Studies Towards the Synthesis of Marine Polysulfide Natural Products

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Abstract

Biologically active compounds isolated from marine sources have had increasing interest in recent years with significant research going into the discovery and isolation of novel marine polysulfide natural products.

Varacin, probably the most widely studied marine polysulfide to date was the subject of much debated structure elucidation attempts, and more recently several successful synthetic approaches have been published. The work published aims to increase our understanding of marine polysulfide compounds existence in nature and determine the origins of their biological activity.

(+)-Aplidium trisulfide which was isolated from *Aplidium Sp.* D in 1989 by Munro *et al* has been shown to exhibit *in vitro* antimicrobial, antileukemic and cytotoxic properties. These intriguing biological effects have led our work towards developing a novel synthetic route toward aplidium trisulfide by both chiral and racemic routes. Aplidium trisulfide is of special significance as it is very rare to isolate enantiomeric compounds from marine sources.

Two other closely related marine alkaloids fasmerianamine A and B are also of synthetic interest to us due to their close resemblance to the structure of aplidium trisulfide. The fasmerianamines were isolated by Copp *et al* from the marine ascidian *Hypsistozoa fasmeriana* in 2001.

Keywords: polysulfide, ascidians, aplidium, trisulfide, varacin, fasmerianamine

Contents

i. Acknowledgments

I would firstly like to thank Dr George W. Weaver for giving me the opportunity to carry out my PhD research under his supervision. I would also like to thank him not only for his endless advice but also for his enthusiasm and encouragement throughout my time at Loughborough University. I would like to thank the EPSRC for sponsoring my research as without funding this work wouldn't have been possible. I would finally like to thank the support staff and many friends that I've made within the chemistry department for their help and advice and for providing an enjoyable place to work.

ii. List of abbreviations

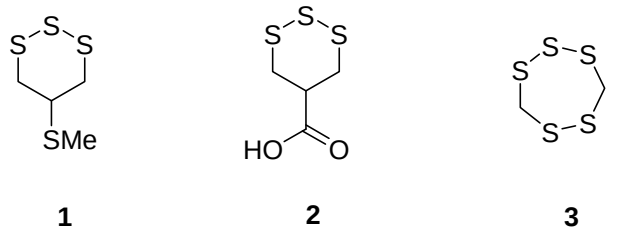
Aq.	-	aqueous
Bn	-	benzyl
Boc	-	*t*-butoxycarbonyl
bp	-	boiling point
bs	-	broad singlet
CD	-	cyclodextrin
d	-	doublet
DCM	-	dichloromethane
DDQ	-	2,3-dichloro-5,6-dicyano-benzoquinone
DEAD	-	diethyl azodicarboxylate
DMAD	-	dimethylacetylene dicarboxylate
DMAP	-	4-dimethylaminopyridine
DMF	-	dimethylformamide
DMSO	-	dimethylsulfoxide
dd	-	doublet of doublets
EI	-	electron ionisation
ES	-	electrospray
FAB	-	fast atom bombardment
GC	-	gas chromatography
HRMS	-	high resolution mass spectrum
IR	-	infrared
m	-	multiplet
mCPBA	-	*meta*-chloroperbenzoic acid
mp	-	melting point
NBS	-	N-bromosucinimide
NTS	-	N-thiocyanatosuccinimide
PDC	-	pyridinium dichromate
RBF	-	round bottom flask
s	-	singlet
t	-	triplet
TBAF	-	tetra-n-butylammonium fluoride
TBDMSCl	-	*t*-butyldimethylsilylchloride

TBDPSCl	-	*t*-butyldiphenylsilylchloride
TCDI	-	thiocarbonyldiimidazole
TEA	-	triethylamine
TEOC	-	2-(trimethylsilyl)ethoxycarbonyl
TFA	-	trifluoroacetic acid
TFAA	-	trifluoroacetic anhydride
THF	-	tetrahydrofuran
q	-	quartet
quat.	-	quaternary
vs	-	very strong

1 - Introduction

Biologically active compounds isolated from marine tunicates have been an area of increasing interest since the late 1980's. It is noteworthy that some 90% of reported tunicate secondary metabolites are nitrogenous with many compounds displaying remarkable bioactivity.[1] For this reason the newly isolated polysulfide secondary metabolites are of great biological and synthetic interest.

Although a wide range of marine polysulfides have now been isolated, characterised and biologically tested, they were not in fact the first polysulfur containing compounds to be studied. 5-Methylthio-1,2,3-trithiane[2, 3] **(1)**, 5-carboxyl-1,2,3-trithiane[4] **(2)**, and lenthionine[5, 6, 7] **(3)** are three more basic structure polysulfides which have been isolated from less exotic sources.

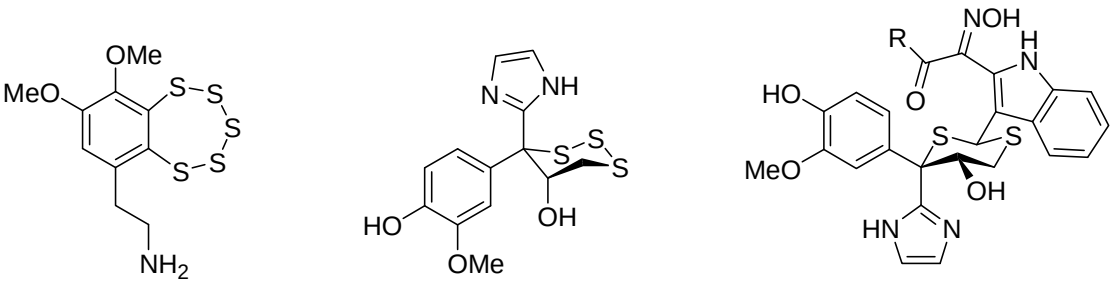


1 **2** **3**

Figure 1: Three naturally occurring polysulfides derivatives

5-Methylthio-1,2,3-trithiane **(1)** has been isolated by gas-phase extraction from the green alga *Chara globulares* and was identified by GC-MS and ^{1}H NMR spectroscopy.[2] Interestingly, 5-carboxyl-1,2,3-trithiane **(2)** has been isolated from the lower part of the asparagus shoot by extracting with ethanol.[4] The 1,2,3,5,6-pentathiepane lenthionine **(3)** has been isolated from Shiitake mushrooms and was the first cyclic polysulfide to be isolated from an organism. However, in the first reported isolation it was suggested that lentionine was not a compound present in Shiitake mushroom but was a product of enzyme action on an unknown precursor whilst the mushrooms were immersed in water. Further work on this by Chen *et al.* led to the isolation of eighteen different sulphur containing compounds and it is now believed these compounds originate from lentinic acid.[8]

In 1989 one of the first marine polysulfide compounds (+)-Aplidium trisulfide **(5)** was isolated from a marine tunicate. (+)-Aplidium trisulfide was isolated from methanol/water extracts of *Aplidium sp. D* found in New Zealand by Munro *et al*. The compound was purified by HPLC and isolated as a yellow gum. Later screening showed that Aplidium trisulfide exhibites *in vitro* antimicrobial, antileukemic and cytotoxic properties.[9] Enantiomeric compounds from marine sources are very rare, the (-)-enantiomer was more recently isolated by Copp *et al.* from *Hypsistozoa fasmeriana* along with two other novel dithiane alkaloids, fasmerianamine A **(6)** and fasmerianamine B **(7)**.[10]



4 **5** **6.** R = OMe **7.** R = OH

Figure 2: Varacin, aplidium trisulfide and two novel 1,3-dithiane alkaloids

Varacin **(4)** is another well known marine polysulfide natural product which contains a pentathiepin ring and notably has a similar carbon framework to dopamine. Varacin was isolated in 1991 by Ireland *et al.* from the ascidian *Lissoclinum vareau* collected from the Fiji islands. Varacin was screened for biological activity and has shown potent antifungal activity as well as cytotoxicity towards human colon cancer 100 times that of 5-fluorouracil. Varacin was also screened against a range of different cell lines, and preliminary results have shown that varacin damages DNA.[11]

The examples already mentioned are just a few of the many marine polysulfide compounds which have now been discovered. Many of the polysulfides isolated exhibit some type of biological activity and this is a major reason for our interest in this area. The fact that little synthetic work has been carried out on the synthesis of marine polysulfide compounds also opens up an area of unexplored research.

Most structural, synthetic and biological work that has been carried out to date has focused around pentathiepins, and varacin in particular, with several reported syntheses.[38,50,53] For this reason we planned to investigate a route towards the synthesis of Aplidium trisulfide **(5)**, and secondly the two recently discovered 1,3-dithiane compounds **(6)** and **(7)**, all of which, to our knowledge have received no synthetic interest to date. Another important reason for our search for a total synthetic route is that only minute quantities can be isolated from nature by harvesting large numbers of tunicates and thus damaging the marine environment.

1.1 - Ascidians

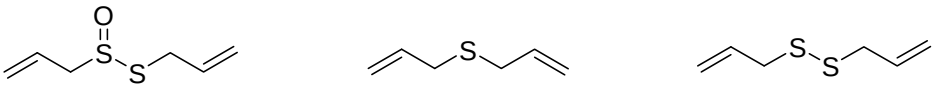
Although 70% of our globe is covered by oceans they remain largely untapped in the search for new medicinal and pharmacological agents. The oceans are full of living organisms and contain more flora and fauna than the land. It is only therefore logical that we now turn to marine organisms in the search for more and varied biologically active natural products. Throughout the course of evolution marine organisms have adapted to harsh environments, which have led to them developing unique metabolites to aid their survival. It is such secondary metabolites from ascidians that have now come to light in the last 20 years which are of great interest and in particular the highly biologically active polysulfide compounds.[12]

Ascidians, also known more commonly as tunicates or sea squirts, are marine filter-feeding animals which often go unnoticed. Tunicates are so called due their "tunic" like sac which embodies them, and sea squirts because of the apparent squirt of water they expel when disturbed. The sedentary adult forms can either be solitary or colonial. Solitary forms live alone whereas colonial ascidians are able to bud off and form colonies which are often mistaken for other encrusting marine life such as sponges.[15]

Although many ascidians go unnoticed as they just look like slimy sacs, ascidians are actually more closely related to humans than any other invertebrate group.[13] Larval ascidians have been observed to have chordate structures including; nerve cords (primarily in early development), a 'notochord' or firm rod of cells beneath the nerve cord (similar to a human backbone), a buccal siphon (where water enters) and an atrial siphon (where water is expelled). The pharynx which occupies a large part of the body has numerous gill slits which act as a sieve for food. Mucus produced allows the filtered food to be moved into the upper digestive tract, this movement is aided by cilia. Ascidians also have a tubular heart which has been found to contract in dual directions.[14]

1.2 – Biological Activity

The use of organosulfur compounds to control infectious disease goes back thousands of years, where homeopathic medicine extracts and oils from vegetables such as garlic, onions, shallots, chives and scallions, were used successfully to treat bacterial infections.[16] For example, Allicin **(8)** has now been identified as the primary agent responsible for garlic's antibacterial properties.[17] Allicin has been shown to have potent *in vitro* antibiotic activity against many bacteria including *E. coli* and *S. aureus*.[18] The likely mode of action of Allicin involves reaction of the thiosulfinate with cellular thiols to produce a mixed disulfide.[19]

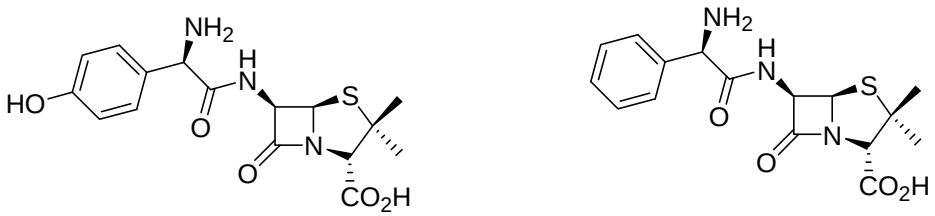


8 **9** **10**

Figure 3: Sulfur containing compounds from garlic

Two other compounds found in garlic, diallyl sulfide **(9)** and diallyl disulfide **(10)** have been found to exhibit potent activity against methicillin resistant *S. aureus* (MRSA).[20] The mechanism of action is not yet fully understood but undoubtedly relies on the sulfur functionality.[21]

It is important to note though, that the presence of sulfur in a biologically active molecule may not actually give the compound its biological effects. For example, in beta-lactam antibiotics such as amoxicillin **(11)** and ampicillin **(12)**, the sulfur atom is not believed to be involved in the mechanism of action.



11 **12**

Figure 4: beta-lactam antibiotics

Many marine polysulfide compounds are extremely biologically active and display antibacterial, antifungal, or anticancer properties. However, in most cases, the reason for their biosynthesis or use within an organism, and the mechanism of their biological action remains widely unknown.

Organosulfur compounds which contain thiols are often relatively reactive. Thiols can act as strong nucleophiles or reducing agents depending on the electrophile present and the reaction environment. Di- and tri-sulfides can act as electrophiles when in the presence of thiophilic nucleophiles, resulting in sulfur-sulfur bond cleavage.

It is important to note, that although free thiols can be responsible for biological activity, they will also have the potential to dimerise which will reduce their biological activity. Metal-thiol coordination can prevent these dimers forming without destroying the overall activity of the thiol.

A mechanistically interesting group of biologically active trisulfides which utilise the nucleophilic activity are the enediyne antibiotics. Calichemicin **(13)** and the closely related structure of Namenamicin **(14)** have both been shown to exhibit potent anti-tumour activity.[22, 23]

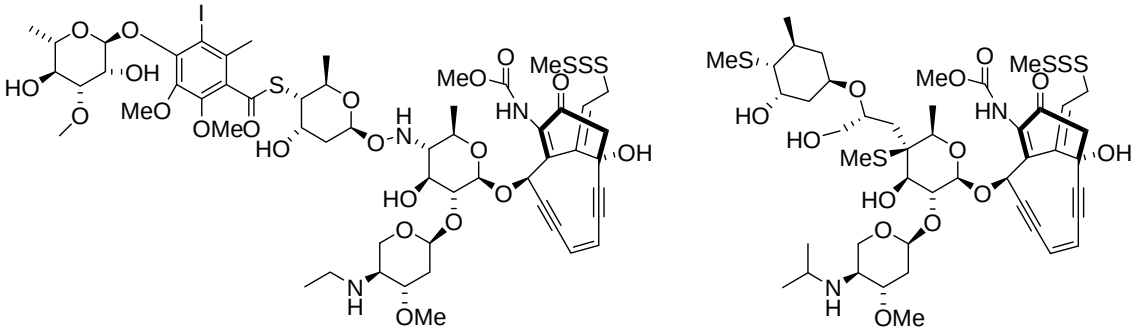
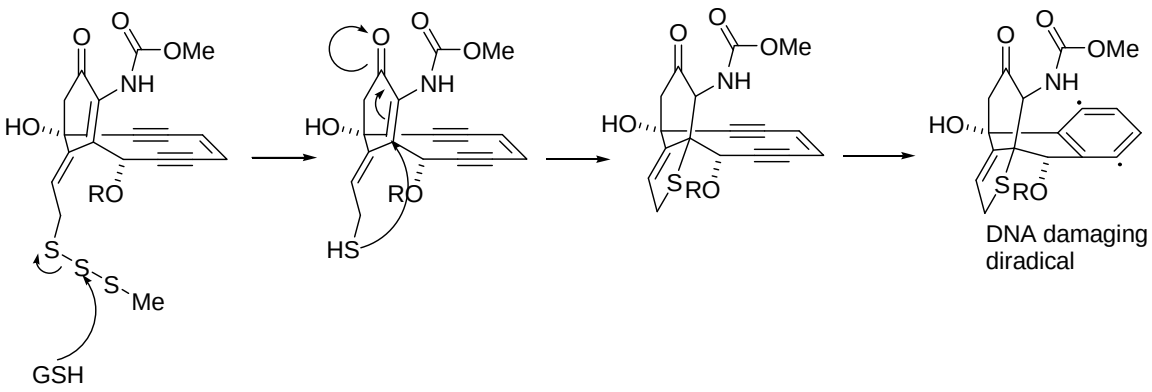


Figure 5: Enediyne antibiotics

Both compounds have been shown to undergo a cascade of intramolecular reactions resulting in the formation of a highly reactive diradical species (scheme 1). In the first step of the process, reaction of the trisulfide group with glutathione generates a free

thiolate anion which in turn undergoes a Michael-type addition across the α,β-unsaturated ketone. This subtle change in hybridization of the carbons allows the enediyne to undergo a Bergman cycloaromatization[93], producing the phenylene diradical. These diradicals are believed to cleave DNA by sequentially stripping off hydrogen atoms along the minor grove of the double helix. The sugar radical then reacts with O_2 to form unstable peroxides.[24]



Scheme 1: Enediyne cascade reaction

Although there are many biologically active compounds with a single sulfur or linear chain of sulfur atoms, it is much rarer to find biologically active compounds containing a polysulfide ring. One example, leinamycin **(15)** represents a new class of DNA-damaging agents which has an interesting dual mechanism of action.

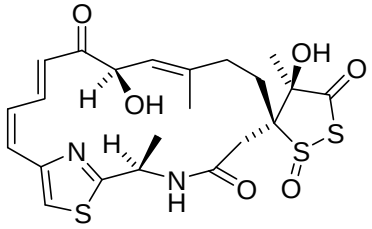


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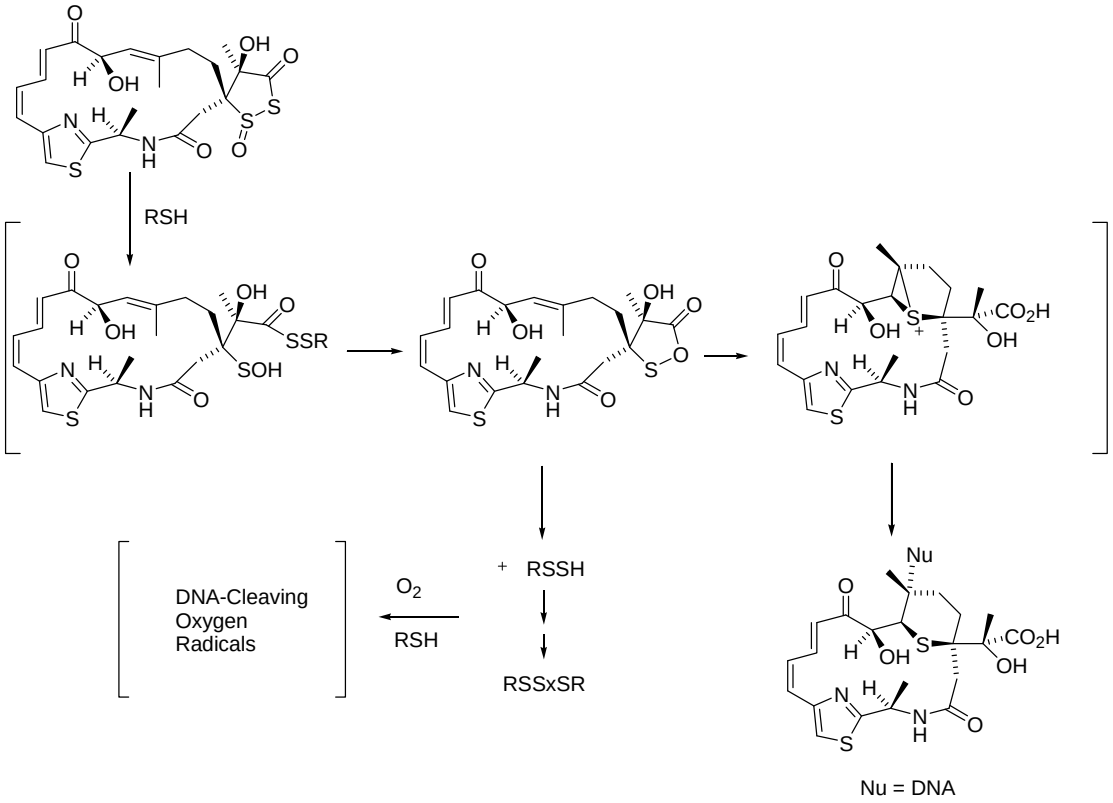
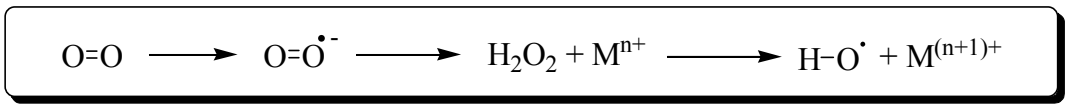
Figure 6: Structure of leinamycin

In 1997 Gates investigated into the biological activity of leinamycin which has been shown to exhibit potent antitumour activity. Gates found that leinamycin reacted with intercellular thiols yielding an electrophilic oxathiolanone (scheme 2). This is then trapped via an intramolecular reaction to yield an episulfonium alkylating species which can then alkylate the N^7 residue of guanine leading to its cytotoxic behaviour.[25]



Scheme 2: Routes of action of Leinamycin's Bioactivity [25]

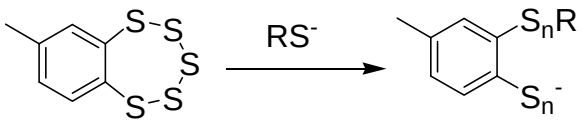
Gates also found that polysulfides formed during the formation of the episulfonium alkylating species could also produce cell damaging hydroxyl radicals. This led Gates to believe that leinamycin's bioactivity could also be due to a thiol-dependant conversion of molecular oxygen to a hydroxyl radical via a trace metal dependant Fenton reaction (scheme 3). Leinamycins biological activity is now believed to be due to both alkylating and cleaving mechanisms.



Scheme 3: Hydroxyl radical produced via a Fenton reaction

Gates' finding that leinamycin is a thiol-dependant DNA-cleaving agent may also be relevant to other polysulfide containing natural products such as varacin, lissoclinotoxin and even disulfides such as polycarpine.

Gates continued his research into polysulfide activity by examining an analogue of varacin, 7-methylbenzopentathiepin **(16)**. Similar cytotoxic results were recorded for the analogue as previously found for varacin, reinforcing the idea that 7-methylbenzopentathiepin is also thiol-mediated in its DNA-cleaving activity.[26]



16 **17**

Scheme 4: Thiol reaction with 7-methylbenzopentathiepin

Additionally Gates found that the reactivity of polysulfide anions **(17)** generated in the reaction with thiols are key intermediates in the generation of the oxygen radicals responsible for cleaving DNA. The oxygen radical most likely converts to hydrogen peroxide, then forming the highly reactive hydroxyl radical which then leads to either sugar-phosphate or sugar-base cleavage.

Recently Greer has produced a theoretical study which investigated a novel S_3-cleavage in the decomposition of pentathiepins. He postulated an inter-conversion between the pentathiepin and an open chain polysulfur anion intermediate. Further theoretical calculations were performed by Greer, and these provided evidence for an open chain polysulfur anion intermediate (**18)**, from which S_3 is able to dissociate from due to the weak bonds between sulfur four and sulfur five.[27]

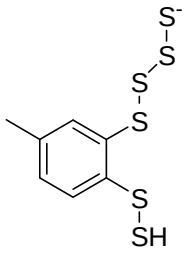


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Figure 7: Open chained polysulfide before S_3 loss

Chan attempted to answer the question of polysulfide bioactivity through the effectiveness of converting circular super-coiled DNA into the circular relaxed form. His investigation showed that polysulfide compounds such as varacin do indeed

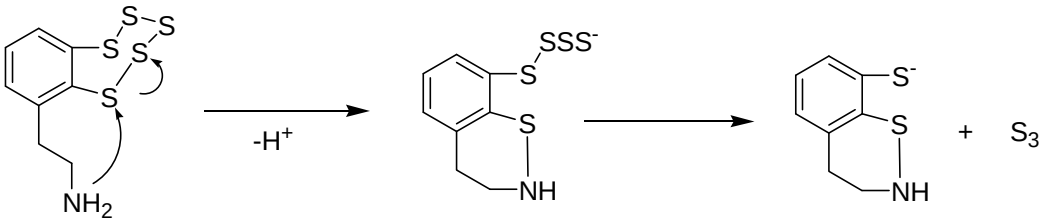
cleave DNA, and further investigations into the activation of the compounds showed that thiols were necessary to initiate DNA cleaving activity. Chan also investigated the effects of pH on the activity and found that at acidic pH the cleaving activity is significantly higher than at lower pH levels.[29]

In an attempt to determine the reactive species involved in the DNA cleavage, Chan also observed the effects of a range of nucleophiles and free radical scavengers and found that the DNA cleaving reaction was reduced by the addition of superoxide radical scavenger dithiothreitol (DTT). Chan also found that the catalase enzyme (which reduces H_2O_2 concentration) exhibited significant inhibitory effects on the DNA cleaving reaction, providing a vast amount of evidence that the DNA cleaving reaction is indeed radical mediated.[30]

In 2002 Greer examined the question 'why are some pentathiepins more biologically active than others?' It was already known that the polysulfide ring is very important for the compounds biological activity, but several active compounds also contained a remotely bonded amine substituent.[28]

It had been suggested that the open chain polysulfide was possibly the product of an intramolecular ring opening reaction involving the adjacent amine group present on varacin. Sato has previously reported that the presence of the amine group does in fact enhance the biological activity of the pentathiepin.[31]

Greer devised a computational study to examine the amines role in the biological activity of pentathiepin compounds. The study showed that primary or secondary amines were able to allow for an intramolecular addition to the pentathiepin ring near to the S1 atom. This leads to nucleophilic attack, followed by sulfur ring opening and finally results in the loss of S_3 (scheme 5).[28]



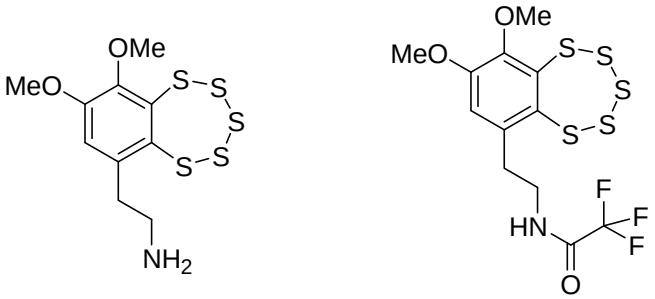
Scheme 5: The role of the amine in the loss of S_3

The loss of the S_3 had already been reported as being a key intermediate in the generation of hydroxyl radicals involved in the cleaving of DNA. Greer was therefore able to conclude that amines play an important role in the generation of these intermediates and this may have a dramatic affect on the activity of a particular polysulfide.

1.3 - Discovery: Isolation and Characterisation

1.3.1 - Varacin

In 1990 Davidson *et al.* isolated the benzopentathiepin varacin **(19)** from a sample of *Lissoclinum vareau*, a lavender coloured encrusting species found in the Fiji islands. Varacin was isolated by homogenising 55g of freeze dried tissue and using solvent partitioning to isolated 360 mg of $CHCl_3$ soluble material. Silica gel column chromatography followed by reverse-phase HPLC yielded 40 mg (0.07%) of varacin as a light brown glass.[11]



19 **20**

Figure 8: Varacin and its trifluoroacetamide derivative

The structure of varacin was first predicted by Davidson to have the formula $C_{10}H_{13}NO_2S_5$ from the FAB mass spectrum of the trifluoroacetamide protected amine **(20)** which displayed a prominent ion at m/z 435. High resolution electron impact ionisation mass spectrometry was used to confirm the accurate mass of 434.9378 for $C_{12}H_{12}F_3NO_3S_5$. Additionally the ^{13}C NMR spectrum showed the expected ten carbon signals, including six aromatic. ^1H NMR spectroscopy also showed two strongly coupled methylene signals at δ 3.15 and 3.25 ppm and a singlet at δ 7.07 ppm for a suspected lone proton on the penta-substituted benzene ring. Confirmation of this structure was obtained by reducing varacin with tert-butoxy-aluminium hydride, and then quenching with methyl iodide to yield (**21).**

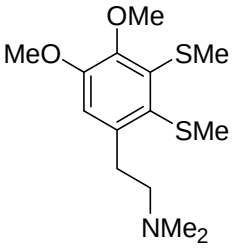


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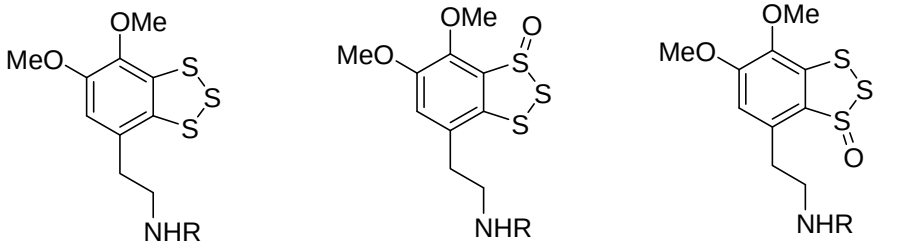
Figure 9: Reduced form of varacin

The mass spectrum of the second compound (**21)** confirmed the loss of three sulphur atoms and the addition of four methyl groups, indicating that the structure predicted for **(19)** was indeed correct.

Three structurally similar marine polysulfides varacin A **(22)**, B **(23)** and C **(24)** were later isolated by Makarieva *et al*. in 1995 from the ascidian *Polycitor Sp*. from tissue samples collected in the Sea of Japan. Ethanol extraction was carried out on fresh tissue samples and the ethanol extract was shown to have potent antimicrobial activity.[32]



22. R = H
22a. R = $COCH_3$

23. R = H
23a. R = $COCH_3$

24. R = H
24a. R = $COCH_3$

Figure 10: Varacin's A-C

The crude extracts were then purified by several stages of silica gel column chromatography yielding a mixture of the active components. At this stage identification of varacin **(19)** was carried out using NMR and mass spectrometry methods. The acetates of varacin A-C **(22a/23a/24a)** were then isolated by treatment of the crude mixture with Ac_2O/pyridine followed by HPLC. The previously undescribed acetate of varacin **(25)** was also isolated and this showed loss of S_2 in the FABMS giving peaks at both m/z 381 and 317.

The ^{1}H NMR spectra of **(25)** and **(22a)** were very similar apart from the aromatic proton signal shifting from 7.13 ppm to 6.49 ppm respectively. This led Makarieva to believe that there was a structural difference in the sulfur ring. The NMR data gathered together with FABMS and EIMS data allowed Makarieva to conclude that the structure of varacin A was indeed **(22)**.

It had previously been reported though that benzopentathiepins are capable of decomposing into elemental sulfur and benzotrithioles,[33] which meant there were some questions over whether varacin A was in fact a natural product. Makarieva decided to investigate into this and found that solutions of **(19)** or **(25)** would readily equilibrate to mixtures of **(19)** and **(22)**, or **(25)** and **(22a)** respectively.[32]

19. R = H
25. R = $COCH_3$

22. R = H
22a. R = $COCH_3$

Scheme 6: Benzopentathiepin/benzotrithiole equilibrium

Approximately 10 - 20% conversion of the benzopentathiepin to benzotrithiole was detected at room temperature after 100 h in MeOH-*d4*, and 45% conversion was seen after 1 year. Refluxing benzopentathiepin in pyridine for 20 min also yielded around 45% conversion to the benzotrithiole. Interestingly the addition of S_8 to an equilibrated mixture under the same conditions would lead to the regeneration of the benzopentathiepin and depletion of the benzotrithiole by as much as 10% in 15 min.

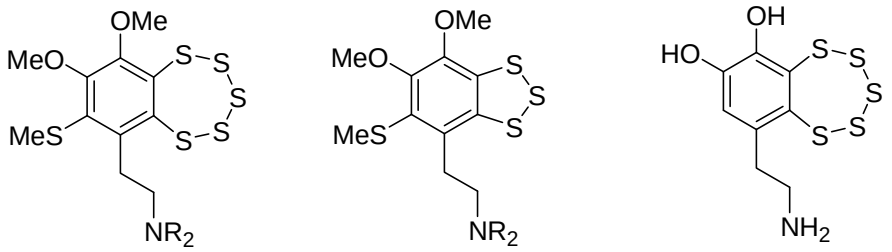
The acetates of varacin B **(23a)** and C **(24a)** which were also formed were shown by EIMS and FABMS to have just the addition of one oxygen atom compared to **(22a)**. The EIMS of both varacin B and C showed the loss of one oxygen atom and gave the expected peak at m/z 317 suggesting that the two isomers contained an *S*-oxide.[34, 35] IR spectroscopy also revealed the characteristic absorption of a C-SO-S at 1085 cm^{-1}.

Finally, ^{1}H NMR spectroscopy showed that the methylene signals for **(23a)** were shifted downfield, this combined data allowed Makarieva to conclude that varacin B was the 3-*S*-oxide and varacin C was the 1-*S*-oxide.

Further studies to see whether varacin B and C were formed due to decomposition of varacin were carried out in MeOH and Makarieva found that neither compound was formed after 1 year. Therefore it is likely that the *S*-oxides are natural products.

Biological testing which was later carried out on varacin A-C and their acetates showed potent *in vitro* antifungal and antimicrobial activity. This goes against earlier suggestions that the amine group side chain is necessary for benzopentathiepins to exhibit biological activity.[32]

In 1994 in their search for new PKC inhibitors, Faulkner and Compagnone discovered a range of varacin type compounds isolated from *Lissoclinum* and *Eudistoma sp.* ascidians. N,N-dimethyl-5-(methylthio) varacin **(26)** and 5-(methylthio) varacin **(27)** were isolated along with their corresponding trithianes **(28)** and **(29)** as reportedly inseparable mixtures.[36]



26 = Me
27 = H

28 = Me
29 = H

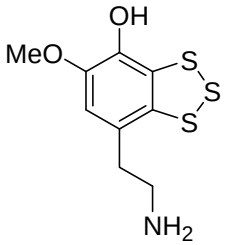
30

Figure 11: Further varacin type structures isolated by Faulkner and Compagnone [36]

Although the trithiane and pentathiepin analogues were inseparable, Faulkner and Compagnone went on to screen the mixtures for PKC inhibition. The mixture of **(27)** and **(29)** proved the most potent (IC_{50} = 0.3 μg/ml) along with another newly isolated compound 3,4-desmethyl varacin **(30)** which had similar activity.

1.3.2 - Lissoclinotoxin

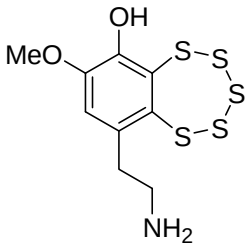
In 1991 Guyot and Litaudon reported the isolation of the first lissoclinotoxin, which would later be found to be one of a series of different lissoclinotoxin structures. Lissoclinotoxin A was isolated from the ascidian *Lissoclinum perforatum* using methanol extraction followed by silica gel chromatography and further preparative HPLC purification. Spectral analysis carried out by Guyot and Litaudon led them to report the structure of lissoclinotoxin A as **(31)**.[37]



31

Figure 12: The originally proposed structure for lissoclinotoxin A.[37]

Davidson *et al.* lay question to the assigned structure of lissoclinotoxin A whilst publishing work on the synthesis of varacin in 1993.[38] Davidson originally suggested that lissoclinotoxin was more likely to possess the structure **(32)**, but after carrying out synthetic work, concluded that it was more likely to be the regioisomer **(33)**. At this point Davidson decided to name the synthetic polysulfide **(32)** isolissoclinotoxin.[39]



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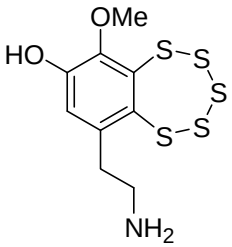
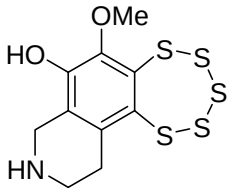


33

Figure 13: The newly confirmed structure of lissoclinotoxin **(32)** and the synthetic polysulfide isolissoclinotoxin **(33)**.[39]

A year later in 1994 Guyot and Litaudon *et al*. published two further papers, both detailing the newly isolated compound lissoclinotoxin B **(34)**, but also confirming the revised structure of lissoclinotoxin as **(33)**.[40,41]

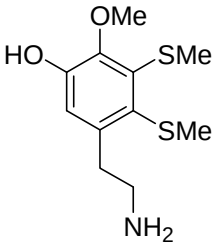
Lissoclinotoxin B was isolated as a minor product from the extraction of *Lissoclinum perforatum* as a yellow powder after extensive silica gel chromatographic purification. ^{1}H NMR spectra showed that lissoclinotoxin B only differed from spectra of lissoclinotoxin A in the absence of one aromatic proton suggesting it was likely that B was a cyclised derivative of A. Further long-range heteronuclear correlation experiments (HMBC) confirmed that lissoclinotoxin B was indeed **(34)**.



34

Figure 14: The structure of lissoclinotoxin B

Later in 1994, Searle and Molinski reported the isolation of lissoclinotoxin A which they now reported as being chiral, along with two new natural products, lissoclinotoxin C **(35)** and D **(36)**, isolated from *lissoclinum sp.* collected near the Great Barrier Reef, Australia. Biological screening of the three toxins showed that lissoclinotoxin A and D both exhibited antifungal activity against *Candida albicans*.[42]



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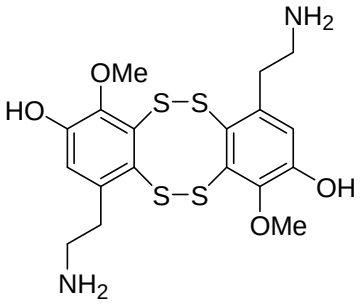

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Figure 15: The structures of lissoclinotoxin C and D

Lissoclinotoxin C **(35)** was isolated as it *N*-trifluoroacetamide as a colourless amorphous solid and showed a close structural relationship to lissoclinotoxin A **(32)**. High resolution FABMS gave a formula of $C_{11}H_{17}NO_2S_2$, (m/z 260.0799, $M+H^+$), revealing only two sulfurs and two extra carbons. ^{1}H NMR spectroscopy showed an

additional two SCH_3 groups when compared to the spectrum of lissoclinotoxin A leading to structure **(35)** being assigned as Lissoclinotoxin C.

Mass spectrometry directly on lissoclinotoxin D was unsuccessful, but by derivatising to form the corresponding *N*-trifluoroacetamide, both positive ($M+H^+$, m/z 651) and negative ($M-H^-$, m/z 649) parent ions were observed in the FABMS. The possibility of lissoclinotoxin D being a degradation product is ruled out due to the lack of similar dimer formation in the FABMS of lissoclinotoxin A's *N*-trifluoroacetamide product.

The homo-dimer was assigned due to only a single aryl proton being observed in the ^1H NMR spectrum. The "head-to-tail" structure was assigned due to it being the more energetically favourable but Searle and Molinski did not rule out the possibility of a "head-to-head" type structure (Figure 16).[42]

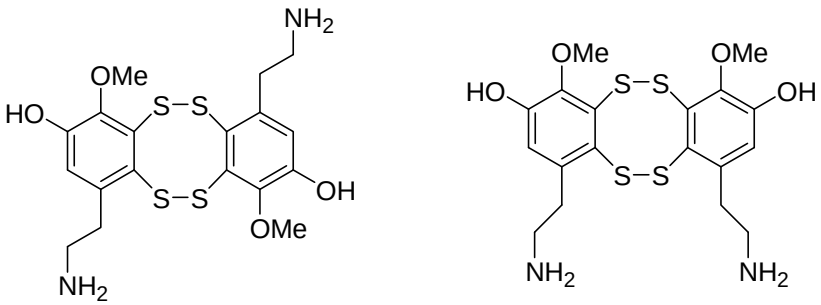


Figure 16: The two possible structures of lissoclinotoxin D

As well as the isolation of these two new lissoclinotoxins, Searle and Molinski also concluded that lissoclinotoxin A is chiral due to the diastereotopic protons observed for the side chain methylene groups in the ^1H NMR spectrum. The benzylic H_2 signals (δ 3.20, ddd, 1H, J = 6.4, 8.4, 13.4 Hz and δ 3.28, ddd, 1H, J = 6.4, 8.4, 13.4 Hz), and the vicinal H_2 signals (δ 3.55, 1H, m and δ 3.62, 1H, m) were resolved and interpreted at 500 MHz. The four mutually coupled protons do not give rise to signals with the commonly expected AAXX spin coupling pattern, but appear as an ABXY pattern with four distinct chemical shifts and geminal couplings ('J 13.4 Hz).[42]

Searle and Molinski further conclude that it is most likely that chirality is due to a high barrier to ring inversion of the pentathiepin ring. The higher barrier of approximately 29 kcalmol^{-1} being due to a unfavourable eclipsing of the sulfur lone pairs when passing through the transition state (Figure 17).[42]

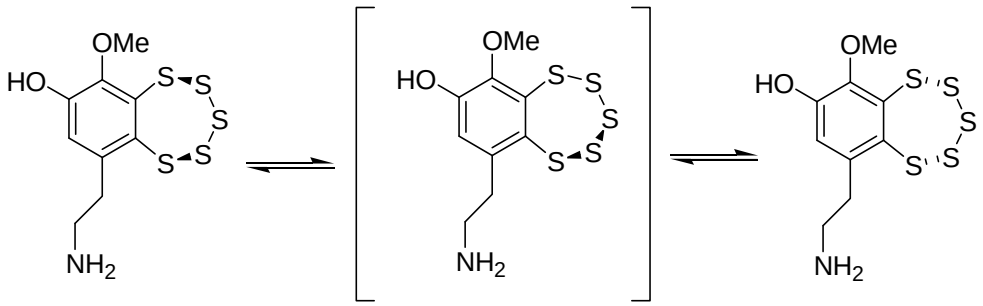
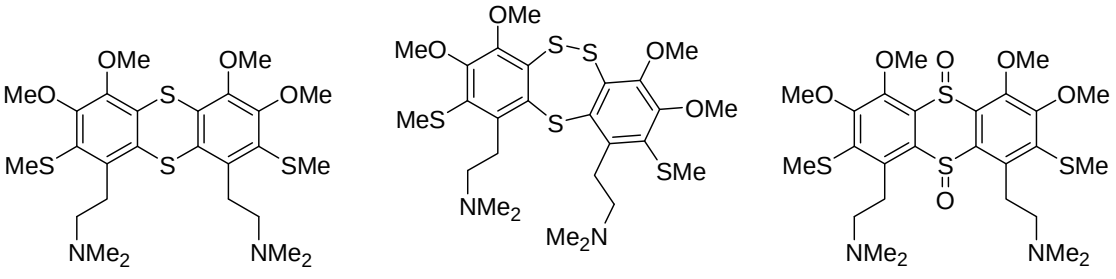


Figure 17: Lissoclinotoxin A ring inversion

In 2003, Ireland and co-workers isolated two new natural products lissoclinotoxin E **(37)** and lissoclinotoxin F **(38)**, along with the previously isolated lissoclin disulfoxide[44] **(39)** from methanol extracts of the Philippine didemnid ascidian. When screened for biological activity, lissoclinotoxin E and F both showed IC_{50} value of 2.3 and 1.5 µg/ml respectively towards a PTEN-deficient human breast carcinoma cell line.[43]

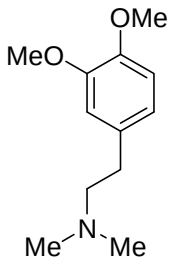


37 **38** **39**

Figure 18: The structures of lissoclinotoxin E and F, and lissoclin disulfoxide.

The major metabolite lissoclinotoxin E, and minor metabolite lissoclinotoxin F were both isolated as a light brown film using solvent partitioning and semi-preparative HPLC methods. HRCIMS, and ^{1}H and ^{13}C NMR spectroscopy were predominantly used to assign the gross structures. The structure relationship between **(37)** and **(38)**

was confirmed via a desulfurization method using Raney nickel in methanol at 90°C which yielded pure 2-(3,4-dimethoxyphenyl)-*N*,*N*-dimethylethanamine **(40)**.[45]



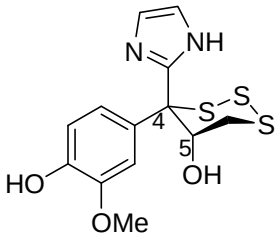
40

Figure 19: The product of desulfurization of lissoclinotoxin E and F

In order to determine the stereochemistry of lissoclinotoxin E and F, Ireland *et al*. performed a computational study using MacroModel software. The data recorded allowed them to assign lissoclinotoxin E **(37)** and F **(38)** as the *trans* and *cis* isomers respectively. Unfortunately though, due to small discrepancies in their data they noted that the other three possible isomers could not be excluded. Attempts at gaining crystalline material suitable for X-ray crystal analysis also proved unsuccessful, and to date there has been no reports of any crystalline derivatives of the lissoclinotoxin family.[43]

1.3.3 - Aplidium trisulfide

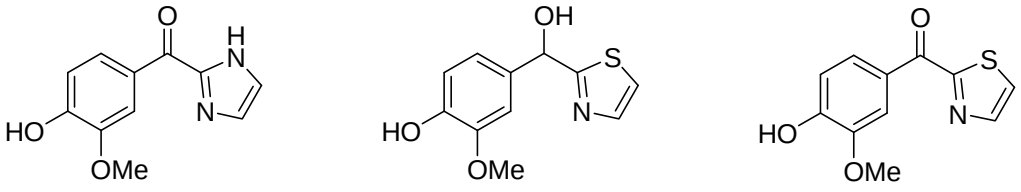
In 1989 as part of a search for new biologically active compounds from marine organisms, Munro *et al* discovered that methanol-toluene extracts from the ascidian Aplidium *Sp. D* exhibited in vitro antimicrobial, antileukemic and cytotoxic properties.[9] Purification of a freshly prepared methanol-water extract using reverse phase chromatography yielded *cis*-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-4-(2"-imidazolyl)-1, 2, 3-trithiane **(5)** as a yellow gum (48 mg, 0.05%).



5

Figure 20: The structure of *cis*-5-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-4-(2"-imidazolyl)-1, 2, 3-trithiane

Interestingly Munro found that the same methanol-water extract when left at room temperature for one month did not yield **(5),** but instead yielded the previously reported ketone **(41)**.[46] The imidazole containing metabolite **(41)** had previously been isolated by Schmitz and Arabshahi in 1988 from *Aplidium pliciferum* along with two other thiazole containing metabolite **(42)** and **(43)**.

