An isoxazole approach to the coleophomones

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An Isoxazole Approach to the Coleophomones

by

Wing Hoi (Angella) YUEN

A Doctoral Thesis Submitted in Partial Fulfillment of the Requirements

For Award of Doctor of Philosophy of Loughborough University

(May 2007)

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Abstract

Coleophomones, metabolites reported first in a Japanese patent in 1998 and then by Merck in 2000 from a *Coleophoma* fungus, have antifungal and antibacterial properties and inhibit bacterial cell-wall transglycosylase and human heart chymase. Their unique molecular architecture contains a cyclic tricarbonyl moiety embedded in an 11-membered macrocycle. In our synthetic strategy the reactive β,β-tricarbonyl structure is masked as an isoxazole to allow elaboration elsewhere in the molecule. We have investigated two isoxazole based approaches to these targets: 1) via an isoxazole ring with ketone or ester substituents; and 2) via a reduced benzisoxazole.

The formation of isoxazole building blocks for the two approaches was by nitrile oxide 1,3-dipolar cycloaddition. Several substituted phenylisoxazole diesters were made from approach 1 successfully, however, the attempt for 6-membered ring closure failed. For approach 2, a number of benzisoxazoles with different substituted phenyl groups were made in moderate to good yield. The side chain additions towards these building blocks have also been elaborated, and the formation of 11-membered macrocycles have been attempted by ring closing metathesis (RCM) with Grubbs II catalyst.

Precursors for total synthesis of coleophomone A, B, C and D have been made. Irradiation reactions have been used to prepare oxime precursors for coleophomone D and use of co-solvent (HMAP and DMPU) was applied in the synthesis to alkylate the benzisoxazole ring.
Acknowledgement

I would like give my gratitude to my supervisors Professor Ray Jones and Doctor George Weaver for their consideration and help throughout PhD studies in both practical and theoretical work. Without their fruitful knowledge and experience, my studies can never be finished this smoothly and successfully. Thanks to all the academic staffs for their valuable advice; and to all the technical staffs and people in laboratories (F001, F009, F201 and F402) for their help and support. Especially Doctor Mark Edgar for the NMR spectrometers analysis; Doctor Mark R J Elsegood for the X-Ray crystallography and Mr. John C Kershaw for the mass spectrum analysis. I would also like to thanks my family for their warmest concern and non-stop supports throughout the years. Thank you!
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Abbreviation

Acetonitrile MeCN
Acetyl Ac
Benzyl bromide BnBr
N-Bromosuccinimide NBS
t-Butyldiphenylchlorosilane TBDPSCl
n-Butyllithium nBuLi
t-Butyllithium tBuLi
N-Chlorosuccinimide NCS
Chlorotrimethylsilane (trimethylsilyl chloride) TMSCl
Density functional theory DFT
1,5-Diazabicyclo[4.3.0]non-5-ene DBU
2,3-Dichloro-5,6-dicyanobenzoquinone DDQ
Dichloromethane DCM
1-[3-((Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride EDCI
4-(Dimethylamino)pyridine DMAP
N,N-Dimethylformamide DMF
N,N'-Dimethyl propylene urea DMPU
Dimethylsulfoxide DMSO
Ethanol EtOH
Ethyl acetate EtOAc
Frontier molecular orbitals FMO
Hexamethylphosphoramide HMPA
Lithium diisopropylamide LDA
Methanol MeOH
Pyridinium chlorochromate PCC
Ring closing metathesis RCM
Ring opening metathesis polymerization ROMP
Tetrahydrofuran THF
Toluenesulphonic acid TsOH
Triethylamine Et₃N
1.0 Introduction

The aim of the work described in this thesis is to approach the synthesis of the coleophomones and analogues by an isoxazole route.

The coleophomones have antifungal and antibiotic activity, as they inhibit both the bacterial cell wall transglycosylase and human heart chymase. Coleophomones and analogues are molecules having a unique cyclic tricarbonyl structure embedded in an 11-membered macrocycle.

Coleophomones A and B exist in equilibrium via an aldol interconversion, B and C are geometric isomers. Coleophomone D belongs to the same family but without the 11-membered macrocycle.

We have proposed two routes to these heterocyclic tricarbonyl natural products using isoxazoles. Route 1 is through an isoxazole ring with ketone or ester substituents, and route 2 is through a reduced benzisoxazole, but before outlining these proposals, we should present some more background on the natural products.

1.1 What are Coleophomones?

Coleophomones were first reported in a Japanese patent in 1998 on behalf of the Shionogi Pharmaceutical Co. The three coleophomones A (1), B (2) and C (3) identified at this stage were isolated from a fungal broth of *Stachybotrys cylindrospora*. The fourth member of the family, coleophomone D (4) was disclosed one year later in another patent by the same company. It was isolated from *Stachybotrys parvispora Hughes* fungal broth. In 2000, a Merck research group published a paper describing coleophomone A and B that they isolated from an
acetone extraction of a liquid fermentation of *Coleophoma* sp. (MF6338),\(^3\) which is a fungus isolated from an unidentified plant litter collected in the Sierra Villuercas (Spain).

Coleophomones were proven to inhibit human heart chymase and transglycosylase in the formation of bacterial cell walls. Human heart chymase is responsible for converting angiotensin I to angiotensin II.\(^4\) Angiotensin II has been suggested to have various important local effects on the heart tissue, which include myocyte hypertrophy and interstitial fibrosis that lead to pathological structural remodeling and thereby predispose to ventricular dysfunction and symptomatic heart failure.\(^5\) Transglycosylase catalyses the polymerization of disaccharide-pentapeptide units from lipid II to form uncrosslinked peptidoglycan.\(^6\) Peptidoglycan, also called murein, is the primarily substance for formation of the bacterial cell wall, which is essential to the survival of many bacteria. Coleophomones A and B show weak antibacterial
activity against aerobic bacteria. With these properties, coleophomones can be envisaged as antifungal and antibacterial substances, or for use to treat diseases such as hypertension and congestive heart failure.

1.2 Structure of the Coleophomones
Coleophomones are structurally novel compounds containing a unique molecular architecture with a cyclic tricarbonyl moiety. They comprise a compact carbon framework and multiple inter-connected rings. Coleophomones A, B and C have an 11-membered macrocycle, a bridging carbocycle complete with a quaternary centre, a fused aromatic ring and an ethereal oxygen (Figure 1).

![Figure 1](image)

Coleophomones A and B exist in equilibrium and have a molecular formula C_{25}H_{26}O_{5}; they are isomeric to each other and can be interconverted by an aldol reaction. Coleophomones B and C are stereoisomers, with an E- and Z-macrocycle respectively. Coleophomone D does not display the 11-membered macrocycle. It exists as a complex mixture of isomers (Scheme 1). Retro-aldol ring-opening, bond rotations and tautomerisation of the enolised 1,3-dicarbonyl system, and aldol closure gives rise to this mixture of coleophomones D_{1}-D_{4}.
1.3 Outline of the Retrosynthesis

The aim of this project is to attempt a synthesis of the coleophomone natural products and analogues through an isoxazole building block. We planned to synthesise the building block from two approaches (Scheme 2). The first approach (Approach 1) involves the di-alkylation of methyl 5-methoxycarbonylmethyl-3-arylisoxazole-4-carboxylate (5) followed by ring closure of a six-membered ring to achieve the building block, while the second approach (Approach 2) involves forming a ring-closed structure, 6-methyl-3-aryl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) before alkylation.

In this project, a key principle of our strategy is to mask the highly polar, potentially reactive $\beta,\beta'$-tricarbonyl moiety as an isoxazole until it is necessary to reveal it. This should allow elaboration reactions to be completed on the non-polar core of the
Introduction

structure.

Coleophomone A, B, C

Wittig or RCM

Coleophomone D

Approach 1

Approach 2

(11) isoxazole building block

Scheme 2
The building block isoxazoles for the first and second approaches were to be prepared by cycloaddition of a nitrile oxide, prepared from an aromatic aldehyde oxime (7), with an enamine (8) derived from an acetonedicarboxylate (9) (Approach 1) or a cyclohexane-1,3-dione (10) (Approach 2), respectively (Scheme 2). The aromatic aldehyde oxime (7) could have different substituent groups on the aromatic ring, depending on which coleophomones we are targetting.

Approach 1 proposes cycloaddition of a nitrile oxide, prepared from an aldehyde oxime (7) chlorinated by N-chlorosuccinimide, with an enamine (8) derived from acetonedicarboxylate (9) and pyrrolidine. Alkylations will be carried out at the C5 substituent of the isoxazole cycloaddition product (11) to give the two carbon chains needed in the natural product. After alkylation and manipulation, the esters should be closed by an aldol closure to form a 6-membered ring, thereby completing the isoxazole building block (12). From the building block, we propose to furnish the 11-membered macrocycle by joining the carbon chain from the cyclohexanone ring with the carbon chain on the aromatic ring, by Wittig reaction or ring closing metathesis; the latter is illustrated. Finally, the isoxazole N-O bond will be cleaved and the product hydrolysed to reform the highly reactive enolised dicarbonyl function.

In a similar fashion, isoxazole ring formation in Approach 2 is through cycloaddition of a nitrile oxide with 5-methylcyclohexane-1,3-dione (10) to yield the isoxazole (6) with an already-closed 6-membered ring. Carbon chains will be added to the C5 carbon, followed by double bond generation at the α,β position. Alternatively, we can undertake these transformations in the reverse order by forming the double bond first to yield an aromatised structure (11), and then perform the alkylations. These should yield the same building block (12). The 11-membered macrocycle will be closed by
Wittig reaction or ring closing metathesis as mentioned above, and isoxazole cleavage-hydrolysis will afford the potentially reactive tricarbonyl group. Note that either C5 or C7 alkylated benzisoxazoles (12) are useful, as these positions become equivalent after N-O cleavage-hydrolysis.

Synthesis of coleophomone D does not require ring closure of an 11-membered macrocycle. The synthesis steps are the same as for coleophomones A, B and C, with the ring closing step omitted. We will try to compare the efficiency, yield and cost between Approaches 1 and 2, in order to figure out the best synthetic route towards these valuable natural products and its analogues.

2.0 Use of Isoxazole as a Masked Dicarbonyl

Isoxazole is often used as a masking ring for the polar di- or tricarbonyl moiety during a synthesis, due to its strong and broad tolerance to many reactions.

In our project, isoxazole will be used to mask the polar tricarbonyl structure of the coleophomones. The use of isoxazole as a building block allows elaborations around the non-polar core of the molecule, with the highly reactive tricarbonyl moiety masked as a five-membered isoxazole ring (Figure 2).
The reactive groups of the structure are covered up until required. The masking principle can be used because the N-O bond can be easily cleaved to regenerate the functional groups. The use of isoxazoles in this way is well preceded.

2.1 Isoxazole

Isoxazole was first proposed by Claisen in 1888 and the name monoazole was suggested. It was later named isoxazole by Hantsch. There were two isoxazole compounds isolated as early as 1852, although the structures were not arranged until 1946. Many isoxazole derivatives have been shown to possess a range of pharmacological activities, which are of considerable interest to medicinal chemists.

The isoxazole ring is numbered as below (Figure 3). The three ring positions available for substitution were indicated as α (alpha), β (beta) and γ (gamma).

![Figure 3](image)

Method of Preparation

Isoxazole ring synthesis can be classified according to their ring closure pattern into the following five main types (Figure 4): two (3+2), one (3+1+1) and two (4+1) processes.
The (3+2) methods can be further divided into two types, the [CCC + NO] and [CNO + CC] processes. These two processes involve oximation of 1,3-dicarbonyl compounds and cycloaddition of nitrile oxides to unsaturated compounds. An example of the frequently used [CCC + NO] process is condensation between hydroxylamine and a three carbon atom component, such as a 1,3-diketone or α,β-unsaturated ketone (Scheme 3). The method relevant to this thesis is the (3+2) [CNO + CC] process.

[CNO + CC] Processes

The most common method for constructing an isoxazole ring by a [CNO + CC] process is a 1,3-dipolar cycloaddition involving a 1,3-dipole and dipolarophile, such as a nitrile oxide with an alkene or an alkyne.

While a nitrile oxide is used as the 1,3-dipole in the ring formation, the dipolarophile can be any kind of alkene or alkyne. As the nitrile oxide is highly reactive, it is
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usually generated *in situ* in the present of excess dipolarophile to allow immediate cycloaddition. The 1,3-dipolar cycloaddition process to form an isoxazole is regioselective and stereoselective and is controlled by the energy difference between the HOMO and LUMO of dipole and dipolarophile. This will be discussed in a later section, where we will also look at different methods of generating nitrile oxides.

Nitrile oxides can react with an alkene to give an isoxazoline by method a),\(^1\), and then to yield the isoxazole ring by further elimination or dehydrogenation. On the other hand, the isoxazole ring can be formed directly by reacting a nitrile oxide with an alkyne (Scheme 4).

\[ \text{nitrile oxide} + \text{alkene} \rightarrow \text{isoxazoline} \]

\[ \text{nitrile oxide} + \text{alkyne} \rightarrow \text{isoxazole} \]

\[ \text{Scheme 4} \]

However, it has been shown that alkynes are much less reactive dipolarophiles\(^2\) than alkenes, therefore, isoxazole ring formation is preferable by reacting with an alkene rather than an alkyne. For example, styrene is ten times more reactive than phenylacetylene and methyl acrylate is six times more reactive than methylpropionate.\(^2\) In the case of conjugated enynes, competition between the two
dipolarophilic sites occurs and the products of double bond reaction always dominate over those from the triple bond. Furthermore, a mono-substituted bond is always more reactive than a disubstituted unsaturated bond. The reaction between benzonitrile oxide (13) and vinylacetylene (14) is a very good example (Scheme 5),\textsuperscript{22,23} where the isoxazoline is the first formed product.

\begin{center}
\begin{align*}
(13) \quad & \text{Ph}^{-} \text{C}^\equiv \text{N}^{-} \text{O}^{-} \\
+ \quad & \text{H}_2\text{C} \equiv \text{C} \equiv \text{CH} \\
\rightarrow \quad & \text{Ph}^{-} \text{C}^\equiv \text{N}^{-} \text{O}^{-} \\
\text{(14)} \quad & \text{Ph}^{-} \text{C} \equiv \text{N}^{-} \text{O}^{-} \\
\end{align*}
\end{center}

Scheme 5

\section*{2.2 Isoxazole Reactions}

The isoxazole ring shows some aromatic character with the oxygen atom acting as an electron-donating group and nitrogen atom as an electron-withdrawing group. C4 is the preferred position for electrophilic substitution and its reactivity is affected by the substituents at C3 and C5. Electron-donating groups activate the electrophilic substitution, while electron-withdrawing groups deactivate it. The C3 proton is the most acidic proton in the ring. The N-O bond is the weakest bond among the five bonds and can be cleaved by some controlled reaction conditions (Figure 5). Many other chemical properties have been reported since the 1960s.\textsuperscript{24}
Electrophilic Substitutions

Only the C4 position of isoxazole can undergo electrophilic substitutions. It can be attacked by electrophiles to perform several well-known substitutions, such as nitration, sulfonation, halogenation and chloroalkylation.

4-Nitroisoxazole can be generated in low yield by heating isoxazole with nitric acid and sulfuric acid. Sulfonation of isoxazole occurs less readily than nitration, the 4-sulfonated isoxazole being obtained only in a very low yield under drastic conditions with chlorosulfonic acid. Nitration and sulfonation of 3,5-dialkylisoxazoles works better than for non-substituted isoxazoles. Halogenations and chloroalkylations always give C4 substitution (Scheme 6).
Nucleophilic Reactions

Nucleophilic substitutions usually occur at the C3 and C5 positions. They may also take place at C4 with a strong nucleophile when C3 and C5 leaving groups are not available. The 3-halogen group can be displaced by methoxy group as a nucleophile, and then hydrolysed under acidic conditions (Scheme 7). Nucleophilic substitution reactions can take place on side chains as well.

If the attacking nucleophile is a base, it will cause the isoxazole ring of C3 unsubstituted isoxazoles to open (Scheme 8).
Side Chain Reactions

Normally, no electrophilic reactions take place at the C3 and C5 carbons, but the side chains at C3 and C5 can be elaborated under basic conditions. Protons at C3 and C5 substituents can be removed by strong base, such as LDA and BuLi. Quenching by an electrophile allows addition onto those side chains. C5 substituents are comparatively more reactive than those at the C3 position.

Taking the reactivity of 3,5-dimethylisoxazole (15) as an example\textsuperscript{31,32} 3-methyl and 5-methyl can be deprotonated\textsuperscript{26} to yield a carbanion and the results have shown that the 5-carbanion is more reactive than the 3-carbanion for electrophilic attacks (Figure 6).

The C4 position sometimes competes with C3 and C5, depending on the pattern of the isoxazole substitutions (Scheme 9). Work conducted by Ross \textit{et al.}\textsuperscript{33} and Suschitzky \textit{et al.}\textsuperscript{34} shows some examples of these reactions.
2.3 Isoxazole Ring Opening

The isoxazole ring acts as a mask for highly reactive functional groups, allowing elaboration at the rest of the molecule in an organic synthesis. After reactions on the non-polar core have been performed, the isoxazole can be cleaved to reveal the functional groups. The comparatively weak N-O bond of the isoxazole can be cleaved and hydrolysed to reveal the 1,3-dicarbonyl functionality.\textsuperscript{35}

The unmasking can be achieved by hydrogenolysis of the isoxazole to cleave the N-O bond. The enamino ketone or imine-enol yielded can be further converted into the dicarbonyl moiety by hydrolysis or diazotization (Figure 7).\textsuperscript{36} Hydrogenolysis has been carried out over different catalysts, such as Raney nickel,\textsuperscript{37,38} palladium charcoal\textsuperscript{39} and platinum black etc.\textsuperscript{40}
Isoxazole ring opening by hydrogenation usually works very well, however, one of the disadvantages is the reduction of unsaturated bonds in the side chains. To avoid this drawback, other reduction reagents such as molybdenum hexacarbonyl, samarium diiodide, TiCl₃ and sodium in moist ether or ethanol can be a better choice.

In the presence of moist Mo(CO)₆, an isoxazole is transformed into a β-enamino ketone followed by water hydrolysis to yield the 1,3-amino ketone. The nitrogen atom of the isoxazole coordinates with the Mo metal to form a complex. Although this complex is stable at room temperature, the N-O bond breaks down under reflux (Scheme 10). However, the full mechanism for this reaction is still not confirmed.

Scheme 10

Cleavage with SmI₂ involves electron transfer; and a radical anion is formed as an
intermediate (Scheme 11). An excess of reagent, about 2 equivalents, is needed for the ring opening using SmI₂.

\[
\begin{align*}
\text{N-O} & \rightarrow \text{radical anion} \\
\text{radical anion} & \rightarrow \text{NH₂O} \\
\end{align*}
\]

Scheme 11

Other less common ring cleavage methods included deprotonation by base at C3 position, which has been mentioned before and ozonolysis. Instead of breaking the N-O bond, ozonolysis open the isoxazole ring at the double bond between C4 and C5, so is not relevant to the unmasking strategies.

3.0 1,3-Dipolar Cycloaddition\textsuperscript{17, 57, 58, 59}

Cycloaddition reactions are commonly used in organic synthesis to assemble four, five and six membered heterocycles. The three most important types are a) Diels-Alder reactions, b) [2+2] cycloadditions and c) 1,3-dipolar cycloadditions (Figure 8).
The 1,3-Dipolar cycloaddition is one of the most efficient methods of making five-membered rings. It is related to the Diels-Alder reaction, a \([4\pi + 2\pi]\) process, with the \(4\pi\)-electron component as a 1,3-dipole rather than a diene.\(^{48}\) To create a five-membered ring by cycloaddition, a three-atom, four-electron ‘diene’ is required, which is called a 1,3-dipole (a\(-\)b\(-\)c),\(^{49}\) and a multiply bonded two-atom section, the dipolarophile (d\(-\)e) (Figure 8). The 1,3-dipole and the dipolarophile can be two molecules reacting in an intermolecular fashion or two parts of the same molecule reacting in an intramolecular process. 1,3-Dipolar cycloaddition can account for the stereo- and regio-selectivity of the products formed. It goes via a \(6\pi\)-electron aromatic transition to yield the five-membered heterocycle.
The isoxazoles in this project were made from nitrile oxide cycloaddition, which is a 1,3-dipolar cycloaddition reaction, using a dipole derived from an aldehyde and an enamine as dipolarophile.

3.1 The 1,3-Dipole

A 1,3-dipole is a three-atom fragment, (a-b-c) in which can be presented in two canonical forms, sextet and octet. The sextet has six electrons in the outer shell of atom a, while the octet has eight electrons. An atom with six electrons in the outermost shell would be unstable, therefore, the 1,3-dipole usually has more than one resonance form and the octet form is drawn as the preferred form.

There are two main types of 1,3-dipolar compounds. Type 1 has a 1,3-dipolar canonical form, which has a double bond between atom a and b on the sextet form and a triple bond on that atom in the octet resonance form, and a central sp-hybridised atom (Figure 9). This type of 1,3-dipole is linear and is also known as the propargyl-allenyl type.
Type 2 has a dipolar canonical form, which has a single bond between atom a and b in the 1,3-dipolar sextet form and a double bond between these atoms for the octet form (Figure 10). Molecules of this 1,3-dipole type have a central sp²-hybridised atom. They are bent and are called the allyl anion type.

The possible elements for atom a, b and c are suggested in the following table (Table 1).
Examples of some common 1,3-dipolar intermediates are shown in Figures 11 & 12 below.
The 1,3-dipoles used in our experiments contain C, N and O atoms. They are called nitrile oxides and belong to type 1 in the categories mentioned above. They have an electrophilic end and a nucleophilic end (Figure 13).

The table below lists common type 2 1,3-dipoles and their corresponding structures:

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<th>Structure</th>
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<tr>
<td>Azomethine imines</td>
<td>( \overset{-}{NR}^+ ) ( \overset{+}{NR}^- ) ( \overset{-}{N}^+ ) ( \overset{+}{N}^- ) ( \overset{-}{O}^+ ) ( \overset{+}{O}^- )</td>
</tr>
<tr>
<td>Azomethine ylides</td>
<td>( \overset{-}{CR_2} ) ( \overset{+}{CR_2} ) ( \overset{-}{NR}^+ ) ( \overset{+}{NR}^- )</td>
</tr>
<tr>
<td>Nitrones</td>
<td>( \overset{-}{CR_2} ) ( \overset{+}{CR_2} ) ( \overset{-}{O}^+ ) ( \overset{+}{O}^- )</td>
</tr>
<tr>
<td>Carbonyl ylides</td>
<td>( \overset{-}{R'_2} \overset{+}{C=O} \overset{-}{CR_2} ) ( \overset{-}{R'_2} \overset{+}{C=O} \overset{-}{CR_2} )</td>
</tr>
<tr>
<td>Thiocarbonyl ylides</td>
<td>( \overset{-}{R'_2} \overset{+}{C=S} \overset{-}{CR_2} ) ( \overset{-}{R'_2} \overset{+}{C=S} \overset{-}{CR_2} )</td>
</tr>
<tr>
<td>Ozone</td>
<td>( \overset{-}{O} \overset{+}{O} ) ( \overset{-}{O} \overset{+}{O} )</td>
</tr>
</tbody>
</table>

**Figure 12**

**Figure 13**
3.2 The Dipolarophile

A dipolarophile is a two-atom $2\pi$-electron unsaturated compound (d-e), which is not limited to an alkene or an alkyne. Many other multiply bonded structures containing elements other than carbon can be dipolarophiles (Figure 14).

$$R-C\equiv\equiv X-R'$$

sp or sp$^2$-hybridised

Figure 14

Examples of some common dipolarophile units are shown in (Figure 15) below.

<table>
<thead>
<tr>
<th>Common dipolarophile functions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$C\equiv C$</td>
<td>Alkene</td>
</tr>
<tr>
<td>$C=\equiv C$</td>
<td>Alkyne</td>
</tr>
<tr>
<td>$C=\equiv N$</td>
<td>Diazo</td>
</tr>
<tr>
<td>$C=\equiv N$</td>
<td>Nitrile</td>
</tr>
<tr>
<td>$C=\equiv O$</td>
<td>Carbonyl</td>
</tr>
<tr>
<td>$C=\equiv S$</td>
<td>Thione</td>
</tr>
</tbody>
</table>

Figure 15
3.3 FMO Theory and Mechanism of 1,3-Dipolar Cycloaddition

A 1,3-dipolar cycloaddition involves the formation of two $\sigma$ bonds from one $\pi$ bond and one lone pair. During the cycloaddition the lone pair from atom $c$ forms a $\sigma$ bond with the dipolarophile, while the $\pi$ bond of the dipolarophile forms a $\sigma$ bond with the dipole atom $a$, moving the $\pi$ bond between $a$ and $b$ towards the positively charged central atom $b$ (Scheme 13).

The success of the reaction depends on the favourable interaction between a filled $\pi$-orbital of one reactant and an empty $\pi^*$-orbital of the other. This interaction must be sterically feasible and the orbitals must be of the correct phase for interaction. The smaller the energy gap, the stronger is the interaction and the higher the reactivity. The reactivity can be explained by the energy difference between the FMOs (Frontier Molecular Orbitals). The HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) of the 1,3-dipole interacting with the LUMO and HOMO of the dipolarophile, respectively (Figure 16), are the key FMO interactions considered.
The electrons involved in the new σ bond formation come from the HOMO because they are the least tightly held and thus most reactive. 53

1,3-Dipolar cycloadditions can be classified into three types, depending on the relative disposition of the FMOs of the 1,3-dipole and dipolarophile (Figure 17). HOMO-controlled reactions (Type 1), are those in which the interaction of the dipole HOMO with the dipolarophile LUMO is greatest. LUMO-controlled reactions (Type 2), are those in which the interaction of the dipole LUMO with the dipolarophile HOMO is greatest. And HOMO-LUMO-controlled reactions (Type 3), have both the FMO interactions as significant.

Electron-donating substituents in a dipole, which raise the dipole HOMO energy, or electron-withdrawing substituents in a dipolarophile that lower the dipolarophile LUMO energy, accelerate Type 1 reactions. In contrast, electron-withdrawing substituents in a dipole which lower the dipole LUMO energy, or electron-donating groups in a dipolarophile that raise the dipolarophile HOMO energy, accelerate Type 2 reactions. Type 3 reactions will be accelerated by an increase of either FMO interaction. 54
1,3-Dipolar cycloaddition reactions involve a $4\pi$-electron dipole and a $2\pi$-electron dipolarophile through a $6\pi$-electron transition state. However, it is as yet impossible to generate a direct mechanistic proof for this cycloaddition, therefore, this type of reaction has been considered as a "no mechanism" reaction. Several mechanisms have been suggested, and these include a concerted or stepwise process.

The concerted mechanism was proposed by Huisgen, which involves a cyclic five-atom transition state. The $4\pi$ electrons of the 1,3-dipole interact with the $\pi$ bond of the dipolarophile in the transition state. The mechanism is usually drawn as below, (Figure 18) for nitrones and nitrile oxides.
An alternative stepwise mechanism was suggested by Firestone,\textsuperscript{57,58} who proposed that the cycloaddition involves a biradical intermediate or a zwitterion (Figure 19).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure18.png}
\caption{Figure 18}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure19.png}
\caption{Figure 19}
\end{figure}
There are possible stereo- and regio-isomers formed from 1,3-dipolar cycloaddition (Figure 20). Selectivity usually favours one of the isomers over the others.

\[
\begin{align*}
\text{Stereoisomers} & \quad X=YZ & \quad \rightarrow & \quad X=YZ \\
R1 & \quad R3 & \quad R2 & \quad R4
\end{align*}
\]

\[
\begin{align*}
\text{Regioisomers} & \quad A=B & \quad \rightarrow & \quad A=B
\end{align*}
\]

The stereochemistry of the products depends on the geometry of approach of the two components of the 1,3-dipolar cycloaddition, with \textit{endo} and \textit{exo} transition states being possible. The configuration of the dipolarophile is usually retained, which is strong evidence in favour of a concerted one-step mechanism.

The stereochemical issue does not apply in the case of nitrile oxides reacting with enamines to form planar isoxazoles in our proposed synthesis. In this case, the focus is on the regiochemistry. Regioselectivity is a result of small energy differences between two regioisomeric transition states.

Consider the addition of diazomethane (16) to methyl methacrylate (17) as an example. The interaction between HOMO of dipole and LUMO of dipolarophile is dominant in this cycloaddition. The coefficients at C3 and C4 are larger than the other
end of the fragment for both 1,3-dipole and dipolarophile, respectively. Therefore, the larger coefficients interact with each other to yield the isomer A as a major product (Scheme 14).

Scheme 14

In organic synthesis, 1,3-dipolar cycloadditions are used to generate heterocyclic structures as part of the target product or (as in our proposals) as a masking ring for sensitive functional groups. Another well-known 1,3-dipolar cycloaddition is ozonolysis, in which ozone is the 1,3-dipole reacting with a dipolarophile alkene to result in cleavage of the alkene.

4.0 Nitrile Oxides

Nitrile oxides have been known for a long time, and their applications are still under investigation. Nitrile oxides are generally not stable towards moisture and therefore are prepared in situ. The two π bonds formed between the C and N atoms of the nitrile oxides restrict their configuration to linear (Figure 21).

Figure 21
4.1 Formation

There are four common methods to generate nitrile oxides: dehydrohalogenation of C-halogenated oximes, dehydration of nitroalkenes, thermolysis of furoxans and oxidation of aldoximes.59

Dehydrohalogenation of Hydroximoyl Chlorides

In 1894, Werner and Buss60 introduced the dehydrohalogenation method. This method involved two steps, starting from an aldoxime. Aldoxime (18) can be C-halogenated by different halogenating agents, such as N-chlorosuccinimide, N-bromosuccinimide, chlorine or t-butyl hypochlorite to give an α-halonitroso compound (19) that tautomerises to a hydroximoyl chloride. This compound can be isolated but it decomposes gradually in air. The halogenated oxime (19) obtained then undergoes dehydrohalogenation to yield nitrile oxide (20) in situ. A base like triethylamine or pyridine is usually added slowly as a dehydrohalogenating agent. An example is shown below (Scheme 15).

![Reaction Scheme 15](image)

The two steps mentioned above can be combined into one-pot by skipping the isolation of halogenated oxime.
Dehydration of Nitroalkanes

This is an effective one-step reaction for both aromatic and aliphatic nitrile oxide formation. Hoshino and Mukaiyama \(^6\) introduced phenyl isocyanate (21) and triethylamine as the dehydrating agent for nitroalkane dehydration in 1960. The mechanism is as below (Scheme 16).

\[
\begin{align*}
R-C-N^+O^- & \xrightarrow{\text{Et}_3N} R-C=N+O^- \\
& \xrightarrow{\text{Et}_3N} R-C=N^-O^- \\
& \xrightarrow{\text{Et}_3N} \text{R-}C\equiv N\equiv O
\end{align*}
\]

Scheme 16

Di-tert-butyl dicarbonate (Boc\(_2\)O) can be used instead of phenyl isocyanate, which leads to respective N- or O-tert-butoxycarbonyl (Boc) protected products. The byproducts resulting from this reaction are readily separable from the nitrile oxide cycloadducts.\(^6\)

Thermolysis of Furoxans

Nitrile oxides dimerise to yield furoxans (22) as a stable heterocyclic product.\(^5\) In reverse, nitrile oxides can be regenerated under thermal conditions (Scheme 17).\(^4\) Preferably, the nitrile oxide is generated in the presence of dipolarophiles to avoid re-dimerisation. One of the drawbacks from this method is the rearrangement of nitrile oxide at high temperature to give isocyanate (23).
Oxidation of Aldoximes

Oxidation of aldoximes to approach nitrile oxides is carried out using different oxidising agents in mild conditions. The commonly used reagents are manganese dioxide, lead tetraacetate, chlorobenzotriazole and diammonium hexanitratocerate.

Summary of Nitrile Oxide Formation

\[
\begin{align*}
&X = \text{Halogen} \\
&\text{Dehydrohalogenation} \\
&\text{Oxidation} \\
&\text{Dehydration} \\
&\text{Dimerisation} \\
&1,3-\text{Dipolar cycloaddition}
\end{align*}
\]
4.2 Regioselectivity of Nitrile Oxides

For an electron-rich and conjugated dipolarophile, the dipole LUMO is in control and leads to a C5 substituent from a mono-substituted dipolarophile. For an electron-deficient dipolarophile, a HOMO-LUMO control is dominant, the regioselectivity is decreased and a mixture of C4 and C5 substituted product is obtained from mono-substituted dipolarophiles (Figure 18).\(^57\)

![Figure 18](image)

However, comparing the effect from number of substituents, the effect of electronegative substituents is much smaller. Research shown that mono-substituted alkenes tend to give C5 substituted isomers as the predominant regioselectivity. This fact is backed up by the FMO calculations.\(^67\)

Cycloaddition of nitrile oxides to 1,2-disubstituted alkenes may give a mixture of two regioisomers. The dominant regioisomer depends on the substituents present, however,
the predictions from FMO calculations do not apply to every single case. Taking the acetal (24) and thioacetal (25) substituent as an example (1), the FMO calculation predicts isomer A (C4) as the major product. However, it failed to predict the major product for the thioacetal. The result is in reverse of the prediction, as isomer B (C5) is afforded as the major product (Scheme 19).\textsuperscript{68} One explanation for this result is steric interaction between the phenyl group and bulky sulfur groups, which increases the energy of transition state for isomer A, therefore yielding isomer B.

Another example (2) is with carbonyl substituents. FMO calculation predicts the formation of C4 amide isomer (A) as the major product for tertiary amides (27). A contrasting result is obtain, C5 isomer (B) is generated as the major product (Scheme 20). The calculation by density functional theory (DFT) suggests a repulsion force caused by the phenyl group of the nitrile oxide and an ethyl group from the amide sterically disfavours the C4 transition state.\textsuperscript{69}
Other factors such as hydrogen bonding may also alter the regioselectivity of cycloaddition reactions.

5.0 Previous Synthesis

The unique structure of coleophomones has drawn the attention of several organic chemists, especially after the potential use as hypertension and congestive heart failure drugs was realised. There are papers published in the last few years about synthesis toward the target product.

