Aziridine–Metathesis based
Approaches to Alkaloid Synthesis

A Thesis presented by

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As Partial Fulfilment of the Requirements for the Award of the Degree of Doctor of Philosophy of Imperial College London

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Dedicated to my family 献给已故的爷爷和奶奶：卢兰生和莫三。
再献给：阿姑：卢惠兰；
父亲：卢毅坚；
母亲：龙桂琼；
大哥：卢卓飞；
大嫂：李洁金；
侄子：卢泽峰，卢泽邦

For Bill Armstrong on the occasion of his 80th birthday
Abstract

The aim of the project is to synthesise (−)-morphine utilising aziridine and metathesis chemistry. The thesis is divided into three chapters.

Chapter 1 provides brief reviews on the subjects of total synthesis of morphine; ring-rearrangement metathesis (RRM) and regioselective ring-opening of aziridines.

Chapter 2 focuses on the research findings in the past three years. Two routes, A and B, were investigated in attempts to synthesise morphine (Scheme 1). In route A, sulfonyl cyclopentene II was prepared from ring-closing metathesis of a diene precursor, which was synthesised from lithiated cinnamylsulfone and butadiene monoxide. Subsequently, RRM reactions of several α-SO₂Ph allyl derivatives of II were investigated and some interesting results were obtained. The synthesis of 2,3-trans vinylaziridine III was achieved in seven steps beginning with a Grignard reaction of (4-methoxyphenyl)magnesium bromide with butadiene monoxide. Subsequently, some highly regioselective ring-opening reactions of III with sulfur-stabilised anionic nucleophiles were achieved. However, in an attempt to synthesise compound I from II and III, no reaction was observed. This led to the investigation of route B, in which five methods for the synthesis of compound IV were investigated. The practical approach deployed a novel Al-mediated substitution of the 4-tosyl group of the tosyl tetrahydropyridine counterpart of IV, prepared from V and III, with a phenylthio group.

Scheme 1

Chapter 3 provides the experimental details and characterisation data.
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Abbreviations

Ac    acetyl
acac  acetylacetonate
AcOH  acetic acid
ADDP  1,1’-(azodicarbonyl)dipiperidine
(aq.) aqueous
Ar    aryl
Bn    benzyl
Boc   tert-butyloxy carbonyl
br    broad
Bu    butyl
CI    chemical ionisation
d    doublet
dba   dibenzylidene acetone
dd    doublet of doublets
ddd   doublet of doublet of doublets
diast. diastereomer
dr    diastereomeric ratio
dt    doublet of triplets
DBU   1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD  diethyl azodicarboxylate
DIAD  diisopropyl azodicarboxylate
DIBAL-H diisobutylaluminium hydride
DMAP  N,N-dimethylaminopyridine
DMDO  dimethyldioxirane
DMF   N,N-dimethylformamide
DMPU  1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidone
DMSO  dimethylsulfoxide
ee    enantiomeric excess
ESI   electrospray ionisation
equiv equivalent(s)
Et    ethyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>RRM</td>
<td>ring-rearrangement metathesis</td>
</tr>
<tr>
<td>SES</td>
<td>2-(trimethylsilyl)ethylsulfonyl</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>S_N1</td>
<td>unimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>S_N2</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBDMS</td>
<td><em>tert</em>-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</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>$N,N,N',N'$-tetramethyl-1,2-ethylenediamine</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
</tr>
</tbody>
</table>
**Stereochemical Notation**

Throughout this report, to aid rapid visual identification of relative and absolute stereochemical configuration, the Maehr convention has been adopted.\(^1\) Thus, solid and broken lines denote racemates, whilst solid and broken wedges imply absolute configurations. For the latter, narrowing of both solid and broken wedges denotes increasing distance from viewer.

---

**Morphine Numbering**

In this report, the following morphine numbering system is adopted.

\[ (-)-\text{morphine} \]
1. Introduction

1.1 Historical Aspects of Morphine

Morphine, the active principle of opium, was the first alkaloid discovered.\textsuperscript{2,3} Its isolation from opium poppy, \textit{Papaver somniferum}, was attempted by a number of scientists.\textsuperscript{4} At the beginning of the 19th century Séguin in France and Sertürner in Germany both independently completed the isolation of morphine.\textsuperscript{5} However, since Séguin’s work was not published until 1814, the discovery of morphine is generally attributed to Sertürner in the year 1805.\textsuperscript{2,4,5} Sertürner named the white crystalline powder morphinum, after Morpheus, the Greek god of dreams. He realised that morphinum, or morphine as we know it, belonged to a group of previously unknown natural products. The term alkaloid, vegetable alkali, was adopted for this family of compounds.\textsuperscript{6}

