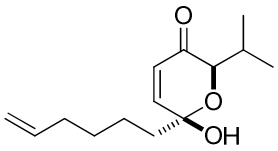
A 0 °C solution of furfuryl alcohol **414** (1.46 g, 6.64 mmol) in dichloromethane (33 mL) was treated with *meta*-chloroperoxybenzoic acid (1.64 g, 7.30 mmol) and the resulting opaque solution was stirred at 0 °C for 1 hour. The mixture was allowed to warm up to room temperature and the reaction stirred for a further 2 hours. The reaction was cooled to 0 °C and quenched by slow addition of saturated aqueous sodium bicarbonate (10 mL). The resulting emulsion was allowed to separate and was then extracted with dichloromethane (3x 15 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* and the residue obtained purified by flash column chromatography (silica gel, 30% diethyl ether in petroleum spirits) to give 1.19 g (75% yield) of lactol **416** as a mixture of anomers (α:β, 7.9:1).

Major anomer 416α.



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (1H, d, J = 10.2 Hz, *CH*CHCO), 6.03 (1H, d, J = 10.2 Hz, CH*CH*CO), 5.77 (1H, m, CH_2CHCH_2), 4.98 (1H, dq, J = 17.1, 1.9 Hz, CH_2CHCH_2), 4.93 (1H, d, J = 10.2 Hz, CH_2CHCH_2), 4.32 (1H, d, J = 2.7 Hz, CO*CH*(O)CH), 2.42 (1H, m, $CH(CH_3)_2$), 2.05 (2H, m, CH_2CHCH_2), 1.82–1.81 (2H, m, CH_2C(O)OH), 1.54–1.35 (4H, m, CH_2CH_2), 1.00 (3H, d, J = 7.0 Hz, $CH(CH_3)_2$), 0.83 (3H, d, J = 6.8 Hz, $(CH(CH_3)_2)$.

Minor anomer 416β

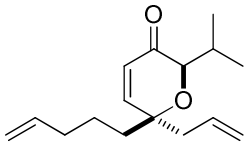


^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (1H, d, J = 10.3 Hz, *CH*CHCO), 6.00 (1H, d, J = 10.3 Hz, CH*CH*CO), 5.77 (1H, m, CH_2CHCH_2), 5.00–4.91 (2H, m, CH_2CHCH_2), 3.90 (1H, d, J = 4.1 Hz, CO*CH*(O)CH), 2.42 (1H, m, $CH(CH_3)_2$), 2.05 (2H, m, CH_2CHCH_2), 1.85–1.76 (2H, m, CH_2C(O)OH), 1.54–1.37 (4H, m, CH_2CH_2), 1.00 (3H, d, J = 6.9 Hz, $CH(CH_3)_2$), 0.90(3H, d, J = 6.8 Hz, $CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 221.1 [M−OH]$^+$ (100%), HRMS found 261.1461, $C_{14}H_{22}NaO_3$ requires 261.1466 [M + Na]$^+$.

ν_{max}(film)/cm^{-1}: 3429, 2966, 2931, 1671, 1382, 908.

6-Allyl-6-(pent-4-enyl)-2-*iso*propyl-6H-pyran-3-one, 409.



A solution of lactol **397** (0.99 g, 4.76 mmol) in anhydrous dichloromethane (23 mL) was treated with allyltrimethylsilane (1.58 mL, 9.99 mmol) and the resulting mixture was cooled to −78 °C. The reaction mixture was then treated by the slow addition of $BF_3{\cdot}OEt_2$ (1.78 mL, 14.1 mmol) and the resulting solution was stirred for 30 minutes at −78 °C. The reaction was then allowed to warm to room temperature and stirred for a further 2 hours. Once the reaction was complete,

as determined by TLC analysis, the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with dichloromethane (2x 10mL). The combined organic phases were washed sequentially with saturated sodium hydrogen carbonate (10 mL), water (2x 10 mL) and brine (10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 8% diethyl ether in petroleum spirits) to afford 945 mg (80 % yield) of desired bis-alkenyl product **409** as a clear oil.

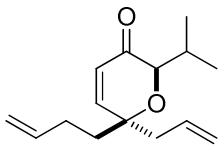
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (1H, d, J = 10.4 Hz, *CH*CHCO), 5.96 (1H, d, J = 10.4 Hz, CH*CH*CO), 5.78–5.65 (2H, m, CH_2*CH*CH_2), 5.07–4.85 (4H, m, *CH*$_2$CHCH$_2$), 4.02 (1H, d, J = 2.6 Hz, CO*CH*(O)CH), 2.51 (1H, ddt, J = 8.0, 6.5, 1.0 Hz, C(O)*CH*$_2$CHCH2), 2.34–2.40 (1H, m, *CH*(CH$_3$)$_2$), 2.32–2.30 (1H, m, C(O)*CH*$_2$CHCH$_2$), 2.00–2.01 (2H, m, *CH*$_2$CHCH$_2$), 1.70–1.64 (1H, m, *CH*$_2$CH$_2$), 1.53–1.44 (2H, m, CH$_2$*CH*$_2$), 1.30–1.22 (1H, m, *CH*$_2$CH$_2$), 0.95 (3H, d, J = 7.0 Hz, CH(*CH*$_3$)$_2$), 0.79 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.7 (CHCH*C*O), 154.6 (*C*HCHCO), 138.4 (CH_2*C*HCH$_2$), 132.6 (CH_2*C*HCH$_2$), 126.6 (CH*C*HCO), 118.6 (*C*H$_2$CHCH$_2$), 114.7 (CH_2CHCH$_2$), 78.5 (CO*C*H(O)CH), 75.7 (CH*C*(O)CH$_2$), 39.7 (CH_2CH*C*H$_2$), 38.0 (CH_2CH*C*H$_2$), 33.8 (*C*H$_2$C(O)), 29.1 (*C*H(CH$_3$)$_2$), 22.7 (CH_2*C*H$_2$CH$_2$), 19.2(CH(*C*H$_3$)$_2$), 16.9 (CH(*C*H$_3$)$_2$).

m/z [EI$^+$(+ve)] 249.2 [M]$^+$ (100%), HRMS found 249.1849, $C_{16}H_{25}O_2$ requires 249.1855 [M + H]$^+$.

ν_{max} (film)/ cm^{-1}: 2924, 1709, 1381, 911.

6-Allyl-6-(but-3-enyl)-2-*iso*propyl-6H-pyran-3-one, 417.



A solution of the lactol **415** (1.36 g, 6.45 mmol) in anhydrous dichloromethane (32 mL) was treated with allyltrimethylsilane (2.15 mL, 13.54 mmol) and the resulting mixture was cooled to −78 °C. The reaction mixture was then treated by the slow addition of $BF_3{\cdot}OEt_2$ (2.44 mL, 19.3 mmol) and the resulting solution stirred for 30 minutes at −78 °C. The reaction was then allowed to warm to room temperature and stirred for a further 2 hours. Once the reaction was complete, as determined by TLC analysis, the reaction was quenched with saturated

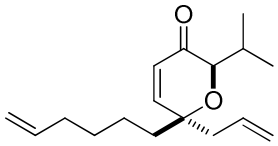
aqueous ammonium chloride (10 mL) and extracted with dichloromethane (2x 15 mL). The combined organic phases were washed sequentially with saturated sodium hydrogen carbonate (10 mL), water (2× 10 mL) and brine (10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude residue was then purified by flash column chromatography (silica gel, 20-50% dichloromethane in petroleum spirits) to afford 876 mg (58 % yield) of the desired bisalkenyl product **417**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (1H, d, J = 10.4 Hz, *CH*CHCO), 5.98 (1H, d, J = 10.4 Hz, CH*CH*CO), 5.80– 5.68 (2H, m, CH_2*CH*CH_2), 5.09–5.02 (2H, m, *CH*$_2$CHCH$_2$), 4.94 (1H, dq, J = 17.1, 1.7 Hz, *CH*$_2$CHCH$_2$), 4.88 (1H, dq, J = 10.2, 1.6 Hz, *CH*$_2$CHCH$_2$), 4.03 (1H, d, J = 2.5 Hz, CO*CH*(O)CH), 2.51 (1H, dd, J = 14.2, 6.4 Hz, CH$_2$CH*CH*$_2$), 2.39 (1H, m, *CH*(CH$_3$)$_2$), 2.29 (1H, m, CH$_2$CH*CH*$_2$), 2.19 (1H, m, CH$_2$CH*CH*$_2$), 1.93 (1H, m, CH$_2$CH*CH*$_2$), 1.80 (1H, ddd, J = 13.6, 11.9, 4.7 Hz, CH$_2$*CH*$_2$), 1.54 (1H, ddd, J = 13.6, 11.6, 4.7 Hz, *CH*$_2$CH$_2$), 0.96 (3H, d, J = 7.0 Hz, CH(*CH*$_3$)$_2$), 0.80 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.7 (CHCH*C*O), 154.3 (*C*HCHCO), 138.4 (CH$_2$*C*HCH$_2$), 132.5 (CH$_2$*C*HCH$_2$), 126.7 (CH*C*HCO), 118.8 (*C*H$_2$CHCH$_2$), 114.6 (*C*H$_2$CHCH$_2$), 78.6 (CO*C*H(O)CH), 75.5 (CH*C*(O)CH$_2$), 39.8 (CH$_2$CH*C*H$_2$), 37.8 (CH$_2$CH*C*H$_2$), 29.1 (*C*H(CH$_3$)$_2$), 27.9 (CH$_2$*C*H$_2$), 19.2 (CH(*C*H$_3$)$_2$), 16.0 (CH(*C*H$_3$)$_2$). m/z [EI$^+$(+ve)] 235.2 [M]$^+$, (100%), HRMS found 235.1693, $C_{15}H_{23}O_2$ requires 235.1698 [M]$^+$.

ν_{max} (film)/ cm^{-1}: 2964, 2930, 1686, 1061, 910.

6-Allyl-6-(hex-5-enyl)-2-*iso*propyl-6H-pyran-3-one, 418.



A solution of the lactol **416** (926 mg, 3.88 mmol) in anhydrous dichloromethane (20 mL) was treated with allyltrimethylsilane (1.29 mL, 8.16 mmol) and the resulting mixture was cooled to −78 °C. The reaction mixture was then treated by the slow addition of $BF_3{\cdot}OEt_2$ (1.48 g, 11.6 mmol) and the resulting solution stirred for 30 minutes at −78 °C. The reaction was then allowed to warm to room temperature and stirred for a further 2 hours. Once the reaction was complete, as determined by TLC analysis, the reaction was quenched with saturated aqueous ammonium chloride (15 mL) and extracted with dichloromethane (3x 20

mL). The combined organic extracts were washed sequentially with saturated sodium hydrogen carbonate (10 mL), water (2x 10 mL) and brine (10 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude residue was then purified by flash column chromatography (silica gel, 7% diethyl ether in petroleum spirits) to afford 778 mg (56% yield) of the desired bisalkenyl product **418**.

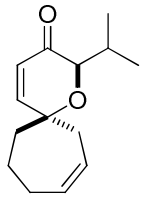
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (1H, d, J = 10.4 Hz, *CH*CHCO), 6.02 (1H, d, J = 10.4 Hz, CH*CH*CO), 5.75–5.73 (2H, m, CH_2CHCH_2), 5.13–5.07 (2H, m, CH_2CHCH_2), 4.97 (1H, dq, J = 17.1, 1.6 Hz, CH_2CHCH_2), 4.91 (1H, d, J = 10.2 Hz, CH_2CHCH_2), 4.04 (1H, d, J = 2.6 Hz, CO*CH*(O)CH), 2.54 (1H, dd, J = 14.2, 6.3 Hz, CH_2CHCH_2), 2.43 (1H, m, $CH(CH_3)_2$), 2.32 (1H, dd, J = 14.2, 8.2 Hz, CH_2CHCH_2), 2.02 (2H, m, J = 6.9 Hz, CH_2CHCH_2), 1.71 (1H, m, $CH_2CH_2CH_2$), 1.54–1.43 (2H, m, $CH_2CH_2CH_2$), 1.41–1.33 (2H, m, $CH_2CH_2CH_2$), 1.23 (1H, m, $CH_2CH_2CH_2$), 1.00 (3H, d, J = 7.0 Hz, $CH(CH_3)_2$), 0.84 (3H, d, J = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9 (CHCH*C*O), 154.7 (*C*HCHCO), 138.8 (CH_2CHCH_2), 132.7 (CH_2CHCH_2), 126.6 (CH*C*HCO), 118.6 (CH_2CHCH_2), 114.5 (CH_2CHCH_2), 78.6 (CO*C*H(O)CH), 75.8 (CH*C*(O)CH_2), 39.7 (CH_2CHCH_2), 38.5 (CH_2CHCH_2), 33.6 ($CH_2CH_2CH_2$), 29.2 ($CH(CH_3)_2$), 29.1 ($CH_2CH_2CH_2$), 22.9 ($CH_2CH_2CH_2$), 19.2 ($CH(CH_3)_2$), 16.0 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 263.2 $[M]^+$ (100%), HRMS found 263.2007 $C_{17}H_{27}O_2$ requires 263.2012 $[M]^+$.

ν_{max} (film)/ cm^{-1}: 3075, 2928, 1686, 1640, 1388, 911.

2-*Iso*propyl-1-oxaspiro[5.6]dodeca-4,8-dien-3-one, **410**.



A solution of bisalkenyl pyranone **409** (52 mg, 0.21 mmol) in dichloromethane (2 mL) in a darkened reaction vessel was treated with 5 mol% first generation Grubbs catalyst (8.6 mg, 10.5 μmol). The resulting mixture was then stirred and heated to reflux for 15 hours. The resulting black solution was concentrated *in vacuo* and the crude residue obtained was purified by flash column chromatography (silica gel, 7% diethyl ether in petroleum spirits) to give 29 mg (65% yield) of spirocycle **410** as a clear oil

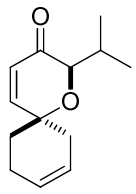
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (1H, d, *J* = 10.4 Hz, *CH*CHCO), 5.94 (1H, m, CH*CH*CO), 5.91 (1H, d, *J* = 10.3 Hz, *CH*CH), 5.50 (1H, m, CH*CH*), 3.94 (1H, d, *J* = 2.8 Hz, CO*CH*(O)CH), 2.53 (1H, dd, *J* = 14.9, 5.9 Hz, CHCH*CH*$_2$), 2.46 (1H, dd, *J* = 14.9, 7.1 Hz, CHCH*CH*$_2$), 2.38 (1H, m, *CH*(CH_3)$_2$), 2.23 (1H, m, CHCH*CH*$_2$), 2.16 (1H, m, CHCH*CH*$_2$), 2.03 (1H, m, CH_2*CH*$_2$), 1.85 (1H, m, CH_2*CH*$_2$), 1.77 (1H, m, *CH*$_2$$CH_2$), 1.57 (1H, m, *CH*$_2$$CH_2$), 0.99 (3H, d, *J* = 6.9 Hz, CH(*CH*$_3$)$_2$), 0.83 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4 (CHCH*C*O), 155.5 (*C*HCHCO), 134.4 (*C*HCH), 125.0 (CH*C*H), 124.9 (CH*C*HCO), 78.4 (CO*C*H(O)CH), 72.6 (CH*C*(O)CH_2), 43.2 (CHCH*C*H$_2$), 33.4 (CHCH*C*H$_2$), 28.8 (*C*H(CH_3)$_2$), 28.4 (CH_2*C*H$_2$), 21.3 (*C*H$_2$$CH_2$), 19.3 (CH(*C*H$_3$)$_2$), 16.0 (CH(*C*H$_3$)$_2$).

m/z [EI$^+$(+ve)] 220.1 [M]$^+$ (100%).

ν_{max} (film)/ cm^{-1}: 2923, 1648,1368, 912.

2-*Iso*propyl-1-oxaspiro[5.5]undeca-4,8-dien-3-one, **419**.



Procedure A

A solution of bisalkenyl pyranone **417** (128 mg, 0.55 mmol) in dichloromethane (10 mL) in a darkened reaction vessel was treated with 5 mol% first generation Grubbs catalyst (22.5 mg, 27 μmol). The resulting mixture was then stirred and heated to reflux for 4 hours. The resulting black solution was concentrated *in vacuo* and the crude residue obtained was purified by flash column chromatography (silica gel, 40-60% dichloromethane in petroleum spirits) to give 88 mg (78% yield) of spirocycle **419** as a clear oil

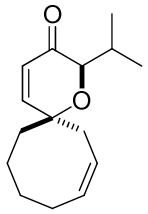
Method B

A solution of bisalkenyl pyranone **417** (72 mg, 0.31 mmol) in dichloromethane (1.5 mL) was treated with 5 mol% of Grubbs second generation catalyst (13 mg, 15 μmol). The resulting red solution was placed in a microwave reactor and heated to 100 ^{o}C for 6 minutes, then cooled to room temperature. The resulting black solution was concentrated *in vacuo* and the crude residue obtained was

purified by flash column chromatography (silica gel, 40-60% dichloromethane in petroleum spirits) to give 53 mg (85% yield) of spirocycle **419** as a clear oil

^{1}H NMR(500 MHz, $CDCl_3$): δ 6.84 (1H, d, J = 10.3 Hz, *CH*CHCO), 5.91 (1H, d, J = 10.3 Hz, CH*CH*CO), 5.70 (1H, m, *CH*CH), 5.52 (1H, m, CH*CH*), 3.95 (1H, d, J = 2.9 Hz, CO*CH*(O)CH), 2.37–2.24 (3H, m, CHCH*CH*$_2$, CHCH*CH*$_2$ and *CH*(CH_3)$_2$), 2.13 (1H, m, CHCH*CH*$_2$), 2.03 (1H, m, CHCH*CH*$_2$), 1.80 (1H, m, *CH*$_2$CH$_2$), 1.68 (1H, m, *CH*$_2$CH$_2$), 0.92 (3H, d, J = 6.9 Hz, CH(*CH*$_3$)$_2$), 0.80 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$).
^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5 (CHCH*C*O), 154.2 (*C*HCHCO), 126.9 (*C*HCH), 125.6 (CH*C*HCO), 122.6 (CH*C*H), 78.4 (CO*C*H(O)CH), 71.3 (CH*C*(O)CH$_2$), 32.8 (CH$_2$*C*H$_2$), 30.4 (CHCH*C*H$_2$), 28.8 (*C*H(CH$_3$)$_2$), 21.9 (CHCH*C*H$_2$), 19.1 (CH(*C*H$_3$)$_2$), 16.1 (CH(*C*H$_3$)$_2$).
m/z [EI$^+$(+ve)] 207.1 [M]$^+$ (100%). HRMS found 207.1380, $C_{13}H_{19}O_2$ requires 207.1385 [M]$^+$.
ν_{max} (film)/ cm^{-1}: 2965, 2926, 1687.

2-*Iso*propyl-1-oxaspiro[5.7]trideca-4,8-dien-3-one, 420.



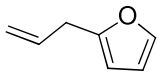
A solution of bisalkenyl pyrone **418** (121 mg, 0.46 mmol) in dichloromethane (10 mL) in a darkened reaction vessel was treated with 5 mol% first generation Grubbs catalyst (18.9 mg, 23 μmol). The resulting mixture was then stirred and heated to reflux for 18 hours. The resulting black solution was concentrated *in vacuo* and the crude residue obtained was purified by flash column chromatography (silica gel, 20-60% dichloromethane in petroleum spirits) to give 28 mg (26% yield) of spirocycle **420** as a clear oil
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (1H, d, J = 10.4 Hz, *CH*CHCO), 5.94 (1H, d, J = 10.4 Hz, CH*CH*CO), 5.85 (1H, m, *CH*CH), 5.49 (1H, m, CH*CH*), 4.05 (1H, d, J = 2.9 Hz, CO*CH*(O)CH), 2.52 (1H, dd, J = 13.5, 8.1 Hz, CHCH*CH*$_2$), 2.44–2.37 (2H, m, CHCH*CH*$_2$, *CH*(CH_3)$_2$), 2.19–2.14 (2H, m, CHCH*CH*$_2$), 1.88–1.76 (2H, m, *CH*$_2$CH$_2$CH$_2$), 1.66 (1H, m, CH$_2$*CH*$_2$CH$_2$), 1.61–1.42 (3H, m, CH$_2$*CH*$_2$CH$_2$, CH$_2$CH$_2$*CH*$_2$), 1.02 (3H, d, J = 6.9 Hz, CH(*CH*$_3$)$_2$), 0.83 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.3 (CHCH*C*O), 155.4 (*C*HCHCO), 133.4 (*C*HCH), 125.9 (CH*C*HCO), 125.3 (CH*C*H), 78.8 (CO*C*H(O)CH), 65.9 (*C*HC(O)CH_2), 37.3 (CHCH*C*H_2), 29.8 (*C*H$(CH_3)_2$), 28.9 (CHCH*C*H_2), 26.8 (CH_2CH_2*C*H_2), 19.3 (*C*$H_2CH_2CH_2$), 15.9 (CH_2*C*H_2CH_2), 15.3 (2 × CH(*C*$H_3)_2$).