5.1 Nicolaou’s Synthesis \(^{70,71}\)

Nicolaou approached the synthesis of coleophomones A, B and C by a different approach to our proposal. They started with a commercially available phenol (28), which was transformed into acetonide/primary alcohol (29).\(^{72}\) The primary alcohol (29) was protected as its para-bromobenzoate ester, the protecting group chosen for easy crystallization due to the para-bromobenzoate group. The acetal group was removed by p-TsOH, followed by MnO\(_2\)-mediated benzylic oxidation to generate the phenolic aldehyde (30). K\(_2\)CO\(_3\) was used to alkylate the phenolic aldehyde (30) with
3-bromo-2-methylpropene. The resulting aldehyde was then converted into its acyl cyanide congener (31) by Nagata’s reagent followed by PCC oxidation to yield (31). Compound (31) was coupled with bisalkylated 1,3-cyclohexanedione (32), in the presence of triethylamine and 4-DMAP to yield the fully substituted precursor (33). 4-DMAP has a crucial role as an additive in the acyl cyanide coupling reaction.

Bisalkylated 1,3-cyclohexanedione (32) was made from a four-step protocol starting with 5-methyl-1,3-cyclohexanedione (34). Dione (34) was refluxed in methanol with catalytic amounts of concentrated H₂SO₄, and then alkylated by prenyl bromide in the presence of LiHMDS. The second alkylation with prenyl bromide was achieved slowly using LDA as base (Scheme 21).
The core structure of coleophomones was made up to this stage. To furnish the natural product, substituted precursor (33) was protected using diazomethane, to yield a mixture of three products (35), (36) and (37). Two of these protected precursors (35) and (36) were subjected to ring closing metathesis by Grubbs II catalyst to furnish the 11-membered macrocycle. The ring closed products E- (38) and Z- (39) were brought through a one-pot phenylselenide formation/oxidation/syn-elimination sequence to afford the \( \alpha,\beta \)-unsaturation in (40) and (41). The \textit{para}-bromobenzoate ester was removed by methanolic potassium carbonate solution to approach (42) and (43).
Alcohol (42) was oxidized using MnO₂ to afford colephomone B, while (43) was oxidized using freshly prepared Collins reagent to yield coleophomone C (Scheme 22).
Introduction

Scheme 22
Nicolaou has also tried synthesising coleophomone A from coleophomone B according to the information in the report from Merck, which stated that "coleophomones A and B exist in equilibrium with each other under physiological conditions".\(^3\)

Starting from (33), the para-bromobenzoate group was removed by K\(_2\)CO\(_3\) and the alcohol oxidised using manganese dioxide to afford a mixture of two isomeric products (44) and (45) (1:1.6). Alcohol (45) was oxidised using CrO\(_3\)-2py (Collins reagent) to give (46), which was ready for 11-membered macrocycle formation. Various olefin metathesis conditions have been tried but the 11-membered macrocycle ring closure was unsuccessful and therefore, the synthesis of coleophomone A was not completed (Scheme 23).
Nicolaou has also tried the total synthesis of coleophomone D. Starting from 1,2-dimethylanisole (48), an aldehyde (49) was made by a radical tribromination, and elimination under acetolysis. This aldehyde (49) was then treated with Nagata’s reagent to afford cyanohydrin (50) as a major product and its regioisomer (51). The mixture of (50) and (51) was oxidised by PCC to yield the acyl cyanide (52). Acylating agent (52) was put forward to couple with (53) in Et₃N to afford the precursor (54), which was reacted with methanolic K₂CO₃ to remove the acetate protecting group. The deprotected precursor (55) was then oxidised by MnO₂ to give coleophomone D (Scheme 24).
Scheme 24
The coupling reactant (53) was made from 1,3-cyclohexadione (34). It was treated with a catalytic amount of concentrated H₂SO₄ and then alkylated by prenyl bromide in the presence of LiHMDS. The second alkylation was performed with LDA and HMPA to afford (57). With the key additive HMPA, (57) was again reacted with LDA and PhSeCl to afford the phenylselenyl intermediate, which was oxidised by H₂O₂, and hydrolysed in a special protocol using LiOH in methanol-water, to yield the desired coupling block (53).

5.2 Suzuki’s Synthesis

A fungal metabolite was reported by Shionogi researchers as a coleophomone-related fungal metabolite and its relatively stable derivative, ammonia adduct (58) was made. Suzuki was trying to synthesise this ammonia adduct (58) and the biosynthetically expected structure (59), using an isoxazole route. This allows direct access to the cyclic structure.

![Reported ammonia adduct (58) and Biosynthetically expected structure (59)](image)

Starting with aldehyde (60), it was converted into a dioxolane followed by treatment with t-BuLi and DMF to yield a protected aldehyde (61). Compound (61) was made into an oxime and then the nitrile oxide by hydroxylamine hydrochloride and NCS. The corresponding nitrile oxide (62) was condensed with 1,3-cyclohexadione (34) to
yield the fused isoxazole (63). The isoxazole (63) was alkylated by prenyl bromide in the presence of LDA and HMPA. A second alkylation was carried under the same conditions resulting in a di-alkylated precursor (65). A phenylselenyl group was added affording (66). The isoxazole ring was opened by Mo(CO)_6 at this stage by a selective reduction of only the N-O bond. Subsequent oxidative C-Se bond cleavage-elimination was achieved by H_2O_2 oxidation to give the unsaturated vinylogous amide (67). The targeted cyclic aminal (59) was obtained upon removal of the acetal with aqueous HCl (Scheme 25).
Introduction

Scheme 25

The reported ammonia adduct (58) was also made by a similar method. It started with 2-methoxybenzaldehyde (68), brominated\(^{76}\) to serve as starting material for the
preparation of aldehyde (70). It was then converted into nitrile oxide, condensed with (34) and then alkylated and ring-opened as stated previously for the biosynthetically expected structure, to yield (58) (Scheme 26). This sets out a general approach towards coleophomone-related structures that was published as we began our programme, and acts as good precedent for our own studies.
6.0 Result and Discussion

We are aiming to synthesize the coleophomones and analogues by an isoxazole route. The very reactive polar tricarbonyl system seen in the coleophomones is masked by the isoxazole ring in the synthesis process, allowing elaboration of the rest of the molecule to be achieved.

To achieve our target isoxazole building block (12), we proposed two routes. Approach 1 is through cycloaddition of a nitrile oxide, prepared from an aldehyde oxime (7), with an enamine (8) derived from an acetonedicarboxylate (9) to generate a diester (5), and the 6-membered ring will be closed by aldol closure after alkylation and manipulation. Approach 2 is through cycloaddition of a nitrile oxide with 5-methylcyclohexane-1,3-dione (10), followed by alkylation. The synthetic
equivalence of (12) and its C5 bis-alkyl regioisomer has been mentioned previously.

6.1 Formation of the 1,3-Dipole
The isoxazole ring was made by a 1,3-dipolar cycloaddition, using a 1,3-dipole and a dipolarophile. In our synthesis, the 1,3-dipole was formed from the chlorinated oxime (74), which was obtained from the corresponding oxime by chlorination using NCS. Dehydrohalogenation by Et₃N gave the nitrile oxide (75) in situ. The chlorinated oxime has to be used immediately, since exposure to air would cause gradual decomposition: The 1,3-dipole attacked the double bond of the dipolarophile in a concerted step to form initially the isoxazoline ring (Scheme 27). We have built in a substituent (on the dipolarophile) that will then eliminate to give the isoxazole.

![Scheme 27](image)

6.2 Phenyl Group as Isoxazole Substituent
6.2.1 Approach 1
To begin our synthesis, we have chosen the simplest non-substituted benzaldehyde oxime (76) as a first example. The chlorinated benzaldehyde oxime (77) was used as a 1,3-dipole and dimethyl-3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) as a dipolarophile. The benzaldehyde oxime was chlorinated by N-chlorosuccinimide
under reflux in chloroform,\textsuperscript{78} and the reaction mixture was checked by TLC to ensure complete chlorination before pyrrolidine enamine (8) and triethylamine were added to the reaction mixture. A catalytic amount of amine base, triethylamine, was used to speed up and increase the yield of the reactions.\textsuperscript{79} This reaction had to be performed under an atmosphere of nitrogen as the nitrile oxide formed \textit{in situ} is highly reactive. Dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) was prepared from dimethyl 1,3-acetonedicarboxylate (9) and pyrrolidine at reflux under a Dean-Stark trap (Scheme 28),\textsuperscript{80} and used without further purification.

\begin{align*}
\text{(76)} & \quad \text{OH} \\
\text{N} \quad \text{O} \\
\text{(77)} & \quad \text{Cl} \\
\text{crude}
\end{align*}

\begin{align*}
\text{NCS, CHCl}_3, \quad \text{reflux} \\
\text{pyrrolidine, Dean-Stark reflux} \\
\text{MeO} \quad \text{O} \quad \text{Me}
\end{align*}

\begin{align*}
\text{(77)} & \quad \text{N} \quad \text{OH} \\
\text{MeO} \quad \text{O} \quad \text{OMe} \\
\text{crude} \\
\text{crude (8)} \\
\text{Scheme 28}
\end{align*}

Different ratios of enamine to oxime were tried to give the best yield of product, methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (Table 2). The yield increased from 17 \% to 44 \% as the ratio of enamine to oxime was increased to 8:1. However, the purification of the product by flash column chromatography became more difficult as the amount of enamine used was increased, therefore, the 6:1 ratio was chosen as optimum. Use of chlorinated oxime that had been partially purified by partition between DCM and water, instead of un-extracted crude material,
increased the yield of (5) to 55%.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Chlorinated Oxime</th>
<th>Enamine</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not extracted with</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>DCM/H₂O</td>
<td>1</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Extracted</td>
<td>1</td>
<td>6</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 2

6.2.1.1 Attempts at 6-Membered Ring Closure

To make the isoxazole building block through Approach 1, we needed to ring close between the two esters to form a 6-membered ring. The methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) was reacted with methylmagnesium bromide in an attempt to convert one ester into a methyl ketone in order to yield a precursor for ring closure. Looking at the structure, the ester A should be less reactive than the ester B due to the conjugation (Scheme 29). However, a mixture of products, included diketone and diol (which were seen from the IR spectra), was obtained and the spectra were difficult to assign. This may due to insufficient selectivity between these two esters.
Methyllithium was also tried for the same purpose. The methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) was converted into 5-carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78) by aqueous sodium hydroxide in a 81% yield. The diacid was then reacted with methyllithium in an attempt to convert the carboxylic acid into a ketone (Scheme 30). However, again, a mixture of products was formed due to difficulty in controlling the selectivity of the reaction.

Due to this failure to modify suitably the two ester termini, we moved the focus to alkylation, with ring closure to be completed at a later stage.
6.2.1.2 Side Chain Elaboration

Methyl iodide was initially used in a model reaction to methylate methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5). The diester was deprotonated by 2.0 equiv. of LDA in dry THF at -78 °C, and then quenched by excess methyl iodide. However, this reaction failed, possibly because methyl iodide was highly volatile and lost from the reaction. 1-Bromo-3-methyl-2-butene was chosen as the second alkylating reagent, because the carbon chain was same as the one needed for the target molecule. Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) was again deprotonated by 2.0 equiv. of LDA at -78 °C and alkylated by 1.0 equiv. of 1-bromo-3-methyl-2-butene to yield methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) at 70 % (Scheme 31).

After the success of mono-alkylation, a second alkylation was tried. Using the same alkylation reagent (1-bromo-3-methyl-2-butene), the dialkylated product, methyl 5-[1-methoxycarbonyl-4-methyl-1-(3-methylbut-2-enyl)pent-3-enyl]-3-phenylisoxazole-4-carboxylate (80) was made successfully from the mono-alkylated product, after deprotonation by 1.5 equiv. of n-BuLi at -78 °C in dry THF. The best yield so far is 23 %. We attempted to modify the yield of the second alkylation by using a palladium(0) complex, tetrakis(triphenylphosphine)palladium(0) (Figure 19), well known to assist such couplings, as a catalyst.

![Figure 19](attachment:figure19.png)
Methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) was deprotonated again by n-BuLi (1.5 equiv.) in dry THF, and 10 mol % of Pd(PPh₃)₄ was added followed by the 1-bromo-3-methylbut-2-ene. Di-alkylated product (80) was obtained in 25%. This showed that the palladium complex did not have any marked effect on the yield of the di-alkylated product (Scheme 31). Di-alkylated product could only be made by a two-step process: di-alkylation by a one-pot reaction was not successful using either LDA or n-BuLi as the base with excess alkylation agent.
The second alkylation was not successful if LDA was used instead of n-BuLi, as the base. LDA was made from n-butyllithium and diisopropylamine, since n-BuLi is a stronger base than LDA. The pKa value of n-BuLi is 45, while LDA is 35. Therefore, deprotonation by n-BuLi was more efficient. On the other hand, LDA is a much bulkier base comparing to n-BuLi, the hindered structure making it less nucleophilic. 1.5 Equiv. of n-BuLi should be sufficient because it is highly reactive towards other functional groups, and the reaction could be adversely affected if too much was added.

6.2.1.3 Use of Weinreb Amide

There are many reagents available for converting esters into ketones, such as Grignard reagents, and other organometallic agents. However, these reagents may convert the ester into alcohol instead of ketone if the conditions are not carefully controlled.\textsuperscript{84} During the organometallic reaction, the ester is first converted to a ketone, and if it cannot be controlled at this stage, a second attack of the reagent will convert the ketone further into an alcohol (Scheme 32). An ester is less reactive than a ketone due to the electron density donated by the lone pair of electrons from the "ether" oxygen attached to the carbonyl carbon.

![Scheme 32](image-url)
In order to prevent the second nucleophilic attack, a Weinreb amide can be used. Weinreb amides are highly effective towards a wide range of nucleophiles, and work efficiently to generate ketone from carboxylic acid. Even in the presence of excess organometallic reagents, the stabilised tetrahedral intermediate prevents formation of alcohol from a second nucleophilic addition (Scheme 33).

At the intermediate stage, chelation of the metal ion between alkoxide and the oxygen atom of the N-methoxy group avoids further addition of nucleophiles. Only on an acidic work-up, is the tetrahedral intermediate released to give a ketone. Any excess of the organometallic reagents will be hydrolysed at the same time of the acidic work-up, therefore preventing second addition and alcohol formation.\(^{85}\)

The use of Weinreb amides has proved to be a very efficient reaction for generation of ketones instead of alcohols from carboxylic acid. Weinreb amides are usually formed from a carboxylic acid group, therefore, esters needed to be converted into carboxylic acid by hydrolysis before proceeding.
Weinreb Amide Formation

After the success of our enolate alkylations, we then returned to the ring closure. To close the six-membered ring, the ester groups needed to be converted into ketones. Grignard reaction had been tried previously (see earlier), but a mixture of ketones and alcohols were obtained.

*Scheme 34*

Use of Weinreb amides prevents the formation of alcohols, so was relevant to our studies. We attempted treatment of the diester, methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) with N,O-dimethylhydroxylamine hydrochloride and AlMe₃ as a Lewis acid, at reflux in dry DCM to yield the Weinreb amide (81) in a single step, but the yield was comparatively low at just 4%. It was suggested that Weinreb amides usually could not been formed directly from esters. Therefore, we had to first convert the two ester groups into carboxylic acids by sodium hydroxide in MeOH/H₂O to afford, 5-carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78) in 81% yield. It was then reacted with N,O-dimethylhydroxylamine hydrochloride, N-methylmorpholine and
EDCI to give the corresponding Weinreb amide, 5-\[(N\text{-methoxy-}N\text{-methylcarbamoyl})\text{methyl}\]-3-phenylisoxazole-4-carboxylic acid 
N-methoxy-N-methylamide (81) in 48 % yield (Scheme 34). The EDCI acted as an activator for the carboxylic acid groups.

Formation of ketones was tried again by reacting the Weinreb amide with a methyl Grignard reagent.\(^\text{86}\) To the Weinreb amide (81), 1 equiv. of methylmagnesium bromide was added in dry THF at 0 °C to form a ketone. However, no ketone was found. The fractions collected from the column were starting material and some unidentified materials.

Other methods to generate ketones have also been attempted. We planned to use an anhydride as a precursor for Grignard alkylation. We thought that carbonyl group A of the anhydride (82) should be more reactive than the carbonyl group B, because B was conjugated with the isoxazole ring. Therefore, if we reacted 3-phenyl-7\textit{H}-pyrano[3,4-\textit{d}]/isoxazole-4,6-dione (82) with methyl Grignard reagent, the methyl group should attack the carbonyl group A, forming a methyl ketone, while the other end would remain as a carboxylic acid after acidic work-up (Scheme 35).
We attempted to prepare the anhydride 3-phenyl-7H-pyrano[3,4-d]isoxazole-4,6-dione (82) from the dicarboxylic acid, 5-carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78) by three different conditions shown in the table below (Table 3). However, the expected anhydride structure (82) was not isolated from all the reaction conditions we tried.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetic anhydride, pyridine</td>
<td>Dry DCM</td>
<td>Reflux</td>
<td>4 h</td>
<td>Unidentified product</td>
</tr>
<tr>
<td>2</td>
<td>TsOH</td>
<td>Toluene</td>
<td>Reflux</td>
<td>16 h</td>
<td>Unidentified product</td>
</tr>
<tr>
<td>3</td>
<td>Acetic anhydride</td>
<td>Dry DCM</td>
<td>Reflux</td>
<td>2 h</td>
<td>Unidentified product</td>
</tr>
</tbody>
</table>

Table 3

6.2.2 Approach 2

In the second approach, the isoxazole building block 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) was also constructed by a 1,3-dipolar cycloaddition in 61% yield, using phenylhydroximoyl chloride (83)
as a 1,3-dipole precursor and 5-methylcyclohexane-1,3-dione (10) as a dipolarophile in the presence of sodium isopropoxide (Scheme 36). The phenylhydroximoyl chloride (83) used for approach 2 was prepared from commercial benzaldehyde oxime (76) and N-chlorosuccinimide at 50 °C in chloroform. The preparation of chlorinated oxime was similar to Approach 1, and it was extracted by DCM and then used directly without purification. It was used immediately after it was made, or stored under nitrogen in a refrigerator for a short period of time. The hydroximoyl chloride (83) was dehydrohalogenated to give a nitrile oxide, which was ready to attack the enol form of dione (10) in a 1,3-dipolar cycloaddition manner (Scheme 36).

\[ \begin{align*}
\text{(76)} & \\
\text{NCS} & \\
\text{100% crude} & \\
\text{(83)} & + \\
\text{sodium isopropoxide} & \\
\text{(10)} & \text{61%}
\end{align*} \]

Scheme 36

\[ \begin{align*}
\text{1,3-dipolar cycloaddition} & \\
\text{Base} & \\
\text{H}^+ & \\
\end{align*} \]

\[ \begin{align*}
\text{6.2.2.1 } \alpha,\beta-\text{Unsaturation} & \\
\text{The 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz}[d]\text{isoxazol-4-one (6) was reacted with several reagents to try to generate a double bond at the } \alpha,\beta\text{-position to the ketone} & \\
\end{align*} \]
group, as that is the oxidation level required in the natural product (Scheme 37). The first attempt used bromination followed by elimination of the bromide as HBr.

Bromine was added to ketone (6) at room temperature for bromination at the α-position,\(^8\) starting material disappeared but a mixture of brominated products was obtained instead of one α-brominated product, possibly because bromine is volatile and difficult to measure accurately in the small scale we used. Deshielded C5 and C7 protons confirmed the formation of brominated products. Next, chlorotrimethylsilane was used with triethylamine to generate a silyl enol ether, \textit{in situ}, followed by \textit{N}-bromosuccinimide to brominate (6), but starting material was recovered. The hoped for reaction sequence is shown below (Scheme 38).
Result and Discussion

The alternative method of using LDA as a base to deprotonate the ketone and form the silyl enol ether before bromination was also tried (Scheme 39). However, starting material was recovered again.

![Scheme 39]

As the reactions above were performed in one step without isolation of any intermediate product, silyl enol ether formation was doubted. t-Butlyldiphenylchlorosilane was used instead of chlorotrimethylsilane,\textsuperscript{90} with LDA (1.2 equiv.) in THF at -78 °C, to produce a silyl enol ether, which should be stable enough to be isolated to confirm the formation of the intermediate, silyl enol ether. Starting material was recovered, proving that the silyl enol ether was not formed.

Phenylselenium bromide is another common reagent used in sequences for the generation of \( \alpha,\beta \)-unsaturation. \( \text{6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenz}[d]\text{isoxazol-4-one (6)} \) was deprotonated by LDA in dry THF and then reacted with phenylselenium bromide.\textsuperscript{91} Without purification, the crude product was oxidised by sodium periodidate and sodium hydrogen carbonate.\textsuperscript{92} Starting material was recovered instead of the \( \alpha,\beta \)-unsaturated product. The required mechanism is as below (Scheme 40).
Use of DDQ is also a very common method for generation $\alpha$,$\beta$-unsaturation by dehydrogenation. DDQ was added to 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[$d$]isoxazol-4-one (6) and the mixture was refluxed in 1,4-dioxane over two days. Still none of the expected product was formed. The following is a summary of reactions tried for generation of the $\alpha$,$\beta$-unsaturation generation (Table 4).
### Summary of reagents and conditions used for generating the α,β-unsaturation

<table>
<thead>
<tr>
<th>Base</th>
<th>Reactant</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>Br₂</td>
<td>CHCl₃</td>
<td>RT, 3 h</td>
<td>Mixture of C₃, C₅, C₃/C₅ brominated products</td>
</tr>
<tr>
<td>Et₂N</td>
<td>TMSCI, NBS</td>
<td>Dry THF</td>
<td>Reflux, 2 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>LDA</td>
<td>TMSCI, NBS</td>
<td>Dry THF</td>
<td>-78°C, 4 h; 80°C, 1½ h</td>
<td>S.M.</td>
</tr>
<tr>
<td>LDA</td>
<td>TMSCI, Br₂</td>
<td>Dry THF</td>
<td>-78°C, 4 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>LDA</td>
<td>TBDPSCl</td>
<td>Dry THF</td>
<td>-78°C, 5 min</td>
<td>S.M.</td>
</tr>
<tr>
<td>LDA</td>
<td>NBS</td>
<td>Dry THF</td>
<td>RT, 1 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>LDA</td>
<td>PhSeBr, NaIO₄</td>
<td>Dry THF, Water</td>
<td>RT, &gt;24 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>LDA</td>
<td>PhSeBr</td>
<td>Dry THF</td>
<td>RT, &gt;24 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>---</td>
<td>DDQ</td>
<td>1,4-dioxane</td>
<td>Reflux, 50 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>---</td>
<td>i) Br₃⁻, ii) DBU</td>
<td>DCM</td>
<td>RT, 3 h</td>
<td>Non-brominated</td>
</tr>
<tr>
<td>---</td>
<td>i) Br₃⁻, ii) DBU</td>
<td>DCM, DMF</td>
<td>0°C, 1 h</td>
<td>50°C, 1 h</td>
</tr>
</tbody>
</table>

Table 4

After many failed reactions, tests were carried out to investigate whether the proton at the alpha position is exchangeable or not. d₄-Methanol (CD₃OD) was added to 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) after attempted deprotonation with LDA (THF, -78 °C). A reduction of ¹H NMR signal of the α-methylene group by proton exchange with d₄-methanol would prove that the alpha
proton is exchangeable under these conditions. However, no reduction of the integral for this signal was observed and we concluded that the alpha proton cannot be exchanged under the conditions we had tried.

After reviewing the data, we returned to bromination and found a paper, by Bode et al., which had shown that bromination by pyridinium hydrobromide perbromide is easier to carry out, because the perbromide is a more convenient reagent as it could be weighed out much more accurately and it reacts less vigorously. 5-Bromo-6-methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (85) was generated in 66% yield by pyridinium hydrobromide perbromide with glacial acetic acid in DCM (Scheme 41). Bromide (85) was then reacted with DBU in DMF at 50°C to yield 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84), 41%. Debrominated material (6) was recovered if the reaction was carried out in DCM at 0°C. We presume these different results were due to the polarity of the solvent. The elimination product exists as its phenolic tautomer (84) rather than the cyclohexanedione form, due to aromatic stabilisation. The structure of the mono-bromo intermediate (85) was confirmed by an X-ray crystal structure determination (Figure 20).

![Scheme 41](image_url)
The C-5 and C-7 protons of 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) were difficult to assign in the NMR spectra as they are under a similar environment. In an attempt to assign the $^1$H NMR spectrum, 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) was converted into 4-acetoxy-6-methyl-3-phenylbenzo[d]isoxazole (86) (Figure 21) by acetic anhydride. A nOe (nuclear Overhauser enhancement) spectrum was performed to investigate the proton-proton interaction. An interaction between the ester methyl and proton c (at C-5) but not proton a (at C-7) was expected, as the proton at position c was located closer to the ester methyl. However, both the protons a and c appeared to be interacting with the ester methyl. No conclusion was drawn and the two proton peaks remain unassigned.
Continuing with the approach 2, further bromination was carried out on the aromatised isoxazole building block, 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) with a view to provide a substrate for a coupling reaction. Bromine was added dropwise to 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84), and either 5-bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (87) or 7-bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (88) was isolated in 18% yield (Scheme 42), as one of the unidentified a or c proton signals disappeared from the NMR spectrum. The unambiguous proof of formation of either product would be potentially useful for our synthesis.

Since the identification of the position of bromination was uncertain, methylation was carried out on 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) to help clarify the reactivity of the compound. Looking at the molecule, it was anticipated that soft methyl iodide and hard methyl trifluoromethanesulfonate should attack the soft and
hard nucleophilic positions of the molecule, respectively. Unfortunately, after LDA deprotonation and electrophile addition, no alkylation was observed and starting material was recovered in both reactions (Scheme 43).

Next, we tried to deprotonate 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) with 3 equiv. of LDA (THF, -78 °C) and reacted with 1-bromo-3-methyl-2-butene with the hope that either the C5 or C7 position would be attacked. However, instead of C-alkylation, the hydroxyl group was attacked to form O-alkyl product 6-methyl-4-(3-methyl-but-2-enyloxy)-3-phenyl-benzo[d]isoxazole (89) in 58 % yield. In similar fashion, reaction with dimethyl sulfate formed 4-methoxy-6-methyl-3-phenyl-benzo[d]isoxazole (90) in 36 % yield (Scheme 44).
Result and Discussion

However, when we deprotonated the brominated phenol, 5-bromo-6-methyl-3-phenyl-benzo[d]isoxazol-4-ol (87) or the 7-bromo isomer (88) by LDA and then reacted with 1-bromo-3-methyl-2-butene, an unexpected C-alkylation at either C5 or C7 was observed. We could not give an explanation for this switch in reactivity, but this unexpected attack at the aromatic carbon was just what we wanted for our carbon chain to be added on for the target molecule (Scheme 45). As the aromatic protons have not been assigned from the spectra of 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84), we could not identify which carbon, C5 or C7 was actually brominated and thus which had been alkylated in the reactions above, but tentatively we assume the C5 (ortho) position is more reactive and is brominated, and thus alkylation is at C7 to give (91). Either the C5 alkylated or C7 alkylated product could be useful for further reactions towards our final targets.
6.2.2.2 C-Alkylation of Cyclohexenone (6)

An alternative approach to introduce the alkyl groups into the 6-membered ring required in Approach 2, is to attempt alkylation before introducing unsaturation into the ring. We thus examined C-alkylation of ketone (6). Deprotonation using the hindered and non-nucleophilic base, lithium diisopropylamide (LDA) in dry THF is a very common and effective method for alkylation. LDA is made from n-butyllithium (n-BuLi) and diisopropylamine, with the lithium cation coordinated with the nitrogen of the diisopropylamide anion. The negatively charged nitrogen atom is responsible for deprotonation of an acidic carbon. The use of co-solvent, hexamethylphosphoramide (HMPA) (Figure 22) helps to coordinate the lithium cation extremely powerfully, reducing aggregation and separating it further from the diisopropylamide anion, allowing the latter to approach closer to the carbon to be deprotonated. The lithium cation is solvated leaving the anion unsolvated and very reactive (Scheme 46), therefore, increasing the efficiency of the LDA deprotonation for bulky groups or around electron-rich functional groups.
Result and Discussion

Hexamethyl phosphoramide (HMPA)  N,N'-dimethylpropylene urea (DMPU)

Figure 22

HMPA is a highly polar solvent with strong dipole moment. One of its major drawbacks is its toxicity, since it is a very carcinogenic chemical. Special handling and disposal precautions are necessary for this chemical, therefore a replacement has been introduced, N,N'-dimethylpropylene urea (DMPU) (Figure 22). DMPU is far less toxic than HMPA, but with similar properties and the same effect as HMPA as a co-solvent. It has a dipole moment at $14.1 \times 10^{-30}$ Cm.$^{97}$

In the earlier discussion of phenylselenation of (6), we have mentioned that the C5 deprotonation of 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) could not be verified under the conditions of LDA as the base in dry THF at -78°C under atmosphere of nitrogen.$^{98}$
Result and Discussion

To promote this deprotonation and subsequent alkylation reaction, a method of using HMPA as a co-solvent was suggested.\textsuperscript{74} We applied this methodology to the deprotonation of 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6), which had failed previously. LDA (2 equiv.) in THF:HMPA (6:1) at -78 °C was used to deprotonate the C5 position, which was then alkylated by 1-bromo-3-methyl-2-butene (1 equiv.). A mixture of mono-alkylated product, 6-methyl-5-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (92) and di-alkylated product, 6-methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (93) was isolated at 21 % yield for each product as well as 21 % of unchanged starting material.

The \textsuperscript{1}H NMR signal of the C5 protons of 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) was deshielded more by the adjacent ketone when compared to the C7 protons. The C5 protons were recorded at 2.64 ppm (\textit{J} 10.0 & 17.4 Hz) and 3.13 ppm (\textit{J} 4.8 & 17.4 Hz), while C7 protons were recorded at 2.30 ppm (\textit{J} 11.1 & 16.0 Hz) and 2.61 ppm (\textit{J} 3.8 & 16.0 Hz). After dialkylation, the signal of the C5 protons were absent, leaving only the peaks at 2.45 ppm (\textit{J} 11.1 & 16.0 Hz) and 2.73 ppm (\textit{J} 3.8 & 16.0 Hz), which are signals representing the C7 protons. The NMR signals and \textit{J} values indicated the alkylation was performed at C5 to give (92) and (93).

After this success in alkylation on C5, we tried to add a phenylselenyl group at the C7 position under similar conditions, in order to introduce the required unsaturation. Using the di-alkylated product (93), HMPA was used as co-solvent with THF at -78 °C and LDA to deprotonate the C7 carbon, which then was attacked with
phenylselenium bromide. 50% of the phenylselenyl product 6-methyl-5,5-bis-(3-methyl-but-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (94) was obtained. Purification of this product was very difficult, and impurity peaks were still found in the proton NMR spectrum after a second chromatographic separation. These peaks possibly derived from the co-solvent HMPA. After this, oxidative elimination of the phenylselenyl group was attempted using sodium periodate and sodium hydrogen carbonate to give a double bond before isoxazole ring opening, but starting material was recovered. However, the phenylselenyl group was eliminated successfully by reversing the order of the steps, and first, by ring opening the isoxazole with Mo(CO)$_6$ in moist acetonitrile$^9$ and then oxidation with H$_2$O$_2$ to yield 2-[1-amino-1-phenyl-meth-(E)-ylidene]-5-methyl-6,6-bis-(3-methyl-but-2-enyl)-cyclohex-4-ene-1,3-dione (95) in 30% (Scheme 47). The yield obtained was always higher when these reactions were performed on a small scale than a large scale.
Looking back at the coleophomone target molecules, we observed that putting carbon chains on either C5 or C7 positions of benzisoxazole (6) would give us the same product after elimination of the phenylselenyl group, as these positions become...
equivalent by bond rotation after the isoxazole ring is opened and the enamine hydrolysed (Scheme 48).100

Therefore, as an alternative sequence we attempted to put a phenylselenyl group at the C5 position first. The use of HMPA as co-solvent for LDA deprotonation was applied to phenylselenyl group addition on the C5 carbon, to afford 6-methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96) in 25 % (Scheme 49), in contrast to earlier findings with LDA in THF alone (see above).
Next we attempted to further alkylate 6-methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96) at the C7 position using 1-bromo-3-methylbut-2-ene and LDA in THF:HMPA (6:1). We anticipated that despite the increased acidity of (96) at C-5, deprotonation and alkylation at C-7 might be favoured on steric grounds. However, the formation of the desired mono-alkylated product, 6-methyl-7-(3-methyl-but-2-enyl)-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (97) and di-alkylated product, 6-methyl-7,7-bis-(3-methyl-but-2-enyl)-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (98), could not be confirmed because the NMR spectrum after column chromatography was not clear enough to be fully analysed. If the alkylated phenylselenyl product formation is confirmed, the phenylselenyl group would be removed by oxidative elimination to give α,β-unsaturation in a similar way to that described earlier (Scheme 50).
Because of the toxicity issues with HMPA, the alternative additive DMPU was also tried for the C5 alkylation of ketone (6). Reactions with DMPU replacing HMPA were carried using the same conditions, and the results are compiled in the following table (Table 5). Different ratios of LDA and alkylating reagent have also been tried, and the optimum condition for mono-alkylated product so far was using 2 equiv. of LDA and 1 equiv. of alkylating reagent. Some of these results refer to the ortho substituted phenyl group, which will be introduced in the following section.
<table>
<thead>
<tr>
<th>Starting material &amp; alkylating reagent</th>
<th>Co-solvent</th>
<th>LDA</th>
<th>Alkylating reagent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(C5-Monoalkylated, C5-Dialkylated, SM)</td>
</tr>
<tr>
<td>N-O</td>
<td>HMPA</td>
<td>2.00 eq</td>
<td>1.00 eq</td>
<td>21, 21, 20 (92), (93), (6)</td>
</tr>
<tr>
<td>PhSeBr</td>
<td>HMPA</td>
<td>2.50 eq</td>
<td>2.02 eq</td>
<td>13, 13, 11 (92), (93), (6)</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>1.50 eq</td>
<td>1.02 eq</td>
<td>6, 17, 10 (92), (93), (6)</td>
</tr>
<tr>
<td>N-O</td>
<td>HMPA</td>
<td>1.20 eq</td>
<td>1.00 eq</td>
<td>25 (96)</td>
</tr>
<tr>
<td>PhSeBr</td>
<td>DMPU</td>
<td>1.50 eq</td>
<td>1.02 eq</td>
<td>20 (96)</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>2.50 eq</td>
<td>1.02 eq</td>
<td>23, 10, (126), (127), (117)</td>
</tr>
<tr>
<td></td>
<td>HMPA</td>
<td>1.20 eq</td>
<td>1.00 eq</td>
<td>11, 7, 42 (124), (125), (117)</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>1.20 eq</td>
<td>1.02 eq</td>
<td>20, (124), (125), (117)</td>
</tr>
</tbody>
</table>

Table 5
6.2.3 Conclusion

We have developed a good base of synthesis towards the isoxazole building blocks for both proposed approaches to the coleophomone system. For Approach 1, we have successfully elaborated by alkylation the side chains at C3. However, we failed to complete the ring closure of the 6-membered ring to afford a benzisoxazole, even with the use of Weinreb amide to help forming ketones.

