Applications of Imino-Diels–Alder Reactions in Synthesis

A thesis presented by

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Declaration of Originality

The work reported in this thesis is my own and information derived from the published and unpublished work of others has been appropriately referenced.
Abstract
The aim of the project was to synthesise (−)-morphine utilising a tethered intramolecular imino-Diels–Alder reaction.

This thesis begins by providing brief reviews on the subjects of total synthesis of morphine and asymmetric imino-Diels–Alder reaction.

The major section focuses on the research findings in the past four years. Starting with investigations in the development of a novel stereoselective imino-Diels–Alder reaction of methyl propargyl ether derived (1E,3Z)-1-silyloxy-3-(phenylthio)-1,3-dienes with trans-2-phenylcyclohexyl glyoxylate derived N-tosylimine. Following with the progress made so far to synthesise triene II; this was envisaged to be prepared from the enantiomerically pure alcohol III and allylic halide IV. The alcohol III was prepared in a five-step sequence from p-anisaldehyde. However, the synthesis of the allylic halide IV from D-lyxose was more challenging and problematic. Initial efforts for its synthesis via a route incorporating the Ohira–Bestmann reaction caused an unwanted epimerisation. Further efforts, through an eleven-step sequence including Wittig dibromomethylation and intramolecular ene–yne metathesis gave V or VI. However, the reductive eliminations to give the alcohol precursor to IV were unsuccessful.

Experimental details and characterisation data are provided at the end of the thesis.
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## 2 Abbreviations

| Ac  | acetyl                                      |
| ADDP | 1,1′-(azodicarbonyl)dipiperidine            |
| atm | atmosphere                                  |
| br  | broad                                       |
| brsm| based on recovered starting material        |
| bp  | boiling point                               |
| BHT | 2,6-bis(1,1-dimethyl ethyl)-4-methylphenol  |
| "Bu| normal-butyl                                |
| cat.| catalytic                                   |
| CI  | chemical ionisation                         |
| CSA | camphorsulfonic acid                        |
| d   | doublet                                     |
| DABCO | 1,4-diazabicyclo[2.2.2]octane              |
| DBDMH| 1,3-dibromo-5,5-dimethyl hydantoin          |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene          |
| DBS | dibenzosuberyl                              |
| DMAP| 4-dimethylaminopyridine                     |
| DMF | N,N-dimethylformamide                       |
| DMSO| dimethylsulfoxide                           |
| dr  | diastereomeric ratio                        |
| EDG | electron donating group                     |
| ee  | enantiomeric excess                         |
| equiv| equivalents                                 |
| ESI | electrospray ionisation                     |
| Et  | ethyl                                       |
| EtOAc| ethyl acetate                               |
| EtOH| ethanol                                     |
| EWG | electron withdrawing group                  |
| h   | hours                                       |
| HMDS| hexamethyl disilazide                       |
| HOMO| highest occupied molecular orbital          |
IMDA intramolecular Diels–Alder
IR infra-red
KHMDST ketonium bis(trimethylsilyl)amide
LDA lithium diisopropylamide
LiHMDS lithium bis(trimethylsilyl)amide
LUMO lowest occupied molecular orbital
m multiplet
m-CPBA meta-chloroperbenzoic acid
Me methyl
MeOH methanol
min minutes
MMPP magnesium monoperoxyphthalate
mp melting point
Ms methanesulfonyl
NBS N-bromosuccinimide
NCS N-chlorosuccinimide
NMR nuclear magnetic resonance
nOe nuclear Overhauser effect
o- ortho-
p- para-
PCC pyridinium chlorochromate
Ph phenyl
Pht phthalimidyld
PMP 1,2,2,6,6-pentamethylpiperidine
PrOH isopropyl alcohol
q quartet
Rf retention factor
rt room temperature
s singlet
s- sec-
t triplet
t- tert-
TBDPS tert-butyldiphenylsilyl
TBS tert-butyldimethylsilyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate (triflate)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N,N,N',N'$-tetramethylethane-1,2-diamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>tolyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>$para$-toluenesulfonyl</td>
</tr>
<tr>
<td>$v_{\text{max}}$</td>
<td>infrared absorption maximum</td>
</tr>
<tr>
<td>wt</td>
<td>weight</td>
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3 Stereochemical Notation

Throughout this report, the Maehr\textsuperscript{1} convention of indicating relative and absolute stereochemistry has been adopted. Hence, solid and broken lines are used to denote racemates, whilst solid and broke wedges are used to denote absolute configuration. Furthermore, the narrowing of both solid and broken wedges implies increasing distance from the viewer.

![Racemate and Single enantiomer](image)

**Figure 1.** Illustration of the Maehr\textsuperscript{1} convention.

4 Morphine Numbering

Throughout this report, the following morphine numbering system will be adopted unless otherwise stated.

![(-)-morphine](image)

**Figure 2.** (-)-morphine numbering system.
5 Introduction

Morphine 1 was the first active alkaloid to be isolated from the opium poppy plant, *Papaver somniferum*, in 1804 by Sertürner. He named the benzylisoquinoline alkaloid “morphium” after the Greek god of dreams, Morpheus; as it was known for causing sleepiness and feelings of euphoria. Predominantly today, morphine is used as a potent opiate analgesic but the 3,6-diacetyl ester of it, diamorphine (heroin) 2, is abused as an illicit narcotic.

![Diagram of morphine and diacetylmorphine](image)

**Figure 3.** Structures of morphine 1 and diacetylmorphine 2.

The entire supply of morphine used today for both medicinal and recreational proposes comes from natural opium, which is mainly cultivated in Afghanistan, Australia, India and Turkey. So far, there still has not been a practical synthesis to morphine that competes with this natural supply. Since Gulland and Robinson reported the structure of morphine in 1925; there have been numerous total and formal syntheses of this alkaloid, which have been detailed in several reviews and articles. In particular, the review by Blakemore and White contains an excellent account of the history, biological action and biosynthesis of morphine.
5.1 Biosynthesis of Morphine

The biosynthesis of (–)-morphine 1 is well understood (Scheme 1), although the mechanism is not completely elucidated. Dopamine 4 and p-hydroxyphenylacetaldehyde 5, which are derived from L-tyrosine 3, undergo a stereoselective Pictet–Spengler reaction to give (S)-norcoclaurine 6. Subsequent oxidation and methylation give (S)-reticuline 7, which undergoes an inversion of configuration by an oxidation–reduction sequence to yield (R)-reticuline 8. Following conversion of (R)-reticuline 8 into salutaridine 9 by α-phenolic oxidation, reduction of the ketone gives salutaridinol 10. Acetylation and spontaneous cyclisation yields thebaine 11, which undergoes demethylation to give neopinone 12. This readily isomerises to codeinone 13, which is reduced to (–)-codeine 14. Finally, demethylation of (–)-codeine 14 affords (–)-morphine 1.
Scheme 1. Biosynthesis of (−)-morphine 1.

1. L-tyrosine 3

2. dopamine 4

3. (S)-norcoclaurine synthase

4. (S)-norcoclaurine 6

5. (R)-reticuline 8

6. (S)-reticuline 7

7. salutaridine 9

8. salutaridinol 10

9. salutaridinol 7-O-acetyltransferase

10. thebaine 11

11. neopinone 12

12. codeinone 13

13. (−)-codeine 14

14. (−)-morphine 1

(unknown enzyme) demethylation

(unknown enzyme) demethylation
5.2 Total Syntheses of Morphine

Since the first total synthesis of morphine was accomplished by Gates and Tschudi in 1952, over 20 total and formal syntheses have been reported. The syntheses described below were chosen because either they were groundbreaking for their time and/or are the most efficient routes to morphine.

5.2.1 Rice’s synthesis

To date the most efficient and possibly practical route to large-scale manufacture of morphine has been Rice’s biomimetic approach, published in 1980 (Scheme 2). Direct condensation of 3-methoxyphenethylamine and acid 15, which was derived from isovanillin, gave the corresponding amide. Subsequent, Bischler–Napieralski cyclisation and reduction gave tetrahydroisoquinoline 16. A sequence of Birch reduction, formylation, ketalisation, and regioselective bromination afforded the crude ketal intermediate, which was readily hydrolysed to ketone 17.

Scheme 2. Rice’s biomimetic approach to (±)-dihydrocodeinone 19.

\[ \begin{align*}
\text{a)} & \quad 3\text{-Methoxyphenethylamine (1.0 equiv), } 200 \, ^\circ\text{C, 2 h; b) } \text{POCl}_3 \text{ (6.4 equiv), MeCN, reflux, 60 min; c) } \text{NaCNBH}_3 \text{ (1.0 equiv), aqueous } \text{MeOH, reflux, 90 min; d) } \text{Li (23 equiv), } \text{NH}_3, \text{ THF/}^\text{t}{\text{-BuOH}}, -55 \, ^\circ\text{C, 4 h; e) } \text{PhOCHO} \text{ (1.5 equiv), EtOAc, reflux, 45 min; f) } \text{MsOH} \text{ (cat.), ethylene glycol (3 equiv), THF, rt, 60 min; then } \text{NBS} \text{ (1.05 equiv), } 0 \, ^\circ\text{C, 30 min; followed by } 88\% \text{ HCO}_2\text{H/H}_2\text{O, rt, 60 min; g) } 14\% \text{ NH}_4\text{F.HF, TfOH, 0 } ^\circ\text{C, 96 h; h) aqueous } \text{HCl, MeOH, reflux, 18 h; i) } \text{Br}_2 \text{ (1.1 equiv), AcOH, rt, 2 h; then aqueous } \text{NaOH, CHCl}_3; j) \text{H}_2, 10\% \text{ Pd/C (cat.), } \text{NaOAc} \text{ (5.0 equiv), aqueous CH}_3\text{O, AcOH.}
\end{align*} \]
Grewe cyclisation\textsuperscript{12} of 17 yielded only morphinan 18, as the bromine substituent at C1 acted as a blocking group preventing \textit{para} coupling. Following hydrolysis of amide 18 and \(\alpha\)-bromination of the ketone, the dihydrofuran ring of 19 was formed by base-induced ring closure. Finally, cleavage of the aryl bromide and methylenation of the amine concurrently by hydrogenation over palladium in a mixture of aqueous formaldehyde and acetic acid gave (\(\pm\))-dihydrocodeinone 19. The conversion of 19 to (\(\pm\))-codeine 14 was achieved using the method reported by Weller and Rapoport.\textsuperscript{13} Subsequent, \(O\)-demethylenation of (\(\pm\))-codeine provided (\(\pm\))-morphine.\textsuperscript{14} Although, Rice’s synthesis of (\(\pm\))-dihydrocodeinone 19 proceeded in an overall yield of 29\% over 10 steps, its main disadvantage was that resolution of the racemate was required to give the active opiate.

\subsection*{5.2.2 Overman’s synthesis}

The first asymmetric total synthesis of (–)-dihydrocodeinone 19 and hence (–)-morphine 1 was published in 1993 by Overman and co-workers\textsuperscript{15} (Scheme 3). Asymmetric reduction of enone 20 with catecholborane in the presence of (\(R\))-oxazaborolidine catalyst 26 afforded the corresponding (\(S\))-alcohol in >96\% ee. Subsequent condensation with phenyl isocyanate, selective dihydroxylation and diol protection gave allylic carbamate 21. Treatment of 21 with the lithium dibutylcuprate and phenyltrimethylsilyllithium provided an allylsilane intermediate, which was subjected to acetonide deprotection. Following periodate cleavage of the resultant diol and treatment of the corresponding \(\beta,\gamma\)-unsaturated aldehyde with debenzosuberylamine and sodium cyanoborohydride provided homoallylic amine 22. Condensation of 22 with aldehyde 23, which was derived from isovanillin, produced an iminium ion which was trapped intramolecularly by the allylsilane to yield octahydroisoquinoline 24. Intramolecular Heck cyclisation of 24 afforded morphinan 25. After cleavage of the benzyl ether, the dihydrofuran ring of 19 was formed by treatment of the resultant alcohol with CSA and 3,5-dinitroperoxybenzoic acid. Finally, oxidation and then hydrogenolysis of the DBS group in the presence of formaldehyde provided (–)-dihydrocodeinone 19.
**Scheme 3.** Overman’s asymmetric approach to (−)-dihydrocodeinone 19.\(^{15}\)

Overman’s synthesis of (−)-dihydrocodeinone 19 proceeded in an overall yield of 4.4% over 14 steps. The main advantage of this asymmetric synthesis was that the unnatural enantiomer of morphine could be synthesised by using the other enantiomeric form of the oxazaborolidine catalyst.

**5.2.3 Mulzer’s synthesis**

In 1996, Mulzer *et al.*\(^{16}\) published their phenanthrene-based approach to morphine (Scheme 4). This was only the second phenanthrene-based synthesis since the first was reported by Ginsburg and co-workers\(^ {17}\) in 1954.
Scheme 4. Mulzer’s phenanthrene-based approach to (−)-dihydrocodeinone 19.\textsuperscript{16}

a) Cl\(_2\) (1.2 equiv), AcOH, 10 °C, 2 h; then reflux, 10 min; b) (COCl\(_2\))\(_2\) (2.2 equiv), benzene, 50 °C, 2 h; then SnCl\(_4\) (3.5 equiv), 0 °C, 36 h; c) HCO\(_2\)Me (2.0 equiv), NaOMe (1.5 equiv), benzene, reflux, 3 h; then rt, 12 h; d) Et\(_3\)N (2.0 equiv), methyl vinyl ketone (1.3 equiv), MeOH, 0 °C→rt, 3 d; followed by KOH (4.0 equiv), dioxane/H\(_2\)O, rt, 3 h; e) vinylmagnesium chloride (4.0 equiv), CuI (2.0 equiv), THF, −78→0 °C, 3 h; then TMSCl (5.0 equiv), Et\(_3\)N (6.0 equiv), 0 °C→rt, 60 min; f) NBS (1.2 equiv), THF, −78 °C→rt, 4 h; g) only 31, DMF, 140 °C, 20 min; h) TMSCl (4.6 equiv), ethylene glycol/CH\(_2\)Cl\(_2\), rt, 18 h; i) BH\(_3\)·SMe\(_2\) (5.0 equiv), THF, −15 °C→rt, 18 h; then aqueous H\(_2\)O\(_2\), NaOH, rt, 20 h; j) H\(_2\), Raney Ni (cat.), KOH (1.0 equiv), MeOH, rt, 5 h; k) PhSO\(_2\)NHMe (1.5 equiv), ADDP (1.5 equiv), PBu\(_3\) (1.5 equiv), benzene, 0 °C→rt, 24 h; l) (BzO)\(_2\) (cat.), NBS (1.05 equiv), CCl\(_4\), reflux, 10 min; then Et\(_3\)N, reflux, 10 min; m) Li (140 equiv), NH\(_3\), THF/\(^\circ\)BuOH, −78 °C, 30 min; n) aqueous HCl, 90 °C, 60 min.
Chlorination of carboxylic acid 27, followed by intramolecular Friedel–Crafts acylation gave tetralone 28, as the chlorine substituent at C1 directed the cyclisation into the less reactive aromatic position. Activation of 28 as its formyl derivative, followed by a sequence of Robinson annulation and retro-Claisen cleavage afforded racemic phenanthrene 29. This was resolved by chiral phase chromatography on cellulose triacetate. Conjugate addition of the vinylcuprate to (−)-phenanthrone 29 gave the corresponding enolate, which was treated with trimethylsilyl chloride to give silyl enol ether 30. Subsequent bromination of 30 gave a 3:1 mixture of diastereomeric bromides 31 and 32. However, the undesired minor bromide 32 could be recycled back to 30, by reduction with zinc in the presence of trimethylsilyl chloride. Heating of bromide 31 in DMF, initiated the intramolecular transetherification to form the dihydrofuran ring of 33. After protection of ketone 33 as the ketal, a sequence of hydroboration and oxidation of the vinyl moiety, followed by hydrogenation of the aryl chloride afforded alcohol 34. Conversion of alcohol 34 to the corresponding sulfonamide and introduction of unsaturation between C9-C10 gave the substrate that underwent concomitant cyclisation to form 35, when the sulfonamide was removed using dissolving metal conditions. Finally, hydrolysis of the ketal yielded (−)-dihydrocodeinone 19. Mulzer’s synthesis of (−)-dihydrocodeinone 19 was quite efficient and proceeded in an overall yield of 11.5% over 15 steps. However, again the synthesis required resolution of racemic phenanthrene 29.

5.2.4 Magnus’ synthesis

Recently, Magnus et al.\textsuperscript{5d} have published an efficient synthesis to (±)-codeine 14 via an interesting intramolecular phenol para-alkylation of 37 (Scheme 5). Suzuki coupling of 2-bromoisoavanillin 36 with cyclotriboroxane 42 gave the corresponding biaryl compound, which was treated with a mixture of ethyl vinyl ether, bromine and Hünig’s base to afford ether 37. Treatment of 37 with caesium fluoride led to the intramolecular phenol para-alkylation to give dienone 38, as a single compound because the epimers at the C16 lactol are mirror images of each other (axial symmetry of the dienone). Subsequent Henry-aldol reaction of 38 was followed by a reduction sequence to give tetracycle 39, as a 1:1 mixture of epimers. Exposure of 39 to reductive amination conditions yielded morphinan 40.
*Scheme 5.* Magnus’ intramolecular phenol alkylation approach to (±)-codeine 14.\(^{5d}\)

Treatment of the ethyl carbamate derivative of 40 with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave the corresponding bromohydrin, which on exposure to base gave epoxide 41. Ring opening of epoxide 41 with sodium thiophenolate, was followed by a sequence of oxidation, thermal elimination and reduction to give (±)-codeine 14. Even though Magnus’ synthesis of (±)-codeine 14
proceeded in an overall yield of 20% over 13 steps, it still gave a racemic mixture that would require resolution to give the active alkaloid. However, they are examining the enantioselective nitroaldol reaction of 38 to subsequently afford (−)-codeine 14.

Although a fully synthetic route to morphine would be unlikely to compete with the natural production and supply unless it were produced in 6–8 steps from inexpensive materials, the synthesis of it continues to attract significant interest from many chemists. This is due to its densely functionalised structure, which features a pentacyclic skeleton and five contiguous stereocentres, being a challenging test ground for different methodologies.
5.3 Our Proposed Synthesis of (−)-morphine

Our proposed synthetic route to (−)-morphine 1 intends to make use of a tethered intramolecular Diels–Alder (IMDA) reaction involving an \( N \)-tosylimine heterodienophile (Scheme 6).

Scheme 6. Proposed route to (−)-morphine.

It is believed that triene 46 would undergo a diastereoselective hetero-IMDA reaction to form cycloadduct 45. Then reductive cleavage of the benzylic ether linkage in the key intermediate 45 is envisaged to give the Heck cyclisation substrate 44. The intramolecular Heck reaction of 44,\(^{18}\) followed by double bond reduction is predicted to give tricyclic intermediate 43. Subsequent oxidation, methylation, ring-closing metathesis (RCM) and ketal hydrolysis would give diol 42. Finally, diiodination of
the electron-rich arene and palladium(0)-catalysed cyclisation\(^{19}\) would give the pentacyclic skeleton of (–)-morphine.

The key substrate feature that renders the imino-IMDA asymmetric is the disposable benzylic ether linkage acting like a chiral auxiliary and directing the \(\text{exo}\) approach of the diene to the more accessible face of the \(N\)-tosylimine dienophile. Alongside the exploration of this route to (–)-morphine, the development of diastereo- and enantioselective intermolecular imino-Diels–Alder reactions using chiral auxiliaries attached to the \(N\)-tosylimine will be investigated.

The following review intends to give an overview of recent developments in the area of asymmetric imino-Diels–Alder reactions using chiral auxiliaries.

### 5.4 Asymmetric Imino-Diels–Alder Reactions

Since, the first reported imino-Diels–Alder reaction over 65 years ago,\(^{20}\) the versatility of the reaction to regio- and stereoselectively construct nitrogen heterocyclic rings has been widely explored, as described in numerous reviews.\(^{21,22}\) Interest in this reaction is still as current as ever due to its ability to rapidly and efficiently synthesise functionalised piperidines, which are common structural components for many aminoacids and biologically active compounds, such as morphine.\(^{23}\)

The use of chiral catalysts or auxiliaries to control the stereochemical outcome of the cycloaddition to favour one enantiomer or diastereomer over another, has led to the development of asymmetric imino-Diels–Alder reactions. The former allows the formation of enantiomerically pure compounds from achiral substrates by coordination of the diene/dienophile to a chiral catalyst, which forces the approach of the dienophile/diene from the less hindered face.\(^{24}\) In the latter, addition of a prochiral diene/dienophile to a chiral dienophile/diene carrying the removable chiral auxiliary, which controls the topicity, leads to the formation of a diastereomerically pure adduct. Regenerative cleavage of the chiral auxiliary then furnishes an enantiomerically pure compound.\(^{25}\)
Since Walborsky et al.\textsuperscript{26} published the first asymmetric Diels–Alder reaction utilising a chiral directing group attached to the dienophile, there has been substantial progress in the development of new chiral auxiliary groups. One such example is chiral 8-phenylmenthol developed by Corey and co-workers\textsuperscript{27} for the enantioselective synthesis of intermediates useful for the preparation of naturally occurring prostaglandins. The Lewis acid (AlCl\textsubscript{3})-catalysed reaction of acrylate ester 47 with 5-benzyloxymethylcyclopentadiene 48 afforded the \textit{endo}-norbornenecarboxylic ester (1S)-49 in 89\% yield and 97\% de (Scheme 7).

\textit{Scheme 7.} Illustration of the stereochemical control \textit{via} the use of a chiral auxiliary.\textsuperscript{25}

The (–)-8-phenylmenthyl ester group on the dienophile 47 causes steric shielding of the diastereotopic \textit{si}-face thereby promoting addition of diene 48 to the \textit{re}-face. Therefore, cycloadduct (1S)-49 is obtained in a significant excess over (1R)-49. Further manipulation of (1S)-49 and cleavage of the chiral auxiliary, gives ketone 50 as a single enantiomer. Without the chiral directing group (R*=H) the addition of diene 48 to the two enantiotopic dienophile faces would occur at the same rate, giving a 1:1 mixture of enantiomers (1R)-49 and (1S)-49.\textsuperscript{25}
There have been many comprehensive reviews\textsuperscript{28} detailing the developments of asymmetric imino-Diels–Alder reactions. The following review intends to give an overview of recent developments of this reaction using covalently attached chiral auxiliary groups as the source of stereochemical control. It will focus mainly on reports from the year 2000 onwards. Advancements in the area of chiral catalysts for asymmetric imino-Diels–Alder reactions will not be covered.

The review will be organised by the three basic variations of the imino-Diels–Alder reaction (Scheme 8). The most common variant uses the imine as the dienophile to construct piperidines, and the other two variants use azadienes.\textsuperscript{21}

\textit{Scheme 8.} Three variations of the imino-Diels–Alder reaction.

5.4.1 \textbf{Imine dienophile}

Normally, the imine dienophile variant of the imino-Diels–Alder reaction requires the use of activated dienes or imines with electron withdrawing group substituents. However, the low reactivity of some imine dienophiles can be overcome by the use of Lewis or Brønsted acid catalysis. Recently, the use of both an activated dienophile and Lewis acid in Diels–Alder reactions has become commonplace; coordination of the acid to the dienophile makes it more electrophilic, often increasing both reaction rate and stereoselectivity.

An example of an asymmetric imino-Diels–Alder reaction using both an electron deficient chiral $N$-sulfinyl imine dienophile and a Lewis acid to improve the
stereoselectivity has been reported by Gautun and co-workers\textsuperscript{29} (Scheme 9 and Table 1).

**Scheme 9.** Imino-Diels–Alder reaction of dienophile 51 with diene 52.\textsuperscript{29}

\begin{center}
\begin{tabular}{llllll}
Entry & Lewis Acid & Solvent & Temperature & Reaction Time & Ratio of 53:54 & Yield \\
1 & - & CH\textsubscript{2}Cl\textsubscript{2} & 50 °C & 40 h & 7:3 & 62\% \\
2 & BF\textsubscript{3}·OEt\textsubscript{2} (1.0 equiv) & CH\textsubscript{2}Cl\textsubscript{2} & −78 °C & 90 min & 4:1 & 63\% \\
\end{tabular}
\end{center}

The Lewis acid-promoted cycloaddition between the doubly activated \textit{N-}\textit{tert}-butanesulfinyl \textit{α}-imino ester 51 and Danishefsky’s diene 52 gave dihydropyridinones 53 and 54 in an improved diastereomeric ratio of 4:1, in comparison to the thermal uncatalysed reaction where the ratio was 7:3. Attempts to make the reaction catalytic by using 10 mol \% of BF\textsubscript{3}·OEt\textsubscript{2} failed, probably due to inhibition of the Lewis acid by strong coordination to the imine nitrogen atom.\textsuperscript{29}

Similarly, García-Mera and co-workers\textsuperscript{30} have published the Lewis acid-activated diastereoselective imino-Diels–Alder reaction of a chiral glyoxylate-derived electron deficient imine and cyclopentadiene (Scheme 10).
Scheme 10. Imino-Diels–Alder reaction of the (−)-8-phenylmenthyl glyoxylate 55 derived imine with cyclopentadiene.\textsuperscript{30}

The iminium salt generated \textit{in situ} from the reaction of (−)-8-phenylmenthyl glyoxylate 55, benzylamine, trifluoroacetic acid and boron trifluoride etherate, was reacted with cyclopentadiene to give a mixture of diastereomeric cycloadducts in an \textit{exo}/\textit{endo} ratio of 91:9. The \textit{exo} adducts 56 and 57 were obtained in a diastereomeric ratio of 88:12. The high \textit{exo} selectivity can be explained by the requirement of the cyclopentadiene to approach the (E)-configured dienophile from the trajectory minimising the steric interaction between the methylene group of the diene and the bulky benzyl group of the dienophile (Figure 4).\textsuperscript{31}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{transition_state_model}
\caption{Transition state model.\textsuperscript{31}}
\end{figure}

The formation of \textit{exo} adduct 56 as the major diastereomer was as a result of the diene approaching the less hindered \textit{si}-face of the dienophile, which was not shielded by the phenyl group of the chiral auxiliary. Chromatographic purification allowed isolation of the major cycloadduct 56, which was treated with lithium aluminium hydride to cleave the chiral auxiliary and afford enantiomerically pure alcohol 60 (Scheme 11).
**Scheme 11.** Reductive cleavage of the chiral auxiliary to afford alcohol 60.\(^{31}\)

![Scheme 11](image)

a) LiAlH\(_4\) (6.0 equiv), Et\(_2\)O, 0 °C→rt, 5 h; R* = (1R)-8-phenylmenthyl.

During research\(^{32}\) into the preparation of the various diastereomers of 8-phenylmenthol and their application as chiral auxiliaries in imino-Diels–Alder reactions;\(^{31}\) García-Mera and co-workers\(^{33}\) developed (+)-(1\(R,\)endo)-2-benzobornenol 61 as a novel π-stacking chiral auxiliary in order to enhance asymmetric induction (Scheme 12).

**Scheme 12.** Synthesis and cycloaddition with cyclopentadiene of the (+)-(1\(R,\)endo)-2-benzobornenyl glyoxylate derived imine.\(^{34}\)

![Scheme 12](image)

a) Acryloyl chloride (2.1 equiv), Et\(_3\)N (2.0 equiv), DMAP (0.14 equiv), CH\(_2\)Cl\(_2\), 0 °C→rt, 2 h; b) OsO\(_4\) (1.5 mol %), NaIO\(_4\) (2.1 equiv), water/dioxane, rt, 2 h; c) PhCH\(_2\)NH\(_2\) (1.1 equiv), TFA (1.1 equiv), BF\(_3\)·OEt\(_2\) (1.1 equiv), cyclopentadiene (2.4 equiv), CH\(_2\)Cl\(_2\), −78 °C, 6 h.

The diastereoselective imino-Diels–Alder reaction between the N-benzyl imine of glyoxylate 62 and cyclopentadiene gave only the exo cycloadducts with a (1S):(1R) diastereomeric ratio of 63:37.\(^{34}\) Although the asymmetric induction was lower for this
reaction than with the analogous (−)-8-phenylmenthol chiral auxiliary (dr 88:12), only \textit{exo} selectivity was observed.

Many of the most widely used chiral auxiliaries for asymmetric synthesis are often derived from natural products, such as (−)-8-phenylmenthol, which sometimes means one or the other enantiomer, is not available. Hence, the natural enantiomer of the auxiliary does not necessarily give the product with the desired configuration. However, this problem does not arise with non-natural auxiliaries, as both enantiomers can be obtained by resolution of a racemate. Also, with non-natural auxiliaries there is the added advantage that their structure can be optimised for use in target specific asymmetric reactions.\textsuperscript{34,35}

Optically active 1-phenylethylamine is one of the most common non-natural chiral auxiliaries used in asymmetric synthesis.\textsuperscript{35} However, many novel non-natural chiral auxiliaries have been developed to improve asymmetric induction, such as \textit{endo}-2-benzobornenol \textsuperscript{61}.\textsuperscript{33} Another example is 1-mesitylethylamine designed by Hashimoto and co-workers.\textsuperscript{35} Application of the (1\textit{S})-mesitylethylamine auxiliary in the asymmetric imino-Diels–Alder reaction between aldimine \textsuperscript{64} and Danishefsky’s diene \textsuperscript{52} showed improved diastereoselectivity in comparison to (1\textit{S})-phenylethylamine (Scheme 13 and Table 2).

\textit{Scheme 13.} Imino-Diels–Alder reaction of aldimine \textsuperscript{64} with diene \textsuperscript{52}.\textsuperscript{35}
Table 2. Conditions tried for the imino-Diels–Alder reaction between 64 and 52.35,36

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Ratio of 65:66</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>BF₃·OEt₂</td>
<td>CH₂Cl₂</td>
<td>−78 °C</td>
<td>8 h</td>
<td>85:15</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>Mesityl</td>
<td>BF₃·OEt₂</td>
<td>CH₂Cl₂</td>
<td>−78→0 °C</td>
<td>24 h</td>
<td>99:1</td>
<td>59%</td>
</tr>
</tbody>
</table>

The use of (1S)-phenylethylamine as an efficient chiral auxiliary for the diastereoselective imino-Diels–Alder reaction of imine 67 with cyclopentadiene has been reported by Trifonova and Andersson (Scheme 14).37

Scheme 14. Diastereoselective cycloaddition of imine 67 with cyclopentadiene.37

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{a} & \quad 74\% \\
\text{NPh} & \quad \text{67} & \quad \rightarrow & \quad \text{NPh} & \quad \text{68} \\
\end{align*}
\]

a) TFA (1.0 equiv), BF₃·OEt₂ (1.0 equiv), cyclopentadiene (2.0 equiv), CH₂Cl₂, −78 °C→rt, overnight.

The crude mixture of the cycloadducts from the reaction showed an exo/endo selectivity of 85:15. The diastereomeric ratio of the exo products was 99:1. Hence, only the major exo cycloadduct 68 was isolated in a yield of 74% from the crude mixture. Again, the high exo selectivity can be explained by the requirement of the cyclopentadiene to approach the (E)-configured dienophile from the trajectory that minimises the steric interaction between the methylene group of the diene and the bulky 1-phenylethyl group of the dienophile (Figure 5). The high diastereoselectivity was due to the diene approaching the less hindered si-face of the dienophile, which was not shielded by the 1-phenylethyl group of the chiral auxiliary.
The enantiomer (1R)-phenylethylamine has also been successfully used as a chiral auxiliary for the diastereoselective cycloaddition between imine 69 and 1,3-cyclohexadiene (Scheme 15).  

**Scheme 15.** Diastereoselective cycloaddition of imine 69 with 1,3-cyclohexadiene.  

\[
\begin{align*}
69 & \quad \text{Ph} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{Et} \\
& \quad \text{a} \quad \rightarrow \\
70 & \quad \text{ex}
\end{align*}
\]

70 exo 65%  
71 endo 8%  

a) TFA, BF₃·OEt₂, 1,3-cyclohexadiene, CH₂Cl₂, −80 °C → rt, 72 h.

Chromatographic purification allowed isolation of the major cycloadduct 70, which Maison and Adiwidjaja have derivatised further to afford enantiomerically pure pipecolic acid derivative 72 (Scheme 16).

**Scheme 16.** Synthesis of pipecolic acid derivative 72 from cycloadduct 70.  

\[
\begin{align*}
70 & \quad \text{Ph} \quad \text{CO}_2\text{Et} \\
& \quad \text{a} \quad \rightarrow \\
72 & \quad \text{OH}
\end{align*}
\]

72  

a) O₃, MeOH, −80 °C; then Me₂S, rt; followed by NaBH₄.
The diastereoselective Lewis acid-mediated imino-Diels–Alder reactions between (−)-8-phenylmenthol derivatised $2^H$-azirine 73 and various activated/non-activated dienes has been achieved by Somfai and co-workers (Scheme 17 and Table 3).^39

**Scheme 17.** Imino-Diels–Alder reaction between $2^H$-azirine 73 and various dienes.\(^3^9\)

![Scheme 17](image)

R* = (−)-8-phenylmenthyl

**Table 3.** Various dienes and conditions used in the [4+2] cycloadditions with $2^H$-azirine 73.\(^3^9\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene (^*)</th>
<th>Lewis Acid</th>
<th>Temperature</th>
<th>de</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>-</td>
<td>$-75\rightarrow-40,^\circ\mathrm{C}$</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>MgBr(_2)·OEt(_2)</td>
<td>$-100,^\circ\mathrm{C}$</td>
<td>96%</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>ZnCl(_2)·OEt(_2)</td>
<td>$-100\rightarrow-90,^\circ\mathrm{C}$</td>
<td>87%</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>cyclopentadiene</td>
<td>-</td>
<td>$-78\rightarrow-40,^\circ\mathrm{C}$</td>
<td>8%</td>
<td>99%</td>
</tr>
<tr>
<td>5</td>
<td>cyclopentadiene</td>
<td>MgBr(_2)·OEt(_2)</td>
<td>$-100,^\circ\mathrm{C}$</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>6</td>
<td>cyclopentadiene</td>
<td>ZnCl(_2)·OEt(_2)</td>
<td>$-100,^\circ\mathrm{C}$</td>
<td>58%</td>
<td>99%</td>
</tr>
</tbody>
</table>

\(^*\)all the reactions were performed in CH\(_2\)Cl\(_2\).

The diastereoselectivity was explained by the chelation of the nitrogen and the carbonyl group by the Lewis acid locking the conformation of the azirine,\(^4^0\) the
phenyl group of the auxiliary shielding the re-face of the dienophile from attack by the diene (Figure 6).\textsuperscript{39}

![Transition state model](image)

**Figure 6.** Transition state model.

The strategy of employing two chiral directing groups on the imine dienophile to further improve the asymmetric induction in imino-Diels–Alder reactions has been used by García-Mera et al.\textsuperscript{41} (Scheme 18).

**Scheme 18.** Imino-Diels–Alder reaction of iminium 78 with cyclopentadiene.\textsuperscript{30}

![Reaction scheme](image)

a) \((1R)\)-Phenylethylamine (1.0 equiv), \(\text{CH}_2\text{Cl}_2\), 0 °C, 60 min; then TFA (1.0 equiv), \(\text{BF}_3\cdot\text{OEt}_2\) (1.0 equiv), −78 °C; b) cyclopentadiene (2.0 equiv), −78 °C, 5 h; \(R^* = (1R)\)-8-phenylmenthyl.

The glyoxylate-derived imine salt 78, possessing the (−)-8-phenylmenthyl and \((1R)\)-phenylethyl groups, on reaction with cyclopentadiene gave only the exo cycloadduct 79. The high diastereoselectivity can be explained by the need for coplanarity of the phenyl ring of (−)-8-phenylmenthyl and the maximum distance between this bulky substituent and the \((1R)\)-phenylethyl group. This places the methyl group of the \((1R)\)-phenylethyl auxiliary backwards to the re-face of the dienophile and so the diene exclusively attacks from the less sterically hindered si-face (Figure 7).\textsuperscript{30}
Figure 7. Transition state model.\textsuperscript{30}

The double asymmetric induction approach has also been used by Gálvez and co-workers\textsuperscript{42} for the imino-Diels–Alder reaction between imine 80 and Danishefsky’s diene 52 (Scheme 19).

Scheme 19. Imino-Diels–Alder reaction of imine 80 and diene 52.\textsuperscript{42}

\begin{align*}
\text{Ph} & \text{N} \quad \text{H} \quad \text{O} \quad \text{Bn} \quad \text{OBn} \\
\text{80} \quad \text{+} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{OTMS} \quad \text{a} \quad 75\% \\
\quad \text{52} \quad \text{81}
\end{align*}

a) ZnI\textsubscript{2} (1.0 equiv), MeCN, –20 °C, 4 h.

Once again the diastereoselectivity of the reaction can be explained by looking at the transition state model of the reaction (Figure 8). The structure of the imine dienophile is locked by the chelation of the Lewis acid and the preferred conformation of the (1S)-phenylethyl group that minimises 1,3-allylic strain. Therefore, in the intermediate complex, both the phenyl and benzyloxymethyl groups block the si-face of the dienophile. Hence, the diene only attacks from the re-face of the imine.
The mechanism of Lewis acid-mediated reactions between unactivated imines and electron-rich dienes, such as Danishefsky’s diene 52, is a matter of debate and seems to vary with the structure of the reactants. In the above case it has been proven that the reaction proceeds via a stepwise tandem Mannich–Michael-type process, as intermediate 82 has been detected (Figure 9).

Figure 8. Transition state model.

Figure 9. Mannich intermediate 82.

5.4.2 1-Azadiene

The 1-azadiene version of the imino-Diels–Alder reaction is less well developed than the imine dienophile version, because electron-deficient 1-azadienes are less reactive towards electron-deficient dienophiles. However, 1-azadienes do undergo inverse electron demand Diels–Alder reactions, and theoretical studies have shown the terminal nitrogen atom lowers the energy of the LUMO of the diene. A number of researchers have been able to promote the imino-Diels–Alder reaction by introducing an EDG or EWG on to the nitrogen atom of the diene to decrease the HOMO–LUMO energy difference, and in turn increase the reactivity of the diene towards the selected dienophile.
The highly diastereoselective inverse electron demand imino-Diels–Alder reaction of N-sulfonyl-1-aza-1,3-butadiene 83 with enol ether 84 bearing a novel lactam chiral auxiliary, has been reported by Boger and co-workers (Scheme 20).  

Scheme 20. Imino-Diels–Alder reaction of diene 83 with enol ether dienophile 84.  

![Scheme 20](image)

a) CHCl₃, 23 °C, 48 h.

The cycloaddition gave a mixture of diastereomeric cycloadducts in an endo/exo ratio of 98:2. The endo adducts were obtained in a diastereomeric ratio of 96:4, but only the major cycloadduct 85 was isolated. The high endo selectivity is thought to result from the possible secondary orbital interaction along with a transition state anomeric effect, where the nitrogen lone pair and the C–O σ-bond of the dienophile lay trans periplanar to each other in the endo boat transition state (Figure 10). The facial selectivity arises due to the diene approaching the dienophile from the re-face, which is not sterically hindered by the chiral auxiliary.

![Figure 10](image)

Figure 10. Transition state model.
An interesting asymmetric intramolecular imino-Diels–Alder reaction has been reported by Steinhagen and Corey\textsuperscript{46} for the synthesis of tetrahydroquinolines (Scheme 21).


![Scheme 21](image)

a) Cs\textsubscript{2}CO\textsubscript{3} (2.5 equiv), CH\textsubscript{2}Cl\textsubscript{2}, rt, 40 h.

Treatment of carbamate 86 with caesium carbonate induces elimination of hydrogen chloride to generate the o-azaxylylene, which undergoes a stereoselective intramolecular [4+2] cycloaddition to give tetrahydroquinolines 87.

![Figure 11](image)

Figure 11. Transition state model.

The high selectivity in formation of 87 is due to the dienophile approaching exo to the 1-azadiene rather than endo, as there would be a steric clash between the cyclohexene and o-azaxylylene rings (Figure 11).