HRMS found 257.1512, $C_{15}H_{22}NaO_2$ requires 257.1517 $[M+Na]^+$.

ν_{max} (film)/ cm^{-1}: 3154, 2932, 1685, 1383, 908.

2-Allylfuran, 421.[246]



A solution of furan **86** (1.61 mL, 22.0 mmol) in anhydrous THF (110 mL) at 0 °C was treated with *n*BuLi (8.84 mL, 22.1 mmol, 2.5 M in hexanes) and the resulting mixture allowed to warm up to room temperature. The solution was stirred for 24 hours at room temperature, at which point the allyl bromide (1.91 mL, 22.1 mmol) was added slowly. The resulting reaction mixture was then stirred at room temperature for a further 24 hours. The reaction was then poured onto ice and the resulting mixture diluted with diethyl ether (100 mL). The resulting brown liquid was then stirred for 20 minutes after which it was extracted with diethyl ether (2x 30 mL). The combined organic extracts were washed with water (2× 20 mL), brine (1× 20 mL) and then dried over sodium sulfate. The solvent was removed under reduced pressure to give 1.71 g (72% yield) alkene **421** in as clear oil.

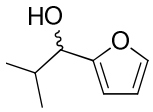
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (1H, q, J = 0.9 Hz, Ar-*H*), 6.17 (1H, dd, J = 3.2, 1.9 Hz, Ar-*H*), 5.89 (1H, dd, J = 3.2, 0.9 Hz, Ar-*H*), 5.85-5.77 (1H, m, CH_2*CH*), 5.04-4.98 (2H, m, *C*H_2CH), 3.27 (2H, d, J = 2.6 Hz, CH*C*H_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1 (Ar-*C*), 141.5 (Ar-*C*), 134.2 (CH_2*C*H), 117.1 (*C*H_2CHCH_2), 110.5 (Ar-*C*), 105.7 (Ar-*C*), 32.8 (CH_2CH*C*H_2).

m/z [EI^+(+ve)] 108.1 $[M]^+$ (99%).

ν_{max} (neat)/cm^{-1}. 3076, 2927, 1639, 995, 915.

1-Furan-2-yl-2-methyl-propan-1-ol, 423.[255]



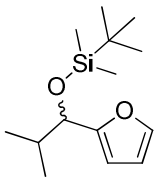
To a stirred solution of furan **86** (5.34 mL, 73.4 mmol), *N,N,N′,N′*-tetramethylethylenediamine (11.01 mL, 73.4mmol) in anhydrous diethyl ether (150 mL) at 0 °C was added slowly *n*BuLi (32.3 mL, 80.7 mmol, *2.5 M* in hexanes). The solution was stirred for 2 hours then cooled to -78 °C and *iso*butyraldehyde (7.33 mL, 80.74 mmol) added and stirred for 3 hours. Warmed to room temperature, water (50 mL) added and diluted with diethyl ether (50 mL). The organic layer was separated and washed sequentially with water (2 *x* 50 mL) and brine (50 mL) and dried over sodium sulfate. Solvents were removed *in vacuo* and the residue obtained was purified by flash column chromatography (30% ethyl acetate: petroleum spirits) gave 1-furan-2-yl-2-methyl-propan-1-ol **423** was obtained, 10.3 g in 99% yield.

^{1}H NMR(400 MHz, $CDCl_3$): *δ* 7.37 (1H, dd, *J* = 2.0, 1.2 Hz, Ar-*H*), 6.33 (1H, dd, *J* = 3.2, 2 Hz, Ar-*H*), 6.27 (1H, dd, *J* = 3.6, 1.0 Hz, Ar-*H*), 4.37 (1H, d, *J* = 6.8 Hz, CH*CH*OH), 2.17-2.05 (1H, m, *CH*$(CH_3)_2$), 1.94 (1H, bs, OH), 1.02 (3H, d, CH(*CH*$_3$)$_2$, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 156.8 (Ar-*C*), 141.8 (Ar-*C*), 110.3 (Ar-*C*), 106.7 (Ar-*C*), 73.7 (*C*HOH), 33.7 (*C*H$(CH_3)_2$), 18.9 (CH(*C*H$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$). m/z [EI$^+$(+ve)] 140.1 [M]$^+$ (100%), HRMS found 140.0841, $C_8H_{12}O_2$ requires 140.0837 [M]$^+$.

ν_{max} (film)/ cm^{-1}: 3321, 1556, 2941

***tert*Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane, 424.**



A suspension of sodium hydride (3.67 g, 91.8 mmol) in anhydrous tetrahydrofuran (100 mL) was cooled to 0 °C and a solution of 1-furan-2-yl-2-methyl-propan-1-ol **423** (10.3 g, 73.4 mmol) in anhydrous tetrahydrofuran (85 mL) was added. The reaction was stirred for 30 minutes and then treated with *tert*butyldimethylsilyl chloride (22.1 g, 146 mmol). The reaction was then stirred

for 5 hours until completion, as indicated by TLC analysis. Once complete the reaction was treated with water (75 mL) and diethyl ether (75 mL) and the organic layer was separated and washed sequentially with water (2 x 50 mL) and brine (20 mL). The organic phase was concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum spirits) to give 17.1 g (92% yield) of silyl ether **424** as a clear oil.

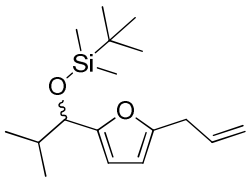
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (1H, dd, *J* = 1.6, 0.8 Hz, Ar-*H*), 6.28, (1H, dd, *J* = 3.2, 2.0 Hz, Ar-*H*) 6.12 (1H, dd, *J* = 3.2, 0.8 Hz, Ar-*H*), 4.30 (1H, d, *J* = 6.8 Hz, *CH*OSi), 2.00 (1H, m, *CH*(CH_3)$_2$), 0.98 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$), 0.85 (9H, s, C(*CH*$_3$)$_3$), 0.72 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$), 0.00 (3H, s, *CH*$_3$Si), -0.16 (3H, s, *CH*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (Ar-*C*), 140.9 (Ar-*C*), 109.8 (Ar-*C*), 106.3 (Ar-*C*), 74.2 (*CH*OSi), 31.6 (*C*H(CH$_3$)$_2$), 26.2 (C(*C*H$_3$)$_3$), 25.8 (CH(*C*H$_3$)$_2$), 22.7 (*C*(CH$_3$)$_3$) 18.6 (CH(*C*H$_3$)$_2$), -5.0 (Si(*C*H$_3$)$_2$), -5.3 (Si(*C*H$_3$)$_2$).

m/z [EI$^+$(+ve)] 254.2 [M]$^+$ (100%), HRMS found 254.1698, $C_{14}H_{26}O_2Si$ requires 254.1702 [M]$^+$.

ν_{max} (film)/ cm^{-1}: 3440, 2958, 1637

[1-(5-Allyl-furan-2-yl)-2-methyl-propoxy]-*tert*butyl-dimethyl-silane, 425.



*tert*Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane **424** (2.69 g, 10.5 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL) and cooled to 0 ^{o}C. *n*BuLi (6.32 mL, 15.8 mmol, 2.5 M in hexanes) was then added and the resulting solution was stirred for 2 hours at 0 ^{o}C. The orange/brown solution was treated with freshly distilled allyl bromide (1.37 mL, 15.8 mmol) and stirred for 12 hours at room temperature. The reaction was quenched with water (50 mL) and diluted with diethyl ether (50 mL). The phases were separated and the organic layer was washed with water (2x 50 mL) and brine (20 mL) and concentrated *in vacuo*. Purification with flash column chromatography (silica gel, petroleum spirits) gave 2.69 g of **425** in 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (1H, d, *J* = 2.8 Hz, Ar-*H*), 5.97-5.87 (1H, m, CH_2*CH*CH_2), 5.92 (1H, d, *J* = 3.2 Hz, Ar-*H*), 5.11 (2H, m, CH*CH*$_2$), 4.25 (1H, d, *J* =

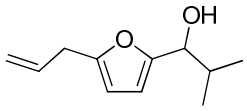
8.8 Hz, *CH*OSi), 3.36 (2H, d, *J* = 6.4 Hz, *CH*$_2$CH), 2.02-1.97 (1H, m, (CH$_3$)$_2$*CH*), 0.95 (3H, d, *J* = 6.8 Hz, *CH*$_3$CH), 0.87 (9H, s, C(*CH*$_3$)$_3$), 0.80 (3H, d, *J* = 6.8 Hz, *CH*$_3$CH), 0.02 (3H, s, *CH*$_3$Si), -0.13 (3H, s, *CH*$_3$Si).

^{13}C NMR (100 MHz, CDCl$_3$): *δ* 155.5 (Ar-*C*), 152.3 (Ar-*C*), 134.3 (CH$_2$*C*HCH$_2$), 116.5 (CH*C*H$_2$), 107.0 (Ar-*C*), 105.8 (Ar-*C*), 74.2 (*C*HOSi), 34.2 (*C*H(CH$_3$)$_2$), 32.6 (Ar*C*H$_2$CH), 25.8 (*C*(CH$_3$)$_3$), 18.9 (CH*C*H$_3$), 18.4 (CH*C*H$_3$), 18.3 (C(*CH*$_3$)$_3$), -4.87 (*C*H$_3$Si), -5.18 (*C*H$_3$Si).

m/z [EI$^+$(+ve)] 294.2 [M]$^+$ (100%), HRMS found 294.2019, C$_{17}$H$_{30}$O$_2$Si requires 294.2015 [M]$^+$.

ν_{max} (film)/ cm^{-1}: 2962, 2097, 1672, 1643, 1078, 835, 777.

1-(5-Allylfuran-2-yl)-2-methylpropan-1-ol, 426.



To a stirred solution of [1-(5-Allyl-furan-2-yl)-2-methyl-propoxy]-*tert*butyl-dimethyl-silane **425** (2.68 g, 9.14 mmol) in anhydrous THF (10 mL) at 0 °C was added tetrabutylammonium fluoride (18.3 mL, 18.38 mmol, 1 M in THF). The reaction was stirred at 0 °C for 10 minutes and then at room temperature for a further 12 hours. Once complete by TLC analysis, the reaction was diluted with diethyl ether (20 mL), water (10 mL) was then added and the biphasic solution was stirred for 30 minutes. The organic extracts were washed with water (2x 10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue purified via flash column chromatography (5% diethyl ether in petroleum spirits) to give 1.59 g (97% yield) alcohol **426** as a clear oil.

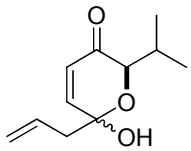
^{1}H NMR (500 MHz, CDCl$_3$): δ 6.02 (1H, d, *J* = 3.0 Hz, Ar-*H*), 5.84 (2H, m, Ar-*H* and CH$_2$*CH*CH$_2$), 5.04 (1H, m, *CH*$_2$CHCH$_2$), 5.01 (1H, m, *CH*$_2$CHCH$_2$), 4.20 (1H, d, *J* = 7.2 Hz, *CH*OH), 3.27 (2H, d, *J* = 6.5 Hz, Ar*CH*$_2$CHCH$_2$), 1.98 (1H, sept, *J* = 7.0 Hz, *CH*(CH$_3$)$_2$), 0.93 (3H, d, *J* = 6.7 Hz, CH(*CH*$_3$)$_2$), 0.76 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, CDCl$_3$): δ 154.8 (Ar-*C*), 153.9 (Ar-*C*), 133.9 (*C*H$_2$CHCH$_2$), 116.9 (CH$_2$*C*HCH$_2$), 107.3 (Ar-*C*), 105.9 (Ar-*C*), 73.6 (*C*HOH), 33.2 (*C*H(CH$_3$)$_2$), 32.6 (CH$_2$CH*C*H$_2$), 18.9 (CH(*C*H$_3$)$_2$), 18.4 (CH(*C*H$_3$)$_2$).

m/z [EI$^+$(+ve)] 163.1 [M-OH]$^+$ (100%), HRMS found 181.0281, C$_{11}$H$_{17}$O$_2$ 181.1229 [M]$^+$.

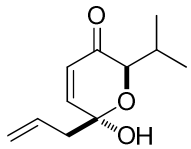
ν_{max} (neat)/cm^{-1}. 3426, 2965, 1681, 835, 777.

6-Hydroxy-2-*iso*propyl-6-Allyl-6H-pyran-3-one, 427.



A 0 °C solution of furfuryl alcohol **426** (801 mg, 4.44 mmol) in dichloromethane (15 mL) was treated with *meta*-chloroperoxybenzoic acid (1.08 g, 4.89 mmol) and the resulting opaque solution was stirred at 0 °C for 1 hour. The mixture was allowed to warm up to room temperature and the reaction was stirred for a further 2 hours. Once the reaction was complete, as determined by TLC analysis, the reaction was cooled to 0 °C and quenched by slow addition of saturated aqueous sodium bicarbonate solution (8 mL). The resulting emulsion was allowed to separate and was then extracted with dichloromethane (3x 20 mL). The combined organic extracts were washed with water (1x 10 mL), brine (1x 10 mL) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* and the residue obtained purified by flash column chromatography (silica gel, 10-50% diethyl ether in petroleum spirits) to give 709 mg (81% yield) of Lactol **427** as mixture of anomers (7.8:1, α:β) as a clear oil

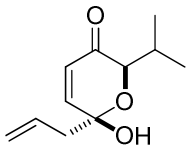
Major Anomer 427α



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (1H, d, J = 10.2 Hz, *CH*CHCO), 5.95 (1H, d, J = 10.1 Hz, CH*CH*CO), 5.81 (1H, m, CH_2*CH*CH_2), 5.18–5.12 (2H, m, *CH*$_2$CHCH_2), 4.26 (1H, d, J = 2.8 Hz, CO*CH*(O)CH), 3.10(1H, bs, OH), 2.58 (1H, dd, J = 13.6, 6.3 Hz, CH_2CH*CH*$_2$), 2.43 (1H, dd, J = 13.6, 8.3 Hz, CH_2CH*CH*$_2$), 2.35 (1H, m, *CH*$(CH_3)_2$), 0.93 (3H, d, J = 7.4 Hz, CH(*CH*$_3$)$_2$), 0.76 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1 (CHCH*C*O), 147.4 (*C*HCHCO), 131.2 (CH_2*C*HCH_2), 127.8 (CH*C*HCO), 120.7 (*C*H_2CHCH_2), 92.8 (*C*(O)OH), 78.2 (CO*C*H(O)CH), 45.8 (CH_2CH*C*H_2), 28.7 (*C*H$(CH_3)_2$), 19.0 (CH(*C*H_3)$_2$), 16.0 (CH(*C*H_3)$_2$).

Minor anomer 427β



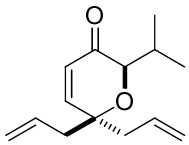
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (1H, d, J = 9.8 Hz, *CH*CHCO), 5.97 (1H, d, J = 9.8 Hz, CH*CH*CO), 5.81 (1H, m, CH_2*CH*CH_2), 5.18–5.12 (2H, m, *CH*$_2$CHCH_2), 3.89 (1H, d, J = 4.4 Hz, CO*CH*(O)CH), 3.32 (1H, bs, OH), 2.61 (1H, m, CH_2CH*CH*$_2$), 2.42 (1H, m, CH_2CH*CH*$_2$), 2.34 (1H, m, *CH*$(CH_3)_2$), 0.92 (3H, d, J = 8.2 Hz, CH(*CH*$_3$)$_2$), 0.84 (3H, d, J = 6.0 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.4 (CHCH*C*O), 149.9 (*C*HCHCO), 130.8 (CH_2*C*HCH_2), 127.5 (CH*C*HCO), 120.6 (*C*H_2CHCH_2), 94.6 (*C*(O)OH), 82.1 (CO*C*H(O)C), 41.7 (CH_2CH*C*H_2), 29.0 (*C*H$(CH_3)_2$), 18.9 (CH(*C*H_3)$_2$), 16.8 (CH(*C*H_3)$_2$).

m/z [EI$^+$(+ve)] 179.1 [M-OH]$^+$ (100%), HRMS found 219.0992, $C_{11}H_{16}NaO_3$ 219.0997 [M+Na]$^+$.

ν_{max} (film)/ cm^{-1}: 3403, 2965, 2932, 1691, 1466, 909.

6,6-Diallyl-2-*iso*propyl-6H-pyran-3-one, 428.



A solution of the lactol **427** (441 mg, 2.24 mmol) in anhydrous dichloromethane (11 mL) was treated with allyltrimethylsilane (747 μL, 4.70 mmol) and the resulting mixture was cooled to −78 °C. The reaction mixture was then treated by the slow addition of $BF_3{\cdot}OEt_2$ (851 μL, 6.72 mmol) and the resulting solution stirred for 30 minutes at −78 °C. The reaction was then allowed to warm to room temperature and was stirred for a further 5 hours. Once the reaction was complete, as determined by TLC analysis, the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (3x 20 mL). The combined organic extracts were washed sequentially with saturated sodium hydrogen carbonate (1× 10 mL), water (2× 10 mL) and brine (1× 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude residue was then purified by flash column chromatography (silica gel, 5% ethyl acetate in petroleum spirits) to afford 452 mg (81% yield) of the desired

bisalkenyl product **428**.

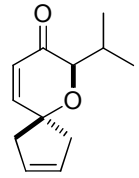
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (1H, d, J = 10.4 Hz, C*H*CHCO), 5.95 (1H, d, J = 10.4 Hz, CHC*H*CO), 5.75 (2H, m, CH_2CHCH_2), 5.11–5.00 (4H, m, CH_2CHCH_2), 4.04 (1H, d, J = 2.6 Hz, CO*CH*(O)CH), 2.51 (1H, ddt, J = 14.3, 6.3, 1.3 Hz, CH_2CHCH_2), 2.39 (2H, m, $CH(CH_3)_2$ and CH_2CHCH_2), 2.31–2.23 (2H, m, CH_2CHCH_2), 0.96 (3H, d, J = 7.0 Hz, $CH(CH_3)_2$), 0.80 (3H, d, J = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.6 (CHCHCO), 153.0 (CHCHCO), 131.9 (CH_2CHCH_2), 131.3 (CH_2CHCH_2), 125.3 (CHCHCO), 117.9 (CH_2CHCH_2), 117.3 (CH_2CHCH_2), 75.7 (COCH(O)CH), 74.4 ($CHC(O)CH_2$), 42.0 (CH_2CHCH_2), 37.9 (CH_2CHCH_2), 28.1 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 14.9 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 221.2 $[M]^+$ (95%), HRMS found 221.1536, $C_{14}H_{21}O_2$ requires 221.1542 $[M]^+$.

ν_{max} (film)/cm^{-1}:2964, 2930, 1690, 1366, 1060.

7-*Iso*propyl-6-oxaspiro[4.5]deca-2,9-dien-8-one, 433.



