


# The Synthesis of Benzisothiazole and Benzothiazole Natural Products

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## Abstract

Chapter 1 gives an introduction to benzisothiazole and benzothiazole natural products. It explores the scope of natural products that are known within these families and discusses what they are used for, how they have been made and how they may have been biosynthesised. Chapter 1 provides a review of each family of natural products in turn.

Chapter 2 describes the total synthesis of the benzisothiazole natural products aulosirazole and pronqodine A, and a series of unnatural analogues. The Chapter begins with a short discussion on the use of the Diels-Alder reaction for the formation of naphthoquinones, then illustrates this strategy for the first synthesis of aulosirazole. The chapter continues with the synthesis of pronqodine A, a structurally similar natural product. The Chapter ends with an evaluation of these compounds as inhibitors of indoleamine-2,3-dioxygenase.

Chapter 3 contains work towards the synthesis of the benzothiazole containing natural product erythrazole A. The first half of the Chapter focuses on the formation of the heterocyclic core, originally attempting to use a biomimetic strategy but switching to an approach utilising the oxidative cyclisation of thioamides. The second half of the Chapter discusses many routes to synthesise and introduce the terpene derived side chain.

Chapter 4 contains experimental detail for the work carried out.

## Acknowledgements

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## Abbreviations

| | |
|---|---|
| [O] | Oxidation |
| °C | Degrees Celsius |
| Å | Ångström |
| Ac | Acetyl |
| AhR | Aryl hydrocarbon receptor |
| AMP | Adenosine monophosphate |
| Ar | Aromatic |
| ATP | Adenosine triphosphate |
| BMI | B lymphoma Mo-MLV insertion region |
| Bn | Benzyl |
| CAN | Ammonium cerium(IV) nitrate |
| CoA | Coenzyme A |
| COX-2 | Cyclooxygenase 2 |
| Cys | Cysteine |
| D | Deuterium |
| d | Doublet |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DIBAL-H | Diisobutylaluminium hydride |
| DIPEA | Diisopropylethylamine |
| DMAP | 4-Dimethylaminopyridine |
| DME | 1,2-Dimethoxyethane |
| DMF | *N*,*N*-Dimethylformamide |

| | |
|---|---|
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone |
| DMSO | Dimethylsulfoxide |
| E | Electrophile |
| EI | Electron impact |
| eIF-2 | Eukaryotic Initiation Factor 2 |
| EOM | Ethoxymethyl ether |
| eq | Equivalent(s) |
| ESI | Electrospray ionisation |
| Et | Ethyl |
| EtOAc | Ethyl acetate |
| EWG | Electron-withdrawing group |
| Fod | 1,1,1,2,2,3,3-Heptafluoro-7,7-dimethyl-4,6-octanedionate |
| GCN2 | General control nonderepressible 2 |
| GLK1 | Glucokinase 1 |
| h | Hour(s) |
| HOMO | Highest occupied molecular orbital |
| HRMS | High resolution mass spectrometry |
| HTS | High throughput screening |
| *i*-Am | Isoamyl |
| $IC_{50}$ | Half maximal inhibitory concentration |
| IDO | Indoleamine 2,3-dioxygenase |
| IFN | Interferon |
| *i*Pr | Isopropyl |

| | |
|---|---|
| IR | Infrared |
| *J* | Coupling constant |
| JAK | Janus Kinase |
| $K_i$ | Inhibitor constant |
| KYN | *N*-Formylkynurenine |
| LDA | Lithium diisopropylamide |
| LUMO | Lowest unoccupied molecular orbital |
| *m* | *meta* |
| m | Multiplet |
| *m*-CPBA | *m*-chloroperbenzoic acid |
| Me | Methyl |
| min | Minute(s) |
| mol | Mole(s) |
| mp | Melting point |
| Ms | Methansulfonyl |
| mTOR | Mammalian target of rapamycin |
| NBS | N-bromosuccinimide |
| *n*Bu | Normal-butyl |
| NMR | Nuclear magnetic resonance |
| NQO1 | NAD(P)H dehydrogenase (quinone 1) |
| Ns | Nitrobenzenesulfonyl |
| Nu | Nucleophile |
| *o* | *ortho* |
| *p* | *para* |
| PG | Prostaglandin |

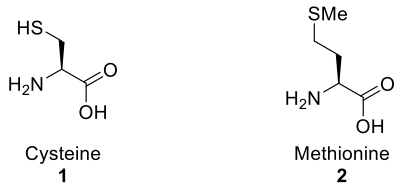
| | |
|---|---|
| Ph | Phenyl |
| PIFA | [Bis(trifluoroacetoxy)iodo]benzene |
| Pin | Pinacol |
| ppm | Part per million |
| *p*-TSA | *p*-Toluenesulfonic acid |
| Py | Pyridine |
| q | Quartet |
| ROS | Reactive oxygen species |
| rt | Room temperature |
| s | Singlet |
| SEM | 2-(Trimethylsilyl)ethoxymethyl |
| SM | Starting material |
| Sp. | Species |
| T | Temperature |
| t | Triplet |
| TBDPS | *tert*-Butyldiphenylsilyl |
| *t*-Bu | *tert*-Butyl |
| Tf | Trifluoromethanesulfonyl |
| TFAA | Trifluoroacetic anhydride |
| THF | Tetrahydrofuran |
| THP | Tetrahydropyran |
| TLC | Thin layer chromatography |
| TMEDA | Tetramethylethylenediamine |
| TMS | Trimethylsilyl |
| TOF | Time of flight |

| | |
|---|---|
| Trp | Tryptophan |
| Ts | 4-Toluenesulfonyl |
| δ | Chemical shift |
| ν | Frequency |
| $\Phi_{BI}$ | Relative bioluminescent quantum yield |

# 1. Introduction to nitrogen and sulfur containing heterocycles

## 1.1. N, S- heterocycles in Nature

Sulfur has been known since ancient times and is found naturally in its elemental form in many places around the globe and was known to both the Assyrian and Babylonian empires. Referred to in the bible and other ancient texts as brimstone, sulfur has had a large influence on human society often associated with destruction. It is thought to be a key ingredient in Greek fire as well as gunpowder which has shaped much of our history.




Cysteine **1** Methionine **2**

*Figure 1.* Sulfur containing amino acids cysteine and methionine

Sulfur is intrinsically linked to life on earth, in the form of the amino acids cysteine **1** and methionine **2**, well before the evolution of humans (Figure 1). As well as being vital for the formation and function of proteins, sulfur is found in a variety of heterocyclic metabolites in Nature.




**3** **4**

*Figure 2.* Thiazole (**3**) and isothiazole (**4**) isomers

A number of different heterocycles containing both nitrogen and sulfur have been isolated from Nature of which the thiazole moiety **3** is the most common (Figure 2). Vitamin B1, thiamine **5** is an essential nutrient and is required by all animals for life. It is a cofactor which is responsible for the decarboxylation of pyruvic acid and catalysing many umpolung reactions in biology. The thiazole moiety is also

present in many ribosomally synthesised and post translationally modified peptide natural products such as plantazolicin A **6,** as a result of the condensation of cysteine (Figure 3).

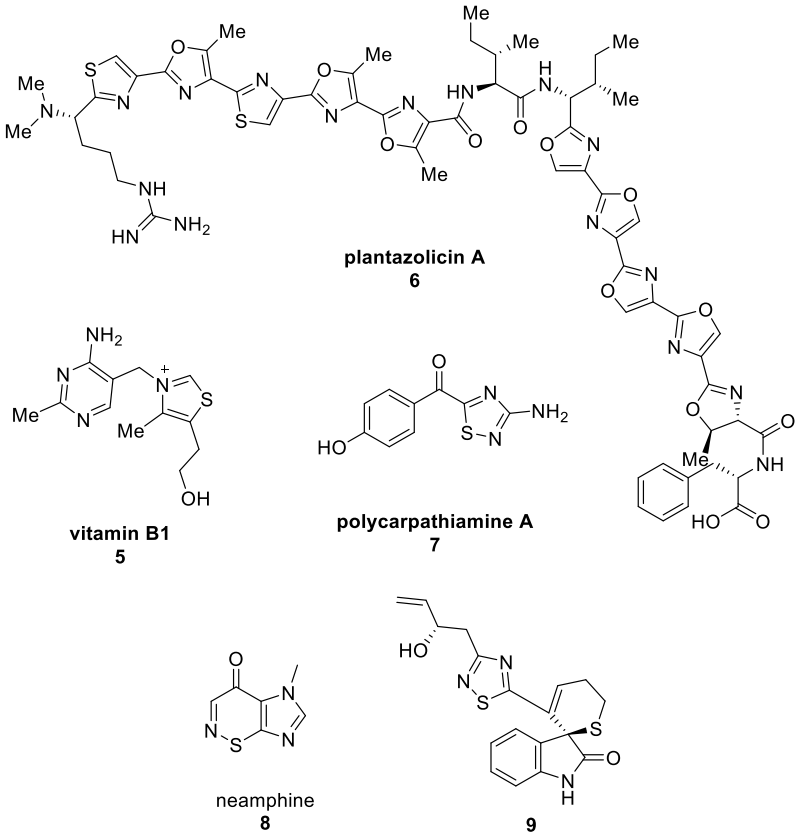



*Figure 3.* Examples of natural products with heterocycles containg both nitrogen and sulfur

Other sulfur containing heterocycles are much rarer, such as the thiadiazole ring present in the polycarpathiamine A **7** and compound **9** isolated from the roots of a plant used in traditional Chinese medicine or the peculiar thiazinone ring present in neamphine **8** (Figure 3).[1–4] Of interest to us are two groups of heterocyclic natural products containing fused isothiazole and thiazole heterocycles as represented by their simplest incarnations, benzisothiazole **10** and benzothiazole **11 (**Figure 4).

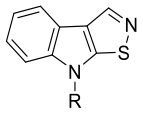



*Figure 4.* Benzoisothiazole **10** and benzothiazole **11**

In the following Chapter we discuss these two groups of natural products in more detail discovering their uses, biosynthetic origins and synthetic approaches used to synthesis these heterocycles.

## 1.2 Benzisothiazole natural products

The benzisothiazole group of natural products is very small with fewer than 10 isolated examples. The most studied examples of fused isothiazole natural products are two phytoalexins isolated from the green and white mustard plant respectively brassilexin **12**,[5] and sinalexin **13 (**Figure 5**)**.[6]

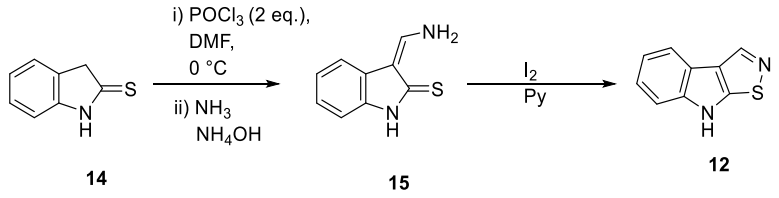



R=H Brassilexin **12**
R=OMe Sinalexin **13**

*Figure 5. Natural products brassilexin **3** and sinalexin **4***

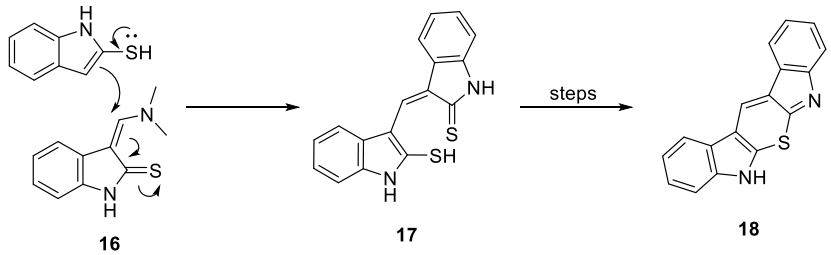
Phytoalexins are secondary metabolites produced by plants in the presence of fungal infections;[7] both brassilexin **12** and sinalexin **13** are known to inhibit the growth of fungi at micromolar concentrations.[8–10] Although effective at inhibiting the growth of a number of pathogens, resistant species have already been identified. Resistance is reported to occur *via* detoxification and elimination of the phytoalexins. In the fungus *Sclerotinia sclerotiorum* this proceeds primarily by the attachment of highly polar pendant sugars but also by reductive opening of the isothiazole ring.[8]

Due to the interest in brassilexin and sinalexin and other non-natural derivatives from the agrichemical community two efficient and short syntheses are known, both of which make use of the Vilsmeier formylation conditions.



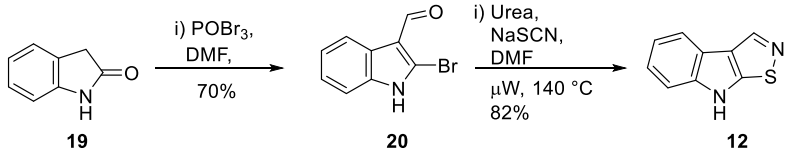

*Scheme 1. Pedras et al.* synthesis of brassilexin

Pedras *et al.* first synthesised brassilexin in 2005 by applying Vilsmeier formylation conditions with an ammonia quench to form enamine **15** from indoline-2-thione **14.** Interestingly both the temperature and stoichiometry of phosphoryl chloride were important to prevent formation of side product **17** during the formylation step. Dimerisation occurs by nucleophilic attack from the 3-position of the indole tautomer of **14** into unsaturated thioamide **16** to give **17** after the elimination of dimethylamine. Ring closure and loss of hydrogen sulfide gives **18**.



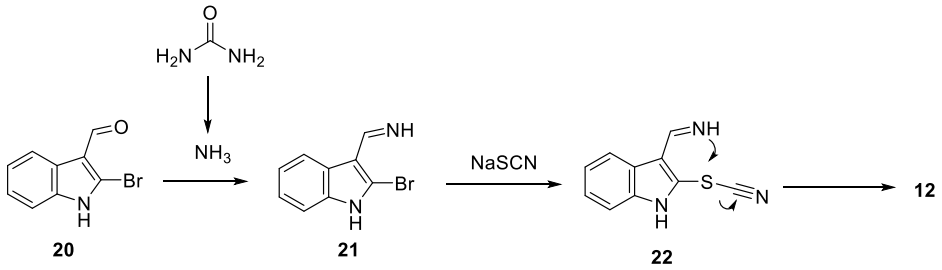

*Scheme 2.* Side reaction during the synthesis of brassilexin

Once conditions were optimised Pedras *et al.* were able to eliminate the side reaction completely and without isolation were able to treat enamine **15** with iodine to form the isothiazole ring and complete the synthesis of brassilexin in 71% yield from **14**. Sinalexin was also synthesised in this manner.[11]



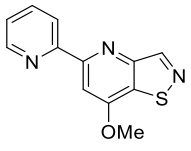

*Scheme 3. Bezbaruah et. al.* synthesis of brassilexin

In 2012 Bezbaruah *et al.* synthesised brassilexin using a different approach. Rather than beginning the synthesis with indoline-2-thione **14** readily available 2-oxindole **19** was used as a starting point. Upon treatment of **19** with dimethylformamide and phosphoryl tribromide not only does formylation occur at the desired 3-position but additionally bromination occurs at the 2-position. Bezbaruah then utilised a microwave reactor to carry out a multiple component reaction in the final step.




*Scheme 4. Multi-component synthesis of brassilexin*

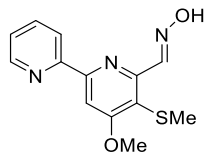
Under the forcing conditions decomposition of urea occurs to give ammonia which condenses with the aldehyde. An aromatic substitution reaction occurs between the thiocyanate anion and the 2-position of the indole to give **22**. Finally an intramolecular substitution reaction can occur on the sulfur atom with cyanide being the leaving group to give **12** in 82% yield.[12]




SF238F
**23**

*Figure 6.* SF2738F **23**

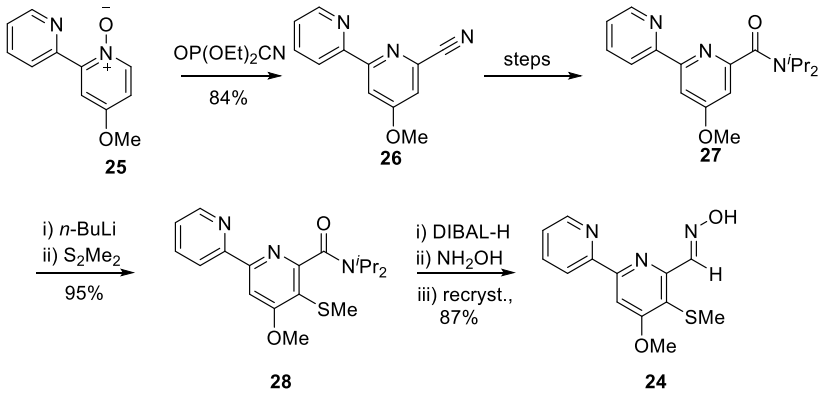
SF2738F **23** was isolated in 1994 from a species of *Streptomyces* and unusually for isothiazole containing natural products was not found to have antimicrobial activity.[13] However it was later found that SF2738F showed potential in the treatment of Parkinson's disease increasing cell viability in the presence of 1-methyl-4-phenylpyrimidium, a standard model for Parkinson's disease.[14]




Collismycin A
**24**

*Figure 7.* Collismycin A

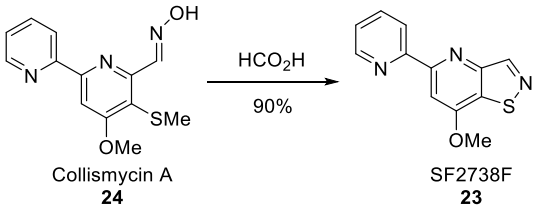
Although no total synthesis of SF2738F has been formally completed, piecing literature together shows that this has indirectly been accomplished. In the isolation paper SF2738A, which later became known as collismycin A, was also identified. López-Ogalla *et al.* identified collismycin A as a potent neuroprotector agent and developed a multi-gram synthesis requiring no chromatography.[15]




*Scheme 5.* López-Ogalla *et al*. synthesis of collismycin A

The nitrile is introduced to bipyrdine **25** in one step using diethyl cyanophosphonate which activates the pyridine N-oxide and acts as a source of cyanide enabling the transformation to be carried out with one reagent. After formation of amide **27** the thioether was introduced by using an *ortho* lithiation stratergy. Both the diisopropylamide and methyoxy groups mutually direct deprotonation to the *ortho* position and dimethyl disulfide was used as the electrophile. The synthesis of collismycin A was completed by partial reduction of the amide followed by condensation with hydroxylamine.[15]

Although the work carried out by López-Ogalla *et al.* ends with the synthesis of collismycin A (Scheme 5) it has been shown that collismycin A can be converted into SF2738F.



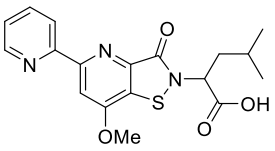

Collismycin A
**24**

SF2738F
**23**

*Scheme 6.* Conversion of collismycin A **24** to SF2738F **23**

Gomi *et al.* demonstrated the relationship between the two natural products by refluxing collismycin A **23** in formic acid. Formation of the isothiazole ring occurred in high yield to give SF2738F **22** thus showing that if desired synthesis of SF2738F could be achieved on large scale.[13]

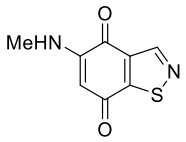
Due to the interest in the aforementioned properties of the collismycin family of natural products Garcia *et al*. investigated the biosynthetic pathway for the formation of collismycin A.




**29**

*Figure 8.* Collismycin SN

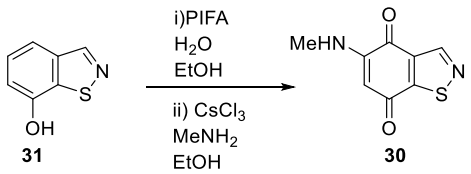
As part of the investigation into the biosynthetic pathway in *Streptomyces* sp. CS40 gene editing was used to mutate key enzymes. The mutation of a methyltransferase resulted in the premature termination of the pathway and collismycin SN was isolated and identified as an intermediate in the synthesis of collismycin A. Although produced by a bacteria and likely to exist briefly in Nature, human modification of the organism was required in order to isolate collismycin SN. The question remains is collismycin SN truly a natural product?




**30**

*Figure 9.* Pronqodine A

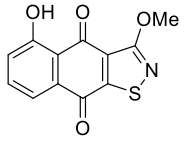
Pronqodine A **30** was isolated in 2013 from a different species of *Steptomyces*. The fused isothiazolebenzoquione exhibited interesting biological activity. In NQO1 expressing cells pronqodine A was shown to possess $IC_{50}$ values in the nanomolar concentration against the production of prostaglandins, PGE2, PGF1α and $PGD_2$. Mechanistically, it is thought this occurs *via* the production of reactive oxygen species (ROS) generated from the redox cycling of pronqodine A. NQO1 reduces pronqodine A **30** to the hydroquinone which will then autooxidise producing ROS which have been shown to inhibit the action of the COX-2 enzyme in converting arachidonic acid to the prostaglandin.[16] Non-steroidal anti-inflammatory agents have potential analgesic effects and also could be potential useful in the treatment of an array of inflammation and immune disorders which can be regulated by the control of chemical messengers in the body.




**31** **30**

*Scheme 7.* Synthesis of pronqodine A

Nakae *et al*. also report the first total synthesis of pronqodine A from the known compound **31** in 23% over two steps.

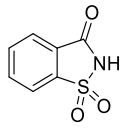



**32**

*Figure 10.* Aulosirazole

The final example of a fused isothiazole natural product, aulosirazole is a naphthoquinoneisothiazole isolated from *Aulosira fertilissima* a species of green-blue algae found in Okinawa, Japan in 1986. The yellow extract was tested against the Corbett assay and showed selective cytotoxicity against solid tumour and leukemia cells lines compared to that of normal cells. The structure was then elucidated to be as shown in Figure 5 and further evaluation of aulosirazole **32** biological activity was undertaken. Aulosirazole was found to have an $IC_{50}$ of 350 ng/mL against KB (a human nasopharyngeal carcinoma) and 45 ng/mL against LoVo (a human colorectal adenocarcinoma).[17] Prior to the beginning of these studies no work towards the synthesis of aulosirazole had been reported.

Although outside of the remit of this Chapter it would be remiss not to mention one of the earliest examples of a synthetic chemical with properties that were exploited by industry, saccharin.



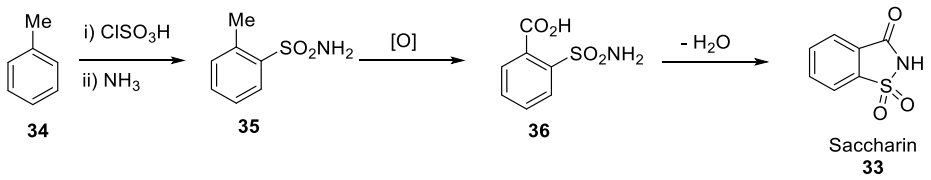

Saccharin
**33**

*Figure 11.* Saccharin

Saccharin was discovered by chance in 1879 at Johns Hopkins University by Constantin Fahlberg. The story goes that when Fahlberg was eating his dinner one evening after working on the oxidation products of toluene derivatives he noticed that his bread was surprisingly sweet. After eliminating the bread as the source of the sweetness he realised that it must have been something on his hands and returned to his laboratory and tasted the chemicals and reactions he had been working with that day. One of the reaction mixtures consisted of *o*-sulfobenzoic acid, phosphorus(V) chloride and ammonia which had been heated during the course of the day.[18] He identified saccharin as the product of this reaction and provided tasting notes in his 1879 publication:

"but if a few drops of the cold aqueous solution (of saccharin) be place in an ordinary goblet full of water, then the latter tastes like the sweetest syrup."- Constantin Fahlber 1879[19]

With the identification of the first artificial sweetener a new chemical industry was born.




*Scheme 8.* Synthesis of Saccharin from toluene

Saccharin can be synthesised from toluene in a two step process. Initially toluene **34** is treated with chlorosulfonic acid followed by ammonia sequentially. This gives sulfonamide **35** which upon oxidation gives benzoic acid **36** heating this product gives saccharin **33**. This process is carried out on an industrial scale to provide for the demand of artificial sweeteners.[20]

This review on fused isothiazole natural products highlights how rare this group of compounds are. Only five known compounds have been isolated of this type and although research has been carried out on the natural products containing no substitution at the 3-position of the isothiazole ring little work has been carried out into the synthesis of natural products containing substituents such as aulosirazole.

## 1.3 Biosynthesis of benzisothiazole natural products

It is also interesting to investigate the methods Nature uses to synthesise these natural products.

In addition to brassilexin **12** a number of other sulfur containing indoles have also been identified including: brassinin, cyclobrassinin and cyclobrassinin monosulfoxide (Figure 12).[21,22]

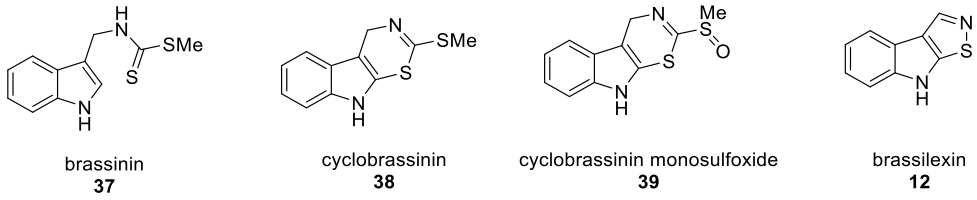
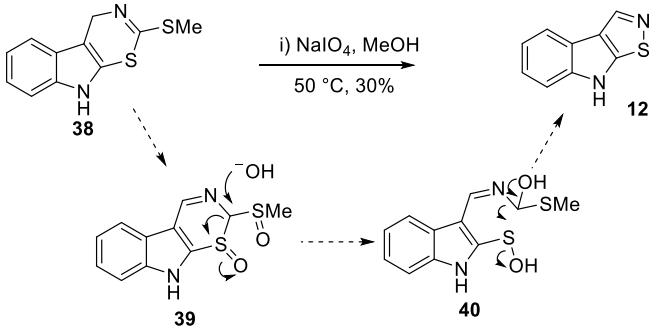


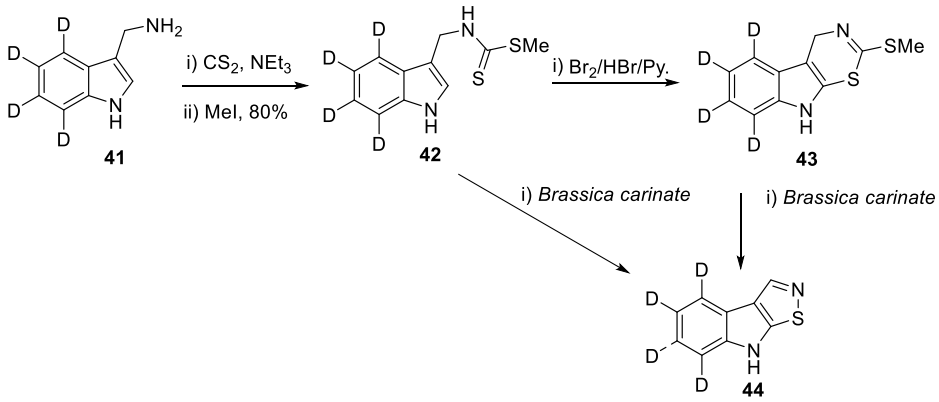

*Figure 12.* Related sulfur containing natural products

Given the visible similarities between these compounds and their isolation from members of the same family of Cruciferae, Barbier *et al.* postulated that brassilexin could be synthesised from cyclobrassinin.




*Scheme 9.* Conversion of cyclobrassinin **38** into brassilexin **10**

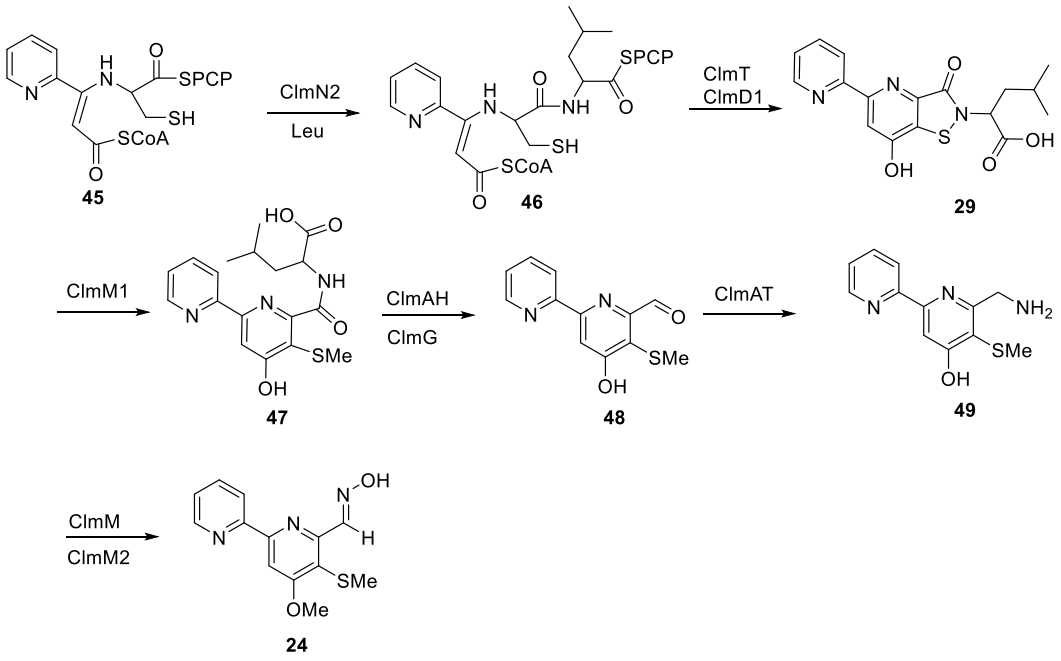
Barbier *et al.* showed that the conversion could be accomplished using the oxidant sodium periodate. The transformation proceeded in a 30% yield and helps validate the hypothesis that cyclobrassinin is a biogenic precursor to brassilexin.[23] Barbier also proposed a mechanism for this ring contraction; the benzothiazinone is initially attacked by water opening the 6-membered ring to give orthoester equivalent **40**. The 5-membered ring is formed by sigma bond migration in a similar manner to the mechanism suggested by Szabó *et al*.[24,25] Barbier later demonstrated that cyclobrassinin monosulfoxide **39** could also be converted chemically into brassilexin **12** in a 80% yield.[22]




*Scheme 10.* Validation of biosynthetic precursors to brassilexin

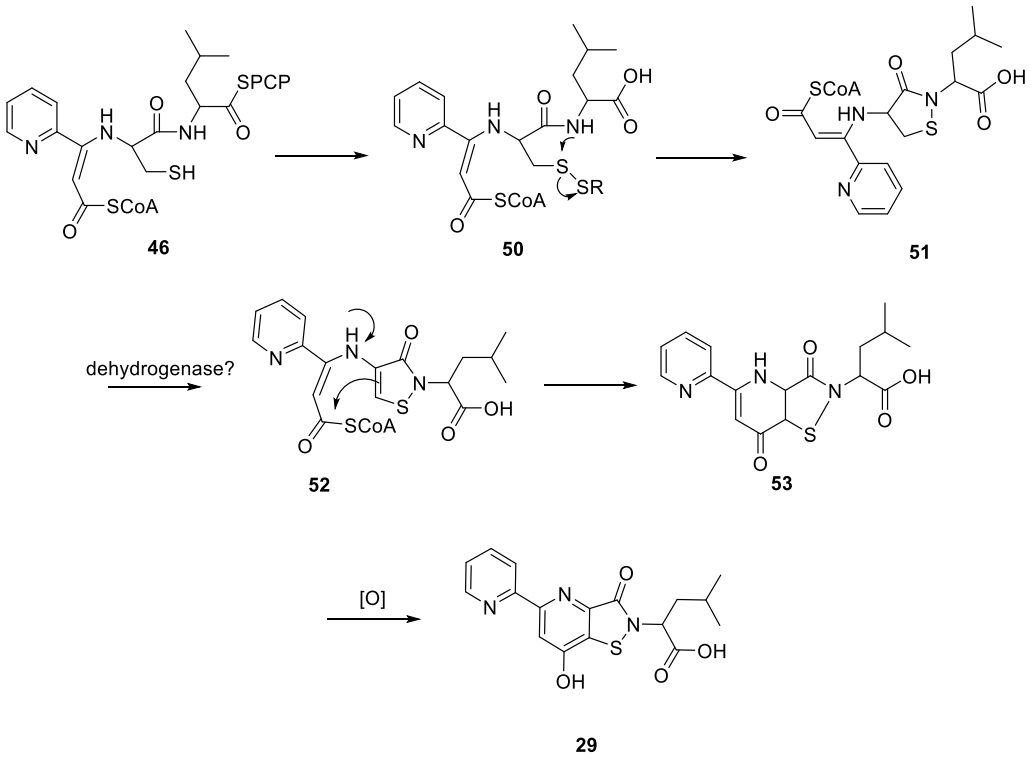
Further to the work demonstrating that the benzothiazinone ring contraction can be carried out synthetically. Pedras *et al.* demonstrated that this transformation is also carried out in Nature. Deuterium labelled versions of the proposed biosynthetic precursors for brassilexin, $D_4$-brassinin **42** and $D_4$-cyclobrassinin **43** were synthesised. A solution of the precursor was taken up by a leaf from the *B. carinata* which was known to produce brassilexin. Once the precursors were inside the leaf, a fungus, *P. lingam*, was applied to the outside of the leaf to stimulate the synthesis of the phytoalexins. It was found that both **42** and **43** were converted to $D_4$-brassilexin **44** confirming them both as biosynthetic precursors to brassilexin.[26]

Due to the aforementioned interest in collismycin A as a neuroprotective compound, Garcia *et al.* investigated its biosynthesis. After identifying the gene cluster coding for the synthesis of collismycin A and identifying a number of proteins Garcia *et al.* carried out a series of inactivation experiments, and structure similarity searches to identify the functions and propose a biosynthesis.[27]




*Scheme 11*. Proposed biosynthesis of collismycin A

A combination of polyketide and nonribosomal peptide synthesis is utilised in the synthesis of collismycin A. Formation of an amide between **45** and leucine is one of the first steps in the synthesis of the isothiazolone heterocycle; the exact role of leucine is unknown although it has been suggested that it is required for recognition by the enzyme responsible for cyclisation.[27] Once **46** has been formed, a cyclisation takes place although the genes and proteins involved have not been identified. Garcia *et al.* tentatively suggest that a thioesterase and a dehydrogenase may be part of the process.[28]

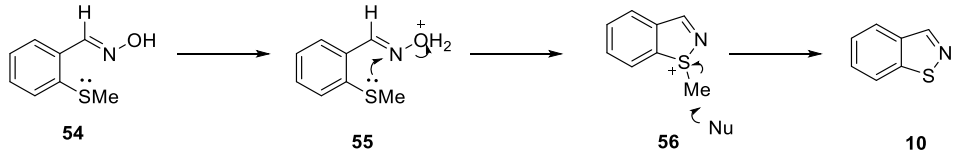



*Scheme 12.* Speculative mechanism for benzisothizolone synthesis

From the small amount of information on the enzymes associated with this double cyclisation event a speculative mechanism could be suggested. Although the mechanism for forming a nitrogen sulfur bond from constituents present in **46** is not known it is plausible that this could proceed *via* an oxidation of the thiol to a disulfide which would be electrophilic allowing nucleophilic attack of the amide lone pair to result in the formation of **51**. The suggested dehydrogenase enzyme could form isothiazolone **52**. The second pyridine ring could then be formed by nucleophilic attack of the enamine onto the carbonyl releasing coenzyme A. This cyclisation would be a 6-exo-trig cyclisation 'allowed' by Baldwins rules.[29] With the formation of **53** tautomerisation and oxidation would give the isolated product collismycin SN **29**.

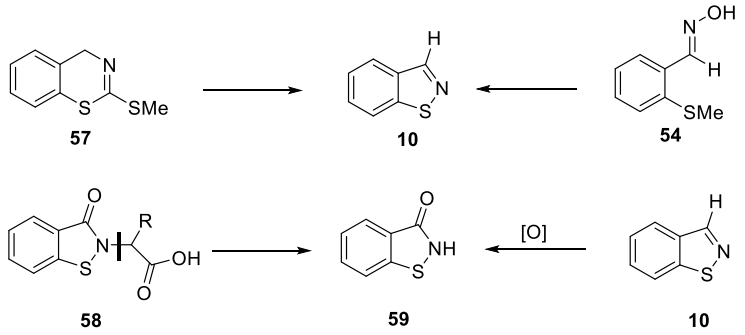
The remainder of the synthesis of collismycin A is outlined in Scheme 11. The oxime moiety is rare in Nature but is thought to be formed by oxidation of an

amine by a cytochrome P450 as previously reported by Kelly *et al.*[30] Due to the previously discussed chemical conversion of collimycin A into benzisothiazole containing SF2738F and the isolation of both natural products from the same bacteria it seems feasible to suggest that the conversion could also occur in Nature (Scheme 13).




*Scheme 13.* Proposed mechanism of benzisothiazole formation

In summary, the current literature on the biosynthesis of benzisothiazoles and benzisothiazolones suggests that multiple routes are possible. Barbier and Pedras have shown that in the case of the brassilexin the nitrogen sulfur bond is formed by a ring contraction of **57.** However the collismycin family of natural products suggest that oximes such as **54** may also give benzisothiazoles.




*Scheme 14.* Summary of biosynthesis of isothiazole and isothiazolone heterocycles

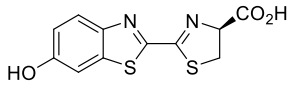
Aulosirazole **31** is unique in that it is the only example of an isolated natural product from an unadulterated organism which is in a higher oxidation state with an oxygen in the 3-position. We have seen from the biosynthesis of collimycin A that Nature can form isothiazolone rings with nitrogen substituents from a combination of polyketide and nonribosobal peptide path ways. Alternatively

oxidation of **8** could occur by one of the myriad of cytochrome P450 enzymes which are known to oxidise heterocycles.[31,32]

## 1.4 Benzothiazole natural products

The benzothiazole family of natural products have received more attention than the previously discussed benzisothazole natural products and are the subject of a number of reviews. This is in part due to the variety of applications the benzothiazole moiety have found in pharmaceuticals and as tools for probing biological systems.[33–35]

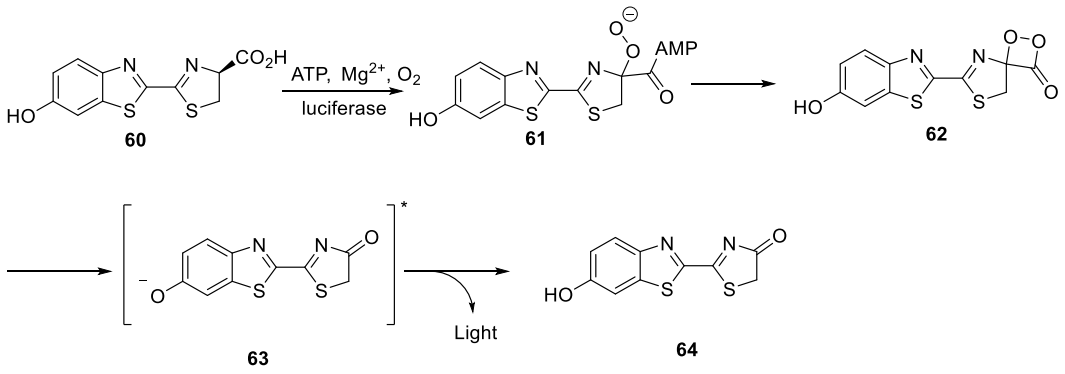
Of the benzothiazole natural products, luciferin **60** has received the greatest attention due to its lustrous properties. First isolated from 15,000 fireflies in 1957, luciferin was found to be the molecule responsible for bioluminescence.[36]




**60**

*Figure 13.* Luciferin **60**

Luciferin itself is not luminescent but may be oxidised by a luciferase enzyme. The luciferase forms an activated adenylate ester **61** which ring closes to form an unstable dioxetanone ring **62**. This 4 membered ring then spontaneously collapses extruding carbon dioxide and leaving **63** in an excited singlet state. In an excited singlet state the electrons are still paired and may return to the ground state by emitting a photon in a spin allowed transition completing the process of bioluminescence.[37]




*Scheme 15*. Bioluminescence of luciferin[37]

The wavelength of the emitted photon varies depending on the difference in energy between the ground and excited states. As such changing the structure of luciferin **60** results in photons of different wavelengths being emitted. Woodroofe *et al*. synthesised a number of analogues by varying the heterocyclic core and found that a range of wavelengths were detected (Figure 14). In addition to changing the wavelength of light emitted it was also found that the benzothiazole core had the greatest relative bioluminescence quantum yield of the synthesised molecules.[38]

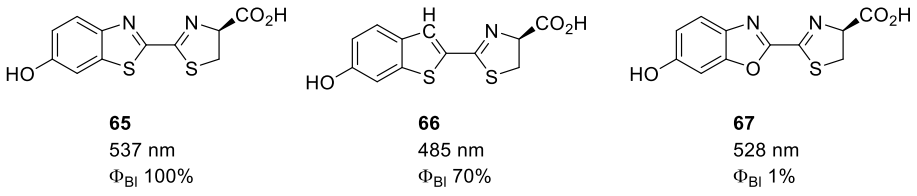
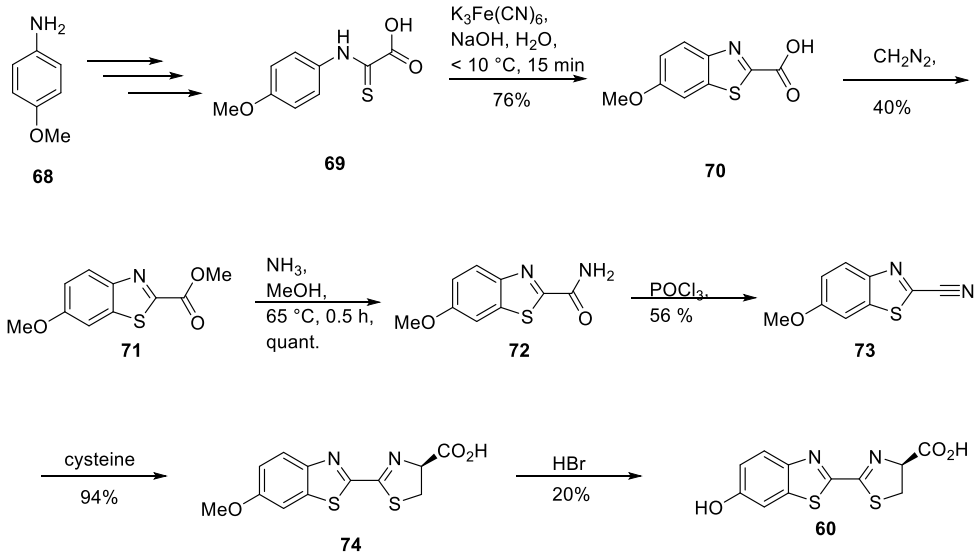



*Figure 14*. Luciferin analogues their emission wavelengths and relative bioluminescence quantum yield[38]

Light as a result of a biological transformation is so important that luciferin assays are run universally and kits are commercially available to make it accessible to all. As a tool, luciferin assays have been used to monitor and probe a seemingly endless range of biological processes.[37,39]

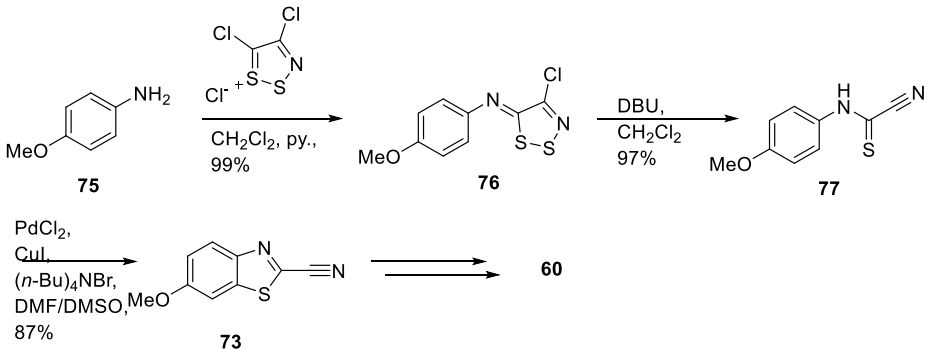
Luciferin **60** has received much attention since 1957, perhaps initially because of the excitement fluorescence can inspire, and later when the practical applications

became apparent. The first synthesis came from White *et al.* in 1962. After carrying out an amide coupling and functional group interconversions, the key benzothiazole heterocycle was formed oxidatively from thioamide **69**. The synthesis was carried out on large scale and was able to produce 0.743 g of luciferin **60**.[40]



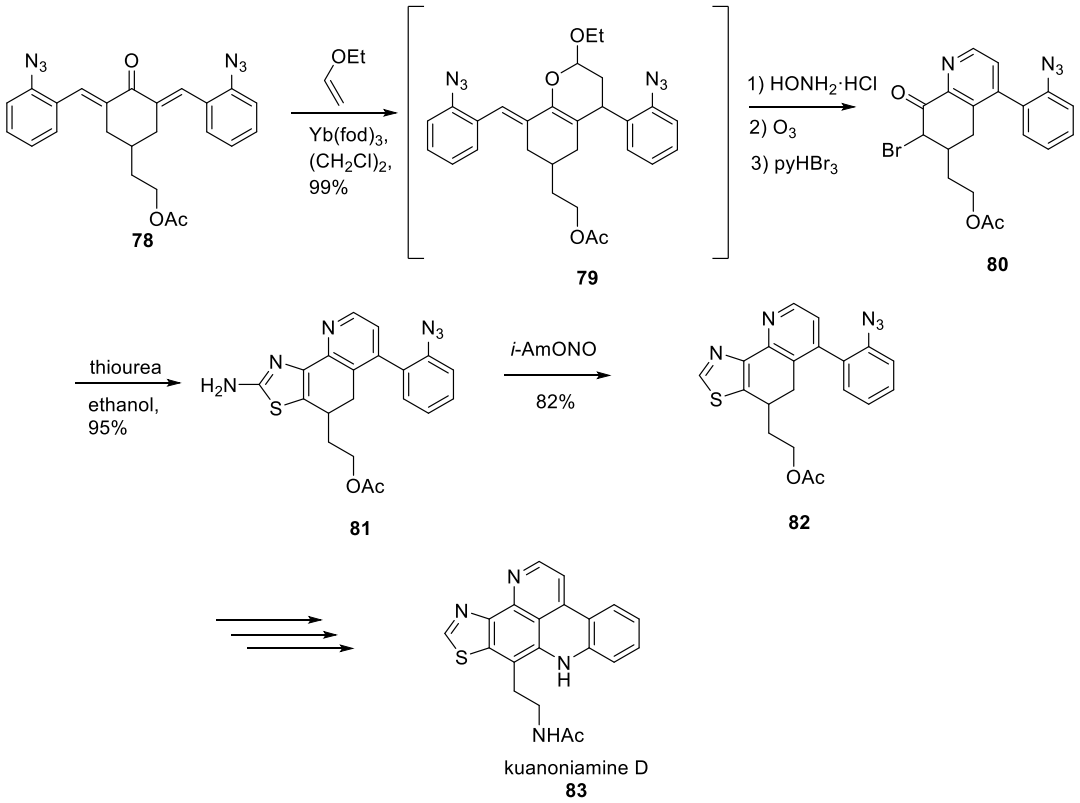

*Scheme 16.* White *et al.* 1963 synthesis of luciferin **60**[40]

Although White *et al.* were able to successfully synthesise 0.743 g of luciferin using this sequence, it is very linear with eight steps and requires multiple manipulations of carbonyl functionalities. Half a century later, the synthesis of luciferin has been optimised and condensed into five steps with a 42% overall yield.[41]




*Scheme 17.* McCutcheon *et al.* 2015 synthesis of luciferin **58**[41]

The use of dithiazolium chloride (Appel's salt) for the synthesis of luciferin was first introduced by McCutcheon in 2012.[42] First synthesised by Appel in 1985 the dithiazolium is a highly electrophilic source of the desired thioamide and nitrile with no functional group manipulation being required.[43] Thioamide **77** was cyclised using palladium and copper and the remainder of this synthesis was carried out in a similar manner to the original synthesis by White *et al*. completing the synthesis in 84% total yield. After over half a century from the initial synthesis McCutcheon's synthesis improves the total yield by 74% and has four fewer steps.[41]

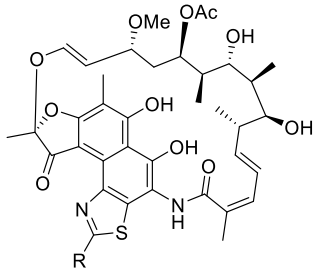



*Scheme 18.*Ciufolini's 1992 synthesis of kuanoniamine D

The synthesis of benzothiazoles with no substituent at the 2-position such as in the kuanoniamine D **83** provides a different challenge to that provided by luciferin, which can be overcome using chemistry developed almost 130 years ago by Traumann. Traumann showed that thiazoles could be synthesised from α -halo ketones and thiourea in a highly efficient manner.[44]

Ciufolini *et al.* synthesised kuanoniamine D in 1992 beginning with symmetrical di-alkene **78**. Dialkene **78** was desymmetrised using an ytterbium catalysed vinyl ether addition across the enone to give **79** which can be treated with hydroxylamine to afford the pyridine.[45] Ozonolysis is then able to oxidatively cleave the remaining alkene to give the ketone which can be α -brominated to give **80**. Treatment with thiourea gives the aminothiazole which upon treatment with *iso*-amyl nitrite is deaminated to give the unsubstituted benzothiazole **82**.