For Approach 2, we have successfully prepared the benzisoxazole, and looked at the alkylation of the C5 and C7 positions using co-solvent, and generation of the required $\alpha,\beta$-unsaturation by different methods, such as phenylselenyl oxidative elimination and bromination. These investigations provided with valuable information to apply to the isoxazole building blocks having substituted phenyl substituents, described in the next section, as well as towards the target natural products.

6.3 o-Substituted Phenyl Group as Isoxazole Substituent

6.3.1 Formation of Building Blocks

After reactions using phenyl group as the aromatic isoxazole substituent, we decided to also investigate substituted aromatic groups, which should look more like our target molecule. We chose an ortho-substituted phenyl ring, 2-hydroxybenzaldehyde oxime (104) as the next trial aromatic substituent (Scheme 51).
The elaboration of ortho-substituted building block would be based on the same retrosynthetic analysis, namely the two approaches from the benzaldehyde oxime: forming an isoxazole with diesters for the first approach and generating the isoxazole with a pre-formed six-membered ring for the second approach.

Before chlorinating the commercial 2-hydroxybenzaldehyde oxime (104), we decided to first mask the reactive alcohol function at the ortho position (Scheme 52). We attempted to protect the o-hydroxy group by different groups, namely benzyl, allyl and 1,4-dibromobut-2-ene. Our initial plan was that, after the isoxazole ring was formed by the 1,3 dipolar cycloaddition, the benzyl or allyl group would be removed by strong acid or hydrogenation, allowing the recovered o-hydroxy group to be coupled with a carbon chain.

2-Benzoyloxybenzaldehyde oxime (105) was isolated in just 1 % yield on reacting benzyl bromide and potassium carbonate with 2-hydroxybenzaldehyde oxime (104) in
dry acetone at reflux. Allyl bromide was used with similar reaction conditions to yield allyl protected product, 2-allyloxybenzaldehyde oxime (106) in just 3 % yield.

![Chemical reaction diagram]

1,4-Dibromobut-2-ene was also tried as a masking group using similar conditions to those employed with benzyl bromide and allyl bromide. However, a mixture of products was obtained from the reaction (Scheme 53), and the spectra were difficult to identify; we deduced that both single and double alkylation had occurred. We had planned that a remote bromide could act as alkylating agent for a benzisoxazole later in the synthesis.
The yields of the benzyl and allyl protected products, 2-benzyloxybenzaldehyde oxime (105), and 2-allyloxybenzaldehyde oxime (106), were not good enough for continuing with the sequence. The problem of low yield might have been caused by the reactive oxime hydroxyl group or nitrogen atom reacting instead of or as well as, the O-hydroxy group. We also found that the whole amount of crude material was not collected after column chromatography. We decided to start with the commercial salicyaldehyde instead of the oxime to solve these issues (Scheme 54).
2-Hydroxybenzaldehyde (109) was deprotonated by potassium carbonate and then reacted with benzyl bromide or allyl bromide, in dry THF under reflux to generate the protected products, 2-benzyloxybenzaldehyde (110) and 2-allyloxybenzaldehyde (111) in 75% and 93% yield, respectively. Some other conditions have been tried (Table 6) but these give the best yield of protected aldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting agent</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzyl bromide</td>
<td>Dry acetone</td>
<td>K₂CO₃, KI, reflux</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>Benzyl bromide</td>
<td>Dry THF</td>
<td>K₂CO₃, reflux</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>Allyl bromide</td>
<td>Dry acetone</td>
<td>K₂CO₃, reflux</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>Allyl bromide</td>
<td>Dry THF</td>
<td>K₂CO₃, reflux</td>
<td>93%</td>
</tr>
</tbody>
</table>

Table 6

After the protected α-hydroxy aldehydes were obtained, further reactions were performed to convert both protected aldehydes, 2-benzyloxybenzaldehyde (110) and 2-allyloxybenzaldehyde (111) into their oximes using 2 equiv. of hydroxylamine hydrochloride and 4 equiv. of sodium acetate in water/ethanol. 2-Benzylloxybenzaldehyde oxime (105) and 2-allyloxybenzaldehyde oxime (106) were collected as crude products under these conditions in > 100% yield.

To progress our two synthetic approaches now that we had obtained the crude oximes, we needed to make the corresponding isoxazole diester and isoxazole with a fused six-membered ring. The crude 2-benzylloxybenzaldehyde oxime (105) was treated with NCS in chloroform at reflux and then work up by extraction with DCM gave the chlorinated oxime, 2-benzylloxyphenylhydroximoyl chloride (112) in good yield.
Without purification, this reactive chlorinated oxime was used directly. For the first approach, we heated the pyrrolidine enamine of dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (in excess) with 2-benzyloxyphenylhydroximoyl chloride (112) and triethylamine in chloroform at reflux to yield the isoxazole diester, methyl 5-methoxycarbonylmethyl-3-(2-benzyloxyphenyl)isoxazole-4-carboxylate (113) in 8% (based on oxime). For the second approach, the chlorinated oxime (112) was stirred with 5-methylcyclohexane-1,3-dione (10) in sodium isopropoxide, which was prepared by dissolving sodium metal in propan-2-ol carefully. 3-(2-Benzylxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (114) was isolated in a 5% yield (based on oxime) (Scheme 55). These low cycloaddition yields are based on crude oxime so are minimum yields. There may also be steric effects of the bulky benzyloxy group, hindering the approach of 1,3-dipole to dipolarophile.

Scheme 55
For the crude 2-allyloxybenzaldehyde oxime (106), chlorination using exactly the same condition was used to form the chlorinated oxime, 2-allyloxy-phenylhydroximoyl chloride (115). This was reacted without purification with the same pyrrolidine enamine (8) and with 5-methylcyclohexane-1,3-dione (10) in attempts to form the isoxazole diester, methyl-3-(2-allyloxy-phenyl)-5-methoxycarbonylmethyl-isoxazole-4-carboxylate (116) and the isoxazole with a fused six-membered ring, 3-(2-allyloxy-phenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[\textit{d}]isoxazol-4-one (117) respectively (Scheme 56).

However, neither of the expected products was isolated, instead, two unpredicted products were obtained from both of the above reactions. After analysis of the $^1$H and $^{13}$C NMR spectra, we concluded the compounds were the intramolecular cyclisation product (118) and unsymmetrically dimerised product (119), i.e. the nitrile oxide.
formed in the dehydrohalogenation step had reacted in either intramolecular or intermolecular mode with the allyl double bond before addition of the dipolarophile (Scheme 57).\textsuperscript{104} The formation of intramolecularly cyclised product (118) was proved by \textsuperscript{1}H NMR spectroscopy. Peaks around 3.15 ppm, 3.78 ppm and 4.01 ppm corresponded to protons at a, b and c, respectively. The dimerised adduct (119) was suggested from its \textsuperscript{1}H NMR spectrum, as a 2:1 ratio of aromatic peaks to allyl protons was observed.

As the tactic of protecting the o-hydroxy group by benzyl and allyl groups was not proving very effective, we changed our plan and decided to attempt the cycloaddition...
directly with the unprotected 2-hydroxybenzaldehyde oxime (104) for both approaches.

6.3.2 Approach 1

2-Hydroxybenzaldehyde oxime (104) was heated at reflux with NCS and pyridine in chloroform and then worked-up by extraction with DCM, to afford 2-hydroxyphenylhydroximoyl chloride (120) in 100% crude, which was used without purification. The 2-hydroxyphenylhydroximoyl chloride (120) was then reacted with 6 equiv. of the pyrrolidine enamine (8) with dropwise addition of triethylamine in chloroform to yield methyl 5-methoxycarbonylmethyl-3-(2-hydroxy-phenyl)-isoxazole-4-carboxylate (107) as the product in 7% (Scheme 58). We are unclear whether the unprotected alcohol function at ortho position was responsible for the low yield. Although the yield is not yet satisfactory, we wished to carry on further investigation with this cycloadduct.

![Scheme 58](image-url)
Looking at our target molecule, we planned to put a carbon chain on the alcohol group in order to allow further reaction to finish the 11-membered macrocycle by metathesis. Allyl bromide was chosen to allylate the hydroxy group, so methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate (107) was deprotonated by potassium carbonate in dry THF and reacted with allyl bromide. Unfortunately, none of the expected product (116) was obtained, instead the oxygen from the deprotonated phenol attacked the ester at C4, forming a six-membered ring instead of reacting with the allyl bromide, and 27% of the (4-oxo-4H-chromeno[4,3-c]isoxazol-3-yl)-acetic acid methyl ester (121) was observed (Scheme 59). A project student from our group discovered that this lactone formation also occurred slowly under room temperature after extended storage of crude isoxazole (107).
Although no expected product was obtained, (4-oxo-4H-chromeno[4,3-c]isoxazol-3-yl)acetic acid methyl ester (121) would still be very useful for approaching our target molecule. We might alkylate the C3 methylene substituent of (121) and re-open the lactone ring by hydrolysis. However, we did not have time to explore this further.

In addition, we have also tried ring closure from methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate (107) to form the fused 6-membered ring. To form a possible precursor for ring closure, we tried converting diester (107) into the diacid, 5-carboxymethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylic acid (122) by treatment with 5M hydrochloric acid under reflux. Without purification, the pale yellow solid was treated with K₂CO₃ and allyl bromide to allylate the hydroxyl group. We understood that there were several acidic protons, which could potentially be deprotonated to give different allylated products. However, none of the predicted products were obtained. Instead, surprisingly, 3-acetyl-4-amino-chromen-2-one (123) was isolated in 51 % yield. The structure of (123) was determined by an X-ray crystal structure determination (Figure 23). We suggest that (107) could have undergone decarboxylation during the acidic hydrolysis, and that lactone closure might be caused by K₂CO₃. The isoxazole ring opening, however, requires a reductive process that we cannot explain satisfyingly (Scheme 60).
Result and Discussion

Scheme 60
6.3.3 Approach 2

For the second approach, 2-hydroxybenzaldehyde oxime (104) was again heated under refluxed with NCS and pyridine in chloroform. After extraction, the crude product was stirred with 5-methylcyclohexane-1,3-dione (10) in sodium isopropoxide, in propan-2-ol to yield 3-(2-hydroxy-phenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) in 52 % (based on oxime) (Scheme 61).
Result and Discussion

Using a similar strategy as in Approach 1, we planned to put a carbon chain on the phenolic group followed by another on the C5 carbon to allow a coupling reaction or a ring closing metathesis to furnish the 11-membered macrocycle (Scheme 62).

3-(2-Hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) was deprotonated by potassium carbonate in dry THF and then reacted with allyl bromide to yield 3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) in 43 %. Ketone (117) was further deprotonated by LDA in dry THF with HMPA as a co-solvent at -78 °C. Allyl bromide was added at -78 °C to give both mono-allylated and di-allylated products.
Result and Discussion

5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) and 5,5-diallyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (125) in 11 % and 7 %, respectively (Scheme 63). Reactions using DMPU instead of HMPA gave similar yields. The evidence of C-5 alkylation was deduced from the $^1$H NMR spectra. The C5 protons next to a ketone in (117) were shifted more downfield: 2.70 ppm ($J$ 9.7 and 17.0 Hz) and 3.08 ppm ($J$ 5.2 and 17.0 Hz), compared to the C7 protons: 2.39 ppm ($J$ 11.0 and 15.9 Hz) and 2.65 ppm ($J$ 3.6 and 15.9 Hz). Those C5 signals disappeared after dialkylation, leaving only signals at 2.28 ppm ($J$ 11.0 and 15.9 Hz) and 2.86 ppm ($J$ 3.6 and 15.9 Hz), which represented the C7 protons. The $J$ value patterns provided a very clear confirmation of protons that disappeared after alkylation, therefore the position of alkylation.

Besides allyl bromide, we also tried C5 alkylation with 1-bromo-3-methylbut-2-ene. 3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) was
deprotonated by 2.5 equiv. of LDA in THF:DMPU (6:1) at -78 °C, followed by adding 1-bromo-3-methylbut-2-ene. Mono-alkylated product, 3-(2-allyloxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]-isoxazol-4-one (126) and di-alkylated product 3-(2-allyloxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (127) were isolated in 23 % and 10 %, respectively (Scheme 64). Again, C-5 alkylation was suggested by the disappearance of the more downfield signal representing C5 protons (similar to the situations discussed above). We now had available four potential substrates, (124)-(127), for ring-closing metathesis.
6.3.3.1 Ring-Closing Metathesis (RCM)

Ring-closing metathesis has recently been used widely in many natural product syntheses. It is a very effective method to form different ring systems, especially medium and large rings in natural product synthesis. Ring-closing metathesis offers rearrangement of carbon-carbon double bonds in the presence of metal carbene complexes. It is one variety of alkene (olefin) metathesis.

Introduction

There are three main types of alkene metathesis reactions: 1) ring-closing metathesis (RCM), 2) cross metathesis and 3) ring-opening metathesis polymerisation (ROMP) (Figure 3). Ring-closing metathesis is a reaction that closes rings from acyclic dienes promoted by the catalysts. Ring opening metathesis polymerisation is, as its name implies, a reaction where a cyclic olefin is ring opened by the catalyst and then polymerises with another unit. Cross metathesis takes place intermolecularly between two olefins to yield a “dimerised” product (Figure 24). ROMP processes will not be further discussed here.

Ring-closing metathesis has been demonstrated to work efficiently despite different conformations of the starting material. No matter whether the conformation of the starting material is in the suitable arrangement or not, by modifying the reaction conditions, such as amount of catalyst added, time of addition, temperature and reaction time, macrocyclisation of the molecule can usually be achieved. This big advantage circumvented the usual considerations of ring closure for large ring systems (ring carbon $\geq 9$).
Result and Discussion

Catalysts

Although there are a lot of metal carbene catalysts developed from transition metal salts and their complexes with organometallic compounds, the most commonly used are molybdenum and ruthenium complexes. They are also known as Schrock and Grubbs catalysts, respectively. The catalysts can be used with a solid support.\textsuperscript{108}

Schrock catalyst is highly reactive towards a broad range of sterically or electronically varied substrates. However, it is highly sensitivity to air, moisture or even trace amounts of impurities present in solvent, which means reaction using Schrock catalyst has to be carried out in an inert atmosphere within a closed system. Its drawbacks also include moderate to poor functional group tolerance.\textsuperscript{109}

Grubbs catalysts are much more stable in air compared with the Schrock systems. They can be weighed out in open air without significantly reducing catalytic reactivity.\textsuperscript{110} They have a very good functional group tolerance towards many different functional groups, like most ethers, alcohols, secondary amides, carbamates.
and sulfonamides. Compared to Grubbs I catalyst, the second generation, Grubbs II catalyst has a higher thermal stability and is less sensitive to double bond substitution in alkene substrates (Figure 25).\textsuperscript{107}

\begin{align*}
\text{Cl}_2\text{PCy}_3 \quad \text{Cl} \quad \text{PCy}_3 \\
\text{Cl} \quad \text{PCy}_3 \\
\text{Cl} \quad \text{PCy}_3 \\
\text{Mes} \quad \text{N} \quad \text{Mes} \\
\text{Cl} \quad \text{Ru} \quad \text{Ph} \\
\text{Cl} \quad \text{PCy}_3 \\
\text{Pr} \quad \text{N} \quad \text{Pr'} \\
\text{(F}_3\text{C})_2\text{MeCO} \quad \text{Ph} \\
\text{(F}_3\text{C})_2\text{MeCO} \\
\end{align*}

Grubbs I catalyst \quad \text{Grubbs II catalyst} \quad \text{Schrock catalyst}

Figure 25

**Mechanism**

Ring-closing metathesis has an entirely different mechanism to other ring-closing reactions. It includes a new carbon-carbon bond formation through a four-membered metallacycle with the metal catalyst.

The mechanism of the ring closing metathesis proceeds through a series of [2+2] cycloadditions. The following is an example of a ring-closing metathesis reaction catalyzed by Grubbs II catalyst (Scheme 65).
The first step of the reaction is a [2+2] cycloaddition of the carbene complex (128) to one of the alkenes, forming a four-membered ring (129) containing the metal. Then, the same type of reaction occurs in reverse, cleaving two bonds of the four-membered ring, and generating a new carbene complex (130) with styrene as a leaving group. An intramolecular [2+2] cycloaddition occurs between the new carbene complex and the second alkene, in order to close the five-membered ring. A second metallacyclobutane (131) is made in this stage, which decomposes in the same way as before to give a methylene carbene complex and the product (132) required. This new carbene complex then attacks another molecule and repeats the cycle. The ring closing metathesis reaction cycle is reversible, so generation of a volatile leaving alkene will
drive the reaction forwards. In the case above, ethene is generated in every cycle after the first cycle (when Ru=CH₂ was generated and used as the catalyst).

**Attempted RCM to Form the 11-Membered Macrocyle**

To approach our target molecule, we need to furnish the 11-membered macrocycle and we decided to use Grubbs II catalyst to attempt the RCM reaction. Beginning with a simpler version, the mono-C-allylated product, 5-allyl-3-(2-allyloxy-phenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) was reacted with Grubbs II catalyst in dry DCM under reflux to attempt to form a closed 11-membered ring molecule. A low concentration (0.01M) of 5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) was used to avoid dimerisation instead of intramolecular ring closure.¹¹² The ¹H NMR spectrum shows some indications of the product we needed, however, the mass spectrum did not match (Scheme 66).

Another ring-closing reaction was performed under the same condition and using Grubbs II catalyst with the di-allylated product 5,5-diallyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (125). 5-Cyclopentene-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (134) was isolated in 27 % yield. It proved that the Grubbs II catalyst we were using was active. Also it showed that the RCM between two adjacent allyl chains was much more efficient than two alkenyl chains that are far away from each other.
Result and Discussion

The failure of RCM to close the 11-membered ring may be caused by the rigidity of the structure of 5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124), reducing the flexibility of the molecule, and not allowing the two chains to come close enough for the catalyst to coordinate in a 4-membered ring. Molecular modeling by Spartan also showed a repulsive force by the carbonyl oxygen. The oxygen is sterically blocking the carbon chains (Figure 26).
Since ring closure of the 11-membered ring in our isoxazole system was unsuccessful, we were prompted to further our investigation in this area. We have tried ring closing a 12-membered ring, see if a larger ring size would allow a better conformation for the ring-closing metathesis to occur. In the same way as before, 3-(2-hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) was deprotonated by potassium carbonate in dry THF and then reacted with 4-bromo-but-1-ene to yield 3-(2-but-3-enyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (135), which has one more carbon atom than allyl derivative (117), in 4%. It was further deprotonated by LDA in dry THF and DMPU as a co-solvent at -78 °C. Allyl bromide was added at -78 °C to quench the reaction and give both mono-allylated and di-allylated product, 5-allyl-3-(2-but-3-enyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (136) and 5,5-diallyl-3-(2-but-3-enyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo-[d]isoxazol-4-one (137), both in 21% yield (Scheme 67). Mono-allylated product (136), was brought forward for RCM with Grubbs II catalyst in DCM at 40 °C. However, none of the desired product (138) was obtained and starting material recovered. The result suggested a ring with one more carbon (12-membered ring) also cannot be closed. The reason is probably the same as the 11-membered case, namely the rigidity and size of ring.
Thus, it seemed that the rigidity of the isoxazole ring disallowed the formation of 11-membered macrocycle. To overcome this problem, we decided to open the isoxazole ring. Isoxazole rings can be opened by a range of different reagents, SmI₂, Raney nickel and iron complex, Fe₂(CO)₉ etc. As a model reaction the isoxazole ring of 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) was opened successfully by Mo(CO)₆ (in moist MeCN) and hydrogen to yield 2-(amino-phenyl-methylene)-5-methylcyclohexane-1,3-dione (139) in 18 % for both conditions. Allyloxy substituted isoxazole, 3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) was opened by the Mo(CO)₆ protocol to yield 2-[(2-allyloxyphenyl)aminomethylene]-5-methylcyclohexane-1,3-dione (140) in 47 %. Hydrogenation was not tried in this case because the double bond of the allyl group
would be reduced at the same time. However, we were not able to ring-open the mono-C-allylated product, 5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) (Scheme 68). We have tried Mo(CO)$_6$, Raney nickel and SmI$_2$ reactions but none of these were able to open the isoxazole ring, and starting material was recovered. We have no idea why the isoxazole ring-opening of this compound was not successful, although we doubted whether it was affected by other active co-ordinating groups present in the molecule, since compounds (6) and (117) reacted successfully.

Scheme 68

6.3.4 Conclusion

Based on the information from compounds with an non-substituted phenyl group, we have made available the o-substituted phenylisoxazole building blocks, with different o-substituents, like hydroxyl, allyl and benzyl. We have looked at alkylation of the
hydroxyl group for approach 1, and an unexpected cyclised product was obtained. Nevertheless, this lactone might still be potentially useful for further synthesis.

For approach 2, we have applied our alkylation experience to the o-hydroxyphenylisoxazole building block to yield a precursor for an 11-membered macrocycle. However, the ring-closing metathesis by Grubbs II catalyst was unsuccessful.

6.4 Bis-o-Substituted Phenyl Group as Isoxazole Substituent
(Attempted Synthesis towards Colephomones A, B and C)

6.4.1 Formation of Building Blocks
Further to reactions using an ortho-substituted phenyl group as the aromatic isoxazole substituent, we decided also to investigate other substituted aromatic groups, which have the same aromatic substitution pattern as our target molecules, colephomones A, B and C. We have chosen a bis-ortho-substituted phenyl derivative, 2-bromo-6-methoxybenzaldehyde oxime (142) as the aromatic precursor. The OMe group acted as a protected form of OH, and the Br would be used for coupling to carbon substituents.

We could not find a suitable bis-ortho-substituted oxime commercially available, therefore, we prepared 2-bromo-6-methoxybenzaldehyde oxime (142) from o-anisaldehyde (143). o-Anisaldehyde (143) was reacted with N,N'-dimethylethylene diamine in ethanol to yield 2-(2-methoxyphenyl)-1,3-dimethylimidazolidine (144) in 72 %. i-BuLi was added to freshly distilled imidazolidine product (144), which was then treated with dibromotetrachloroethane after stirring in room temperature for 6 hours.
2-Bromo-6-methoxybenzaldehyde (145) was obtained in 35% as a yellow solid after acidic aqueous work-up. This aldehyde (145) was converted into oxime in the presence of hydroxylamine hydrochloride and sodium acetate to give 100% crude yield of 2-bromo-6-methoxybenzaldehyde oxime (142) (Scheme 69).

![Scheme 69](image)

6.4.2 Approach 1

2-Bromo-6-methoxybenzaldehyde oxime (142) was heated at reflux in chloroform with NCS and pyridine then extracted by DCM. Without purification, 2-bromo-6-methoxyphenylhydroximoyl chloride (146) was treated with 6 equiv. of pyrrolidine enamine (8) and triethylamine to yield methyl 5-methoxycarbonylmethyl-3-(2-bromo-6-methoxyphenyl)isoxazole-4-carboxylate (147) in just 5% (Scheme 70). The only reason for this low yield that we can propose is the steric effect of the two ortho substituents hindering 1,3-dipolar cycloaddition. Due to the time limitations, we decided not to carry forward as the yield was not yet good enough.
6.4.3 Approach 2

For the second approach, 2-bromo-6-methoxybenzaldehyde oxime (142) was brought to reflux with NCS and pyridine in chloroform. The extracted crude material was stirred with 5-methylcyclohexane-1,3-dione (10) in sodium isopropoxide to give 3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (148) in a decent 75% yield (based on 5-methylcyclohexane-1,3-dione) (Scheme 71).
3-(2-Bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (148) was reacted with allyl bromide or 1-bromo-3-methylbut-2-ene in LDA with DMPU as a co-solvent to yield the products shown in the table below (Table 7). In the \(^1\)H NMR spectra of alkylated products, the disappearance of the more downfield signals between 2.66-3.16 ppm, which represent protons next to the ketone group, suggested C5 alkylations.

<table>
<thead>
<tr>
<th>Starting material &amp; alkylating reagent</th>
<th>Co-solvent</th>
<th>reagents</th>
<th>Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(148)</td>
<td>DMPU</td>
<td>LDA 2.10 equiv.</td>
<td>(149)</td>
<td>18 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alkylating reagent 1.20 equiv.</td>
<td>(150)</td>
<td>17 %</td>
</tr>
<tr>
<td>(148)</td>
<td>DMPU</td>
<td>LDA 2.10 equiv.</td>
<td>(151)</td>
<td>22 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alkylating reagent 2.00 equiv.</td>
<td>(152)</td>
<td>23 %</td>
</tr>
</tbody>
</table>

Table 7
Result and Discussion

To synthesise the natural products coleophomones A, B and C, we needed to generate a double bond between the C6- and C7 positions. The di-alkylated product, 3-(2-bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (152) was chosen because the carbon chains are closest to those required in the final product. (152) was deprotonated by LDA in the presence of DMPU and then treated with phenylselenium bromide to yield 3-(2-bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (153) in 41 % (Scheme 72).
Result and Discussion

We attempted to ring-open the isoxazole of 3-(2-bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (153), and then oxidise the phenylselenyl group to give double bond in one-pot. However, no ring-opened product was resulted. It was assumed the Mo(CO)$_6$ failed to ring-open the isoxazole.

Sml$_2$ has been tried but failed as well. We have reversed the sequence of ring-opening and oxidation, i.e. an initial oxidation, but again no product was obtained. Lack of
time prevented further study along this route.

6.4.4 Conclusion

A bis-ortho-substituted isoxazole building block was made for both approach 1 and 2. Carbon chains and a phenylselenyl group were added on the C5 and C7 carbons respectively in approach 2 towards the structure of coleophomones. However, the isoxazole ring opening by Mo(CO)$_6$, Raney nickel and SmI$_2$ was unsuccessful. Therefore, we were unable to advance the synthesis towards coleophomones A, B and C. Deprotection-alkenylation of the phenolic group, and elaboration of the bromo substituent by coupling, remain to be studied.

6.5 o,m-Substituted Phenyl Group as Isoxazole Substituent

(Attempted Synthesis towards Coleophomone D)

6.5.1 Formation of Building Blocks

To syntheses coleophomone D, an ortho-meta-disubstituted benzaldehyde oxime was needed. 2-Acetoxymethyl-3-methoxybenzaldehyde oxime (154) was selected as a suitable 1,3-dipole precursor carrying substituents appropriate to coleophomone D. Oxime (154) was made from 2,3-dimethylanisole (155) by an initial photolytic bromination.$^{114}$ 2,3-Dimethylanisole (155) and freshly recrystallised NBS in CCl$_4$ was stirred under nitrogen, while being exposed to a 300 watt high intensity tungsten lamp. The reaction mixture was heated to reflux by the lamp. After 5 hours, 93 % of the desired tri-brominated product, 2-bromomethyl-3-(dibromomethyl)anisole (156) was obtained. A range of brominated products were collected with different equivalents of NBS and reaction conditions (Scheme 73), as demonstrated in the table below (Table 8).
**Table 8**

<table>
<thead>
<tr>
<th>NBS (equiv)</th>
<th>Solvent</th>
<th>Lamp (watt)</th>
<th>Time (h)</th>
<th>Product*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>cyclohexane</td>
<td>150</td>
<td>2</td>
<td>mono</td>
</tr>
<tr>
<td>3.0</td>
<td>cyclohexane</td>
<td>150</td>
<td>overnight</td>
<td>mono + di</td>
</tr>
<tr>
<td>3.0</td>
<td>CCl₄</td>
<td>150</td>
<td>3</td>
<td>Mono + di</td>
</tr>
<tr>
<td>3.0</td>
<td>CCl₄</td>
<td>150</td>
<td>overnight</td>
<td>Di</td>
</tr>
<tr>
<td>3.0</td>
<td>cyclohexane (10 mol % AIBN)</td>
<td>300</td>
<td>overnight</td>
<td>Di</td>
</tr>
<tr>
<td>3.0</td>
<td>CCl₄</td>
<td>300</td>
<td>5</td>
<td>Tri</td>
</tr>
<tr>
<td>4.0</td>
<td>CCl₄</td>
<td>300</td>
<td>overnight</td>
<td>Tetra</td>
</tr>
</tbody>
</table>

* mono (157), di (158), tri (156) and tetra (159) bromo derivatives

This photolytic bromination method was developed by Box's group in 1990, using NBS in CCl₄ under a 250 W outdoor spot light. Due to a delay with restrictions on purchasing CCl₄, we started initially to perform the bromination in a less toxic solvent,
cyclohexane (instead of CCl₄) with NBS under a 150 W high intensity tungsten lamp. However, only mono (157) and di (158) brominated products were observed, with 2.1 equiv. and 3.0 equiv. NBS respectively. No further product beyond di-bromination was achieved under this condition. Once we received the CCl₄, we attempted the same bromination again. However, surprisingly, a same result was observed even when we used CCl₄ with NBS under a 150 W high intensity tungsten lamp. We have contacted Box, the original author, regarding the conditions they used. He agreed with our observation of mono (157) and di (158) brominated products formation, and could not find any significant error in our reactions. We decided to use a higher intensity tungsten lamp with extended reaction time as our last trial. A 300 W high intensity tungsten lamp was shone onto the reaction mixture in CCl₄, and the tetra brominated compound was finally obtained.

We found that tri- and tetra- brominated products (156) and (159) could only be made by reactions with CCl₄ and 300 watt tungsten lamp. Any other conditions only produced mono- and di- brominated products (157) and (158). Tetrabromo (159) is crystalline, and we were able to obtain an X-ray crystal structure (Figure 26).

![Figure 26: X-ray crystal structure of (159) Appendix III](image)
The desired oxime (154) was made from tri-brominated product, 2-bromomethyl-3-(dibromomethyl)anisole (156). The tribromo compound was stirred with anhydrous sodium acetate in glacial acetic acid to yield 2-acetoxymethyl-3-methoxybenzaldehyde (160) in 65%. Further reaction with hydroxylamine hydrochloride and sodium acetate resulted in a 100% crude yield of 2-acetoxymethyl-3-methoxybenzaldehyde oxime (154) (Scheme 74).

Approach 1 was not tried on the ortho-meta-disubstituted benzaldehyde oxime, as the yield from the previous reactions with bis-ortho-substituted oxime was not satisfactory. Therefore, we moved on to Approach 2.

6.5.2 Approach 2
2-Acetoxymethyl-3-methoxybenzaldehyde oxime (154) was treated with NCS and pyridine in chloroform. The extracted crude product was stirred with 5-methylcyclohexane-1,3-dione (10) in sodium isopropoxide to yield 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-
4-one (162) in 38% yield (based on 5-methylcyclohexane-1,3-dione) (Scheme 75).

\[
\text{AcO} \quad \text{N} \quad \text{OH} \\
\text{MeO} \quad \text{(154)} \\
\rightarrow \text{NCS} \\
\text{AcO} \quad \text{N} \quad \text{Cl} \\
\text{MeO} \\
100\% \text{ crude} \ (161)
\]

\[
\text{Sodium isopropoxide} \text{ MeD} \rightarrow \text{NMR}
\]

\[
\text{Scheme 75}
\]

3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (162) was deprotonated by LDA with DMPU as co-solvent and then reacted with 1-bromo-3-methylbut-2-ene to yield mono-alkylated product, 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (163) and di-alkylated product, 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (164) in 15% and 23% respectively. Evidence of C5 alkylations was shown by disappearance of the C5 proton signals in the $^1$H NMR spectrum of (162). The more deshielded C5 protons next to the ketone at 2.62 ppm ($J$ 9.7 & 16.9 Hz) and 3.10 ppm ($J$ 5.0 & 16.9 Hz) were absent after alkylations, showing the protons at C5 were replaced by alkylating groups.

After the carbon chains addition, we next attempted double bond generation at C-6 and C-7, which again was needed for the coleophomone D. Di-alkylated product (164)
was treated with LDA and phenylselenium bromide in DMPU to yield 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (165) in 39%. The isoxazole ring was opened by Mo(CO)$_6$, without purification, and the crude product was further treated with H$_2$O$_2$ to oxidise the phenylselenyl group which then underwent elimination to produce the double bond. 2-[1-Amino-1-[3-methoxy-2-(2-oxo-propoxy)-phenyl]-meth-(E)-ylidene]-5-methyl-6,6-bis-(3-methyl-but-2-enyl)-cyclohex-4-ene-1,3-dione (166) was obtained in 20% (Scheme 76). Due to the time limitations, we have not been able to continue to coleophomone D.
However, the steps left should be very straightforward. According to Nicolaou's research, the carbonyl group at the ortho position of (166) can be made by simple removal of the acetyl group using K₂CO₃ in MeOH followed by oxidation with MnO₂. Hydrolysis of the enaminoketone at some stage should yield coleophomone D (Scheme 77).
6.5.3 Conclusion

An o,p-disubstituted phenylisoxazole building block was made for approach 2. We successfully performed reactions, such as alkylation, isoxazole ring opening and phenylselenyl group elimination to generate a double bond on the building block. These work well and developed an isoxazole route towards the natural target molecule, coleophomone D.

7.0 Final Conclusion

Two approaches to syntheses of the coleophomones A, B, C and D have been tried. Although we have not completed the total synthesis, we have made the precursors for the coleophomone family by an isoxazole route. A precursor (166) for coleophomone D was made in an overall yield of 0.41% from 2-acetoxymethyl-3-methoxybenzaldehyde oxime (154) with
5-methylcyclohexane-1,3-dione (10). According to Nicolaou’s work, we will be able to make the final product easily by deprotecting our precursor (166) to generate the hydroxyl group and oxidise to aldehyde.