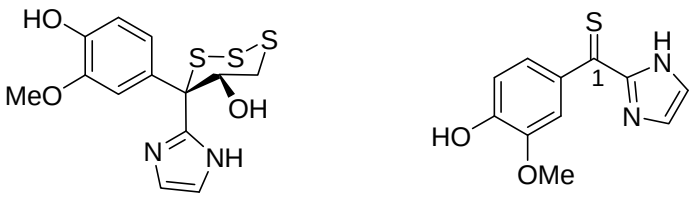


41 **42** **43**

Figure 21: Three previously isolated metabolites from Aplidium pliciferum[46]

Attempts by Munro to re-isolate **(41)** from the freshly prepared ascidian extracts failed to yield **(41)** suggesting that the ketone was not a naturally occurring metabolite of Aplidium *Sp. D*. Further to this Munro found no evidence for the occurrence of the thiazole containing metabolites.

Munro decided to investigated further the stability of Aplidium trisulfide **(5)** and he found that although **(5)** was stable for one month in acidic solution (4% TFA in CD_3OD), a change occurred over a period of weeks in slightly alkaline (0.02% NaOH w/v in CD_3OD) or neutral conditions giving a mixture of **(5)** and two new compounds **(44)** and **(45)**.



44 **45**

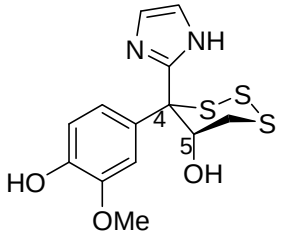
Figure 22: The two products of the decomposition of **(5)** in neutral or basic conditions

Compound **(44)** was characterised as an isomer of **(5)** due to it possessing the same ^{1}H-^{13}C long range couplings as determined by HMBC, as well as showing the same LRMS and HRMS data. Comparison of ^{1}H and ^{13}C NMR data of **(5)** with **(44)** showed that the two compounds differed by stereochemical inversion at C-4.

Further nOe experiments showed that the naturally occurring trithiane **(5)** exists as a skewed boat conformation in solution and is assigned as 4R, 5S, where as **(44)** exists as a 4S, 5S structure.

The second compound formed through the storage of **(5)** in neutral or alkaline CD_3OD was noted as having very similar ^{1}H and ^{13}C NMR data as of that of the ketone **(41),** suggesting the presence of a conjugated electron withdrawing group at C-1. Munro found that upon acidification of this solution to stop further decomposition, signals from the new compound diminished and new signals from the ketone **(41)** appeared. The transformation to **(41)** was complete after 2 days at room temperature. All attempts at utilising HPLC separation to isolate the transient intermediate proposed as **(45)** proved unsuccessful, only yielding further ketone. This is consistent with the instability of the thione in aqueous acidic solution.

Later in 2001 Copp and co-workers discovered that extracts from the delicate pink stalked ascidian *Hypsistozoa fasmeriana* found off the coast of New Zealand exhibited a wide range of biological activities. Specimens of *H. fasmeriana* were collected by scuba from Leigh Harbour and Tutukaka, and kept freeze dried until use. The freeze dried samples were extracted with MeOH and CH_2Cl_2 and the crude extract partitioned between water and CH_2Cl_2. C18 Flash chromatography and semi preparative HPLC were used to isolate (-)-**(5)** as a TFA salt (8mg, 0.18%).[10]



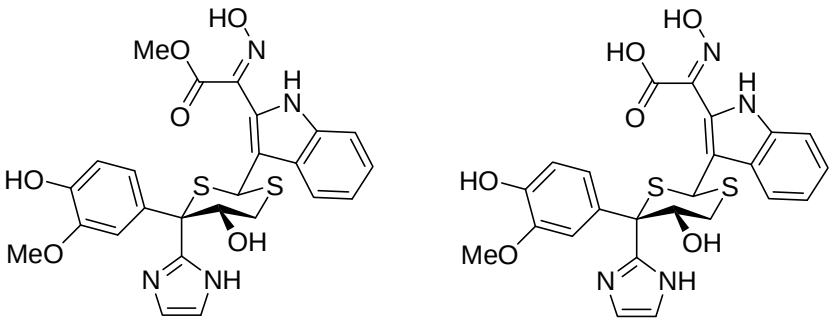
(+)-**5**
(-)-**5**

Figure 23: Both (+) and (-) enantiomers of the trisulfide now isolated

All spectral data obtained for the (-) enantiomer were identical to that previously report for the (+) enantiomer except the chiroptical properties which were equal in magnitude but opposite in sign at every wavelength measured.

1.3.4 - Fasmerianamine

In 2001, as well as isolating the newly discovered (-) enantiomer of the aplidium trisulfide Copp and co-workers also discovered two entirely new dithiane alkaloids **(46)** and **(47)** from *Hypsistozoa fasmeriana.*[10] Unfortunately neither of the dithianes were found to exhibit biological activity but never the less they represent an interesting and novel class of enantiomeric marine polysulfides.



46 **47**

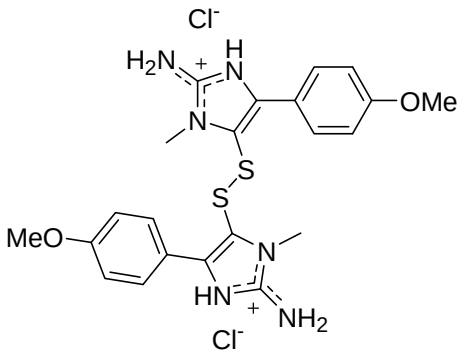
Figure 24: The structure of fasmerianamine A **(46)**, and fasmerianamine B **(47)**

Several features of the fasmerianamines ^{1}H NMR spectra were similar to those of aplidium trisulfide **(5)**, which aided structural elucidation. The dithianes were isolated as a 2:1 mixture (A:B), and characterised by NMR spectroscopy and mass spectrometry. A molecular formula of $C_{26}H_{24}N_4O_6S_2$ was established for **(46)** using HRFABMS. Extensive NMR spectroscopy allowed Copp to assign the relative stereochemistry of **(46)** as (8α, 10β, 11β)-methyl-2-[3-[11-hydroxy-10-(22-hydroxy-21-methoxyphenyl)-10-(18*H*-imidazol-14-yl)-9,13-dithian-8-yl]-1*H*-indol-2-yl]-2-oximoacetate.

The ^{1}H NMR data for **(47)** was almost identical to that of **(46)** apart from the absence of a methyl singlet at δ 4.02. This was replaced by a broad resonance at δ 13.10 which suggested the presence of a carboxylic acid functionality.

1.3.5 - Polycarpine

Polycarpine was first isolated by Fenical in 1996 when investigating the ascidian *Polycarpa clavata*. Fenical had originally investigated *Polycarpa clavata* in 1990, which had resulted in the isolation of polycarpamines A-E. These unusual, bioactive metabolites contained a high percentage of sulfur and novel functional groups. To further explore these interesting metabolites a full exploration was undertaken in 1996, leading, ultimately to the isolation of the novel dimeric disulfide alkaloid, polycarpine dihydrochloride **(48)**.

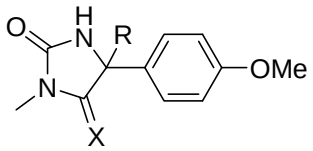


48 – polycarpine dihydrochloride

49 – polycarpine (free base)

Figure 25: The structure of polycarpine

Isolation of polycarpine dihydrochloride was achieved by extraction of the crude plant material with 70 % MeOH/CH_2Cl_2, followed by partitioning of the extract into hexane, ethyl acetate, n-butanol and water. Gel-filtration of the n-butanol fraction, followed by mild chromatography yielded polycarpine hydrochloride as the sole metabolite. Fenical found that if silica gel was used to perform the chromatography polycarpine was isolated as the free base **(49)**, with three other degradation products **(50-52)**, though this was later over come by using silica flash chromatography and reversed phase HPLC.



50 – R = OMe, X = S

51 – R = OH, X = S

52 – R = OMe, X = O

Figure 26: Polycarpine: products of degradation

The pure polycarpine hydrochloride was isolated as orange rods, with a melting point of 201-203 °C. The molecular formula $C_{22}H_{24}N_6O_2S_2$ was established using HRFABMS and the isotope cluster which was observed confirmed that only two sulphur atoms were present. The symmetry element was confirmed by ^{13}C NMR where only 11 carbon atoms were observed rather than the expected 22.

The dicationic nature of the metabolite was confirmed by exposure to acetate salts in water, which led to the formation of **(52)**, which contained two acetate counter ions.

The remaining structural assignments were achieved by using combined spectral methods. In particular 2D-NMR hetero-correlation methods and nOe experiments. HMBC correlations were able to link the aromatic proton at C-7 to that at C-5, and correlation of the C-11 N-methyl protons to C-1 and C-3.

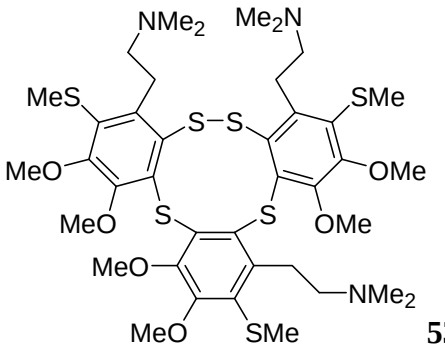
To meet the requisite molecular formula, a disulfide bridge linking two identical halves is required to be positioned at C1 and C1', resulting in structure **(48)** as the only reasonable candidate.

The free base of polycarpine was isolated as an orange non-crystalline solid, and was similar in NMR and mass spectrum to the dihydrochloride form. However, only seven resonances were observed in the carbon spectrum, and the proton spectrum had a significant broadening of the resonances seen at 3.14 and 7.37, suggesting the compound actually exists as a tautomeric mixture in solution.

Polycarpine dihydrochloride has been found to be cytotoxic toward the human colon tumor cell line HCT-116 at 0.9 μg/ml.

1.3.6 - Lissoclibadin

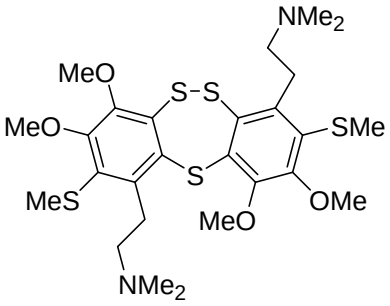
To date, seven lissoclibadins have been isolated from various ascidians. Lissoclibadin 1 **(53)** was the first of these to be isolated and characterised when found in the ethanol extract of the ascidian *Lissoclinium* sp. by Namikoshi *et al*.[47]



53

Lissoclibadin 1 was isolated as the tris-TFA salt, with the molecular weight 887 and formula ($C_{39}H_{57}N_3O_6S_7$) being deduced from HRFABMS. The ^{1}H and ^{13}C spectra indicated the presence of three identical aromatic amine moieties. By subtracting the sum of the three aromatic moieties from the molecular formula of **(53)**, Namikoshi was able to ascertain that the compound must contain four additional sulfur atoms, and from this, that the aromatic moieties were joined by one disulphide bond and two sulphide bonds, giving a 10 membered polysulfide ring.

Later in 2005, Namikoshi, when continuing to investigate extracts from the ascidian *Lissoclinium* sp, isolated Lissoclibadins 2 **(54)** and 3 **(55)** from the *n*-BuOH layer.[48]



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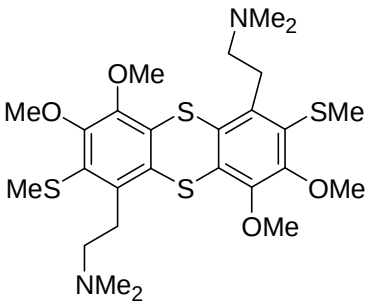

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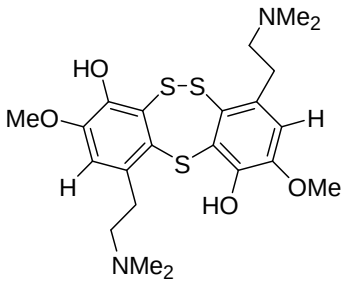
Figure 27: The structures of Lissoclibadin 2 and 3.

Both lissoclibadin 2 and 3 were isolated as bis-TFA salts. Interestingly, lissoclibadin 2 was found to have the same molecular formula and weight as lissoclinotoxin F **(37)**, and lissoclibadin 3 was found to have the same molecular formula and weight as lissoclinotoxin E **(38)**.[48] Spectral analysis of each compound showed that both lissoclibadin 2 and 3 contained two aromatic amine moieties with the same formula as in lissoclibadin 1, and lissoclinotoxins E and F. However, lissoclinotoxin F, shows symmetric ^{1}H and ^{13}C signals in relation to the aromatic amine units, whereas lissoclibadin 2 shows two sets of signals corresponding to each of the moieties indicating the molecule is not of a symmetrical shape. Further, lissoclibadin 2 showed an nOe correlation between the OMe of one moiety and the NMe_2 of the other, proving the compound must be of unsymmetrical shape and enabling the structure of lissoclibadin 2 to be correctly assigned. In the case of lissoclibadin 3, ^{1}H and ^{13}C data showed only one set of signals corresponding to the aromatic amine units, indicating that unlike lissoclibadin 2, lissoclibadin 3 had a symmetric structure. This posed an interesting problem, as lissoclinotoxin E had also previously been assigned the same symmetrical structure, yet the data for the two compounds was not identical. Namikoshi used the nOe correlation between the OMe and NMe found in lissoclibadin 3 as evidence that the aromatic amine moieties in lissoclibadin 3 had to have a *trans* orientation, resulting in the structure of lissoclinotoxin E being assigned the *cis* orientation.

In 2006, four further lissoclibadins were isolated by Nakazawa *et al*.[49] This time from the ascidian *Lissoclinum* cf. *badium.*. The four new compounds Lissoclibadin 4 **(56)**, 5 **(57)**, 6 **(58)** and 7 **(59)** were isolated in Manado, Indonesia, from ethanol extracts.



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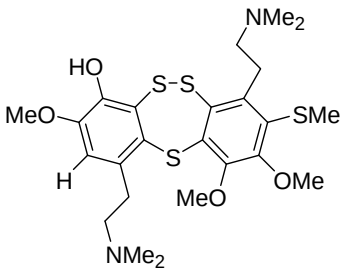

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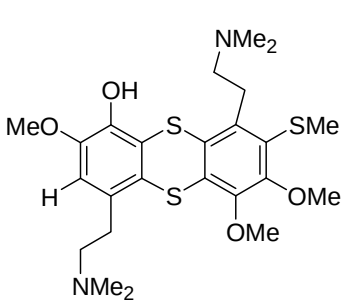

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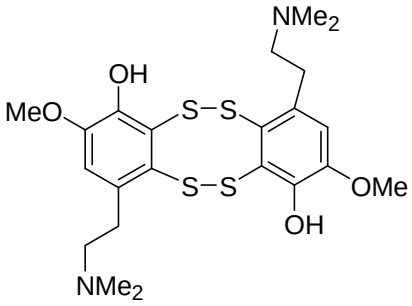

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Figure 28: The structures of Lissoclibadin 4-7.

The four new lissoclibadin compounds were all isolated as the bis-TFA salt. In all cases the molecular weights and formulas were deduced from HRFABMS and NMR studies.

Lissoclibadin 4 gave a molecular weight of 482 and formula of $C_{22}H_{30}N_2O_4S_3$. As with lissoclibadin 2 **(54)**, ^{1}H and ^{13}C spectra showed the existence of two identical aromatic amine moieties, however in the case of lissoclibadin 4, the aromatic moieties were substituted slightly differently to lissoclibadin 2, with an OH in place of an OMe group and a proton replacing the SMe group. Subtraction of these units from the total molecular formula of the compound left three sulphur atoms, indicating that the units were connected as in lissoclibadin 2, with one disulphide bond and one sulphide bond, and as in the case of lissoclibadin 2, the asymmetric structure indicated by the NMR data meant that only antiparallel orientation could be possible, leading to the structure being assigned as shown. Similar structural analysis on lissoclibadins 5-7 lead to their structures also being assigned as shown.

All of the isolated lissoclibadins 1 to 7 have shown various bioactivities, such as antifungal activity, antibacterial activity and inhibition of protein kinase C.

For example Namikoshi found that lissoclibadin 1 **(53)** inhibited the growth of the marine bacterium *R. atlantica* strain TUF-D11 (15.2mm at 20 µg/disk) but interestingly was not active against *E. coli* IAM 12119T, *S. aureus* IAM 12544T, *S. cerevisiae* IAM 1438T, *M. hiemalis* IAM 6088 at 50 µg/disk.

Namikoshi also found that lissoclibadins 1 to 3 showed cytotoxicity against the human leukemia cell line HL-60 at IC50 values of 0.37 (0.33), 0.21 (0.13), and 5.5 (3.16) μM (μg/mL), respectively.

Whereas, the more recently discovered lissoclibadins 4-7 (**56-59**) did show weak antibacterial activity against *S. aureus* and *E. coli*, two of the dimeric lissoclibadins compounds **(57)** and **(58)** also showed modest anti-yeast activity against *S. cerevisiae*. Nakazawa postulated that it was possible that the phenol group in **(57)** and **(58)** may mediate their antimicrobial activity but as yet no actual mechanism of action has been proposed for these compounds.

1.4 - Previous Polysulfide Synthesis

1.4.1 - Behar and Danishefsky (varacin)

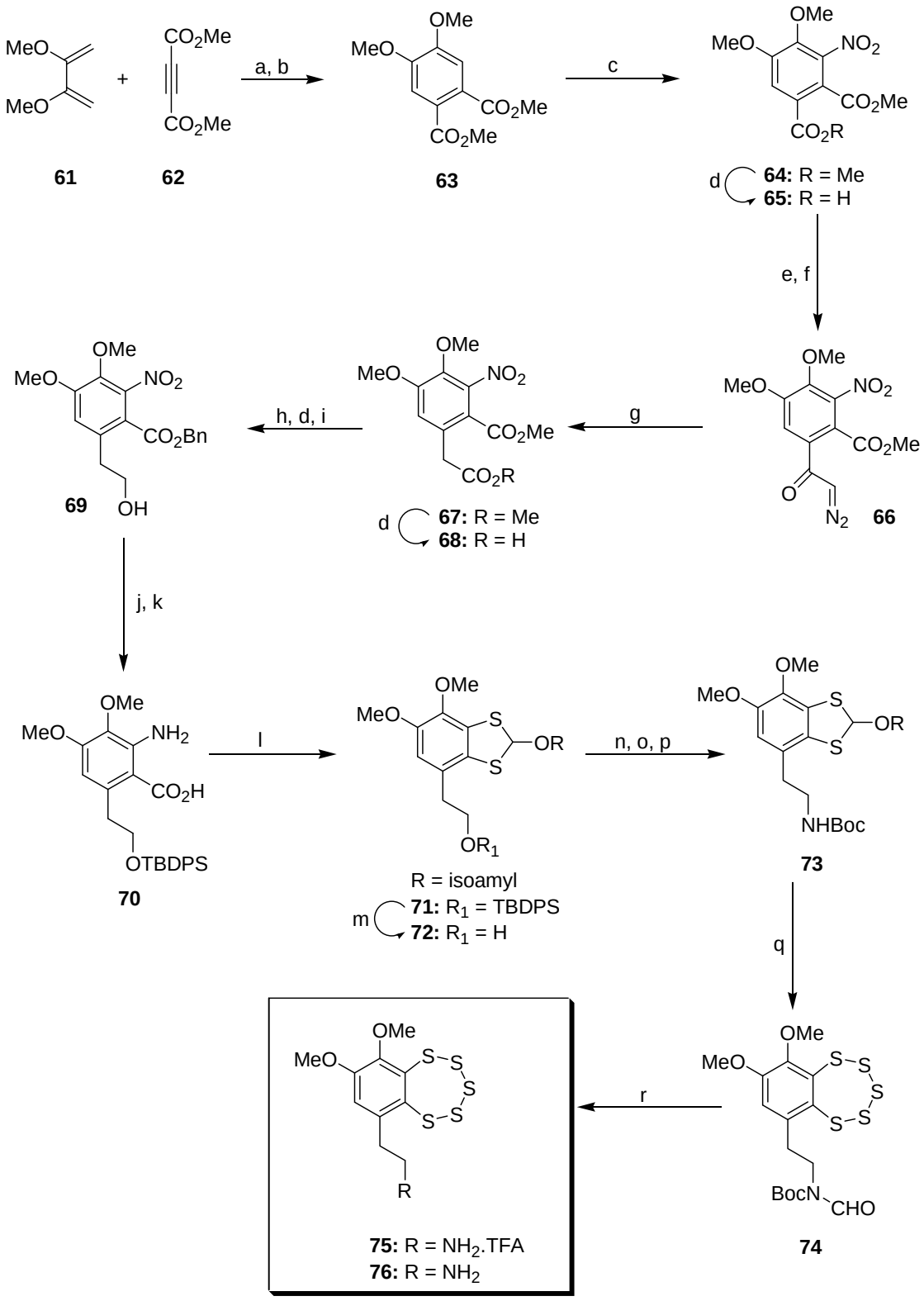
Behar and Danishefsky[50] presented the first publication on their attempted synthesis of varacin in May 1993. Their work was spurred on by their broader interest in polysulfide containing anti-tumour antibiotics, but it was necessary to overcome several problems during the synthesis. Most noticeably were the problems of interaction between the primary amino and pentathiepin groups, which had previously been documented as incompatible, and the actual incorporation of the pentathiepin ring onto an aromatic ring was to prove a challenge.

The synthesis (scheme 7) began with a Diels-Alder reaction between 2, 3-dimethoxy-1, 3-butadiene **(61)** and dimethylacetylene dicarboxylate **(62)** (DMAD). The product was immediately oxidized with DDQ to yield diester **(63)**. Treatment of the diester **(63)** with nitronium tetrafluoroborate (NO_2BF_4) in sulfolane (tetramethylene sulfone) yielded the corresponding nitrodiester **(64)**. At this point it was necessary to distinguish between the methyl ester groups to continue the synthesis. This was accomplished by hydrolyzing the less hindered methyl ester group to yield the carboxylic acid (**65)**, and then converting this to its corresponding acid chloride. This could then be treated with excess diazomethane to yield the diazoketone **(66)**. Silver benzoate was then used to promote a Wolff rearrangement to first yield the methyl ester **(67)** and then the acid **(68)**. Reduction with borane followed by reaction with LiOH provided the required benzyl ester **(69)**, silylation of the primary alcohol and hydrogenation of the nitro and benzyl ester yielded the protected anthranilic acid **(70)**.

Once the formation of the acid had been completed, the next step was the incorporation of sulphur into the molecule. To achieve this, the previously synthesized acid compound **(70)** was reacted with isoamyl nitrite in the presence of carbon disulphide and isoamyl alcohol. The compound was then directly subjected to thermal decomposition under the assumption that the previous reaction would have yielded the diazonium carboxylate salt. This assumption proved to be correct when thermal decomposition yielded the expected compound **(71)** in 40% yield. The installation of the nitrogen substituents was achieved in two steps by removal of the silyl protecting group to yield the alcohol, and then a subsequent Mitsunobu reaction

using phthalimide to yield **(73)**. It was found to be necessary to be able to remove the amino protecting group with mild acidic conditions, as harsher conditions resulted in decomposition of the pentathiepin ring, as such the *tert*-butyl carbamate protecting group was used **(73)**.

The pentathiepin ring posed the most unique problem. Behar and Danishefsky found a solution to this synthetic step by the treatment of **(73)** with S_2Cl_2 which resulted in both the removal of the ortho ester and the formation the pentathiepin ring **(74)**. Finally removal of the nitrogen protecting groups was performed using methanolic HCl. The resulting compound was then purified using reversed-phase HPLC to yield the trifluoroacetate salt of varacin **(75)**. However, the actual synthesis of free varacin **(76)** was found to pose a further problem due to the aforementioned interaction between the amino group and the pentathiepin ring. All the desalting techniques used resulted in rapid decomposition, thought to be initiated by the free amino group attacking the pentathiepin ring. This led Behar to believe that varacin is only stable at physiological pH as it is able to exist in protonated form.



Scheme 7: (a) PhMe, $CHCl_3$, Reflux; (b) DDQ, PhMe [78% for 2 steps] (c) NO_2BF_4, sulfolane [77%]; (d) LiOH, THF, H_2O [quantitative]; (e) PhMe, $(COCl)_2$, cat.DMF; (f) excess CH_2N_2, Et_2O [79% from **65**]; (g) Silver Benzoate, TEA, MeOH [76%]; (h) BH_3.THF, THF; (i) BnBr, $NaHCO_3$, TBAI, DMF (92%

from **68**); (j) TBDPSCl, TEA, DMAP, DCM [90%]; (k) H_2, $Pd(OH)_2$, THF; H_2, Pd-C, EtOH [94%]; (l) isoamyl nitrate, isoamyl alcohol, CS_2, 1,2-dichloroethane, 75^oC [40%]; (m) TBAF, THF [93%]; (n) phthalimide, DEAD, PPh_3, THF; (o) hydrazine, EtOH; (p) $(Boc)_2O$, DMAP, DCM [55% from **72**]; (q) S_2Cl_2, THF; (r) MeOH, HCl [46% from **73**]

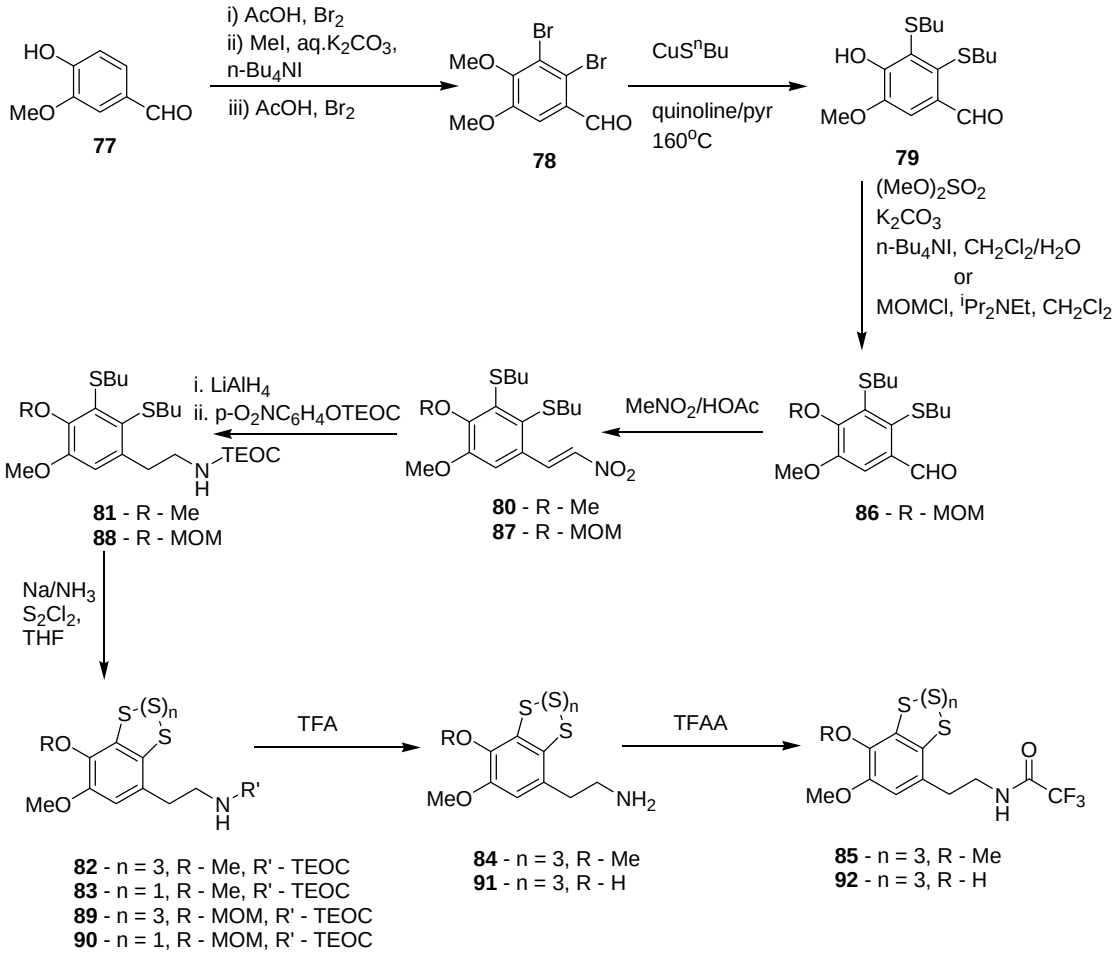
1.4.2 - Davidson (varacin)

Before the synthesis of varacin by Behar and Danishefsky[50] and Davidson,[38] there was much discussion over the actual structure of varacin because the structure had been assigned purely on spectroscopic data, and there remained the question of if the compound existed solely as a pentathiepin compound or as a mixture of pentathiepin and trithiane ring systems. Davidson decided that a total synthesis of varacin would provide a definitive answer to this question.

Davidson's approach was to form the pentathiepin ring via the addition of sulfur monochloride (S_2Cl_2) to an appropriate pre-constructed dithiol or dithiolate precursor.[38] To arrive at the dithiolate precursor Davidson used a route in which vanillin **(77)** was converted to 2,3-dibromoveratraldehyde **(78)** in three steps, this was found to be more efficient than using a single step process. To incorporate the sulphur into the compound the aldehyde **(78)** was treated with cuprous *n*-butylmercaptide in quinoline/pyridine to yield a mixture of **(79)** and the two possible monodemethylated compounds. The aldehyde **(79)** was methylated and then treated with nitromethane in $HOAc/NH_4OAc$ to give the nitro compound **(80)**, which was subsequently reduced with $LiAlH_4$ to give the phenethylamine side chain, which was protected with a β-(trimethylsilyl)ethoxycarbonyl group to yield **(81)**. Removal of the *n*-butyl groups to yield the dithiolate compound was effected by treating compound **(81)** with Na/NH_3. The addition of S_2Cl_2 to the dithiolate yielded two products **(82)** and **(83).** Separation of these compounds was achieved using flash-chromatography or reversed phase HPLC. Compounds **(82)** and **(83)** were found to give very similar NMR spectra, however, Davidson was able to identify some significant differences which enabled each compound to be identified. From these Davidson was able to indentify compound **(82)** as the benzopentathiepin and **(83)** as the benzotrithiane.

Exposure of **(82)** to TFA in chloroform provided the trifluoroacetate salt of varacin **(84)** and the spectroscopic data matched that reported for the natural product. Davidson obtained further confirmation of the presence of a pentathiepin ring by the conversion of the TFA salt of varacin into the *N*-trifluoroacetamide **(85)** with TFAA. HRMS of this compound gave a molecular ion consistent with the formula $C_{12}H_{12}F_3NO_3S_5$. However, despite repeated attempts Davidson also found that

deprotection of **(82)** to yield free varacin resulted in rapid decomposition into several uncharacterisable products.



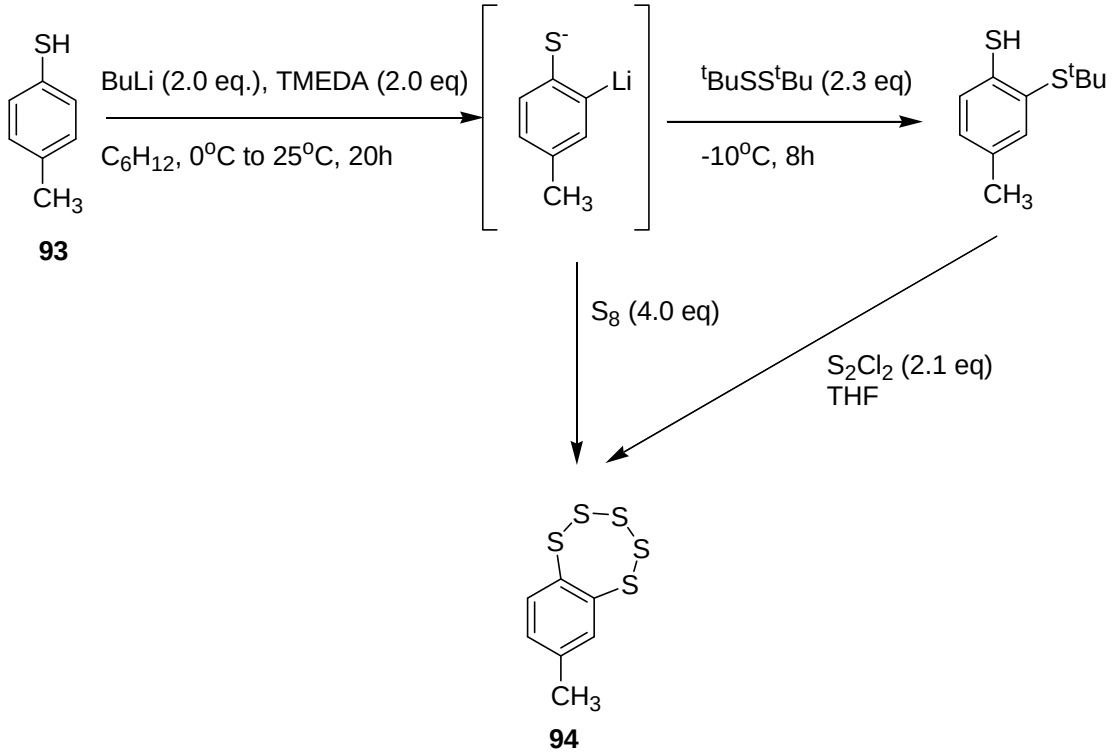
Scheme 8: Davidson's synthesis of varacin

1.4.3 - Davidson (isolissoclinotoxin A)

During his synthesis of varacin, Davidson also examined structure of lissoclinotoxin A by the synthesis of isolissoclinotoxin A.[39] The Davidson's synthesis of isolissoclinotoxin A follows the same synthetic route as that used in the previous synthesis of varacin up to compound **(79)** where instead of methylating the free alcohol a MOM group was used instead. This enables the protecting group to be easily removed to yield the required compound. The MOM protected compound **(86)** was then treated with nitromethane in $HOAc/NH_4OAc$ to give the nitro compound **(87)**, which was subsequently reduced with $LiAlH_4$ to give the phenethylamine side chain, which was protected with a β-(trimethylsilyl)ethoxycarbonyl group to yield **(88)**. As in the previous synthesis of varacin the SBu groups were reduced using Na/NH_3 which was followed directly with treatment of the dithiolate groups with S_2Cl_2 resulting in the formation of a 3:2 mixture of compounds **(89)** and **(90)**. These compounds where found to have many of the spectral characteristic observed in the varacin intermediates **(82)** and **(83)**, enabling Davidson to postulate that **(89)** contained a pentathepin ring and **(90)** a trithiane ring. Further evidence of this was obtained by the conversion of **(89)** to the TFA salt **(91)**, which was then further reacted with TFAA to yield the *N*-trifluoroacetamide derivative **(92).** HRMS of compound **(92)** was found to show that the compound had a molecular formula of $C_{11}H_{10}F_3NO_3S_5$, consistent with the presence of a pentathiepin ring.

1.4.4 - Still & Toste (varacin)

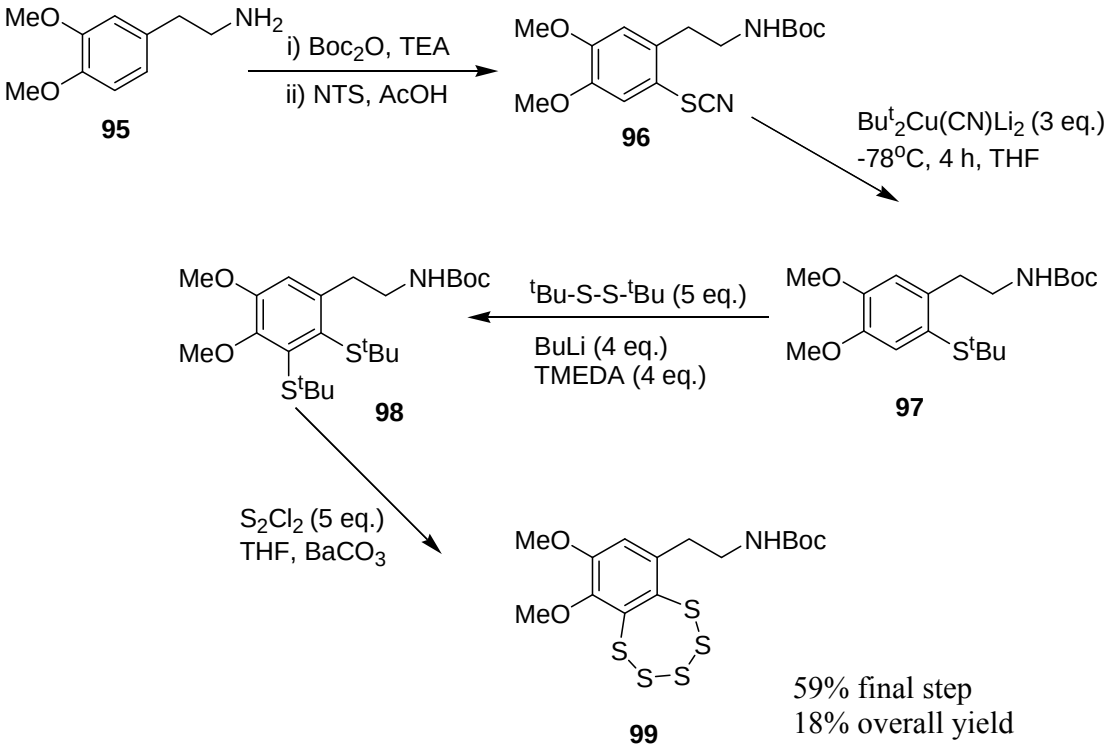
Still and Toste[53] in their attempts to synthesis the polysulfide varacin decided on an approach that introduced only a single sulphur using S_2Cl_2 in a method first reported by Chenard and co-workers. This system was initially investigated using the model system shown in scheme 8, where *p*-toluenethiol **(93)** is doubly lithiated and then S_8 is used to yield 7-methylbenzopentathiepin **(94)** in 56% yield. However, due to contamination of 7-methylbenzopentathiepin via this method, a more reliable route was devised in which the lithiated *p*-toluenethiol is treated with di-*tert*-butyl disulfide and then treated with S_2Cl_2 to yield 7-methylbenzopentathiepin **(94)** in 86% yield after purification via chromatography.



Scheme 9: Initial test reaction

With these encouraging results in hand a full synthesis of varacin was then attempted using 3,4-dimethoxyphenethylamine **(95)** as the starting material. After protection of the NH_2 group, the compound was thiocyanated using an electrophilic thiocyanation procedure developed by Toste *et al.*,[54] which used NTS, to yield the thiocyanate **(96)**. This was then converted to tert-butyl sulphide **(97)** using $Bu^t{}_2Cu(CN)Li_2$ in a ligand

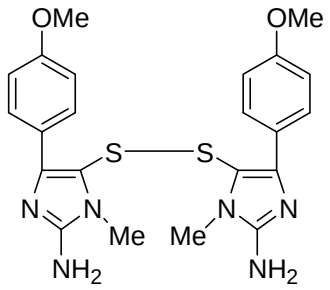
exchange reaction also developed by Toste and co workers. Lithiation and reaction with di-*tert*-butyl disulfide yielded the desired bisulfide **(98)** in good yield. Initially the key step of the reaction, the formation of the pentathiepin ring, proved problematic, however the synthesis was finally achieved by the addition of $BaCO_3$ to the reaction with S_2Cl_2 to yield the Boc-protected compound **(99)** in 59% yield after chromatography. The reaction gave an overall yield of 18%.



Scheme 10: Still & Toste's route

1.4.5 – Novikov (polycarpine)

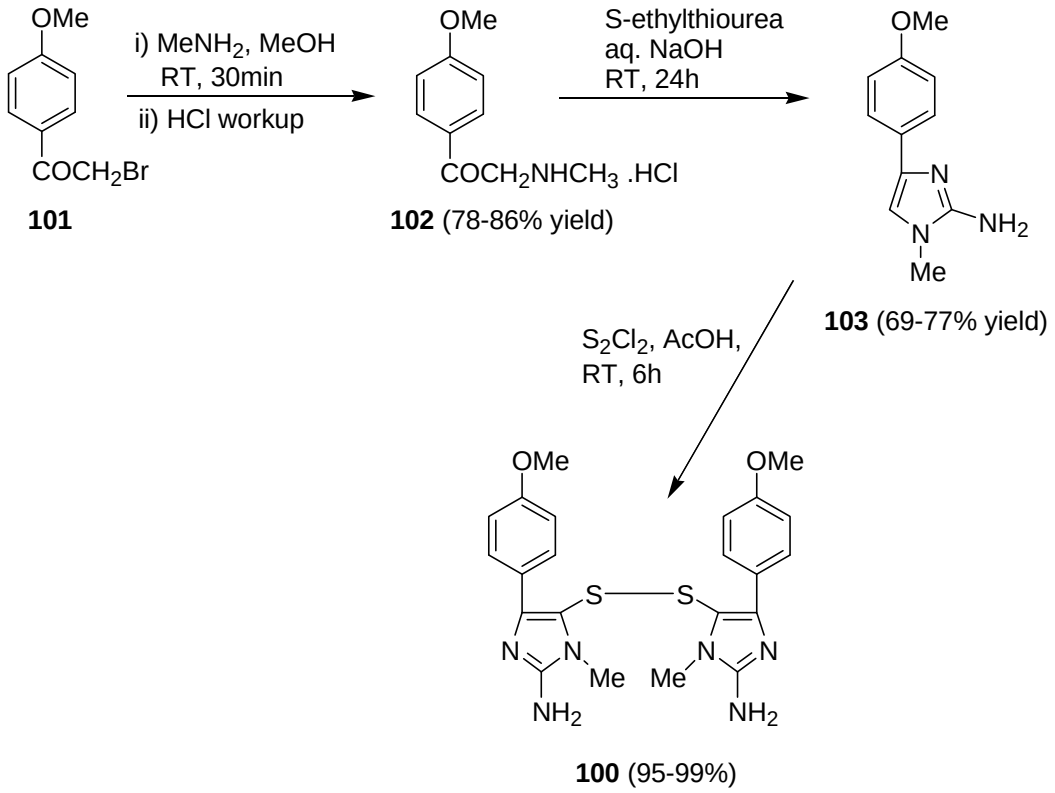
Bis[2-amino-4-(4-methoxyphenyl)-1-methyl-5-imidazolyl]disulfide dihydrochloride **(100)** (polycarpine) was recently isolated from *Polycarpa aurata* from the Pacific ocean by Novikov,[86] and has also been found more recently in *Polycarpa clavata* in the Indian Ocean, Western Australia by Fenical and Kang.[85]



100

Figure 29: Structure of polycarpine

Polycarpine is interesting as it presents both high biological activity and a new structural type of alkaloid from ascidians. However, to date only one synthetic approach has been published. Novikov *et al.*[86] decided to investigate polycarpines structure-activity relationship by developing a simple and general synthesis to it and other related compounds using a key intermediate **(103)**. Polycarpine was prepared in three steps from commercially available p-methoxyphenacyl bromide **(101)** in 57% overall yield (Scheme 11).



Scheme 11: Synthesis of polycarpine

Nucleophilic substitution of the bromine was performed using a large excess of $MeNH_2$ to yield the amine, though due to the instability of the free base the compound was isolated as the HCl salt **(102)**. Conversion of the salt to the aminoimidazole **(103)** was achieved using S-ethylthiourea in water in the presence of NaOH. The final step used S_2Cl_2 in acetic acid to couple the two molecules of **(103)** via a disulfide bridge. Six other analogues were also prepared in a similar manner.

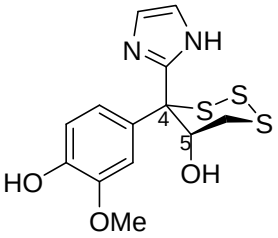
All of the disulfides prepared were tested *in-vitro* against 60-75 lines of cancer cells, with polycarpine **(100)** showing significant anti-tumour activity.

2 - Results and Discussion

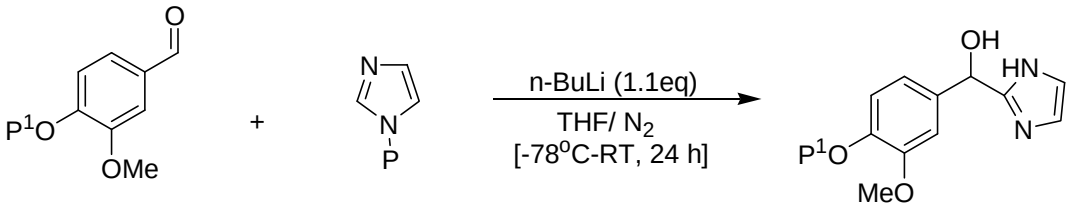
2.1 - Initial route

2.1.1 - Formation of the key secondary alcohols

The goal of synthesising the naturally occurring Aplidium trisulfide (4R, 5S) initially in racemic form was approached firstly by attempting to construct the non-sulfur containing section of the molecule. It was thought by introducing the main imidazole and benzene segments first that the labile sulfur ring would then be able to be formed in a later step limiting the chances of damaging the ring with harsh reagents and conditions.



It was therefore set out to form the alcohol **(104)** from the cheap and commercially available starting materials of vanillin and imidazole. Before we proceeded with the coupling of imidazole and vanillin it was necessary to use two different protection groups to prevent side reactions or other by-products forming. The hydroxyl group on vanillin was therefore protected using both benzyl **(105)** and TBDMS **(106)** protection groups, and imidazole was protected as shown in scheme 11 with the dimethylaminomethyl group. This group was used due to its ability to coordinate to the lithium cation and stabalise the imidazole carbanion, as well as the ease of deprotection during a later step.