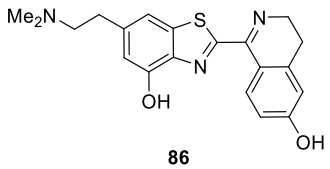
The rifamycin family of natural products have found fame for their use as antibiotics, especially as a treatment for tuberculosis. They are thought to be inhibitors of RNA polymerases, and as such prevent the transfer of genetic information from the DNA stopping the replication of the bacteria.[46,47]



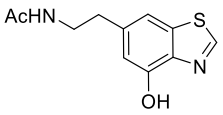

Rifamycin P R=H **84**
Rifamycin Q R= $CH_2OH$ **85**

*Figure 15.* Rifamycin P and Q

Two members of the rifamycin family, P **84** and Q **85**, have been identified to contain a benzothiazole ring, both isolated by Cricchio *et al*. in 1980.[48] Although no synthesis of rifamycin has been completed, Cricchio *et al.* further explored the relationship between a number of rifamycin natural products in order to ascertain how the benzothiazole ring arises in Nature. These investigations will be discussed in Chapter 1.5.



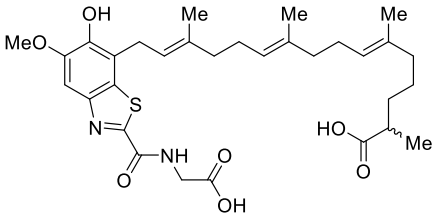

**86**



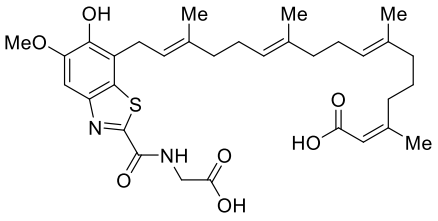

**87**

*Figure 16.* Violatinctamine **86** and related benzothiazole **87**

Violatinctamine **86** was isolated in 2004 from a marine tunicate collected in Kenya. The name arises from the colour of the tunicate it is isolated from and in fact violatinctamine is reported to be orange in colour.[49] Despite much investigation within the Moody group, a synthesis of violatinctamine remains challenging.[50] More recently a structurally related compound **87** has been identified this time from a terrestrial source in the form of an ant. It is interesting that compounds that are so strikingly similar can be isolated from such diverse sources indicating that these functions could be ubiquitous.[51]




**88**




**89**

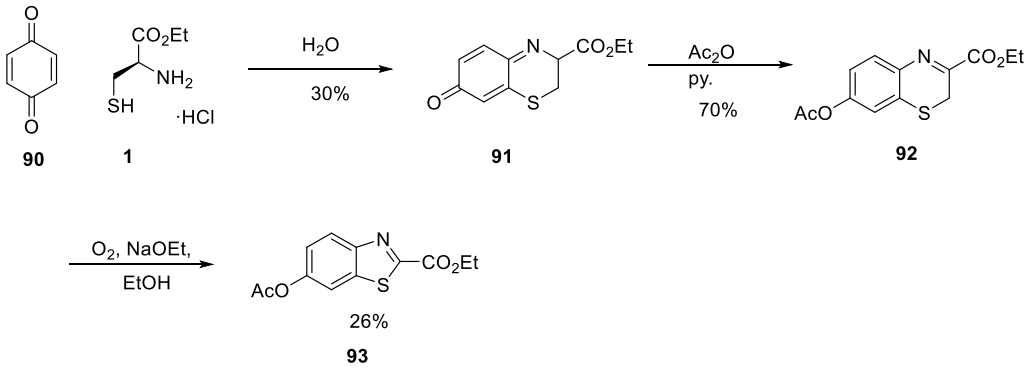
*Figure 17.* Erythrazole A **88** and B **89**

Erythrazoles A and B were isolated in 2011 from a marine bacteria of the genus *erythrobacter*. Hu and MacMillan identified the natural products during a HTS while searching for molecules that modulate epigenetic regulation. As the erythrazole natural products themselves display no activity in the assay, they were in the same fraction as two other undisclosed compounds which were active and thus were elucidated to the scientific community. Currently nothing is known about the function of the natural products, and the combination of a terpene side chain attached to a polyketide derived core provides an interesting synthetic target.[52]

Although not an exclusive list of known benzothiazole natural products, this short review highlights the rarity of benzothiazole natural products as well as displaying the diversity of structure and properties these molecules exhibit. Although the properties of some members of this family of natural products have been well explored and utilised, others such as erythrazole A **88** remain a complete mystery.

## 1.5 Biosynthesis of benzothiazole natural products

McCapra *et al*. first proposed the biosynthesis of luciferin **60** in 1975, and showed that the transformation was chemically viable in the laboratory (Scheme 19).[53]




*Scheme 19.* Proposed biosynthetic route to luciferin[53]

McCapra proposed that the benzothiazole heterocycles could be biosynthesised from benzoquinone and cysteine, both commonly found in Nature. A number of radiolabelling experiments were undertaken to test this hypothesis. Okada *et al*. carried out the first radiolabelling experiment using $^{14}C$ labelled *p*-benzoquinone and labelled hydroquinone which was injected into live fireflies and was shown to be incorporated into luciferin shown in blue (Figure 18).[54]

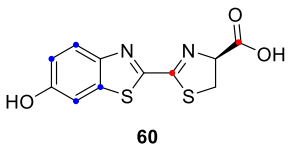
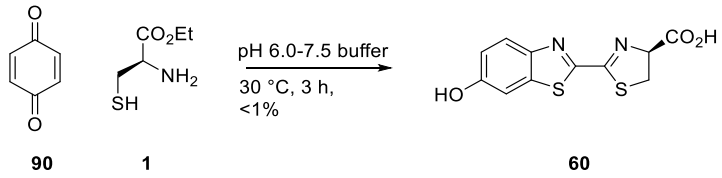



*Figure 18.* Locations of $^{14}C$ in luciferin **60**. Results from Okada et al. shown in blue and results from McCapra shown in red.

McCapra showed that $^{14}C$ labelled cysteine was also incorporated into luciferin supporting the proposed biosynthesis.[55] The final piece of evidence was provided by Kanie *et al*. in 2016.[56]

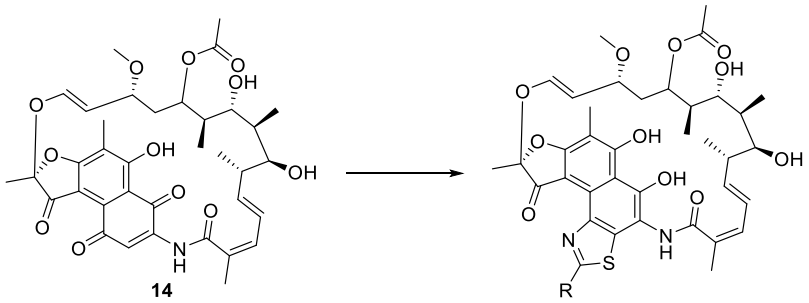



**90** **1** **60**

*Scheme 20.* One pot synthesis of luciferin **60**

Kanie *et al*. demonstrate that luciferin forms spontaneously from benzoquinone and cysteine in buffered aqueous conditions, albeit in a <1% yield. This shows that luciferin can be formed without enzymes or catalysis and may arise spontaneously.

The biosynthesis of rifamycins P and Q (**84** & **85**) was investigate by Cricchio *et al.* who used a series of $^{14}C$ and $^{35}S$ labelled cysteine to prove that they were indeed biosynthesised by the addition of cysteine to rifamycin S **94**.[57]

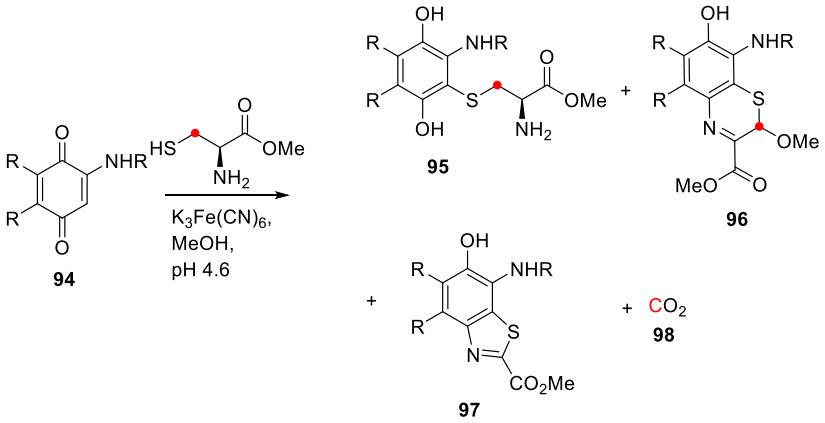



*Scheme 21.* Conversion of rifamycin S to rifamycin Q or P

In addition to the labelling experiment it was also shown that rifamycin Q **85** is derived by enzymatic reduction of the 2-carboxylate benzothiazole. Interestingly when [3-$^{14}C$]-cysteine was used no radiolabel was present in the product. This suggests that the 3-position carbon is extruded during the ring contraction.[58]

This led Cricchio *et al.* to further investigate the mechanism of this reactions, again using radiolabelling experiments. Reacting cysteine methyl ester with

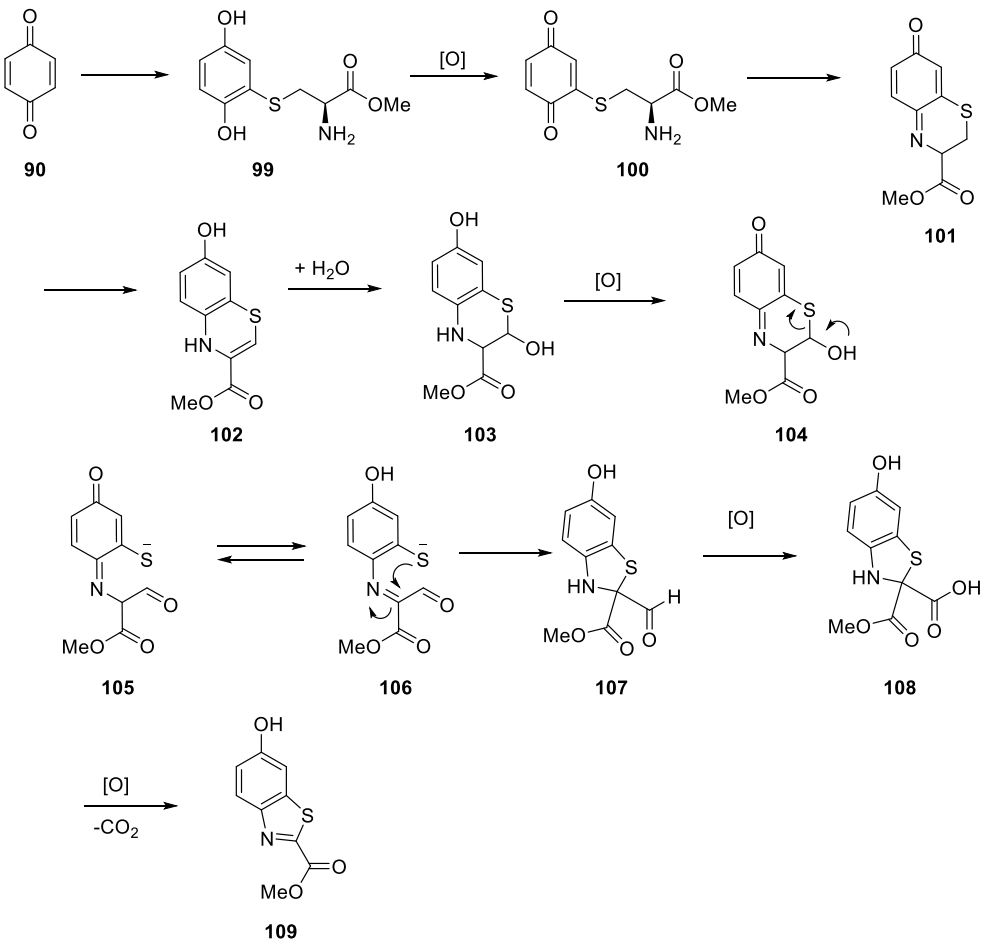
rifamycin S **94** in the presence of potassium ferricyanide resulted in the formation of many products some that were deemed to be intermediates in the formation of the thiazole ring.[57]




*Scheme 22*. Cricchio *et al.* reaction of rifimycin S **94** with radio labelled cysteine

The first observation from this shows that the 5-membered ring arises from the ring contraction of a larger 6 membered ring. In addition the presence of radioactivity identified in carbon dioxide shows that the carbon of the amino acid side chain is extruded in an oxidised form.

The mechanism begins with the conjugate addition of cysteine to benzoquinone followed by oxidation allowing an intramolecular condensation of the amino acid amine to form a quinone imine **101**. At this point there must be a rearrangement to the aromatic hydroquinone form **102** as well as forming the conjugated double bond.




*Scheme 23.* Proposed mechanism of thiazine ring contraction

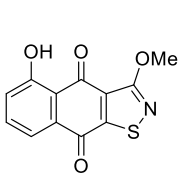
Addition of water to the 1, 4-unsaturated carbonyl would give rise to a thiohemiacetal **103**. The resulting ring opened form is able to tautomerise to a form in which the 2-position of the amino acid is electrophilic. Ring closure can then occur either at the 2-position or the 3-position. Baldwin's rules would suggest that ring closure on the 3-position in a 6-exo-trig would be preferred however these rules can only be applied to first row elements as the sulfur orbitals are larger and thus have less geometric constraint and the 5-endo-trig product can also be formed.[29]

The final step is the decarboxylation and oxidation of the heterocyclic ring. Although deformylation is possible, Cricchio *et al.* report the production of carbon dioxide and therefore a final oxidation step must occur before the decarboxylation.

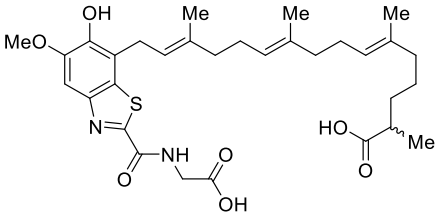
Although when using the methyl ester only the 3-position carbon is extruded as gas, presumably when cysteine is used in Nature there is no selectivity between the two carboxyl groups.

## 1.6 Project aims

Chapter one has so far provided an overview as to the research currently undertaken into benzisothiazole and benzothiazole natural products. It highlights how rare these groups of natural products are as well as demonstrating how useful it is to study and understand the properties of these molecules that Nature makes.




**32**




**88**

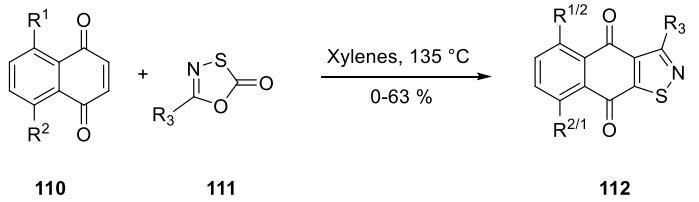
*Figure 19.* Aulosirazole **32** and erythrazole A **88**

The following Chapters aim to increase our knowledge of these compounds. Efforts will be focused on two natural products; aulosirazole **32** and erythrazole A **88**. In this study we aim to develop strategies to synthesis both these natural products in order to test and evaluate the properties of the molecules.

# 2. Synthesis and biological evaluation of benzisothiazoles

## 2.1 The total synthesis of aulosirazole

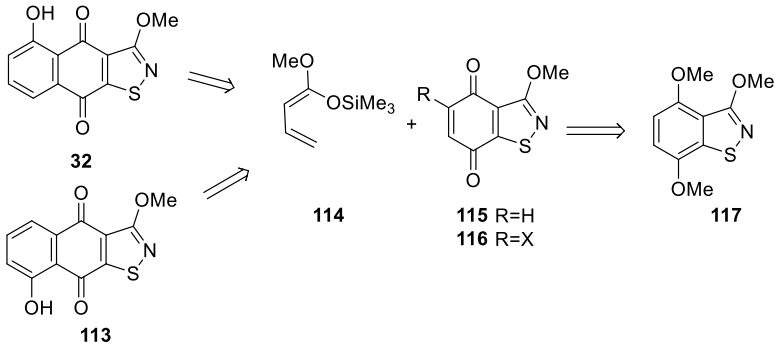
Previous work within the Moody group towards the synthesis of aulosirazole focused on the use of a 1,3-dipolar cycloaddition between a nitrile sulfide, which was formed *in situ*, and quinone to form the isothiazole ring.[17]




*Scheme 24.* Isothiazole formation by 1,3-dipolar cycloaddition

However, the reactions were of varying yield and also gave mixtures of regioisomers. $R^3$ was restricted to aryl or ester functionalities due to limitations of the chemistry; conversion of $R^3$ into the desired methoxy moiety proved unsuccessful.[59]

The failure to introduce the methoxy group bought about the inception of a new route (Scheme 25). Since its discovery by Diels and Alder, the eponymous reaction has become a useful tool in total synthesis and would be a reliable last step in the synthesis of aulosirazole **32**.[60–62]

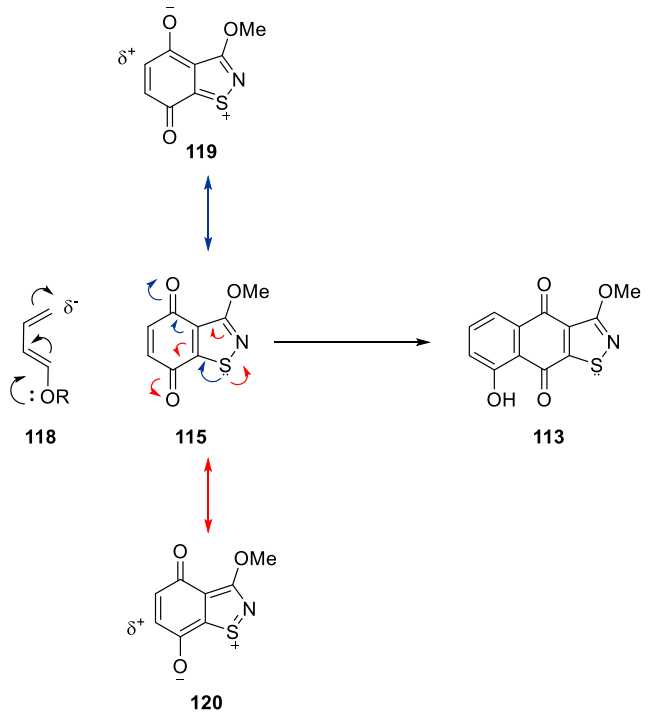



*Scheme 25.* Retrosynthesis of aulosriazole **32**

The regiochemical outcome of the Diels-Alder reaction was considered from the start. The Diels-Alder reaction takes place between an electron rich diene and an electron poor dienophile; therefore the HOMO of the former and LUMO of the latter must be considered as they are the orbitals which will be closest in energy. Houk states that "The larger terminal coefficient on each addend will become bonded preferentially in the transition state." In order to predict the regiochemical outcome we must predict the relative sizes of the orbital coefficients.[63]

A way of doing this is by looking at the different canonical forms the substrate can adopt. In the case of the diene this is relatively simple, as arrows may be pushed from the oxygen lone pair into the diene giving a negative charge at the opposite end of the diene. Assigning the symbol $\delta^-$ at this position designates the largest orbital coefficient of the HOMO.

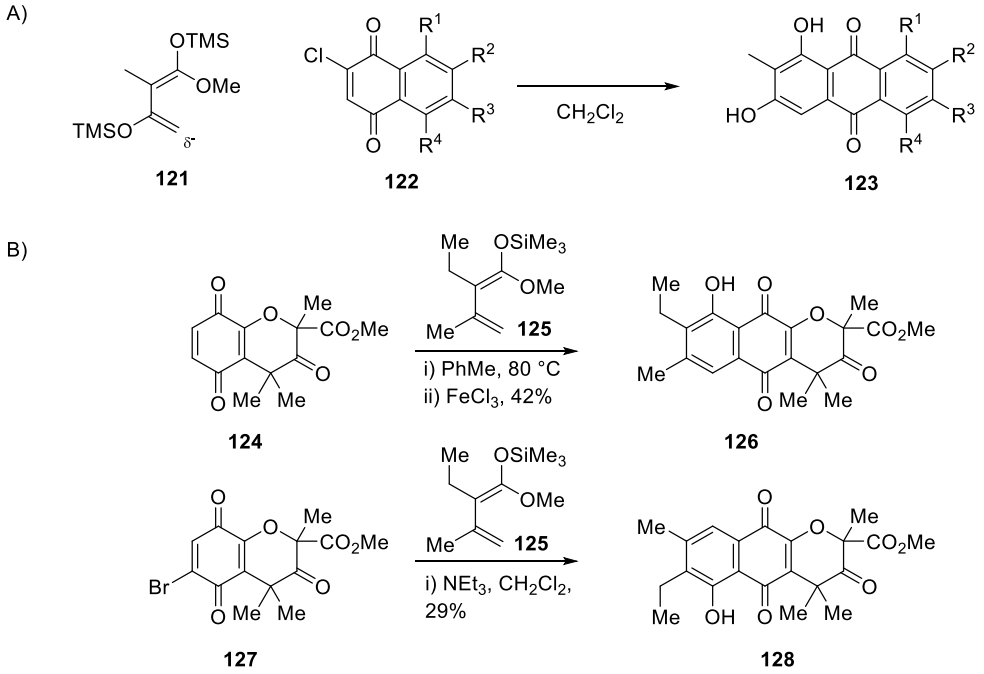
Predicting the orbital coefficient for the LUMO, quinone **115**, is slightly more complex as two possible canonical forms can be drawn as shown in Scheme 26. Application of the *principle of least motion* as proposed by Rice and Teller, then reviewed by Hine, would conclude that the blue arrows represent the canonical form which has a greater contribution to the molecular orbital as the electronic structure changes the least.[64]




*Scheme 26.* Regioselectivity of the Diels Alder reaction between diene **118** and quinone **115**

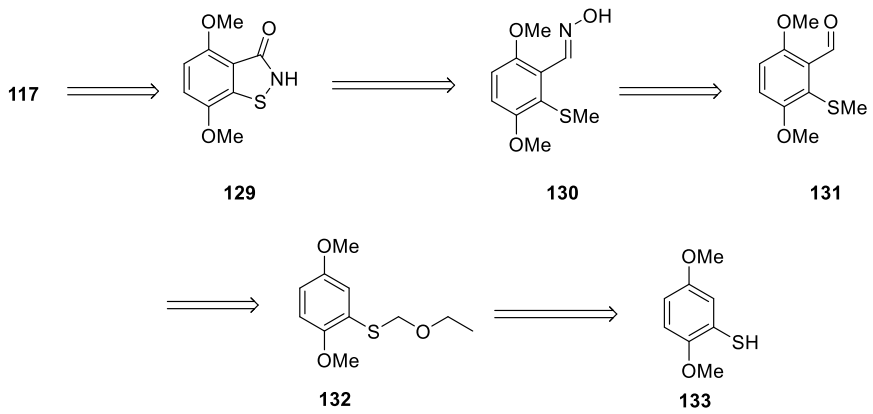
If we then combine our two predicted largest orbital coefficients we see that the undesired isomer **113** would be obtained as the product of the Diels-Alder reaction. Although this is inconvenient Brassard has shown that the selectivity can be manipulated by incorporating halogen atoms into the dieneophile (Scheme 27).[65,66]

Brassard demonstrated that irrespective of the substitution of the naphthoquinone addition of terminus of the diene with the largest orbital coefficient occurred at the unhalogenated position. This is exemplified by the synthesis of the reported structure of annulin B **126** where introduction of a halogen results in complete reversal of the Diels-Alder reaction (Scheme 27 B).[67]



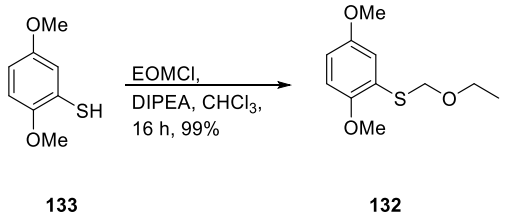

*Scheme 27*. Brassard's synthesis of rubiadins[65]B) Brassard's rule applied to the synthesis of annulin B

Aulosirazole is in a higher oxidation state than other isothiazole natural products; selective O-methylation of benzisothiazolone **129** would give **117**. The oxidative formation of benzisothiazolones from *ortho*-substituted oxime thioethers is reported in patent literature and provides a sensible disconnection of the N, S-bond to potential accessible retrons.[68,69]



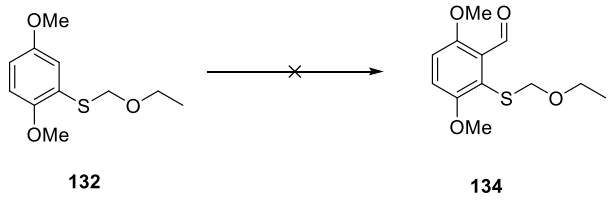

*Scheme 28.* Retrosynthesis of aulosirazole **32** continued

The aldehyde functionality could be introduced by *ortho*-lithiation of **132**. Thioether **132** was chosen as it was thought that the protecting group may also help direct *ortho*-lithiation and could be synthesised in one step from 2,5-dimethoxythiophenol.




*Scheme 29.* Thiophenol protection

Alkylation of **133** with the chloride of the directing group gave **132** in excellent yield. With **132** in hand *ortho*-lithiation was attempted.




*Scheme 30.* Lithiation of **132**

| Entry | Lithiating agent | Temp. °C/Time | Solvent/ Additive | $E^+$ | Result |
|---|---|---|---|---|---|
| 1 | *n*-BuLi | -78/3 min | THF/ TMEDA | *N*-formylpiperidine | SM |

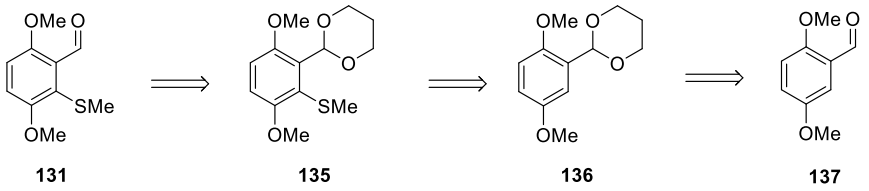
| | | | | | |
|---|---|---|---|---|---|
| 2 | *n*-BuLi | -78/ 30 min | THF | DMF | SM |
| 3 | *n*-BuLi | -78/ 30 min | THF/ TMEDA | DMF | SM |
| 4 | *n*-BuLi | 0/ 1 h | $Et_2O$/ TMEDA | DMF | degradation |
| 5 | *n*-BuLi | -78 - -20/ 1h | Hexanes/ TMEDA | MeOD | degradation |
| 6 | *t*-BuLi | -78/ 1 min | THF | DMF | SM |
| 7 | *t*-BuLi | -78/ 20 min | THF | DMF | SM |
| 8 | *t*-BuLi | -78/ 40 min | THF | DMF | SM +degradation |

*Table 1.* Attempted lithiation conditions

The reactivity of organolithium reagents is known to relate to the aggregation state of the reagent itself. In general the lower the aggregation state the more available and reactive the organolithium reagent is.[70] *n*-Butyllithium is known to exist in as a hexamer in hydrocarbon solvents, a tetramer in THF solution and as a dimer in hexane with N,N,N',N'-tetramethylethylenediame (TMEDA) as an additive.[71] However at -78 °C only starting material remained when using *n*-butyllithium in THF, THF with TMEDA, or hexanes with TMEDA.

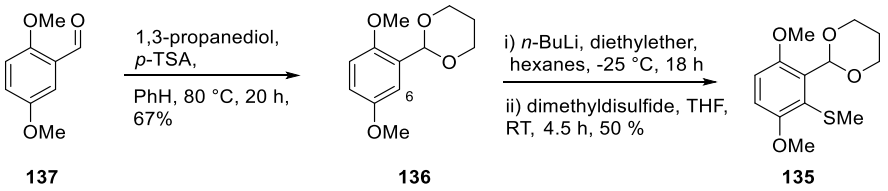
In the case of entry 5 in Table 1 deuterium was used as the electrophile and no desired product was identified at lower temperatures. Upon warming it was found that degradation occurred this was confirmed by Entry 4 which also showed instability at relatively warm temperatures.

*t*-Butyllithium is a highly reactive organolithium reagent that exists as a monomer in THF, however, even at -78 °C degradation was seen before lithiation occurred.[72]




*Scheme 31.* Alternative disconnection of **131**

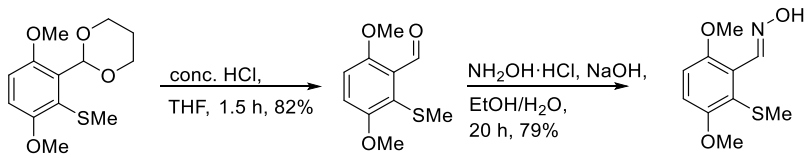
Initially the disconnection was made to introduce the aldehyde *via ortho*-lithiation rather than to introduce the thioether, this decision was made to avoid using dimethyl disulfide as the electrophile as it is toxic, flammable and highly malodorous. However, this was not possible and Scheme 31 outlines an alternative route.




**137** **136** **135**

*Scheme 32*. Synthesis of **135**

Formation of acetal **136** was completed using Dean-Stark conditions to drive the reaction to completion by the azeotropic removal of water.[73] A modified procedure of Sato *et al.* was used to successfully introduce the thioether giving **135**.[74,75] Ortho directing groups behave in an additive manner therefore selectivity for the 6 position of **135** is obtained as it is between a methoxy and acetal, both of which are able to coordinate to the organolithium reagent.[76]

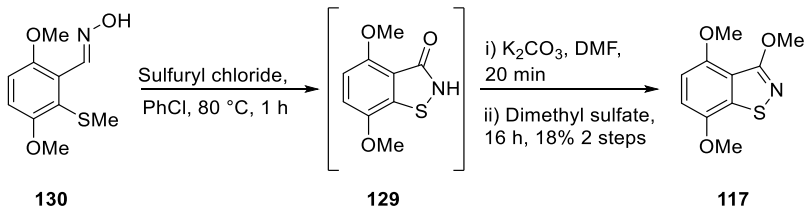



**135** **131** **130**

*Scheme 33.* Carbonyl manipulation to give **130**

With the desired substitution pattern established manipulation of the carbonyl gave oxime **130** the desired precursor to forming the key isothiazole ring. Deprotection of acetal **135** was carried out using concentrated hydrochloric acid. It is worth noting that attempts to reduce the volume of THF prior to dilution and extraction with ethyl acetate led to aliphatic impurities which were found to hinder purification. Hydroxylamine hydrochloride, which is more nucleophilic than

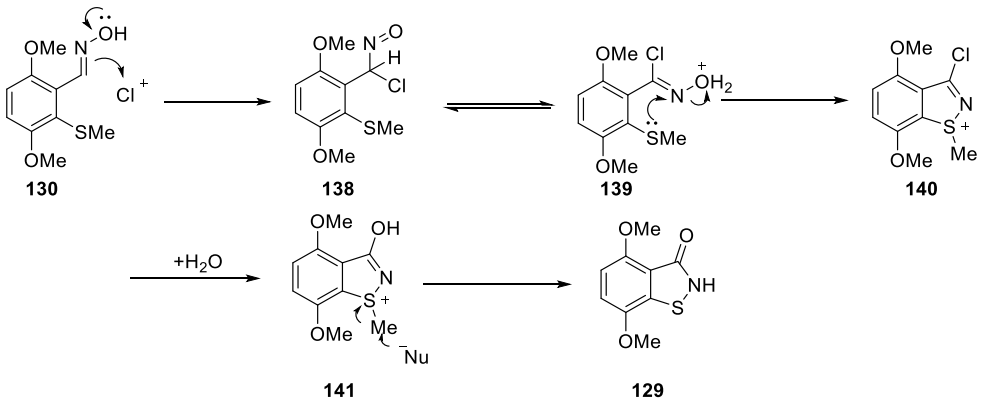
ammonia due to the alpha effect, in the presence of base was used to form oxime **130** in good yield.[77]




**130** **129** **117**

*Scheme 34.* Formation and methylation of benzisothiazolone **130**

Preliminary work carried out by Liu and Moody showed that the conditions used in the formation of benzisothiazolone **129** were optimal.[59] Attempts made to isolate **129** prior to methylation were found to be more challenging due to the similarity in polarity between the product and impurities and it was also found that no improvement to yield was found over the two step process.




**130** **138** **139** **140**

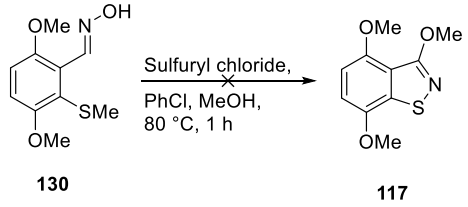
**141** **129**

*Scheme 35.* Speculative mechanism for the benzisothiazolone formation

A speculative mechanism for the formation of a benzisothiazolone from an oxime and thioether is outlined in Scheme 35. Chlorination of oximes with chlorine is well documented, sulfuryl chloride acts as a source of electrophilic chlorine and so the proposed mechanism begins with the chlorination of oxime **130**.[78,79] Activation of the oxime hydroxyl group as a leaving group leads to intramolecular attack of the sulfur lone pair on to the nitrogen. The ring closure would be categorized as a *5-exo-trig* ring closure according to Baldwin's rules for ring closure; although this

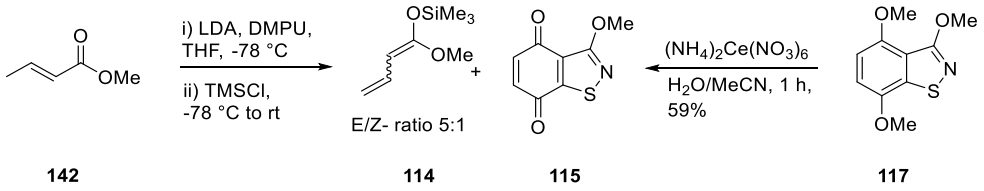
is an allowed transformation the rules are generally not applicable due to the larger sizes of elements from the second row. Hydrolysis of the chloride and removal of the methyl group gives **129**.

From Scheme 35 we see the 'amide' like portion of the isothiazolone ring is formed by hydrolysis of the chloride. As such it was speculated that addition of methanol to the reaction mixture could lead to **117** directly in one step from **130**.



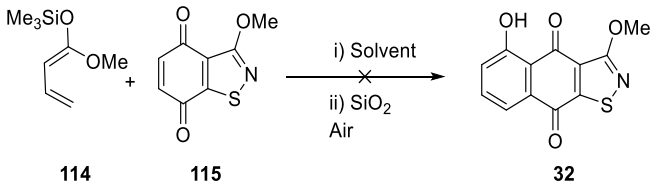

*Scheme 36.* Attempted one step formation of **117**

Unfortunately addition of methanol to the reaction mixture did not lead to desired methoxy benzisothiazole **117** but instead gave only degradation products.




*Scheme 37.* Synthesis of diene **144** and dienophile **115**

Diene **114** was prepared following the procedure of Ratjen *et al*. and purified by vacuum distillation.[80] The unhalogenated quinone dienophile was synthesised by oxidising **117** with the single electron oxidant ammonium cerium nitrate.



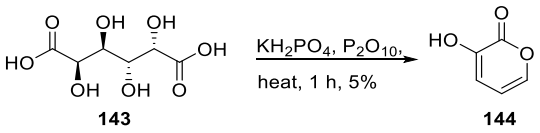

*Scheme 38.* Diels-Alder reaction

| Diene equivalents | Solvent | Temperature | Result |
|---|---|---|---|
| 1.2 | $CH_2Cl_2$ | rt | Degradation |
| 1.2 | PhMe | rt | Degradation |
| As solvent | - | rt | Degradation |

*Table 2*. Conditions for trialed Diels-Alder reaction

Diels-Alder reactions between quinone dieneophiles and similar dienes to **114** have been previously reported by Nawrat *et al*.[81,82] In this reaction the oxidation of the dihydroxy product occurs spontaneously in the presence of silica in air. However it was found that only degradation to highly polar products occurred. Diene **114** and similar dienes are notoriously difficult to handle due to their moisture sensitivity and as such we were interested in a bench stable alternative that would allow for further investigation of the Diels-Alder step.

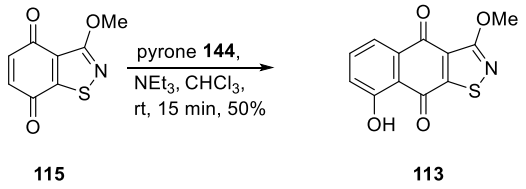
The use of pyrones as dienes in Diels-Alder reactions was first reported in 1931 by the men themselves.[83] Corey *et al.* first reported the use of 3-hydroxy-2-pyrone as a diene in Diels-Alder reactions as a vinylketene equivalent and it has found use as a bench stable diene since.[84–87]




*Scheme 39.* Synthesis of 3-hydroxy-2-pyrone

3-Hydroxy-2-pyrone **144** was synthesised by the method described by Wiley *et al*.[88] Mucic acid **143,** monobasic potassium phosphate and phosphorus pentoxide

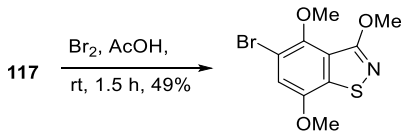
were heated using a hot Bunsen burner for 1 hour during which time the mixture turned molten and pyrone **144** was collected by distillation.




**115** **113**

*Scheme 40*. Diels-Alder reaction of unhalogenated dienophile **115**

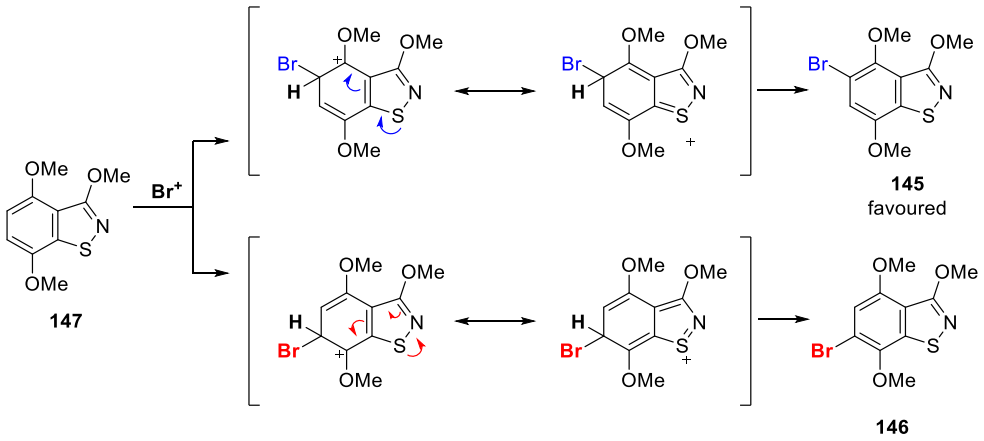
In the presence of base, both the Diels-Alder reaction and aerobic oxidation between **115** and **144** proceeded spontaneously at room temperature. In concordance with our hypothesis the unnatural isomer of aulosirazole **113** was formed. With this knowledge we were confident that the synthesis of aulosirazole could be completed using the strategy developed by Brassard.