A solution of bisalkenyl pyrone (58 mg, 0.26 mmol) in dichloromethane (3 mL) in a darkened reaction vessel was treated with 5 mol% first generation Grubbs catalyst (10.8 mg, 13 μmol). The resulting mixture was then stirred and heated to reflux for 3 hours. The resulting black solution was concentrated *in vacuo* and the crude residue obtained purified by flash column chromatography (silica gel, 5% ethyl acetate in petroleum spirits) to give 44 mg of product **433** (85% yield) as a clear oil

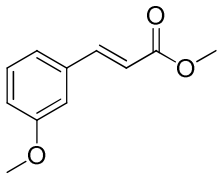
^{1}H NMR(500 MHz, $CDCl_3$): δ 6.96 (1H, d, J =10.2 Hz, *CH*CHCO), 5.96 (1H, d, J = 10.2 Hz, CH*CH*CO), 5.97 (1H, m, CH_2CH), 5.75 (1H, m, CH*CH*), 3.97 (1H, d, J = 2.9 Hz *CH*OC), 2.85 (1H, dquint, = 16.9, 4.0 Hz, $CHCH_2CH_2$), 2.72 (1H, d, J = 17.2, 1.9 Hz, $CHCH_2CH_2$), 2.68-2.63 (1H, dm, $CHCH_2CH_2$), 2.50-2.45 (1H, d, $CHCH_2CH_2$), 2.41 (1H, septd, J = 6.9, 2.9 Hz, $CH(CH_3)_2$), 1.00 (3H, d, J = 7.0 Hz, $CH(CH_3)_2$), 0.88 (3H, d, J = 6.9 Hz, $CH(CH_3)_2$). .

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9 (CHCHCO), 154.6(CHCHCO), 128.4 (CHCH), 127.7 (CHCHCO), 124.5 (CHCH), 82.1 (COCH(O)CH), 80.0 ($CHC(O)CH_2$), 46.8 ($CHCHCH_2$), 40.0 ($CHCHCH_2$), 28.4 ($CH(CH_3)_2$), 19.0 ($CH(CH_3)_2$), 16.1 ($CH(CH_3)_2$).

m/z [EI$^+$(+ve)] 193.1 [M]$^+$ (90%), HRMS found 193.1223, $C_{12}H_{17}O_2$ requires 193.1229 [M]$^+$.

ν_{max} (film)/ cm^{-1}: 2928, 1686, 1476, 1383.

Methyl-(*E*)-3-(3-methoxyphenyl)-acrylate, 442.[262]



To a refluxing solution of methyl (triphenylphosphoranylidene) acetate (23.8 g, 71.0 mmol) in anhydrous dichloromethane (185 mL) was added 3-methoxybenzaldehyde **441** (4.83 mL, 35.5 mmol). The resulting mixture was refluxed at reflux for a further 10 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo* and adsorbed directly onto silica. Purification with flash column chromatography (silica gel, elution with 20% diethyl ether in petroleum spirits) afforded 6.20 g (91% yield) of ester **442** as a single *E* isomer.

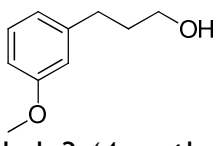
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (1H, d, *J* = 16.0 Hz, Ar*CH*CH), 7.32 (1H, t, *J* = 8.0, Ar-*H*), 7.15-7.13 (1H, m, Ar-*H*), 7.07-7.06 (1H, m, Ar-*H*), 6.96 (1H, ddd, *J* = 8.4, 2.8, 0.8, Ar-*H*), 6.46(1H, d, *J* = 16.0, ArCH*CH*), 3.85 (3H, s, O*CH*$_3$), 3.83 (3H, s, CO_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4 (*C*O), 159.9 (Ar-*C*), 144.8 (Ar-*C*), 135.8 (Ar-*C*), 129.9 (Ar-*C*), 120.7 (Ar-*C*), 118.1 (*C*HCH), 116.1 (Ar-*C*), 113.0 (CH*C*H), 55.3 (O*C*H$_3$), 51.7 (CO_2CH_3).

m/z [EI$^+$(+ve)] 192.0 [M]$^+$ (100%), 161.02 [M-OCH$_3$]$^+$ (26%), HRMS found 192.0785, $C_{11}H_{12}O_3$ requires 192.0786 [M$^+$].

ν_{max} (film)/ cm^{-1}: 1700, 1639, 1434, 783, 679

3-(3-Methoxyphenyl)-propan-1-ol.[263]



To a stirred solution of (*E*)-methyl 3-(4-methoxyphenyl) acrylate **442** (5.05 g, 26.9 mmol) in tetrahydrofuran (270 mL) at 0 ^{o}C was added slowly lithium aluminium hydride solution (8.07 mL, 8.07 mmol, 1 M in diethyl ether). The

resulting suspension was heated under reflux and stirred for 10 hours. The reaction was cooled to 0 ^{o}C and diluted with diethyl ether (200 mL) and sequentially treated with water (2.2 mL), 15% NaOH solution (2.2 mL) and water (6.6 mL). To the resulting opaque white suspension was stirred for 30 minutes was added anhydrous sodium sulfate and stirred for a further 30 minutes. The solids were filtered off and washed with diethyl ether (3x 50 mL) then concentrated *in vacuo*. Purification using flash column chromatography (silica gel, elution with 30-50% diethyl ether in petroleum spirits), gave 3.26 g (73% yield) of the desired saturated alcohol.

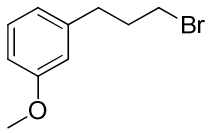
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (1H, dt, J = 7.7, 0.8 Hz, Ar-*H*), 6.84-6.76 (3H, m, Ar-*H*), 3.83 (3H, s, OCH_3) 3.71 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$), 2.72 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$), 1.93 (2H, m, $CH_2CH_2CH_2$), 1.74 (1H, bs, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (Ar-*C*), 143.5 (Ar-*C*), 129.4 (Ar-*C*), 120.9 (Ar-*C*), 114.3 (Ar-*C*), 111.1 (Ar-*C*) 62.2 ($CH_2CH_2CH_2$), 55.2 (OCH_3), 34.1 ($CH_2CH_2CH_2$), 32.1 ($CH_2CH_2CH_2$).

m/z [EI^{+}(+ve)] 166.0 [M]$^{+}$ (100%), HRMS found 166.0995, $C_{10}H_{14}O_2$ requires 166.0994 [M^{+}].

ν_{max} (film)/ cm^{-1}: 3291, 2861, 1504, 1292

1-(3-Bromopropyl)-3-methoxybenzene, 443.[261]



To a solution of 3-(4-methoxyphenyl)propan-1-ol (3.16 g, 19.0 mmol) in dichloromethane (190 mL) was added carbon tetrabromide (24.9 g, 76.0 mmol) and triphenylphosphine (19.9 g, 76.0 mmol). The reaction was stirred until completion by TLC analysis (3 hours). The solvent was evaporated under reduced pressure and the solids formed were adsorbed directly onto silica and purified by flash column chromatography (silica gel, 5 % diethyl ether in petroleum spirits) to give 3.32 g (77 % yield) of the desired bromide **443**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (1H, m, Ar-*H*), 6.82-6.79 (3H, m, Ar-*H*), 3.84 (3H, s, OCH_3), 3.44 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$), 2.80 (2H, t, J = 7.2 Hz, $CH_2CH_2CH_2$), 2.21 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$).

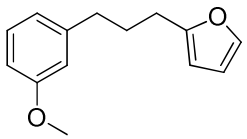
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (Ar-*C*), 142.2 (Ar-*C*), 129.5 (Ar-*C*), 120.9 (Ar-*C*), 114.4 (Ar-*C*), 111.5 (Ar-*C*), 55.2 (OCH_3), 34.1 ($CH_2CH_2CH_2$), 33.8 ($CH_2CH_2CH_2$),

33.1 (CH_2Br).

m/z [EI^+(+ve)] ^{79}Br-228.0 $[M]^+$ (100%), HRMS [M^+] found 228.0151, $C_{10}H_{13}O^{79}Br$ requires 228.0150. ^{81}Br-230.0 $[M]^+$ (97%), HRMS [M^+] found 230.0129, $C_{10}H_{13}O^{81}Br$ requires 230.0129.

ν_{max} (film)/ cm^{-1}: 3016, 3014, 1625, 1503, 832.

2-(3-(3-Methoxyphenyl)propyl)-furan, 444.



Furan **86** (328 μL, 4.52 mmol) in anhydrous tetrahydrofuran (22 mL) was cooled to 0 °C and treated with *n*BuLi (1.8 mL, 4.52 mmol). The reaction was warmed to room temperature and stirred for 20 hours at which time the reaction cooled back down to 0 °C and a solution of bromide **443** (1.03 g, 4.52 mmol) in anhydrous tetrahydrofuran (10 mL) was added. The reaction mixture was then stirred for a further 4 hours. The resulting brown solution was diluted with diethyl ether (15 mL) and water (10 mL) was added and stirred for 30 minutes. The organic phase was washed with water (2x 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 4% dichloromethane in petroleum spirits) afforded 507 mg (52%) of the aromatic compound **444** as a clear oil.

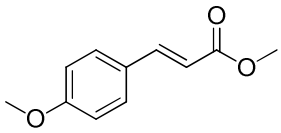
^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (1H, dd, J = 1.7, 0.7 Hz, Ar-*H*), 7.25-7.19 (2H, m, Ar-*H*), 6.81-6.74 (1H, m, Ar-*H*), 6.29 (2H, dd, J = 3.1, 1.9 Hz, Ar-*H*), 6.01 (1H, dd, J = 3.1, 0.8, Ar-*H*), 3.81 (3H, s, OCH_3), 2.66 (4H, q, J = 7.2 Hz, $CH_2CH_2CH_2$), 1.99 (2H, quint, J = 7.6 Hz, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (Ar-*C*), 155.9 (Ar-*C*), 142.2 (Ar-*C*), 140.8 (Ar-*C*), 129.5 (Ar-*C*), 120.4 (Ar-*C*), 114.4 (Ar-*C*), 111.1 (Ar-*C*), 110.1 (Ar-*C*), 104.9 (Ar-*C*), 55.2 (OCH_3), 35.3 ($CH_2CH_2CH_2$), 34.1 ($CH_2CH_2CH_2$), 27.5 ($CH_2CH_2CH_2$).

m/z [EI^+(+ve)] 216.1 $[M]^+$ (100%), HRMS found 216.1151, $C_{14}H_{16}O_2$, requires 216.1150 [M^+].

ν_{max} (film)/ cm^{-1}: 2938, 1601, 1584, 1261

Methyl-(*E*)-3-(4-methoxyphenyl)-acrylate, 447.[264]



To a refluxing solution of methyl (triphenylphosphoranylidene) acetate (24.5 g, 73.4mmol) in anhydrous dichloromethane (185 mL) was added 4-methoxybenzaldehyde **446** (4.99 mL, 36.7mmol). The resulting mixture was refluxed at reflux for a further 10 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo* and adsorbed directly onto silica. Purification with flash column chromatography (silica gel, elution with 20% diethyl ether in petroleum spirits) afforded 6.41 g (91% yield) of ester **447** as a single *E* isomer.

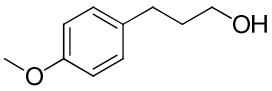
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 16.0 Hz, Ar*CH*CH), 7.38 (2H, dd, *J* = 8.8, 2.0 Hz, Ar-*H*), 6.81 (2H, dd, *J* = 8.8, 2.0 Hz, Ar-*H*), 6.21 (1H, d, *J* = 16.0 Hz, ArCH*CH*), 3.74 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (*C*O), 161.4 (Ar-*C*), 144.5 (*C*HCH), 129.7 (2x Ar-*C*), 127.1 (Ar-*C*), 115.3 (CH*C*H), 114.3 (2x Ar-*C*), 55.4 (O*C*H_3), 51.6 ($CO_2C$$H_3$).

m/z [EI$^+$(+ve)] 192.1 $[M]^+$ (100%), 161.1 $[M\text{-}OCH_3]^+$ (20%), HRMS found 192.0788, $C_{11}H_{12}O_3$ requires 192.0786 [M^+].

ν_{max} (film)/ cm^{-1}: 1681, 1599, 1485, 787.

3-(4-Methoxyphenyl)-propan-1-ol, 448.[265]



To a stirred solution of (*E*)-methyl 3-(4-methoxyphenyl) acrylate **447** (2.13 g, 11.1 mmol) in tetrahydrofuran (55 mL) at 0 ^{o}C was added slowly lithium aluminium hydride solution (15.8 mL, 55.4 mmol, 3.5 M in diethyl ether). The resulting suspension was heated under reflux and stirred for 10 hours. The reaction was cooled to 0 ^{o}C and diluted with diethyl ether (100 mL) and sequentially treated with water (2.2 mL), 15% NaOH solution (2.2 mL) and water (6.6 mL). To the resulting opaque white suspension was stirred for 30 minutes was added anhydrous sodium sulfate and stirred for a further 30 minutes. The solids were filtered off and washed with diethyl ether (3x 50 mL) then concentrated *in vacuo*. Purification using flash column chromatography (silica gel, elution with 30-50% diethyl ether in petroleum spirits), gave 1.31 g (71%

yield) of the desired saturated alcohol **448**.

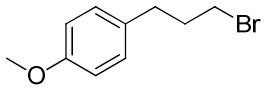
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (2H, d, J = 8.6 Hz, Ar-*H*), 6.87 (2H, d, J = 8.6 Hz, Ar-*H*), 3.82 (3H, s, OCH_3), 3.70 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$), 2.69 (2H, t, J = 7.6 Hz, $CH_2CH_2CH_2$), 1.93-1.86 (2H, m, $CH_2CH_2CH_2$), 1.35 (1H, bs, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (Ar-*C*), 133.9 (Ar-*C*), 129.3 (2x Ar-*C*), 113.8 (2x Ar-*C*), 62.3 ($CH_2CH_2CH_2$), 55.3 (OCH_3), 34.5 ($CH_2CH_2CH_2$), 31.2 ($CH_2CH_2CH_2$).

m/z [EI$^+$(+ve)] 166.1 [M]$^+$ (100%), HRMS found 166.0995, $C_{10}H_{14}O_2$ requires 166.0994 [M$^+$].

ν_{max} (film)/ cm^{-1}: 3410, 2871, 1521, 1269

1-(3-Bromopropyl)-4-methoxybenzene, 449.[266]



To a solution of 3-(4-methoxyphenyl)propan-1-ol **448** (1.31 g, 7.89 mmol) in dichloromethane (80 mL) was added carbon tetrabromide (10.3 g, 31.3 mmol) and triphenylphosphine (8.20 g, 31.3 mmol). The reaction was stirred until completion by TLC analysis (3 hours). The solvent was evaporated under reduced pressure and the solids formed were adsorbed directly onto silica and purified by flash column chromatography (silica gel, 5 % diethyl ether in petroleum spirits) to give 1.42 g (79 % yield) of the desired bromide **449**.

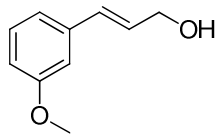
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (2H, d, J = 8.4 Hz, Ar-*H*), 6.76 (2H, d, J = 8.8 Hz, Ar-*H*), 3.71 (3H, s, OCH_3), 3.30 (2H, t, J = 6.4 Hz, $CH_2CH_2CH_2$), 2.64 (2H, t, J = 7.2 Hz, $CH_2CH_2CH_2$), 2.05 (2H, quin, J = 6.4 Hz, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (Ar-*C*), 132.6 (Ar-*C*), 129.5 (2x Ar-*C*), 113.9 (2x Ar-*C*), 55.3 (OCH_3), 34.4 ($CH_2CH_2CH_2$), 33.2 ($CH_2CH_2CH_2$), 33.1 ($CH_2CH_2CH_2$).

m/z [EI$^+$(+ve)] ^{79}Br-228.0 [M]$^+$ (100%), HRMS found 228.0151, $C_{10}H_{13}O^{79}Br$, requires 228.0150 [M$^+$]. ^{81}Br-230.0 (100%), HRMS found 230.0132, $C_{10}H_{13}O^{81}Br$ requires 230.0129 [M$^+$].

ν_{max} (film)/ cm^{-1}: 3030, 3004, 1612, 1510, 829.

(*E*)-3-(3-Methoxy-phenyl)-prop-2-en-1-ol, 451.[268]



A stirred solution of (*E*)-3-(3-Methoxy-phenyl)-acrylic acid methyl ester **442** (5.07 g, 26.4 mmol) in anhydrous dichloromethane (130 mL) was cooled to -78 °C and treated with diisobutylaluminium hydride (58.1 mL, 58.1 mmol, 1 M in dichloromethane) and stirred for 3 hours. Warmed to 0 °C and diluted with diethyl ether (75 mL). The reaction was quenched with water (1.05 mL), 15% aqueous sodium hydroxide (1.05 mL) and water (5.75 mL) sequentially. The cloudy suspension was stirred for 30 minutes and was then treated with sodium sulfate and stirred for a further 30 minutes. The solids formed were filtered through celite and washed with diethyl ether (3x 100 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20-40% diethyl ether in petroleum ether) gave 3.08 g (71% yield) of allylic alcohol **451** as a clear oil.

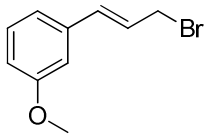
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.01 (1H, d, *J* = 7.6 Hz, Ar-*H*), 6.95 (1H, t, *J* = 2.0 Hz, Ar-*H*), 6.84 (1H, ddd, *J* = 8.0, 2.4, 0.4 Hz, Ar-*H*), 6.60 (1H, d, *J* = 16.0 Hz, Ar*CH*CH), 6.40 (1H, dt, *J* = 15.9, 5.7 Hz, CH*CH*CH_2), 4.33 (2H, bs, CH_2OH), 3.83 (3H, s, O*CH*$_3$), 2.21 (1H, bs, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (Ar-*C*), 138.2 (Ar-*C*), 130.9 (*C*HCH), 129.6 (Ar-*C*), 128.9 (*C*HCH_2), 119.2 (Ar-*C*), 113.3 (Ar-*C*), 111.9 (Ar-*C*), 63.6 (*C*H_2OH), 55.2 (O*C*H_3).

m/z [EI$^+$(+ve)] 164.1 [M]$^+$ (100%), HRMS found 164.0838, $C_{10}H_{12}O_2$, requires 164.0837 [M$^+$].

ν_{max} (film)/ cm^{-1}: 3161, 2360, 1652.

(*E*)-1-(3-Bromoprop-1-enyl)-3-methoxybenzene, 452.[267]



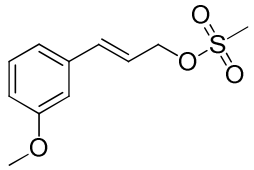
To a refluxing solution of (*E*)-3-(3-methoxy-phenyl)-prop-2-en-1-ol **451** (967 mg, 5.89 mmol) in dichloromethane (30 mL) was added carbon tetrabromide (7.72 g, 23.6 mmol) and triphenylphosphine (6.19 g, 23.6 mmol). The reaction was

stirred for 3 hours until completion by TLC analysis. The reaction mixture was concentrated under reduced pressure and the solids formed were adsorbed directly onto silica and purified by flash column chromatography (silica gel, 5 % diethyl ether in petroleum spirits) to give 891 mg (67 % yield) of the desired allylic bromide **452**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, t, J = 7.5 Hz, Ar-*H*), 7.24 (2H, m, Ar-*H*), 6.92 (1H, m, Ar-*H*), 6.80 (1H, d, J = 15.1 Hz, Ar*CH*CH), 6.34 (1H, dt, J = 15.7, 5.2 Hz, Ar*CH*CH_2), 3.92 (2H, d, J = 6.2, CH_2OH), 3.83 (3H, s, O*CH*$_3$).

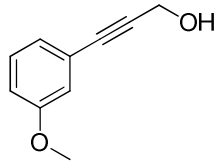
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (Ar-*C*), 138.9 (Ar-*C*), 132.9 (*C*HCH), 129.1 (Ar-*C*), 122.7 (*C*HCH_2), 119.7 (Ar-*C*), 113.6 (Ar-*C*), 113.4 (Ar-*C*), 55.2 (O*C*H$_3$), 36.1 (*C*H_2Br).

(*E*)-3-(3-Methoxyphenyl)-allyl methanesulfonate, 453.[270]



To a stirred solution of (*E*)-3-(3-methoxy-phenyl)-prop-2-en-1-ol, **451** (499 mg, 3.05 mmol) in tetrahydrofuran (20 mL) at 0 ^{o}C was added mesyl chloride (344 μL, 4.57 mmol). The resulting solution was stirred for 10 minutes and then treated with triethylamine (848 μL, 6.09 mmol) for a further 2 hours. The mixture was diluted with diethyl ether (20 mL) and 10% aqueous hydrochloride acid solution (5 mL) was added. The phases were separated and the organic layer was washed with saturated sodium bicarbonate solution (5 mL) and brine (10 mL), then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was taken on to the next step without further purification.