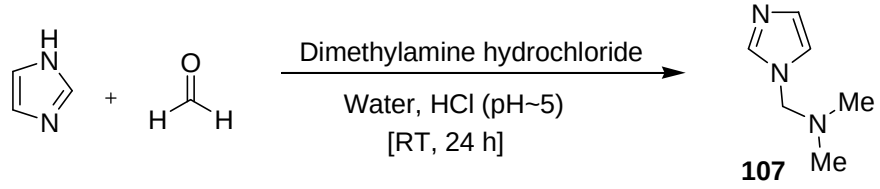
105. P^1 = Bn
106. P^1 = TBDMS

107. P = CH_2NMe2

104

Scheme 12: Synthesis of key secondary alcohols

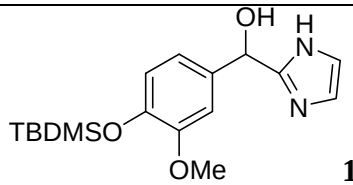
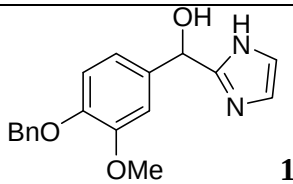
All protection steps gave near quantitative yields but as was later found the benzyl protection of the alcohol was favourable over the TBDMS protection. This was due to the fact that the benzyl protected products yielded a highly crystalline sample allowing simple and easy purification via recrystalisation. It was also observed that the TBDMS protection was labile on a flash silica column, leading to reduced yields.



Scheme 12: Imidazole protection

The addition of **(107)** to the aldehyde was carried out using n-BuLi in hexane (2.5M) to deprotonate the imidazole at the 2-position. This was then reacted with the aldehyde forming the secondary alcohol **(104)**. The formation of **(104)** was confirmed by ^{1}H NMR as the spectrum showed a new signal at 5.8ppm for the C<u>H</u>OH proton. The IR spectrum also showed a new hydroxyl stretch at 3190cm^{-1}, as well as the absence of an aldehyde signal confirming the formation of a secondary alcohol.

A range of other interesting secondary alcohol structures were also sythesised using both N-methylimidazole and thiazole in place of **(107)**. Different functionalities were also introduced onto the benzene moiety yielding several other secondary alcohols with dimethoxy- and 1,3-dioxole-analogues, these are tabulated below.

Secondary Alcohol	Yield (%)
 **108**	**82**
 **109**	**73**

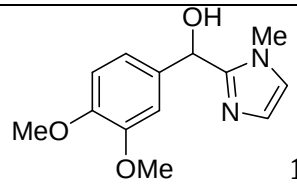
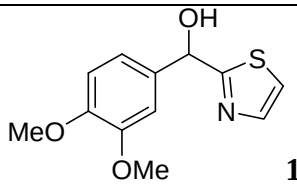
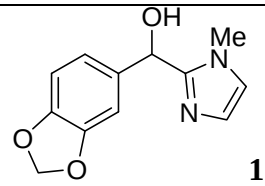
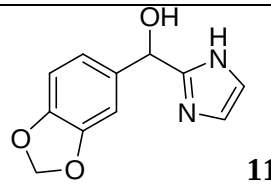
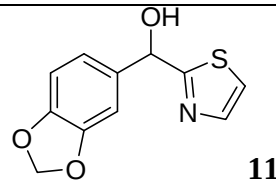
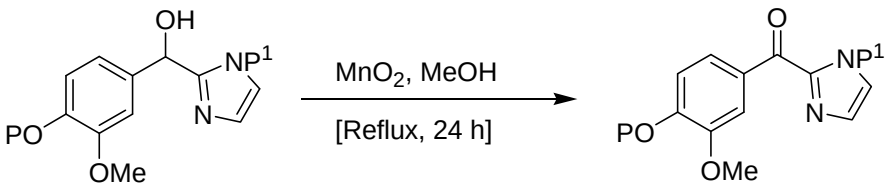
 **110**	**98**
 **111**	**95**
 **112**	**92**
 **113**	**88**
 **114**	**70**

Table 1: Yields of key secondary alcohols

2.1.2 - Manganese Dioxide Oxidation

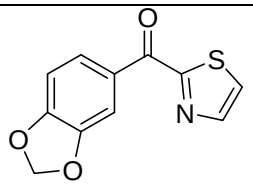
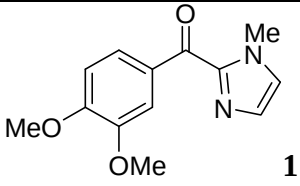
As the secondary alcohol was of limited use for the addition of a further carbon atom to form the necessary quaternary centre it was decided to firstly oxidise the alcohol to the corresponding ketone **(115)**. This would then allow us to introduce a nucleophilic source of carbon and form the desired quaternary centre. The oxidation was achieved by refluxing the corresponding secondary alcohol with 5 equivalents of MnO_2 in methanol for 24 h. The resulting black mixture is then simply filtered through a pad of celite giving the corresponding ketone on evaporation of the filtrate.



115

Scheme 13: General reaction for MnO_2 oxidation

This procedure proved to be very reproducible giving good yields of a range of different ketones. The ketones needed no further purification and could be used directly in further reaction steps. A range of ketones were synthesised and these are tabulated below.

Ketone	Yield (%)
 **116**	95
 **117**	97

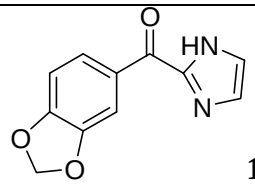
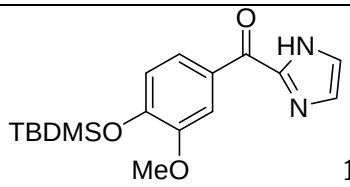
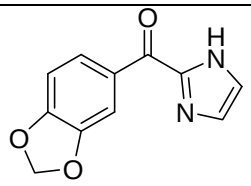
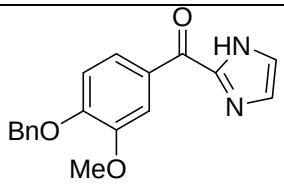
 **118**	90
 **119**	93
 **120**	96
 **121**	84

Table 2: Range of ketones and their yields

The formation of the ketones was confirmed by IR spectra where a strong carbonyl stretch was observed for each compound around 1650 cm^{-1}. Further evidence was obtained from the X-ray crystal structure of the piperonal (Figure 30) and benzyl protected (Figure 31) derived ketones.

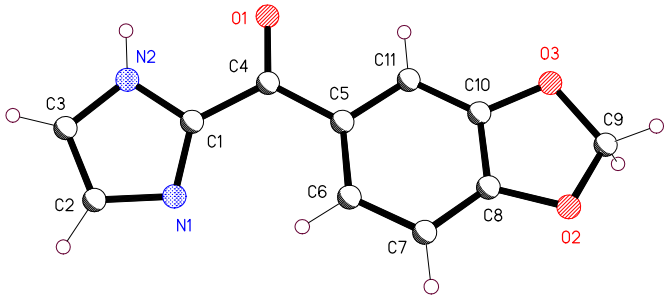


Figure 30: Crystal structure of benzo[1,3]dioxol-5-yl-(1H-imidazol-2-yl) -methanone **(120)**

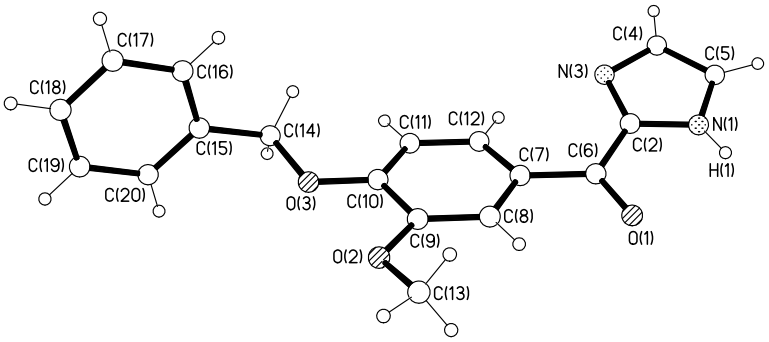
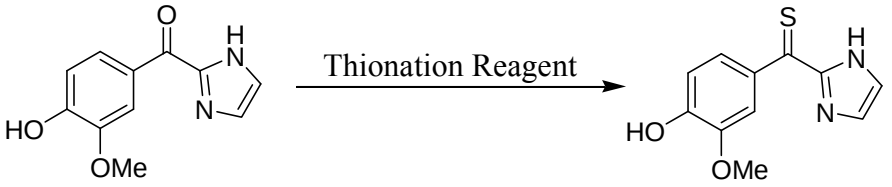


Figure 31: Crystal structure of (4-Benzyloxy-3-methoxyphenyl)-(1*H*-imidazol-2-yl)-methanone **(121)**

2.1.3 - Thioketone Formation

With a range of ketones in hand we wanted to investigate forming the previously reported thioketone **(122)** which had been isolated from extracts of the Aplidium sp. D. There were two main reasons for this suggested next step, firstly the thioketones would offer a interesting set of new compounds which would be challenging to make, and secondly this step may offer a novel way of introducing sulfur into the structure at an early stage which may prove useful when going forward towards the synthesis of aplidium trisulfide.



122

Scheme 14: General thionation reaction

Although this seemed a relatively simplistic target it is known that thiocarbonyl compounds can be inherently unstable as they photo-oxidise in air to give the corresponding ketone, sulfur and sulfoxide[94], as well as being hydrolytically unstable. It was therefore decided to firstly use benzophenone as a test ketone as it is cheap and comercially available and this would not involve using up our own sythesised ketone product. Benzophenone is also known to yield a bright blue thioketone which is reasonably stable compared to less bulky thioketones, and the highly unstable thioaldehydes.[95]

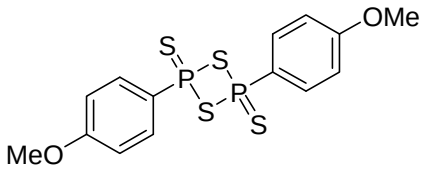


Figure 32: Structure of Lawesson's reagent

Lawesson's Reagent was firstly used to do the conversion using toluene as a solvent and refluxing the reaction mixture for 12 h. This yielded a blue solid in 88% crude yield, but the IR spectrum suggested small amounts of ketone were still present due to

a weak carbonyl stretch. The ^{1}H NMR also revealed a number of aromatic containing impurities which we expected had come from the degraded Lawesson's reagent. Column chromatography was therefore attempted to purify the thioketone but this yielded benzophenone starting material and a small amount of an unidentifiable aromatic mixture.

As purification by column chromatography resulted in the thioketone decomposing we decided to try other methods which may not require further purification. P_4S_{10} had previously been used to form thioketones[88] and more recently it has been coupled with other reagents such as $NaHCO_3$[57] and Al_2O_3[58] in attempts to try and increase yields and allow reactions to be conducted at room temperature. Previously the draw back of using P_4S_{10} as a thionation reagent has been that a large excess has had to be used to achieve moderate conversion to the thioketone. We therefore decided to try a range of solvents and conditions using benzophenone before going on to try and form **(66)**. Acetonitrile was initially used as a solvent due to the reported success of Nivard *et al*[57] in forming thiocarbonyl compounds much faster in polar solvents compared with widely used toluene.

Reagent/s	**Solvent**	**Temp. (^{o}C)**	**Time (hrs)**	**Yield (%)**
P_4S_{10}	CH_3CN	25^{o}C	24	93*
P_4S_{10}	DMF	25^{o}C	24	87*
P_4S_{10}/Al_2O_3	CH_3CN	25^{o}C	24	94*
P_4S_{10}/Al_2O_3	Dioxane	Reflux	1	Complex mixture
$P_4S_{10}/NaHCO_3$	CH_3CN	25^{o}C	24	78*
$P_4S_{10}/NaHCO_3$	DMF	25^{o}C	24	91*
$P_4S_{10}/NaHCO_3$	Toluene	Reflux	48	89*
Al_2S_3	Toluene	25^{o}C	24	Starting material
Al_2S_3	Toluene	Reflux	72	Starting material
Al_2S_3	THF	Reflux	72	Starting material

Table 3: Range of conditions used in forming the thioketone (**crude yields*.)

When using P_4S_{10} and acetonitrile as a solvent thiobenzophenone was formed in a good crude yield which was comparable to Nivard's yields of ~90%. We also found that the corresponding thioacetamide was formed as had previously been reported in the literature by Nivard. The thioacetamide was observed in the ^{1}H NMR spectra with

a peak at 1.1ppm. This by-product was also formed when using P_4S_{10}/Al_2O_3 and $P_4S_{10}/NaHCO_3$ with acetonitrile. Interestingly Kaushik[58] did not report the formation of thioacetamide during his work using P_4S_{10}/Al_2O_3 reagents. Due to the presence of a carbonyl peak in the IR spectrum of the crude product purification by column chromatography was attempted to yield the pure thioketone. Attempts using light petroleum/ethyl acetate eluent on silica gel yielded further samples contaminated with ketone. Purification was therefore put on hold in hope of a better conversion process.

Due to the incomplete reaction and formation of thioacetamide we decided to try a different solvent. Dioxane was chosen as a readily available dry solvent, but due to the insolubility of the reagents it was decided to reflux the mixture to increase solubility. This unfortunately led to the reaction mixture turning into a solid which was insoluble in both organic solvents and water. A sample of the material formed was submitted for mass spectrometry but the results proved inconclusive. We were therefore unable to conclude what reaction had taken place but we postulate that the mixture underwent a complex polymerisation involving ring opening of dioxane.

DMF was another readily available polar solvent which we next trialled. This gave the characteristic bright blue thiobenzophenone, but an inability to remove the high boiling point residual DMF without destroying the thioketone meant that this was not the best solvent to use.

Using $P_4S_{10}/NaHCO_3$ and refluxing in toluene also led to the formation of thiobenzophenone in good crude yield with the only impurity being a small amount of benzophenone. This was the most promising procedure so far for the formation of thioketone.

We also wanted to experiment into other sources of sulfur which may facilitate the conversion of ketones to thioketones. To our knowledge aluminium sulfide had not been used before so we tried reacting this with benzophenone using toluene then THF as the solvent. Unfortunately even after refluxing a mixture of benzophenone and aluminium sulfide for extended durations no reaction was observed and only starting material was recovered. From this brief work it appears that aluminium sulfide is not a reactive enough form of sulfide to undergo this type of reaction.

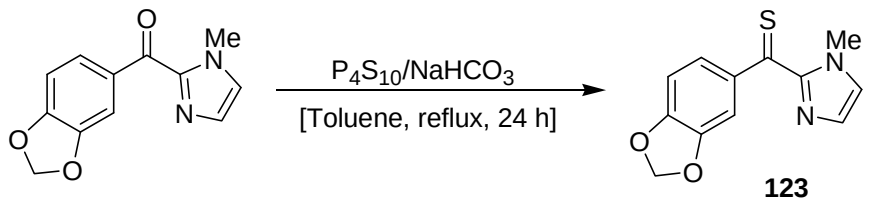
Reactions with no solvents also interested us due to the previously observed problems of P_4S_{10} reacting with acetonitrile and dioxane, and also the environmental benefits of solvent-less reactions. Therefore we went ahead and stirred our test substrate, benzophenone, with 2 equivalents of the reagents at room temperature for either 24 or 72 h (table 4). Reagents were pre-ground in a pestle and mortar for 10 minutes as suggested in Kaushik's paper, before being stirred in a round bottom flask with a magnetic stirrer bar for the remainder of the reaction time. The solid was then extracted with small portions of DCM.

Solid state reactions (No Solvent)			
Ketone Substrate	Reagent/s	Time (hrs)	Yield (%)
Benzophenone	P_4S_{10}	24	84
Benzophenone	P_4S_{10}/Al_2O_3 (1:1)	24	87
Benzophenone	Al_2S_3	72	SM

Table 4: Solid state reaction conditions

Both P_4S_{10} and P_4S_{10}/Al_2O_3 yielded the bright blue thiobenzophenone in good yields, although the ^1H NMR spectra revealed that there was again benzophenone impurity in the samples and this continued to be a problem as column chromatography led to further decomposition of the thioketone. Al_2S_3 gave no reaction under these conditions and work up yielded the starting material benzophenone.

At this stage it was decided to try our most successful method, $P_4S_{10}/NaHCO_3$ refluxing in toluene, on our own pre-synthesised ketone and hopefully forming the corresponding thioketone **(123)**.



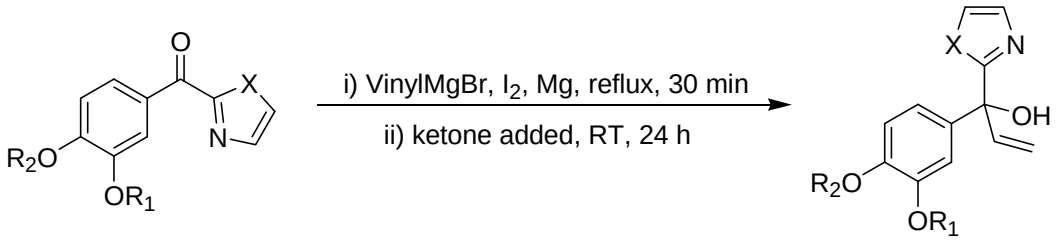
Scheme 15: Attempted formation of Benzo[1,3]dioxol-5-yl-(1-methyl-1H-imidazol-2-yl)methanethione

A difficulty in determining whether any thioketone was forming was a major problem. Thin layer chromatography showed no evidence of product forming and there was no observed colour change as with the thiobenzophenone formation. Upon workup the reaction yielded only starting material and no thioketone was observed. Several further attempts were made to repeat the reaction using the other pre-synthesised ketone analogues but in all cases no desired product could be isolated. Attempts were also made to use GC-MS to analyse the reaction mixture to see if small quantities of the thioketone were formed in-situ but only the ketone was observed in the mass spectrum.

2.1.4 - Grignard Addition

Due to the problems in forming the thioketone intermediates it was decided to continue toward the synthesis of Aplidium trisulfide by using a Grignard addition to the previously formed ketone intermediates. A Grignard addition was first attempted using commercially available vinyl magnesium bromide (2.5M in THF). It was quickly observed that the commercially available Grignard gave poor yields, typically around 40-50% so it was decided that making the fresh Grignard *in situ* using an alkyl or alkenyl bromide and magnesium may be more effective.

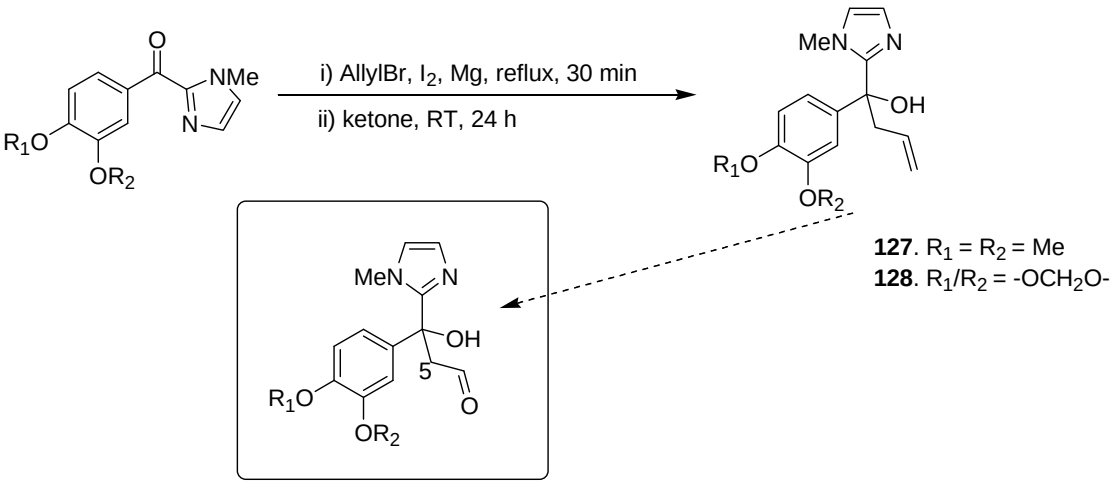
Formation of the Grignard was achieved by refluxing vinyl bromide with excess magnesium turnings and a crystal of iodine in THF for 30 min. At this stage the reaction was cooled to room temperature and the ketone was added in THF and the reaction mixture stirred for 24 h. Formation of the tertiary alcohol was confirmed by a strong hydroxyl stretch in the IR spectra ~3100cm^{-1} and later by ^{1}H and ^{13}C NMR spectroscopy. A range of tertiary alcohols **(124-126)** were isolated in good yields.



124. X = NH, R_1/R_2 = OCH_2O (76% yield)
125. X = S, R_1/R_2 = OCH_2O (80% yield)
126. X = NMe, R_1 = R_2 = OMe (89% yield)

Scheme 16: Vinyl Grignard addition products

The Grignard addition proved to be a reliable reaction and gave us a simple route to create the new quaternary centre. Although the new quaternary centre is formed as a racemate due to optically inactive reagents being used, other concurrent work was investigating an alternative asymmetric route toward aplidium trisulfide and this will be discussed later.



Scheme 17: Allyl Grignard addition product

Due to the ease of carrying out the vinyl Grignard additions to the ketone intermediates it was decided to make some other interesting analogues containing the allyl group **(127)** and **(128)** instead of the vinyl group. It was thought that these compounds may also be useful in synthesising simplified trisulfide structures which did not contain the additional hydroxyl group at the 5-position, as is present in the structure of aplidium trisulfide. It was also thought that the allyl group may later be converted to an aldehyde group by osonolysis as shown in scheme 17.

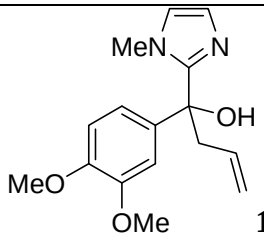
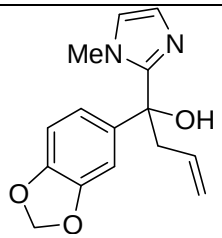
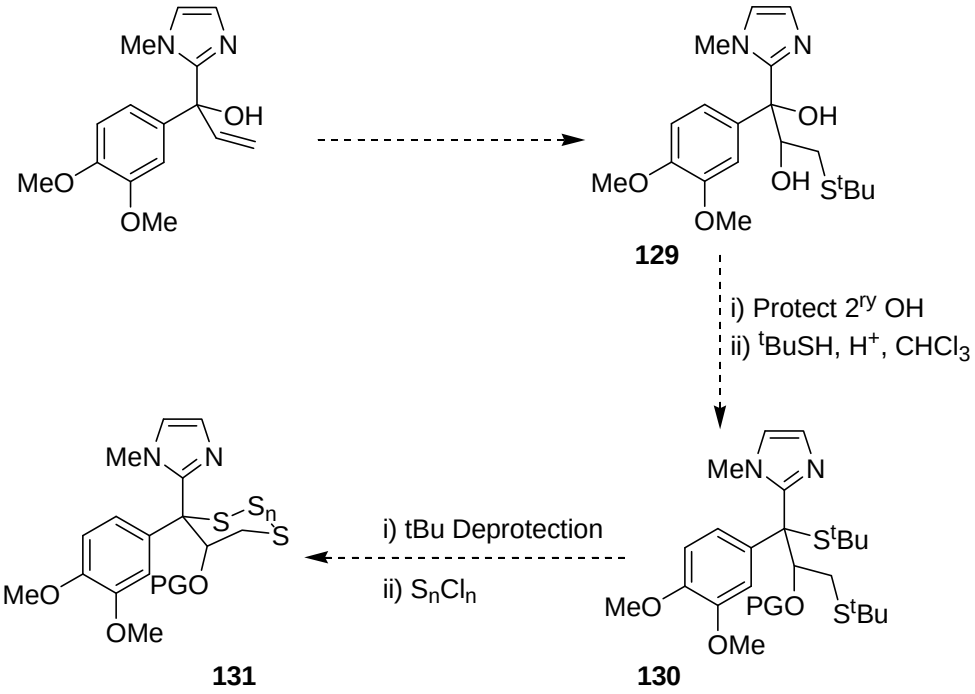
Compound	Yield (%)
 **127**	**82**
 **128**	**49**

Table 5: Allylmagnesium bromide addition products

2.1.5 - Functionalising the Olefin

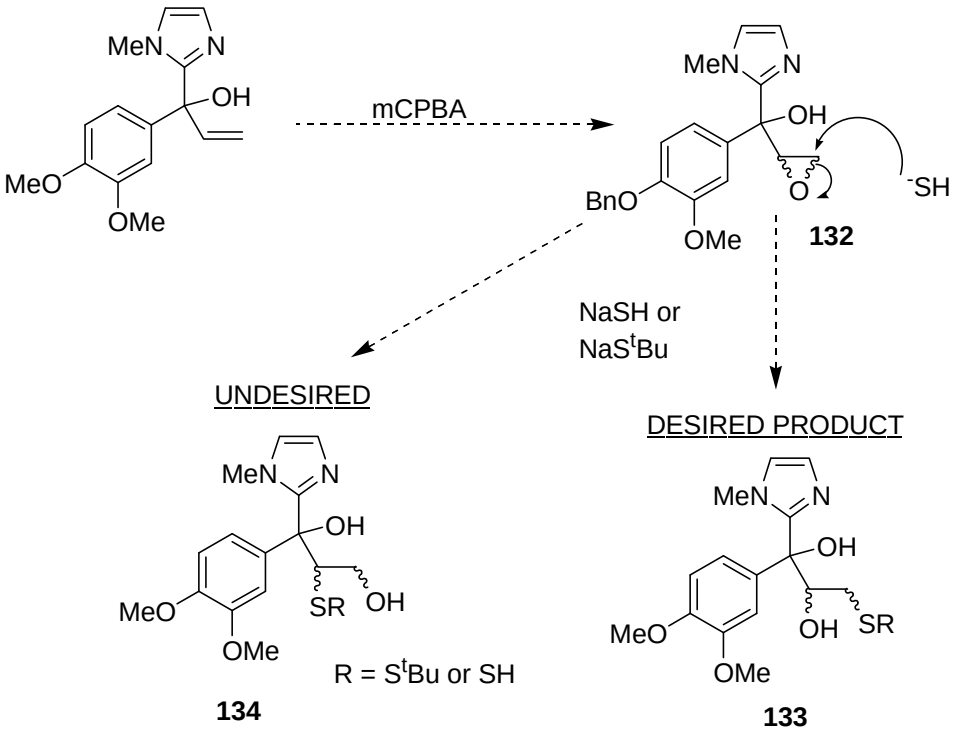
Now that we had completed the synthesis of the main carbon back-bone with the imidazole group present, our next step would have to allow us to introduce some functionality to the terminal alkene. The new functionality would have to allow further steps in order to form the trisulfide ring via the addition of sulfur, and also allow the formation of a secondary alcohol at the 5 position. The compound **(129)** was therefore targeted as a useful intermediate. Creating a *t*-butyl thioether **(130)** at the terminal carbon was important as this could be deprotected at a later stage and reacted with S_2Cl_2 to form a range of different sized sulfur containing rings **(131)**.



Scheme 18: Possible functionalisation of the olefin

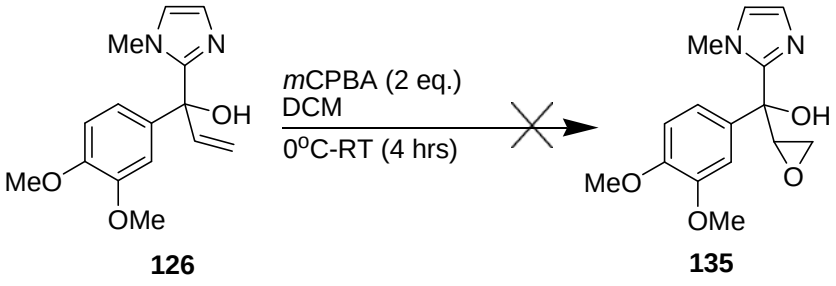
Firstly we decided that forming the epoxide (**132)** on the terminal alkene would generate a useful synthetic intermediate. It was hoped that the epoxide could be formed in a good yield by using mCPBA. The epoxide could then be opened with a nucleophilic source of sulfur in a later step, giving the secondary alcohol **(133)**, and a terminal thio- group on work up. One possible problem with this synthetic route is the ring opening step. In our perceived reaction the sulfur nucleophile would need to attack at the epoxides terminal carbon. The alternative is that the epoxide opens at the

non-terminal carbon giving the product **(134)**. We consider this a less likely product due to it being sterically less favourable to open in this way.



Scheme 19: Possible epoxide formation and ring opening with a nucleophilic source of sulfur

The epoxidation was attempted on the N-methylimidazole derivative **(126)**, scheme 20, by carrying out the addition of 2 equivalents of *m*CPBA (77%) in DCM at 0^{o}C and then allowing the reaction to warm to 25^{o}C over 4 hours. The reaction yielded a dark orange oil which was unidentifiable by ^{1}H NMR spectroscopy. Column chromatography on silica gel was attempted to purify the mixture but none of the desired product **(135)** was isolated.



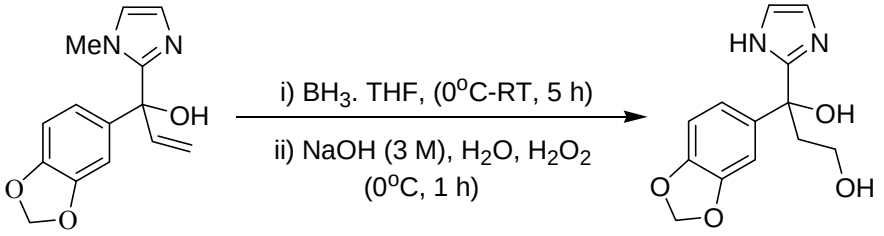
Scheme 20: mCPBA epoxidation of terminal alkene

Possible reasons for the reaction yielding an inseparable mixture of products could be either that the tertiary alcohol ring opened the epoxide or the imidazole double bond could also have reacted with the excess *m*CPBA. For this reason the reaction was repeated with a single equivalent of *m*CPBA to determine if the ring opening was occurring, and if so could we isolate this product.

The reaction was repeated and monitored closely by TLC. After 4 hours some starting material was still observed on the TLC plate but there were several new spots apparent. Work up followed by preparative TLC was carried out in attempts to isolate the major products. Despite repeated attempts to identify the products using ^{1}H NMR spectroscopy our efforts proved inconclusive.

A second attempt at epoxidising the alkene was tried using the well known Sharpless asymmetric epoxidation method discovered by Sharpless and Katsuki in 1980.[59] The procedure which requires 10 mol% $Ti(i\text{-}OPr)_4$, 1.1 eq. *t*BuOOH and one optical isomer of diethyl tartrate only works for allylic alcohols. The method was therefore trialled on the allylic alcohol substrates **(127)** and **(128)**. Unfortunately in each case the reaction only yielded ca. 65-70% recovery of starting material after column chromatography.

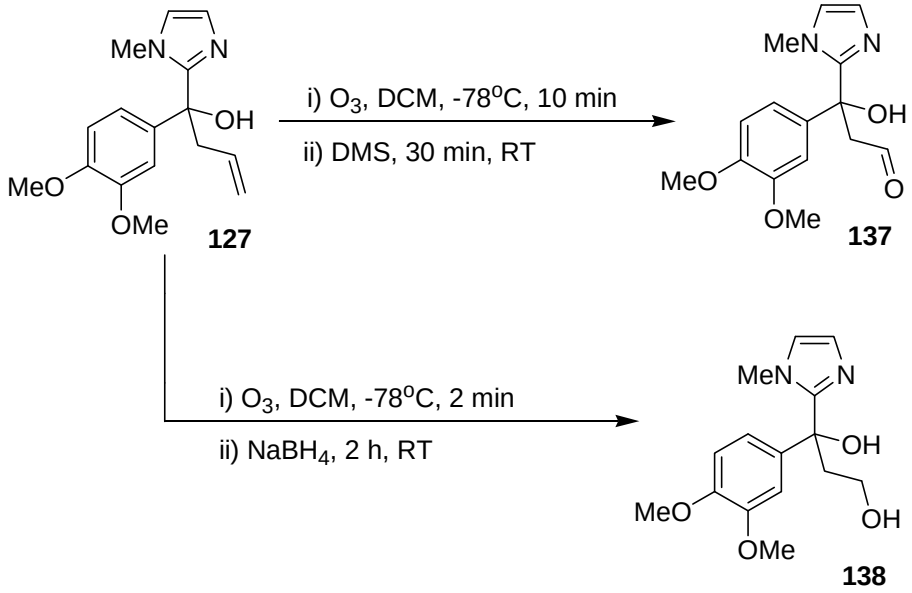
A hydroboration/oxidation reaction was next tried using both $THF.BH_3$ (Scheme 21) and separately 9-BBN. The BH_3 method had the advantages that it will react with three equivalents of the alkene to yield the trialkylborane, together with the ease in handling the reagent as a 1M solution in THF. Hydroboration/oxidation was envisaged as a useful step in forming the desired primary alcohol **(136)**. Both sources of borane were trialled but unfortunately only starting material was recovered from the reactions.



128 **136**

Scheme 21: Attempted hydroboration/oxidation reaction

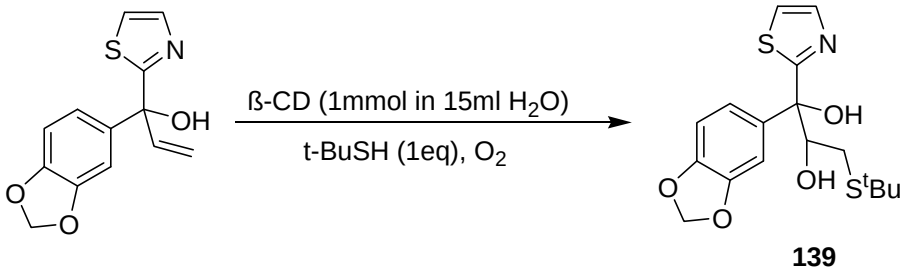
Ozonolysis of pre-synthesised allyl containing substrates such as **(127)** was another possible reaction which we could utilise in order to functionalise the terminal alkene. This was carried out using two different methods show in scheme 22. The reaction mixture from the first attempted ozonolysis was quenched with DMS in order to try and form the aldehyde. Unfortunately the reaction yielded a complex mixture of products as was observed in the ^{1}H NMR spectrum. Although several aldehyde peaks were present at ~9.5ppm no products could be isolated after column chromatography.



Scheme 22: Ozonolysis and reductive ozonolysis reactions

We thought the reason for the ozonolysis yielding a complex mixture of products may have been due to two reasons. One possibility being that the aldehyde formed maybe unstable or could have also reacted further with itself. Another problem could be that ozonolysis of the imidazole ring is occurring and forming other reactive or unstable aldehydes. For this reason a second method was tried with a shortened ozonolysis period of just 2 min. The reaction was then quenched with $NaBH_4$ in an attempt to form the terminal hydroxyl containing compound **(138)**. Unfortunately this gave a similar complex mixture as previously seen in the ^{1}H NMR spectra. Therefore it was decided to discontinue the ozonolysis work on this type of substrate as it was most likely that we would be unable to limit the amount of ozone present so not to ozonolyse the imidazole group.

As the attempted methods so far to functionalise the olefin had proven quite harsh, with the ozonolysis possibly breaking open the imidazole ring, and the *m*CPBA epoxidation possibly forming the imidazole N-oxide it was decided to look for a milder reaction. In one particular paper by Rao *et al* they explored the use of β-CD in a new and environmentally benign procedure that formed β-hydroxysulfides efficiently and in good yields.[56] We thought this type of reaction would allow us to form some very useful intermediates so we set about their method on our own substrate to try and form compound **(139)**.



139

Scheme 23: Attempted β-hydroxysulfides formation

At first the reaction was attempted at room temperature stirring for 24 hours but this yielded only starting material. We then considered two ways to possibly make the reaction proceed; raising the temperature to speed up the reaction, and by using more equivalents of the thiol. Although there were no problems envisaged by increasing the equivalents of thiol, apart from odour, raising the temperature of a reaction containing volatile t-butyl thiol may lead to less thiol in the reaction mixture. With the boiling point of t-butyl thiol being 62-65°C it was decided to carry out the reaction in a closed flask with minimal headspace when using the thiol at elevated temperatures. Several substrates were trialled containing both the imidazole and thiazole groups as well as attempts at changing the thiol to thio-phenol (Table 6). Unfortunately we could not replicate Rao's success and no reaction with any of our substrates was observed.

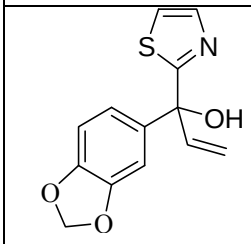
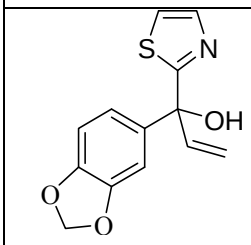
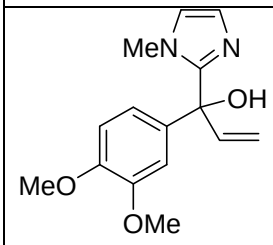
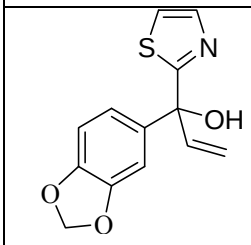
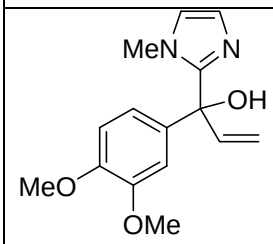
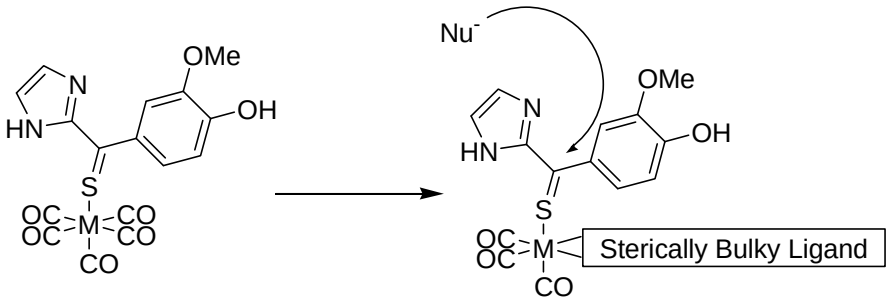
Alkene	Thiol	Eq. of thiol	Temp. (^{o}C)	Yield (%)
	*t*-butyl	1	25	SM
	*t*-butyl	2	25	SM
	*t*-butyl	2	60	SM
	phenyl	2	60	SM
	*t*-butyl	5	25	SM

Table 6: The range of substrates and reaction conditions trialled for attempted formation of corresponding β-hydroxysulfide

2.2 – Thiocarbonyl-metal complexes

Due to the previous problems associated with forming a stable thioketone intermediate, another area of interest to us was in forming thiocarbonyl-metal complexes as had previously been reported by Reid[64] and Gingerich.[65] Their work was of interest to us for two main reasons, firstly this may allow us to form a more stable thiocarbonyl species, and secondly that the complexes previously reported may allow further work into ligand exchange and the possibility of an asymmetric route towards aplidium trisulfide using sterically hindered ligands. If this was possible it would be envisaged that a nucleophile would have a preferential side of attack.



Scheme 24: Proposed route for asymmetric work

Reid's method of forming a reactive metal complex species involved using tetrabutylammonium iodide and chromium or tungsten hexacarbonyl, heating in diglyme and then filtering the mixture to yield the corresponding salt.

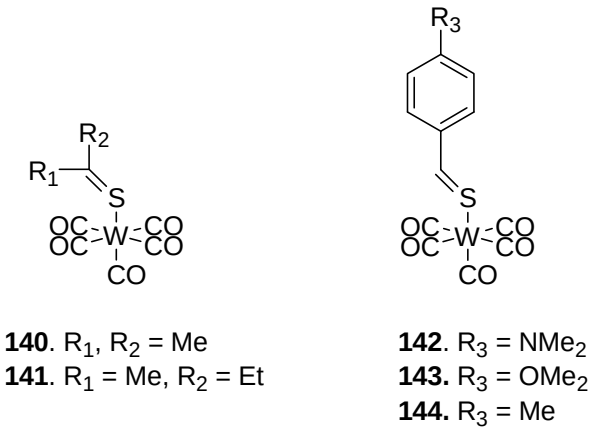
This procedure was carried out under nitrogen using both the tungsten and chromium hexacarbonyl starting materials and successfully yielded the corresponding salts. Confirmation of the iodo-metal complex formation was observed by the characteristic C=O stretches present in the IR spectra. Reaction of the iodo-tungsten and iodo-chromium complexes with benzophenone was attempted *in-situ* due to the instability of the complexes. Reactions were carried out in THF at room temperature but no new products were observed when using either of the complexes, and as Gingerich's procedure seemed more promising at the time no further work was carried out to study the reactivity of these iodo-metal complexes.

On the other hand Gingerich had initially formed a reactive mononuclear salt containing the species $[M(CO)_5(SH)]^-$ using metal hexacarbonyl's (scheme 25). Several analogue compounds were prepared containing tungsten, chromium and molybdenum metal centres.

$$M(CO)_6 + [(Ph_3P)_2N]SH \longrightarrow [(Ph_3P)_2N][M(CO)_5(SH)] + CO$$

Scheme 25: Angelici and Gingerich's previous work

Gingerich found that the tungsten analogue could be isolated as a solid in good yield of 93% where as the yellow chromium analogue discoloured in air after 4 hours. The molybdenum analogue was reportedly too unstable to isolate pure. For these reasons the thio-tungsten complex was chosen for further reactivity studies. Further research showed that $[W(CO)_5SH]^-$ could be reacted with sterically unhindered ketones such as acetone and methylethylketone as well as a range of para-substituted benzaldehyde compounds to form tungsten-thiocarbonyl complexes such as **(140-144)**. A reduction in yield was noted when using sterically hindered carbonyl substrates.



140. R_1, R_2 = Me
141. R_1 = Me, R_2 = Et

142. R_3 = NMe_2
143. R_3 = OMe_2
144. R_3 = Me

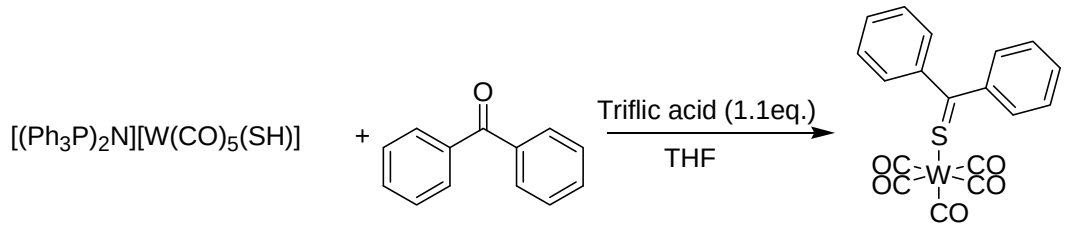
Figure 33: Previous thiocarbonyl products

We decided to initially try and repeat Gingerich's work on less sterically demanding aldehydes before attempting to form a thiocarbonyl-metal complex containing our pre-synthesised ketones.

The thio-tungsten salt was initially formed following Gingerich's procedure achieving a comparible yield of 84% of a yellow solid. IR bands at 2052, 1932(vs), 1851 were used to confirm the products formation.

Next, we decided to trial one of Gingerich's reported reactions using readily available anisaldehyde as a substrate. The corresponding thioaldehyde-tungsten complex was isolated as a purple oil in 6% yield after column chromatography, much lower than the reported 32% yield.

Although this was a poor yield we decided that it would be worthwhile to attempt the formation of a thioketone-tungsten complex. This was initially attempted using benzophenone as a substrate. The reaction yielded 2% of a bright purple compound after column chromatography. The compound showed a strong carbonyl absorption at 1932cm^{-1} in the IR spectrum, and a shift at δ 206.9 in the ^{13}C NMR spectrum, characteristic of a C=S carbon. HRMS confirmed the product as $C_{18}H_{10}SO_5W$ (M^+) m/z 521.9755.



Scheme 26: Formation of [W(CO)$_5${S=C(C$_6$H$_5$)$_2$}]

Despite several attempts using fresh batches of the tungsten salt and freshly distilled THF the reaction could not be repeated on our own ketone substrates **(116-121)**. This is possibly due to steric hinderance.

2.3 – Key sulfide intermediates

2.3.1 – Retrosynthesis

Due to the difficulties with introducing functionality to the terminal alkenes as previously discussed, it was decided that a more convergent synthesis was needed where functionality could be incorporated during the addition of the C_5/C_6 unit.

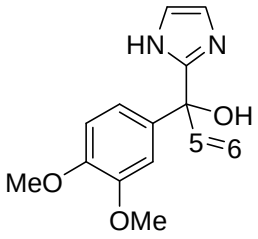
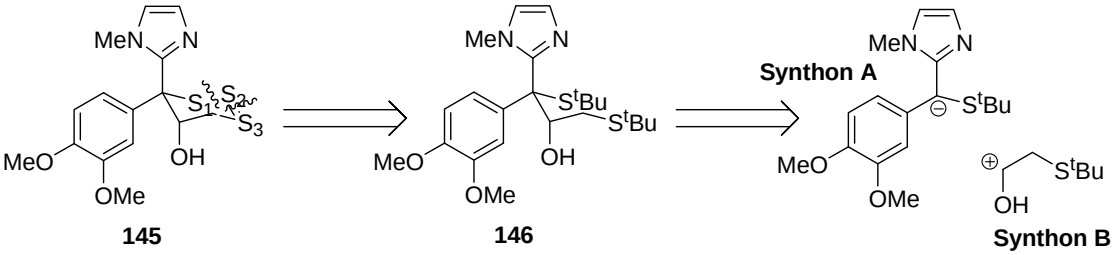


Figure 34: Vinyl containing substrate difficult to functionalise

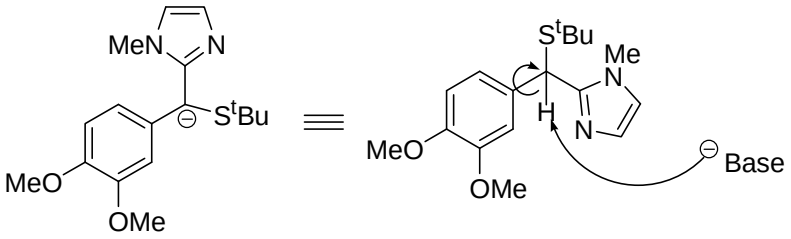
Retrosynthetically it was still thought that forming the 1,2,3-trithiane should be the final synthetic step due to the expected instability of the trithiane ring, therefore we decided the first disconnections should be at S_1-S_2 and S_2-S_3 (Scheme 27). The presence of di-*t*-butyl groups would allow for a protected thiol to be deprotected and ring closed using sulfur monochloride.