**145**

*Scheme 41*. Bromination of **117**

Bromination of **117** was carried out, but unfortunately scaling up of this reaction proved unsuccessful and material was obtained by running multiple 0.15 mmol reactions simultaneously and combining for work up. The regioselectivity of bromination is key to the success of this strategy; herein lies the true beauty of the methodology. The same factors that contribute to the regiochemical outcome of the Diels-Alder reaction of the quinone also are the same factors that control bromination of **117** (Scheme 42).




*Scheme 42.* Regiochemical outcome of bromination

The same mesomeric effect of the sulfur heteroatom in the isothiazole ring that controls the Diels-Alder reaction can also stabilise the Wheland intermediate formed during electrophilic aromatic substitution. This effect provides greater stabilisation to the 5 substitute therefore favouring **145** as the product of bromination. The regiochemistry was confirmed by X-ray crystallography **(**Figure 20**)**.

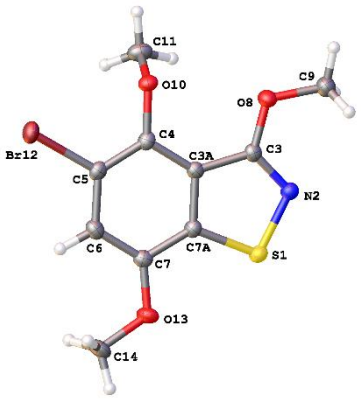
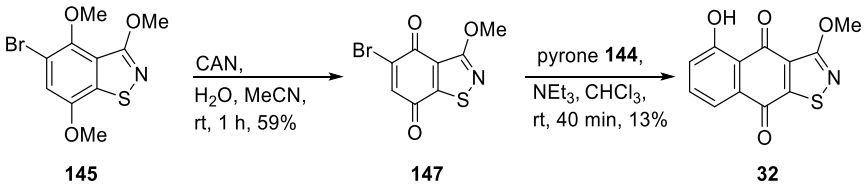


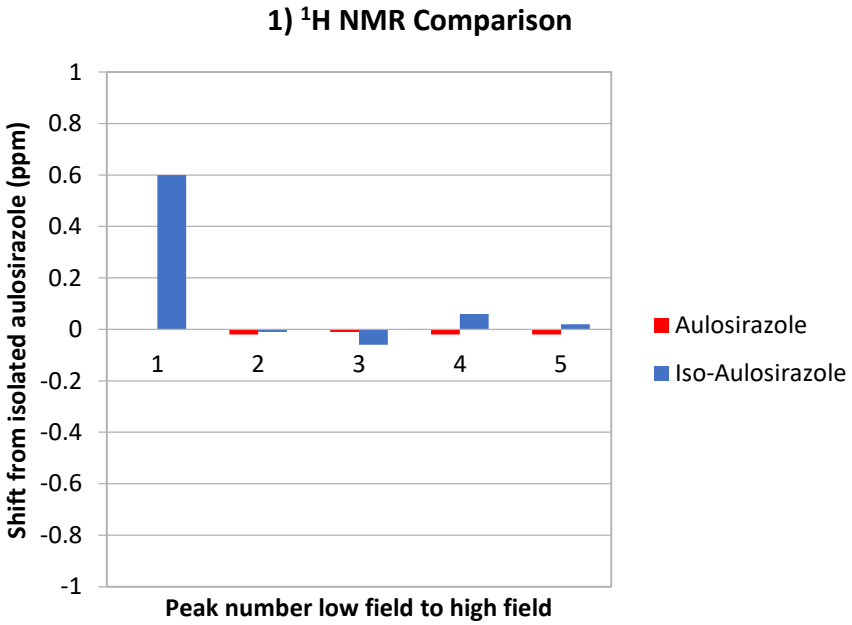

*Figure 20.* X-ray crystallographic confirmation of **145**

The overall effect of this is that a complete reversal of selectivity during the Diels-Alder reaction with aulosirazole **32** being successfully synthesised in 13% yield with no isomer **113** being formed.




*Scheme 43. Synthesis of aulosriazole **32***

Data collected from synthetic aulosirazole **32** and its isomer **113** were compared to that of the isolated sample as reported by Stratmann *et al.*[17] Both $^{1}H$ and $^{13}C$ NMR data were compared to that of the isolated samples and matched with great fidelity affirming the structure and completion of the total synthesis of aulosirazole **32** and its isomer **113**.



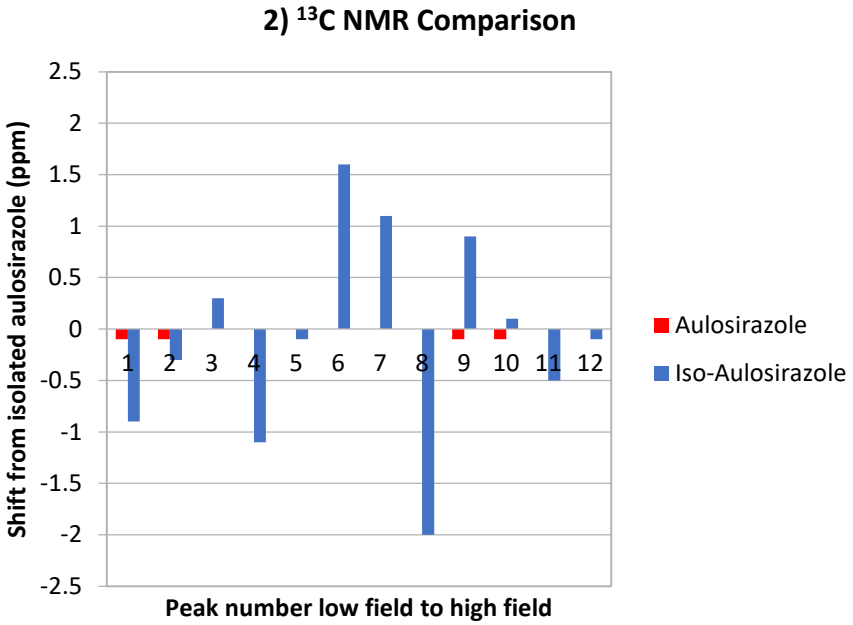
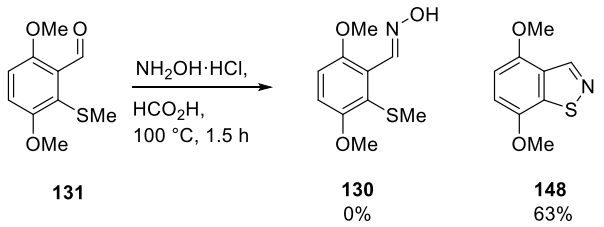



*Figure 21*. 1) $^{1}$H NMR comparison of natural and synthetic aulosirazole 2) $^{13}$C NMR comparison of natural and synthetic aulosirazole

## 2.2 The total synthesis of pronqodine A and analogues

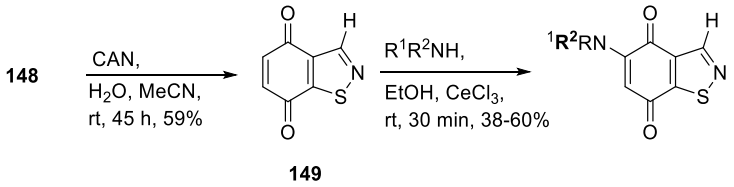
Serendipitously during our work towards the synthesis of aulosirazole **32** while investigating the formation of oxime **130** under acid conditions we found that no oxime **130** was isolated but rather ring closure occurred to give benzisothiazole **148** Scheme 44.




*Scheme 44. Benzisothiazole formation*

This result may be unsurprising considering the formation of benzisothiazoles from *meta*- substituted oximes and thioethers has been described since the late 1970's, but our one pot procedure seems to hold advantages over previously reported thermolysis reactions.

We then applied it to the synthesis of pronqodine A **30** and analogues.




*Scheme 45.* Synthesis of pronqodine A and analouges

| Entry | Amine | Yield |
|---|---|---|
| 1 | $H_2NMe$ | 42% (**30**) |
| 2 | $H_2NBn$ | 38% (**150**) |
| 3 | $HN(CH_2)_4$ | 60% (**151**) |

*Table 3.* Synthesis of pronqodine A and analogues

Oxidation of **148** was carried out using ammonium cerium nitrate to give quinone **149**. Conjugate addition of amine to the quinone was carried out according to the

procedure of Nakae *et al.*, used during their synthesis of pronqodine A **30**.[16] Cerium(III) chloride is a Lewis acid which is able to coordinate to two Lewis bases. Presumably this added to enhance selectivity by coordinating between the sulfur and carbonyl in the 7 position, thus directing addition to the 5 position.[89] Using this method we synthesised pronqodine A **30**, along with analogues **150** and **151**. These examples show that primary, secondary and benzylic amines can act as nucleophiles adding into quinone **149**.

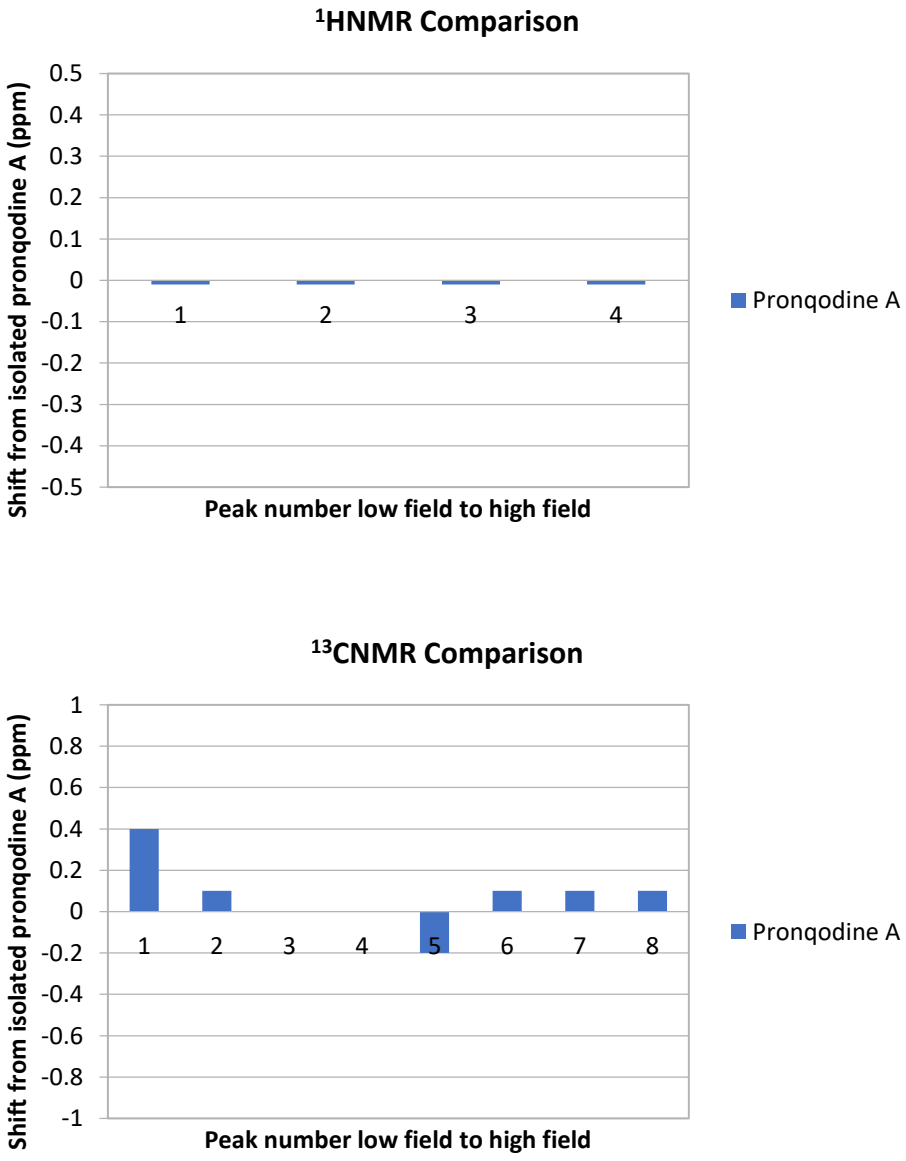
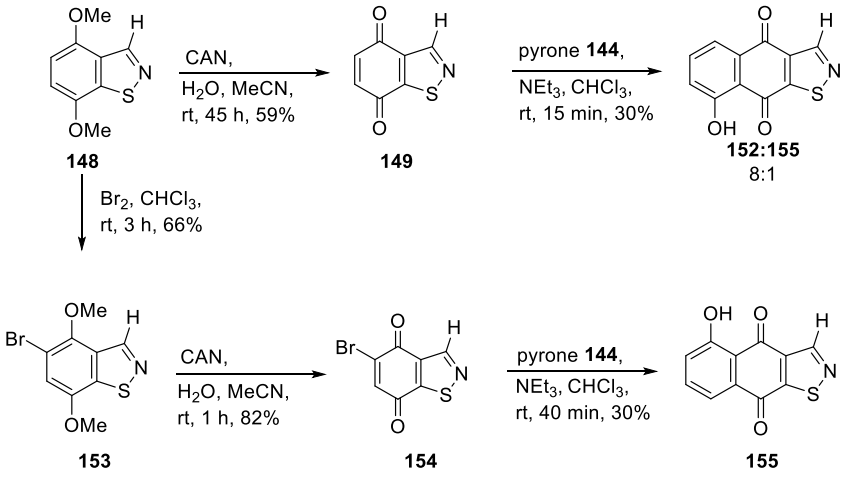



*Figure 22.* 1) $^{1}$H NMR comparison of natural and synthetic pronqodine A 2) $^{13}$C NMR comparison of natural and synthetic pronqodine A

Once again upon completion of the natural product the data was compared and shown to only vary a small degree in the $^{13}C$ NMR and we were confident that the data for synthetic **30** matched that of the isolated pronqodine A **30**.




*Scheme 46.* Synthese of desmethoxy analogues of aulosirazole

With quinone **149** available it was decided that cross-over compounds could be synthesised between aulosirazole and pronqodine A. Using the strategy developed for the total synthesis of aulosirazole the synthesis of Diels-Alder adducts of desmethoxy-isothiazolequinones **152** and **155** was undertaken.

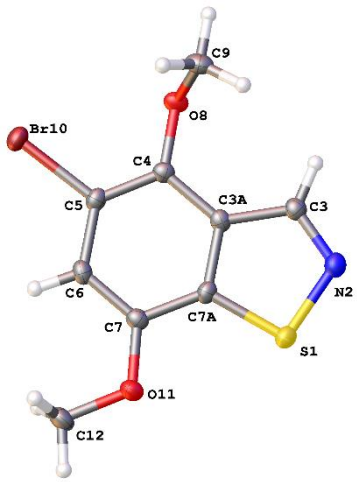


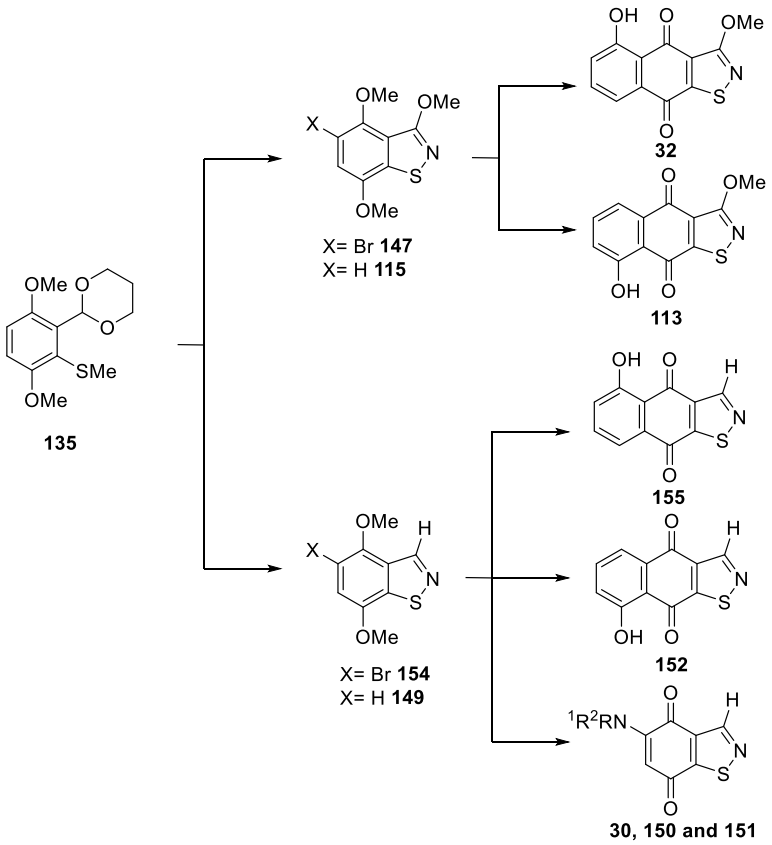

*Figure 23.* Structural confirmation of **153**

The synthesis of the desmethoxy- analogues of aulosirazole were carried using the same strategy and reagents as for aulosirazole. In the case of the synthesis of **152** it

was found that rather than obtaining solely the 8-hydroxy isomer an 8:1 mixture was obtained of **152** and **155** respectively. Once again Brassard's strategy for reversing the inherent regioselectivity worked exquisitely giving **155** as a single regioisomer.

## 2.3 Summary of the synthesis of benzisothiazole natural products

The synthesis of aulosirazole **32**, pronqidine A **30** and a number of analogues has successfully been achieved using a divergent route as outlined in Scheme 47. In addition to completing the synthesis of the target molecules a number of analogues have been made validating the possibility of further functionalising the quinones using either Diels-Alder reactions or aza-Michael addition if desired.

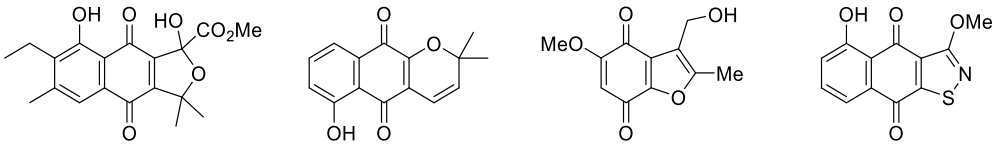



*Scheme 47.* Summary of the synthesis of aulosirazole and pronqodine A

## 2.4 Biological evaluation of aulosirazole, pronqodine A and their analogues

Aulosirazole was reported to display selective inhibition for solid tumours, including murine colon C38 and human lung H125 cancer cell lines, over leukemia cell lines L1210 and P388. In addition to this it was also demonstrated that aulosirazole inhibits a human nasophyrangeal carcinoma (KB) and a human colorectal adenocarcinoma with $IC_{50}$ values of 350 and 45 ng/mL respectively.[17] Our objective therefore was to investigate the origins and possible mechanism for the reported biological action.

All quinones in Figure 24 are known to be inhibitors of indoleamine 2,3-dioxygenase (IDO). Stark similarities between synthesised compounds and literature benzoquinones and naphthoquinones led us to believe the same mode of action could be possible for our series of quinones.[90–92]




**156** $K_i$ = 0.69 μM

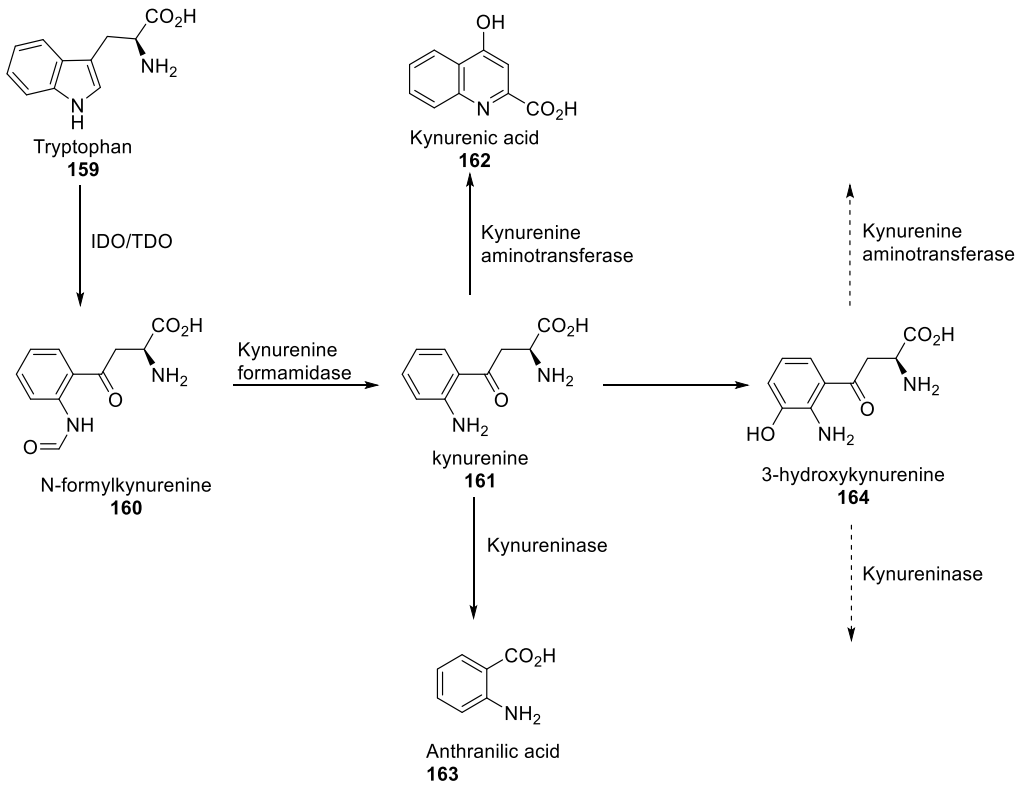
**157** $IC_{50}$ = 0.19 μM

**158** $IC_{50}$ = 0.24 μM

**32** $IC_{50}$ = ?

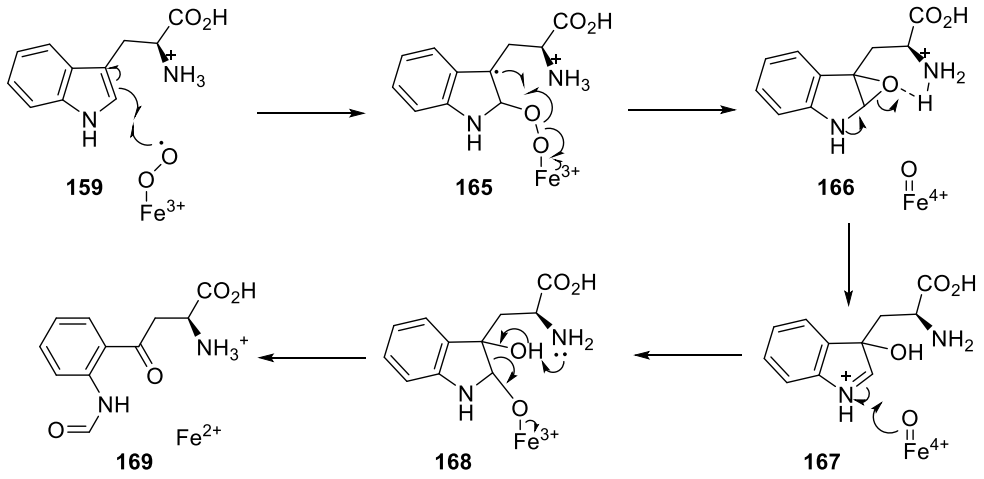
*Figure 24.* Known IDO inhibitors 1) Annulin A **156**[90] 2) **157** naphthoquinone[91] 3) benzofuranquinone **158**

The chemical role of IDO is to oxidatively cleave the indole 2,3-bond of tryptophan (Trp) **159** to give *N*-formylkynurenine **160**, the first and rate limiting step of the kynurenine (KYN) pathway (Scheme 48).[93]




*Scheme 48.* Kynurenine pathway

The active site of IDO contains a haem unit which adds oxygen across the double bond. Although a number of mechanisms have been suggested for this transformation, computational studies carried out by Capece *et al*. claim the mechanism laid out in Scheme 49.[94]




*Scheme 49*. Proposed mechanism for the catabalism of tryptophan[94]

It is suggested that radical addition of oxygen pre-bound to the haem centre occurs first. Homolytic cleavage of the O-O bond oxidises the iron(III) to iron(IV). Epoxide **166** is opened to give a cation which can be stabilised by forming an iminium which oxygen can then add into to form **168**. The 2,3-bond is then cleaved in a concerted process which ends with the elimination of iron(II) which is then available to bind another molecule of triplet oxygen so the process can start again.

Although the chemistry of the enzyme is interesting in its own right, the consequences of the protein expression are what makes it an interesting therapeutic target. IDO is expressed by a small number of healthy cells and suppresses the local immune system. Expression of IDO in the placenta and uterus is important for reproduction as it prevents the hosts immune system targeting foreign cells of the foetus allowing it to develop.[95]

Immune escape is thought to be key to the survival and growth of tumours; by suppressing the immune system they are able to avoid mechanisms designed to detect and kill defected cells.[96] A study carried out Theate *et al.* showed that 58% of 866 tested tumour samples tested expressed IDO and when looking at families

of tumours such as endometrial carcinoma and cervical carcinoma the proportion of tumour samples expressing IDO were 94% and 83% respectively.[95] The high prevalence of IDO in tumour cells suggest that it plays a large role in the survival of these tumour cells.

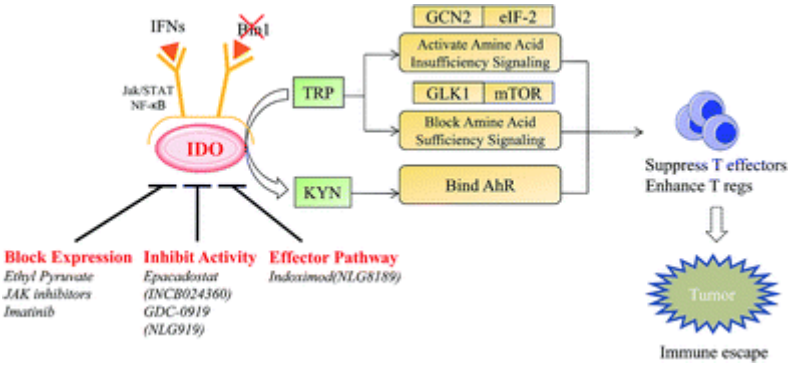



*Figure 25.* Mechanism of immune escape reproduced from Qian et al.[97]

Expression of IDO leads to a depletion of Trp in the local environment, which leads to the suppression of T effector cells and the proliferation of T regulatory cells ($T_{reg}$) through two independent pathways (Figure 25). A third pathway also exists as KYN, a catabolite of Trp, also has similar effects.[97] T effectors, in general, promote the immune response and includes cytotoxic T cells ($T_C$) which are able to destroy tumour cells, and T helper cells ($T_H$) which further activate $T_c$ cells and macrophages. $T_{reg}$ have the opposite effect and suppress the immune system.[98] The overall effect of this is that the tumor cell is able to avoid the immune system's mechanisms for detecting and destroying corrupted cells. A positive feedback loop is also proposed by Chen increasing the expression of IDO and $T_{reg}$ cells.[99]

It has been suggested that small molecule inhibitors of IDO could increase the effectiveness of current chemotherapies or be combined with other immune system modulators to delay tumour growth.[100,101]

Our compounds were tested in function assay by our collaborators at the University of Colorado, Denver. Activity was measured by assessing the ability for rhIDO to catabolise tryptophan in the presence of our inhibitors. From this the $IC_{50}$ of our inhibitors could be calculated.[102]

| Compound | $IC_{50}$ (nM) | Percent activity remaining of IDO | | | |
|---|---|---|---|---|---|
| | | 0.1 µM | 1 µM | 10 µM | 100 µM |
| Aulosirazole (**32**) | 80.3±4.3 | 31.7±0.4 | 7.2±1.0 | 1.2±0.4 | 2.1±0.7 |
| 113 | 71.3±1.4 | 29.9±0.6 | 2.2±0.2 | 0 | 0 |
| 155 | 78.9±1.3 | 36.0±0.3 | 9.4±0.2 | 2.5±0.1 | 2.3±0.1 |
| **152** | 80.8±0.7 | 38.1±0.4 | 10.5±0.1 | 0.5±0.2 | 0 |
| pronqodine A **(30)** | 131.5±28.5 | 51.1±1.5 | 15.4±0.1 | 3.0±0.1 | 5.9±0.1 |
| **150** | 83.3±2.9 | 40.0±1.7 | 6.3±0.2 | 0 | 0 |
| **151** | 541.5±16.2 | 73.4±1.4 | 25.7±0.3 | 5.5±0.1 | 2.6±0.2 |
| menadione | 887.4±15.8 | 86.0±1.6 | 44.9±0.6 | 10.8±0.1 | 0 |
| juglone | 16,413.5 ±1197.6 | 94.2±0.7 | 84.9±0.3 | 53.5±0.7 | 4.5±0.1 |

*Table 4.* Inhibition of rhIDO for aulosirazole **32**, pronqodine A **30** and analogues

All compounds proved to be inhibitors of IDO. Aulosirazole **32** and three analogues all had similar $IC_{50}$ values of around 80 nM and are the most potent inhibitors of IDO synthesised within the Moody group to date (Figure 26).[92,103]

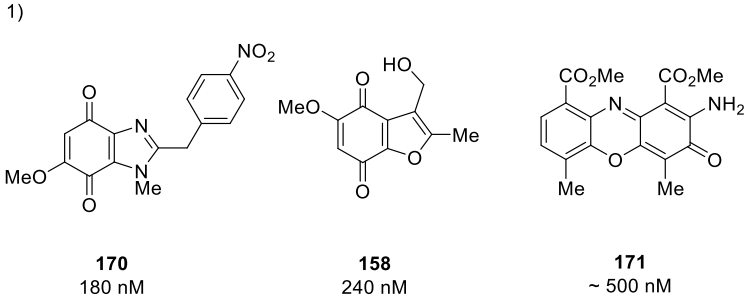


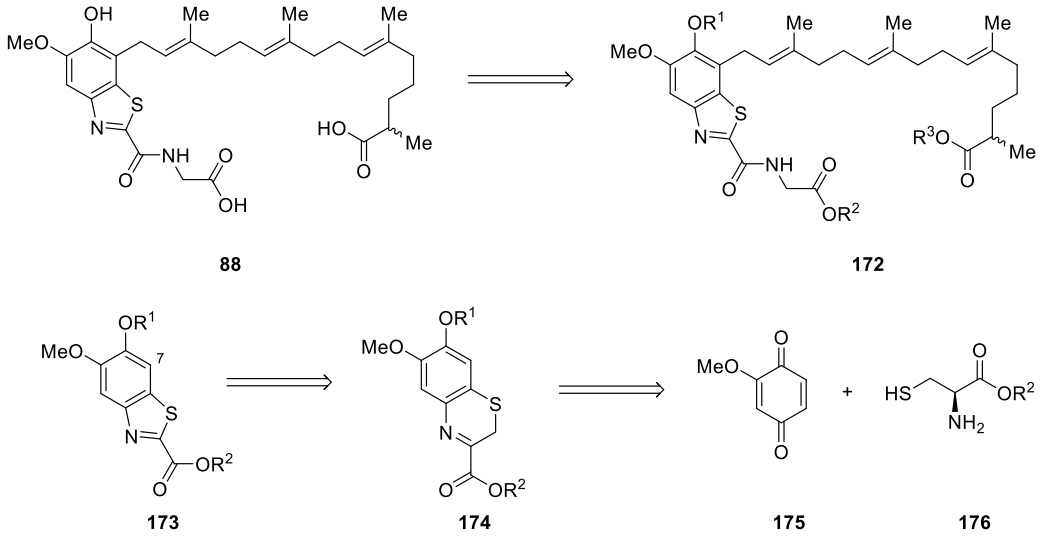

*Figure 26. Previous IDO inhibitors from within the Moody group*[92,103]

Pronqodine A and pyrrolidine analogue **151** had comparatively poor inhibition. Interestingly as pyrrolidine analogue **150** possesses a tertiary amine it is unable to act as a hydrogen bond donating group. As it is significantly the weakest inhibitor, it could suggest that a hydrogen bonding group in that area is important for activity.

# 3. Work towards the synthesis of benzothiazole natural products

## 3.1 Biosynthetic approach to erythrazole A

Retrosynthetic analysis (Scheme 50) of erythrazole A **88** was undertaken. The geranylgeraniol derived terpene chain would be introduced towards the end of the synthesis due to the promiscuous reactivity of the multiple alkenes present, in addition to the central location of the bond. Many strategies are available for the introduction of the terpene side chain including organometallic chemistry, such as by directed *ortho*-lithiation or metal halogen exchange, or *via* direct C-alkylation at the 7-position of **173.**[104,105]

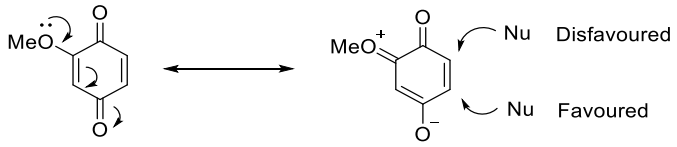



*Scheme 50.* Retrosynthetic analysis of erythrazole A **88**

Another important consideration is the judicious selection of protecting groups. Due the ability for terpenes to cyclise in the presence of acid and their easy hydrogenation, a protecting group must be labile to either base or nucleophiles such as fluoride. As such methyl esters would be ideal protecting groups for acids in compound **172,** and $R^1$ could be a silyl ether protecting group as they can be removed easily with fluoride.

An additional problem is the high level of oxygen substitution on the aromatic ring. Introduction of phenolic ethers either *via* Ullman condensation or oxidation is not always trivial, and as such having oxygen substitution present at both the 5- and 6-positions from the beginning would be preferred.

The highly substituted aromatic ring of **173** could be synthesised from the biomimetic ring contraction of **174**. It was hypothesised that **174** could be obtained from the addition of cysteine to 2-methoxyquinone **175**.

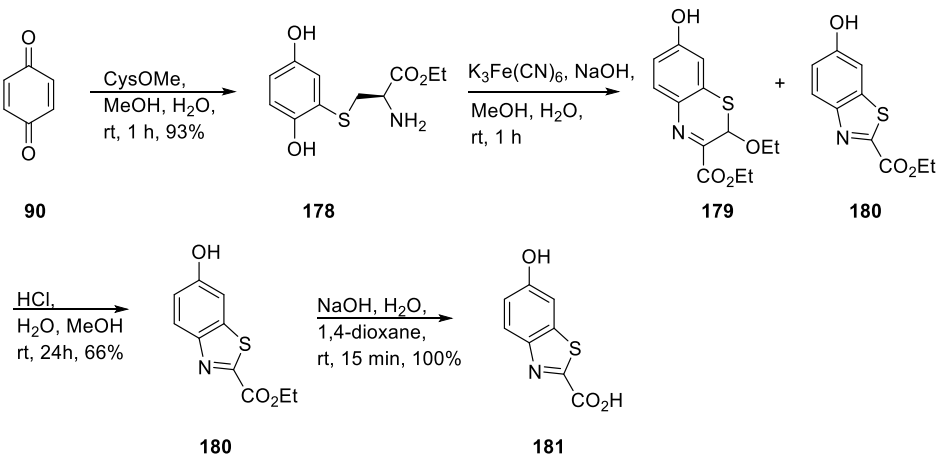



**175** **177**

*Scheme 51. Canonical forms of 2-methoxyquinone*

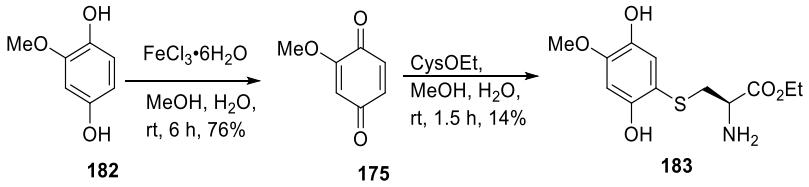
Due to the resonance effect of the methoxy group it was predicted that the conjugate addition of a nucleophile *para*- to this would be favoured (Scheme 51).[106]

Early work on the addition of cysteine to benzoquinone was carried out by Crescenzi *et al*.[107] In addition McCapra *et al.* investigated the oxidative cyclisation of the cysteine adduct to form the thiazine ring.[53,55] The work of Lowik *et al*. utilised these methods for the synthesis of 6-hydroxybenzothiazole-2-carboxylic acid (Scheme 52).[108]



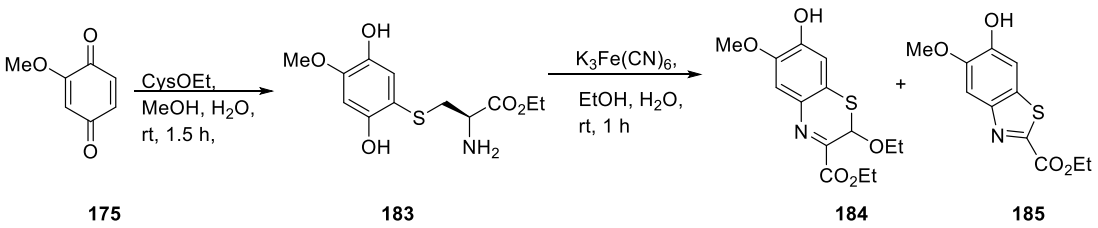

*Scheme 52.* Reported synthesis of 6-hydroxybenzothiazole-2-carboxylic acid by Lowik et al.[108]

Using this work as a starting point, we set about our investigations. Quinone **175** was synthesised in one step from the commercially available 2-methoxyhydroquinone **182** in 76% yield.



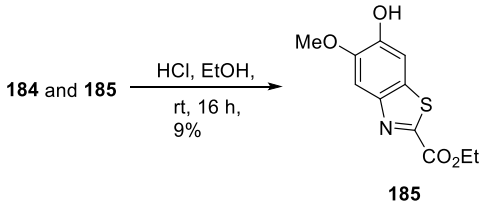

*Scheme 53.* Synthesis of **183**

Addition of cysteine ethyl ester to **175** was carried out using the reported conditions.[108] Unfortunately the desired cysteine adduct **183** was only isolated in 14% yield. No other isomers were isolated however, possibly due to the highly polar nature of the molecule causing difficulties with isolation. As the oxidative cyclisation step was also carried out in aqueous conditions, it was decided that the two steps could be telescoped without isolation of intermediate **183**.




*Scheme 54*. Oxidation cyclisation of **183**

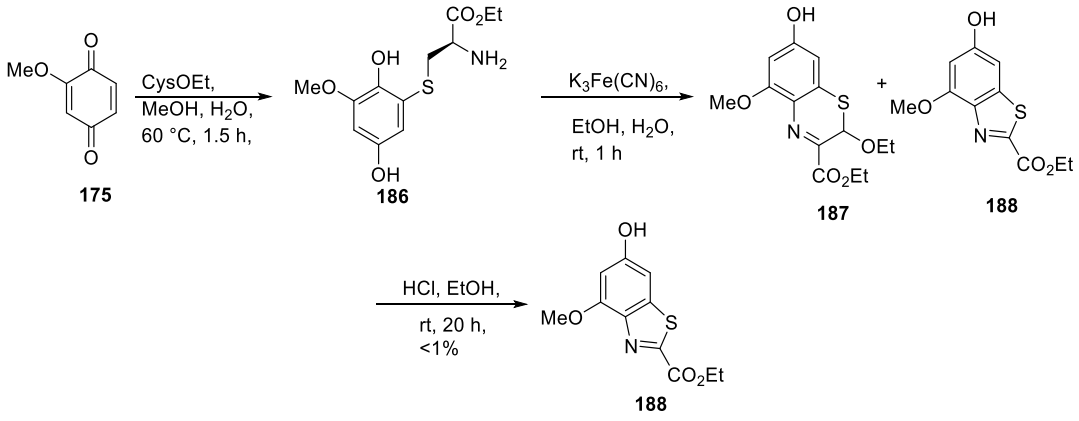
After the formation of **183,** the reaction mixture was washed with ethyl acetate allowing for the removal of any organic soluble by-products. The resulting aqueous solution was then treated with the conditions reported by McCapra *et al.*[55] giving an inseparable mixture of **184** and **185** (Scheme 54).




*Scheme 55.* Acid mediated ring contraction of **184**

As discussed in Chapter 1.3, **184** is an intermediate in the synthesis of **185** therefore the mixture was treated with hydrochloric acid to complete the ring contraction of the thiazine ring. The telescoped process gave a 9% yield of intermediate **185** from 2-methoxybenzoquinone.

It was found that by carrying out the initial addition of cysteine to quinone **175** at higher temperature only the 5-methoxy isomer **188** was obtained albeit in a <1% total yield over the 3 steps.

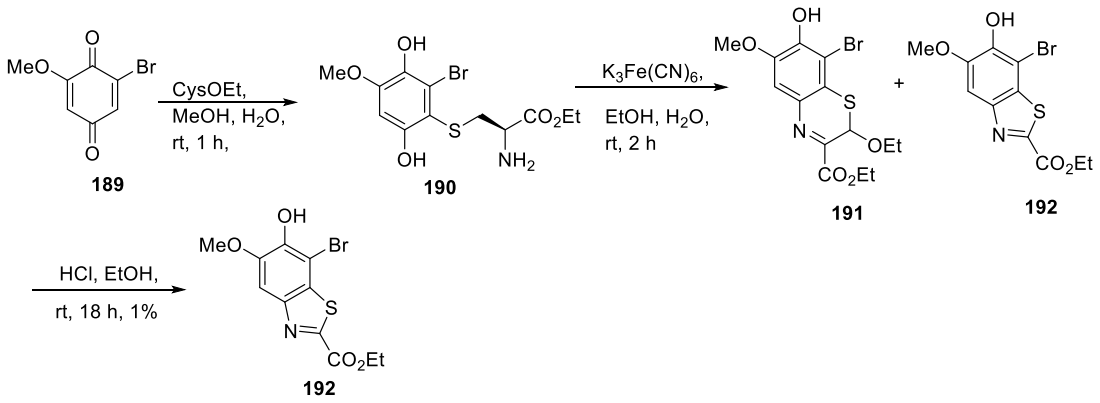



*Scheme 56.* Higher temperature effect of regiochemistry

Although the *para*-methoxy group should give some kinetic control over the regiochemical outcome of the reaction at higher temperatures, this is not the case

as there is enough energy present to overcome the activation energy at both positions. As such it is plausible that product **185** is the thermodynamic product of the reaction with substitution occurring at the least electron rich position.

Although not explicit in our retrosynthesis (Scheme 50), the presence of a halogen atom at the 7- position of **175** could be beneficial for the introduction of the desired terpene side chain. In addition the inductive electron withdrawing effects of the halogen may also reduce the energy of the LUMO and improve the initial conjugate addition of cysteine ethyl ester.

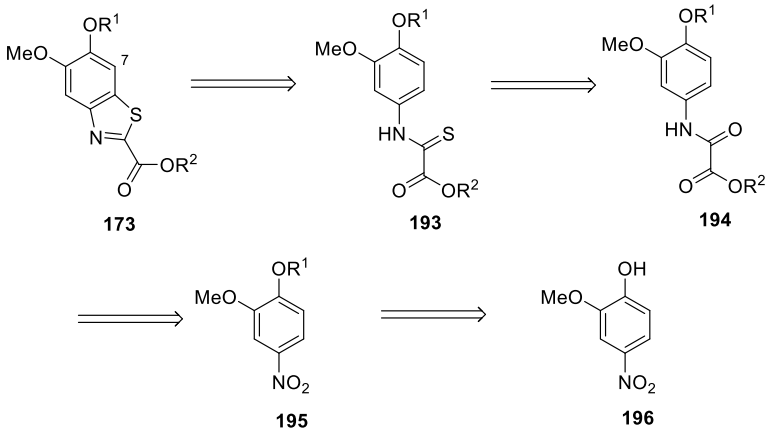



*Scheme 57.* Synthesis of halogenated benzothiazole **192**

Thus the commercially available 2-bromo-6-methoxybenzoquinone **189** was chosen as the starting material for this reaction. The telescoped process was applied with the addition of cysteine ethyl ester, oxidation with potassium ferricyanide to give a mixture of **191** and **192** and finally the acid promoted ring contraction of the thiazine ring to give **192** (Scheme 57). Once again however it was found that this process occurred in very poor yield of 1% and was unsuitable for scaling up. Due to being unable to find a scalable and reliable method for the synthesis of the core of erythrazole A, it was decided that a new route needed to be investigated.