5.4.3 2-Azadiene

The nature of 2-azadienes tends to make them more reactive than 1-azadienes, and also better dienes for Lewis acid-mediated imino-Diels–Alder reactions.\textsuperscript{21} They can undergo normal or inverse electron demand imino-Diels–Alder reactions, depending on the substitution pattern around the 2-azadiene.
A diastereoselective imino-Diels–Alder reaction between 2H-azirine 88 bearing the (1R)-10-(N,N-diethylsulfomyl)isobornyl auxiliary and 2-azadiene 89 has been reported by Alves et al. (Scheme 22).47

**Scheme 22.** Imino-Diels–Alder reaction between 2H-azirine 88 and 2-azadiene 89.47

A diastereoselective imino-Diels-Alder reaction between 2H-azirine 88 bearing the (1R)-10-(N,N-diethylsulfomyl)isobornyl auxiliary and 2-azadiene 89 has been reported by Alves et al. (Scheme 22).47

The cycloaddition solely gave *endo* selectivity products 90 and 91 in a diastereomeric ratio of 6:1. Attempts at improving the diastereoselectivity by using a Lewis acid (MgBr$_2$·OEt$_2$) resulted in a complex mixture of products with no cycloadduct formed. The diastereoselectivity was explained by the favoured and disfavoured approach of the diene to the two different conformers, *s-cis* and *s-trans*, which the 2H-azirine 88 adopts (Figure 12).47

**Figure 12.** Transition state model.47

In the favoured approach the diene attacks from the less hindered *si*-face of the dienophile, whereas in the disfavoured approach it attacks from the *re*-face. An
improvement in diastereoselectivity due to a steric effect from the methylene group of the isobornyl auxiliary, was observed when a more bulky diene was used (Scheme 23).

**Scheme 23.** Imino-Diels–Alder reaction between 2H-azirine 88 and 2-azadiene 92.47

![Scheme 23](image)

a) Toluene, rt, 3 d; Ar = p-anisyl and R* = (1R)-10-(N,N-diethylsulfometyl)isobornyl.

The concept of using chiral auxiliaries attached to heterodienes has been much less explored than the heterodienophile approach.48 However, Andersson and co-workers49 have reported the imino-Diels–Alder reaction of the chiral aromatic imine 95 with cyclopentadiene, where the imine acts as a 2-azadiene instead of a dienophile (Scheme 24).

**Scheme 24.** Imino-Diels–Alder reaction of aromatic imine 95 with cyclopentadiene.49

![Scheme 24](image)

a) TFA (1.1 equiv), BF3·OEt2 (1.1 equiv), cyclopentadiene (1.1 equiv), CH2Cl2, −78 °C→rt, overnight.

The high diastereoselectivity achieved in the formation of tetrahydroquinoline 96 was due to the cyclopentadiene approaching the (E)-configured protonated imine from the trajectory that is not hindered by the phenyl group of the (S)-(+) -ethyl mandelate auxiliary (Figure 13).
Figure 13. Transition state model.

5.5 Conclusion

Alongside a brief review of some classical total syntheses of morphine, our retrosynthetic approach to this alkaloid has been proposed (Scheme 6), where the key step is a diastereoselective imino-IMDA reaction to form cycloadduct 45. Since the predicted selectivity is as a result of a tethered chiral directing group, a review into the area of asymmetric imino-Diels–Alder reactions using chiral auxiliaries was also presented. The foregoing discussion showed that, in general, (−)-8-phenylmenthol and (1S)- or (1R)- phenylethylamine are particularly effective chiral auxiliaries for achieving high levels of asymmetric induction. The presence of a Lewis or Brønsted acid catalyst tended to improve the selectivity of the [4+2] cycloaddition in some cases. Additionally, the use of two chiral directing groups on imine dienophiles for a double asymmetric induction effect gave very high levels of diastereoselectivity. Finally, the review showed that asymmetric imino-Diels–Alder reactions provide a rapid and efficient method for the synthesis of a variety of chiral heterocycles.
6 Results and Discussion

6.1 Stereoselective Diels–Alder Reactions for Piperidine Synthesis

The Craig group has been actively involved in the development of enantioselective routes to nitrogen heterocycles. Previous research\(^\text{50}\) has successfully synthesised enantiomerically pure 2-alkyl 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines \(100\) via reaction of lithiated \(\beta\)-sulfonyl acetal \(97\) with amino acid derived \(N\)-tosylaziridines \(98,\ ^{51}\) followed by acid-catalysed cyclisation (Scheme 25).

**Scheme 25.** Synthesis of tetrahydropyridines \(100\).\(^{50}\)

Another approach to substituted tetrahydropyridines investigated within the group,\(^{52}\) was the imino-Diels–Alder cycloaddition reactions between highly electron-rich dienes \(101\) with the activated \(N\)-tosylimine \(102\) derived from ethyl glyoxylate (Scheme 26).

**Scheme 26.** Hetero-[4+2] cycloaddition.\(^{52}\)

---

a) \(^{t}\)BuLi (1.1 equiv), THF/TMEDA (4:1), \(-78\, {^\circ}\text{C}, 20\) min, then \(98\) (1.0 equiv), \(-78\, {^\circ}\text{C} \rightarrow\text{rt, 30 min, followed by AcOH/THF (1.0 equiv); b) TMSCl (6.0 equiv), MeCN, rt, 20 min; c) \(^{t}\)BuOK (0.1 equiv), \(^{t}\)BuOH (10 equiv), THF.

---

a) CHCl\(_3\), \(-50\, {^\circ}\text{C, 30 min. For R = H J\text{H-2,H-3 6.5 Hz and R = Me J\text{H-2,H-3 5.5 Hz.}}\)
The cycloaddition was highly *endo* selective with respect to the dienophile ester because for the cycloadduct 103 where the R substituent was a methyl group only the all *cis* geometry was isolated, which was confirmed by X-ray crystallography analysis. However, for the simple diene where the R substituent was hydrogen, $^1$H-NMR analysis of the crude product did show the presence of the other diastereomer. The observed *endo/exo* ratio in this case was 10:1. The high *endo* selectivity was thought to arise from the electronic effect of the dienophile ester and the steric bulk of the *N*-tosyl group working cooperatively (Figure 14).

![Figure 14. Illustration of the *exo* and *endo* transition states.](image)

Therefore, the plan for the current research was to develop diastereo- and enantioselective versions of the above mentioned imino-Diels–Alder reaction, by using chiral analogues of *N*-tosylimine 102; where the ethyl group of the ester was replaced by *trans*-2-phenylcyclohexyl$^{53}$ and (−)-8-phenylmenthyl$^{54}$ groups to give *N*-tosylimines 104 and 105 (Figure 15).

![Figure 15. Structure of the chiral *N*-tosylimines 104 and 105.](image)
The diastereoselectivity was expected to arise as a result of the *endo* approach of diene *106* to the more accessible face of the imine, which was not shielded by the phenyl group of the chiral auxiliary (Scheme 27).

**Scheme 27.** Stereoselective hetero-[4+2] cycloaddition.

Separation of the diastereoisomers from the imino-Diels–Alder reaction and cleavage of the auxiliary by ester hydrolysis or reduction was expected to give the enantiomerically pure piperidine.

The work presented herein describes the progress made so far towards the development of the diastereo- and enantioselective versions of the imino-Diels–Alder reaction of diene *106* with *N*-tosylimines *104* and *105*.

### 6.1.1 Diene synthesis

The best method found from the previous work carried out in the group by Beligny\textsuperscript{52} for the synthesis of \((1E,3Z)-1\)-silyloxy-3-(tolylthio)-1,3-dienes *101*, was by treatment of the \((E)-\alpha,\beta\)-unsaturated aldehydes *109b* with the silylating agent in the presence of base.\textsuperscript{55} In turn, aldehydes *109* were synthesised according to a procedure developed by Tso and Chen\textsuperscript{56} involving lithiation of 1-(tolylthio)-3-methoxy-1-propyne *107*, followed by treatment with the various alkyl halides to give allenyl ethers *108*. Acidic
hydrolysis of 108 gave 109 as a mixture of geometric isomers, which were separable by chromatography (Scheme 28).

**Scheme 28.** Method for the preparation of dienes 101.

\[
\begin{align*}
\text{MeO} & \quad \text{STol} \quad \text{a, b} \quad \text{MeO} \quad \text{STol} \quad \text{c} \quad \text{STol} + \text{STol} \\
\text{107} & \quad \text{108} & \quad \text{109a} & \quad \text{109b} \\
& & (Z)-isomer & (E)-isomer \\
& & R=H & 36\% \\
& & R=Me & 35\% \\
& & R=Ph & 74\% \\
& & & 30\% \\
& & & 13\% \\
\end{align*}
\]

a) LDA (1.1 equiv), THF, $-78^\circ C$, 10 min; b) RCH\textsubscript{2}I or RCH\textsubscript{2}Br (1.2–1.5 equiv), $-78\rightarrow0^\circ C$; c) 1.0 M HCl, Et\textsubscript{2}O, rt; d) TBSOTf (1.2 equiv), Et\textsubscript{2}O, 0 °C; e) Et\textsubscript{3}N (1.4 equiv), 0 °C→rt.

Scheme 28 shows the phenyl derivative of the α,β-unsaturated aldehyde 109 was only isolated as the (Z)-isomer. Therefore, a method for partially isomerising the (Z)-isomer 109\textsubscript{a} to the (E)-isomer 109\textsubscript{b} by DBU base treatment was also developed (Scheme 29).

**Scheme 29.** Isomerisation of the (Z)-isomer 109\textsubscript{a} to the (E)-isomer 109\textsubscript{b}.

\[
\begin{align*}
\text{O} & \quad \text{STol} \quad \text{d, e} \quad \text{O} \quad \text{STol} \\
\text{109a} & \quad \text{109b} \\
& & R=H & 73\% \\
& & R=Me & 47\% \\
& & R=Ph & 48\% \\
\end{align*}
\]

a) DBU (2.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}, rt, 3 h; b) AcOH (2.0 equiv), rt.
This route for the synthesis of the desired dienes was repeated, replacing the tolylthio with the analogous phenylthio substituent for the current research, as the diphenyl disulfide reagent required was considerably cheaper than di-\textit{p}-tolyl disulfide.

### 6.1.1.1 Synthesis of 1-phenylthio-3-methoxy-1-propyne

Initially, the synthesis of the 1-phenylthio-3-methoxy-1-propyne \textbf{110} was attempted by the method reported by Miller \textit{et al.}\textsuperscript{57} which used phenylsulfenyl chloride \textbf{111} as the electrophilic reagent to quench the anion generated by the treatment of methyl propargyl ether with \textit{n}-BuLi (Scheme 30). Phenylsulfenyl chloride \textbf{111} was prepared according to the procedure reported by Barrett \textit{et al.}\textsuperscript{58} However, due to the instability of \textbf{111}; it was replaced by diphenyl disulfide as the electrophilic reagent.\textsuperscript{59}

**Scheme 30.** Synthesis of 1-phenylthio-3-methoxy-1-propyne \textbf{110}.\textsuperscript{57}

\[
\text{MeO} \overset{\text{a, b}}{\longrightarrow} \text{MeO} \overset{83\%}{\longrightarrow} \text{SPh}
\]

\textbf{110}

a) \textit{n}-BuLi (1.3 equiv), THF, \textit{−}78 °C, 15 min; b) PhSCl (1.14 equiv), \textit{−}78→0 °C, 1 h.

Disappointingly, quenching the anion with diphenyl disulfide produced the desired product \textbf{110} in a yield of only 59%, because a considerable amount of by-product \textbf{112} was isolated. A plausible mechanism for the formation of the by-product involves nucleophilic attack on the triple bond of \textbf{110} by lithium thiophenoxide produced from the initial reaction (Scheme 31).

**Scheme 31.** Mechanism for the formation of by-product \textbf{112}.
Therefore, diphenyl disulfide was replaced with S-phenyl benzenethiosulfonate 113, because the more weakly nucleophilic lithium phenylsulfinate by-product would be less likely to attack the triple bond. Using these modified conditions 110 was formed as the sole product in a yield of 91%.

The drawback of using S-phenyl benzenethiosulfonate 113 as the electrophilic reagent was its cost. Hence, a practical method for multi-gram synthesis of 113 was investigated.60,61 The best procedure was found to be the selective oxidation of diphenyl disulfide using 30 wt % aqueous hydrogen peroxide (Scheme 32).62

Scheme 32. Synthesis of 113 by the oxidation of diphenyl disulfide.62

![Scheme 32](image)

a) ~30 wt % Aqueous H₂O₂ (2.0 equiv), AcOH, rt, 48 h.

6.1.1.2 Synthesis of the α,β-unsaturated aldehydes

The synthesis of the α,β-unsaturated aldehydes were carried out according to the method previously described (vide supra).52

Scheme 33. Preparation of the α,β-unsaturated aldehydes.

![Scheme 33](image)

a) LDA (1.1 equiv), THF, −78 °C, 15 min; b) RCH₂I or RCH₂Br (1.2–1.5 equiv), −78→−10 °C; c) 1.0 M HCl, Et₂O, rt, 2–6 h.
The results are summarised below (Table 4). The combined yields of the different analogues of the two isomers were consistently above 70%. However, the ratios of (Z)- to (E)-isomers increased with increasing steric bulk of R.

**Table 4.** Results for the different α,β-unsaturated aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>Ratio of (Z):(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>73%</td>
<td>1.0:4.6</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>73%</td>
<td>1.0:2.0</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>77%</td>
<td>1.0:1.4</td>
</tr>
</tbody>
</table>

The results for the partial isomerisation of the (Z)-isomer in to the (E)-isomer using the sterically hindered base DBU (Scheme 34) are detailed in Table 5.

**Scheme 34.** Isomerisation of the unsaturated aldehydes.

\[
\begin{align*}
\text{(Z)-isomer} & \quad \text{a, b} \\
\downarrow & \\
\text{(E)-isomer}
\end{align*}
\]

a) DBU (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}, rt, 1–15 h; b) AcOH (1.0 equiv), rt.

**Table 5.** Results for the partial isomerisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reaction Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>2 h</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>15 h</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>60 min</td>
<td>43%</td>
</tr>
</tbody>
</table>
When performing the partial isomerisation of the α,β-unsaturated aldehydes, it was found that the concentration of the reaction was crucial as concentrations ≥ 0.2 M led to aldol condensation by-products 118 (Figure 16). The optimal concentration for the isomerisation was determined to be 0.07 M.

![Chemical structure](image)

8 possible diastereomers 118

**Figure 16.** Aldol condensation by-products 118.

DABCO was tried as an alternative base to DBU for the partial isomerisation, to determine if the isomerisation could be driven to completion. However, the yields were lower than those for DBU.

### 6.1.1.3 Synthesis of the (1E,3Z)-1-silyloxy-3-(phenylthio)-1,3-dienes

Previously, the method for the formation of the electron-rich dienes was by the reaction of the (E)-isomer of the α,β-unsaturated aldehydes with TBSOTf to form the oxonium species, followed by treatment with base to afford the (1E,3Z)-geometric dienes. However, repetition of this method gave very impure (30–65% purity) diene products in poor yields (36–48%). Therefore, the decision was taken to revert back to the literature method by Trost et al., in which the base was added to reaction mixture before the silylating agent. This simple change led to significant improvements in the purities and yields of the dienes (Scheme 35).
Scheme 35. Preparation of the electron-rich dienes.

![Diagram of diene synthesis](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Purity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>115b</td>
<td>69%</td>
<td>68%</td>
</tr>
<tr>
<td>Me</td>
<td>116b</td>
<td>70%</td>
<td>76%</td>
</tr>
<tr>
<td>Ph</td>
<td>117b</td>
<td>63%</td>
<td>69%</td>
</tr>
</tbody>
</table>

a) Et₃N (1.4 equiv), Et₂O, 0 °C, 5 min; b) TBSOTf (1.2 equiv), 0 °C→rt.

A possible reason for why the order of addition of the base and silylating agent was so critical to the formation of the dienes was that the dienes are known to be very labile in the presence of acid. Triflic acid may have been present in the moisture-sensitive TBSOTf reagent. Thus, by having the base present before the addition of the TBSOTf, any acid introduced during the addition of TBSOTf would be quenched, preventing decomposition. Also, due to the acid sensitivity of the dienes, purification by chromatography was performed on base-washed silica. Furthermore, due to the instability of the dienes, storage for long periods of time led to decomposition. So, they were synthesised and used in the Diels–Alder reactions on the same day.

Only the (E)-isomers of the α,β-unsaturated aldehydes could be used in the synthesis of the (1E,3Z)-1-silyloxy-3-(phenylthio)-1,3-dienes because the work by Beligny had shown that the (Z)-isomer gave a mixture of all possible diene geometric isomers; the (E)-isomer selectively gave the (1E,3Z)-diene. This was presumed to be due to steric interactions occurring for certain conformations of the (E)-isomer, preventing free rotation around the C1–C2 and C3–C4 bonds, and hence favouring only one conformation that would undergo the diene formation reaction (Scheme 36).
Scheme 36. Origin of diene formation selectivity.

In comparison, for the (Z)-isomer such steric interactions do not occur, and so all the conformers are possible. All these conformers can undergo the diene formation reaction to give all four possible geometric isomers (Scheme 37).

Scheme 37. Formation of all four geometric isomers of the diene.
6.1.2 Synthesis of N-tosylimine dienophiles

Bélini

52 had previously found the best route to N-tosylimine 102 was from the thermal [2+2] cycloaddition of ethyl glyoxylate and p-toluenesulfonyl isocyanate to give the cyclic intermediate 122, which underwent cycloreversion with extrusion of carbon dioxide to give 102 (Scheme 38).

**Scheme 38.** Method for the preparation N-tosylimine 102.

![Scheme 38](image)

a) TsNCO (1.0 equiv), toluene, reflux, 3 d.

The drawback of this method was the long reaction time of 3 days, but literature precedents revealed that this could be reduced to a few hours by the addition of a sub-stoichiometric amount of aluminium chloride.

63,64 The synthesis of the trans-2-phenylcyclohexyl glyoxylate was attempted, so that the [2+2] cycloaddition-cycloreversion with p-toluenesulfonyl isocyanate could be investigated to prepare the N-tosylimine derivative.

6.1.2.1 Synthesis of trans-2-phenylcyclohexyl glyoxylate

Synthesis of trans-2-phenylcyclohexyl glyoxylate 126 was successfully performed on a multi-gram scale following the procedure described by Whitesell et al.

65 The method involved the cuprous iodide-catalysed ring opening of cyclohexene oxide with phenylmagnesium bromide to afford a racemic mixture of trans-2-phenylcyclohexanol 123, which was condensed with 1-bromoacetic acid to give trans-2-phenylcyclohexyl bromoacetate 124. Treatment of 124 with silver nitrate gave trans-2-phenylcyclohexyl (nitrooxy)acetate 125, which was expected to provide glyoxylate 126 upon reaction with sodium acetate in DMSO. However, treatment of 125 with anhydrous sodium acetate in dry DMSO gave a crude equilibrium mixture of trans-2-phenylcyclohexyl glyoxylate 126 and the geminal diol 127 (Scheme 39).
Scheme 39. Preparation of an equilibrium mixture of 126 and 127.

\[
\begin{align*}
\text{123} & \quad \text{a)} \quad \text{PhMgBr (1.5 equiv), CuI (0.16 equiv), THF, } -30 \to 0 \degree C, \text{ 2 h; } \\
\text{124} & \quad \text{b)} \quad \text{1-bromoacetic acid (2.5 equiv), } p-\text{TSA·H}_2\text{O (0.03 equiv), benzene, reflux, 16 h; } \\
\text{125} & \quad \text{c)} \quad \text{AgNO}_3 (3.0 equiv), \text{ MeCN, rt, 72 h; } \\
\text{126} & \quad \text{d)} \quad \text{NaOAc (1.0 equiv), DMSO, rt, 2 h.}
\end{align*}
\]

a) PhMgBr (1.5 equiv), CuI (0.16 equiv), THF, −30→0 °C, 2 h; b) 1-bromoacetic acid (2.5 equiv), p-TSA·H₂O (0.03 equiv), benzene, reflux, 16 h; c) AgNO₃ (3.0 equiv), MeCN, rt, 72 h; d) NaOAc (1.0 equiv), DMSO, rt, 2 h.

Attempted dehydration of the equilibrium mixture according the literature procedure,⁶⁵ by heating under reduced pressure for 60 min followed by distillation under reduced pressure, failed to give solely the glyoxylate.

Synthesis of the \textit{trans}-2-phenylcyclohexyl glyoxylate 126 was also attempted by the ozonolysis of \textit{trans}-2-phenylcyclohexyl acrylate 128 (Scheme 40).⁶⁶ Disappointingly, the isolated product from the ozonolysis contained only a very small quantity of the glyoxylate, and mainly consisted of the geminal diol with other unknown by-products.

Scheme 40. Attempted synthesis of 126 via ozonolysis.

\[
\begin{align*}
\text{123} & \quad \text{a)} \quad \text{Acryloyl chloride (2.0 equiv), Et₃N (2.0 equiv), DMAP (0.14 equiv), CH}_2\text{Cl}_2, \text{ 0 }\degree\text{ C, 2.5 h; } \\
\text{128} & \quad \text{b, c)} \quad \text{O}_3/\text{O}_2, \text{ MeOH/CH}_2\text{Cl}_2, -78 \degree\text{ C, 1 h; } \\
\text{126} & \quad \text{c)} \quad \text{Me}_2\text{S (6.0 equiv), } -25 \degree\text{ C} \to \text{rt, 14 h.}
\end{align*}
\]

a) Acryloyl chloride (2.0 equiv), Et₃N (2.0 equiv), DMAP (0.14 equiv), CH₂Cl₂, 0 °C, 2.5 h; b) O₃/O₂, MeOH/CH₂Cl₂, −78 °C, 1 h; c) Me₂S (6.0 equiv), −25 °C→rt, 14 h.

The equilibrium mixture of the glyoxylate 126 and geminal diol 127 was used to investigate the formation of \textit{trans}-2-phenylcyclohexyl 2-tosyliminoacetate 104.
6.1.2.2 Synthesis of trans-2-phenylcyclohexyl 2-tosyliminoacetate via the glyoxylate

Initially, the glyoxylate was treated with \( p \)-toluenesulfonyl isocyanate as described previously (Scheme 41).

**Scheme 41.** Attempted formation of \( N \)-tosylimine 104.

\[
\begin{align*}
\text{126} & + \quad \text{127} \rightarrow \quad \text{104} \\
+ & \text{a} \\
\text{a) TsNCO (1.0 equiv), toluene, reflux, 3 d.}
\end{align*}
\]

However, after prolonged heating the reaction had not reached completion, and attempted purification by column chromatography led to decomposition. Repetition of the reaction using two equivalents of \( p \)-toluenesulfonyl isocyanate, followed by purification of the crude product by recrystallisation from ethyl acetate, gave 26% of hemiaminal 129 (Figure 17) contaminated with \( p \)-toluenesulfonamide. Consequently, other known methods for the formation of imines were tried (Table 6).

**Figure 17.** Structure of hemiaminal 129.

The condensation of the equilibrium mixture of glyoxylate 126 and diol 127 with \( p \)-toluenesulfonamide gave hemiaminal 129 (Entries 1 and 2), after isolation and purification by recrystallisation. This indicated that the electron-poor imine was moisture-sensitive. Accordingly, the decision was taken not to isolate the \( N \)-tosylimine 104 and use the generated imine *in situ* for the Diels–Alder reaction.
The Kresze reaction\textsuperscript{67} of ethyl glyoxylate and \(N\)-sulfinyl-\(p\)-toluenesulfonamide has been shown by Weinreb and co-workers,\textsuperscript{64} to be a good way of synthesising the corresponding \(N\)-tosylimine. Thus, \(N\)-sulfinyl-\(p\)-toluenesulfonamide \textsuperscript{130} was synthesised according to the procedure by Kresze and Wucherpfennig.\textsuperscript{68} Thermal [2+2] cycloaddition of \textsuperscript{130} with glyoxylate \textsuperscript{126}, followed by cycloreversion with expulsion of sulfur dioxide to form \(N\)-tosylimine \textsuperscript{104}, when followed by \textsuperscript{1}H-NMR spectroscopy appeared to go to completion (Entry 3). However, the subsequent \textit{in situ} use of \textsuperscript{104} in the imino-Diels–Alder reaction with diene \textsuperscript{120} failed.

\textit{Table 6}. Results for the attempted synthesis of \(N\)-tosylimine \textsuperscript{104}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Equivalents of Reagent</th>
<th>Reaction Time*</th>
<th>Concentration</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsNH\textsubscript{2}</td>
<td>2.0</td>
<td>3 d</td>
<td>0.11 M</td>
<td>52% (hemiaminal)</td>
</tr>
<tr>
<td>2</td>
<td>TsNH\textsubscript{2} †</td>
<td>1.0</td>
<td>2 h</td>
<td>0.20 M</td>
<td>81% (hemiaminal)</td>
</tr>
<tr>
<td>3</td>
<td>TsN=S=O‡</td>
<td>1.5</td>
<td>13 h</td>
<td>0.07 M</td>
<td>used \textit{in situ}</td>
</tr>
<tr>
<td>4</td>
<td>TsN=PPh\textsubscript{3}</td>
<td>1.0</td>
<td>32 h</td>
<td>0.24 M</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>TsN=PBu\textsubscript{3} †</td>
<td>2.0</td>
<td>2 d</td>
<td>0.29 M</td>
<td>used \textit{in situ}</td>
</tr>
<tr>
<td>6</td>
<td>TsN=PBu\textsubscript{3} †</td>
<td>1.25</td>
<td>3 h</td>
<td>1.08 M</td>
<td>used \textit{in situ}</td>
</tr>
</tbody>
</table>

*All the reactions were performed in dry toluene and heated under reflux.
†In the presence of 4Å molecular sieves.
‡In the presence of MgSO\textsubscript{4}.

An alternative method involving aza-Wittig reaction of glyoxylate \textsuperscript{126} and an \(N\)-tosyliminophosphorane was investigated. The triphenyl-phosphine \textsuperscript{131} and tri-\textit{n}-butylphosphine \textsuperscript{132} derivatives of the \(N\)-tosyliminophosphorane were synthesised according to the procedure by Bittner \textit{et al.}\textsuperscript{69} (Scheme 42). Here, redox-condensation reaction of the diethyl azodicarboxylate (DEAD) oxidant and the phosphine reducing agent give a betaine intermediate, which reacts with the \(p\)-toluenesulfonamide to yield the phosphorane and the diethyl hydrazinedicarboxylate by-product. The classical method for the synthesis of iminophosphoranes by the Staudinger\textsuperscript{70} reaction of azides with phosphines was tried.\textsuperscript{71} However, the yields were considerably lower.
Scheme 42. Synthesis of N-tosyliminophosphoranes 131 and 132.

\[
\begin{align*}
\text{Scheme 42. Synthesis of N-tosyliminophosphoranes 131 and 132.}^{69} \\
\begin{array}{c}
\text{O} & \text{S} & \text{O} \\
\text{NH}_2 & + & \text{PR}_3 \\
\end{array}
\xrightarrow{\text{a}}
\begin{array}{c}
\text{O} & \text{S} & \text{O} \\
\text{N} & \text{PR}_3 \\
\end{array}
\end{align*}
\]

\( R = \text{Ph} \) \quad 85\% \\
\( R = \text{Bu} \) \quad 60\%

131 \\
132

a) DEAD (1.0 equiv), THF, 0 °C→rt, 30–45 min.

The attempted aza-Wittig reaction of iminophosphorane 131 with the equilibrium mixture of glyoxylate 126 and diol 127 gave only starting material after 32 h of heating under reflux (Entry 4). Hence, the more nucleophilic tri- \( n \)-butylphosphine analogue of the N-tosyliminophosphorane was tried. When two equivalents of iminophosphorane 132 was reacted with the mixture of 126 and 127 at the low reaction concentration of 0.29 M the reaction took 2 days to reach completion by NMR spectroscopy (Entry 5). Therefore, to improve the reaction time, the concentration of the reaction mixture was increased to ~1.0 M, which resulted in complete reaction after 3 hours of heating under reflux (Entry 6). In addition to increasing the concentration, 4Å activated molecular sieves were added to the reaction mixture to absorb any water present in the reaction mixture, to prevent the hemiaminal forming. As mentioned above, the N-tosylimine 104 formed from the aza-Wittig reaction was used in situ in the subsequent imino-Diels-Alder reaction (vide infra).

6.1.2.3 Attempted synthesis of trans-2-phenylcyclohexyl 2-tosyliminoacetate via the \( \alpha \)-bromoglycinate

As there had been problems with the synthesis, purity and stability of the highly reactive N-tosylimine 104 from the glyoxylate; an alternative route to it via dehydrobromination of \( \alpha \)-bromoglycinate 137 was investigated (vide infra).

Whiting and co-workers\(^{72}\) had observed poor yields (5–25\%) for the Diels–Alder reaction of cyclopentadiene with the electron-deficient imine 134; where the imine was also generated in situ by the aza-Wittig reaction of N-sulfonylphosphinamide 133 with ethyl glyoxylate in refluxing toluene (Scheme 43).
Scheme 43. Imino-Diels–Alder reaction between cyclopentadiene with imine 134.\(^{72}\)

\[
\begin{align*}
\text{EtO}_2\text{C} & + \text{N}^\text{Ph} & \text{a} & \rightarrow \text{EtO}_2\text{C} & \text{b} & \rightarrow \text{COEt} \\
133 & & & 134 & & 135 \\
\end{align*}
\]

a) Toluene, reflux; b) cyclopentadiene (2.0 equiv), reflux.

In the same paper Whiting and co-workers reported various attempts to synthesise imine 134, such as by thermal [2+2] cycloaddition-cycloreversion reaction of the glyoxylate with the corresponding isocyanate. However, they were not able to isolate the imine in a pure state using this method. Also, their attempts at the condensation of the glyoxylate with benzenesulfonamide, followed by \textit{in situ} trapping of the unstable imine 134 with cyclopentadiene, resulted in low yields (<23%) of the cycloadduct. They found that the best method for the synthesis of imine 134 and the subsequent Diels–Alder reaction was by base-promoted dehydrobromination of \(\alpha\)-bromoglycinate 136; followed by the \textit{in situ} trapping of imine 134 with cyclopentadiene to give cycloadduct 135 (Scheme 44).

Scheme 44. Synthesis of imine 134 by dehydrobromination of \(\alpha\)-bromoglycinate 136.

\[
\begin{align*}
\text{H} & \text{N}^\text{Ph} & \text{a} & \rightarrow \text{EtO}_2\text{C} & \text{b} & \rightarrow \text{COEt} \\
\text{Br} & & & 134 & & 135 \\
136 & & & & & \\
\end{align*}
\]

a) \(\text{tPr}_2\text{NEt} (1.0 \text{ equiv}), \text{toluene, } 0 \^\circ\text{C}, 30 \text{ min} \); b) cyclopentadiene (10 equiv), 0 \^\circ\text{C}, 60 min.
Encouraged by this report, synthesis of \textit{trans}-2-phenylcyclohexyl 2-bromo-2-tosylaminoacetate 137 (Figure 18) was attempted, as a better route to \textit{N}-tosylimine 104.

![Structure of α-bromoglycinate 137.](image)

\textit{Figure 18.} Structure of α-bromoglycinate 137.

Initially, the synthesis of \textit{N}-tosylglycinate 140 was attempted via Gabriel\textsuperscript{73} synthesis from the chloroacetate 138 (Scheme 45). However, low yields for the last two steps rendered this route impractical. A considerable amount of \textit{trans}-2-phenylcyclohexanol 123 was isolated, as well as 140, indicating the hydrazine had attacked the carbonyl bond of the \textit{N},\textit{N}-phthaloylglycine 139.

\textit{Scheme 45.} Synthesis of \textit{N}-tosylglycinate 140 via Gabriel synthesis.\textsuperscript{73}

\begin{align*}
\text{123} \xrightarrow{a} \text{138} & \quad \text{96\%} \\
\text{138} \xrightarrow{b} \text{139} & \quad \text{53\%} \\
\text{123} \xrightarrow{c, d} \text{140} & \quad \text{17\%}
\end{align*}

a) Chloroacetyl chloride (1.27 equiv), DMAP (0.01 equiv), CH\textsubscript{2}Cl\textsubscript{2}, reflux, 14.5 h; b) potassium phthalimide (1.0 equiv), DMF, 100 °C, 5 h; c) hydrazine monohydrate (1.0 equiv), EtOH, reflux, 4 h; d) TsCl (1.5 equiv), Et\textsubscript{3}N, (1.5 equiv), EtOH, rt, 21 h.

Therefore, the alternative route by esterification of \textit{trans}-2-phenylcyclohexanol 123 with \textit{N}-tosylglycine 141 was tried. This gave 140 in a yield of 75\% (Scheme 46). \textit{N}-tosylglycine 141 was prepared following the procedure by Kotha and Singh\textsuperscript{74}.
Scheme 46. Synthesis of N-tosylglycinate 140 via esterification.

\[
\begin{align*}
&\text{HO} & & \text{NHTs} \\
&\text{141} & & \text{O} \\
&\text{a, b, c} & & 40\% \\
&\text{HO} & & \text{NH}_2 \\
&\text{140} & & \text{Ph} \\
&\text{123} & & \text{Ph} \\
&\text{d} & & 75\% \\
\end{align*}
\]

a) 2.0 M NaOH, water, rt, 5 min; b) TsCl (1.4 equiv), rt, 3 h; c) 2.0 M HCl, 0 °C, 30 min; d) p-TSA·H$_2$O (0.1 equiv), benzene, reflux, 22 h.

With N-tosylglycinate 140 in hand, various photobromination conditions were tried to form α-bromoglycinate 137. Unfortunately, it was unable to be isolated cleanly in a reasonable yield. Thus, the base promoted dehydrobromination to form N-tosylimine 104 was never investigated.

6.1.3 Imino-Diels–Alder reaction

The only successful imino-Diels–Alder reaction has been between the electron-rich diene 121 and the freshly made solution of N-tosylimine 104 in toluene, which was prepared by the aza-Wittig reaction (vide supra). Tetrahydropyridine 142 was isolated in a yield of 24% and diastereomer ratio of 5:1, determined by $^1$H-NMR analysis (Scheme 47). Attempts at increasing the diastereoselectivity by performing the reaction at room temperature failed, as only starting materials were recovered.
**Scheme 47.** Imino-Diels–Alder reaction between diene 121 and dienophile 104.

![Scheme 47](image)

a) Toluene, reflux, 3 h. For 142 $J_{H-2,H-3}$ 2.0 Hz.

In this case, the major imino-Diels–Alder product was the *exo* diastereomer, with respect to the dienophile ester. This was assigned by comparison of the $^1$H-NMR coupling constant between H-2 and H-3 with the observed coupling constant for the *exo* imino-Diels–Alder cycloadduct product obtained in the previous work (Scheme 48). The observed coupling constant was 2.0 Hz for the *exo* product. The *eso* geometry of the adduct 144 in the prior work was verified by X-ray crystallography studies on the crystalline sulfone derivative 145.

**Scheme 48.** Imino-Diels–Alder reaction between diene 143 and *N*-tosylimine 102.

![Scheme 48](image)

a) CHCl$_3$, −50 °C→rt, 30 min; b) NaHCO$_3$ (2.8 equiv), *m*-CPBA (2.5 equiv) 50 °C→rt, 45 min. For 145 $J_{H-2,H-3}$ 2.0 Hz.
The low yield of the imino-Diels–Alder reaction of diene 121 with $N$-tosylimine 104 and the problems with the synthesis of 104, led to the decision not to investigate this diastereoselective imino-Diels–Alder reaction any further at this stage.

### 6.1.4 Future work

In addition to optimising the imino-Diels–Alder reaction of (1E,3Z)-1-silyloxy-3-(phenylthio)-1,3-dienes with $N$-tosylimine 104 by looking at solvent, temperature and concentration effects; investigation into the enantioselective version of the reaction will be pursued, by synthesising and using the (−)-8-phenylmenthyl derivative of the imine.
6.1.5 Conclusion

In summary, the synthesis of the hydrogen 119, methyl 120 and phenyl 121 analogues of the (1E,3Z)-1-silyloxy-3-(phenylthio)-1,3-diene have been successfully performed. The synthesis of the trans-2-phenylcyclohexyl 104 derivative of the N-tosylimine dienophile has been attempted via various methods, but the only successful method was by aza-Wittig reaction of glyoxylate 126 with iminophosphorane 132. However, because of the instability of glyoxylate derived imines; imine 104 was used in situ in the imino-Diels–Alder reaction with diene 121. The yield of tetrahydropyridine 142 was 24% and the observed diastereomer ratio was 5:1.
6.2 Diastereoselective Intramolecular Diels–Alder Reactions for an Approach to (−)-morphine

Previous research in the Craig group has looked at the intramolecular Diels–Alder (IMDA) reactions of trienes, in which the diene and dienophile have been tethered using a temporary covalent linkage. Silaketal,\textsuperscript{75} tertiary and benzylic ether,\textsuperscript{76} and acetal\textsuperscript{77} linkages were used to attain highly stereoselective IMDA reactions. Additionally, chiral diester tethers were developed to give diastereoselective IMDA reactions (Scheme 49).\textsuperscript{78} Cleavage of the chiral diester auxiliary by ester hydrolysis or reduction gave overall products of regio- and stereoselective intermolecular [4+2] cycloadditions.

Scheme 49. IMDA reaction of a tethered heterotriene.\textsuperscript{78}

![Scheme 49](image)

\begin{align*}
\text{146} & \xrightarrow{\text{a}} \text{147} & \text{148} & \xrightarrow{\text{a}} \text{149} & \text{150} \\
\text{cis:trans:trans} & = 5:1:1 \\
\end{align*}

\text{a) TsNCO (2.4 equiv), toluene, 125 °C, 16 h.}

The plan for the current research was the use of a tethered IMDA reaction involving an N-tosylimine heterodienophile for the synthesis of an advanced intermediate in the synthesis of (−)-morphine 1 (Scheme 6). The key idea was to tether the diene and the heterodienophile using a disposable benzylic ether linkage,\textsuperscript{79} which contains the stereochemical information required ultimately to render the cycloaddition asymmetric.

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Scheme 6. Proposed route to (−)-morphine.

The highly selective formation of cycloadduct 45 in the hetero-IMDA reaction of triene 46 was predicted on account of the exo-directing effect of the N-Ts moiety and the preferred pseudoequatorial disposition of the aryl group, which was positioned on the sterically less demanding exo surface of the bicyclo[4.3.0] product.

Synthesis of triene 46 was envisaged by alkylation\(^8^0\) of the enantiomerically pure alcohol 152 with allylic halide 151, followed by desilylation and oxidation to the aldehyde. Reaction of the aldehyde with iminophosphorane 131 (TsN=PPh\(_3\)) in the presence of a sub-stoichiometric amount of RuCl\(_2\)(PPh\(_3\))\(_3\) would give the N-tosylimine (Scheme 50).\(^8^1\)
Scheme 50. Synthesis of triene 46.

The work presented herein describes the progress made thus far towards the synthesis of triene 46.

a) Ag₂O; b) TBAF; c) Dess–Martin periodinane; d) TsN=PPh₃, RuCl₃(PPh₃)₃ catalyst.
6.2.1 Synthesis of the enantiomerically pure alcohol

Enantiomerically pure alcohol 152 was prepared in a five-step sequence starting from \( p \)-anisaldehyde (Scheme 51). Quantitative protection of the aldehyde as the dimethyl acetal 153,\(^{82,83}\) followed by lithium-iodine exchange, with acidic work-up gave 2-iodo-4-methoxybenzaldehyde 154.\(^{84,85}\) Wittig methylenation and subsequent Sharpless asymmetric dihydroxylation using AD-mix-\(\beta^{86}\) gave diol 156 in high selectivity of 97% ee, which was determined by chiral HPLC. For comparison, the racemic diol was synthesised using Upjohn dihydroxylation conditions.\(^{87}\) The selective mono-silylation of the primary alcohol furnished the alcohol 152, which was contaminated with a TBDPS derived siloxane impurity.

Scheme 51. Synthesis of enantiomerically pure alcohol 152.

\[
\begin{align*}
\text{a) Trimethyl orthoformate (2.9 equiv), } p\text{-TSA-H}_2\text{O (0.1 equiv), CH}_2\text{Cl}_2, \text{ rt, 48 h; b) } ^t\text{BuLi (1.13 equiv), Et}_2\text{O, } -78 \degree\text{C} \rightarrow -25 \degree\text{C}, 3.5 \text{ h; then I}_2 (1.0 \text{ equiv), Et}_2\text{O, } -78 \degree\text{C}, 30 \text{ min; followed by treatment with 2.0 M HCl, Et}_2\text{O, rt, 4.5 h; c) Ph}_3\text{PCH}_3\text{Br (1.0 equiv), } ^{n}\text{BuLi (1.0 equiv), THF, rt, 15 min; then 154, THF, rt, 16.5 h; d) AD-mix-}\beta, ^t\text{BuOH/H}_2\text{O (1:1), 0 }\degree\text{C} \rightarrow \text{rt, 16 h; e) TBDPSCI (1.2 equiv), imidazole (2.4 equiv), THF, rt} \rightarrow 40 \degree\text{C, 3 h.}\n\end{align*}
\]
6.2.2 Progress toward the synthesis of the allylic halide

Having successfully synthesised alcohol 152, the focus shifted to the synthesis of the allylic halide 151. The envisaged route for the synthesis of 151 was from lactol 159 (Scheme 52), which would be derived from D-lyxose.