3-(Methoxy-phenyl)-prop-2-yn-1-ol, 463.[279]



3-Iodoanisole **464** (6.53 g, 54.8 mmol) in acetonitrile (270 mL) was treated with Bis(triphenylphosphine)palladium(II) dichloride (4.81 g, 6.85 mmol), copper iodide (2.61 g, 13.7 mmol) and triethylamine (38.5 mL, 274 mmol). The resulting

yellow solution was treated with propargyl alcohol **465** (3.94 mL, 65.8 mmol) and the reaction was heated to reflux and stirred for 10 hours. Once complete, by TLC analysis, the solids were filtered off and washed with diethyl ether (2x 50 mL), the filtrate was evaporated and the residue obtained was purified by flash column chromatography (30% ethyl acetate in petroleum) to give 7.37 g (83% yield) of the desired alkyne **463** as a brown oil.

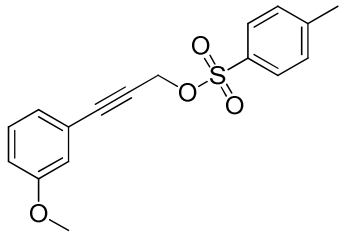
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (1H, dd, *J* = 8.0, 0.8 Hz, Ar-*H*), 7.04 (1H, dt, *J* = 7.6, 0.8 Hz, Ar-*H*), 6.98 (1H, dd, *J* = 2.4, 1.2 Hz, Ar-*H*), 6.89 (1H, ddd, *J* = 8.4, 2.8, 0.6 Hz, Ar-*H*), 4.49 (2H, s, *C*H_2OH), 3.79 (3H, s, OCH_3), 1.70 (1H, s, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (Ar-*C*), 129.4 (Ar-*C*), 124.2 (Ar-*C*), 123.5 (Ar-*C*), 116.5 (Ar-*C*), 115.1 (Ar-*C*), 87.0 (C*C*), 85.7 (*C*CH_2), 55.3 (O*C*H_3), 51.7 (*C*H_2OH).

m/z [EI$^+$(+ve)] 162.1 $[M]^+$ (100%), HRMS found 162.0679, $C_{10}H_{10}O_2$, requires 162.0681 $[M^+]$.

ν_{max} (film)/ cm^{-1}: 3374, 3002, 2938, 2227, 1603, 855, 782, 687.

3-(3-Methoxyphenyl)prop-2-ynyl 4-methylbenzenesulfonate, 467.



A solution of alkyne alcohol **463** (509 mg, 3.14 mmol) in diethyl ether (20 mL) was treated with 4-methylbenzenesulfonyl chloride (628 mg, 3.30 mmol) and the solution was cooled to 0 °C and stirred for 30 minutes. Powdered potassium hydroxide (881 mg, 15.7 mmol) was added in 3 portions over 20 minutes and the heterogeneous mixture stirred for a further 2 hours. Water (10 mL) and diethyl ether (20 mL) were added and the biphasic mixture was stirred for 30 minutes. The organic phase was washed with water (2x 10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 972 mg (97% yield) of tosylate **467**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7.22 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.08 (1H, t, *J* = 7.9 Hz, Ar-*H*), 6.79-6.74 (2H, m, Ar-*H*), 6.68 (1H, dd, *J* = 1.3 Hz, Ar-*H*), 4.84 (2H, s, C*CH*$_2$O), 3.67 (3H, s, O*CH*$_3$), 2.29 (3H, s, Ar*CH*$_3$).

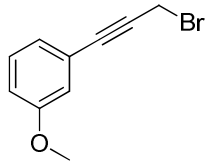
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (Ar-*C*), 145.2 (Ar-*C*), 133.3 (Ar-*C*), 130.3 (Ar-

C), 129.8 (Ar-*C*), 129.4 (Ar-*C*), 128.2 (Ar-*C*), 127.0 (Ar-*C*), 124.2 (Ar-*C*), 122.4 (Ar-*C*), 116.9 (Ar-*C*), 115.4 (Ar-*C*), 88.9 (*C*CCH$_2$), 80.4 (C*C*CH$_2$), 58.6 (OCH$_3$), 55.3 (CC*C*H$_2$), 21.6 (ArCH$_3$).

m/z [EI$^+$(+ve)] 316.1 [M]$^+$ (100%), HRMS found 316.0772, $C_{17}H_{16}O_4S$, requires 316.0769 [M$^+$].

ν_{max} (film)/ cm^{-1}: 2852, 2233, 1595, 1319, 1176, 759.

1-(3-Bromo-prop-1-ynyl)-3-methoxy-benzene, 468.

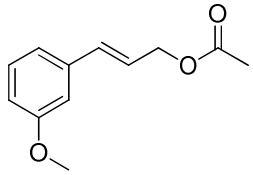


To a solution of 3-(Methoxy-phenyl)-prop-2-yn-1-ol **463** (367 mg, 2.26 mmol) in dichloromethane (15 mL) was added carbon tetrabromide (2.99 g, 9.05 mmol) and triphenylphosphine (2.37 g, 9.05 mmol). The reaction was stirred for 3 hours until completion by TLC analysis, solvent was evaporated under reduced pressure. Crude solids were adsorbed directly onto silica and purified by flash column chromatography (silica gel, 5 % diethyl ether in petroleum spirits), affording 232 mg (46% yield) of **468** as a brown oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.16 (1H, dd, *J* = 7.6, 0.6 Hz, Ar-*H*), 6.97 (1H, d, *J* = 7.6 Hz, Ar-*H*), 6.90-6.89 (1H, m, Ar-*H*), 6.84-6.82 (1H, Ar-*H*), 4.09 (2H, s, CH$_2$*Br*), 3.73 (3H, s, OCH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ 160.2 (Ar-*C*), 130.5 (Ar-*C*), 122.9 (Ar-*C*), 115.8 (Ar-*C*), 115.1 (Ar-*C*), 114.0 (Ar-*C*), 85.7 (C*C*CH$_2$), 80.9 (*C*CCH$_2$), 55.2 (OCH$_3$), 12.2 C*C*H$_2$Br.

(*E*)-3-(3-methoxyphenyl)-allyl acetate, 469.[283]



A solution of (*E*)-3-(3-Methoxy-phenyl)-prop-2-en-1-ol **451** (5.49 g, 33.5 mmol) was dissolved in dichloromethane (100 mL) at 0 ^{o}C. Triethylamine (6.99 mL, 50.2 mmol) and dimethylaminopyridine (409 mg, 3.45 mmol) were added and the reaction mixture was stirred for 30 minutes, then treated with acetic anhydride

(4.45 mL, 50.2 mmol). The mixture was stirred for a further 12 hours until completion, monitored by TLC analysis. Water (20 mL) and dichloromethane (50 mL) were added and the organic phase was washed with water (2x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification with flash column chromatography (silica gel, 20% diethyl ether in petroleum ether) gave 5.94 g (86% yield) of allylic acetate **469**.

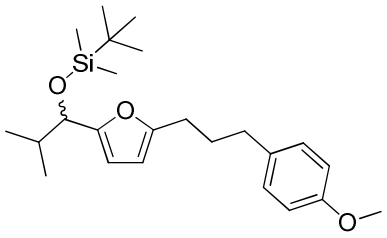
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.15 (1H, t, *J* = 7.9 Hz, Ar-*H*), 6.90 (1H, d, *J* = 7.7 Hz, Ar-*H*), 6.84 (1H, t, *J* = 2.0 Hz, Ar-*H*), 6.74 (1H, ddd, *J* = 8.2, 2.5, 0.7 Hz, Ar-*H*), 6.54 (1H, d, *J* = 15.8 Hz, *CH*CHCH$_2$), 6.19 (1H, dt, *J* = 15.8, 6.4 Hz, CH*CH*CH$_2$), 4.64 (2H, d, *J* = 6.4 Hz, CH*CH$_2$*), 3.73 (3H, s, OCH_3), 2.02 (3H, s, CO*CH$_3$*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (*C*OCH_3), 159.8 (Ar-*C*), 137.7 (Ar-*C*), 134.1 (*C*HCH), 129.6 (Ar-*C*), 123.5 (Ar-*C*), 119.3 (CH*C*H), 113.8 (Ar-*C*), 111.8 (Ar-*C*), 65.0 (CH*C*H$_2$), 55.2 (O*C*H$_3$), 21.0 (CO*C*H$_3$).

m/z [EI$^+$(+ve)] 206.1 [M]$^+$ (100%), HRMS found 206.0945, $C_{12}H_{14}O_3$, requires 206.0943 [M$^+$].

ν_{max} (film)/ cm^{-1}: 2941, 2835, 1735, 1490, 1259, 775.

_tert_Butyl-(1-(5-(3-(4-methoxyphenyl)propyl)furan-2-yl)-2-methylpropoxy) dimethylsilane, 450.



To a stirred 0 °C solution of *tert*Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane **424** (992 mg, 3.89 mmol) in anhydrous tetrahydrofuran (10 mL) was added slowly *n*BuLi (1.16 mL, 5.84 mmol, 2.5 M solution in hexanes). The solution was stirred at 0 °C for 10 minutes and the yellow solution was allowed to attain room temperature over an hour. Cooled to -78 °C the now brown solution was treated with a solution of bromide **449** (10 mL, 5.07 mmol, 0.5 M in tetrahydrofuran) and stirred for 1 hour, then for a further 12 hours at room temperature. The mixture was diluted with diethyl ether (10 mL) and quenched with saturated ammonium chloride solution (5 mL) and the layers separated. The organic phase

was washed with water (2x 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether) gave 1.03 g of silyl ether bicycle **450** (38% yield) as clear oil that was inseparable from remaining bromide **449**.

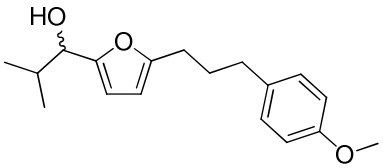
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (2H, d, J = 9.2 Hz, Ar-*H*), 6.85 (2H, d, J = 9.4 Hz, Ar-*H*), 6.01 (1H, d, J = 3.0 Hz, Ar-*H*), 5.89 (1H, d, J = 3.0 Hz, Ar-*H*), 4.24 (1H, d, J = 7.0 Hz, *CH*OSi), 3.79 (3H, s, O*CH*$_3$), 2.59 (4H, t, J = 7.7 Hz, *CH*$_2$CH$_2$*CH*$_2$), 2.05-1.98 (1H, m, *CH*(CH$_3$)$_2$), 1.94-1.87 (2H, m, CH$_2$*CH*$_2$CH$_2$), 0.96 (3H, d, J = 6.7 Hz, CH(*CH*$_3$)$_2$), 0.87 (9H, s, SiC(*CH*$_3$)$_3$), 0.79 (3H, d, J = 6.8 Hz, CH(*CH*$_3$)$_2$), 0.02 (3H, s, SiCH$_3$), -0.13 (SiCH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (Ar-*C*), 155.0 (Ar-*C*), 154.5 (Ar-*C*), 132.4 (Ar-*C*), 129.4 (2x Ar-*C*), 113.9 (2x Ar-*C*), 106.9 (Ar-*C*), 105.3 (Ar-*C*), 74.3 (*C*HOSi), 55.3 (O*C*H$_3$), 34.4 (CH$_2$CH$_2$*C*H$_2$), 33.2 (*C*H$_2$CH$_2$CH$_2$), 30.2 (*C*H(CH$_3$)$_2$), 27.5 (CH$_2$*C*H$_2$CH$_2$), 25.9 (C(*C*H$_3$)$_3$), 18.8 (CH(*C*H$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$), 18.3 (*C*(CH$_3$)$_3$), -4.8 (Si*C*H$_3$), -5.2 (Si*C*H$_3$).

m/z [EI$^+$(+ve)] 402.3 [M]$^+$ (100%), HRMS found 402.2594, $C_{24}H_{38}O_3Si$, requires 402.2590 [M$^+$].

ν_{max} (film)/ cm^{-1}: 2955, 2932, 2856, 1512, 1247

1-(5-(3-(4-Methoxyphenyl)propyl)furan-2-yl)-2-methylpropan-1-ol, 470.



To a stirred solution of *tert*Butyl(1-(5-(3-(4-methoxyphenyl)propyl)furan-2-yl)-2-methylpropoxy)dimethylsilane, **450** (595 mg, 1.48 mmol) in tetrahydrofuran (4 mL) at 0 °C was added tetrabutylammonium fluoride (2.96 mL, 2.96 mmol) and the resulting solution was stirred for 48 hours. Water (5 mL) and diethyl ether (10 mL) were added and the phases were separated. The organic layer was then washed with water (2x 5 mL), brine (5 mL) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to afford 418 mg (98% yield) of alcohol **470** that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (2H, d, J = 8.6 Hz, Ar-*H*), 6.73 (2H, d, J = 8.6 Hz, Ar-*H*), 6.01 (1H, d, J = 3.1 Hz, Ar-*H*), 5.82 (1H, d, J = 3.0 Hz, Ar-*H*), 4.19 (1H, dd, J = 7.1, 5.2, *CH*OH), 3.69 (3H, s, OCH$_3$), 2.50 (4H, q, J = 7.5 Hz,

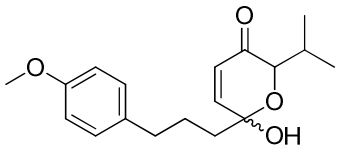
*CH2*CH_2*CH*$_2$), 2.03-1.95 (1H, m, *CH*(CH_3)$_2$), 1.82 (2H, quint, *J* = 5.6 Hz, *CH2*CH_2*CH*$_2$), 1.69 (1H, d, *J* = 5.2 Hz, OH), 0.92 (3H, d, *J* = 6.7 Hz, CH(*CH*$_3$)$_2$), 0.75 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 157.8 (Ar-*C*), 155.3 (Ar-*C*), 154.5 (Ar-*C*), 134.0 (Ar-*C*), 129.4 (2x Ar-*C*), 113.8 (2x Ar-*C*), 107.1 (Ar-*C*), 105.3 (Ar-*C*), 73.7 (*C*HOH), 55.3 (O*C*H_3), 34.3 ($CH_2CH_2CH_2$), 33.3 (*C*$H_2CH_2CH_2$), 29.9 (CH_2*C*H_2CH_2), 27.5 (*C*H(CH_3)$_2$), 18.8 (CH(*C*H_3)$_2$), 18.4 (CH(*C*H_3)$_2$).

m/z [EI$^+$(+ve)] 288.2 [M]$^+$ (100%), HRMS found 288.1729, $C_{18}H_{24}O_3$ requires 288.1725 [M$^+$].

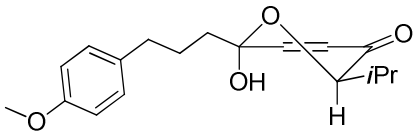
ν_{max} (film)/ cm^{-1}: 3432, 1613, 1511, 1244, 1035.

6-Hydroxy-2-*iso*propyl-6-(3-(4-methoxyphenyl)propyl)-2H-pyran-3(6H)-one, 469.



To a stirred solution of 1-(5-(3-(4-Methoxyphenyl)propyl)furan-2-yl)-2-methylpropan-1-ol, **470** (452 mg, 1.56 mmol), in dichloromethane (9 mL) at 0 °C was added 3-chloroperoxybenzoic acid (423 mg, 1.72 mmol). The white suspension was stirred for 30 minutes at 0 °C then a further 4 hours at room temperature until completion TLC analysis. The reaction was cooled to 0 °C and diluted with dichloromethane (10 mL) then quenched by the slow addition of saturated sodium hydrogen carbonate solution (5 mL) and stirred for a further 30 minutes. The resulting emulsion was allowed to separate and was then extracted into dichloromethane (3x 10 mL). The organic layer was washed with water (2x 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 30% diethyl ether in petroleum spirits) afforded 306 mg (65% yield) of lactol **469** as a mixture of anomers (7:1, α to β) and as clear oil

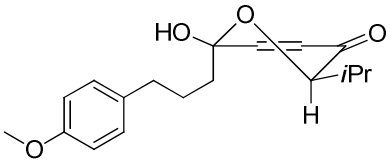
6-α-Hydroxy-2-*iso*propyl-6-(3-(4-methoxyphenyl)propyl)-2H-pyran-3(6H)-one, 469α.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar-*H*), 6.74 (1H, d, *J* = 10.2 Hz, *CH*CH), 6.04 (1H, d, *J* = 10.2 Hz, *CH*CO), 4.34 (1H, d, *J* = 2.7 Hz, CO*CH*), 3.79 (3H, s, OCH_3), 2.64-2.59 (2H, m, $CH_2CH_2CH_2$), 2.67-2.43 (2H, m, $CH_2CH_2CH_2$), 1.88-1.81 (2H, m, $CH_2CH_2CH_2$), 1.79-1.68 (1H, m, $CH(CH_3)_2$), 1.59 (1H, bs, OH), 1.03 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 0.92 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8 (CO), 157.9 (Ar-*C*), 147.3 (Ar-*C*), 133.8 (Ar-*C*), 129.3 (Ar-*C*), 127.9 (Ar-*C*), 113.9 (Ar-*C*), 94.0 (O*C*O), 78.2 (CO*C*H), 55.3 (OCH_3), 41.2 ($CH_2CH_2CH_2$), 34.7 ($CH_2CH_2CH_2$), 28.7 ($CH(CH_3)_2$), 25.4 ($CH_2CH_2CH_2$), 19.1 ($CH(CH_3)_2$), 16.2($CH(CH_3)_2$).

6-β-Hydroxy-2-*iso*propyl-6-(3-(4-methoxyphenyl)propyl)-2H-pyran-3(6H)-one, 469β.



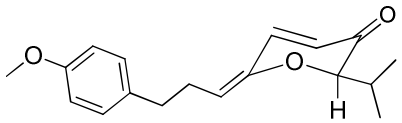
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar-*H*), 6.81 (1H, d, *J* = 9.8 Hz, *CH*CH), 6.00 (1H, d, *J* = 10.3 Hz, *CH*CO), 3.85 (1H, d, *J* = 4.7 Hz, CO*CH*), 3.79 (3H, s, O*CH*$_3$), 2.64-2.59 (2H, m, $CH_2CH_2CH_2$), 2.67-2.43 (2H, m, $CH_2CH_2CH_2$), 1.88-1.81 (2H, m, $CH_2CH_2CH_2$), 1.79-1.68 (1H, m, $CH(CH_3)_2$), 1.26 (1H, bs, OH), 1.01 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$), 0.88 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3 (CO), 167.0 (Ar-*C*), 150.3 (Ar-*C*), 133.8 (Ar-*C*), 129.3 (Ar-*C*), 127.4 (Ar-*C*), 155.1 (Ar-*C*), 81.9 (O*C*O), 77.2 (CO*C*H), 55.3 (OCH_3), 41.2 ($CH_2CH_2CH_2$), 34.7 ($CH_2CH_2CH_2$), 28.7 ($CH(CH_3)_2$), 24.8 ($CH_2CH_2CH_2$), 19.1 ($CH(CH_3)_2$), 16.2($CH(CH_3)_2$).

m/z [CI^+ (+ve), (*iso*butane)] 305.2 $[M+H]^+$ (100%), HRMS found 305.1756, $C_{18}H_{25}O_4$ requires 305.1753 $[M+H]^+$.

ν_{max} (film)/ cm^{-1}: 3431, 1675, 1613, 1511.

2-*iso*Propyl-6-(3-(4-methoxyphenyl)propylidene)-2H-pyran-3(6H)-one, 472.



A solution of 6-Hydroxy-2-*iso*propyl-6-(3-(4-methoxyphenyl)propyl)-2H-pyran-3(6H)-one **471** in dichloromethane (0.1 M with respect to lactol) was cooled to -78 °C. The solution was treated with Lewis acid (see below for specific reagents) and stirred for 2 hours at -78 °C. The reaction was diluted diethyl ether (5 mL) and quenched with water (2 mL). The phases were separated and the organic layer was washed with water (2x 2 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20% diethyl ether in petroleum spirits) gave **472** as a clear oil.