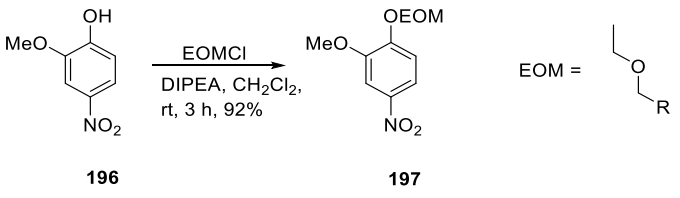
### 3.2 Luciferin inspired route to erythrazole A

As we considered intermediate **173** still to be the key compound for the synthesis of erythrazole A we focused our attention on an alternative disconnection of intermediate **173**. As such we decided that the carbon-sulfur bond could be formed using the nucleophilic character of thioamides to form the thiazole ring, a strategy used by White *et al.*[40] in the total synthesis of luciferin.



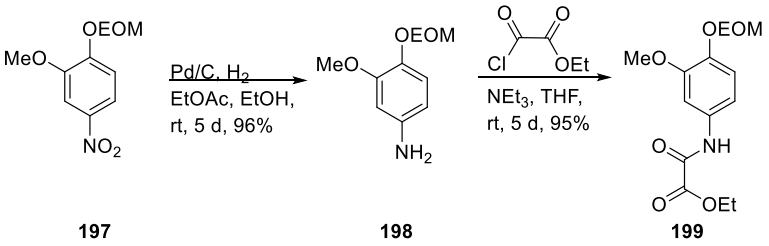

*Scheme 58*. Second retrosynthesis of erythrazole A

The thioamide could be formed from amide **194** that would be formed *via* an amide formation with commercially available ethyl chlorooxoacetate. As we would need to select an appropriate protecting group for the synthesis, 4-nitroguaiacol **196** seemed like the ideal starting material enabling us to easily choose an appropriate protecting group from the beginning of the synthesis. The ethylmethyl ether (EOM) protecting group seemed ideal as not only would it protect the phenolic proton but it is also known to act as a directing group for *ortho*-lithiation.[76]




*Scheme 59*. EOM protection of 4-nitroguaiacol **196**

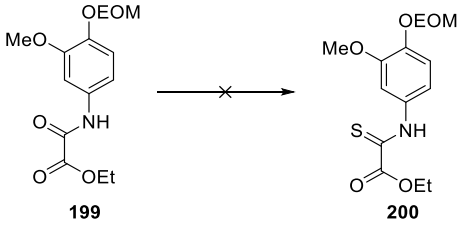
4-Nitroguaiacol **196** was protected in high yield using chloromethyl ethyl ether in the presence of diisopropylethylamine. As the EOM protecting group is acid labile hydrogenation was used in order to reduce nitro compound **197** to aniline **198**.




*Scheme 60*. Synthesis of amide **85**

Prolonged exposure to air resulted in the degradation of aniline **198** and so it was immediately reacted with ethyl chlorooxoacetate to give the amide **199.**

The formation of oxalyl thioamides is well reported in literature using either Lawesson's reagent or phosphorus pentasulfide[109–112] However all conditions only resulted in decomposition of starting material and were unsuccessful in promoting the formation of thioamide **200 (**Table 5**),** even those carried out at lower temperatures.[113] Mass spectrometry suggests that the EOM protecting group was removed under all conditions unveiling a phenol which may react with either Lawesson's reagent or phosphorus pentasulfide resulting in decomposition.

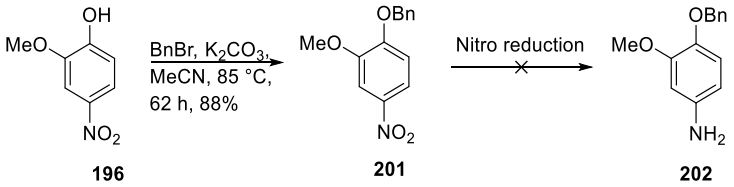



*Scheme 61*. Attempted formation of thioamide **86**

| Sulfur source | Solvent | Temperature (°C) | Result |
|---|---|---|---|
| Phosphorus pentasulfide | Xylene | 140 | Degradation |
| Lawesson's reagent | Toluene | 110 | Degradation |
| Lawesson's reagent | THF | rt | Degradation |

*Table 5. Attempted conditions for thioamide formation*

It was decided that an alternative, more robust, protecting group would be required which is stable to the thioamide formation conditions. It was decided that the benzyl protecting group would be suitable as it is stable to a wide range of conditions.[114] 4-Nitroguaiacol **196** was benzylated in 88% yield to give **201**.




*Scheme 62.* Benzylation of 4-nitroguaicol

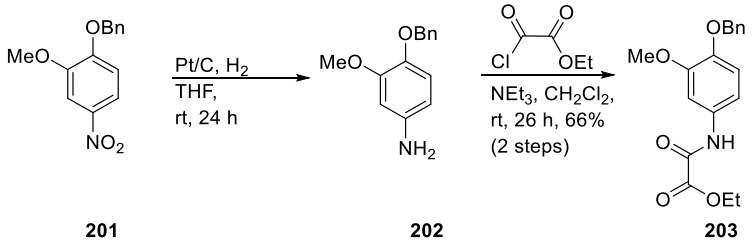
| Reducing agent | Solvent | Temperature (°C) | Result |
|---|---|---|---|
| Fe | Acetic acid | 100 | Degradation |
| Fe | Acetic acid | Rt | Degradation |
| Fe | HCl/EtOH | rt | Degradation |
| Zn | HCl/EtOH | rt | Degradation |
| In | $NH_4$·Cl/EtOH | rt | Degradation |

*Table 6.* Reduction conditions

As benzyl protecting groups are removed under hydrogenation conditions, the use of metal/acid reductions were considered. Initially the reduction was attempted at 100 °C, but baseline degradation products were formed. Even at lower temperatures the iron and acidic conditions also lead to degradation (Table 6). The same results were seen when the proton source was changed to dilute hydrochloric acid. Indium in ammonium chloride has been reported for the reduction of

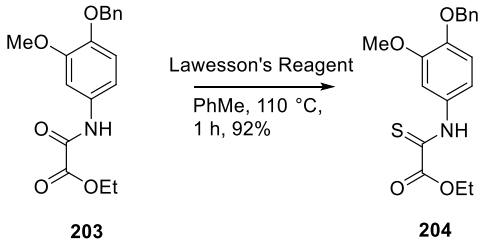
aromatic nitro groups under mild conditions, but once again the desired aniline **202** was not formed.[115]

Although hydrogenation conditions using palladium are known to remove benzyl ethers, other catalysts do not. Thus we carried out the reduction using Pt/C which cleanly reduces the nitro group to give **202** without removing the benzyl group (Scheme 63).



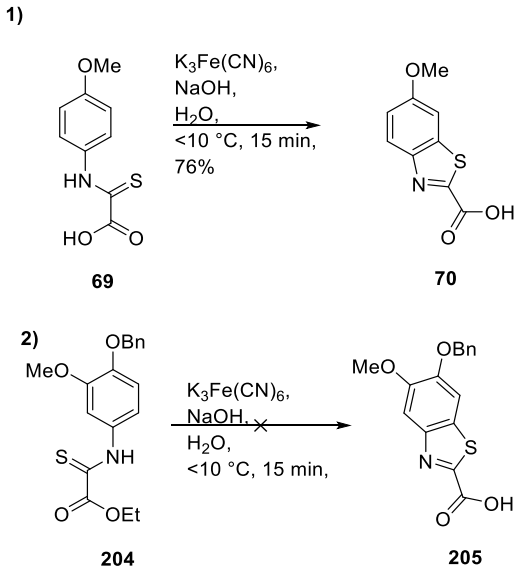

*Scheme 63.* Reduction and amide formation of **89**

Compound **202** was found to rapidly colourise and begin to decompose upon exposure to air, therefore **202** was not isolated but used directly in the next step. The amide formation was found to proceed more efficiently in dichloromethane rather than THF to give **203** in a 66% yield over two steps.



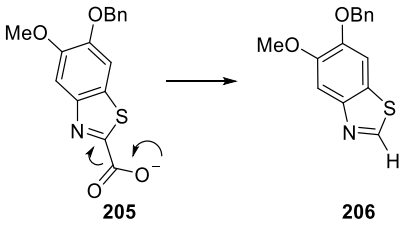

*Scheme 64.* Formation of **204**

Formation of thioamide **204** proceeded in high yield with Lawesson's reagent in boiling toluene, overcoming the previous route's limitations. With **204** in hand we were able to investigate the oxidative cyclisation as reported by White *et al*.[40,116,117] using aqueous potassium ferricyanide and sodium hydroxide (Scheme 65.1).



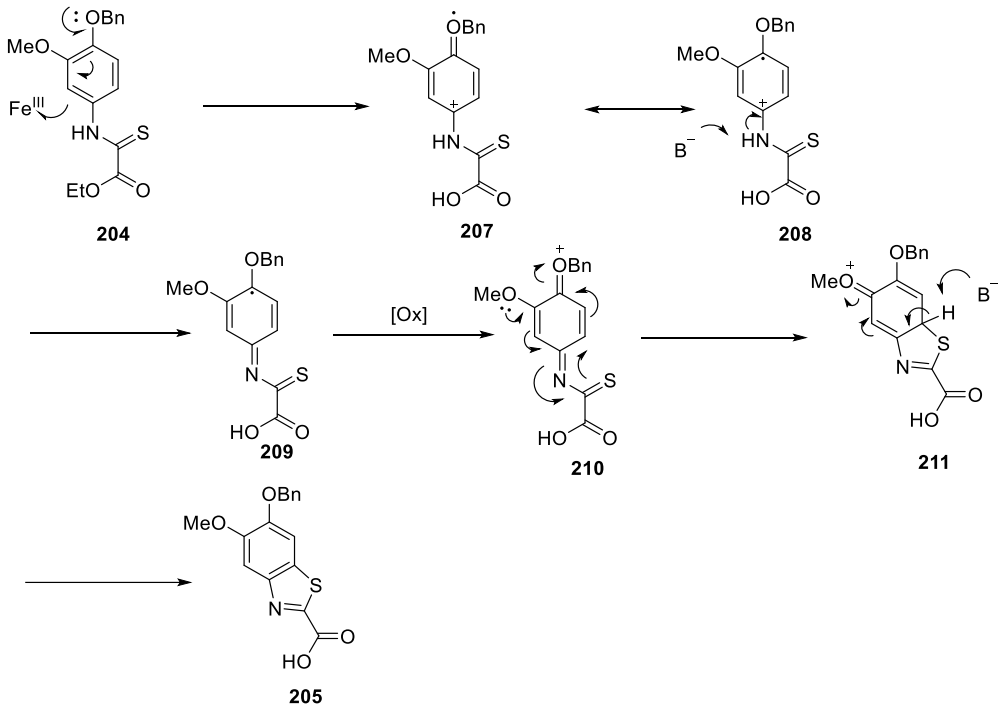

*Scheme 65.* 1) reported synthesis by White et al.[40] 2) Attempted synthesis of **205**

Due to the similarities between **69** and **204** it was thought that the same transformation could be undertaken in order to form **205**. Despite these similarities no desired product was identified, but rather mass spectrometry of the reaction mixture showed **206** to be the only product. However, attempts to isolate this product failed.



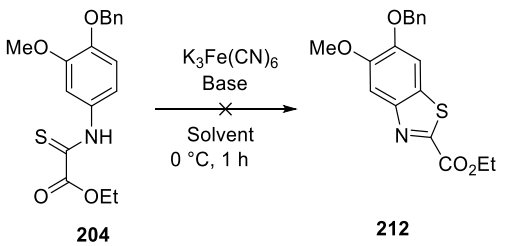

*Scheme 66.* Possible decarboxylation product **206**

Although 2-carboxybenzothiazoles are reported to be thermally unstable, it is unknown in this instance whether the decarboxylation takes place after benzothiazole ring formation or on an unstable intermediate during the reaction (Scheme 66).[108]




*Scheme 67*. Proposed mechanism of the oxidatitve cyclisation of thioamides

Our proposed mechanism begins with the single electron oxidation of the aromatic ring to form the radical cation **207**. A further oxidation gives benzoquinone imine **210** and conjugate addition of the thioamide forms the crucial ring. Additionally this mechanism also sheds light on why the desired regiochemistry is obtained, as in Scheme 51 intermediate **210** has a methoxy group which directs conjugate addition to occur on the less electron rich alkene. Rearomatisation should then give the desired benzothiazole. This proposed mechanism suggests that although a base is required an alternative base that is unable to hydrolyse an ester may be able to carry out this transformation without decarboxylation.




*Scheme 68*. Benzothiazole formation

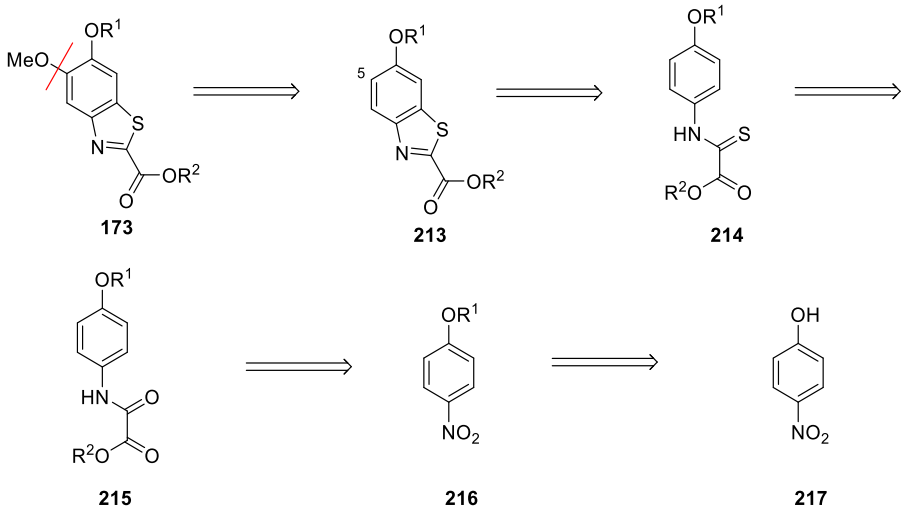
| Entry | Base | Solvent | Result |
|---|---|---|---|
| 1 | NaOH (1 M) | $H_2O$ | **206** |
| 2 | NaOH (0.5 M) | $H_2O$ | SM + **212** |
| 3 | NaOH (1.1 eq) | $H_2O$ | SM |
| 4 | KOH (1.1 eq) | $H_2O$ | SM |
| 5 | - | MeCN/$H_2O$ | SM |
| 6 | - | THF/$H_2O$ | SM |
| 7 | $K_2CO_3$ | MeCN/$H_2O$ | SM |
| 8 | $K_2CO_3$ | $H_2O$ | SM |
| 9 | $Na_2CO_3$ | $H_2O$ | SM |
| 10 | $CsCO_3$ | $H_2O$ | SM |
| 11 | DIPEA | $H_2O$ | SM + **212** |
| 12 | DBU | $H_2O$ | **212** |

*Table 7.* Screening of base for benzothiazole formation

Lowering the concentration of sodium hydroxide appeared to prevent the formation of decarboxylation product **206.** However, the reaction did not proceed to completion even after 1 h. Even lower concentrations of hydroxide base (Entries 3-4) show no conversion. A co-solvent was necessary for solubility in the absence of a base (Entries 5-6) but no reaction took place. While non-nucleophilic carbonate bases showed no reaction (Entries 7-10), amine bases showed some reaction taking place with DBU giving complete conversion (Entry 12). Unfortunately, it was found upon increasing the scale from 0.003 mmol that no reaction occurred. This made this route unviable and an alternative was considered.

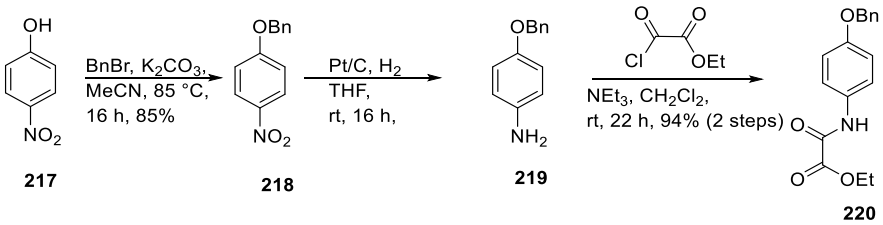
### 3.3 Synthesis of the benzothiazole core of erythrazole A

It was therefore considered that the more electron rich di-oxygenated species was too electronically different to the substrate reported by White *et al*.[40] An alternative was to synthesise a more similar substrate with a late stage introduction of the methoxy moiety at the 5- position of **213** either by Ullman chemistry, or oxidation.[118–121]




*Scheme 69*. Retrosynthetic analysis of **173**

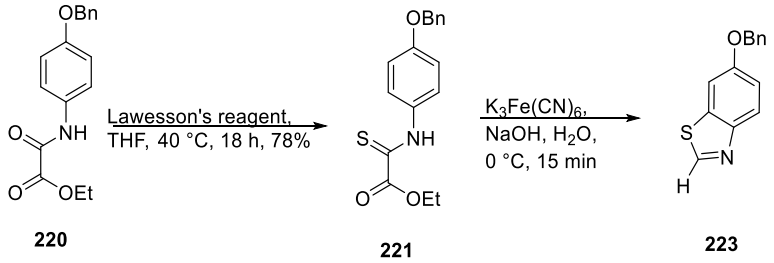
Once again a benzyl protecting group was selected for $R^1$ as it was known to tolerate the thioamide formation conditions and should be similar to the methyl ether group used in the synthesis of luciferin. Unlike the methyl ether, this protecting group should be removed easily by hydrogenation.




*Scheme 70*. Synthesis of **220**

The synthesis of amide **220** was carried out using the same conditions used for the synthesis of the di-oxygenated species **203** giving **220** in an 80% yield from the starting *para*-nitrophenol **217** (Scheme 70).

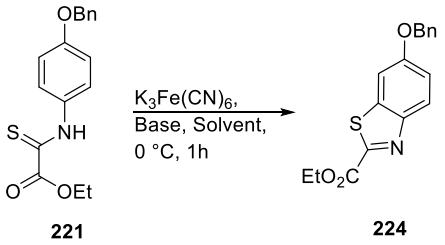
When previously employed thioamide formation conditions were applied to **220** this only led to degradation of the starting material. Alternative conditions were found using Lawesson's reagent in THF which is known to proceed at room temperature rather than requiring high temperatures such as with toluene.[109,111] In the synthesis of **221** no reaction was seen at room temperature however we were able to obtain **221** in 78% yield when warmed to 40 °C.




**220** **221** **223**

*Scheme 71*. Benzothiazole formation

Once again attempts to use the reported conditions by White *et al.*[40] unfortunately showed decarboxylated product **223** was forming during the reaction; however isolation eluded us.

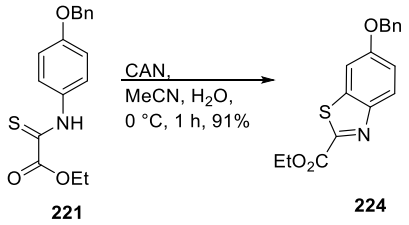



*Scheme 72.* Alternative reaction conditions for the formation of **224**

| Entry | Base | Solvent | Result |
|---|---|---|---|
| 1 | DBU | $H_2O$ | SM |
| 2 | $K_2CO_3$ | $H_2O$ | SM |
| 3 | - | MeCN/$H_2O$ | SM |
| 4 | - | THF/$H_2O$ | SM |

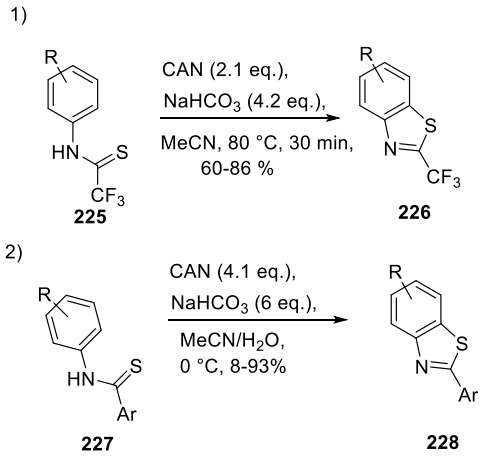
*Table 8.* Reaction conditions and results

Alternative reaction conditions (Table 8) were attempted using conditions which seemed promising in our initial investigation shown in Table 7. However all of these attempts were fruitless and gave no desired benzothiazole **224**.




*Scheme 73.* Benzothiazole synthesis using CAN

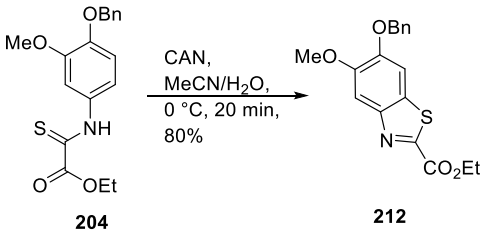
Serendipitously the first alternative oxidant used was ammonium cerium nitrate which was chosen as it is well known to oxidise *para*-substituted aromatics to both quinones and quinone imines.[102,122] Additionally it was found that there are two further reports of the use of CAN in the formation of benzisothiazoles.




*Scheme 74.* 1) 2-Trifluoromethylbenzothiazole synthesis. [123] 2) 2-Arylbenzothiazole synthesis.[124]

Zhu *et al*.[123] reported the synthesis of 2-trifluoromethylbenzothiazoles in 2011 using CAN as an oxidant following this in 2014 Chen *et al.*[124] reported that similar conditions were used in order to for 2-arylbenzothiazoles (Scheme 74). Our example is the first time that this these conditions have been shown to be able to be applied to the oxalyl system **221**.

With this in mind we looked towards applying these conditions to the synthesis of the di-oxygenated benzothiazole (Scheme *75*).

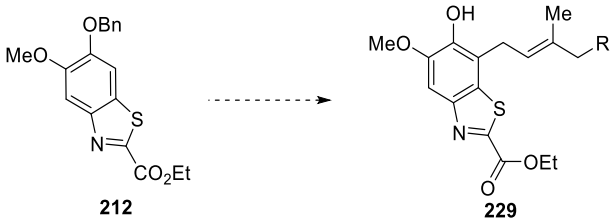



Scheme 75. Synthesis of benzothiazole **212**

Pleasingly the reaction proceeded effectively in a very good yield of 80% giving the desired benzothiazole **212** with the correct regiochemistry and no sign of decarboxylation occurring. The addition of sodium hydrogencarbonate had no effect on the reaction.

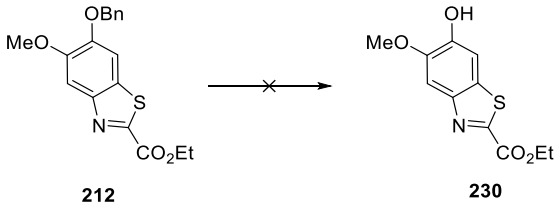
## 3.4 Functionalisation of benzothiazole core of erythrazole A

After successfully developing a scalable route to benzothiazole **212,** we set about investigating further functionalisation to introduce the desired terpene sidechain.




*Scheme 76.* Functionalisation of benzothiazole core

We began by removing the phenolic benzyl protecting group. The use of hydrogenation is well documented for the deprotection of benzyl groups; however at atmospheric pressure only starting material was recovered with both palladium on carbon and Pearlman's catalyst in a variety of solvents.[114] Transfer hydrogenation using ammonium formate as the hydrogen source at an elevated temperature also failed to give phenol **230**.[125]

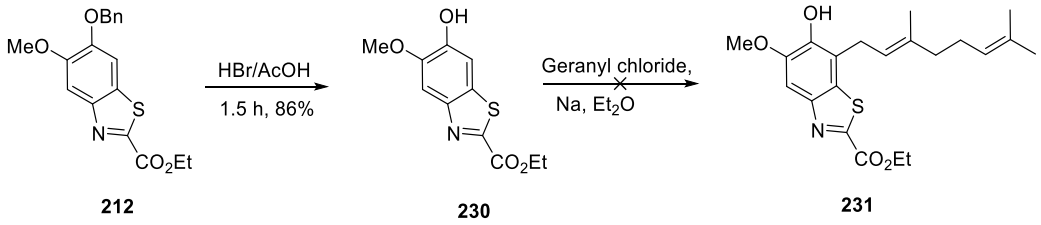



*Scheme 77.* Attempted hydrogenolysis

| Entry | Palladium souce | Hydrogen source | Solvent | Result |
|---|---|---|---|---|
| 1 | Pd/C | $H_2$ | EtOH/EtOAc | SM |
| 2 | Pd/C | $H_2$ | MeOH | SM |
| 3 | Pd/C | $H_2$ | AcOH | SM |
| 4 | $Pd(OH)_2$ | $H_2$ | EtOAc | SM |
| 5 | Pd/C | $NH_4HCO_2$ | EtOH | SM |

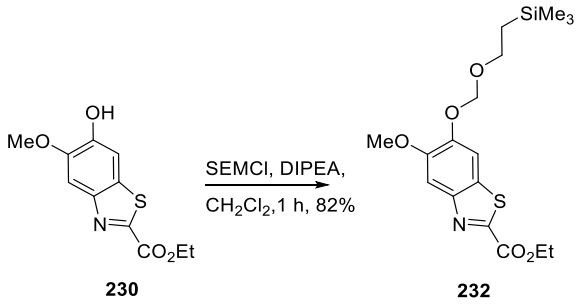
*Table 9.* Conditions of attempted benzyl hydrogenolysis

Although hydrogenolysis was unsuccessful it was found hydrogen bromide in acetic acid was able to carry out the transformation effectively at room temperature giving phenol **230** in 86% yield.




*Scheme 78.* Benzyl deprotection and attempted C-alkylation

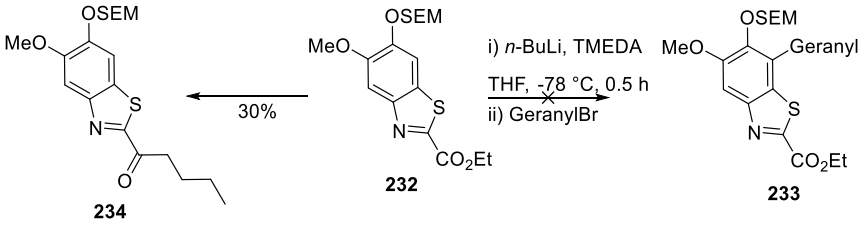
Yamada *et. al.* reported the *C*-alkylation of phenol with geranyl chloride in 90% yield using sodium metal, but on our substrate these conditions did not give the desired *ortho*- alkylated phenol.[104] A classical method for forming new bonds with arenes is directed *ortho*- lithiation, where a strong base deprotonates an arene at a position next to the directing group. Although a deprotonated phenol can act as a directing group we choose to use the SEM directing group as it can be removed with both acid conditions or by using a fluoride source and is also known to act as a directing group.[76,114]




*Scheme 79.* Introduction of the SEM directing group

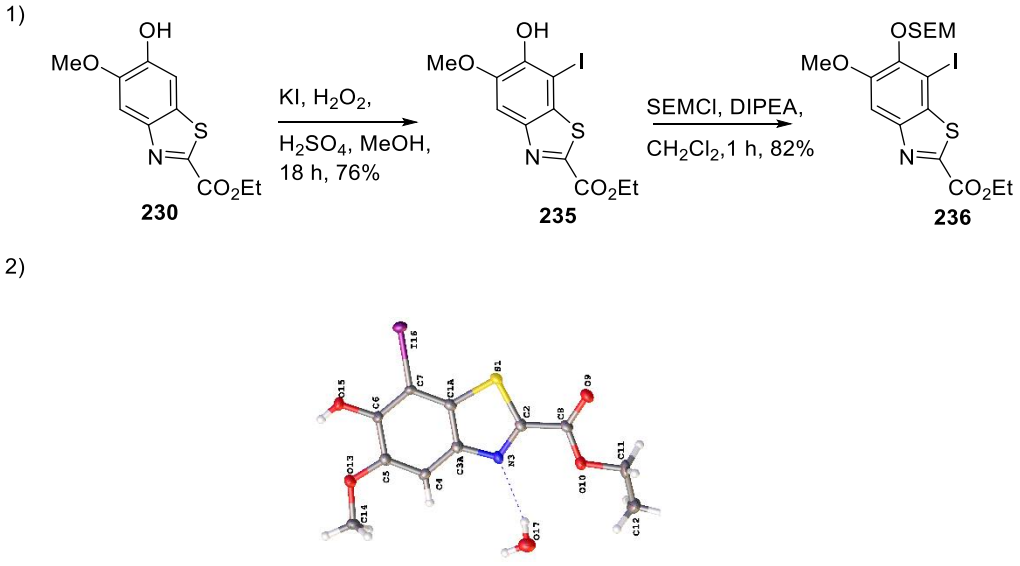
With the directing group in place we were then able to attempt to deprotonate the arene. *n*-Butyllithium was chosen as base and the reaction was carried out in THF using TMEDA as an additive. Organolithium reagents exist in high aggregation states, often as hexamers in apolar solvents, and the use of polar solvents or additives which are able to co-ordinate to the lithium can break up aggregates to

give dimers or monomers of the reagent. These are more reactive than their higher aggregation state counterparts so are able to deprotonate aromatic rings more easily.[70,76,126]




*Scheme 80.* Attempted ortho lithiation

It was found that rather than deprotonating the aromatic ring the *n*-butyllithium instead acted as a nucleophile reacting with the ester to give **234**. As well as being highly basic with a pka of *ca*. 50, organolithium reagents are also able to insert in to carbon halogen bonds. The rate of halogen exchange is thought to be much faster than that of deprotonation; it was therefore hoped that the rate of insertion may be quicker than that of the nucleophilic attack on the ester preventing formation of the side product and giving the desired functionalised benzothiazole.




*Scheme 81*. 1) Synthesis of halogenated core 2) Structural confirmation of **235**

The iodination was undertaken using potassium iodide and hydrogen peroxide with catalytic sulfuric acid to give **235** and the structure of which was confirmed

by X-ray crystallography. Once again a SEM directing group was used to protect the free phenol giving **236** in 82% yield.

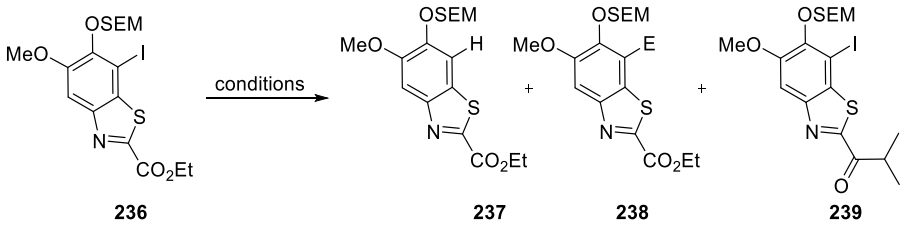



*Table 10.* Halogen exchange route to a functionalised core

| Entry | Conditions | Temp (°C) | Metal halogen exchange T | $E^+$ | T (h) | Results |
|---|---|---|---|---|---|---|
| 1 | *n*-BuLi, TMEDA, THF | -78 | 10 min | Geranyl bromide | 4 | **SM** **237** (trace) |
| 2 | $^i$Pr-MgCl·LiCl, CuI, THF | rt | 15 min | Geranyl bromide | 18 | **SM** **239** (trace) |
| 3 | $^i$Pr-MgCl·LiCl, THF | -50 | 30 min | *p*-chlorobenzaldehyde | 14 | SM |
| 4 | $^i$Pr-MgCl·LiCl, THF | -30 | 20 min | *p*-chlorobenzaldehyde | 1 | SM **237** (trace) **239** (trace) |
| 5 | Mg, $I_2$, THF | 60 | 1 h | $H^+$ | 2 | SM |

*Table 11.*Attempted organometallic route to introducing a side chain. All reactions were carried out on a 0.05 mmol scale and products were identified by high resolution mass spectroscopy.

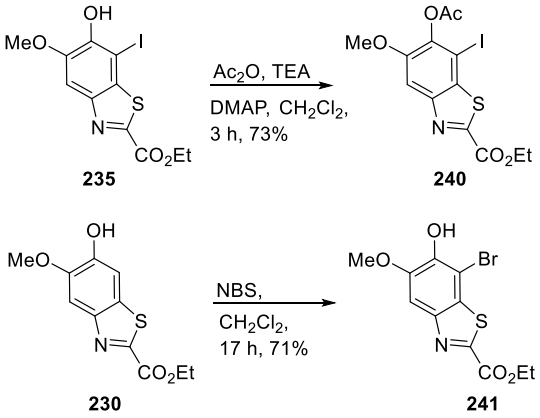
With **236** in hand we then attempted to functionalise the core using lithiation or Grignard chemistry. Although metal-halogen exchange had taken place to some degree which is demonstrated by the presence of **237,** no reaction with the desired electrophile took place (Table 11, entry 1). A similar result was found using iso-propylmagnesium chloride lithium chloride complex which was developed by

Knochel who coined the term ‘turbo Grignard’ to describe its reactivity.[127,128] Table 11, entry 4 shows that at lower temperatures the Grignard reagent is unreactive, possibly due to the electron rich nature of the heterocycle which slows the halogen-magnesium exchange rate.[129] When the temperature is raised to rt a side reaction occurs and addition of the *iso*-propyl group to the ester takes place (entry 2). Attempts to find a happy medium at -30 °C gave a mixture of starting material, **237** and **239** (entry 4). Although this suggests that some halogen-metal exchange occurs no reaction was seen with *para*-chlorobenzaldehyde suggesting even the Grignard intermediate is unable to react possibly due to steric hindrance.

Transition metal catalysis has become a stalwart of organic chemisty with the Suzuki-Miyaura reaction being an archetypal example.[130] In order to investigate cross coupling as a potential route to forming the key carbon-carbon bond a number of precursors were chosen.

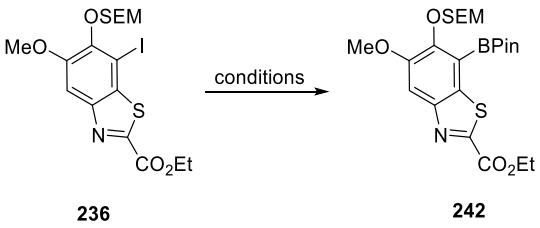
Gerbino *et. al.* have reported the cross-coupling of prenyl side-chains with aromatic systems using either the aromatic or the prenyl group as the boronic ester.[131] They also demonstrated that the coupling could be carried out with either an aromatic iodide or bromide and in the presence of a free phenol.

With plausible precursors **235** and **236** already in hand, we proceeded to synthesise the remaining precursors. Compound **240** was synthesised by treating phenol **235** with acetic anhydride in the presence of catalytic 4-dimethylaminopyridine to give **240** in a good yield.




*Scheme 82.* Synthesis of **240** and **241**

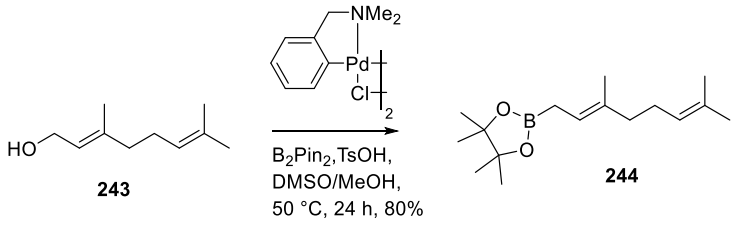
Bromination was carried out using *N*-bromosuccinamide to give **241** in 71% yield. The final compound to be synthesised was the boronic ester derivative which in theory could be formed *via* Miyaura borylation.[132, 133] In practice however, it was found that all of the conditions attempted did not give borylated product **242** and only starting material was isolated. Due to work carried out by both Organ and Buchwald groups we were still optimistic that we would be able to perform a Suzuki-Miyaura cross-coupling using a terpene derived boronic ester.[134, 135]




*Scheme 83.* Miyaura borylation

| Entry | Catalyst | Base | Solvent | | Temp. | Result |
|---|---|---|---|---|---|---|
| 1 | $PdCl_2(dppf)$ | KOAc | Dioxane | $(BPin)_2$ | 100 °C | SM |
| 2 | $Pd(OAc)_2$, CyJohnPhos | TEA | Dioxane | PinBH | 50 °C | SM |
| 3 | CuI | NaH | THF | PinBH | 70 °C | SM |

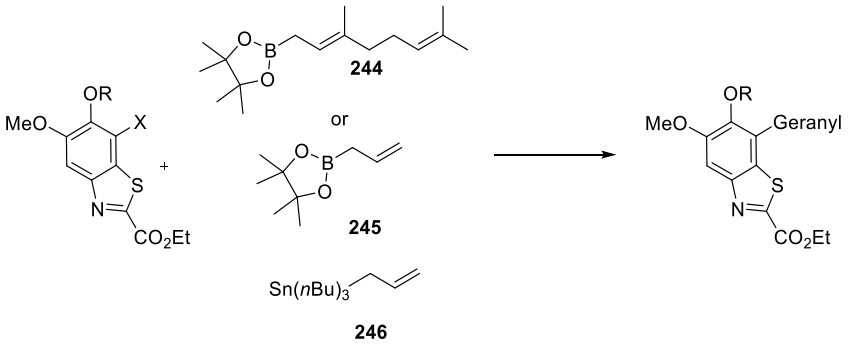
*Table 12.* Miyaura borylation conditions




*Scheme 84*. Borylation of geraniol

The pinacol boronic ester of geraniol was synthesised using the method of Aggarwal *et. al*. directly from commercially available geraniol.[136] Cross coupling reactions were then attempted.

Table 13 shows that benzothiazole core is unstable to the majority of the reaction conditions. Initially it was thought that this was a recurrence of the instability of benzothiazole core towards decarboxylation. Although the Suzuki cross-coupling requires a base to form a boronate species which undergoes transmetalation the Stille reaction does not require base. Entries 13 and 14 are both base-free Stille couplings and undergo degradation at 50 °C.[137] It was thought therefore that the incompatibility was between the benzothiazole and the palladium at elevated temperatures.

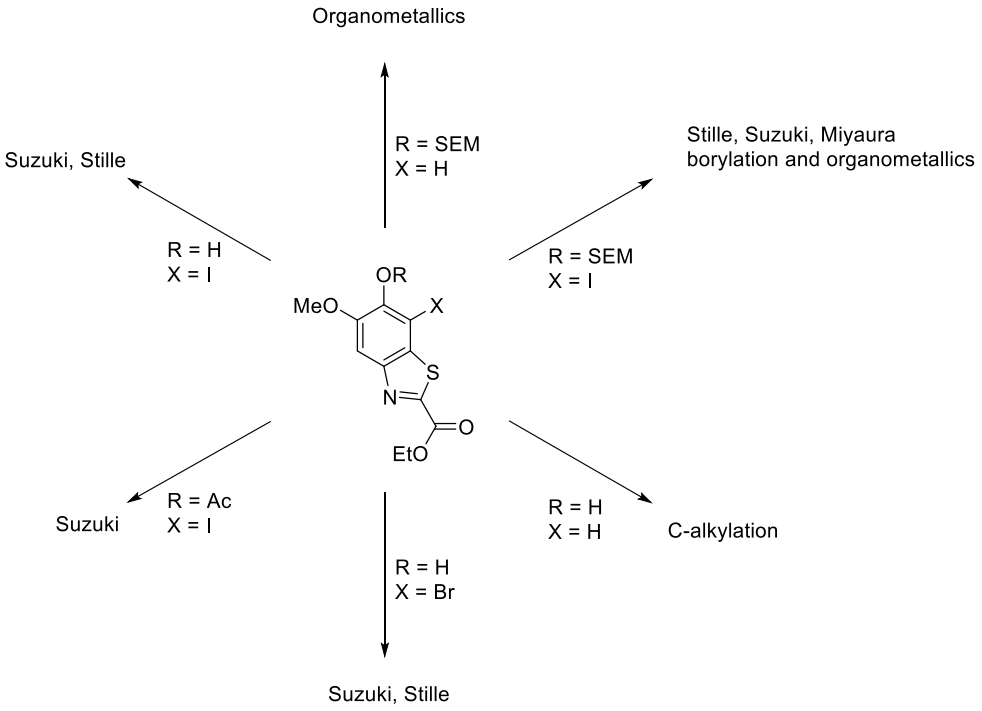



*Scheme 85*. Cross-coupling of allyl metals

| Entry | R=, X=, Coupling partner | Reagents | Solvent | Temp. | Result |
|---|---|---|---|---|---|
| 1 | SEM, I, **244** | $PdCl_2$(dppf), $Cs_2CO_3$ | DMF | 70 °C (μW) | Degradation |
| 2 | H, I, **244** | $Pd(OAc)_2$, $K_2CO_3$ | DMF | 30 °C | SM |
| 3 | H, I, **244** | $Pd(PPh_3)_2Cl_2$, $K_2CO_3$ | Dioxane/$H_2O$ | 90 °C | Degradation |
| 4 | H, I, **244** | Pd/C, $K_2CO_3$ | Dioxane/$H_2O$ | 95 °C | Degradation |
| 5 | H, I, **244** | PEPPSI-iPr, $Cs_2CO_3$ | DMF | 70 °C (μW) | Degradation |
| 6 | Ac, I, **244** | PEPPSI-iPr, $Cs_2CO_3$ | DMF | 70 °C (μW) | Degradation |
| 7 | Ac, I, **245** | PEPPSI-iPr, KOH | THF | 60 °C | Degradation |
| 8 | H, I, **245** | PEPPSI-iPr, KOH | THF | 60 °C | Degradation |
| 9 | Ac, I, **245** | $PdCl_2$/*t*-BuXPhos, $K_3PO_4$ | THF/$H_2O$ | 60 °C | Degradation |
| 10 | H, I, **245** | $PdCl_2$/*t*-BuXPhos, $K_3PO_4$ | THF/$H_2O$ | 60 °C | Degradation |
| 11 | Ac, I, **245** | $Pd(PPh_3)_4$, CsF | THF | 60 °C | Degradation |
| 12 | H, Br, **245** | $Pd(PPh_3)_4$, $K_2CO_3$ | DME/$H_2O$ | 110 °C | Degradation |
| 13 | H, I, **246** | $Pd(dba)_3 \cdot CHCl_3$/$PPh_3$, CuI | DMF | 50 °C | Degradation |
| 14 | H, Br, **246** | $Pd(dba)_3 \cdot CHCl_3$/$PPh_3$, CuI | DMF | 50 °C | Degradation |

*Table 13*, Cross-coupling conditions

Scheme 86 summarises the routes and reactions, attempted to introduce a geranyl or allyl function group to the desired 7-position, of the benzothiazole core. A wide range of attempts were made to introduce a model group directly to the 7-position all of which failed either due to lack of reactivity, promiscuous reactivity or degradation of the starting materials. Work on this synthetic approach was halted and an alternative route to erythrazole A was considered.