The isoxazole ring-opening of (153) was unsuccessful using Mo(CO)₆, Raney nickel and SmI₂. However, we are confident that the cleavage can be achieved by another suitable reagent. As long as the ring opening is successful, coleophomones A, B and C could be synthesed from it. The compound (153) was made in an overall yield of 1.78%.

Comparing the two approaches we have tried, we concluded that route 2 is more effective than route 1. Route 1) was through the isoxazole ring with ketone or ester substituents and route 2) through a reduced benzisoxazole. The attempts at formation of a six-membered ring between the two esters for route 1 were not successful, and a low yield was obtained from the 1,3-dipolar cycloaddition.

Although the natural target molecules were not achieved, we have made available several analogues of the coleophomone family, which could be very valuable compounds.
8.0 Experimental - General

**Infrared spectra** were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer as liquid films, nujol mulls, chloroform solutions, neat (from evaporation of an acetonitrile or dichloromethane solution) or in KBr discs as stated.

**NMR spectra** were measured on either a Bruker AC Broadband HX 5mm probe 250 MHz or 400 MHz Avance 5mm B.B. dual gradients probe FTNMR spectrometer using CDCl$_3$, d$_4$-methanol, d$_6$-acetone or d$_6$-DMSO as the solvent as indicated. Coupling constant ($J$) values are given in Hz.

**Mass spectra** were measured by JEOL SX 102 high resolution spectrometer, and EPSRC National Mass Spectrometry Service Centre (University of Wales Swansea).

**Flash column chromatography** was performed with silica gel 60 (40-63 µ, 230-400 mesh, 60 A), unless stated otherwise. TLC analyses were performed on Merck UV active aluminium plates coated with 0.2 mm silica 60 F$_{254}$ or on alumina plastic plates.

**Melting point** measurement was performed on Gallenkamp hot stage or Stuart Scientific (SMP3) melting point apparatus and they are mostly uncorrected.

**Combustion microanalysis** was performed on a Perkin Elmer Analyser 2400 CHN and by Warwick Analytical Service. Results are given as percentages.

Commercial reagents were normally used without further purification, unless stated. Dry tetrahydrofuran (THF) was freshly distilled from sodium over pre-dried THF.
Experimental with benzophenone. Dichloromethane, ethyl acetate and petroleum ether (40-60 °C) were distilled according to standard methods for general use. Reagents were purified when necessary using standard procedures. Standard techniques were employed for handling air-sensitive reagents and all air-sensitive reaction were carried out under a nitrogen atmosphere.

8.1 Experimental

*Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5)*

\[
\begin{align*}
\text{Benzaldehyde oxime (1.36 g, 11.24 mmol) in chloroform (50 ml) was added to} \\
\text{N-chlorosuccinimide (1.64 g, 12.36 mmol) in chloroform (50 ml). The mixture was} \\
\text{then heated under reflux in a 3-necked flask under an atmosphere of nitrogen for 1.5 h.} \\
\text{The solution was checked by TLC to confirm that no N-chlorosuccinimide was} \\
\text{present. After cooling to room temperature, dimethyl} \\
\text{3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (15.33 g, 67.44 mmol) was added in one} \\
\text{portion, followed by triethylamine (1.70 ml, 12.36 mmol) in chloroform (5 ml)} \\
\text{dropwise over 45 min. The reaction mixture was heated under reflux at an atmosphere} \\
\text{of nitrogen for 3 h and then left to stir at room temperature for 16 h. The reaction} \\
\end{align*}
\]
mixture was concentrated \textit{in vacuo} to yield a yellow oil, which was purified by flash column chromatography on silica gel using petroleum ether:ethyl acetate (5:3 v/v) as eluent to yield methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (1.32 g, 43 \%) as a yellow oil; MS (EI+) found 275.0798, C_{14}H_{13}NO_{5}; requires 275.0794; \nu_{\text{max}} \text{(neat)/cm}^{-1} 1741 (C=O), 2848, 2873 and 2953 (CH_{2}, CH_{3}); \delta_{H} (250MHz; CDCl_{3}) 3.75 (s, 6H, 2 x CH_{3}), 4.19 (s, 2H, CH_{2}) and 7.40-7.44 (m, 3H, 3 x Ar-H), 7.62-7.65 (m, 2H, 2 x Ar-H); \delta_{C} (100MHz; CDCl_{3}) 33.5 (2 x CH_{3}), 37.6 (CH_{2}), 109.8 (C), 128.1 (2 x Ar-CH), 129.4 (2 x Ar-CH), 121.0 (Ar-CH), 132.4 (Ar-C), 161.4 (C), 161.8 (C), 167.3 (C), and 171.3 (C).

Product in 55 \% was obtained if DCM extracted chlorinated oxime was used.

\textit{6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6)}

\[
\begin{align*}
\text{N} & \equiv \text{OH} \quad + \quad \begin{array}{c}
\text{O} \\
\text{C}
\end{array} \\
\text{(83)} & \quad \text{Sodium isopropoxide} \\
\text{(10)} & \quad \text{(6)}
\end{align*}
\]

To a solution of sodium isopropoxide prepared from sodium (0.45 g, 19.60 mmol) in isopropyl alcohol (100 ml), were added successively 5-methylcyclohexane-1,3-dione (10) (2.47 g, 19.60 mmol) and phenylhydroximoyl chloride (83) (1.47 g, 9.37 mmol). After stirring for 1 h at room temperature, the reaction mixture was poured into water (50 ml), and extracted with ethyl acetate (1 x 300 ml, 2 x 50 ml). The combined organic layer was washed with brine (2 x 100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash
column chromatography using petroleum ether:diethyl ether (2:1 v/v) as eluent to yield 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) (1.30 g, 61 %) as a white solid; mp 105-106 °C; MS (EI+) found 227.0947, C_{14}H_{13}NO_{2}; requires 227.0946; \nu_{max} (CHCl_3)/cm^{-1} 1687 (C=N), 1720 (C=O), 2872, 2927 and 2958; \delta_H (400MHz; CDCl_3) 1.17 (d, J 6.6, 3H, CH_3), 2.30 (dd, J 11.1 and 16.0, 1H, OCCH_2), 2.46-2.50 (m, 1H, CH), 2.61 (dd, J 3.8 and 16.0, 1H, OCCH_2), 2.64 (dd, J 10.0 and 17.4, 1H, O=CCH_2), 3.13 (dd, J 4.8 and 17.4, 1H, O=CCH_2) and 7.37-7.43 (m, 3H, 3 x Ar-H), 7.97-8.01 (m, 2H, 2 x Ar-H); \delta_C (100MHz; CDCl_3) 20.8 (CH_3), 30.3 (CH), 31.3 (CH_2), 47.2 (CH_2), 114.0 (C), 128.4 (2 x Ar-CH), 129.2 (2 x Ar-CH), 130.6 (Ar-CH), 132.4 (Ar-C), 159.9 (C), 182.0 (C) and 191.6 (C).

Dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8)

Dimethyl 1,3-acetonedicarboxylate (17.00 g, 97.61 mmol) and pyrrolidine (8.22 ml, 98.89 mmol) were heated in dry toluene (165 ml) at reflux under a Dean-Stark trap for 2 h. Water was separated (1.77 ml, 97.61 mmol) and the solvent was evaporated in vacuo to give dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (22.10 g, 100 %) as a yellow oil, which was used without purification, MS (FAB+) found 228.1233 [M+H], C_{11}H_{17}NO_{4}; requires 228.1236 [M+H]; \nu_{max} (neat)/cm^{-1} 1740 (C=O), 2870 and 2949 (CH_2, CH_3); \delta_H (250MHz; CDCl_3) 1.88-1.94 (m, 4H, CH_2CH_2), 3.18-3.35
Experimental

(\text{m}, 4\text{H}, \text{CH}_2\text{NCH}_2), 3.57 (\text{s}, 3\text{H}, \text{CH}_3), 3.69 (\text{s}, 3\text{H}, \text{CH}_3), 4.12 (\text{s}, 2\text{H}, \text{CH}_2) \text{ and } 4.56 (\text{s}, 1\text{H}, \text{CH}); \delta \text{C} (100\text{MHz}; \text{CDCl}_3) 25.1 (\text{CH}_2\text{CH}_2), 35.5 (\text{CH}_2), 48.0 (\text{CH}_2\text{NCH}_2), 49.8 (\text{CH}_3), 50.1 (\text{CH}_3), 52.2 (\text{CH}), 154.6 (\text{C}), 169.3 (\text{C}) \text{ and } 170.2 (\text{C}).

5-Carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78)

Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (4.46 g, 16.21 mmol) was heated at reflux with sodium hydroxide (1.62 g, 40.53 mmol) in water (30 ml) and methanol (10 ml) for 16 h. After reflux, the solution was cooled, filtered and acidified by concentrated hydrochloric acid to pH 1. The resultant white solid was filtered and washed with dry ether (5 ml) to yield 5-carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78) (0.75 g, 81 %) as a light yellow solid; mp 192-193 °C; MS (FAB+) found 248.0565 [M+H], C_{12}H_{10}NO_5; requires 248.0559 [M+H]; \nu_{\text{max}} (\text{Nujol})/\text{cm}^{-1} 1642 (\text{C}=\text{N}), 1728 (\text{C}=\text{O}), 2863 \text{ and } 2944 (\text{CH}_2); \delta \text{H} (250\text{MHz}; \text{d}_6-\text{DMSO}) 4.20 (\text{s}, 2\text{H}, \text{CH}_2), 7.49-7.53 (\text{m}, 3\text{H}, 3 \times \text{Ar-H}), 7.62-7.65 (\text{m}, 2\text{H}, 2 \times \text{Ar-H}) \text{ and } 13.18 (\text{broad peak}, 2\text{H}, 2 \times \text{OH}); \delta \text{C} (100\text{MHz}; \text{d}_6-\text{DMSO}) 36.8 (\text{CH}_2), 109.7 (\text{C}), 128.1 (2 \times \text{Ar-CH}), 129.2 (2 \times \text{Ar-CH}), 129.9 (\text{Ar-CH}), 132.3 (\text{Ar-C}), 161.1 (\text{C}), 161.7 (\text{C}), 167.2 (\text{C}) \text{ and } 171.1 (\text{C}).
Experimental

\textbf{Methyl}

5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) (Method A)

\[ \text{Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (0.10 g, 0.36 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (2.0 equiv.; 0.72 mmol), which was prepared from \textit{n}-butyllithium (2.5 M solution in hexanes; 0.29 ml, 0.73 mmol) and diisopropylamine (0.12 ml, 0.84 mmol) in dry THF (2 ml) at 0 °C. The resulting mixture was allowed to stir at -78 °C for 30 min. 1-Bromo-3-methyl-2-butene (0.04 ml, 0.36 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (5 ml) was added and the mixture was extracted with diethyl ether (3 x 15 ml). The combined extracts were washed with brine (1 x 30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) (0.09 g, 70%) as a yellowish oil; MS (EI+) found 343.1419 [M+H]+, \textit{C}_{19}\text{H}_{21}\text{NOS}; requires 343.1420 [M+H]+; \nu_{\text{\text{max}}} (\text{neat})/\text{cm}^{-1} 1734 (\text{C=O}), 2336 and 3012 (\text{CH}_2, \text{CH}_3); \delta_{\text{H}} (400\text{MHz}; \text{CDCl}_3) 1.51 (s, 3\text{H}, \text{CH}_3), 1.57 (s, 3\text{H}, \text{CH}_3), 2.70-2.80 (m, 2\text{H}, \text{CH}_2), 3.65 (s, 3\text{H}, \text{CH}_3), 3.67 (s, 3\text{H}, \text{CH}_3), 4.48 (dd, J 6.4 and 8.9, 1\text{H}, \text{CHCOOMe}), \]
5.00-5.04 (m, 1H, CH) and 7.34-7.42 (m, 3H, 3 x Ar-H), 7.53-7.57 (m, 2H, 2 x Ar-H);
$\delta_{C}$ (100MHz, CDCl$_3$) 17.7 (CH$_3$), 25.7 (CH$_3$), 28.7 (CH$_2$), 44.8 (CH), 51.5 (CH$_3$),
52.6 (CH$_3$), 58.7 (CH), 109.3 (C), 119.2 (C), 128.1 (2 x Ar-CH), 129.3 (2 x Ar-CH),
129.9 (Ar-CH), 135.6 (Ar-C), 161.9 (C), 162.4 (C), 169.8 (C) and 174.6 (C).

Methyl

$5$-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79)

(Method B)

Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (0.12 g, 0.45 mmol) in dry
THF (5 ml) was added to n-butyllithium (2.5 M in hexane) (2.5 equiv.,
0.45 ml, 1.12 mmol) at -78 °C. The reaction was stirred for 15 min before
1-bromo-3-methyl-2-butene (0.11 ml, 0.98 mmol) was added also at -78 °C. The
reaction mixture was allowed to warm to room temperature and stirred overnight.
Saturated sodium hydrogen carbonate solution (5 ml) was added, the reaction mixture
was then extracted with diethyl ether (3 x 15 ml) and the combined extracts were
Experimental

washed with brine (1 x 30 ml). The organic extract was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (3:1 v/v) as eluent. Only mono-alkylated product, methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) was obtained (0.06 g; 47 %) as a yellowish oil. Spectroscopic data as reported above.

Methyl

5-[1-methoxycarbonyl-4-methyl-1-(3-methylbut-2-enyl)pent-3-enyl]-3-phenylisoxazole-4-carboxylate (80)

(Method A)

Methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) (0.11 g, 0.32 mmol) in dry THF (5 ml) was added to n-butyllithium (2.5 M in hexane) (1.5 equiv., 0.19 ml, 0.48 mmol) at -78 °C. The reaction was stirred for 30 min before 1-bromo-3-methyl-2-butene (0.04 ml, 0.38 mmol) was added also at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (5 ml) was added, the reaction mixture was then extracted with diethyl ether (3 x 10 ml) and the combined extracts were washed with brine (1 x 30 ml). The organic extract was dried over
magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield methyl 5-[1-methoxycarbonyl-4-methyl-1-(3-methylbut-2-enyl)pent-3-enyl]-3-phenylisoxazole-4-carboxylate (80) (0.03 g, 23%) as a yellow oil; MS (FAB+) found 412.2130 [M+H], C_{24}H_{29}NO_{5}; requires 412.2124 [M+H]; \nu_{\text{max}} \text{(neat)/cm}^{-1} 1734 \text{(C=O), 2363 and 3052 (CH}_2, \text{CH}_3); \delta_H \text{(400MHz; CDCl}_3) 1.48 \text{(s, 6H, 2 x CH}_3), 1.60 \text{(s, 6H, 2 x CH}_3), 2.75-2.84 \text{(m, 4H, 2 x CH}_2), 3.60 \text{(s, 3H, CH}_3), 3.62 \text{(s, 3H, CH}_3), 4.89-4.94 \text{(m, 2H, 2 x CH)} and 7.36-7.41 \text{(m, 3H, 3 x Ar-H)}, 7.52-7.54 \text{(m, 2H, 2 x Ar-H)}; \delta_C \text{(100MHz; CDCl}_3) 17.8 \text{(2 x CH}_3), 26.0 \text{(2 x CH}_3), 30.3 \text{(2 x C), 32.7 (2 x CH}_2), 44.7 \text{(2 x CH), 51.5 (CH}_3), 52.1 \text{(CH}_3), 53.7 \text{(C), 117.6 \text{(C), 128.1 (2 x Ar-CH), 129.3 (2 x Ar-CH), 129.8 (Ar-CH), 136.0 (Ar-C), 162.1 (C), 162.9 (C), 172.0 (C) and 177.7 (C).}

*Methyl*

5-[1-methoxycarbonyl-4-methyl-1-(3-methylbut-2-enyl)pent-3-enyl]-3-phenylisoxazole-4-carboxylate (80) (Method B)

\[
\begin{align*}
\text{(79)} & \quad \quad \quad \quad \text{1.2 equiv. } n-\text{BuLi,} \\
& \quad \quad \quad \quad \text{Pd(O) 10%} \\
\text{(80)} & \quad \quad \quad \quad \text{1.2 equiv. } \text{Br} \\
\end{align*}
\]

Methyl 5-(1-methoxycarbonyl-4-methylpent-3-enyl)-3-phenylisoxazole-4-carboxylate (79) (0.19 g, 0.55 mmol) in dry THF (5 ml) was added to n-butyllithium (2.5 M in
hexane) (1.2 equiv., 0.26 ml, 0.65 mmol) at -78 °C. The reaction was stirred for 30 min before Pd(PPh₃)₄ (10 %; 0.06 g, 0.05 mmol) was added. After stirring for further 5 min, 1-bromo-3-methyl-2-butene (0.08 ml, 0.65 mmol) was added also at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (5 ml) was added, the reaction mixture was then extracted with diethyl ether (3 x 15 ml) and the combined extracts were washed with brine (1 x 30 ml). The organic extract was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield methyl 5-[1-methoxycarbonyl-4-methyl-1-(3-methylbut-2-enyl)pent-3-enyl]-3-phenylisoxazole-4-carboxylate (80) (0.06 g, 25 %) as a yellow oil. Spectroscopic data as reported above.

5-[(N-methoxy-N-methylcarbamoyl)methyl]-3-phenylisoxazole-4-carboxylic acid N-methoxy-N-methylamide (81) (Method A)

5-Carboxymethyl-3-phenylisoxazole-4-carboxylic acid (78) (0.04 g, 0.13 mmol) was dissolved in dry DCM (10 ml). N,O-Dimethylhydroxylamine hydrochloride in dry
Experimental

DCM (2 ml) and \(N\)-methylmorpholine (0.03 ml, 0.27 mmol) were added to the reaction at 0 °C followed by EDCI (0.05 g, 0.27 mmol) in dry DCM (1 ml) again at 0 °C. The mixture was stirred at 0 °C for 1 h. Cold hydrochloric acid (1 M; 3 ml) was added to the reaction mixture, and the mixture was extracted with DCM (10 ml). The organic layer was washed with saturated sodium hydrogencarbonate solution (3 ml) and then dried by magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude material was purified by flash column chromatography using methanol (10 %) in DCM as eluent to yield 5-[(\(N\)-methoxy-\(N\)-methylcarbamoyl)methyl]-3-phenylisoxazole-4-carboxylic acid \(N\)-methoxy-\(N\)-methylamide (81) (0.23 g, 48 %) as a yellowish brown oil; MS (EI+) found 334.1394 [M+H], \(C_{16}H_{19}N_{3}O_{5}\); requires 334.1397 [M+H]; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 1574, 1614 (amide) and 1754; \(\delta_{H}\) (400MHz; CDCl\(_3\)) 3.13 (s, 3H, CH\(_3\)), 3.22 (s, 3H, CH\(_3\)), 3.78 (s, 3H, OCH\(_3\)), 4.16 (s, 3H, OCH\(_3\)), 5.07 (s, 2H, CH\(_2\)), 7.41-7.48 (m, 3H, 3 x Ar-H) and 7.64-7.68 (m, 2H, 2 x Ar-H); \(\delta_{C}\) (100MHz; CDCl\(_3\)) 30.5 (CH\(_2\)), 32.4 (2 x CH\(_3\)), 61.6 (2 x OCH\(_3\)), 112.4 (C), 127.5 (2 x Ar-C), 127.5 (C), 128.1 (C), 128.7 (2 x Ar-C), 129.3 (C), 130.0 (Ar-C) and 167.3 (2 x C=O).
**Experimental**

5-[(N-methoxy-N-methylcarbamoyl)methyl]-3-phenylisoxazole-4-carboxylic acid

*N*-methoxy-*N*-methylamide (81)

( Method B )

\[
\begin{align*}
\text{OMe} & \\
\text{N,O-Dimethylhydroxylamine} & \text{hydrochloride} & \text{OMe} \\
\text{AIMe} & 3 & I \\
\end{align*}
\]

\[N,O\text{-Dimethylhydroxylamine hydrochloride (12.76 g, 130.79 mmol) was dissolved in}
\text{dry DCM (100 ml) under an atmosphere of nitrogen at -10 °C. Trimethylaluminium}
(2.0 M in hexane) (65.39 ml, 130.79 mmol) was added dropwise at -10 °C, and the}
reaction was stirred for 1 h. Methyl 5-methoxycarbonylmethyl-3-phenylisoxazole-4-carboxylate (5) (6.00 g, 21.80 mmol)
in dry DCM (20 ml) was added at -10 °C over 1 h by syringe. The mixture was then
left to stir at room temperature overnight. Water (100 ml) was added at 0 °C to quench
the reaction. It was then extracted with DCM (3 x 100 ml). The combined organic
fractions were dried by sodium sulfate, filtered and evaporated under reduced pressure.
The crude material was purified by flash column chromatography using petroleum
ether:ethyl acetate (1:1 v/v) as the eluent to yield the product 5-[(N-methoxy-N-methylcarbamoyl)methyl]-3-phenylisoxazole-4-carboxylic acid
*N*-methoxy-*N*-methylamide (81) (0.32 g, 4 %) as a brown oil. Spectroscopic data as
reported above.
**Phenylhydroximoyl chloride (83)**

Benzaldehyde oxime (3.73 g, 30.82 mmol) in chloroform (30 ml) and pyridine (0.25 ml, 3.07 mmol) were mixed in a reaction flask. The mixture was stirred under the atmosphere of nitrogen and the temperature was raised to 50 °C. *N*-Chlorosuccinimide (4.53 g, 33.90 mmol) was added to the mixture and stirred at 50 °C for 3 h. The reaction mixture was diluted by DCM (200 ml). The organic layer was washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the phenylhydroximoyl chloride (83) (3.90 g, 81 %) as greenish-yellow crystals. The solid was unstable, unless stored under nitrogen in a refrigerator. $v_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 785 (CCl), 1526, 3147 and 3316 (OH broad peak); $\delta_H$ (250MHz; CDCl$_3$) 7.30-7.35 (m, 3H, 3 x Ar-H), 7.71-7.74 (m, 2H, 2 x Ar-H) and 9.06 (broad peak, H, OH). Unstable compound, decomposed during MS and carbon NMR studies.
Pyridinium hydrobromide perbromide (0.17 g, 0.53 mmol) was added to 6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[e]isoxazol-4-one (6) (0.10 g, 0.44 mmol) in DCM (10 ml). Glacial acetic acid (1.2 ml) was added and the mixture was warmed slightly. The colour of the reaction changed to pale yellow. The reaction was stirred at room temperature for 3 h. It was then extracted with diethyl ether (1 x 15 ml). The combined extracts were washed with water (2 x 15 ml), dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield 5-bromo-6-methyl-3-phenyl-4,5,6,7-tetrahydrobenz[e]isoxazol-4-one (85) (0.09 g, 66 %) as a pale yellow solid; mp 133-134 °C; MS (EI+) found 305.0050 (Br7); C14H12NO2Br; requires 305.0051 (Br7); v_max (CHCl3)/cm⁻¹ 738 (CBr), 1697 (C=O) and 2985 (CH2,CH3); δ_H(400MHz; CDCl3) 1.32 (d, J 4.0, 3H, CH3), 2.43-2.45 (m, 1H, MeCH), 2.86 (dd, J 10.6 and 17.7, 1H, OCCH2), 3.00 (dd, J 4.9 and 17.7, 1H, OCCH2), 4.41 (d, J 2.7, 1H, CH) and 7.46-7.50 (m, 3H, 3 x Ar-H), 8.01-8.03 (m, 2H, 2 x Ar-H); δ_C (100MHz; CDCl3) 18.6 (CH3), 27.9 (CH2), 34.4 (CH), 58.3 (CH), 111.4 (C), 128.5 (2 x Ar-CH), 129.1 (2 x Ar-CH), 130.8 (Ar-CH), 132.1 (Ar-C), 160.7 (C), 180.8 (C) and 185.2 (C).
5-Bromo-6-methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[\textit{d}]isoxazol-4-one (85) (0.05 g, 0.22 mmol) was dissolved in dry DMF (3 ml). The solution was heated to 50 °C under an atmosphere of nitrogen and 1,5-diazabicyclo[4.3.0]non-5-ene (0.04 ml, 0.26 mmol) was added dropwise. The mixture was stirred at 50 °C for 1 h. Saturated sodium hydrogen carbonate solution (5 ml) was added to quench the reaction mixture. Diethyl ether (10 ml) was added and the mixture was washed with brine (4 x 10 ml). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield 6-methyl-3-phenylbenzo[\textit{d}]isoxazol-4-ol (84) (0.02 g, 41 %) as a white powder; mp 176-177 °C; MS (FAB+) found 226.0874 [M+H], C_{14}H_{11}NO_2; requires 226.0868 [M+H]; v_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1633, 1650, 1693 (C=\text{N}), 1712, 1731 (C=\text{O}), 2356, 2985 (CH_3), 3053 and 3416; δ_\text{H} (400MHz; d_4-MeOH) 2.33 (s, 3H, CH_3), 6.45 (s, 1H, CH), 6.81 (s, 1H, CH) and 7.38-7.40 (m, 3H, 3 x Ar-H), 7.88-7.90 (m, 2H, 2 x Ar-H); δ_\text{C} (100MHz; d_4-MeOH) 22.0 (CH_3), 101.7 (CH), 108.9 (C), 110.8 (CH), 129.2 (2 x Ar-CH), 130.4 (2 x Ar-CH), 130.7 (Ar-CH), 130.8 (Ar-C), 144.6 (C), 154.0 (C), 159.1 (C) and 167.9 (C); Found C, 74.44; H, 4.77; N, 5.93; C_{14}H_{11}NO_2 requires C, 74.65; H, 4.92; N, 6.22.
4-Acetoxy-6-methyl-3-phenylbenzo[d]isoxazole (86)

6-Methyl-3-phenylbenzo[d]isoxazol-4-ol (84) (0.04 g, 0.06 mmol) was dissolved in DCM (5 ml). Acetic anhydride (0.01 ml, 0.06 mmol) and pyridine (0.01 ml, 0.06 mmol) were added. The reaction mixture was heated at reflux for 4 h. Solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (4:1 v/v) as eluent to yield 4-acetoxy-6-methyl-3-phenylbenzo[d]isoxazole (86) (0.02 g, 100%) as a white powder; mp 94 °C; MS (EI+) found 267.0898, C_{16}H_{13}NO_{3}; requires 267.0895; \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 1685, 1701 (\text{C}=\text{O}), 2358 and 2988 (\text{CH}_3); \delta_{\text{H}}(400\text{MHz}; \text{CDCl}_3) 1.87 (s, 3H, \text{CH}_3), 2.47 (s, 3H, OCOCH_3), 6.81 (s, 1H, CH), 7.27 (s, 1H, CH) and 7.44-7.45 (m, 3H, 3 x Ar-H), 7.65-7.68 (m, 2H, 2 x Ar-H); \delta_{\text{C}}(100\text{MHz}; \text{CDCl}_3) 19.9 (\text{CH}_3), 20.5 (\text{CH}_3), 100.9 (\text{C}), 107.6 (\text{CH}), 116.7 (\text{CH}), 127.9 (\text{C}), 129.1 (2 x \text{Ar-CH}), 130.8 (2 x \text{Ar-CH}), 131.2 (\text{Ar-CH}), 131.3 (\text{Ar-C}), 144.3 (\text{C}), 153.9 (\text{C}), 159.0 (\text{C}) and 167.7 (\text{C}); Found C, 72.19; H, 5.12; N, 5.29; C_{16}H_{13}NO_{3} requires C, 71.90; H, 4.90; N, 5.24.
Experimental

5-Bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (87)

or 7-bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (88)

Bromine (0.02 ml, 0.36 mmol) was added dropwise to a mixture of 6-methyl-3-phenylbenzo[d]isoxazol-4-ol (84) (0.08 g, 0.36 mmol) in methanol (5 ml), glacial acetic acid (0.5 ml) and water (5 ml). The reaction vessel was cooled in ice throughout the addition. After stirring the mixture vigorously over a period of 3.5 h, brine (10 ml) was added to saturate the reaction mixture. The two layers were separated and the aqueous layer was extracted with diethyl ether (2 x 30 ml). The combined organic phase was washed with saturated sodium hydrogen carbonate solution (3 x 30 ml) and brine (1 x 30 ml), dried over magnesium sulfate, filtered and concentrated in vacuo to yield the crude product. The crude product was purified by flash column chromatography using petroleum ether:diethyl ether (1:1 v/v) as eluent to yield the bromo-derivative (87) or (88) (0.02 g, 18 %); mp 195-196 °C; MS (FAB+) found 302.9889 (Br79), C14H10NO2Br79; requires 302.9895 (Br79); νmax (CHCl3)/cm⁻¹ 731 (CBr), 1687, 1720 (C=O) and 2895 (CH3); δH (250MHz; CDCl3) 2.73 (s, 3H, CH3), 6.34 (s, 1H, Ar-CH) and 7.49-7.54 (m, 3H, 3 x Ar-H), 7.92-7.96 (m, 2H, 2 x Ar-H); δC (100MHz; CDCl3) 22.0 (CH3), 101.9 (CH), 110.0(C), 115.4 (CBr), 129.7 (2 x Ar-CH), 130.8 (2 x Ar-CH), 131.0 (Ar-CH), 131.2 (Ar-C), 144.8 (C), 154.2 (C), 159.3 (C) and 168.0 (C); Position of bromination cannot be identified by nOe.
Experimental

6-Methyl-4-(3-methylbut-2-enyloxy)-3-phenylbenzo[d]isoxazole (89)

6-Methyl-3-phenylbenzo[d]isoxazol-4-ol (84) (0.02 g, 0.07 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (3.0 equiv.; 0.21 mmol), which was prepared from n-butyllithium (2.5 M solution in hexanes; 0.09 ml, 0.21 mmol) and diisopropylamine (0.04 ml, 0.26 mmol) in dry THF (2 ml) at 0 °C. The resulting mixture was allowed to stir at -78 °C for 15 min. 1-Bromo-3-methyl-2-butene (0.01 ml, 0.09 mmol) was added at -78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (5 ml) was added and the mixture was extracted with DCM (3 x 15 ml). The combined organic layer was washed with brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:diethyl ether (10:1 v/v) as eluent to yield 6-methyl-4-(3-methylbut-2-enyloxy)-3-phenylbenzo[d]isoxazole (89) (0.01 g, 58 %) as a yellow oil; MS (FAB+) found 294.1498 [M+H], C19H19NO2; requires 294.1494 [M+H]; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 1617, 1672 and 2919 (CH\(_2\), CH\(_3\)); \( \delta_{\text{H}} \) (250MHz; CDCl\(_3\)) 1.61 (s, 3H, CH\(_3\)), 1.70 (s, 3H, CH\(_3\)), 2.42 (s, 3H, CH\(_3\)), 4.51 (d, \( J = 6.8 \), 2H, OCH\(_2\)), 5.34-5.38 (m, 1H, CHC), 6.43 (s, 1H, ArH), 6.92 (s, 1H, Ar-H), 7.36-7.40 (m, 3H, 3 x Ar-H), 7.89-7.91 (m, 2H, 2 x Ar-H); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 18.1 (CH\(_3\)), 18.3 (CH\(_3\)), 22.4 (CH\(_3\)), 25.7 (Me\(_2\)C), 65.3 (CH), 102.5 (CH), 106.3 (C), 118.8 (CH), 127.9 (2 x
Experimental

Ar-C), 129.1 (Ar-C), 129.6 (Ar-C), 129.9 (2 x Ar-C) 138.4 (CH2O), 142.7 (C), 153.5 (C), 157.8 (C) and 166.3 (C).

4-Methoxy-6-methyl-3-phenylbenzo[d]isoxazole (90)

6-Methyl-3-phenylbenzo[d]isoxazol-4-ol (84) (0.02 g, 0.07 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (3.0 equiv; 0.21 mmol), which was prepared from n-butyllithium (2.5 M solution in hexanes; 0.09 ml, 0.21 mmol) and diisopropylamine (0.04 ml, 0.26 mmol) in dry THF (2 ml) at 0 °C. The resulting mixture was allowed to stir at -78 °C for 15 min. Dimethyl sulfate (0.12 ml, 0.09 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (5 ml) was added and the mixture was extracted with DCM (3 x 15 ml). The combined organic layer was washed with brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:diethyl ether (10:1 v/v) as eluent to yield 4-methoxy-6-methyl-3-phenylbenzo[d]isoxazole (90) (0.06 g, 36 %) as a yellow oil, MS (EI+) found 239.0948, C15H13N02; requires 239.0946; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 1621, 1669 (C=N) and 2939 (CH\(_2\), CH\(_3\)); \( \delta_H \) (250MHz; CDCl\(_3\)) 2.43 (s, 3H, CH\(_3\)), 4.45 (s, 3H, OCH\(_3\)), 6.42 (s, 1H, ArH), 6.90 (s, 1H, Ar-H), 7.36-7.40 (m, 3H, 3
Experimental x Ar-H), 7.89-7.90 (m, 2H, 2 x Ar-H); δc (100MHz; CDCl3) 22.5 (CH₃), 102.3 (C), 127.5 (2 x Ar-C), 129.5 (Ar-C), 129.8 (Ar-C), 129.9 (2 x Ar-C) 139.2 (CH₃O), 143.4 (C), 153.5 (C), 157.8 (C) and 166.3 (C).