Scheme 27: Retrosynthesis to give synthon A and B

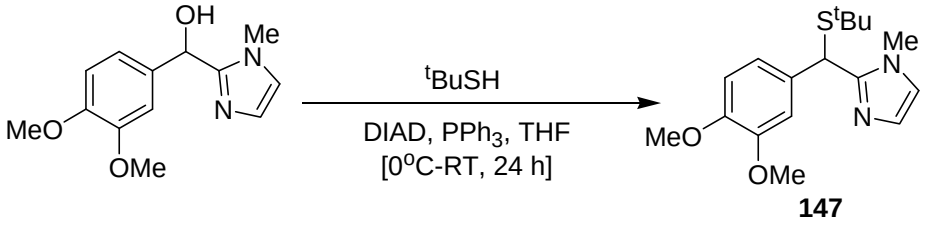
2.3.2- 'Synthon A'

Compound **(147)** was chosen as the synthetic equivalent to synthon A. We thought that by using a strong enough base this was a viable deprotonation due to the stabilising effect of the neighbouring sulfur, although it was hoped that the carbanion would still exhibit reasonable nucleophilicity.



'Synthon A' **147**

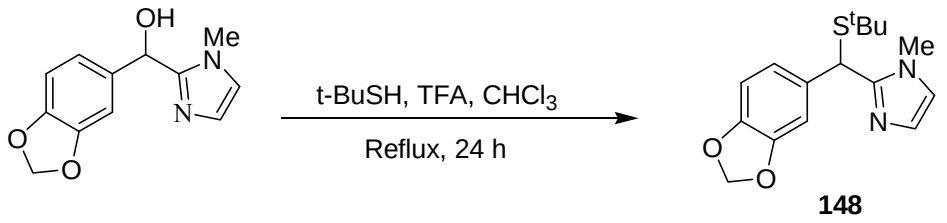
Forming the sulfide **(147)** was first attempted via a Mitsunobu type reaction (Scheme 28) using a presynthesised secondary alcohol.



Scheme 28: Mitsunobu reaction to form sulfide

The reaction yielded a dark orange oil which was purified by silica column chromatography using a light petroleum: ethyl acetate (10:1) eluent. Unfortunately this only led to the recovery of the starting material (80%). The same procedure was also repeated using n-butylthiol in place of t-butylthiol, as it was thought that the n-butyl chain may be less sterically demanding allowing the reaction to proceed. This was not the case though and again the starting material (76%) was recovered.

At this stage it became apparent that there was a more fundamental reaction which we could try. A simple nucleophilic substitution reaction using acid to aid the loss of water and form the corresponding sulfide was a possibility (Scheme 29).



148

Scheme 29: Acid catalysed S_N1 reaction to form sulfide

This reaction worked well using TFA and gave **(148)** as an orange oil in 90% yield. The crude product was also clean and needed no purification. Confirmation that the sulfide had formed was evident in the IR spectra where the hydroxyl peak in the starting material was now absent. ^{1}H NMR spectroscopy also confirmed that the product had been formed due to the 1H, s, C<u>H</u>OH shifting form 5.85ppm in the starting material to 5.26ppm in the product. Final confirmation of the structure was achieved when after long term storage several small crystals formed in the storage tube. Utilising single crystal X-ray diffraction allowed us to elucidate the crystal structure (Figure 35).

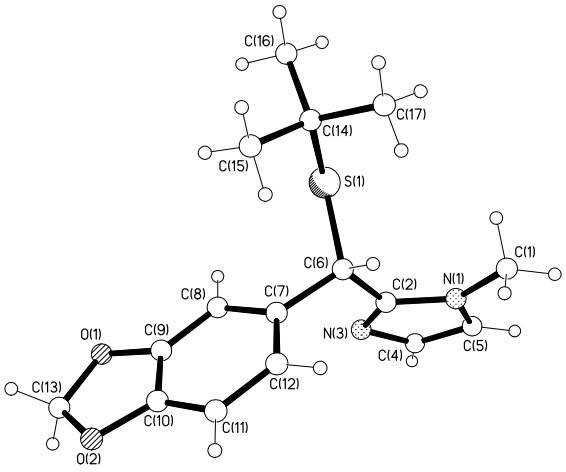


Figure 35: X-ray crystal structure of 2-(Benzo[1,3]dioxol-5-yl-tert-butylsulfanyl-methyl)-1-methyl-1*H*-imidazole

Following this success the same procedure was repeated with several other secondary alcohols to give a range of interesting sulfide analogues **(149-154)** (Table 7). Each new compound was isolated as a yellow-orange oil, as was found with the original product. Due to the possibility of gaining further X-ray crystal structures of these

novel sulfides a range of recrystallisation techniques were carried out in attempt to gain crystals but unfortunately no further crystals were isolated.

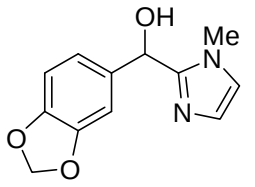
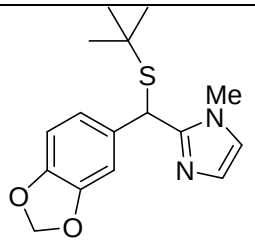
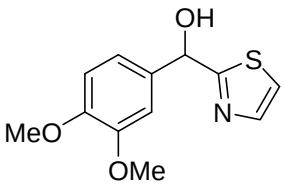
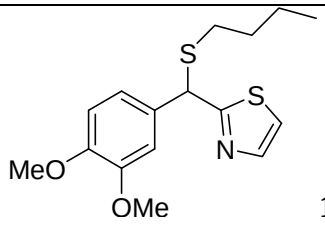
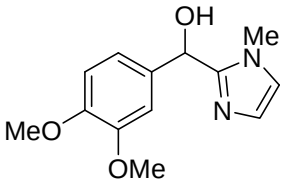
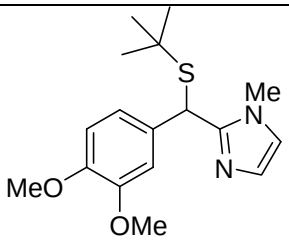
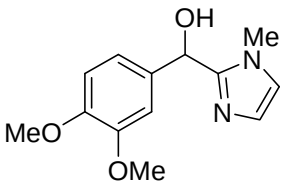
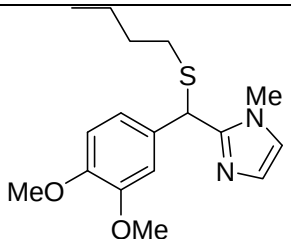
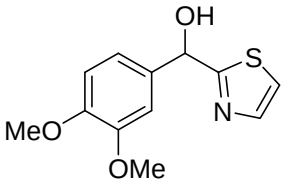
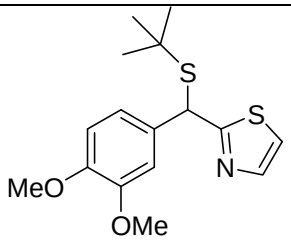
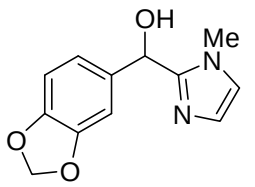
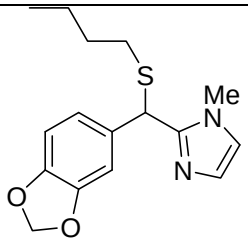
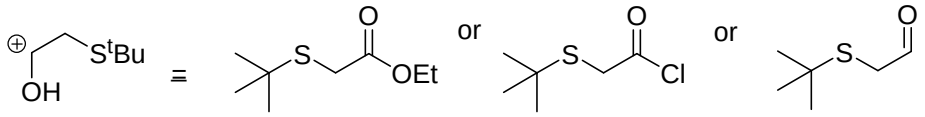
Alcohol	Thiol (2 eq)	Solvent	Time (h)	Sulfide	Yield (%)
	*t*-BuSH	$CHCl_3$	24	 **149**	90
	*n*-BuSH	$CHCl_3$	24	 **150**	96
	*t*-BuSH	$CHCl_3$	24	 **151**	99
	*n*-BuSH	$CHCl_3$	24	 **152**	95
	*t*-BuSH	$CHCl_3$	24	 **153**	98
	*n*-BuSH	$CHCl_3$	24	 **154**	92

Table 7: The range of sulfides formed from their corresponding secondary alcohols

2.3.3 – 'Synthon B'

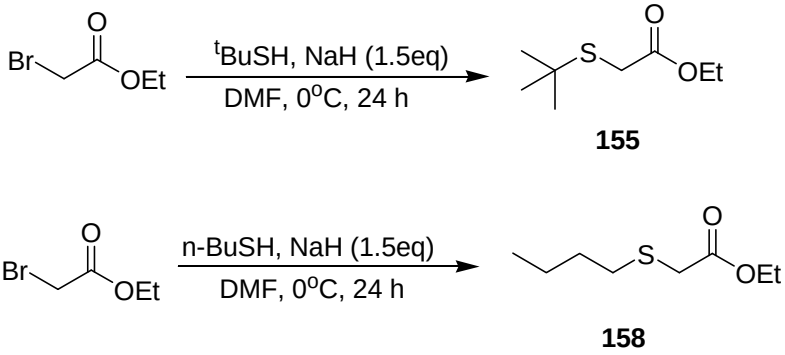
Once we had formed compound **(148)** and a range of analogues **(149-154)** we decided to investigate possible synthetic equivalents to 'synthon B' which could be used to complete the main carbon backbone structure of Aplidium trisulfide. There were several immediate options **(155-157)** and each compound had positives and negatives for their formation and use in the coupling reaction.



155 **156** **157**

Figure 36: Synthetic equivalents to synthon B

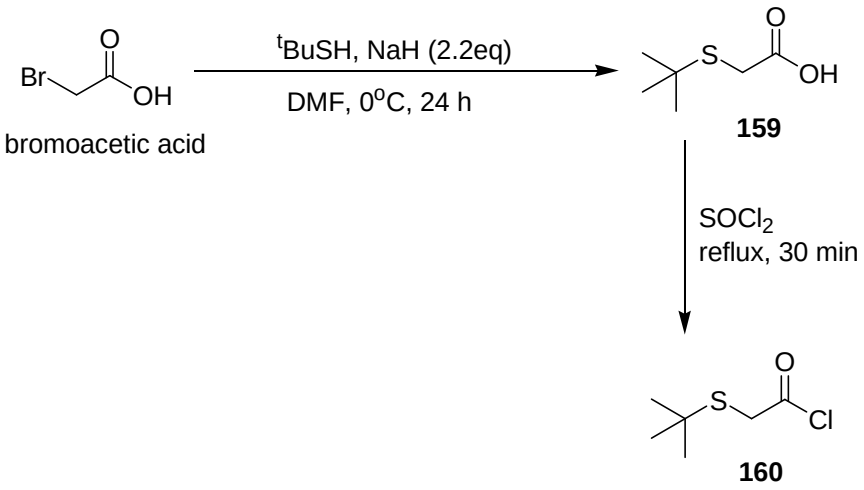
The ester was foreseen as the easiest synthetic target due to its chemical stability but probably the most un-reactive due to the non-favourable loss of EtO^- in the coupling reaction. Although this compound could prove to be less reactive at a later stage, due to the straight forward synthesis we went ahead and made a small batch of the β-t-butylsulfide ester **(155)** and also the n-butylsulfide analogue **(158)**.



Scheme 30: Formation of two different β-sulfide esters

The esters **(155)** and **(158)** were isolated as light yellow oils in good yields of 99 and 95% respectively. The crude product appeared clean in the ^{1}H NMR spectrum so no further purification was carried out.

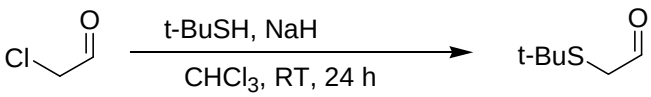
Formation of the acid chloride **(160)** was not quite as simple as forming the esters, but we managed to synthesise the acid chloride in two steps from bromoacetic acid as shown in scheme 31 via the corresponding carboxylic acid **(159)**.



Scheme 31: Formation of acid chloride via corresponding carboxylic acid

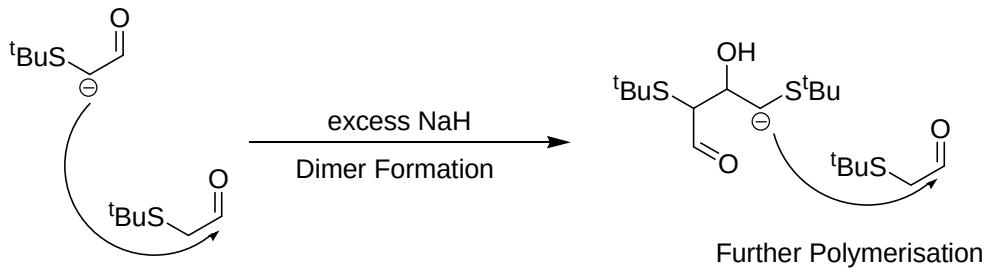
Formation of the acid chloride was confirmed by IR spectroscopy when the carbonyl band shifted from 1710 cm^{-1} to 1793 cm^{-1} indicative of the acid chloride carbonyl. ^{1}H NMR spectroscopy also confirmed the acid chloride had been formed, but we were unable to obtain a clean ^{13}C NMR spectrum and mass spectra due to the acid chloride hydrolysing back to the carboxylic acid.

Formation of the β-sulfide aldehydes proved to be challenging targets. One possible starting material was chloro-acetaldehyde but this was only available commercially in aqueous solution. Extraction of the acetaldehyde was carried out into chloroform and the extraction was confirmed by ^{1}H NMR spectroscopy. Transformation of the chloro-acetaldehyde into the β-sulfide aldehydes was then attempted using NaH (1.1eq) and thiol (1eq) but this failed to yield the desired product.



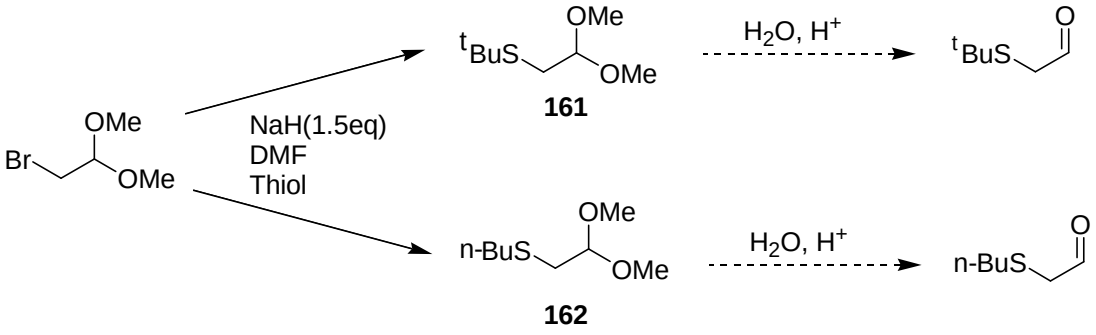
Scheme 32: Attempted formation of the β-sulfide aldehyde

Instead of the desired product a complex mixture was isolated which we were unable to purify by silica gel chromatography. We were therefore unable to determine what type of reaction had occurred but due to the large multiplet in the ^{1}H NMR spectra at 0.9 - 1.2 ppm characteristic of a t-butylsulfide, it led us to believe that a possible polymerisation had occurred between sulfide anions and other units of the reactive aldehyde.



Scheme 33: Possible polymerisation of sulfides

At this stage we thought it maybe sensible to look at using a protected form of the aldehyde as the aldehyde it self seemed to be too reactive. 2-Bromo-1,1-dimethoxy-ethane was commercially available so we decided to work on this building block. As previous, we used both n-BuSH and t-BuSH in the nucleophilic substitution. The substitutions were carried out giving good yields of compounds **(161)** and **(162)**, in 79% and 97% respectively.



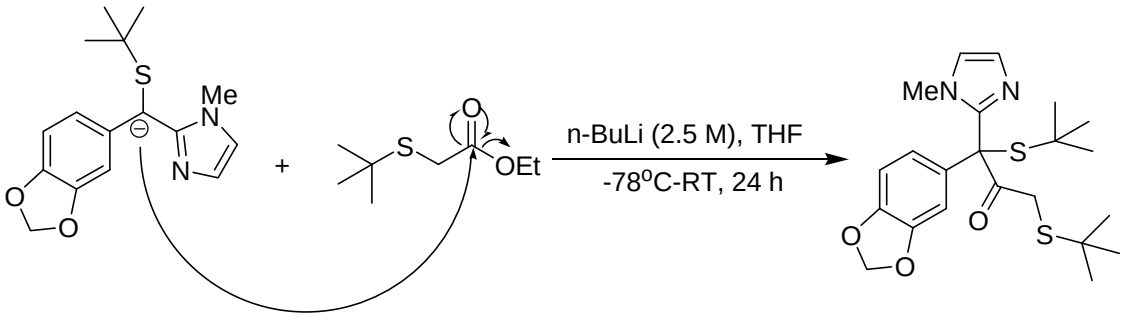
Scheme 34: Sulfide acetal formation and attempted Deprotection

Deprotection of the acetal was attempted using aq.HCl in MeOH but the reaction yielded a complex mixture of products. Silica gel column chromatography was carried out but unfortunately none of the desired product could be isolated.

2.3.4 – Convergent Step

Now that we had a range of synthetic equivalents it was decided to attempt the possible coupling reactions to complete the main carbon backbone structure of aplidium trisulfide.

The first attempted convergent step was between the imidazole containing sulfide and the t-butylsulfide ethyl ester. The formation of the anion was carried out using n-BuLi (2.5 M, 1.1eq) in THF at -78^{o}C. The ester was then added and the reaction mixture was allowed to return to room temperature and stirred overnight. The reaction yielded a crude orange oil which was purified by silica gel column chromatography. Unfortunately, even though TLC suggested the presence of new products, attempts at isolating these proved unsuccessful and only the aromatic containing sulfide was re-isolated.

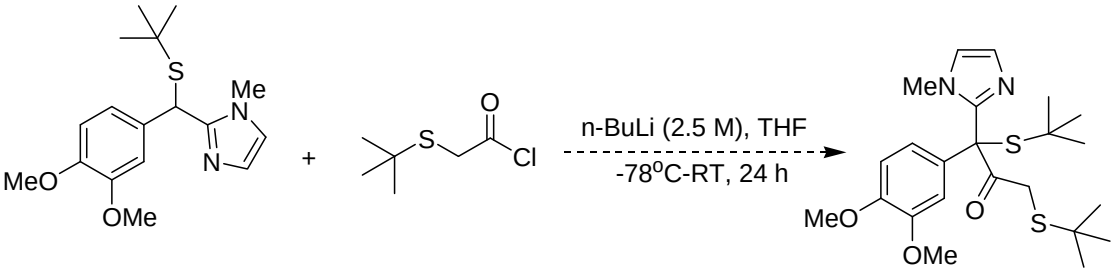


Scheme 35: Attempted coupling of the sulfide anion with sulfide ester

This work was repeated several times taking care to ensure anhydrous conditions while using a range of the previously synthesised analogue compounds but again no new products could be isolated in any case.

We thought the possible low reactivity of the ester may be a reason for the reaction not yielding the clean desired product so we next decided to react the acid chloride containing sulfide with the carbanion in the hope that this would be much more reactive and form the desired product.

The reaction was carried out in the same way as previously attempted using a slight excess of n-BuLi to form the carbanion and then adding the acid chloride while stirring at -78^{o}C. At this stage we were very keen to form compound **(163)** as this would be an exciting and key step towards synthesising aplidium trisulfide.



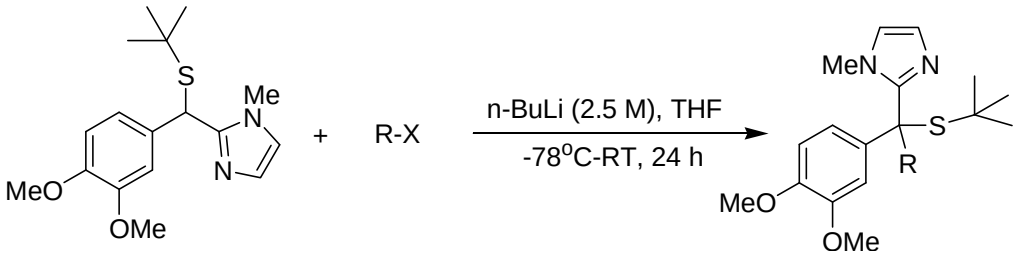
163

Scheme 36: Attempted acid chloride coupling

To our disappointment only the aromatic containing sulfide was recovered but no other products were isolated even after careful column chromatography. This led us to believe that either the anion wasn't being formed, or stabilisation of the anion meant that this was not a reactive intermediate. Further work would need to determine if this carbanion could be formed.

2.3.5 – Sulfide Alkylation

As the convergent synthesis was not proceeding as we had hoped it was decided to investigate some other interesting alkylations on the proposed sulfide anion (Scheme 37). Methyl iodide seemed an obvious way to determine whether or not the anion was being formed, as well as demonstrating the carbanion reactivity.



Scheme 37: Sulfide anion alkylation

We therefore attempted to create the anion in exactly the same way as previously discussed, but this time we reacted the anion with methyl iodide. To our surprise the reaction yielded the desired product on our first attempt in 90% yield. The product displayed a new 3H, s at δ 2.17 in the ^{1}H NMR spectrum. HRMS confirmed the product as $C_{18}H_{27}N_2O_2S$ m/z 335.1788.

The methyl iodide reaction was repeated on the piperonal derived substrate and yielded 70% product. Further reactions were carried out using allyl bromide and benzyl bromide to investigate how sterics would affect the carbanions reactivity. This allowed us to form a range of novel compounds (Table 8).

Unfortunately both the benzyl bromide and allyl bromide additions yielded crude mixtures which appeared impure by ^{1}H NMR spectroscopy. Column chromatography was therefore carried out to isolate the pure compounds and further characterise the products. This led to poor yields for both products.

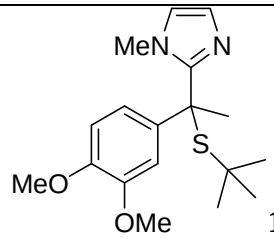
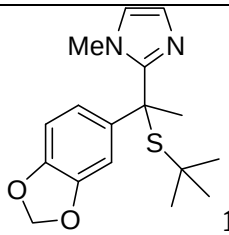
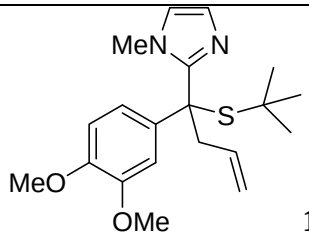
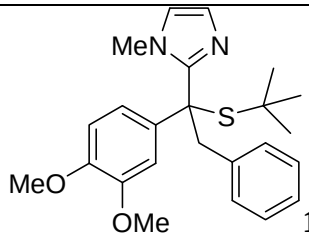
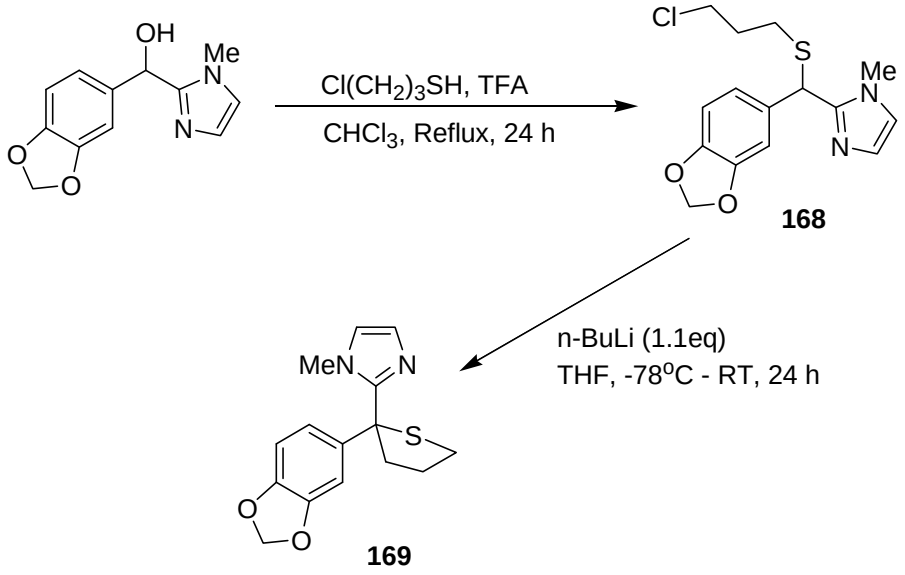
Compound	Yield (%)
 **164**	90
 **165**	70
 **166**	11
 **167**	8

Table 8: Sulfide alkylation products and their yields

2.3.6 – Attempted Synthesis of Cyclic Mono-Sulfide

Another interesting synthetic step that we wanted to investigate was the use of an intramolecular cyclisation reaction to form cyclic monosulfides such as **(169)**. We attempted to make the target compound by firstly synthesising **(168)** using 3-chloropropane-1-thiol and our previously developed procedure for forming sulfides. The sulfide **(168)** was isolated in 85% yield after silica gel column chromatography.

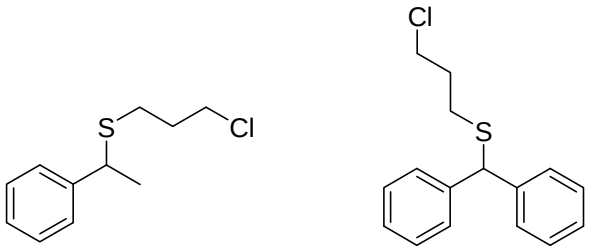


Scheme 38: Attempted formation of cyclic mono-sulfide

Cyclisation was then attempted using n-BuLi (2.5 M, 1.1eq) to deprotonate at -78^{o}C. The reaction was then allowed to warm to room temperature and stirred for a further 24 h. On work up the reaction yielded a dark orange oil which appeared to be a mix of many different products visible by TLC and ^{1}H NMR spectroscopy. Column chromatography proved challenging as the separation between spots was minimal. Repeat work was attempted increasing the solvent volume and adding the n-BuLi dropwise over 1 hour. This again yielded a complex mixture and after several attempts at purification this was discontinued as no clean products could be isolated.

Two further compounds **(170)** and **(171)** were synthesised in an attempt to study the cyclisation further. It was thought that the phenylethanol derived substrate **(170)** may undergo the cyclisation faster due to less steric hindrance, and the diphenylmethanol

substrate may further show us the effects of anion delocalisation. It was found that neither compound readily cyclised when using n-BuLi to deprotonate, this could possibly be due to the delocalisation of the anion once formed around the benzene ring.

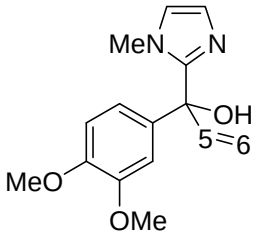


170 **171**

Figure 36: Two further chloropropanethiol compounds

2.4 - Less Hindered Route

Due to the previously discussed problems with introducing functionality at the C5 and C6 positions of the tertiary alcohol, it was decided that other possible synthetic routes may prove more fruitful.



Whilst looking through the literature a paper by Hibert[87] described how a Friedel-Craft Acylation could be carried out to form the ketone **(174)**. This type of intermediate would be useful for our synthesis of aplidium trisulfide analogues. It could be envisaged that chlorine would be substituted for a sulfide group using tBuSH, and that an imidazole nucleophile could be added to the ketone forming the tertiary alcohol **(172)** with a new quaternary centre. The tertiary alcohol **(172)** would be absent of any functionality at the 5-position where the hydroxyl group is present in aplidium trisulfide), but this route may allow us to investigate the trisulfide forming step before having the additional consideration of the 5-hydroxy group.

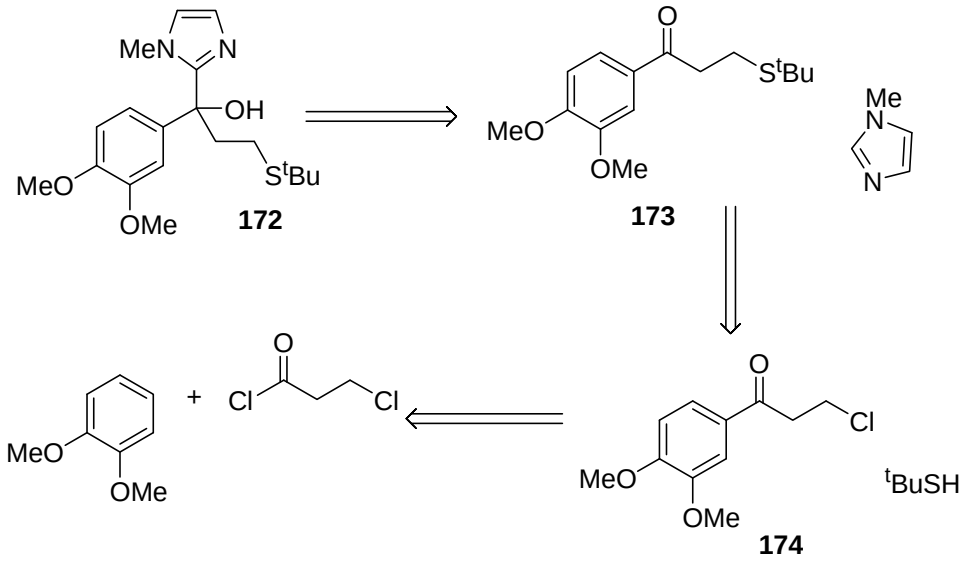
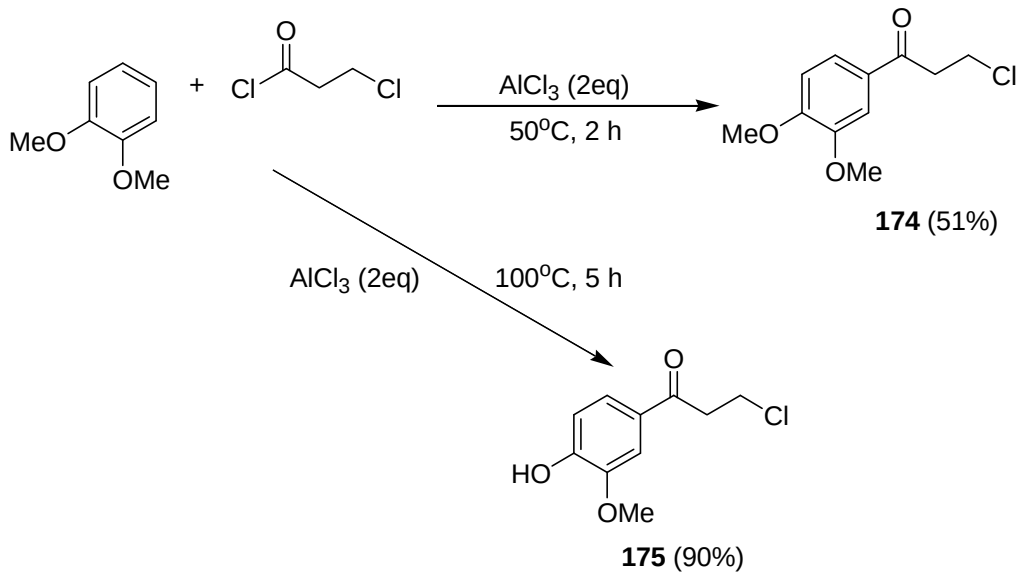


Figure 37: Proposed new route to key intermediate **(172)**

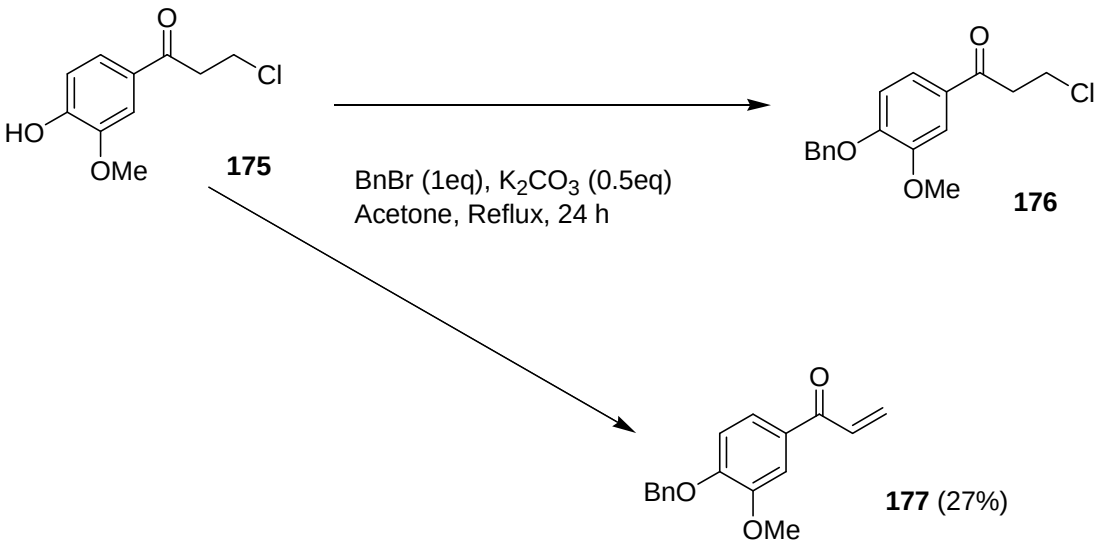
The Friedel-Craft acylation was not as straight forward to carry out as we had hoped. Reacting the acid chloride and veratrole at 50°C for 2 hours gave just 51% yield of product **(174)** upon work up. We suspected the reaction yield was low due to a dark black sticky residue which coated the reaction flask making it difficult to handle and extract.

The reaction was repeated at 100°C for 5 hours to determine whether a better yield could be gained. Unexpectedly, workup of the reaction mixture yielded 90% of the closely related *para*-demethylated product **(175)**. This was evident due to the O-H stretch in the IR spectrum at 3392cm^{-1} and the absence of a CH_3 peak at δ ~3.7 in the ^{1}H NMR spectrum. HRMS confirmed the loss of a single methyl group $C_{10}H_{11}ClO_3$ found m/z 214.0391.



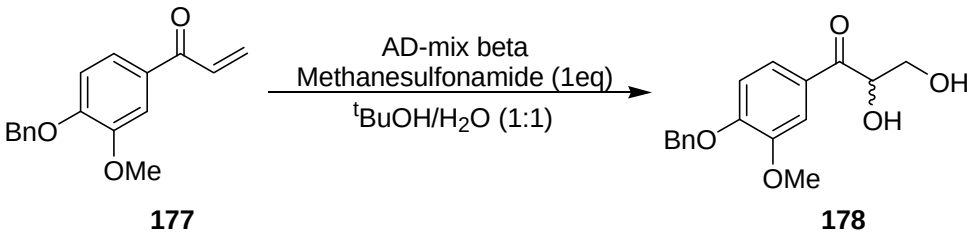
Scheme 39: Friedel-Craft Acylation products

Due to the much improved yield of **(175)** we decided to carry this product through our originally devised route. It was first necessary to carry out protection on the *para*-alcohol. A benzyl protection was chosen as this had previously been carried out using readily available benzylbromide, potassium carbonate as a base and refluxing in acetone for 24 hours.



Scheme 40: Unexpected benzyl protection product **(177)**

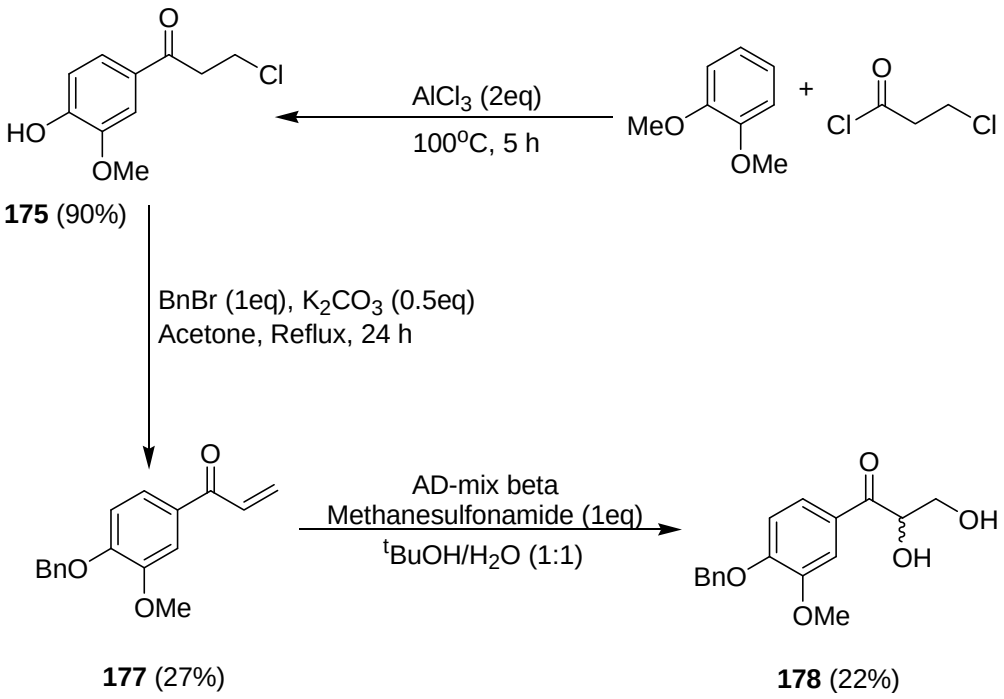
Work up of the reaction yielded a mixture of products as visible by ^{1}H NMR spectroscopy. Column chromatography was carried out on silica gel using a light petroleum: ethyl acetate (10:1) eluent. This yielded the enone **(177)** in 27% yield. This once again was not our intended product but led us to rethink our synthetic route. It was therefore decided to attempt a Sharpless dihydroxylation on the enone. The reaction was attempted using the commercially available AD-mix beta which is required at 1.4g per mmol of substrate. One equivalent of methanesulfonamide was also added to aid the hydrolysis step.



Scheme 41: Sharpless dihydroxylation

Upon workup the reaction yielded a crude mixture which was purified by column chromatography on silica gel. This yielded the dihydroxylated product in 22% yield. The dihydroxylated product showed a strong broad absorbance at 3389cm^{-1} in the IR spectrum and the expected 3 protons at δ 3.6, 3.9 and 5.0 ppm in the ^{1}H NMR

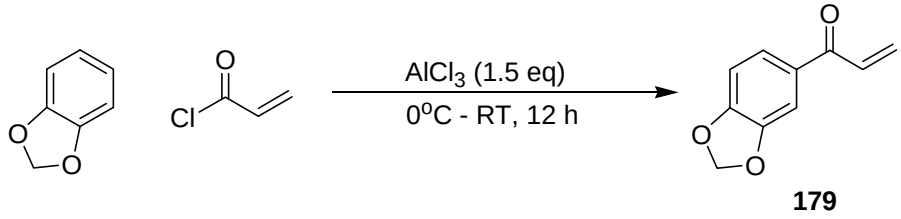
spectrum in place of the previously observed vinyl protons. HRMS confirmed the product as $C_{17}H_{18}O_5$ with m/z 302.1151.



Scheme 42: Three step synthesis of dihydroxylated product

The three step process was repeated in attempts to form more of **(178)**. The plan was then to carry out a diol protection and investigate whether an imidazole anion would attack the carbonyl group as previously demonstrated for aldehydes. It was found that the dihydroxylation step was very unrepeatability and due to the low yields of the dihydroxylated product using the three step process (Scheme 42) a more efficient route was sought.

Direct formation of the enone was next investigated using the benzo[1,3]dioxole analogue and reacting with 1 equivalent of acryloyl chloride.

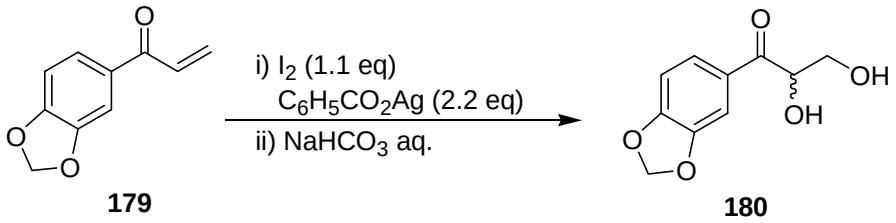


Scheme 43: Friedel-Craft enone formation

The addition of $AlCl_3$ to the reaction mixture was this time carried out at 0°C, and then the reaction was allowed to warm to RT overnight. This method worked much better than the previously used refluxing methodology and upon workup yielded the desired product in 91% yield. Recrystallisation of the product in diethyl ether removed low level impurities that were present in the ^1H NMR spectrum. The product exhibited a strong carbonyl stretch at 1737 cm^{-1} in the IR spectrum.

As small amount of dihydroxylation product had been previously been isolated it was decided to briefly repeat this work on the enone substrate **(179)**. This was unsuccessful and resulted in reisolation of the starting material as had been the case with repeat attempts at forming **(178)**.

Another well known method of forming diols is the Prévost reaction.[89] 2 Equivalents of silver carboxylate is needed to form the trans dicarboxylate which can then hydrolysed to the trans-1,2-diol under basic conditions. This was therefore attempted on the enone **(179)** using the readily available reagents iodine and silver benzoate in toluene.

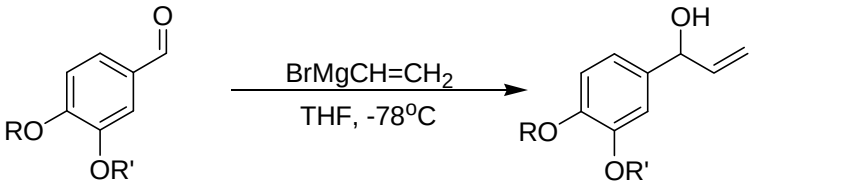


179 **180**

Scheme 44: Attempted Prévost reaction

Unfortunately the reaction yielded quantitative recovery of the starting material. The Woodward-Brutcher modification of the Prévost reaction[90] was also attempted with the addition of aqueous acetic acid. It was thought that this method may be more reproducible and less dependant on dry reaction conditions. The modification also has the benefit of only requiring 1 equivalent of silver benzoate as the orthocarboxylate is directly hydrolysed to give a cis-1,2-diol. Unfortunately the modified conditions also led to recovery of starting material.

At the same time as studying reactions of the electron deficient olefin in the enone system we decided to investigate reactions of allylic alcohols. This would allow us to understand whether certain reactions attempted on the tertiary alcohol substrates could be carried out on less hindered allylic systems. The allylic alcohols **(105)** and **(106)** were therefore synthesised from the corresponding aldehydes using a Grignard reaction in good yields of 95 and 89% respectively.

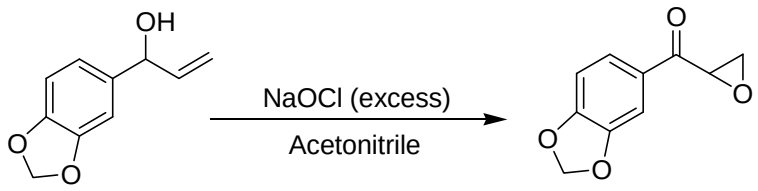


181: R = R' = Me (95%)
182: R + R' = -CH_2- (89%)

Scheme 45: Grignard to form allylic alcohol

Epoxidation of the alkene was attempted using mCPBA as had previously been performed on the tertiary more hindered alcohols. The mCPBA reaction was carried out under the exact same conditions as previously used. It was again found that the reaction yielded a complex mixture of products as observed by ^{1}H NMR spectroscopy. Purification by silica gel chromatography was attempted but this led to further impure uncharactorisable fractions. It was postulated that the epoxidation reaction was occurring but the hydroxyl group may be further reacting via a Payne type rearrangement or undergoing further intermolecular reactions with other epoxide containing molecules to form a complex mixture of products.

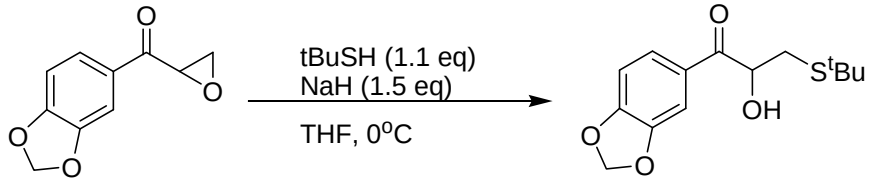
A further reaction which was therefore tried was a multiple oxidation using sodium hypochlorite solution. This was carried out using excess oxidising agent in acetonitrile. This was to aid the solubility of the substrate. Upon work up the reaction yielded the epoxy-ketone **(183)** in 71% yield.



182 **183** (71%)

Scheme 46: Sodium hypochlorite oxidation

Oxidation of the allylic alcohol to the epoxide was confirmed by ^{1}H NMR spectroscopy where the expected protons at. 2.9 (1H, dd, *J* = 2.6, 6.4 Hz, CHC<u>H</u>H), 3.0 (1H, dd, *J* = 4.6, 6.4 Hz, CHCH<u>H</u>), 4.1 (1H, dd, *J* = 2.6, 4.6 Hz, C<u>H</u>CH$_2$) were clearly observed. Oxidation of the hydroxyl group was confirmed by IR spectroscopy as the product showed a strong carbonyl stretch at 1678 cm^{-1}. Final confirmation was obtained from the FAB-HRMS with a peak observed at m/z 210.0759 corresponding to $C_{10}H_{12}NO_4$ the M+NH_4^+ ion.