Subsequently, explanations of the molecular structure of morphine caused great controversy. Intensive investigation was carried out but it remained unsolved for a long period.\textsuperscript{2,4,5} In 1847 Laurent correctly deduced the empirical formula of morphine as $\text{C}_{17}\text{H}_{19}\text{NO}_3$.\textsuperscript{2,3} Further progress was made by Knorr and Hörlein whose conclusion was published in 1907 (1 in Figure 1).\textsuperscript{2,3} They believed that C-15 was connected to C-5, a hypothesis which was challenged by Gulland and Robinson who showed, for the first time, the structure for morphine as 2, with C-15 connected to C-13 (Figure 1).\textsuperscript{2,3,4}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1}
\end{figure}
1.2 Biosynthesis of Morphine

The morphine alkaloids contain a class of structurally related compounds with medicinal value.\(^7\) Morphine itself has a unique clinical importance due to its superior broad-spectrum analgesic properties. Despite some of its detrimental side effects, it continues to be one of the most widely used clinical drugs for alleviation of severe pain.\(^3\,^7\)

Three types of mammalian opioid receptors, \(\delta\), \(\kappa\) and \(\mu\) have been identified.\(^8\) The expression of morphine’s interaction with the \(\mu\) receptor is thought to be the key contribution to its analgesic effect. The mechanisms of its action in affecting the human central nervous and immune systems have received a lot of attention.\(^9\) The mechanism for its function is thought to be similar to the body’s own painkiller endorphins, a family of polypeptides. Additionally, recent discoveries showed that the affinity between morphine and the binding site of the \(\mu\) receptor is much higher.\(^8\)

It has been found that human bodies need morphine and produce it intracellularly at a nanomolar level.\(^9\) Morphine is also present in toad skin, cow brain, adrenal glands and various mammalian tissues.\(^10,11,12\) The biosynthesis of \((--)\)-morphine is well studied, as depicted in Scheme 2, although the mechanism is still not fully elucidated. Amine 3 and aldehyde 4 both derive from L-tyrosine. Pictet–Spengler reaction of 3 with 4 gives \((S)\)-norcodaurine, which provides all the non-\(N\)-methyl carbon atoms required in morphine. Subsequent oxidation, methylation and epimerisation gave \((R)\)-reticuline 5. The next key carbon–carbon bond formation was achieved by a diphenolic coupling via intermediate 6 to give salutaridine. Following the syntheses of several analogues, morphine is obtained in an extremely concise manner.\(^13\)
Scheme 2
1.3 Total Synthesis of Morphine

The distinctive architecture of morphine, which possesses five rings, five contiguous stereocentres and a compact arrangement of functionality, has attracted synthetic chemists for decades. Since the first total synthesis was accomplished by Gates in 1952, over 20 others have been published.

1.3.1 Rice’s Approach to Morphine

The biomimetic route of Rice, published in 1980, has offered the most efficient and probably the only synthetically feasible route to produce morphine in bulk (Scheme 3). Homologation of benzaldehyde 7 gave acid 8, which was coupled with amine 9 to give the corresponding amide. Subsequent Bischler–Napieralski reaction mediated by POCl3 followed by reduction of the tetrahydroisoquinolinium intermediate gave tetrahydroisoquinoline 10. Compound 10 was subjected to Birch reduction followed by formylation, ketalisation and regioselective bromination. The resulting ketal was then deprotected to give ketone 11. Compound 11 was then converted to morphinan 12 after a Grewe cyclisation, initiated by hydrogen fluoride-ammonia complex in trifluoromethanesulfonic acid, which is a very practical way to construct the tetracyclic ring structure of morphine. The bromine substituent acts as a blocking group to prevent the undesired coupling. After hydrolysis of amide 12, the dihydrofuran ring of 13 was formed via regioselective α-bromination of the ketone followed by base-induced ring closure. Finally, dihydrocodeinone 13 was prepared after cleavage of the aryl bromide bond and methylation of the resulting amine simultaneously by hydrogenation over palladium in a mixture of aqueous formaldehyde and acetic acid. Morphine was then synthesised in another five steps from 13.
Having a sequence of 16 steps and total yield of 16%, Rice’s method is highly efficient. However, the main disadvantage of this synthesis was that it required a final resolution of (±)-morphine.