5-Bromo-6-methyl-7-(3-methylbut-2-enyl)-3-phenyl-benzo[d]isoxazol-4-ol (91) or 7-bromo-6-methyl-5-(3-methylbut-2-enyl)-3-phenyl-benzo[d]isoxazol-4-ol

\[
\text{N} \quad \text{O} \quad \begin{array}{c}
\text{Br} \\
\text{HO} \\
\text{Br}
\end{array} \quad \xrightarrow{2.0 \text{ equiv. LDA}} \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{Br}
\end{array} \quad \begin{array}{c}
\text{HO} \\
\text{Br}
\end{array}
\]

5-Bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (87) or 7-bromo-6-methyl-3-phenylbenzo[d]isoxazol-4-ol (88) (0.03 g, 0.11 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (2.0 equiv.; 0.21 mmol), which was prepared from n-butyllithium (2.5 M solution in hexane) (0.09 ml, 0.21 mmol) and diisopropylamine (0.04 ml, 0.26 mmol) in dry THF (2 ml) at 0 °C. The resulting mixture was allowed to stir at -78 °C for 30 min. 1-Bromo-3-methyl-2-butene (0.01 ml, 0.13 mmol) was added at -78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (3 ml) was added and the mixture was extracted with DCM (3 x 10 ml). The combined organic layer was washed with brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:ethyl acetate (10:1 v/v) as eluent to yield
Experimental

5-bromo-6-methyl-7-(3-methylbut-2-enyl)-3-phenylbenzo[d]isoxazol-4-ol (91) or
7-bromo-6-methyl-5-(3-methylbut-2-enyl)-3-phenyl-benzo[d]isoxazol-4-ol (0.01 g,
30 %) as yellow crystals; mp 137 – 138 °C; MS (EI+) found 371.0531 (Br79),
C19H18NO2Br79; requires 371.0521 (Br79); νmax (nujol)/cm⁻¹ 736 (CBr), 1651, 2252,
2978 (CH₂, CH₃) and 3153 (OH); δH (400MHz; CDCl₃) 1.25 (s, 3H, CH₃), 1.54 (s, 3H,
CH₃), 2.70 (s, 3H, CH₃), 4.04 (d, J 7.2, 2H, CH₂), 4.95-4.99 (m, 1H, CH), 7.43-7.48
(m, 3H, 3 x Ar-H) and 7.84-7.86 (m, 2H, 2 x Ar-H); δC (100MHz; CDCl₃) 17.7 (CH₃),
24.0 (CH₃), 25.8 (CH₃), 72.1 (CH₂), 100.0 (CMe₂), 114.1 (Ar-C), 115.7 (Ar-C), 118.4
(CH), 127.9 (Ar-C), 128.6 (2 x Ar-C), 129.6 (2 x Ar-C), 130.4 (Ar-C), 140.0 (CBr),
140.8 (COH), 149.2 (C), 158.2 (C) and 162.0 (C); Found C, 61.11; H, 4.89; N, 3.96;
C₁₉H₁₈NO₂Br requires C, 61.30; H, 4.87; N, 3.76.
6-Methyl-5-\((3\text{-methylbut-2-enyl})\)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazole-4-one (92) and 6-Methyl-5,5-bis-\((3\text{-methylbut-2-enyl})\)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazole-4-one (93) (Method A)

\[
\begin{align*}
\text{N-O} & \quad 2.0 \text{ equiv. LDA, THF:HMPA (6:1)} \\
\text{N-O} & \quad 1.0 \text{ equiv. Br}^+ \\
\end{align*}
\]

\(n\)-Butyllithium (2.5 M solution in hexanes; 0.18 ml, 0.45 mmol) and diisopropylamine (0.07 ml, 0.54 mmol) were added to dry THF (3 ml), followed by HMPA (0.5 ml) at 0 °C to make a LDA solution. The mixture was left to stir at 0 °C for 15 min. 6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazole-4-one (6) (0.05 g, 0.22 mmol) in dry THF (2 ml) at -78 °C was added dropwise to this freshly prepared solution of LDA (2.0 equiv.; 0.45 mmol). The resulting mixture was allowed to stir at -78 °C for 15 min. 1-Bromo-3-methyl-2-butene (0.03 ml, 0.22 mmol) was added at -78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (5 ml) was added and the mixture was extracted with DCM (3 x 10 ml). The combined organic fraction was washed with water (3 x 30 ml)
and brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:diethyl ether (2:1 v/v) as eluent to yield the mono-alkylated product, 6-methyl-5-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (92) (0.02 g, 21 %) as a yellow oil; MS (EI+) found 295.1573, C_{19}H_{21}NO_{2}; requires 295.1572; \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} \ 1689 \ (\text{C}=\text{O}), 2304, 2985 \text{ and } 3053 \ (\text{CH}_2, \ \text{CH}_3); \ \delta_H (400\text{MHz}; \text{CDCl}_3) 1.11 \ (d, \ J \ 6.1, \ 3H, \ \text{CH}_3), 1.60 \ (s, \ 3H, \ \text{CH}_3), 1.64 \ (s, \ 3H, \ \text{CH}_3), 2.31-2.41 \ (m, \ 1H, \ \text{MeCH}), 2.34 \ (dd, \ J \ 11.2 \text{ and } 16.1, \ 1H, \ \text{OCCH}_2), 2.52-2.66 \ (m, \ 2H, \ \text{CH}_2), 2.65 \ (dd, \ J \ 3.9 \text{ and } 16.1, \ 1H, \ \text{OCCH}_2), 2.84-2.86 \ (m, \ 1H, \ \text{O=CCH}), 5.02-5.05 \ (m, \ 1H, \ \text{CHCMe}_2), 7.39-7.42 \ (m, \ 3H, \ 3 \times \ \text{Ar-H}) \text{ and } 7.98-8.01 \ (m, \ 2H, \ 2 \times \ \text{Ar-H}); \ \delta_C (100\text{MHz}; \text{CDCl}_3) 18.0 \ (\text{CMe}), 19.3 \ (\text{CMe}), 25.9 \ (\text{CMe}), 28.1 \ (\text{CH}_2), 33.1 \ (\text{Ar-C}), 42.2 \ (\text{Ar-C}), 46.0 \ (\text{Ar-C}), 53.5 \ (\text{CMe}_2), 113.7 \ (\text{C}=\text{O}), 119.3 \ (\text{CCH}), 128.5 \ (2 \times \ \text{Ar-C}), 129.2 \ (2 \times \ \text{Ar-C}), 130.5 \ (\text{Ar-C}), 135.3 \ (\text{Ar-C}), 159.9 \ (\text{C}), 181.0 \ (\text{C}) \text{ and } 184.3 \ (\text{C}); \text{ and the di-alkylated product,}

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (93) (0.02 g, 21 %) as a yellow oil; MS (EI+) found 363.2201, C_{24}H_{29}NO_{2}; requires 363.2198; \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} \ 1682 \ (\text{C}=\text{O}), 2305, 2986 \text{ and } 3052 \ (\text{CH}_2, \ \text{CH}_3); \ \delta_H (400\text{MHz}; \text{CDCl}_3) 1.03 \ (d, \ J \ 6.6, \ 3H, \ \text{CH}_3), 1.42 \ (s, \ 3H, \ \text{CH}_3), 1.52 \ (s, \ 3H, \ \text{CH}_3), 1.57 \ (s, \ 3H, \ \text{CH}_3), 1.61 \ (s, \ 3H, \ \text{CH}_3), 2.37-2.78 \ (m, \ 5H, \ \text{CH} \text{ and } 2 \times \ \text{CH}_2), 2.45 \ (dd, \ J \ 11.1 \text{ and } 16.0, \ 1H, \ \text{OCCH}_2), 2.73 \ (dd, \ J \ 3.8 \text{ and } 16.0, \ 1H, \ \text{OCCH}_2), 4.72-4.76 \ (m, \ 1H, \ \text{CCH}), 5.03-5.07 \ (m, \ 1H, \ \text{CCH}), 7.38-7.42 \ (m, \ 3H, \ 3 \times \ \text{Ar-H}) \text{ and } 7.98-8.00 \ (m, \ 2H, \ 2 \times \ \text{Ar-H}); \ \delta_C (100\text{MHz}; \text{CDCl}_3) 14.6 \ (\text{CH}_3), 17.7 \ (\text{CH}_3), 18.0 \ (\text{CH}_3), 26.1 \ (2 \times \ \text{CH}_3), 32.5 \ (\text{CH}_2), 33.2 \ (\text{CH}_2), 34.8 \ (\text{CH}), 44.8 \ (\text{CH}_2), 44.9 \ (\text{C}), 114.5 \ (\text{C}=\text{O}), 118.2 \ (\text{CH}), 118.6 \ (\text{CH}), 127.6 \ (\text{Ar-C}), 128.4 \ (2 \times \ \text{Ar-C}), 129.3 \ (2 \times \ \text{Ar-C}), 130.5 \ (\text{Ar-C}), 135.6 \ (\text{CMe}_2), 135.6 \ (\text{CMe}_2), 159.9 \ (\text{C}), 186.9 \ (\text{C}) \text{ and } 192.0 \ (\text{C}).
6-Methyl-5-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (92)

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (93)

(Method B)

\[
\begin{align*}
\text{n-Butyllithium (2.5 M solution in hexanes; 2.83 ml, 7.07 mmol) and diisopropylamine (1.01 ml, 7.21 mmol) were added in dry THF (9 ml) at 0 °C, followed by DMPU (1.5 ml) to make a LDA solution. It was stirred for 20 min. 6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazole-4-one (6) (1.07 g, 4.71 mmol) in dry THF (5 ml) was added dropwise to this solution of LDA (1.5 equiv.; 7.07 mmol) at -78 °C. The resulting mixture was allowed to stir at -78 °C for 90 min. 1-Bromo-3-methyl-2-butene (0.56 ml, 4.80 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added and the mixture was extracted with DCM (3 x 20 ml). The combined extracts were washed with water (3 x 30 ml) and }
\end{align*}
\]
then brine (1 x 30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:diethyl ether (2:1 v/v) as eluent to yield mono-alkylated product, 6-methyl-5-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (92) (0.08 g, 6 %) and di-alkylated product, 6-methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (93) (0.30 g, 17 %). Spectroscopic data as reported above.

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (94) (Method A)

![Diagram](image)

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (93) (0.02 g, 0.05 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (1.5 equiv.; 0.07 mmol) and HMPA, which was prepared from n-butyllithium (2.5 M solution in hexanes; 0.03 ml, 0.07 mmol) and diisopropylamine (0.01 ml, 0.09 mmol) in dry THF (3 ml) at 0 °C, followed by HMPA
Experimental

(0.5 ml). The resulting mixture was allowed to stir at -78 °C for 10 min. Phenylselenium bromide (0.02 g, 0.06 mmol) was added at -78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (5 ml) was added and the mixture was extracted with DCM (3 x 10 ml). The combined organic fraction was washed with water (3 x 30 ml) and brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:ethyl acetate (8:1 v/v) as eluent to yield 6-methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (94) (0.01 g, 50 %) as a brown oil; MS (EI+) found 520.1750 (Se$^{80}$) [M+H], C$_{30}$H$_{33}$N$_{2}$O$_{2}$Se$_{80}$; requires 520.1749 (Se$^{80}$) [M+H]; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 1651, 1672 (C=O), 2335, 2974 and 3001 (CH$_{2}$, CH$_{3}$); $\delta_{H}$ (400MHz; CDCl$_{3}$) 1.24 (d, J 0.8, 3H, CH$_{3}$), 1.50 (s, 12H, 4 x CH$_{3}$), 2.32-2.44 (m, 2H, CH$_{2}$), 2.51-2.61 (m, 2H, CH$_{2}$), 2.72-2.80 (m, 1H, CHMe), 3.74 (d, J 11.3, 1H, CHSe), 4.86-4.87 (m, 1H, CH), 5.20-5.23 (m, 1H, CH), 7.11-7.25 (m, 3H, 3 x Ar-H), 7.39-7.42 (m, 3H, 3 x Ar-H), 7.47-7.58 (m, 2H, 2 x Ar-H) and 7.95-7.97 (m, 2H, 2 x Ar-H); $\delta_{C}$ (100MHz; CDCl$_{3}$) 14.6 (CH$_{3}$), 17.7 (CH$_{3}$), 18.0 (CH$_{3}$), 26.1 (2 x CH$_{3}$), 32.5 (CH$_{2}$), 33.2 (CH$_{2}$), 34.8 (CH), 51.5 (CH), 44.9 (C), 114.5 (C=O), 118.2 (CH), 118.6 (CH), 127.6 (Ar-C), 128.4 (2 x Ar-C), 129.3 (2 x Ar-C), 129.5 (2 x Ar-C), 130.5 (Ar-C), 131.6 (Ar-C), 135.6 (CM$_{2}$), 135.6 (CM$_{2}$), 138.2 (2 x Ar-C), 159.9 (C), 186.9 (C) and 192.0 (C).
Experimental

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (94)

(Method B)

n-Butyllithium (2.5 M solution in hexanes; 1.45 ml, 3.63 mmol) and diisopropylamine (0.52 ml, 3.70 mmol) was added in dry THF (12 ml) at 0 °C, followed by DMPU (2 ml) to make a LDA solution. It was stirred for 20 min. 6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (93) (0.66 g, 1.81 mmol) in dry THF (5 ml) was added dropwise to this solution of LDA (2.0 equiv.; 3.63 mmol) at -78 °C. The resulting mixture was allowed to stir at -78 °C for 60 min. Phenylselenium bromide (0.44 g, 1.85 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added. The mixture was extracted with DCM (3 x 20 ml), and the combined extracts were washed with water (3 x 30 ml) and then brine (1 x 30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (10:1 v/v) as eluent to yield 6-methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (94).
nzo[d]isoxazol-4-one (94) (0.36 g, 39 %) as a brown oil. Spectroscopic data as reported above.

2-[1-Amino-1-phenyl-meth-(E)-ylidene]-5-methyl-6,6-bis-(3-methyl-but-2-enyl)-cyclohex-4-ene-1,3-dione (95)

![Chemical structure](image)

6-Methyl-5,5-bis-(3-methylbut-2-enyl)-3-phenyl-7-phenylselenyl-4,5,6,7-tetrahydro-benzo[d]isoxazol-4-one (94) (6.90 g, 13.31 mmol) was dissolved in acetonitrile (30 ml) and water (10 ml). Molybdenum hexacarbonyl (3.51 g, 13.31 mmol) was added to the reaction and the mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was treated with hydrogen peroxide (3 ml) dropwise at 0 °C. It was then left to stir at room temperature overnight. The reaction was filtered through celite and charcoal bath and then poured into ice (20 g). The mixture was extracted with DCM (30 ml). The organic layer was washed with water (3 x 20 ml) and then treated with sodium sulphite solution (10 %) (10 ml). The extracted organic layer was dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield a residue. This crude product was purified by flash column chromatography using DCM as eluent to yield the product, 2-[1-amino-1-phenyl-meth-(E)-ylidene]-5-methyl-6,6-bis-(3-methyl-but-2-enyl)-cyclo
Experimental

hex-4-ene-1,3-dione (95) (1.45 g, 30%) as a light yellow viscous oil. MS (FAB+) found 364.2271 [M+H], C_{24}H_{29}NO_2; requires 364.2277 [M+H]; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1617, 1620 (NH_2), 2936, 3403 (C=O); \delta_H (400MHz; CDCl_3) 1.21 (d, J 3.1, 3H, CH_3), 1.51 (d, J 2.5, 12H, 4 x CH_3), 2.11-2.25 (m, 4H, 2 x CH_2), 4.71-5.01 (m, 2H, CH), 5.74 (s, 1H, NH_2), 6.41 (s, 1H, NH_2), 7.32-7.41 (m, 3H, 3 x Ar-H), 7.46 (s, 1H, CH) and 7.74-7.78 (m, 2H, 2 x Ar-H); \delta_C (400MHz; CDCl_3) 15.5 (CH_3), 18.1 (2 x CH_3), 18.9 (2 x CH_3), 47.9 (2 x CH_2), 114.7 (C), 127.5 (2 x Ar-C), 128.2 (C), 128.6 (3 x Ar-C), 130.1 (CH), 130.2 (CH), 131.9 (CH), 135.8 (C), 135.9 (C), 156.9 (C), 160.7 (C), 185.8 (C) and 191.6 (C).

6-Methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96)

![Chemical structure](attachment:image)

6-Methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96) (0.05 g, 0.24 mmol) in dry THF (2 ml) at -78 °C was added dropwise to a freshly prepared solution of LDA (1.2 equiv.; 0.29 mmol) and HMPA, which was prepared from n-butyllithium (2.5 M solution in hexanes; 0.11 ml, 0.29 mmol) and diisopropylamine (0.04 ml, 0.35 mmol) in dry THF (3 ml) at 0 °C, followed by HMPA (0.5 ml). The resulting mixture was allowed to stir at -78 °C for 15 min. Phenylselenium bromide (0.07 g, 0.29 mmol) was added at -78 °C, the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (5 ml) was added and the
mixture was extracted with DCM (3 x 10 ml). The combined organic fraction was washed with water (3 x 30 ml) and brine (1 x 30 ml), dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:ethyl acetate (8:1 v/v) as eluent to yield 6-methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96) (0.02 g, 25 %) as a brown oil; MS (EI+) found 384.0496 (Se80) [M+H], C20H17NO2Se80; requires 384.0497 (Se80) [M+H]; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 1685 and 1685 (C=O); \( \delta_{\text{H}} \) (400MHz; CDCl3) 1.34 (d, J 6.6, 3H, CH3), 2.58-2.74 (m, 1H, CHMe), 2.85 (dd, J 11.1 and 16.0, 1H, OCCH2), 2.95 (dd, J 3.9 and 16.0, 1H, OCCH2), 3.89 (d, J 3.2, 1H, SeCH), 7.18-7.22 (m, 3H, 3 x Ar-H), 7.36-7.38 (m, 3H, 3 x Ar-H), 7.50-7.52 (m, 2H, 2 x Ar-H) and 7.84-7.86 (m, 2H, 2 x Ar-H); \( \delta_{\text{C}} \) (100MHz; CDCl3) 20.8 (CH3), 30.3 (CH), 31.3 (CH2), 50.1 (CH), 114.0 (C), 128.4 (2 x Ar-CH), 129.2 (2 x Ar-CH), 129.5 (2 x Ar-C), 130.6 (Ar-CH), 131.5 (Ar-C), 138.2 (2 x Ar-C), 132.4 (Ar-C), 159.9 (C), 182.0 (C) and 191.6 (C);
6-Methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96)

(Method B)

\[ \text{LDA 1.5 equiv., THF:DMPU (6:1)} \]

\[ 1.0 \text{ equiv. PhSeBr} \]

\[ \text{n-Butyllithium (2.5 M solution in hexanes; 2.83 ml, 7.07 mmol) and diisopropylamine (1.01 ml, 7.21 mmol) was added in dry THF (9 ml) at 0°C, followed by DMPU (1.5 ml) to make a LDA solution. It was stirred for 20 min. 6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (6) (1.07 g, 4.71 mmol) in dry THF (5 ml) was added dropwise to this solution of LDA (1.5 equiv.; 7.07 mmol) at -78°C. The resulting mixture was allowed to stir at -78°C for 90 min. Phenylselenium bromide (1.13 g, 4.80 mmol) was added at -78°C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added. The mixture was extracted with DCM (3 x 20 ml). The combined extracts were washed with water (3 x 30 ml) and then brine (1 x 30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (8:1 v/v) as eluent to yield 6-methyl-3-phenyl-5-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (96) (0.36 g, 20%) as brown oil. Spectroscopic data as reported above.} \]
**2-Benzyloxybenzaldehyde oxime (105)**

2-Hydroxybenzaldehyde oxime (104) (5.00 g, 36.46 mmol) was dissolved in dry acetone (50 ml) under an atmosphere of nitrogen. Potassium carbonate (5.04 g, 36.46 mmol) was added, followed by benzyl bromide (4.34 g, 36.46 mmol). The reaction mixture was heated under reflux for 16 h. After the reaction was cooled to room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate (100 ml), and then washed with saturated sodium hydroxide solution (1M; 3 x 50 ml) and brine (50 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude oil was purified by flash column chromatography using petroleum ether:ethyl acetate (3:1 v/v) as eluent to yield 2-benzyloxybenzaldehyde oxime (105) (0.05 g, 1 %) as a yellow oil; MS (El+) found 227.0943, C14H13N02; requires 227.0946; \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \) 1620 (C=\( \equiv \)N), 2877 and 3280 (OH); \( \delta_{\text{H}} \) (400MHz; CDCl\(_3\)) 5.02 (s, 2H, CH\(_2\)Ph), 6.87-6.79 (m, 2H, 2 x Ar-H), 7.23-7.32 (m, 6H, 5 x Ar-H, OAr-H), 7.65 (d, J 7.6, 1H, Ar-H), 8.50 (s, 1H, N=\( \equiv \)CH) and 9.73 (broad peak, 1H, NOH); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 70.5 (CH\(_2\)) 112.6 (NCH), 120.9 (Ar-C), 121.2 (Ar-C), 127.4 (Ar-C), 128.1 (Ar-C), 128.2 (Ar-C), 128.46 (Ar-C), 128.7 (Ar-C), 128.7 (Ar-C), 131.3 (Ar-C), 136.6 (Ar-C), 146.5 (C) and 157.4 (OC).
To a solution of hydroxylamine hydrochloride (3.21 g, 46.24 mmol) and sodium acetate (7.59 g, 92.52 mmol) in water (50 ml), 2-benzyloxybenzaldehyde (110) (4.91 g, 23.13 mmol) in ethanol (50 ml) was added. The reaction mixture was heated to 70 °C for 10 min and then cooled down to room temperature. The reaction was stored in a refrigerator overnight. If crystals were not formed, the solution was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield the crude product, 2-benzyloxybenzaldehyde oxime (105) (6.30 g crude) as a yellow oil; MS (EI+) found 227.0943, C_{14}H_{13}NO_2; requires 227.0946; ν_{max} (neat)/cm^{-1} 1620 (C=N), 2877 and 3280 (OH); δ_H (400MHz; CDCl_3) 5.02 (s, 2H, CH_2Ph), 6.87-6.79 (m, 2H, 2 x Ar-H), 7.23-7.32 (m, 6H, 5 x Ar-H, OAr-H), 7.65 (d, J 7.6, 1H, Ar-H), 8.50 (s, 1H, N=CH) and 9.73 (broad peak, 1H, NOH); δ_C (100MHz; CDCl_3) 70.5 (CH_2) 112.6 (NCH), 120.9 (Ar-C), 121.2 (Ar-C), 127.4 (Ar-C), 128.1 (Ar-C), 128.2 (Ar-C), 128.5 (Ar-C), 128.7 (Ar-C), 128.7 (Ar-C), 131.3 (Ar-C), 136.6 (Ar-C), 146.5 (C) and 157.4 (OC).
2-Alyloxybenzaldehyde oxime (106)

2-Hydroxybenzaldehyde oxime (104) (5.00 g, 36.46 mmol) was dissolved in dry acetone (50 ml) under an atmosphere of nitrogen. Potassium carbonate (5.04 g, 36.46 mmol) was added, followed by allyl bromide (3.16 ml, 36.46 mmol). The reaction mixture was heated under reflux for 16 h. After the reaction was cooled to room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate (100 ml), and then washed with saturated sodium hydroxide solution (1M, 3 x 50 ml) and brine (50 ml). The organic layer was dried by sodium sulfate and evaporated to dryness under reduced pressure. The crude oil was purified by flash column chromatography using petroleum ether:ethyl acetate (3:1 v/v) as eluent to yield 2-allyloxybenzaldehyde oxime (106) (0.19 g, 3 %) as a yellow oil; MS (EI+) found 177.0789, C10H11NO2; requires 177.0790; νmax (neat)/cm⁻¹ 1649 (C=N), 2887 and 3283 (OH); δH (400MHz; CDCl₃) 4.44 (d, J 8.3, 2H, OCH₂), 5.16 (d, J 10.6, 1H, =CH₂), 5.28 (d, J 10.6, 1H, =CH₂), 5.88-5.93 (m, 1H, CH), 6.75-6.85 (m, 2H, 2 x Ar-H), 7.17-7.20 (m, 1H, Ar-H), 7.59-7.61 (m, 1H, Ar-H), 8.47 (s, 1H, N=CH) and 9.62 (broad peak, 1H, NOH); δC (100MHz; CDCl₃) 13.1 (CH₂), 20.0 (CH), 68.1 (OCH₂),111.4 (N=CH), 119.8 (Ar-C), 125.8 (Ar-C), 130.4 (Ar-C), 131.8 (Ar-C), 145.5 (C) and 155.6 (OC).
To a solution of hydroxylamine hydrochloride (4.20 g, 60.42 mmol) and sodium acetate (9.91 g, 120.84 mmol) in water (50 ml), 2-allyloxybenzaldehyde (111) (4.90 g, 30.21 mmol) in ethanol (50 ml) was added. The reaction mixture was heated to 70 °C for 10 min and then cooled down to room temperature. The reaction was stored in a refrigerator overnight. If crystals were not formed, the solution was extracted with ethyl acetate (3 x 100 ml). The combined organic layers was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield the crude product, 2-allyloxybenzaldehyde oxime (106) (6.48 g crude) as a yellow oil. Spectroscopic data as reported above.
2-Hydroxybenzaldehyde oxime (104) (3.00 g, 21.88 mmol) was dissolved in chloroform (100 ml), followed by addition of pyridine (0.22 ml, 2.74 mmol). The mixture was stirred under an atmosphere of nitrogen, when the temperature was raised to 50 °C. N-Chlorosuccinimide (2.98 g, 22.31 mmol) was added to the mixture which was stirred at 50 °C for 2 h. The reaction mixture was diluted by DCM (60 ml). The organic layer was washed by water (2 x 40 ml) and brine (50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product, 2-hydroxyphenylhydroximoyl chloride (120) (4.28 g crude) as a crude yellow oil; MS (EI+) found 171.0079 (Cl\textsuperscript{35}), C\textsubscript{7}H\textsubscript{7}NO\textsubscript{2}Cl\textsuperscript{35}; requires 171.0087; \nu_{\text{max}} (neat)/cm\textsuperscript{-1} 758 (CCI), 1606, 3047 and 3306 (OH board peak); \delta\textsubscript{H} (400MHz; CDCl\textsubscript{3}) 6.92-6.84 (m, 2H, 2 x Ar-R), 7.28-7.17 (m, 1H, Ar-H), 7.72 (d, J 8.4, 1H, Ar-H), 8.71 (s, broad peak, 1H, NOH) and 10.13 (s, broad peak, 1H, OH); \delta\textsubscript{C} (100MHz; CDCl\textsubscript{3}) 115.8 (C), 117.0 (Ar-C), 120.4 (Ar-C), 129.4 (Ar-C), 132.2 (Ar-C), 142.4 (C) and 156.2 (C).
Experimental

*Methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate* (107)

![Chemical Structure](image)

Dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (5.40 g, 23.78 mmol) and 2-hydroxyphenylhydroximoyl chloride (120) (0.68 g, 3.96 mmol) was dissolved in chloroform (50 ml). Triethylamine (0.55 ml, 3.96 mmol) was added dropwise over 30 min. The reaction mixture was heated under reflux at an atmosphere of nitrogen for 3 h and then left to stir at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* to yield a yellow oil, which was purified by flash column chromatography on silica gel using petroleum ether:ethyl acetate (5:3 v/v) as eluent to yield methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate (107) (0.08 g, 7 %) as a yellow oil; MS (FAB+) found 292.0818 [M+H], C_{14}H_{15}NO_{6}; requires 292.0821 [M+H]; νmax (neat)/cm⁻¹ 1740 (C=O), 2360, 2955 (CH₂, CH₃) and 3410 (OH); δH (400MHz; CDCl₃) 3.75 (s, 3H, CH₃), 3.79 (CH₃), 4.35 (s, 2H, CH₂), 7.40-7.36 (m, 1H, Ar-H), 7.61-7.59 (m, 1H, Ar-H), 8.10 (d, J 8.0, 1H Ar-H) and 9.82 (s, 1H, OH); δC (100MHz; CDCl₃) 30.2 (CH₂), 40.7 (CH₃), 49.9 (CH₃), 105.2 (C), 111.0 (C), 118.0 (Ar-C), 124.5 (Ar-C), 125.4 (Ar-C), 133.2 (Ar-C), 153.4 (C), 156.2 (C), 156.4 (C), 166.1 (C) and 171.7 (C).
3-(2-Hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108)

To a solution of sodium isopropoxide prepared from sodium (0.09 g, 3.96 mmol) in isopropyl alcohol (50 ml), were added successively 5-methylcyclohexane-1,3-dione (10) (0.50 g, 3.96 mmol) and 2-hydroxyphenylhydroximoyl chloride (120) (0.68 g, 3.96 mmol). After stirring for 4 h at room temperature, the reaction mixture was poured into water (30 ml), and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine (2 x 50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate:petroleum ether (1:1 v/v) as eluent to yield 3-(2-hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) (0.50 g, 52 %) as yellow crystals; mp 125-126 °C; MS (FAB+) found 244.0968 [M+H], C14H13NO3; requires 244.0974 [M+H]; \( \nu_{\text{max}} \) (nujol)/cm\(^{-1} \) 1692 (C=O), 2952 and 3118 (OH); \( \delta_{\text{H}} \) (400MHz; CDCl\(_3\)) 1.22 (d, J 6.4, 3H, CH\(_3\)), 2.38 (dd, J 11.2 and 16.0, 1H, OCCH\(_2\)), 2.43-2.55 (m, 1H, CCH), 2.69 (dd, J 3.6 and 16.0, 1H, OCCH\(_2\)), 2.70 (dd, J 10.4 and 16.7, 1H, O=CCH\(_2\)), 3.18 (dd, J 4.8 and 16.7, 1H, O=CCH\(_2\)), 7.07-7.00 (m, 2H, 2 x Ar-H), 7.38-7.35 (m, 1H, Ar-H), 8.61 (d, J 8.0, 1H, Ar-H) and 9.49 (s 1H, OH); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 20.6 (CH\(_3\)), 29.8 (CHMe), 31.0 (CH\(_2\)), 47.4 (CH\(_2\)), 112.8 (C), 114.5 (C), 117.4 (Ar-C), 119.8 (Ar-C), 132.2 (Ar-C), 132.5 (Ar-C), 156.6 (C), 159.4 (C), 181.6 (C) and 191.8 (C); Found C, 69.01; H, 5.43; N, 5.81; C\(_{14}H_{13}NO_3\) requires C, 69.12; H, 5.39; N, 5.76.
2-Benzyloxybenzaldehyde (110)<sup>116</sup>

\[
\begin{align*}
\text{OH} & \quad \text{BnBr, } K_2CO_3 \\
\text{H} & \quad \text{reflux} & \quad \text{H} \\
\end{align*}
\]

2-Hydroxybenzaldehyde (109) (3.81 ml, 36.46 mmol) in dry THF was treated with anhydrous potassium carbonate (5.04 g, 36.46 mmol). The slurry was stirred under nitrogen for 10 min at room temperature and was treated with benzyl bromide (4.78 ml, 40.11 mmol). The reaction mixture was warmed at reflux for 16 h and allowed to cool to room temperature. Water (200 ml) was added to dilute the reaction and then extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water (200 ml) and then brine (200 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (8:1 v/v) as eluent to yield 2-benzyloxybenzaldehyde (110) (5.6 g, 75 %) as yellow crystals; mp 48-49 °C (lit<sup>116</sup> m.p. 48 – 49 °C); MS (El+) found 212.0836, C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>; requires 212.0837; \( \nu_{\text{max}} \) (CHCl<sub>3</sub>/cm) 1600, 1708 (C=O), 2911, 3033, 3062 (CH<sub>2</sub>); \( \delta_{\text{H}} \) (400MHz; CDCl<sub>3</sub>) 5.01 (s, 2H, CH<sub>2</sub>), 6.90-6.87 (m, 2H, 2 x Ar-H), 7.30-7.21 (m, 6H, 6 x Ar-H), 7.71 (d, J 7.6, 1H, Ar-H) and 10.42 (s, 1H, CHO); \( \delta_{\text{C}} \) (100MHz; CDCl<sub>3</sub>) 70.4 (CH<sub>2</sub>), 113.1 (Ar-C), 121.0 (Ar-C), 125.2 (C), 127.4 (Ar-C), 127.6 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 128.8 (Ar-C), 129.2 (Ar-C), 136.2 (Ar-C), 161.1 (C), 189.7 (CHO) and 196.7 (C).
2-Hydroxybenzaldehyde (109) (3.81 ml, 36.46 mmol) in dry THF was treated with anhydrous potassium carbonate (5.04 g, 36.46 mmol). The slurry was stirred under nitrogen for 10 min at room temperature and was treated with allyl bromide (3.48 ml, 40.11 mmol). The reaction mixture was warmed at reflux for 16 h and allowed to cool to room temperature. Water (200 ml) was added to dilute the reaction mixture which was then extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water (200 ml) and then brine (200 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (9:1 v/v) as eluent to yield the product 2-allyloxybenzaldehyde (111) (5.6 g, 93%) as a yellow oil; MS (EI+) found 162.0683, C₁₀H₁₀O₂; requires 162.0681; ν max (neat)/cm⁻¹ 1647, 1688 (C=O), 2862, 3076 (CH₂); δ₇ (400MHz; CDCl₃) 4.65 (dd, J 3.2 and 5.2, 2H, OCH₂), 6.00 (d, J 10.6, 1H, =CH₂), 6.13 (d, J 10.6, 1H, =CH₂), 6.13-6.00 (m, 1H, CH), 7.03-6.96 (m, 2H, 2 x Ar-H), 7.54-7.50 (m, 1H, Ar-H), 7.83 (d, J 7.6, 1H, Ar-H) and 10.53 (CHO); δC (100MHz; CDCl₃) 69.1 (CH₂), 112.9 (Ar-C), 118.0 (OCH₂), 120.8 (Ar-C), 125.0 (C), 128.4 (Ar-C), 132.4 (CH), 135.9 (Ar-C), 160.9 (C) and 189.7 (CHO).
Experimental

2-Benzylxyphenylhydroximoyl chloride (112)

![Diagram of the reaction](image)

2-Benzylxybenzaldehyde oxime (105) (6.70 g, 29.48 mmol) was dissolved in chloroform (50 ml), and pyridine (0.25 ml, 3.07 mmol) was added. The solution was then heated to 50 °C, while N-chlorosuccinimide (4.33 g, 32.43 mmol) was added. The reaction mixture was heated under reflux for 16 h. After the mixture was cooled to room temperature, DCM (100 ml) was added. The mixture was then washed with water (2 x 50 ml) and brine (50 ml). The combined organic layer was dried by sodium sulfate and evaporated to dryness under reduced pressure to yield 2-benzylxyphenylhydroximoyl chloride (112) (7.60 g, 100 %) as a crude yellow oil; MS (EI+) found 261.0552, C_{14}H_{12}NO_{2}Cl; requires 261.0557; ν_{max} (neat)/cm^{-1} 752 (CCI) and 3028 (OH); δ_{H} (400MHz; CDCl3) 5.12 (s, 2H, CH₂), 6.87-7.58 (m, 9H, 9 x Ar-H), 8.49 (s, broad peak, 1H, NOH) and 10.41 (s, broad peak, 1H, OH); δ_{C} (100MHz; CDCl3) 70.3 (CH₂), 127.8 (Ar-C), 128.4 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 131.0 (Ar-C), 131.9 (Ar-C), 133.9 (Ar-C), 136.6 (C), 153.1 (C), 156.0 (C) and 156.7 (C). The crude product was used without purification as it is very reactive.
**Methyl 5-methoxycarbonylmethyl-3-(2-benzylxyphenyl)isoxazole-4-carboxylate (113)**

![Chemical formula](image)

Dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (1.70 g, 7.50 mmol) and 2-benzylxyphenylhydroximoyl chloride (112) (0.33 g, 1.25 mmol) was dissolved in chloroform (30 ml). Triethylamine (0.21 ml, 1.50 mmol) was added dropwise over 15 min. The reaction mixture was heated under reflux at an atmosphere of nitrogen for 3 h and then left to stir at room temperature for 16 h. The reaction mixture was concentrated in vacuo to yield a yellow oil, which was purified by flash column chromatography on silica gel using petroleum ether:ethyl acetate (5:3 v/v) as eluent to yield methyl 5-methoxycarbonylmethyl-3-(2-benzylxyphenyl)isoxazole-4-carboxylate (113) (0.04 g; 8 %) as a yellow oil; MS (EI+) found 381.1231, C_{21}H_{19}NO_{6}; requires 381.1212; \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} 1696 (C=N), 1718, 1743 (C=O), 2344, 2360, 2950, 3031 (CH_{2}, CH_{3}); \delta_{H}(400\text{MHz}; CDCl_{3}) 3.48 (s, 3H, COOCH_{3}), 3.67 (s, 3H, COOCH_{3}), 4.09 (s, 2H, CH_{2}COOMe), 4.99 (s, 2H, CH_{2}Ph), 7.00-6.96 (m, 2H, 2 x Ar-H), 7.20-7.18 (m, 3H, 3 x Ar-H), 7.25-7.23 (m, 3H, 3 x Ar-H) and 7.40-7.37 (m, 2H, 2 x Ar-H); \delta_{C}(100\text{MHz}; CDCl_{3}) 33.2 (CH_{2}), 51.6 (CH_{3}), 52.7 (CH_{3}), 70.3 (CH_{2}Ph), 111.6 (C), 112.3 (Ar-C), 118.1 (C), 120.9 (Ar-C), 126.8 (Ar-C), 127.7 (Ar-C), 128.4 (Ar-C), 128.6 (Ar-C), 130.5 (Ar-C), 131.5 (Ar-C), 136.7 (C), 156.8 (C), 160.4 (C), 161.8 (C), 167.4 (C) and 169.6 (C).
Experimental

3-(2-Benzylxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (114)

To a solution of sodium isopropoxide prepared from sodium (0.03 g, 1.25 mmol) in isopropyl alcohol (20 ml), were added successively 5-methylcyclohexane-1,3-dione (10) (0.16 g, 1.25 mmol) and 2-benzylxyphenylhydroximoyl chloride (112) (0.33 g, 1.25 mmol). After stirring for 16 h at room temperature, the reaction mixture was poured into water (30 ml), and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine (2 x 50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:diethyl ether (5:1 v/v) gradually changed to petroleum ether:diethyl ether (1:1) as eluent to yield 3-(2-benzylxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (114) (0.02 g, 5 %) as a yellow oil; MS (FAB+) found 334.1436 [M+H], C21H19N03; requires 334.1443 [M+H]; vmax (neat)/cm⁻¹ 1701 (C=O), 2247, 2872, 2958, 3032, 3064 (CH₂, CH₃); δH (400MHz; CDCl₃) 1.05 (d, J=6.8, 3H, CH₃), 2.06 (dd, J=11.1 and 15.9, 1H, OCCH₂), 2.35-2.24 (m, 1H, CHMe), 2.33 (dd, J=3.5 and 15.9, 1H, OCCH₂), 2.54 (dd, J=9.6 and 16.9, 1H, O=CCH₂), 3.06 (dd, J=4.8 and 16.9, 1H, O=CCH₂) 4.97 (s, 2H, CH₂), 6.99-6.97 (m, 2H, 2 x Ar-H), 7.23-7.18 (m, 3H, 3 x Ar-H), 7.28-7.24 (m, 3H, 3 x Ar-H) and 7.39-7.37 (m, 2H, 2 x Ar-H); δC (100MHz; CDCl₃) 20.7 (CH₃), 30.4 (CHMe), 31.0 (CH₂), 46.6 (CH₂), 70.4 (CH₂Ph), 112.4 (Ar-C), 117.3 (C), 120.7 (Ar-C), 127.1 (Ar-C), 127.9 (Ar-C), 128.3 (Ar-C), 128.6 (Ar-C), 130.5
Experimental

(Ar-C), 131.7 (Ar-C), 136.9 (C), 157.2 (C), 157.5 (C), 171.2 (C), 180.2 (C) and 191.1 (C).