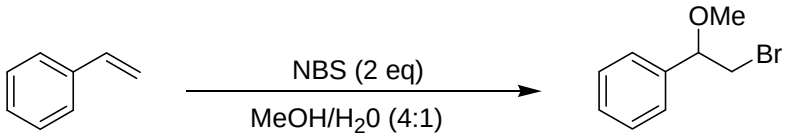


183 **184**

Scheme 47: Attempted epoxide opening reaction

Attempt at ring opening the epoxide proved challenging. The chosen conditions used sodium hydride to firstly deprotonate the t-butyl thiol in a solution of THF at 0°C. The keto-epoxide **(183)** was then added drop wise in a solution of THF and the reaction mixture allowed to warm to RT. Work up yielded a mixture of products as visible by ^{1}H NMR spectroscopy. Attempts to isolate a major product using column chromatography and preparative TLC proved unsuccessful. A possible problem with this reaction may be the reactivity of the sulfur anion which was formed, which could have either reacted with the epoxide as we had hoped, or possibly the ketone group. The epoxide could also have ring opened at the terminal or secondary site giving further mixtures of products.

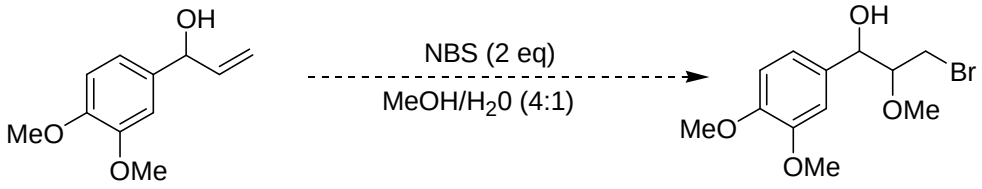
Another reaction of interest to us was in using a bromination agent to form a bromonium ion from an alkene. Carrying the reaction out in alcohol can reportedly yield the corresponding alkoxybromide.[82] This was initially attempted using N-bromosucinimide on a styrene substrate with methanol/water (4:1) as a mixed solvent.



185

Scheme 48: Methoxybromide formation from styrene

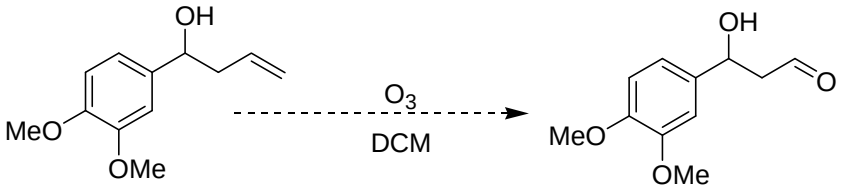
The reaction afforded an 80% yield of the desired methoxybromide which was confirmed by comparable data to that previously reported by Phukan.[82] Disappointingly repeating the exact procedure on the allylic alcohol **(181)** only yielded starting material. This reaction was repeated to confirm our findings but this time carrying out the reaction over an extended period of 24 hours instead of the 2 hours used for the styrene substrate. Unfortunately only starting material was recovered confirming this allylic alcohols low reactivity to NBS.



181 **186**

Scheme 49: Attempted methoxybromide formation

Ozonolysis had previously been attempted on the tertiary alcohol structure with little success. This was assumed to be due to the compatibility of the imidazole group when trying to oxidise only the terminal alkene. To study this further we synthesised the alcohol **(187)** from the corresponding aldehyde using allylmagnesium bromide. This was achieved in a good yield of 79%.



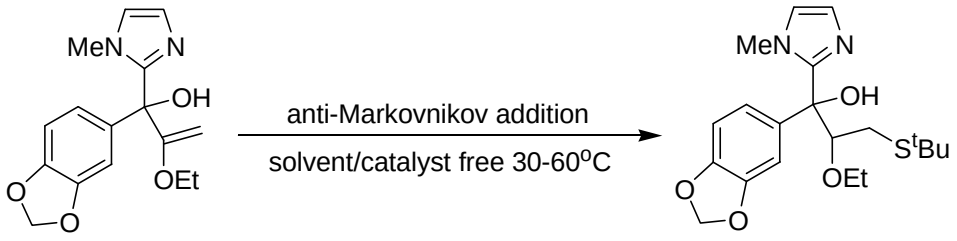
187 **188**

Scheme 50: Ozonolysis of the allyl Grignard product

The ozonolysis reaction was then carried out in DCM. It was found to be difficult to control the amount of O_3 entering the reaction flask by tuning the flow rate as a theoretical stoichiometric amount of O_3 yielded starting material. For this reason the second reaction was left running for 5 minutes before quenching with DMS and carrying out TLC analysis on the mixture. The TLC plate was visualised under a UV light source where the mixture now appeared as a long streak running 2/3rds the

length of the plate. As there were no identifiable spots present it was decided not to attempt column chromatography purification.

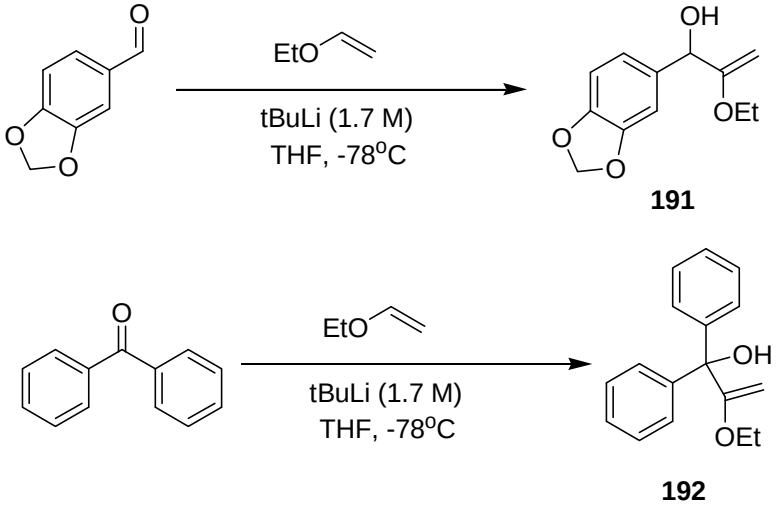
A recent paper by Lin *et al*[91] demonstrated the anti-Markovnikov addition of thiols to vinyl ethers. This was of interest to us for introducing sulfur into the carbon backbone structure in the proposed reaction scheme 51.



189 **190**

Scheme 51: anti-Markovnikov thiol addition

Compound **(189)** was therefore targeted as a useful synthetic intermediate although the initially trial reactions were carried out on piperonal and benzophenone substrates. One equivalent of t-BuLi (1.7 M) was used to form the ethylvinyl ether anion at -78°C in THF. Addition of the carbonyl compound was carried out at -78°C before allowing the reaction mixture to gradually warm back to room temperature. The reaction of both the piperonal and benzophenone substrates proceeded well using this procedure yielding the corresponding alcohols in 61% **(191)** and 77% **(192)** yield respectively.



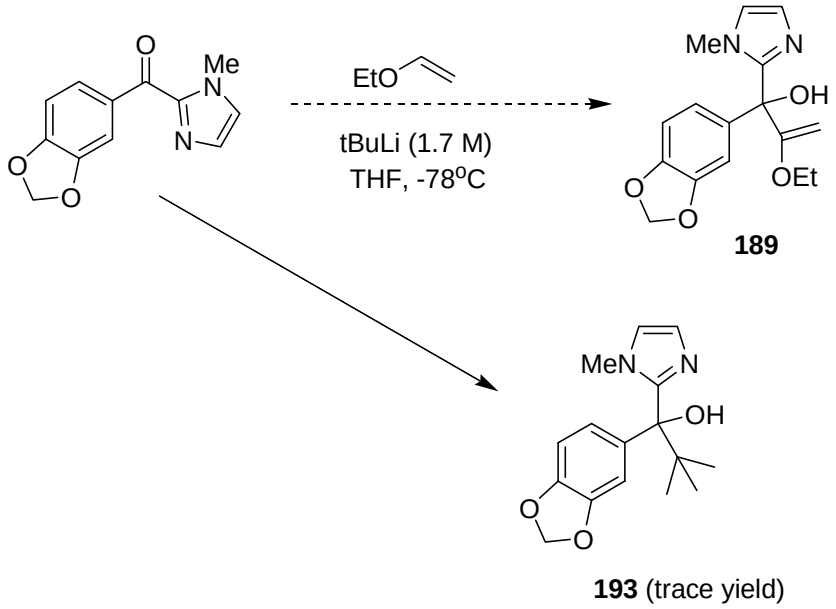
191

192

Scheme 52: Ethylvinyl ether additions

Following the successful ethylvinyl ether additions on both an aldehyde and ketone substrate we were relatively confident that the reaction would proceed on our imidazole containing ketone substrates. We carried out the reaction under the same pre-determined conditions in an attempt to form the target compound **(189)** but after the initial work up it was evident from the ^{1}H NMR spectrum that the reaction had not proceeded as cleanly as previously observed.

The crude mixture was therefore purified by silica gel column chromatography using light petroleum:ethyl acetate (10:1) eluent. This afforded a trace yield of a colourless oil. Interestingly, IR spectroscopy suggested the presence of a hydroxyl group due to a stretch at 3482cm^{-1}, and ^{1}H NMR spectroscopy suggested the presence of a t-butyl group due to the peak at 1.18 ppm which integrated to approximately 9 protons. Due to the presence of the correct number of aromatic protons we tentatively assign the structure of the *t*-butyl addition product **(193)**.



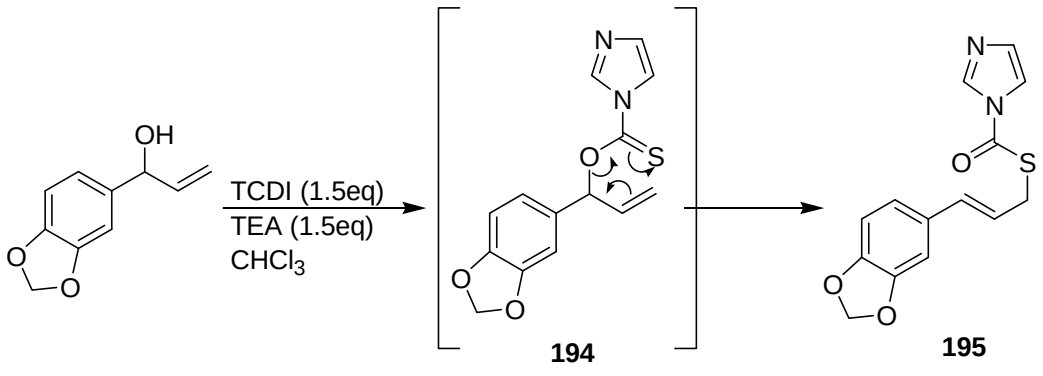
Scheme 53: Attempted ethylvinyl ether addition to an imidazole containing ketone

Unfortunately time did not allow for an investigation into thiol additions to the earlier synthesised vinyl ethers **(191)** and **(192)** as planned due to more promising work in the area of sulfur containing [3,3] sigmatropic rearrangement.

2.5 - [3,3] Rearrangements

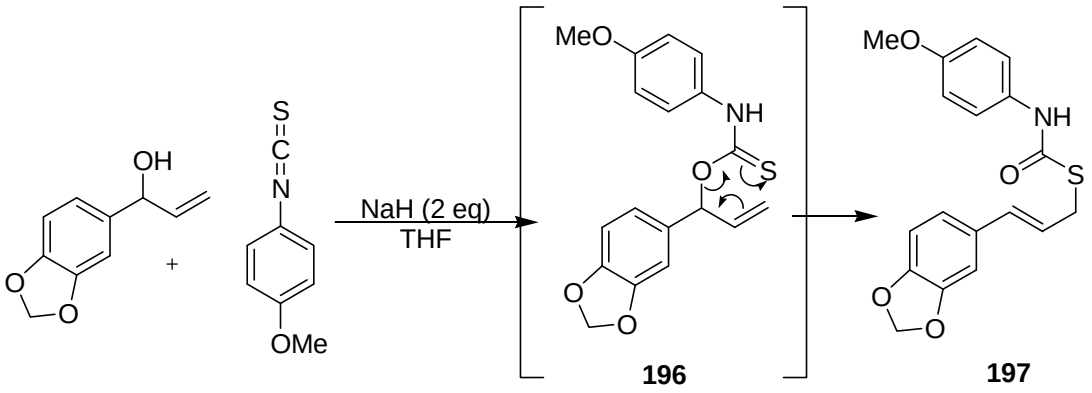
The Claisen rearrangement[23] is well known as one of the most powerful reactions for the stereoselective formation of carbon-carbon bonds. Although the Claisen rearrangement has been widely studied, the thio-Claisen rearrangement has had limited attention since it was first reported in 1962 by Kwart and Hackett.[92] We decided to investigate the use of a thio-Claisen rearrangement as a practical tool for introducing sulphur to an allylic alcohol substrate.

Our investigation initially began using the widely available reagent thiocarbonyl diimidazole (TCDI) as a source of sulfur. The corresponding allylic alcohol was stirred with an excess of TEA in chloroform before adding the TCDI. It was found that at room temperature the reaction yielded starting material after 48 hours, but when the reaction was refluxed for 24 hours a distinct product spot was observed on the TLC plate. Aqueous work-up was followed by silica gel column chromatography yielding a yellow solid with a mp = 184-185°C. The new product exhibited a new carbonyl stretch at 1600cm^{-1} in the IR spectrum and the absence of the original O-H was also noted. ^{1}H NMR spectroscopy suggested the formation of **(195)** due to two new alkene protons present at 6.04 and 6.55 ppm. A coupling constant of 15.6Hz indicated that the transalkene had been formed. One anomaly that was noticed in the NMR spectra of the product was that no imidazole protons or carbons were observed, suggesting that the imidazole group may not be present in the product. We therefore eagerly awaited the mass spectrometry results which we hoped would help deduce the structure. Unfortunately mass spectrometry results proved inconclusive and a major ion was not observed. We therefore postulate that the reaction went via the thionocarbamate intermediate **(194)** and we tentatively assign the product as **(195)**.



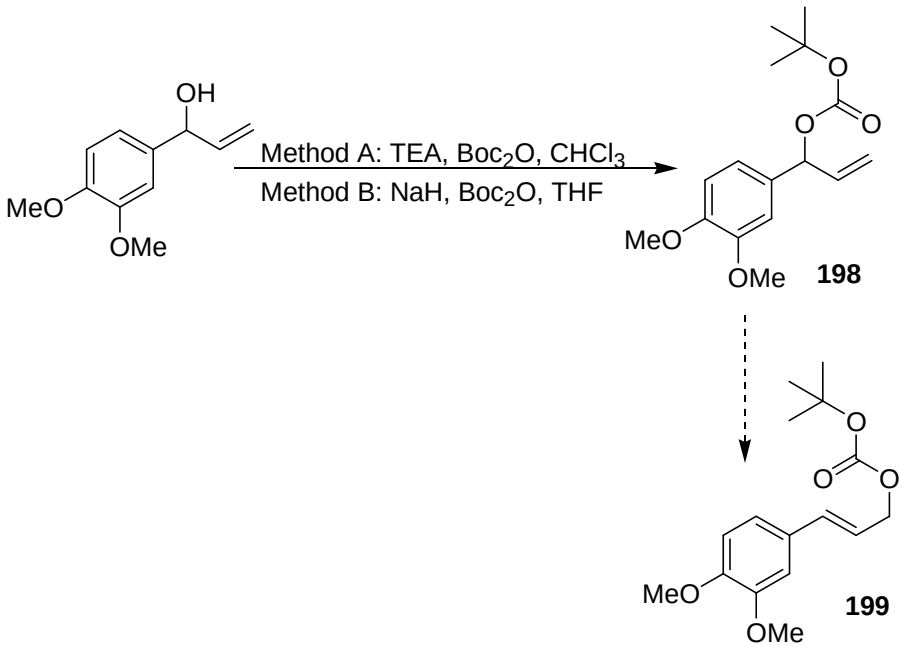
Scheme 54: thio-Claisen reaction using TCDI

A similar reaction utilising an isothiocyanate was also carried out. This was initially attempted using the same TEA/chloroform procedure as previously used but this was unsuccessful and yielded starting material even after 48 hours refluxing. We were intrigued as to why the reaction would not precede using an isothiocyanate under these conditions so attempted a further reaction using sodium hydride to deprotonate the allylic alcohol in THF at 0°C. The isothiocyanate was then added and the reaction allowed to return to room temperature overnight. An aqueous work up followed by recrystallisation yielded a white solid with mp = 239-241°C. The ^{1}H NMR spectrum exhibited a NH proton at 6.95 ppm as a broad singlet. The two alkene protons were again observed at 6.00 and 6.40 ppm with a 15.6 Hz coupling constant. HRMS confirmed the product as having the formula $C_{18}H_{18}NO_4S$ and m/z 344.0948 leading us to assign the structure **(197)**.



Scheme 55: thio-Claisen rearrangement using isothiocyanate

One final reaction that was attempted was the rearrangement of a similar carbonic acid intermediate **(198)**. It was thought that this may undergo a similar rearrangement through a cyclic transition state to form the transalkene **(199).** The rearrangement was attempted using Boc_2O and both the previously used reaction conditions. Unfortunately in both cases the suggested intermediate was isolated and the rearrangement to form **(199)** was not observed.



Scheme 56: Attempted carbonic acid rearrangment

The thio-Claisen rearrangement had worked and sulfur had been successfully incorporated forming **(197)**. Further work to functionalise the new double bond in **(197)** is needed to develop the synthesis further. It is not clear why the attempted Claisen rearrangement of **(198)** failed, but it may be due to the higher stability of the C=O bond in the carbonate ester compared to the relatively weak C=S bond in the thionocarbamate **(196)**.

2.6 - Conclusions

Throughout this research the most challenging aim has been to work towards the total synthesis of aplidium trisulfide. Although the complete total synthesis was not achieved I believe the research carried out has made a real advancement toward this previously unattempted target molecule.

The work initially afforded a catalogue of key secondary alcohol compounds containing the imidazole group and aromatic substituents present in aplidium trisulfides structure. These compounds were successfully oxidised using a manganese dioxide procedure which proved to be high yielding and a reproducible process which led to the synthesis of a variety of closely related ketones. A Grignard reaction was then utilised to form a range of allylic alcohols. This step demonstrated the formation of the hindered quaternary carbon centre which is present in the main carbon backbone structure of aplidium trisulfide.

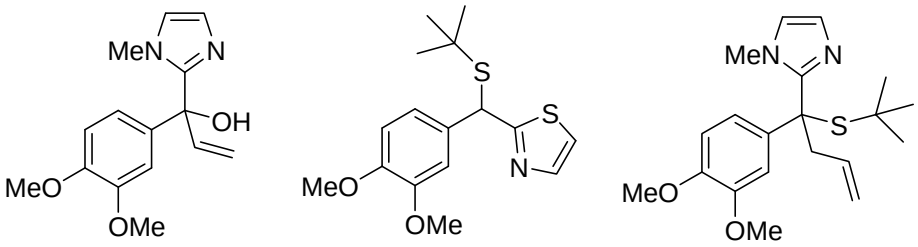


Figure 38: Synthetic advancements toward aplidium trisulfide

Difficulties in the synthesis arose when attempting to functionalise the olefin of the carbon backbone structure. This proved to be a major hurdle and we are unable to report an effective way to gain functionality at this site. Whilst the initial proposed route became hampered due to unsuccessful attempts at functionalisation, this led to a number of new and diverse ideas.

Going back to the secondary alcohol stage allowed us to rethink our proposed synthesis. At this stage we came up with a more convergent synthesis towards aplidium trisulfide and this led us to introduce sulfur into the structure at an earlier stage. A range of butylthioether compounds were synthesised. The presence of the butylthioether was to facilitate the formation of the trisulfide ring during the proposed

final step. t-Butylthioether groups have previously been shown to react with a range of sulfur chlorides and form polysulfide ring. So the introduction of a thioether was a key synthetic step.

Synthesis of both ester and acid chlorides containing a thioether group was completed successfully and these compounds were necessary for the convergent step. Unfortunately the proposed convergent step proved unsuccessful which was disappointing due to the highly desired product.

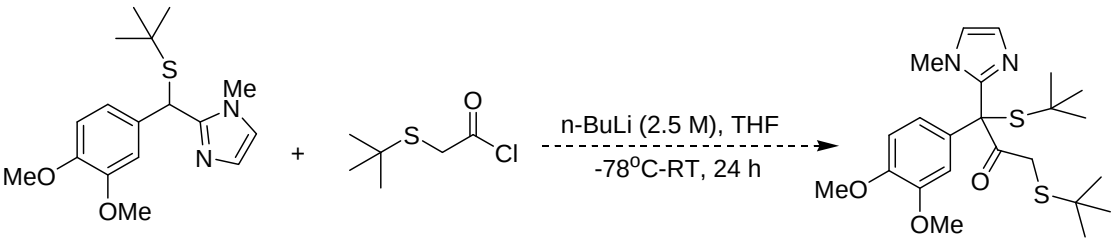


Figure 39: Unsuccessful convergent step

More successful work followed where we demonstrate that a carbanion can be formed adjacent to the sulfur atom and a range of alkylhalides could be reacted with the anion to form a quaternary centre. We discovered that steric hindrance had a large effect, reducing the yield of sterically demanding products.

Problems were also encountered when attempting to form thioketone compounds due to their inherently instability. This led us to investigate the use of organometallic chemistry in forming stabilised thioketone metal complexes. Isolation of the bright purple thiobenzophenone-tungsten complex was successful and proved that hindered ketones could be used in this type of reaction, but due to the extremely poor yields our direction moved away from this exciting avenue of research.

Finally we embarked upon a new “less hindered” synthetic route. This was designed to get around the problems previously encountered when trying to functionalise a sterically hindered olefin. At this stage of the research time was short and many reactions were tried unsuccessfully without further repeat work or optimisation. This would be an area where further research may prove fruitful. Ethylvinyl ether additions to benzaldehyde type compounds were not fully utilised and it would be interesting to investigate the use of thiol additions to vinyl ether containing compounds.

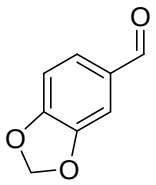
Experimental

3.1 - General Information

Infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Thin film spectra were recorded using dichloromethane to load the samples onto a sodium chloride plate. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively using a Bruker DPX 400MHz instrument using $CDCl_3$ as the solvent unless otherwise stated. ^{1}H and ^{13}C NMR shifts are reported in ppm using tetramethylsilane as the internal reference. Mass spectra were recorded using a Jeol-SX102 instrument, using electron impact (EI) or fast atom bombardment (FAB) techniques, or by the EPSRC national mass spectrometry service at the University of Wales, Swansea, using electrospray (ES) techniques. Melting points were recorded using an Electrothermal-IA 9100 melting point instrument. Chromatographic purification was carried out using Merk-Kieselgel 60H silica gel as the absorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium backed plates and were observed under UV radiation of wavelength 254 nm or via staining with a solution of phosphomolybdic acid (PMA) in ethanol and then drying. Reactions requiring anhydrous conditions were carried out using glassware dried overnight at 130^{o}C, freshly distilled solvents and done under an atmosphere of nitrogen unless otherwise stated. Light petroleum was distilled from calcium chloride. Dichloromethane and ethanol were distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium using benzophenone as an indicator. All other solvents were used as obtained. Aqueous work-ups were carried out using de-ionised water.

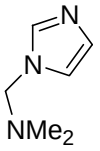
3.2 – Synthetic Procedures

Preparation of benzo[1,3]dioxole-4-carbaldehyde [60]



Piperonyl alcohol (7.61 g, 50 mmol) and PDC (9.41 g, 25 mmol) were stirred in DCM (100 ml) at 25°C for 24 h. Diethyl ether (100 ml) was then added and the solution filtered through a pad of celite which was further washed with diethyl ether (2 x 50 ml). The organic filtrate was then evaporated to dryness yielding 6.13 g (82%) of a white solid; mp = 34-35 °C (lit.[1] mp = 36 °C); ν_{max}(film)/cm^{-1} 1668 (C=O), 1621, 1597, 1494, 1447, 1417, 1273, 1094, 1034, 927, 864, 811, 785; δ_H (400 MHz $CDCl_3$) 5.96 (2H, s, C$\underline{H}_2$), 6.85 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 7.24 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 7.32 (1H, dd, *J* = 1.6, 8.0 Hz, C$\underline{H}_{arom}$), 9.72 (1H, s, C$\underline{H}$); δ_C (100 MHz $CDCl_3$) 102.1 (CH_2), 106.9 (CH), 108.4 (CH), 128.7 (CH), 131.9 (quat), 148.7 (quat), 153.1 (quat), 190.4 (CO).

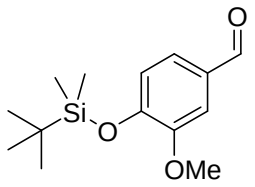
Preparation of imidazol-1-ylmethyldimethylamine [61]



Imidazole (17.02 g, 250 mmol) and dimethylamine hydrochloride (20.64 g, 250 mmol) were dissolved in water (50 ml). Conc. HCl was added to achieve pH~4. Aq. formaldehyde (22.3 ml, 300 mmol) was then added and the reaction was stirred for 24 h. The mixture was then basified with 20% KOH solution and extracted with DCM (3 x 100 ml). The combined organic layers were then dried over $MgSO_4$ and evaporated to dryness yielding 26.78 g (86%) of a colourless oil; ν_{max} (film)/cm^{-1} 3107, 2942, 2831, 1504, 1455, 1214, 1074, 1050 cm^{-1}; δ_H (400 MHz $CDCl_3$) 2.17 (6H, s, 2 x C$\underline{H}_3$), 4.56 (2H, s, C$\underline{H}_2$), 6.88 (1H, t, *J* = 1.2 Hz, C$\underline{H}$), 6.95 (1H, t, *J* = 1.2 Hz, C$\underline{H}$),

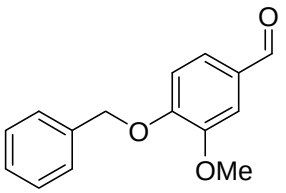
7.40 (1H, s, C<u>H</u>); δ_C (100 MHz $CDCl_3$) 41.8 (2 x CH_3), 69.2 (CH_2), 119.8 (CH), 128.9 (CH), 137.6 (CH).

Preparation of 4-(*tert*-butyldimethylsilanyloxy)-3-methoxybenzaldehyde [62]



Vanillin (7.61 g, 50 mmol) and imidazole (5.11 g, 75 mmol) were dissolved in DCM (75 ml) and stirred for 15 min. TBDMSCl (9.80 g, 65 mmol) in DCM (40 ml) was then added and the reaction was stirred at room temperature for 24 h. Water (75 ml) was added and the reaction extracted with DCM (3 x 75 ml). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness yielding 12.83 g (96%) of a clear yellow oil; ν_{max}(film)/cm^{-1} 2929, 2856, 1697 (C=O), 1592, 1504, 1289, 1152; δ_H (400 MHz $CDCl_3$) 0.01 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.81 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.66 (3H, s, OC<u>H</u>$_3$), 6.76 (1H, d, J = 8.0 Hz, C<u>H</u>$_{arom}$), 7.17 (2H, m, 2 x C<u>H</u>$_{arom}$), 9.65 (1H, s, C<u>H</u>); δ_C (100 MHz $CDCl_3$) -3.6 (2 x CH_3), 18.0 (quat), 25.7 (3 x CH_3), 56.1 (CH_3), 109.0 (CH), 114.6 (CH), 127.7 (CH), 129.6 (quat), 147.5 (quat), 152.2 (quat), 191.2 (CO).

Preparation of 4-benzyl-3-methoxybenzaldehyde [63]



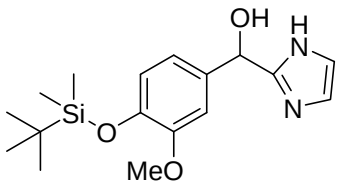
Vanillin (7.61 g, 50 mmol) and potassium carbonate (8.29 g, 60 mmol) in acetone (300 ml) were placed in a round bottomed flask. Benzyl bromide (8.55 g, 50 mmol) was then added slowly and once the addition was complete the reaction mixture was refluxed for 24 h. Water (200 ml) was then added, and the mixture extracted with

ethyl acetate (3 x 100 ml). The combined organic layers were then dried over $MgSO_4$ and evaporated to dryness yielding a yellow solid. This was then recrystallised from DCM-light petroleum to yield 11.02 g (91%) of a white powder; ν_{max} (film)/cm^{-1} 2936, 1681 (C=O), 1585, 1507, 1268, 1135, 1030; δ_H (400 MHz $CDCl_3$) 3.91 (3H, s, $OC\underline{H}_3$), 5.21 (2H, s, $C\underline{H}_2$), 6.97 (1H, d, *J* = 8.0 Hz, $C\underline{H}_{arom}$), 7.37 (7H, m, 7 x $C\underline{H}_{arom}$), 9.80 (1H, s, C<u>H</u>O); δ_C (100 MHz $CDCl_3$) 55.0 (CH_3), 70.9 (CH_2), 109.3 (CH), 112.3 (CH), 113.8 (CH), 117.8 (CH), 126.7 (CH), 127.2 (CH), 128.2 (CH), 128.8 (CH), 130.3 (quat), 136.0 (quat), 150.0 (quat), 153.6 (quat), 191.0 (CO).

General Procedure for the Formation of Key Secondary Alcohols

The corresponding imidazole/thiazole (10 mmol) was stirred in THF (10 ml) at -78^oC under an atmosphere of nitrogen. n-BuLi in hexane (2.5 M, 12 mmol) was then added drop-wise and the reaction mixture stirred for 15 min. The required aldehyde (10 mmol) was then added and the reaction was allowed to return to room temperature and stirred for 24 h. The reaction was then quenched with water (25 ml) and extracted with ethyl acetate (3 x 25ml). The organic fractions were then combined, dried over $MgSO_4$ and evaporated to dryness yielding the crude secondary alcohol. Silica column chromatography was carried out using petrol:ethyl acetate (10:1) eluent affording the pure product.

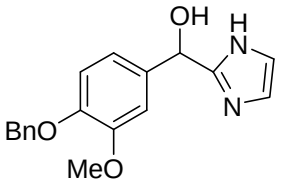
[4-(*tert*-Butyldimethylsilanoxy)-3-methoxyphenyl]-(1*H*-imidazol-2-yl)-methanol



Prepared as general procedure for the synthesis of key secondary alcohols using pre-synthesised 4-(*tert*-butyldimethylsilanyloxy)-3-methoxybenzaldehyde (2.66 g, 10 mmol) and imidazol-1-ylmethyldimethylamine (1.25 g, 10 mmol) yielding 2.75 g (82%) of a white powder; mp 226-227 ^oC; ν_{max}(film)/cm^{-1} 3300 (O-H), 2953, 2357,

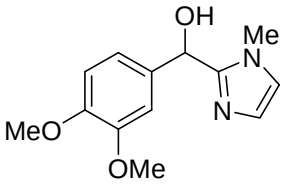
1667, 1513, 1462, 1283, 1075; δ_H (400 MHz DMSO) 0.01 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.84 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.63 (3H, s, OC<u>H</u>$_3$), 5.65 (1H, s, C<u>H</u>OH), 6.68 (3H, m, 3 x C<u>H</u>$_{arom}$), 6.89 (1H, s, C=NC<u>H</u>), 6.99 (1H, d, *J* = 2.0Hz, NHC<u>H</u>) [O<u>H</u> and N<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 4.7 (2 x CH_3), 18.1 (quat), 25.5 (3 x CH_3), 55.2 (CH_3), 69.4 (CH), 110.6 (CH), 115.9 (CH), 118.6 (CH), 119.7 (CH), 126.7 (CH), 137.0 (quat), 143.1 (quat), 150.0 (quat), 150.3 (quat); HRMS [ES] ($M+H^+$), $C_{17}H_{27}N_2O_3Si$ requires m/z 335.1712, found m/z 335.1785.

(4-Benzyloxy-3-methoxyphenyl)-(1*H*-imidazol-2-yl)-methanol



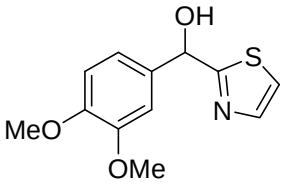
Prepared as general procedure for the synthesis of key secondary alcohols using pre-synthesised 4-benzyl-3-methoxybenzaldehyde (2.42 g, 10 mmol) and Imidazol-1-ylmethyl-dimethyl-amine (1.25 g, 10 mmol), yielding 2.26 g (73%) of a white powder; mp 189-190 ^oC; ν_{max}(film)/cm^{-1} 3190 (O-H), 1589, 1514, 1457, 1415, 1229, 1135, 1071cm^{-1}; δ_H (400 MHz $CDCl_3$) 3.77 (3H, s, OC<u>H</u>$_3$), 5.04 (2H, s, C<u>H</u>$_2$), 5.75 (1H, s, C<u>H</u>OH), 6.76 (2H, m, 2 x C<u>H</u>$_{arom}$), 6.86 (2H, s, NHC<u>H</u>C<u>H</u>), 6.90 (1H, s, C<u>H</u>$_{arom}$), 7.21 (5H, m, 5 x C<u>H</u>$_{arom}$) [O<u>H</u> and N<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 55.5 (CH_3), 69.4 (CH_2), 69.9 (CH), 110.4 (CH), 113.1 (CH), 118.3 (CH), 127.6 (2 x CH), 127.7 (3 x CH), 128.3 (2 x CH), 136.2 (quat), 137.2 (quat), 146.7 (quat), 148.7 (quat), 150.3 (quat); HRMS [EI] (M^+), $C_{18}H_{18}N_2O_3$ requires m/z 310.1322, found m/z 310.1317.

(3,4-Dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol



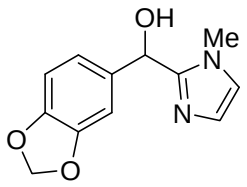
Prepared as general procedure for the synthesis of key secondary alcohols using 3,4-dimethoxybenzaldehyde (16.62 g, 100 mmol) and 1-methylimidazole (8.21 g, 100 mmol) yielding 24.18 g (98%) of a yellow oil; ν_{max}(film)/cm^{-1} 3187 (O-H), 1593, 1512, 1456, 1439, 1297, 1271, 1083; δ_H (400 MHz $CDCl_3$) 3.31 (3H, s, NC$\underline{H}_3$), 3.69 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$), 5.81 (1H, s, C$\underline{H}$OH), 6.61 (1H, s, C$\underline{H}_{arom}$), 6.65 (3H, s, C$\underline{H}_{arom}$ and NC$\underline{H}$C$\underline{H}$N), 6.87 (1H, s, C$\underline{H}_{arom}$) [O$\underline{H}$ and N$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 33.2 (CH_3), 55.8 (2 x CH_3), 68.6 (CH), 109.3 (CH), 110.7 (CH), 118.1 (CH), 122.0 (CH), 125.9 (CH), 134.2 (quat), 148.1 (quat), 148.8 (quat), 149.3 (quat); HRMS [EI] (M^+), $C_{13}H_{16}N_2O_3$ requires m/z 249.1234, found m/z 249.1235.

(3,4-Dimethoxyphenyl)-thiazol-2-yl-methanol



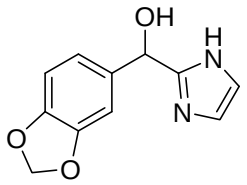
Prepared as general procedure for the synthesis of key secondary alcohols using 3,4-dimethoxybenzaldehyde (4.15 g, 25 mmol) and thiazole (2.13 g, 25 mmol) yielding 5.99 g (95%) of a yellow oil; ν_{max}(film)/cm^{-1} 3203 (O-H), 2963, 2397, 1515, 1503, 1481, 1260, 1024; δ_H (400 MHz $CDCl_3$) 3.80 (3H, s, OC$\underline{H}_3$), 3.81 (3H, s, OC$\underline{H}_3$), 5.95 (1H, s, C$\underline{H}$OH), 6.80 (1H, d, J = 8.0 Hz, C$\underline{H}_{arom}$), 6.94 (2H, m, 2 x C$\underline{H}_{arom}$), 7.25 (1H, d, J = 3.2 Hz, SC$\underline{H}$), 7.68 (1H, d, J = 3.2 Hz, NC$\underline{H}$) [O$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 13.1 (quat), 21.3 (quat), 54.8 (2 x CH_3), 52.8 (CH), 108.4 (CH), 109.9 (CH), 118.1 (CH), 118.7 (CH), 132.9 (quat), 141.3 (CH), 148.2 (quat); HRMS [EI] ($M+H^+$), $C_{12}H_{14}NO_3S$ requires m/z 252.0689, found m/z 252.0693.

Benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanol



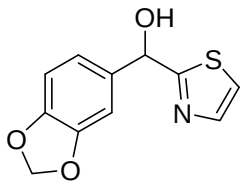
Prepared as general procedure for the synthesis of key secondary alcohols using piperonal (3.75 g, 25 mmol) and 1-methylimidazole (2.05 g, 25 mmol) yielding 5.36 g (92%) of a white solid; mp = 109-112°C; ν_{max}(film)/cm^{-1} 3113 (O-H), 1549, 1482, 1456, 1437, 1287, 1251, 1103; δ_H (400 MHz $CDCl_3$) 3.34 (3H, s, NC<u>H</u>$_3$), 5.73 (1H, s, C<u>H</u>OH), 5.85 (2H, s, OC<u>H</u>$_2$O), 6.67 (3H, m, 3 x C<u>H</u>$_{arom}$), 6.74 (1H, d, *J* = 1.2 Hz, NCH$_3$C<u>H</u>), 6.77 (1H, d, *J* = 1.2 Hz, C=NC<u>H</u>) [O<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 33.1 (CH_3), 68.8 (CH), 101.0 (CH_2), 107.0 (CH), 108.0 (CH), 119.7 (CH), 122.1 (CH), 126.2 (CH), 135.0 (quat), 147.0 (quat), 147.8 (quat), 149.1 (quat); HRMS [EI] ($M+H^+$), $C_{12}H_{13}N_2O_3$ requires m/z 233.0921, found m/z 233.0921.

Benzo[1,3]dioxol-5-yl-(1*H*-imidazol-2-yl)-methanol



Prepared as general procedure for the synthesis of key secondary alcohols using piperonal (0.75 g, 5 mmol) and pre-synthesised imidazol-1-ylmethyldimethylamine (0.63 g, 5 mmol) yielding 0.96 g (88%) of a yellow oil; ν_{max}(film)/cm^{-1} 3195 (O-H), 2891, 2579, 1548, 1504, 1486, 1442, 1362, 1301, 1263, 1235, 1183, 1101, 1038, 933; δ_H (400 MHz DMSO-d_6) 5.69 (1H, s, C<u>H</u>OH), 6.03 (2H, s, C<u>H</u>$_2$), 6.19 (1H, bs, O<u>H</u>), 6.76 (2H, s, 2 x C<u>H</u>$_{arom}$) 6.89 (1H, s, C<u>H</u>$_{arom}$) [imidazole protons not observed]; δ_C (100 MHz DMSO-d_6) 69.3 (CH), 100.7 (CH_2), 106.8 (CH), 107.6 (CH), 119.5 (CH), 137.4 (quat), 146.1 (quat), 146.9 (quat), 150.2 (quat) [N<u>C</u>H<u>C</u>H not observed]; HRMS [EI] (M^+), $C_{11}H_{10}N_2O_3$ requires m/z 218.0691, found m/z 218.0695.

Benzo[1,3]dioxol-5-ylthiazol-2-ylmethanol

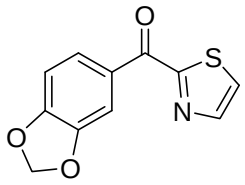


Prepared as general procedure for the synthesis of key secondary alcohols using piperonal (0.88 g, 5.9 mmol) and thiazole (0.50 g, 5.9 mmol) yielding 0.97 g (70%) of a orange oil; ν_{max}(film)/cm^{-1} 3311 (O-H), 2928, 1681, 1603, 1502, 1496, 1442, 1246, 1094, 1038, 929; δ_H (400 MHz $CDCl_3$) 5.88 (3H, m, C<u>H</u>$_2$ and C<u>H</u>OH), 6.71 (1H, d, *J* = 7.6 Hz, C<u>H</u>$_{arom}$), 6.86 (2H, m, 2 x C<u>H</u>$_{arom}$), 7.21 (1H, d, *J* = 3.2 Hz, SC<u>H</u>), 7.62 (1H, d, *J* = 3.2 Hz, NC<u>H</u>) [O<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 73.6 (CH), 101.2 (CH_2), 107.1 (CH), 108.3 (CH), 119.6 (CH), 120.4 (CH), 135.5 (quat), 142.3 (CH), 147.7 (quat), 148.0 (quat), 174.5 (quat); HRMS [EI] (M^+), $C_{11}H_9NO_3S$ requires m/z 235.0303, found m/z 235.0306.

General Procedure for MnO_2 Oxidation of Secondary Alcohols

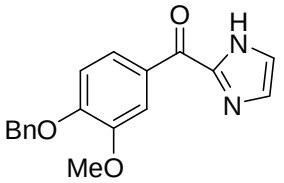
The pre-synthesised secondary alcohol (4 mmol) and activated MnO_2 (20 mmol) were refluxed in methanol (10 ml) for 24 h. The mixture was then filtered warm through a pad of celite and the solids further washed with chloroform (3 x 25 ml). The combined organic filtrate was then evaporated to dryness yielding the corresponding ketone.

Benzo[1,3]dioxol-5-yl-thiazol-2-ylmethanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using benzo[1,3]dioxol-5-ylthiazol-2-ylmethanol (0.90 g, 3.8 mmol) and MnO_2 (1.66 g, 19.2 mmol) yielding 0.85 g (95%) of a yellow oil; ν_{max}(film)/cm^{-1} 2359, 1639 (C=O), 1599, 1499, 1478, 1438, 1388, 1352, 1297, 1264, 1241, 1117, 1077, 1035, 926; δ_H (400 MHz $CDCl_3$) 6.01 (2H, s, OC$\underline{H}_2$O), 6.86 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 7.62 (1H, d, *J* = 3.0 Hz, SC$\underline{H}$), 7.91 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 8.01 (1H, d, *J* = 3.0 Hz, NC$\underline{H}$), 8.26 (1H, dd, *J* = 8.4, 1.6 Hz, C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 101.9 (CH_2), 108.1 (CH), 110.7 (CH), 125.9 (CH), 128.4 (CH), 129.5 (quat), 144.6 (CH) [4 x quat not detected]; HRMS [ES] ($M+H^+$), $C_{11}H_8NO_3S$ requires m/z 234.0217, found, 234.0219.

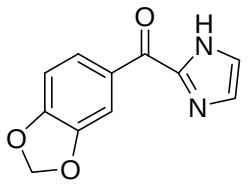
(4-Benzyloxy-3-methoxyphenyl)-(1*H*-imidazol-2-yl)-methanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using (4-benzyloxy-3-methoxyphenyl)-(1*H*-imidazol-2-yl)-methanol (0.62 g, 2 mmol) and MnO_2 (0.87 g, 10 mmol), yielding 0.52 g (84%) of a yellow solid; mp 172-174 ^oC; ν_{max}(film)/cm^{-1} 1633, 1624, 1511, 1463, 1327, 1310, 1253, 1173, 1150 ; δ_H (400 MHz $CDCl_3$) 3.99 (3H, s, OC$\underline{H}_3$), 5.28 (2H, s, OC$\underline{H}_2$Ph), 6.97 (1H, d, *J* = 8.5 Hz, C$\underline{H}_{arom}$), 7.25-7.45 (7H, m, 5 x C$\underline{H}_{arom}$ and NHC$\underline{H}$C$\underline{H}$N), 8.10 (1H, d, *J* =1.4 Hz, C$\underline{H}_{arom}$), 8.50 (1H, dd, *J* = 8.5 and 1.4 Hz, C$\underline{H}_{arom}$) [N$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 56.1 (CH_3), 70.8 (CH_2), 112.2 (CH), 113.1 (CH), 119.7 (CH), 126.6 (CH), 127.2 (2 x CH), 128.1 (CH), 128.6 (2 x CH), 128.7 (quat), 131.6 (CH), 136.3 (quat), 145.5 (quat),

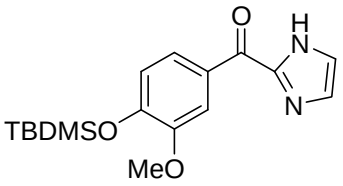
149.2 (quat), 152.9 (quat), 179.9 (quat). HRMS [EI] (M^+), $C_{18}H_{16}N_2O_3$ requires m/z 308.1157, found m/z 308.1161.

Benzo[1,3]dioxol-5-yl-(1*H*-imidazol-2-yl)-methanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using benzo[1,3]dioxol-5-yl-(1*H*-imidazol-2-yl)-methanol (0.87 g, 4 mmol) and MnO_2 (1.74 g, 20 mmol), yielding 0.77 g (90%) of a yellow solid; mp 182-185^oC; ν_{max}(film)/cm^{-1} 3280, 2361, 1623, 1594, 1442, 1395, 1249, 1121; δ_H (400 MHz $CDCl_3$) 6.07 (2H, s, OC$\underline{H}_2$O), 6.93 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 7.29 (1H, s, NHC$\underline{H}$), 7.38 (1H, s, C=NC$\underline{H}$), 8.06 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 8.49 (1H, dd, *J* = 1.6, 8.0 Hz, C$\underline{H}_{arom}$) [N$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 101.8 (CH_2), 108.1 (CH), 110.5 (CH), 119.7 (CH), 128.3 (CH), 129.9 (quat), 131.6 (CH), 147.9 (quat), 152.3 (quat) [2 x quat not detected]; HRMS [ES] ($M+H^+$), $C_{11}H_9N_2O_3$ requires m/z 217.0608, found m/z 217.0608.