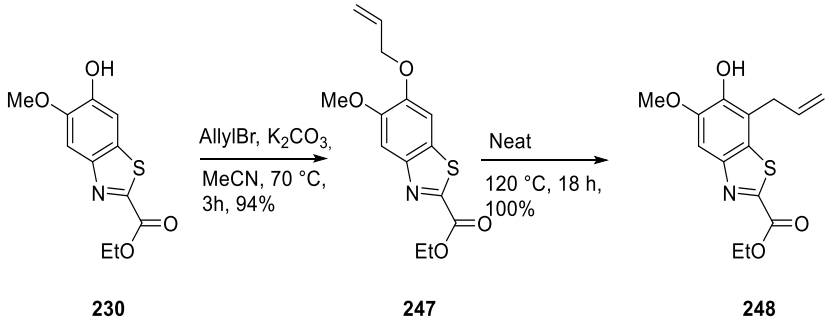

*Scheme 86.* Summary of attempted functionalisation of the benzothiazole core

## 3.5 Application of the Claisen rearrangement towards the synthesis of erythrazole A

In 1912 Ludwig Claisen published the first example of the eponymous [3,3] sigmatropic rearrangement; over a hundred years later the reaction is still in common use as a reliable method for forming carbon-carbon bonds.[138–141] Forming bonds between heteroatoms and carbon is often considered easier due to the difference in electronegativity between the two atoms. Being able to form this

bond then rearranging it into more challenging to make carbon-carbon bond with only heat is a valuable tool.

Initially a simple model was used to demonstrate that carrying out a Claisen rearrangement on this substrate would be possible. Compound **248** was chosen as the model substrate as it could be formed in one step from existing material *via* alkylation with allyl bromide.

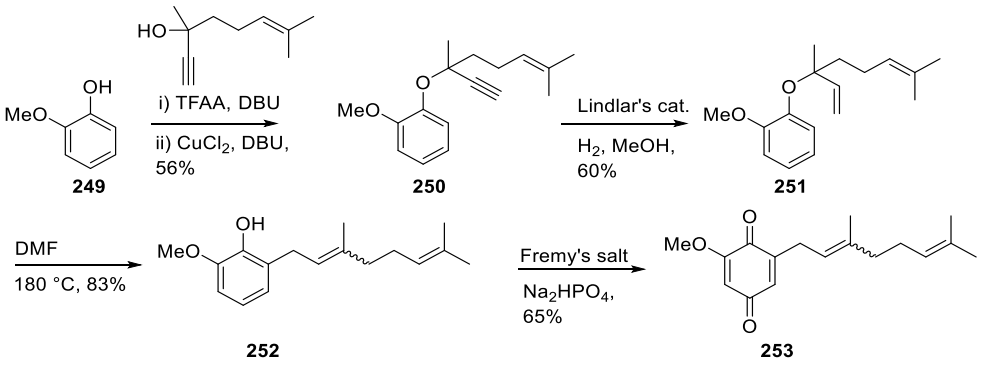



**230** **247** **248**

*Scheme 87*. Model Claisen rearrangement of **248**

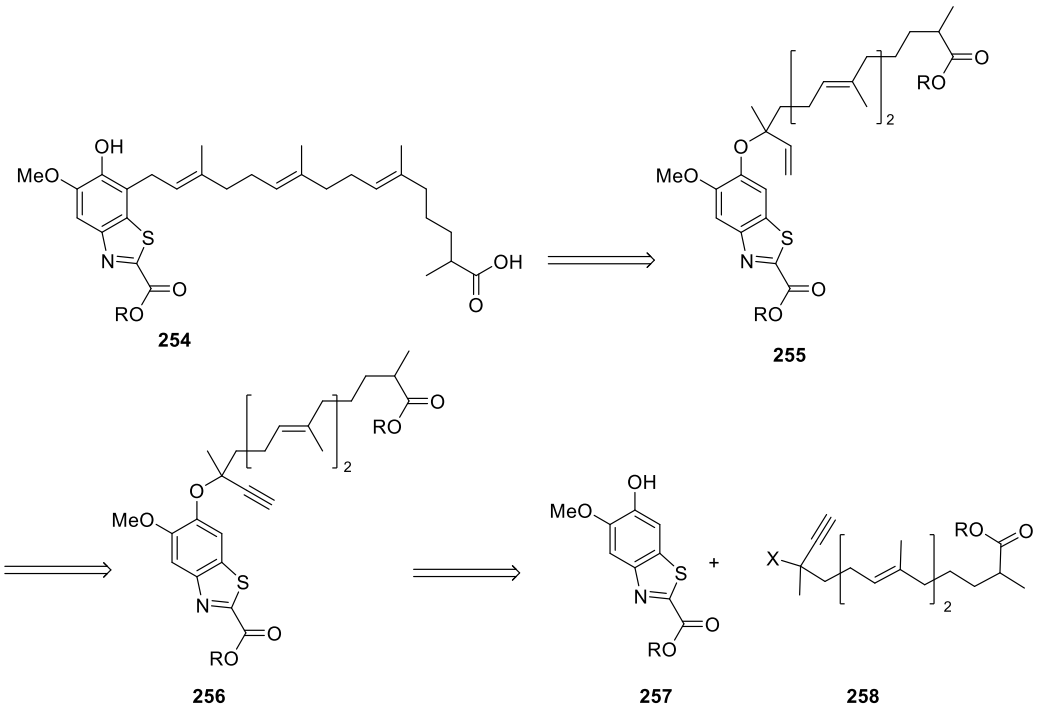
The beige solid was then heated neat at 120 °C in an oven for 18 hours during which time the Claisen rearrangement took place giving **248** in quantitative yield. This demonstrated that the transformation could be undertaken on the desired substrate and investigating the synthesis of a suitable side chain would be worthwhile.

Previous work within the Moody group provides a starting point for our retrosynthesis. Davis *et al.* completed the total synthesis of verapliquinones A and B in 1995 using the Claisen rearrangement to form the key carbon-carbon bond (Scheme 88).



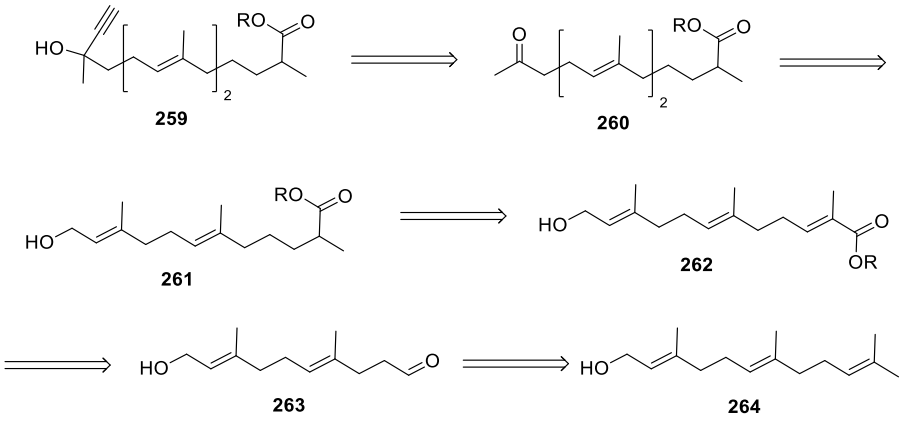

*Scheme 88.* Davis et al. total synthesis of verapliquinone A and B

In order to form **250**, the phenol needed to be alkylated. Substituted allyl halides or their equivalents are known to undergo substitution *via* a $S_N1$ mechanism forming an allylic cation which can react with the nucleophile at either end giving a mixture of products. Godfrey *et. al.* from Bristol-Myers Squibb discovered that using old needles gave consistent alkylations using DBU and acetonitrile. The old needles had brass Luer locks rather than stainless steel which is more commonly used now. With this knowledge they were able to develop novel conditions using copper chloride as a catalyst to give high yielding reproducible reactivity.[142]




*Scheme 89.* Reterosynthesis of erythrazole A

With this information in hand we were able to retrosynthesise erythrazole A using the work previously carried out within the group discussed above. Our analysis leads to **258,** a derivative of a farnesyl terpene chain where X could be a either a carbonate, electron poor ester or halide (Scheme 89).

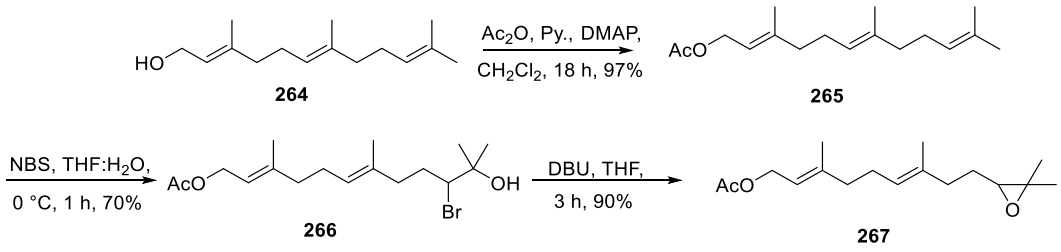



*Scheme 90. Reterosynthesis of side chain*

Propargylic alcohol **259** will be formed by addition of a Grignard reagent to ketone **260** which should proceed with high chemoselectivity over addition to the

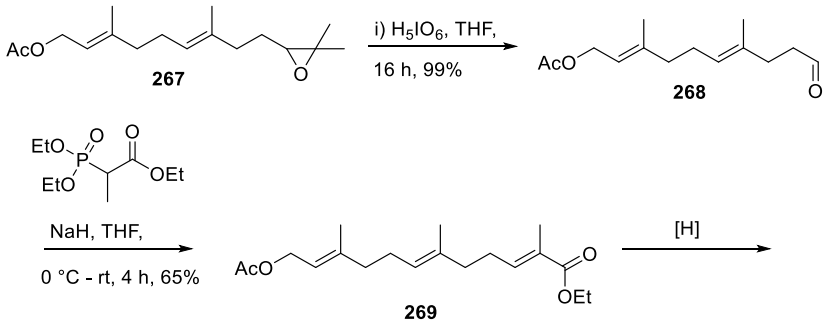
ester. The alkylation of allyl halides with α -ketoesters followed by decarboxylation is reported for terpenes allowing **260** to be synthesised from **261**.[143] Compound **261** could be formed by the 1,4-reduction of unsaturated ester **262** for which a number of methods are known.[144] Olefination reactions have been used to form modified terpene chains, often to facilitate the introduction of deuterium for mechanistic experiments. In addition to this, the synthesis of the desired aldehyde is reported from farnesol.[145]

The synthesis began with the protection of commercially available *trans, trans*-farnesol with an acetate group. This protecting group was chosen based upon literature precedent for the subsequent steps and may give some regioselectivity for the formation of the bromohydrin. The protection of the alcohol as an ester will make the allyl alcohol less electron rich which in turn may give greater selectivity for the electrophilic bromination of the terminal alkene.[145]




*Scheme 91*. Synthesis of epoxide **267**

Bromohydrin **266** was isolated in 70% yield and no other isomers were identified. Potassium carbonate and methanol are the commonly employed conditions for the elimination as the conditions remove the ester protecting group concurrently. However in our case we wanted to keep the acetate protecting group, and so we used the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene to form epoxide **267** in 90% yield leaving the protecting group intact.




*Scheme 92.* Synthesis of unsaturated ester **269**

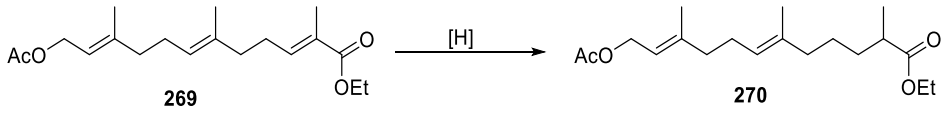
Analogous to the cleavage of diols with sodium periodate, periodic acid is able to cleave epoxides to give aldehyde **268**. Olefination was then carried out using a Horner-Wadsworth-Emmons (HWE) reaction between aldehyde **268** and triethyl 2-phosphonopropionate. The HWE reaction gives high *E* selectivity due to the reversibility of the oxophosphetane formation step which allows the thermodynamic *E* product to form; in our case a greater than 95:5 E:Z ratio was observed by $^{1}$H NMR. Chemoselective reduction of **269** in a 1, 4-manner would complete the functionalisation of the right hand side of the terpene.

Despite attempting many different conditions we were unable to successfully reduce the desired bond selectively. Magnesium and zinc are known as selective reducing agents for the 1,4- reduction of unsaturated esters as is Stryker's reagent, however all were unreactive in this instance (Table 14, entries 1-7).[146–149]

As expected no reaction was seen with sodium borohydride in methanol although in the presence of nickel(II) chloride a mixture of starting material, correct mass and over reduced products were identified. In addition to this with lithium aluminium hydride there was also evidence of ester reduction of the acetate protecting group (Table 14 entries 8-14). Interestingly the presence of the nickel(II) salt may lead to a markedly different reaction mechanism as they are known to be reduced to metal borides the most notable of these being Brown's catalyst or P-2 nickel which is a catalyst used in hydrogenation.[150,151] In addition to

the presence of a hydrogenation catalyst sodium borohydride is known to be unstable in methanol and forms hydrogen readily, so it is plausible that these reactions are undergoing a transfer hydrogenation reaction rather than nucleophilic addition of a hydride.[152]

Hydrosilylation and hydroboration of **269** also proved to be fruitless. Even under catalysis conditions with Wilkinson's catalyst no 1,4-addition of cataecholborane was observed (Table 14, entries17-19).[153,154] Samarium (II) iodide and sodium dithionite are both single electron reducing agents which have been shown to selectively reduce conjugated double bonds but both of these seem to cause no change in starting material **269 (**Table 14**,** entries 20-21).[155,156] The final conditions attempted to undertake the desired transformation uses Nature's machinery in order to enact the 1,4-reduction of **269** but once again no reaction was seen (Table 14, entry 22).[157]



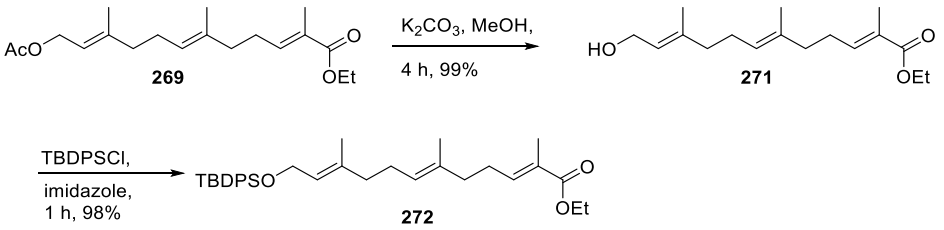

**269** **270**

*Scheme 93.* 1,4-reduction of **269**

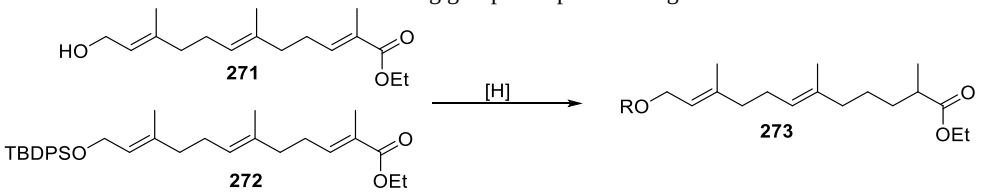
| | Reagents | Solvent | Conditions | Result |
|---|---|---|---|---|
| 1 | Zn, HCl, | MeOH | rt, sonication | SM |
| 2 | Zn, $NiCl_2$, | $H_2O$, Dioxane | rt, sonication | SM |
| 3 | Mg | MeOH | rt, sonication | SM |
| 4 | Mg, HCl, | MeOH | rt, sonication | SM |
| 5 | Stryker's, PMHS | PhMe | rt | SM |
| 6 | Stryker's reagent | PhMe | rt | SM |
| 7 | Stryker's reagent | THF | rt- 40 °C | SM |
| 8 | $Cu_2Cl_2$, $NaBH_4$, | MeOH | 0 °C -rt | SM |
| 9 | $CuCl_2$, $NaBH_4$ | MeOH | 0 °C -rt | SM |
| 10 | $NaBH_4$ | DMSO | rt | SM |
| 11 | $NaBH_4$ | EtOH | rt | SM |
| 12 | $NaBH_4$ | MeOH | rt | Complex mixture |
| 13 | $LiBH_4$, $NiCl_2$ | MeOH | 0 °C -rt | Complex mixture |
| 14 | $LiAlH_4$, CuI | THF | 0 °C | Complex mixture |
| 15 | $(PPh_3)_3CuBH_4$ | THF | rt | SM |
| 16 | $(PPh_3)_3CuBH_4$ | PhMe | rt | SM |
| 17 | $Et_3SiH$, $ClRh(PPh_3)_3$ | $H_2O$ | 70 °C | SM |
| 18 | $Pd(PPh_3)_3Cl$, catecholborane | THF | -60 °C | SM |
| 19 | Catecholborane | THF | rt | SM |
| 20 | $SmI_2$ | MeOH | rt | SM |
| 21 | $Na_2S_2O_4$, $NaHCO_3$, | $H_2O$/Dioxane | 90 °C | SM |
| 22 | Baker's yeast | $H_2O$, DMSO | rt | SM |

*Table 14.* Attempted reductions of **269**

After the initial conditions screen shown in Table 14 it was decided that further investigation into the use of borohydrides could prove beneficial. The presence of the acetate protecting group proved to be an added complication and as such was removed using potassium carbonate in methanol to give **271**. The alcohol could then be protected as a silyl ether which would not undergo reduction in the presence of borohydrides. With both the free alcohol **271** and the silyl ether **272** we were able to further investigate reducing the conjugated double bond.




*Scheme 94*. Protecting group manipulation to give **272**



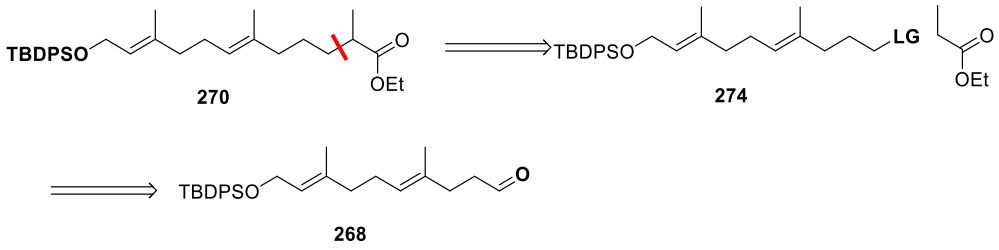

*Scheme 95*. 1,4-reduction of **271** or **272**

| | SM | Reagents | Solvent | Conditions | Result |
|---|---|---|---|---|---|
| 1 | 271 | $NaBH_4$, $NiCl_2$ | MeOH | RT | Complex mixture |
| 2 | 271 | $NaBH_4$, $NiCl_2$ | MeOH | 0 °C | Complex mixture |
| 3 | 271 | $NaBH_4$, $NiCl_2$ | MeOH | -20 °C | Complex mixture |
| 4 | 271 | $NaBH_4$ | MeOH | 0 °C -rt | SM |
| 5 | 271 | $NaBH_4$, $CoCl_2$ | MeOH | -20 °C | Complex mixture |
| 6 | 271 | $NaBH_4$, $PdCl_2$ | MeOH | -20 °C | Complex mixture |
| 7 | 272 | $NaBH_4$, $NiCl_2$ | MeOH | -20 °C | Complex mixture |
| 8 | 271 | $LiAlH_4$, CuI | THF | 0 °C | 1,2- and 1,4- reduction |
| 9 | 271 | $LiAlH_4$, CuI | THF | -78 °C | SM |

*Table 15.* Attempted reductions of **271** and **272**

Even with the acetate protecting group removed, complex, inseparable, mixtures were obtained of starting material, **273**, isomers of **273** and also over reduced products were obtained when using sodium borohydride and nickel(II) chloride at room temperature, the same was also found for the silyl protected **272** (Table 15, entries 1 and 4). Reducing the temperature did not appear to have any effect on the outcome of the reaction with the same mixture still being observed by MS (Table 15, entries 1-3). It was thought that different metal salts would give different reactive species and as such may give different results; however the same mixture was found with both salts of cobalt and palladium.[158] Lithium aluminium hydride in the presence of copper(I) iodide gave a mixture of 1,2- and 1,4- reduction at 0 °C and no reaction was seen when the temperature was reduced to -78 °C.

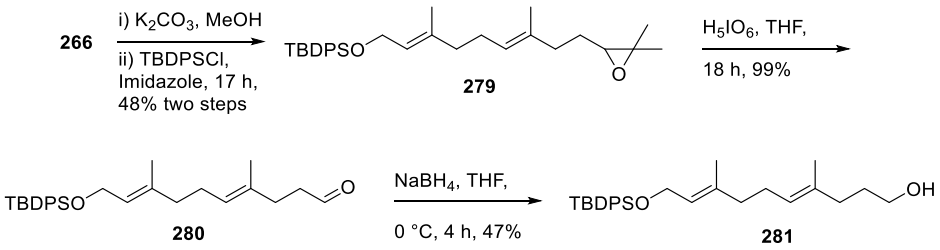
Due to the number of failed attempted conditions for the 1,4- reduction of our unsaturated ester a new route was planned to circumvent this difficult transformation. It was decided that the single bond would be formed directly *via* alkylation.




*Scheme 96.* Alkylation retrosynthesis of **270**

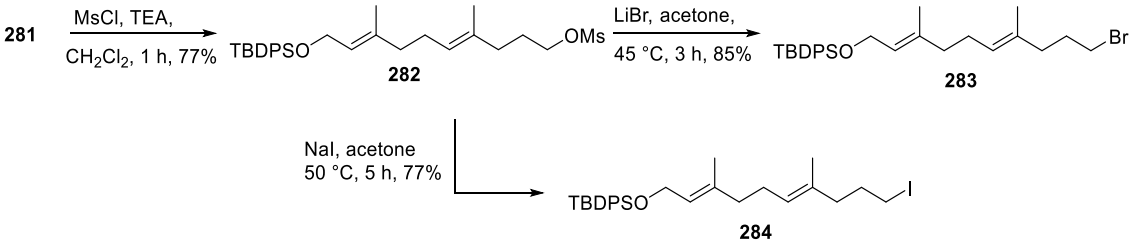
The initial disconnection was made α to the ester as an ester enolate is a sensible disconnection to be the nucleophile. As a result the terminal carbon will have to be the electrophilic partner and a leaving group would need to be present. The leaving group would be in the same position as the previously synthesised aldehyde so it would just require functional group manipulation in order to have a halogen at the desired position. In addition to this it was also decided that a silyl protecting group

would be used as the acetate has been shown to be susceptible to nucleophilic acttack.



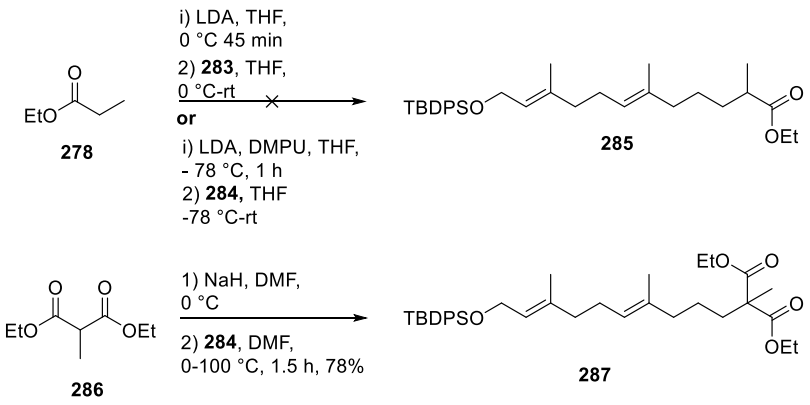

*Scheme 97.* Synthesis of **281**

Rather than using DBU to form the epoxide as previously discussed potassium carbonate in methanol was used. Methanolysis of the acetate protecting group occurs and the alcohol can then be protected with a bulky silyl group. The remainder of the synthesis to alcohol **281** was carried out in the manner previously discussed.



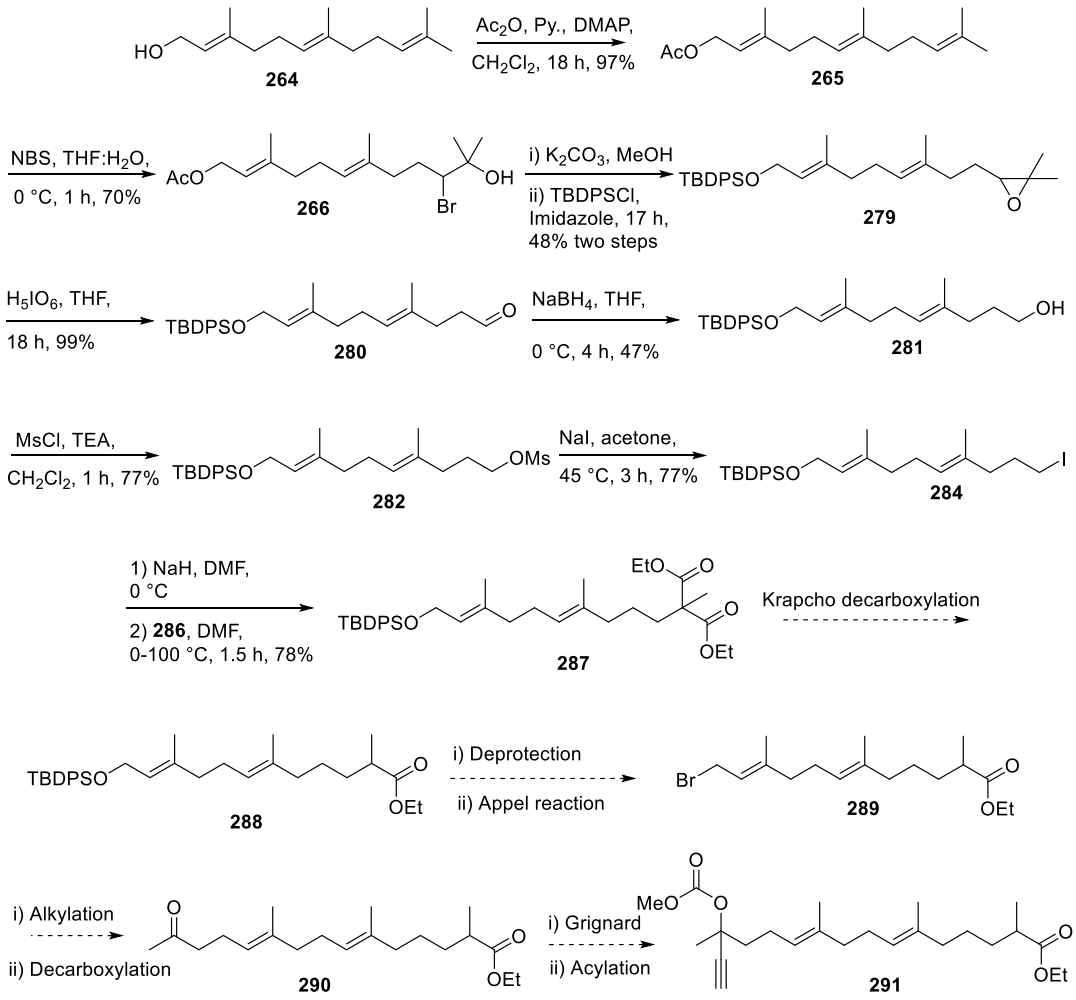

*Scheme 98.* Synthesis of **283** and **284**

The alkylation of both bromide **283** and iodide **284** with ethyl propionate were unsuccessful. In both cases no reaction was observed and starting material remained. This poor alkylation has been previously reported for a similar substrate by Nanda *et al.* who found that the alkylation could be improved greatly from <15% to 95% by using an enolate equivalent in the guise of malonate **286**. Using the reported conditions the alkylation was successfully carried out in 78% yield (Scheme 99).[159]




*Scheme 99.* Alkylation with enolate equivalents

With the successful formation of the challenging single bond we decided that it was a good opportunity to review the current and future route. The key bond for the side chain of erythazole A had been formed with the current route being nine steps from commercially available farnesol. With the bond in place, functionalisation of the left hand side of **287** would complete the desired precursor introducing the side chain to the core.

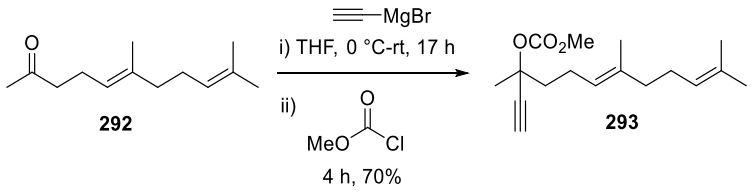



*Scheme 100.* Summary of side chain synthesis and remaining route

The formation of geranylacetone and the propagylic carbonate derivative from geraniol has been previously reported.[143,160,161] The similarity between this work and our planned route led us to believe that a similar route could be used to complete the synthesis of **291**. However, due to the availability of starting material and time constraints no further progress was made on this. In addition due to the number of modifications for the route to be successful, the resulting process takes a cumbersome 17 steps and an alternative route may need to be reconsidered as discussed in Chapter **3.7**.

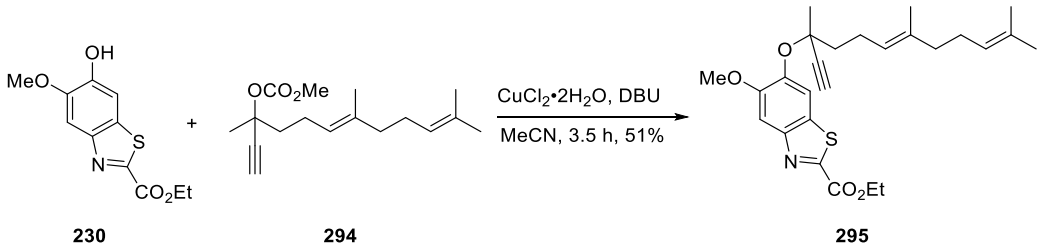
## 3.6 Farnesyl model system

It was deemed due to time constraints that a more accurate model of the phenol coupling and Claisen rearrangement would be more beneficial than repeating previous synthesis and literature work. Commercially available geranylacetone was chosen as the starting material for the model system as it contained the same number of double bonds as the natural product side chain.




*Scheme 101.* Alkylation and acylation of **292**

A one pot procedure was used for the alkylation and acylation of **292**. The anion formed by addition of ethynyl magnesium bromide to the ketone was reacted with methyl chloroformate to form **293**.

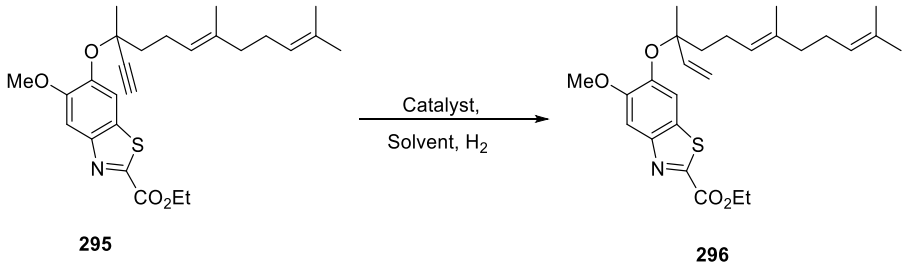



*Scheme 102.* Coupling of key fragments **230** and **294**

The coupling of the two fragments was carried out by a procedure reported by Godfrey *et al*. The stoichiometry of catalyst used is very important in this reaction as at higher concentrations homocoupling of the alkyne competes with the phenol alkylation. Therefore 0.05 mol% of catalyst was used and no homocoupling was seen and the reaction could be repeated in a reliable fashion.[142]

Our search for a suitable catalyst for the hydrogenation of alkyne **295** began with the iconic Lindlar's catalyst which is well known for the *Z*-selective reduction of alkynes to alkenes. Lindlar's catalyst has a reputation for having variable reactivity

depending on manufacturing process and suppliers and therefore catalysts from both Strem and Sigma-Aldrich were used. Lindlar's catalyst consists of palladium on calcium carbonate poisoned by lead; however as little detail is publicly available on each supplier's exact manufacturing process, the ratio of each component is unknown. Although it has been shown to be successful for the partial hydrogenation of similar alkynes, in our case no hydrogenation of any of the Π bonds in **295** was observed using catalyst from either supplier.[162–164]



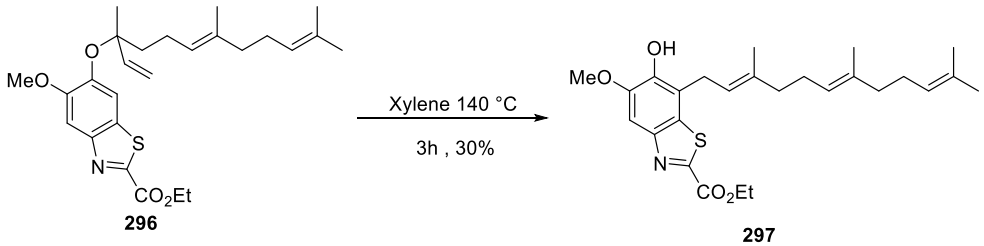

**295** **296**

*Scheme 103.* Chemoselective alkyne hydrogenation

| | Catalyst | Poison | Solvent | Result |
|---|---|---|---|---|
| 1 | Lindlar (Strem) | | MeOH | Over reduction |
| 2 | Lindlar (Strem) | | EtOAc/EtOH | SM |
| 3 | Lindlar (Sigma-Aldrich) | | MeOH | SM |
| 4 | Lindlar (Sigma-Aldrich) | | EtOAc/EtOH | SM |
| 5 | Pd/$BSO_4$ | | EtOAc | SM |
| 6 | Pd/C | | EtOAc | Over reduction |
| 7 | Pd/C | Quinoline (7:1) | EtOAc | SM |
| 8 | Pd/C | Quinoline (0.5:1) | EtOAc | over reduction |
| 9 | Pd/C | Quinoline (1:1) | EtOAc | 71**% 4:1** |

*Table 16.* Alkyne reduction conditions

Palladium on carbon is perhaps the most commonly used hydrogenation catalyst and is used regularly to reduce alkenes but less commonly used in the partial reduction of alkynes as rapid over reduction can occur (Table 16, entry 6). During an early synthesis of vitamin E Isler *et. al.* reported the use of Pd/C with quinoline as a hydrogenation catalyst for a partial reduction of an alkyne, however, no details were given of the molar ration of quinoline:palladium. Initially a large excess of quinoline was used, but no reactivity was observed. It was found that a 1:1 ratio of quinoline:palladium was optimal for the partial reduction of **295** (Table 16 entries 7-9). The quinoline is able to bind to the palladium thus reducing the reactivity of the catalyst as there are fewer binding sites available for the alkyne to bind which in turn reduces the probability of hydrogen and alkyne meeting on the surface before the alkyne is desorbed. The selectivity for partial hydrogenation is a result of the relative binding affinity of the alkyne compared to the alkene. Alkynes are known to bind more strongly to palladium surfaces and therefore will have a longer half-life on the surface, increasing the probability of encountering a molecule of hydrogen while on the surface. The alkene on the other hand is absorbed and desorbed more rapidly so will react much slower.[165,166] Using these conditions were able to reduce the terminal alkyne of **295** to give **296** in a 4:1 ratio with an unidentified over reduced product.



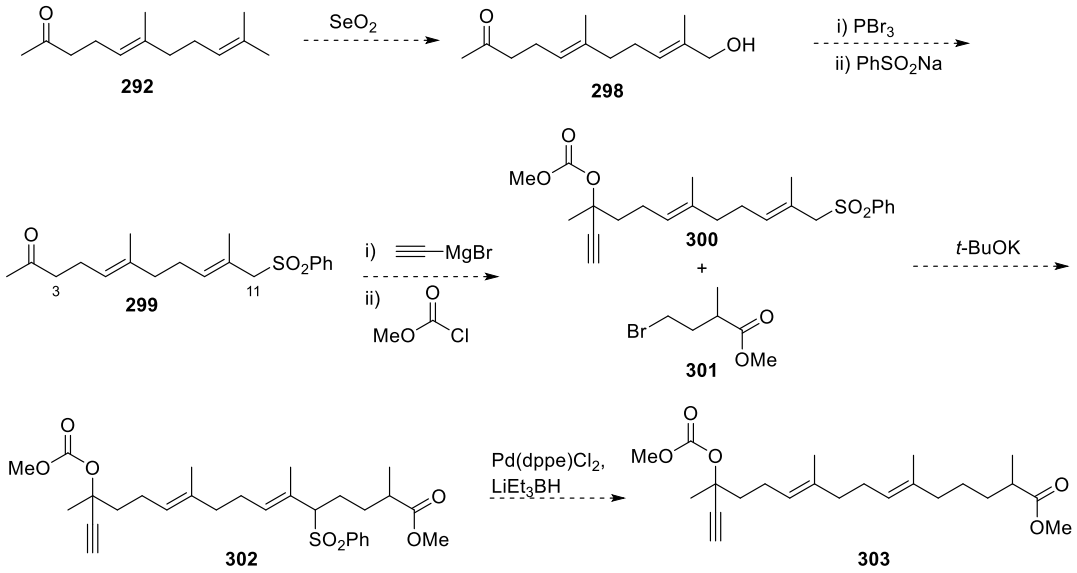

*Scheme 104.* Synthesis of **297**

The Claisen rearrangement was realised by heating in xylenes. The [3,3]-sigmatropic rearrangement occurred in a 30% yield after chromatography with 3 mg of product being isolated. The success of this model system bodes well for the current strategy for installing the sidechain of erythrazole A.

## 3.7 Conclusions and future work

Although the total synthesis of erythrazole A remains outstanding, large inroads have been made into developing a route which could be applied successfully. A scalable synthesis of the benzothiazole core was achieved with conditions being developed that were able to oxidatively form the thiazole ring while retaining the ester moiety.

Although work towards the terpene sidechain remains incomplete large strides have been made into the completion of the desired sidechain. Formation of the key single bond *via* an alkylation reaction is auspicious for the completion of the sidechain using this route. Alternatively, due to the length of the current route, a shorter route inspired by the work of Baj *et al.* into the recent synthesis of menaquinone 7 could be considered.[167]




*Scheme 105.* Alternative synthesis of **303**

It is proposed that the synthesis would begin with the allylic oxidation of commercially available geranyl acetone **292**, a step which is well documented in

literature.[168,169] Alcohol **298** may be converted into a sulfone using Appel chemistry followed by substitution with a sulfinic acid sodium salt as carried out by Baj *et al.* At this point the ketone would be functionalised by the addition as shown previously in Scheme 101. The $pK_a$'s of carbons 3 and 11 of **299** would both be around 20, as such selectively deprotonating 11 would be difficult. Compound **300** only has one acidic position and as such deprotonation and alkylation could occur selectively. Finally desulfonation could be carried out using palladium and super hydride, again as reported by Raj *et al.*[167] Although this would be the ideal route with no protecting groups in use, compatibility between the propagylic carbonate and some of the described conditions may lead to protecting groups being required. However in its idealised format the longest linear route would be 7 steps, this is significantly reduced from 17 steps the currently employed route takes.

Although work on the synthesis of the sidechain is still required, the synthesis of **295** (Scheme 115) confirms that propargylic carbonate **300** is indeed a good target to aim for. Geranyl acetone has the same number and type of Π functionality in the side chain, and as such is a good model. It has been successfully demonstrated that this chain can be introduced to the heterocyclic core using a Claisen rearrangement and, in some ways more importantly, that semihydrogenation of alkyne **295** can be achieved using palladium on charcoal poisoned with quinoline.

Overall much progress has been made towards the synthesis of erythrazole A with workable routes to all portions of the molecule being available. The advanced model also demonstrates that the end strategy is tenable. With the passing of time the synthesis of erythrazole could be attained using the discussed strategy.

# 4. Experimental

## 4.1 General

Anhydrous acetonitrile and dimethylformamide were used as supplied. THF was dried by distillation under nitrogen from benzophenone ketyl, and dichloromethane was distilled under nitrogen from calcium hydride. *N*,*N*-Diisopropylethylamine and triethylamine were distilled under nitrogen from potassium hydroxide and stored under argon. Light petroleum refers to the petroleum fraction with boiling point 40-60 °C and ether denotes diethyl ether.

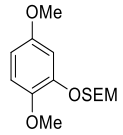
Solution phase IR were recorded using a Perkin-Elmer 1600 FTIR instrument with the solvent given in each case. ATR solid phase IR were recorded using a Bruker Alpha FTIR instrument. High resolution mass spectra were recorded using a Bruker TOF mass spectrometer with electrospray ionisation.

Merck TLC Silica gel 60 $F_{254}$ plates were used for thin-layer chromatography and visualised using basic aqueous potassium permanganate solution and ultraviolet light. Flash chromatography was carried out using the specified eluent, with Aldrich technical grade 60 Å 230 – 400 mesh silica gel.

A range of instruments were used to record NMR spectra; Jeol 270, Bruker DPX400, Bruker AV(III)400, Bruker AV(III)400hd, Bruker AV400, Bruker AV(III)500 and Bruker AV(III)800 at the given frequency. The deuterated solvent used is specified in each case. ACD labs was used to process and reference NMR spectra according to residual solvent, with chemical shifts reported in ppm. Peak multiplicity was reported with the following abbreviations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; and m, multiplet, with coupling constants reported in Hertz. DEPT experiments were used to assign C, CH, $CH_2$ or $CH_3$ from the $^{13}C$ spectra. Complex structure elucidation was carried out using HSQC, COSY and HMBC experiments when needed.

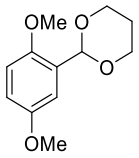
## 4.2 Procedures

**(2,5-Dimethoxyphenyl)(ethoxymethyl)sulfane (132)**



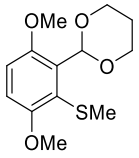

Sequentially, chloromethyl ethyl ether (0.1 mL, 1.18 mmol) and diisopropylamine (0.13 mL, 95.3 mg, 0.74 mmol) were added to a solution of 2,5-dimethoxythiophenol (0.09 mL, 100 mg, 0.59 mmol) in dichloromethane (5 mL) and the mixture stirred at rt for 16 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water (3 × 20 mL), and dried over magnesium sulfate. The volatiles were removed *in vacuo* to give the *title compound* as a colourless oil (135 mg, 100%); (Found: M+$Na^+$ 251.0702. $C_{11}H_{16}Na_1O_3S_1$ requires 251.0712); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3008, 2941, 2903, 2836, 1599, 1490; $\delta_H$ (400 MHz; $CDCl_3$) 7.16 (1H, d, *J* 3.0, ArH), 6.76 (1H, d, *J* 9.2, ArH), 6.70 (1H, dd, *J* 9.2, 3.0, ArH) 5.00 (2H, s, SC$\underline{H_2}$O), 3.81 (3H, s, OMe), 3.74 (3H, s, OMe), 3.65 (2H, q, *J* 7.2, OC$\underline{H_2}CH_3$), 1.19 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 154.0 (C), 151.6 (C), 125.3 (C), 116.6 (CH), 112.2 (CH), 111.6 (CH), 74.0 ($CH_2$), 64.0 ($CH_2$), 56.4 ($CH_3$), 55.7 ($CH_3$), 14.8 ($CH_3$).