3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117)

K₂CO₃, allyl bromide

reflux

3-(2-Hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) (0.27 g, 1.09 mmol) was dissolved in dry THF (20 ml). Potassium carbonate (0.15 g, 1.11 mmol) was added to the mixture and then stirred for 10 min. After that, the allyl bromide (0.10 ml, 1.20 mmol) was added and the reaction mixture was heated under reflux for 16 h. Water (50 ml) was added after the reaction was cooled to room temperature, then ethyl acetate (3 x 30 ml) was added to extract the solution. The combined organic layer was extracted with water (50 ml) and then brine (50 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield 3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) (0.13 g, 43 %) as yellow crystals; mp 111-112 °C; MS (FAB+) found 284.1287 [M+H], C₁₇H₁₇NO₃; requires 284.1287 [M+H]; νₓ (nujol)/cm⁻¹ 1603, 1689 (C=O) and 2956;
Experimental

$\delta_H(400\text{MHz}; \text{CDCl}_3)$ 1.22 (d, $J$ 6.5, 3H, CH$_3$), 2.39 (dd, $J$ 11.0 and 15.9, 1H, OCCH$_2$), 2.46-2.62 (m, 1H, CHMe), 2.65 (dd, $J$ 3.6 and 15.9, 1H, OCCH$_2$), 2.70 (dd, $J$ 9.7 and 17.0, 1H, O=CCH$_2$), 3.08 (dd, $J$ 5.2 and 17.0, 1H, O=CCH$_2$), 4.65-4.67 (m, 2H, OCH$_2$), 5.31 (d, $J$ 10.1, 1H, =CH$_2$), 5.57 (d, $J$ 16.8, 1H, =CH$_2$), 6.04-6.08 (m, 1H, =CH), 6.99-7.04 (m, 2H, 2 x Ar-H), 7.39-7.43 (m, 1H, Ar-H) and 8.06 (d, $J$ 8.0, 1H, Ar-H); $\delta_C(100\text{MHz}; \text{CDCl}_3)$ 21.0 (CH$_3$), 30.2 (CH$_2$), 30.8 (CHMe), 46.3 (CH$_2$), 69.2 (=CH$_2$), 113.3 (Ar-C), 115.9 (C), 117.1 (OCH$_2$), 118.3 (Ar-C), 131.1 (Ar-C), 132.4 (Ar-C), 132.7 (=CH), 134.6 (C), 156.8 (C), 160.9 (C), 163.7 (C) and 191.2 (C); Found C, 71.95; H, 5.82; N, 5.09; C$_{17}$H$_{17}$NO$_3$ requires C, 72.07; H, 6.05; N, 4.94.

(_4-Oxo-4H-chromeno[4,3-c]isoxazol-3-yl)acetic acid methyl ester (121)

![Chemical structure](image)

Methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate (107) (0.08 g, 0.29 mmol) was dissolved in dry THF (20 ml). Potassium carbonate (0.04 g, 0.29 mmol) was added to the mixture and then stirred for 10 min. After that, the allyl bromide (0.03 ml, 0.31 mmol) was added and the reaction mixture was heat under reflux for 16 h. Water (50 ml) was added after the reaction was cooled to room temperature. Ethyl acetate (3 x 30 ml) was added to extract the solution and the combined organic layer was extracted with water (50 ml) and then brine (50 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under
reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (8:1 v/v) as eluent to yield (4-oxo-4H-chromeno[4,3-c]isoxazol-3-yl)acetic acid methyl ester (121) (0.02 g, 27 %) as a viscous yellow oil (solidified in refrigerator); MS (EI+) found 259.0483, C_{13}H_{9}NO_{5}; requires 259.0481; ν_{max} (CHCl_{3})/cm^{-1} 1635, 1741 (C=O) and 2934 (CH_{2}, CH_{3}); δ_{H}(400MHz; CDC_{6}) 2.99 (s, 2H, CH_{2}), 3.76 (s, 3H, CH_{3}), 4.72-4.76 (m, 1H, OCCH), 5.02-5.13 (m, 2H, =CH_{2}), 5.68-5.81 (m, 1H, CH), 7.36-7.39 (m, 2H, 2 x Ar-H), 7.58-7.62 (m, 1H, Ar-H) and 8.08-8.11 (m, 1H, Ar-H); δ_{C} (100MHz; CDC_{6}) 34.0 (CH_{2}), 42.8 (CH), 53.1 (CH_{3}), 104.7 (C), 111.1 (C), 118.0 (Ar-C), 118.9 (CH_{2}), 124.4 (Ar-C), 125.3 (Ar-C), 132.8 (−CH), 133.2 (Ar-C), 153.3 (C), 156.1 (C), 156.2 (C), 168.3 (C) and 175.4 (C).

3-Acetyl-4-amino-chromen-2-one (123)

\[
\text{OH} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{O}
\end{array} \quad \begin{array}{c}
\text{OMe}
\end{array} \quad \begin{array}{c}
\text{Me}
\end{array} \\
(107)
\]

\[
\text{i) 5M HCl, glacial acid} \quad \text{ii) K_{2}CO_{3}} \\
(123)
\]

Methyl 5-methoxycarbonylmethyl-3-(2-hydroxyphenyl)isoxazole-4-carboxylate (107) (0.08 g, 0.29 mmol) was treated with hydrochloric acid (5M; 3 ml) in glacial acetic acid (15 ml). The mixture was heated at reflux for 3 h. The reaction was evaporated under reduced pressure to yield the crude product. The residue was dissolved in dry acetone (20 ml) and heated under reflux with potassium carbonate (0.04 g, 0.29 mmol) for 3 h. After the reaction was cooled to room temperature, the solvent was evaporated
and the residue was dissolved in ethyl acetate (30 ml). This mixture was washed with saturated sodium hydroxide solution (1M; 3 x 30 ml) and brine (50 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude oil was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield 3-acetyl-4-amino-chromen-2-one (123) (0.04 g, 59 %) as a pale yellow solid; mp 70 - 71 °C; MS (EI+) found 204.0658 [M+H], C_{11}H_{9}NO_{3}; requires 204.0655 [M+H]; ν_{max} (CDCl₃)/cm⁻¹ 1734, 2921 (C=O) and 3329 (NH₂); δₜ (400MHz; CDCl₃) 2.72 (s, 3H, CH₃), 6.95-6.99 (m, 1H, Ar-H), 7.05 (dd, J 1.0 & 8.0, 1H, Ar-H), 7.35-7.39 (m, 1H, Ar-H), 7.82 (dd, J 1.0 & 8.0, 1H, Ar-H), 10.72 (s, 1H, NH₂) and 10.85 (s, 1H, NH₂); δetty (400MHz; CDCl₃) 12.1 (CH₃), 110.7 (C), 117.2 (Ar-C), 119.7 (Ar-C), 126.0 (Ar-C), 129.8 (C), 132.5 (Ar-C), 153.5 (C), 156.8 (C), 157.9 (C) and 160.8 (C); Found C, 65.21; H, 4.63; N, 6.82; C_{11}H_{9}NO_{3} requires C, 65.02; H, 4.46; N, 6.89.
5-Allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) and 5,5-Diallyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (125) (Method A)

\[
\text{LDA 1.2 equiv., THF:HMPA (6:1)} \\
1.0 \text{ equiv. allyl bromide}
\]

\[\text{(117)} \quad \text{(124)} \quad \text{(125)}\]

\[
\begin{align*}
n-\text{Butyllithium (2.5 M solution in hexanes; 0.22 ml, 0.54 mmol) and diisopropylamine} \\
(0.08 \text{ ml, 0.55 mmol) was added in dry THF (6 ml) at 0^\circ C, followed by HMPA (1 ml) to make a LDA solution. The mixture was then stirred for 10 min. 3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) (0.13 g, 0.45 mmol) in dry THF (2 ml) was added dropwise to this solution of LDA (1.2 equiv.; 0.54 mmol) at -78^\circ C. The resulting mixture was allowed to stir at -78^\circ C for 30 min. Allyl bromide (0.04 ml, 0.45 mmol) was added at -78^\circ C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added and the mixture was extracted with DCM (3 x 30}
\end{align*}
\]
The combined extracts were washed with water (3 x 50 ml) and then brine (1 x 50 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield, mono-allylated product 5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124) (0.02 g, 11 %) as a yellow oil; MS (EI+) found 324.1594 [M+H], C_{20}H_{21}NO_{3}; requires 324.1594 [M+H]; \nu_{\text{max}} \,(\text{neat})/\text{cm}^{-1} 1676, 1680 (C=O), 2919 and 2976; \delta_{\text{H}} \,(400\text{MHz}; \text{CDCl}_3) 1.19 \,(d, \, J \, 6.4, \, 3H, \, \text{CH}_3), \, 2.38-2.50 \,(m, \, 2H, \, \text{CH}_2), \, 2.41 \,(dd, \, J \, 11.0 \, \text{and} \, 16.0, \, 1H, \, \text{OCCH}_2), \, 2.59-2.76 \,(m, \, 1H, \, \text{CHMe}), \, 2.77 \,(dd, \, J \, 3.6 \, \text{and} \, 16.0, \, 1H, \, \text{OCCH}_2), \, 3.18 \,(m, \, 1H, \, \text{O}=\text{CCH}), \, 4.65-4.68 \,(m, \, 2H, \, \text{CH}_2), \, 5.05-5.10 \,(m, \, 2H, \, \text{OCH}_2), \, 5.33 \,(dd, \, J \, 10.2, \, 1H, \, \text{OCCH}_2), \, 5.59 \,(dd, \, J \, 16.7, \, 1H, \, \text{CH}), \, 5.72-5.88 \,(m, \, 1H, \, \text{CH}), \, 6.06-6.13 \,(m, \, 1H, \, \text{CH}), \, 7.00-7.07 \,(m, \, 2H, \, 2 \times \text{Ar-H}), \, 7.41-7.47 \,(m, \, 1H, \, \text{Ar-H}) \, \text{and} \, 8.07-8.10 \,(m, \, 1H, \, \text{Ar-H}); \delta_{\text{C}} \,(100\text{MHz}; \text{CDCl}_3) 19.9 \,(\text{CH}_3), \, 28.4 \,(\text{CH}_2), \, 30.1 \,(\text{CH}_2), \, 32.4 \,(\text{CHMe}), \, 53.3 \,(\text{CH}), \, 60.4 \,(\text{CH}_2), \, 113.3 \,(\text{Ar-C}), \, 116.0 \,(\text{C}), \, 117.2 \,(=\text{CH}_2), \, 117.3 \,(=\text{CH}_2), \, 121.0 \,(\text{Ar-C}), \, 131.1 \,(\text{Ar-C}), \, 132.7 \,(\text{Ar-C}), \, 133.1 \,(\text{CH}), \, 133.8 \,(\text{C}), \, 136.0 \,(\text{CH}), \, 156.8 \,(\text{C}), \, 161.1 \,(\text{C}), \, 162.0 \,(\text{C}) \, \text{and} \, 192.7 \,(\text{C}); \, \text{and} \, \text{di-allylated product}, 5,5-diallyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (125) (0.01 g, 7 %) as a yellow oil; MS (EI+) found 364.1905 [M+H], C_{23}H_{25}NO_{3}; requires 364.1907 [M+H]; \nu_{\text{max}} \,(\text{neat})/\text{cm}^{-1} 1686 (C=O), 2919 and 2977; \delta_{\text{H}} \,(400\text{MHz}; \text{CDCl}_3) 1.16 \,(d, \, J \, 6.9, \, 3H, \, \text{CH}_3), \, 2.11-2.23 \,(m, \, 2H, \, \text{CCH}_2), \, 2.26-2.31 \,(m, \, 2H, \, \text{CCH}_2), \, 2.28 \,(dd, \, J \, 11.0 \, \text{and} \, 16.0, \, 1H, \, \text{OCCH}_2), \, 2.51-2.62 \,(m, \, 1H, \, \text{CHMe}), \, 2.86 \,(dd, \, J \, 3.6 \, \text{and} \, 16.0, \, 1H, \, \text{OCCH}_2), \, 4.67-4.69 \,(m, \, 2H, \, \text{OCH}_2), \, 5.04-5.07 \,(m, \, 4H, \, 2 \times \text{CH} = \text{CH}_2), \, 5.33 \,(d, \, J \, 10.0, \, 1H, \, \text{OCCH}_2), \, 5.60 \,(d, \, J \, 16.8, \, 1H, \, \text{OCCH}_2), \, 5.62-5.78 \,(m, \, 2H, \, 2 \times \text{CH}), \, 6.02-6.12 \,(m, \, 1H, \, \text{CH}), \, 6.99-7.05 \,(m, \, 2H, \, 2 \times \text{Ar-H}), \, 7.38-7.43 \,(m, \, 1H, \, \text{Ar-H}) \, \text{and} \, 8.08-8.10 \,(m, \, 1H, \, \text{Ar-H}); \delta_{\text{C}} \,(100\text{MHz}; \text{CDCl}_3) 15.3 \,(\text{CH}_3), \, 27.8 \,(\text{CH}_2), \, 35.2 \,(\text{CHMe}), \, 35.4 \,(\text{CH}_2),
5-Aryl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (124)

(124)

n-Butyllithium (2.5 M solution in hexanes; 2.5 equiv., 14.02 ml, 35.05 mmol) and diisopropylamine (5.02 ml, 35.75 mmol) was added in dry THF (30 ml) at 0 °C, followed by DMPU (5 ml) to make a LDA solution. It was stirred for 30 min. 3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) (4.00 g, 14.02 mmol) in dry THF (5 ml) was added dropwise to this solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 90 min. Allyl bromide (1.21 ml, 14.30 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (60 ml) was added and the mixture was extracted with DCM (3 x 60 ml). The combined extracts were washed with water (4 x 60 ml) and then brine (1 x 100 ml). The organic extracts were dried over sodium sulfate, filtered
and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield 5-allyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[\textit{d}]isoxazol-4-one (124) (0.91 g, 20%) as a yellow oil. Spectroscopic data as reported before.

\[
\text{3-(2-Allyloxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[\textit{d}]isoxazol-4-one (126) and 3-(2-Allyloxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[\textit{d}]isoxazol-4-one (127)}
\]

\[
\text{n-Butyllithium (2.5 M solution in hexanes; 2.5 equiv., 0.21 ml, 0.53 mmol) and diisopropylamine (0.08 ml, 0.54 mmol) was added in dry THF (6 ml) at 0 °C,}
\]
Experimental followed by DMPU (1 ml) to make a LDA solution. It was then stirred for 15 min. 3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (117) (0.06 g, 0.21 mmol) in dry THF (2 ml) was added dropwise to this solution of LDA at -78 °C. The resulting mixture was allowed to stir at -78 °C for 10 min. 1-Bromo-3-methylbut-2-ene (0.03 ml, 0.22 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogencarbonate solution (10 ml) was added and the mixture was extracted with DCM (3 x 20 ml). The combined extracts were washed with water (4 x 20 ml) and then brine (1 x 30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield both mono-alkylated product, 3-(2-allyloxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (126) (0.02 g, 23 %) as a yellow oil; MS (EI+) found 352.1917 [M+H], C_{22}H_{22}NO_3; requires 352.1913 [M+H]; ν_max (neat)/cm⁻¹ 1693, 1698 (C=O), 2927 and 2963; δ_H (400MHz; CDCl₃) 1.18 (d, J 6.5, 3H, CH₃), 1.70 (s, 3H, CH₃), 1.71 (s, 3H, CH₃), 2.35-2.46 (m, 3H, OCCH₂ & CH₂), 2.71-2.77 (m, 1H, CHMe), 2.79 (dd, J 3.6 and 15.9, 1H, OCCH₂), 3.21 (m, 1H, O=CCH₂), 4.67-4.70 (m, 2H, OCH₂), 5.08-5.27 (m, 1H, =CH), 5.32 (d, J 10.0, 1H, =CH₂), 5.58 (d, J 16.5, 1H, =CH₂), 6.03-6.13 (m, 1H, CH=), 7.00-7.07 (m, 2H, 2 x Ar-H), 7.42-7.44 (m, 1H, Ar-H) and 8.06-8.10 (m, 1H, Ar-H); δ_C (100MHz; CDCl₃) 19.9 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 28.4 (CH₂), 30.1 (CH₂), 32.4 (CHMe), 53.3 (CH), 60.4 (CH₂), 113.3 (Ar-C), 116.0 (C), 117.5 (OCH₂), 117.5 (C), 121.0 (Ar-C), 131.2 (Ar-C), 132.8 (Ar-C), 133.7 (CH), 133.8 (C), 136.2 (CH), 156.9 (C), 161.4 (C), 162.2 (C) and 192.8 (C). and di-alkylated product, 3-(2-allyloxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (127) (0.01 g, 10 %) as a yellow oil; MS (EI+) found 420.2540
Experimental

[M+H], C_{27}H_{33}NO_{3}; requires 420.2539 [M+H]; \nu_{\text{max}} \text{(neat)/cm}^{-1} 1675, 1684 (C=O), 2915 and 2962; \delta_{\text{H}} (400MHz; CDCl_{3}) 1.17 (d, J 6.9, 3H, CH_{3}) 1.68 (s, 3H, CH_{3}), 1.69 (s, 3H, CH_{3}), 1.70 (s, 3H, CH_{3}), 1.71 (s, 3H, CH_{3}), 2.40-2.51 (m, 4H, 2 x CH_{2}), 2.69-2.73 (m, 1H, CHMe), 2.78 (dd, J 11.0 and 16.0, 1H, OCCH_{2}) 3.22 (dd, J 3.6 and 16.0, 1H, OCCH_{2}), 4.65-4.71 (m, 2H, OCH_{2}), 5.03-5.19 (m, 2H, 2 x =CH), 5.31 (d, J 10.0, 1H, =CH_{2}), 5.59 (d, J 16.8, 1H, =CH_{2}), 6.02-6.14 (m, 1H, =CH), 7.00-7.07 (m, 2H, 2 x Ar-H), 7.38-7.45 (m, 1H, Ar-H) and 8.08-8.11 (m, 1H, Ar-H); \delta_{\text{C}} (100MHz; CDCl_{3}) 18.0 (CH_{3}), 25.9 (CH_{3}), 26.0 (CH_{3}), 26.1 (CH_{3}), 26.2 (CH_{3}), 29.4 (CH_{2}), 32.8 (CHMe), 35.3 (CH_{2}), 37.3 (CH_{2}), 52.7 (C), 69.1 (CH_{2}), 113.4 (Ar-C), 116.3 (C), 117.3 (CH_{2}), 118.0 (C), 118.1 (C), 120.8 (Ar-C), 131.3 (Ar-C), 132.5 (Ar-C), 132.7 (CH), 133.2 (CH), 133.7 (C), 134.2 (CH), 156.8 (C), 161.3 (C), 161.3 (C) and 194.7 (C).

5-Spirocyclopentene-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (134)

\[ \text{5,5-Diallyl-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (125)} \] (0.13 g, 0.36 mmol) was dissolved in dry DCM under an atmosphere of nitrogen. Grubbs II catalyst (20 mol\%, 0.06 g, 0.07 mmol) was added and the reaction
was heated to 40 °C for 3.5 h. The reaction mixture was then filtered through celite and charcoal. Water (10 ml) was added to the filtrate and the mixture was extracted by DCM (3 x 10 ml). The combined organic layer was washed with brine (30 ml), dried by sodium sulfate, filtered and evaporate under reduced pressure. The crude material was purified by flash column chromatography using petroleum ether:ether acetate (2:1 v/v) as eluent to yield the product 5-spirocyclopentene-3-(2-allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (134) (0.03 g, 27 %) as a yellow oil; MS (EI+) found 336.1595 [M+H], C_{21}H_{21}N_{0}O_{3}; requires 336.1600 [M+H]; \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} 1684 (\text{C=O}) and 2925; \delta_{\text{H}} (400MHz; CDCl_{3}) 1.03 (d, J 6.8, 3H, CH_{3}), 2.39 (dd, J 11.0 and 16.0, 1H, OCCH_{2}), 2.50-2.56 (m, 1H, CH), 2.59 (dd, J 3.6 and 15.9, 1H, OCCH_{2}), 2.69-2.79 (m, 2H, CH_{2}), 3.05-3.14 (m, 2H, CH_{2}), 4.62 (d, J 10.1, 1H, =CH_{2}), 4.79 (d, J 16.8, 1H, =CH_{2}), 5.23-5.27 (m, 1H, =CH), 5.51-5.59 (m, 2H, OCH_{2}), 5.98-6.07 (m, 1H, =CH), 6.35-6.41 (m, 1H, =CH), 6.93-7.03 (m, 2H, 2 x Ar-H), 7.26-7.31 (m, 1H, Ar-H) and 7.98-8.03 (m, 1H, Ar-H); \delta_{\text{C}} (400MHz; CDCl_{3}) 15.4 (CH_{3}), 26.6 (CH_{2}), 26.7 (CH_{2}), 37.6 (CH_{2}), 39.2 (CH_{2}), 68.3 (CH_{2}), 110.5 (C), 112.3 (Ar-C), 112.6 (Ar-C), 116.2 (CH_{2}), 119.9 (CH), 120.0 (CH), 123.0 (CH), 127.6 (Ar-C), 130.1 (C), 131.3 (Ar-C), 155.6 (C), 160.2 (C), 161.1 (C), 167.1 (C) and 170.3 (C).
3-(2-Hydroxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (108) (6.00 g, 24.77 mmol) was dissolved in dry THF (50 ml). Potassium carbonate (3.49 g, 25.26 mmol) was added to the mixture and then stirred for 10 min. After that, the 4-bromobut-l-ene (2.51 ml, 24.77 mmol) was added and the reaction mixture was heated under reflux for 16 h. Water (50 ml) was added after the reaction was cooled to room temperature. The mixture was extracted with ethyl acetate (3 x 40 ml), and the combined organic layer was extracted with water (50 ml) and then brine (50 ml). The organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield 3-[2-(but-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (135) (0.31 g, 4 %) as a oil; MS (EI+) found 297.1360, C_{18}H_{19}NO_{3}; requires 297.1365; ν_{max} (neat)/cm^{-1} 1601, 1693 (C=O) and 2956; δ_{H} (400MHz; CDCl_{3}) 1.08 (d, J 2.4, 3H, CH_{3}), 2.41 (dd, J 11.0 and 15.9, 1H, OCCH_{2}), 2.52-2.64 (m, 1H, CH), 2.62 (dd, J 3.6 & 15.9, 1H, OCCH_{2}), 2.70 (dd, J 9.8 and 16.9, 1H, O=CCH_{2}), 3.10 (dd, J 5.0 and 16.9, 1H, O=CCH_{2}), 3.85-3.90 (m, 2H, CH_{3}), 5.09-5.22 (m, 3H, CH_{2} & CH),
5.77-5.99 (m, 2H, OCH₂), 6.99-7.05 (m, 2H, 2 x Ar-H), 7.41-7.43 (m, 1H, Ar-H) and 8.04-8.06 (m, 1H, Ar-H); $\delta_c$ (400MHz; CDCl₃) 20.9 (CH₃), 30.3 (CH₂), 30.8 (CH), 46.3 (CH₂), 68.2 (CH₂), 113.0 (Ar-C), 117.2 (CH₂), 117.5 (CH), 117.6 (CH₂), 120.8 (Ar-C), 126.8 (Ar-C), 131.1 (Ar-C), 157.2 (C), 163.8 (C), 171.2 (C), 177.5 (C), 191.4 (C) and 200.0 (C).

5-Allyl-3-[2-(but-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (136) and

5,5-Diallyl-3-[2-(but-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]-isoxazol-4-one (137)

\[ \text{LDA 1.2 equiv., THF:DMU (8:1)} \]
\[ \text{1.0 equiv. allyl bromide} \]

n-Butyllithium (2.5 M solution in hexanes; 1.2 equiv., 0.61 ml, 1.52 mmol) and diisopropylamine (0.22 ml, 1.55 mmol) was added in dry THF (3 ml) at 0 °C,
Experimental

followed by DMPU (1 ml) to make a LDA solution. It was then stirred for 10 min.

3-[2-(But-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (135) (0.30 g, 1.01 mmol) in dry THF (3 ml) was added dropwise to the solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 30 min. Allyl bromide (0.09 ml, 1.03 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (10 ml) was added, and the mixture was extracted with DCM (3 x 10 ml). The combined organic extracts were washed with water (3 x 10 ml) and then brine (30 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield, mono-allylated product, 5-allyl-3-[2-(but-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (136) (0.07 g, 21 %) as a yellowish oil; MS (FAB+) found 338.1758 [M+H], C21H23NO3; requires 338.1757 [M+H]; νmax (neat)/cm⁻¹ 1603, 1693 (C=O) and 2955; δH (400MHz; CDCl3) 1.21 (d, J 6.8, 3H, CH3), 2.41-2.47 (m, 3H, OCCH2 and CH2), 2.62 (dd, J 3.6 & 15.9, 1H, OCCH2), 2.72-2.76 (m, 1H, CH), 3.17 (m, 1H, O=CCH2), 4.14 (t, J 6.4, 2H, CH2, 5.05-5.22 (m, 5H, 2 x CH2 & CH), 5.73-5.89 (m, 2H, CH2), 5.90-6.03 (m, 1H, =CH), 6.99-7.05 (m, 2H, 2 x Ar-H), 7.41-7.43 (m, 1H, Ar-H) and 8.07-8.09 (m, 1H, Ar-H); δC (400MHz; CDCl3) 19.9 (CH3), 28.4 (CH2), 32.4 (CH2), 32.6 (CH), 53.3 (CH), 68.2 (CH2), 101.3 (C), 102.0 (CH), 112.6 (CH), 113.0 (Ar-C), 116.0 (C), 116.3 (CH2), 117.2 (CH2), 117.3 (CH2), 120.8 (Ar-C), 131.1 (Ar-C), 132.4 (Ar-C), 157.2 (C), 162.0 (C), 184.2 (C) and 192.7 (C); and di-allylated product, 5,5-diallyl-3-[2-(but-3-enyloxy)phenyl]-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (137) (0.08 g, 21 %) as a yellowish oil; MS (FAB+) found 378.2066 [M+H], C24H27N03; requires 378.2069 [M+H]; νmax (neat)/cm⁻¹ 1609, 1690 (C=O) and 2928; δH (400MHz; CDCl3) 1.09 (d, J
Experimental

6.4, 3H, CH₃), 2.04-2.21 (m, 2H, CH₂), 2.38-2.49 (m, 1H, CH), 2.48 (m, 2H, CH₂), 2.62 (m, 2H, CH₂), 4.14 (t, J 6.8, 2H, CH₂), 5.05-5.16 (m, 7H, 3 x CH₂ & CH), 5.63-5.86 (m, 3H, CH₂ & CH), 5.87-6.02 (m, 1H, CH), 6.99-7.05 (m, 2H, 2 x Ar-H), 7.43-7.45 (m, 1H, Ar-H) and 8.08-8.10 (m, 1H, Ar-H); δC (400MHz; CDCl₃) 19.5 (CH₃), 27.8 (CH₂), 30.7 (CH₂), 32.1 (CH₂), 32.9 (CH₂), 68.2 (CH₂), 101.3 (C), 102.0 (2 x CH), 113.0 (Ar-C), 116.7 (CH₂), 116.3 (C), 116.5 (C), 117.2 (CH₂), 117.4 (CH), 117.6 (CH₂), 118.4 (CH₂), 120.8 (Ar-C), 131.2 (Ar-C), 132.3 (Ar-C), 157.2 (C), 162.1 (C), 175.5 (C) and 200.6 (C).

2-(Aminophenylmethylene)-5-methylcyclohexane-1,3-dione (139)

(Method A)

6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) (0.03 g, 0.12 mmol) was dissolved in acetonitrile (3 ml), molybdenum hexacarbonyl (0.03 g, 0.12 mmol) was added and the reaction was heated at reflux overnight. After cooling to room temperature, the reaction mixture was filtered through celite, and then washed with ethyl acetate (30 ml). The organic layer was evaporated under reduced pressure to give the crude product. The crude material was purified by flash column chromatography with or with Fluka aluminium oxide (basic type pH 9.5 ± 0.5, 50-150 μ) using MeOH (2 %) in DCM as the eluent to yield the product, 2-(aminophenylmethylene)-5-methylcyclohexane-1,3-dione (139) (0.01g, 35 %) as a
yellow solid; mp 104 °C; MS (EI+) found 230.1185 [M+H], \( C_{14}H_{15}NO_2 \); requires 230.1181 [M+H]; \( v_{\text{max}} \) (DMSO)/cm\(^{-1} \) 1664 (NH bending), 2124, 2250 and 3450 (NH\(_2\)); \( \delta_H \) (400MHz; DMSO) 0.99 (s, 3H, CH\(_3\)), 2.09-2.18 (m, 3H, CH\(_2\) \& CH), 2.33-2.41 (m, 2H, CH\(_2\)), 7.24-7.27 (m, 2H, 2 x Ar-H), 7.36-7.45 (m, 3H, 3 x Ar-H), 9.19 (s, 1H, NH\(_2\)) and 11.61 (s, 1H, NH\(_2\)); \( \delta_C \) (400MHz; DMSO) 20.7 (CH\(_3\)), 25.9 (CH), 46.6 (2 x CH\(_2\)), 114.2 (C), 127.2 (2 x Ar-C), 127.8 (2 x Ar-C), 129.2 (Ar-C), 133.6 (C), 153.8 (C), 173.2 (C) and 175.6 (C); Found C, 72.94; H, 6.65; N, 6.32; \( C_{14}H_{15}NO_2 \) requires C, 73.34; H, 6.59; N, 6.11.