### 1.3.2 Overman’s Approach to Morphine

The first asymmetric total synthesis of (−)-morphine was achieved by Overman et al. (Scheme 4). Cyclohexenol 16 was synthesised in 93% yield and over 96% ee by enantioselective reduction of cyclohexanone 14 with catechol borane in the presence of (R)-oxazaborolidine catalyst 15. The introduction of chirality in this step allows the final product (−)-morphine to be produced without any resolution. Allylic alcohol 16 was then transformed to allylsilane 17 in five steps involving a condensation with phenyl isocyanate, transformation of the terminal olefin to the corresponding acetonide, SN2' displacement of the carbamate, deprotection of the acetonide followed by cleavage of the resulting diol, and treatment of the resulting aldehyde with dibenzosuberylamine (DBS-NH₂). Condensation of 17 and aldehyde 18 resulted in the formation of 19 in which (E)-iminium ion is orientated towards to the face opposite to the silyl group. Subsequent cyclisation gave product 20, which upon treatment with a palladium catalyst underwent a Heck reaction to give unsaturated morphinan 21. After cleavage of the benzyl ether of 21, the final ring of the core skeleton was formed by treatment...
with camphorsulfonic acid and 3,5-dinitroperoxybenzoic acid. Intermediate 22 was then converted into 23 in three steps, from which (−)-morphine was prepared in another five steps following Rice’s route.

Scheme 4

Overman’s asymmetric method also allowed the synthesis of the other enantiomer by adopting the enantiomeric form of the proline-derived catalyst 15. The success of the iminium ion-allylsilane cyclisation and the formation of the quaternary stereocentre by an intramolecular Heck reaction also highlighted the efficiency of this approach. This route, like many others, primarily focused on the construction of the N-norreticuline moiety. Several phenanthrene-based approaches to morphine have been reported, such as Ginsburg in 1954,\textsuperscript{19} Mulzer\textsuperscript{20} and White\textsuperscript{21}, both in the 1990s.
1.3.3 White’s Approach to Morphine

Due to the interest of the pharmacological properties of the unnatural enantiomer, White’s synthesis focused on (+)-morphine (Scheme 5).\textsuperscript{21} Stobbe condensation\textsuperscript{22} of isovanillin 24 and dimethyl succinate 25, followed by a chiral rhodium catalysed asymmetric hydrogenation\textsuperscript{23} and bromination gave intermediate 26. Intramolecular Friedel–Crafts reaction of 26, hydrogenolysis of the resulting aryl bromide and saponification gave 27. Condensation of 27 with methyl formate was followed by treatment with methyl vinyl ketone to give 28, which was subjected to a Robinson annulation to yield the phenanthrene framework 29. Substrate 29 was then transformed into tetracyclic intermediate diazo ketone 30 in nine steps. The formation of the quaternary carbon centre 13 of the pentacyclic nucleus of 31 was achieved by rhodium(II)-catalysed carbenoid C–H insertion from diazo ketone 30. (+)-Morphine was then synthesised from 31 in another ten steps. The overall yield of White’s approach is moderate (\textit{ca.} 3\%). This synthesis can be easily used to prepared the natural (−)-morphine by controlling the stereochemistry of 26.

Scheme 5
1.3.4 Parker’s Approach to Morphine

Parker et al. made use of a tandem radical ring closure to construct the morphine core structure in an extremely efficient manner (Scheme 6).\textsuperscript{24} Mono-protected diol 33 was obtained from aryl amine 32 in a seven-step transformation. Mitsunobu coupling of 33 and phenol 34 followed by deprotection of the resulting alcohol yielded substrate 35 with the aromatic ring placed behind the cyclohexene. When treated with Bu$_3$SnH and AIBN, aryl bromide 35 underwent the planned cascade sequence to afford 38. The final ring of morphine, the piperidine ring, was formed when tosylamide 38 was exposed to dissolving metal conditions. It was believed that the ring closure was facilitated by $N$-centred radicals. Swern oxidation of 39 gave ketone 40, which was transformed to (\textendash)-morphine according to literature procedures.\textsuperscript{17,25}

![Scheme 6](image-url)
Morphine is currently produced mostly by extraction from the natural plant opium.\textsuperscript{26} Although India and Australia are the two biggest legal suppliers for morphine, a large proportion of opium is grown in the world’s politically unstable areas and in order to secure the supply of morphine alternative means should be explored. However, synthetic manufacturing of morphine will only be favourable if a short sequence (6–8 steps) is achieved.\textsuperscript{26} This may seem almost unobtainable given the state-of-the-art chemistry, but from that point of view this molecule still provides a major challenge. In addition, given the unique structure of morphine, many synthetic chemists continue to use this molecule as a test ground for different methodologies.

### 1.4 The Craig Group Proposed Route to Morphine Synthesis

The Craig group has a keen interest in natural product synthesis\textsuperscript{27,28,29} and has been very active in exploring the synthesis of morphine in recent years.\textsuperscript{30,31} Our current proposal intends to take advantage of the methodologies of regioselective vinylaziridine ring-opening mediated by sulfones and ring-rearrangement metathesis (RRM) (Scheme 7).