**2,5-Dimethoxybenzaldehyde dioxane acetal (136)**



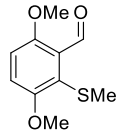

*p*-Toluenesulfonic acid (45 mg, 0.24 mmol) was added to 2,5-dimethoxybenzaldehyde (10 g, 60 mmol) and 1,3-propanediol (7.6 g, 100 mmol) in benzene (50 mL). The mixture was heated at reflux for 20 h using Dean-Stark apparatus. The reaction mixture was washed with sodium bicarbonate (20 mL), water (2 × 20 mL) followed by brine (20 mL). The organics were dried over sodium sulfate then the volatiles were removed under vacuum to give a brown oil. The crude product was purified by vacuum distillation (0.8 mbarr) to give the title compound **15** as a yellow oil (9.01 g, 67%); (Found: $M^+$ 225.1132. C12H17O4 requires 225.1121); $\delta_H$ (400 MHz; $CDCl_3$) 7.23 (1 H, d, *J* 3, ArH), 6.89-6.83 (2 H, m, ArH), 5.88 (1 H, s, CH), 4.3-4.26(2 H, m, $CH_2$), 4.07-4.00 (2 H, m, $CH_2$), 3.82 (3 H, s, OMe), 3.83 (2 H, m, OMe), 2.33-2.21 (1 H, m, CH), 1.49-1.42 (1 H, m, CH); $\delta_C$ (100 MHz; $CDCl_3$) 153.9 (C), 150.6 (C), 127.7 (C), 115.9 (CH), 112.3 (CH), 111.9 (CH), 96.8 (CH), 67.6 ($CH_2$), 56.4 (CH), 55.8 (CH), 25.9 ($CH_2$). The data were consistent with literature.[170]

**2-(3,6-Dimethoxy-2-(methylthio)phenyl)-1,3-dioxane (135)**



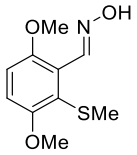

Under an atmosphere of argon, 2-(2,5-dimethoxyphenyl)-1,3-dioxane[1] (8.5 g, 38 mmol) was dissolved in ether (85 mL) and hexane (425 mL). At -25 °C, *n*-butyllithium in hexanes (2.38 M; 23.9 mL) was added dropwise over 40 min forming a pale yellow turbid reaction mixture. The reaction mixture was left to stand at -25 °C for 18 h, then dimethyl disulfide (6.88 mL, 85 mmol) in THF (100 mL) was added, and the reaction mixture was stirred for 4.5 h while returning to rt. The volatiles were removed under reduced pressure to give a light brown oil. The residue was purified by column chromatography on silica (10-30% ethyl acetate/light petroleum) to give the *title compound* as a yellow oil (3.9 g, 50%); (Found: $M+H^+$, 271.1003. $C_{13}H_{19}O_4S$ requires 271.0999); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3000, 2928, 1584, 1474, 1256; $\delta_H$ (400 MHz; $CDCl_3$) 6.91 (1H, d, *J* 9.0, ArH), 6.81 (1H, d, *J* 9.0, ArH), 6.51 (1H, s, ArC<u>H</u>), 4.28 (2H, m, CH), 3.99 (2H, m, CH), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 2.35 (4H, m, SMe + CH), 1.41 (1H, m, CH); $\delta_C$ (100 MHz; $CDCl_3$) 154.5 (C), 152.8 (C), 130.4 (C), 126.0 (C), 114.2 (CH), 112.5 (CH), 100.5 (CH), 67.8 ($CH_2$) 57.4 ($CH_3$), 56.6 ($CH_3$), 25.9 ($CH_2$), 19.1 ($CH_3$).

**3,6-Dimethoxy-2-(methylthio)benzaldehyde (131)**



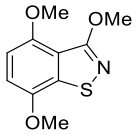

2-(3,6-Dimethoxy-2-(methylthio)phenyl)-1,3-dioxane (3.9 g, 14 mmol) was dissolved in THF (200 mL), concentrated hydrochloric acid (70 mL) was added, and the reaction mixture stirred at rt for 1.5 h. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate and the solvent was removed under vacuum to give an orange oil. The residue was purified by column chromatography on silica (10-20% ethyl acetate/light petroleum) to give a yellow residue which was triturated with cold ether to give the *title compound* as yellow oil that solidifies over time (2.5 g, 82%); (Found: M +$Na^+$, 235.0407. $C_{10}H_{12}NaO_3S$ requires 235.0399); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3005, 2962, 2940, 2839, 1689, 1575, 1469; $\delta_H$ (400 MHz; $CDCl_3$) 10.57 (1H, s, CHO), 7.03 (1H, d, *J* 9.1, ArH), 6.90 (1H, d, *J* 9.1, ArH), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 2.41 (3H, s, SMe); $\delta_C$ (100 MHz; $CDCl_3$) 191.7 (CH), 154.2 (C), 154.1 (C), 128.8 (C), 128.6 (C), 116 (CH) 112 (CH), 56.8 ($CH_3$), 56.7 ($CH_3$), 19.0 ($CH_3$).

**3,6-Dimethoxy-2-(methylthio)benzaldehyde oxime (130)**



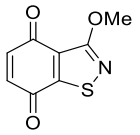

3,6-Dimethoxy-2-(methylthio)benzaldehyde (1.0 g, 4.7 mmol) was dissolved in water (20 mL) and ethanol (10 mL). Hydroxylamine hydrochloride (1.15 g, 16.5 mmol) was added forming a turbid solution to which sodium hydroxide (1.32 g, 33 mmol) was added. The reaction mixture was stirred at rt for 20 h then diluted with water (50 mL). The aqueous layer was extracted with dichloromethane (5 × 30 mL) and the organic layers were combined, dried over magnesium sulfate and the volatiles were removed *in vacuo* to give the *title compound* as a colourless solid (0.87 g, 79%); mp 166-168 °C; (Found: $M+H^+$, 228.0696. $C_{10}H_{14}NO_3S$ requires 228.0689); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3577, 3255, 3002, 2963, 2938, 2838, 1578, 1473; $\delta_H$ (400 MHz; $CDCl_3$) 9.37 (1H, br, OH), 8.30 (1H, s, CHN), 6.91 (2H, s, ArH) 3.90 (3H, s, OMe), 3.86 (3H, s, OMe), 2.35 (3H, s, SMe); $\delta_C$ (100 MHz; $CDCl_3$) 154.2 (C), 152.3 (C), 147.4 (CH), 126.8 (C), 124.3 (C), 112.3 (CH), 111.7 (CH), 56.5 ($CH_3$), 56.3 ($CH_3$), 18.9 ($CH_3$).

**3,4,7-Trimethoxybenz[*d*]isothiazole (117)**



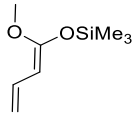

3,6-Dimethoxy-2-(methylthio)benzaldehyde oxime (390 mg, 1.71 mmol) was dissolved in chlorobenzene and heated to 80 °C. Sulfuryl chloride (0.136 mL, 1.71 mmol) was added and the reaction mixture stirred at 80 °C for 30 min. The volatiles were removed *in vacuo* and the resulting dark yellow residue taken up in DMF (10 mL). Potassium carbonate (0.93 g, 6.84 mmol) was added and the suspension was stirred at rt for 20 min. Dimethyl sulfate (0.323 mL, 3.42 mmol) was added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (4 x 25 mL). The organic layers were combined, washed with water (4 x 100 mL), dried over magnesium sulfate, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography on silica (5% ethyl acetate/light petroleum) to give the *title compound* (70 mg, 18 %) as a beige solid; mp 110-112 °C; (Found: M + $H^+$, 226.0533. $C_{10}H_{12}NO_3S$ requires 226.0532); $\lambda_{max}$ (methanol)/nm 3010, 2967, 2942, 2936, 1685, 1666, 1573, 1493, 1461, 1440, 1293; $\delta_H$ (400 MHz; $CDCl_3$) 6.78 (1H, d, *J* 8.4, ArH), 6.67 (1H, d, *J* 8.4, ArH), 4.20 (3H, s, OMe), 3.94 (3H, s, OMe), 3.93 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 164.0 (C), 151.0 (C), 146.8 (C), 144.9 (C), 116.7 (C), 108.6 (CH), 106.0 (CH), 56.7 ($CH_3$), 56.6 ($CH_3$), 56.2 ($CH_3$).

**3-Methoxybenz[*d*]isothiazole-4,7-dione (115)**



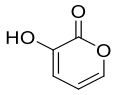

To a solution of 3,4,7-trimethoxybenz[*d*]isothiazole (67 mg, 0.30 mmol) in acetonitrile (10 mL) was added a solution of ammonium cerium(IV) nitrate (406 mg, 0.0.74 mmol) in water (10 mL). The mixture was stirred at rt for 45 min, then diluted with water (50 mL), and extracted with ethyl acetate (3 × 25 mL). The organic extracts were combined, washed with water (3 × 30 mL), brine (30 mL), dried over magnesium sulfate, filtered and the volatiles were removed *in vacuo.* The residue was purified by column chromatography on silica (5% ethyl acetate/light petroleum) to give the *title compound* as a yellow solid (41 mg, 71%); mp 127-130 °C; (Found: M+$Na^+$, 217.9880. $C_8H_5NNaO_3S$ requires 217.9882); $\lambda_{max}$ (methanol)/nm 248 (log ε 4.13), 337 (log ε 3.37), 389 (log ε 3.42); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 1668, 1536, 1478; $\delta_H$ (400 MHz; $CDCl_3$) 6.90 (1H, d, *J* 10.1, C=C<u>H</u>), 6.83 (1H, d, *J* 10.1, C=C<u>H</u>), 4.19 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 179.1 (C), 179.0 (C), 167.3 (C), 163.7 (C), 139.6 (CH), 136.8 (CH), 121.0 (C), 57.2 ($CH_3$).

**1-Methoxy-1-trimethylsiloxybutadiene (114)**



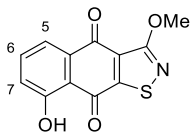

Using basewashed glassware and under an atmosphere of argon, at -10 °C *n*-butyllithium (1.82 M; 55 mL) was added slowly to diisopropylamine (14 mL, 100 mmol) in THF (75 mL) then stirred for 30 min at -10 °C. The freshly prepared lithiumdiisopropylamide was then cooled to -78 °C and DMPU (14.5 mL, 120 mmol) was added and stirred for 10 min while maintaining the same temperature to form a milky white suspension. At -78 °C methyl crotonate (10.6 mL, 100 mmol) was added dropwise over 20 min then stirred for a further 30 min to form a clear yellow solution. Trimethylsilychloride (20 mL, 157 mmol) was added and stirred at -78 °C for a further 20 min before being stirred for 2 h while warming to rt. The volatiles was removed under vacuum to give a yellow gum which was washed with pentane (200 mL) which was then filtered and the solvent removed under vacuum to give a yellow oil. The oil was purified by vacuum distillation to give the *title compound* as colourless oil which was used directly in the next reaction; bp 40 °C/1.7 mmHg (lit.[171] 31-34 °C/0.6 mmHg)

**3-Hydroxy-2*H*-pyran-2-one (144)**



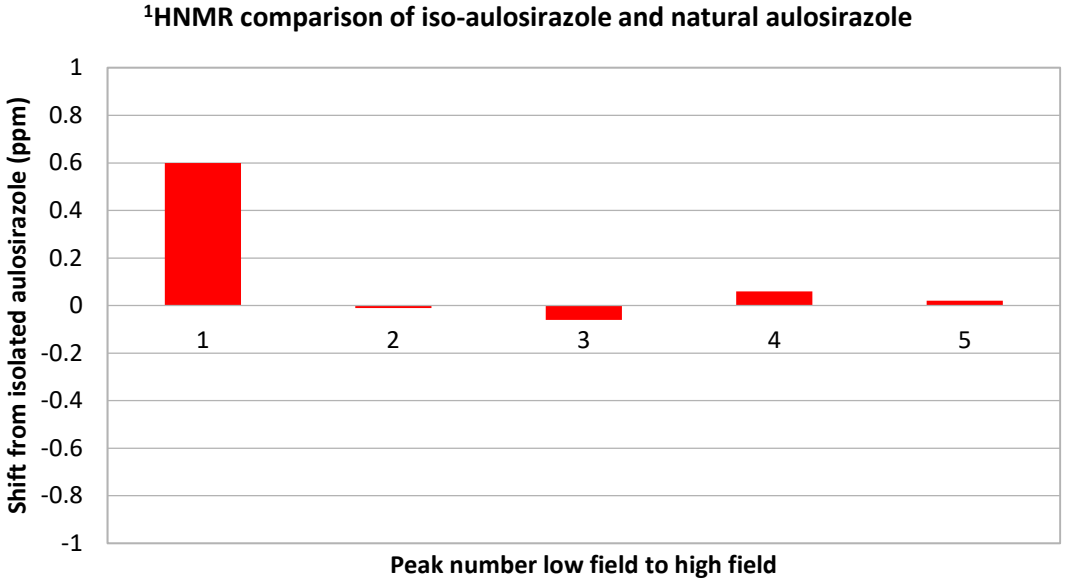

Mucic acid (10 g, 47 mmol) and monobasic potassium phosphate (10 g, 73 mmol) were ground together then added to a 250 mL round bottomed flask. Phosphorus pentoxide (6 g, 42 mmol) was stirred in quickly then a short path distillation kit was equipped leading to a smaller 50 mL round bottomed flask. The 250 mL round bottomed flask was heated from the top with a Bunsen burner on high heat for 1 h. A black solid formed on top of the solid with a refluxing molten phase underneath, a vapour was emitted and collected by distillation. The collected acidic residue was neutralised by addition of $NaOH_{(aq)}$ (1M) then diluted with water (50 mL). The aqueous layer was continually extracted with ether for 24 h. The organic layer was collected and the solvent removed *in vacuo* the resulting solid was then recrystallised from 2:1 hexanes: ethyl ether to give the *title compound* as a yellow solid (284 mg, 5%);(Found: $M+Na^+$ 135.0042. $C_5H_4Na_1O_3$ requires 135.0053); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3484 (br), 3045, 2963, 1706, 1659, 1424, 1392; $\delta_H$ (400 MHz; $CDCl_3$) 7.18 (1H, dd, *J* 5.2, 1.7, H1), 6.70 (1H, dd, *J* 6.9, 1.7, H3), 6.54 (1H, br, OH), 6.24 (1H, dd, *J* 6.9, 5.2, H2); $\delta_C$ (100 MHz; $CDCl_3$) 161.6 (C), 142.4 (C), 142.1 (CH), 114.5 (CH), 107.1 (CH).

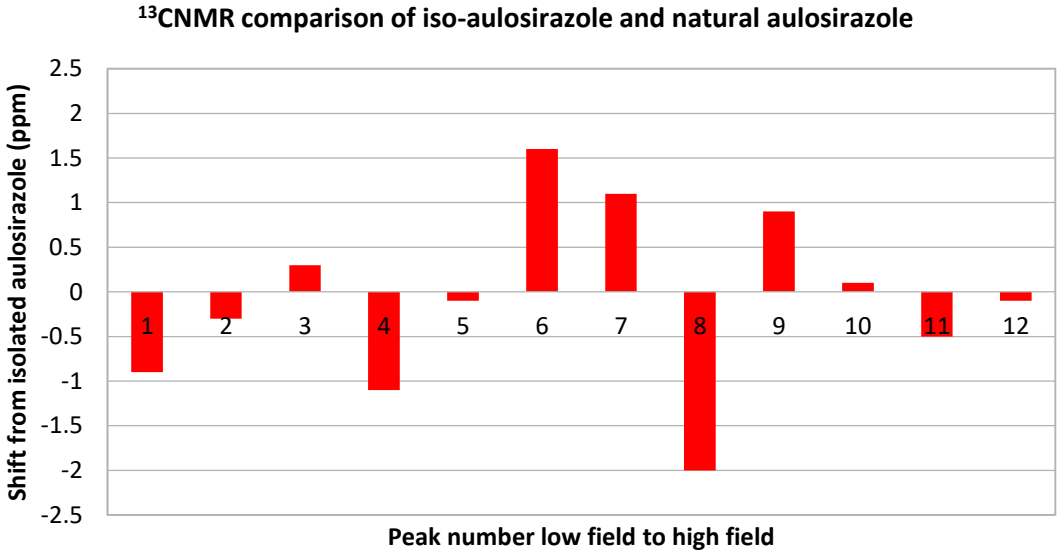
**8-Hydroxy-3-methoxynaphth[2,3-*d*]isothiazole-4,9-dione (113)**



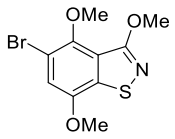

Triethylamine (1 mg, 0.01 mmol) was added to a solution of 3-methoxybenz[*d*]isothiazole-4,7-dione (20 mg, 0.1 mmol) and 3-hydroxy-2*H*-pyran-2-one[172] (17 mg, 0.15 mmol) in $CHCl_3$ (0.5 mL). The reaction mixture was stirred at rt for 15 min, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (5% ethyl acetate/light petroleum) to give the *title compound* as a yellow solid (13 mg, 50%); mp 186-187 °C; (Found: $M+Na^+$, 283.9991. $C_{12}H_7NNaO_4S$ requires 283.9988); $\lambda_{max}$ (methanol)/nm 217 (log ε 4.46), 247 (log ε 4.01), 274 (log ε 3.92) 349 (log ε 3.48), 416 (log ε 3.76); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3004, 1672, 1637, 1574; $\delta_H$ (400 MHz; $CDCl_3$) 11.85 (1H, s, OH), 7.83 (1H, m, H-5), 7.73 (1H, dd, *J* 8.2, 8.0, H-6), 7.31 (1H, dd, *J* 8.2, 0.8, H-7), 4.26 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 182.4 (C), 176.3 (C), 168.0 (C), 165.2 (C), 163.0 (C), 137.8 (CH), 134.1 (C), 124.3 (CH), 123.0 (C), 120.5 (CH), 115.4 (C), 57.3 ($CH_3$).

**Figure S2**. Comparison of the $^{1}$H NMR and $^{13}$C NMR spectra of 8-hydroxy-3-methoxynaphth[2,3-*d*]isothiazole-4,9-dione and natural aulosirazole.[2]



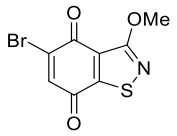



**5-Bromo-3,4,7-trimethoxybenz[*d*]isothiazole (145)**



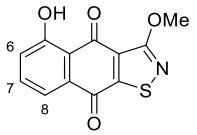

3,4,7-Trimethoxybenz[*d*]isothiazole (23 mg, 0.1 mmol) was dissolved in acetic acid (1 mL) followed by the addition of bromine (0.1 mM in acetic acid; 1 mL). The reaction mixture was stirred for 1.5 h at rt. The reaction mixture was diluted with water (25 mL) then extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (5 x 25 mL) and brine (25 mL) then dried over magnesium sulfate, filtered then the solvent removed *in vacuo*. The residue was purified by column chromatography on silica (5% ethyl acetate/ petrol) to give the *title compound* as a beige solid (11 mg, 49%); (Found: M + $H^+$, 303.9627. $C_{10}H_{11}{}^{79}BrO_3S$ requires 303.9638); $\lambda_{max}$ (methanol)/nm 3011, 2938, 2855, 1684, 1670, 1576, 1457; $\delta_H$ (400 MHz; $CDCl_3$) 6.97 (1H, s, H-6), 4.21 (3H, s, OMe), 3.95 (3H, s, OMe), 3.92 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 162.4 (C), 148.4 (C), 147.2 (C), 143.6 (C), 120.6 (C), 112.7 (C), 112.2 (CH), 62.5 ($CH_3$), 56.5 ($CH_3$), 56.2 ($CH_3$).

**5-Bromo-3-methoxybenz[*d*]isothiazole-4,7-dione (147)**



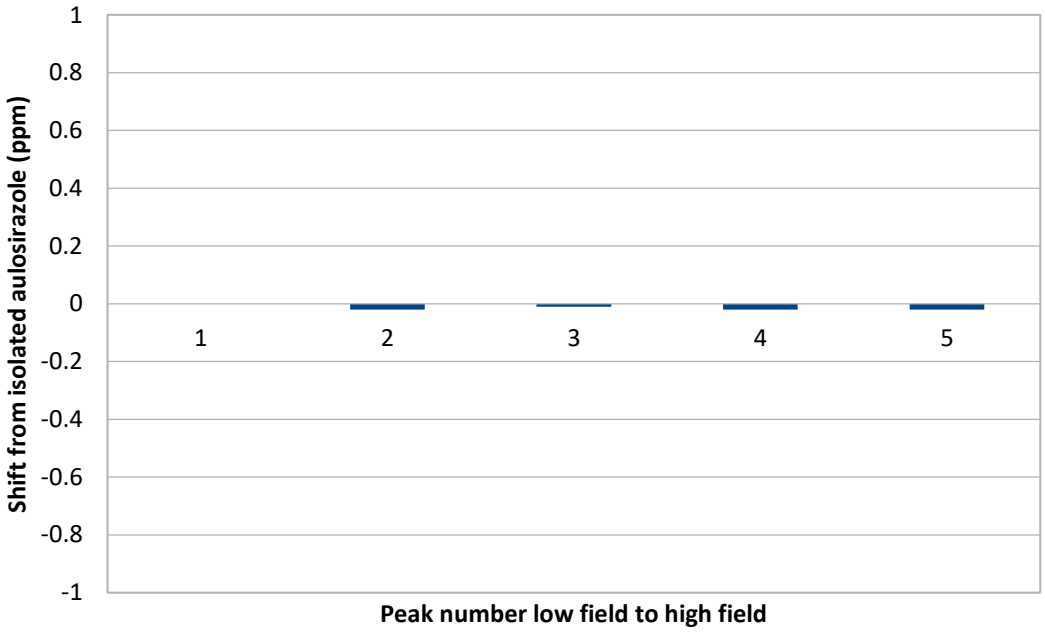

To a solution of 5-bromo-3,4,7-trimethoxybenz[*d*]isothiazole (45 mg, 0.15 mmol) in acetonitrile (5 mL) was added a solution of ammonium cerium(IV) nitrate (202 mg, 0.37 mmol) in water (5 mL). The reaction mixture was stirred rt for 45 min, diluted with water (50 mL), and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (3 × 30 mL), brine (30 mL), dried over magnesium sulfate, and the volatiles were removed *in vacuo.* The residue was purified by column chromatography on silica (5% ethyl acetate/light petroleum) to give the *title compound* as a yellow solid (25 mg, 61%); mp 181-182 °C; (Found: $M+H^+$, 273.9166. $C_8H_5{}^{79}BrNO_3S$ requires 273.9168); $\lambda_{max}$ (methanol)/nm 277 (log ε 3.84) 341 (log ε 3.40) 397 (log ε 3.24); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2939, 1683, 1536, 1478; $\delta_H$ (400 MHz; $CDCl_3$) 7.43 (1H, s, H-6), 4.20 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 176.1 (C), 171.1 (C), 167.6 (C), 164.1 (C), 142.1 (C), 138.3 (CH), 119.7, 57.3 ($CH_3$).

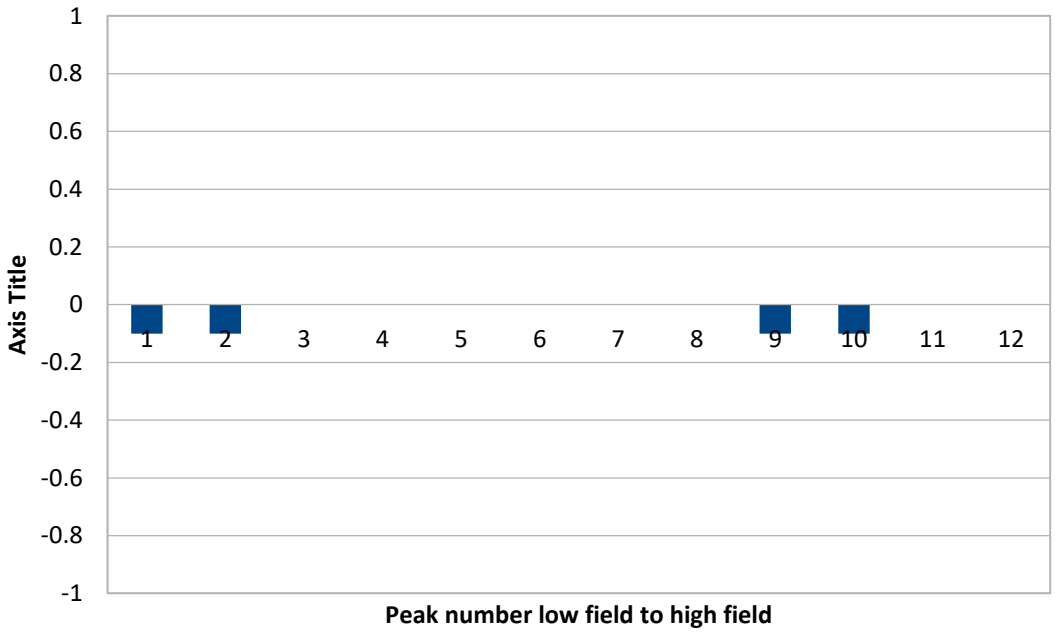
**5-Hydroxy-3-methoxynaphth [2,3-*d*]isothiazole-4,9-dione (Aulosirazole 32)**



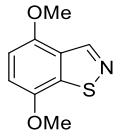

To a solution of 5-bromo-3-methoxybenz[*d*]isothiazole-4,7-dione (25 mg, 0.091 mmol) and 3-hydroxy-2*H*-pyran-2-one (12.3 mg, 0.109 mmol) in $CHCl_3$ (0.5 mL) was added triethylamine (1 mg, 0.01 mmol), and the reaction mixture stirred for 40 min. A further portion of 3-hydroxy-2*H*-pyran-2-one (12.3 mg, 0.109 mmol) was added and stirring was continued at rt for 20 h. The reaction mixture was purified by column chromatography (3% ethyl acetate/light petroleum) to give the *title compound* as a yellow solid (3 mg, 13%); mp 192-193 °C; (Found: $M+Na^+$, 283.9976. $C_{12}H_7NNaO_4S$ requires 283.9988); $\lambda_{max}$ (methanol)/nm 216 (log ε 4.38), 247 (log ε 3.94), 273 (log ε 3.81), 342 (log ε 3.27), 424 (log ε 3.68); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2929, 1674, 1640, 1478; $\delta_H$ (400 MHz; $CDCl_3$) 12.4 (1H, s, OH), 7.78 (1H, dd, *J 8*, 1.2, H-8), 7.64 (1H, dd, *J* 8.4, 8.0, H-7) 7.33 (1H, dd, *J* 8.4, 1.2, H-6), 4.23 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 183.4 (C), 176.7 (C), 167.7 (C), 166.4 (C), 163.1 (C), 136.2 (CH), 133.0 (C), 126.3 (CH), 122.2 (C), 120.5 (CH), 155.9 (C), 57.4 ($CH_3$). The data was consistent with literature.[2]

**Figure S1**. Comparison of the $^{1}H$ NMR and $^{13}C$ NMR spectra of synthetic aulosirazole and natural aulosirazole.[2]



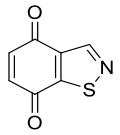



**4,7-Dimethoxybenz[*d*]isothiazole (148)**



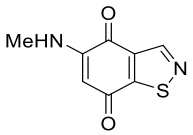

3,6-Dimethoxy-2-(methylthio)benzaldehyde (400 mg, 1.8 mmol) and hydroxylamine hydrochloride (170 mg, 2.45 mmol) were dissolved in formic acid (15 mL) and the reaction mixture heated at reflux for 1.5 h. The reaction mixture was then diluted with water (50 mL) the pH was adjusted to *ca.* 7 by addition of potassium hydroxide then extracted with dichloromethane (3 x 50 mL). The organic layers were combined, washed with water (50 mL), brine (50 mL) then dried over magnesium sulfate, filtered and the volatiles remove *in vacuo* to give the *title compound* as a beige solid (300 mg, 63%); mp 51-53 °C; (Found: M + $H^+$, 196.0435. $C_9H_{10}NO_2S$ requires 196.0427); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2962, 2938, 2909, 2840, 1602, 1501,1462, 1432; $\delta_H$ (400 MHz; $CDCl_3$) 9.00 (1H, s, H-3), 6.80 (1H, d, *J* 8.3, ArH), 6.69 (1H, d, *J* 8.3, ArH), 3.98 (6H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 152.5 (CH), 150.2 (C), 146.7. (C), 143.7 (C), 129.1 (C), 107.4 (CH), 104.8 (CH), 56.0 ($CH_3$), 55.8 ($CH_3$).

**Benz[*d*]isothiazole-4,7-dione (149)**



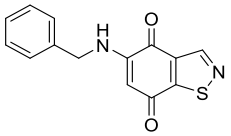
4,7-Dimethoxybenz[*d*]isothiazole (200 mg, 2.6 mmol) was dissolved in acetonitrile (40 mL), ammonium cerium(IV) nitrate (1.4 g, 2.5 mmol) was added followed by the addition of water (40 mL). The reaction mixture was stirred at rt for 1 h. No change was seen by TLC and a further portion of ammonium cerium(IV) nitrate (0.7 g, 1.2 mmol) was added and stirred at room temperature for 1 h. The volume was reduced *in vacuo* to *ca.* 40 mL, extracted with ethyl acetate (3 x 40 mL) then dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica (10% ethyl acetate/light petroleum) to give the *title compound* as yellow crystals (118 mg, 59%); mp 149-150 °C; (Found; $M+H^+$, 165.9959 $C_7H_4NO_2S$ requires 165.9963); $\lambda_{max}$ (methanol)/nm 202 (log ε 4.04), 236 (log ε 4.07), 332 (log ε 3.57); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1672, 1637, 1595, 1517, 1349; $\delta_H$ (400 MHz; $CDCl_3$) 8.97 (1H, s, H-3), 6.97 (1H, d, *J* 10.3, C=CH) 6.89 (1H, d, *J* 10.3, C=CH); $\delta_C$ (100 MHz; $CDCl_3$) 180.2 (C), 178.7 (C), 161.8 (C), 155.9 (CH), 138.5 (CH), 137.9 (CH) 135.9 (C).

**5-(Methylamino)benz [*d*]isothiazole-4,7-dione (pronqodine A 30)**



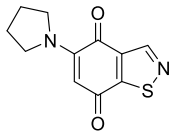

To a solution of benz[*d*]isothiazole-4,7-dione (250 mg, 1.5 mmol) in ethanol (25 mL) was added methylamine in ethanol (33%; 0.28 mL) and cerium(III) chloride (55 mg, 0.15 mmol). The reaction mixture was stirred at rt for 1 h. The volume was reduced by half under reduced pressure, then partitioned between dichloromethane (100 mL) and water (100 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The organic layers were then combined, washed with water (4 x 100 mL), brine (100 mL) then dried over magnesium sulfate before being filtered and the volatiles removed under vacuum. The purple residue was purified by flash chromatography on silica (40-60% ethyl acetate/light petroleum) to give the *title compound* as a purple solid (112 mg, 42%); mp 233-235 °C; (Found: M + $H^+$, 195.0225. $C_8H_7N_2O_2S$ requires 195.0223); $\lambda_{max}$ (methanol)/nm 217 (log ε 4.31), 280 (log ε 3.97), 481 (log ε 3.51); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3395, 3011, 1682, 1619, 1599, 1518, 1424; $\delta_H$ (400 MHz; $CDCl_3$) 8.88 (1H, s, H-3) 6.11 (1H, br, NH), 5.59 (1H, s, H-6), 2.98 (3H, d, *J* 5.5, NMe); $\delta_C$ (100 MHz; $CDCl_3$) 176.5 (C), 175.9 (C), 167.9 (C), 155.4 (CH), 150.0 (C), 133.3 (C), 98.7 (CH), 29.7 ($CH_3$). The data was consistent with literature.[3]

**5-(Benzylamino)benz[*d*]isothiazole-4,7-dione (150)**



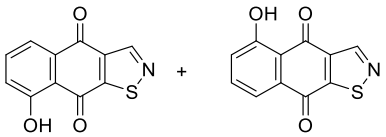
To a solution of benz[*d*]isothiazole-4,7-dione (50 mg, 0.30 mmol) and cerium(III) chloride (11 mg, 0.03 mmol) in ethanol (5 mL) was added benzylamine (0.083 mL, 0.76 mmol). The reaction mixture was stirred for 30 min at rt. The reaction mixture was diluted with water (20 mL) then extracted with dichloromethane (4 × 10 mL). The organic layers were combined the washed with water (3 × 20 mL), dried over magnesium sulfate then the volatiles removed under vacuum. The purple residue was purified by flash chromatography on silica (20 % ethyl acetate/light petroleum) to give the *title compound* as a purple solid (31 mg, 38%); mp 185-186 °C; (Found: $M+H^+$, 271.0535. $C_{14}H_{11}N_2NaO_2S$ requires 271.0536); $\lambda_{max}$ (methanol)/nm 271 log ε 4.03), 480 (log ε 3.41); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 3379, 1682, 1595,1518; $\delta_H$ (400 MHz; $CDCl_3$) 8.89 (1H, s, H-3), 7.43-7.31 (5H, m, ArH), 6.34 (1H, br, NH), 5.66 (1H, s, H-6), 4.41 (1H, Br, $CH_2$), 4.40 (2H, d, *J* 6, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 176.7 (C), 176.1 (C), 167.5 (C), 155.4 (CH), 148.7 (C), 135.1 (C), 133.4 (C), 129.2 (CH), 128.5 (CH), 127.7 (CH) 99.8 (CH), 47.4 ($CH_2$).

**5-(Pyrrolidin-1-yl)benz[*d*]isothiazole-4,7-dione (151)**



To a solution of benz[*d*]isothiazole-4,7-dione (50 mg, 0.30 mmol) and cerium(III) chloride (11 mg, 0.03 mmol) in ethanol (5 mL) was added pyrrolidine (0.062 mL, 0.76 mmol). The reaction mixture was stirred for 30 min at rt the reaction mixture was then diluted with water (20 mL) then extracted with dichloromethane (3 × 10 mL). The organic layers were combined, washed with water (3 × 20 mL), dried over magnesium sulfate then the volatiles removed under vacuum. The purple solid was purified by flash chromatography on silica (30 % ethyl acetate/light petroleum) to give the *title compound* as a purple solid (42 mg, 60%); mp 231-232 °C; (Found: $M+H^+$, 235.0541. $C_{11}H_{11}N_2O_2S$ requires 235.0536); $\lambda_{max}$ (methanol)/nm 236 log ε 4.00), 287 (log ε 3.72), 505 (log ε 3.48); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 1681, 1604, 1555,1520; $\delta_H$ (400 MHz; $CDCl_3$) 8.84 (1H, s, H-3), 5.61 (1H, s, H-6), 4.01 (2H, br, $CH_2$), 3.40 (2H, br, $CH_2$), 2.03 (4H, br, 2 × $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 177.8 (C), 175.5 (C), 166.5 (C), 155.8 (CH), 149.5 (C), 134.4 (C), 103.2 (CH), 51.7 (br, 2 × $CH_2$), 26.7 ($CH_2$), 23.8 ($CH_2$).

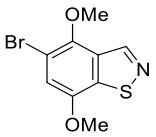
**A mixture of 8-hydroxynaphtho[2,3-d]isothiazole-4,9-dione and 5-hydroxynaphtho[2,3-d]isothiazole-4,9-dione (desmethoxy aulosirazole) (152)**




8:1

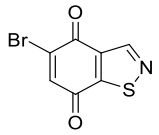
3-Hydroxy-2*H*-pyran-2-one (34 mg, 0.3 mmol) was added to a solution of benz[*d*]isothiazole-4,7-dione (40 mg, 0.2 mmol) and triethylamine (0.1 mmol; 3 μL) in chloroform (1 mL). The reaction mixture was stirred for 30 min then the volatiles removed under vacuum to give a green residue. The residue was purified by flash chromatography on silica (5% ethyl acetate and light petroleum) to give the *title compounds* as an inseparable yellow solid (14 mg, 30 %); (Found; M + $H^+$, 230.9991 $C_{11}H_5NO_3S$ requires 230.9990); $\lambda_{max}$ (methanol)/nm 220 (log ε 5.37), 269 (log ε 4.93), 308 (log ε 4.73), 419 (log ε 4.67); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2927, 2855, 1702, 1675, 1574, 1520; Major product; $\delta_H$ (400 MHz; $CDCl_3$) 11.93 (1H, s, OH), 9.10 (1H, s, H-3), 7.83 (1 H, dd, *J* 7.5, 1.1, ArH), 7.73 (1H, dd, *J* 7.5, 8.4, ArH), 7.34 (1H, dd, *J* 8.4, 1.1, ArH); Minor product $\delta_H$ (400 MHz; $CDCl_3$) 12.24 (1H, s, OH), 9.11 (1H, s, H-3), 7.83 ( H, m, ArH), 7.70 (1H, m, ArH), 7.37 (1H, dd, *J* 8.5, 1.1, ArH); Combined $\delta_C$ (100 MHz; $CDCl_3$) 182.4 (C), 177.6 (C), 163.5 (C), 163.4 (C), 163.2 (C), 157.1 (CH), 156.5 (C), 138.0 (C), 137.8 (CH), 136.8 (CH), 133.6 (C), 126.1 (CH), 125.1 (CH), 120.8 (CH), 120.7 (CH), 115.6 (C).

**5-Bromo-4,7-dimethoxybenz[d]isothiazole (153)**



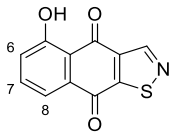

Bromine (25 mg, 0.15 mmol; 8 μL) in chloroform (1 mL) was added to 4,7-dimethoxybenz[*d*]isothiazole (30 mg, 0.15 mmol) in chloroform (3 mL). The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with water (10 mL), then extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with sodium hydrogen carbonate (20 mL), brine (20 mL) then dried over magnesium sulfate. The residue was purified by flash chromatography on silica (5 % ethyl acetate and light petroleum) to give the *title compound* as a colorless solid (28 mg, 66%); mp 118 °C; (Found; $M+H^+$, 273.9519. $C_9H_9{}^{79}BrNO_2S$ requires 273.9532); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2967, 1685, 1573, 1493; $\delta_H$ (400 MHz; $CDCl_3$) 8.94 (1H, s, H-3), 6.97 (1H, s, ArH), 4.03 (3H, s, OMe), 3.98 (3H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 151.8 (CH), 148.9 (C), 147.0 (C), 143.3 (C), 132.4 (C), 111.7 (C), 111.5 (CH), 62.4 ($CH_3$), 56.4 ($CH_3$).

**5-Bromobenz[*d*]isothiazole-4,7-dione (154)**



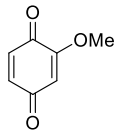

5-Bromo-4,7-dimethoxybenz[d]isothiazole (40 mg, 0.15 mmol) was dissolved in acetonitrile (4 mL), ammonium cerium(IV) nitrate (200 mg, 0.36 mmol) in water (4 mL) was added. The reaction mixture was stirred at rt for 1 h, diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate, the volatiles removed under reduced pressure to give an orange residue. The residue was purified by flash chromatography on silica (5% ethyl acetate and light petroleum) to give the *title compound* as a yellow solid (30 mg, 82%); (Found: M+$Na^+$, 265.8884. $C_7H_2{}^{79}BrNaNO_2S$ requires 265.8882); $\lambda_{max}$ (methanol)/nm 203 (log ε 3.97), 230 (log ε 3.89), 276 (log ε 3.91), 314 (log ε 3.59); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 1685, 1666, 1572, 1518; $\delta_H$ (500 MHz; $CDCl_3$) 9.00 (1H, s, H-3), 7.49 (1H, s, H-6); $\delta_C$ (125 MHz; $CDCl_3$) 175.7 (C), 172.8 (C), 162.2 (C), 156.6 (CH), 140.8 (C), 139.2 (CH), 134.6 (C).

**5-Hydroxynaphtho[2,3-*d*]isothiazole-4,9-dione (desmethoxy aulosirazole) (155)**



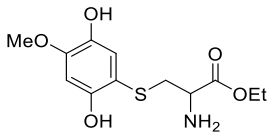

Triethylamine (0.2 mmol; 3 μL) was added to 5-bromobenz[*d*]isothiazole-4,7-dione (22 mg, 0.1 mmol) and 3-hydroxy-2*H*-pyran-2-one (15 mg, 0.15 mmol) in chloroform (1 mL). The reaction mixture was stirred at room temperature for 14 h then the volatiles were removed under vacuum. The residue was purified by flash chromatography on silica (5% ethyl acetate and light petroleum) to give the *title compound* as a yellow solid (6.7 mg, 30%); mp 169-170 °C; (Found: $M+H^+$, 232.0067. $C_{11}H_6NO_3S$ requires 232.0063); $\lambda_{max}$ (methanol)/nm 216 (log ε 5.4), 269 (log ε 4.99), 306 (log ε 4.69), 418 (log ε 4.69); $\delta_H$ (400 MHz; $CDCl_3$) 12.25 (1H, s, OH), 9.11 (1H, s, H-3), 7.85 (1H, dd, *J* 7.4, 1.1, H8), 7.71 (1H, dd, *J* 8.5, 7.4, H7), 7.38 (1H, dd, *J* 8.5, 1.1 H6); $\delta_C$ (100 MHz; $CDCl_3$) 184.2 (C), 176.3 (C), 164.4 (C), 163.2 (C), 156.5 (CH), 137.3 (C), 136.8 (CH), 133.4 (C), 126.1 (CH), 120.8 (CH), 115.6 (C).

**Methoxybenzoquinone *(*175*)***



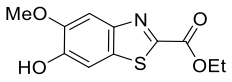

Iron (III) chloride (135 g, 500 mmol) in water (500 mL) was added in one portion to 2-methoxyhydroquinone (14 g, 100 mmol). The reaction mixture was stirred at room temperature for 18 h and the resulting precipitate was collected by filtration and washed with water (50 mL). The solid was dried *in vacuo* for 4 days to give the *title compound* as a green solid (11.75 g, 85%); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3043, 2940, 2978, 1681, 1654, 1625, 1595; $\delta_H$ (400 MHz; $CDCl_3$) 6.72 (2H, s, C=CH), 5.95 (1H, s, C=CH), 3.84 (3H, s, OC$\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 187.5 (C), 181.7 (C), 158.6 (C), 137.2 (CH), 134.5 (CH), 107.7 (CH), 55.2 ($CH_3$). The data was consistent with literature.[92]

**Ethyl S-(2,5-dihydroxy-4-methoxyphenyl)cysteinate (183)**



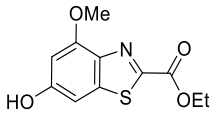

A solution of 2-methoxy-1,4-benzoquinone (276 mg, 2 mmol) in methanol (15 mL) and THF (5 mL) was added dropwise over 10 min to a solution of L-cysteine ether ester (371 mg, 2 mmol) in water (5 mL) and the reaction mixture was stirred at rt for 1.5 h. The resulting solution was diluted with water (10 mL) then washed with ethyl acetate (3 × 20 mL). The aqueous layer was collected and volatiles removed under vacuum. The residue was purified by flash chromatography on silica (5-10% methanol/$CH_2Cl_2$). The *title compound* was collected as a red gum (80 mg, 14%); (Found: $M+H^+$, 288.0885. $C_{12}H_{18}NO_5S$ requires 288.0900); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 3552, 3006, 2929, 1733, 1620; $\delta_H$ (400 MHz; $CDCl_3$) 7.02 (1H, s, ArH), 6.51 (1H, s, ArH), 4.16 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 3.85 (3H, s, $OCH_3$), 3.47 (1H, dd, *J* 9.3, 4.3, $NH_2C\underline{H}R_2$), 3.16 (1H, dd, *J* 13.9, 4.3, $SC\underline{H}_2$), 2.72 (1H, dd, *J* 13.9, 9.3, $SCH_2$), 1.25 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$); $\delta_C$ (100 MHz; $CDCl_3$) 173.4 (C), 152.8 (C), 149.7 (C), 139.1 (C), 121.6 (CH), 107.9 (C), 100.2 (CH), 61.8 ($CH_2$), 55.9 ($CH_3$), 52.9 (CH), 40.8 ($CH_2$), 13.9 ($CH_3$).

**Ethyl 6-hydroxy-5-methoxybenzo*[d]*thiazole-2-carboxylate (185)**



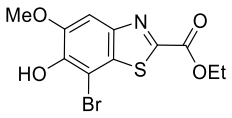

A solution of 2-methoxy-1,4-benzoquine (690 mg, 5 mmol) in methanol (25 mL) was added dropwise over 1.5 h to L-cysteine ethyl ester (928 mg, 5 mmol) in water (12.5 mL) then stirred at rt for 20 min. The reaction mixture was washed with ethyl acetate (2 × 20 mL) then the aqueous was collected and diluted with water (20 mL) and ethanol (35 mL). Potassium ferricyanide (9.88 g, 30 mmol) was added in one portion then stirred for 3 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, dried over magnesium sulfate then the volatiles removed under vacuum to give a black residue. The residue was dissolved in ethanol (50 mL) then aq. HCl (1M; 50 mL) was added and stirred at room temperature for 16 h. The reaction mixture was diluted with water (100 mL) then extracted with dichloromethane (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over magnesium sulfate then the volatiles removed under vacuum. The resulting residue was purified by flash chromatography on silica (40% ethyl acetate/light petroleum) to give the *title compound* as a beige solid (111 mg, 9%); (Found: $M+H^+$, 254.0477. $C_{11}H_{12}NO_4S$ requires 254.0482); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3690, 3606, 2530, 3011, 2928, 1714, 1602; $\delta_H$ (400 MHz; $CDCl_3$) 7.62 (1H, s, ArH), 7.40 (1H, s, ArH), 6.22 (1H, s, OH), 4.51 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 3.98 (3H, s, $OC\underline{H}_3$), 1.46 (3H, t, $OCH_2C\underline{H}_3$); $\delta_C$ (100 MHz; $CDCl_3$) 195.6 (CH), 169.6 (C), 140.9 (C), 136.3 (CH), 136.0 (CH), 122.9 (CH), 121.5 (C), 119.8 (CH), 25.4 ($CH_3$).