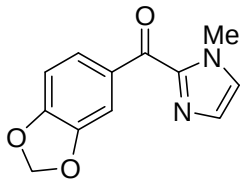
[4-(*tert*-Butyldimethylsilanoxy)-3-methoxyphenyl]-(1*H*-imidazol-2-yl)-methanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using [4-(*tert*-butyldimethylsilanoxy)-3-methoxyphenyl]-(1*H*-imidazol-2-yl)-methanol (0.50 g, 1.4 mmol) and MnO_2 (0.61 g, 7.0 mmol), yielding 0.43 g (93%) of a orange oil; ν_{max}(film)/cm^{-1} 2958, 1681, 1587, 1514, 1462, 1416, 1259, 1096; δ_H (400 MHz

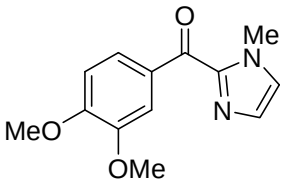
DMSO-d_6) 0.01 (6H, s, Si(C$\underline{H}_3$)$_2$), 0.85 (9H, s, SiC(C$\underline{H}_3$)$_3$), 3.75 (3H, s, OC$\underline{H}_3$), 6.81 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 6.98 (1H, s, NHC$\underline{H}$), 7.17 (1H, s, C=NC$\underline{H}$), 8.02 (1H, d, *J* = 2.0 Hz, C$\underline{H}_{arom}$), 8.21 (1H, dd, *J* = 2.0, 8.4 Hz, C$\underline{H}_{arom}$) [N$\underline{H}$ not observed]; δ_C (100 MHz DMSO-d_6) -4.1 (2 x CH_3), 25.5 (3 x CH_3), 55.5 (CH_3), 113.8 (CH), 114.8 (CH), 121.1 (CH), 126.2 (CH), 127.2 (quat), 130.6 (CH), 145.1 (quat), 147.1 (quat), 151.9 (quat), 178.9 (quat) [1 x quat not detected]; HRMS [EI] (M^+), $C_{17}H_{24}N_2O_3Si$ requires m/z 332.1556, found m/z 332.1559.

Benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanol (2.32 g, 10 mmol) and MnO_2 (4.35 g, 50 mmol), yielding 2.20 g (96%) of a white solid; mp = 295-297 ^oC; ν_{max}(film)/cm^{-1} 2358, 1766, 1633 (C=O), 1598, 1440, 1396, 1357, 1257, 1234, 1094, 1036; δ_H (400 MHz $CDCl_3$) 3.97 (3H, s, NC$\underline{H}_3$), 5.97 (2H, s, OC$\underline{H}_2$O), 6.82 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 7.01 (1H, s, CH_3NC$\underline{H}$), 7.12 (1H, s, C=NC$\underline{H}$), 7.72 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), (1H, dd, *J* = 1.6, 8.0 Hz, C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 36.4 (CH_3), 101.7 (CH_2), 107.8 (CH), 110.6 (CH), 126.5 (CH), 127.8 (CH), 129.0 (CH), 131.6 (quat), 143.2 (quat), 147.6 (quat), 151.7 (quat), 182.2 (quat); HRMS [ES] ($M+H^+$), $C_{12}H_{11}N_2O_3$ required 231.0764, found 231.0764.

(3,4-Dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanone



Prepared as general procedure for the MnO_2 oxidation of secondary alcohols using (3,4-dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol (1.24 g, 5 mmol) and MnO_2 (2.17 g, 25 mmol), yielding 1.19 g (97%) of a white solid; mp = 172-173 ^oC; ν_{max}(film)/cm^{-1} 1631 (C=O), 1582, 1508, 1446, 1416, 1263, 1226, 1075, 1020, 768; δ_H (400 MHz $CDCl_3$) 3.84 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 3.97 (3H, s, NC$\underline{H}_3$), 6.86 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 7.01 (1H, s, CH_3NC$\underline{H}$), 7.12 (1H, s, C=NC$\underline{H}$), 7.77 (1H, d, *J* = 2.0Hz, C$\underline{H}_{arom}$), 8.08 (1H, dd, *J* = 2.0, 8.4 Hz, C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 35.3 (CH_3), 54.9 (2 x CH_3), 108.9 (CH), 111.6 (CH), 125.4 (2 x CH), 127.9 (CH), 128.9 (quat), 142.3 (quat), 147.5 (quat), 152.2 (quat), 181.5 (quat); HRMS [EI] (M^+), $C_{13}H_{14}N_2O_3$ requires m/z 246.1004, found m/z 246.1004.

Preparation of $[W(CO)_5I]$ $[N(Bu)_4]$ [64]

Tetrabutylammonium iodide (0.50 g, 1.4 mmol) was heated with an excess of tungsten hexacarbonyl (1.00 g, 2.8 mmol) in diglyme (20 ml) at 120^oC for 4 h. The mixture was filtered hot under N_2, and addition of hexane to the filtrate afforded 0.85 g (91%) of a yellow solid. IR spectra were recorded to confirm the carbonyl stretches and then the product was carried through without further purification. ν_{max}(film)/cm^{-1} 2058, 1909, 1836.

Preparation of $[Cr(CO)_5I]$ $[N(Bu)_4]$ [64]

Tetrabutylammonium iodide (0.50 g, 1.4 mmol) was heated with an excess of chromium hexacarbonyl (1.00 g, 4.5 mmol) in diglyme (20 ml) at 120°C for 4 h. The mixture was filtered hot under N_2, and addition of hexane to the filtrate afforded 0.72 g (95%) of a yellow solid. IR spectra were recorded to confirm the carbonyl stretches and then the product was carried through without further purification. ν_{max}(film)/cm^{-1} 2055, 1914, 1849.

Preparation of $[W(CO)_5SH]$ $[(Ph_3P)_2N]$ [65]

Sodium hydrosulfide (0.15 g, 2.7 mmol) and bis(triphenylphosphoranylidene)-ammonium chloride (1.15 g, 2.0 mmol) were dissolved in ethanol (10 ml). The mixture was stirred at RT for 1.5 h and then the volatile components were removed under vacuum. THF (20 ml) and tungsten hexacarbonyl (0.74 g, 2.1 mmol) were then added and the mixture refluxed for 1.5 h. The mixture was then filtered under N_2 and the resulting filtrate reduced under vacuum yielding 1.51 g (84%) of a yellow solid; mp 115-117°C (lit. mp[65] = 116 – 119 °C); ν_{max}(film)/cm^{-1} 2052, 1932(vs), 1851.

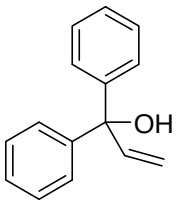
Preparation of $[W(CO)_5\{S=C(C_6H_4)OMe\}]$ [65]

$[(Ph_3P)_2N][W(CO)_5SH]$ (1.79 g, 2.0 mmol) and *p*-anisaldehyde (0.27 ml, 2.2 mmol) were stirred in THF (10 ml) with an excess of magnesium sulphate. Triflic acid (0.19 ml, 2.2 mmol) was then added dropwise to the reaction during which the solution turned a deep purple. The mixture was then reduced under vacuum and the resulting residue was purified via column chromatography eluting with light petroleum: ethyl acetate (99:1) to afford 0.057 g (6%) of the title compound as a purple oil; ν_{max}(film)/cm^{-1} 2067, 1919(vs), 1592, 1262, 1162; δ_H (400 MHz $CDCl_3$) 3.92 (3H, s, $OC\underline{H}_3$), 6.94 (2H, dd, *J* 2.6, 9.4 Hz, 2 x $C\underline{H}_{arom}$), 7.83 (2H, dd, *J* 2.6, 9.4 Hz, $C\underline{H}_{arom}$), 9.89 (1H, s, S=C$\underline{H}$); HRMS [EI](M^+), $C_{13}H_8SO_6W$ requires m/z 473.9524, found m/z 473.9530.

Preparation of $[W(CO)_5\{S=C(C_6H_5)_2\}]$

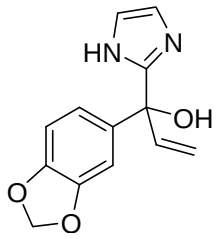
$[(Ph_3P)_2N][W(CO)_5SH]$ (1.79 g, 2.0 mmol) and benzophenone (0.40 g, 2.2 mmol) were stirred in THF (10 ml) with an excess of magnesium sulphate. Triflic acid (0.19 ml, 2.2 mmol) was then added dropwise to the reaction during which the solution turned a deep purple. The mixture was then reduced under vacuum and the resulting residue was purified via column chromatography eluting with light petroleum: ethyl acetate (99:1) to afford 0.021 g (2%) of the title compound as a purple oil. ν_{max}(film)/cm^{-1} 2067, 1932(vs); δ_H (400 MHz $CDCl_3$) 7.12 - 7.64 (8H, m, 8 x C<u>H</u>$_{arom}$), 7.80 - 7.83 (2H, m, 2 x C<u>H</u>$_{arom}$); δ_C (100MHz $CDCl_3$) 128.3, 128.9, 130.1, 132.4, 171.2 (C=O), 206.9 (C=S); HRMS [EI](M^+), $C_{18}H_{10}SO_5W$ requires m/z 521.9753, found m/z 521.9755.

Preparation of 1,1-diphenyl-prop-2-en-1-ol [66]



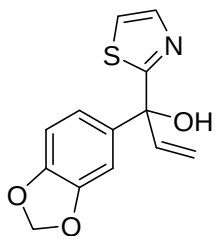
An excess of magnesium turnings were stirred vigorously overnight under N_2 to give a clean reaction surface. THF (10 ml) was then added to the flask along with a crystal of iodine. Vinyl bromide solution (1M in THF, 2.4 ml, 2.4 mmol) was then added dropwise and the mixture was refluxed for 30 min. Benzophenone (0.40 g, 2.0 mmol) was then added and the solution was stirred for 12 h then quenched with ice. The resulting mixture was extracted with DCM (3 x 25 ml) and the combined organic fractions then washed with water (50 ml) and brine (50 ml). The organic was then evaporated to dryness yielding a white solid, 0.37 g (87%); mp = 68-70^oC (lit. mp[67] = 72-73^oC); ν_{max}(film)/cm^{-1} 3468 (O-H), 3057, 1597, 1446, 1318, 1276, 1176, 1072, 1029, 920; δ_H (400 MHz $CDCl_3$) 2.25 (1H, s, O<u>H</u>), 5.29 (2H, m, CH=C<u>H</u>$_2$), 6.49 (1H, dd, *J* = 8.8, 16.2 C<u>H</u>=CH_2) 7.16 - 7.31 (10H, m, 10 x C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 79.4 (quat), 113.9 (CH_2), 127. 1 (4 x CH), 127.3 (2 x CH), 128.2 (4 x CH), 143.5 (CH), 145.7 (2 x quat).

Preparation of 1-benzo[1,3]dioxol-5-yl-1-(1*H*-imidazol-2-yl)-prop-2-en-1-ol



Vinyl bromide solution (1 M in THF, 0.46 ml, 0.46 mmol) was added dropwise to an excess of magnesium turnings in THF (5 ml) and the solution refluxed for 1 h. Benzo[1,3]dioxol-5-yl-(1*H*-imidazol-2-yl)-methanone (0.050 g, 0.23 mmol) in THF (5 ml) was then added and the reaction was stirred for 12 h. Ice was then added to quench the reaction and the resulting mixture was extracted with DCM (3 x 20ml). The organic fractions were combined, dried over $MgSO_4$ and evaporated to dryness yielding 39 mg (76%) of a yellow oil; ν_{max}(film)/cm^{-1} 3149 (O-H), 2923, 1502, 1484, 1434, 1240, 1162, 1094, 1039; δ_H (400 MHz $CDCl_3$) 5.20 – 5.25 (2H, m, CHC$\underline{H}_2$), 5.86 (2H, s, OC$\underline{H}_2$O), 6.42 (1H, dd, *J* = 10.4, 17.2 Hz, C$\underline{H}$CH_2), 6.66 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 6.75 (1H, dd, *J* = 1.6, 8.4 Hz, C$\underline{H}_{arom}$), 6.83 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 6.88 (2H, s, NC$\underline{H}$C$\underline{H}$) [O$\underline{H}$ and N$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 100.2 (CH_2), 106.3 (CH), 106.9 (CH), 113.7 (CH_2), 118.8 (CH), 119.6 (CH), 122.3 (CH), 136.3 (quat), 140.3 (CH), 146.2 (quat), 146.7 (quat), 149.9 (quat) [1 x quat not detected]; HRMS [EI] (M^+), $C_{13}H_{12}N_2O_3$ requires m/z 244.0848, found. m/z 244.0849.

Preparation of 1-benzo[1,3]dioxol-5-yl-1-thiazol-2-yl-prop-2-en-1-ol



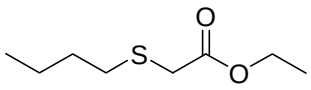
Vinyl bromide solution (1 M in THF, 1.2 ml, 1.2 mmol) was added dropwise to an excess of magnesium turnings in THF (5 ml). The mixture was then refluxed for 1 h and then allowed to cool. Benzo[1,3]dioxol-5-yl-thiazol-2-yl-methanone (0.23 g, 1

mmol) was then added in THF (5 ml) and the reaction was stirred for 12 h. An aqueous work up was carried out extracting with DCM (3 x 25 ml). The combined organic fractions were further washed with water (25 ml) and brine (25 ml). The organic was then dried over $MgSO_4$, evaporated to dryness giving 0.21 g (80%) of an orange oil; ν_{max}(film)/cm^{-1} 3165 (O-H), 2931, 1507, 1498, 1478, 1253, 1123, 1099, 1027; δ_H (400 MHz $CDCl_3$) 5.27 (2H, dd, *J* = 10.4, 17.2 Hz, CHC$\underline{H}_2$), 5.85 (2H, s, OC$\underline{H}_2$O), 6.45 (1H, dd, *J* = 10.4, 17.2, Hz, C$\underline{H}$CH$_2$), 6.67 (1H, d, *J* = 12.4 Hz, C$\underline{H}_{arom}$), 6.84 (1H, dd, *J* = 1.6, 12.4 Hz, C$\underline{H}_{arom}$), 6.89 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 7.19 (1H, d, *J* = 3.4 Hz, SC$\underline{H}$), 7.63 (1H, d, *J* = 3.4 Hz, NC$\underline{H}$) [O$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 77.5 (quat), 100.3 (CH_2), 106.8 (CH), 107.2 (CH), 114.1 (CH_2), 118.3 (CH), 118.8 (CH), 136.8 (quat), 140.5 (CH), 141.4 (CH), 146.2 (quat), 146.7 (quat), 175.4 (quat); HRMS [ES] ($M+H^+$), $C_{13}H_{12}NO_3S$ requires m/z 262.0532, found m/z 262.0529.

General Procedure (A) for the synthesis of sulfides

The corresponding thiol (6 mmol) was stirred in DMF (5 ml) under an atmosphere of nitrogen at 0 ^oC. NaH (9 mmol) was added and the mixture was stirred for 10 min. The bromoacetate/acetal (6 mmol) was then added and the reaction stirred at room temperature for 24 h. Water (25 ml) was added to quench, and then extraction was carried out with diethyl ether (3 x 25 ml). The combined organic fractions were washed with water (25 ml) then dried over $MgSO_4$. Evaporation to dryness yielded the clean crude product.

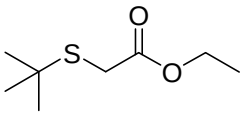
n-Butylsulfanylacetic acid ethyl ester [68]



Prepared as general procedure (A) for the synthesis of sulfides using n-butylthiol (0.54 g, 6 mmol) and ethyl bromoacetate (1.00 g, 6 mmol), yielding 1.01 g (95%) of a yellow oil; ν_{max}(film)/cm^{-1} 2957, 2929, 2871, 1734 (C=O), 1464, 1411, 1379, 1365,

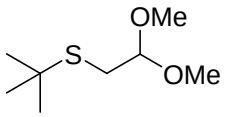
1272, 1203, 1131, 1030; δ_H (400 MHz $CDCl_3$) 0.84 (3H, t, *J* = 4.8 Hz, $S(CH_2)_3C\underline{H}_3$), 1.19 (3H, t , *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.35 (2H, m, $SCH_2CH_2C\underline{H}_2$), 1.53 (2H, m, $SCH_2C\underline{H}_2CH_2$), 2.57 (2H, t, *J* = 7.6 Hz, $SC\underline{H}_2CH_2CH_2$), 3.14 (2H, s, $C\underline{H}_2C{=}O$), 4.13 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$); δ_C (100 MHz $CDCl_3$) 12.7 (CH_3), 13.2 (CH_3), 20.8 (CH_2), 30.3 (CH_2), 31.3 (CH_2), 32.7 (CH_2), 60.2 (CH_2), 169.6 (quat).

tert-Butylsulfanylacetic acid ethyl ester [69]



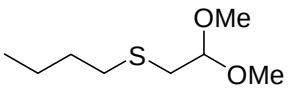
Prepared as general procedure (A) for the synthesis of sulfides using tert-butylthiol (0.54 g, 6 mmol) and ethyl bromoacetate (1.00 g, 6 mmol), yielding 1.05 g (99%) of a yellow oil; ν_{max}(film)/cm^{-1} 2960, 2864, 1734 (C=O), 1460, 1365, 1271, 1201, 1133, 1031; δ_H (400 MHz $CDCl_3$) 1.19 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.27 (9H, s, $C(C\underline{H}_3)_3$), 3.21 (2H, s, $C\underline{H}_2C{=}O$), 4.12 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$); δ_C (100 MHz $CDCl_3$) 14.1 (CH_3), 30.6 (3 x CH_3), 31.8 (CH_2), 42.9 (quat), 61.2 (CH_2), 171.1 (quat).

2-(2,2-Dimethoxyethylsulfanyl)-2-methylpropane [70]



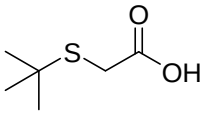
Prepared as general procedure (A) for the synthesis of sulfides using t-butylthiol (0.54 g, 6 mmol) and 2-bromo-1,1-dimethoxyethane (1.01 g, 6 mmol), yielding 0.85 g (79%) of a yellow oil; ν_{max}(film)/cm^{-1} 2958, 2828, 1459, 1363, 1163, 1060, 980, 964; δ_H (400 MHz $CDCl_3$) 1.24 (9H, s, $C(C\underline{H}_3)_3$), 2.67 (2H, d, *J* = 5.6 Hz, $SC\underline{H}_2$), 3.29 (6H, s, 2 x $OC\underline{H}_3$), 4.43 (1H, t, *J* = 5.6 Hz, $C\underline{H}(OCH_3)_2$); δ_C (100 MHz $CDCl_3$) 29.8 (3 x CH_3), 29.9 (quat), 40.9 (CH_2), 52.2 (2 x CH_3), 102.9 (CH).

1-(2,2-Dimethoxyethylsulfanyl)-butane [71]



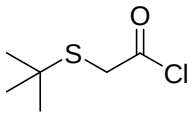
Prepared as general procedure (A) for the synthesis of sulfides using n-butylthiol (0.54 g, 6 mmol) and 2-bromo-1,1-dimethoxyethane (1.01 g, 6 mmol), yielding 1.03 g (97%) of a yellow oil; ν_{max}(film)/cm^{-1} 2955, 2927, 2871, 2828, 1464, 1366, 1222, 1190, 1120, 1058, 985, 965; δ_H (400 MHz $CDCl_3$) 0.86 (3H, t, *J* = 4.8 Hz, $S(CH_2)_3C\underline{H}_3$), 1.34 (2H, m, $SCH_2CH_2C\underline{H}_2$), 1.49 (2H, m, $SCH_2C\underline{H}_2CH_2$), 2.51 (2H, t, *J* = 7.2 Hz, $SC\underline{H}_2CH_2CH_2$), 2.61 (2H, d, *J* = 5.6 Hz, $SC\underline{H}_2CH$), 6.09 (6H, s, $OC\underline{H}_3$), 4.42 (1H, t, *J* = 5.6 Hz, $C\underline{H}(OCH_3)_2$); δ_C (100 MHz $CDCl_3$) 11.2 (CH_3), 21.6 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 34.4 (CH_2), 53.7 (2 x CH_3), 104.5 (CH).

Preparation of tert-butylsulfanyl-acetic acid [72]



tert-Butylthiol (0.496 g, 5.5 mmol) and bromoacetic acid (0.695 g, 5.0 mmol) were stirred in DMF (5 ml) at 0^{o}C. NaH (60%, 0.440 g, 11.0 mmol) was then added and the reaction stirred at room temperature overnight. Water (25 ml) was added to quench the reaction and then the mixture was acidified to ~pH 5 with aq.HCl. The mixture was then extracted with diethyl ether (3 x 25 ml). The combined organic fractions were further washed with water (3 x 25 ml) to remove residual DMF. The organic was then dried over $MgSO_4$, filtered and reduced to dryness yielding 0.639 g (97%) of a yellow oil; ν_{max}(film)/cm^{-1} 2924, 1710 (C=O), 1459, 1420, 1365, 1296, 1160, 933; δ_H (400 MHz $CDCl_3$) 1.28 (9H, s, $C(CH_3)_3$), 3.26 (2H, s, SCH_2) [O$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 30.6 (3 x CH_3), 31.2 (CH_2), 43.4 (quat), 177.6 (quat); HRMS [EI] (M^+), $C_6H_{12}O_2S$ requires m/z 148.0558, found m/z 148.0555.

Preparation of tert-butylsulfanylacetyl chloride [73]

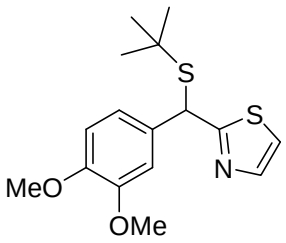


tert-Butylsulfanyl-acetic acid (0.10 g, 0.68 mmol) was stirred in $SOCl_2$ (1 ml) at 60 ^oC for 1 hour. The mixture was then cooled and the excess $SOCl_2$ was removed under pressure on a rotary evaporator yielding 0.098 g (88%) of an orange oil; ν_{max}(film)/cm^{-1} 2922, 1793 (C=O), 1457, 1375, 1168, 1007, 961; δ_H (400 MHz $CDCl_3$) 1.27 (9H, s, $C(CH_3)_3$), 3.69 (2H, s, CH_2). [^{13}C NMR and HRMS - not recorded due to the unstable nature of the acid chloride.]

General Procedure (B) for the synthesis of sulfides

The corresponding pre-synthesised secondary alcohol (5 mmol), thiol (10 mmol) and TFA (10 mmol) were refluxed in $CHCl_3$ (20 ml) for 24 h. The reaction was then basified with aqueous $NaHCO_3$ and extracted into $CHCl_3$ (3 x 25 ml). The organic fractions were combined, washed with water (25 ml) and dried over $MgSO_4$. Evaporating the organic to dryness yielded the clean crude product.

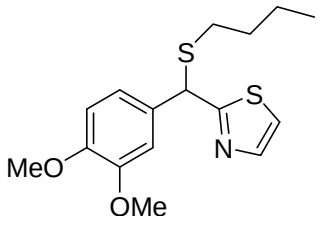
2-[tert-Butylsulfanyl-(3,4-dimethoxy-phenyl)methyl]-thiazole



Prepared as general procedure (B) for the synthesis of sulfides using tert-butylthiol (1.80 g, 20 mmol), TFA (2.28 g, 20 mmol) and (3,4-dimethoxyphenyl)-thiazol-2-yl-methanol (2.51 g, 10 mmol), yielding 3.17 g (98%) of a dark orange oil; ν_{max}(film)/cm^{-1} 2956, 2358, 1590, 1513, 1462, 1416, 1263, 1140, 1026; δ_H (400 MHz

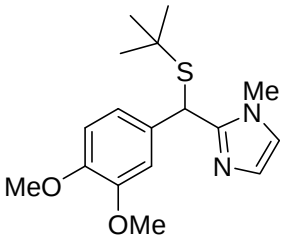
$CDCl_3$) 1.22 (9H, s, C($C\underline{H}_3$)$_3$), 3.78 (3H, s, O$C\underline{H}_3$), 3.81 (3H, s, O$C\underline{H}_3$), 5.41 (1H, s, $(CH_3)_3CSC\underline{H}$), 6.73 (1H, d, J = 8.4 Hz, $C\underline{H}_{arom}$), 6.92 (1H, dd, J = 2.0, 8.4 Hz, $C\underline{H}_{arom}$), 6.96 (1H, d, J = 2.0 Hz, $C\underline{H}_{arom}$), 7.18 (1H, d, J = 3.6 Hz, SC$\underline{H}$CH), 7.62 (1H, d, J = 3.6 Hz NC$\underline{H}$); δ_C (100 MHz $CDCl_3$) 30.7 (3 x CH_3), 45.4 (quat), 49.3 (CH), 55.8 (2 x CH_3), 111.1 (CH), 118.1 (CH), 119.8 (CH), 120.2 (CH), 133.7 (quat), 142.6 (CH), 148.4 (quat), 149.1 (quat), 174.9 (quat); HRMS [ES] ($M+H^+$), $C_{16}H_{22}NO_2S_2$ requires m/z 324.1086, found m/z 324.1088.

2-[n-Butylsulfanyl-(3,4-dimethoxyphenyl)methyl]-thiazole



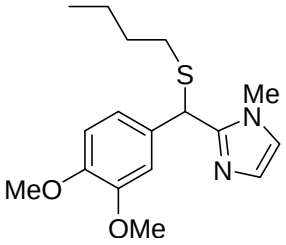
Prepared as general procedure (B) for the synthesis of sulfides using n-butylthiol (1.80 g, 20 mmol), TFA (2.28 g, 20 mmol) and (3,4-dimethoxyphenyl)-thiazol-2-yl-methanol (2.51 g, 10 mmol), yielding 3.09 g (96%) of a orange oil; ν_{max}(film)/cm^{-1} 2954, 1590, 1513, 1462, 1416, 1262, 1139, 1026, 764; δ_H (400 MHz $CDCl_3$) 0.87 (3H, t, J = 7.2 Hz, S(CH_2)$_3C\underline{H}_3$), 1.40 (2H, m, $SCH_2CH_2C\underline{H}_2$), 1.58 (2H, m, $SCH_2C\underline{H}_2CH_2$), 2.52 (2H, m, $SC\underline{H}_2CH_2CH_2$), 3.87 (3H, s, O$C\underline{H}_3$), 3.88 (3H, s, O$C\underline{H}_3$), 5.42 (1H, s, $CH_2SC\underline{H}$), 6.82 (1H, d, J = 8.0 Hz, $C\underline{H}_{arom}$), 7.01 (1H, dd, J = 2.0, 8.0 Hz, $C\underline{H}_{arom}$), 7.06 (1H, d, J = 2.0 Hz, $C\underline{H}_{arom}$), 7.28 (1H, d, J = 3.2 Hz, SC$\underline{H}$CH), 7.71 (1H, d, J = 3.2 Hz, NC$\underline{H}$); δ_C (100 MHz $CDCl_3$) 13.7 (CH_3), 21.9 (CH_2), 31.1 (CH_2), 32.4 (CH_2), 51.3 (CH), 55.9 (2 x CH_3), 111.0 (CH), 111.1 (CH), 119.9 (CH), 120.5 (CH), 132.0 (quat), 142.6 (CH), 148.7 (quat), 149.1 (quat), 173.1 (quat); HRMS [ES] ($M+H^+$), $C_{16}H_{22}NO_2S_2$ requires m/z 324.1086, found m/z 324.1088.

2-[tert-Butylsulfanyl-(3,4-dimethoxyphenyl)-methyl]-1-methyl-1*H*-imidazole



Prepared as general procedure (B) for the synthesis of sulfides using tert-butylthiol (0.90 g, 10 mmol), TFA (1.14 g, 10 mmol) and (3,4-dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol (1.24 g, 5 mmol), yielding 1.58 g (99%) of a orange oil; ν_{max}(film)/cm^{-1} 2955, 1589, 1513, 1462, 1411, 1363, 1334, 1262, 1235, 1139, 1026; δ_H (400 MHz $CDCl_3$) 1.18 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.46 (3H, s, NC<u>H</u>$_3$), 3.77 (6H, s, 2 x OC<u>H</u>$_3$), 5.34 (1H, s, (CH$_3$)$_3$CSC<u>H</u>), 6.70 (2H, m, 2 x C<u>H</u>$_{arom}$), 6.86 (2H, m, C<u>H</u>$_{arom}$ and CH$_3$NC<u>H</u>), 6.97 (1H, d, J = 2.0 Hz, NC<u>H</u>); δ_C (100 MHz $CDCl_3$) 31.1 (3 x CH$_3$), 33.4 (CH$_3$), 43.7 (CH), 44.5 (quat), 55.9 (2 x CH$_3$), 110.6 (CH), 111.4 (CH), 119.7 (CH), 121.6 (CH), 127.2 (CH), 131.7 (quat), 147.5 (quat), 148.1 (quat), 148.9 (quat); HRMS [ES] (M+H$^+$), $C_{17}H_{25}N_2O_2S$ requires m/z 321.1631, found m/z 321.1629.

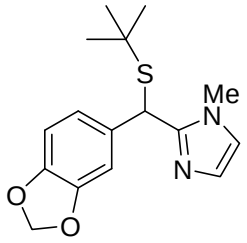
2-[n-Butylsulfanyl-(3,4-dimethoxyphenyl)-methyl]-1-methyl-1*H*-imidazole



Prepared as general procedure (B) for the synthesis of sulfides using n-butylthiol (0.90 g, 10 mmol), TFA (1.14 g, 10 mmol) and (3,4-dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol (1.24 g, 5 mmol), yielding 1.51 g (95%) of a orange oil; ν_{max}(film)/cm^{-1} 2953, 1602, 1512, 1464, 1419, 1338, 1261, 1234, 1140, 1026; δ_H (400 MHz $CDCl_3$) 0.75 (3H, t, J = 7.2 Hz, S(CH$_2$)$_3$C<u>H</u>$_3$), 1.23 (2H, m, SCH$_2$CH$_2$C<u>H</u>$_2$), 1.44 (2H, m, SCH$_2$C<u>H</u>$_2$CH$_2$), 2.37 (2H, m, SC<u>H</u>$_2$CH$_2$CH$_2$), 3.39 (3H, s, NC<u>H</u>$_3$), 3.74 (3H,

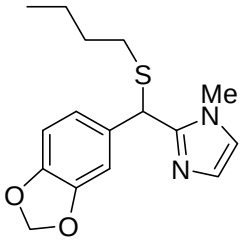
s, OC<u>H</u>$_3$), 3.79 (3H, s, OC<u>H</u>$_3$), 5.12 (1H, s, SC<u>H</u>), 6.68 (2H, m, C<u>H</u>$_{arom}$ and CH$_3$NC<u>H</u>), 6.82 (1H, ddd, *J* = 0.4, 2.0, 8.4 Hz, C<u>H</u>$_{arom}$), 6.88 (1H, d, *J* = 1.2 Hz, C=NC<u>H</u>), 6.91 (1H, d, *J* = 2.0 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 13.5 (CH_3), 21.6 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 33.2 (CH_3), 45.8 (CH), 55.9 (2 x CH_3), 110.4 (CH), 111.2 (CH), 120.3 (CH), 121.7 (CH), 127.2 (CH), 130.8 (quat), 146.5 (quat), 148.3 (quat), 149.1 (quat); HRMS [ES] ($M+H^+$), $C_{17}H_{25}N_2O_2S$ requires m/z 321.1631, found m/z 321.1629.

2-(Benzo[1,3]dioxol-5-yl-tert-butylsulfanylmethyl)-1-methyl-1*H*-imidazole



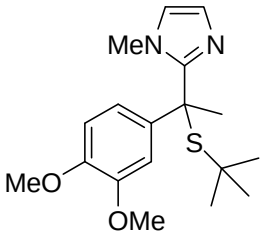
Prepared as general procedure (B) for the synthesis of sulfides using t-butylthiol (0.090 g, 1 mmol), TFA (0.114 g, 1 mmol) and benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanol (0.116 g, 0.5 mmol), yielding 0.14 g (90%) of a orange oil; ν_{max}(film)/cm^{-1} 2956, 1682, 1608, 1501, 1442, 1364, 1281, 1246, 1159, 1123, 1096, 1037, 928, 793, 739; δ_H (400 MHz $CDCl_3$) 1.10 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.45 (3H, s, NC<u>H</u>$_3$), 5.26 (1H, s, SC<u>H</u>), 5.82 (1H, d, *J* = 1.6 Hz, OCH<u>H</u>O), 5.83 (1H, d, *J* = 1.6 Hz, OCH<u>H</u>O), 6.70 (1H, d, *J* = 1.2 Hz, CH$_3$NC<u>H</u>), 6.71 (1H, d, *J* = 8.0 Hz, C<u>H</u>$_{arom}$), 6.74 (1H, ddd, *J* = 0.8, 2.0, 8.0 Hz, C<u>H</u>$_{arom}$), 6.84 (1H, d, *J* = 1.2 Hz, C=NC<u>H</u>), 6.94 (1H, d, *J* = 2.0 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 29.9 (3 x CH_3), 32.4 (CH_3), 42.5 (CH), 43.6 (quat), 100.1 (CH_2), 105.9 (CH), 106.7 (CH), 120.1 (CH), 120.7 (CH), 126.6 (CH), 132.1 (quat), 145.9 (quat), 146.2 (quat), 146.8 (quat); HRMS [ES] ($M+H^+$), $C_{16}H_{21}N_2O_2S$ requires m/z 305.1318, found m/z 305.1320.

2-(Benzo[1,3]dioxol-5-ylbutylsulfanylmethyl)-1-methyl-1*H*-imidazole



Prepared as general procedure (B) for the synthesis of sulfides using n-butylthiol (0.180 g, 2 mmol), TFA (0.150 g, 1 mmol) and benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanol (0.232 g, 1 mmol), yielding 0.28g (92%) of a orange oil; ν_{max}(film)/cm^{-1} 2956, 1723, 1486, 1243, 1037, 931, 794; δ_H (400 MHz $CDCl_3$) 0.81 (3H, t, *J* = 7.4 Hz, $S(CH_2)_3C\underline{H}_3$), 1.28 (2H, m, $SCH_2CH_2C\underline{H}_2$), 1.45 (2H, m, $SCH_2C\underline{H}_2CH_2$), 2.38 (2H, m, $SC\underline{H}_2CH_2CH_2$), 3.44 (3H, s, $NC\underline{H}_3$), 5.11 (1H, s, $SC\underline{H}$), 5.87 (1H, d, *J* = 1.6 Hz, $OCH\underline{H}O$), 5.88 (1H, d, *J* = 1.6 Hz, $OC\underline{H}HO$), 6.67 (1H, d, *J* = 8.0 Hz, $C\underline{H}_{arom}$), 6.74 (2H, m, $C\underline{H}_{arom}$ and $CH_3NC\underline{H}$), 6.91 (2H, m, $C\underline{H}_{arom}$ and $C{=}NC\underline{H}$); δ_C (100 MHz $CDCl_3$) 12.6 (CH_3), 20.9 (CH_2), 30.1 (CH_2), 30.4 (CH_2), 32.2 (CH), 44.8 (CH_3), 100.1 (CH_2), 106.8 (CH), 107.7 (CH), 120.4 (CH), 120.7 (CH), 126.1 (CH), 131.1 (quat), 145.3 (quat), 145.9 (quat), 146.9 (quat); HRMS [ES] ($M+H^+$), $C_{16}H_{21}N_2O_2S$ requires m/z 305.1318, found m/z 305.1320.

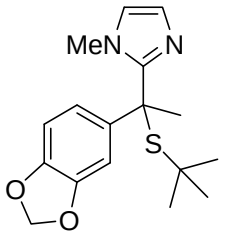
Preparation of 2-[1-tert-butylsulfanyl-1-(3,4-dimethoxyphenyl)-ethyl]-1-methyl-1*H*-imidazole



2-[tert-Butylsulfanyl-(3,4-dimethoxyphenyl)-methyl]-1-methyl-1*H*-imidazole (0.160 g, 0.5 mmol) was stirred at -78^{o}C in THF (5 ml). n-BuLi (2.5 M in hexane, 0.24 ml, 0.6 mmol) was added dropwise and the mixture stirred for 15 min. Methyl iodide (0.085 g, 0.6 mmol) was added and the reaction allowed to warm to room temperature and stir for 24 h. Water (25 ml) was then added and the mixture extracted with DCM

(3 x 25 ml). The combined organic layers were further washed with water (25 ml), dried over $MgSO_4$ then evaporated to dryness yielding 0.151 g (90%) of a yellow oil; ν_{max}(film)/cm^{-1} 2958, 2358, 1506, 1456, 1258, 1143, 1082, 1026, 804; δ_H (400 MHz $CDCl_3$) 1.07 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.17 (3H, s, SCC<u>H</u>$_3$), 3.26 (3H, s, NC<u>H</u>$_3$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.79 (3H, s, OC<u>H</u>$_3$), 6.60 (1H, dd, *J* = 2.0, 8.4 Hz, C<u>H</u>$_{arom}$), 6.69 (1H, d, *J* = 8.4 Hz, C<u>H</u>$_{arom}$), 6.74 (1H, d, *J* = 2.0 Hz, C<u>H</u>$_{arom}$), 6.78 (1H, d, *J* = 1.2 Hz, CH_3NC<u>H</u>), 6.93 (1H, d, *J* = 1.2 Hz, C=NC<u>H</u>); δ_C (100 MHz $CDCl_3$) 30.4 (3 x CH_3), 34.1 (CH_3), 34.3 (CH_3), 46.2 (quat), 51.2 (quat), 54.7 (CH_3), 54.9 (CH_3), 108.1 (CH), 109.7 (CH), 116.7 (CH), 121.6 (CH), 125.1 (CH), 138.2 (quat), 146.6 (quat), 147.7 (quat), 148.2 (quat); HRMS [ES] ($M+H^+$), $C_{18}H_{27}N_2O_2S$ requires m/z 335.1788, found m/z 335.1788.

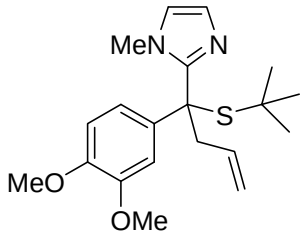
Preparation of 2-(1-benzo[1,3]dioxol-5-yl-1-tert-butylsulfanylethyl)-1-methyl-1*H*-imidazole



2-(Benzo[1,3]dioxol-5-yl-tert-butylsulfanylmethyl)-1-methyl-1*H*-imidazole (0.100 g, 0.33 mmol) was stirred at -78^{o}C in THF (5 ml). n-BuLi (2.5 M in hexane, 0.16 ml, 0.40 mmol) was added dropwise and the mixture stirred for 20 min. Methyl iodide (0.056 g, 0.40 mmol) was added and the reaction allowed to warm to room temperature and stir for 24 h. Water (25 ml) was then added and the mixture extracted with DCM (3 x 25 ml). The combined organic fractions were further washed with water (25 ml), dried over $MgSO_4$ then evaporated to dryness yielding 0.074 g (70%) of a yellow oil; ν_{max}(film)/cm^{-1} 2955, 2358, 2339, 1504, 1484, 1362, 1242, 1105, 1037, 936, 807; δ_H (400 MHz $CDCl_3$) 1.10 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.16 (3H, s, SCC<u>H</u>$_3$), 3.32 (3H, s, NC<u>H</u>$_3$), 6.56 (1H, d, *J* = 1.8 Hz, OCH<u>H</u>O), 6.57 (1H, d, *J* = 1.8 Hz, OC<u>H</u>HO), 6.60 (1H, dd, *J* = 2.0, 8.0 Hz, C<u>H</u>$_{arom}$), 6.65 (1H, d, *J* = 8.0 Hz, C<u>H</u>$_{arom}$), 6.68 (1H, d, *J* = 2.0 Hz, C<u>H</u>$_{arom}$), 6.81 (1H, d, *J* = 1.2 Hz, CH_3NC<u>H</u>), 7.01 (1H, d, *J* = 1.2 Hz, C=NC<u>H</u>); δ_C (100 MHz $CDCl_3$) 30.9 (3 x CH_3), 34.1 (CH_3), 34.4 (CH_3), 46.5

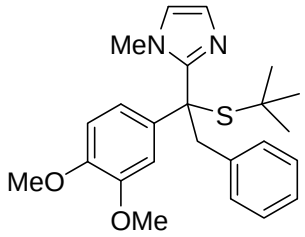
(quat), 51.2 (quat), 100.2 (CH_2), 105.5 (CH), 107.1 (CH), 117.8 (CH), 121.9 (CH), 124.1 (CH), 126.1 (quat), 145.4 (quat), 146.9 (quat), 148.1 (quat); HRMS [ES] ($M+H^+$), $C_{17}H_{23}N_2O_2S$ requires m/z 319.1475, found m/z 319.1474.

Preparation of 2-[1-tert-butylsulfanyl-1-(3,4-dimethoxyphenyl)-but-3-enyl]-1-methyl-1*H*-imidazole



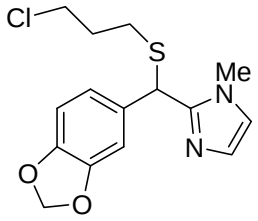
2-[tert-Butylsulfanyl-(3,4-dimethoxyphenyl)-methyl]-1-methyl-1*H*-imidazole (0.160 g, 0.5 mmol) was stirred in THF (2 ml) at -78°C. n-BuLi (2.5 M in hexane, 0.24 ml, 0.6 mmol) was then added dropwise. The mixture was stirred for 15 min then allyl bromide (0.073 g, 0.6 mmol) was added. The reaction was then allowed to return to room temperature and stirred for 24 h. The reaction was then quenched with water (25 ml) and extracted with DCM (3 x 25 ml). The combined organic fractions were then washed with water (25ml), dried over $MgSO_4$, and evaporated to dryness yielding 0.163 g of a crude orange oil. Column chromatography on silica gel was carried out using light petroleum:ethyl acetate (10:1) eluent, yielding the title compound in a yield of 0.038 g (22%) as a yellow oil; ν_{max}(film)/cm^{-1} 2956, 1513, 1463, 1408, 1362, 1260, 1145, 1026, 915, 804, 765, 697; δ_H (400 MHz $CDCl_3$) 1.06 (9H, s, $C(C\underline{H}_3)_3$), 3.18 (4H, m, $NC\underline{H}_3$ and $CCH\underline{H}CH=CH_2$), 3.52 (1H, q, *J* = 7.6 Hz, $CC\underline{H}HCH=CH_2$), 3.72 (3H, s, $OC\underline{H}_3$), 3.79 (3H, s, $OC\underline{H}_3$), 4.76 (1H, dd, *J* = 2.0, 17.2 Hz, $CCH_2CH=C\underline{H}H$), 4.87 (1H, dt, *J* = 1.2, 10.0 Hz, $CCH_2CH=CH\underline{H}$), 5.79 (1H, m, $CCH_2C\underline{H}=CH_2$), 6.59 (2H, m, 2 x $C\underline{H}_{arom}$), 6.67 (1H, d, *J* = 7.2 Hz, $C\underline{H}_{arom}$), 6.75 (1H, d, *J* = 1.2 Hz, $CH_3NC\underline{H}$), 6.94 (1H, d, *J* = 1.2 Hz, $C=NC\underline{H}$); δ_C (100 MHz $CDCl_3$) 30.6 (3 x CH_3), 33.7 (CH_3), 46.3 (quat), 46.5 (CH_2), 54.1 (quat), 54.7 (CH_3), 54.9 (CH_3), 108.9 (CH), 109.3 (CH), 116.6 (CH_2), 117.9 (CH), 121.6 (CH), 125.0 (CH), 133.3 (CH), 134.9 (quat), 146.6 (quat), 147.4 (quat), 147.9 (quat); HRMS [ES] ($M+H^+$), $C_{20}H_{29}N_2O_2S$ requires m/z 361.1944, found m/z 361.1946.

Preparation of 2-[1-tert-butylsulfanyl-1-(3,4-dimethoxyphenyl)-2-phenylethyl]-1-methyl-1*H*-imidazole



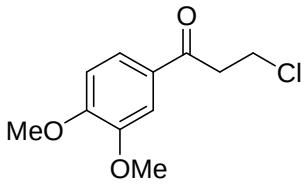
2-[tert-Butylsulfanyl-(3,4-dimethoxyphenyl)-methyl]-1-methyl-1*H*-imidazole (0.160 g, 0.5 mmol) was stirred in THF (2 ml) at -78°C. n-BuLi (2.5 M in hexane, 0.24 ml, 0.6 mmol) was then added dropwise. The reaction was stirred for 15 min then benzyl chloride (0.076 g, 0.6 mmol) was added. The reaction was then allowed to return to room temperature and stirred for a further 24 h. The reaction was then quenched with water (25 ml) and extracted with DCM (3 x 25 ml). The combined organic fractions were washed with water (25 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.195 g of a crude dark orange oil. Column chromatography on silica gel was carried out using light petroleum:ethyl acetate (8:1) eluent, yielding 0.032 g (16%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 2954, 1601, 1511, 1462, 1409, 1362, 1259, 1144, 1077, 1027, 912; δ_H (400 MHz $CDCl_3$) 1.13 (9H, s, C(C$\underline{H}_3$)$_3$), 3.16 (3H, s, NC$\underline{H}_3$), 3.44 (3H, s, OC$\underline{H}_3$), 3.79 (4H, m, OCH_3 and PhCH$\underline{H}$), 3.98 (1H, m, PhC$\underline{H}$H), 6.55 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 6.74-7.02 (9H, m, 7 x C$\underline{H}_{arom}$ and C=NC$\underline{H}$C$\underline{H}$NCH$_3$); δ_C (100 MHz $CDCl_3$) 30.9 (3 x CH_3), 33.9 (NCH_3), 46.9 (quat), 47.4 (CH_2), 54.7 (2 x CH_3), 121.6 (CH), 121.9 (CH), 123.9 (CH), 124.8 (CH), 125.1 (CH), 125.7 (CH), 125.8 (2 x CH), 130.9 (2 x CH), 134.6 (quat), 136.1 (quat), 147.9 (quat), [3 x quat not detected]; HRMS [ES] (M+H$^+$), $C_{24}H_{31}N_2O_2S$ requires 411.2101, found 411.2097.