Scheme 52. Retrosynthetic route to lactol 159 from allylic halide 151.

It was anticipated that lactol 159 would be converted into alkyne 158 via a Corey–Fuchs reaction; Demailly and co-workers had shown that aldoses, such as D-ribose, when subjected to Corey–Fuchs dibromomethylenation followed by treatment with n-BuLi gave the corresponding alkyne (Scheme 53). Treatment of alkyne 158 with Grubbs’ second-generation catalyst would provide vinyloxepin 157 by ene–yne metathesis. Sequential bromination, reductive elimination and bromination would then give 151.
Scheme 53. Demailly’s synthesis of glyco-1-ynitols.\textsuperscript{89}

Scheme 54. Synthesis of allyl ether 164 from D-\((−)\)-lyxose.

6.2.2.1 Attempted synthesis of lactol 159

Allyl ether 164 was prepared from D-\((−)\)-lyxose via a sequence of benzylolation,\textsuperscript{90} acetonide protection\textsuperscript{91} and allylation of the remaining hydroxyl under standard conditions (Scheme 54).

Unfortunately, attempted debenzylation by sodium/ammonium or lithium/naphthalene\textsuperscript{92} reduction either gave deprotection of the allyl ether and/or isomerisation to the propenyl ether 166. Lewis acid-mediated debenzylation\textsuperscript{93,94} conditions gave deprotection of the acetonide (Scheme 55).
**Scheme 55.** Attempted debenzylation of 164.

![Scheme 55 Diagram](image_url)

a) Sodium (5.0 equiv), liquid NH₃, THF, −78 °C→rt, 14 h; b) lithium (3.0 equiv), naphthalene (4.0 equiv), THF, −78 → −10°C, 13.5 h; c) SnCl₄ (1.0 equiv), CH₂Cl₂, rt, 30 min; d) BBr₃ (1.0 equiv), CH₂Cl₂, −10 °C→rt, 30 min.

Attempted hydrolysis of the analogous methyl glycoside 170 (Scheme 56) by treatment with trimethylsilyl iodide⁹⁵ or trichloromethylsilane/sodium iodide⁹⁶ gave exclusively decomposition products.

**Scheme 56.** Synthesis of 170 from D-(−)-lyxose.

![Scheme 56 Diagram](image_url)

a) AcCl (0.5 equiv), MeOH, 50 °C, 3 h; b) 2,2-dimethoxypropane (3.5 equiv), p-TSA·H₂O (0.02 equiv), acetone, rt, 6 h; c) NaH (1.7 equiv), DMF, 0 °C, 30 min, then allyl bromide (2.0 equiv), 0 °C→rt, 60 min.
6.2.2.2 Revised route to the allylic halide via Ohira–Bestmann homologation

Since selective deprotection of the precursors to lactol 157 had proved unsuccessful, a revised approach to allylic halide 151 was proposed (Scheme 57). It was envisaged formation of 151 could be achieved by reductive elimination of vinyloxepin 171 under desulfonylative ring-opening conditions, followed by bromination of the liberated primary alcohol. Vinyloxepin 171 would be synthesised by ene–yne metathesis of sulfone 172; which in turn would be formed by treatment of epoxide 173 with sodium thiophenolate, oxidation of the thioether to the sulfone and allylation of the alcohol. Epoxide 173 would be synthesised via selective tosylation of diol 174, followed by treatment of the tosylate with base. Literature precedent existed for the synthesis of diol 174 from lactol 165 by the Ohira–Bestmann modification of the Seyferth–Gilbert homologation.101

Scheme 57. Revised route to allylic halide 151 starting from lactol 165.

Both catalytic and transfer hydrogenolysis of ether 163 afforded lactol 165 in quantitative yields, but on scale-up the latter was more reliable. Lactol 165 was exposed to the Ohira–Bestmann reagent under basic conditions with the intention of obtaining alkyne 174. However, alkyne 177 was obtained, which was epimeric at the propargylic stereocentre (Scheme 59). Initially, during the research investigations we were not aware that this epimerisation had occurred, and proceeded to attempt to synthesise allylic halide 151 with this epimer. The Ohira–Bestmann reagent 176 was
synthesised by treatment of the anion of dimethyl 2-oxopropylphosphonate 175 with \( p \)-toluenesulfonyl azide\(^{103} \) according to the procedure developed by Vandewalle and co-workers.\(^{104} \) Phosphonate 175 was prepared by the direct Michaelis–Arbuzov\(^{105} \) reaction between trimethyl phosphite and \textit{in situ} generated iodoacetone (Scheme 58).\(^{106,107} \)

\textit{Scheme 58.} Synthesis of the Ohira–Bestmann reagent 176.

\[
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\end{array} \quad \xrightarrow{a} \quad \begin{array}{c}
\text{MeO} \\
\text{P} \\
\text{MeO} \\
\text{MeO} \\
\end{array} \quad \xrightarrow{b} \quad \begin{array}{c}
\text{MeO} \\
\text{P} \\
\text{MeO} \\
\text{N} \text{N} \\
\end{array} \\
175 \quad \text{60%} \quad 91\% \quad 176 \\
\end{array}
\]

a) KI (1.0 equiv), acetone/MeCN, rt, 1 h; then P(O\text{Me})\text{3} (1.0 equiv), rt, 21 h; followed heating at 50 °C, 6 h; b) NaH (1.1 equiv), toluene/THF, 0 °C, 1 h; then TsN\text{3} (1.05 equiv), toluene, 0 °C→rt, 3 h.

\textit{Scheme 59.} Synthesis of tosylate 178 from 163.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{BnO}^+ \\
\text{OH} \\
\end{array} \quad \xrightarrow{a} \quad \text{quantitative} \\
163 \quad \xrightarrow{b} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{OH} \\
\text{OH} \\
\end{array} \quad \text{46%} \\
165 \quad \text{88.5:11.5 dr} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{OH} \\
\text{OH} \\
\end{array} \quad \xrightarrow{c} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OH} \\
\text{OH} \\
\end{array} \quad \text{88%} \\
177 \quad \text{178} \\
\end{array}
\]

a) Ammonium formate (2.5 equiv), 10 wt % Pd/C (0.33 equiv), MeOH, reflux, 45 min; b) K\text{2}CO\text{3} (3.0 equiv), MeOH, reflux; then 176 (3.0 equiv), MeOH, added \textit{via} syringe pump over a period of 8 h; followed by 14.5 h, reflux; c) Bn\text{2}SnO (0.05 equiv), Et\text{3}N (1.5 equiv), TsCl (1.25 equiv), CH\text{2}Cl\text{2}, 0 °C→rt, 5 h.

Selective tosylation was achieved using conditions reported by Martinelli \textit{et al.};\(^{108} \) where using dibutyltin oxide as a catalyst increases the rate and regioselectivity of the
reaction. The dibutyltin oxide forms a five-membered chelate between the diol, which effectively activates the primary hydroxyl and protects the secondary hydroxyl group.

With tosylate 178 in hand formation of thioether 180 via the epoxide was investigated (Scheme 60). Treatment of 178 with sodium thiophenolate gave an inseparable mixture of vinyl sulfide 179 and thioether 180. Both cis- and trans-isomers of the vinyl sulfide were observed in the crude 1H-NMR spectrum, but the minor trans-isomer was not isolated. Formation of the vinyl sulfides probably occurred by radical attack of the terminal triple bond by thiophenolate. Vinyl sulfide 179 and thioether 180 could be separated after oxidation to the sulfone using magnesium monoperoxyphthalate (MMPP).

Scheme 60. Investigations into the formation of thioether 180.

Further investigations showed that treatment of tosylate 178 with other bases such as, potassium carbonate or Triton®-B (benzytrimethylammonium hydroxide) gave complete conversion to the epoxide by TLC analysis; which when treated in situ with thiophenol gave thioether 180 as the sole product (Table 7). However, scale-up of the latter conditions from 0.3 mmol to 5.9 mmol caused the yield to decrease, as formation of methyl ether 182 was observed (Figure 19). This was as a result of Triton®-B being supplied as a 40 wt % solution in methanol.
Table 7. Conditions investigated for the formation of thioether 180.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Reaction Time*</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ (3.0 equiv)</td>
<td>THF</td>
<td>reflux</td>
<td>8 h</td>
<td>6 h</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>Triton®-B (3.0 equiv)</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>5 min</td>
<td>60 min</td>
<td>84%</td>
</tr>
</tbody>
</table>

*After the addition of 1.0 equivalents of PhSH

Figure 19. Structure of methyl ether 182.

Because formation of thioether 180 from the tosylate was still a problem on a large scale, an alternative method was envisaged via the Ohira–Bestmann reaction of lactol 183 (Scheme 61).

Scheme 61. Alternative route to thioether 180.

The synthesis of lactol 183 was accomplished in a three-step sequence, beginning with the acetonide protection$^{109}$ of D-lyxose, followed by conversion to the bis(thioether) 184 under standard conditions.$^{110}$ The configuration of the bis(thioether) 184 was determined by X-ray crystallographic analysis (Appendix I). Selective hydrolysis$^{111}$ of the anomeric carbon-sulfur bond gave lactol 183; removal of mercuric
salts was achieved by a sodium sulfide treatment during work-up. Subjection of lactol 183 to the Ohira–Bestmann reagent using the conditions developed by Demailly and co-workers gave alkyne 180, plus a trace amount of enol ether 185 (Scheme 62).

**Scheme 62.** Synthesis of alkyne 180 via lactol 183.

![Scheme 62](image)

Having established an efficient route to alkyne 180, the focus shifted to the next challenge, which was the synthesis of vinyloxepin 187 by the intramolecular ene–yne metathesis of allyl ether 186. It was decided to investigate the ene–yne metathesis on alkyne 180 and not the sulfone derivative 181, as there was literature precedent suggesting that thioethers did not poison Grubbs’ second-generation catalyst. Alkyne 180 was allylated under standard conditions to give allyl ether 186 in nearly quantitative yield (Scheme 63).
Scheme 63. O-Allylation of alkyne 180.

\[
\begin{align*}
\text{180} & \xrightarrow{a} \text{186} \\
& \text{98%}
\end{align*}
\]

a) NaH (1.5 equiv), DMF, 0 °C; then a solution of 180 (1.0 equiv) and allyl bromide (1.5 equiv) in DMF added, 0 °C→rt, 60 min.

In initial experiments, exposure of 186 to Grubbs’ second-generation catalyst (5 mol %) in dichloromethane (0.05 M) at room temperature for 48 h gave 13% of compound 189, the product of cross-metathesis of the expected vinyloxepin 187, together with 21% of unreacted 186. In an effort to increase the turnover rate of the catalyst,\textsuperscript{115} an analogous reaction was conducted under an atmosphere of ethylene; this gave in 70% yield the vinyloxepin 187 and the ethylene-alkyne cross-metathesis product 188 as an inseparable 4:3 mixture (Scheme 64). Similar reactivity in the presence of ethylene has been reported by Mori et al.\textsuperscript{116}

Scheme 64. Ene–yne metathesis of 186 in the presence of ethylene.

\[
\begin{align*}
\text{186} & \xrightarrow{a} \text{187} & \text{188} \\
& 40\% & 30\%
\end{align*}
\]

a) Grubbs’ 2\textsuperscript{nd}-generation catalyst (10 mol %), ethylene atmosphere, CH\textsubscript{2}Cl\textsubscript{2} (0.03 M), rt, 17 h.

In further experiments, allyl ether 186 was treated with 10 mol % Grubbs’ second-generation catalyst in dichloromethane (0.05 M) under reflux conditions for 3.5 h, giving 187 in 42% yield (Scheme 65). However, the product readily decomposed at higher concentrations and elevated temperatures, and as a consequence could be stored only as a dilute solution in dichloromethane for short periods.
Scheme 65. Ene–yne metathesis of 186.

186

\[ \text{Scheme 65. Ene–yne metathesis of 186.} \]

\[ \text{186} \xrightarrow{a} 187 \text{ (42\%)} + 189 \text{ (12\%)} \]

a) Grubbs’ 2nd-generation catalyst (10 mol %), CH\(_2\)Cl\(_2\) (0.05 M), reflux, 3.5 h.

The decomposition product was determined to be a dimer, the product of a highly stereo- and regioselective Diels–Alder reaction of vinyloxepin 187 with itself (Scheme 66). X-ray crystallography confirmed the regiochemistry of the cycloadduct 190 (Figure 20, Appendix II). Dimerisations of 7-membered vinyloxepins via thermal or Lewis acid-catalysed Diels–Alder reaction have previously been reported.\(^{117}\)

Scheme 66. Dimerisation of vinyloxepin 187.

187

\[ \text{Scheme 66. Dimerisation of vinyloxepin 187.} \]

\[ \text{187} \xrightarrow{a} 190 \text{ (87\%)} \]

a) vacuum, rt, 48 h.
Figure 20. The molecular structure of cycloadduct 190.

The X-ray crystallographic analysis showed stereocentres C-4 and C-26 were epimeric. Since the structure of the bis(thioether) 184 had already been confirmed by X-ray crystallography (Appendix I), the epimerisation must have occurred during the Ohira–Bestmann homologation. Analysis of the literature\textsuperscript{89,118} showed that there was precedent for such unwanted base–acid reactivity occurring during the Ohira–Bestmann reaction. Esterification of alkyne 180 gave a 3,5-dinitrobenzoate (Scheme 67), which was shown by X-ray crystallography to be 191, which was epimeric at the propargylic stereocentre (Figure 21, Appendix III).


\[
\begin{array}{c}
\text{O} & \text{O} & \text{OH} \\
\text{O} & \text{O} & \text{SPh} \\
\end{array}
\xrightarrow{a} \\
\begin{array}{c}
\text{O} & \text{O} & \text{SPh} \\
\text{O} & \text{O} & \text{NO}_2 \\
\end{array}
\]

\begin{itemize}
\item a) 3,5-Dinitrobenzoyl chloride (1.1 equiv), Et\textsubscript{3}N (1.5 equiv), THF, 0 °C→rt, 3 h.
\end{itemize}
Before it had been established that epimerisation had occurred, the reductive elimination to give trienol 193 was attempted (Scheme 68). However, treatment of vinyloxepin 187 with lithium naphthalenide$^{119}$ failed to effect the elimination and only starting material was recovered. Therefore, a two-step strategy via E1cB elimination to give triene 192, followed by desulfurisation with Raney nickel was investigated.

**Scheme 68.** Formation of trienol 193.

\[ \text{187} \xrightarrow{\text{a}} \text{193} \]

\[ \text{192} \xrightarrow{\text{b}} \text{54\%} \xrightarrow{\text{Raney Ni}} \]

a) Lithium (6.0 equiv), naphthalene (6.0 equiv), THF, $-78 \degree C \to rt$, 4 h; b) $^n$BuLi (2.0 equiv), THF, $-78 \to 0 \degree C$, 30 min.
Treatment of vinyloxepin 187 with n-BuLi gave triene 192. Only the (E)-isomer was isolated, but a small trace of the (Z)-isomer was observed in the crude ¹H-NMR spectrum. Desulfurisation was not investigated, as interest shifted at this stage to the synthesis of the correct epimer required for the synthesis of allylic halide 151.

6.2.2.3 Investigations into the synthesis of alkyne 195

Since the Ohira–Bestman homologation was causing unwanted epimerisation, an alternative route for the synthesis of the required alkyne 195 was investigated. This involved Wittig iodomethylenation¹²⁰ to give (Z)-iodoalkene 194, which would be subjected to base-mediated elimination (Scheme 69).¹²¹ Unfortunately, under a diverse range of conditions tried, all failed to provide (Z)-iodoalkene 194.

Scheme 69. Formation of alkyne 195 via (Z)-iodoalkene 194.

Similarly, attempted Wittig chloromethylenation¹²² and Corey–Fuchs dibromomethylenation⁸⁹ reactions, failed to give the corresponding haloalkenes. Another method of forming alkynes from lactols via the Colvin rearrangement¹²³ has been reported by Myers et al.¹²⁴ (Scheme 70), and this too was attempted unsuccessfully. The low reactivity of 2,3-O-isopropylidene lactol derivatives of D-lyxose with organolithium reagents has also been observed by Singh and co-workers.¹²⁵
Scheme 70. Formation of alkyne 197 from lactol 196.\textsuperscript{124}

\[
\begin{align*}
\text{HO} & \quad \text{LiO} \\
\text{196} & \quad \text{TMS} \\
\text{(1.2 equiv)} & \quad \text{LDA (2.4 equiv)} \\
\text{THF, } -78 \ ^\circ\text{C} & \rightarrow \text{rt.}
\end{align*}
\]

Due to difficulties of forming alkyne 195 from lactol 183, a new route via lactone 200 was envisaged (Scheme 71), whereby Wittig iodomethylation\textsuperscript{120} would give iodoalkene 201, which would be treated with butyllithium to furnish alkyne 195.

Scheme 71. New route to alkyne 195.

Oxidation of lactol 183 with a dimethyl sulfoxide-acetic anhydride mixture\textsuperscript{126} gave lactone 200 (Scheme 72), plus the Pummerer rearrangement\textsuperscript{127} product 202 and acetate 203 as minor by-products (Figure 22). Alternative oxidations were tried, such as Swern,\textsuperscript{128} TPAP\textsuperscript{129} and PCC,\textsuperscript{130} but these were not as high-yielding.
Disappointingly, the subsequent Wittig iodomethylation did not give 201 and only starting material was recovered.

**Scheme 72. Oxidation to lactone 200.**

![Scheme 72](image)

a) Ac₂O (18 equiv), DMSO, rt, 22 h; b) ICH₂PPh₃I (4.0 equiv), ’BuOK or LiHMDS (4.0 equiv), THF, rt, 30 min; then 200, rt→reflux, 17 h.

**Figure 22.** By-products from the oxidation of lactol 183.

Pleasingly, Wittig chloromethylation did give the analogous chloroalkene 205 but in poor yield. The two-step sequence via the chlorohydrin 204 proved to be the better route (Scheme 73) and gave chloroalkene 205 in a yield of 61% over two-steps. Chlorohydrin 204 was obtained as a mixture of diastereomers, with the hydroxyl group *cis* to the H-2, H-3 and H-4 protons for the major isomer, as determined by nOe interactions between OH and H-2 & H-4 protons. Treatment of the chloroalkene 205 with ”BuLi did not provide alkyne 195, but instead gave numerous decomposition products.
Scheme 73. Synthesis of chloroalkene 205.

a) CICH₂PPh₃Cl (4.0 equiv), n-BuLi (4.0 equiv), TMEDA (4.0 equiv), THF, rt, 30 min; then 200, rt, 90 min; b) ICH₂Cl (1.5 equiv), n-BuLi (1.5 equiv), THF, −78 °C, 90 min; c) Et₃N (10 equiv), MsCl (3.0 equiv), CH₂Cl₂, 0 °C→rt, 30 min; d) n-BuLi (2.0 equiv), THF, −78 °C→rt, 60 min.

The feasibility of reductive elimination of dichloroolefins to give acetylenic alcohols through lithium insertion has been demonstrated by Yadav *et al.*₁³¹ (Scheme 74).

Scheme 74. Synthesis of acetylenic alcohols from lactones.¹³¹

a) Lithium sand (6.0 equiv), THF, reflux, 30 min.
Encouraged by this precedent, dichloroolefin 211 was prepared according to a procedure by Lakhrissi and Chapleur (Scheme 75).\textsuperscript{132} However, treatment of dichloroolefin 211 with freshly prepared lithium sand\textsuperscript{133} failed to effect the reductive elimination to give alkyne 195 and only starting material was recovered. Similar unreactivity has been observed by Myers and Goldberg.\textsuperscript{124}

\textit{Scheme 75.} Synthesis of dichloroolefin 211 and attempted reductive elimination.\textsuperscript{131}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {200};
\node (b) at (2,0) {211};
\node (c) at (4,0) {195};
\draw[->,thick] (a) -- (b) node[midway,above] {98\%} node[below] {a};
\draw[->,dashed] (b) -- (c) node[midway,above] {b};
\end{tikzpicture}
\end{center}

a) PPh\textsubscript{3} (4.0 equiv), CCl\textsubscript{4} (24.0 equiv) added via syringe pump, THF, reflux, 30 min; a) lithium sand (6.0 equiv), THF, reflux, 5.5 h.

It was thought that the unreactivity of the dichloroolefin 211 could be overcome by using the dibromoolefin 213, as bromine–lithium exchange requires less energy.\textsuperscript{134} The dibromoolefin 213 was prepared via Wittig dibromomethylation\textsuperscript{135} and the two-step protocol through the dibromohydrin 212 (Scheme 76).\textsuperscript{136} The former proved to be higher-yielding and more reliable on scale-up. Again, dibromohydrin 212 was obtained as a mixture of diastereomers, with the hydroxyl group \textit{cis} to the H-2, H-3 and H-4 protons for the major isomer, as determined by nOe interactions between OH and H-2 & H-4 protons.
**Scheme 76.** Synthesis of dibromoolefin 213.

![Scheme 76 Diagram](image)

a) PPh₃ (4.0 equiv), CBr₄ (2.0 equiv), toluene, rt, 30 min; then 200, reflux, 60 min; b) CH₂Br₂ (4.0 equiv), LDA (2.0 equiv), THF, −78 °C, 60 min; c) Et₃N (10 equiv), MsCl (3.0 equiv), CH₂Cl₂, 0 °C→rt, 30 min.

Several reagents known to effect halogen–metal exchange in the Corey–Fuchs reaction, such as n-butyllithium, methyl lithium/lithium bromide complex, ethyl magnesium bromide and magnesium were used in conjunction with dibromoolefin 213; the results are summarised below (Scheme 77 and Table 8).

**Scheme 77.** Synthesis of alkyne 195 from dibromoolefin 213.

![Scheme 77 Diagram](image)
**Table 8.** Conditions tried for the formation of alkyne 195 from dibromoolefin 213.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Equivalents</th>
<th>Temperature*</th>
<th>Reaction Time</th>
<th>Yield of 215</th>
<th>Yield of 195</th>
<th>(E):(Z)† of 215</th>
<th>Yield of 195</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>2.0</td>
<td>−78 °C→rt</td>
<td>30 min</td>
<td>21%</td>
<td>1.0:2.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi</td>
<td>3.0</td>
<td>−78 °C</td>
<td>10 min</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeLi·LiBr</td>
<td>5.0</td>
<td>−78→−20 °C</td>
<td>60 min</td>
<td>16%</td>
<td>1.0:4.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EtMgBr</td>
<td>4.0</td>
<td>0 °C→rt</td>
<td>10 min</td>
<td>88%</td>
<td>1.0:2.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rieke Mg</td>
<td>10.0</td>
<td>rt→reflux</td>
<td>4 h</td>
<td>33%</td>
<td>1.0:4.7</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SmI₂</td>
<td>5.0</td>
<td>−78 °C→rt</td>
<td>90 min</td>
<td>100%</td>
<td>1.0:2.4</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*All the reactions were carried out in THF.
†The (E)- and (Z)-isomers were assigned by nOe analysis. A nOe observed between HC≡C and H-3 for the (Z)-isomer.

Treatment of dibromoolefin 213 with Rieke\textsuperscript{40} magnesium was the only reaction that gave a reasonable amount of alkyne 195 (Entry 5). However, attempts to improve the yield by increasing the equivalents of magnesium or the temperature of the reaction, by changing the solvent to diglyme, were unsuccessful. Since, most of the reagents gave bromoalkene 215 in varying yields instead of alkyne 195 (Entries 1, 3, 4 and 6), it was decided to investigate the treatment of this with the different halogen-metal exchange reagents (Scheme 78 and Table 9).

**Scheme 78.** Synthesis of alkyne 195 from bromoalkene 215.
Table 9. Conditions tried for the formation of alkyne 195 from bromoalkene 215.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Equivalents</th>
<th>Temperature*</th>
<th>Reaction Time</th>
<th>Yield of 185</th>
<th>Yield of 195</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>3.0</td>
<td>−78→0 °C</td>
<td>90 min</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi</td>
<td>2.5</td>
<td>−78→0 °C</td>
<td>90 min</td>
<td>28%</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>t-BuLi</td>
<td>2.5</td>
<td>−78 °C→rt</td>
<td>2.5 h</td>
<td>25%</td>
<td>36%</td>
</tr>
<tr>
<td>4</td>
<td>Rieke Mg</td>
<td>10.0</td>
<td>rt→reflux</td>
<td>4 h</td>
<td>-</td>
<td>21%</td>
</tr>
</tbody>
</table>

*All the reactions were carried out in THF.

The more basic t-BuLi was better for the bromine-lithium exchange, as it gave enol ether 185 and alkyne 195 in greater yields (Entry 2) than n-BuLi and Rieke magnesium (Entries 1 and 4). Increasing the temperature before the reaction was quenched did not improve the yield or ratio of 185 to 195 (Entry 3).

6.2.2.4 Ene–yne metathesis investigations

Having found a way of synthesising alkyne 195, the intramolecular ene–yne metathesis of allyl ether 218 was investigated (Scheme 79).

Scheme 79. Synthesis of allyl ether 218.

a) EtMgBr (4.0 equiv), THF, 0 °C→rt, 10 min; b) t-BuLi (2.5 equiv), THF, −78→0 °C, 90 min; c) NaH (1.5 equiv), DMF, 0 °C; then a solution of 195 (1.0 equiv) and allyl bromide (1.5 equiv) in DMF added, 0 °C→rt, 30 min.
In initial experiments, the conditions established for the previous ene–yne metathesis on epimer 186 were tried. However, when allyl ether 218 was exposed to Grubbs’ second-generation catalyst (10 mol %) in dichloromethane (0.05 M) under reflux conditions for 3.5 h, only starting material was recovered. In further experiments, allyl ether 218 was treated with 10 mol % Grubbs’ second-generation catalyst in toluene (0.05 M) under reflux conditions for 30 min; giving vinyloxepin 219 in 17% yield and the cross-metathesis by-product 220 in 7% yield. Attempts at increasing the yield of the metathesis reaction by changing the solvent to 1,2-dichloroethane or the catalyst to Hoveyda–Grubbs’ second-generation catalyst failed. However, treatment of allyl ether 218 with 20 mol % Grubbs’ second-generation catalyst in dichloromethane (0.05 M) under microwave irradiation conditions for 5 min, gave vinyloxepin 219 in 36% yield and 220 in 4% yield (Scheme 80). A major unidentified by-product (15% yield by weight) was also isolated from this reaction. It was believed to be derived from cross-metathesis of the vinyloxepin 219 with an unknown fragmentation product of itself.

Scheme 80. Ene–yne metathesis of 218.

Interestingly, vinyloxepin 219 did not readily decompose to the dimer \emph{via} a Diels–Alder reaction with itself, which was unlike the epimer. Treatment of vinyloxepin 219 with \textsuperscript{t}BuLi did not give triene 221 \emph{via} E1cB elimination, but instead gave trienol 222 (Scheme 81). The unusual reactivity observed here could be due to the protons in the \(\alpha\)-position to the sulfide being in a sterically encumbered position preventing deprotonation. Reductive elimination was also tried on 219 to give the corresponding trienol 224 by treatment with sodium naphthalenide, but was unsuccessful and gave decomposition of the starting material.
**Scheme 81.** Formation of trienol 222.

\[
\begin{align*}
\text{219} & \quad \xrightarrow{a} \quad 28\% \quad \text{222} \\
\end{align*}
\]

a) "BuLi (1.0 equiv), THF, −78→0 °C, 90 min.

In order to overcome this unwanted reactivity, it was proposed that oxidation of the sulfide to the sulfone would give vinyloxepin 223, which then could be subjected to reductive elimination with sodium amalgam to give trienol 224.

**Scheme 82.** Oxidation to the sulfone.

\[
\begin{align*}
\text{219} & \quad \xrightarrow{a} \quad \text{223} & \quad \xrightarrow{c} \quad 31\% \quad \text{224} \\
\text{218} & \quad \xrightarrow{b} \quad 89\% \quad \text{225} \\
\end{align*}
\]

a) MMPP.6H$_2$O (5.0 equiv), MeOH, rt, 90 min; b) MMPP.6H$_2$O (5.0 equiv), MeOH, rt, 5 min; c) Grubbs’ 2nd-generation catalyst (20 mol %), CH$_2$Cl$_2$ (0.05 M), microwave irradiation, 70 °C, 5 min; d) Na(Hg) (10 equiv), Na$_2$HPO$_4$ (4.8 equiv), MeOH/THF, rt, 60 min.
Oxidation of the sulfide of vinylloxepin 219 to the sulfone with MMPP was unsuccessful. However, oxidation of the allyl ether 218 did give the corresponding sulfone 225, which was exposed to Grubbs’ second-generation catalyst under microwave irradiation conditions to afford vinylloxepin 223 (Scheme 82). Treatment of vinylloxepin 223 with sodium amalgam failed to effect the reductive elimination and only starting material was recovered.

**6.2.3 Future work**

Further optimisation of the ene–yne metathesis reaction to afford vinylloxepin 223 will be required by using alternative catalysts and solvents, plus other reducing agents known to effect reductive elimination reactions of sulfones will need to be tested. Then, with trienol 224 in hand, bromination will finally give allylic halide 151. Subsequently, synthesis of triene 46 can be pursued as described in Scheme 50 and the envisaged stereoselective hetero-IMDA reaction of it can be tried.

**Scheme 50.** Synthesis of triene 46.

![Scheme 50](image)

a) Ag₂O; b) TBAF; c) Dess–Martin periodinane; d) TsN=PPh₃, RuCl₂(PPh₃)₃ catalyst.
6.2.4 Conclusion

To sum up, the synthesis of the enantiomerically pure alcohol 152 has been achieved in a five-step sequence starting from $p$-anisaldehyde. However, the synthesis of the allylic halide 151 from D-lyxose has been problematic. Initial efforts for its synthesis via the route incorporating the Ohira–Bestmann reaction of lactol 183 gave alkyne 180, which was epimeric at the propargylic stereocentre. Further efforts, through a sequence of Wittig dibromomethylation, mono-debromination and reductive elimination on lactone 200 eventually gave alkyne 195; which underwent $O$-allylation and intramolecular ene–yne metathesis to give vinyloxepin 219. Unfortunately, the attempted E1cB elimination on 219 did not give the expected triene 221, but instead gave trienol 222. Therefore, an alternative route via ene–yne metathesis on sulfone 225 and the subsequent reductive elimination to give trienol 224, which could undergo bromination to give allylic halide 151, was investigated. Disappointingly, when vinyloxepin 223 was treated with sodium amalgam, it failed to undergo the reductive-elimination. Hence, future endeavours will focus on investigating alternative reducing agents for the reductive elimination.

Interestingly, the vinyloxepin 187 product from the ene–yne metathesis on the epimer readily underwent a highly stereo- and regioselective Diels–Alder reaction with itself, to give dimer 190.
7 Experimental

General Directions. Standard laboratory techniques were employed when handling air-sensitive reagents and all reactions were performed under a nitrogen atmosphere unless otherwise stated.

Microwave. All microwave reactions were performed in a Biotage initiator upgraded to version 2.5 and cooled using compressed air (4 bar).

Ozonolysis. Ozone gas was generated from oxygen gas using a Triogen LAB2B ozone generator.

Solvents and reagents. All solvents and reagents were used as received from the supplier unless otherwise noted. Hexane refers to the fraction of petroleum boiling between 67–70 °C. Petrol refers to the fraction of light petroleum-ether boiling between 40–60 °C. Anhydrous THF and Et₂O were distilled from sodium-benzophenone ketyl under nitrogen prior to use. Dry toluene was distilled from sodium under a nitrogen atmosphere. Anhydrous CH₂Cl₂, acetonitrile, Et₃N, DMSO and DBU were distilled from CaH₂ under nitrogen. Dry ‘PrOH was distilled from CaO under a nitrogen atmosphere. Dry acetone was distilled from K₂CO₃ onto 4Å molecular sieves under an atmosphere of nitrogen. Water was distilled using a Merit W4000 system.

Chromatography. Flash column chromatography was performed using silica gel (BDH) according to the method of W.C. Still et al. or using Biotage SNAP Flash Cartridges on a Biotage Isolera Flash Purification System. Thin-layer chromatography was performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck 60 F₂₅₄), which were developed using standard visualising agents: UV fluorescence (254 & 366 nm) and/or ammonium molybdate, potassium permanganate and vanillin.

Melting points. These were determined on Stuart Scientific SMP1 or BÜCHI B-545 melting point apparatus and are uncorrected.

Optical rotations. These were determined on an Optical Activity LtD, AA-10 Automatic or polAAr 3000 Automatic, polarimeter at 589 nm (Na D-line) with a path length of 1 dm. Concentrations (c) are quoted in g/100 mL and specific rotations ([α]D) are quoted in units of 10⁻¹ deg cm² g⁻¹ at the specified temperature (T).

Infrared spectroscopy. Spectra were recorded on a Perkin–Elmer, Spectrum RX FT-IR or Spectrum One FT-IR, spectrometer as thin films on NaCl plates or neat.
**NMR spectroscopy.** All $^1$H and $^{13}$C NMR spectra were recorded at 400 and 101 MHz, respectively, on a Bruker Ultra-Shield AV400 spectrometer. Chemical shifts ($\delta_{\text{H}}$ and $\delta_{\text{C}}$) are expressed in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants ($J$) are reported to the nearest 0.5 Hz.

**Mass spectrometry.** Low-resolution mass spectra (m/z) and high-resolution mass spectra were recorded on a Micromass AutoSpec Premier spectrometer.

**Elemental analyses.** These were performed at the microanalytical laboratories of the London Metropolitan University.
To a stirred solution of methyl propargyl ether (3.08 g, 43.9 mmol, 1.0 equiv) in dry THF (100 mL) at –78 ºC, was added n-BuLi (18.5 mL of 2.37 M solution in hexanes, 43.9 mmol, 1.0 equiv) dropwise. After 30 min, to the resultant yellow solution observed at –78 ºC, was added dropwise a solution of S-phenyl benzenethiosulfonate (11.0 g, 43.9 mmol, 1.0 equiv) in dry THF (50 mL). The reaction mixture was allowed to slowly warm to –10 ºC. After 60 min, a 10% water–THF solution (100 mL) was slowly added to the reaction mixture. The quenched reaction mixture was diluted with Et₂O (100 mL) and water (100 mL). The aqueous layer was extracted with Et₂O (3 x 100 mL). Then, the combined organic layers were washed with water (2 x 200 mL), brine (2 x 200 mL), dried (MgSO₄) and concentrated under reduced pressure to give a yellow oil. Purification by Kugelrohr distillation gave 1-phenylthio-3-methoxy-1-propyne (110) (7.11 g, 91%) as a colourless oil; bp 160 ºC (3.0 mmHg); Rf 0.33 (10% Et₂O–petrol); νmax (neat) 2181, 1099, 739, 688 cm⁻¹; δH (CDCl₃, 400 MHz) 7.46 (2H, d, J 7.5 Hz, ortho PhS), 7.36 (2H, t, J 7.5 Hz, meta PhS), 7.25 (1H, t, J 7.5 Hz, para PhS), 4.36 (2H, s, CH₂), 3.45 (3H, s, OCH₃); δC (CDCl₃, 101 MHz) 132.4 (ipso PhS), 129.3 (meta PhS), 126.8 (para PhS), 126.4 (ortho PhS), 95.2 (C-2), 73.6 (C-1), 60.8 (C-3), 57.6 (OCH₃); m/z (CI) 196 [M+NH₄]⁺, 181, 164 [M–CH₃]+, 149 [M–OCH₃]+ (Found: [M+NH₄]⁺, 196.0761. C₁₀H₁₀OS requires [M+NH₄]⁺, 196.0796). Data in agreement with previous reported literature values.
Phenylsulfenyl chloride (111).\textsuperscript{58}

![Phenylsulfenyl chloride (111)](image)

To a stirred mixture of thiophenol (10.0 mL, 97.4 mmol, 1.0 equiv) and dry triethylamine (0.11 mL, 0.78 mmol, 0.01 equiv) in dry \(n\)-pentane (50 mL) at 0 °C, was added sulfuryl chloride (9.08 mL, 112 mmol, 1.15 equiv) dropwise. The resultant orange-red solution was slowly warmed to room temperature. After 60 min, the reaction mixture was concentrated under reduced pressure at room temperature. The red liquid residue obtained was purified by short-path distillation to give phenylsulfenyl chloride \textit{111} (12.1 g, 86%) as a blood-red liquid; bp 42–43 °C (1.5 mmHg) [lit.\textsuperscript{58} bp 41–42 °C (1.5 mmHg)]; \(R_f\) 0.33 (100% petrol); \(\nu_{\text{max}}\) (neat) 3061, 1576, 1474, 1439, 745, 685 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.73–7.70 (2H, m, \textit{ortho} PhSCl), 7.49–7.44 (3H, m, \textit{meta} & \textit{para} PhSCl); \(\delta_C\) (CDCl\(_3\), 101 MHz) 135.6 (ipso PhSCl), 131.8 (\textit{ortho} PhSCl), 130.2 (\textit{para} PhSCl), 129.4 (\textit{meta} PhSCl); \(m/z\) (CI) 327 [3M–3Cl]\(^+\), 268, 218 [2M–2Cl]\(^+\), 159, 126 109 [M–Cl]\(^+\), 102. Data in agreement with previous reported literature values.\textsuperscript{58}
To a stirred suspension of diphenyl disulfide (10.0 g, 45.8 mmol, 1.0 equiv) in glacial acetic acid (40 mL) at room temperature was added dropwise hydrogen peroxide (10.6 g, 29.4 wt % aqueous solution, 91.6 mmol, 2.0 equiv) over a period of 15 min. Then, the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was cooled to 0 °C and quenched with water (100 mL). The organic layer was separated, dissolved in CHCl₃ (30 mL), washed with saturated aqueous NaHCO₃ solution (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a pale yellow semi-crystalline solid. Purification by recrystallisation from MeOH gave S-phenyl benzenethiosulfonate 113 (8.50 g, 74%) as a white square plates; mp 43.0–44.0 °C (MeOH) [lit.¹⁴² mp 44–45 °C (diethyl ether/hexane)]; Rₛ 0.18 (10% Et₂O–petrol); vₘₐₓ (film) 1322, 1149, 755, 748, 683, cm⁻¹; δ_H (CDCl₃, 400 MHz) 7.62–7.58 (3H, m, ortho PhSO₂ & para PhSO₂), 7.50 (1H, tt, J 6.5 & 2.5 Hz, para PhS), 7.46–7.42 (2H, m, meta PhSO₂), 7.39–7.34 (4H, m, ortho PhS & meta PhS); δ_C (CDCl₃, 101 MHz) 142.9 (ipso PhSO₂), 136.6 (meta PhSO₂), 133.7 (para PhSO₂), 131.5 (para PhS), 129.5 (ortho PhS), 128.8 (meta PhS), 127.8 (ipso PhS), 127.6 (ortho PhSO₂); m/z (CI) 518 [2M+NH₄]⁺, 268 [M+NH₄]⁺, 250 [MH]⁺. Data in agreement with previous reported literature values.⁶²
(Z)-3-(Phenylthio)but-2-enal (115a) and (E)-3-(phenylthio)but-2-enal (115b).