**Ethyl 6-hydroxy-4-methoxybenzo[*d*]thiazole-2-carboxylate (188)**



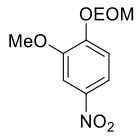

A solution of 2-methoxy-1,4-benzoquine (690 mg, 5 mmol) in methanol (25 mL) was added dropwise over 1 h to a solution of L-cysteine ethyl ester (928 mg, 5 mmol) in water (12.5 mL) at 60 °C. The reaction mixture was diluted with water (50 mL) then washed with ethyl acetate (2 × 50 mL). Ethanol (35 mL) was added followed by potassium ferricyanide (9.88 g, 30 mmol) the reaction mixture was then stirred for 1 h. The reaction mixture was extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, dried over magnesium sulfate then the volatiles removed under vacuum to give a black residue. The residue was dissolved in ethanol (50 mL) then aq. HCl (1M; 50 mL) was added and stirred at room temperature for 20 h. The reaction mixture was extracted with dichloromethane (2 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over magnesium sulfate then the volatiles removed under vacuum. The resulting residue was purified by flash chromatography on silica (30-40% ethyl acetate/ light petroleum) to give the *title compound* as a beige solid (18 mg, <1%); (Found: $M+Na^+$, 254.0487. $C_{11}H_{11}N\,NaO_4S$ requires 254.0482); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3690, 3590, 3011, 2930, 1737, 1711, 1602; $\delta_H$ (400 MHz; $CDCl_3$) 6.94 (1H, d, *J* 2.1, ArH), 6.57 (1H, d, *J* 2.1, ArH), 4.49 (2H, q, *J* 7.1, $OC\underline{H_2}CH_3$), 3.95 (3H, s, $OCH_3$), 1.42 (3H, t, *J* 7.1, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 160.9 (C), 157.7 (C), 155.7 (C), 153.9 (C), 139.9 (C), 138.7 (C), 98.4 (CH), 98.3 (CH), 62.8 ($CH_2$), 56.0 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 7-bromo-6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (192)**



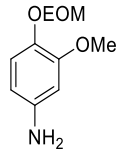

A slurry of 2-bromo-6-methoxy-1,4-benzoquinone (1.09 g, 5 mmol) in methanol (25 mL) was added dropwise to L-cysteine ethyl ester (928 mg, 5 mmol) over 1 h. The resulting solution was diluted with water (50 mL) then washed with ethyl acetate (2 × 50 mL). The aqueous phase was collected and ethanol (35 mL) was added followed by potassium ferricyanide (9.88 g, 30 mmol) and stirred at rt for 2 h. The reaction mixture was extracted with ethyl acetate (2 × 50 mL) the organic layers were then combined, washed with brine, dried over magnesium sulfate then the volatiles removed under vacuum. The resulting residue was dissolved in ethanol (50 mL) then aq. HCl (50 mL) was added and stirred for 18 h before being extracted with dichloromethane (3 × 50 mL). The organic extracts were combined and volatiles removed under vacuum to give a dark red residue which was purified by flash chromatography on silica (30-40% ethyl acetate/light petroleum) to give the *title compound* as a beige solid (15 mg, 1%); (Found: $M+H^+$, 331.9576. $C_{11}H_{11}{}^{79}BrNO_4S$ requires 331.9587); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3690, 3517, 3011, 2855, 1736, 1713, 1495; $\delta_H$ (400 MHz; $CDCl_3$) 7.62 (1H, s, ArH), 6.43 (1H, s, OH), 4.54 (2H, q, *J* 7.2, $OC\underline{H_2}CH_3$), 4.03 (3H, s, $OCH_3$), 1.48 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$)160.4 (C), 156.0 (C), 147.9 (C), 145.5 (C), 144.8 (C), 104.8 (CH), 97.9 (C), 62.9 ($CH_2$), 56.8 ($CH_3$), 14.3 ($CH_3$).

**1-(Ethoxymethoxy)-2-methoxy-4-nitrobenzene (197)**



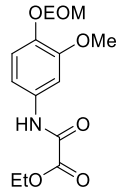

Under an atmosphere of argon chloromethyl ethyl ether (0.278 mL, 3 mmol) was added to a solution of 4-nitroguaiacol (338 mg, 2 mmol) and diisopropylethylamine (0.522 mL, 3 mmol) in $CH_2Cl_2$ (10 mL). The reaction mixture was stirred at room temperature for 3 h then evaporated onto silica gel. The residue was purified by flash chromatography (25% ethyl acetate/light petroleum) to give the *title compound* as a pale yellow oil (417 mg, 92%); (Found: M+$Na^+$, 250.0682. $C_{10}H_{13}NNaO_5$ requires 250.0686); $\nu_{max}$ (CHCl3)/$cm^{-1}$ 3098, 2980, 1589, 1519, 1393; $\delta_H$ (400 MHz; $CDCl_3$) 7.85 (1H, dd, *J* 8.9, 2.6, ArH), 7.75 (1H, d, *J* 2.6, ArH), 7.23 (1H, d, *J* 8.9, ArH), 5.36 (2H, s, OC$\underline{H_2}$O), 3.95 (3H, s, OC$\underline{H_3}$), 3.76 (2H, q, *J* 7.2, OC$\underline{H_2}CH_3$), 1.21 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 152.2 (C), 149.3 (C), 142.2 (C), 117.5 (CH), 114.1 (CH), 106.8 (CH), 93.8 ($CH_2$), 65.0 ($CH_2$), 56.3 ($CH_3$), 15.0 ($CH_3$).

**4-(Ethoxymethoxy)-3-methoxyaniline (198)**



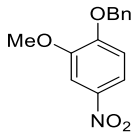

To a solution of 1-(ethoxymethoxy)-2-methoxy-4-nitrobenzene (1.135 g, 5 mmol) in ethyl acetate (25 mL) and ethanol (25 mL) was added 10% palladium on carbon (530 mg, 0.5 mmol) the suspension was stirred rapidly under an atmosphere of hydrogen for 5 days. The black solid was removed by filtration and the filtrate concentrated under vacuum to give the *title compounds* as a red oil (950 mg, 96%) which was used directly in the next step; (Found: $M+H^+$, 198.1131. $C_{10}H_{16}NO_3$ requires 198.1125); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 3447, 3373, 3009, 2979, 1621, 1512; $\delta_H$ (400 MHz; $CDCl_3$) 6.96 (1H, d, *J* 8.5, ArH), 6.29 (1H, d, *J* 2.5, ArH), 6.20 (1H, dd, *J* 8.5, 2.5, ArH), 5.14 (2H, s, $OC\underline{H_2}O$), 3.81 (3H, s, $OCH_3$), 3.77 (2H, q, *J* 7.1, $OC\underline{H_2}CH_3$), 1.23 (3H, t, *J* 7.1, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 150.9 (C), 142.2 (C), 139.3 (C), 119.1 (CH), 106.7 (CH), 100.5 (CH), 95.2 ($CH_2$), 64.1 ($CH_2$), 55.7 ($CH_3$), 15.1 ($CH_3$).

**Ethyl 2-((4-(ethoxymethoxy)-3-methoxyphenyl)amino)-2-oxoacetate (199)**



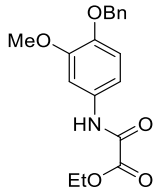

To a solution of 4-(Ethoxymethoxy)-3-methoxyaniline (450 mg, 2.27 mmol) in THF was added sequentially triethylamine (0.38 mL, 2.72 mmol) and ethyl chlorooxoacetate (0.254 mL, 2.27 mmol). The reaction mixture was stirred at rt for 5 days over which time a colorless precipitated formed. The precipitate was removed by filtration and the filtrate collected and volatiles removed under vacuum to give a red residue. The residue was purified by flash chromatography on silica (30% ethyl acetate/light petroleum) to give the *title compound* as a yellow oil (480 mg, 95%); (Found: $M+H^+$, 298.1281. $C_{14}H_{20}NO_6$ requires 298.1285); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3389, 3007, 2982, 1707, 1605; $\delta_H$ (400 MHz; $CDCl_3$) 8.85 (1 H, br, NH), 7.52 (1 H, d, *J* 2.4, ArH), 7.15 (1 H, d, *J* 8.7, ArH), 6.97 (1 H, dd, *J* 8.7, 2.4, ArH), 5.25 (2 H, s, $OCH_2O$), 4.40 (2 H, q, *J* 7.2, $O\underline{CH_2}CH_3$), 3.88 (3 H, s, OMe), 3.76 (2 H, q, *J* 7.1, $OC\underline{H_2}CH_3$), 1.42 (3 H, t, *J* 7.2, $OCH_2C\underline{H_3}$), 1.21 (3 H, t, *J* 7.1, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 161.1 (C), 153.7 (C), 150.0 (C), 144.2 (C), 131.3 (C), 116.7 (CH), 111.9 (CH), 104.5 (CH), 94.3 ($CH_2$), 64.4 ($CH_2$), 63.7 ($CH_2$), 55.9 ($CH_3$), 15.1 ($CH_2$), 14.0 ($CH_2$).

**1-Benzyloxy-2-methoxy-4-nitrobenzene (201)**



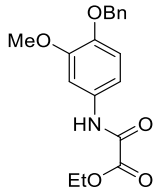

To 4-nitroguaiacol (600 mg, 3.55 mmol) and potassium carbonate (981 mg, 7 mmol) in acetonitrile (10 mL) was added benzyl bromide (0.5 mL, 4.25 mmol) the reaction mixture was stirred at reflux for 20 h. The reaction mixture was diluted with water (50 mL) then extracted with ethyl acetate (3 × 50 mL) the organics were combined, washed with water (2 × 50 mL), brine (50 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a yellow solid (850 mg, 92 %); mp 79 °C; (Found: $M^+Na$, 282.0732. $C_{14}H_{13}NNaO_4$ requires 282.0737); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3095, 3042, 2938, 1591, 1518; $\delta_H$ (400 MHz; $CDCl_3$) 7.85 (1H, dd, *J* 8.9, 2.5, ArH), 7.77 (1H, d, *J* 2.5, ArH), 7.45-7.35 (5H, m, ArH), 6.93 (1H, d, *J* 8.9, ArH), 5.26 (2H, s, $OCH_2$), 3.97 (3H, s, $OCH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 153.5 (C), 149.2 (C), 141.5 (C), 135.5 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.2 (CH), 117.5 (CH), 111.7 (CH), 106.6 (CH), 71.0 ($CH_2$), 56.2 ($CH_3$), 33.5 ($CH_2$).

**Ethyl 2-((4-benzyloxy-3-methoxyphenyl)amino)-2-oxoacetate (203)**



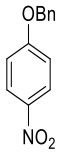

1-(Benzyloxy)-2-methoxy-4-nitrobenzene (7.77 g, 30 mmol) and 5% Pt/C (585 mg, 3 mmol) were stirred in THF (150 mL) under an atmosphere of hydrogen for 16 h. Further 5% Pt/C (585 mg, 3 mmol) was added and stirred at rt under an atmosphere of hydrogen for 4 h. The reaction mixture was filtered and the filtrate collected and volatiles removed under vacuum to give a red oil. The red oil was dissolved in dichloromethane (200 mL) then triethylamine (6.26 mL, 45 mmol) was added and the mixture cooled to 0 °C. Ethyl chlorooxoacetate (4.00 mL, 36 mmol) was added and stirred at rt for 2 h. At 0 °C triethylamine (2.78 mL, 20 mmol) followed by ethyl chlorooxoacetate (1.66 mL, 15 mmol) were added then stirred at rt for 72 h. The reaction mixture was washed with saturated potassium carbonate$_{(aq)}$ (4 × 200 mL), brine (2 × 200 mL). The pink precipitate was removed by filtration. The organic layer was collected and dried over magnesium sulfate. The residue was purified by flash chromatography on silica (15% ethyl acetate/light petroleum) to give the *title compound* as a beige oil (5.28 g, 54%); (Found: $M^-$, 328.1198. $C_{18}H_{18}NO_5$ requires 328.1190); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3389, 3011, 2940, 1761, 1706; $\delta_H$ (400 MHz; $CDCl_3$) 8.89 (1H, br, NH), 7.44 (1H, d, *J* 2.5, ArH), 7.41-7.25 (5H, m, ArH), 6.98 (1H, dd, *J* 8.6, 2.5, ArH), 6.82 (1H, d, 8.6, ArH), 5.1 (2H, s, OC$\underline{H}_2$Ar), 4.35 (2H, q, *J* 7.2, OC$\underline{H}_2$CH$_3$), 3.85 (3H, s, OCH$_3$-), 1.37 (3H, t, *J* 7.1, OCH$_2$C$\underline{H}_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.9 (C), 153.6 (C), 149.7 (C), 145.5 (C), 137.8 (C), 130.4 (C), 128.4 (CH), 127.7 (CH), 127.2 (CH), 114.2 (CH), 111.7 (CH), 104.6 (CH), 71.1 ($CH_2$), 63.4 ($CH_2$), 55.8 ($CH_3$).e

**Ethyl 2-((4-benzyloxy-3-methoxyphenyl)amino)-2-thioxoacetate (204)**



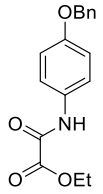

Ethyl 2-((4-benzyloxy-3-methoxyphenyl)amino)-2-oxoacetate (576 mg, 1.6 mmol) was dissolved in toluene at 110 °C then Lawesson's reagent (486 mg, 1.2 mmol) was added and stirred at reflux for 1 h. The reaction mixture was cooled, diluted with ethyl acetate (100 mL), washed with water (3 × 200 mL), filtered, washed with brine (100 mL) then dried over sodium sulfate. The volatiles were removed under vacuum to give a red residue which was purified by flash chromatography on silica (15% ethyl acetate/light petroleum) to give the *title compound* as a red oil which solidified over time (507 mg, 92%); mp 75-76 °C; (Found: M-H, 344.0960. $C_{18}H_{18}NO_4S$ requires 344.0962); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3316, 2993, 2940, 1750, 1709, 1600, 1513; $\delta_H$ (400 MHz; $CDCl_3$) 10.50 (1H, br, NH), 7.96 (1H, d, *J* 2.6, ArH), 7.45-7.30 (6H, m, ArH), 6.90 (1H, d, *J* 8.6, ArH), 5.18 (2H, s, OC$\underline{H_2}$), 4.43 (2H, q, *J* 7.2, OC$\underline{H_2}CH_3$), 3.91 (3H, s, OMe), 1.45 (3H, t, *J* 7.2, $OCH_2\underline{CH_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 177.6 (C), 159.9 (C), 149.4 (C), 146.9 (C), 136.6 (C), 131.7 (C), 128.6 (CH), 128.0 (CH), 127.2 (CH), 114.2 (CH), 113.6 (CH), 106.0 (CH), 71.1 ($CH_2$), 64.5 ($CH_2$), 56.1 ($CH_3$).

**1-Benzyloxy-4-nitrobenzene (218)**



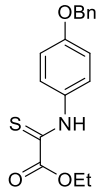

A suspension of 4-nitrophenol (2.25 g, 16 mmol), potassium carbonate (4.4 g, 32 mmol) and benzyl bromide (2.25 mL, 19.2 mmol) in acetonitrile (75 mL) were heat at 85 °C for 16 h. Upon addition of water (100 mL) to the reaction mixture the a colourless precipitate was formed which was collected by filtration and dried under vacuum to give the *title compound* as a colourless solid (3.11 g, 85%); mp 105 °C; (Found: $M+Na^+$, 252.0633, $C_{13}H_{11}NNaO_3$ requires 252.0631); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3089, 3042, 2938, 1608, 1594, 1517, 1381; $\delta_H$ (400 MHz; DMSO) 7.31 (2H, d, *J* 9.2, ArH), 6.58-6.44 (5H, m, ArH), 6.32 (2H, d, *J* 9.2, ArH), 4.36 (2H, s, $OCH_2$); $\delta_C$ (100 MHz; DMSO) 163.6 (C), 140.9 (C), 135.9 (C), 128.5 (CH), 128.1 (CH), 127.8 (CH), 125.8 (CH), 115.2 (CH), 70.1 ($CH_2$).

**Ethyl 2-((4-(benzyloxy)phenyl)amino)-2-oxoacetate (220)**



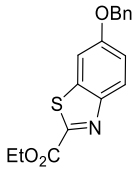

1-Benzyloxy-4-nitrobenzene (5.73 g, 25 mmol) was dissolved in THF (250 mL) and 5% Pt/C (490 mg, 2.5 mmol) was added and stirred under an atmosphere of hydrogen for 88 h. The reaction mixture was filtered and the volatiles removed under vacuum. The resulting residue was dissolved in $CH_2Cl_2$ (250 mL) triethylamine (5.2 mL, 37.5 mmol) followed by ethyl chlorooxoacetate (3.34 mL, 30 mmol) were added and the solution stirred for 20 h. The reaction mixture was washed with water (100 mL), citric acid (2 × 100 mL), brine (100 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give a brown residue which was purified by flash chromatography (25% ethyl acetate/petrol) followed by recrystallization twice from ethyl acetate/petrol to give the *title compound* as colourless needles (4.58 g, 61%); mp 102 °C; (Found: C, 68.32; H, 5.72; N, 4.65. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68%.); (Found: M+H$^+$, 300.1225, $C_{17}H_{18}NO_4$ requires 300.1230); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3389, 3043, 3008, 1706, 1596, 1532; $\delta_H$ (400 MHz; $CDCl_3$) 8.81 (1H, br, NH), 7.57 (2H, d, *J* 9.0, ArH), 7.45-7.32 (5H, m, ArH), 6.98 (2H, d, *J* 9.0, ArH), 5.07 (2H, s, C$\underline{H}_2$), 4.42 (2H, q, *J* 7.2, OC$\underline{H}_2$CH$_3$), 1.44 (3H, t, *J* 7.2, OCH$_2$C$\underline{H}_3$); $\delta_C$ (100 MHz; $CHCl_3$) 161.2 (C), 156.3 (C), 153.8 (C), 136.8 (C), 129.9 (C), 128.7 (CH), 128.1 (CH), 127.5 (CH), 121.5 (CH), 115.3 (CH), 70.3 ($CH_2$), 63.7 ($CH_2$), 14.0 ($CH_3$).

**Ethyl 2-((4-(benzyloxy)phenyl)amino)-2-thioxoacetate (221)**



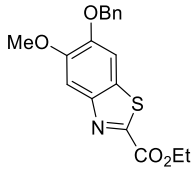

To a solution of ethyl 2-((4-(benzyloxy)phenyl)amino)-2-oxoacetate (300 mg, 1 mmol) in THF (25 mL) was added Lawesson's reagent (202 mg, 0.5 mmol) and the reaction mixture was stirred at room temperature for 20 h. A further portion of Lawesson's reagent (202 mg, 0.5 mmol) was added and the reaction mixture stirred at 40 °C for 35 h. The volatiles were removed under vacuum and the red residue was purified by flash chromatography on silica (25% ethyl acetate/light petroleum) to give the *title compound* as an orange solid (245 mg, 78%); mp 113 °C; (Found: $M^+H$, 316.0997, $C_{17}H_{18}NO_3S$ requires 316.1002); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3317, 3043, 2993, 1710, 1609, 1510; $\delta_H$ (400 MHz; $CDCl_3$) 10.5 (1H, br, NH), 7.92 (2H, d, *J* 8.9, ArH), 7.45-7.33 (5H, m, ArH), 7.03 (2H, d, *J* 8.9, ArH), 5.10 (2H, s, C$\underline{H}_2$), 4.44 (2H, q, *J* 7.2, OC$\underline{H}_2$$CH_3$), 1.46 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$); $\delta_C$ (100 MHz; $CHCl_3$) 178.2 (C), 159.9 (C), 157.4 (C), 136.5 (C), 131.1 (C), 128.7 (CH), 128.2 (CH), 127.5 (CH), 123.6 (CH), 115.1 (CH), 70.3 ($CH_2$), 64.5 ($CH_2$), 14.0 ($CH_3$).

**Ethyl 6-(benzyloxy)benzo[*d*]thiazole-2-carboxylate (224)**



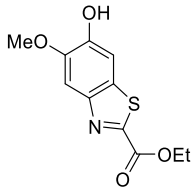

To a solution of ethyl 2-((4-(benzyloxy)phenyl)amino)-2-thioxoacetate (20 mg, 0.06 mmol) in MeCN (2 mL) was added CAN (138 mg, 0.25 mmol) in water (2 mL) the reaction mixture was stirred for 1 h at rt. The reaction mixture was diluted with water (10 mL) then extracted with ethyl acetate (2 × 10 mL). The organic extracts were combined, washed with water (2 × 20 mL), brine (20 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a brown residue (18 mg, 91%); (Found: $M+H^+$, 314.0845, $C_{17}H_{16}NO_3S$ requires 314.0845); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3051, 3002, 1715, 1603,1553; $\delta_H$ (400 MHz; $CDCl_3$) 8.12 (1H, d, *J* 9.1, ArH), 7.48-7.35 (6H, m, ArH), 7.27 (1H, dd, *J* 9.1, 2.5, ArH), 5.17 (2H, s, OC$\underline{H_2}$Ar), 4.54 (2H, q, *J* 7.2, OC$\underline{H_2}CH_3$), 1.49 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CHCl_3$) 183.0 (C), 158.7 (C), 138.6 (C), 136.1 (C), 128.8 (CH), 128.3 (CH), 127.5 (CH), 128.2 (CH), 118.1 (CH), 104.7 (CH), 70.7 ($CH_2$), 62.9 ($CH_2$), 14.3 ($CH_3$).

**Ethyl 6-(benzyloxy)-5-methoxybenzo[*d*]thiazole-2-carboxylate (212)**



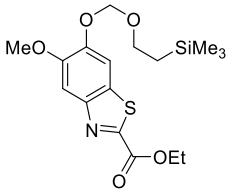

At 0 °C to a solution of ethyl 2-((4-(benzyloxy)-3-methoxyphenyl)amino)-2-thioxoacetate (103.6 mg, 0.3 mmol) in MeCN (10 mL) was added CAN (658 mg, 1.2 mmol) in water (10 mL). The reaction mixture was stirred for 20 min then diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combine, washed with water (2 × 30 mL), brine (30 mL) then dried over magnesium sulfate to give the *title compound* as a beige solid (83 mg, 81%); mp 116 °C; (Found: $M+H^+$, 344.0961, $C_{18}H_{18}NO_4S$ requires 344.0951); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3009, 1714, 1607, 1497; $\delta_H$ (400 MHz; $CDCl_3$) 7.66 (1H, s, ArH), 7.45-7.31 (6H, m, ArH), 5.24 (2H, s, $CH_2$), 4.52 (2H, q, *J* 7.1, $OC\underline{H_2}CH_3$), 3.97 (3H, s, OMe), 1.47 (3H, t, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CHCl_3$) 160.7 (C), 156.2 (C), 150.9 (C), 149.9 (C), 148.2 (C), 136.1 (C), 129.8 (C), 128.7 (CH), 128.2 (CH), 127.3 (CH), 106.0 (CH), 104.1 (CH), 71.3 ($CH_2$), 62.8 ($CH_2$), 56.2 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (230)**



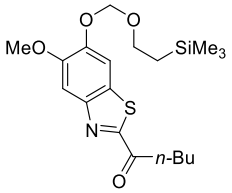

Ethyl 6-(benzyloxy)-5-methoxybenzo[*d*]thiazole-2-carboxylate (1.05 g, 3 mmol) was dissolved in hydrobromic acid in acetic acid (33%, 20 mL) and the solution was stirred at rt for 1.5 h. The reaction mixture was poured into saturated sodium hydrogen carbonate (500 mL) then extracted with ethyl acetate (2 × 50 mL). The organics were combined, washed with sodium hydrogen carbonate (2 × 100 mL), brine (100 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give a beige residue which was purified by flash chromatography on silica (40-50% ethyl acetate/light petroleum) to give the *title compound* as a colourless solid (653 mg, 86%); mp 172 °C; (Found $M+Na^+$ 276.0306. $C_{11}H_{11}NNaO_4S$ requires 276.0301); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 3531, 3006, 1713; $\delta_H$ (400 MHz; $CDCl_3$) 7.63 (1H, s, ArH), 7.40 (1H, s, ArH), 6.17 (1H, br, OH), 4.52 (2H, m, $OC\underline{H}_2CH_3$), 3.99 (3H, s, OMe), 1.49 (3H, m, $OCH_2C\underline{H}_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.7 (C), 155.8 (C), 147.8 (C), 147.5 (C), 147.4 (C), 130.7 (C), 105.3 (CH), 105.2 (CH), 62.8 ($CH_2$), 58.2 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 5-methoxy-6-((2-(trimethylsilyl)ethoxy)methoxy)benzo[*d*]thiazole-2-carboxylate (232)**



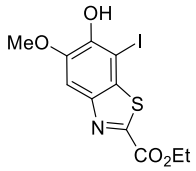

To a solution of ethyl 6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (50 mg, 0.2 mmol) and diisopropylethylamine (38 μL, 0.3 mmol) in $CH_2Cl_2$ (5 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (53 μL, 0.3 mmol) and the reaction mixture was stirred at rt for 1 h. The volatiles were removed under vacuum to give a light yellow residue which was purified by flash chromatography on silica ( 15-20% ethyl acetate/light petroleum) to give the *title compound* as a beige gum (63 mg, 82%); (Found $M+H^+$ 384.1294. $C_{17}H_{26}NO_5SSi^+$ requires 384.1295); $\nu_{max}$ (ATR)/$cm^{-1}$ 2952, 1738, 1710, 1549; $\delta_H$ (400 MHz; $CDCl_3$) 7.69 (1H, s, ArH), 7.66 (1H, s, ArH), 5.39 (2H, s, $OC\underline{H_2}O$), 4.52 (2H, q, *J* 7.2, $OC\underline{H_2}CH_3$), 3.96 (3H, s, OMe), 3.83 (2H, t, *J* 8.3, $OC\underline{H_2}CH_2Si$), 1.47 (3h, t, *J* 7.2, $OCH_2C\underline{H_3}$), 0.98 (2H, t, *J* 8.3, $OCH_2C\underline{H_2}Si$), 0.01 (9H, s, $SiMe_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.7 (C), 156.7 (C), 150.7 (C), 148.6 (C), 148.5 (C), 129.8 (C), 106.56 (CH), 106.0 (CH), 94.2 ($CH_2$), 66.9 ($CH_2$), 62.8 ($CH_2$), 56.1 ($CH_3$), 18.1 ($CH_2$), 14.3 ($CH_3$), 1.4 ($CH_3$).

**1-(5-Methoxy-6-((2-(trimethylsilyl)ethoxy)methoxy)benzo[*d*]thiazol-2-yl)pentan-1-one (234)**

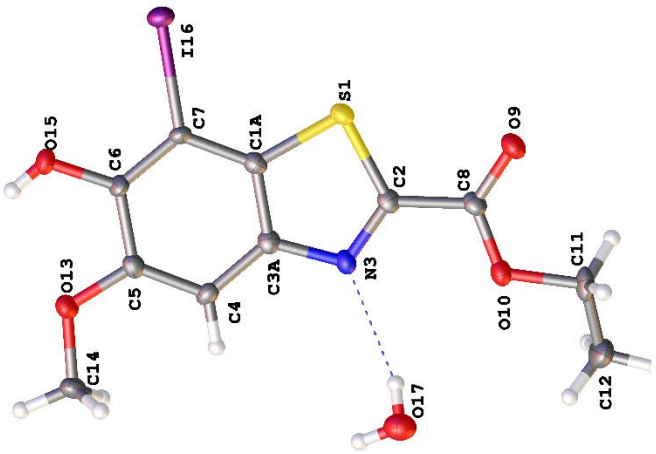



A solution of ethyl 5-methoxy-6-((2-(trimethylsilyl)ethoxy)methoxy)benzo[*d*]thiazole-2-carboxylate (38 mg, 0.1 mmol) and TMEDA (18 μL, 0.11 mmol) in THF (5 mL) was prepared under an atmosphere of argon at -78 °C. To this was added *n*-butyllithium in hexanes (2.4 M; 0.05 mL) the reaction was stirred at -78 °C temperature for 30 min. Geranyl bromide (0.396 mL, 0.2 mmol) was added and the reaction mixture was allowed to warm to rt over 2 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with ammonium chloride (2 × 40 mL), brine (40 mL), dried over magnesium sulfate and the volatiles were removed under vacuum. The residue was purified by flash chromatography on silica (10-20% ethyl acetate/light petroleum) to give a colourless gum (12 mg, 30%); (Found $M+Na^+$ 418.1472. $C_{19}H_{29}NNaO_4SSi^+$ requires 418.1484); $\nu_{max}$ (ATR)/$cm^{-1}$ 3692, 3605, 3006, 2960, 1681, 1602; $\delta_H$ (400 MHz; $CDCl_3$) 7.70 (1H, s, ArH), 7.61 (1H, s, ArH), 5.40 ($OC\underline{H_2}O$), 3.99 (3H, s, OMe), 3.84 (2H, t, *J* 8.5, $OC\underline{H_2}CH_2Si$), 3.23 (2H, t, *J* 7.5, $C\underline{H_2}CH_2CH_2CH_3$), 1.79 (2H, m, $CH_2C\underline{H_2}CH_2CH_3$), 1.46 (2H, m, $CH_2CH_2C\underline{H_2}CH_3$), 0.98 (5H, m, $CH_2CH_2CH_2C\underline{H_3}$+ $OCH_2C\underline{H_2}Si$), 0.00 (9H, s, $SiMe_3$); $\delta_C$ (100 MHz; $CDCl_3$) 195.2 (C), 165.3 (C), 150.7 (C), 149.9 (C), 148.6 (C), 130.5 (C), 106.9 (CH), 105.9 (CH), 94.2 ($CH_2$), 66.9 ($CH_2$), 56.2 ($CH_3$), 38.2 ($CH_2$), 26.2 ($CH_2$), 22.4 ($CH_2$), 18.1 ($CH_2$), 13.9 ($CH_3$), 1.42 ($CH_3$).

**Ethyl 6-hydroxy-7-iodo-5-methoxybenzo[*d*]thiazole-2-carboxylate (235)**

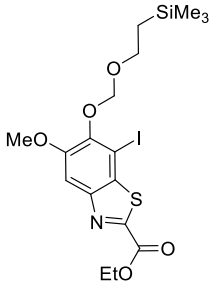



To a solution of ethyl 6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (383 mg, 1.5 mmol), potassium iodide (249 mg, 1.5 mmol) and sulfuric acid (0.12 mL) in methanol (50 mL) was added hydrogen peroxide in water (30%, 0.34 mL) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and water (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL) then the organics were combined, washed with water (2 × 50 mL), brine (50 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give a colourless residue which was purified by flash chromatography on silica (30-40% ethyl acetate/light petroleum) to give the *title compound* as a colourless solid (430 mg, 76%); mp 173 °C (dec); (Found $M+Na^+$ 401.9268. $C_{11}H_{10}INNaO_4S$ requires 401.9267); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 3515, 3008, 1715, 1602; $\delta_H$ (400 MHz; $CDCl_3$) 7.62 (1H , s, ArH), 6.62 (1H, br, OH), 4.53 (2H, q, *J* 7.2, $OC\underline{H_2}CH_3$), 4.01 (3H, s, OMe), 1.48 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 198.4 (C), 160.6 (C), 154.7 (C), 147.7 (C), 146.7 (C), 144.4 (C), 138.4 (C), 105.6 (CH), 62.9 ($CH_2$), 56.7 ($CH_3$), 14.3 ($CH_3$).



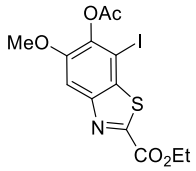
**Ethyl 7-iodo-5-methoxy-6-((2-**

**(trimethylsilyl)ethoxy)methoxy)benzo[*d*]thiazole-2-carboxylate (236)**



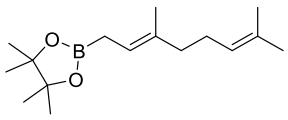

To a solution of ethyl 6-hydroxy-7-iodo-5-methoxybenzo[*d*]thiazole-2-carboxylate (76 mg, 0.2 mmol) and diisopropylethylamine (38 μL, 0.3 mmol) was added 2-(trimethylsilyl)ethoxymethyl chloride (53 μL, 0.3 mmol) and the reaction mixture was stirred at rt for 1 h. The volatiles were removed under vacuum to give a light yellow residue which was purified by flash chromatography on silica (15-20% ethyl acetate/light petroleum) to give the *title compound* as a beige solid (72 mg, 71%); mp 112 °C; (Found $M+Na^+$ 532.0085. $C_{17}H_{24}INNaO_5SSi^+$ requires 532.0087); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3009, 2957, 1716, 1639; $\delta_H$ (400 MHz; $CDCl_3$) 7.67 (1H, s, ArH), 5.32 (2H, s, $OC\underline{H_2}O$), 4.54 (2H, q, *J* 7.1, $OC\underline{H_2}CH_3$), 3.99 (2H, t, *J* 8.7, $OC\underline{H_2}CH_2Si$), 3.93 (3H, s, OMe), 1.48 (3H, t, *J* 7.1, $OCH_2C\underline{H_3}$), 1.00 (2H, t, *J* 8.7, $OCH_2C\underline{H_2}Si$), 0.03 (9H, s, $SiMe_3$);

**Ethyl 6-acetoxy-7-iodo-5-methoxybenzo[*d*]thiazole-2-carboxylate (240)**



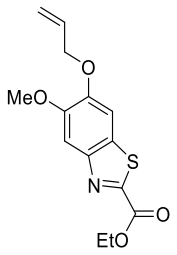

To a solution of ethyl 6-hydroxy-7-iodo-5-methoxybenzo[*d*]thiazole-2-carboxylate (100 mg, 0.26 mmol), acetic anhydride (32 mg, 0.31 mmol) and triethylamine (0.11 mL, 0.8 mmol) in $CH_2Cl_2$ (10 mL)was added DMAP (3 mg, 0.024 mmol) the reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and then washed with saturated sodium hydrogen carbonate (3 × 20 mL), brine (20 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a beige solid (80 mg, 73%); mp 170 °C; (Found $M+Na^+$ 443.9375. $C_{13}H_{13}INO_5S$ requires 443.9373); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3042, 2941, 1775, 1718, 1638; $\delta_H$ (400 MHz; $CDCl_3$) 7.70 (1H, s, ArH), 4.54 (2H, q, *J* 7.2, $OC\underline{H_2}CH_3$), 3.90 (3H, s, OMe), 2.41 (3H, s, Me), 1.48 (3H, t, *J* 7.2, $OCH_2C\underline{H_3}$); $\delta_C$ (100 MHz; $CDCl_3$) 167.8 (C), 160.3 (C), 157.9 (C), 151.6 (C), 148.7 (C), 142.7 (C), 136.9 (C), 107.2 (C), 63.2 ($CH_2$), 56.5 ($CH_3$), 20.7 ($CH_3$), 14.2 ($CH_3$).

**(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (244)**



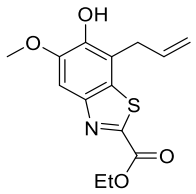
Geraniol (0.58 mL, 3.3 mmol) was dissolved in methanol (6.5 mL) and DMSO (6.5 mL) and degassed with argon for 10 min. *p*-TsOH (30 mg, 0.165 mmol), bis(pinacolato)diboron (1.68 g, 6.6 mmol) and di-μ- chlorobis{2-[(dimethylamino)methyl]phenyl-C,N}dipalladium(II) (46 mg, 0.083 mmol) were added and the reaction mixture was stirred at 50 °C under an atmosphere of argon for 24 h. The reaction mixture was filtered through silica, washed with light petroleum and the volatiles were removed under vacuum. The residue was dissolved in ether (50 mL) and water (50 mL). The aqueous layer was extracted with ether (50 mL) then the organics were combined and dried over magnesium sulfate. The volatiles were removed under vacuum loading the residue onto silica which was then purified by flash chromatography on silica (2% ether and light petroleum) to give the title compound as a colourless oil (700 mg, 80%); (Found M+$Na^+$ 287.2159. $C_{16}H_{29}BNaO_2$ requires 287.2153); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2978, 2923, 1446, 1369; $\delta_H$ (400 MHz; $CDCl_3$) 5.25 (1H, t, *J* 7.5, $CH_2C\underline{H}$=C), 5.10 (1H, t, *J* 6.7, $CH_2C\underline{H}$=C), 2.1-1.96 (4H, m, 2 × $CH_2$), 1.68 (3H, s, Me), 1.65-1.57 (8H, m, 2 × Me + $CH_2$), 1.24 (12H, s, 4 × Me); $\delta_C$ (100 MHz; $CDCl_3$) 135.1 (C), 131.1 (C), 124.5 (CH), 118.5 (CH), 83.0 (C), 39.7 ($CH_2$), 26.8 ($CH_2$), 25.7 ($CH_3$), 24.7 ($CH_3$), 17.7 ($CH_3$), 15.9 ($CH_3$). $\delta_B$ (128 MHz; $CDCl_3$) 33.1. The data was consistent with literature.[173]

**Ethyl 6-(allyloxy)-5-methoxybenzo[*d*]thiazole-2-carboxylate (247)**



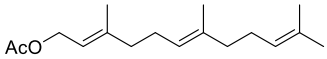

To a suspension of ethyl 6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (253 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) in acetonitrile (10 mL) was added allyl bromide (0.95 mL, 1.1 mmol). The reaction mixture was heated at 70 °C for 3 h then diluted with $CH_2Cl_2$ (10 mL) and water (10 mL). The aqueous layer was washed further with $CH_2Cl_2$ (2 × 10 mL) then the organic layers were combined, washed with water (30 mL), brine (30 mL) then dried over magnesium sulfate to give the *title compound* as a light yellow solid (276 mg, 94%); (Found: $M+H^+$ 294.0802. $C_{14}H_{16}NO_4S$ requires 294.0795); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2981, 2934, 1732, 1705, 1605, 1549; $\delta_H$ (400 MHz; $CDCl_3$) 7.66 (1H, s, ArH), 7.32 (1H, s, ArH), 6.12 (1H, ddt, *J* 17.3, 10.6, 5.4, =C<u>H</u>$CH_2$), 5.47 (1H, dq, *J* 17.3, 1.5, <u>H</u>$_t$H$_c$C=CH), 5.36 (1H, dq, *J* 10.5, 1.5, H$_t$<u>H</u>$_c$C=CH), 4.71 (2H, dt, *J* 5.4, 1.5, $CH_2$=CH-C<u>H</u>$_2$), 4.52 (2H, q, *J* 7.1, OC<u>H</u>$_2$$CH_3$), 3.96 (3H, s, $OCH_3$), 1.47 (3H, t, *J* 7.1, $OCH_2$C<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.8 (C), 156.1 (C), 150.7 (C), 149.7 (C), 148.0 (C), 132.3 (CH), 129.8 (C), 118.8 ($CH_2$), 105.9 (CH), 103.5 (CH), 70.2 ($CH_2$), 62.8 ($CH_2$), 56.1 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 7-allyl-6-hydroxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (248)**



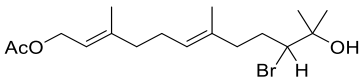

Ethyl 6-(allyloxy)-5-methoxybenzo[*d*]thiazole-2-carboxylate (7 mg, ) was heated neat at 120 °C for 18 h to give the desired compound as an orange gum (7 mg, 100%); (Found: $M+H^+$ 294.0795. $C_{14}H_{16}NO_4S$ requires 294.0795); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3445, 2983, 1710, 1489; $\delta_H$ (400 MHz; $CDCl_3$) 7.56 (1H, s, ArH), 6.15 (1H, br, OH), 5.95 (1H, ddt, *J*17.1, 10.0, 6.4, =C<u>H</u>$CH_2$), 5.16 (1H, dq, *J* 17.1, 1.6, <u>H</u>$_t$H$_c$C=CH), 5.11 (1H, dq, *J* 10.0, 1.6, H$_t$<u>H</u>$_c$C=CH), 4.52 (2H, q, OC<u>H</u>$_2$$CH_3$), 4.00 (3H, s, $OCH_3$), 3.66 (2H, dt, *J* 6.4, 1.6, $CH_2$=CH-C<u>H</u>$_2$), 1.47 (4H, t, *J* 7.1, $OCH_2$C<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.9 (C), 155.4 (C), 147.8 (C), 146.6 (C), 144.3 (C), 133.4 (CH), 131.8 (C), 116.9 ($CH_2$), 103.6 (CH), 62.7 ($CH_2$), 56.4 ($CH_3$), 33.7 ($CH_2$) 14.3 ($CH_3$).