With boron trifluoride diethyl etherate

Lactol (51 mg, 0.17 mmol), dichloromethane (1.7 mL), $BF_3.OEt_2$ (43 μL, 0.34 mmol) gave 31 mg **472** in 64% yield.

With silicon tetrachloride

Lactol (46 mg, 0.15 mmol), dichloromethane (1.5 mL), $SiCl_4$ (452 μL, 0.45 mmol, 1 M in dichloromethane) gave 33 mg **472** in 76% yield.

With ethyl aluminium chloride

Lactol (49 mg, 0.16 mmol), dichloromethane (1.6 mL), $SiCl_4$ (478 μL, 0.48 mmol, 1 M in hexanes) gave 13 mg **472** in 29% yield.

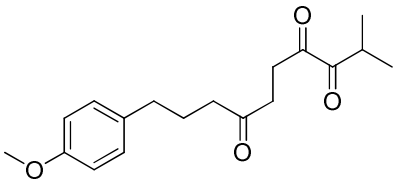
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.79 (2H, d, *J* = 10.3 Hz, Ar-*H*), 6.76 (1H, d, *J* = 6.5 Hz, *CH*CH), 5.86 (1H, d, *J* = 9.8 Hz, *CH*CO), 5.02 (1H, t, *J* = 7.5 Hz,CH_2*CH*CH), 4.13 (1H, d, *J* = 4.7 Hz, CO*CH*),3.72 (3H, s, OCH_3), 2.63 (2H, t, *J* = 7.5 Hz, *CH*$_2$$CH_2$CH), 2.49 (2H, q, *J* = 7.6 Hz, CH_2*CH*$_2$CH), 2.18-2.12 (1H, m, *CH*$(CH_3)_2$), 0.96 (3H, d, *J* = 6.9 Hz, CH(*CH*$_3$)$_2$), 0.84 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2 (CO), 157.9 (Ar-*C*), 151.1 (CH*C*), 147.1 (*C*HCH), 141.1 (Ar-*C*), 133.6 (Ar-*C*), 129.3 (CH*C*O), 122.1 (Ar-*C*), 119.3 (Ar-*C*), 113.8 (Ar-*C*), 85.4 (CH_2*C*HC), 77.3 (CH*C*O), 55.3 (OCH_3), 34.2 (*C*H_2CH_2CH), 31.7 (*CH*$(CH_3)_2$), 27.6 (CH_2*CH*$_2$CH), 18.9 (CH(*CH*$_3$)$_2$), 16.8(CH(*CH*$_3$)$_2$).

m/z [EI$^+$(+ve)] 286.1 $[M]^+$ (100%), HRMS found 286.1566, $C_{18}H_{22}O_3$ requires 286.1569 $[M]^+$.

ν_{max} (film)/ cm^{-1}: 2966, 1685, 1612, 830.

10-(4-methoxyphenyl)-2-methyldecane-3,4,7-trione, 473.



6-Hydroxy-2-*iso*propyl-6-(3-(4-methoxyphenyl)propyl)-2H-pyran-3(6H)-one **471** (46 mg, 0.149 mmol) in dichloromethane (1.5 mL) was cooled to -78 °C. The solution was treated with chloro tri*iso*propoxytitanium (IV) (449 μL, 0.45 mmol) and stirred for 2 hours. The reaction was diluted with diethyl ether (5 mL) and quenched then water (2 mL). The phases were separated and the organic layer was washed with water (2x 2 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20% diethyl ether in petroleum spirits) gave 24 mg (55% yield) of **473** in as a green oil.

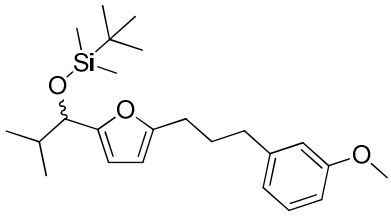
^{1}H NMR (400 MHz, $CDCl_3$): *δ*.7.08 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.82 (2H, d, *J* = 8.6 Hz, Ar-*H*), 3.78 (3H, s, OCH_3), 3.35 (1H, sept, *J* = 6.9 Hz, *CH*$(CH_3)_2$), 2.94 (2H, t, *J* = 6.1 Hz, CO*CH*$_2$$CH_2$), 2.74 (2H, t, *J* = 6.2 Hz, $COCH_2$*CH*$_2$), 2.56 (2H, t, *J* = 7.5 Hz, *CH*$_2$$CH_2CH_2$), 2.45 (2H, t, *J* = 7.4 Hz, CH_2CH_2*CH*$_2$), 1.88(2H, quint, *J* = 7.4 Hz, CH_2*CH*$_2$$CH_2$), 1.11 (6H, d, *J* = 6.9 Hz, CH*(CH$_3$)$_2$*).

^{13}C NMR (100 MHz, $CDCl_3$): *δ*.208.6 (CH_2*C*OCH_2), 202.8 (CO*C*OCH), 198.9 (*C*H$_2$*C*OCO), 157.9 (Ar-*C*), 133.5 (Ar-*C*), 129.4 (2x Ar-*C*), 113.8 (2x Ar-*C*), 55.3 (O*C*H$_3$), 41.6 (CH_2CH_2*C*H$_2$), 36.2 (CO*C*H$_2$$CH_2$), 34.1 (*C*H$_2$$CH_2CH_2$), 33.8 (*CH*$(CH_3)_2$), 30.6 ($COCH_2$*C*H$_2$), 25.5 ($CH_2CH_2$*C*H$_2$), 17.4 (2x CH(*C*H$_3$)$_2$).

m/z [EI$^+$(+ve)] 304.2 [M]$^+$ (100%), HRMS found 304.1673, $C_{18}H_{24}O_4$ requires 304.1674 [M$^+$].

ν_{max} (film)/ cm^{-1}: 2067, 1704, 1613, 831.

_tert_Butyl(1-(5-(3-(3-methoxyphenyl)propyl)furan-2-yl)-2-methylpropoxy) dimethylsilane, 481.



A solution of *tert*Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane **424** (1.95 g, 7.66 mmol) in anhydrous tetrahydrofuran (40 mL) at 0 °C was treated slowly with *n*BuLi (3.44 mL, 8.42 mmol, 2.45 M solution in hexanes). The solution was stirred for 10 minutes at 0 °C and the yellow solution was allowed to attain room temperature over an hour. The resulting brown solution was cooled to -78 °C and treated with a solution of freshly distilled bromide **443** (20 mL, 8.42 mmol, 0.4 M in tetrahydrofuran) and stirred for 1 hour, then for a further 12 hours at room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and quenched by the slow addition of saturated ammonium chloride solution (5 mL). The layers were separated and the organic phase was washed with water (2x 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum spirits) gave as an oil an inseparable mixture of desired silyl ether **481** and bromide **443** (2.77 g, 87:13 silyl ether:bromide).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.18 (1H, m, Ar-*H*), 6.81-6.73 (3H, m, Ar-*H*), 6.02 (1H, d, *J* = 3.0 Hz, Ar-*H*), 5.89 (1H, d, *J* = 3.0 Hz, Ar-*H*), 4.24 (1H, d, *J* = 7.0 Hz, *CH*OSi), 3.79 (3H, s, O*CH*$_3$), 2.62 (4H, t, *J* = 7.4 Hz, *CH*$_2$CH$_2$*CH*$_2$), 2.05-1.99 (1H, m, *CH*(CH$_3$)$_2$), 1.96-1.90 (2H,m ,CH$_2$*CH*$_2$CH$_2$), 0.96 (3H, d, *J* = 6.7 Hz, CH(*CH*$_3$)$_2$), 0.87 (9H, s, SiC(*CH*$_3$)$_3$), 0.79 (3H, d, *J* = 6.8 Hz, CH(*CH*$_3$)$_2$), 0.02 (3H, s, Si*CH*$_3$), -0.13 (3H, s, Si*CH*$_3$).

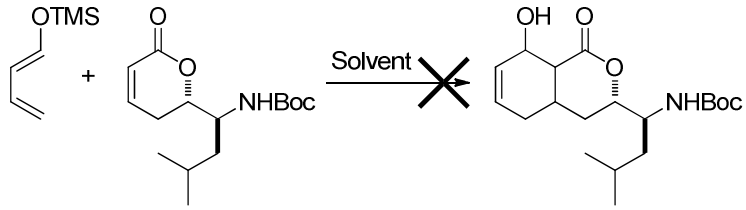
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (Ar-*C*), 151.4 (Ar-*C*), 151.2 (Ar-*C*), 142.1 (Ar-*C*), 129.8 (Ar-*C*), 120.6 (Ar-*C*), 115.2 (Ar-*C*), 113.2 (Ar-*C*), 108.7 (Ar-*C*), 104.3 (Ar-*C*), 74.3 (*C*HOSi), 55.2 (O*C*H$_3$), 35.3 (*C*H(CH$_3$)$_2$), 34.3 (CH$_2$CH$_2$*C*H$_2$), 29.8 (*C*H$_2$CH$_2$CH$_2$), 27.2 (CH$_2$*C*H$_2$CH$_2$), 25.9 (C(*C*H$_3$)$_3$), 18.8 (CH(*C*H$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$),18.5 (*C*(CH$_3$)$_3$) -4.8 (Si*C*H$_3$), -5.2 (Si*C*H$_3$).

m/z [EI$^+$(+ve)] 288.2 [M]$^+$ (100%), HRMS found 288.1730, $C_{18}H_{24}O_3$ requires 288.1725 [M$^+$].

ν_{max} (film)/ cm^{-1}: 3432, 1613, 1511, 1244, 1035

7. Appendices

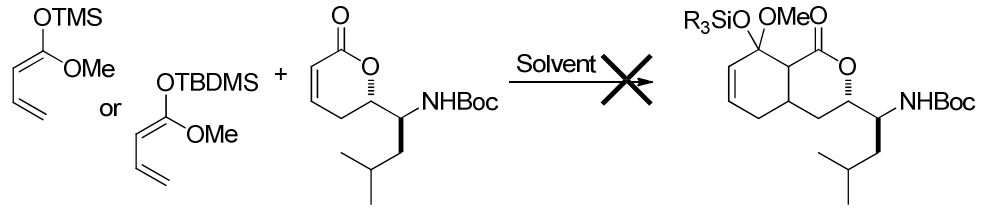
7.1. Appendix 1 - Reaction of diene 208 and dienophile 198



Equivalent's Diene	Solvent[a]	Lewis Acid	Temperature
1.1	CH_2Cl_2	-	Reflux
1.1	CH_2Cl_2	-	Reflux (sealed tube)
1.1	Benzene	-	Reflux
1.1	Benzene	-	Reflux (sealed tube)
2.0	Toluene	-	Reflux
2.0	Xylene	-	Reflux
1.15	CH_2Cl_2	Me_3Al	Reflux
1.2	CH_2Cl_2	$AlCl_3$	Reflux
1.2	CH_2Cl_2	Et_2AlCl	Reflux
1.15	CH_2Cl_2	Me_3Al	Reflux (sealed tube)
1.15	Benzene	Me_3Al	Reflux
1.15	Benzene	Et_2AlCl	Reflux
1.15	Benzene	Me_3Al	Reflux (sealed tube)
2.0	Toluene	$AlCl_3$	Reflux
2.0	Xylene	$AlCl_3$	Reflux

[a] Reactions were run at concentrations of 0.2 M with respect to dienophile 198.

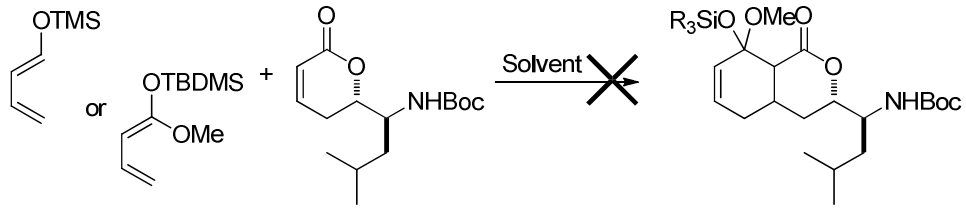
7.2. Appendix 2 - Reaction of modified dienes 202 and 206



Diene (Equiv)	Solvent	Lewis Acid	Temperature
202	CH_2Cl_2	-	Reflux
202	CH_2Cl_2	Me_3Al	Reflux
202	Benzene	-	Reflux
202	Benzene	Me_3Al	Reflux
206	CH_2Cl_2	-	Reflux
206	CH_2Cl_2	$AlCl_3$	Reflux
206	Benzene	-	Reflux
206	Toluene	$AlCl_3$	Reflux
206	Toluene	-	Reflux
206	Toluene	-	Reflux (sealed tube)
206	Xylene	-	Reflux

[a] Reactions were run for at least 24 hours and at 0.2 M with respect to dienophile and with 1.1 equivalents of diene and monitored by TLC.

7.3. Appendix 3 - Microwave conditions.



Diene [a]	Solvent	Lewis Acid	μW conditions [b]
208 (1.5)	CH_2Cl_2	-	130°C for 11 mins
206 (1.2)	CH_2Cl_2	-	130°C for 22 mins
206 (1.2)	CH_2Cl_2	Me_3Al	130°C for 22 mins
206 (1.2)	CH_2Cl_2	$AlCl_3$	130°C for 11 mins
206 (1.4)	DCM (0.4 M)	-	130°C for 20 mins
206 (1.2)	Benzene	Me_3Al	200°C for 20 mins
206 (1.2)	Benzene	$AlCl_3$	200°C for 20 mins
208 (2.0)	Toluene (0.1 M)	-	180°C for 30 mins
208 (2.0)	Toluene (0.3 M)	-	180°C for 30 mins
208 (2.0)	Toluene (0.1 M)	$AlCl_3$	180°C for 30 mins
208 (3.0)	Toluene	-	180°C for 30 mins
208 (4.0)	Toluene	-	180°C for 30 mins
208 (5.0)	Toluene	-	180°C for 30 mins
208 (2.0)	Toluene	-	180°C for 2 hr
208 (5.0)	Toluene	-	180°C for 2 hr
208 (5.0)	Toluene	-	200°C for 2 hr
208 (2.0)	Diphenyl ether	-	250°C for 1 hr
208 (5.0)	Diphenyl ether	-	250°C for 1 hr

[b] Number of diene equivalents [b] μW conditions were applied temperatures and durations, pressures increased as a result up to 5 bar with the toluene and diphenyl ether experiments

[a] Number of diene equivalents [b] μW conditions were applied temperatures and durations, pressures increased as a result up to 5 bar with the toluene and diphenyl ether experiments.

7.4. Appendix 4 - Neat Diels Alder series.

Diene	µW conditions
208 (2.0)	250°C for 30 mins
208 (3.0)	250°C for 30 mins
208 (6.0)	250°C for 2 hr

Number of diene equivalents in parentheses.

7.5. Appendix 5 – X-ray data for 198

Table 1. Crystal data and structure refinement for 198.

Identification code	198
Empirical formula	C_{15} H_{25} N O_4
Formula weight	283.36
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	?, ?
Unit cell dimensions	a = 10.3366(15) A alpha = 90 deg. b = 10.3366(15) A beta = 90 deg. c = 27.883(6) A gamma = 120 deg.
Volume	2580.0(7) A^3
Z, Calculated density	7, 1.277 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	1078
Crystal size	? x ? x ? mm
Theta range for data collection	3.16 to 27.48 deg.
Limiting indices	13<=h<=13, -13<=k<=13, -35<=l<=36
Reflections collected / unique	36960 / 3940 [R(int) = 0.2909]
Completeness to theta = 27.48	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3940 / 1 / 186
Goodness-of-fit on F^2	0.943
Final R indices [I>2sigma(I)]	R1 = 0.0906, wR2 = 0.1864
R indices (all data)	R1 = 0.2407, wR2 = 0.2395
Absolute structure parameter	1(3)
Largest diff. peak and hole	0.192 and -0.180 $e.A^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 198.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	7440(5)	8896(5)	62(1)	70(1)
O(2)	5622(6)	7224(6)	-379(2)	98(2)
O(3)	12589(4)	10529(5)	158(1)	76(1)
O(4)	11797(5)	10698(5)	908(1)	74(1)
N(1)	10611(5)	10764(5)	244(1)	59(1)
C(1)	6291(8)	7505(9)	2(3)	77(2)
C(2)	5972(9)	6463(8)	377(3)	93(2)
C(3)	6900(10)	6715(10)	731(3)	114(3)
C(4)	8237(8)	8184(8)	788(2)	85(2)
C(5)	8040(7)	9366(8)	547(2)	67(2)
C(6)	9439(6)	10873(7)	492(2)	60(2)
C(7)	11694(7)	10690(7)	471(2)	63(2)

C(8)	13977(8)	10632(9)	325(2)	76(2)
C(9)	14561(9)	10326(10)	-133(2)	109(3)
C(10)	14954(8)	12113(9)	537(2)	88(2)
C(11)	13630(9)	9328(9)	683(3)	100(2)
C(12)	9125(7)	12038(7)	258(2)	73(2)
C(13)	10111(11)	13587(9)	411(4)	121(3)
C(14)	11663(9)	14151(10)	427(4)	131(4)
C(15)	9682(13)	14617(10)	152(4)	153(4)

Table 3. Bond lengths [A] and angles [deg] for 198.

O(1)-C(1)	1.341(8)
O(1)-C(5)	1.466(6)
O(2)-C(1)	1.221(7)
O(3)-C(7)	1.342(7)
O(3)-C(8)	1.461(7)
O(4)-C(7)	1.223(6)
N(1)-C(7)	1.321(7)
N(1)-C(6)	1.448(7)
C(1)-C(2)	1.417(10)
C(2)-C(3)	1.310(10)
C(3)-C(4)	1.463(11)
C(4)-C(5)	1.494(9)
C(5)-C(6)	1.513(8)
C(6)-C(12)	1.540(8)
C(8)-C(10)	1.471(10)
C(8)-C(9)	1.513(9)
C(8)-C(11)	1.569(9)
C(12)-C(13)	1.467(10)
C(13)-C(14)	1.408(11)
C(13)-C(15)	1.524(12)
C(1)-O(1)-C(5)	118.2(5)
C(7)-O(3)-C(8)	119.8(5)
C(7)-N(1)-C(6)	122.8(4)
O(2)-C(1)-O(1)	117.2(6)
O(2)-C(1)-C(2)	125.0(7)
O(1)-C(1)-C(2)	117.9(7)
C(3)-C(2)-C(1)	122.4(7)
C(2)-C(3)-C(4)	120.4(7)
C(3)-C(4)-C(5)	110.9(6)
O(1)-C(5)-C(4)	110.6(5)
O(1)-C(5)-C(6)	106.0(4)
C(4)-C(5)-C(6)	115.9(5)
N(1)-C(6)-C(5)	112.0(5)
N(1)-C(6)-C(12)	111.7(5)
C(5)-C(6)-C(12)	112.4(5)
O(4)-C(7)-N(1)	123.4(5)
O(4)-C(7)-O(3)	125.9(5)
N(1)-C(7)-O(3)	110.6(5)
O(3)-C(8)-C(10)	110.0(6)
O(3)-C(8)-C(9)	101.3(5)
C(10)-C(8)-C(9)	114.7(6)
O(3)-C(8)-C(11)	110.2(6)
C(10)-C(8)-C(11)	112.4(5)
C(9)-C(8)-C(11)	107.5(6)
C(13)-C(12)-C(6)	115.3(5)
C(14)-C(13)-C(12)	119.2(9)
C(14)-C(13)-C(15)	113.3(8)
C(12)-C(13)-C(15)	109.8(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 198.
The anisotropic displacement factor exponent takes the form:-2 π^2 [h^2 a*^2 U^{11} + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
O(1)	66(3)	93(3)	36(2)	-3(2)	0(2)	30(3)	
O(2)	91(4)	90(4)	71(3)	-10(3)	-9(3)	14(3)	
O(3)	67(3)	121(4)	44(2)	9(2)	7(2)	50(3)	
O(4)	77(3)	108(3)	43(2)	4(2)	-1(2)	51(3)	
N(1)	61(3)	80(3)	34(2)	-4(2)	0(2)	34(3)	
C(1)	46(4)	84(5)	78(5)	0(4)	14(4)	14(4)	
C(2)	71(5)	75(5)	96(5)	15(4)	15(5)	9(4)	
C(3)	85(6)	109(7)	115(6)	49(5)	8(5)	23(6)	
C(4)	91(5)	84(5)	62(4)	20(3)	0(3)	30(5)	
C(5)	59(4)	98(5)	40(3)	-10(3)	-6(3)	37(4)	
C(6)	68(4)	85(5)	35(3)	-2(3)	-4(3)	45(4)	
C(7)	63(4)	91(5)	40(3)	-1(3)	-4(3)	42(3)	
C(8)	76(5)	103(6)	64(4)	8(4)	-1(3)	56(5)	
C(9)	106(6)	177(9)	83(5)	3(5)	19(4)	101(7)	
C(10)	78(5)	113(6)	88(5)	20(5)	-6(4)	58(5)	
C(11)	114(6)	111(6)	91(5)	24(4)	-8(4)	69(5)	
C(12)	67(4)	84(5)	65(4)	-12(3)	-14(3)	36(4)	
C(13)	131(8)	87(6)	132(7)	10(5)	-55(6)	44(6)	
C(14)	75(6)	84(6)	213(11)	16(6)	26(6)	24(5)	
C(15)	180(10)	93(7)	173(9)	16(6)	-64(8)	58(7)	

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 198.

	x	y	z	U(eq)
H(1A)	10603	10746	-64	70
H(2A)	5069	5566	371	111
H(3A)	6709	5956	948	137
H(4A)	9090	8167	650	102
H(4B)	8435	8415	1126	102
H(5A)	7315	9505	734	81
H(6A)	9809	11234	817	71
H(9A)	14386	10818	-396	163
H(9B)	14054	9269	-192	163
H(9C)	15614	10695	-103	163
H(10A)	15146	12873	304	132
H(10B)	15880	12186	633	132
H(10C)	14473	12245	811	132
H(11A)	13301	9516	984	149
H(11B)	14517	9267	733	149
H(11C)	12859	8402	552	149
H(12A)	9211	11986	-87	88
H(12B)	8102	11769	328	88
H(13A)	9832	13604	746	145
H(14A)	11889	13655	677	196
H(14B)	12165	15205	492	196
H(14C)	11995	13980	125	196
H(15A)	10156	15577	306	230
H(15B)	8617	14194	164	230
H(15C)	10002	14731	-176	230

7.6. Appendix 6 – X-Ray data for 244

Table 1. Crystal data and structure refinement for 244.