To a stirred solution of 1-phenylthio-3-methoxy-1-propyne 110 (2.00 g, 11.2 mmol, 1.0 equiv) in dry THF (80 mL) at −78 ºC, was added dropwise a freshly prepared solution of LDA (1.32 g, 12.3 mmol, 1.1 equiv) in THF (30 mL). After 15 min, iodomethane (838 µL, 13.5 mmol, 1.2 equiv) was added dropwise to the orange solution observed at −78 ºC. The reaction mixture was allowed to slowly warm to −10 ºC. Then, the reaction was quenched with a 20% water–THF solution (30 mL), diluted with Et₂O (50 mL) and water (50 mL). The aqueous layer was extracted with Et₂O (4 x 75 mL). Then, the combined organic layers were concentrated under reduced pressure, dissolved in Et₂O (50 mL) and treated with aqueous HCl solution (50 mL, 1.0 M). The mixture was stirred at room temperature for 6 h. The aqueous layer was extracted with Et₂O (3 x 100 mL). Then, the combined organic layers were washed with saturated aqueous NaHCO₃ solution (2 x 200 mL), water (2 x 200 mL), brine (2 x 200 mL), dried (MgSO₄) and concentrated under reduced pressure to give a brown residue. Purification by chromatography (10% Et₂O–petrol) gave (Z)-3-(phenylthio)but-2-enal 115a (261 mg, 13%) as an orange oil; R_f 0.44 (30% Et₂O–petrol); ν_max (neat) 1660, 1581, 1156, 750, 691 cm⁻¹; δ_H (CDCl₃, 400 MHz) 10.09 (1H, d, J 6.5 Hz, H-1), 7.54 (2H, d, J 7.0 Hz, ortho PhS), 7.50–7.40 (3H, m, meta & para PhS), 6.18 (1H, d, J 6.5 Hz, H-2), 1.99 (3H, s, H-4); δ_C (CDCl₃, 101 MHz) 189.3 (C-1), 160.8 (C-3), 134.8 (ortho PhS), 130.0 (ipso PhS), 129.5 (meta PhS), 129.4 (para PhS), 126.2 (C-2), 25.1 (C-4); m/z (CI) 374 [2M+NH₄]⁺, 230, 213, 196 [M+NH₄]⁺, 179 [MH]⁺ (Found: [MH]⁺, 179.0535. C₁₀H₁₀O requires [MH]⁺, 179.0531); and gave (E)-3-(phenylthio)but-2-enal 115b (1.19 g, 60%) as an orange oil; R_f 0.35 (30% Et₂O–petrol); ν_max (neat) 1659, 1592, 1155, 757, 691 cm⁻¹; δ_H (CDCl₃, 400 MHz) 9.82 (1H, d, J 8.0 Hz, H-1), 7.52–7.44 (5H, m, PhS), 5.51 (1H, d, J 8.0 Hz, H-2), 2.48 (3H, s, H-4); δ_C (CDCl₃, 101 MHz) 187.4 (C-1), 165.6 (C-3), 135.6 (ortho PhS), 130.4 (para PhS), 129.9 (meta PhS), 128.3 (ipso PhS), 122.1 (C-2), 18.5 (C-4); m/z (CI) 374

(Z)-3-(Phenyllthio)pent-2-enal (116a) and (E)-3-(phenylthio)pent-2-enal (116b).

To a stirred solution of 1-phenylthio-3-methoxy-1-propyne 110 (2.00 g, 11.2 mmol, 1.0 equiv) in dry THF (70 mL) at −78 ºC, was added dropwise a freshly prepared solution of LDA (1.32 g, 12.3 mmol, 1.1 equiv) in THF (30 mL). After 15 min, iodoethane (1.08 mL, 13.5 mmol, 1.2 equiv) was added dropwise to the orange solution observed at −78 ºC. The reaction mixture was allowed to slowly warm to 0 ºC. After 3 h, water (10 mL) was added slowly to the reaction mixture. The aqueous layer was extracted with Et₂O (3 x 25 mL). Then, the combined organic layers were concentrated under reduced pressure, diluted in THF (50 mL) and treated with aqueous HCl solution (25 mL, 1.0 M). The mixture was stirred at room temperature for 2 h, before being diluted with Et₂O (30 mL). The aqueous layer was extracted with Et₂O (2 x 50 mL). Then, the combined organic layers were washed with saturated aqueous NaHCO₃ solution (50 mL), water (50 mL), brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a brown-orange residue. Purification by chromatography (10% Et₂O–petrol) gave (Z)-3-(phenylthio)pent-2-enal 116a (513 mg, 24%) as a yellow-orange oil; Rf 0.51 (30% Et₂O–petrol); \( \nu_{\text{max}} \) (neat) 2974, 1670, 1572, 1542, 1148, 750, 693 cm⁻¹; \( \delta_{\text{H}} \) (CDCl₃, 400 MHz) 10.19 (1H, d, \( J \) 6.5 Hz, H-1), 7.44–7.34 (5H, m, PhS), 6.13 (1H, d, \( J \) 6.5 Hz, H-2), 2.27 (2H, q, \( J \) 7.5 Hz, H-4), 1.08 (3H, t, \( J \) 7.5 Hz, H-5); \( \delta_{\text{C}} \) (CDCl₃, 101 MHz) 190.1 (C-1), 165.7 (C-3), 134.1 (ortho PhS), 133.8 (ipso PhS), 129.4 (meta PhS), 129.3 (para PhS), 126.6 (C-2), 30.5 (C-4), 13.1 (C-5); \( m/z \) (Cl) 385 [2M+H]⁺, 221, 210 [M+NH₄]⁺, 193 [MH]⁺ (Found: [MH]⁺, 193.0679. C₁₁H₁₂OS requires [MH]⁺, 193.0687); and gave (E)-3-(phenylthio)pent-2-enal 116b (1.06 g, 49%) as an orange oil; \( R_f \) 0.38 (30% Et₂O–petrol); \( \nu_{\text{max}} \) (neat) 2975, 2935, 1658, 1578, 1153, 752, 691 cm⁻¹; \( \delta_{\text{H}} \) (CDCl₃, 400 MHz) 9.82 (1H, d, \( J \) 8.0 Hz,
H-1), 7.52–7.45 (5H, m, PhS), 5.41 (1H, d, J 8.0 Hz, H-2), 2.86 (2H, q, J 7.5 Hz, H-4), 1.41 (3H, t, J 7.5 Hz, H-5); δC (CDCl₃, 101 MHz) 187.0 (C-1), 172.7 (C-3), 135.6 (ortho PhS), 130.3 (para PhS), 129.9 (meta PhS), 128.3 (ipso PhS), 121.2 (C-2), 26.1 (C-4), 16.0 (C-5); m/z (CI) 385 [2M+H]⁺, 367, 301, 273, 210 [M+NH₄]⁺, 193 [MH]⁺ (Found: [MH]⁺, 193.0680. C₁₁H₁₂OS requires [MH]⁺, 193.0687).

(Z)-4-Phenyl-3-(phenylthio)but-2-enal (117a) and (E)-4-phenyl-3-(phenylthio)but-2-enal (117b).

To a stirred solution of 1-phenylthio-3-methoxy-1-propyne 110 (3.45 g, 19.4 mmol, 1.0 equiv) in dry THF (100 mL) at −78 ºC, was added dropwise a freshly prepared solution of LDA (2.28 g, 21.3 mmol, 1.1 equiv) in THF (50 mL). After 15 min, benzyl bromide (3.45 mL, 29.0 mmol, 1.5 equiv) was added dropwise to the orange solution observed at −78 ºC. The reaction mixture was allowed to slowly warm to −10 ºC. Then, the reaction was quenched with a 20% water–THF solution (50 mL). The aqueous layer was extracted with Et₂O (4 x 130 mL). Then, the combined organic layers were concentrated under reduced pressure, dissolved in Et₂O (100 mL) and treated with aqueous HCl solution (100 mL, 1.0 M). The mixture was stirred at room temperature for 2 h. The aqueous layer was extracted with Et₂O (3 x 75 mL). Then, the combined organic layers were washed with saturated aqueous NaHCO₃ solution (2 x 350 mL), water (2 x 350 mL), brine (2 x 350 mL), dried (MgSO₄) and concentrated under reduced pressure to give a brown residue. Purification by chromatography (10% Et₂O–petrol) gave (Z)-4-phenyl-3-(phenylthio)but-2-enal 117a (1.56 g, 32%) as an orange oil; Rₚ 0.38 (30% Et₂O–petrol); νₘₐₓ (neat) 1666, 1570, 1535, 1134, 746 cm⁻¹; δH (CDCl₃, 400 MHz) 10.18 (1H, d, J 6.5 Hz, H-1), 7.46–7.38 (5H, m, PhS & Ph), 7.30–7.23 (3H, m, PhS & Ph), 6.99 (2H, dd, J 7.5 & 2.0 Hz, ortho Ph), 6.10 (1H, d, J 6.5 Hz, H-2), 3.55 (2H, s, H-4); δC (CDCl₃, 101 MHz) 190.0 (C-1), 162.6 (C-3), 136.4 (ipso Ph), 134.4 (ortho PhS), 130.0 (ipso PhS), 129.4 (meta PhS), 129.3 (para PhS &
para Ph), 129.0 (ortho Ph), 128.6 (meta Ph), 127.1 (C-2), 43.3 (C-4); m/z (CI) 509 [2M+H]⁺, 272 [M+NH₄]⁺, 255 [MH]⁺ (Found: [MH]⁺, 255.0844. C₁₀H₁₄OS requires [MH]⁺, 255.0844); and gave (E)-4-phenyl-3-(phenylthio)but-2-enal 117b (2.21 g, 45%) as an orange oil; Rf 0.30 (30% Et₂O–petrol); νmax (neat) 1659, 1579, 1556, 1142, 751 cm⁻¹; δH (CDCl₃, 400 MHz) 9.91 (1H, d, J 7.5 Hz, H-1), 7.50–7.45 (5H, m, PhS & Ph), 7.43–7.31 (5H, m, PhS & Ph), 5.61 (1H, d, J 7.5 Hz, H-2), 4.18 (2H, s, H-4); δC (CDCl₃, 101 MHz) 187.3 (C-1), 168.1 (C-3), 137.2 (ipso PhS), 134.4 (ipso Ph), 130.4 (para PhS), 130.0 (meta PhS), 129.0 (ortho Ph), 128.6 (meta Ph), 127.3 (para Ph), 122.9 (C-2), 37.9 (C-4); m/z (CI) 509 [2M+H]⁺, 272 [M+NH₄]⁺, 255 [MH]⁺ (Found: [MH]⁺, 255.0847. C₁₀H₁₄OS requires [MH]⁺, 255.0844).

(E)-3-(Phenylthio)but-2-enal (115b).

To a stirred solution of (Z)-3-(phenylthio)but-2-enal 115a (295 mg, 1.65 mmol, 1.0 equiv) in dry CH₂Cl₂ (24 mL) at room temperature, was added DBU (247 µL, 1.65 mmol, 1.0 equiv). The reaction was stirred at room temperature for 2 h and then glacial acetic acid (94.6 µL, 1.65 mmol, 1.0 equiv) was added. The organic layer was washed with saturated aqueous NaHCO₃ solution (2 x 25 mL), water (2 x 25 mL), brine (2 x 25 mL), dried (MgSO₄) and concentrated under reduced pressure to give a brown oil. Purification by chromatography (10% Et₂O–petrol) gave (E)-3-(phenylthio)but-2-enal 115b (106 mg, 36%) as an orange oil; Rf 0.24 (30% Et₂O–petrol); νmax (neat) 1657, 1592, 1581, 1155, 758, 692 cm⁻¹; δH (CDCl₃, 400 MHz) 9.82 (1H, d, J 7.5 Hz, H-1), 7.53–7.43 (5H, m, PhS), 5.51 (1H, dq, J 7.5 & 1.0 Hz, H-2), 2.48 (3H, d, J 1.0 Hz, H-4); δC (CDCl₃, 101 MHz) 187.3 (C-1), 165.6 (C-3), 135.6 (ortho PhS), 130.4 (para PhS), 130.0 (meta PhS), 128.3 (ipso PhS), 122.1 (C-2), 18.5 (C-4); m/z (CI) 357 [2M+H]⁺, 196 [M+NH₄]⁺, 179 [MH]⁺ (Found: [MH]⁺, 179.0531. C₁₀H₁₀OS requires [MH]⁺, 179.0531).
(E)-3-(Phenylthio)pent-2-enal (116b).

\[
\begin{align*}
\text{116a} & \quad \rightarrow \\
\text{116b}
\end{align*}
\]

To a stirred solution of (Z)-3-(phenylthio)pent-2-enal 116a (670 mg, 3.48 mmol, 1.0 equiv) in dry CH₂Cl₂ (50 mL) at room temperature, was added DBU (521 µL, 3.48 mmol, 1.0 equiv). The reaction was stirred at room temperature for 15 h and then glacial acetic acid (199 µL, 3.48 mmol, 1.0 equiv) was added. The organic layer was washed with saturated aqueous NaHCO₃ solution (2 x 50 mL), water (2 x 50 mL), brine (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure to give an orange oil. Purification by chromatography (10% Et₂O–petrol) gave (E)-3-(phenylthio)pent-2-enal 116b (328 mg, 49%) as an orange oil; Rf 0.37 (30% Et₂O–petrol); νmax (neat) 2976, 1659, 1575, 1153, 751, 692 cm⁻¹; δH (CDCl₃, 400 MHz) 9.82 (1H, d, J 7.5 Hz, H-1), 7.52–7.43 (5H, m, PhS), 5.41 (1H, d, J 7.5 Hz, H-2), 2.85 (2H, q, J 7.5 Hz, H-4), 1.41 (3H, t, J 7.5 Hz, H-5); δC (CDCl₃, 101 MHz) 187.0 (C-1), 172.7 (C-3), 135.6 (ortho PhS), 130.3 (para PhS), 130.0 (meta PhS), 128.3 (ipso PhS), 121.2 (C-2), 26.2 (C-4), 16.0 (C-5); m/z (CI) 385 [2M+H]+, 210 [M+NH₄]+, 193 [MH]+ (Found: [MH]+, 193.0678. C₁₁H₁₂OS requires [MH]+, 193.0687).
(E)-4-Phenyl-3-(phenylthio)but-2-enal (117b).

To a stirred solution of (Z)-4-phenyl-3-(phenylthio)but-2-enal 117a (1.35 g, 5.31 mmol, 1.0 equiv) in dry CH₂Cl₂ (75 mL) at room temperature, was added DBU (793 µL, 5.31 mmol, 1.0 equiv). The reaction was stirred at room temperature for 1 h and then glacial acetic acid (304 µL, 5.31 mmol, 1.0 equiv) was added. The organic layer was washed with saturated aqueous NaHCO₃ solution (2 x 75 mL), water (2 x 75 mL), brine (2 x 75 mL), dried (MgSO₄) and concentrated under reduced pressure to give an orange oil. Purification by chromatography (10% Et₂O–petrol) gave (E)-4-phenyl-3-(phenylthio)but-2-enal 117b (585 mg, 43%) as an orange oil; Rₚ 0.30 (30% Et₂O–petrol); ʋ_max (neat) 1657, 1579, 1142, 750, 692 cm⁻¹; δ_H (CDCl₃, 400 MHz) 9.91 (1H, d, J 7.5 Hz, H-1), 7.50–7.44 (5H, m, PhS & Ph), 7.41–7.32 (5H, m, PhS & Ph), 5.61 (1H, d, J 7.5 Hz, H-2), 4.18 (2H, s, H-4); δ_C (CDCl₃, 101 MHz) 187.3 (C-1), 168.1 (C-3), 137.2 (ipso PhS), 135.6 (ortho PhS), 134.4 (ipso Ph), 130.4 (para PhS), 130.0 (meta PhS), 129.0 (ortho Ph), 128.6 (meta Ph), 127.3 (para Ph), 122.9 (C-2), 37.9 (C-4); m/z (CI) 509 [2M+H]⁺, 272 [M+NH₄]⁺, 255 [MH]⁺ (Found: [MH]⁺, 255.0838. C₁₆H₁₄OS requires [MH]⁺, 255.0844).
(E)-1-tert-Butyldimethylsilyloxy-3-(phenylthio)-1,3-butadiene (119).

To a stirred solution of (E)-3-(phenylthio)but-2-enal 115b (140 mg, 0.785 mmol, 1.0 equiv) in dry Et₂O (39 mL) at 0 ºC, was added dry triethylamine (153 µL, 1.10 mmol, 1.4 equiv). After 5 min, tert-butylidemethylsilyl trifluoromethanesulfonate (216 µL, 0.942 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred for 30 min at 0 ºC. The reaction mixture was slowly allowed to warm to room temperature over a period of 30 min. Additional triethylamine (0.75 mL) was added to the biphasic reaction mixture. Then, concentration under reduced pressure gave a red-orange residue. Purification by chromatography on base washed silica (5% Et₂O–petrol) gave (E)-1-tert-butyldimethylsilyloxy-3-(phenylthio)-1,3-butadiene 119 (226 mg, 69% purity determined by ¹H-NMR, 68%) as a pale yellow oil; Rf 0.77 (10% Et₂O–petrol); v_{max} (neat) 2956, 2938, 2858, 1643, 1255, 1174, 839, 785, 740, 690, 677 cm⁻¹; δ_{H} (CDCl₃, 400 MHz) 7.39 (2H, dd, J 7.0 & 1.5 Hz, ortho PhS), 7.30 (2H, dd, J 7.5 & 7.0 Hz, meta PhS), 5.35 (1H, s, H-4), 5.13 (1H, s, H-4), 0.86 (9H, s, SiC(CH₃)₃ TBSO), -5.4 (Si(CH₃)₂ TBSO); m/z (CI) 475, 307, 293 [MH]⁺, 235 [M–t-Bu]⁺, 183 [M–SPh]⁺.
(1E,3Z)-1-tert-Butyldimethylsilyloxy-3-(phenylthio)-1,3-pentadiene (120).

![Chemical Structure](image)

To a stirred solution of (E)-3-(phenylthio)pent-2-enal 116b (107 mg, 0.556 mmol, 1.0 equiv) in dry Et$_2$O (28 mL) at 0 ºC, was added dry triethylamine (108 µL, 0.779 mmol, 1.4 equiv). After 5 min, tert-butyltrimethylsilyl trifluoromethanesulfonate (153 µL, 0.668 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred for 30 min at 0 ºC. The reaction mixture was slowly allowed to warm to room temperature over a period of 30 min. Additional triethylamine (0.5 mL) was added to the biphasic reaction mixture. Then, concentration under reduced pressure gave a red-orange residue. Purification by chromatography on base washed silica (5% Et$_2$O–petrol) gave (1E,3Z)-1-tert-butyldimethylsilyloxy-3-(phenylthio)-1,3-pentadiene 120 (185 mg, 70% purity determined by $^1$H-NMR, 76%) as a yellow oil; R$_f$ 0.76 (10% Et$_2$O–petrol); $\nu_{\text{max}}$ (neat) 2955, 2930, 2858, 1644, 1255, 1203, 1161, 839, 783, 738, 689 cm$^{-1}$; $\delta_{\text{H}}$ (CDCl$_3$, 400 MHz) 7.26–7.21 (5H, m, PhS), 6.83 (1H, d, $J$ 11.5 Hz, H-1), 6.09 (1H, q, $J$ 7.0 Hz, H-4), 5.83 (1H, d, $J$ 11.5 Hz, H-2), 1.96 (3H, d, $J$ 7.0 Hz, H-5), 0.83 (9H, s, SiC(CH$_3$)$_3$ TBSO), 0.02 (6H, s, Si(CH$_3$)$_2$ TBSO); $\delta_{\text{C}}$ (CDCl$_3$, 101 MHz) 144.9 (C-1), 136.5 (ipso PhS), 132.4 (C-4), 128.8 (C-3), 128.6 (ortho PhS), 127.3 (meta PhS), 125.1 (para PhS), 113.9 (C-2), 25.6 (SiC(CH$_3$)$_3$ TBSO), 18.2 (SiC(CH$_3$)$_3$ TBSO), 15.7 (C-5), −5.4 (Si(CH$_3$)$_2$ TBSO); $m/z$ (CI) 307 [MH]$^+$, 197 [M–SPh]$^+$, 191 [M–TBS]$^+$, 132, 90.

101
(1E,3Z)-1-tert-Butyldimethylsilyloxy-4-phenyl-3-(phenylthio)-1,3-butadiene (121).

\[
\begin{align*}
\text{O} & \quad \text{SPh} \\
\text{Ph} & \quad \text{TBSO} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

To a stirred solution of (E)-4-phenyl-3-(phenylthio)but-2-enal 117b (110 mg, 0.432 mmol, 1.0 equiv) in dry \(\text{Et}_2\text{O}\) (22 mL) at 0 °C, was added dry triethylamine (84.2 µL, 0.605 mmol, 1.4 equiv). After 5 min, tert-butyldimethylsilyl trifluoromethanesulfonate (119 µL, 0.519 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was slowly allowed to warm to room temperature over a period of 1 h. Additional triethylamine (0.4 mL) was added to the biphasic reaction mixture. Then, concentration under reduced pressure gave a red-orange residue. Purification by chromatography on base washed silica (5% \(\text{Et}_2\text{O}–\text{petrol}\)) gave (1E,3Z)-1-tert-butyldimethylsilyloxy-4-phenyl-3-(phenylthio)-1,3-butadiene 121 (174 mg, 63% purity determined by \(^1\text{H}-\text{NMR}, 69\%\)) as a yellow oil; \(R_f\) 0.65 (10% \(\text{Et}_2\text{O}–\text{petrol}\)); \(v_{\text{max}}\) (neat) 2955, 2930, 2857, 1637, 1255, 1133, 839, 783, 690 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.64 (2H, d, \(J\) 7.0 Hz, ortho PhS), 7.38–7.24 (7H, m, PhS & Ph), 7.13 (1H, tt, \(J\) 7.0 & 1.5 Hz, para PhS), 6.96 (1H, d, \(J\) 11.5 Hz, H-1), 6.92 (1H, s, H-4), 5.93 (1H, d, \(J\) 11.5 Hz, H-2), 0.83 (9H, s, Si(CH\(_3\))\(_3\) TBSO), 0.03 (6H, s, Si(CH\(_3\))\(_2\) TBSO); \(\delta_C\) (CDCl\(_3\), 101 MHz) 147.3 (C-1), 136.7 (ipso Ph), 136.3 (ipso PhS), 134.0 (C-4), 129.6 (ortho PhS), 128.9 (meta PhS), 128.6 (C-3), 128.0 (meta Ph), 127.9 (ortho Ph), 127.3 (para Ph), 125.5 (para PhS), 114.5 (C-2), 25.5 (Si(CH\(_3\))\(_3\) TBSO), 18.2 (Si(CH\(_3\))\(_3\) TBSO), −5.4 (Si(CH\(_3\))\(_2\) TBSO); \(m/z\) (Cl) 369 [MH]\(^+\), 259 [M–SPh]\(^+\), 132, 90.
trans-2-Phenylcyclohexanol (123).\textsuperscript{65}

\[
\begin{array}{c}
\text{C} \quad \text{O} \\
\text{Ph} \\
\text{123}
\end{array}
\]

To stirred magnesium turnings (2.19 g, 90.2 mg atom\textsuperscript{−1}, 1.5 equiv) at room temperature was added a solution of bromobenzene (14.6 g, 93.2 mmol, 1.6 equiv) in dry THF (20 mL) dropwise over a period of 60 min. The resulting Grignard solution was stirred at room temperature for 30 min and then cuprous iodide (1.77 g, 9.32 mmol, 0.16 equiv) was added. The mixture was cooled to −30 °C and then a solution of cyclohexene oxide (5.90 g, 60.1 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise over a period of 30 min. After the addition was complete, the reaction mixture was warmed slowly to 0 °C and stirred for 2 h. The mixture was quenched by being poured into cold saturated aqueous NH\textsubscript{4}Cl solution (70 mL). The organic layer was washed with saturated aqueous NH\textsubscript{4}Cl solution (3 x 25 mL). Then, the combined aqueous layers were extracted with Et\textsubscript{2}O (3 x 100 mL). The combined organic layers were dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to give a cream coloured solid. Purification by recrystallisation from \textit{n}-pentane gave trans-2-phenylcyclohexanol \textbf{123} (6.05 g, 57\%) as white needles; mp 56.0 °C (\textit{n}-pentane) [lit.\textsuperscript{65} mp 56.5–57.0 °C (pentane)]; R\textsubscript{f} 0.43 (30% EtOAc–petrol); \nu_{\text{max}} (film) 3293, 2930, 1445, 1060, 1050, 745, 696 cm\textsuperscript{−1}; \delta\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 7.39–7.25 (5H, m, Ph), 3.70 (1H, td, \textit{J} 10.0 & 4.5 Hz, H-1), 2.64 (1H, ddd, \textit{J} 12.5, 10.0 & 3.5 Hz, H-2), 2.17–2.14 (1H, m, H-3 & H-6), 1.91–1.88 (2H, m, H-3 & H-6), 1.81–1.78 (1H, m, H-3 & H-6), 1.62–1.31 (4H, m, H-4 & H-5); \delta\textsubscript{C} (CDCl\textsubscript{3}, 101 MHz) 143.2 (ipso Ph), 128.8 (meta Ph), 127.9 (ortho Ph), 126.9 (para Ph), 74.4 (C-1), 53.2 (C-2), 34.4 (C-6), 33.3 (C-3), 26.1 (C-4), 25.1 (C-5); \textit{m/z} (Cl) 370 [2M+NH\textsubscript{4}]\textsuperscript{+}, 266, 194 [M+NH\textsubscript{4}]\textsuperscript{+}, 176 [M]\textsuperscript{+}, 158, 130. Data in agreement with previous reported literature values.\textsuperscript{65}
**trans-2-Phenylcyclohexyl bromoacetate (124)**

A stirred mixture of *trans*-2-phenylcyclohexanol 123 (5.00 g, 28.3 mmol, 1.0 equiv), 1-bromoacetic acid (9.80 g, 70.9 mmol, 2.5 equiv) and *p*-toluenesulfonic acid monohydrate (162 mg, 0.851 mmol, 0.03 equiv) in benzene (75 mL) was heated under reflux with azeotropic removal of water for 16 h. Then, the mixture was cooled to room temperature and poured into cold saturated aqueous NaHCO₃ solution (150 mL). The aqueous layer was extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with brine (2 x 200 mL), dried (MgSO₄) and concentrated under reduced pressure to give crude *trans*-2-phenylcyclohexyl bromoacetate 124 (8.15 g, 97%) as a pale yellow oil; R$_f$ 0.68 (30% EtOAc–petrol); ν$_{max}$ (neat) 2935, 1732, 1278, 1167, 1013, 756, 700 cm$^{-1}$; δ$_{H}$ (CDCl₃, 400 MHz) 7.32–7.21 (5H, m, Ph), 5.05 (1H, td, J 10.5 & 4.5 Hz, H-1), 3.59 (1H, d, J 12.5 Hz, CH$_2$), 3.53 (1H, d, J 12.5 Hz, CH$_2$), 2.73 (1H, ddd, J 12.5, 10.5 & 4.0 Hz, H-2), 2.23–2.15 (1H, m, H-3 & H-6), 2.00–1.91 (2H, m, H-3 & H-6), 1.87–1.81 (1H, m, H-3 & H-6), 1.66–1.35 (4H, m, H-4 & H-5); δ$_{C}$ (CDCl₃, 101 MHz) 166.5 (C=O), 142.5 (ipso Ph), 128.4 (meta Ph), 127.5 (ortho Ph), 126.6 (para Ph), 78.2 (C-1), 49.6 (C-2), 33.8 (C-6), 32.0 (C-3), 26.0 (CH$_2$), 25.7 (C-4), 24.7 (C-5); m/z (Cl) 614, 612, 610 [2M+NH$_4$]$^+$, 474, 472, 316, 314 [M+NH$_4$]$^+$, 176 [M–COCH$_2$]$^{79}$Br$^+$, 158 [M–OCOCCH$_2$]$^{81}$Br$^+$, 143, 130. Data in agreement with previous reported literature values.
trans-2-Phenylcyclohexyl (nitrooxy)acetate (125).\textsuperscript{65}

![Structural formula](image)

To a stirred solution of trans-2-phenylcyclohexyl bromoacetate 124 (2.00 g, 6.73 mmol, 1.0 equiv) in dry acetonitrile (30 mL), was added silver nitrate (3.43 g, 20.2 mmol, 3.0 equiv). The mixture was stirred at room temperature for 72 h and then concentrated under reduced pressure to give a grey solid suspended in a yellow oil, which was extracted with Et\(_2\)O (30 mL). The grey solid silver bromide was removed and washed with Et\(_2\)O (3 x 5 mL). Then, the combined organic layers were washed with water (2 x 30 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (10% EtOAc–petrol) gave trans-2-phenylcyclohexyl (nitrooxy)acetate 125 (1.70 g, 90%) as white fine needles; mp 51.0–52.0 °C (Et\(_2\)O); R\(_f\) 0.36 (10% EtOAc–petrol); \(\nu_{\text{max}}\) (film) 1750, 1292, 1231, 1065, 848, 752, 700 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.33–7.18 (5H, m, Ph), 5.11 (1H, td, \(J\) 11.0 & 4.5 Hz, H-1), 4.67 (1H, d, \(J\) 17.0 Hz, CH\(_2\)), 4.52 (1H, d, \(J\) 17.0 Hz, CH\(_2\)), 2.72 (1H, ddd, \(J\) 12.5, 11.0 & 3.5 Hz, H-2), 2.23–2.14 (1H, m, H-3), 2.00–1.91 (2H, m, H-5 & H-6), 1.85–1.81 (1H, m, H-4), 1.66–1.33 (4H, m, H-3, H-4, H-5 & H-6); \(\delta_C\) (CDCl\(_3\), 101 MHz) 165.1 (C=O), 142.3 (ipso Ph), 128.5 (meta Ph), 127.3 (ortho Ph), 126.8 (para Ph), 78.4 (C-1), 66.9 (CH\(_2\)), 49.6 (C-2), 33.7 (C-6), 32.1 (C-3), 25.6 (C-4), 24.7 (C-5); \(m/z\) (Cl) 297 [M+NH\(_4\)]\(^+\), 250, 158, 130, 108. Data in agreement with previous reported literature values.\textsuperscript{65}
**trans-2-Phenylcyclohexyl glyoxylate (126) and trans-2-phenylcyclohexyl 2,2-dihydroxyacetate (127).**

A mixture of **trans-2-phenylcyclohexyl (nitrooxy)acetate 125** (3.00 g, 10.7 mmol, 1.0 equiv) and anhydrous sodium acetate (881 mg, 10.7 mmol, 1.0 equiv) in dry DMSO (40 mL), was stirred at room temperature for 2 h. Then, the reaction mixture was poured into ice-brine solution (50 mL). The solution was extracted with Et₂O (5 x 100 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution (400 mL), water (400 mL), dried (MgSO₄) and concentrated under reduced pressure to give an equilibrium mixture of **trans-2-phenylcyclohexyl glyoxylate 126** and **trans-2-phenylcyclohexyl 2,2-dihydroxyacetate 127** (2.19 g, 88%) as a white amorphous solid; mp 89.0–91.0 °C (Et₂O); Rₓ 0.40 (50% EtOAc–petrol); νₘₐₓ (film) 3354, 1743, 1230, 1087, 753, 699 cm⁻¹; δₓ (CDCl₃, 400 MHz) 9.16 (1H, s, CHO 126), 7.33–7.27 (2H, m, meta Ph), 7.24–7.21 (3H, m, ortho Ph & para Ph), 5.17 (1H, ddd, J 11.0, 10.5 & 4.5 Hz, H-1 126), 5.09 (1H, ddd, J 11.0, 10.5 & 4.5 Hz, H-1 127), 4.94 (1H, br s, CH(OH)₂ 127), 2.83 (1H, ddd, J 12.5, 11.0 & 4.0 Hz, H-2 126), 2.76 (1H, ddd, J 12.5, 11.0 & 4.0 Hz, H-2 127), 2.23–2.14 (1H, m, H-3 & H-6), 2.02–1.92 (2H, m, H-3 & H-6), 1.87–1.83 (1H, m, H-3 & H-6), 1.69–1.36 (4H, m, H-4 & H-5); δₓ (CDCl₃, 101 MHz) 183.9 (CHO 126), 158.5 (C=O), 142.3 (ipso Ph 127), 142.0 (ipso Ph 126), 128.5 (ortho Ph), 127.5 (meta Ph), 126.9 (para Ph), 86.8 (CH(OH)₂ 127), 79.2 (C-1 126), 78.6 (C-1 127), 49.9 (C-2 127), 49.5 (C-2 126), 33.5 (C-6), 31.9 (C-3), 25.6 (C-4), 24.7 (C-5); m/z (Cl) 250 [2M+NH₄]⁺/[M]⁺, 232 [M]⁺/[M–H₂O]⁺, 194, 176, 158, 108.
trans-2-Phenylcyclohexyl acrylate (128).

![Chemical Structure]

To a stirred solution of trans-2-phenylcyclohexanol 123 (2.00 g, 11.3 mmol, 1.0 equiv) and DMAP (194 mg, 1.59 mmol, 0.14 equiv) in dry CH$_2$Cl$_2$ (12 mL) at 0 °C, was added triethylamine (3.15 mL, 22.7 mmol, 2.0 equiv). Then, acryloyl chloride (1.84 mL, 22.7 mmol, 2.0 equiv) was added dropwise to the reaction mixture over a period of 15 min. The reaction mixture was stirred at 0 °C for 2.5 h, before being quenched with water (6 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 3 mL) and the combined organic layers were concentrated to give an orange residue. The residue was dissolved in Et$_2$O (6 mL) and washed with water (6 mL). The aqueous layer was extracted with Et$_2$O (3 x 6 mL) and then the combined organic layers were dried (MgSO$_4$) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (10% EtOAc–petrol) gave trans-2-phenylcyclohexyl acrylate 128 (1.31 g, 50%) as a colourless oil; R$_f$ 0.74 (50% EtOAc–petrol); $\nu_{\text{max}}$ (neat) 3030, 2935, 2859, 1720, 1636, 1620, 1194, 808, 756, 700 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.30–7.27 (2H, m, meta Ph), 7.21–7.17 (3H, m, ortho & para Ph), 6.18 (1H, dd, $J$ 17.0 & 1.5 Hz, trans CH=CH$_2$), 5.89 (1H, dd, $J$ 17.0 & 10.5 Hz, CH=CH$_2$), 5.65 (1H, dd, $J$ 10.5 & 1.5 Hz, cis CH=CH$_2$), 5.06 (1H, td, $J$ 11.0 & 4.5 Hz, H-1), 2.74 (1H, ddd, $J$ 12.5, 11.0 & 4.0 Hz, H-2), 2.23–2.18 (1H, m, H-3), 2.01–1.80 (3H, m, H-4, H-5 & H-6), 1.66–1.35 (4H, m, H-3, H-4, H-5 & H-6); $\delta_C$ (CDCl$_3$, 101 MHz) 165.5 (C=O), 143.1 (ipso Ph), 130.0 (CH$_2$), 128.7 (CH), 128.3 (meta Ph), 127.5 (ortho Ph), 126.4 (para Ph), 76.2 (C-1), 49.7 (C-2), 33.9 (C-6), 32.3 (C-3), 25.8 (C-4), 24.8 (C-5); $m/z$ (CI) 248 [M$^+$NH$_4^+$], 231 [MH$^+$], 176, 158 (Found: [MH$^+$], 231.1384. C$_{15}$H$_{18}$O$_2$ requires [MH$^+$], 231.1385) (Found: C, 78.15; H, 7.87%. C$_{15}$H$_{18}$O$_2$ requires C, 78.23; H, 7.88%).
**N-Sulfinyl-p-toluenesulfonamide (130).**

\[ \text{TsNH}_2 + \text{SOCl}_2 \rightarrow \text{TsN=S=O} \]

A stirred mixture of \( p \)-toluenesulfonamide (1.00 g, 5.84 mmol, 1.0 equiv) and thionyl chloride (1.80 mL, 24.7 mmol, 4.23 equiv) was heated under reflux for 3 d. Then, cooled to room temperature and concentrated under reduced pressure to remove the unreacted thionyl chloride. Further residual traces of thionyl chloride were removed by entrainment with benzene (3 x 10 mL) to give a give dark orange semi-solid. Purification by Kugelrohr distillation gave \( N \)-sulfinyl-\( p \)-toluenesulfonamide 130 (235 mg, 19%) as a yellow solid; bp 150 °C (3.0 mmHg) [lit.\(^{144}\) bp 130–140 °C (0.06 mmHg)]; mp 63.0 °C [lit.\(^{144}\) mp 47–51 °C]; \( R_f \) 0.70 (50% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 1373, 1188, 1081, 810 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\), 400 MHz) 7.96 (2H, d, \( J \) 8.5 Hz, ortho Ts), 7.44 (2H, d, \( J \) 8.5 Hz, meta Ts), 2.52 (3H, s, CH\(_3\)); \( \delta_C \) (CDCl\(_3\), 101 MHz) 146.8 (para Ts), 141.7 (ipso Ts), 130.3 (meta Ts), 127.1 (ortho Ts), 21.9 (CH\(_3\)); \( m/z \) (CI) 225, 208, 189, 174, 156, 139, 108, 52. Data in agreement with previous reported literature values.\(^{143,144}\)

**4-Methyl-\( N \)-(triphenylphosphoranylidene)benzenesulfonamide (131).**

\[ \text{O} \]

To a stirred solution of triphenylphosphine (1.31 g, 4.99 mmol, 1.0 equiv) and \( p \)-toluenesulfonamide (855 mg, 4.99 mmol, 1.0 equiv) in dry THF (10 mL) at 0 °C was added diethyl azodicarboxylate (787 µL, 4.99 mmol, 1.0 equiv) in dry THF (5 mL) dropwise. The reaction mixture was allowed to warm to room temperature. After 30 min of stirring at room temperature, the reaction mixture was concentrated under reduced pressure to give a yellow solid, which was washed with Et\(_2\)O (3 x 10 mL). Purification by recrystallisation from absolute EtOH gave 4-methyl-\( N \)-(triphenylphosphoranylidene)benzenesulfonamide 131 (1.84 g, 85%) as colourless.
square plates; mp 190.0 °C (absolute EtOH) [lit.\textsuperscript{69} mp 190 °C (EtOH)]; \(R_f\) 0.02 (50% Et\(_2\)O–petrol); \(v_{\text{max}}\) (film) 1438, 1268, 1141, 1113, 723, 692 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.77 (6H, ddd, \(J = 13.0, 7.0 \text{ & } 2.0 \text{ Hz, ortho PPh}_3\)), 7.60 (3H, td, \(J = 7.0 \text{ & } 2.0 \text{ Hz, para PPh}_3\)), 7.52 (2H, d, \(J = 8.0 \text{ Hz, ortho Ts}\)), 7.48 (6H, td, \(J = 7.0 \text{ & } 3.0 \text{ Hz, meta PPh}_3\)), 7.03 (2H, d, \(J = 8.0 \text{ Hz, meta Ts}\)), 2.33 (3H, s, CH\(_3\)); \(\delta_C{[H]}\) (CDCl\(_3\), 101 MHz) 143.4 (ipso Ts), 140.5 (para Ts), 133.2 (d, \(J = 11.0 \text{ Hz, meta PPh}_3\)), 132.7 (meta Ts), 128.8 (para PPh\(_3\)), 127.4 (d, \(J = 105.0 \text{ Hz, ipso PPh}_3\)), 125.7 (ortho Ts), 21.3 (CH\(_3\)); \(\delta_P{[H,C]}\) (CDCl\(_3\), 162 MHz) 14.4 (PPh\(_3\)); \(m/z\) (CI) 423 [MH\(^+\)], 251, 235, 194. Data in agreement with previous reported literature values.\textsuperscript{69}

4-Methyl-N-(tri-\textit{n}-butylphosphoranylidene)benzenesulfonamide (132).\textsuperscript{145}

![Chemical structure of 4-Methyl-N-(tri-\textit{n}-butylphosphoranylidene)benzenesulfonamide (132)](image)

To a stirred solution of tri-\textit{n}-butylphosphine (1.23 mL, 4.99 mmol, 1.0 equiv) and \(p\)-toluenesulfonamide (855 mg, 4.99 mmol, 1.0 equiv) in dry THF (10 mL) at 0 °C was added diethyl azodicarboxylate (787 µL, 4.99 mmol, 1.0 equiv) in dry THF (5 mL) dropwise. The reaction mixture was allowed to warm to room temperature. After 45 min, the reaction mixture was washed with aqueous NaOH solution (25 mL, 2.0 M), water (25 mL), brine (25 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a yellow semi-crystalline solid. Purification by recrystallisation from cyclohexane gave 4-methyl-N-(tri-\textit{n}-butylphosphoranylidene)benzenesulfonamide 132 (1.11 g, 60%) as white square plates; mp 52.0 °C (cyclohexane) [lit.\textsuperscript{145} mp 54 °C (cyclohexane)]; \(R_f\) 0.44 (50% EtOAc–petrol); \(v_{\text{max}}\) (film) 2958, 1257, 1138 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.82 (2H, d, \(J = 8.0 \text{ Hz, ortho Ts}\)), 7.22 (2H, d, \(J = 8.0 \text{ Hz, meta Ts}\)), 2.39 (3H, s, CH\(_3\) Ts), 1.96–1.89 (6H, m, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu), 1.53–1.34 (12H, m, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu), 0.91 (9H, t, \(J = 7.0 \text{ Hz, CH}_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu); \(\delta_C{[H]}\) (CDCl\(_3\), 101 MHz) 143.9 (ipso Ts), 140.8 (para Ts), 128.9 (meta Ts), 125.7 (ortho Ts), 24.9 (d, \(J = 62.5 \text{ Hz, CH}_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu), 24.0 (d, \(J = 16.0 \text{ Hz, CH}_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu), 23.5 (d, \(J = 4.0 \text{ Hz, CH}_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu), 21.4 (CH\(_3\) Ts), 13.5 (CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) Bu); \(\delta_P{[H,C]}\) (CDCl\(_3\), 162 MHz) 36.4 (PPh\(_3\)); \(m/z\) (CI) 388, 372 [MH\(^+\)], 218, 194 (Found: [MH\(^+\)],...
372.2126. C_{19}H_{34}NO_{2}PS requires [MH]^+, 372.2126). Data in agreement with previous reported literature values.\textsuperscript{145}