2-(Aminophenylmethylene)-5-methylcyclohexane-1,3-dione (139)

(METHOD B)

![Chemical Structure]

Palladium on carbon (10 %) was added carefully to dry ethanol (10 ml) in a flask under an atmosphere of nitrogen. 6-Methyl-3-phenyl-4,5,6,7-tetrahydrobenz[d]isoxazol-4-one (6) (0.03 g, 0.12 mmol) in ethanol (10 ml) was added to the palladium/carbon slurry whilst stirring vigorously. The reaction vessel was evacuated and then purged with nitrogen three times, then evacuated and purged with hydrogen three times, eventually being left under an atmosphere of hydrogen. The reaction mixture was left stirring vigorously for 24 h at room temperature. The reaction vessel was then evacuated and purged with nitrogen three times, and the reaction mixture was filtered using a celite pad. The solvent was
removed under reduced pressure to yield the crude product, which was passed through or with Fluka aluminium oxide (basic type pH 9.5 ± 0.5, 50-150 μ) using MeOH (2 %) in DCM as the eluent to yield the product 2-(aminophenylmethylene)-5-methylcyclohexane-1,3-dione (139) (0.01 g, 35 %) as a yellow solid. Spectroscopic data as reported above.

2-[(2-Allyloxyphenyl)aminomethylene]-5-methylcyclohexane-1,3-dione (140)

3-(2-Allyloxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (99) (0.06 g, 0.23 mmol) was dissolved in moist acetonitrile (10 ml), molybdenum hexacarbonyl (0.06 g, 0.23 mmol) was added and the reaction was heated at reflux overnight. After cooling to room temperature, the reaction mixture was filtered through celite and then washed with ethyl acetate (30 ml). The organic layer was then evaporated under reduced pressure to give a crude product. The crude material was purified by flash column chromatography with or with Fluka aluminium oxide (basic type pH 9.5 ± 0.5, 50-150 μ) using petroleum ether:ether acetate (1:1 v/v) as the eluent to yield the product 2-[(2-allyloxyphenyl)aminomethylene]-5-methylcyclohexane-1,3-dione (140) (0.03 g, 47 %) as a yellow solid, mp 72 - 73 °C; MS (FAB+) found 286.1451 [M+H], C17H19N03; requires 286.1443 [M+H]; \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1667 (NH bending), 1733.
Experimental

(C=O), 2358, 2949 and 3459 (NH₂); δ₁ (400MHz; CDCl₃) 1.65-1.69 (m, 3H, CH₃), 2.34-2.39 (m, 1H, CH), 3.68-3.70 (m, 2H, CH₂), 4.22-4.24 (m, 2H, CH₂), 4.69-4.71 (m, 2H, OCH₂), 5.38 (d, J 10.2, 1H, =CH₂), 5.46 (d, J 16.4, 1H, =CH₂), 5.84 (s, 1H, NH₂), 6.01-6.13 (m, 1H, =CH), 6.98 (d, J 8.4, 1H, Ar-H), 7.09-7.11 (m, 1H, Ar-H), 7.44-7.46 (m, 1H, Ar-H), 7.81 (s, 1H, NH₂) and 8.22 (dd, J 2.0 & 8.0, 1H, Ar-H); δc (400MHz; CDCl₃) 24.3 (CH₃), 33.7 (CH), 63.3 (CH₂), 69.1 (CH₂), 69.9 (=CH₂), 112.7 (Ar-C), 116.3 (C), 119.4 (OCH₂), 121.5 (Ar-C), 124.1 (C), 132.1 (=CH), 132.7 (Ar-C), 133.3 (Ar-C), 134.6 (C), 156.3 (C), 158.1 (C) and 184.1 (C); Found C, 71.85; H, 6.70; N, 4.91; C₁₇H₁₉N₀₃ requires C, 71.56; H, 6.71; N, 4.91.

2-(2-Methoxyphenyl)-1,3-dimethylimidazolidine (144)²

![Chemical structure](image)

o-Anisaldehyde (3.00 g, 22.04 mmol) and N,N'-dimethylethylenediamine (2.33 g, 26.44 mmol) in ethanol (100 ml) was stirred at room temperature overnight. Magnesium sulfate (ca. 4.50 g) was added, and the resulting mixture was stirred for a further 15 min. The reaction mixture was filtered and washed with diethyl ether and the solvent was removed under reduced pressure. The crude product was distilled (b.p. 98–102 °C/3mbar) (lit. b.p. 96–100 °C/2mbar) to yield the product 2-(2-methoxyphenyl)-1,3-dimethylimidazolidine (144) (3.28 g, 72 %) as a solid; mp 41–42 °C; MS (EI+) found 207.1494 [M+H], C₁₂H₁₈N₂O; requires 207.1497 [M+H];
Experimental

$\nu_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 1600, 2777 and 2940; $\delta_H$ (400 MHz; CDCl$_3$) 2.11 (s, 6H, 2 x NCH$_3$), 2.50-2.54 (m, 2H, 2 x CHH), 3.23-3.27 (m, 2H, 2 x CHH), 3.72 (s, 3H, OCH$_3$), 3.98 (s, 1H, CH), 6.79 (d, $J$ 8.3, 1H, Ar-H), 6.87-9.30 (m, 1H, Ar-H), 7.15-7.19 (m, 1H, Ar-H) and 7.58-7.60 (m, 1H, Ar-H); $\delta_C$ (400 MHz; CDCl$_3$) 39.6 (2 x CH$_3$), 53.5 (2 x CH$_2$), 55.4 (OCH$_3$), 82.7 (CH), 110.3 (Ar-C), 121.1 (Ar-C), 127.5 (C), 128.8 (Ar-C), 129.2 (Ar-C) and 158.9 (C).

2-Bromo-6-methoxybenzaldehyde (145)$^{117}$

To a solution of freshly distilled 2-(2-methoxyphenyl)-1,3-dimethylimidazolidine (144) (1.00 g, 4.85 mmol) in dry THF (40 ml) was added t-BuLi (2.5 M in hexanes) (5.82 ml, 14.54 mmol) dropwise by syringe over 1 h. The mixture was stirred under nitrogen at room temperature for 6 h. A solution of 1,2-dibromotetrachloroethane (5.00 g, 14.54 mmol) in dry THF (10 ml) was then slowly added, and the mixture was stirred at room temperature overnight. Hydrochloric acid (2M; 150 ml) was added to quench the reaction, which was stirred for 30 min at room temperature. The organic layer was separated and the aqueous layer extracted with chloroform (2 x 50 ml). The combined organic extract was washed with aqueous ammonia chloride (100 ml), and the aqueous layer was extracted with chloroform (2 x 50 ml). The organic layers were again combined, dried by magnesium sulfate, filtered and evaporated under reduced
Experimental pressure. The crude product was purified by flash column chromatography using petroleum ether:diethyl ether (7:3 v/v) as eluent to yield the product 2-bromo-6-methoxybenzaldehyde (145) (0.36 g, 35 %) as a yellow solid; mp 57–58 °C (lit. 57.5–58 °C); MS (EI+) found 214.9712 (Br79) [M+H], C8H7O2Br; requires 214.9708 (Br79) [M+H]; \( \nu_{\text{max}} \) (CHCl3)/cm\(^{-1} \) 785 (C-Br), 1691 (C=O), 2882 and 3075; \( \delta_{\text{H}} \) (400MHz; CDCl3) 3.83 (s, 3H, OCH3), 6.85 (dd, \( J = 8.4 \& 14.0 \), 1H, Ar-H), 7.04 (d, \( J = 8.4 \), 1H, Ar-H), 7.28 (m, 1H, Ar-H) and 10.41 (s, 1H, CHO); \( \delta_{\text{C}} \) (400MHz; CDCl3) 55.2 (CH3), 110.0 (Ar-C), 125.4 (Ar-C), 123.7 (C), 133.8 (Ar-C), 135.4 (C), 161.0 (C) and 189.3 (C).

2-bromo-6-methoxybenzaldehyde oxime (142)

To a solution of hydroxylamine hydrochloride (0.31 g, 4.46 mmol) and sodium acetate (0.72 g, 8.78 mmol) in water (50 ml), 2-bromo-6-methoxybenzaldehyde (145) (0.47 g, 2.19 mmol) in ethanol (20 ml) was added. The reaction mixture was heated to 70 °C for 10 min and then cooled down to room temperature. The reaction was stored in a refrigerator overnight. If crystals were not formed, the solution was extracted with ethyl acetate (3 x 30 ml). The combined organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield 2-bromo-6-methoxybenzaldehyde oxime (142) (0.61 g, 100 %) as a pale yellow
crude solid (the crude product was further purified by recrystallization with DCM/MeOH for combustion analysis); mp 186-187 °C; MS (ES+) found 229.9812 (Br\(^{79}\)) [M+H], C\(_8\)H\(_8\)NO\(_2\)Br\(^{79}\); requires 229.9811 (Br\(^{79}\)) [M+H]; \(\nu_m\) (CHCl\(_3\))/cm\(^{-1}\) 721 (C-Br) and 2958 (OH); \(\delta_H\) (400MHz; CDCl\(_3\)) 3.92 (s, 3H, OCH\(_3\)), 6.88-6.94 (m, 1H, Ar-H), 7.05-7.20 (m, 1H, Ar-H), 7.24-7.28 (m, 1H, Ar-H), 8.56 (s, 1H, NCH) and 10.05 (s, 1H, OH); \(\delta_C\) (400MHz; CDCl\(_3\)) 56.1 (OCH\(_3\)), 109.8 (Ar-C), 114.3 (C), 122.4 (C), 130.9 (Ar-C), 135.0 (C), 145.5 (NCH) and 158.9 (C); Found C, 41.66; H, 3.60; N, 6.05; C\(_8\)H\(_8\)NO\(_2\)Br requires C, 41.77; H, 3.51; N, 6.09.

2-Bromo-6-methoxyphenylhydroximoyl chloride (146)

2-Bromo-6-methoxybenzaldehyde oxime (142) (0.61 g, 2.65 mmol) was dissolved in chloroform (50 ml), followed by addition of pyridine (0.21 ml, 2.65 mmol). The mixture was stirred under an atmosphere of nitrogen, when the temperature was raised to 50 °C. N-Chlorosuccinimide (0.36 g, 2.70 mmol) was added to the mixture which was stirred at 50 °C for 2 h. The reaction mixture was diluted by DCM (50 ml). The organic layer was washed with water (2 x 50 ml) and brine (50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product, 2-bromo-6-methoxyphenylhydroximoyl chloride (146) (0.72 g, 100 %) as a yellow crude oil; MS (EI+) found 263.9431 (Br\(^{79}\), Cl\(^{35}\)) [M+H], C\(_8\)H\(_7\)NO\(_2\)Br\(^{79}\)Cl\(^{35}\); requires
Methyl 5-methoxycarbonylmethyl-3-(2-bromo-6-methoxyphenyl)isoxazole-4-carboxylate (147)

Dimethyl 3-(1-pyrrolidino)pent-2-ene-1,5-dioate (8) (1.80 g, 7.94 mmol) and 2-bromo-6-methoxyphenylhydroximoyl chloride (146) (0.35 g, 1.32 mmol) were dissolved in chloroform (50 ml). Triethylamine (0.18 ml, 1.32 mmol) was added dropwise over 30 min. The reaction mixture was heated under reflux at an atmosphere of nitrogen for 3 h and then left to stir at room temperature for 16 h. The reaction mixture was concentrated in vacuo to yield a yellow oil, which was purified by flash column chromatography on silica gel using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield methyl 5-methoxycarbonylmethyl-3-(2-bromo-6-methoxyphenyl)isoxazole-4-carboxylate (147) (0.03 g, 5 %) as a yellow oil; MS (EI+) found 383.0002 (Br<sup>79</sup>), C<sub>13</sub>H<sub>14</sub>NO<sub>5</sub>Br<sup>79</sup>; requires 383.0004 (Br<sup>79</sup>); v<sub>max</sub> (neat)/cm<sup>-1</sup> 1629, 1708, 1752 (C=O), 2846 and 2951; δ<sub>H</sub> (400MHz; CDCl<sub>3</sub>) 3.68 (s, 3H, OCH<sub>3</sub>), 3.72 (s,
Experimental

3H, OCH₃), 3.84 (s, 3H, OCH₃), 5.20 (s, 2H, CH₂), 6.85-6.93 (m, 1H, Ar-H) and
7.27-7.28 (m, 2H, 2 x Ar-H); δC (400MHz; CDCl₃) 38.2 (CH₂), 51.1 (CH₃), 52.2
(CH₃), 56.0 (OCH₃), 110.7 (Ar-C), 116.4 (C), 123.9 (C), 124.5 (Ar-C), 132.2 (Ar-C),
158.8 (C), 161.4 (C), 161.7 (C), 171.2 (C), 181.1 (C) and 190.1 (C).

3-(2-Bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one
(148)

To a solution of sodium isopropoxide prepared from sodium (0.03 g, 1.02 mmol) in
isopropyl alcohol (50 ml), were added successively 5-methylcyclohexane-1,3-dione
(10) (0.13 g, 1.02 mmol) and 2-bromo-6-methoxyphenylhydroximoyl chloride (146)
(0.27 g, 1.02 mmol). After stirring overnight at room temperature, the reaction mixture
was poured into water (50 ml), and extracted with DCM (3 x 50 ml). The combined
organic layer was washed with brine (2 x 100 ml), dried over sodium sulfate, filtered
and concentrated under reduced pressure. The crude product was purified by flash
column chromatography using ethyl acetate:petroleum ether (1:1 v/v) as eluent to
yield 3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-
tetrahydrobenzo[d]isoxazol-4-one (148) (0.26 g, 75 %) as a yellow viscous oil; MS
(nanospray) found 335.0164 (Br⁷⁹), C₁₃H₁₄NO₃Br⁷⁹; requires 335.0163 (Br⁷⁹); νmax
(DCM)/cm⁻¹ 713 (C-Br), 1692 (C=O) and 2959; δH (400MHz; CDCl₃) 1.21 (dd, J 6.4,
3H, CH$_3$), 2.26-2.31 (m, 1H, OCCH$_2$), 2.43-2.57 (m, 1H, CH), 2.52 (dd, J 2.8 & 16.0, 1H, OCCH$_2$), 2.66-2.72 (m, 1H, O=CCH$_2$), 3.16 (d, J 4.8 & 17.2, 1H, O=CCH$_2$), 3.71 (s, 3H, OCH$_3$), 6.90-6.93 (m, 1H, Ar-H) and 7.24-7.27 (m, 2H, 2 x Ar-H); $\delta$C (400MHz; CDCl$_3$) 20.8 (CH$_3$), 30.4 (CH), 31.0 (CH$_2$), 46.4 (CH$_2$), 56.2 (OCH$_3$), 110.1 (Ar-C), 115.4 (C), 123.9 (C), 124.8 (Ar-C), 131.8 (Ar-C), 134.5 (C), 156.0 (C), 158.9 (C), 180.8 (C) and 191.0 (C).

5-Allyl-3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (149) and
5,5-Diallyl-3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (150)

\( \begin{align*} n\text{-Butyllithium (2.5 M solution in hexanes; 2.1 equiv., 1.10 ml, 2.75 mmol)} \end{align*} \) and diisopropylamine (0.40 ml, 2.81 mmol) was added in dry THF (26 ml) at 0 °C,
Experimental

followed by DMPU (6 ml) to make a LDA solution. It was stirred for 10 min.
3-(2-Bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (148) (0.44 g, 1.31 mmol) in dry THF (10 ml) was added dropwise to this solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 30 min. Allyl bromide (0.13 ml, 1.57 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (30 ml) was added and the mixture was extracted with DCM (3 x 50 ml). The combined extract was washed with water (3 x 30 ml) and then brine (1 x 100 ml). The organic extract was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1 v/v) as eluent to yield, mono-allylated product

5-allyl-3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (149) (0.09 g, 18 %) as a yellow oil; MS (FAB+) found 376.0544 (Br^79) [M+H], C_{18}H_{18}NO_{3}Br^{79}; requires 376.0548 (Br^79) [M+H]; \nu_{\text{max}} (\text{neat})/ \text{cm}^{-1} 778 (C-Br), 1693 (C-O) and 2963; \delta_{\text{H}} (400MHz; CDCl\text{_3}) 1.18 (d, J 6.4, 3H, CH\text{_3}), 2.28-2.42 (m, 3H, OCCH\text{H} & CH\text{_2}), 2.45-2.53 (m, 1H, CH), 2.55 (dd, J 2.8 & 16.0, 1H, OCCH\text{H}), 2.95-3.03 (m, 1H, O=CCH), 3.73 (s, 3H, OCH\text{H}), 5.16-5.24 (m, 2H, =CH\text{_2}), 5.71-6.01 (m, 1H, =CH), 6.91-6.93 (m, 1H, Ar-H) and 7.24-7.31 (m, 2H, 2 x Ar-H); \delta_{\text{C}} (400MHz; CDCl\text{_3}) 19.0 (CH\text{_3}), 33.6 (CH), 41.5 (CH), 45.2 (CH\text{_2}), 45.6 (CH\text{_2}), 56.2 (OCH\text{H}), 110.0 (Ar-C), 115.2 (C), 118.5 (=CH\text{_2}), 124.1 (C), 124.1 (C), 124.9 (Ar-C), 131.8 (Ar-C), 134.3 (=CH), 156.1 (C), 158.9 (C), 182.4 (C) and 190.8 (C); and
di-allylated product

5,5-diallyl-3-(2-bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (150) (0.09 g, 17 %) as a yellow oil; MS (FAB+) found 416.0864 (Br^79) [M+H], C_{21}H_{22}NO_{3}Br^{79}; requires 416.0861 (Br^79) [M+H]; \nu_{\text{max}} (\text{neat})/ \text{cm}^{-1} 779 (C-Br),
1693 (C=O) and 2964; δ_H (400MHz; CDCl_3) 1.02 (d, J 2.0, 3H, CH\_3), 2.21-2.41 (m, 3H, OCCHH \& CH\_2), 2.45-2.61 (m, 4H, CH, OCCHH \& CH\_2), 3.68 (s, 3H, OCH\_3), 5.03-5.09 (m, 4H, 2 x =CH\_2), 5.41-5.79 (m, 2H, 2 x =CH), 6.83-6.87 (m, 1H, Ar-H) and 7.18-7.22 (m, 2H, 2 x Ar-H); δ_C (400MHz; CDCl\_3) 12.9 (CH\_3), 37.2 (CH\_2), 37.6 (CH\_2), 43.0 (CH\_2), 52.3 (CH), 55.2 (OCH\_3), 109.0 (Ar-C), 116.2 (C), 118.3 (=CH\_2), 118.5 (=CH\_2), 123.0 (C), 123.1 (C), 123.8 (Ar-C), 131.6 (Ar-C), 131.7 (=CH), 132.0 (=CH), 157.8 (C), 163.1 (C), 175.8 (C), 189.8 (C) and 191.3 (C).

3-(2-Bromo-6-methoxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (151) and 3-(2-Bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (152)

\[ \text{OMe} \quad \text{N} \quad \text{O} \quad \text{Br} \]
\[ \text{BrO} \]

(148)

\[ \text{OMe} \quad \text{N} \quad \text{O} \quad \text{Br} \]
\[ \text{BrO} \]

(151)

2.1 equiv. LDA, THF:DMPU (6:1)

2.0 equiv. Br

(152)

\[ n\text{-Butyllithium (2.5 M solution in hexanes; 2.1 equiv., 2.30 ml, 5.75 mmol) and} \]
diisopropylamine (0.82 ml, 5.86 mmol) was added in dry THF (30 ml) at 0 °C, followed by DMPU (8 ml) to make a LDA solution. It was stirred for 15 min. 3-(2-Bromo-6-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (148) (0.92 g, 2.74 mmol) in dry THF (18 ml) was added dropwise to this solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 10 min. 1-Bromo-3-methyl but-2-ene (0.64 ml, 5.47 mmol) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (40 ml) was added, and the mixture was extracted with DCM (3 x 50 ml). The combined organic extract was washed with water (3 x 30 ml) and then brine (1 x 100 ml). The organic extract was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield both mono-alkylated product, 3-(2-bromo-6-methoxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (151) (0.24 g, 22 %) as a yellow oil; MS (EI+) found 403.0780 (Br79), C20H12NO3Br79; requires 403.0778 (Br79); νmax (neat)/cm⁻¹ 731 (C-Br), 1570, 1694 (C=O) and 2965; ¹H (400MHz; CDCl3) 1.08 (d, J 5.9, 3H, CH3), 1.53 (s, 3H, CH3), 1.55 (s, 3H, CH3), 2.11-2.41 (m, 3H, OCCHH & CH2), 2.51-2.63 (m, 2H, OCCHH & CH), 2.86 (m, 1H, O=CCH), 3.64 (s, 3H, OCH3), 5.17-5.21 (m, 1H, =CH), 6.83-6.86 (m, 1H, Ar-H) and 7.16-7.23 (m, 2H, 2 x Ar-H); ¹C (400MHz; CDCl3) 20.9 (CH3), 24.6 (2 x CH3), 28.4 (CH2), 34.6 (CH2), 50.9 (CH), 54.5 (CH), 55.3 (OCH3), 108.2 (Ar-C), 117.1 (C), 121.5 (C), 123.1 (Ar-C), 131.2 (Ar-C), 131.9 (=CH), 152.1 (C), 153.1 (C), 157.9 (C), 171.2 (C), 183.1 (C) and 191.3 (C); and di-alkylated product, 3-(2-bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (152) (0.30 g, 23 %) as a yellow oil; MS
Experimental

(FAB+) found 472.1480 [M+H] (Br)\textsuperscript{79}, C\textsubscript{25}H\textsubscript{30}NO\textsubscript{3}Br\textsuperscript{79}; requires 472.1487 [M+H] (Br)\textsuperscript{79}; \(\nu\)\textsubscript{max} (neat)/cm\textsuperscript{-1} 777 (C-Br), 1597, 1698 (C=O) and 2974; \(\delta\)\textsubscript{H} (400MHz; CDCl\textsubscript{3}) 1.04 (d, \(J = 6.3\), 3H, CH\textsubscript{3}), 1.49 (s, 3H, CH\textsubscript{3}), 1.51 (s, 3H, CH\textsubscript{3}), 1.53 (s, 3H, CH\textsubscript{3}), 1.55 (s, 3H, CH\textsubscript{3}), 2.20-2.51 (m, 3H, OCCHH & CH\textsubscript{2}), 2.51-2.62 (m, 4H, CH, OCCHH & CH\textsubscript{2}), 3.70 (s, 3H, OCH\textsubscript{3}), 5.14-5.21 (m, 2H, 2 x =CH), 6.82-6.89 (m, 1H, Ar-H) and 7.19-7.25 (m, 2H, 2 x Ar-H); \(\delta\)\textsubscript{C} (400MHz; CDCl\textsubscript{3}) 22.0 (CH\textsubscript{3}), 25.7 ( 2 x CH\textsubscript{3}), 25.8 (2 x CH\textsubscript{3}), 28.5 (CH\textsubscript{2}), 28.9 (CH\textsubscript{2}), 34.1 (CH\textsubscript{2}), 51.2 (CH), 56.2 (OCH\textsubscript{3}), 108.2 (Ar-C), 117.0 (C), 121.2 (C), 122.4 (C), 123.9 (Ar-C), 131.6 (Ar-C), 131.9 (=CH), 132.0 (=CH), 152.6 (C), 153.1 (C), 157.9 (C), 165.4 (C), 171.1 (C), 182.0 (C) and 192.5 (C).

3-(2-Bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (153)

\(\text{n-Butyllithium (2.5 M solution in hexanes; 0.51 ml, 1.27 mmol) and diisopropylamine (0.18 ml, 1.30 mmol) was added in dry THF (16 ml) at 0 °C, followed by DMPU (6 ml) to make an LDA solution. The mixture was stirred for 20 min.}

3-(2-Bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydronobenzo[d]isoxazol-4-one (152) (0.30 g, 0.64 mmol) in dry THF (10 ml) was added
Experimental dropwise to this solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 60 min. Phenylselenium bromide (0.22 g, 0.95 mmol) in dry THF (10 ml) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (30 ml) was added, and the mixture was extracted with DCM (3 x 30 ml). The combined extract was washed with water (50 ml) and then brine (50 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (3:1 v/v) as eluent to yield 3-(2-bromo-6-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylseleny l-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (153) (0.16 g, 41 %) as a brown oil. MS (FAB+) found 628.0959 [M+H] (Br⁺, Se⁻⁸), C₃₁H₃₄N₃O₃Br⁺Se⁻⁸₀; requires 628.0966 [M+H] (Br⁺, Se⁻⁸₀); \[\nu_{\text{max}}\text{(neat)/cm}^{-1}\] 734 (C-Br), 1573, 1616 (C=O), 2925 and 2963; δH (400MHz; CDCl₃) 1.03 (d, J 5.9, 3H, CH₃), 1.53 (s, 3H, CH₃), 1.55 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.59 (s, 3H, CH₃), 2.21-2.50 (m, 5H, CH & 2 x CH₂), 2.50-2.61 (m, 1H, CH), 3.70 (s, 3H, OCH₃), 4.97-5.13 (m, 1H, =CH), 5.19-5.31 (m, 1H, =CH), 6.83-6.71 (m, 1H, Ar-H), 7.17-7.20 (m, 2H, 2 x Ar-H), 7.28-7.34 (m, 3H, 3 x Ar-H) and 7.56-7.61 (m, 2H, 2 x Ar-H); δC (400MHz; CDCl₃) 22.0 (CH₃), 25.7 (2 x CH₃), 25.9 (2 x CH₃), 28.7 (CH₂), 28.9 (CH₂), 48.2 (CH), 51.3 (CH), 56.1 (OCH₃), 108.2 (Ar-C), 117.1 (C), 121.3 (C), 122.4 (C), 123.9 (Ar-C), 129.5 (2 x Ar-C), 131.6 (2 x Ar-C), 131.9 (=CH), 132.1 (=CH), 138.1 (2 x Ar-C), 152.4 (C), 153.1 (C), 157.8 (C), 165.1(C), 171.3 (C), 181.9 (C) and 192.6 (C).
2,3-Dimethylanisole (0.20 g, 1.47 mmol) and N-bromosuccinimide (0.78 g, 4.41 mmol) were dissolved in carbon tetrachloride (75 ml) and the mixture was stirred under nitrogen for 5 h, while being exposed to a 300 watt high intensity tungsten lamp. The solution was cooled to room temperature, the suspended succinimide was removed by filtration and the solvent was evaporated. The residue was recrystallised from hexane:chloroform (5:1 v/v) to yield the product 2-bromomethyl-3-(dibromomethyl)anisole (156) (0.51 g, 93 %) as a white solid; mp 84–85 °C (Lit.114 84–85 °C); $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 797 (C-Br), 1698 and 2836; $\delta_H$ (400MHz; CDCl$_3$) 3.73 (s, 3H, OCH$_3$), 4.67 (s, 2H, CH$_2$), 6.72 (t, $J$ 7.6, 1H, Ar-H), 6.95 (s, 1H, CH), 7.24 (t, $J$ 8.0, 1H, Ar-H), 7.43 (d, $J$ 7.8, 1H Ar-H); $\delta_C$ (400MHz; CDCl$_3$) 22.9 (CH$_2$), 35.8 (CH), 55.4 (OCH$_3$), 110.8 (Ar-C), 121.8 (Ar-C), 123.9 (C), 129.4 (Ar-C), 140.3 (C) and 156.8 (C).
2-Bromomethyl-3-methylanisole (157)\textsuperscript{114}

2,3-Dimethylanisole (5.00 g, 36.71 mmol) and \textit{N}-bromosuccinimide (6.53 g, 36.71 mmol) were dissolved in cyclohexane (300 ml) and the mixture was stirred under nitrogen for 1.5 h, while being exposed to a 150 watt high intensity tungsten lamp. The solution was cooled to room temperature, the suspended succinimide was removed by filtration and the solvent was evaporated. The residue was recrystallised from hexane:diethyl ether (5:1 v/v) to yield the product 2-bromomethyl-3-methylanisole (157) (2.01 g, 25 \%) as a white solid; m.p. 48-50 °C; MS (FAB\textsuperscript{+}) found 213.9999 [M-H] \textit{(Br}\textsuperscript{79}), \textit{C}_{9}\textit{H}_{11}\textit{OBr}\textsuperscript{79}; requires 213.9993 [M-H] \textit{(Br}\textsuperscript{79}); \textit{v}_{\text{max}} (\text{CHCl}_{3})/\text{cm}^{-1} 775 (C-Br), 1586 and 3415; \delta_{\text{H}} (400MHz; \text{CDCl}_{3}) 2.31 (s, 3H, CH\textsubscript{3}), 3.77 (s, 3H, OCH\textsubscript{3}), 4.66 (s, 2H, CH\textsubscript{2}), 6.70 (m, 2H, 2 x Ar-H) and 7.08 (t, \textit{J} 8.0, 1H, Ar-H); \delta_{\text{C}} (400MHz; \text{CDCl}_{3}) 18.4 (CH\textsubscript{3}), 54.4 (OCH\textsubscript{3}), 56.5 (CH\textsubscript{2}), 107.2 (Ar-C), 122.0 (Ar-C), 125.9 (C), 127.5 (Ar-C), 136.9 (C) and 157.0 (C).
2,3-Bis(bromomethyl)anisole (158)

2,3-Dimethylanisole (2.5 g, 18.36 mmol) and N-bromosuccinimide (6.86 g, 38.55 mmol) were dissolved in cyclohexane (150 ml) and the mixture was stirred under nitrogen for 3 h, while being exposed to a 150 watt high intensity tungsten lamp. The solution was cooled to room temperature, the suspended succinimide was removed by filtration and the solvent was evaporated. The residue was recrystallised from hexane:diethyl ether (5:1 v/v) to yield the product 2,3-bis(bromomethyl)anisole (158) (1.62 g, 30 %) as a white solid; mp 69-70 °C (Lit.\textsuperscript{114} 69-70 °C); MS (FAB+) found 291.9100 (Br\textsuperscript{+}); requires 291.9098 (Br\textsuperscript{+}); \( \nu \)\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 796 (C-Br), 2835 and 2960; \( \delta \)\textsubscript{H} (400MHz; CDCl\textsubscript{3}) 3.76 (s, 3H, OCH\textsubscript{3}), 4.51 (s, 2H, CH\textsubscript{2}), 4.68 (s, 2H, CH\textsubscript{2}), 6.75 (d, J 8.4, 1H, Ar-H), 6.85 (d, J 3.8, 1H, Ar-H) and 7.15 (t, J 16.4, 1H, Ar-H); \( \delta \)\textsubscript{C} (400MHz; CDCl\textsubscript{3}) 22.8 (CH\textsubscript{2}), 29.1 (CH\textsubscript{2}), 55.1 (OCH\textsubscript{3}), 110.4 (Ar-C), 121.8 (Ar-C), 124.0 (C), 129.0 (Ar-C), 136.9 (C) and 156.8 (C).
2,3-Bis(dibromomethyl)anisole (159)\textsuperscript{114}

\[
\begin{align*}
\text{OMe} & \quad \text{4.0 equiv. NBS, CCl}_4, \quad 300 \text{ W tungsten lamp} \\
\end{align*}
\]

2,3-Dimethylanisole (0.20 g, 1.47 mmol) and N-bromosuccinimide (1.05 g, 5.88 mmol) were dissolved in carbon tetrachloride (75 ml) and the mixture was stirred under nitrogen overnight, while being exposed to a 300 watt high intensity tungsten lamp. The solution was cooled to room temperature, the suspended succinimide was removed by filtration and the solvent was evaporated. The residue was recrystallised from hexane:chloroform (5:1 v/v) to yield the product 2,3-bis(dibromomethyl)anisole (159) (0.60 g, 90 %) as a white solid; mp 148-149.5 °C (Lit.\textsuperscript{114} 149-150 °C); MS (FAB+) found 370.8082 [M-Br-H] \(\text{Br}_7\text{OBr}_4\); requires 370.8075 [M-Br-H] \(\text{Br}_7\); \(\nu\max (\text{CDCl}_3)/\text{cm}^{-1} 748 (\text{C-Br}), 1902, 1975, 2535 \) and 3740; \(\delta_H (400\text{MHz; CDCl}_3) 3.88 (s, 3H, OCH}_3), 6.78 (dd, J 0.8 & 8.4, 1H, Ar-H), 7.40 (t, J 8.4, 1H, Ar-H), 7.54 (s, 1H, CH), 7.68 (dd, J 0.8 & 8.0, 1H, Ar-H) and 7.77 (s, 1H, CH); \(\delta_C (400\text{MHz; CDCl}_3) 28.8 (\text{CH}), 37.0 (\text{CH}), 56.41 (\text{OCH}_3), 111.16 (\text{Ar-C}), 124.3 (\text{C}), 125.7 (\text{Ar-C}), 131.5 (\text{Ar-C}), 144.2 (\text{C}) \) and 151.8 (C).
2-Bromomethyl-3-(dibromomethyl)anisole (156) (11.49 g, 30.81 mmol) and anhydrous sodium acetate (9.10 g, 110.93 mmol) were dissolved in glacial acetic acid (100 ml) and the stirred solution was heated at reflux overnight. The acetic acid was evaporated, the residue was dissolved in ethyl acetate, the salts were removed by filtration, and the filtrate was stirred with hydrochloric acid (0.5M) (100 ml). After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 80 ml). The combined organic solution was dried over magnesium sulfate, filtered, evaporated and the crude material was purified by flash column chromatography using petroleum ether:ethyl acetate (3:2 v/v) as the eluent to yield the product 2-acetoxymethyl-3-methoxybenzaldehyde (160) (4.17 g, 65 %) as a yellow oil; MS (FAB+) found 207.0652 [M-H], C_{11}H_{12}O_{4}; requires 207.0657 [M-H]; \nu_{\text{max}} (CHCl_{3})/cm^{-1} 1659 and 1737 (C=O); \delta_{H} (400MHz; CDCl_{3}) 2.05 (s, 3H, CH_{3}), 3.90 (s, 3H, OCH_{3}), 5.57 (s, 2H, CH_{2}), 7.17-7.19 (m, 1H, Ar-H), 7.50-7.53 (m, 2H, 2 x Ar-H) and 10.29 (s, 1H, CHO); \delta_{C} (400MHz; CDCl_{3}) 21.0 (CH_{3}), 55.9 (CH_{2}), 56.2 (OCH_{3}), 116.23 (Ar-C), 122.56 (C), 122.82 (Ar-C), 130.26 (Ar-H), 137.0 (C), 158.5 (C), 171.1 (C=O) and 191.7 (CHO).
Experimental