Identification code	244
Empirical formula	C_{12} H_{13} O_3
Formula weight	205.22
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	P21/n
Unit cell dimensions	a = 6.2961(11) A alpha = 90 deg. b = 8.7626(18) A beta = 90.705(5) deg. c = 18.718(3) A gamma = 90 deg.
Volume	1032.6(3) A^3
Z, Calculated density	4, 1.320 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	436
Crystal size	0.1 x 0.1 x 0.4 mm
Theta range for data collection	3.18 to 27.48 deg.
Limiting indices	-8<=h<=8, -11<=k<=11, -24<=l<=24
Reflections collected / unique	13411 / 2353 [R(int) = 0.0612]
Completeness to theta = 27.48	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2353 / 0 / 192
Goodness-of-fit on F^2	1.119
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.1050
R indices (all data)	R1 = 0.0674, wR2 = 0.1257
Largest diff. peak and hole	0.232 and -0.258 $e.A^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 244.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(3)	11708(2)	4056(1)	1987(1)	31(1)
O(1)	5333(2)	4401(1)	1092(1)	32(1)
O(2)	7225(2)	4751(1)	2064(1)	29(1)
C(8)	10919(3)	5579(2)	2013(1)	26(1)
C(9)	8900(3)	5588(2)	2443(1)	26(1)
C(10)	9004(3)	4852(2)	3179(1)	28(1)
C(6)	8465(3)	5880(2)	968(1)	26(1)
C(11)	10736(3)	5581(2)	3635(1)	33(1)
C(5)	7959(3)	6375(2)	280(1)	30(1)
C(7)	6899(3)	4975(2)	1364(1)	26(1)
C(4)	9446(3)	7194(2)	-101(1)	31(1)
C(2)	11903(3)	7008(2)	883(1)	29(1)
C(1)	10437(3)	6188(2)	1275(1)	26(1)
C(12)	6858(3)	4994(2)	3540(1)	35(1)
C(3)	11409(3)	7508(2)	200(1)	31(1)

Table 3. Bond lengths [A] and angles [deg] for 244.

O(3)-C(8)	1.425(2)
O(1)-C(7)	1.213(2)
O(2)-C(7)	1.338(2)
O(2)-C(9)	1.461(2)
C(8)-C(1)	1.508(2)
C(8)-C(9)	1.513(2)
C(9)-C(10)	1.521(2)
C(10)-C(11)	1.518(3)
C(10)-C(12)	1.523(3)
C(6)-C(1)	1.388(2)
C(6)-C(5)	1.392(2)

C(6)-C(7)	1.472(2)
C(5)-C(4)	1.385(3)
C(4)-C(3)	1.380(3)
C(2)-C(3)	1.383(2)
C(2)-C(1)	1.387(2)
C(7)-O(2)-C(9)	120.20(13)
O(3)-C(8)-C(1)	111.51(13)
O(3)-C(8)-C(9)	108.58(13)
C(1)-C(8)-C(9)	108.94(14)
O(2)-C(9)-C(8)	110.19(13)
O(2)-C(9)-C(10)	104.48(13)
C(8)-C(9)-C(10)	116.90(14)
C(11)-C(10)-C(9)	110.75(15)
C(11)-C(10)-C(12)	110.52(15)
C(9)-C(10)-C(12)	109.80(15)
C(1)-C(6)-C(5)	120.96(16)
C(1)-C(6)-C(7)	119.90(15)
C(5)-C(6)-C(7)	119.12(16)
C(4)-C(5)-C(6)	119.36(17)
O(1)-C(7)-O(2)	117.67(16)
O(1)-C(7)-C(6)	123.91(16)
O(2)-C(7)-C(6)	118.41(15)
C(3)-C(4)-C(5)	120.02(17)
C(3)-C(2)-C(1)	120.59(17)
C(2)-C(1)-C(6)	118.74(16)
C(2)-C(1)-C(8)	122.67(16)
C(6)-C(1)-C(8)	118.57(15)
C(4)-C(3)-C(2)	120.33(17)

Symmetry transformations used to generate equivalent atoms

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 244.
The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	30(1)	30(1)	34(1)	4(1)	4(1)	5(1)
O(1)	28(1)	35(1)	32(1)	-2(1)	-3(1)	-3(1)
O(2)	28(1)	33(1)	26(1)	1(1)	-2(1)	-4(1)
C(8)	27(1)	26(1)	26(1)	1(1)	-2(1)	-2(1)
C(9)	27(1)	24(1)	26(1)	-1(1)	-3(1)	-1(1)
C(10)	32(1)	25(1)	27(1)	0(1)	0(1)	2(1)
C(6)	27(1)	25(1)	26(1)	-2(1)	0(1)	0(1)
C(11)	37(1)	33(1)	28(1)	1(1)	-3(1)	0(1)
C(5)	31(1)	30(1)	28(1)	-2(1)	-3(1)	0(1)
C(7)	28(1)	24(1)	27(1)	-2(1)	-1(1)	2(1)
C(4)	37(1)	32(1)	24(1)	2(1)	-1(1)	1(1)
C(2)	31(1)	26(1)	28(1)	-2(1)	2(1)	-1(1)
C(1)	29(1)	23(1)	26(1)	-2(1)	0(1)	2(1)
C(12)	38(1)	36(1)	30(1)	0(1)	4(1)	-2(1)
C(3)	35(1)	28(1)	30(1)	1(1)	4(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 244.

	x	y	z	U(eq)
H(10)	10430(30)	6670(30)	3688(11)	40(6)
H(4)	6590(30)	6110(20)	79(9)	25(5)
H(8)	8390(30)	6670(20)	2482(9)	20(4)
H(6)	11960(30)	6290(20)	2264(9)	25(5)

H(9)	9320(30)	3750(20)	3092(9)	27(5)
H(13)	6500(30)	6060(30)	3578(10)	35(5)
H(12)	10730(30)	5120(20)	4132(12)	36(5)
H(3)	9090(30)	7520(20)	-584(10	30(5)
H(2)	12460(30)	8110(20)	-68(10)	39(5)
H(1)	13330(30)	7260(20)	1097(10)	36(5)
H(15)	5700(40)	4480(20)	3250(12)	41(6)
H(14)	6910(40)	4500(30)	4035(13)	46(6)
H(11)	12190(40)	5450(30)	3429(12)	52(6)
H(7)	12900(50)	4080(30)	1723(14)	67(8)

7.7. Appendix 7 – X- Ray data for 261

Table 1. Crystal data and structure refinement for 261.

Identification code	**261**
Empirical formula	$C_{15}H_{18}O_3$
Formula weight	246.31
Temperature	100 K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 1 21/c 1
Unit cell dimensions	a = 19.150(13) A alpha = 90 deg. b = 5.058(3) A beta = 97.09(2) deg. c = 12.838(10) A gamma = 90 deg.
Volume	1234.0(15) A^3
Z, Calculated density	4, 1.326 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	528
Crystal size	0.20 x 0.08 x 0.08 mm
Theta range for data collection	3.198 to 23.255 deg.
Limiting indices	-21<=h<=21, -5<=k<=5, -14<=l<=14
Reflections collected / unique	7318 / 1765 [R(int) = 0.207]
Completeness to theta = 22.790	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1765 / 1 / 166
Goodness-of-fit on F^2	0.8991
Final R indices [I>2sigma(I)]	R1 = 0.0771, wR2 = 0.1382
R indices (all data)	R1 = 0.1909, wR2 = 0.1766
Largest diff. peak and hole	1.00 and -1.12 $e.A^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 261.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3398(2)	10491(9)	3782(3)	41
O(5)	2372(2)	11354(8)	1944(3)	33
C(8)	3898(3)	9640(12)	564(5)	32
C(9)	2871(3)	11639(13)	1291(5)	31
C(13)	1096(3)	9815(13)	2763(5)	37
O(16)	2785(2)	13508(8)	674(3)	38
C(19)	3470(3)	9779(11)	1361(5)	29
C(23)	542(3)	10050(13)	3513(5)	41
C(28)	4581(3)	6205(13)	1512(5)	37
C(37)	4450(3)	7840(12)	634(5)	36
C(48)	519(3)	7620(12)	4207(5)	43
C(50)	2383(3)	8912(12)	2596(5)	35
C(57)	3595(3)	8150(12)	2243(5)	29
C(62)	4157(3)	6348(12)	2303(5)	40
C(65)	1817(3)	6911(12)	4074(5)	37

C(68)	3131(3)	8388(12)	3085(5)	36
C(72)	1828(3)	9304(11)	3355(5)	30
C(76)	1244(3)	7100(13)	4816(5)	42

Table 3. Bond lengths [A] and angles [deg] for 261.

O(1)-C(68)	1.442(7)
O(1)-H(2)	0.89(4)
O(5)-C(9)	1.355(7)
O(5)-C(50)	1.491(7)
C(8)-C(19)	1.388(8)
C(8)-C(37)	1.390(8)
C(8)-H(81)	0.950
C(9)-O(16)	1.231(7)
C(9)-C(19)	1.478(8)
C(13)-C(23)	1.522(8)
C(13)-C(72)	1.533(7)
C(13)-H(131)	0.950
C(13)-H(132)	0.950
C(19)-C(57)	1.397(8)
C(23)-C(48)	1.522(8)
C(23)-H(231)	0.950
C(23)-H(232)	0.950
C(28)-C(37)	1.396(8)
C(28)-C(62)	1.377(9)
C(28)-H(281)	0.950
C(37)-H(371)	0.950
C(48)-C(76)	1.530(8)
C(48)-H(481)	0.950
C(48)-H(482)	0.950
C(50)-C(68)	1.515(7)
C(50)-C(72)	1.541(8)
C(50)-H(501)	0.950
C(57)-C(62)	1.405(8)
C(57)-C(68)	1.488(9)
C(62)-H(621)	0.950
C(65)-C(72)	1.524(8)
C(65)-C(76)	1.541(9)
C(65)-H(651)	0.950
C(65)-H(652)	0.950
C(68)-H(681)	0.950
C(72)-H(721)	0.950
C(76)-H(761)	0.950
C(76)-H(762)	0.950
C(68)-O(1)-H(2)	108(4)
C(9)-O(5)-C(50)	118.2(5)
C(19)-C(8)-C(37)	119.9(6)
C(19)-C(8)-H(81)	119.4
C(37)-C(8)-H(81)	120.7
O(5)-C(9)-O(16)	115.5(6)
O(5)-C(9)-C(19)	119.8(6)
O(16)-C(9)-C(19)	124.7(7)
C(23)-C(13)-C(72)	111.5(5)
C(23)-C(13)-H(131)	110.1
C(72)-C(13)-H(131)	109.2
C(23)-C(13)-H(132)	108.9
C(72)-C(13)-H(132)	107.7
H(131)-C(13)-H(132)	109.5
C(9)-C(19)-C(8)	120.7(6)
C(9)-C(19)-C(57)	118.6(6)
C(8)-C(19)-C(57)	120.7(6)
C(13)-C(23)-C(48)	112.3(5)

C(13)-C(23)-H(231)	108.7
C(48)-C(23)-H(231)	107.8
C(13)-C(23)-H(232)	109.1
C(48)-C(23)-H(232)	109.3
H(231)-C(23)-H(232)	109.5
C(37)-C(28)-C(62)	120.1(6)
C(37)-C(28)-H(281)	120.3
C(62)-C(28)-H(281)	119.7
C(28)-C(37)-C(8)	119.9(7)
C(28)-C(37)-H(371)	119.7
C(8)-C(37)-H(371)	120.4
C(23)-C(48)-C(76)	110.3(5)
C(23)-C(48)-H(481)	110.5
C(76)-C(48)-H(481)	110.6
C(23)-C(48)-H(482)	107.8
C(76)-C(48)-H(482)	108.2
H(481)-C(48)-H(482)	109.5
O(5)-C(50)-C(68)	109.0(5)
O(5)-C(50)-C(72)	106.6(5)
C(68)-C(50)-C(72)	116.8(5)
O(5)-C(50)-H(501)	108.3
C(68)-C(50)-H(501)	108.4
C(72)-C(50)-H(501)	107.5
C(19)-C(57)-C(62)	118.7(6)
C(19)-C(57)-C(68)	118.9(6)
C(62)-C(57)-C(68)	122.4(6)
C(57)-C(62)-C(28)	120.7(6)
C(57)-C(62)-H(621)	119.3
C(28)-C(62)-H(621)	120.0
C(72)-C(65)-C(76)	112.9(5)
C(72)-C(65)-H(651)	109.1
C(76)-C(65)-H(651)	110.4
C(72)-C(65)-H(652)	106.7
C(76)-C(65)-H(652)	108.1
H(651)-C(65)-H(652)	109.5
C(50)-C(68)-C(57)	109.4(5)
C(50)-C(68)-O(1)	111.9(5)
C(57)-C(68)-O(1)	108.2(5)
C(50)-C(68)-H(681)	109.1
C(57)-C(68)-H(681)	109.1
O(1)-C(68)-H(681)	109.1
C(50)-C(72)-C(13)	111.6(5)
C(50)-C(72)-C(65)	110.1(5)
C(13)-C(72)-C(65)	110.7(5)
C(50)-C(72)-H(721)	108.5
C(13)-C(72)-H(721)	108.2
C(65)-C(72)-H(721)	107.6
C(65)-C(76)-C(48)	111.4(5)
C(65)-C(76)-H(761)	108.8
C(48)-C(76)-H(761)	108.6
C(65)-C(76)-H(762)	109.2
C(48)-C(76)-H(762)	109.4
H(761)-C(76)-H(762)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 261.
The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^2 U^{11} + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	50(3)	40(3)	33(3)	-1(3)	5(2)	-2(2)
O(5)	40(3)	29(3)	29(3)	2(2)	4(2)	6(2)

C(8)	33(4)	31(4)	30(4)	-3(3)	1(3)	2(3)
C(9)	31(4)	26(4)	35(4)	-2(4)	6(4)	-4(3)
C(13)	33(4)	40(4)	38(4)	3(4)	2(3)	3(3)
O(16)	44(3)	35(3)	33(3)	4(2)	3(2)	-2(2)
C(19)	28(4)	25(4)	32(4)	4(3)	-6(3)	2(3)
C(23)	46(5)	33(4)	43(5)	6(3)	6(4)	8(4)
C(28)	32(4)	36(4)	43(5)	-2(4)	3(4)	2(3)
C(37)	38(4)	36(4)	35(4)	-11(3)	5(3)	-1(3)
C(48)	53(5)	37(4)	42(5)	-2(3)	17(4)	-3(4)
C(50)	25(4)	31(4)	46(5)	8(4)	-5(3)	-4(3)
C(57)	31(4)	28(4)	28(4)	-10(3)	-1(3)	1(3)
C(62)	47(4)	31(4)	38(5)	6(3)	-2(4)	5(4)
C(65)	40(4)	33(4)	37(4)	3(3)	2(4)	6(3)
C(68)	47(5)	28(4)	31(4)	0(3)	2(4)	-11(3)
C(72)	37(4)	23(4)	31(4)	-2(3)	10(3)	-3(3)
C(76)	61(5)	31(4)	35(4)	2(3)	6(4)	-4(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 261.

	x	y	z	U(eq)
H(81)	3806	10774	-27	47
H(131)	1108	11388	2362	49
H(132)	981	8359	2307	49
H(231)	652	11532	3958	58
H(232)	94	10303	3118	58
H(281)	4958	4974	1564	53
H(371)	4743	7731	90	52
H(481)	176	7836	4675	59
H(482)	397	6146	3762	59
H(501)	2233	7470	2149	45
H(621)	4246	5231	2899	58
H(651)	2267	6707	4467	46
H(652)	1717	5417	3633	46
H(681)	3143	6777	3467	48
H(721)	1958	10798	3785	49
H(761)	1357	8517	5292	57
H(762)	1232	5492	5196	57
H(2)	3180(30)	10410(130)	4360(40)	50

7.8. Appendix 8 – X-Ray data for 264

Table 1. Crystal data and structure refinement for 264

Identification code	**264**
Empirical formula	$C_{17}H_{16}O_3$
Formula weight	268.30
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Pc
Unit cell dimensions	a = 12.826(5) Å α= 90°. b = 7.712(2) Å β= 91.105(19)°. c = 6.916(3) Å γ = 90°.
Volume	683.9(4) $Å^3$
Z	2
Density (calculated)	1.303 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	284

Crystal size	0.20 x 0.20 x 0.08 mm^3
Theta range for data collection	1.59 to 29.97°
Index ranges	-18<=h<=17, -10<=k<=9, -9<=l<=9
Reflections collected	11845
Independent reflections	3782 (R(int) = 0.0465)
Observed reflections (>2sigma(I))	3011
Completeness to theta = 29.97°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9929 and 0.9825
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3782 / 2 / 185
Goodness-of-fit on F^2	1.023
Final R indices (I>2sigma(I))	R1 = 0.0463, wR2 = 0.1051
R indices (all data)	R1 = 0.0646, wR2 = 0.1149
Absolute structure parameter	-0.9(10)
Largest diff. peak and hole	0.334 and -0.165 e.$Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å2) for 264
U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)	
O(1)	0.67391(11)	1.14513(16)	0.21976(19)	0.0244(3)	
O(2)	0.56260(10)	0.93766(16)	0.28384(17)	0.0214(3)	
O(3)	0.53289(11)	0.67266(18)	-0.02699(19)	0.0279(3)	
C(1)	0.83906(14)	0.9027(3)	0.1581(3)	0.0259(4)	
C(2)	0.91110(15)	0.7787(3)	0.1035(3)	0.0296(4)	
C(3)	0.87838(16)	0.6092(3)	0.0635(3)	0.0281(4)	
C(4)	0.77443(16)	0.5625(3)	0.0824(3)	0.0257(4)	
C(5)	0.70136(14)	0.6854(2)	0.1382(2)	0.0211(4)	
C(6)	0.73436(15)	0.8547(3)	0.1754(3)	0.0214(4)	
C(7)	0.65680(14)	0.9895(2)	0.2268(2)	0.0203(4)	
C(8)	0.58683(15)	0.6453(2)	0.1529(3)	0.0225(4)	
C(9)	0.54193(14)	0.7526(2)	0.3149(3)	0.0206(4)	
C(10)	0.42548(14)	0.7342(3)	0.3422(3)	0.0236(4)	
C(11)	0.38640(15)	0. 8493(3)	0.5064(3)	0.0294(4)	
C(12)	0.27748(15)	0.8039(2)	0.5677(3)	0.0234(4)	
C(13)	0.19026(15)	0.8675(3)	0.4681(3)	0.0278(4)	
C(14)	0.09075(15)	0.8264(3)	0.5285(3)	0.0379(6)	
C(15)	0.07723(19)	0.7218(3)	0.6883(3)	0.0419(6)	
C(16)	0.1631(2)	0.6567(3)	0.7863(4)	0.0451(6)	
C(17)	0.26268(18)	0.6990(3)	0.7279(3)	0.0340(5)	

Table 3. Bond lengths [Å] and angles [°] for 264.