\textit{trans-2-Phenylcyclohexyl chloroacetate (138)\textsuperscript{146}}

![Structural diagram]

To a stirred solution of \textit{trans-2-phenylcyclohexanol} 123 (500 mg, 2.84 mmol, 1.0 equiv) and DMAP (3.18 mg, 0.028 mmol, 0.01 equiv) in dry CH\textsubscript{2}Cl\textsubscript{2} (9.5 mL) was added chloroacetyl chloride (287 µL, 3.60 mmol, 1.27 equiv) at room temperature. The reaction mixture was heated under reflux for 14.5 h. Then, the mixture was cooled to room temperature and washed with saturated aqueous NaHCO\textsubscript{3} solution (2 x 9.5 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to give crude \textit{trans-2-phenylcyclohexyl chloroacetate} 138 (619 mg, 96%) as a colourless oil; R\textsubscript{f} 0.73 (50% EtOAc–petrol); $\nu_{\text{max}}$ (neat) 2937, 1759, 1736, 1188, 757, 700 cm$^{-1}$; $\delta$\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 7.39–7.20 (5H, m, Ph), 5.06 (1H, td, $J$ 10.5 & 4.5 Hz, H-1), 3.82 (1H, d, $J$ 15.0 Hz, CH\textsubscript{2}), 3.71 (1H, d, $J$ 15.0 Hz, CH\textsubscript{2}), 2.72 (1H, ddd, $J$ 12.5, 11.0 & 3.5 Hz, H-2), 2.23–2.14 (1H, m, H-3), 2.00–1.90 (2H, m, H-4 & H-6), 1.87–1.80 (1H, m, H-4), 1.67–1.32 (4H, m, H-3, H-5 & H-6); $\delta$\textsubscript{C} (CDCl\textsubscript{3}, 101 MHz) 166.6 (C=O), 142.5 (ipso Ph), 128.4 (meta Ph), 127.5 (ortho Ph), 126.7 (para Ph), 78.3 (C-1), 49.6 (C-2), 33.6 (C-6), 32.1 (C-3), 26.0 (CH\textsubscript{2}), 25.7 (C-4), 24.7 (C-5); m/z (CI) 272, 270 [M+NH\textsubscript{4}]\textsuperscript{+}, 194, 176 [M–COCH\textsubscript{2}^{35}\text{Cl}+H]\textsuperscript{+}, 158, 130. Data in agreement with previous reported literature values.\textsuperscript{146}
**trans-2-Phenylcyclohexyl 2-(1,3-dioxoisindolin-2-yl)acetate (139).**

A stirred mixture of *trans*-2-phenylcyclohexyl chloroacetate 138 (500 mg, 1.98 mmol, 1.0 equiv) and potassium phthalimide (366 mg, 1.98 mmol, 1.0 equiv) in dry DMF (10 mL) was heated at 100 °C for 5 h. Then, the reaction mixture was cooled to room temperature, diluted with Et₂O (10 mL), filtered and the white filter cake was washed with Et₂O (10 mL). The filtrate was washed with water (3 x 10 mL), dried (MgSO₄) and concentrated under reduced pressure to give a cream coloured gum. Purification by chromatography (10% Et₂O–petrol) gave a white gum, which was dissolved in Et₂O (15 mL), washed with aqueous NaOH solution (15 mL, 2.0 M), water (15 mL), dried (MgSO₄), and concentrated under reduced pressure to give *trans*-2-phenylcyclohexyl 2-(1,3-dioxoisindolin-2-yl)acetate 139 (378 mg, 53%) as a colourless gum; *R*ₐ 0.64 (50% EtOAc–petrol); *ν*ₘₐₓ (neat) 1776, 1747, 1724, 1210, 956, 715, 700 cm⁻¹; *δ*<sub>H</sub> (CDCl₃, 400 MHz) 7.86 (2H, dd, *J* 5.5 & 3.0 Hz, Phth-5,8), 7.75 (2H, dd, *J* 5.5 & 3.0 Hz, Phth-6,7), 7.27–7.21 (3H, m, *meta* & *para* Ph), 7.12 (2H, dd, *J* 7.5 & 3.0 Hz, *ortho* Ph), 5.00 (1H, ddd, *J* 11.0, 10.5 & 4.5 Hz, H-1), 4.19 (1H, d, *J* 17.2 Hz, CH₂), 4.13 (1H, d, *J* 17.2 Hz, CH₂), 2.66 (1H, ddd, *J* 12.5, 11.0 & 3.5 Hz, H-2), 2.24–2.21 (1H, m, H-3), 1.96–1.87 (2H, m, H-5 & H-6), 1.81–1.78 (1H, m, H-5), 1.63–1.28 (4H, m, H-3, H-4 & H-6); *δ*<sub>C</sub> (CDCl₃, 101 MHz) 167.2 (C=O), 166.5 (C=O, Phth), 142.4 (*ipso* Ph), 134.1 (Phth-6,7), 132.0 (Phth-5,8), 128.4 (*meta* Ph), 127.2 (*ortho* Ph), 126.6 (*para* Ph), 123.5 (Phth-4,9), 78.0 (C-1), 49.5 (C-2), 38.9 (CH₂), 33.7 (C-6), 32.1 (C-3), 25.7 (C-4), 24.6 (C-5); *m/z* (Cl) 381 [M+NH₄]<sup>+</sup>, 252, 234, 176 [M–COCH₃NPhth+H]<sup>+</sup>, 158 (Found: [M+NH₄]<sup>+</sup>, 381.1784. C₂₂H₂₁NO₄ requires [M+NH₄]<sup>+</sup>, 381.1814).
To a stirred suspension of glycine (7.50 g, 100 mmol, 1.0 equiv) in water (20 mL) was added an aqueous NaOH solution (50 mL, 2.0 M) at room temperature. After 5 min, p-toluenesulfonyl chloride (26.7 g, 140 mmol, 1.4 equiv) was added portionwise to the colourless solution over a period of 30 min. Reaction mixture was stirred at rt for 3 h and then the unreacted p-toluenesulfonyl chloride was removed by filtration. The filtrate was acidified with an aqueous HCl solution (45 ml, 2.0 M) to pH 2 at 0 °C. The solution was stirred at rt for 30 min until most of the N-tosyl glycine had precipitated out of solution. Then, the white solid precipitate was isolated by filtration under reduced pressure, washed with water (2 x 20 mL) and dried in a vacuum desiccator to give N-tosylglycine 141 (9.11 g, 40%) as a white amorphous solid; mp 131.0–133.0 °C (water) [lit.\textsuperscript{74} mp 147 °C]; R\textsubscript{f} 0.22 (10% MeOH–CH\textsubscript{2}Cl\textsubscript{2}); ν\textsubscript{max} (film) 3269, 1719, 1335, 1158 cm\textsuperscript{-1}; δ\textsubscript{H} (D\textsuperscript{6}-Acetone, 400 MHz) 7.79 (2H, d, J \textasciitilde 8.0 Hz, ortho Ts), 7.40 (2H, d, J \textasciitilde 8.0 Hz, meta Ts), 3.77 (2H, s, CH\textsubscript{2}), 2.43 (3H, s, CH\textsubscript{3} Ts); δ\textsubscript{C} (D\textsuperscript{6}-Acetone, 101 MHz) 169.4 (C=O), 143.1 (para Ts), 137.9 (ipso Ts), 129.5 (meta Ts), 127.0 (ortho Ts), 43.6 (CH\textsubscript{2}), 20.5 (CH\textsubscript{3} Ts); m/z (Cl) 476 [2M+NH\textsubscript{4}]\textsuperscript{+}, 305, 247 [M+NH\textsubscript{4}]\textsuperscript{+}, 230 [MH]\textsuperscript{+}, 201, 108. Data in agreement with previous reported literature values.\textsuperscript{74}
trans-2-Phenylcyclohexyl 2-(tosylamino)acetate (140).

\[ \text{Ph} \quad \text{O} \quad \text{NHTs} \]

\[ \text{HO} \quad \text{C} \quad \text{NHTs} \]

\[ \text{Ph} \quad \text{O} \quad \text{NHTs} \]

A stirred solution of trans-2-phenylcyclohexanol 123 (500 mg, 2.84 mmol, 1.0 equiv), N-tosylglycine 141 (650 mg, 2.84 mmol, 1.0 equiv) and p-toluenesulfonic acid monohydrate (54.0 mg, 0.284 mmol, 0.1 equiv) in benzene (14 mL) was heated under reflux with azeotropic removal of water for 22 h. Concentrated under reduced pressure to give a pale yellow solid residue, which was dissolved in EtOAc (10 mL) and washed with water (2 x 10 mL). Combined aqueous layers were extracted with EtOAc (2 x 10 mL). The combined organic fractions were washed with brine (20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to give a pale yellow solid. Purification by recrystallisation from 50% EtOAc–petrol gave trans-2-phenylcyclohexyl 2-(tosylamino)acetate 140 (821 mg, 75%) as a white amorphous solid; mp 92.0–93.0 °C (petrol); R\textsubscript{f} 0.26 (30% EtOAc–petrol); \( v \)\textsubscript{max} (film) 3284, 2935, 1744, 1336, 701, 662 cm\(^{-1}\); \( \delta \)\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 7.65 (2H, d, \( J \) 8.0 Hz, ortho Ts), 7.29 (2H, d, \( J \) 8.0 Hz, meta Ts), 7.26 (2H, dd, \( J \) 8.0 & 7.0 Hz, meta Ph), 7.19 (1H, tt, \( J \) 7.0 & 1.0 Hz, para Ph), 7.12 (2H, dd, \( J \) 8.0 & 1.0 Hz, ortho Ph), 4.88 (1H, ddd, \( J \) 11.0, 10.5 & 4.5 Hz, H-1), 4.78 (1H, br t, \( J \) 5.0 Hz, NH), 3.58 (1H, dd, \( J \) 17.5 & 5.0 Hz, CH\textsubscript{2}), 3.39 (1H, dd, \( J \) 17.5 & 5.0 Hz, CH\textsubscript{2}), 2.62 (1H, ddd, \( J \) 12.5, 11.0 & 3.5 Hz, H-2), 2.45 (3H, s, CH\textsubscript{3} Ts), 1.98–1.92 (2H, m, H-3), 1.87–1.78 (2H, m, H-5), 1.62–1.51 (2H, m, H-6), 1.48–1.29 (2H, m, H-4); \( \delta \)\textsubscript{C} (CDCl\textsubscript{3}, 101 MHz) 168.0 (C=O), 143.7 (ipso Ph), 142.4 (para Ts), 136.1 (ipso Ts), 129.7 (meta Ts), 128.4 (meta Ph), 127.3 (ortho Ts), 127.2 (ortho Ph), 126.7 (para Ph), 78.2 (C-1), 49.5 (C-2), 43.9 (CH\textsubscript{2}), 33.3 (C-6), 32.0 (C-3), 25.6 (C-4), 24.6 (C-5), 21.6 (CH\textsubscript{3} Ts); \( m/z \) (CI) 405 [M+NH\textsubscript{4}]\textsuperscript{+}, 295, 247, 158 (Found: [M+NH\textsubscript{4}]\textsuperscript{+}, 405.1861. \( C_{21}H_{25}NO_4S \) requires [M+NH\textsubscript{4}]\textsuperscript{+}, 405.1848) (Found: C, 64.94; H, 6.45; N, 3.56%. \( C_{21}H_{25}NO_4S \) requires C, 65.09; H, 6.50; N, 3.61%).
(2S,3R,6R)-(trans-2-Phenylcyclohexyl) 6-(tert-butyldimethylsilyloxy)-3-phenyl-4-(phenylthio)-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (142).

A solution of trans-2-phenylcyclohexyl 2-tosyliminoacetate 104 (166 mg, 0.431 mmol, 1.7 equiv) was prepared in situ by heating under reflux the equilibrium mixture of trans-2-phenylcyclohexyl glyoxylate 126 and trans-2-phenylcyclohexyl 2,2-dihydroxyacetate 127 (100 mg, 0.431 mmol, 1.7 equiv) with 4-methyl-N-(tri-n-butylphosphoranylidene) benzenesulfonamide 132 (200 mg, 0.538 mmol, 1.25 equiv) in dry toluene (1.5 mL) for 40 h. To the freshly prepared solution of 104 at room temperature was added a solution of (1E,3Z)-1-tert-butyldimethylsilyloxy-4-phenyl-3-(phenylthio)-1,3-butadiene 121 (96 mg, 0.259 mmol, 1.0 equiv) in dry toluene (0.5 mL). The reaction mixture was heated under reflux for 3 h. Then, concentrated under reduced pressure to give an orange oil. Purification by chromatography (20% Et₂O–petrol) gave (2S,3R,6R)-(trans-2-phenylcyclohexyl) 6-(tert-butyldimethylsilyloxy)-3-phenyl-4-(phenylthio)-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate 142 (47 mg, 24%, 5:1 dr) as a yellow oil; Rf 0.29 (20% Et₂O–petrol); νmax (film) 2923, 1733, 1249, 1169, 754, 700 cm⁻¹; δH (CDCl₃, 400 MHz) 7.37–7.20 (15H, m, Ph, Ph’ & PhS), 6.89 (2H, d, J 8.5 Hz, ortho Ts), 6.83 (2H, d, J 8.5 Hz, meta Ts), 5.56 (1H, d, J 4.0 Hz, H-5), 5.19 (1H, ddd, J 11.0, 10.5 & 4.5 Hz, H-1’), 4.84 (1H, d, J 4.0 Hz, H-6), 4.56 (1H, br d, J 2.0 Hz, H-2), 3.98 (1H, br d, J 2.0 Hz, H-3), 2.94 (1H, ddd, J 13.0, 11.0 & 3.5 Hz, H-2’), 2.26 (3H, s, CH₃ Ts), 2.01–1.79 (4H, m, H-3’ & H-6’), 1.67–1.40 (4H, m, H-4’ & H-5’), 0.59 (9H, s, Si(CH₃)₂ TBSO), −0.06 (3H, s, Si(CH₃)₂ OTBS), −0.13 (3H, s, Si(CH₃)₂ OTBS); δC (CDCl₃, 101 MHz) 170.4 (C=O), 143.7 (C-4), 141.9 (ipso Ph’), 140.2 (para Ts), 137.8 (ipso Ph), 135.8 (ipso Ts), 135.4 (ipso PhS),
134.5 (ortho PhS), 129.2 (meta PhS), 129.1 (meta Ts), 128.8 (meta Ph), 128.7 (meta Ph’), 128.6 (ortho Ts), 128.4 (ortho Ph), 127.3 (para Ph’), 127.2 (ortho Ph’), 126.5 (para Ph), 126.2 (para PhS), 124.7 (C-5), 77.8 (C-1’), 66.2 (C-6), 49.3 (C-2), 47.0 (C-2’), 35.4 (C-3), 31.5 (C-6’), 25.7 (C-3’), 25.7 (Si(CH₃)₃ OTBS), 25.4 (CH₃ Ts), 24.6 (C-4’), 21.3 (C-5’), 17.6 (Si(CH₃)₃ OTBS), −4.8 (Si(CH₃)₂ OTBS), −4.9 (Si(CH₃)₂ OTBS); m/z (ESI) (Found: [M+Na]⁺, 776.2894. C₄₃H₅₁NO₅S₂Si requires [M+Na]⁺, 776.2876).

*p-Anisaldehyde dimethyl acetal (153).*¹⁴⁷

![p-Anisaldehyde dimethyl acetal (153)](image)

To a stirred colourless solution of *p*-anisaldehyde (8.74 mL, 72.0 mmol, 1.0 equiv) in dry CH₂Cl₂ (45 mL) at room temperature under an atmosphere of argon, was added trimethyl orthoformate (23.1 mL, 209 mmol, 2.9 equiv), followed by *p*-toluenesulfonic acid monohydrate (1.37 g, 7.20 mmol, 0.1 equiv). Purple solution observed at the end of addition. The reaction mixture was stirred at room temperature for 48 h. Then, concentration under reduced pressure gave a purple oil. Purification by reduced pressure distillation gave *p*-anisaldehyde dimethyl acetal *153* (13.1 g, quantitative) as a colourless oil; bp 120.0 °C (1.35 mmHg) [lit.⁸⁵ bp 120–121 °C (14 mmHg)]; R₆ 0.45 (50% EtOAc–iso-hexane); νmax (neat) 1613, 1511, 1246, 1170, 1099, 1049, 1033, 981, 911, 820 cm⁻¹; δH (CDCl₃, 400 MHz) 7.37 (2H, d, J 9.0 Hz, ortho Ar), 6.89 (2H, d, J 9.0 Hz, meta Ar), 5.35 (1H, s, CH(OMe)₂), 3.80 (3H, s, OMe), 3.31 (6H, s, CH(OMe)₂); δC (CDCl₃, 101 MHz) 159.7 (para Ar), 130.4 (ipso Ar), 127.9 (ortho Ar), 113.5 (meta Ar), 103.1 (CH(OMe)₂), 55.3 (CH(OMe)₂), 52.6 (OMe); m/z (CI) 204, 182 [M]+, 151 [M–OMe]+, 136. Data in agreement with previous reported literature values.¹⁴⁷
2-Iodo-4-methoxybenzaldehyde (154).\textsuperscript{84}

\[ \text{MeO} - \text{O} = \text{O} \]

\[ \text{OMe} \]

\[ \text{OMe} \]

\[ \text{OMe} \]

\begin{align*}
\text{To a stirred colourless solution of } p\text{-anisaldehyde dimethyl acetal 153 (3.00 g, 16.5 mmol, 1.0 equiv) in dry Et}_2\text{O (59 mL) at } -78 \degree \text{C under an atmosphere of argon was added tert-butyllithium (10.9 mL, 18.6 mmol, 1.13 equiv, 1.7 M in pentane) in one portion. Reaction mixture warmed to } -25 \degree \text{C and stirred for 3.5 h. Orange solution observed with fine yellow precipitate. Then, the reaction mixture was re-cooled to } -78 \degree \text{C and a solution of iodine (4.18 g, 16.5 mmol, 1.0 equiv) in dry Et}_2\text{O (44 mL) was added dropwise over a period of 30 min. Reaction mixture slowly allowed to warm up to room temperature over a period of 16 h. Reaction mixture quenched with } i\text{-PrOH (5.0 mL) and then poured into ice/water (75g/75 mL) mixture. Acidified with aqueous HCl solution (75 mL, 2.0 M) and extracted with Et}_2\text{O (2 x 150 mL). The combined organic extracts were concentrated under reduced pressure to half the original volume and treated again with aqueous HCl solution (150 mL, 2.0 M). Stirred at room temperature for 4.5 h. Layers separated and organic layer washed with water (75 mL), saturated aqueous NaHCO}_3\text{ solution (2 x 75 mL), water (75 mL), brine (2 x 75 mL), dried (Na}_2\text{SO}_4\text{) and concentrated under reduced pressure to give a brown residue. Purification by chromatography (1→6% EtOAc–iso-hexane) gave 2-iodo-4-methoxybenzaldehyde 154 (1.80 g, 42%) as white needles; mp 113.0 \degree \text{C (EtOAc)} \text{[lit.}\textsuperscript{84} \text{mp 105–107 } \degree \text{C (CH}_2\text{Cl}_2\text{)]; R}_f \text{ 0.24 (5% EtOAc–iso-hexane); } \nu_{\text{max}} \text{ (neat) } 1661, 1579, 1558, 1235, 1018, 879, 858, 814 \text{ cm}^{-1}; \delta_{\text{H}} \text{ (CDCl}_3\text{, 400 MHz) 9.93 (1H, d, } J = 1.0 \text{ Hz, CHO), 7.85 (1H, d, } J = 8.5 \text{ Hz, H-6), 7.44 (1H, d, } J = 2.5 \text{ Hz, H-3), 6.99 (1H, ddd, } J = 8.5, 2.5 \text{ & 1.0 Hz, H-5), 3.88 (3H, s, OMe); \delta_{\text{C}} \text{ (CDCl}_3\text{, 101 MHz) 194.5 (CHO), 164.3 (C-4), 131.6 (C-6), 128.6 (C-1), 125.3 (C-3), 114.8 (C-5), 102.3 (C-2), 55.9 (OMe); m/z (CI) 280 [M+NH}_4^+, 263 [MH]^+, 154, 151, 137. Data in agreement with previous reported literature values.}\textsuperscript{84}}\]

116
2-Iodo-4-methoxy-1-vinylbenzene (155).

\[
\begin{align*}
\text{154} & \quad \text{I} & \quad \text{OMe} \\
\text{155} & \quad \text{I} & \quad \text{OMe}
\end{align*}
\]

To a stirred suspension of methyltriphenylphosphonium bromide (0.893 g, 2.50 mmol, 1.0 equiv) in dry THF (10.4 mL) at room temperature under an atmosphere of argon was added \textit{n}-butyllithium (3.12 mL, 2.5 mmol, 1.0 equiv, 0.80 M in hexanes) dropwise over a period of 5 min. At the end of addition a bright red-orange solution was observed. The reaction mixture was stirred at room temperature for 15 min, before the addition of a solution of 2-iodo-4-methoxybenzaldehyde \textbf{154} (0.655 g, 2.50 mmol, 1.0 equiv) in dry THF (10.4 mL). At the end of addition an orange solution was observed. After 16.5 h at room temperature, reaction mixture quenched with saturated aqueous \(\text{NH}_4\text{Cl}\) solution (6.5 mL) and then followed by the addition of water (6.5 mL). Layers separated and aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 \times 20 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated under reduced pressure to give an orange residue. Purification by chromatography (0→5% EtOAc–iso-hexane) gave 2-iodo-4-methoxy-1-vinylbenzene \textbf{155} (460 mg, 71%) as a colourless oil; \(\text{R}_f\), 0.59 (30% EtOAc–iso-hexane); \(\nu_{\text{max}}\) (neat) 1593, 1478, 1284, 1235, 1027, 1013, 981, 843, 812 \(\text{cm}^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.42 (1H, d, \(J\) 8.5 Hz, H-6), 7.36 (1H, d, \(J\) 2.5 Hz, H-3), 6.88 (1H, ddd, \(J\) 8.5, 2.5 & 0.5 Hz, H-5), 6.83 (1H, ddd, \(J\) 17.0, 11.0 & 0.5 Hz, \(HC=CH_2\)), 5.51 (1H, dd, \(J\) 17.0 & 1.0 Hz, \textit{trans} \(HC=CH_2\)), 5.20 (1H, dd, \(J\) 11.0 & 1.0 Hz, \textit{cis} \(HC=CH_2\)), 3.78 (3H, s, OMe); \(\delta_C\) (CDCl\(_3\), 101 MHz) 159.3 (C-4), 139.8 (HC=CH\(_2\)), 133.3 (C-1), 126.5 (C-6), 124.0 (C-3), 114.9 (HC=CH\(_2\)), 114.8 (C-5), 99.8 (C-2), 55.5 (OMe); \(m/z\) (CI) 538 [2M+NH\(_4\)]\(^+\), 521 [2M+H\(^+\)], 393 [2M–I]\(^+\), 302, 278 [M+NH\(_4\)]\(^+\), 261 [MH]\(^+\), 146, 133 [M–I]\(^+\), 118 (Found: [MH]\(^+\), 260.9781. \(\text{C}_9\text{H}_9\text{IO}\) requires [MH]\(^+\), 260.9776) (Found: C, 41.49; H, 3.58%. \(\text{C}_9\text{H}_9\text{IO}\) requires C, 41.56; H, 3.49%).
To a stirred yellow solution of AD-mix-β (1.90 g) in water (8.5 mL) and tert-butanol (2.1 mL) at 0 °C was added a solution of 2-iodo-4-methoxy-1-vinylbenzene 155 (400 mg, 1.54 mmol, 1.0 equiv) in tert-butanol (2.1 mL). The reaction mixture was quenched with saturated aqueous Na₂SO₃ solution (10 mL) and then extracted with CHCl₃ (3 x 40 mL). The combined organic extracts were washed with brine (60 mL), dried (MgSO₄) and concentrated under reduced pressure to give a white solid. Purification by chromatography (10→60% EtOAc–iso-hexane) gave (R)-1-(2-iodo-4-methoxyphenyl)ethane-1,2-diol 156 (325 mg, 72%, 97% ee by chiral HPLC, Chiralpak IC, 10% absolute EtOH–heptane, 1.0 mL/min) as a white amorphous solid; mp 83.0–85.0 °C (EtOAc); Rₙ 0.18 (50% EtOAc–iso-hexane); [α]D²⁰ −38.3 (c 0.120, CHCl₃); νmax (neat) 3256, 1596, 1232, 1082, 1017, 897, 855, 823, cm⁻¹; δH (CDCl₃, 400 MHz) 7.42 (1H, dd, J 8.5 & 0.5 Hz, H-6), 7.35 (1H, d, J 2.5 Hz, H-3), 6.94 (1H, dd, J 8.5 & 2.5 Hz, H-5), 4.99 (1H, ddd, J 8.0, 3.0 & 0.5 Hz, CHOH), 3.83 (1H, dd, J 11.5 & 3.0 Hz, CH₂OH), 3.79 (3H, s, OMe), 3.51 (1H, dd, J 11.5 & 8.0 Hz, CH₂OH); δC (CDCl₃, 101 MHz) 159.5 (C-4), 134.3 (C-1), 127.8 (C-6), 124.5 (C-3), 114.6 (C-5), 97.5 (C-2), 77.4 (CHOH), 66.6 (CH₂OH), 55.6 (OMe); m/z (CI) 606 [2M+NH₄]⁺, 588 [2M]⁺, 462 [2M–I]⁺, 329, 312 [M+NH₄]⁺, 294 [M]⁺, 277 [M–OH]⁺, 186, 168 [M–I]⁺, 154, 137 (Found: [M+NH₄]⁺, 312.0099. C₉H₁₁IO₃ requires [M+ NH₄]⁺, 312.0097) (Found: C, 36.66; H, 3.86%. C₉H₁₁IO₃ requires C, 36.76; H, 3.77%).
(R)-2-tert-Butyldiphenylsilyloxy-1-(2-iodo-4-methoxyphenyl)ethanol (152).

To a stirred colourless solution of (R)-1-(2-iodo-4-methoxyphenyl)ethane-1,2-diol 156 (100 mg, 0.340 mmol, 1.0 equiv) in dry THF (0.68 mL) at room temperature under an atmosphere of argon, was added tert-butyldiphenylsilyl chloride (0.106 mL, 0.408 mmol, 1.2 equiv), followed by imidazole (55.6 mg, 0.816 mmol, 2.4 equiv). Then, the cloudy white reaction mixture was heated at 40 °C for 3 h. Followed by concentration under reduced pressure to give an amorphous white solid, which was dissolved in water (1.5 mL) and extracted with CH$_2$Cl$_2$ (3 x 1.5 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure to give a colourless oil. Purification by chromatography (0→15% EtOAc–iso-hexane) gave (R)-2-tert-butyldiphenylsilyloxy-1-(2-iodo-4-methoxyphenyl)ethanol 152 (124 mg, 69%, 92% purity by LCMS) as a colourless gum; $R_f$ 0.54 (20% EtOAc–iso-hexane); $[\alpha]_D^{28} -28.2$ (c 0.078, CHCl$_3$); $\nu_{\text{max}}$ (neat) 3262, 1598, 1563, 1107, 1036, 821, 736 cm$^{-1}$; $\delta$ H (CDCl$_3$, 400 MHz) 7.73–7.34 (11H, m, 2 x Ph TBDPS & H-6), 7.26 (1H, d, $J$ 2.5 Hz, H-3), 6.89 (1H, dd, $J$ 8.5 & 2.5 Hz, H-5), 4.98 (1H, dd, $J$ 8.5 & 3.5 Hz, CHO$_2$), 3.88 (1H, dd, $J$ 10.5 & 3.5 Hz, CH$_2$OTBDPS), 3.75 (3H, s, OMe), 3.47 (1H, dd, $J$ 10.5 & 8.5 Hz, CH$_2$OTBDPS), 1.08 (9H, s, (C(CH$_3$)$_3$) TBDPS); $\delta$ C (CDCl$_3$, 101 MHz) 159.5 (C-4), 135.7 & 135.6 (ortho Ph), 134.1 (C-1), 133.0 & 132.9 (ipso Ph), 129.9 & 129.8 (para Ph), 128.1 (C-6), 127.9 & 127.8 (meta Ph), 124.2 (C-3), 114.4 (C-5), 97.4 (C-2), 77.1 (CH$_2$OTBDPS), 67.9 (CHO$_2$), 55.5 (OMe), 26.9 (C(CH$_3$)$_3$ TBDPS), 19.3 (C(CH$_3$)$_3$ TBDPS); $m/z$ (CI) 550 [M+NH$_4$]$^+$, 532 [M]$^+$, 515 [M–OH]$^+$, 424 [M–I+NH$_4$]$^+$, 406 [M–I+H]$^+$, 391 [M–OH–I+3H]$^+$, 327, 304, 216 (Found: [M+NH$_4$]$^+$, 550.1292. C$_{25}$H$_{29}$IO$_3$Si requires [M+ NH$_4$]$^+$, 550.1274).
To a stirred suspension of D-(-)-lyxose (5.00 g, 33.3 mmol, 1.0 equiv) in benzyl alcohol (25 mL) at room temperature was added acetyl chloride (1.00 mL, 14.0 mmol, 0.42 equiv). Then, the reaction mixture was heated at 50 °C. After 19 h, the brown solution observed was cooled to room temperature and poured slowly into Et₂O (50 mL) with stirring. Product was allowed to crystallise at rt over a period of 4 h and then overnight at 0 °C. Product isolated by filtration under reduced pressure and washed with Et₂O (3 x 25 mL) to give benzyl-α-D-lyxopyranoside 162 (7.18 g, 90%) as a fine white powder; mp 145.0 °C (Et₂O) [lit.\textsuperscript{148} mp 144 °C]; R\textsubscript{f} 0.51 (20% MeOH–CHCl\textsubscript{3}); [\textalpha]\textsubscript{D}\textsuperscript{18} +84.3 (c 0.70, MeOH) [lit.\textsuperscript{148} [\textalpha]\textsubscript{D}\textsuperscript{22} +83.0 (c 3.10, MeOH)]; \nu\textsubscript{max} (film) 3332, 2924, 2853, 1456, 1376, 1061, 737 cm\textsuperscript{-1}; \delta\textsubscript{H} (MeOD, 400 MHz) 7.37–7.28 (5H, m, OBn), 4.77 (1H, s, H-1), 4.74 (1H, d, J 12.0 Hz, CH\textsubscript{2} OBn), 4.52 (1H, d, J 12.0 Hz, CH\textsubscript{2} OBn), 3.86–3.81 (2H, m, H-2 & H-4), 3.73–3.68 (2H, m, H-3 & equatorial H-5), 3.52 (1H, t, J 10.0 Hz, axial H-5); \delta\textsubscript{C} (MeOD, 101 MHz) 137.6 (ipso OBn), 128.0 (meta OBn), 127.6 (ortho OBn), 127.4 (para OBn), 99.7 (C-1), 71.3 (C-3), 70.4 (C-2), 68.8 (CH\textsubscript{2} OBn), 67.1 (C-4), 62.9 (C-5); \textit{m/z} (CI) 498 [2M+NH\textsubscript{4}]\textsuperscript{+}, 258 [M+NH\textsubscript{4}]\textsuperscript{+}, 248, 240 [M]\textsuperscript{+}, 209, 150 [M–Bn+H]\textsuperscript{+}. Data in agreement with previous reported literature values.\textsuperscript{148}
To a stirred suspension of benzyl-α-D-lyxopyranoside 162 (7.00 g, 29.1 mmol, 1.0 equiv) and p-toluenesulfonic acid monohydrate (111 mg, 0.583 mmol, 0.02 equiv) in acetone (98 mL) at room temperature was added 2,2-dimethoxypropane (12.5 mL, 102 mmol, 3.5 equiv). The reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was diluted with hexane/Et$_2$O (1:1, 200 mL) and washed with saturated aqueous NaHCO$_3$ solution (3 x 50 mL). The combined aqueous layers were extracted with Et$_2$O (3 x 150 mL). Then, the combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (20% EtOAc–petrol) gave 1-O-benzyl-2,3-isopropylidene-α-D-lyxopyranoside 163 (7.71 g, 94%) as fine white needles; mp 66.0 °C (EtOAc) [lit.$^{148}$ mp 62 °C]; R$_f$ 0.20 (30% EtOAc–petrol); [α]$_D^{18}$ +86.0 (c 1.00, CH$_2$Cl$_2$) [lit.$^{148}$ [α]$_D^{22}$ +86.2 (c 3.10, CH$_2$Cl$_2$)]; $\nu_{\text{max}}$ (film) 3424, 1376, 1223, 1140, 1090, 1075, 998, 863, 732, 695 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.38–7.31 (5H, m, OBn), 4.86 (1H, d, $J$ 2.5 Hz, H-1), 4.84 (1H, d, $J$ 11.5 Hz, CH$_2$ OBn), 4.60 (1H, d, $J$ 11.5 Hz, CH$_2$ OBn), 4.28–4.26 (1H, m, H-3), 2.97 (1H, d, $J$ 7.5 Hz, OH), 1.48 (3H, s, C(CH$_3$)$_2$), 1.37 (3H, s, C(CH$_3$)$_2$); $\delta_C$ (CDCl$_3$, 101 MHz) 136.7 (ipso OBn), 128.6 (meta OBn), 128.2 (ortho OBn), 128.1 (para OBn), 109.5 (C(CH$_3$)$_2$), 97.3 (C-1), 76.1 (C-3), 74.4 (C-2), 69.8 (CH$_2$ OBn), 67.4 (C-4), 63.1 (C-5), 27.3 (C(CH$_3$)$_2$), 25.6 (C(CH$_3$)$_2$); $m/z$ (CI) 298 [M+NH$_4$]$^+$, 280 [M]$^+$, 263 [M–OH]$^+$, 240 [M–C(CH$_3$)$_2$+2H]$^+$, 190 [M–Bn+H]$^+$, 131, 108. Data in agreement with previous reported literature values.$^{148}$
To a stirred suspension of sodium hydride (146 mg, 6.06 mmol, 1.7 equiv, 60% dispersion in mineral oil) in dry DMF (6 mL) at 0 °C, was added a solution of 1-O-benzyl-2,3-isopropylidene-α-D-lyxopyranoside 163 (1.00 g, 3.57 mmol, 1.0 equiv) in dry DMF (6 mL) over a period of 15 min. The pale yellow suspension was stirred at 0 °C for 30 min. Then, allyl bromide (621 µL, 7.13 mmol, 2.0 equiv) was added dropwise over a period of 5 min. The reaction mixture was allowed to slowly warm up to room temperature. After 60 min, the reaction mixture was quenched by the dropwise addition of MeOH (2.0 mL). Concentration under reduced pressure gave a pale yellow residue, which was dissolved in CHCl₃ (15 mL) and washed with saturated aqueous NaHCO₃ solution (10 mL). The aqueous layer was extracted with CHCl₃ (2 x 5 mL). Then, the combined organic layers were washed with water (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (5% EtOAc–petrol) gave 4-O-allyl-1-O-benzyl-2,3-isopropylidene-α-D-lyxopyranoside 164 (1.09 g, 96%) as a colourless oil; Rₛ 0.48 (20% EtOAc–petrol); [α]D²⁰ +43.5 (c 0.115, CH₂Cl₂); vₘₐₓ (neat) 1374, 1243, 1220, 1140, 1076, 1057, 1012, 699 cm⁻¹; δH (CDCl₃, 400 MHz) 7.38–7.30 (5H, m, OBn), 5.94 (1H, dddd, J 17.0, 10.5, 6.0 & 5.5 Hz, CH=CH₂), 5.32 (1H, dq, J 17.0 & 1.0 Hz, trans CH=C₂H₃), 5.21 (1H, dq, J 10.5 & 1.0 Hz, cis CH=C₂H₃), 4.95 (1H, d, J 1.5 Hz, H-1), 4.78 (1H, d, J 12.0 Hz, CH₂ OBn), 4.54 (1H, d, J 12.0 Hz, CH₂ OBn), 4.25 (1H, dt, J 5.5 & 1.0 Hz, OCH₂CH=CH₂), 4.24–4.21 (1H, m, H-4), 4.17 (1H, dd, J 6.0 & 1.5 Hz, H-3), 4.13 (1H, dt, J 6.0 & 1.0 Hz, OCH₂ CH₂CH₂), 3.72–3.59 (2H, m, H-5), 3.63 (1H, d, J 6.0 Hz, H-2), 1.52 (3H, s, C(CH₃)₂), 1.37 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 137.0 (ipso OBn), 134.7 (OCH₂CH=CH₂), 128.5 (meta OBn), 128.2 (ortho OBn), 127.9 (para OBn), 117.4 (OCH₂CH=CH₂), 109.2 (C(CH₃)₂), 96.9 (C-1), 77.2 (C-4), 75.5 (C-3), 74.7 (C-2), 71.1 (OCH₂CH=CH₂), 69.2 (CH₂ OBn), 59.2 (C-5), 28.0 (C(CH₃)₂), 26.3 (C(CH₃)₂); m/z (CI) 658 [2M+NH₄]⁺, 550, 338
Methyl-α-D-lyxopyranoside (168).\textsuperscript{149}

\[
\text{HO} \quad \text{OH} \quad \text{HO} \quad \text{HO} \\
\text{HO} \quad \text{O} \quad \text{MeO} \\
\text{OH} \quad \text{OH} \quad \text{OH} \\
\text{MeO}^{-1} \quad \text{O} \quad 5
\]

To a stirred suspension of D-(−)-lyxose (5.00 g, 33.3 mmol, 1.0 equiv) in dry MeOH (67 mL) at room temperature under an atmosphere of argon was added acetyl chloride (1.19 mL, 16.7 mmol, 0.5 equiv). Then, the reaction mixture was heated at 50 °C. After 3 h, the pale yellow solution observed was cooled to room temperature and neutralised with Ag\textsubscript{2}CO\textsubscript{3} (3.5 g) to pH 7. Then, the reaction mixture was treated with charcoal and filtered through a pad of celite. Concentration under reduced pressure gave an orange oil, which solidified on standing at room temperature. Purification by recrystallisation twice from EtOAc (25 mL) gave methyl-α-D-lyxopyranoside 168 (3.44 g, 63\%) as a white granular crystals; mp 102.0–104.5 °C (EtOAc) [lit.\textsuperscript{149} mp 107.4–108.0 °C]; R\textsubscript{f} 0.37 (20% MeOH–CHCl\textsubscript{3}); [\alpha]\textsubscript{D}\textsuperscript{29} +65.0 (c 0.68, MeOH) [lit.\textsuperscript{149} [\alpha]\textsubscript{D}\textsuperscript{25} +55.2 (c 0.62, H\textsubscript{2}O)]; \nu\textsubscript{max} (neat) 3183, 1086, 1044, 1005, 970 cm\textsuperscript{-1}; \delta_H (MeOD, 400 MHz) 4.54 (1H, dt, J 3.0 & 0.5 Hz, H-1), 3.78 (1H, td, J 9.0 & 5.0 Hz, H-4), 3.73 (1H, t, J 3.0 Hz, H-2), 3.66–3.62 (2H, m, H-3 & equatorial H-5), 3.42 (1H, ddd, J 11.0, 9.0 & 0.5 Hz, axial H-5), 3.37 (3H, s, OMe); \delta_C (MeOD, 101 MHz) 103.2 (C-1), 72.7 (C-3), 71.7 (C-2), 68.6 (C-4), 64.1 (C-5), 55.6 (OMe); m/z (CI) 346 [2M+NH\textsubscript{4}]\textsuperscript{+}, 199, 182 [M+NH\textsubscript{4}]\textsuperscript{+}, 150 [M–CH\textsubscript{3}+H]\textsuperscript{+}. Data in agreement with previous reported literature values.\textsuperscript{149}
To a stirred suspension of methyl-α-D-lyxopyranoside 168 (3.00 g, 18.3 mmol, 1.0 equiv) and p-toluenesulfonic acid monohydrate (69.6 mg, 0.366 mmol, 0.02 equiv) in acetone (61 mL) at room temperature under an atmosphere of argon, was added 2,2-dimethoxypropane (7.84 mL, 64.0 mmol, 3.5 equiv). The reaction mixture was stirred at room temperature for 6 h. Then, the reaction mixture was diluted with iso-hexane/Et₂O (1:1, 122 mL) and washed with saturated aqueous NaHCO₃ solution (3 x 40 mL). The combined aqueous layers were extracted with Et₂O (3 x 100 mL). Then, the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a colourless oil. Purification by chromatography (10–60% EtOAc–iso-hexane) gave 1-O-methyl-2,3-isopropylidene-α-D-lyxopyranoside 169 (2.88 g, 77%) as colourless needles; mp 51.5–52.0 °C (EtOAc) [lit.¹⁴⁹ mp 51.4–52.6 °C]; Rf 0.17 (50% EtOAc–iso-hexane); [α]D²⁵ +51.4 (c 0.111, EtOH) [lit.¹⁴⁹ [α]D²⁵ +48.3 (c 0.8, EtOH)]; v_max (neat) 3425, 1379, 1219, 1138, 1072, 1059, 953, 908, 860 cm⁻¹; δH (CDCl₃, 400 MHz) 4.65 (1H, d, J 2.5 Hz, H-1), 4.24 (1H, dd, J 6.0 & 4.5 Hz, H-3), 4.14 (1H, dd, J 6.0 & 2.5 Hz, H-2), 3.87–3.82 (2H, m, H-4 & equatorial H-5), 3.74–3.71 (1H, m, axial H-5), 3.47 (3H, s, OMe), 1.52 (3H, s, C(CH₃)₂), 1.36 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 109.6 (C(CH₃)₂), 99.9 (C-1), 76.0 (C-3), 74.3 (C-2), 67.2 (C-4), 63.2 (C-5), 27.5 (C(CH₃)₂), 25.5 (C(CH₃)₂); m/z (CI) 222 [M+NH₄]+, 205 [MH]+, 190 [M–CH₃+H]+. Data in agreement with previous reported literature values.¹⁴⁹
4-O-Allyl-1-O-methyl-2,3-isopropylidene-α-D-lyxopyranoside (170).