2-Acetoxymethyl-3-methoxybenzaldehyde oxime (154)

To a solution of hydroxylamine hydrochloride (5.70 g, 82.03 mmol) and sodium acetate (13.46 g, 164.09 mmol) in water (80 ml), was added 2-acetoxymethyl-3-methoxybenzaldehyde (160) (8.54 g, 41.02 mmol) in ethanol (80 ml). The reaction mixture was heated to 70 °C for 10 min, and then cooled down to room temperature. The reaction was stored in a refrigerator overnight. If crystals were not formed, the solution was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was dried by sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield 2-acetoxymethyl-3-methoxybenzaldehyde oxime (154) (9.17 g, 100 %) as a pale yellow solid (the crude product was further purified for combustion analysis); mp 142-143 °C; MS (ES+) found 223.0838, C_{11}H_{13}NO_4; requires 223.0839; ν_{max} (CHCl_3)/cm^{-1} 1691, 1731 (C=O) and 3370; δ_{H} (400MHz; CDCl_3) 2.07 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.33 (s,2H, CH_2), 6.94-6.97 (m, 1H, Ar-H), 7.32-7.38 (m, 2H, 2 x Ar-H) and 8.42 (s, 1H, NCH); δ_{C} (400MHz; CDCl_3) 21.1 (CH_3), 55.9 (OCH_3), 57.3 (CH_2), 112.0 (Ar-C), 119.3 (Ar-C), 121.9 (C), 130.1 (Ar-C), 133.1 (C), 148.6 (CHN), 158.2 (C) and 170.2 (C=O); Found C, 59.38; H, 5.86; N, 6.49; C_{11}H_{13}NO_4 requires C, 59.19; H, 5.87; N, 6.27.
2-Acetoxymethyl-3-methoxyphenylhydroximoyl chloride (161)

To 2-acetoxymethyl-3-methoxybenzaldehyde oxime (154) (6.64 g, 29.75 mmol) in chloroform (100 ml) was added pyridine (2.40 ml, 29.75 mmol) in a reaction flask. The mixture was stirred under an atmosphere of nitrogen and the temperature was raised to 50 °C. N-Chlorosuccinimide (4.05 g, 30.34 mmol) was added to the mixture and stirred at 50 °C for 2 h. The reaction mixture was diluted by DCM (50 ml). The organic layer was washed with water (2 x 80 ml) and brine (100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product, 2-acetoxymethyl-3-methoxyphenylhydroximoyl chloride (161) (7.68 g, 100 %) as a yellow crude oil; MS (EI+) found 257.0454 (CI^{35}), C_{11}H_{12}NO_3Cl^{35}; requires 257.0455; ν_{max} (neat)/cm^{-1} 667 (C-Cl), 1792 (C=O) and 3402; δ_H (400MHz; CDCl3) 2.07 (s, 3H, CH3), 3.85 (s, 3H, OCH3), 5.28 (s, 2H, CH2), 7.01-7.26 (m, 1H, Ar-H) and 7.32-7.45 (m, 2H, 2 x Ar-H); δ_C (400MHz; CDCl3) 20.0 (CH3), 54.9 (OCH3), 56.6 (CH2), 110.2 (Ar-C), 120.9 (Ar-C), 121.0 (C), 129.1 (Ar-H), 132.9 (C), 157.8 (C), 169.5 (C=O) and 169.9 (C).
Experimental

3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (162)

To a solution of sodium isopropoxide prepared from sodium (0.68 g, 29.77 mmol) in isopropyl alcohol (150 ml), were added successively 5-methylcyclohexane-1,3-dione (10) (5.63 g, 44.64 mmol) and 2-acetoxymethyl-3-methoxyphenylhydroximoyl chloride (161) (7.67 g, 29.77 mmol). After stirring overnight at room temperature, the reaction mixture was poured into water (150 ml), and extracted with DCM (3 x 60 ml). The combined organic layer was washed with brine (2 x 100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:2 v/v) as eluent to yield 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (162) (3.73 g, 38 %) as a yellow viscous oil; MS (FAB+) found 330.1350 [M+H], C_{18}H_{19}NO_{5}; requires 330.1342 [M+H]; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1690 and 1735 (C=O); \delta_{\text{H}} (400\text{MHz}; \text{CDCl}_3) 1.16 (d, J 6.8, 3H, CH\text{3}), 1.96 (s, 3H, CH\text{3}), 2.21 (dd, J 11.0 & 15.9, 1H, OC\text{CH2}), 2.41-2.53 (m, 2H, CH \& OC\text{CH2}), 2.62 (dd, J 9.7 & 16.9, 1H, O=OC\text{CH2}), 3.10 (dd, J 5.0 & 16.9, 1H, O=OC\text{CH2}), 3.80 (s, 3H, OCH\text{3}), 5.19 (s, 2H, OCH\text{2}), 6.93-6.97 (m, 1H, Ar-H) and 7.21-7.34 (m, 2H, 2 \times Ar-H); \delta_{\text{C}} (400\text{MHz}; \text{CDCl}_3) 20.9 (\text{CH3}), 21.1 (\text{CH3}), 30.5 (\text{CH2}), 31.08 (\text{CH2}), 46.64 (\text{CH}), 55.90 (\text{OCH3}), 57.85 (\text{OCH2}), 112.5 (\text{Ar-C}), 115.0 (C), 121.5 (\text{Ar-C}), 130.2 (\text{Ar-C}), 137.0 (C), 142.0
Experimental

(C), 158.6 (C), 170.9 (C), 181.1 (C) and 191.5 (C).

3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-
tetrahydrobenzo[d]isoxazol-4-one (163) and 3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-
4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (164)

\[\text{(162)} \quad \begin{array}{c}
\text{AcO} \\
\text{MeO}
\end{array}
\]

\[\text{(163)} \quad \begin{array}{c}
\text{AcO} \\
\text{MeO}
\end{array}
\]

\[2.1 \text{ equiv. LDA, THF:DMPU (6:1)}
\]

\[2.0 \text{ equiv. } \text{Br} \]

\[\text{(164)} \quad \begin{array}{c}
\text{AcO} \\
\text{MeO}
\end{array}
\]

\(n\)-Butyllithium (2.5 M solution in hexanes; 2.1 equiv., 9.52 ml, 23.79 mmol) and diisopropylamine (3.40 ml, 24.27 mmol) was added in dry THF (30 ml) at 0 °C, followed by DMPU (8 ml) to make a LDA solution. It was stirred for 15 min. 3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-
4-one (162) (3.73 g, 11.33 mmol) in dry THF (18 ml) was added dropwise to this solution of LDA and DMPU at -78 °C. The resulting mixture was allowed to stir at -78 °C for 10 min. 1-Bromo-3-methybut-2-ene (2.64 ml, 22.66 mmol) was added at
-78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogen carbonate solution (40 ml) was added and the mixture was extracted with DCM (3 x 50 ml). The combined extract was washed with water (3 x 30 ml) and then brine (1 x 100 ml). The organic extract was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (2:1 v/v) as eluent to yield both mono-alkylated product, 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (163) (0.66 g, 15 %) as a yellow oil; MS (FAB+) found 397.1891 [M+H], C$_{23}$H$_{27}$NOS; requires 397.1889 [M+H]; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 1695, 1737 (C=O) and 2966; $\delta_{\text{H}}$(400MHz; CDCl$_3$) 1.16 (d, $J$ 5.5, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$), 1.60 (s, 3H, CH$_3$), 2.07 (s, 3H, CH$_3$), 2.24 (dd, $J$ 11.0 and 15.9, 1H, CH$_2$), 2.41-2.54 (m, 4H, CH, CH$_2$ & CH$_3$), 2.97-3.08 (m, 1H, CH), 3.75 (s, 3H, OCH$_3$), 5.19 (s, 2H, OCH$_2$), 5.24-5.27 (m, 1H, CH), 6.83-6.86 (m, 1H, Ar-H), 6.94-6.98 (m, 1H, Ar-H) and 7.25-7.43 (m, 1H, Ar-H); $\delta_{\text{C}}$ (400MHz; CDCl$_3$) 20.7 (CH$_3$), 21.0 (CH$_3$), 25.8 (2x CH$_3$), 30.1 (CH$_2$), 42.8 (CH$_2$), 43.2 (CH), 51.9 (CH), 55.8 (OCH$_3$), 57.6 (OCH$_2$), 108.2 (Ar-C), 111.2 (Ar-C), 117.3 (C), 121.9 (C), 129.6 (Ar-C), 130.1 (=CH), 151.2 (C), 153.1 (C), 158.7 (C), 165.7 (C), 170.7 (C), 181.2 (C) and 190.8 (C); and di-alkylated product, 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (164) (1.23 g, 23 %) as a yellow oil; MS (FAB+) found 465.2514 [M+H], C$_{28}$H$_{32}$NOS; requires 465.2515 [M+H]; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 1589, 1737 (C=O) and 2968; $\delta_{\text{H}}$(400MHz; CDCl$_3$) 1.17 (d, $J$ 5.1, 3H, CH$_3$), 1.57 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 1.62 (s, 3H, CH$_3$), 1.65 (s, 3H, CH$_3$), 2.03 (s, 3H, CH$_3$), 2.24-2.34 (m, 3H, CH & CH$_2$), 2.41-2.65 (m, 2H, CH & CH$_2$), 3.05-3.11 (m, 2H, CH$_2$), 3.77 (s, 3H, OCH$_3$), 5.19 (s, 2H, OCH$_2$), 5.16-5.23 (m, 2H, 2 x CH), 6.82-6.86
Experimental

(m, 1H, Ar-H), 6.92-6.96 (m, 1H, Ar-H) and 7.23-7.28 (m, 1H, Ar-H); δC (400MHz; CDCl₃) 20.8 (CH₃), 21.0 (CH₃), 25.7 (2 x CH₃), 25.9 (2 x CH₃), 29.6 (CH₂), 30.1 (CH₂), 43.2 (CH₂), 51.9 (CH), 55.6 (OCH₃), 57.6 (OCH₂), 106.3 (Ar-C), 110.9 (Ar-C), 117.2 (C), 121.2 (C), 122.6 (C), 129.5 (Ar-C), 130.1 (=CH), 130.2 (=CH), 152.3 (C), 153.3 (C), 158.6 (C), 163.2 (C), 165.6 (C), 171.1 (C), 181.0 (C) and 191.3 (C).

3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (165)

3-(2-Acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis(3-methylbut-2-enyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (164) (1.23 g, 1.81 mmol) in dry THF (10 ml) was added dropwise to a solution of LDA and DMPU at -78 °C, which was prepared by adding n-butyllithium (2.5 M solution in hexanes; 2.11 ml, 5.28 mmol) and diisopropylamine (0.76 ml, 5.39 mmol) in dry THF (16 ml) at 0 °C, followed by DMPU (6 ml). The resulting mixture was allowed to stir at -78 °C for 60 min. Phenylselenium bromide (0.94 g, 3.96 mmol) in dry THF (10 ml) was added at -78 °C, and the mixture was allowed to warm to room temperature and stirred overnight. Saturated sodium hydrogencarbonate solution (30 ml) was added and the mixture was
extracted with DCM (3 x 30 ml). The combined extract was washed with water (50 ml) and then brine (50 ml). The organic extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (3:1 v/v) as eluent to yield 3-(2-acetoxymethyl-3-methoxyphenyl)-6-methyl-5,5-bis-(3-methylbut-2-enyl)-7-phenylselenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (165) (0.64 g, 39 %) as a brown oil. MS (FAB+) found 622.2069 (M+H), C_{34}H_{39}NO_{2}Se^{80}; requires 622.2072 (Se^{80}) [M+H]; ν_{max} (neat)/cm⁻¹ 1731 (C=O), 2912 and 2964; δ_{H} (400MHz; CDCl₃) 1.04 (d, J 5.8, 3H, CH₃), 1.58 (s, 3H, CH₃), 1.60 (s, 3H, CH₃), 1.62 (s, 3H, CH₃), 1.65 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 2.22-2.33 (m, 4H, 2 x CH₂), 2.41-2.64 (m, 2H, 2 x CH), 3.83 (s, 3H, OCH₃), 4.97-5.12 (m, 1H, =CH), 5.20-5.45 (m, 1H, =CH), 5.19 (s, 2H, OCH₂), 6.85-6.92 (m, 1H, Ar-H), 6.93-7.12 (m, 1H, Ar-H), 7.23-7.27 (m, 3H, 3 x Ar-H), 7.38-7.44 (m, 1H, Ar-H) and 7.58-7.62 (m, 2H, 2 x Ar-H); δ_{C} (400MHz; CDCl₃) 20.7 (CH₃), 21.2 (CH₃), 25.6 (2 x CH₃), 25.9 (2 x CH₃), 29.5 (CH₂), 30.1 (CH₂), 49.2 (CH), 51.8 (CH), 55.5 (OCH₃), 57.6 (OCH₂), 106.2 (Ar-C), 117.3 (C), 119.6 (Ar-C), 121.3 (C), 122.5 (C), 129.5 (2 x Ar-C), 130.1 (=CH), 130.2 (Ar-C), 130.3 (=CH), 131.6 (Ar-C), 138.1 (2 x Ar-C), 151.2 (C), 153.6 (C), 158.7 (C), 163.1 (C), 165.5 (C), 171.2 (C), 181.2 (C) and 191.3 (C).
2-[1-Amino-1-(2-acetoxymethyl-3-methoxyphenyl)-meth-(E)-ylidene]-5-methyl-6,6-
bis(3-methyl-but-2-enyl)cyclohex-4-ene-1,3-dione (166)

3-(2-Bromo-6-methoxyphenyl)-6-methyl-5,5-bis(3-methylbut-2-enyl)-7-phenyl-
selenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (165) (7.14 g, 11.50 mmol) was
dissolved in acetonitrile (30 ml) and water (10 ml). Molybdenum hexacarbonyl (3.04
g, 11.50 mmol) was added to the reaction, and the mixture was heated under reflux for
3 h. After cooling to room temperature, the reaction mixture was treated with
hydrogen peroxide (27.5 wt % in H2O) (3 ml) dropwise at 0 °C. It was then left to stir
at room temperature overnight. The reaction was filtered through celite and charcoal
bath and then poured into ice (20 g). The mixture was extracted with DCM (30 ml).
The organic layer was washed with water (3 x 20 ml) and then neutralised with
sodium sulfite (10 %) (20 ml). The extracted organic layer was dried over sodium
sulfate, filtered and evaporated to dryness under reduced pressure to give the crude.
The crude product was purified by flash column chromatography using petroleum
ether:ethyl acetate (7:1) as eluent to yield the product,
2-[1-amino-1-(2-acetoxymethyl-3-methoxyphenyl)-meth-(E)-ylidene]-5-methyl-6,6-
bis(3-methyl-but-2-enyl)cyclohex-4-ene-1,3-dione (166) (1.04 g, 20 %) as a light
yellow viscous oil. MS (FAB+) found 466.2610 [M+H], C28H35NO5; requires
466.2593 [M+H]; \( \nu_{\text{max}} \) (CHCl3)/cm\(^{-1}\) 1678, 1771 (C=O), 2713 and 3410 (NH2); \( \delta_H \)
Experimental

(400MHz; CDCl₃) 1.18 (d, J 6.5, 3H, CH₃), 1.50 (s, 12H, 4 x CH₃), 1.99 (d, J 7.4, 2H, CH₂), 2.00 (s, 3H, CH₃), 2.44 (d, J 7.2, 2H, CH₂), 3.74 (s, 3H, OCH₃), 4.21-4.62 (m, 2H, 2 x CH), 5.18 (s, 1H, NH₂), 5.23 (s, 2H, OCH₂), 5.32 (s, 1H, NH₂), 6.80-6.84 (m, 1H, Ar-H), 6.92-6.94 (m, 1H, Ar-H), 7.24-7.29 (m, 1H, Ar-H) and 7.45 (d, J 1.5, 1H, CH); δc (400MHz; CDCl₃) 15.0 (CH₃), 17.3 (2 x CH₃), 17.6 (2 x CH₃), 26.0 (CH₃), 47.0 (2 x CH₂), 55.6 (OCH₃), 64.8 (CH₂), 117.8 (C), 125.5 (2 x Ar-C), 127.5 (Ar-C), 128.2 (Ar-C), 130.0 (CH), 130.1 (CH), 131.2 (CH), 134.2 (C), 135.3 (C), 158.6 (C), 161.3 (C), 170.3 (C), 187.2 (C) and 191.5 (C).

2,3-Bis(acetoxymethyl)anisole (167)¹¹⁴

2,3-Bis(bromomethyl)anisole (158) (1.64 g, 4.40 mmol) and anhydrous sodium acetate (1.30 g, 15.83 mmol) were dissolved in glacial acetic acid (20 ml) and then heated under reflux overnight. The acetic acid was evaporated, the residue was dissolved in ethyl acetate, the salts were removed by filtration, and the filtrate was stirred with hydrochloric acid (0.5 M) (10 ml). After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 30 ml). The combined organic solution was dried over magnesium sulfate, filtered, evaporated and the crude was purified by flash column chromatography using petroleum ether:ethyl acetate (3:2 v/v) as the eluent to yield the product 2,3-bis(acetoxymethyl)anisole (167) (0.31 g, 28 %)
as a white solid; mp 90–92 °C (Lit. 90–91 °C); MS (FAB) found 252.0995, C_{13}H_{16}O_{5};
requires 252.0998; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1746 (\text{C}=\text{O}) and 2853; \delta_{\text{H}} (400\text{MHz}; \text{CDCl}_3)
2.05 (s, 3H, CH\text{\textsubscript{3}}), 2.08 (s, 3H, CH\text{\textsubscript{3}}), 3.85 (s, 3H, OCH\text{\textsubscript{3}}), 5.19 (s, 2H, CH\text{\textsubscript{2}}), 5.27 (s, 2H, CH\text{\textsubscript{2}}), 6.93 (d, J 8.4, 1H, Ar-H), 7.02 (d, J 7.6, 1H, Ar-H) and 7.34 (t, J 8.0, 1H, Ar-H); \delta_{\text{C}} (400\text{MHz}; \text{CDCl}_3) 20.9 (\text{CH}_3), 21.0 (\text{CH}_3), 55.8 (\text{OCH}_3), 57.6 (\text{CH}_2), 63.9 (\text{CH}_2), 111.2 (\text{Ar-C}), 121.9 (\text{Ar-C}), 122.5 (\text{C}), 130.1 (\text{Ar-C}), 137.0 (\text{C}), 158.6 (\text{C}), 170.7 (\text{C}) and 170.9 (\text{C}).
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Appendix I

X-Ray crystal structure of 5-Bromo-6-methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-one (85)
Table 1. Crystal data and structure refinement for (85).

<table>
<thead>
<tr>
<th>Identification code</th>
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</tr>
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<tbody>
<tr>
<td>Chemical formula</td>
<td>C₁₄H₁₂BrNO₂</td>
</tr>
<tr>
<td>Formula weight</td>
<td>306.16</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P₂₁/c</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>7.8801(5) Å</td>
</tr>
<tr>
<td>b</td>
<td>11.1370(7) Å</td>
</tr>
<tr>
<td>c</td>
<td>14.1152(9) Å</td>
</tr>
<tr>
<td>Cell volume</td>
<td>1232.39(14) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.650 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>3.328 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>616</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>colourless, 0.41 x 0.27 x 0.19 mm³</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>5683 (θ range 2.33 to 28.39°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker SMART 1000 CCD diffractometer</td>
</tr>
<tr>
<td>ω rotation with narrow frames</td>
<td></td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>2.33 to 28.90°</td>
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<tr>
<td>Index ranges</td>
<td>h -10 to 10, k -14 to 14, l -18 to 18</td>
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<td>Completeness to θ = 26.00°</td>
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<tr>
<td>Intensity decay</td>
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<tr>
<td>Reflections collected</td>
<td>10595</td>
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<tr>
<td>Independent reflections</td>
<td>2988 (R̂ = 0.0195)</td>
</tr>
<tr>
<td>Reflections with F² &gt; 2σ</td>
<td>2575</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
<td>0.318 and 0.531</td>
</tr>
<tr>
<td>Structure solution</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Weighting parameters a, b</td>
<td>0.0712, 1.8709</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
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</tr>
<tr>
<td>Final R indices [F² &gt; 2σ]</td>
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</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0455, wR2 = 0.1230</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.066</td>
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<tr>
<td>Largest and mean shift/su</td>
<td>0.001 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.706 and -0.556 e Å⁻³</td>
</tr>
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</table>
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for (85). $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^0$ tensor.

<table>
<thead>
<tr>
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<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>-0.0863(2)</td>
<td>0.6916(2)</td>
<td>0.46033(15)</td>
<td>0.0248(4)</td>
</tr>
<tr>
<td>N(1)</td>
<td>-0.1322(3)</td>
<td>0.6463(2)</td>
<td>0.54835(19)</td>
<td>0.0237(5)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.0105(3)</td>
<td>0.6156(2)</td>
<td>0.59902(19)</td>
<td>0.0179(5)</td>
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<tr>
<td>C(2)</td>
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<td>0.6388(2)</td>
<td>0.5462(2)</td>
<td>0.0176(5)</td>
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<tr>
<td>C(3)</td>
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<td>0.6853(2)</td>
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<tr>
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<td>0.3856(2)</td>
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<td>C(7)</td>
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<td>0.6255(3)</td>
<td>0.5628(2)</td>
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<td>0.0257(6)</td>
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<td>C(10)</td>
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<td>0.5358(3)</td>
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<td>C(14)</td>
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<td>Br(1)</td>
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<td>0.85107(3)</td>
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Table 3. Bond lengths [Å] and angles [°] for (85).

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<th>Length [Å]</th>
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<td>C(2)–C(7)</td>
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<td>1.527(4)</td>
</tr>
<tr>
<td>C(5)–C(14)</td>
<td>1.530(4)</td>
</tr>
<tr>
<td>C(6)–Br(1)</td>
<td>1.972(3)</td>
</tr>
<tr>
<td>C(8)–C(13)</td>
<td>1.396(4)</td>
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<tr>
<td>C(9)–C(10)</td>
<td>1.385(5)</td>
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<tr>
<td>C(11)–C(12)</td>
<td>1.371(5)</td>
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<td>C(3)–O(1)–N(1)</td>
<td>108.3(2)</td>
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<td>C(2)–C(1)–C(8)</td>
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<td>C(3)–C(2)–C(7)</td>
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</tr>
<tr>
<td>C(2)–C(3)–C(4)</td>
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<tr>
<td>C(6)–C(5)–C(4)</td>
<td>111.5(2)</td>
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<tr>
<td>C(4)–C(5)–C(14)</td>
<td>111.5(3)</td>
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<td>C(5)–C(6)–Br(1)</td>
<td>111.3(2)</td>
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<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle [°]</th>
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<td>O(1)–C(3)–O(1)</td>
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<td>N(1)–C(1)–C(2)</td>
<td>1.442(4)</td>
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<td>C(2)–C(1)–C(2)</td>
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<td>C(4)–C(5)–C(6)</td>
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<td>C(6)–C(5)–C(14)</td>
<td>1.527(4)</td>
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<tr>
<td>C(7)–C(6)–Br(1)</td>
<td>1.218(4)</td>
</tr>
<tr>
<td>C(8)–C(9)–C(10)</td>
<td>1.402(4)</td>
</tr>
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<td>C(10)–C(11)–C(12)</td>
<td>1.394(5)</td>
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<table>
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<th>Bond</th>
<th>Angle [°]</th>
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<tr>
<td>C(3)–O(1)–N(1)</td>
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<td>N(1)–C(1)–C(8)</td>
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<td>C(3)–C(2)–C(7)</td>
<td>136.3(3)</td>
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<td>O(1)–C(3)–C(4)</td>
<td>121.0(2)</td>
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<td>C(5)–C(6)–Br(1)</td>
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<td>C(7)–C(6)–Br(1)</td>
<td>105.25(19)</td>
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Table 4. Hydrogen coordinates and isotropic displacement parameters (Å²) for (85).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(4A)</td>
<td>0.1768</td>
<td>0.8141</td>
<td>0.3781</td>
<td>0.027</td>
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<tr>
<td>H(4B)</td>
<td>0.1034</td>
<td>0.6990</td>
<td>0.3189</td>
<td>0.027</td>
</tr>
<tr>
<td>H(5)</td>
<td>0.3342</td>
<td>0.5835</td>
<td>0.3717</td>
<td>0.030</td>
</tr>
<tr>
<td>H(6)</td>
<td>0.5521</td>
<td>0.6421</td>
<td>0.4875</td>
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</tr>
<tr>
<td>H(9)</td>
<td>-0.2354</td>
<td>0.6402</td>
<td>0.7112</td>
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</tr>
<tr>
<td>H(10)</td>
<td>-0.2694</td>
<td>0.5517</td>
<td>0.8579</td>
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</tr>
<tr>
<td>H(11)</td>
<td>-0.0591</td>
<td>0.4229</td>
<td>0.9293</td>
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<tr>
<td>H(12)</td>
<td>0.1868</td>
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<td>0.8568</td>
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<tr>
<td>H(13)</td>
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<td>H(14A)</td>
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<td>H(14C)</td>
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</table>

Table 5. Torsion angles [°] for (85).

<p>| | | | | |</p>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>Bond Angle</td>
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<td>--------------</td>
<td>-------------</td>
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<td>C(1)-C(8)-C(13)-C(12)</td>
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Appendix
Appendix II

X-Ray crystal structure of (123).
Table 1. Crystal data and structure refinement for (123).

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<th>Identification code</th>
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<td>Formula weight</td>
<td>203.19</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>orthorhombic, Pna2₁</td>
</tr>
</tbody>
</table>
| Unit cell parameters| \( \begin{align*} 
    a &= 11.2713(16) \text{ Å} \\
    b &= 19.538(3) \text{ Å} \\
    c &= 4.0480(6) \text{ Å} \\
\end{align*} \) |
| Cell volume         | 891.4(2) Å³ |
| Z                   | 4 |
| Calculated density  | 1.514 g/cm³ |
| Absorption coefficient \( \mu \) | 0.112 mm⁻¹ |
| \( F(000) \)        | 424 |
| Crystal colour and size | colourless, 0.62 × 0.17 × 0.13 mm³ |
| Reflections for cell refinement | 2694 (θ range 2.76 to 26.98°) |
| Data collection method | Bruker SMART 1000 CCD diffractometer |
| \( \theta \) range for data collection | 2.08 to 28.94° |
| Index ranges        | h -14 to 14, k -25 to 25, l -5 to 5 |
| Completeness to \( \theta = 26.00° \) | 100.0 % |
| Intensity decay      | 0% |
| Reflections collected | 7541 |
| Independent reflections | 1246 (R_{int} = 0.0408) |
| Reflections with \( F^2 > 2\sigma \) | 1017 |
| Absorption correction | semi-empirical from equivalents |
| Min. and max. transmission | 0.934 and 0.986 |
| Structure solution  | direct methods |
| Refinement method   | Full-matrix least-squares on \( F^2 \) |
| Weighting parameters a, b | 0.0388, 0.3691 |
| Data / restraints / parameters | 1246 / 1 / 144 |
| Final R indices \([ F^2 > 2\sigma ]\) | \( R_1 = 0.0354, wR2 = 0.0817 \) |
| R indices (all data) | \( R_1 = 0.0522, wR2 = 0.0916 \) |
| Goodness-of-fit on \( F^2 \) | 1.035 |
| Absolute structure parameter | \(-10(10)\) |
| Largest and mean shift/su | 0.000 and 0.000 |
| Largest diff. peak and hole | 0.251 and -0.171 e Å⁻³ |
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for (123). \( U_{eq} \) is defined as one third of the trace of the orthogonalized \( U^i \) tensor.

<table>
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<th></th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( U_{eq} )</th>
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</thead>
<tbody>
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<td>O(1)</td>
<td>0.99165(14)</td>
<td>0.72230(7)</td>
<td>0.1643(5)</td>
<td>0.0271(4)</td>
</tr>
<tr>
<td>C(1)</td>
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<td>0.78964(11)</td>
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<td>0.0234(5)</td>
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<tr>
<td>O(2)</td>
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<td>0.0291(4)</td>
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<tr>
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<tr>
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</tr>
<tr>
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<td>0.0283(6)</td>
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<td>0.0272(5)</td>
</tr>
<tr>
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<td>0.0227(5)</td>
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Table 3. Bond lengths [Å] and angles [°] for (123).

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<th>Angle [°]</th>
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<tr>
<td>C(2)–C(3)</td>
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<tr>
<td>C(3)–N(1)</td>
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<td>C(4)–C(9)</td>
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<tr>
<td>C(5)–C(6)</td>
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<tr>
<td>C(7)–C(8)</td>
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<tr>
<td>C(10)–O(3)</td>
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<tr>
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</tr>
<tr>
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<td>119.8(2)</td>
<td></td>
</tr>
<tr>
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<tr>
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<tr>
<td>C(7)–C(8)–C(9)</td>
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<tr>
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<td>C(3)–C(2)–C(1)</td>
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<td>C(1)–C(2)–C(10)</td>
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<td>N(1)–C(3)–C(4)</td>
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Table 4. Hydrogen coordinates and isotropic displacement parameters (Å²) for (123).

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<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
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<td>H(1A)</td>
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<tr>
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Table 5. Torsion angles [°] for (123).

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</tr>
<tr>
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<td>-1.3(3)</td>
</tr>
<tr>
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</tr>
<tr>
<td>C(4)-C(5)-C(6)-C(7)</td>
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<td>C(6)-C(7)-C(8)-C(9)</td>
<td>2.1(4)</td>
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<td>1.7(3)</td>
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<tr>
<td>C(3)-C(4)-C(9)-C(8)</td>
<td>-178.7(2)</td>
</tr>
<tr>
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<td>-2.6(4)</td>
</tr>
<tr>
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</table>

Table 6. Hydrogen bonds for (123) [Å and °].

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<th>d(H-A) [Å]</th>
<th>d(D-A) [Å]</th>
<th>&lt;(DHA) [°]</th>
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Symmetry operations for equivalent atoms
' x-1/2, -y+3/2, z-1
Appendix III

X-Ray crystal structure of 2,3-Bis(dibromomethyl)anisole (159)

The data were collected at 150(2)K on a Bruker Apex II CCD diffractometer. The structure was solved by direct methods and refined on $F^2$ using all the reflections*. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Parameters for data collection and refinement are summarised in Table 1. There are both $\pi-\pi$ and Br-Br interactions in the lattice.

<table>
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<tr>
<td>Space group</td>
<td>P2(1)/c</td>
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<tr>
<td>Unit cell dimensions</td>
<td>\begin{align*} a &amp; = 7.9770(3) \text{ Å} &amp; \alpha = 90^\circ. \ b &amp; = 22.1919(9) \text{ Å} &amp; \beta = 106.6220(10)^\circ. \ c &amp; = 6.8715(3) \text{ Å} &amp; \gamma = 90^\circ. \end{align*}</td>
</tr>
<tr>
<td>Volume</td>
<td>1165.59(8) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>2.575 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>13.775 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>840</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.36 x 0.12 x 0.04 mm³</td>
</tr>
<tr>
<td>Crystal description</td>
<td>colourless lath</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.84 to 31.90°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11&lt;=h&lt;=11, -32&lt;=k&lt;=31, -10&lt;=l&lt;=9</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>14001</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3749 [R(int) = 0.0397]</td>
</tr>
<tr>
<td>Completeness to theta = 27.50°</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.6088 and 0.0829</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3749 / 0 / 128</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.029</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0284, wR2 = 0.0608</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0467, wR2 = 0.0659</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.00264(16)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.900 and -0.775 e.A⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for (159).

$U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U(\text{eq})$</th>
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<td>7048(1)</td>
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<td>5624(1)</td>
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<td>5655(1)</td>
<td>8544(1)</td>
<td>20(1)</td>
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Table 3. Bond lengths [Å] and angles [°] for (159).

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<th>Bond/Angle</th>
<th>Value</th>
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<td>C(2)-C(3)</td>
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<td>C(2)-C(8)</td>
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<td>1.391(4)</td>
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<tr>
<td>C(4)-C(5)</td>
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</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.394(3)</td>
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<tr>
<td>C(6)-C(8)</td>
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<tr>
<td>C(6)-C(7)</td>
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<td>C(7)-Br(2)</td>
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<tr>
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<tr>
<td>C(8)-C(9)</td>
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<td>C(2)-O(1)-C(1)</td>
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</tr>
<tr>
<td>O(1)-C(2)-C(3)</td>
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<td>O(1)-C(2)-C(8)</td>
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<td>121.0(2)</td>
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<td>C(6)-C(7)-Br(2)</td>
<td>111.62(16)</td>
</tr>
<tr>
<td>C(6)-C(7)-Br(1)</td>
<td>110.72(15)</td>
</tr>
<tr>
<td>Br(2)-C(7)-Br(1)</td>
<td>109.52(12)</td>
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<td>C(6)-C(8)-C(2)</td>
<td>118.1(2)</td>
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<td>C(6)-C(8)-C(9)</td>
<td>124.6(2)</td>
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<td>Br(3)-C(9)-Br(4)</td>
<td>110.94(12)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

xiv
Table 4. Anisotropic displacement parameters (Å² x 10³) for (159). The anisotropic displacement factor exponent takes the form: 

\[-2\pi²[ h² a² U_{11} + ... + 2 h k a b U_{12} ]\]

<table>
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<th>$u^{33}$</th>
<th>$u^{23}$</th>
<th>$u^{13}$</th>
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<td>17(1)</td>
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<td>7(1)</td>
<td>-3(1)</td>
</tr>
</tbody>
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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (159).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
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<th>z</th>
<th>U(eq)</th>
</tr>
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