Preparation of 2-[benzo[1,3]dioxol-5-yl-(3-chloropropylsulfanyl)-methyl]-1-methyl-1*H*-imidazole



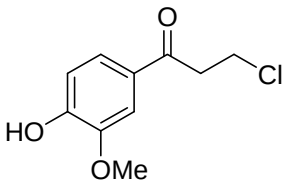
Benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanol (0.348 g, 1.5 mmol), 3-chloropropane-1-thiol (0.332 g, 3 mmol) and TFA (0.342 g, 3 mmol) were refluxed in chloroform (20 ml) for 24 h. The mixture was allowed to cool and basified with aq. $NaHCO_3$. Diethyl ether (3 x 50 ml) was used to extract the mixture, and the combined organic layers were washed with water (50 ml). The organic phase was then dried over $MgSO_4$ and evaporated to dryness yielding 0.61 g of a crude orange oil. Column chromatography using silica gel and light petroleum: ethyl acetate (5:1) eluent afforded 0.413 g (85%) of the title compound as a orange oil; ν_{max}(film)/cm^{-1} 2902, 1501, 1486, 1366, 1243, 1197, 1124, 1095, 1037, 929, 793; δ_H (400 MHz $CDCl_3$) 1.86 (2H, m, $SCH_2C\underline{H}_2CH_2Cl$), 2.53 (2H, m, $SC\underline{H}_2CH_2CH_2Cl$), 3.38 (3H, s, $NC\underline{H}_3$), 3.52 (2H, m, $SCH_2CH_2C\underline{H}_2Cl$), 5.08 (1H, s, $SC\underline{H}$), 5.83 (1H, d, *J* = 1.2 Hz, $OCH\underline{H}O$), 5.85 (1H, d, *J* = 1.2 Hz, $OC\underline{H}HO$), 6.64 (1H, d, *J* = 8.0 Hz, $C\underline{H}_{arom}$), 6.74 (2H, m, $CH_3NC\underline{H}$ and $C\underline{H}_{arom}$), 6.89 (2H, m, $C\underline{H}_{arom}$ and $C{=}NC\underline{H}$); δ_C (100 MHz $CDCl_3$) 27.6 (CH_2), 30.7 (CH_2), 32.1 (CH_3), 42.5 (CH_2), 44.8 (CH), 100.1 (CH_2), 106.5 (CH), 107.6 (CH), 120.4 (CH), 121.2 (CH), 126.2 (CH), 130.9 (quat), 144.9 (quat), 146.2 (quat), 147.1 (quat); HRMS [ES] ($M+H^+$), $C_{15}H_{18}{}^{35}ClN_2O_2S$ requires m/z 325.0772, found m/z 325.0773.

Preparation of 3-chloro-1-(3,4-dimethoxyphenyl)-propan-1-one [74]



Veratrole (1.38 g, 10 mmol), 3-chloropropionyl chloride (1.52 g, 12 mmol) and $AlCl_3$ (2.67 g, 20 mmol) were heated at 50°C for 2 h. Iced water (50 ml) was added and the mixture was extracted with DCM (3 x 50 ml). The combined organic layers were then washed with water (50 ml), dried over $MgSO_4$ and evaporated to dryness yielding 2.03 g of a crude yellow solid. Recrystallisation from diethyl ether yielded 1.17 g (51%) of the title compound as a white solid; ν_{max}(film)/cm^{-1} 1672 (C=O), 1587, 1513, 1425, 1357, 1271, 1168, 1022; δ_H (400 MHz $CDCl_3$) 3.34 (2H, t, *J* = 7.2 Hz, C$\underline{H}_2$CO), 3.83-3.89 (8H, m C$\underline{H}_2$Cl and 2 x OC$\underline{H}_3$), 6.83 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 7.46 (1H, d, *J* = 2.0 Hz, C$\underline{H}_{arom}$), 7.52 (1H, dd, *J* = 2.0, 8.4 Hz, C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 39.1 (CH_2), 40.8 (CH_2), 56.0 (2 x CH_3), 110.0 (2 x CH), 122.9 (CH), 129.7 (quat), 149.2 (quat), 153.7 (quat), 195.3 (quat); HRMS [EI] (M^+), $C_{11}H_{13}{}^{35}ClO_3$ requires m/z 228.0548, found m/z 228.0550.

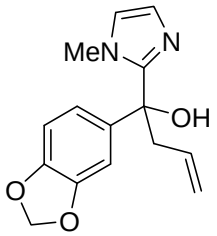
Preparation of 3-chloro-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one [75]



Veratrole (0.69 g, 5 mmol), 3-chloropropionyl chloride (0.76 g, 6 mmol) and $AlCl_3$ (1.33 g, 10 mmol) were heated at 100°C for 5 h. Iced water (50 ml) was added and the mixture was extracted with DCM (3 x 50 ml). The combined organic layers were then washed with water (50 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.96 g (90%) of a yellow oil; ν_{max}(film)/cm^{-1} 3392 (O-H), 1669 (C=O), 1589, 1515, 1426, 1348, 1275, 1187, 1030; δ_H (400 MHz $CDCl_3$) 3.33 (2H, t, *J* = 6.8 Hz,

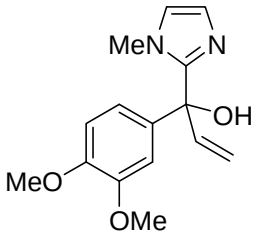
C=OC$\underline{H}_2$), 3.86 (5H, m, C$\underline{H}_2$Cl and OC$\underline{H}_3$), 6.83 (1H, d, *J* = 8.4 Hz, C$\underline{H}_{arom}$), 7.46 (2H, m, C$\underline{H}_{arom}$) [O$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 36.3 (CH_2), 39.7 (CH_2), 55.1 (CH_3), 108.9 (CH), 113.1 (CH), 122.5 (CH), 128.3 (quat), 145.8 (quat), 149.9 (quat), 194.4 (quat); HRMS [EI] (M^+), $C_{10}H_{11}{}^{35}ClO_3$ requires m/z 214.0394, found m/z 214.0391.

Preparation of 1-benzo[1,3]dioxol-5-yl-1-(1-methyl-1*H*-imidazol-2-yl)-but-3-en-1-ol



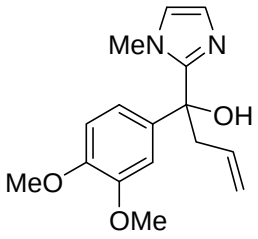
Benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanone (0.30 g, 1.3 mmol) was stirred in THF (5 ml) at 0^{o}C. Allylmagnesium chloride solution (2.0 M in THF, 1.30 ml, 2.6 mmol) was then added. The reaction was then stirred at room temperature for 24 h. Water (25 ml) was then added to quench the reaction and the mixture was extracted with diethyl ether (3 x 25 ml). The combined organic layers were then washed with brine (50 ml) and water (50 ml). The organic phase was then dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.243 g of a crude dark brown oil. Column chromatography on silica gel using light petroleum: ethyl acetate (10:1) as eluent afforded 0.173 g (49%) of the title compound as a yellow solid; mp = 163-165^{o}C; ν_{max}(film)/cm^{-1} 3124 (O-H), 2876, 1481, 1446, 1340, 1246, 1143, 1076, 1040, 931, 903, 812, 740; δ_H (400 MHz $CDCl_3$) 2.74 (1H, dd, *J* = 7.2, 14.0 Hz, CC$\underline{H}$HCH=CH_2), 3.18 (1H, dd, *J* = 7.2, 14.0 Hz, CCH$\underline{H}$CH=CH_2), 3.29 (3H, s, NC$\underline{H}_3$), 3.71 (1H, bs, O$\underline{H}$), 5.08 (2H, m, CH=C$\underline{H}_2$), 5.77-5.88 (3H, m, OC$\underline{H}_2$O and C$\underline{H}$=CH_2), 6.64 (2H, m, 2 x C$\underline{H}_{arom}$), 6.66 (1H, d, *J* = 1.2 Hz, CH_3NC$\underline{H}$), 6.73 (1H, m, C$\underline{H}_{arom}$), 6.78 (1H, d, *J* = 1.2 Hz, C=NC$\underline{H}$); δ_C (100 MHz $CDCl_3$) 33.1 (CH_3), 46.6 (CH_2), 73.1 (quat), 99.9 (CH_2), 105.2 (CH), 106.7 (CH), 117.5 (CH), 119.3 (CH_2), 121.8 (CH), 124.8 (CH), 132.7 (CH), 137.1 (quat), 145.4 (quat), 146.5 (quat), 148.8 (quat); HRMS [FAB] (M+H^+), $C_{15}H_{17}N_2O_3$ requires m/z 273.1239, found m/z 273.1236.

Preparation of 1-(3,4-dimethoxyphenyl)-1-(1-methyl-1*H*-imidazol-2-yl)-prop-2-en-1-ol



(3,4-Dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanone (0.50 g, 2.0 mmol) was stirred in THF (7.5 ml) at 0^{o}C. Vinylmagnesium bromide (1.0 M in THF, 10.0 ml, 10.0 mmol) was added and the reaction was allowed to return to room temperature and stirred for 12 h. The reaction was then quenched with water (50 ml), and extracted with DCM (3 x 50 ml). The combined organic layers were then washed with water (100 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.49 g (89%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 3107 (O-H), 2952, 1591, 1510, 1463, 1410, 1258, 1234, 1136, 1026, 913, 741; δ_H (400 MHz $CDCl_3$) 3.33 (3H, s, NC$\underline{H}_3$), 3.84 (3H, s, OC$\underline{H}_3$), 3.89 (3H, s, OC$\underline{H}_3$), 5.26 (2H, m, CH=C$\underline{H}_2$), 6.68-6.94 (6H, m, C$\underline{H}$=CH_2 and 3 x C$\underline{H}_{arom}$ and CH_3NC$\underline{H}$C$\underline{H}$N) [O$\underline{H}$ not observed]; δ_C (100 MHz $CDCl_3$) 34.2 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 75.7 (quat), 109.2 (CH), 110.6 (CH), 113.5 (CH_2), 118.3 (CH), 123.0 (CH), 126.1 (CH), 135.2 (quat), 141.7 (CH), 148.4 (quat), 148.9 (quat), 149.8 (quat); HRMS [ES] (M+H$^+$), $C_{15}H_{19}N_2O_3$ requires m/z 275.1390, found m/z 275.1391; Elemental Analysis, requires C 65.68; H 6.61; N 10.21, found C 65.33; H 6.29; N 10.21.

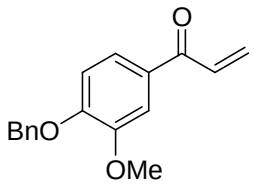
Preparation of 1-(3,4-dimethoxyphenyl)-1-(1-methyl-1*H*-imidazol-2-yl)-but-3-en-1-ol



(3,4-Dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanone (0.50 g, 2.0 mmol) was stirred in THF (7.5 ml) at 0^{o}C. Allylmagnesium bromide (2.0 M in THF, 5.0 ml,

10.0 mmol) was added and the reaction was allowed to return to room temperature and stirred for 12 h. The reaction was then quenched with water (50 ml) and extracted with DCM (3 x 50 ml). The combined organic layers were then washed with water (100 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.47 g (82%) as a yellow oil; ν_{max}(film)/cm^{-1} 3132 (O-H), 2869, 1476, 1459, 1329, 1285, 1171, 1044, 1010, 962, 902, 815, 751; δ_H (400 MHz $CDCl_3$) 2.75 (1H, dd, *J* = 8.0, 13.6 Hz, CC<u>H</u>HCH=CH_2), 3.28 (4H, m, CCH<u>H</u>CH=CH_2 and NC<u>H</u>$_3$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.78 (3H, s, OC<u>H</u>$_3$), 5.15 (2H, m, CH=C<u>H</u>$_2$), 5.81-5.90 (1H, m, C<u>H</u>=CH_2), 6.68 (3H, m, 2 x C<u>H</u>$_{arom}$ and CH_3NC<u>H</u>), 6.78 (1H, s, C<u>H</u>$_{arom}$), 6.85 (1H, d, *J* = 0.8Hz, C=NC<u>H</u>) [O<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 34.1 (CH_3), 47.7 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 74.1 (quat), 108.5 (CH), 110.6 (CH), 117.4 (CH), 120.6 (CH_2), 122.8 (CH), 125.9 (CH), 133.9 (CH), 136.6 (quat), 147.9 (quat), 148.7 (quat), 149.8 (quat); HRMS [ES] ($M+H^+$), $C_{16}H_{21}N_2O_3$ requires m/z 289.1547, found m/z 289.1551.

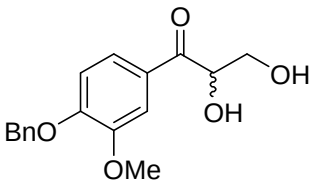
Preparation of 1-(4-benzyloxy-3-methoxyphenyl)-propenone



3-Chloro-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (0.86 g, 4.0 mmol), benzyl bromide (0.68 g, 4.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) were heated under reflux in acetone (15 ml) for 24 h. Water (50 ml) was added and then the mixture was extracted with chloroform (3 x 50 ml). The combined organic fractions were then washed with water (50 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.94 g of a crude orange oil. Column chromatography on silica gel using light petroleum: ethyl acetate (10:1) eluent afforded 0.29 g (27%) of the title compound as a clear colourless oil; ν_{max}(film)/cm^{-1} 1668 (C=O), 1587, 1566, 1502, 1475, 1436, 1309, 1301, 1278, 1244, 1193, 1138, 1091, 1022; δ_H (400 MHz $CDCl_3$) 3.95 (3H, s, OC<u>H</u>$_3$), 5.24 (2H, s, PhC<u>H</u>$_2$O), 5.86 (1H, dd, *J* = 1.6, 10.4 Hz, CH=CH<u>H</u>), 6.42 (1H, dd, *J* = 1.6, 17.2 Hz, CH=C<u>H</u>H), 6.91 (1H, d, *J* = 8.4 Hz, C<u>H</u>$_{arom}$), 7.17 (1H, dd, *J* = 10.4, 17.2 Hz, C<u>H</u>=CH_2), 7.30-7.43 (5H, m, 5 x C<u>H</u>$_{arom}$), 7.51 (1H, dd, *J* = 2.0, 8.4

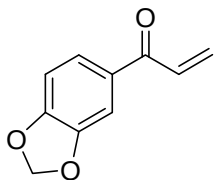
Hz, C<u>H</u>$_{arom}$), 7.59 (1H, d, *J* = 2.0 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 56.1 (CH_3), 70.8 (CH_2), 111.1 (CH), 112.1 (CH), 123.2 (CH), 127.2 (2 x CH), 128.0 (CH), 128.8 (2 x CH), 129.1 (CH_2), 130.6 (quat), 131.9 (CH), 136.2 (quat), 149.7 (quat), 152.5 (quat), 189.2 (quat); HRMS [EI] (M^+), $C_{17}H_{16}O_3$ requires m/z 268.1100, found m/z 268.1104.

Preparation of 1-(4-benzyloxy-3-methoxyphenyl)-2,3-dihydroxypropan-1-one



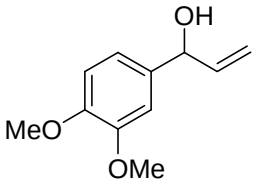
1-(4-Benzyloxy-3-methoxyphenyl)-propenone (0.268 g, 1.0 mmol), AD-mix β (1.4 g per mmol of substrate), and methylsulfonamide (0.095 g, 1.0 mmol) were stirred in ^{t}BuOH/H_2O (1:1, 10 ml) for 24 h. Sodium sulfite (1.5 g, 12.0 mmol) was then added and the reaction stirred for a further 30 min. The reaction was then extracted with chloroform (3 x 50 ml). The combined organic fractions were washed with aq. KOH (2.0 M, 50 ml), dried over $MgSO_4$ and evaporated to dryness yielding 0.180 g of a crude dark orange oil. Column chromatography on silica gel using light petroleum: ethyl acetate (2:1) eluent yielded 0.065 g (22%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 3389 (O-H), 2924, 1670 (C=O), 1589, 1557, 1539, 1511, 1456, 1418, 1267, 1108, 1016; δ_H (400 MHz $CDCl_3$) 3.64 (1H, dd, *J* = 5.2, 11.6 Hz, C<u>H</u>HOH), 3.90 (4H, m, CH<u>H</u>OH and OC<u>H</u>$_3$), 5.02 (1H, m, C<u>H</u>OH), 5.16 (2H, s, PhC<u>H</u>$_2$O), 6.85 (1H, d, *J* = 8.4 Hz, C<u>H</u>$_{arom}$), 7.24-7.31 (7H, m, 7 x C<u>H</u>$_{arom}$) [2 x O<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 55.1 (CH_3), 64.8 (CH_2), 69.9 (CH_2), 73.0 (CH), 109.9 (CH), 111.1 (CH), 122.2 (CH), 125.5 (2 x CH), 126.2 (CH), 126.9 (quat), 127.2 (2 x CH), 134.9 (quat), 148.8 (quat), 152.4 (quat), 196.5 (quat); HRMS [EI] (M^+), $C_{17}H_{18}O_5$ requires m/z 302.1154, found m/z 302.1151.

Preparation of 1-benzo[1,3]dioxol-5-yl-propenone [76]



Benzo[1,3]dioxole (0.61 g, 5 mmol) and acryloyl chloride (0.45 g, 5 mmol) were dissolved in DCM (10 ml) and the mixture stirred at 0 ^{o}C. $AlCl_3$ (1.0 g, 7.5 mmol) was then added in several small portions. The mixture was stirred for 15 min at 0 ^{o}C then allowed to return to room temperature overnight. The mixture was then filtered through a pad of celite, and the solid washed with DCM (3 x 25 ml). The combined organic layers were then reduced under vacuum to yield a crude yellow oil. Recrystallisation from diethyl ether yielded 0.80 g (91%) of the title compound as a clear colourless oil; ν_{max}(film)/cm^{-1} 2356, 1737 (C=O), 1633, 1602, 1496, 1462, 1402, 1334, 1292, 1231, 1142, 1112, 1059, 1015, 980; δ_H (400 MHz $CDCl_3$) 5.76 (2H, s, OC$\underline{H}_2$O), 5.96 (1H, dd, *J* = 1.2, 10.4 Hz, CH=CH$\underline{H}$), 6.25 (1H, dd, *J* = 10.4, 17.2 Hz, C$\underline{H}$=CH$_2$), 6.52 (1H, dd, *J* = 1.2, 17.2 Hz, CH=C$\underline{H}$H), 7.17 (3H, m, 3 x C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 77.3 (CH_2), 116.0 (CH), 123.5 (CH), 127.4 (CH), 127.7 (CH), 133.0 (CH_2), 140.6 (quat), 147.5 (quat), 163.9 (quat), 171.2 (quat); HRMS [FAB] ($M+H^+$), $C_{10}H_9O_3$ requires m/z 177.0552, found m/z 177.0547.

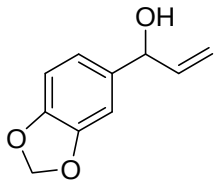
Preparation of 1-(3,4-dimethoxyphenyl)-prop-2-en-1-ol [77]



3,4-Dimethoxybenzaldehyde (1.66 g, 10 mmol) was stirred in THF (10 ml) at -78^{o}C. Vinylmagnesium bromide solution (1.0 M in THF, 20 ml, 20 mmol) was added dropwise and the mixture stirred at -78 ^{o}C for 30 min. The reaction was then allowed to warm to room temperature and stirred overnight. Water (25 ml) was added to quench, and the mixture extracted with DCM (3 x 50 ml). The combined organic

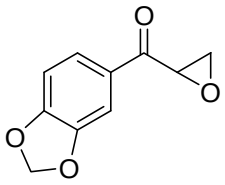
layers were washed with water (50 ml) and brine (50 ml), then dried over $MgSO_4$, filtered and reduced under vacuum to yield 1.84 g (95%) of the title compound as a light yellow oil; ν_{max}(film)/cm^{-1} 3476 (O-H), 2935, 1514, 1462, 1260, 1233, 1138, 1026, 922; δ_H (400 MHz $CDCl_3$) 3.69 (6H, s, 2 x OC<u>H</u>$_3$), 4.92 (1H, d, *J* = 5.2 Hz, C<u>H</u>OH), 5.01 (1H, dt, *J* = 1.4, 10.0 Hz, CH=C<u>H</u>H), 5.15 (1H, dt, *J* = 1.4, 17.2 Hz, CH=CH<u>H</u>), 5.87 (1H, m, C<u>H</u>=CHH), 6.67 (1H, d, *J* = 8.0 Hz, C<u>H</u>$_{arom}$), 6.72 (1H, dd, *J* = 1.6, 8.0 Hz, C<u>H</u>$_{arom}$), 6.76 (1H, d, *J* = 1.6 Hz, C<u>H</u>$_{arom}$) [O<u>H</u> not observed]; δ_C (100 MHz $CDCl_3$) 55.6 (CH_3), 55.8 (CH_3), 74.4 (CH), 108.8 (CH), 110.3 (CH), 114.2 (CH_2), 118.5 (CH), 135.3 (quat), 140.5 (CH), 148.2 (quat), 148.8 (quat); HRMS [EI] (M^+), $C_{11}H_{14}O_3$ requires m/z 194.0937, found m/z 194.0937.

Preparation of 1-benzo[1,3]dioxol-5-yl-prop-2-en-1-ol [78]



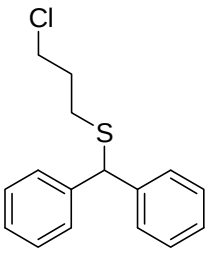
Piperonal (3.0 g, 20 mmol) was stirred in THF (10 ml) at -78^{o}C. Vinylmagnesium bromide solution (1.0 M in THF, 30 ml, 30 mmol) was added dropwise and the mixture stirred at -78^{o}C for 30 min. The reaction was then allowed to warm to room temperature and stirred overnight. Water (25 ml) was added to quench, and the mixture extracted with DCM (3 x 50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), then dried over $MgSO_4$, filtered and reduced under vacuum to yield 3.18 g (89%) of the title compound as a light yellow oil; ν_{max}(film)/cm^{-1} 3372 (O-H), 2890, 1501, 1487, 1442, 1246, 1092, 1038, 990; δ_H (400 MHz $CDCl_3$) 2.75 (1H, s, O<u>H</u>), 4.96 (1H, m, C<u>H</u>OH), 5.06 (1H, dt, *J* = 1.2, 10.4 Hz, CH=CH<u>H</u>), 5.19 (1H, dt, *J* = 1.2, 17.2 Hz, CH=C<u>H</u>H), 5.87 (3H, m, OC<u>H</u>$_2$O and C<u>H</u>=CH$_2$), 6.64 (1H, d, *J* = 7.6 Hz, C<u>H</u>$_{arom}$), 6.69 (1H, dd, *J* = 1.6, 7.6 Hz, C<u>H</u>$_{arom}$), 6.73 (1H, d, *J* = 1.6 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 74.7 (CH), 100.9 (CH_2), 106.4 (CH), 108.1 (CH), 114.9 (CH_2), 119.5 (CH), 136.8 (quat), 140.3 (CH), 146.9 (quat), 147.7 (quat); HRMS [FAB] (M^+), $C_{10}H_{10}O_3$ requires m/z 178.0630, found m/z 178.0630.

Preparation of benzo[1,3]dioxol-5-yl-oxiranyl-methanone



1-Benzo[1,3]dioxol-5-yl-prop-2-en-1-ol (0.534 g, 3 mmol) was dissolved in acetonitrile (2.5 ml) and NaOCl (5 ml, 10% aq. solution) was added. The reaction was then stirred at room temperature for 72 h. The mixture was then extracted with $CHCl_3$ (3 x 25 ml) and the combined organic layers were washed with water (50 ml), dried over $MgSO_4$, filtered, and reduced under vacuum yielding 0.41 g (71%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 1678 (C=O), 1602, 1503, 1446, 1392, 1350, 1257, 1109, 1036, 930, 896; δ_H (400 MHz $CDCl_3$) 2.88 (1H, dd, *J* = 2.6, 6.4 Hz, CHC<u>H</u>H), 3.03 (1H, dd, *J* = 4.6, 6.4 Hz, CHCH<u>H</u>), 4.09 (1H, dd, *J* = 2.6, 4.6 Hz, C<u>H</u>CH_2), 6.01 (2H, s, OC<u>H</u>$_2$O), 6.80 (1H, d, *J* = 8.4 Hz, C<u>H</u>$_{arom}$), 7.42 (1H, d, *J* = 1.8 Hz, C<u>H</u>$_{arom}$), 7.63 (1H, dd, *J* = 1.8, 8.4 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 47.5 (CH_2), 50.9 (CH), 102.1 (CH_2), 108.0 (CH), 108.2 (CH), 125.0 (CH), 130.2 (quat), 148.4 (quat), 152.6 (quat), 192.5 (quat); HRMS [FAB] ($M+NH_4^+$), $C_{10}H_{12}NO_4$ requires m/z 210.0761, found m/z 210.0759.

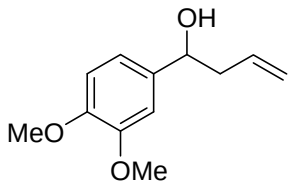
Preparation of [1-(3-chloro-propylsulfanyl)-benzyl]-benzene



Diphenylmethanol (0.276 g, 1.5 mmol) and 3-chloropropane-1-thiol (0.332 g, 3 mmol) were stirred in $CHCl_3$ (10 ml) in a RBF with a reflux condenser attached. TFA (0.342 g, 3 mmol) was added and the mixture was refluxed for 24 h. Aq. $NaHCO_3$ (25 ml) was then added and the mixture extracted with $CHCl_3$ (3 x 25 ml). The combined

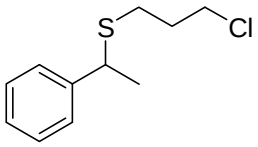
organic layers were washed with brine (50 ml), water (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.397 g (96%) of the title compound as a clear yellow oil; ν_{max}(film)/cm^{-1} 3023, 2914, 1949, 1887, 1804, 1597, 1492, 1448, 1308, 1269, 1185, 1076, 1029, 748, 701; δ_H (400 MHz $CDCl_3$) 1.85 (2H, m, $SCH_2C\underline{H}_2CH_2Cl$), 2.39 (2H, t, *J* = 6.8 Hz, $SC\underline{H}_2CH_2CH_2Cl$), 3.43 (2H, t, *J* = 6.8 Hz, $SCH_2CH_2C\underline{H}_2Cl$), 5.03 (1H, s, $SC\underline{H}$), 7.06-7.32 (10H, m, 10 x $C\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 29.4 (CH_2), 31.8 (CH_2), 43.2 (CH_2), 54.3 (CH), 127.0 (2 x CH), 128.5 (4 x CH), 129.1 (4 x CH), 141.6 (2 x quat); HRMS [FAB] ($M\text{-}H^+$), $C_{16}H_{16}{}^{35}ClS$ requires m/z 275.0661, found m/z 275.0657.

Preparation of 1-(3,4-dimethoxy-phenyl)-but-3-en-1-ol [81]



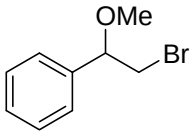
3,4-Dimethoxybenzaldehyde (5.0 g, 30 mmol) was stirred in THF (20 ml) at -78 ^oC. Allylmagnesium bromide (2.0 M in THF, 30 ml, 60 mmol) was added in several portions and the solution allowed to stir for 15 min. The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with iced water (50 ml), and the resulting mixture extracted with diethyl ether (3 x 75 ml). The combined organic layers were washed with brine (2 x 150 ml), dried over $MgSO_4$, filtered and reduced under vacuum to yield 4.91 g (79%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 3480 (O-H), 2933, 1515, 1463, 1417, 1262, 1234, 1152, 1139, 1027, 916; δ_H (400 MHz $CDCl_3$) 2.26 (1H, bs, $O\underline{H}$), 2.41 (2H, t, *J* = 6.8 Hz), 3.77 (3H, s, $OC\underline{H}_3$), 3.79 (3H, s, $OC\underline{H}_3$), 4.58 (1H, t, *J* = 6.4 Hz, $C\underline{H}OH$), 5.04 (2H, m, $CH=C\underline{H}_2$), 5.71 (1H, m, $C\underline{H}=CH_2$), 6.79 (3H, m, 3 x $C\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 43.7 (CH_2), 55.8 (2 x CH_3), 73.1 (CH), 108.9 (CH), 110.8 (CH), 117.8 (CH), 118.1 (CH_2), 134.6 (CH), 138.9 (quat), 148.3 (quat), 149.0 (quat); HRMS [EI] (M^+), $C_{12}H_{16}O_3$ requires m/z 208.1094, found m/z 208.1092.

Preparation of [1-(3-chloro-propylsulfanyl)-ethyl]-benzene



1-Phenylethanol (0.183 g, 1.5 mmol) and 3-chloropropane-1-thiol (0.332 g, 3 mmol) were stirred in $CHCl_3$ (10 ml) in a RBF with a reflux condenser attached. TFA (0.342 g, 3 mmol) was then added, and the mixture was refluxed for 24 h. Aq. $NaHCO_3$ (25 ml) was added and the mixture extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were washed with brine (50 ml), water (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.30 g (93%) of the title compound as a clear yellow oil; ν_{max}(film)/cm^{-1} 2922, 1941, 1884, 1809, 1599, 1445, 1308, 1269, 1086, 1019, 753; δ_H (400 MHz $CDCl_3$) 1.47 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 1.81 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.39 (2H, m, $SC\underline{H}_2CH_2$), 3.47 (2H, m, $CH_2C\underline{H}_2Cl$), 3.89 (1H, q, J = 6.5 Hz, $C\underline{H}CH_3$), 7.13 - 7.28 (5H, m, 5 x $C\underline{H}_{arom}$); HRMS [FAB] ($M+H^+$), $C_{11}H_{15}{}^{35}ClS$ requires m/z 215.0656, found m/z 215.0658.

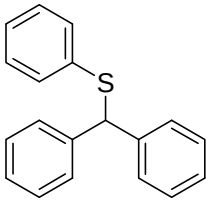
Preparation of (±)-(2-bromo-1-methoxyethyl)-benzene [82]



Styrene (2.0 g, 19.2 mmol) and NBS (6.83 g, 38.4 mmol) were stirred at room temperature in MeOH:H_2O (25 ml, 4:1) for 2 h. Conc. sodium thiosulfate aq. solution (50 ml) was then added and the mixture was stirred for 10 min before being extracted with $CHCl_3$ (3 x 50 ml). The combined organic layers were then washed with water (100 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 3.3 g (80%) of the title compound as a yellow oil; ν_{max}(film)/cm^{-1} 2933, 1683, 1453, 1209, 1111, 765; δ_H (400 MHz $CDCl_3$) 3.30 (3H, s, $OC\underline{H}_3$), 3.48 (1H, dd, J = 6.0, 10.6 Hz, $C\underline{H}HBr$), 3.57 (1H, dd, J = 2.4, 10.8 Hz, $CH\underline{H}Br$), 4.39 (1H, dd, J = 4.0, 8.4 Hz,

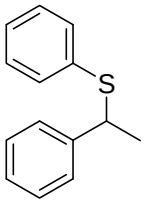
C<u>H</u>OCH_3), 7.26 – 7.39 (5H, m, 5 x CH_{arom}); δ_C (100 MHz $CDCl_3$) 35.2 (CH_2), 56.2 (CH_3), 82.4 (CH), 124.9 (2 x CH), 127.8 (2 x CH), 128.1 (CH), 138.0 (quat).

Preparation of diphenyl-methylthiophenyl ether [83]



Diphenylmethanol (3.68 g, 20 mmol) and benzenethiol (2.20 g, 20 mmol), were stirred in $CHCl_3$ (15 ml) and TFA (2.97 ml, 40 mmol) was added dropwise. The mixture was then refluxed for 24 h. Aq. $NaHCO_3$ (25 ml) was added and the mixture extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 4.72 g (86%) of a yellow solid; mp = 185 - 186 ^oC; ν_{max}(film)/cm^{-1} 3023, 1951, 1597, 1581, 1490, 1445, 1402, 1191, 1075, 1029, 734, 698; δ_H (400 MHz $CDCl_3$) 5.62 (1H, s, SC<u>H</u>), 7.30 – 7.46 (15H, m, 15 x C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 56.4 (CH), 126.6 (CH), 126.7 (2 x CH), 128.5 (2 x CH), 128.7 (4 x CH), 128.9 (2 x CH), 130.6 (4 x CH), 136.4 (quat), 141.3 (2 x quat); HRMS [FAB] (M^+), $C_{19}H_{16}S$ requires m/z 276.0793, found m/z 276.0786.

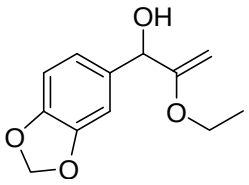
Preparation of 1-phenyl-ethanethiophenyl ether [84]



1-Phenylethanol (2.44 g, 20 mmol) and benzenethiol (2.20 g, 20 mmol), were stirred in $CHCl_3$ (15 ml) and TFA (2.97 ml, 40 mmol) was added dropwise. The mixture was then refluxed for 24 h. Aq. $NaHCO_3$ (25 ml) was added and the mixture extracted

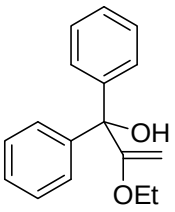
with $CHCl_3$ (3 x 25 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 4.12 g (96%) of a yellow oil; ν_{max}(film)/cm^{-1} 3024, 2965, 1599, 1581, 1491, 1450, 1371, 1220, 1087, 1048, 1025, 832, 747, 697; δ_H (400 MHz $CDCl_3$) 1.79 (3H, d, *J* = 6.5 Hz, CHC<u>H</u>$_3$), 4.20 (1H, q, *J* = 6.5 Hz, SC<u>H</u>), 6.89 – 7.27 (10H, m, 10 x C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 22.3 (CH_3), 44.5 (CH), 126.3 (CH), 127.3 (2 x CH), 127.7 (2 x CH), 128.5 (CH), 128.8 (2 x CH), 132.6 (2 x CH), 143.4 (quat), 145.7 (quat); HRMS [FAB] (M^+), $C_{14}H_{14}S$ requires m/z 214.0816, found m/z 214.0819.

Preparation of 1-benzo[1,3]dioxol-5-yl-2-ethoxy-prop-2-en-1-ol



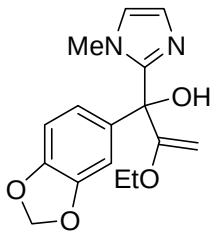
Ethyl vinyl ether (0.36 g, 5 mmol) was stirred in THF (5 ml) at -78 ^oC. t-BuLi (1.7 M in hexane, 2.94 ml, 5 mmol) was added dropwise and the mixture stirred for 30 min. Piperonal (0.30 g, 2 mmol) in THF (5 ml) was then added and the reaction mixture was stirred for 12 h at RT. The mixture was quenched with ethanol (2 ml) at 0 ^oC, then iced water (25 ml) was added to the mixture and extracted with diethyl ether (3 x 25 ml). The combined organic layers were then washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.27 g (61%) of the title compound as a clear light yellow oil; ν_{max}(film)/cm^{-1} 3455 (O-H), 2975, 2891, 1502, 1487, 1441, 1244, 1094, 1038, 933, 810; δ_H (400 MHz $CDCl_3$) 1.24 (3H, t, *J* = 7.2 Hz, OCH$_2$C<u>H</u>$_3$), 2.56 (1H, bs, O<u>H</u>), 3.74 (2H, q, *J* = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 4.06 (1H, d, *J* = 2.0 Hz, C=C<u>H</u>H), 4.19 (1H, d, *J* = 2.0 Hz, C=CH<u>H</u>), 5.01 (1H, d, *J* = 4.8 Hz, C<u>H</u>OH), 5.93 (2H, s, OC<u>H</u>$_2$O), 6.77 (1H, d, *J* = 8.0 Hz, C<u>H</u>$_{arom}$), 6.88 (1H, dd, *J* = 1.6, 8.0 Hz, C<u>H</u>$_{arom}$), 6.93 (1H, d, *J* = 1.6 Hz, C<u>H</u>$_{arom}$); δ_C (100 MHz $CDCl_3$) 14.3 (CH_3), 64.1 (CH_2), 74.6 (CH), 82.1 (CH_2), 100.8 (CH_2), 107.2 (CH), 108.5 (CH), 120.2 (CH), 135.5 (quat), 146.6 (quat), 148.0 (quat), 162.7 (quat); HRMS [FAB] (M^+), $C_{12}H_{14}O_4$ requires m/z 222.0892, found m/z 222.0893.

Preparation of 2-ethoxy-1,1-diphenyl-prop-2-en-1-ol

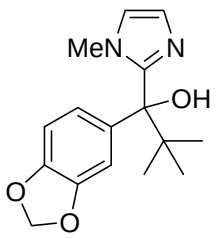


Ethyl vinyl ether (0.14 g, 2 mmol) was stirred in THF (4 ml) at -78 ^{o}C. t-BuLi (1.7 M in hexane, 1.76 ml, 3 mmol) was added dropwise and the mixture was stirred for 15 min. Benzophenone (0.36 g, 2 mmol) in THF (5 ml) was then added and the reaction was stirred for 24 h at RT. The mixture was quenched with methanol (2.5 ml) at 0 ^{o}C, then iced water (25 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic layers were then washed with brine (25 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.39 g (77%) of the title compound as a clear colourless oil; ν_{max}(film)/cm^{-1} 3563 (O-H), 2976, 1490, 1446, 1256, 1170, 1066, 1032, 972, 820, 761, 699; δ_H (400 MHz $CDCl_3$) 1.14 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 3.47 (1H, s, O$\underline{H}$), 3.71 (3H, m, $OC\underline{H}_2CH_3$ and C=C$\underline{H}$H), 4.19 (1H, d, *J* = 2.8 Hz, C=CH$\underline{H}$), 7.11 – 7.43 (10H, m, 10 x $C\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 15.2 (CH_3), 63.7 (CH_2), 81.2 (quat), 86.7 (CH_2), 126.4 (2 x CH), 127.1 (4 x CH), 128.0 (4 x CH), 144.8 (2 x quat), 164.1 (quat); HRMS [FAB] (M^+), $C_{17}H_{18}O_2$ requires m/z 254.1307, found m/z 254.1306.

Attempted preparation of 1-benzo[1,3]dioxol-5-yl-2-ethoxy-1-(1-methyl-1H-imidazol-2-yl)-prop-2-en-1-ol (189)



189



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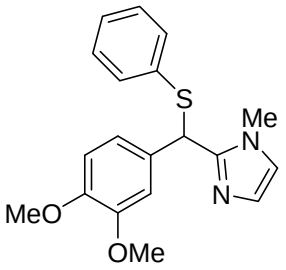
Ethyl vinyl ether (0.22 g, 3 mmol) was stirred in THF (5 ml) at -78 ^{o}C. t-BuLi (1.7 M in hexane, 1.76 ml, 3 mmol) was added dropwise and the mixture stirred for 15 min.

Benzo[1,3]dioxol-5-yl-(1-methyl-1*H*-imidazol-2-yl)-methanone (0.46 g, 2 mmol) in THF (7.5 ml) was then added and the mixture was stirred at -78 ^{o}C –> RT overnight. The reaction was quenched with ethanol (2 ml) at 0 ^{o}C followed by iced water (25 ml). The mixture was extracted with diethyl ether (3 x 25 ml) and the combined organic layers further washed with water (50 ml). The organic was then dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.31 g of a crude mixture. Column chromatography on silica gel with a light petroleum: ethyl acetate (10:1) eluent gave a trace yield of the compound tentatively assigned as the *t*-butyl addition product **(193)**; ν_{max}(film)/cm^{-1} 3482 (O-H), 2988, 1564, 1533, 1481, 1429, 1209, 1078, 801, 763; δ_H (400 MHz $CDCl_3$) 1.18 (9H, s), 3.13 (3H, s), 5.86 (1H, d, *J* = 1.5 Hz), 5.88 (1H, d, *J* = 1.5 Hz), 6.47 – 6.79 (5H, m). No parent ion detected in mass spectrum.

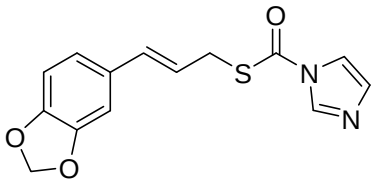
Preparation of 2-[(3,4-dimethoxy-phenyl)-phenylsulfanylmethyl]-1-methyl-*1H*-imidazole



(3,4-Dimethoxyphenyl)-(1-methyl-1*H*-imidazol-2-yl)-methanol (0.49 g, 2 mmol), benzenethiol (0.44 g, 4 mmol) and TFA (0.46 g, 4 mmol) in $CHCl_3$ (10 ml) were refluxed for 48 h. Water (20 ml) was then added and the mixture extracted with $CHCl_3$ (3 x 20 ml). The combined organic layers were then washed with aq. $NaHCO_3$ (2 x 50 ml) then dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.67 g (98%) of the title compound as a orange oil; ν_{max}(film)/cm^{-1} 2932, 2359, 1582, 1512, 1462, 1336, 1261, 1139, 1025, 740, 691; δ_H (400 MHz $CDCl_3$) 3.19 (3H, s, NC$\underline{H}_3$), 3.65 (3H, s, OC$\underline{H}_3$), 3.70 (3H, s, OC$\underline{H}_3$), 5.30 (1H, s, SC$\underline{H}$), 6.60 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 6.67(1H, d, *J* = 1.2 Hz, NC$\underline{H}$), 6.69 (1H, dd, *J* = 2.0, 8.0 Hz, C$\underline{H}_{arom}$), 6.82 (1H, d, *J* = 2.0 Hz, C$\underline{H}_{arom}$), 6.92 (1H, d, *J* = 1.2 Hz, NC$\underline{H}$), 7.07 – 7.19 (5H, m, 5 x C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 32.2 (CH_3), 49.3 (CH), 55.0 (CH_3), 55.1 (CH_3), 109.9

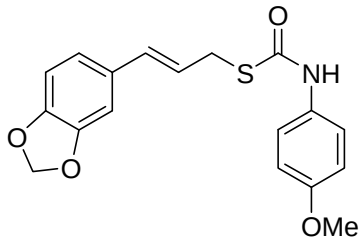
(CH), 110.7 (CH), 119.8 (CH), 120.7 (CH), 126.3 (CH), 126.7 (CH), 128.0 (2 x CH), 128.6 (2 x CH), 129.9 (quat), 133.6 (quat), 145.2 (quat), 147.7 (quat), 148.1 (quat); HRMS [FAB] ($M+H^+$), $C_{19}H_{21}N_2O_2S$ requires m/z 341.1324, found m/z 341.1322.

Preparation of imidazole-1-carbothioic acid S-(3-benzo[1,3]dioxol-5-yl-allyl) ester



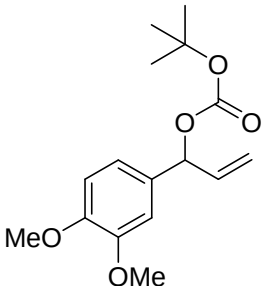
1-Benzo[1,3]dioxol-5-yl-prop-2-en-1-ol (0.36 g, 2 mmol), TCDI (0.53 g, 3 mmol) and TEA (0.30 g, 3 mmol) in $CHCl_3$ (10 ml) were refluxed for 24 h. Water (50 ml) was added and the mixture extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were then washed with water (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.97 g of a crude dark orange oil. Silica gel column chromatography with a light petroleum: ethyl acetate (20:1) eluent yielded 0.11 g (19%) of a yellow solid tentatively assigned as the title compound; mp = 184 - 185 ^oC; ν_{max}(film)/cm^{-1} 2358, 1600, 1485, 1443, 1248, 1035, 973; δ_H (400 MHz $CDCl_3$) 4.18 (2H, dd, *J* = 0.8, 7.6 Hz, C$\underline{H}_2$S), 5.94 (2H, s, OC$\underline{H}_2$O), 6.04 (1H, dt, *J* = 7.6, 15.6 Hz, CH=C$\underline{H}$CH$_2$), 6.55 (1H, d, *J* = 15.6 Hz, C$\underline{H}$=CHCH$_2$), 6.73 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 6.78 (1H, dd, *J* = 1.6, 8.0 Hz, C$\underline{H}_{arom}$), 6.89 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), [imidazole C$\underline{H}$'s not observed]; δ_C (100 MHz $CDCl_3$) 39.7 (CH_2), 101.1 (CH_2), 105.7 (CH), 108.3 (CH), 120.3 (CH), 121.3 (CH), 130.8 (quat), 134.4 (CH), 147.5 (quat), 148.1 (quat), 222.6 (quat), [imidazole $\underline{C}$s not observed].

Preparation of (4-methoxy-phenyl)-thiocarbamic acid S-(3-benzo[1,3]dioxol-5-yl-allyl) ester



1-Benzo[1,3]dioxol-5-yl-prop-2-en-1-ol (0.36 g, 2 mmol) was stirred in THF (7.5 ml) at 0 ^{o}C. Sodium hydride (60% oil disp., 0.16 g, 4 mmol) was added and the mixture was stirred for 15 min. 1-Isothiocyanato-4-methoxybenzene (0.33 g, 2 mmol) was added and the mixture was allowed to stir at RT for 12 h. Water (25 ml) was then added and the mixture was extracted with diethyl ether (3 x 25 ml). The combined organic layers were washed with brine (50 ml) and water (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.42 g of the crude product. Recrystallisation from $CHCl_3$ and hexane afforded 0.21 g (30%) of the title compound as a white solid; mp = 239 – 241 ^{o}C; ν_{max}(film)/cm^{-1} 1642, 1509, 1204, 1029, 966, 929, 822; δ_H (400 MHz $CDCl_3$) 3.70 (5H, m, C$\underline{H}_2$S and OC$\underline{H}_3$), 5.86 (2H, s, OC$\underline{H}_2$O), 6.00 (1H, dt, *J* = 7.6, 15.6 Hz, CH=C$\underline{H}$CH$_2$), 6.40 (1H, d, *J* = 15.6 Hz, C$\underline{H}$=CHCH$_2$), 6.66 (1H, d, *J* = 8.0 Hz, C$\underline{H}_{arom}$), 6.71 (1H, dd, *J* = 1.6, 8.0 Hz, C$\underline{H}_{arom}$), 6.77 (2H, m, 2 x C$\underline{H}_{arom}$), 6.83 (1H, d, *J* = 1.6 Hz, C$\underline{H}_{arom}$), 6.95 (1H, bs, N$\underline{H}$), 7.23 (2H, d, *J* = 8.8 Hz, 2 x C$\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 30.9 (CH_2), 55.5 (CH_3), 101.1 (CH_2), 105.7 (CH), 108.3 (CH), 114.3 (2 x CH), 121.4 (CH), 122.3 (2 x CH), 123.3 (CH), 131.1 (quat), 132.6 (CH), 147.3 (quat), 148.0 (quat) [3 x quat not detected]; HRMS [ES] (M+H$^+$), $C_{18}H_{18}NO_4S$ requires m/z 344.0951, found m/z 344.0948.