To a stirred suspension of sodium hydride (832 mg, 20.8 mmol, 1.7 equiv, 60% dispersion in mineral oil) in dry DMF (20 mL) at 0 °C under an atmosphere of argon, was added a solution of 1-O-methyl-2,3-isopropylidene-α-D-lyxopyranoside 169 (2.50 g, 12.2 mmol, 1.0 equiv) in dry DMF (20 mL) over a period of 10 min. After 30 min at 0 °C, allyl bromide (2.12 mL, 24.5 mmol, 2.0 equiv) was added dropwise over a period of 5 min. The reaction mixture was allowed to slowly warm up to room temperature. After 60 min, the reaction mixture was quenched by the dropwise addition of MeOH (10 mL). Concentration under reduced pressure gave a dark yellow residue, which was dissolved in CHCl₃ (55 mL) and washed with saturated aqueous NaHCO₃ solution (20 mL). The aqueous layer was extracted with CHCl₃ (2 x 10 mL). Then, the combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (5→25% EtOAc–iso-hexane) gave 4-O-allyl-1-O-methyl-2,3-isopropylidene-α-D-lyxopyranoside 170 (2.78 g, 93%) as a colourless oil; Rf 0.29 (20% EtOAc–iso-hexane); [α]D²⁹ +37.5 (c 0.530, CH₂Cl₂); νmax (neat) 1647, 1382, 1371, 1219, 1141, 1087, 1060, 1017, 979, 898, 856 cm⁻¹; δH (CDCl₃, 400 MHz) 5.91 (1H, dddd, J 17.0, 10.5, 6.0 & 5.5 Hz, C=CH₂), 5.30 (1H, dq, J 17.0 & 1.5 Hz, trans CH=CH₂), 5.19 (1H, dq, J 10.5 & 1.5 Hz, cis CH=CH₂), 4.72 (1H, d, J 2.0 Hz, H-1), 4.20 (1H, ddt, J 13.0, 5.5 & 1.5 Hz, OCH₂CH=CH₂), 4.17 (1H, t, J 5.5 Hz, H-3), 4.12 (1H, ddt, J 13.0, 6.0 & 1.5 Hz, OCH₂CH=CH₂), 4.07 (1H, dd, J 5.5 & 2.0 Hz, H-2), 3.64–3.51 (3H, m, H-4 & H-5), 3.40 (3H, s, OMe), 1.53 (3H, s, C(CH₃)₂), 1.36 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 134.7 (OCH₂CH=CH₂), 117.3 (OCH₂CH=CH₂), 109.2 (C(CH₃)₂), 99.4 (C-1), 77.2 (C-3), 75.4 (C-2), 74.5 (C-4), 71.1 (OCH₂CH=CH₂), 59.2 (C-5), 55.4 (OMe), 28.1 (C(CH₃)₂), 26.3 (C(CH₃)₂); m/z (Cl) 506 [2M+NH₄]+, 474 [2M–CH₃+H]+, 344, 302, 262 [M+NH₄]+, 245 [MH]+, 230 [M–CH₃+H]+, 213 [M–OCH₃]+, 169, 100, 97, 85 (Found: [M+NH₄]+, 262.1656.
C₁₂H₂₀O₅ requires [M+NH₄]⁺, 262.1654) (Found: C, 58.98; H, 8.20%. C₁₂H₂₀O₅ requires C, 59.00; H, 8.25%).

2,3-O-Isopropylidene-α-D-lyxofuranose (165).

![Image of chemical structures](image)

A suspension of 1-O-benzyl-2,3-isopropylidene-α-D-lyxopyranoside 163 (1.00 g, 3.56 mmol, 1.0 equiv) and palladium on carbon (1.25 g, 10 wt % on carbon, 1.78 mmol, 0.33 equiv) in MeOH (70 mL) was stirred under a hydrogen atmosphere (4 balloons) for 16 h. Then, filtered through a pad of celite to remove the catalyst, dried (Na₂SO₄) and concentrated under reduced pressure to give 2,3-O-isopropylidene-α-D-lyxofuranoside 165 (678 mg, quantitative, 98:2 dr) as colourless needles; mp 70.0–72.0 °C (MeOH) [lit.¹⁵⁰ mp 76–78 °C]; R_f 0.39 (10% MeOH–CH₂Cl₂); [α]_D²⁴ +25.4 (c 1.735, CHCl₃); ν_max (neat) 3416, 3307, 1379, 1212, 1163, 1098, 1075, 1050, 1036, 980, 891, 857 cm⁻¹; δ_H (CDCl₃, 400 MHz) 5.47 (1H, d, J 2.0 Hz, H-1), 4.86 (1H, dd, J 6.0 & 5.0 Hz, H-3), 4.67 (1H, d, J 6.0 Hz, H-2), 4.31 (1H, q, J 5.0 Hz, H-4), 4.02–3.92 (2H, m, H-5), 2.71 (1H, br d, J 2.0 Hz, OH), 2.10 (1H, br t, J 6.0 Hz, OH), 1.51 (3H, s, C(CH₃)₂), 1.35 (3H, s, C(CH₃)₂); δ_C (CDCl₃, 101 MHz) 112.8 (C(CH₃)₂), 101.1 (C-1), 85.7 (C-2), 80.5 (C-3), 79.8 (C-4), 61.2 (C-5), 25.9 (C(CH₃)₂), 24.5 (C(CH₃)₂); m/z (CI) 208 [M+NH₄]⁺, 190 [M]⁺, 150 (Found: [M+NH₄]⁺, 208.1185. C₈H₁₄O₅ requires [M+NH₄]⁺, 208.1185) (Found: C, 50.58; H, 7.47%. C₈H₁₄O₅ requires C, 50.52; H, 7.42%). Data in agreement with previous reported literature values.¹⁵⁰
2,3-O-Isopropylidene-α-D-lyxofuranose (165).\textsuperscript{150}

![Chemical Structures](image)

A stirred suspension of 1-O-benzyl-2,3-isopropylidene-α-D-lyxopyranoside 163 (2.50 g, 8.92 mmol, 1.0 equiv), ammonium formate (2.81 g, 44.6 mmol, 5.0 equiv) and palladium on carbon (3.13 g, 10 wt % on carbon, 2.94 mmol, 0.33 equiv) in MeOH (178 mL) was heated under reflux for 45 min. Then, filtered through a pad of celite on a hydrophobic frit and concentrated under reduced pressure to give 2,3-O-isopropylidene-α-D-lyxofuranoside 165 (1.63 g, 96%, 97:3 dr) as colourless needles; mp 46.0 °C (MeOH); R\textsubscript{f} 0.37 (10% MeOH–CH\textsubscript{2}Cl\textsubscript{2}); [\alpha]\textsubscript{D}\textsuperscript{27} +13.6 (c 0.184, CHCl\textsubscript{3}); \nu\textsubscript{max} (neat) 3416, 3307, 1378, 1209, 1162, 1063, 1047, 1035, 976, 890, 855 cm\textsuperscript{-1}; \delta\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 5.45 (1H, s, H-1), 4.83 (1H, dd, J 6.0 & 5.0 Hz, H-3), 4.64 (1H, d, J 6.0 Hz, H-2), 4.29 (1H, q, J 5.0 Hz, H-4), 4.00–3.90 (2H, m, H-5), 1.48 (3H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.32 (3H, s, C(CH\textsubscript{3})\textsubscript{2}); \delta\textsubscript{C} (CDCl\textsubscript{3}, 101 MHz) 112.8 (C(CH\textsubscript{3})\textsubscript{2}), 101.1 (C-1), 85.7 (C-2), 80.5 (C-3), 79.3 (C-4), 61.3 (C-5), 26.0 (C(CH\textsubscript{3})\textsubscript{2}), 24.6 (C(CH\textsubscript{3})\textsubscript{2}); m/z (Cl) 208 [M+NH\textsubscript{4}]\textsuperscript{+}, 190 [M]\textsuperscript{+}, 175, 150 (Found: [M+NH\textsubscript{4}]\textsuperscript{+}, 208.1183. C\textsubscript{8}H\textsubscript{14}O\textsubscript{5} requires [M+NH\textsubscript{4}]\textsuperscript{+}, 208.1185) (Found: C, 50.62; H, 7.37%. C\textsubscript{8}H\textsubscript{14}O\textsubscript{5} requires C, 50.52; H, 7.42%). Data in agreement with previous reported literature values.\textsuperscript{150}
Dimethyl-2-oxopropylphosphonate (175).\textsuperscript{107}

\[
\begin{align*}
\text{Cl} & \quad \overset{\text{O}}{\text{C}} \\
\text{MeO} & \quad \overset{\text{O}}{\text{P}} \\
\text{MeO} & \quad \overset{\text{Cl}}{\text{O}}
\end{align*}
\]

175

To a stirred suspension of potassium iodide (89.7 g, 54.0 mmol, 1.0 equiv) in dry MeCN (125 mL) and dry acetone (100 mL) at room temperature, was added chloroacetone (43.0 mL, 54.0 mmol, 1.0 equiv) in one portion. After 60 min, trimethyl phosphite (63.4 mL, 54.0 mmol, 1.0 equiv) was added dropwise over a period of 15 min to the cream viscous reaction mixture. Exotherm observed at the end of the addition. After 21 h, at room temperature the reaction mixture was heated at 50 °C for 6 h. Then, reaction mixture cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure to give a brown-orange oil. Purification by Kugelrohr distillation gave \textit{dimethyl-2-oxopropylphosphonate} 175 (54.2 g, 60%) as a colourless oil; bp 126.0 °C (4.5 mmHg) [lit.\textsuperscript{107} bp 69–70 °C (0.35 mmHg)]; R\textsubscript{f} 0.57 (10% MeOH–CH\textsubscript{2}Cl\textsubscript{2}); \nu\textsubscript{max} (neat) 1716, 1257, 1031, 832 cm\textsuperscript{-1}; \delta\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 3.80 (6H, d, J 11.0 Hz, OMe), 3.12 (2H, d, J 23.0 Hz, CH\textsubscript{2}), 2.33 (3H, s, CH\textsubscript{3}); \delta\textsubscript{C\{H\}} (CDCl\textsubscript{3}, 101 MHz) 199.7 (d, J 6.0 Hz, C=O), 53.1 (d, J 6.0 Hz, OMe), 42.2 (d, J 128.5 Hz, CH\textsubscript{2}), 31.4 (s, CH\textsubscript{3}); \delta\textsubscript{P\{H,C\}} (CDCl\textsubscript{3}, 162 MHz) 22.4 (P(OMe)\textsubscript{2}); m/z (Cl) 392, 375, 357, 350 [2M+NH\textsubscript{4}]\textsuperscript{+}, 333 [2M+H]\textsuperscript{+}, 226, 209, 184 [M+NH\textsubscript{4}]\textsuperscript{+}, 167 [MH]\textsuperscript{+}, 124. Data in agreement with previous reported literature values.\textsuperscript{107}
Dimethyl 1-diazo-2-oxopropylphosphonate (176).\textsuperscript{107}

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{P} \\
175 & \quad \rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{N}_2 \\
176
\end{align*}
\]

To a stirred suspension of sodium hydride (2.12 g, 53.0 mmol, 1.1 equiv, 60% dispersion in mineral oil) in dry toluene (70 mL) and dry THF (25 mL) at 0 °C, was added a solution of dimethyl 2-oxopropylphosphonate 175 (8.00 g, 48.2 mmol, 1.0 equiv) in dry toluene (25 mL) over a period of 10 min. Effervescence observed during addition. Stirred at 0 °C for 60 min. Then, a solution of p-toluenesulfonyl azide (9.97 g, 50.6 mmol, 1.05 equiv) in dry toluene (5.0 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature. After 3 h at rt, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give a yellow oil. Purification by chromatography (50% EtOAc–hexane) gave dimethyl 1-diazo-2-oxopropylphosphonate 176 (8.39 g, 91%) as a yellow oil; R\textsubscript{f} 0.60 (10% MeOH–CH\textsubscript{2}Cl\textsubscript{2}); \nu\textsubscript{max} (neat) 2223, 2125, 1656, 1365, 1272, 1245, 1182, 1023, 835, 804, 784 cm\textsuperscript{-1}; \delta\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 3.85 (6H, d, J 12.0 Hz, OMe), 2.27 (3H, s, CH\textsubscript{3}); \delta\textsubscript{C{H}} (CDCl\textsubscript{3}, 101 MHz) 189.9 (d, J 12.5 Hz, C=O), 53.6 (d, J 6.0 Hz, OMe), 27.1 (CH\textsubscript{3}); \delta\textsubscript{P{H, C}} (CDCl\textsubscript{3}, 162 MHz) 14.3 (P(OMe)\textsubscript{2}); \textit{m/z} (Cl) 402 [2M+NH\textsubscript{4}]+, 385 [2M+H]+, 376, 357, 329, 302, 297, 285, 274, 257, 241, 210 [M+NH\textsubscript{4}]+, 193 [MH]+, 179, 165. Data in agreement with previous reported literature values.\textsuperscript{107}
(2S,3S,4R)-3,4-Isopropylidenedioxy-hex-5-yn-1,2-diol (177).

To a stirred suspension of 2,3-O-isopropylidene-α-D-lyxofuranose 165 (4.84 g, 25.4 mmol, 1.0 equiv) and potassium carbonate (10.6 g, 76.3 mmol, 3.0 equiv) in dry MeOH (70 mL) heated under reflux, was added a solution of dimethyl 1-diazo-2-oxopropylphosphonate 176 (14.7 g, 76.3 mmol, 3.0 equiv) in dry MeOH (57 mL) dropwise over a period of 8 h using a syringe pump. Then, heated under reflux for another 19.5 h. The reaction mixture was filtered through a glass frit to remove the residual inorganics. The filtrate was concentrated under reduced pressure to give an orange residue, which was dissolved in water (250 mL) and then extracted with EtOAc (3 x 250 mL). The combined organic extracts were concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (10→40% EtOAc–hexane) gave (2S,3S,4R)-3,4-isopropylidenedioxy-hex-5-yn-1,2-diol 177 (1.85 g, 39%) as a colourless oil; Rf 0.13 (50% EtOAc–hexane); [α]_D^22 = −22.3 (c 2.15, CHCl_3); ν_max (neat) 3416, 3290, 2122, 1383, 1242, 1214, 1163, 1064, 880 cm⁻¹; δ_H (CDCl_3, 400 MHz) 4.67 (1H, dd, J = 8.0 & 2.0 Hz, H-4), 4.14 (1H, d, J = 8.0 Hz, H-3), 3.78 (3H, br s, H-1 & H-2), 2.70 (1H, br s, OH), 2.58 (1H, d, J = 2.0 Hz, H-6), 2.39 (1H, br s, OH), 1.51 (3H, s, C(CH_3)_2), 1.46 (3H, s, C(CH_3)_2); δ_C (CDCl_3, 101 MHz) 111.1 (C(CH_3)_2), 82.5 (C-3), 80.2 (C-5), 75.2 (C-6), 69.5 (C-2), 66.8 (C-4), 64.6 (C-1), 26.6 (C(CH_3)_2), 26.1 (C(CH_3)_2); m/z (CI) 390 [2M+NH_4]^+, 204 [M+NH_4]^+, 187 [MH]^+, 171 (Found: [MH]^+, 187.0972. C_9H_{14}O_4 requires [MH]^+, 187.0970) (Found: C, 58.05; H, 7.63%. C_9H_{14}O_4 requires C, 58.05; H, 7.58%).
(3S,4S,5R)-3,4-Isopropylidenedioxy-hex-1-yn-5-ol-6-tosylate (178).

To a stirred colourless solution of (2S,3S,4R)-3,4-isopropylidenedioxy-hex-5-yn-1,2-diol 177 (500 mg, 2.69 mmol, 1.0 equiv) in dry CH₂Cl₂ (9 mL) at 0 °C was added triethylamine (0.564 mL, 4.03 mmol, 1.5 equiv), followed by dibutyltin oxide (33.4 mg, 0.134 mmol, 0.05 equiv) and p-toluenesulfonyl chloride (640 mg, 3.36 mmol, 1.25 equiv). The reaction mixture was allowed to warm to room temperature over a period of 60 min. After 5 h at rt, the reaction mixture was filtered through a pad of silica and washed with EtOAc (3 x 10 mL). The combined filtrate and washings were washed with water (15 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (10→20% EtOAc–hexane) gave (3S,4S,5R)-3,4-isopropylidenedioxy-hex-1-yn-5-ol-6-tosylate 178 (802 mg, 88%) as a colourless gum; Rₐ 0.42 (50% EtOAc–hexane); [α]D²² −17.8 (c 0.450, CHCl₃); vmax (neat) 3521, 3282, 2123, 1599, 1372, 1360, 1191, 1177, 1068, 986, 836, 816 cm⁻¹; δH (CDCl₃, 400 MHz) 7.83 (2H, d, J 8.0 Hz, ortho Ts), 7.38 (2H, d, J 8.0 Hz, meta Ts), 4.64 (1H, dd, J 7.5 & 2.0 Hz, H-3), 4.15–4.08 (3H, m, H-4 & H-6), 3.93 (1H, dd, J 9.0, 5.5 & 2.5 Hz, H-5), 2.56 (1H, d, J 2.0 Hz, H-1), 2.47 (3H, s, CH₃ Ts), 2.30 (1H, d, J 9.0 Hz, OH), 1.47 (3H, s, C(CH₃)₂), 1.41 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 145.2 (ipso Ts), 132.6 (para Ts), 129.9 (meta Ts), 128.0 (ortho Ts), 111.3 (C(CH₃)₂), 80.5 (C-4), 80.0 (C-2), 75.4 (C-1), 70.5 (C-6), 67.1 (C-5), 66.4 (C-3), 26.5 (C(CH₃)₂), 26.0 (C(CH₃)₂), 21.7 (CH₃ Ts); m/z (CI) 358 [M+NH₄]⁺, 341 [MH]⁺, 204, 187, 169, 102 (Found: [M+NH₄]⁺, 358.1330. C₁₆H₂₀O₆S requires [M+NH₄]⁺, 358.1324) (Found: C, 56.49; H, 5.92%. C₁₆H₂₀O₆S requires C, 56.46; H, 5.92%).
(3S,4S,5S)-1-(Phenylthio)-3,4-isopropylidenedioxy-hex-1-ene-5-ol-6-thiobenzene (179) and (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene (180).

To a stirred suspension of sodium methoxide (476 mg, 8.81 mmol, 3.0 equiv) in dry MeOH (7.4 mL) at 0 °C was added thiophenol (326 µL, 2.94 mmol, 1.0 equiv). After 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature over a period of 60 min to give a white suspension. Then, a solution of (3S,4S,5R)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-tosylate 178 (1.00 g, 2.94 mmol, 1.0 equiv) in dry MeOH (7.4 mL) was added to the reaction mixture at room temperature. The reaction mixture was heated under reflux for 60 min. Then, cooled to room temperature and concentrated under reduced pressure to give a white solid residue. The residue was dissolved in saturated aqueous NH₄Cl solution (10 mL) and water (10 mL), extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (5→15% Et₂O–hexane) gave (3S,4S,5S)-1-(phenylthio)-3,4-isopropylidenedioxy-hex-1-ene-5-ol-6-thiobenzene 179 (55.4 mg, 5%) and (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 180 (662.5 mg, 81%) as a colourless oil; Rₚ 0.34 and 0.30 (50% Et₂O–hexane); vₘₐₓ (neat) 3470, 3289, 2122, 1584, 1382, 1247, 1214, 1059, 741, 691 cm⁻¹; δₜₜ (CDCl₃, 400 MHz) 7.46–7.23 (15H, m, PhS), 6.52 (1H, d, J 9.5 Hz, H-1, 179), 5.76 (1H, dd, J 9.5 & 9.0 Hz, H-2, 179), 4.94 (1H, t, J 9.0 Hz, H-3, 179), 4.62 (1H, dd, J 7.5 & 2.0 Hz, H-3, 180), 4.27 (1H, dd, J 7.5 & 3.0 Hz, H-4, 180), 3.97 (1H, dd, J 9.0 & 3.0 Hz, H-4, 179), 3.77 (2H, qd, J 7.0 & 3.0 Hz, H-5), 3.16 (2H, dd, J 14.0 & 7.0 Hz, H-6), 3.15 (2H, dd, J 14.0 & 7.0 Hz, H-6), 2.57 (1H, d, J 2.0 Hz, H-1, 180), 2.49 (1H, br d, J 7.0 Hz, OH), 1.50 (6H, s, C(CH₃)₂), 1.46 (6H, s, C(CH₃)₂); δₜ (CDCl₃, 101 MHz, for 180) 135.0 (ipso PhS), 130.3 (ortho PhS), 129.1 (meta PhS), 126.8 (para PhS), 111.0 (C(CH₃)₂), 82.2 (C-4), 80.5 (C-2), 75.1 (C-1), 68.1 (C-5), 66.8 (C-3), 38.2 (C-6), 26.6
To a stirred solution of (3S,4S,5S)-1-(phenylthio)-3,4-isopropylidenedioxy-hex-1-ene-5-ol-6-thiobenzene 179 (6.0 mg, 0.015 mmol, 0.1 equiv) and (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 180 (44.0 mg, 0.158 mmol, 1.0 equiv) in dry MeOH (3.6 mL) at room temperature was added magnesium monoperoxyphthalate (444 mg, 0.898 mmol, 5.7 equiv). After 60 min at rt, the reaction mixture was filtered through a pad celite and then concentrated under reduced pressure to give a colourless gum. The residue was dissolved in saturated aqueous NaHCO₃ solution (3.0 mL), extracted with EtOAc (4 x 5.0 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to give a colourless gum. Purification by prep TLC (50% EtOAc–petrol) gave (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-sulfonyl benzene 181 (30.9 mg, 63%) as an amorphous white solid; mp 86.0–88.0 °C (EtOAc); Rf 0.38 (50% EtOAc–petrol); νmax (neat) 3507, 3293, 1303, 1149, 1058 cm⁻¹; δH (CDCl₃, 400 MHz) 7.98 (2H, d, J 7.0 Hz, ortho PhSO₂), 7.72 (1H, t, J 7.5 Hz, para PhSO₂), 7.62 (2H, dd, J 7.5 & 7.0 Hz, meta PhSO₂), 7.32 (2H, d, H-3), 4.56 (1H, dt, J 9.0 & 3.0 Hz, H-5), 4.08 (1H, dd, J 7.0 & 2.0 Hz, H-3), 3.47 (1H, dd, J 14.5 & 9.0 Hz, H-6), 3.34 (1H, dd, J 14.5 & 3.0 Hz, H-6), 3.00 (1H, br s, OH), 2.58 (1H, d, J 2.0 Hz, H-1), 1.48 (3H, s, C(CH₃)₂), 1.43 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 139.2 (ipso PhSO₂), 134.2 (para PhSO₂), 129.5 (meta PhSO₂), 128.1 (ortho PhSO₂), 114.4 (C(CH₃)₂), 83.1 (C-4), 80.3 (C-2), 75.4 (C-1), 66.1 (C-3), 64.5 (C-5), 59.8 (C-6), 26.4 (C(CH₃)₂), 26.0 (C(CH₃)₂); m/z (CI) 328 [M+NH₄]^+, 311 [MH]^+, 279, 263, 246, 221 (Found: [M+NH₄]^+, 328.1219. C₁₅H₁₈O₅S requires [M+NH₄]^+, 328.1219).
Phenyl 2,3-O-isopropylidene-5-S-phenyl-1,5-dithio-β-D-lyxofuranoside (184).

To a stirred suspension of D-(−)-lyxose (5.00 g, 33.3 mmol, 1.0 equiv) in acetone (120 mL) was added concentrated H$_2$SO$_4$ (302 µL, 5.66 mmol, 0.17 equiv). The reaction mixture was stirred at room temperature for 12 h. Then, neutralised by the addition of Na$_2$CO$_3$ (12.5 g). After stirring for 3 h at room temperature, filtered and concentrated under reduced pressure to give crude 2,3-O-isopropylidene-D-lyxofuranose 165 (6.37 g) as a colourless gum, which was dissolved in dry pyridine (28 mL) with diphenyl disulfide (18.2 g, 83.2 mmol, 2.5 equiv). To this stirred yellow solution at room temperature was added tri-n-butylphosphine (33.3 mL, 133 mmol, 4.0 equiv) dropwise. At the end of addition a dark red solution was observed and during addition an exotherm was observed. After 24 h at room temperature, the reaction mixture was quenched with CH$_2$Cl$_2$ (250 mL). After 30 min, pale yellow solution observed, which was washed with saturated aqueous NaHCO$_3$ solution (250 mL) and water (250 mL). The combined aqueous layers were extracted with CH$_2$Cl$_2$ (4 x 100 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a green residue. Purification by chromatography (0→5% Et$_2$O–hexane) gave phenyl 2,3-O-isopropylidene-5-S-phenyl-1,5-dithio-β-D-lyxofuranoside 184 (9.22 g, 74% over 2 steps) as colourless needles; mp 77.0–79.0 °C (Et$_2$O); R$_f$ 0.27 (20% Et$_2$O–hexane); [α]$_D$ 25° –88.5 (c 1.04, CHCl$_3$); $\nu_{\text{max}}$ (film) 1584, 1209, 1102, 741, 692 cm$^{-1}$; $\delta$H (CDCl$_3$, 400 MHz) 7.52 (2H, d, $J$ 7.0 Hz, ortho PhS), 7.44 (2H, d, $J$ 8.0 Hz, ortho PhS), 7.34–7.21 (6H, m, meta PhS & para PhS), 3.75 (1H, ddd, $J$ 7.5, 6.5 & 4.0 Hz, H-4), 3.39–3.38 (2H, m, H-5), 1.60 (3H, s, C(CH$_3$)$_2$), 1.40 (3H, s, C(CH$_3$)$_2$); $\delta$C (CDCl$_3$, 101 MHz) 135.7 (ipso PhS), 135.5 (ipso PhS), 130.5 (ortho PhS), 129.6 (ortho PhS), 129.0 (meta PhS), 128.9 (meta PhS), 126.9 (para PhS), 126.4 (para PhS), 113.3 (C(CH$_3$)$_2$), 89.8 (C-1), 82.3 (C-2), 80.3 (C-4), 80.0 (C-3), 31.2 (C-5), 26.0 (C(CH$_3$)$_2$),
25.2 (C(CH\textsubscript{3})\textsubscript{2}); m/z (Cl) 392 [M\textsubscript{++NH\textsubscript{4}}], 375 [MH\textsuperscript{+}], 265 [M–SPh\textsuperscript{-}] (Found: [MH\textsuperscript{+}], 375.1077. C\textsubscript{20}H\textsubscript{22}O\textsubscript{3}S\textsubscript{2} requires [MH\textsuperscript{+}], 375.1089) (Found: C, 64.23; H, 6.00%. C\textsubscript{20}H\textsubscript{22}O\textsubscript{3}S\textsubscript{2} requires C, 64.14; H, 5.92%).

2,3-O-Isopropylidene-5-S-phenyl-5-thio-D-lyxofuranose (183).

To a stirred colourless solution of phenyl 2,3-O-isopropylidene-5-S-phenyl-1,5-dithio-\(\beta\)-D-lyxofuranoside 184 (5.78 g, 15.4 mmol, 1.0 equiv) in MeCN/water (51.5 mL, 10:1) at room temperature was added HgCl\textsubscript{2} (8.38 g, 30.9 mmol, 2.0 equiv), followed by red HgO (8.36 g, 38.6 mmol, 2.5 equiv). The orange suspension was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of celite, washing with CH\textsubscript{2}Cl\textsubscript{2} (3 x 50 mL). The combined filtrate and washings were treated with sodium sulfide (15.0 g). After 15 min, the mixture was filtered. The filtrate was washed with 20% aqueous KI solution (125 mL), saturated aqueous NaHCO\textsubscript{3} solution (125 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→20% EtOAc–hexane) gave 2,3-O-isopropylidene-5-S-phenyl-5-thio-D-lyxofuranose 183 (4.03 g, 92%, 93:7 dr) as a colourless oil; R\textsubscript{f} 0.48 (50% EtOAc–hexane); [\(\alpha\)]\textsubscript{D}\textsuperscript{26} = –33.9 (c 1.89, CHCl\textsubscript{3}); \(v_{\text{max}}\) (neat) 3426, 1584, 1210, 1161, 1066, 1012, 866, 739, 691 cm\textsuperscript{-1}; \(\delta\text{H}\) (CDCl\textsubscript{3}, 400 MHz) 7.42 (2H, d, \(J\text{ 7.5 Hz, ortho}\) PhS), 7.31 (2H, t, \(J\text{ 7.5 Hz, meta}\) PhS), 7.22 (1H, t, \(J\text{ 7.5 Hz, para}\) PhS), 5.41 (1H, d, \(J\text{ 2.5 Hz, H-1 major anomer}\)), 4.98 (1H, dd, \(J\text{ 12.0 & 3.5 Hz, H-1 minor anomer}\)), 4.80 (1H, dd, \(J\text{ 6.0 & 3.5 Hz, H-3 major anomer}\)), 4.76 (1H, dd, \(J\text{ 6.0 & 3.5 Hz, H-3 minor anomer}\)), 4.63 (1H, d, \(J\text{ 6.0 Hz, H-2 major anomer}\)), 4.52 (1H, dd, \(J\text{ 6.0 & 3.5 Hz, H-2 minor anomer}\)), 4.33 (1H, td, \(J\text{ 7.0 & 3.5 Hz, H-4, major anomer}\)), 3.91 (1H, d, \(J\text{ 12.0 Hz, OH minor anomer}\)), 3.67 (1H, ddd, \(J\text{ 9.0, 6.0 & 3.5 Hz, H-4 minor anomer}\)), 3.27 (1H, dd, \(J\text{ 13.5 & 7.0 Hz, H-5}\)), 3.24 (1H, dd, \(J\text{ 13.5 & 7.0 Hz, H-5}\)), 2.39 (1H, d, \(J\text{ 2.5 Hz, OH major anomer}\)), 1.56 (3H, s, C(CH\textsubscript{3})\textsubscript{2} minor...
anomer), 1.50 (3H, s, C(CH₃)₂ major anomer), 1.40 (3H, s, C(CH₃)₂ minor anomer), 1.35 (3H, s, C(CH₃)₂ major anomer); δC (CDCl₃, 101 MHz) 135.8 (ipso PhS), 129.5 (ortho PhS), 128.9 (meta PhS), 126.3 (para PhS), 112.7 (C(CH₃)₂), 101.2 (C-1), 85.5 (C-2), 79.9 (C-3), 78.9 (C-4), 32.1 (C-5), 26.1 (C(CH₃)₂), 24.9 (C(CH₃)₂); m/z (CI) 300 [M+NH₄]⁺, 283 [MH]⁺, 265 [M−OH]⁺, 225, 178, 123 (Found: [MH]⁺, 283.1003. C₁₄H₁₈O₄S requires [MH]⁺, 283.1004) (Found: C, 59.62; H, 6.60%. C₁₄H₁₈O₄S requires C, 59.55; H, 6.43%).

(3S,4R,5S)-Tetrahydro-2-methylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (185) and (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yn-5-ol-6-thiobenzene (180).

To a stirred suspension of 2,3-O-isopropylidene-5-S-phenyl-5-thio-D-lyxofuranose 183 (340 mg, 1.20 mmol, 1.0 equiv) and potassium carbonate (499 mg, 3.61 mmol, 3.0 equiv) in dry MeOH (3.2 mL) heated under reflux, was added a solution of dimethyl 1-diazo-2-oxopropylphosphonate (694 mg, 3.61 mmol, 3.0 equiv) in dry MeOH (2.5 mL) dropwise over a period of 8 h via a syringe pump. The reaction mixture was filtered through a glass frit to remove the residual inorganics. The filtrate was concentrated under reduced pressure to give a green residue, which was dissolved in water (18 mL) and then extracted with EtOAc (5 x 18 mL). The combined organic extracts were concentrated under reduced pressure to give a pale green oil. Purification by chromatography (0→10% Et₂O–hexane) gave (3S,4R,5S)-tetrahydro-2-methylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 185 (7.1 mg, 2%) as a colourless oil; Rₚ 0.59 (50% Et₂O–hexane); [α]D⁺²⁵ +104.5 (c 1.57, CHCl₃); vₘₕₐₜ (neat) 1679, 1584, 1223, 1062, 1024, 740, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.43 (2H, d, J 7.5 Hz, ortho PhS), 7.32 (2H, t, J 7.5 Hz, meta PhS), 7.23 (1H, t, J 7.5 Hz, para PhS), 5.05 (1H, d, J 6.0 Hz, H-3), 4.76 (1H, dd, J 6.0 & 4.0 Hz, H-4), 4.50 (1H, s,
C=CH₂), 4.26 (1H, s, C=CH₂), 4.20 (1H, t, J 7.0 & 4.0 Hz, H-5), 3.37–3.28 (2H, m, C₂H₅SPh), 1.51 (3H, s, C(CH₃)₂), 1.27 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 161.3 (C-2), 135.4 (ipso PhS), 129.7 (ortho PhS), 129.1 (meta PhS), 113.4 (C(CH₃)₂), 86.4 (C=CH₂), 81.1 (C-5), 80.1 (C-3), 78.6 (C-4), 32.4 (C₂H₅SPh), 1.51 (3H, s, C(CH₃)₂), 1.27 (3H, s, C(CH₃)₂).

δC (CDCl₃, 101 MHz) 161.3 (C-2), 135.4 (ipso PhS), 129.7 (ortho PhS), 129.1 (meta PhS), 113.4 (C(CH₃)₂), 86.4 (C=CH₂), 81.1 (C-5), 80.1 (C-3), 78.6 (C-4), 32.4 (C₂H₅SPh), 1.51 (3H, s, C(CH₃)₂), 1.27 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 161.3 (C-2), 135.4 (ipso PhS), 129.7 (ortho PhS), 129.1 (meta PhS), 113.4 (C(CH₃)₂), 86.4 (C=CH₂), 81.1 (C-5), 80.1 (C-3), 78.6 (C-4), 32.4 (C₂H₅SPh), 1.51 (3H, s, C(CH₃)₂), 1.27 (3H, s, C(CH₃)₂).

δC (CDCl₃, 101 MHz) 161.3 (C-2), 135.4 (ipso PhS), 129.7 (ortho PhS), 129.1 (meta PhS), 113.4 (C(CH₃)₂), 86.4 (C=CH₂), 81.1 (C-5), 80.1 (C-3), 78.6 (C-4), 32.4 (C₂H₅SPh), 1.51 (3H, s, C(CH₃)₂), 1.27 (3H, s, C(CH₃)₂);

m/z (CI) 296 [M+NH₄]⁺, 279 [MH]⁺, 221 (Found: [MH]⁺, 279.1054). C₁₅H₁₈O₃S requires [MH]⁺, 279.1055) and (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 180 (226 mg, 68%) as a colourless oil; Rf 0.37 (50% Et₂O–hexane); [α]D²⁶ −33.3 (c 0.72, CHCl₃); νmax (neat) 3479, 3289, 2122, 1584, 1247, 1213, 1059, 741, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.43 (2H, d, J 7.5 Hz, ortho PhS), 7.32 (2H, t, J 7.5 Hz, para PhS), 4.62 (1H, dd, J 7.5 & 2.0 Hz, H-3), 4.26 (1H, dd, J 7.5 & 3.0 Hz, H-4), 3.76 (1H, qd, J 7.0 & 3.0 Hz, H-5), 3.16 (1H, dd, J 14.0 & 7.0 Hz, H-6), 2.56 (1H, d, J 2.0 Hz, H-1), 2.50 (1H, br d, J 7.0 Hz, OH), 1.49 (3H, s, C(CH₃)₂), 1.45 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 134.9 (ipso PhS), 130.3 (ortho PhS), 129.1 (meta PhS), 126.8 (para PhS), 111.0 (C(CH₃)₂), 82.2 (C-4), 80.5 (C-2), 75.1 (C-1), 68.1 (C-5), 66.7 (C-3), 38.2 (C-6), 26.6 (C(CH₃)₂), 26.0 (C(CH₃)₂); m/z (CI) 296 [M+NH₄]⁺, 279 [MH]⁺, 263 [M−CH₃]⁺, 221 [M−OC(CH₃)₂+H]⁺, 203 (Found: [MH]⁺, 279.1048). C₁₅H₁₈O₃S requires [MH]⁺, 279.1055) (Found: C, 64.84; H, 6.65%. C₁₅H₁₈O₃S requires C, 64.72; H, 6.52%).

(3S,4R,5S)-3,4-Isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene (186).

To a stirred suspension of sodium hydride (511 mg, 12.8 mmol, 1.5 equiv, 60% dispersion in mineral oil) in dry DMF (21 mL) at 0 °C, was added a solution (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 180 (2.37 g, 8.51 mmol, 1.0 equiv) and allyl bromide (1.11 mL, 12.8 mmol, 1.5 equiv) in dry DMF (21 mL). Effervescence observed during addition. Then the reaction mixture was allowed
to warm to room temperature. After 60 min, at room temperature the reaction mixture was quenched with MeOH (5 mL). Concentrated under reduced pressure to give a pale yellow semi-solid residue, which was dissolved in CHCl$_3$ (100 mL) and washed with saturated aqueous NaHCO$_3$ solution (100 mL). Aqueous layer was extracted with CHCl$_3$ (3 x 75 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (0→5% Et$_2$O–hexane) gave (3S,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene 186 (2.66 g, 98%) as a colourless oil; $\text{R}_f$ 0.62 (50% Et$_2$O–hexane); $\left[\alpha\right]_D^{24} = -42.9$ (c 1.12, CHCl$_3$); $\nu_{\text{max}}$ (neat) 3287, 2119, 1647, 1584, 1060, 739, 690 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.42 (2H, dd, $J$ 8.0 & 1.5 Hz, ortho PhS), 7.32 (2H, t, $J$ 8.0 Hz, meta PhS), 7.22 (1H, tt, $J$ 8.0 & 1.5 Hz, para PhS), 5.88 (1H, ddt, $J$ 17.0, 10.5 & 6.0 Hz, H=C=CH$_2$), 5.21 (1H, dq, $J$ 17.0 & 1.5 Hz, trans HC=CH$_2$), 5.17 (1H, dq, $J$ 10.5 & 1.5 Hz, cis HC=CH$_2$), 4.59 (1H, dd, $J$ 7.5 & 2.0 Hz, H-3), 4.35 (1H, dd, $J$ 7.5 & 3.5 Hz, H-4), 4.19 (1H, ddt, $J$ 12.5, 6.0 & 1.5 Hz, CH$_2$CH=CH$_2$), 4.03 (1H, ddt, $J$ 12.5, 6.0 & 1.5 Hz, CH$_2$CH=CH$_2$), 3.59 (1H, td, $J$ 6.5 & 3.5 Hz, H-5), 3.21 (1H, dd, $J$ 13.5 & 6.5 Hz, H-6), 3.17 (1H, dd, $J$ 13.5 & 6.5 Hz, H-6), 2.55 (1H, d, $J$ 2.0 Hz, H-1), 1.47 (3H, s, C(CH$_3$)$_2$), 1.45 (3H, s, C(CH$_3$)$_2$); $\delta_C$ (CDCl$_3$, 101 MHz) 135.9 (ipso PhS), 134.2 (HC=CH$_2$), 129.8 (ortho PhS), 129.0 (meta PhS), 126.4 (para PhS), 117.8 (HC=CH$_2$), 110.7 (C(CH$_3$)$_2$), 81.9 (C-4), 80.8 (C-2), 75.7 (C-5), 74.9 (C-1), 72.1 (CH$_2$CH=CH$_2$), 66.3 (C-3), 34.5 (C-6), 26.6 (C(CH$_3$)$_2$), 26.0 (C(CH$_3$)$_2$); $m/z$ (CI) 336 [M+NH$_4$]$^+$, 319 [MH]$^+$, 261 [M−OCH$_2$CH=CH$_2$]$^+$ (Found: [M+NH$_4$]$^+$, 336.1635. C$_{18}$H$_{22}$O$_3$S requires [M+NH$_4$]$^+$, 336.1633) (Found: C, 68.00; H, 6.87%. C$_{18}$H$_{22}$O$_3$S requires C, 67.89; H, 6.96%).
(Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine (187) and ((3aR,4S,7Z,8aS)-3a,4,6,8a-tetrahydro-8-((1E)-2-((Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepin-8-yl)vinyl)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepine (189).