O(1)-C(7)	1.221(2)
O(2)-C(7)	1.339(2)
O(2)-C(9)	1.468(2)
O(3)-C(8)	1.428(2)
O(3)-H(1)	1.03(4)
C(1)-C(2)	1.387(3)
C(1)-C(6)	1.400(3)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.399(3)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.390(3)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.393(3)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.395(3)
C(5)-C(8)	1.507(3)

C(6)-C(7)	1.486(3)
C(8)-C(9)	1.516(3)
C(8)-H(8A)	1.0000
C(9)-C(10)	1.516(2)
C(9)-H(9A)	1.0000
C(10)-C(11)	1.534(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.509(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(17)	1.388(3)
C(12)-C(13)	1.392(3)
C(13)-C(14)	1.387(3)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.382(4)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.377(4)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.385(3)
C(16)-H(16A)	0.9500
C(17)-H(17A)	0.9500
C(7)-O(2)-C(9)	119.98(14)
C(8)-O(3)-H(1)	100(2)
C(2)-C(1)-C(6)	119.08(19)
C(2)-C(1)-H(1A)	120.5
C(6)-C(1)-H(1A)	120.5
C(1)-C(2)-C(3)	119.93(18)
C(1)-C(2)-H(2A)	120.0
C(3)-C(2)-H(2A)	120.0
C(4)-C(3)-C(2)	120.57(18)
C(4)-C(3)-H(3A)	119.7
C(2)-C(3)-H(3A)	119.7
C(3)-C(4)-C(5)	120.09(19)
C(3)-C(4)-H(4A)	120.0
C(5)-C(4)-H(4A)	120.0
C(4)-C(5)-C(6)	119.00(17)
C(4)-C(5)-C(8)	122.74(17)
C(6)-C(5)-C(8)	118.21(16)
C(5)-C(6)-C(1)	121.31(17)
C(5)-C(6)-C(7)	119.76(16)
C(1)-C(6)-C(7)	118.89(17)
O(1)-C(7)-O(2)	117.96(16)
O(1)-C(7)-C(6)	123.77(17)
O(2)-C(7)-C(6)	118.27(16)
O(3)-C(8)-C(5)	111.55(15)
O(3)-C(8)-C(9)	112.26(15)
C(5)-C(8)-C(9)	108.82(14)
O(3)-C(8)-H(8A)	108.0
C(5)-C(8)-H(8A)	108.0
C(9)-C(8)-H(8A)	108.0
O(2)-C(9)-C(8)	110.52(14)
O(2)-C(9)-C(10)	106.88(14)
C(8)-C(9)-C(10)	115.48(15)
O(2)-C(9)-H(9A)	107.9
C(8)-C(9)-H(9A)	107.9
C(10)-C(9)-H(9A)	107.9
C(9)-C(10)-C(11)	112.01(15)
C(9)-C(10)-H(10A)	109.2
C(11)-C(10)-H(10A)	109.2
C(9)-C(10)-H(10B)	109.2
C(11)-C(10)-H(10B)	109.2
H(10A)-C(10)-H(10B)	107.9

C(12)-C(11)-C(10)	113.03(15)
C(12)-C(11)-H(11A)	109.0
C(10)-C(11)-H(11A)	109.0
C(12)-C(11)-H(11B)	109.0
C(10)-C(11)-H(11B)	109.0
H(11A)-C(11)-H(11B)	107.8
C(17)-C(12)-C(13)	118.67(18)
C(17)-C(12)-C(11)	120.09(19)
C(13)-C(12)-C(11)	121.23(18)
C(14)-C(13)-C(12)	120.4(2)
C(14)-C(13)-H(13A)	119.8
C(12)-C(13)-H(13A)	119.8
C(15)-C(14)-C(13)	120.3(2)
C(15)-C(14)-H(14A)	119.8
C(13)-C(14)-H(14A)	119.8
C(16)-C(15)-C(14)	119.7(2)
C(16)-C(15)-H(15A)	120.2
C(14)-C(15)-H(15A)	120.2
C(15)-C(16)-C(17)	120.3(2)
C(15)-C(16)-H(16A)	119.9
C(17)-C(16)-H(16A)	119.9
C(16)-C(17)-C(12)	120.7(2)
C(16)-C(17)-H(17A)	119.6
C(12)-C(17)-H(17A)	119.6

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å2) for 264.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0306(7)	0.0226(7)	0.0199(6)	-0.0010(6)	0.0003(5)	-0.0034(5)
O(2)	0.0236(6)	0.0195(6)	0.0210(7)	-0.0006(5)	-0.0004(5)	0.0001(5)
O(3)	0.0326(7)	0.0303(8)	0.0207(7)	-0.0018(6)	-0.0020(6)	-0.0055(6)
C(1)	0.0255(10)	0.0344(11)	0.0180(9)	-0.0016(8)	0.0005(7)	-0.0039(8)
C(2)	0.0236(9)	0.0450(12)	0.0201(10)	-0.0018(9)	0.0007(8)	0.0004(8)
C(3)	0.0303(10)	0.0327(11)	0.0214(9)	0.0008(8)	0.0038(8)	0.0101(8)
C(4)	0.0336(10)	0.0259(10)	0.0176(9)	0.0016(8)	0.0019(7)	0.0055(8)
C(5)	0.0279(9)	0.0227(10)	0.0129(8)	0.0028(7)	0.0035(7)	0.0008(7)
C(6)	0.0249(8)	0.0257(10)	0.0138(8)	-0.0006(7)	-0.0006(7)	0.0016(7)
C(7)	0.0251(9)	0.0242(9)	0.0114(7)	-0.0012(7)	-0.0023(7)	-0.0008(7)
C(8)	0.0291(9)	0.0208(9)	0.0177(8)	-0.0018(7)	0.0017(7)	-0.0021(7)
C(9)	0.0249(9)	0.0199(8)	0.0170(8)	0.0012(7)	0.0007(6)	-0.0012(7)
C(10)	0.0236(9)	0.0241(9)	0.0231(9)	-0.0036(8)	0.0015(7)	-0.0036(7)
C(11)	0.0217(9)	0.0339(11)	0.0327(11)	-0.0100(9)	0.0046(8)	-0.0043(8)
C(12)	0.0242(9)	0.0237(9)	0.0222(9)	-0.0057(8)	0.0028(7)	-0.0010(7)
C(13)	0.0312(10)	0.0313(10)	0.0209(10)	-0.0017(8)	0.0003(8)	0.0001(8)
C(14)	0.0227(10)	0.0575(15)	0.0335(12)	-0.0172(11)	-0.0024(9)	0.0019(9)
C(15)	0.0366(12)	0.0501(14)	0.0397(13)	-0.0197(11)	0.0171(10)	-0.0204(11)
C(16)	0.0699(18)	0.0333(13)	0.0330(12)	0.0011(10)	0.0215(12)	-0.0127(11)

C(17)	0.0441(12)	0.0292(11)	0.0288(11)	0.0035(9)	0.0021(9)	0.0069(9)

Table 5. Atomic coordinates and isotropic displacement parameters (Å2) for 264.

	x	y	z	U(eq)
H(1A)	0.8605	1.0186	0.1835	0.031
H(2A)	0.9826	0.8089	0.0931	0.035
H(3A)	0.9276	0.5253	0.0232	0.034
H(4A)	0.7532	0.4466	0.0572	0.031
H(8A)	0.5797	0.5201	0.1881	0.027
H(9A)	0.5779	0.7174	0.4384	0.025
H(10A)	0.4090	0.6116	0.3711	0.028
H(10B)	0.3884	0.7659	0.2203	0.028
H(11A)	0.4346	0.8380	0.6193	0.035
H(11B)	0.3876	0.9719	0.4638	0.035
H(13A)	0.1989	0.9394	0.3580	0.033
H(14A)	0.0316	0.8703	0.4597	0.045
H(15A)	0.0090	0.6949	0.7304	0.050
H(16A)	0.1541	0.5825	0.8944	0.054
H(17A)	0.3215	0.6557	0.7983	0.041
H(1)	0.584(3)	0.756(5)	-0.093(6)	0.099(12)

7.9. Appendix 9 – X-ray data for 276

Table 1. Crystal data and structure refinement for 276.

Identification code	**276**
Empirical formula	C_{13} H_{16} O_3
Formula weight	220.27
Temperature	293 K
Wavelength	1.54180 A
Crystal system, space group	Monoclinic, P 1 21/n 1
Unit cell dimensions	a = 7.5397(8) A alpha = 90 deg.
	b = 15.2598(13) A beta = 99.298(6) deg.
	c = 10.2955(11) A gamma = 90 deg.
Volume	1169.0(2) A^3
Z, Calculated density	4, 1.251 Mg/m^3
Absorption coefficient	0.716 mm^{-1}
F(000)	472
Crystal size	0.30 x 0.10 x 0.08 mm
Theta range for data collection	6.619 to 65.288 deg.
Limiting indices	-8<=h<=7, -14<=k<=17, -12<=l<=11
Reflections collected / unique	4172 / 1859 [R(int) = 0.025]
Completeness to theta = 65.288	93.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.62
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	859 / 0 / 148
Goodness-of-fit on F^2	0.9186
Final R indices [I>2sigma(I)]	R1 = 0.0578, wR2 = 0.1541
R indices (all data)	R1 = 0.0839, wR2 = 0.1765
Largest diff. peak and hole	0.48 and -0.34 $e.A^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 276.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	6864(4)	755(2)	3996(3)	47

C(2)	5997(4)	657(2)	2710(3)	46
C(3)	5233(4)	1428(2)	1963(4)	51
O(4)	5029(3)	2172(1)	2624(2)	54
C(5)	5237(5)	2139(2)	4061(3)	49
C(6)	6949(5)	1657(2)	4605(3)	52
O(7)	8525(3)	2074(2)	4304(3)	64
C(8)	5108(5)	3096(2)	4537(3)	56
C(9)	5110(6)	3110(2)	6014(4)	69
C(10)	5335(7)	4011(3)	6617(5)	101
C(11)	3427(6)	3533(3)	3797(4)	86
O(12)	4803(4)	1442(2)	773(2)	66
C(13)	5927(5)	-163(2)	2096(3)	58
C(14)	6749(5)	-879(2)	2769(4)	62
C(15)	7635(5)	-777(2)	4039(4)	64
C(16)	7686(5)	27(2)	4667(4)	56

Table 3. Bond lengths [A] and angles [deg] for 276.

C(1)-C(2)	1.387(4)
C(1)-C(6)	1.509(4)
C(1)-C(16)	1.399(4)
C(2)-C(3)	1.471(4)
C(2)-C(13)	1.399(4)
C(3)-O(4)	1.344(4)
C(3)-O(12)	1.216(4)
O(4)-C(5)	1.464(4)
C(5)-C(6)	1.512(4)
C(5)-C(8)	1.549(4)
C(5)-H(51)	0.994
C(6)-O(7)	1.426(4)
C(6)-H(61)	0.963
O(7)-H(1)	0.89(3)
C(8)-C(9)	1.521(5)
C(8)-C(11)	1.522(5)
C(8)-H(81)	1.015
C(9)-C(10)	1.506(5)
C(9)-H(91)	1.020
C(9)-H(92)	0.958
C(10)-H(101)	0.978
C(10)-H(102)	1.011
C(10)-H(103)	0.973
C(11)-H(111)	0.993
C(11)-H(112)	1.005
C(11)-H(113)	0.939
C(13)-C(14)	1.385(5)
C(13)-H(131)	0.965
C(14)-C(15)	1.378(6)
C(14)-H(141)	0.922
C(15)-C(16)	1.384(5)
C(15)-H(151)	0.909
C(16)-H(161)	0.964
C(2)-C(1)-C(6)	118.5(3)
C(2)-C(1)-C(16)	119.2(3)
C(6)-C(1)-C(16)	122.2(3)
C(1)-C(2)-C(3)	119.7(3)
C(1)-C(2)-C(13)	120.4(3)
C(3)-C(2)-C(13)	119.8(3)
C(2)-C(3)-O(4)	118.6(3)
C(2)-C(3)-O(12)	123.9(3)
O(4)-C(3)-O(12)	117.5(3)
C(3)-O(4)-C(5)	118.7(2)
O(4)-C(5)-C(6)	109.7(3)
O(4)-C(5)-C(8)	106.6(2)

C(6)-C(5)-C(8)	115.8(3)
O(4)-C(5)-H(51)	107.6
C(6)-C(5)-H(51)	106.8
C(8)-C(5)-H(51)	110.1
C(5)-C(6)-C(1)	108.3(3)
C(5)-C(6)-O(7)	113.2(3)
C(1)-C(6)-O(7)	107.3(3)
C(5)-C(6)-H(61)	107.0
C(1)-C(6)-H(61)	110.2
O(7)-C(6)-H(61)	110.9
C(6)-O(7)-H(1)	114(2)
C(5)-C(8)-C(9)	109.8(3)
C(5)-C(8)-C(11)	110.1(3)
C(9)-C(8)-C(11)	111.1(3)
C(5)-C(8)-H(81)	109.9
C(9)-C(8)-H(81)	109.3
C(11)-C(8)-H(81)	106.5
C(8)-C(9)-C(10)	114.0(4)
C(8)-C(9)-H(91)	110.3
C(10)-C(9)-H(91)	107.1
C(8)-C(9)-H(92)	107.4
C(10)-C(9)-H(92)	105.7
H(91)-C(9)-H(92)	112.2
C(9)-C(10)-H(101)	110.7
C(9)-C(10)-H(102)	114.9
H(101)-C(10)-H(102)	111.0
C(9)-C(10)-H(103)	104.2
H(101)-C(10)-H(103)	105.8
H(102)-C(10)-H(103)	109.7
C(8)-C(11)-H(111)	112.2
C(8)-C(11)-H(112)	107.5
H(111)-C(11)-H(112)	113.7
C(8)-C(11)-H(113)	107.1
H(111)-C(11)-H(113)	107.0
H(112)-C(11)-H(113)	109.2
C(2)-C(13)-C(14)	119.9(3)
C(2)-C(13)-H(131)	117.9
C(14)-C(13)-H(131)	122.2
C(13)-C(14)-C(15)	119.6(3)
C(13)-C(14)-H(141)	120.6
C(15)-C(14)-H(141)	119.8
C(14)-C(15)-C(16)	121.1(3)
C(14)-C(15)-H(151)	117.6
C(16)-C(15)-H(151)	121.3
C(1)-C(16)-C(15)	119.7(3)
C(1)-C(16)-H(161)	121.5
C(15)-C(16)-H(161)	118.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 276.
The anisotropic displacement factor exponent takes the form: $2\pi^2$ [h^2 a^{*2} U^{11} + ... + 2 h k a* b* U^{12}

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	52(2)	42(2)	47(2)	3(1)	6(2)	-2(2)
C(2)	49(2)	43(2)	45(2)	1(1)	3(2)	0(1)
C(3)	53(2)	51(2)	45(2)	0(2)	1(2)	-2(2)
O(4)	68(2)	47(1)	43(1)	-1(1)	-3(1)	4(1)
C(5)	57(2)	45(2)	45(2)	0(1)	6(2)	2(2)
C(6)	62(2)	49(2)	42(2)	1(1)	2(2)	3(2)

O(7)	56(2)	54(1)	78(2)	-15(1)	-1(1)	-5(1)
C(8)	62(2)	46(2)	57(2)	-1(2)	6(2)	5(2)
C(9)	88(3)	61(2)	61(3)	-14(2)	18(2)	0(2)
C(10)	107(4)	98(4)	100(4)	-23(3)	22(3)	-2(3)
C(11)	93(3)	67(3)	90(3)	-14(2)	-7(2)	33(2)
O(12)	86(2)	66(2)	42(2)	2(1)	-2(1)	13(1)
C(13)	66(2)	54(2)	51(2)	-7(2)	6(2)	-6(2)
C(14)	71(3)	40(2)	77(3)	-3(2)	17(2)	-3(2)
C(15)	66(2)	43(2)	82(3)	12(2)	13(2)	8(2)
C(16)	61(2)	51(2)	54(2)	9(2)	1(2)	5(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 276.

	x	y	z	U(eq)
H(51)	4226	1786	4295	62
H(61)	6988	1612	5542	64
H(81)	6169	3449	4329	71
H(91)	6130	2731	6486	90
H(92)	3954	2910	6161	90
H(101)	5204	3991	7546	117
H(102)	6478	4324	6495	117
H(103)	4300	4336	6176	117
H(111)	3274	4139	4109	99
H(112)	2381	3137	3869	99
H(113)	3577	3573	2911	99
H(131)	5278	-209	1211	72
H(141)	6716	-1422	2372	72
H(151)	8160	-1258	4456	81
H(161)	8329	75	5554	66
H(1)	8870(40)	2540(20)	4810(30)	50

7.10. Appendix 10 – X-ray data for 289

Table 1. Crystal data and structure refinement for **289**.

Identification code	**289**
Empirical formula	C_{16} H_{17} N_1 O_4
Formula weight	287.32
Temperature	150 K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 1 21/n 1
Unit cell dimensions	a = 8.3707(4) A alpha = 90 deg.
	b = 7.7537(3) A beta = 94.832(2) deg.
	c = 22.1213(10) A gamma = 90 deg.
Volume	1430.66(11) A^3
Z, Calculated density	4, 1.334 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	608
Crystal size	0.35 x 0.20 x 0.15 mm
Theta range for data collection	1.848 to 27.476 deg.
Limiting indices	-10<=h<=10, -10<=k<=8, -28<=l<=26
Reflections collected / unique	9665 / 3251 [R(int) = 0.0679]
Completeness to theta = 27.476	99.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3251 / 0 / 193
Goodness-of-fit on F^2	0.9678
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1112

R indices (all data)	R1 = 0.1063, wR2 = 0.1332
Largest diff. peak and hole	0.65 and -0.75 e.A^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 289.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)	
O(1)	-1640(2)	4218(2)	2217(1)	29	
C(2)	-1633(2)	6022(3)	2087(1)	24	
C(3)	18(2)	6812(3)	2218(1)	23	
O(4)	1098(2)	6271(2)	1763(1)	24	
C(5)	582(2)	6214(3)	1166(1)	24	
O(6)	1575(2)	5990(2)	808(1)	33	
C(7)	-1158(2)	6406(3)	993(1)	23	
C(8)	-2250(2)	6367(3)	1439(1)	24	
C(9)	-3879(3)	6521(3)	1261(1)	30	
C(10)	-4406(3)	6687(3)	655(1)	35	
C(11)	-3320(3)	6712(3)	217(1)	35	
C(12)	-1695(3)	6571(3)	384(1)	30	
C(13)	856(2)	6289(3)	2830(1)	24	
C(14)	2496(3)	7166(3)	2929(1)	32	
C(15)	3528(2)	6493(3)	3466(1)	25	
N(16)	5040(2)	7236(2)	3623(1)	25	
C(17)	5601(2)	6416(3)	4105(1)	25	
O(18)	4607(2)	5177(2)	4287(1)	31	
C(19)	3293(2)	5254(3)	3866(1)	29	
C(20)	7129(3)	6697(3)	4483(1)	31	
C(21)	-217(3)	6730(3)	3337(1)	37	

Table 3. Bond lengths [A] and angles [deg] for 289.