**(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate (265)**



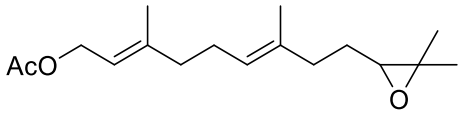

To a solution of farnesol (25 g, 112 mmol) and acetic anhydride (11.71 mL, 124 mmol) in $CH_2Cl_2$ (500 mL) at 0 °C was added pyridine (10.03 mL, 124 mmol) then 4-dimethylaminopyridine (134 mg, 1.1 mmol). The reaction mixture was stirred warming slowly to rt for 18 h. The reaction mixture was washed with saturate sodium hydrogen carbonate (3 × 250 mL), hydrochloric acid (1 M; 3 × 250 mL), brine (250 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a colourless oil (28.87 g, 97%); (Found: $M+Na^+$ 287.1980. $C_{17}H_{28}NaO_2$ requires 287.1982); $\nu_{max}$ (ATR)/$cm^{-1}$ 2965, 2915, 2854, 1738; $\delta_H$ (400 MHz; $CDCl_3$) 5.34 (1H, tq, *J* 7.1, 1.1, $OCH_2C\underline{H}$=C), 5.13-5.06 (2H, m, 2 × C$\underline{H}$=C), 4.58 (2H, d, *J* 7.1, O$C\underline{H}_2$CH=), 2.16-2.02 (6H, m, 3 × $C\underline{H}_2$), 2.05 (3H, s, $C\underline{H}_3CO_2$), 2.00-1.94 (2H, m, $CH_2$), 1.70 (3H, d, *J* 0.5, Me), 1.67 (3H, d, *J* 1.1, Me), 1.59 (6H, s, 2 × Me); $\delta_C$ (100 MHz; $CDCl_3$) 171.1 (C), 142.3 (C), 135.4 (C), 131.3 (C), 124.3 (CH), 123.6 (CH), 118.3 (CH), 61.4 ($CH_2$), 39.7 ($CH_2$), 39.5 ($CH_2$), 26.7 ($CH_2$), 26.2 ($CH_2$), 25.7 ($CH_3$), 21.0 ($CH_3$), 17.7 ($CH_3$), 16.4 ($CH_3$), 16.0 ($CH_3$).The data was consistent with literature.[145]

**(2*E*,6*E*)-10-Bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate (266)**



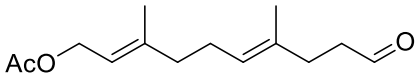

A solution of N-bromosuccinamide (21.55 g, 121 mmol) in THF:water (2:1; 400 mL) was added dropwise to a solution of (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate (28.87 g, 110 mmol) in THF:water (2:1; 350 mL) at 0 °C over 40 min. The reaction mixture was stirred at 0 °C for a further 1 h. The volume was then reduced to *ca.* 500 mL then extracted with ether (2 × 250 mL). The organics were combined then washed with satured sodium hydrogen carbonate (3 × 200 mL), brine (200 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give a faint yellow oil which was purified by flash chromatography on silica (10-15% ethyl acetate/light petroleum) to give the *title compound* as a colourless oil (27.25 g, 70%); (Found: M+$Na^+$ 383.1192. $C_{17}H_{29}{}^{79}BrNaO_3$ requires 383.1192); $\nu_{max}$ (ATR)/$cm^{-1}$ 3448, 2974, 2933, 1735; $\delta_H$ (400 MHz; $CDCl_3$) 5.34 (1H, tq, *J* 7.2, 1.3, $OCH_2C\underline{H}$=C), 5.19 (1H, tq, *J* 6.9, 1.0, C<u>H</u>=C), 4.59 (2H, d, *J* 7.2, $OC\underline{H}_2CH$=), 3.96 (1H, dd, *J* 11.3, 1.9, C<u>H</u>Br), 2.39-2.26 (1H, m, C<u>H</u>$_2$), 2.18-2.04 (4H, m, C<u>H</u>$_2$), 2.05 (3H, s, $C\underline{H}_3CO_2$), 2.04-1.93 (1H, m, C<u>H</u>$_2$), 1.86-1.74 (2H, m, C<u>H</u>$_2$), 1.73 (3H, d, *J* 1.3, C<u>H</u>$_3$), 1.62 (3H, d, *J* 1.0, C<u>H</u>$_3$), 1.37 (3H, s, C<u>H</u>$_3$), 1.36 (3H, s, C<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 171.2 (C), 142.0 (C), 133.6 (C), 125.4 (CH), 118.4 (CH), 72.5 (C), 70.6 (CH), 61.4 ($CH_2$), 39.4 ($CH_2$), 38.1 ($CH_2$), 32.0 ($CH_2$), 26.5 ($CH_3$), 26.1 ($CH_2$), 25.9 ($CH_3$), 21.1 ($CH_3$), 16.5 ($CH_3$), 15.8 ($CH_3$). The data was consistent with literature.[145]

**(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate (267)**



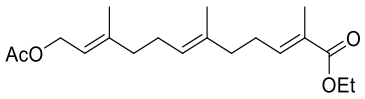

To a solution of (2*E*,6E)-10-bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate (27 g, 75 mmol) in THF (300 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (33.55 mL, 225 mmol). The reaction mixture was warmed to rt while stirring for 3 h. The volume was reduced (ca. 50 mL) then diluted with water (250 mL) and extracted with ethyl acetate (2 × 200 mL). The organic extracts were combined, washed with water (2 × 200 mL), brine (200 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a colourless oil (19 g, 90%); (Found M+Na 303.1928. $C_{17}H_{28}NaO_3$ requires 303.1931); $\nu_{max}$ (ATR)/$cm^{-1}$ 2923, 1736, 1377; $\delta_H$ (400 MHz; $CDCl_3$) 5.35 (1H, tq, *J* 7.1, 1.4, C<u>H</u>=C), 5.16 (1H, tq, *J* 6.9, 1.3, C<u>H</u>=C), 4.60 (2H, d, *J* 6.9, OC<u>H</u>$_2$CH=), 2.71 (1H, t, *J* 6.3, C<u>H</u>-O), 2.24-2.04 (6H, m, C<u>H</u>$_2$), 2.07 (3H, s, C<u>H</u>$_3$CO$_2$), 1.74-1.59 (2H, m, C<u>H</u>$_2$), 1.73 (3H, d, *J* 1.3 C<u>H</u>$_3$), 1.64 (3H, d, *J* 1.4, C<u>H</u>$_3$), 1.32 (3H, s, C<u>H</u>$_3$), 1.28 (3H, s, C<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 171.2 (C), 142.1 (C), 134.6 (C), 124.3 (CH), 118.3 (CH), 64.2 (CH), 61.4 ($CH_2$), 58.4 (C), 39.4 ($CH_2$), 36.3 ($CH_2$), 27.4 ($CH_2$), 26.2 ($CH_2$), 24.9 ($CH_3$), 21.1 ($CH_3$), 18.7 ($CH_3$), 16.5 ($CH_3$), 16.0 ($CH_3$). The data was consistent with literature.[145]

**(2*E*,6*E*)-3,7-dimethyl-10-oxodeca-2,6-dien-1-yl acetate (268)**



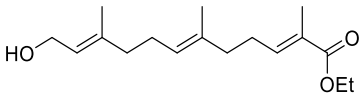

At 0 °C a solution of (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate (140 mg, 0.5 mmol) in THF (6 mL) was added a solution of periodic acid (114mg, 0.5 mmol) in water (3 mL) then stirred for 3 h while warming to rt. The reaction mixture was diluted with water (15 mL) then extracted with ethyl acetate (3 × 10 mL). The organics were combined, washed with brine (20 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum and the resulting residue was purified by column chromatography on silica (10% ethyl acetate/light petroleum) to give the *title compound* as a colorless oil (80 mg, 67%); (Found: $M+Na^+$ 261.1452. $C_{14}H_{22}NaO_3$ requires 261.1467); $\nu_{max}$ (ATR)/$cm^{-1}$ 2920, 1726, 1669, 1445, 1229; $\delta_H$ (400 MHz; $CDCl_3$) 9.72 (1H, t, *J* 1.9, CHO), 5.31 (1H, t, *J* 6.7, CH=C), 5.11 (1H, t, *J* 6.7, CH=C), 4.56 (2H, d, *J* 7,1, OC$\underline{H_2}$CH=C), 2.49 (2H, td, *J* 7.5, 1.9, $CH_{2)}$), 2.30 (2H, t, *J* 7.5, $CH_2$), 2.15-2.06 (2H, m, $CH_2$), 2.03 (3H, s, $CH_2CO$), 2.06-1.98 (2H, m, $CH_2$), 1.67 (3H, s, $CH_3$), 1.60 (3H, s, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 202.6 (CH), 171.1 (C), 141.8 (C), 133.4 (C), 124.7 (CH), 118.5 (CH), 61.3 ($CH_2$), 42.1 ($CH_2$), 39.2 ($CH_2$), 31.8 ($CH_2$), 26.0 ($CH_2$), 21.0 ($CH_3$), 16.4 ($CH_3$), 16.1 ($CH_3$).

**Ethyl (2*E*,6*E*,10*E*)-12-acetoxy-2,6,10-trimethyldodeca-2,6,10-trienoate (269)**



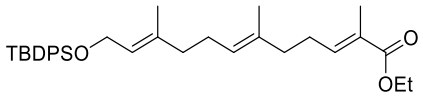

To a suspension of sodium hydride (1.78 g, 74 mmol) in THF (400 mL) at 0 °C was added triethyl 2-phosphonopropionate (15.9 mL, 74 mmol) dropwise over 15 min. The reaction mixture was stirred for a further 40 min during which time the turbid solution became homogenous. (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate (16.08 g, 67.5 mmol) in THF (200 mL) was added dropwise to the reaction mixture over 1 h. The reaction mixture was stirred for a further 3 h while warming to room temperature. The reaction mixture was diluted with saturated ammonium chloride (250 mL) then extracted with ether (100 mL). The organic layer was washed with saturated ammonium chloride (250 mL), water (250 mL), brine (250 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give a pale yellow residue which was purified by column chromatography (5% ethyl acetate:petroleum ether) to give the *title compound*, a >95:5 mixture of E:Z isomers, as a colourless oil (14.16 g, 65%); (Found: M+$Na^+$ 345.2042. $C_{19}H_{30}NaO_4$ requires 345.2036); $\nu_{max}$ (ATR)/$cm^{-1}$ 2924, 2854, 1737, 1707, 1670, 1443; $\delta_H$ (400 MHz; $CDCl_3$) 6.75 (1H, tq, *J* 7.3, 1.4, C<u>H</u>=C), 5.36 (1H, tq, *J* 7.0, 1.1, C<u>H</u>=C), 5.15 (1H, tq, *J* 6.5, 1.4, C<u>H</u>=C), 4.60 (2H, d, *J* 7.3, OC<u>$H_2$</u>=), 4.2 (2H, q, *J* 7.1, OC<u>$H_2$</u>$CH_3$), 2.27 (2H, q, *J* 2.28, C<u>$H_2$</u>), 2.19.2.03 (6H, m, C<u>$H_2$</u>), 2.07 (3H, d, *J* 1.5, C<u>$H_3$</u>CO), 1.84 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.73 (3H, d, *J* 1.6, $CH_3$), 1.63 (3H, d, *J* 1.5, $CH_3$), 1.3 (3H, t, *J* 7.1, $OCH_2C$<u>$H_3$</u>); $\delta_C$ (100 MHz; $CDCl_3$) 171.1 (C), 168.2 (C), 140.0 (C), 141.8 (CH), 134.4 (C), 127.8 (C), 124.5 (CH), 118.4 (CH), 61.4 ($CH_2$), 60.4 ($CH_2$), 39.4 ($CH_2$), 38.2 ($CH_2$), 27.3 ($CH_2$), 26.2 ($CH_2$), 21.0 ($CH_3$), 16.5 ($CH_3$), 16.0 ($CH_3$), 14.3 ($CH_3$), 12.4 ($CH_3$). The data was consistent with literature.[145]

**Ethyl (2*E*,6*E*,10*E*)-12-hydroxy-2,6,10-trimethyldodeca-2,6,10-trienoate (271)**



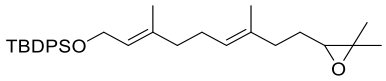

To a solution of ethyl (2*E*,6*E*,10*E*)-12-acetoxy-2,6,10-trimethyldodeca-2,6,10-trienoate (1.61 g, 5 mmol) in ethanol (50 mL) was added potassium carbonate (1.38 g, 10 mmol) and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with water (150 mL) then extracted with ethyl acetate (3 × 50 mL). The organic layers were combined then washed with water (100 mL) then brine (100 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a colourless oil (1.39 g, 99%); (Found: $M+Na^+$ 303.1932. $C_{17}H_{28}NaO_3$ requires 303.1931); $\nu_{max}$ (ATR)/$cm^{-1}$ 3407 (br), 2978, 2929, 1705; $\delta_H$ (400 MHz; $CDCl_3$) 6.74 (1H, tq, *J* 7.2, 1.3, C<u>H</u>=C), 5.41 (1H, tq, *J* 6.9, 1.3, C<u>H</u>=C), 5.14 (1H, tq, *J* 6.7, 1.3, C<u>H</u>=C), 4.23-4.13 (4H, m, HOC<u>$H_2$</u>= + OC<u>$H_2$</u>$CH_3$), 2.31-2.22 (2H, m, $CH_2$), 2.19-2.01 (6H, m, $CH_2$), 1.83 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.68 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.62 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.3 (3H, t, *J* 7.2, $OCH_2C$<u>$H_3$</u>); $\delta_C$ (100 MHz; $CDCl_3$) 168.4 (C), 142.0 (CH), 139.2 (C), 134.2 (C), 127.7 (C), 124.7 (CH), 123.6 (CH), 60.4 ($CH_2$), 59.4 ($CH_2$), 39.4 ($CH_2$), 38.2 ($CH_2$), 27.1 ($CH_2$), 26.1 ($CH_2$), 16.2 ($CH_3$), 15.9 ($CH_3$), 14.3 ($CH_3$), 12.4 ($CH_3$). The data was consistent with literature.[145]

**Ethyl (*2E*,6*E*,10E)-12-((*tert*-butyldiphenylsilyl)oxy)-2,6,10-trimethyldodeca-2,6,10-trienoate (272)**




To a solution of ethyl (2*E*,6*E*,10*E*)-12-hydroxy-2,6,10-trimethyldodeca-2,6,10-trienoate (CB756) (280 mg, 1mmol) and imidazole (272 mg, 4 mmol) in $CH_2Cl_2$ (10 mL) was added *tert*-butyl(chloro)diphenylsilane (0.260 mL, 1.1 mmol). Then reaction mixture was stirred at rt for 1 h, then diluted with $CH_2Cl_2$ (30 mL), washed with hydrochloric acid (1M; 2 × 50 mL) and brine (50 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a pale yellow oil (508 mg, 98%); (Found: $M+C_3H_5N_2^+$ 587.3671. $C_{36}H_{51}N_2O_{3S}Si$ requires 587.3663); $\nu_{max}$ (ATR)/$cm^{-1}$ 2956, 2929, 2855, 1707, 1648; $\delta_H$ (400 MHz; $CDCl_3$) 7.81-7.67 (4H, m, ArH), 7.48-7.37 (6H, m, ArH), 6.78 (1H, tq, *J* 7.3, 1.5, H̲C=CCO$_2$Et), 5.42 (1H, tq, *J* 6.4, 1.3, OCH$_2$CH̲=C), 5.19 (1H, t, *J* 6.8, CH̲=), 4.26 (2H, d, *J* 6.4, OCH̲$_2$C=C), 4.22 (2H, q, *J* 7.1, OCH̲$_2$CH$_3$), 2.36-2.22 (2H, m, CH̲$_2$), 2.17-2.06 (4H, m, 2 × CH̲$_2$), 2.05-1.99 (2H, m, CH̲$_2$), 1.86 (3H, s, CH̲$_3$), 1.66 (3H, d, *J* 1.3, CH̲$_3$), 1.48 (3H, d, *J* 1.2, CH̲$_3$), 1.32 (3H, t, *J* 7.1, OCH$_2$CH̲$_3$) 1.08 (9H, s, C(CH̲$_3$)$_3$) ; $\delta_C$ (100 MHz; $CDCl_3$) 168.3 (C), 141.9 (CH), 136.9 (C), 135.6 (CH), 135.2 (C), 134.1 (C), 129.5 (CH), 127.6 (CH), 124.9 (CH), 124.1 (CH), 61.2 ($CH_2$), 60.4 ($CH_2$), 39.4 ($CH_2$), 38.3 ($CH_2$), 27.4 ($CH_2$), 26.9 ($CH_3$), 26.3 ($CH_2$), 16.4 ($CH_3$), 16.0 ($CH_3$), 14.3 ($CH_3$), 12.4 ($CH_3$). The data was consistent with literature.[174]

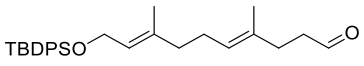
***tert*-Butyl(((2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)oxy)diphenylsilane (279)**




To a solution of (2*E*,6*E*)-10-bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate (18 g, 50 mmol) in methanol (100 mL) was added potassium carbonate (34.5 g, 250 mmol). The reaction mixture was stirred at rt for 64 h then the volatiles were removed under vacuum. The resulting slurry was triturated with ether (3 × 100 mL) the organics were combined and the volatiles were removed under vacuum to give a yellow oil (5.3 g) which was used in the next step without further purification.

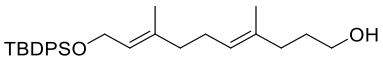
The residue was dissolved in $CH_2Cl_2$ (100 mL) and imidazole (5.99 g, 88 mmol) followed by *tert*-butyl(chloro)diphenylsilane (6.3 mL, 24 mmol) were added. The reaction mixture was stirred at rt for 17 h then washed with hydrochloric acid (1 M; 3 × 100 mL), brine (100 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give a pale yellow oil which was used without further purification (11.4 g, 48%); (Found: M+ $C_3H_5N_2^+$ 545.3563. $C_{34}H_{49}O_2Si$ requires 545.3558); $\nu_{max}$ (ATR)/$cm^{-1}$ 2958, 2929,2855, 1471,1461; $\delta_H$ (400 MHz; $CDCl_3$) 7.85-7.63 (4H, m, ArH), 7.50-7.34 (6H, m, ArH), 5.43 (1H, tq, *J* 6.3, 1.3, CH=), 5.20 (1H, tq, *J* 6.8, 1.2, CH=), 4.28 (2H, d, *J* 6.3, O$C\underline{H_2}$CH=), 2.74 (1H, t, *J* 6.2, CHO), 2.23-1.99 (6H, m, 3 × $CH_2$), 1.74-1.59 (2H, m, $CH_2$), 1.65 (3H, d, *J* 1.4, $CH_3$), 1.48 (3H, d, *J* 1.3, $CH_3$), 1.32 (3H, s, $CH_3$), 1.28 (3H, s, $CH_3$), 1.10 (9H, s, $C(C\underline{H_3})_3$); $\delta_C$ (100 MHz; $CDCl_3$) 137.0 (C), 135.6 (CH), 135.4 (C), 134.1 (C), 129.5 (CH), 127.6 (CH), 124.7 (CH), 124.1 (CH), 64.3 (CH), 61.2 ($CH_2$), 58.5 (C), 39.5($CH_2$), 36.3 ($CH_2$), 27.5 ($CH_2$), 26.9 ($CH_3$), 26.6 ($CH_3$), 26.4 ($CH_2$), 24.9 ($CH_3$), 19.2 (C), 18.8 ($CH_3$), 16.4 ($CH_3$), 16.1 ($CH_3$). The data was consistent with literature.[174]

**(4*E*,8*E*)-10-((*tert*-Butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dienal (280)**



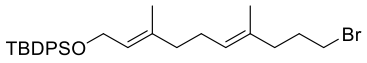

To a solution of ethyl (2*E*,6*E*,10*E*)-12-((*tert*-butyldiphenylsilyl)oxy)-2,6,10-trimethyldodeca-2,6,10-trienoate (10.4 g, 22 mmol) in THF (200 mL) at 0 °C was added periodic acid (5.51 g, 24 mmol) in water (100 mL). The reaction mixture was stirred for 18 h while warming to rt then diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (2 × 200 mL) the organics were combined, washed with brine (200 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum to give a pale yellow oil which was used without further purification (9.48 g, 99%); (Found: M+$C_3H_5N_2^+$ 503.3088. $C_{31}H_{43}N_2O_2Si$ requires 503.3088); $\nu_{max}$ (ATR)/$cm^{-1}$ 2929, 2891, 2855, 1723, 1471; $\delta_H$ (400 MHz; $CDCl_3$) 9.73 (1H, t, *J* 1.9, C<u>H</u>O), 7.81-7.66 (4H, m, ArH), 7.46-7.34 (6H, m, ArH), 5.38 (1H, tq, *J* 6.3, 1.2, C<u>H</u>=), 5.15 (1H, tq, *J* 7.0, 1.3, C<u>H</u>=), 4.23 (2H, d, *J* 6.28, OC<u>$H_2$</u>=), 2.50 (2H, tdd, *J* 6.9, 2.0, 0.7, $CH_2$), 2.36-2.26 (2H, m, $CH_2$), 2.13-2.06 (2H, m, $CH_2$), 2.03-1.96 (2H, m, $CH_2$), 1.62 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.45 (3H, d, *J* 1.3, C<u>$H_3$</u>), 1.06 (9H, s, C(C<u>$H_3$</u>)$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 202.7 (CH), 136.8 (C), 135.6 (CH), 134.8 (CH), 134.1 (C), 133.2 (C), 129.6 (CH), 129.5 (CH), 127.7 (CH), 127.6 (CH), 125.1 (CH), 124.3 (CH), 61.2 ($CH_2$), 42.2 ($CH_2$), 39.3 ($CH_2$), 31.8 ($CH_2$), 26.9 ($CH_3$), 26.6 ($CH_3$), 26.2 ($CH_2$), 19.2 (C), 16.3 ($CH_3$), 16.2 ($CH_3$). The data was consistent with literature.[174]

**(4*E*,8*E*)-10-((*tert*-Butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dien-1-ol (281)**




To a solution of (4*E*,8*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dienal (7.44 g, 17 mmol) in THF (100 mL) at 0 °C was added sodium borohydride (713 mg, 18.8 mmol) and the reaction mixture was stirred for 2 h while warming to rt. The reaction mixture was diluted with water (100 mL) then extracted with ethyl acetate (2 × 75 mL). The organics were combined, washed with sat. sodium hydrogen carbonate (2 × 100 mL), brine (100 mL) then dried over magnesium sulfate. The volatiles were removed under vacuum and the residue purified by column chromatography on silica (15-20% ethyl acetate:petroleum ether) to give the *title compound* as a colourless oil (3.46 g, 47%); (Found: $M+C_3H_5N_2^+$ 505.3242. $C_{31}H_{45}N_2O_2Si$ requires 505.4245); $\nu_{max}$ (ATR)/$cm^{-1}$ 3307 (br), 3070, 3047, 2929, 2855, 1471; $\delta_H$ (400 MHz; $CDCl_3$) 7.78-7.68 (4H, m, ArH), 7.52-7.36 (6H, m, ArH), 5.43 (1H, tq, *J* 6.3, 1.3, C<u>H</u>=), 5.20 (1H, tq, *J* 7, 1.3, C<u>H</u>=), 4.27 (2H, dq, *J* 6.3, 0.9, OC<u>H</u>$_2$CH=), 3.65 (2H, t, *J* 6.5, C<u>H</u>$_2$OH), 2.20-1.98 (6H, m, 3 × $CH_2$), 1.79-1.68 (2H, m, $CH_2$), 1.66 (3H, d, *J* 1.3, $CH_3$), 1.48 (3H, d, *J* 1.3, $CH_3$), 1.09 (9H, s, C(C<u>H</u>$_3$)$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 136.9 (C), 135.6 (CH), 134.8 (C), 134.1 (C), 129.5 (CH), 127.6 (CH), 124.5 (CH), 124.2 (CH), 62.7 ($CH_2$), 61.2 ($CH_2$), 39.4 ($CH_2$), 35.9 ($CH_2$), 30.7 ($CH_2$), 26.9 ($CH_3$), 26.2 ($CH_2$), 19.2 (C), 16.3 ($CH_3$), 15.9 ($CH_3$).

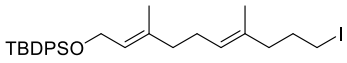
**(((2*E*,6*E*)-10-Bromo-3,7-dimethyldeca-2,6-dien-1-yl)oxy)(tert-butyl)diphenylsilane (283)**




To a solution of **(**4*E*,8*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dien-1-ol (150 mg, 0.34 mmol) and triethylamine (0.1 mL, 0.68 mmol) in $CH_2Cl_2$ (6 mL) was added methanesulfonyl chloride (0.03 mL, 0.38 mmol). The reaction mixture was stirred at rt for 4 h then washed with hydrochloric acid (1 M; 3 × 10 mL), brine (10 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give a colorless oil (100 mg).

The resulting oil was taken up in dry acetone (5 mL) and lithium bromide (25 mg, 0.28 mmol) was added. The reaction mixture was heated to 45 °C for 3 h, diluted with ether (20 mL) then washed with water (20 mL), sodium thiosulfate (1M; 10 mL), brine (10 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a colorless oil (80 mg, 47%); (Found: $M+C_3H_5N_2^+$ 567.2374. $C_{31}H_{44}{}^{79}BrN_2OSi$ requires 567.2406); $\nu_{max}$ (ATR)/$cm^{-1}$ 2929, 2855, 1471, 1461; $\delta_H$ (400 MHz; $CDCl_3$) 7.88-7.63 (4H, m, ArH), 7.51-7.36 (6H, m, ArH), 5.39 (1H, tq, *J* 6.3, 1.3, C<u>H</u>=), 5.18 (1H, tq, *J* 6.9, 1.2, C<u>H</u>=), 4.24 (2H, dd, *J* 6.3, 0.9, $OCH_2C$=), 3.36 (2H, t, *J* 6.7, $CH_2Br$), 2.15-1.90 (8H, m, 4 × $CH_2$), 1.61 (3H, d, *J* 1.3, $CH_3$), 1.45 (3H, d, *J* 1.2, $CH_3$), 1.06 (9H, s, $C(C\underline{H}_3)_3$); $\delta_C$ (100 MHz; $CDCl_3$) 136.8 (C), 135.6 (CH), 134.1 (C), 133.2 (C), 129.5 (CH), 127.6 (CH), 125.5 (CH), 124.2 (CH), 61.2 ($CH_2$), 39.4 ($CH_2$), 37.8 ($CH_2$), 33.5 ($CH_2$), 30.9 ($CH_2$), 26.9 ($CH_3$), 26.3 ($CH_2$), 19.2 (C), 16.3 ($CH_3$), 15.9 ($CH_3$).

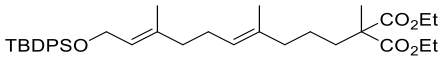
***tert*-Butyl(((2*E*,6*E*)-10-iodo-3,7-dimethyldeca-2,6-dien-1-yl)oxy)diphenylsilane (284)**




To a solution of **(**4*E*,8*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dien-1-ol (1.31 g, 3 mmol) and triethyl amine (0.85 mL, 6 mmol) in $CH_2Cl_2$ (30 mL) was added methanesulfonyl chloride (0.25 mL, 3.3 mmol). The reaction mixture was stirred at rt for 4 h then washed with hydrochloric acid (1 M; 3 × 50 mL), brine (30 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give a colorless oil (1.36 g).

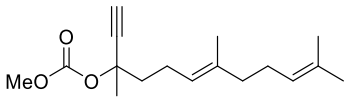
The resulting oil was taken up in dry acetone (26 mL) then sodium iodide (1.18 g, 7.9 mmol) was added and the reaction mixture was heated to 50 °C for 5 h then the volatiles removed under vacuum. The residue was taken up in ether (50 mL) then washed with water (50 mL), sodium thiosulfate (1M; 2 × 50 mL) and brine then dried over magnesium sulfate. The volatiles were removed under vacuum and the residue purified by column chromatography on silica (10% ethyl acetate:petroleum ether) to give the *title compound* as a colourless oil (1.09 g, 66%); (Found: $M+C_3H_5N_2^+$ 615.2259. $C_{31}H_{44}IN_2OSi$ requires 615.2262); $\nu_{max}$ (ATR)/$cm^{-1}$ 2956, 2928, 2855, 1471, 1460; $\delta_H$ (400 MHz; $CDCl_3$) 7.78 – 7.67 (4H, m, ArH), 7.49 – 7.36 (6H, m, ArH), 5.42 (1H, tq, *J* 6.3, 1.3, CH=), 5.21 (1H, tq, *J* 6.9, 1.3, CH=), 4.26 (2H, dq, *J* 6.2, 0.9, OC$\underline{H_2}$CH=), 3.16 (2H, t, *J* 7.0, C$\underline{H_2}$I), 2.17 – 2.00 (6H, m, 3 × $CH_2$), 1.98 – 1.88 (2H, m, $CH_2$), 1.62 (3H, dd, *J* 1.5, 0.8, $CH_3$), 1.48 (3H, q, *J* 0.8, $CH_3$), 1.08 (9H, s, C(C$\underline{H_3}$)$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 136.9 (C), 135.6 (CH), 134.1 (C), 133.0 (C), 129.5 (CH), 127.6 (CH), 125.6 (CH), 124.2 (CH), 61.2 ($CH_2$), 40.0 ($CH_2$), 39.4 ($CH_2$), 31.6 ($CH_2$), 26.9 ($CH_3$), 26.3 ($CH_2$), 19.2 (C), 16.3 ($CH_3$), 15.9 ($CH_3$), 6.7 ($CH_2$).

**Diethyl 2-((4*E*,8*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dien-1-yl)-2-methylmalonate (287)**



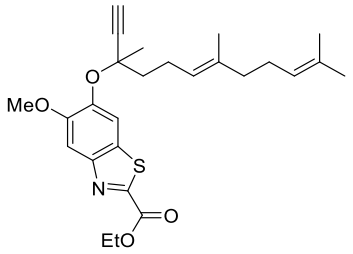

Diethyl methylmalonate (137 mg, 0.78 mmol) and sodium hydride (60%; 31 mg, 0.78 mmol) in DMF (2.5 mL) were stirred at 0 °C for 20 min. *tert*-Butyl(((2*E*,6*E*)-10-iodo-3,7-dimethyldeca-2,6-dien-1-yl)oxy)diphenylsilane (430 mg, 0.78 mmol) in DMF (2 mL) was added and stirred for 30 min at 0 °C. The reaction mixture was heated to 100 °C for 1.5 h then cooled and diluted with water (50 mL). The suspension was extracted with ether (2 × 30 mL). The organics were then combined, washed with lithium chloride solution (5%; 2 × 50 mL), brine (50 mL) and dried over magnesium sulfate. The volatiles were removed under vacuum to give the *title compound* as a colourless oil (360 mg, 78%); (Found: M+ $C_3H_5N_2$ 661.4047. $C_{39}H_{57}N_2O_5Si$ requires 661.4037); $\nu_{max}$ (ATR)/$cm^{-1}$ 2930, 2856, 1730, 1461; $\delta_H$ (400 MHz; $CDCl_3$) 7.79 – 7.65 (4H, m, ArH), 7.50 – 7.35 (6H, m, ArH), 5.41 (1H, tq, *J* 6.3, 1.1, CH=), 5.15 (1H, tq, *J* 7.9, 1.8, CH=), 4.25 (1H, d, *J* 6.7, $OCH_2CH$=), 4.20 (2H, q, *J* 7.1, 2× $OC\underline{H_2}CH_3$), 2.12-2.06 (2H, m, $CH_2$), 2.05-1.97 (4H, m, $CH_2$), 1.89 – 1.79 (2H, m, $CH_2$), 1.60 (3H, d, *J* 1.4, $CH_3$), 1.47 (3H, d, *J* 1.3, $CH_3$), 1.43 (3H, s, $CH_3$), 1.42 – 1.29 (2H, m, $CH_2$), 1.27 (6H, t, *J* 7.1, $OCH_2C\underline{H_3}$), 1.08 (9H, s, $C(C\underline{H_3})_3$); $\delta_C$ (100 MHz; $CDCl_3$) 172.5 (C), 137.1 (C), 135.6 (CH), 134.5 (C), 134.1 (C), 129.5 (CH), 127.6 (CH), 124.6 (CH), 124.0 (CH), 61.2 ($CH_2$), 61.1 ($CH_2$), 53.6 (C), 39.7 ($CH_2$), 39.5 ($CH_2$), 35.1 ($CH_2$), 26.9 ($CH_3$), 26.4 ($CH_2$), 22.5 ($CH_2$), 19.9 ($CH_3$), 19.2 (C), 19.4 ($CH_3$), 19.8 ($CH_3$), 14.1 ($CH_3$).

**(*E*)-3,7,11-Trimethyldodeca-6,10-dien-1-yn-3-ol (293)**



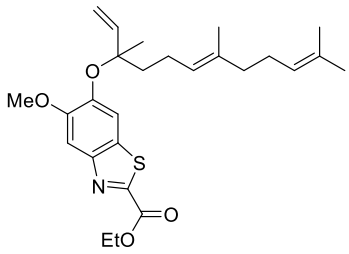
At 0 °C ethynylmagnesium bromide (0.5 M; 13.2 mL, 6.6 mmol) was added dropwise to geranyl acetone (582 mg, 3 mmol) in THF (30 mL) then stirred warming to rt for 17 h. Methyl chloroformate (0.64 mL, 6.9 mmol) was added and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with ethyl acetate (200 mL), then washed with hydrochloric acid (1M; 2 × 100 mL), brine (100 mL) then dried over $MgSO_4$. The volatiles were removed under vacuum and the residue purified by column chromatography (5% ethyl acetate:petroleum ether) to give the *title compound* as a colourless oil (0.585 g, 70%); (Found: $M+Na^+$ 301.1769. $C_{17}H_{26}NaO_3$ requires 301.1774); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2958, 2919, 2854, 2119 (w), 1753, 1439; $\delta_H$ (400 MHz; $CDCl_3$) 5.21-5.02 (2H, m, 2 × CH=), 3.77 (3H, s, $OCH_3$), 2.63 (1H, s, CH), 2.29-2.12 (2H, m, $CH_2$), 2.11-1.94 (5H, m, $CH_2$), 1.89-1.79 (1H, m, $CH_2$), 1.73 (3H, s, $CH_3$), 1.68 (3H, d, *J* 1.3, $CH_3$), 1.63 (3H, s, $CH_3$), 1.61 (3H, s, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 153.6 (C), 136.1 (C), 131.4 (C), 124.2 (CH), 122.8 (CH), 83.1 (CH), 76.9 (C), 73.9 CH), 54.4 ($CH_3$), 41.3 ($CH_2$), 39.6 ($CH_2$), 26.7 ($CH_2$), 26.3 ($CH_3$), 25.7 ($CH_3$, 22.8 ($CH_2$), 17.7 ($CH_3$), 16.0 ($CH_3$). The data was consistent with literature.[143]

**Ethyl (*E*)-5-methoxy-6-((3,7,11-trimethyldodeca-6,10-dien-1-yn-3-yl)oxy)benzo[*d*]thiazole-2-carboxylate (295)**



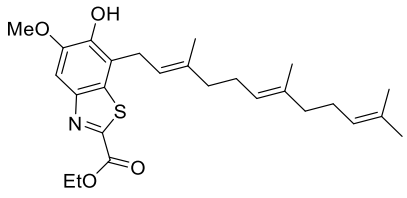

A solution of ethyl 6-hydroxy-5-methoxybenzo[d]thiazole-2-carboxylate (200 mg, 0.8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL, 0.88 mmol) in acetonitrile (8 mL) was cooled to 0 °C under an atmosphere of argon. Copper(II) chloride in acetonitrile (0.1M; 0.4 mL, 0.004 mmol) and (*E*)-3,7,11-trimethyldodeca-6,10-dien-1-yn-3-ol (245 mg, 0.88 mmol) were added sequentially then stirred for 2.5 h while warming to rt. The reaction mixture was diluted with ethyl acetate (30 mL), washed with hydrochloric acid (1M; 3 × 30 mL), brine (30 mL) then dried over $MgSO_4$. The volatiles were removed under vacuum and the residue purified by column chromatography (20% ethyl acetate/light petroleum) to give the *title compound* as a colorless oil (184 mg, 52%); (Found: $M+H^+$ 456.2211. $C_{26}H_{34}NO_4S$ requires 456.2203.); $\nu_{max}$ (ATR)/$cm^{-1}$ 2865, 2917, 2108, 1739, 1712, 1492, 1464, 1439; $\delta_H$ (400 MHz; $CDCl_3$) 7.96 (1H, s, ArH), 7.67 (1H, s, ArH), 5.19 (1H, t, *J* = 7.0 Hz, =C<u>H</u>), 5.10 (1H, t, *J* = 6.7 Hz, =C<u>H</u>), 4.53 (2H, q, *J* = 7.1, OC<u>H</u>$_2$$CH_3$), 3.91 (3H, s, $OCH_3$ ), 2.65 (1H, s, ≡CH), 2.44 – 2.26 (2H, m, $CH_2$), 2.16 – 1.89 (6H. m, 3 × $CH_2$), 1.69 (3H, s, $CH_3$), 1.66 (3H, s, $CH_3$), 1.65 (3H, s, $CH_3$), 1.61 (3H, s, $CH_3$), 1.48 (3H, t, *J* = 7.1, $OCH_2C$<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 160.7 (C), 157.3 (C), 153.5 (C), 149.6 (C), 146.6 (C), 135.9 (C), 131.4 (C), 128.9 (C), 124.4 (CH), 123.3 (CH), 113.1 (CH), 106.2 (CH), 84.6 (C), 77.8 (C), 75.8 (CH), 62.8 ($CH_2$), 55.9 ($CH_3$), 42.3 ($CH_2$), 39.7 ($CH_2$), 26,7 ($CH_2$), 26.6 ($CH_3$), 25.7 ($CH_3$), 23.1 ($CH_2$), 17.7 ($CH_3$), 16.0 ($CH_3$), 14.3 ($CH_3$).

**Ethyl (*E*)-5-methoxy-6-((3,7,11-trimethyldodeca-1,6,10-trien-3-yl)oxy)benzo[*d*]thiazole-2-carboxylate (296)**



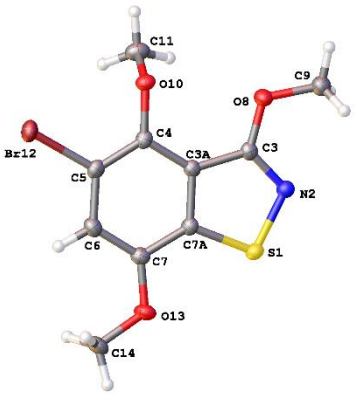

To a solution of ethyl (*E*)-5-methoxy-6-((3,7,11-trimethyldodeca-6,10-dien-1-yn-3-yl)oxy)benzo[*d*]thiazole-2-carboxylate (20 mg, 0.04 mmol) in ethyl acetate was added quinoline in ethyl acetate (0.01 M; 0.2 mL, 0.002 mmol) then Palladium on carbon (10%; 2 mg, 0.002 mmol). The reaction mixture was stirred under an atmosphere of hydrogen for 2 h at rt. The reaction mixture was filtered through celite then the volatiles removed under vacuum to give a 4:1 mixture of the *title compound* as a colorless oil (13 mg, 71%) and an unidentified over reduced product; (Found: $M+H^+$ 458.2358. $C_{26}H_{36}NO_4S$ requires 458.2360.); ); $\nu_{max}$ (ATR)/$cm^{-1}$ 2964, 2923, 2853, 1738, 1713, 1493, 1464 $\delta_H$ NMR (400 MHz; $CDCl_3$) 7.65 (1H, s, ArH), 7.54 (1H, s, ArH), 6.16 (1H, dd, *J* = 17.5, 11.1 Hz, C<u>H</u>=$CH_2$ ), 5.26 (1H, dd, *J* = 11.1, 0.9 Hz, CH=C<u>H</u>$_2$), 5.25 (1H, dd, *J* = 17.5, 0.9 Hz, CH=C<u>H</u>$_2$), 5.17 (1H, t, *J* = 7.1 Hz, =CH), 5.11 (1H, t, *J* = 6.9 Hz, =CH), 4.54 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$$CH_3$ ), 3.92 (3H, s, $OCH_3$), 2.25 – 1.74 (8H, m, 4 × $CH_2$), 1.70 (3H, s, $CH_3$), 1.67 – 1.57 (9H, m, 3 × $CH_3$), 1.50 (6H, m, $CH_3$ + $OCH_2C$<u>H</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.8 (C), 156.7 (C), 153.4 (C), 148.9 (C), 147.3 (C), 142.9 (CH), 135.5 (C), 131.4 (C), 129.0 (C), 124.3 (CH), 123.9 (CH), 115.1 ($CH_2$), 111.9 (CH), 106.1 (CH), 84.1 (C), 62.8 ($CH_2$), 55.9 ($CH_3$), 41.6 ($CH_2$), 39.7 ($CH_2$), 26.7 ($CH_2$), 25.7 ($CH_3$), 22.4 ($CH_2$), 22.0 ($CH_3$), 17.7 ($CH_3$), 15.9 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 6-hydroxy-5-methoxy-7-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzo[*d*]thiazole-2-carboxylate (297)**

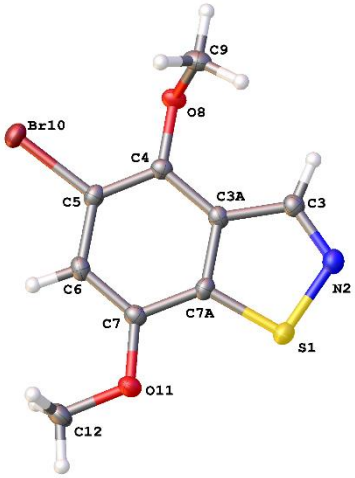



A solution ethyl (*E*)-5-methoxy-6-((3,7,11-trimethyldodeca-1,6,10-trien-3-yl)oxy)benzo[*d*]thiazole-2-carboxylate (10 mg, 0.02 mmol) in xylenes (1 mL) was heat at 140 °C for 3 h. The volatiles were removed under vacuum and the residue purified by column chromatography (20-30% ethyl acetate/light petroleum) to give the *title compound* as a colorless oil (3 mg, 30%); (Found: $M+H^+$ 458.2354. $C_{26}H_{36}NO_4S$ requires 458.2360.); ); $\nu_{max}$ (ATR)/$cm^{-1}$ 3378 (br), 2963, 2923, 2852, 1735, 1710, 1490, 1460; $\delta_H$ (400 MHz; $CDCl_3$) 7.55 (1H, s, ArH), 6.16 (1H, s, OH), 5.36 – 5.26 (1H, m, =CH), 5.24 – 5.04 (2H, m, 2 × =CH), 4.54 (3H, q, *J* = 7.1 Hz, $OC\underline{H_2}CH_3$), 4.01 (3H, s, $OCH_3$), 3.65 (2H, d, *J* = 7.2 Hz, $ArCH_2$), 2.34 – 1.89 (8H, m, 4 × $CH_2$), 1.90 – 1.56 (12H, 4 × $CH_3$), 1.49 (1H, t, *J* = 7.1 Hz, $OCH_2C\underline{H_3}$).

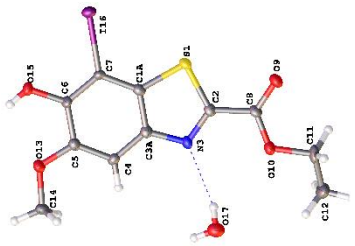
## 4.3 X-ray crystallography data




| | |
|---|---|
| Identification code | CEBCMA |
| Empirical formula | $C_{10}H_{10}NO_3SBr$ |
| Formula weight | 304.16 |
| Temperature/K | 120(2) |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 6.7308(4) |
| b/Å | 18.2244(10) |
| c/Å | 9.2090(5) |
| α/° | 90 |
| β/° | 100.882(5) |
| γ/° | 90 |
| Volume/Å$^3$ | 1109.31(11) |
| Z | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.821 |
| m/mm$^{-1}$ | 6.765 |
| F(000) | 608.0 |
| Crystal size/mm$^3$ | 0.6157 × 0.4808 × 0.4037 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection | 10.922 to 150.08° |
| Index ranges | $-8 \leq h \leq 8$, $-21 \leq k \leq 22$, $-10 \leq l \leq 11$ |
| Reflections collected | 8928 |
| Independent reflections | 2223 [$R_{int}$ = 0.0727, $R_{sigma}$ = 0.0344] |
| Data/restraints/parameters | 2223/0/148 |
| Goodness-of-fit on F$^2$ | 1.129 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0663, $wR_2$ = 0.1723 |
| Final R indexes [all data] | $R_1$ = 0.0669, $wR_2$ = 0.1730 |
| Largest diff. peak/hole / e Å$^{-3}$ | 2.27/-0.71 |




| | |
|---|---|
| Identification code | CEBCMB |
| Empirical formula | $C_9H_8BrNO_2S$ |
| Formula weight | 274.13 |
| Temperature/K | 120(2) |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 4.00452(9) |
| b/Å | 13.3385(3) |
| c/Å | 18.2472(4) |
| α/° | 90 |
| β/° | 91.905(2) |
| γ/° | 90 |
| Volume/Å$^3$ | 974.12(4) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.869 |
| μ/mm$^{-1}$ | 7.541 |
| F(000) | 544.0 |
| Crystal size/mm$^3$ | 0.1915 × 0.0463 × 0.0225 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 8.212 to 148.666 |
| Index ranges | $-4 \leq h \leq 4$, $-16 \leq k \leq 14$, $-21 \leq l \leq 21$ |
| Reflections collected | 3570 |
| Independent reflections | 1897 [$R_{int}$ = 0.0191, $R_{sigma}$ = 0.0248] |
| Data/restraints/parameters | 1897/0/129 |
| Goodness-of-fit on F$^2$ | 1.052 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0243, $wR_2$ = 0.0622 |
| Final R indexes [all data] | $R_1$ = 0.0265, $wR_2$ = 0.0632 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.43/-0.34 |



| | |
|---|---|
| Identification code | CEBCMD |
| Empirical formula | $C_{11}H_{12}INO_5S$ |
| Formula weight | 397.18 |
| Temperature/K | 120(2) |
| Crystal system | orthorhombic |
| Space group | $Pna2_1$ |
| a/Å | 19.8378(5) |
| b/Å | 15.2137(3) |
| c/Å | 4.56532(12) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/Å$^3$ | 1377.84(6) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.915 |
| μ/mm$^{-1}$ | 19.845 |
| F(000) | 776.0 |
| Crystal size/mm$^3$ | 0.331 × 0.0457 × 0.0185 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 7.322 to 148.192 |
| Index ranges | $-22 \leq h \leq 24$, $-18 \leq k \leq 9$, $-5 \leq l \leq 5$ |
| Reflections collected | 4853 |
| Independent reflections | 2493 [$R_{int}$ = 0.0414, $R_{sigma}$ = 0.0473] |
| Data/restraints/parameters | 2493/2/183 |
| Goodness-of-fit on F$^2$ | 1.036 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0361, $wR_2$ = 0.0919 |
| Final R indexes [all data] | $R_1$ = 0.0374, $wR_2$ = 0.0935 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.94/-0.86 |
| Flack parameter | -0.013(8) |

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