To a stirred colourless solution of (3S,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yn-6-thiobenzene 186 (135 mg, 0.424 mmol, 1.0 equiv) in dry CH₂Cl₂ (8.5 mL) was added Grubbs II catalyst (36.0 mg, 0.042 mmol, 0.1 equiv). Then, the reaction mixture was heated under reflux for 3.5 h. Filtered through a pad of silica eluting with hexane (25 mL) and then Et₂O/hexane (1:1, 5 x 10 mL). The filtrate was concentrated under reduced pressure without heating to almost dryness to give a brown liquid. Purification by chromatography (0→20% Et₂O–hexane) gave (Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 187 (56.4 mg, 42%) as a colourless oil; Rₜ 0.33 (20% Et₂O–hexane); [α]D²² −46.3 (c 0.605, CHCl₃); vₘₐₓ (film) 1584, 1236, 1113, 1082, 738, 691 cm⁻¹; δ₁H (CDCl₃, 400 MHz) 7.41 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.31 (2H, t, J 7.5 Hz, meta PhS), 7.20 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 6.38 (1H, dd, J 17.5 & 11.0 Hz, CH=CH₂), 5.79 (1H, br dd, J 5.5 & 3.0 Hz, H-7), 5.56 (1H, d, J 17.5 Hz, trans CH=CH₂), 5.11 (1H, d, J 11.0 Hz, cis CH=CH₂), 4.96 (1H, br d, J 9.5 Hz, H-8a), 4.45 (1H, dd, J 17.5 & 5.5 Hz, H-6), 4.33 (1H, dd, J 9.5 & 7.0 Hz, H-3a), 4.27–4.22 (2H, m, H-4 & H-6), 3.48 (1H, dd, J 13.5 & 3.0 Hz, CH₂SPh), 3.03 (1H, dd, J 13.5 & 9.5 Hz, CH₂SPh), 1.48 (3H, s, C(CH₃)₂), 1.45 (3H, s, C(CH₃)₂); δ₁C (CDCl₃, 101 MHz) 138.5 (C-8), 136.7 (ipsos PhS), 135.2 (CH=CH₂), 129.2 (ortho PhS), 128.9 (meta PhS), 127.9 (C-7), 126.0 (para PhS), 115.6 (CH=CH₂), 109.9 (C(CH₃)₂), 79.4 (C-3a), 75.7 (C-8a), 75.6 (C-4), 67.2 (C-6), 34.2 (CH₂SPh), 27.1 (C(CH₃)₂), 26.8
(C(CH₃)₂); m/z (Cl) 336 [M+NH₄]⁺, 319 [MH]⁺, 261 [M−OC(CH₃)₂+H]⁺ (Found: [MH]⁺, 319.1358. C₁₈H₂₂O₃ requires [MH]⁺, 319.1368) and ((3aR,4S,7Z,8aS)-3a,4,6,8a-tetrahydro-8-((1E)-2-((Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepin-8-yl)vinyl)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepine 189 (15.3 mg, 12%) as a colourless oil; R₉ 0.13 (20% Et₂O–hexane); [α]D 21° −109.7 (c 0.62, CHCl₃); vₜₚ (film) 1584, 1234, 1112, 1081, 735, 690 cm⁻¹; δH (CDCl₃, 400 MHz) 7.41 (4H, d, J 7.5 Hz, ortho PhS), 7.31 (4H, t, J 7.5 Hz, meta PhS), 7.20 (2H, t, J 7.5 Hz, para PhS), 6.60 (2H, s, CH=CH), 5.82 (2H, br d, J 5.5 Hz, H-7), 4.95 (2H, br d, J 8.5 Hz, H-8a), 4.46 (2H, dd, J 18.0 & 5.5 Hz, H-6), 4.33 (2H, dd, J 8.5 & 7.5 Hz, H-3a), 4.28–4.24 (4H, m, H-4 & H-6), 3.48 (2H, dd, J 13.5 & 1.5 Hz, CH₂SPh), 3.03 (2H, dd, J 13.5 & 9.5 Hz, CH₂SPh), 1.48 (6H, s, C(CH₃)₂), 1.45 (6H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 138.3 (C-8), 136.7 (ipso PhS), 129.2 (ortho PhS), 128.9 (meta PhS), 128.5 (CH=CH), 127.4 (C-7), 126.0 (para PhS), 109.8 (C(CH₃)₂), 79.4 (C-3a), 75.7 (C-8a), 75.6 (C-4), 67.3 (C-6), 34.2 (CH₂SPh), 27.1 (C(CH₃)₂), 26.8 (C(CH₃)₂); m/z (Cl) 654, 640, 626 [M+NH₄]⁺, 609 [MH]⁺, 551, [M−OC(CH₃)₂+H]⁺, 513, 457, 443, 349, 279, 261, 243, 221, 170, 126 (Found: [MH]⁺, 609.2358. C₃₄H₄₀O₆S₂ requires [MH]⁺, 609.2345) (Found: C, 67.16; H, 6.54%. C₃₄H₄₀O₆S₂ requires C, 67.08; H, 6.62%).
(3aR,4S,6aS,7S,10bS)-7-((3aR,4S,8aS,Z)-2,2-Dimethyl-4-(phenylthiomethyl)-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-8-yl)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,6a,7,8,9,10b-octahydrobenzo[c][1,3]dioxolo[4,5-e]oxepine (190).

The colourless oil of (Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 187 (54.1 mg, 0.170 mmol, 1.0 equiv) was left for 48 h at room temperature under vacuum to dimerise. Purification by chromatography (0→15% Et\textsubscript{2}O–hexane) gave (3aR,4S,6aS,7S,10bS)-7-((3aR,4S,8aS,Z)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-8-yl)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,6a,7,8,9,10b-octahydrobenzo[c][1,3]dioxolo[4,5-e]oxepine 190 (47.0 mg, 87%) as a white granular solid; R\textsubscript{f} 0.13 (20% Et\textsubscript{2}O–hexane); [\alpha]\textsubscript{D}\textsuperscript{24} −39.5 (c 0.405, CHCl\textsubscript{3}); \nu\textsuperscript{max} (film) 1583, 1075, 1042, 871, 737, 689 cm\textsuperscript{-1}; \delta\textsuperscript{H} (CDCl\textsubscript{3}, 400 MHz) 7.41 (4H, d, J 7.5 Hz, ortho PhS), 7.33–7.29 (4H, m, meta PhS), 7.22–7.17  (2H, m, para PhS), 5.99 (1H, br s, H-10), 5.40 (1H, br s, H-7'),  4.77 (1H, br d, J 7.5 Hz, H-8a'), 4.63 (1H, d, J 9.5 Hz, H-10b), 4.41 (1H, dd, J 17.0 & 5.0 Hz, H-6'), 4.26 (1H, dd, J 9.5 & 6.0 Hz, H-3a), 4.24–4.10 (4H, m, H-3a', H-4', H-4 & H-6'), 3.58–3.33 (4H, m, H-6 & CH\textsubscript{2}SPh), 3.15–2.89 (4H, m, H-6a, H-7 & CH\textsubscript{2}SPh), 2.19 (2H, br s, H-9), 1.67–1.56 (2H, m, H-10), 1.48 (3H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.47 (3H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.45 (3H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.41 (3H, s, C(CH\textsubscript{3})\textsubscript{2}); \delta\textsuperscript{C} (CDCl\textsubscript{3}, 101 MHz) 139.9 (C-10a), 136.7 (ipso PhS), 136.4 (ipso PhS), 133.2 (C-8'), 129.6 (ortho PhS), 129.3 (ortho PhS), 128.9 (meta PhS), 126.7 (C-10), 126.1 (para PhS), 126.0 (para PhS), 123.5 (C-7'), 110.1 (C(CH\textsubscript{3})\textsubscript{2}), 109.9 (C(CH\textsubscript{3})\textsubscript{2}), 80.1 (C-4'), 78.5 (C-3a), 77.1 (C-10b), 76.1 (C-8a'), 75.7 (C-4), 75.1 (C-3a'), 68.5 (C-6), 67.8 (C-6'), 40.1 (C-6a), 37.2 (C-8), 34.2 (CH\textsubscript{2}SPh), 32.5 (CH\textsubscript{2}SPh), 27.3 (C(CH\textsubscript{3})\textsubscript{2}), 27.0 (C(CH\textsubscript{3})\textsubscript{2}), 26.9 (C(CH\textsubscript{3})\textsubscript{2}), 26.8 (C(CH\textsubscript{3})\textsubscript{2}), 23.9
(C-7 & C-10); m/z (Cl) 654 [M+NH₄]⁺, 637 [MH]⁺, 596 [M−OC(CH₃)₂+NH₄]⁺, 579 [M−OC(CH₃)₂+H]⁺, 544, 527, 521, 488, 469, 413, 126 (Found: [MH]⁺, 637.2639. C₃₆H₄₄O₆S₂ requires [MH]⁺, 637.2658) (Found: C, 68.05; H, 6.94%. C₃₆H₄₄O₆S₂ requires C, 67.89; H, 6.96%).

(S)-1-((4R,5S)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(phenylthio)ethyl 3,5-dinitrobenzoate (191).

![Chemical Structure](image)

To a stirred colourless solution of (3S,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 180 (47 mg, 0.169 mmol, 1.0 equiv) in dry THF (0.66 mL) at 0 °C was added triethylamine (35.4 µL, 0.253 mmol, 1.5 equiv), followed by 3,5-dinitrobenzoyl chloride (42.8 mg, 0.186 mmol, 1.1 equiv). Solution turned yellow in colour on addition of the 3,5-dinitrobenzoyl chloride. Reaction mixture was allowed to warm to room temperature. After 3 h at room temperature, the reaction mixture was partitioned between Et₂O (2 mL) and water (2 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 mL). The combined organic layers were washed with brine (2 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow semi-solid. Purification by chromatography (0→5% Et₂O–hexane) gave (S)-1-((4R,5S)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(phenylthio)ethyl 3,5-dinitrobenzoate 191 (53.8 mg, 67%) fine pale yellow needles; Rₜ 0.46 (50% Et₂O–hexane); [α]D¹⁹ −69.0 (c 1.58, CHCl₃); νmax (neat) 3288, 2121, 1713, 1545, 1341, 1277, 1246, 1064, 729, 719, 693, 666 cm⁻¹; δH (CDCl₃, 400 MHz) 9.22 (1H, t, J 2.0 Hz, para Ar(NO₂)₂), 9.03 (2H, d, J 2.0 Hz, ortho Ar(NO₂)₂), 7.42 (2H, dd, J 8.0 Hz, meta PhS), 7.23 (2H, t, J 8.0 Hz, meta PhS), 7.10 (1H, tt, J 8.0 & 1.0 Hz, para PhS), 5.50 (1H, ddd, J 8.0, 5.0 & 3.5 Hz, H-1), 4.54–4.49 (2H, m, H-4 & H-5), 3.44 (1H, dd, J 14.5 & 8.0 Hz, CH₂SPh), 3.36 (1H, dd, J 14.5 & 5.0 Hz, CH₂SPh), 2.62 (1H, d, J 2.0 Hz, C≡CH), 1.53 (3H, s, C(CH₃)₂), 1.49 (3H, s, C(CH₃)₂); δC (CDCl₃,
101 MHz) 161.8 (C=O), 148.6 (meta Ar(NO$_2$)$_2$), 134.6 (ipso Ar(NO$_2$)$_2$), 130.4 (ortho Ar(NO$_2$)$_2$), 129.5 (ortho PhS), 129.1 (meta PhS), 126.9 (para PhS), 122.5 (para Ar(NO$_2$)$_2$), 111.8 (C(CH$_3$)$_2$), 80.9 (C-4), 80.1 (C≡CH), 75.7 (C≡C), 74.0 (C-1), 66.7 (CH$_2$SPh), 26.6 (C(CH$_3$)$_2$), 26.1 (C(CH$_3$)$_2$); m/z (CI) 490 [M+NH$_4$]$^+$, 472 [M]$^+$, 460, 415 [M−OC(CH$_3$)$_2$+H]$^+$, 266, 206 (Found: [M+NH$_4$]$^+$, 490.1295. C$_{22}$H$_{20}$N$_2$O$_8$S requires [M+NH$_4$]$^+$, 490.1284) (Found: C, 56.02; H, 4.30; N, 5.75%. C$_{22}$H$_{20}$N$_2$O$_8$S requires C, 55.93; H, 4.27; N, 5.93%).

**(Z)-3-((4S,5S)-2,2-Dimethyl-5-((E)-2-(phenylthio)vinyl)-1,3-dioxolan-4-yl)penta-2,4-dien-1-ol (192).**

To a stirred colourless solution of (Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 187 (220 mg, 0.691 mmol, 1.0 equiv) in dry THF (3.5 mL) at −78 °C was added $^n$BuLi (314 µL of a 2.25 M solution in hexanes, 1.38 mmol, 2.0 equiv) dropwise. At the end of addition a yellow solution was observed. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and quenched with water (2.0 mL). Layers were separated and the aqueous layer was extracted with Et$_2$O (4 x 5 mL). Combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (10→30% Et$_2$O–hexane) gave (Z)-3-((4S,5S)-2,2-dimethyl-5-((E)-2-(phenylthio)vinyl)-1,3-dioxolan-4-yl)penta-2,4-dien-1-ol 192 (119 mg, 54%) as a yellow oil; R$_f$ 0.19 (50% Et$_2$O–hexane); [α]$_D$$^{21}$ −69.6 (c 0.345, CHCl$_3$); $\nu$$_{max}$ (neat) 3413, 1609, 1583, 1047, 1024, 740, 690 cm$^{-1}$; $\delta$$_{H}$ (CDCl$_3$, 400 MHz) 7.40–7.32 (4H, m, ortho & meta PhS), 7.29 (1H, tt, J 7.0 & 1.5 Hz, para PhS), 6.50 (1H, d, J 15.0 Hz, HC=CH$_2$Ph), 6.35 (1H, dd, J 17.5 & 11.0 Hz, HC=CH$_2$), 6.02 (1H, d, J 7.0 Hz, H-2), 5.63 (1H, dd, J 15.0 & 8.0 Hz, HC=CH$_2$Ph), 5.48 (1H, d, J 17.5 Hz, trans HC=CH$_2$), 5.14 (1H, d, J 11.0 Hz, cis HC=CH$_2$), 4.60 (1H, d, J 8.0 Hz, H-4), 4.33
(1H, t, J 8.0 Hz, H-5), 4.30–4.10 (2H, m, H-1), 2.08 (1H, br t, J 5.5 Hz, OH), 1.53 (3H, s, C(CH$_3$)$_2$), 1.46 (3H, s, C(CH$_3$)$_2$); $\delta$C (CDCl$_3$, 101 MHz) 135.4 (HC=CH$_2$), 134.7 (ipso PhS), 133.5 (C-3), 132.3 (C-2), 130.9 (ortho PhS), 129.5 (HC=CHSPh), 129.3 (meta PhS), 127.6 (para PhS), 126.1 (HC=CHSPh), 115.7 (HC=CH$_2$), 109.6 (C(CH$_3$)$_2$), 80.9 (C-5), 77.9 (C-4), 58.5 (C-1), 27.0 (C(CH$_3$)$_2$), 26.8 (C(CH$_3$)$_2$); m/z (Cl) 336 [M+NH$_4$]$^+$, 278 [M–OC(CH$_3$)$_2$+NH$_4$]$^+$, 261 [M–OC(CH$_3$)$_2$+H]$^+$, 243 [M–OC(CH$_3$)$_2$−OH]$^+$, 168, 151 [M–OC(CH$_3$)$_2$–SPh]$^+$, 133, 97 (Found: [M+NH$_4$]$^+$, 336.1639. C$_{18}$H$_{22}$O$_3$S requires [M+NH$_4$]$^+$, 336.1633) (Found: C, 68.01; H, 6.92%. C$_{18}$H$_{22}$O$_3$S requires C, 67.89; H, 6.96%).
1-O-(Methylthio)methyl-2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxofuranoside (202), 1-O-acetyl-2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxofuranoside (203) and 2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxono-1,4-lactone (200).

![Chemical Structure](image)

To a stirred colourless solution of dry dimethyl sulfoxide (20 mL) and acetic anhydride (7.29 mL, 77.1 mmol, 18.0 equiv) at room temperature, was added 2,3-O-isopropylidene-5-S-phenyl-5-thio-D-lyxofuranose 183 (1.21 g, 4.29 mmol, 1.0 equiv). After 22 h at room temperature, the reaction mixture was partitioned between EtOAc (125 mL) and water (125 mL). Layers were separated and the organic layer was washed with water (125 mL) and then brine (125 mL). This sequence of washing was repeated twice. Combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a yellow liquid. Purification by chromatography (0→40% Et$_2$O–hexane) gave 1-O-(methylthio)methyl-2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxofuranoside 202 (157 mg, 11%) as a pale yellow liquid; $[\alpha]_D^{21}$ +126.7 (c 1.105, CHCl$_3$); $\nu_{\text{max}}$ (neat) 742 (2H, dd, $J$ 7.5 & 1.0 Hz, ortho PhS), 7.31 (2H, t, $J$ 7.5 Hz, meta PhS), 7.21 (1H, tt, $J$ 7.5 & 1.0 Hz, para PhS), 5.36 (1H, s, H-1), 4.77 (1H, dd, $J$ 6.0 & 3.5 Hz, H-3), 4.67–4.61 (3H, m, H-2 & MeSCH$_2$), 4.12 (1H, td, $J$ 7.0 & 3.5 Hz, H-4), 3.30 (1H, dd, $J$ 13.5 & 7.0 Hz, H-5), 2.13 (3H, s, MeSCH$_2$), 1.50 (3H, s, C(CH$_3$)$_2$), 1.35 (3H, s, C(CH$_3$)$_2$); $\delta$C (CDCl$_3$, 101 MHz) 135.8 (ipso PhS), 129.6 (ortho PhS), 128.9 (meta PhS), 126.3 (para PhS), 112.8 (C(CH$_3$)$_2$), 102.7 (C-1), 85.1 (C-2), 79.8 (C-3), 79.0 (C-4), 70.7 (MeSCH$_2$), 31.9 (C-5), 26.1 (C(CH$_3$)$_2$), 24.9 (C(CH$_3$)$_2$), 14.3 (MeSCH$_2$); $m/z$ (Cl) 702 [2M+NH$_4$]$^+$, 360 [M+NH$_4$]$^+$, 343 [MH]$^+$, 330, 313, 281 [M–CH$_2$SMe]$^+$, 265 [M–OCH$_2$SMe]$^+$, 207, 179 (Found: [MH]$^+$, 343.1028. C$_{16}$H$_{22}$O$_4$S$_2$ requires [MH]$^+$, 343.1038) and 1-O-acetyl-2,3-O-isopropylidene-5-S-
phenyl-5-thio-α-D-lyxofuranoside 203 (40.2 mg, 3%) as a colourless oil; Rf 0.38 (50% Et₂O–hexane); [α]D²² –15.7 (c 0.225, CHCl₃); vₚₓₚₜ (neat) 1748, 1584, 1232, 1210, 1103, 1083, 1008, 865, 740, 692 cm⁻¹; δH (CDCl₃, 400 MHz) 7.43 (2H, dd, J 8.0 & 1.5 Hz, ortho PhS), 7.33 (2H, t, J 8.0 Hz, meta PhS), 7.24 (1H, tt, J 8.0 & 1.5 Hz, para PhS), 4.85 (1H, dd, J 6.0 & 3.5 Hz, H-3), 4.70 (1H, d, J 6.0 Hz, H-2), 4.23 (1H, td, J 7.0 & 3.5 Hz, H-4), 3.50 (2H, d, J 7.0 Hz, H-5), 2.06 (3H, s, AcO), 1.52 (3H, s, C(C₃H₇)₂), 1.36 (3H, s, C(C₃H₇)₂); δC (CDCl₃, 101 MHz) 169.5 (C=O AcO), 135.6 (ipso PhS), 129.8 (orth PhS), 129.6 (meta PhS), 129.4 (para PhS), 113.3 (C(CH₃)₂), 100.7 (C-1), 84.9 (C-2), 81.2 (C-4), 80.9 (C-3), 31.4 (C-5), 26.1 (C(CH₃)₂), 25.0 (C(CH₃)₂), 21.1 (CH₃ AcO); m/z (CI) 666 [2M+NH₄]+, 606, 342 [M+NH₄]+, 324 [M]+, 282 [M–Ac+H]+, 265 [M–OAc]+ (Found: [M+NH₄]+, 342.1375). C₁₆H₁₉O₅S requires [M+NH₄]+, 342.1376.

phenyl-5-thio-α-D-lyxono-1,4-lactone 200 (970.5 mg, 79%) as an amorphous white solid; mp 53.0–54.0 °C (Et₂O); Rf 0.19 (50% Et₂O–hexane); [α]D²¹ –26.7 (c 0.75, CHCl₃); vₚₓₚₜ (film) 1788, 1583, 1219, 1186, 1106, 1088, 1008, 979, 743, 692 cm⁻¹; δH (CDCl₃, 400 MHz) 7.47 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.36 (2H, t, J 7.5 Hz, meta PhS), 7.28 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 4.88 (1H, dd, J 5.0 & 3.5 Hz, H-3), 4.81 (1H, d, J 5.0 Hz, H-2), 4.54 (1H, ddd, J 8.5, 6.0 & 3.5 Hz, H-4), 3.41 (1H, dd, J 14.0 & 6.0 Hz, H-5), 3.36 (1H, dd, J 14.0 & 8.5 Hz, H-5), 1.51 (3H, s, C(CH₃)₂), 1.41 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 173.4 (C=O), 134.6 (ipso PhS), 130.5 (ortho PhS), 129.3 (meta PhS), 127.2 (para PhS), 114.2 (C(CH₃)₂), 77.5 (C-4), 76.2 (C-2), 75.9 (C-3), 32.2 (C-5), 26.8 (C(CH₃)₂), 25.9 (C(CH₃)₂; m/z (CI) 298 [M+NH₄]+, 280 [M]+ (Found: [M+NH₄]+, 298.1110. C₁₄H₁₆O₄S requires [M+NH₄]+, 298.1113) (Found: C, 60.06; H, 5.63%. C₁₄H₁₆O₄S requires C, 59.98; H, 5.75%).
1-Chloromethyl-2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxofuranose (204).

To a stirred colourless solution of 2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxono-1,4-lactone 200 (500 mg, 1.78 mmol, 1.0 equiv) in dry THF (3.6 mL) at −78 °C, was added chloroiodomethane (195 µL, 2.68 mmol, 1.5 equiv), followed by addition of n-BuLi (1.06 mL of a 1.38 M solution in hexanes, 2.68 mmol, 1.5 equiv) dropwise over a period of 30 min. After 30 min at −78 °C, the pale yellow reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH₄Cl solution (5.0 mL). The reaction mixture was warmed to rt and then partitioned between Et₂O (10 mL) and water (2 mL). Layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). Combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→10% Et₂O–hexane) gave 1-chloromethyl-2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxofuranose 204 (324 mg, 55%, 91:9 dr) as a colourless gum; [α]D²¹ −49.5 (c 0.97, CHCl₃); Rf 0.42 (50% Et₂O–hexane); νmax (neat) 3437, 1584, 1210, 1161, 1099, 1035, 870, 739, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.43 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.32 (2H, t, J 7.5 Hz, meta PhS), 7.23 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 4.91 (1H, dd, J 6.0 & 3.5 Hz, H-3 major diastereomer), 4.86 (1H, dd, J 6.0 & 3.5 Hz, H-3 minor diastereomer), 4.72 (1H, d, J 6.0 Hz, H-2 minor diastereomer), 4.61 (1H, d, J 6.0 Hz, H-2 major diastereomer), 4.39 (1H, d, J 1.0 Hz, OH minor diastereomer), 4.30 (1H, td, J 7.0 & 3.5 Hz, H-4 major diastereomer), 4.04 (1H, ddd, J 7.5, 6.0 & 3.5 Hz, H-4 minor diastereomer), 3.83 (1H, d, J 11.5 Hz, CH₂Cl major diastereomer), 3.79 (1H, d, J 11.5 Hz, CH₂Cl major diastereomer), 3.66 (1H, d, J 11.5 Hz, CH₂Cl minor diastereomer), 3.52 (1H, dd, J 11.5 & 1.0 Hz, CH₂Cl minor diastereomer), 3.26 (2H, d, J 7.0 Hz, H-5), 3.03 (1H, s, OH major diastereomer), 1.61 (3H, s, C(CH₃)₂ minor diastereomer), 1.51 (3H, s, C(CH₃)₂ major diastereomer), 1.42 (3H, s, C(CH₃)₂ minor diastereomer), 1.36 (3H, s, C(CH₃)₂ major diastereomer); δC
To a stirred colourless solution of 1-chloromethyl-2,3-O-isopropylidene-5-\(\text{S-phenyl-5-thio-\(\alpha\)}-D-lyxofuranose 204 (250 mg, 0.756 mmol, 1.0 equiv) in dry CH\(_2\)Cl\(_2\) (7.6 mL) at 0 °C, was added dry triethylamine (1.06 mL, 7.56 mmol, 10.0 equiv), followed by methanesulfonyl chloride (175 µL, 2.27 mmol, 3.0 equiv). At the end of addition a cloudy pale yellow solution was observed. The reaction mixture was stirred for 30 min at 0 °C. Then was allowed to warm to rt over a period of 30 min. The orange solution observed was quenched with saturated aqueous NaHCO\(_3\) solution (10 mL). Layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). Combined organic layers were washed with saturated aqueous NH\(_4\)Cl solution (3 x 25 mL), water (2 x 25 mL), dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→5% Et\(_2\)O–hexane) gave (\(E,3S,4R,5S\))-tetrahydro-2-chloromethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 205a (28.8 mg, 12%) as a colourless oil; \(R_f\) 0.35 (20% Et\(_2\)O–hexane); \([\alpha]_D^{19}\) +128.6 (c 1.12, CHCl\(_3\)); \(\nu_{\text{max}}\) (neat) 1664, 1585, 1211, 1065, 1007, 924, 740, 692 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.45 (2H, dd, \(J 7.5 \& 1.5\) Hz, ortho PhS), 7.33 (2H, t, \(J 7.5\) Hz, meta PhS), 7.25 (1H, tt, \(J 7.5 \& 1.5\) Hz, para PhS), 7.17 (1H, ddd, \(J 7.5 \& 1.5\) Hz, ipso PhS), 6.86 (1H, d, \(J 7.5\) Hz, ipso PhS), 6.57 (1H, m, ortho PhS), 6.41 (1H, dd, \(J 7.5 \& 1.5\) Hz, meta PhS), 6.30 (1H, d, \(J 7.5\) Hz, meta PhS), 5.59 (1H, broad s), 5.26 (1H, dd, \(J 7.5 \& 1.5\) Hz, meta PhS), 5.00 (2H, d, \(J 7.5\) Hz, ipso PhS), 4.83 (2H, s), 4.54 (1H, m, ortho PhS), 4.19 (2H, t, \(J 7.5\) Hz, ortho PhS), 3.66 (1H, s), 3.49 (2H, q, \(J 7.5\) Hz, ipso PhS), 3.39 (2H, t, \(J 4.0\) Hz, meta PhS), 3.33 (2H, t, \(J 4.0\) Hz, meta PhS), 3.22 (2H, m, ortho PhS), 3.08 (2H, m, meta PhS), 2.46 (1H, dd, \(J 7.5 \& 1.5\) Hz, meta PhS), 2.39 (1H, br d, \(J 1.5\) Hz, ortho PhS), 2.37 (1H, br d, \(J 1.5\) Hz, ortho PhS), 1.46 (2H, m), 1.18 (3H, d, \(J 6.5\) Hz, ipso PhS), 1.07 (3H, d, \(J 6.5\) Hz, ipso PhS).
δH (CDCl₃, 400 MHz) 7.47 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.34 (2H, t, J 7.5 Hz, meta PhS), 7.25 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 7.36 (1H, d, J 1.0 Hz, HC=C), 5.12 (1H, dd, J 6.0 & 1.0 Hz, H-3), 4.86 (1H, dd, J 6.0 & 3.5 Hz, H-4), 4.34 (1H, ddd, J 9.0, 5.5 & 3.5 Hz, H-5), 3.44 (1H, dd, J 13.5 & 5.5 Hz, CH₂SPh), 3.38 (1H, dd, J 13.5 & 9.0 Hz, CH₂SPh), 1.50 (3H, s, C(CH₃)₂), 1.40 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 155.6 (C-2), 135.0 (ipso PhS), 130.1 (ortho PhS), 129.1 (meta PhS), 126.8 (para PhS), 113.8 (C(CH₃)₂), 92.7 (HC=C), 82.4 (C-5), 79.6 (C-3), 78.8 (C-4), 32.0 (CH₂SPh), 26.9 (C(CH₃)₂), 26.1 (C(CH₃)₂); m/z (CI) 332, 330 [M+NH₄]⁺, 315, 313 [MH]⁺, 257, 255 [M–OC(CH₃)₂+H]⁺ (Found: [MH]⁺, 313.0663. C₁₅H₁₇O₃S⁵Cl requires [MH]⁺, 313.0665) (Found: C, 57.62; H, 5.38%. C₁₅H₁₇O₃SCl; requires C, 57.59; H, 5.48%) and (Z,3S,4R,5S)-tetrahydro-2-chloromethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 205b (168 mg, 71%) as an amorphous white solid; mp 75.0–77.0 °C (Et₂O); Rf 0.24 (20% Et₂O–hexane); [α]D²⁰ +144.9 (c 0.635, CHCl₃); νmax (film) 1671, 1584, 1225, 1154, 1075, 1013, 738, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.47 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.34 (2H, t, J 7.5 Hz, meta PhS), 7.25 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 7.36 (1H, d, J 1.0 Hz, HC=C), 5.12 (1H, dd, J 6.0 & 1.0 Hz, H-3), 4.86 (1H, dd, J 6.0 & 3.5 Hz, H-4), 4.34 (1H, ddd, J 9.0, 5.5 & 3.5 Hz, H-5), 3.44 (1H, dd, J 13.5 & 5.5 Hz, CH₂SPh), 3.38 (1H, dd, J 13.5 & 9.0 Hz, CH₂SPh), 1.50 (3H, s, C(CH₃)₂), 1.40 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 155.6 (C-2), 135.0 (ipso PhS), 130.1 (ortho PhS), 129.1 (meta PhS), 126.8 (para PhS), 113.8 (C(CH₃)₂), 92.7 (HC=C), 82.4 (C-5), 79.6 (C-3), 78.8 (C-4), 32.0 (CH₂SPh), 26.9 (C(CH₃)₂), 26.1 (C(CH₃)₂); m/z (CI) 332, 330 [M+NH₄]⁺, 315, 313 [MH]⁺, 257, 255 [M–OC(CH₃)₂+H]⁺ (Found: [MH]⁺, 313.0663. C₁₅H₁₇O₃S⁵Cl requires [MH]⁺, 313.0665) (Found: C, 57.62; H, 5.38%. C₁₅H₁₇O₃SCl; requires C, 57.59; H, 5.48%).
(3S,4R,5S)-Tetrahydro-2-(dichloromethylene)-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (211).

To a stirred colourless solution of 2,3-O-isopropylidene-5-S-phenyl-5-thio-α-D-lyxono-1,4-lactone 200 (1.00 g, 3.57 mmol, 1.0 equiv) and triphenylphosphine (3.74 g, 14.3 mmol, 4.0 equiv) in dry THF (56 mL) heat under reflux, was added carbon tetrachloride (8.26 mL, 85.6 mmol, 24.0 equiv) in dry THF (14 mL) dropwise via syringe pump over a period of 2 h. After 30 min, the orange solution observed was cooled to rt. The reaction mixture was quenched with water (40 mL). Layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 120 mL). Combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (120 mL), water (120 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give an orange semi-solid. Purification by chromatography (0→5% Et$_2$O–hexane) gave (3S,4R,5S)-tetrahydro-2-(dichloromethylene)-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 211 (1.22 g, 98%) as an amorphous white solid; mp 91.0–93.0 °C (Et$_2$O); [α]$_D$ 21 +169.3 (c 0.945, CHCl$_3$); $v_{\text{max}}$ (film) 1662, 1583, 1212, 1064, 1021, 892, 741, 691 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.46 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.34 (2H, t, J 7.5 Hz, meta PhS), 7.26 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 5.29 (1H, d, J 6.0 Hz, H-3), 4.89 (1H, dd, J 6.0 & 3.5 Hz, H-4), 4.29 (1H, ddd, J 8.5, 6.0 & 3.5 Hz, H-5), 3.41 (1H, dd, J 13.5 & 6.0 Hz, CH$_2$SPh), 3.36 (1H, dd, J 13.5 & 8.5 Hz, CH$_2$SPh), 1.51 (3H, s, C(CH$_3$)$_2$), 1.43 (3H, s, C(CH$_3$)$_2$); $\delta_C$ (CDCl$_3$, 101 MHz) 151.8 (C-2), 134.8 (ipso PhS), 130.3 (ortho PhS), 129.2 (meta PhS), 126.9 (para PhS), 113.7 (C(CH$_3$)$_2$), 101.8 (Cl$_2$C=C), 83.0 (C-5), 79.6 (C-3), 79.1 (C-4), 31.9 (CH$_2$SPh), 26.7 (C(CH$_3$)$_2$), 26.0 (C(CH$_3$)$_2$); m/z (Cl) 368, 366, 364 [M+NH$_4$]$^+$, 350, 348, 346 [M]$^+$, 293, 291, 289 [M−OC(CH$_3$)$_2$+H]$^+$, 263 (Found: [M+NH$_4$]$^+$, 364.0539. C$_{15}$H$_{16}$O$_3$S$^{35}$Cl$_2$ requires [M+NH$_4$]$^+$, 364.0541) (Found: C, 51.77; H, 4.57%. C$_{15}$H$_{16}$O$_3$SCl$_2$ requires C, 51.88; H, 4.64%).
1-Dibromomethyl-2,3-\(\text{O}\)-isopropylidene-5-S-phenyl-5-thio-\(\alpha\)-\(\text{D}\)-lyxofuranose (212).

To a stirred colourless solution of 2,3-\(\text{O}\)-isopropylidene-5-S-phenyl-5-thio-\(\alpha\)-\(\text{D}\)-lyxono-1,4-lactone 200 (500 mg, 1.78 mmol, 1.0 equiv) and dibromomethane (501 µL, 7.13 mmol, 4.0 equiv), in dry THF (3.6 mL) at −78 °C, was added chloroiodomethane (195 µL, 2.68 mmol, 1.5 equiv), followed by addition of a freshly prepared solution of LDA (382 mg, 3.57 mmol, 2.0 equiv) in THF (8.7 mL) dropwise over a period of 30 min. At the end of addition a dark yellow solution was observed. After 60 min at −78 °C, the pale yellow reaction mixture was poured into a mixture of saturated aqueous NH\(_4\)Cl solution (10 mL) and Et\(_2\)O (20 mL). Diluted with water (5 mL) and then the layers were separated. Aqueous layer was extracted with Et\(_2\)O (3 x 20 mL). Combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to give a brown liquid. Purification by chromatography (0→5% Et\(_2\)O–hexane) gave 1-dibromomethyl-2,3-\(\text{O}\)-isopropylidene-5-S-phenyl-5-thio-\(\alpha\)-\(\text{D}\)-lyxofuranose 212 (657 mg, 81%, 92:8 dr) as an amorphous white solid; \([\alpha]_D^{20} −20.0 (c 0.60, \text{CHCl}_3)\); \(R_f\) 0.34 (30% Et\(_2\)O–hexane); \(v_{\text{max}}\) (film) 3401, 1583, 1211, 1159, 1102, 1064, 1025, 876, 738, 692 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.42 (2H, dd, \(J\) 8.0 & 1.0 Hz, \textit{ortho} PhS), 7.31 (2H, t, \(J\) 8.0 Hz, \textit{meta} PhS), 5.87 (1H, s, CHBr\(_2\) major diastereomer), 5.72 (1H, s, CHBr\(_2\) minor diastereomer), 4.96–4.91 (2H, m, H-2 & H-3 minor diastereomer), 4.95 (1H, dd, \(J\) 6.0 & 4.0 Hz, H-3 major diastereomer), 4.72 (1H, d, \(J\) 6.0 Hz, H-2 major diastereomer), 4.61 (1H, s, OH minor diastereomer), 4.40 (1H, ddd, \(J\) 8.0, 6.0 & 4.0 Hz, H-4 minor diastereomer), 4.34 (1H, td, \(J\) 7.0 & 4.0 Hz, H-4 major diastereomer), 3.31–3.27 (2H, m, H-5 minor diastereomer), 3.23 (2H, d, \(J\) 7.0 Hz, H-5), 3.11 (1H, s, OH major diastereomer), 1.63 (3H, s, C(CH\(_3\))\(_2\) minor diastereomer), 1.52 (3H, s, C(CH\(_3\))\(_2\) major diastereomer), 1.43 (3H, s, C(CH\(_3\))\(_2\) minor diastereomer), 1.36 (3H, s, C(CH\(_3\))\(_2\) major diastereomer); \(\delta_C\)
(CDCl$_3$, 101 MHz) 135.6 (ipso PhS), 129.8 (ortho PhS), 129.0 (meta PhS), 126.5 (para PhS), 113.1 (C(CH$_3$)$_2$), 104.4 (C-1), 84.1 (C-2), 80.4 (C-3), 79.2 (C-4), 47.6 (CHBr$_2$), 31.6 (C-5), 26.1 (C(CH$_3$)$_2$), 24.7 (C(CH$_3$)$_2$); m/z (Cl) 474, 472 [M+NH$_4$]$^+$, 470, 456, 454 [M]$^+$, 452, 439, 437 [M−OH]$^+$, 435, 394, 392, 376 [M−$^{79}$Br+H]$^+$, 374 [M−$^{81}$Br+H]$^+$, 359 [M−OH−$^{79}$Br+H]$^+$, 357 [M−OH−$^{81}$Br+H]$^+$ (Found: [M+NH$_4$]$^+$, 469.9637. C$_{15}$H$_{18}$O$_4$S$^{79}$Br$_2$ requires [M+NH$_4$]$^+$, 469.9636) (Found: C, 39.58; H, 3.95%. C$_{15}$H$_{18}$O$_4$SBr$_2$ requires C, 39.67; H, 3.99%).

(3$S$,4$R$,5$S$)-Tetrahydro-2-(dibromomethylene)-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (213).