O(1)-C(2)	1.428(3)
O(1)-H(1)	0.87(3)
C(2)-C(3)	1.517(3)
C(2)-C(8)	1.505(3)
C(2)-H(21)	1.000
C(3)-O(4)	1.470(2)
C(3)-C(13)	1.525(3)
C(3)-H(31)	0.983
O(4)-C(5)	1.355(2)
C(5)-O(6)	1.208(2)
C(5)-C(7)	1.482(3)
C(7)-C(8)	1.401(3)
C(7)-C(12)	1.390(3)
C(8)-C(9)	1.392(3)
C(9)-C(10)	1.382(3)
C(9)-H(91)	0.946
C(10)-C(11)	1.383(3)
C(10)-H(101)	0.939
C(11)-C(12)	1.383(3)
C(11)-H(111)	0.934
C(12)-H(121)	0.938
C(13)-C(14)	1.531(3)
C(13)-C(21)	1.533(3)
C(13)-H(131)	0.974
C(14)-C(15)	1.502(3)
C(14)-H(141)	0.999
C(14)-H(142)	0.983
C(15)-N(16)	1.408(3)
C(15)-C(19)	1.333(3)

N(16)-C(17)	1.295(3)
C(17)-O(18)	1.354(2)
C(17)-C(20)	1.483(3)
O(18)-C(19)	1.381(3)
C(19)-H(191)	0.934
C(20)-H(201)	0.973
C(20)-H(202)	0.955
C(20)-H(203)	0.968
C(21)-H(211)	0.963
C(21)-H(212)	0.980
C(21)-H(213)	0.982
C(2)-O(1)-H(1)	109.9(18)
O(1)-C(2)-C(3)	112.09(16)
O(1)-C(2)-C(8)	111.02(17)
C(3)-C(2)-C(8)	110.16(17)
O(1)-C(2)-H(21)	107.2
C(3)-C(2)-H(21)	108.5
C(8)-C(2)-H(21)	107.7
C(2)-C(3)-O(4)	110.88(16)
C(2)-C(3)-C(13)	113.95(17)
O(4)-C(3)-C(13)	105.59(16)
C(2)-C(3)-H(31)	109.0
O(4)-C(3)-H(31)	107.3
C(13)-C(3)-H(31)	109.9
C(3)-O(4)-C(5)	120.89(15)
O(4)-C(5)-O(6)	117.60(18)
O(4)-C(5)-C(7)	118.30(18)
O(6)-C(5)-C(7)	124.1(2)
C(5)-C(7)-C(8)	120.06(19)
C(5)-C(7)-C(12)	119.35(19)
C(8)-C(7)-C(12)	120.56(19)
C(2)-C(8)-C(7)	118.84(18)
C(2)-C(8)-C(9)	122.28(19)
C(7)-C(8)-C(9)	118.7(2)
C(8)-C(9)-C(10)	120.5(2)
C(8)-C(9)-H(91)	119.6
C(10)-C(9)-H(91)	119.9
C(9)-C(10)-C(11)	120.4(2)
C(9)-C(10)-H(101)	120.2
C(11)-C(10)-H(101)	119.4
C(10)-C(11)-C(12)	120.2(2)
C(10)-C(11)-H(111)	120.7
C(12)-C(11)-H(111)	119.1
C(7)-C(12)-C(11)	119.7(2)
C(7)-C(12)-H(121)	118.6
C(11)-C(12)-H(121)	121.7
C(3)-C(13)-C(14)	110.41(17)
C(3)-C(13)-C(21)	109.63(17)
C(14)-C(13)-C(21)	111.67(18)
C(3)-C(13)-H(131)	107.6
C(14)-C(13)-H(131)	108.2
C(21)-C(13)-H(131)	109.1
C(13)-C(14)-C(15)	114.10(19)
C(13)-C(14)-H(141)	108.5
C(15)-C(14)-H(141)	109.1
C(13)-C(14)-H(142)	107.7
C(15)-C(14)-H(142)	107.0
H(141)-C(14)-H(142)	110.4
C(14)-C(15)-N(16)	119.93(18)
C(14)-C(15)-C(19)	132.0(2)
N(16)-C(15)-C(19)	108.08(19)
C(15)-N(16)-C(17)	105.02(18)
N(16)-C(17)-O(18)	113.77(18)

N(16)-C(17)-C(20)	128.8(2)
O(18)-C(17)-C(20)	117.36(19)
C(17)-O(18)-C(19)	104.15(16)
O(18)-C(19)-C(15)	108.98(18)
O(18)-C(19)-H(191)	120.0
C(15)-C(19)-H(191)	131.0
C(17)-C(20)-H(201)	109.3
C(17)-C(20)-H(202)	109.5
H(201)-C(20)-H(202)	109.0
C(17)-C(20)-H(203)	109.3
H(201)-C(20)-H(203)	111.6
H(202)-C(20)-H(203)	108.1
C(13)-C(21)-H(211)	110.7
C(13)-C(21)-H(212)	110.3
H(211)-C(21)-H(212)	107.4
C(13)-C(21)-H(213)	110.6
H(211)-C(21)-H(213)	109.0
H(212)-C(21)-H(213)	108.8

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 289.
The anisotropic displacement factor exponent takes the form:$-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	30(1)	26(1)	0(1)	5(1)	-5(1)
C(2)	25(1)	24(1)	23(1)	-2(1)	5(1)	2(1)
C(3)	27(1)	22(1)	21(1)	-5(1)	1(1)	3(1)
O(4)	22(1)	30(1)	21(1)	-2(1)	2(1)	0(1)
C(5)	25(1)	24(1)	23(1)	1(1)	1(1)	-3(1)
O(6)	27(1)	46(1)	26(1)	0(1)	6(1)	-2(1)
C(7)	25(1)	21(1)	25(1)	0(1)	-1(1)	-2(1)
C(8)	24(1)	20(1)	26(1)	-2(1)	0(1)	-1(1)
C(9)	24(1)	32(1)	34(1)	-1(1)	2(1)	3(1)
C(10)	25(1)	36(1)	44(2)	1(1)	-9(1)	0(1)
C(11)	37(1)	36(1)	28(1)	4(1)	-11(1)	-3(1)
C(12)	31(1)	32(1)	26(1)	1(1)	1(1)	-3(1)
C(13)	27(1)	23(1)	22(1)	-1(1)	1(1)	1(1)
C(14)	32(1)	32(1)	29(1)	1(1)	-5(1)	-5(1)
C(15)	27(1)	25(1)	23(1)	-2(1)	0(1)	-1(1)
N(16)	25(1)	27(1)	23(1)	1(1)	-2(1)	-1(1)
C(17)	24(1)	27(1)	23(1)	-1(1)	4(1)	3(1)
O(18)	28(1)	35(1)	29(1)	8(1)	-2(1)	-1(1)
C(19)	25(1)	26(1)	37(1)	2(1)	-2(1)	-2(1)
C(20)	27(1)	41(1)	25(1)	-1(1)	-1(1)	4(1)
C(21)	35(1)	51(2)	26(1)	-8(1)	0(1)	12(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 289.

	x	y	z	U(eq)
H(21)	-2383	6587	2355	28
H(31)	-73	8074	2194	25
H(91)	-4630	6514	1558	34
H(101)	-5507	6779	536	43
H(111)	-3669	6825	-193	42
H(121)	-937	6563	94	35
H(131)	1023	5047	2822	28
H(141)	2326	8430	2981	38
H(142)	3073	6946	2568	38

H(191)	2432	4502	3897	30
H(201)	7721	5618	4520	37
H(202)	6906	7077	4878	37
H(203)	7739	7591	4301	37
H(211)	359	6584	3729	49
H(212)	-561	7937	3304	49
H(213)	-1172	5989	3311	49
H(1)	-1160(30)	3660(40)	1944(13)	50

7.11. Appendix 11 – X-ray data for 298

Table 1. Crystal data and structure refinement for 298.

Identification code	**298**
Empirical formula	C_{18} H_{20} O_4
Formula weight	1201.36
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system, space group	?, ?
Unit cell dimensions	a = 6.6229(12) A alpha = 90 deg. b = 10.6758(14) A beta = 98.058(6) deg. c = 22.750(3) A gamma = 90 deg.
Volume	1592.7(4) A^3
Z, Calculated density	1, 1.253 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	640
Crystal size	? x ? x ? mm
Theta range for data collection	3.11 to 27.48 deg.
Limiting indices	-8<=h<=8, -13<=k<=13, -29<=l<=29
Reflections collected / unique	20004 / 3649 [R(int) = 0.1898]
Completeness to theta = 27.48	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3649 / 0 / 279
Goodness-of-fit on F^2	0.931
Final R indices [I>2sigma(I)]	R1 = 0.0679, wR2 = 0.1409
R indices (all data)	R1 = 0.1864, wR2 = 0.1920
Largest diff. peak and hole	0.198 and -0.209 $e.A^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 298.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3165(4)	7540(2)	1893(1)	40(1)
O(2)	1331(4)	5138(2)	2233(1)	48(1)
O(3)	4994(4)	4162(2)	1245(1)	43(1)
O(4)	-1587(5)	5971(3)	2432(1)	74(1)
C(1)	2591(5)	6993(3)	910(1)	33(1)
C(2)	2386(5)	8305(3)	955(1)	37(1)
C(3)	2536(6)	9069(4)	468(2)	46(1)
C(4)	2973(6)	8506(4)	-57(2)	51(1)
C(5)	3203(6)	7227(4)	-91(2)	50(1)
C(6)	2983(5)	6433(3)	390(1)	38(1)
C(7)	2016(6)	8564(3)	1585(1)	40(1)
C(8)	2212(5)	6537(3)	1512(1)	34(1)
C(9)	2872(6)	5325(3)	1840(1)	36(1)
C(10)	-255(6)	5977(3)	2120(2)	51(1)
C(11)	-88(5)	6747(3)	1573(2)	41(1)
C(12)	3121(5)	4108(3)	1505(1)	38(1)
C(13)	4891(6)	3344(3)	1756(2)	39(1)
C(103)	-1860(7)	8937(4)	1304(2)	58(1)

C(104)	-172(6)	8197(3)	1676(2)	46(1)
C(105)	-1672(6)	6270(4)	1061(2)	51(1)
C106)	1300(7)	3553(4)	1126(2)	58(1)
C(107)	5085(8)	1961(4)	1656(2)	50(1)

Table 3. Bond lengths [A] and angles [deg] for 298.

C(1)-C(7)	1.455(4)
O(1)-C(8)	1.463(4)
O(2)-C(10)	1.377(4)
O(2)-C(9)	1.463(4)
O(3)-C(12)	1.449(4)
O(3)-C(13)	1.463(4)
O(4)-C(10)	1.207(4)
C(1)-C(6)	1.382(4)
C(1)-C(2)	1.412(5)
C(1)-C(8)	1.508(4)
C(2)-C(3)	1.391(5)
C(2)-C(7)	1.514(4)
C(3)-C(4)	1.401(5)
C(3)-H(1)	1.00(4)
C(4)-C(5)	1.378(5)
C(4)-H(2)	1.01(4)
C(5)-C(6)	1.408(5)
C(5)-H(3)	0.95(4)
C(6)-H(4)	1.05(3)
C(7)-C(104)	1.542(5)
C(7)-H(5)	1.01(3)
C(8)-C(9)	1.526(4)
C(8)-C(11)	1.565(5)
C(9)-C(12)	1.527(4)
C(9)-H(13)	1.06(4)
C(10)-C(11)	1.510(5)
C(11)-C(105)	1.541(6)
C(11)-C(104)	1.568(5)
C(12)-C(13)	1.476(5)
C(12)-C(106)	1.502(5)
C(13)-C(107)	1.502(5)
C(13)-H(16)	1.02(3)
C(103)-C(104)	1.524(6)
C(103)-H(9)	0.95(4)
C(103)-H(7)	1.02(4)
C(103)-H(8)	1.08(5)
C(104)-H(6)	0.98(3)
C(105)-H(10)	0.95(4)
C(105)-H(11)	1.09(4)
C(105)-H(12)	1.03(4)
C(106)-H(15)	1.04(5)
C(106)-H(14)	1.00(5)
C(106)-H(20)	1.00(4)
C(107)-H(18)	1.00(4)
C(107)-H(17)	1.11(4)
C(107)-H(19)	0.99(4)
C(7)-o(1)-C(8)	96.5(2)
C(10)-o(2)-C(9)	112.1(2)
C(12)-o(3)-C(13)	60.9(2)
C(6)-C(1)-C(2)	121.5(3)
C(6)-C(1)-C(8)	135.5(3)
C(2)-C(1)-C(8)	103.0(3)
C(3)-C(2)-C(1)	120.4(3)
C(3)-C(2)-C(7)	133.3(3)
C(1)-C(2)-C(7)	106.3(3)
C(2)-C(3)-C(4)	118.2(3)

C(2)-C(3)-H(1)	120(2)
C(4)-C(3)-H(1)	122(2)
C(5)-C(4)-C(3)	120.8(3)
C(5)-C(4)-H(2)	120(2)
C(3)-C(4)-H(2)	119(2)
C(4)-C(5)-C(6)	121.8(4)
C(4)-C(5)-H(3)	120(2)
C(6)-C(5)-H(3)	119(2)
C(1)-C(6)-C(5)	117.2(3)
C(1)-C(6)-H(4)	122.1(17)
C(5)-C(6)-H(4)	120.6(17)
O(1)-C(7)-C(2)	100.0(3)
O(1)-C(7)-C(104)	100.5(3)
C(2)-C(7)-C(104)	111.1(3)
O(1)-C(7)-H(5)	112.5(19)
C(2)-C(7)-H(5)	116.0(17)
C(104)-C(7)-H(5)	114.6(19)
O(1)-C(8)-C(1)	100.8(2)
O(1)-C(8)-C(9)	105.1(2)
C(1)-C(8)-C(9)	130.2(3)
O(1)-C(8)-C(11)	100.8(2)
C(1)-C(8)-C(11)	108.8(3)
C(9)-C(8)-C(11)	107.1(3)
O(2)-C(9)-C(12)	108.8(3)
O(2)-C(9)-C(8)	103.8(3)
C(12)-C(9)-C(8)	121.5(3)
O(2)-C(9)-H(13)	105.0(18)
C(12)-C(9)-H(13)	109.1(19)
C(8)-C(9)-H(13)	107.6(19)
O(4)-C(10)-o(2)	119.2(3)
O(4)-C(10)-C(11)	129.2(4)
O(2)-C(10)-C(11)	111.5(3)
C(10)-C(11)-C(105)	108.8(3)
C(10)-C(11)-C(104)	114.0(3)
C(105)-C(11)-C(104)	113.9(3)
C(10)-C(11)-C(8)	100.3(3)
C(105)-C(11)-C(8)	117.0(3)
C(104)-C(11)-C(8)	102.1(3)
O(3)-C(12)-C(13)	60.1(2)
O(3)-C(12)-C(106)	116.5(3)
C(13)-C(12)-C(106)	122.3(3)
O(3)-C(12)-C(9)	109.2(3)
C(13)-C(12)-C(9)	114.4(3)
C(106)-C(12)-C(9)	119.2(3)
O(3)-C(13)-C(12)	59.06(19)
O(3)-C(13)-C(107)	116.8(3)
C(12)-C(13)-C(107)	124.3(4)
O(3)-C(13)-H(16)	110.5(18)
C(12)-C(13)-H(16)	114.9(18)
C(107)-C(13)-H(16)	116.9(18)
C(104)-C(103)-H(9)	112(3)
C(104)-C(103)-H(7)	105(3)
H(9)-C(103)-H(7)	107(3)
C(104)-C(103)-H(8)	111(3)
H(9)-C(103)-H(8)	112(4)
H(7)-C(103)-H(8)	110(3)
C(103)-C(104)-C(7)	115.1(3)
C(103)-C(104)-C(11)	117.9(4)
C(7)-C(104)-C(11)	100.2(3)
C(103)-C(104)-H(6)	111.9(19)
C(7)-(104)-H(6)	103(2)
C(11)-C(104)-H(6)	106.8(18)
C(11)-C(105)-H(10)	109(2)

C(11)-C(105)-H(11)	110(2)
H(10)-C(105)-H(11)	110(3)
C(11)-C(105)-H(12)	109(2)
H(10)-C(105)-H(12)	109(3)
H(11)-C(105)-H(12)	111(3)
C(12)-C(106)-H(15)	114(3)
C(12)-C(106)-H(14)	113(3)
H(15)-C(106)-H(14)	103(4)
C(12)-C(106)-H(20)	106(2)
H(15)-C(106)-H(20)	109(3)
H(14)-C(106)-H(20)	112(4)
C(13)-C(107)-H(18)	109.3(19)
C(13)-C(107)-H(17)	110.4(19)
H(18)-C(107)-H(17)	104(3)
C(13)-C(107)-H(19)	109(2)
H(18)-C(107)-H(19)	114(3)
H(17)-C(107)-H(19)	111(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 298.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	48(2)	36(1)	34(1)	-4(1)	2(1)	2(1)
O(2)	58(2)	44(2)	46(1)	15(1)	22(1)	13(1)
O(3)	49(2)	40(1)	42(1)	1(1)	16(1)	2(1)
O(4)	80(2)	71(2)	83(2)	26(2)	57(2)	22(2)
C(1)	31(2)	34(2)	32(2)	2(1)	2(2)	-1(2)
C(2)	36(2)	40(2)	36(2)	-1(2)	7(2)	0(2)
C(3)	52(3)	40(2)	47(2)	7(2)	8(2)	-1(2)
C(4)	64(3)	48(3)	44(2)	7(2)	16(2)	1(2)
C(5)	52(3)	64(3)	35(2)	-1(2)	10(2)	3(2)
C(6)	41(2)	42(2)	30(2)	0(2)	6(2)	1(2)
C(7)	50(3)	31(2)	40(2)	0(2)	5(2)	5(2)
C(8)	37(2)	35(2)	28(2)	-5(1)	5(2)	-1(2)
C(9)	43(2)	37(2)	30(2)	1(2)	11(2)	2(2)
C(10)	57(3)	43(2)	57(2)	12(2)	23(2)	12(2)
C(11)	35(2)	44(2)	47(2)	5(2)	14(2)	8(2)
C(12)	37(2)	38(2)	40(2)	3(2)	9(2)	0(2)
C(13)	46(2)	34(2)	37(2)	4(2)	9(2)	5(2)
C(103)	57(3)	50(3)	69(3)	9(2)	16(2)	16(2)
C(104)	54(3)	44(2)	44(2)	3(2)	18(2)	9(2)
C(105)	29(2)	52(3)	72(3)	7(2)	3(2)	1(2)
C(106)	51(3)	49(3)	69(3)	-16(2)	-5(2)	-3(2)
C(107)	62(3)	41(2)	47(2)	5(2)	9(2)	9(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 298.

	x	y	z	U(eq)
H((6)	-180(50)	8320(30)	2102(15)	38(9)
H((4)	3160(50)	5460(30)	354(14)	46(10)
H((18)	4340(50)	1740(30)	1257(16)	41(9)
H((10)	-2990(70)	6510(40)	1136(16)	65(12)
H((1)	2340(60)	9990(40)	499(15)	60(12)
H((16)	5730(50)	3710(30)	2125(15)	39(9)
H((17)	4270(60)	1420(40)	1969(17)	67(12)
H((2)	3160(60)	9050(40)	-405(18)	75(13)
H((19)	6550(70)	1740(30)	1710(16)	60(12)
H((9)	-1800(70)	8850(40)	890(20)	77(15)

H((11)	-1370(60)	6680(40)	644(19)	72(12)
H((7)	-1560(70)	9860(40)	1407(18)	77(14)
H((13)	4250(60)	5510(30)	2128(16)	58(11)
H((3)	3520(60)	6860(40)	-450(18)	67(12)
H((5)	2480(50)	9410(30)	1752(14)	43(9)
H((12)	-1610(60)	5310(40)	1043(16)	67(12)
H((15)	1590(70)	2700(40)	940(20)	89(15)
H((14)	800(80)	4090(50)	770(20)	100(17)
H((8)	-3340(80)	8690(40)	1420(20)	104(17)
H((20)	240(70)	3440(40)	1397(18)	73(14)

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