Preparation of carbonic acid tert-butyl ester 1-(3,4-dimethoxyphenyl)-allyl ester



Method A:

1-(3,4-Dimethoxyphenyl)-prop-2-en-1-ol (0.29 g, 1.5 mmol), TEA (0.15 g, 1.5 mmol) and Boc_2O (0.33 g, 1.5 mmol) were stirred in $CHCl_3$ (5 ml) at RT for 5 days. Water (25 ml) was added and the mixture extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were washed with water (50 ml), dried over $MgSO_4$, filtered and reduced to dryness yielding 0.51 g of a crude mixture. Silica gel column chromatography with light petroleum: ethyl acetate (10:1) eluent yielded 0.19 g (43%) of the title compound as a white solid (see data overleaf).

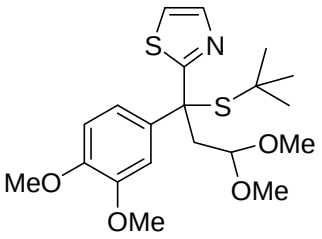
Method B:

1-(3,4-Dimethoxy-phenyl)-prop-2-en-1-ol ol (0.291 g, 1.50 mmol) was stirred in THF (5 ml) at 0 ^oC. Sodium hydride (60% oil disp., 0.054 g, 2.25 mmol) was added and the mixture was stirred for 20 min. Boc_2O (0.327 g, 1.5 mmol) was then added and the mixture was allowed to return to RT and stirred overnight. Iced water (20 ml) was added and the mixture extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with brine (20 ml) and water (20 ml), then dried over $MgSO_4$, filtered and reduced to dryness yielding 0.41 g (93%) of the title compound as a white solid. (see data overleaf).

ν_{max}(film)/cm^{-1} 2981, 2930, 2358, 1809, 1771, 1755, 1738, 1520, 1456, 1371, 1305, 1260, 1212, 1119, 1070; δ_H (400 MHz $CDCl_3$) 1.41 (9H, s, $C(C\underline{H}_3)_3$), 3.78 (3H, s, $OC\underline{H}_3$), 3.80 (3H, s, $OC\underline{H}_3$), 5.17 (2H, m, $CH=C\underline{H}_2$), 5.90 (2H, m, $C\underline{H}C\underline{H}=CH_2$), 6.75 (1H, d, J = 8.0 Hz, $C\underline{H}_{arom}$), 6.80 (1H, d, J = 2.0 Hz, $C\underline{H}_{arom}$), 6.83 (1H, dd, J = 2.0, 8.0 Hz, $C\underline{H}_{arom}$); δ_C (100 MHz $CDCl_3$) 27.5 (3 x CH_3), 55.7 (2 x CH_3), 79.0 (CH), 82.2 (quat), 110.2 (CH), 110.9 (CH), 116.7 (CH_2), 119.8 (CH), 131.2 (quat), 136.2

(CH), 146.7 (quat), 148.9 (quat), 152.7 (quat); HRMS [FAB] (M^+), $C_{16}H_{22}O_5$ requires m/z 294.1467, found m/z 294.1460.

Attempted preparation of 2-[1-tert-butylsulfanyl-1-(3,4-dimethoxyphenyl)-3,3-dimethoxypropyl]-thiazole



2-[tert-Butylsulfanyl-(3,4-dimethoxy-phenyl)-methyl]-thiazole (0.162 g, 0.5 mmol) was stirred in THF (5 ml) at -78 ^oC. n-BuLi (2.5M in hexane, 0.24 ml, 0.6 mmol) was added dropwise and the mixture was stirred for 20 min. 2-Bromo-1,1-dimethoxy-ethane (0.101 g, 0.6 mmol) was then added and the reaction was allowed to return to RT and stirred overnight. Water (20 ml) was added and the mixture was extracted with $CHCl_3$ (3 x 20 ml). The combined organic layers were further washed with water (25 ml), dried over $MgSO_4$, filtered and evaporated to dryness yielding 0.139 g of a crude mixture of products. Silica gel column chromatography using light petroleum: ethyl acetate (20:1) as eluent yielded 0.109 g (67% recovery) of the sulfide starting material, and a trace yield of an unidentifiable product; ν_{max}(film)/cm^{-1} 2957.4, 1511.8, 1460.0, 1259.3, 1026.3, 798.5; δ_H (400 MHz $CDCl_3$) 1.10 (9H, s), 2.46 (2H, m), 3.76 (3H, s), 3.88 (3H, s), 6.71 (1H, d), 7.05 (2H, m), 7.24 (1H, d), 7.64 (1H, d); LRMS (EI) m/z 290 (100%) 274 (12%).

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5 - Appendices

5.1 – X-ray crystal data and structure refinement for 2-(Benzo[1,3]dioxol-5-yl-tert-butylsulfanyl-methyl)-1-methyl-1*H*-imidazole

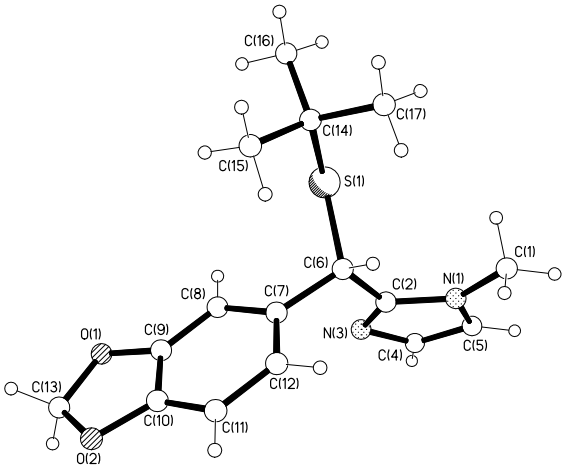

Table 1.

Identification code	gw37dl-(PAR/ME)	
Chemical formula	$C_{16}H_{20}N_2O_2S$	
Formula weight	304.40	
Temperature	150(2) K	
Radiation, wavelength	synchrotron, 0.6911 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 28.261(3) Å	α = 90°
	b = 5.8269(6) Å	β = 111.014(2)°
	c = 20.3766(19) Å	γ = 90°
Cell volume	3132.3(5) $Å^3$	
Z	8	
Calculated density	1.291 g/cm^3	
Absorption coefficient μ	0.213 mm^{-1}	
F(000)	1296	
Crystal colour and size	colourless, 0.10 × 0.05 × 0.03 mm^3	
Reflections for cell refinement	7909 (θ range 3.56 to 29.58°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	

θ range for data collection	1.49 to 25.00°
Index ranges	h –25 to 34, k –7 to 6, l –22 to 24
Completeness to θ = 25.00°	98.3 %
Intensity decay	3%
Reflections collected	17195
Independent reflections	5890 (R_{int} = 0.0620)
Reflections with $F^2>2\sigma$	5441
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.979 and 0.994
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1500, 1.3313
Data / restraints / parameters	5890 / 0 / 389
Final R indices [$F^2>2\sigma$]	R1 = 0.0843, wR2 = 0.2079
R indices (all data)	R1 = 0.0874, wR2 = 0.2129
Goodness-of-fit on F^2	1.068
Extinction coefficient	0.037(6)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	1.577 and –0.533 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.19965(18)	0.5669(8)	0.1535(2)	0.0473(11)
N(1)	0.21050(12)	0.3942(6)	0.20884(17)	0.0329(7)
C(2)	0.18547(13)	0.3564(6)	0.25381(18)	0.0268(7)
N(3)	0.20487(12)	0.1853(6)	0.29641(19)	0.0380(8)
C(4)	0.24441(15)	0.1066(8)	0.2773(2)	0.0425(10)
C(5)	0.24858(13)	0.2330(8)	0.2244(2)	0.0383(10)
C(6)	0.13816(12)	0.4805(6)	0.24920(17)	0.0249(7)
C(7)	0.13510(11)	0.5259(6)	0.32094(18)	0.0232(7)
C(8)	0.11748(12)	0.3576(6)	0.35605(18)	0.0235(7)
C(9)	0.11796(12)	0.4112(6)	0.42163(18)	0.0246(7)
C(10)	0.13485(12)	0.6185(6)	0.45317(18)	0.0255(7)

C(11)	0.15259(13)	0.7847(6)	0.4202(2)	0.0286(8)
C(12)	0.15200(12)	0.7378(6)	0.35339(19)	0.0250(7)
O(1)	0.10308(11)	0.2736(5)	0.46631(15)	0.0373(7)
C(13)	0.1118(2)	0.4087(8)	0.5266(2)	0.0529(12)
O(2)	0.13096(10)	0.6260(5)	0.51851(14)	0.0350(6)
S(1)	0.08664(3)	0.30088(15)	0.19081(4)	0.0265(3)
C(14)	0.03393(12)	0.5003(6)	0.14834(18)	0.0281(7)
C(15)	0.02028(14)	0.6420(7)	0.2012(2)	0.0337(8)
C(16)	–0.00952(14)	0.3388(7)	0.1087(2)	0.0379(9)
C(17)	0.04673(15)	0.6563(8)	0.0966(2)	0.0397(9)
C(1')	0.29973(17)	0.5831(7)	–0.0384(2)	0.0429(10)
N(1')	0.28987(11)	0.3996(5)	0.00341(16)	0.0294(7)
C(2')	0.31640(12)	0.3509(6)	0.07215(17)	0.0239(7)
N(3')	0.29677(12)	0.1770(6)	0.09485(17)	0.0339(7)
C(4')	0.25530(13)	0.1100(7)	0.0368(2)	0.0380(9)
C(5')	0.25088(12)	0.2452(8)	–0.0190(2)	0.0324(8)
C(6')	0.36457(11)	0.4692(6)	0.11490(17)	0.0235(7)
C(7')	0.36700(11)	0.5166(6)	0.18896(17)	0.0216(7)
C(8')	0.38249(12)	0.3491(6)	0.24146(18)	0.0246(7)
C(9')	0.38022(13)	0.4045(6)	0.30556(19)	0.0267(7)
C(10')	0.36373(13)	0.6165(6)	0.31877(19)	0.0273(7)
C(11')	0.34892(14)	0.7811(6)	0.2694(2)	0.0299(8)
C(12')	0.35043(12)	0.7329(6)	0.20320(19)	0.0251(7)
O(1')	0.39367(12)	0.2699(5)	0.36548(14)	0.0386(7)
C(13')	0.3772(3)	0.3995(8)	0.4125(3)	0.0722(19)
O(2')	0.36667(12)	0.6265(5)	0.38799(14)	0.0406(7)
S(1')	0.41556(3)	0.28419(16)	0.10837(5)	0.0257(3)
C(14')	0.46793(12)	0.4855(6)	0.11481(18)	0.0285(8)
C(15')	0.48096(14)	0.6354(7)	0.1805(2)	0.0351(9)
C(16')	0.51139(14)	0.3262(7)	0.1197(2)	0.0388(9)
C(17')	0.45370(16)	0.6349(8)	0.0494(2)	0.0412(9)

Table 3. Bond lengths [Å] and angles [°]

C(1)–N(1)	1.459(5)	N(1)–C(2)	1.362(4)
N(1)–C(5)	1.377(5)	C(2)–N(3)	1.306(5)

C(2)–C(6)	1.493(5)	N(3)–C(4)	1.387(5)
C(4)–C(5)	1.345(6)	C(6)–C(7)	1.518(5)
C(6)–S(1)	1.841(3)	C(7)–C(12)	1.401(5)
C(7)–C(8)	1.406(5)	C(8)–C(9)	1.368(5)
C(9)–C(10)	1.371(5)	C(9)–O(1)	1.387(4)
C(10)–C(11)	1.371(5)	C(10)–O(2)	1.376(4)
C(11)–C(12)	1.383(5)	O(1)–C(13)	1.404(5)
C(13)–O(2)	1.410(5)	S(1)–C(14)	1.842(3)
C(14)–C(15)	1.513(5)	C(14)–C(16)	1.528(5)
C(14)–C(17)	1.530(5)	C(1')–N(1')	1.455(5)
N(1')–C(2')	1.361(4)	N(1')–C(5')	1.368(5)
C(2')–N(3')	1.316(4)	C(2')–C(6')	1.496(4)
N(3')–C(4')	1.390(5)	C(4')–C(5')	1.352(6)
C(6')–C(7')	1.511(5)	C(6')–S(1')	1.842(3)
C(7')–C(8')	1.398(5)	C(7')–C(12')	1.410(5)
C(8')–C(9')	1.369(5)	C(9')–C(10')	1.380(5)
C(9')–O(1')	1.385(4)	C(10')–C(11')	1.344(5)
C(10')–O(2')	1.384(4)	C(11')–C(12')	1.393(5)
O(1')–C(13')	1.423(5)	C(13')–O(2')	1.408(6)
S(1')–C(14')	1.856(3)	C(14')–C(16')	1.514(5)
C(14')–C(17')	1.520(5)	C(14')–C(15')	1.528(5)

C(2)–N(1)–C(5)	106.7(3)	C(2)–N(1)–C(1)	128.0(3)
C(5)–N(1)–C(1)	125.3(3)	N(3)–C(2)–N(1)	112.0(3)
N(3)–C(2)–C(6)	124.4(3)	N(1)–C(2)–C(6)	123.3(3)
C(2)–N(3)–C(4)	104.7(3)	C(5)–C(4)–N(3)	110.8(4)
C(4)–C(5)–N(1)	105.8(3)	C(2)–C(6)–C(7)	112.5(3)
C(2)–C(6)–S(1)	104.4(2)	C(7)–C(6)–S(1)	114.6(2)
C(12)–C(7)–C(8)	119.8(3)	C(12)–C(7)–C(6)	118.7(3)
C(8)–C(7)–C(6)	121.4(3)	C(9)–C(8)–C(7)	117.2(3)
C(8)–C(9)–C(10)	122.6(3)	C(8)–C(9)–O(1)	127.6(3)
C(10)–C(9)–O(1)	109.8(3)	C(9)–C(10)–C(11)	121.3(3)
C(9)–C(10)–O(2)	110.3(3)	C(11)–C(10)–O(2)	128.4(3)
C(10)–C(11)–C(12)	117.7(3)	C(11)–C(12)–C(7)	121.4(3)
C(9)–O(1)–C(13)	104.5(3)	O(1)–C(13)–O(2)	110.9(3)
C(10)–O(2)–C(13)	104.6(3)	C(6)–S(1)–C(14)	105.30(16)
C(15)–C(14)–C(16)	110.5(3)	C(15)–C(14)–C(17)	110.5(3)

C(16)–C(14)–C(17)	110.2(3)	C(15)–C(14)–S(1)	112.3(2)
C(16)–C(14)–S(1)	102.8(2)	C(17)–C(14)–S(1)	110.3(2)
C(2')–N(1')–C(5')	106.6(3)	C(2')–N(1')–C(1')	127.3(3)
C(5')–N(1')–C(1')	126.0(3)	N(3')–C(2')–N(1')	112.1(3)
N(3')–C(2')–C(6')	124.1(3)	N(1')–C(2')–C(6')	123.6(3)
C(2')–N(3')–C(4')	104.5(3)	C(5')–C(4')–N(3')	110.3(3)
C(4')–C(5')–N(1')	106.4(3)	C(2')–C(6')–C(7')	111.8(3)
C(2')–C(6')–S(1')	105.1(2)	C(7')–C(6')–S(1')	115.0(2)
C(8')–C(7')–C(12')	120.2(3)	C(8')–C(7')–C(6')	121.7(3)
C(12')–C(7')–C(6')	118.0(3)	C(9')–C(8')–C(7')	117.1(3)
C(8')–C(9')–C(10')	122.1(3)	C(8')–C(9')–O(1')	128.0(3)
C(10')–C(9')–O(1')	109.9(3)	C(11')–C(10')–C(9')	121.9(3)
C(11')–C(10')–O(2')	128.5(3)	C(9')–C(10')–O(2')	109.6(3)
C(10')–C(11')–C(12')	118.1(3)	C(11')–C(12')–C(7')	120.5(3)
C(9')–O(1')–C(13')	103.9(3)	O(2')–C(13')–O(1')	109.7(4)
C(10')–O(2')–C(13')	104.5(3)	C(6')–S(1')–C(14')	104.45(16)
C(16')–C(14')–C(17')	111.2(3)	C(16')–C(14')–C(15')	111.0(3)
C(17')–C(14')–C(15')	110.2(3)	C(16')–C(14')–S(1')	103.0(3)
C(17')–C(14')–S(1')	110.3(2)	C(15')–C(14')–S(1')	111.0(2)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$)

	x	y	z	U
H(1A)	0.1654	0.5427	0.1191	0.071
H(1B)	0.2244	0.5537	0.1301	0.071
H(1C)	0.2019	0.7202	0.1742	0.071
H(4)	0.2657	–0.0195	0.2986	0.051
H(5)	0.2728	0.2149	0.2023	0.046
H(6)	0.1376	0.6313	0.2255	0.030
H(8)	0.1057	0.2128	0.3351	0.028
H(11)	0.1649	0.9271	0.4425	0.034
H(12)	0.1633	0.8516	0.3290	0.030
H(13A)	0.1363	0.3300	0.5679	0.064
H(13B)	0.0796	0.4280	0.5351	0.064
H(15A)	0.0495	0.7349	0.2289	0.051

H(15B)	0.0107	0.5399	0.2326	0.051
H(15C)	–0.0082	0.7432	0.1764	0.051
H(16A)	–0.0180	0.2428	0.1425	0.057
H(16B)	0.0008	0.2408	0.0771	0.057
H(16C)	–0.0393	0.4292	0.0812	0.057
H(17A)	0.0168	0.7471	0.0699	0.060
H(17B)	0.0570	0.5623	0.0642	0.060
H(17C)	0.0745	0.7595	0.1226	0.060
H(1D)	0.2717	0.5922	–0.0838	0.064
H(1E)	0.3314	0.5513	–0.0462	0.064
H(1F)	0.3028	0.7292	–0.0135	0.064
H(4')	0.2332	–0.0133	0.0364	0.046
H(5')	0.2257	0.2350	–0.0647	0.039
H(6')	0.3661	0.6193	0.0919	0.028
H(8')	0.3941	0.2029	0.2330	0.030
H(11')	0.3377	0.9263	0.2793	0.036
H(12')	0.3402	0.8465	0.1674	0.030
H(13C)	0.3464	0.3287	0.4161	0.087
H(13D)	0.4040	0.3994	0.4599	0.087
H(15D)	0.5088	0.7392	0.1829	0.053
H(15E)	0.4913	0.5375	0.2224	0.053
H(15F)	0.4511	0.7255	0.1783	0.053
H(16D)	0.5013	0.2249	0.0786	0.058
H(16E)	0.5201	0.2336	0.1625	0.058
H(16F)	0.5409	0.4170	0.1211	0.058
H(17D)	0.4830	0.7282	0.0511	0.062
H(17E)	0.4255	0.7358	0.0476	0.062
H(17F)	0.4435	0.5372	0.0075	0.062

Table 5. Torsion angles [°]

C(5)–N(1)–C(2)–N(3)	0.2(5)	C(1)–N(1)–C(2)–N(3)	179.2(4)
C(5)–N(1)–C(2)–C(6)	–173.6(3)	C(1)–N(1)–C(2)–C(6)	5.3(6)
N(1)–C(2)–N(3)–C(4)	–0.7(5)	C(6)–C(2)–N(3)–C(4)	173.1(4)
C(2)–N(3)–C(4)–C(5)	0.9(5)	N(3)–C(4)–C(5)–N(1)	–0.7(5)
C(2)–N(1)–C(5)–C(4)	0.3(5)	C(1)–N(1)–C(5)–C(4)	–178.7(4)

N(3)–C(2)–C(6)–C(7)	41.9(5)	N(1)–C(2)–C(6)–C(7)	−145.0(3)
N(3)–C(2)–C(6)–S(1)	−83.0(4)	N(1)–C(2)–C(6)–S(1)	90.1(4)
C(2)–C(6)–C(7)–C(12)	94.7(4)	S(1)–C(6)–C(7)–C(12)	−146.2(3)
C(2)–C(6)–C(7)–C(8)	−83.0(4)	S(1)–C(6)–C(7)–C(8)	36.1(4)
C(12)–C(7)–C(8)–C(9)	−0.2(5)	C(6)–C(7)–C(8)–C(9)	177.5(3)
C(7)–C(8)–C(9)–C(10)	−0.2(5)	C(7)–C(8)–C(9)–O(1)	−179.3(3)
C(8)–C(9)–C(10)–C(11)	−0.3(5)	O(1)–C(9)–C(10)–C(11)	178.9(3)
C(8)–C(9)–C(10)–O(2)	179.8(3)	O(1)–C(9)–C(10)–O(2)	−1.0(4)
C(9)–C(10)–C(11)–C(12)	1.2(5)	O(2)–C(10)–C(11)–C(12)	−179.0(3)
C(10)–C(11)–C(12)–C(7)	−1.6(5)	C(8)–C(7)–C(12)–C(11)	1.1(5)
C(6)–C(7)–C(12)–C(11)	−176.6(3)	C(8)–C(9)–O(1)–C(13)	179.2(4)
C(10)–C(9)–O(1)–C(13)	0.1(4)	C(9)–O(1)–C(13)–O(2)	0.8(5)
C(9)–C(10)–O(2)–C(13)	1.4(4)	C(11)–C(10)–O(2)–C(13)	−178.5(4)
O(1)–C(13)–O(2)–C(10)	−1.3(5)	C(2)–C(6)–S(1)–C(14)	−151.9(2)
C(7)–C(6)–S(1)–C(14)	84.5(3)	C(6)–S(1)–C(14)–C(15)	−53.9(3)
C(6)–S(1)–C(14)–C(16)	−172.6(2)	C(6)–S(1)–C(14)–C(17)	69.9(3)
C(5')–N(1')–C(2')–N(3')	−0.3(4)	C(1')–N(1')–C(2')–N(3')	178.3(4)
C(5')–N(1')–C(2')–C(6')	175.1(3)	C(1')–N(1')–C(2')–C(6')	−6.3(6)
N(1')–C(2')–N(3')–C(4')	0.4(4)	C(6')–C(2')–N(3')–C(4')	−175.0(3)
C(2')–N(3')–C(4')–C(5')	−0.3(5)	N(3')–C(4')–C(5')–N(1')	0.1(5)
C(2')–N(1')–C(5')–C(4')	0.1(4)	C(1')–N(1')–C(5')–C(4')	−178.5(4)
N(3')–C(2')–C(6')–C(7')	−44.9(4)	N(1')–C(2')–C(6')–C(7')	140.3(3)
N(3')–C(2')–C(6')–S(1')	80.5(4)	N(1')–C(2')–C(6')–S(1')	−94.3(3)
C(2')–C(6')–C(7')–C(8')	82.6(4)	S(1')–C(6')–C(7')–C(8')	−37.2(4)
C(2')–C(6')–C(7')–C(12')	−94.0(3)	S(1')–C(6')–C(7')–C(12')	146.3(3)
C(12')–C(7')–C(8')–C(9')	0.6(5)	C(6')–C(7')–C(8')–C(9')	−175.9(3)
C(7')–C(8')–C(9')–C(10')	−0.4(5)	C(7')–C(8')–C(9')–O(1')	−179.5(3)
C(8')–C(9')–C(10')–C(11')	0.0(6)	O(1')–C(9')–C(10')–C(11')	179.3(3)
C(8')–C(9')–C(10')–O(2')	−178.5(3)	O(1')–C(9')–C(10')–O(2')	0.8(4)
C(9')–C(10')–C(11')–C(12')	0.1(5)	O(2')–C(10')–C(11')–C(12')	178.3(4)
C(10')–C(11')–C(12')–C(7')	0.1(5)	C(8')–C(7')–C(12')–C(11')	−0.5(5)
C(6')–C(7')–C(12')–C(11')	176.1(3)	C(8')–C(9')–O(1')–C(13')	−172.3(5)
C(10')–C(9')–O(1')–C(13')	8.5(5)	C(9')–O(1')–C(13')–O(2')	−14.8(6)
C(11')–C(10')–O(2')–C(13')	171.8(5)	C(9')–C(10')–O(2')–C(13')	−9.8(5)
O(1')–C(13')–O(2')–C(10')	15.4(6)	C(2')–C(6')–S(1')–C(14')	149.3(2)

C(7')–C(6')–S(1')–C(14')	–87.3(3)	C(6')–S(1')–C(14')–C(16')	172.3(2)
C(6')–S(1')–C(14')–C(17')	–68.9(3)	C(6')–S(1')–C(14')–C(15')	53.5(3)

5.2 – X-ray crystal data and structure refinement for (4-Benzyloxy-3-methoxyphenyl)-(1*H*-imidazol-2-yl)-methanone

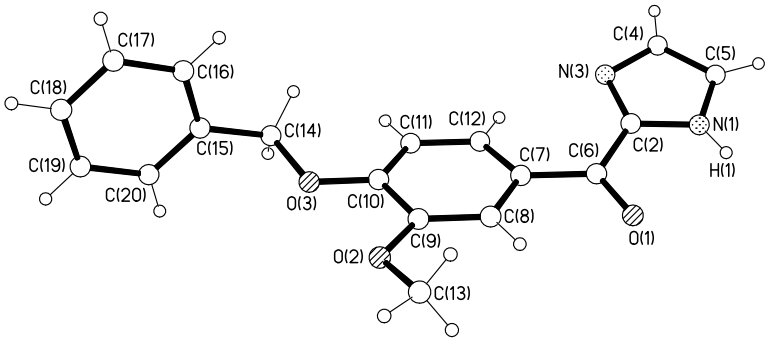

Table 1.

Identification code	gw38-(PAR/ME)	
Chemical formula	$C_{18}H_{16}N_2O_3$	
Formula weight	308.33	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 5.2011(3) Å	α = 90°
	b = 18.7666(10) Å	β = 94.0830(9)°
	c = 15.4067(8) Å	γ = 90°
Cell volume	1499.98(14) $Å^3$	
Z	4	
Calculated density	1.365 g/cm^3	
Absorption coefficient μ	0.094 mm^{-1}	
F(000)	648	
Crystal colour and size	colourless, 0.87 × 0.26 × 0.17 mm^3	
Reflections for cell refinement	6499 (θ range 2.90 to 30.52°)	
Data collection method	Bruker APEX 2 CCD diffractometer	

	ω rotation with narrow frames
θ range for data collection	1.71 to 30.55°
Index ranges	h –7 to 7, k –26 to 25, l –21 to 21
Completeness to θ = 30.55°	99.5 %
Intensity decay	0%
Reflections collected	17552
Independent reflections	4578 (R_{int} = 0.0222)
Reflections with $F^2>2\sigma$	3836
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.922 and 0.984
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0685, 0.2748
Data / restraints / parameters	4578 / 0 / 213
Final R indices [$F^2>2\sigma$]	R1 = 0.0427, wR2 = 0.1117
R indices (all data)	R1 = 0.0514, wR2 = 0.1184
Goodness-of-fit on F^2	1.042
Extinction coefficient	0.0070(15)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.422 and –0.234 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	1.34379(17)	–0.10238(5)	0.46668(6)	0.02428(19)
C(2)	1.14473(18)	–0.08247(5)	0.40961(6)	0.02084(19)
N(3)	1.03789(18)	–0.13885(5)	0.36870(6)	0.0270(2)
C(4)	1.1733(2)	–0.19626(6)	0.40209(8)	0.0310(2)
C(5)	1.3639(2)	–0.17437(6)	0.46241(8)	0.0305(2)
C(6)	1.08270(18)	–0.00636(5)	0.39901(6)	0.01963(18)
O(1)	1.22228(14)	0.03713(4)	0.43987(5)	0.02492(17)
C(7)	0.86497(18)	0.01835(5)	0.33912(6)	0.01938(18)
C(8)	0.85951(19)	0.09155(5)	0.31835(6)	0.02098(19)
C(9)	0.67023(19)	0.11852(5)	0.26021(6)	0.02039(19)

C(10)	0.48069(18)	0.07252(5)	0.22103(6)	0.01939(18)
C(11)	0.47975(18)	0.00092(5)	0.24422(6)	0.02101(19)
C(12)	0.67225(18)	–0.02597(5)	0.30310(6)	0.02037(18)
O(2)	0.65070(15)	0.18779(4)	0.23361(5)	0.02626(17)
C(13)	0.8625(2)	0.23335(6)	0.25883(8)	0.0306(2)
O(3)	0.31358(14)	0.10381(4)	0.16053(4)	0.02286(16)
C(14)	0.1449(2)	0.05673(5)	0.10904(6)	0.0234(2)
C(15)	0.04629(19)	0.09649(5)	0.02876(6)	0.02132(19)
C(16)	0.1688(2)	0.08857(6)	–0.04807(7)	0.0263(2)
C(17)	0.0789(2)	0.12398(6)	–0.12336(7)	0.0302(2)
C(18)	–0.1334(2)	0.16835(6)	–0.12234(7)	0.0295(2)
C(19)	–0.2565(2)	0.17698(6)	–0.04615(7)	0.0296(2)
C(20)	–0.1677(2)	0.14111(6)	0.02932(7)	0.0261(2)

Table 3. Bond lengths [Å] and angles [°]

N(1)–C(5)	1.3570(14)	N(1)–C(2)	1.3620(12)
C(2)–N(3)	1.3326(13)	C(2)–C(6)	1.4708(13)
N(3)–C(4)	1.3674(14)	C(4)–C(5)	1.3729(16)
C(6)–O(1)	1.2347(11)	C(6)–C(7)	1.4832(13)
C(7)–C(12)	1.3876(13)	C(7)–C(8)	1.4103(13)
C(8)–C(9)	1.3791(13)	C(9)–O(2)	1.3648(11)
C(9)–C(10)	1.4131(13)	C(10)–O(3)	1.3616(11)
C(10)–C(11)	1.3904(13)	C(11)–C(12)	1.3966(13)
O(2)–C(13)	1.4261(12)	O(3)–C(14)	1.4424(11)
C(14)–C(15)	1.5030(13)	C(15)–C(16)	1.3915(15)
C(15)–C(20)	1.3934(14)	C(16)–C(17)	1.3888(15)
C(17)–C(18)	1.3839(17)	C(18)–C(19)	1.3862(17)
C(19)–C(20)	1.3936(14)		

C(5)–N(1)–C(2)	107.44(9)	N(3)–C(2)–N(1)	111.08(9)
N(3)–C(2)–C(6)	129.62(9)	N(1)–C(2)–C(6)	119.26(9)
C(2)–N(3)–C(4)	105.16(9)	N(3)–C(4)–C(5)	110.28(10)
N(1)–C(5)–C(4)	106.04(9)	O(1)–C(6)–C(2)	117.96(8)
O(1)–C(6)–C(7)	120.38(9)	C(2)–C(6)–C(7)	121.63(8)
C(12)–C(7)–C(8)	119.39(8)	C(12)–C(7)–C(6)	124.00(8)

C(8)–C(7)–C(6)	116.61(8)	C(9)–C(8)–C(7)	120.45(9)
O(2)–C(9)–C(8)	125.39(9)	O(2)–C(9)–C(10)	114.77(8)
C(8)–C(9)–C(10)	119.82(9)	O(3)–C(10)–C(11)	125.38(8)
O(3)–C(10)–C(9)	114.89(8)	C(11)–C(10)–C(9)	119.72(8)
C(10)–C(11)–C(12)	120.04(9)	C(7)–C(12)–C(11)	120.48(9)
C(9)–O(2)–C(13)	116.72(8)	C(10)–O(3)–C(14)	116.48(7)
O(3)–C(14)–C(15)	107.88(8)	C(16)–C(15)–C(20)	118.93(9)
C(16)–C(15)–C(14)	119.80(9)	C(20)–C(15)–C(14)	121.28(9)
C(17)–C(16)–C(15)	120.80(10)	C(18)–C(17)–C(16)	119.99(10)
C(17)–C(18)–C(19)	119.80(10)	C(18)–C(19)–C(20)	120.29(10)
C(15)–C(20)–C(19)	120.18(10)		

Table 4. Hydrogen coordinates and isotropic displacement parameters (Å^2)

	x	y	z	U
H(1)	1.441(3)	–0.0728(8)	0.4966(9)	0.029
H(4)	1.1401	–0.2444	0.3859	0.037
H(5)	1.4854	–0.2037	0.4946	0.037
H(8)	0.9871	0.1225	0.3446	0.025
H(11)	0.3481	–0.0297	0.2200	0.025
H(12)	0.6712	–0.0750	0.3186	0.024
H(13A)	0.8738	0.2396	0.3221	0.046
H(13B)	0.8366	0.2798	0.2305	0.046
H(13C)	1.0225	0.2119	0.2412	0.046
H(14A)	–0.0008	0.0417	0.1428	0.028
H(14B)	0.2402	0.0136	0.0927	0.028
H(16)	0.3157	0.0586	–0.0490	0.032
H(17)	0.1631	0.1177	–0.1756	0.036
H(18)	–0.1946	0.1928	–0.1737	0.035
H(19)	–0.4021	0.2075	–0.0454	0.036
H(20)	–0.2533	0.1471	0.0813	0.031

Table 5. Torsion angles [°]

C(5)–N(1)–C(2)–N(3)	–0.35(12)	C(5)–N(1)–C(2)–C(6)	–178.49(9)

N(1)–C(2)–N(3)–C(4)	0.67(12)	C(6)–C(2)–N(3)–C(4)	178.55(10)
C(2)–N(3)–C(4)–C(5)	−0.75(13)	C(2)–N(1)–C(5)–C(4)	−0.12(13)
N(3)–C(4)–C(5)–N(1)	0.54(14)	N(3)–C(2)–C(6)–O(1)	−174.56(10)
N(1)–C(2)–C(6)–O(1)	3.18(14)	N(3)–C(2)–C(6)–C(7)	3.47(16)
N(1)–C(2)–C(6)–C(7)	−178.79(9)	O(1)–C(6)–C(7)–C(12)	−167.85(9)
C(2)–C(6)–C(7)–C(12)	14.16(14)	O(1)–C(6)–C(7)–C(8)	12.53(14)
C(2)–C(6)–C(7)–C(8)	−165.46(9)	C(12)–C(7)–C(8)–C(9)	−2.46(14)
C(6)–C(7)–C(8)–C(9)	177.18(9)	C(7)–C(8)–C(9)–O(2)	−178.06(9)
C(7)–C(8)–C(9)–C(10)	−0.13(15)	O(2)–C(9)–C(10)–O(3)	2.26(12)
C(8)–C(9)–C(10)–O(3)	−175.88(8)	O(2)–C(9)–C(10)–C(11)	−179.08(9)
C(8)–C(9)–C(10)–C(11)	2.78(14)	O(3)–C(10)–C(11)–C(12)	175.68(9)
C(9)–C(10)–C(11)–C(12)	−2.83(14)	C(8)–C(7)–C(12)–C(11)	2.41(14)
C(6)–C(7)–C(12)–C(11)	−177.20(9)	C(10)–C(11)–C(12)–C(7)	0.23(14)
C(8)–C(9)–O(2)–C(13)	9.08(14)	C(10)–C(9)–O(2)–C(13)	−168.94(9)
C(11)–C(10)–O(3)–C(14)	−8.41(14)	C(9)–C(10)–O(3)–C(14)	170.16(8)
C(10)–O(3)–C(14)–C(15)	−160.78(8)	O(3)–C(14)–C(15)–C(16)	95.79(11)
O(3)–C(14)–C(15)–C(20)	−84.63(11)	C(20)–C(15)–C(16)–C(17)	−0.51(15)
C(14)–C(15)–C(16)–C(17)	179.08(9)	C(15)–C(16)–C(17)–C(18)	0.67(16)
C(16)–C(17)–C(18)–C(19)	−0.36(17)	C(17)–C(18)–C(19)–C(20)	−0.09(17)
C(16)–C(15)–C(20)–C(19)	0.05(15)	C(14)–C(15)–C(20)–C(19)	−179.53(9)
C(18)–C(19)–C(20)–C(15)	0.25(17)		

Table 6. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1)...O(1')	0.863(14)	2.055(15)	2.8641(11)	155.9(13)

5.3 – X-ray crystal data and structure refinement for Benzo[1,3]dioxol-5-yl-(1*H*-imidazol-2-yl)-methanone

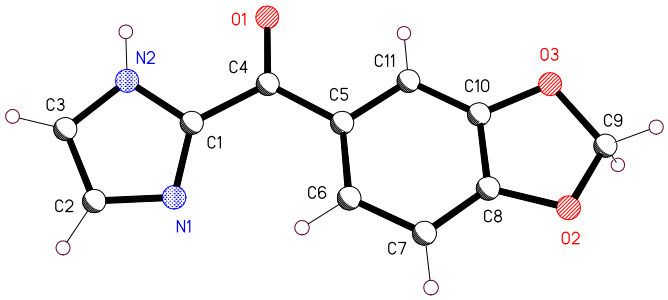

Table 1.

Identification code	gwdl3-(PAR/VM)	
Empirical formula	$C_{11}H_8N_2O_3$	
Formula weight	216.19	
Temperature	150(2) K	
Wavelength	0.84620 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 11.4689(14) Å	α= 90°.
	b = 22.714(3) Å	β= 95.722(2)°.
	c = 7.3010(9) Å	γ = 90°.
Volume	1892.5(4) $Å^3$	
Z	8	
Density (calculated)	1.518 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	896	
Crystal size	0.31 x 0.16 x 0.05 mm^3	
Crystal description	yellow tablet	
Theta range for data collection	3.85 to 33.10°.	
Index ranges	-14<=h<=14, -28<=k<=29, -9<=l<=9	
Reflections collected	6895	
Independent reflections	2020 [R(int) = 0.0528]	
Completeness to theta = 27.50°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.853846	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2020 / 0 / 145	

Goodness-of-fit on F^2	1.090
Final R indices [I>2sigma(I)]	R1 = 0.0441, wR2 = 0.0999
R indices (all data)	R1 = 0.0557, wR2 = 0.1064
Largest diff. peak and hole	0.255 and -0.204 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8096(1)	544(1)	-1759(2)	19(1)
N(1)	7030(1)	630(1)	-2611(2)	22(1)
C(2)	6609(1)	77(1)	-3016(2)	25(1)
C(3)	7416(1)	-339(1)	-2407(2)	25(1)
N(2)	8352(1)	-40(1)	-1623(2)	23(1)
C(4)	8966(1)	973(1)	-940(2)	20(1)
O(1)	9860(1)	771(1)	-78(2)	30(1)
C(5)	8810(1)	1616(1)	-1120(2)	17(1)
C(6)	7919(1)	1879(1)	-2292(2)	19(1)
C(7)	7841(1)	2490(1)	-2476(2)	20(1)
C(8)	8669(1)	2817(1)	-1461(2)	18(1)
O(2)	8806(1)	3418(1)	-1458(2)	24(1)
C(9)	9722(1)	3542(1)	-9(2)	24(1)
O(3)	10291(1)	2995(1)	484(2)	24(1)
C(10)	9556(1)	2564(1)	-295(2)	17(1)
C(11)	9655(1)	1969(1)	-87(2)	19(1)

Table 3. Bond lengths [Å] and angles [°]

C(1)-N(1)	1.330(2)
C(1)-N(2)	1.3592(19)
C(1)-C(4)	1.478(2)
N(1)-C(2)	1.367(2)
C(2)-C(3)	1.366(2)
C(3)-N(2)	1.3494(19)
C(4)-O(1)	1.2364(18)

C(4)-C(5)	1.476(2)
C(5)-C(6)	1.399(2)
C(5)-C(11)	1.416(2)
C(6)-C(7)	1.397(2)
C(7)-C(8)	1.366(2)
C(8)-O(2)	1.3733(17)
C(8)-C(10)	1.385(2)
O(2)-C(9)	1.4417(19)
C(9)-O(3)	1.4328(18)
O(3)-C(10)	1.3768(17)
C(10)-C(11)	1.363(2)

N(1)-C(1)-N(2)	111.08(14)
N(1)-C(1)-C(4)	130.09(14)
N(2)-C(1)-C(4)	118.80(13)
C(1)-N(1)-C(2)	104.71(13)
C(3)-C(2)-N(1)	110.65(14)
N(2)-C(3)-C(2)	105.90(14)
C(3)-N(2)-C(1)	107.66(13)
O(1)-C(4)-C(5)	120.03(14)
O(1)-C(4)-C(1)	116.88(14)
C(5)-C(4)-C(1)	123.08(13)
C(6)-C(5)-C(11)	120.25(14)
C(6)-C(5)-C(4)	123.45(14)
C(11)-C(5)-C(4)	116.24(13)
C(7)-C(6)-C(5)	121.25(14)
C(8)-C(7)-C(6)	117.02(14)
C(7)-C(8)-O(2)	127.97(14)
C(7)-C(8)-C(10)	122.40(14)
O(2)-C(8)-C(10)	109.58(13)
C(8)-O(2)-C(9)	105.65(11)
O(3)-C(9)-O(2)	107.19(11)
C(10)-O(3)-C(9)	105.55(11)
C(11)-C(10)-O(3)	128.16(13)
C(11)-C(10)-C(8)	121.91(13)
O(3)-C(10)-C(8)	109.87(13)
C(10)-C(11)-C(5)	117.17(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$). 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)	18(1)	18(1)	23(1)	1(1)	2(1)	3(1)
N(1)	17(1)	25(1)	24(1)	-2(1)	-2(1)	-1(1)
C(2)	20(1)	27(1)	26(1)	-4(1)	0(1)	-5(1)
C(3)	25(1)	20(1)	30(1)	-4(1)	2(1)	-5(1)
N(2)	18(1)	18(1)	31(1)	1(1)	-1(1)	2(1)
C(4)	17(1)	21(1)	23(1)	2(1)	2(1)	2(1)
O(1)	21(1)	21(1)	46(1)	4(1)	-11(1)	2(1)
C(5)	14(1)	19(1)	19(1)	0(1)	3(1)	0(1)
C(6)	13(1)	22(1)	22(1)	1(1)	-1(1)	-1(1)
C(7)	14(1)	23(1)	22(1)	3(1)	-2(1)	4(1)
C(8)	17(1)	17(1)	19(1)	2(1)	5(1)	3(1)
O(2)	24(1)	16(1)	29(1)	0(1)	-4(1)	1(1)
C(9)	23(1)	20(1)	28(1)	-5(1)	-3(1)	3(1)
O(3)	21(1)	19(1)	30(1)	-5(1)	-5(1)	1(1)
C(10)	14(1)	21(1)	17(1)	-4(1)	2(1)	-1(1)
C(11)	16(1)	21(1)	19(1)	1(1)	0(1)	4(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$).

	x	y	z	U(eq)
H(2)	5860	-6	-3637	30
H(3)	7334	-754	-2513	30
H(2A)	9010	-195	-1116	27
H(6)	7357	1637	-2976	23
H(7)	7238	2670	-3272	24

H(9A)	10290	3825	-443	29
H(9B)	9385	3714	1068	29
H(11)	10265	1798	718	23

Table 6. Torsion angles [°]

N(2)-C(1)-N(1)-C(2)	0.08(17)
C(4)-C(1)-N(1)-C(2)	-177.80(15)
C(1)-N(1)-C(2)-C(3)	0.20(18)
N(1)-C(2)-C(3)-N(2)	-0.41(18)
C(2)-C(3)-N(2)-C(1)	0.44(17)
N(1)-C(1)-N(2)-C(3)	-0.34(18)
C(4)-C(1)-N(2)-C(3)	177.81(13)
N(1)-C(1)-C(4)-O(1)	173.71(15)
N(2)-C(1)-C(4)-O(1)	-4.0(2)
N(1)-C(1)-C(4)-C(5)	-6.6(3)
N(2)-C(1)-C(4)-C(5)	175.66(14)
O(1)-C(4)-C(5)-C(6)	170.07(14)
C(1)-C(4)-C(5)-C(6)	-9.6(2)
O(1)-C(4)-C(5)-C(11)	-7.2(2)
C(1)-C(4)-C(5)-C(11)	173.10(13)
C(11)-C(5)-C(6)-C(7)	0.1(2)
C(4)-C(5)-C(6)-C(7)	-177.06(14)
C(5)-C(6)-C(7)-C(8)	-0.1(2)
C(6)-C(7)-C(8)-O(2)	177.16(13)
C(6)-C(7)-C(8)-C(10)	0.1(2)
C(7)-C(8)-O(2)-C(9)	173.90(15)
C(10)-C(8)-O(2)-C(9)	-8.74(15)
C(8)-O(2)-C(9)-O(3)	14.22(15)
O(2)-C(9)-O(3)-C(10)	-14.32(15)
C(9)-O(3)-C(10)-C(11)	-173.60(15)
C(9)-O(3)-C(10)-C(8)	9.14(15)
C(7)-C(8)-C(10)-C(11)	-0.1(2)
O(2)-C(8)-C(10)-C(11)	-177.68(13)
C(7)-C(8)-C(10)-O(3)	177.31(13)
O(2)-C(8)-C(10)-O(3)	-0.23(16)
O(3)-C(10)-C(11)-C(5)	-176.80(13)

C(8)-C(10)-C(11)-C(5)	0.2(2)
C(6)-C(5)-C(11)-C(10)	-0.1(2)
C(4)-C(5)-C(11)-C(10)	177.23(13)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2A)...O(1)#1	0.88	1.98	2.8273(17)	160.9

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y,-z