![Diagram](image)

To a stirred colourless solution of triphenylphosphine (3.74 g, 14.3 mmol, 4.0 equiv) in dry toluene (7.2 mL) at rt, was added carbon tetrabromide (2.37 g, 7.13 mmol, 2.0 equiv). After 30 min at rt, a yellow suspension observed, to this was added a colourless solution of 2,3-O-isopropylidene-5-$S$-phenyl-5-thio-$\alpha$-D-lyxono-1,4-lactone 200 (1.00 g, 3.57 mmol, 1.0 equiv) in dry toluene (7.2 mL). Reaction mixture heated under reflux for 60 min, brown suspension observed at temperature. Cooled to rt, filtered, washed with hexane (2 x 20 mL), Et$_2$O (2 x 20 mL) and concentrated under reduced pressure to give a yellow semi-solid. Purification by chromatography (0→5% Et$_2$O–hexane) gave (3$S$,4$R$,5$S$)-tetrahydro-2-(dibromomethylene)-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 213 (1.52 g, 97%) as an amorphous white solid; mp 70.0–72.0 °C (Et$_2$O); R$_f$ 0.46 (50% Et$_2$O–hexane); [a]$_{D}^{20}$ +117.1 (c 0.82, CHCl$_3$); $\nu_{\text{max}}$ (film) 1632, 1584, 1207, 1157, 1126, 1075, 1013, 932, 740, 692 cm$^{-1}$; $\delta$H (CDCl$_3$, 400 MHz) 7.46 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.34 (2H, t, J 7.5 Hz, meta PhS), 7.26 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 5.23 (1H, d, J 6.0 Hz, H-3), 4.92 (1H, dd, J 6.0 & 3.5 Hz, H-4), 4.31 (1H, ddd, J 8.5, 6.0 & 3.5 Hz, H-5), 3.40 (1H, dd, J 13.5 & 6.0 Hz, CH$_2$SPh), 3.35 (1H, dd, J 13.5 & 8.5 Hz, CH$_2$SPh), 1.51
(3H, s, C(CH$_3$)$_2$), 1.44 (3H, s, C(CH$_3$)$_2$); $\delta$C (CDCl$_3$, 101 MHz) 155.4 (C-2), 134.8 (ipso PhS), 130.3 (ortho PhS), 129.2 (meta PhS), 126.9 (para PhS), 113.6 (C(CH$_3$)$_2$), 82.7 (C-5), 80.4 (C-3), 79.3 (C-4), 68.7 (Br$_2$C=C), 26.6 (C(CH$_3$)$_2$), 26.1 (C(CH$_3$)$_2$); m/z (CI) 456, 454 [M+NH$_4$]$^+$, 452, 439, 437 [MH]$^+$, 435, 381, 379 [M−OC(CH$_3$)$_2$+H]$^+$, 377, 359 [M−$^{79}$Br+H]$^+$, 357 [M−$^{81}$Br+H]$^+$, 123 (Found: [M+NH$_4$]$^+$, 451.9534. C$_{15}$H$_{16}$O$_3$S$_79$Br$_2$ requires [M+NH$_4$]$^+$, 451.9531) (Found: C, 41.45; H, 3.59%. C$_{15}$H$_{16}$O$_3$SBr$_2$ requires C, 41.31; H, 3.70%).

$(E,3S,4R,5S)$-Tetrahydro-2-bromomethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (215a) and $(Z,3S,4R,5S)$-tetrahydro-2-bromomethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (215b).

![Diagram](image)

To a stirred solution of EtMgBr (1.14 mL of a 3.0 M solution in Et$_2$O, 3.43 mmol, 4.0 equiv) at 0 °C, was added a colourless solution of (3S,4R,5S)-tetrahydro-2-(dibromomethylene)-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 213 (374 mg, 0.857 mmol, 1.0 equiv) in dry THF (7.6 mL). The reaction mixture was allowed to warm to rt and stirred for 10 min. The pale yellow solution observed was quenched with saturated aqueous NH$_4$Cl solution (2.0 mL) and then partitioned between EtOAc (12 mL) and water (1 mL). Layers were separated and the aqueous layer was extracted with EtOAc (4 x 12 mL). Combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a colourless oil. Purification by chromatography (0→5% Et$_2$O–hexane) gave $(E,3S,4R,5S)$-tetrahydro-2-bromomethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 215a (73.9 mg, 24%) as a colourless oil; R$_f$ 0.62 (50% Et$_2$O–hexane); [α]$_D^{21}$ +130.4 (c 0.675, CHCl$_3$); $\nu_{\text{max}}$ (neat) 1658, 1584, 1211, 1137, 1073, 1006, 904, 741, 692 cm$^{-1}$; $\delta$H (CDCl$_3$, 400 MHz) 7.44 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.33 (2H, t, J 7.5 Hz, meta PhS), 7.25 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 5.74 (1H, d, J 1.0 Hz, HC=C), 5.30 (1H, dd, J 6.0 Hz, d, J 1.0 Hz, HC=C)
& 1.0 Hz, H-3), 4.82 (1H, dd, J 6.0 & 3.5 Hz, H-4), 4.17 (1H, ddd, J 7.5, 6.5 & 3.5 Hz, H-5), 3.36 (1H, dd, J 13.5 & 7.5 Hz, CH₂SPh), 3.31 (1H, dd, J 13.5 & 6.5 Hz, CH₂SPh), 1.52 (3H, s, C(CH₃)₂), 1.44 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 157.3 (C-2), 135.1 (ipso PhS), 129.9 (ortho PhS), 129.1 (meta PhS), 126.7 (para PhS), 113.5 (C(CH₃)₂), 83.9 (HC=C), 82.3 (C-5), 79.6 (C-3), 78.5 (C-4), 32.3 (CH₂SPh), 26.6 (C(CH₃)₂), 25.9 (C(CH₃)₂); m/z (CI) 376, 374 [M+NH₄]⁺, 359, 357 [MH]⁺, 301, 299 [M–OC(CH₃)₂]⁺ (Found: [MH]⁺, 357.0163. C₁₅H₁₇O₃S⁷⁹Br requires [MH]⁺, 357.0160) (Found: C, 50.40; H, 4.89%. C₁₅H₁₇O₃SBr; requires C, 50.43; H, 4.80%) and (Z,3S,4R,5S)-tetrahydro-2-bromomethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 215b (196 mg, 64%) as an amorphous white solid; mp 76.0–78.0 °C (Et₂O); Rₓ 0.54 (50% Et₂O–hexane); [α]D²¹ +124.8 (c 0.705, CHCl₃); v_max (film) 1667, 1584, 1272, 1224, 1140, 1118, 1076, 1013, 741, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.47 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.33 (2H, tt, J 7.5 Hz, meta PhS), 7.25 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 5.32 (1H, d, J 1.0 Hz, HC=C), 5.10 (1H, dd, J 5.5 & 1.0 Hz, H-3), 4.89 (1H, dd, J 5.5 & 3.5 Hz, H-4), 4.36 (1H, ddd, J 9.0, 5.5 & 3.5 Hz, H-5), 3.44 (1H, dd, J 13.5 & 5.5 Hz, CH₂SPh), 3.37 (1H, dd, J 13.5 & 9.0 Hz, CH₂SPh), 1.50 (3H, s, C(CH₃)₂), 1.40 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 157.5 (C-2), 135.0 (ipso PhS), 130.1 (ortho PhS), 129.1 (meta PhS), 126.8 (para PhS), 113.8 (C(CH₃)₂), 82.2 (C-5), 79.9 (C-3), 79.0 (C-4), 78.9 (HC=C), 32.1 (CH₂SPh), 26.9 (C(CH₃)₂), 26.1 (C(CH₃)₂); m/z (CI) 376, 374 [M+NH₄]⁺, 359, 357 [MH]⁺, 301, 299 [M–OC(CH₃)₂]⁺ (Found: [MH]⁺, 357.0164. C₁₅H₁₇O₃S⁷⁹Br requires [MH]⁺, 357.0160) (Found: C, 50.55; H, 4.71%. C₁₅H₁₇O₃SBr; requires C, 50.43; H, 4.80%).
(3S,4R,5S)-Tetrahydro-2-methylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan (185) and (3R,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene (195).

To a stirred colourless solution of (Z,3S,4R,5S)-tetrahydro-2-bromomethylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 215b (100 mg, 0.280 mmol, 1.0 equiv) in dry THF (1.4 mL) at −78 °C, was added t-BuLi (479 µL of a 1.46 M solution in hexanes, 0.700 mmol, 2.5 equiv) dropwise. Then, reaction mixture was warmed to 0 °C over a period of 90 min. The orange solution was quenched with saturated aqueous NH₄Cl solution (0.5 mL). Layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 2 mL). Combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→20% Et₂O–hexane) gave (3S,4R,5S)-tetrahydro-2-methylene-3,4-isopropylidenedioxy-5-((phenylthio)methyl)furan 185 (22.2 mg, 28%) as a colourless oil; Rₚ 0.41 (50% Et₂O–hexane); [α]D²¹ +107.7 (c 0.52, CHCl₃); νmax (neat) 1680, 1584, 1273, 1223, 1158, 1105, 1062, 740, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.44 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.33 (2H, t, J 7.5 Hz, meta PhS), 7.24 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 5.06 (1H, d, J 6.0 Hz, H-3), 4.77 (1H, dd, J 6.0 & 4.0 Hz, H-4), 4.52 (1H, s, C=CH₂), 4.28 (1H, s, C=CH₂), 4.21 (1H, ddd, J 7.5, 6.5 & 4.0 Hz, H-5), 3.37 (1H, dd, J 13.5 & 7.5 Hz, CH₂SPh), 3.31 (1H, dd, J 13.5 & 6.5 Hz, CH₂SPh), 1.53 (3H, s, C(CH₃)₂), 1.41 (3H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 161.3 (C-2), 135.4 (ipso PhS), 129.7 (ortho PhS), 129.1 (meta PhS), 126.5 (para PhS), 113.4 (C(CH₃)₂), 86.4 (C=CH₂), 81.1 (C-5), 80.1 (C-3), 78.6 (C-4), 32.4 (CH₂SPh), 26.8 (C(CH₃)₂), 26.0 (C(CH₃)₂); m/z (CI) 279 [MH]+, 221 (Found: [MH]+, 279.1055. C₁₅H₁₈O₄S requires [MH]+, 279.1055) (Found: C, 64.81; H, 6.42%. C₁₅H₁₈O₄S requires C, 64.72; H, 6.52%) and (3R,4S,5S)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene 195 (28.7 mg, 37%) as an amorphous white solid; mp 62.0 °C (Et₂O);
R_f 0.32 (50% Et_2O–hexane); [a]_D^{21} +68.6 (c 0.875, CHCl_3); ν_{max} (film) 3480, 3289, 2114, 1584, 1228, 1044, 865, 742, 692 cm^{-1}; δH (CDCl_3, 400 MHz) 7.47 (2H, dd, J 7.5 & 1.5 Hz, ortho PhS), 7.32 (2H, t, J 7.5 Hz, meta PhS), 7.25 (1H, tt, J 7.5 & 1.5 Hz, para PhS), 4.78 (1H, dd, J 6.5 & 2.0 Hz, H-3), 4.20 (1H, t, J 6.5 Hz, H-4), 4.08 (1H, dddd, J 8.0, 6.5, 4.0 & 3.5 Hz, H-5), 3.22 (1H, dd, J 13.5 & 4.0 Hz, H-6), 3.04 (1H, dd, J 13.5 & 8.0 Hz, H-6), 2.77 (1H, d, J 3.5 Hz, OH), 2.43 (1H, d, J 2.0 Hz, H-1), 1.58 (3H, s, C(CH_3)_2), 1.39 (3H, s, C(CH_3)_2); δC (CDCl_3, 101 MHz) 135.1 (ipso PhS), 130.5 (ortho PhS), 129.0 (meta PhS), 126.8 (para PhS), 11.08 (C(CH_3)_2), 79.3 (C-4), 79.1 (C-2), 76.6 (C-1), 69.6 (C-5), 66.8 (C-3), 37.8 (C-6), 27.3 (C(CH_3)_2), 25.8 (C(CH_3)_2); m/z (Cl) 296 [M+NH_4]^+, 279 [MH]^+, 263 [M−OH+H]^+, 221 [M−OC(CH_3)_2+H]^+, 148 (Found: [MH]^+, 279.1055. C_{15}H_{18}O_3S requires [MH]^+, 279.1055) (Found: C, 64.89; H, 6.70%. C_{15}H_{18}O_3S requires C, 64.72; H, 6.52%).

(3R,4R,5S)-3,4-Isopropylidenedi oxy-5-allyloxy-hex-1- yne-6-thiobenzene (218).

To a stirred suspension of sodium hydride (75.4 mg, 1.89 mmol, 1.5 equiv, 60% dispersion in mineral oil) in dry DMF (3.1 mL) at 0 °C, was added a solution (3R,4S,5S)-3,4-isopropylidenedi oxy-hex-1- yne-5-ol-6-thiobenzene 195 (350 mg, 1.26 mmol, 1.0 equiv) and allyl bromide (164 μL, 1.89 mmol, 1.5 equiv) in dry DMF (3.1 mL). Effervescence observed during addition. Then the reaction mixture was allowed to warm to room temperature. After 30 min, at room temperature the reaction mixture was quenched with MeOH (3.5 mL). Concentrated under reduced pressure to give an orange residue, which was dissolved in CHCl_3 (35 mL) and washed with saturated aqueous NaHCO_3 solution (35 mL). Aqueous layer was extracted with CHCl_3 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→5% Et_2O–hexane) gave (3R,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1- yne-6-
thiobenzene 218 (363 mg, 91%) as a colourless oil; R\textsubscript{f} 0.57 (50% Et\textsubscript{2}O–hexane); [\alpha]_D\textsuperscript{21} +82.8 (c 1.16, CHCl\textsubscript{3}); \nu\textsubscript{max} (neat) 3288, 2113, 1646, 1584, 1229, 1076, 1053, 866, 742, 692 cm\textsuperscript{-1}; \delta\textsubscript{H} (CDCl\textsubscript{3}, 400 MHz) 7.45 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.31 (2H, t, J 7.5 Hz, meta PhS), 7.22 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 5.99 (1H, ddt, J 17.0, 10.5 & 5.5 Hz, HC=CH\textsubscript{2}), 5.32 (1H, dq, J 17.0 & 1.5 Hz, trans HC=CH\textsubscript{2}), 5.19 (1H, dq, J 10.5 & 1.5 Hz, cis HC=CH\textsubscript{2}), 4.72 (1H, dd, J 5.5 & 2.0 Hz, H-3), 4.33 (1H, ddt, J 12.5, 5.5 & 1.5 Hz, CH\textsubscript{2}CH=CH\textsubscript{2}), 4.28 (1H, dd, J 7.0 & 5.5 Hz, H-4), 4.21 (1H, ddt, J 12.5, 5.5 & 1.5 Hz, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.90 (1H, td, J 7.0 & 4.0 Hz, H-5), 3.23 (1H, dd, J 13.5 & 4.0 Hz, H-6), 3.11 (1H, dd, J 13.5 & 7.0 Hz, H-6), 2.42 (1H, d, J 2.0 Hz, H-1), 1.59 (3H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.39 (3H, s, C(CH\textsubscript{3})\textsubscript{2}); \delta\textsubscript{C} (CDCl\textsubscript{3}, 101 MHz) 136.3 (ipso PhS), 135.0 (HC=CH\textsubscript{2}), 130.2 (ortho PhS), 128.9 (meta PhS), 126.4 (para PhS), 117.0 (HC=CH\textsubscript{2}), 110.9 (C(CH\textsubscript{3})\textsubscript{2}), 80.2 (C-4), 79.8 (C-2), 77.7 (C-5), 75.9 (C-1), 72.5 (CH\textsubscript{2}CH=CH\textsubscript{2}), 66.9 (C-3), 36.1 (C-6), 27.5 (C(CH\textsubscript{3})\textsubscript{2}), 26.1 (C(CH\textsubscript{3})\textsubscript{2}); m/z (Cl) 336 [M+NH\textsubscript{4}]\textsuperscript{+}, 319 [MH]\textsuperscript{+}, 261 [M–OCH\textsubscript{2}CH=CH\textsubscript{2}]\textsuperscript{+} (Found: [M+NH\textsubscript{4}]\textsuperscript{+}, 336.1640. C\textsubscript{18}H\textsubscript{22}O\textsubscript{3}S requires [M+NH\textsubscript{4}]\textsuperscript{+}, 336.1633) (Found: C, 67.95; H, 7.02%. C\textsubscript{18}H\textsubscript{22}O\textsubscript{3}S requires C, 67.89; H, 6.96%).
(Z,3aR,4S,8aR)-3a,4,6,8a-Tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine (219) and ((3aR,4S,7Z,8aR)-3a,4,6,8a-tetrahydro-8-((1E)-2-((Z,3aR,4S,8aR)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepin-8-yl)vinyl)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepine (220).

To a stirred colourless solution of (3R,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene 218 (50.0 mg, 0.157 mmol, 1.0 equiv) in dry CH$_2$Cl$_2$ (3.14 mL) was added Grubbs II catalyst (26.7 mg, 0.0314 mmol, 0.2 equiv). Then, the reaction mixture was irradiated at 70 °C in the microwave for 5 min. Filtered through a pad of silica eluting with hexane (5 mL) and then Et$_2$O/hexane (1:1, 20 mL). Concentrated under reduced pressure to give a brown residue. Purification by chromatography (0→20% Et$_2$O–hexane) gave (Z,3aR,4S,8aR)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 219 (17.8 mg, 36%) as a colourless oil; R$_f$ 0.52 (50% Et$_2$O–hexane); $[\alpha]_D^{25}$−156.0 (c 0.925, CHCl$_3$); $\nu$ (neat) 1644, 1610, 1584, 1247, 1216, 1165, 1133, 1055, 740, 692 cm$^{-1}$; $\delta$H (CDCl$_3$, 400 MHz) 7.39 (2H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.31 (2H, t, J 7.5 Hz, meta PhS), 7.20 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 6.40 (1H, dd, J 17.5 & 11.0 Hz, C=CH$_2$), 5.76 (1H, br t, J 3.0 Hz, H-7), 5.35 (1H, d, J 17.5 Hz, meta PhS), 7.20 (1H, tt, J 7.5 & 1.0 Hz, para PhS), 6.40 (1H, dd, J 17.5 & 11.0 Hz, C=CH$_2$), 5.09 (1H, d, J 11.0 Hz, cis CH=CH$_2$), 5.03 (1H, d, J 7.0 Hz, H-8a), 4.66 (1H, dd, J 19.0 & 3.0 Hz, H-6), 4.38 (1H, dd, J 7.0 & 1.5 Hz, H-3a), 4.36 (1H, dd, J 19.0 & 3.0 Hz, H-6), 3.57 (1H, ddd, J 8.0, 5.5 & 1.5 Hz, H-4), 3.24 (1H, dd, J 13.5 & 8.0 Hz, CH$_2$SPh), 3.15 (1H, dd, J 13.5 & 5.5 Hz, CH$_2$SPh), 1.61 (3H, s, C(CH$_3$)$_2$), 1.46 (3H, s, C(CH$_3$)$_2$); $\delta$C (CDCl$_3$, 101 MHz) 139.9 (CH=CH$_2$), 136.5 (ipso PhS), 134.7 (C-7), 133.1 (C-8), 129.0 (ortho PhS & meta PhS), 126.0 (para PhS), 111.9 (CH=CH$_2$), 108.5 (C(CH$_3$)$_2$), 79.2 (C-3a), 77.5 (C-4), 71.6 (C-8a), 70.7 (C-6), 35.4 (CH$_2$SPh), 158
26.5 (C(H₃)₂), 25.5 (C(H₃)₂); m/z (Cl) 336 [M+NH₄]⁺, 319 [MH]⁺, 278 [M–OC(H₃)₂+NH₄]⁺, 261 [M–OC(H₃)₂+H]⁺, 243, 133 (Found: [MH]⁺, 319.1359. C₁₈H₂₂O₃S requires [MH]⁺, 319.1368) and ((3aR,4S,7Z,8aR)-3a,4,6,8a-tetrahydro-8-((1E)-2-((Z,3aR,4S,8aR)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepin-8-yl)vinyI)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepine 220 (2.1 mg, 4%) as a pale yellow oil; Rₜ 0.20 (50% Et₂O–hexane); [α]D¹⁹ −109.1 (c 0.33, CHCl₃); v_max (neat) 1584, 1247, 1216, 1164, 1144, 1050, 1027, 739, 692 cm⁻¹; δH (CDCl₃, 400 MHz) 7.38 (4H, dd, J 7.5 & 1.0 Hz, ortho PhS), 7.31 (4H, t, J 7.5 Hz, meta PhS), 7.20 (2H, tt, J 7.5 & 1.0 Hz, para PhS), 6.33 (2H, s, CH=CH), 5.81 (2H, br t, J 3.0 Hz, H-7), 4.93 (2H, d, J 7.0 Hz, H-8a), 4.67 (2H, dd, J 19.0 & 3.0 Hz, H-6), 4.37 (2H, dd, J 7.0 & 1.5 Hz, H-3a), 4.35 (2H, dd, J 19.0 & 3.0 Hz, H-6), 3.56 (2H, ddd, J 8.0, 5.5 & 1.5 Hz, H-4), 3.23 (2H, dd, J 13.5 & 8.0 Hz, CH₂SPh), 3.14 (2H, dd, J 13.5 & 5.5 Hz, CH₂SPh), 1.59 (6H, s, C(CH₃)₂), 1.44 (6H, s, C(CH₃)₂); δC (CDCl₃, 101 MHz) 136.4 (ipso PhS), 133.9 (C-7), 133.0 (C-8), 130.5 (CH=CH), 129.0 (ortho PhS & meta PhS), 126.0 (para PhS), 108.6 (C(CH₃)₂), 79.0 (C-3a), 77.3 (C-4), 73.3 (C-8a), 70.6 (C-6), 35.4 (CH₂SPh), 26.4 (C(CH₃)₂), 25.6 (C(CH₃)₂); m/z (ESI) (Found: [MH]⁺, 609.2344. C₃₄H₄₀O₆S₂ requires [MH]⁺, 609.2345).

(2S,3R,4Z,6Z)-2,3-Dihydro-2-((phenylthio)methyl)-5-vinlyoxepin-3-ol (222).

To a stirred colourless solution of (Z,3aR,4S,8aR)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 219 (16.0 mg, 0.05 mmol, 1.0 equiv) in dry THF (0.25 mL) at −78 °C, was added n-BuLi (20.8 µL of a 2.42 M solution in hexanes, 0.105 mmol, 1.0 equiv) dropwise. At the end of addition a yellow solution was observed. The reaction mixture was allowed to warm to 0 °C over a period of 90 min and quenched with saturated aqueous NH₄Cl solution (0.25 mL). Layers were separated and the aqueous layer was extracted with Et₂O (3 x 3 mL).
Combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→20% Et₂O–hexane) gave (2S,3R,4Z,6Z)-2,3-dihydro-2-((phenylthio)methyl)-5-vinylloxepin-3-ol 222 (3.7 mg, 28%) as a colourless oil; Rₜ 0.30 (50% Et₂O–hexane); [α]D¹⁹ −40.0 (c 0.10, CHCl₃); vₑₘ₅₉ (neat) 3416, 1646, 1616, 1583, 1088, 1026, 740, 691 cm⁻¹; δH (CDCl₃, 400 MHz) 7.41 (2H, dd, J 8.0 & 1.5 Hz, ortho PhS), 7.32 (2H, t, J 8.0 Hz, meta PhS), 7.23 (1H, tt, J 8.0 & 1.5 Hz, para PhS), 6.56 (1H, d, J 7.5 Hz, H-7), 6.32 (1H, dd, J 17.5 & 11.0 Hz, HC=CH₂), 5.99 (1H, d, J 6.0 Hz, H-4), 5.38 (1H, d, J 17.5 Hz, trans HC=CH₂), 5.31 (1H, d, J 7.5 Hz, H-6), 5.15 (1H, d, J 11.0 Hz, cis HC=CH₂), 4.58 (1H, dd, J 9.0 & 6.0 Hz, H-3), 4.16 (1H, t, J 7.0 Hz, H-2), 3.22 (1H, dd, J 14.0 & 7.0 Hz, CH₂SPh), 3.22 (1H, dd, J 14.0 & 7.0 Hz, CH₂SPh), 1.90 (1H, d, J 9.0 Hz, OH); δC (CDCl₃, 101 MHz) 147.6 (C-7), 138.6 (HC=CH₂), 135.4 (C-5), 133.9 (ipso PhS), 130.5 (C-4), 129.6 (ortho PhS), 129.1 (meta PhS), 126.5 (para PhS), 113.7 (HC=CH₂), 100.5 (C-6), 80.7 (C-2), 70.2 (C-3), 34.3 (CH₂SPh); m/z (CI) 278 [M+NH₄]⁺, 261 [MH]⁺, 243 [M−OH]⁺, 133 (Found: [MH]⁺, 261.0957. C₁₅H₁₆O₂S requires [MH]⁺, 261.0949).

(3R,4R,5S)-3,4-Isopropylidenedioxy-5-allyloxy-hex-1-yne-6-sulfonyl benzene (225).

To a stirred solution of (3R,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene 218 (40.0 mg, 0.126 mmol, 1.0 equiv) in dry MeOH (2.5 mL) at room temperature was added magnesium monoperoxyphthalate hexahydrate (311 mg, 0.628 mmol, 5.0 equiv). After 5 min at rt, the reaction mixture was concentrated under reduced pressure to give a white semi-solid. The residue was partitioned between saturated aqueous NaHCO₃ solution (2.5 mL) and CHCl₃ (2.5 mL). Layers separated and the aqueous layer was extracted with CHCl₃ (3 x 2.5 mL). The combined organic
layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a colourless oil. Purification by chromatography (0→20% Et$_2$O–hexane) gave (3R,4R,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yn-6-sulfonyl benzene (39.1 mg, 89%) as an amorphous white solid; mp 51.0 °C (Et$_2$O); R$_f$ 0.22 (50% Et$_2$O–hexane); [α]$_D$ $^{19}$ +5.0 (c 0.80, CHCl$_3$); $\nu_{\text{max}}$ (film) 3266, 2113, 1586, 1306, 1230, 1147, 1082, 1053, 867, 748, 689 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.95 (2H, dd, $J$ 7.5 & 1.0 Hz, ortho PhSO$_2$), 7.67 (1H, tt, $J$ 7.5 & 1.0 Hz, para PhSO$_2$), 7.58 (2H, t, $J$ 7.5 Hz, meta PhSO$_2$), 5.74 (1H, ddt, $J$ 17.0, 10.5 & 5.5 Hz, HC=CH$_2$), 5.17 (1H, dq, $J$ 17.0 & 1.5 Hz, trans HC=CH$_2$), 5.09 (1H, dq, $J$ 10.5 & 1.5 Hz, cis HC=CH$_2$), 4.79 (1H, dd, $J$ 6.5 & 2.0 Hz, H-3), 4.29 (1H, t, $J$ 6.5 Hz, H-4), 4.25 (1H, td, $J$ 6.5 & 4.0 Hz, H-5), 4.23 (1H, ddt, $J$ 12.0, 5.5 & 1.5 Hz, CH$_2$CH=CH$_2$), 4.03 (1H, ddt, $J$ 12.0, 5.5 & 1.5 Hz, CH$_2$CH=CH$_2$), 3.53 (1H, dd, $J$ 14.5 & 6.5 Hz, H-6), 3.49 (1H, dd, $J$ 14.5 & 4.0 Hz, H-6), 2.57 (1H, d, $J$ 2.0 Hz, H-1), 1.55 (3H, s, C(CH$_3$)$_2$), 1.36 (3H, s, C(CH$_3$)$_2$); $\delta_C$ (CDCl$_3$, 101 MHz) 140.6 (ipso PhSO$_2$), 134.2 (HC=CH$_2$), 133.6 (para PhSO$_2$), 129.2 (meta PhSO$_2$), 128.0 (ortho PhSO$_2$), 117.1 (HC=CH$_2$), 111.1 (C(CH$_3$)$_2$), 79.5 (C-4), 79.0 (C-2), 76.8 (C-1), 74.3 (C-5), 73.8 (CH$_2$CH=CH$_2$), 66.8 (C-3), 57.6 (C-6), 27.2 (C(CH$_3$)$_2$), 25.9 (C(CH$_3$)$_2$); $m/z$ (Cl) 368 [M+NH$_4$]$^+$, 351 [MH]$^+$, 293 [M−OCH$_2$CH=CH$_2$]$^+$, 228, 220, 205, 160, 102 (Found: [M+NH$_4$]$^+$, 368.1530. C$_{18}$H$_{22}$O$_5$S requires [M+NH$_4$]$^+$, 368.1532) (Found: C, 61.79; H, 6.48%. C$_{18}$H$_{22}$O$_5$S requires C, 61.69; H, 6.33%).
To a stirred colourless solution of (3R,4S,5S)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-sulfonyl benzene 225 (200 mg, 0.571 mmol, 1.0 equiv) in dry CH$_2$Cl$_2$ (11.4 mL) was added Grubbs II catalyst (96.9 mg, 0.114 mmol, 0.2 equiv). Then, the reaction mixture was irradiated at 70 °C in the microwave for 5 min. Filtered through a pad of silica eluting with hexane (100 mL) and then Et$_2$O/hexane (1:1, 200 mL). Concentrated under reduced pressure to give a brown residue. Purification by chromatography (0→20% Et$_2$O–hexane) gave (Z,3aR,4S,8aR)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylsulfonyl)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine 223 (62.5 mg, 31%) as a white granular solid; inter alia $R_f$ 0.30 (50% Et$_2$O–hexane); $v_{\text{max}}$ (neat) 1306, 1146, 1084, 749, 689 cm$^{-1}$; $\delta_H$ (CDCl$_3$, 400 MHz) 7.95 (2H, dd, $J$ 7.5 & 1.5 Hz, ortho PhSO$_2$), 7.68 (1H, tt, $J$ 7.5 & 1.5 Hz, para PhSO$_2$), 7.59 (2H, t, $J$ 7.5 Hz, meta PhSO$_2$), 6.41 (1H, dd, $J$ 17.5 & 11.0 Hz, CH=CH$_2$), 5.78 (1H, br t, $J$ 3.0 Hz, H-7), 5.33 (1H, d, $J$ 17.5 Hz, trans CH=CH$_2$), 5.10 (1H, d, $J$ 11.0 Hz, cis CH=CH$_2$), 5.00 (1H, d, $J$ 7.5 Hz, H-8a), 4.42 (1H, dd, $J$ 19.0 & 3.0 Hz, H-6), 4.30 (1H, dd, $J$ 19.0 & 3.0 Hz, H-6), 4.24–4.18 (2H, m, H-3a and H-4), 3.62  (1H, dd, $J$ 15.0 & 9.0 Hz, CH$_2$SO$_2$Ph), 3.29 (1H, dd, $J$ 15.0 & 2.5 Hz, CH$_2$SO$_2$Ph), 1.49 (3H, s, C(CH$_3$)$_2$), 1.41 (3H, s, C(CH$_3$)$_2$); $\delta_C$ (CDCl$_3$, 101 MHz) 140.6 (ipso PhSO$_2$), 139.6 (CH=CH$_2$), 134.5 (C-7), 133.6 (para PhSO$_2$), 132.7 (C-8), 129.1 (meta PhSO$_2$), 127.7 (ortho PhSO$_2$), 112.1 (CH=CH$_2$), 108.7 (C(CH$_3$)$_2$), 80.3 (C-3a), 73.4 (C-4), 71.7 (C-8a), 70.1 (C-6), 58.8 (CH$_2$SO$_2$Ph), 26.3 (C(CH$_3$)$_2$), 25.5 (C(CH$_3$)$_2$); $m/z$ (CI) 382, 368 [M+NH$_4^+$], 324, 310 [M–OC(CH$_3$)$_2$+NH$_4^+$], 293 [M–OC(CH$_3$)$_2$+H]$^+$, 202, 160 (Found: [M+NH$_4^+$]$^+$, 368.1527. C$_{18}$H$_{22}$O$_5$S requires [M+NH$_4$]$^+$, 368.1532).
8 Appendices

8.1 Appendix I

Crystal structure and data for 184.

Crystal data and structure refinement for DC1003.

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Crystal system, space group: Monoclinic, P2(1)

Unit cell dimensions:

\[ a = 7.9938(3) \, \text{Å} \quad \alpha = 90^\circ \]

\[ b = 9.0867(2) \, \text{Å} \quad \beta = \]

\[ c = 13.5097(3) \, \text{Å} \quad \gamma = 90^\circ \]

Volume, Z: 958.55(5) Å³, 2

Density (calculated): 1.298 Mg/m³

Absorption coefficient: 0.293 mm⁻¹

F(000): 396

Crystal colour / morphology: Colourless platy needles

Crystal size: 0.51 x 0.19 x 0.06 mm³

θ range for data collection: 3.09 to 32.93°

Index ranges:

\[-11 \leq h \leq 11, \quad -13 \leq k \leq 13, \quad -20 \leq l \leq 11\]

Reflns collected / unique: 10451 / 6046 [R(int) = 0.0286]

Reflns observed [F>4σ(F)]: 4286

Absorption correction: Analytical

Max. and min. transmission: 0.983 and 0.906

Refinement method: Full-matrix least-squares on F²

Data / restraints / parameters: 6046 / 1 / 226

Goodness-of-fit on F²: 0.858

Final R indices [F>4σ(F)]: R1 = 0.0358, wR2 = 0.0660

R indices (all data): R1 = 0.0562, wR2 = 0.0690

Absolute structure parameter: x+ = 0.02(4), x- = 0.98(4)

Largest diff. peak, hole: 0.280, -0.175 eÅ⁻³

Mean and maximum shift/error: 0.000 and 0.001

Bond lengths [Å] and angles [°] for DC1003.
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8.2 Appendix II

Crystal structure and data for 190.
Crystal data and structure refinement for DC1004.

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C(28)
Mean and maximum shift/error 0.000 and 0.002

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<td>C(43)-C(44)</td>
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C(11)-O(1)-C(2)  117.2(8)
O(1)-C(2)-C(12)  112.0(9)
O(1)-C(2)-C(3)   109.9(7)
C(12)-C(2)-C(3)  114.9(10)
O(20)-C(3)-C(2)  107.8(8)
O(20)-C(3)-C(4) 100.4(9)
C(2)-C(3)-C(4) 116.9(10)
O(22)-C(4)-C(5) 113.5(9)
O(22)-C(4)-C(3) 103.9(8)
C(5)-C(4)-C(3) 111.3(10)
C(6)-C(5)-C(4) 121.7(10)
C(6)-C(5)-C(10) 119.5(9)
C(4)-C(5)-C(10) 118.8(9)
C(5)-C(6)-C(7) 125.9(10)
C(6)-C(7)-C(8) 111.4(10)
C(7)-C(8)-C(9) 111.4(8)
C(25)-C(9)-C(8) 114.1(9)
C(25)-C(9)-C(10) 115.7(8)
C(8)-C(9)-C(10) 107.6(8)
C(5)-C(10)-C(11) 112.4(8)
C(5)-C(10)-C(9) 113.8(8)
C(11)-C(10)-C(9) 113.8(8)
O(1)-C(11)-C(10) 115.1(8)
C(2)-C(12)-S(13) 113.0(9)
C(14)-S(13)-C(12) 102.0(5)
C(15)-C(14)-C(19) 119.8(11)
C(15)-C(14)-S(13) 115.9(8)
C(19)-C(14)-S(13) 124.0(10)
C(16)-C(15)-C(14) 118.8(11)
C(17)-C(16)-C(15) 120.5(13)
C(18)-C(17)-C(16) 120.4(14)
C(17)-C(18)-C(19) 122.6(13)
C(18)-C(19)-C(14) 117.9(13)
C(21)-O(20)-C(3) 106.2(8)
O(20)-C(21)-O(22) 105.1(8)
O(20)-C(21)-C(24) 113.1(11)
O(22)-C(21)-C(24) 109.6(9)
O(20)-C(21)-C(23) 109.0(9)
O(22)-C(21)-C(23) 107.0(9)
C(24)-C(21)-C(23) 112.6(10)
C(4)-O(22)-C(21) 108.9(8)
C(31)-C(25)-C(26) 121.3(9)
C(31)-C(25)-C(9) 123.3(9)
C(26)-C(25)-C(9) 115.4(8)
O(32)-C(26)-C(25) 114.3(8)
O(32)-C(26)-C(27) 102.1(7)
C(25)-C(26)-C(27) 112.0(9)
O(34)-C(27)-C(26) 104.3(9)
O(34)-C(27)-C(28) 112.0(8)
C(26)-C(27)-C(28) 113.1(8)
O(29)-C(28)-C(37) 108.0(10)
O(29)-C(28)-C(27) 108.7(8)
O(29)-C(28)-C(27) 112.1(9)
C(37)-C(28)-C(30) 116.0(8)
O(29)-C(28)-C(37) 114.5(10)
C(25)-C(31)-C(30) 127.4(9)
C(33)-O(32)-C(26) 109.5(8)
O(32)-C(33)-O(34) 107.1(8)
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O(32)-C(33)-C(35) 106.5(11)
O(34)-C(33)-C(35) 109.4(13)
C(36)-C(33)-C(35) 115.2(16)
C(27)-O(34)-C(33) 108.7(7)
C(28)-C(37)-S(38) 107.5(8)
C(39)-S(38)-C(37) 103.2(6)
C(40)–C(39)–C(44) 118.0(12)
C(40)–C(39)–S(38) 125.4(9)
C(44)–C(39)–S(38) 116.5(11)
C(41)–C(40)–C(39) 119.7(12)
C(40)–C(41)–C(42) 124.6(15)
C(43)–C(42)–C(41) 117.1(14)
C(42)–C(43)–C(44) 121.6(13)
C(43)–C(44)–C(39) 119.0(14)
8.3 Appendix III

Crystal structure and data for 191.

Crystal data and structure refinement for DC1005.

Identification code  DC1005
Formula  C22 H20 N2 O8 S
Formula weight 472.46
Temperature 173(2) K
Diffractometer, wavelength OD Xcalibur PX Ultra, 1.54184 Å
Crystal system, space group Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions
\[a = 7.22546(10) \, \text{Å}, \quad \alpha = 90^\circ\]
\[b = 12.76286(16) \, \text{Å}, \quad \beta = 90^\circ\]
\[c = 23.8828(3) \, \text{Å}, \quad \gamma = 90^\circ\]
Volume, Z 2202.41(5) Å³, 4
Density (calculated) 1.425 Mg/m³
Absorption coefficient 1.769 mm⁻¹
F(000) 984
Crystal colour / morphology Yellow needles
Crystal size 0.22 x 0.06 x 0.04 mm³
θ range for data collection 3.70 to 72.39°
Index ranges -8<=h<=8, -15<=k<=15, -28<=l<=29
Reflns collected / unique 8985 / 4266 [R(int) = 0.0223]
Reflns observed [F>4σ(F)] 4016
Absorption correction Analytical
Max. and min. transmission 0.933 and 0.733
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 4266 / 0 / 298
Goodness-of-fit on F² 1.043
Final R indices [F>4σ(F)]
R1 = 0.0268, wR2 = 0.0682
R1+ = 0.0268, wR2+ = 0.0682
R1- = 0.0423, wR2- = 0.1122
R indices (all data) R1 = 0.0292, wR2 = 0.0693
Absolute structure parameter x+ = 0.000(12), x- = ***
Largest diff. peak, hole 0.172, -0.186 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001

Bond lengths [Å] and angles [°] for DC1005.

\[\begin{align*}
C(1)-C(2) & \quad 1.189(3) \\
C(2)-C(3) & \quad 1.471(2) \\
C(3)-O(4) & \quad 1.4272(19) \\
C(3)-C(7) & \quad 1.539(2) \\
O(4)-C(5) & \quad 1.4304(19) \\
C(5)-O(6) & \quad 1.4358(19) \\
C(5)-C(18) & \quad 1.509(3) \\
C(5)-C(17) & \quad 1.517(2) \\
O(6)-C(7) & \quad 1.4183(18) \\
C(7)-C(8) & \quad 1.525(2) \\
C(8)-O(19) & \quad 1.4542(17)
\end{align*}\]
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<td>C(11)-S(10)-C(9)</td>
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<td>C(16)-C(11)-S(10)</td>
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<td>C(20)-O(19)-C(8)</td>
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<td>O(20)-C(20)-O(19)</td>
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C(22)-C(23)-C(24)  123.12(14)
C(22)-C(23)-N(27)  118.32(13)
C(24)-C(23)-N(27)  118.56(14)
C(25)-C(24)-C(23)  116.77(14)
C(24)-C(25)-C(26)  122.79(14)
C(24)-C(25)-N(30)  119.00(14)
C(26)-C(25)-N(30)  118.21(14)
C(25)-C(26)-C(21)  118.64(14)
O(29)-N(27)-O(28)  124.00(14)
O(29)-N(27)-C(23)  117.93(14)
O(28)-N(27)-C(23)  118.07(14)
O(32)-N(30)-O(31)  124.76(14)
O(32)-N(30)-C(25)  117.65(14)
O(31)-N(30)-C(25)  117.57(14)
9 References


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