![Scheme 7](image-url)
It was envisaged that (±)-morphine could be constructed from cyclopentenyl sulfone 45 and vinylaziridine 46. The synthesis of sulfone 45 has been reported via a π-allyl palladium-mediated nucleophilic addition of sodium phenylsulfinate to cyclopentadiene monoxide.32 The preparation of aziridine 46 has been achieved via two routes,30,31 developed by former group members, both starting from butadiene monoxide 47 and the Grignard reagent (4-methoxyphenyl)magnesium bromide 48.

It was believed that the three-membered N-ring of aziridine 46 would undergo a regioselective ring-opening reaction when treated with the α-sulfonyl carbanion of 45. The sulfonyl cyclopentene product 44 would then be subjected to metathesis conditions in an attempt to synthesise sulfonyl cyclohexene 43 via a ring-rearrangement metathesis (RRM). Subsequently, we hoped to form the C12–C13 bond of phenanthrene 42 by a Lewis acid-mediated intramolecular desulfonylative cationic cyclisation of 43. Hydroboration–oxidation of the terminal double bond of 42 followed by an intramolecular Mitsunobu reaction should furnish the piperidine ring of 41. When successful, it would result in the dihydrofuran ring formation. This was expected to include an oxidation of the allylic alcohol of substrate 41 and a hydroxylation of its enol tautomer. After bromination of the aromatic ring, this process would then be concluded by an aromatic substitution by the resulting alcohol to give the pentacyclic skeleton of morphine.

One of the attractive characteristics of this retrosynthesis is that RRM of cyclopentenyl sulfone 44 to cyclohexenyl sulfone 43, arranging the functionality required for the formation of the next two rings. A major aspect of this project also aimed to develop further the methodology of regioselective aziridine ring-opening.

The following reviews intend to give some literature evidence for the feasibility of the unprecedented RRM step proposed, and an overview of recent developments in the area of regioselective aziridine ring-opening.
1.5 Ring-rearrangement Metathesis

Metathesis chemistry has gained tremendous attention from synthetic chemists in recent years. Its unique and easy way of forming and redistributing carbon–carbon bonds makes it one of the most powerful tools in organic chemistry. Moreover, with increasingly robust catalysts being discovered (Figure 2), its impact will continue to expand.

![Well-defined olefin metathesis catalysts](image)

**Figure 2 - Well-defined olefin metathesis catalysts**

1.5.1 RRM of Carbocycles to Heterocycles

Amongst the three fundamental types of metathesis, ring-closing metathesis (RCM), cross metathesis (CM) and ring-opening metathesis polymerisation (ROMP), RCM and ROMP have been most widely used. In recent years the combined intramolecular use of ring-opening metathesis (ROM) and RCM, also recognised as ring-rearrangement metathesis (RRM), has grown rapidly. Investigations have shown that RRM reactions are generally governed by thermodynamic factors. It provides an effective way of forming heterocycles such as 54a, b from their corresponding carbocycles 53a, b by an increase in thermodynamic stability (Figure 3).
Blechert and Schaudt have successfully synthesised the first natural cis-cinnamoyl alkaloid (+)-astrophylline utilising RRM chemistry (Scheme 8). The RRM reaction precursor 57 came from a Mitsunobu substitution of the alcohol of 56 with N-Ns allyl amine. Alcohol 56 derived from optically pure acetate 55 in four steps involving: Pd(0) π-allyl substitution; epimerisation; stannation and [2,3]-Wittig–Still rearrangement. Stereospecific RRM reaction of cyclopentene 57 with catalyst 50 gave bi-tetrahydropyridine 58, which was converted to compound 59 after N-Ns deprotection and acylation. Subjection of 59 to N-Boc deprotection followed by alkyne syn-reduction gave (+)-astrophylline 60.

![Figure 3](image)

**Scheme 8**
1.5.2 RRM of Carbocycles to Carbocycles

In contrast to the transformations described above, converting one carbocycle into another by RRM is more challenging, especially when the ring strain of the product is close to the starting material. Norbornenes are good substrates for RRM owing to their highly strained bridged bicyclic system. Blechert and co-workers have reported the first application of RRM for the synthesis of \([X.3.0]\) carbo-bicycles using olefin substituted norbornenes \(61a–d\) (Scheme 9). Rearranged products \(62a–d\) were easily obtained under mild reaction conditions. The presence of ethylene was necessary in order to suppress polymerisation. Notably, even the relatively strained bicyclo[6.3.0]undecene \(62d\) was synthesised in good yield.

![Scheme 9](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(61a)</td>
<td>(62a)</td>
<td>80%</td>
</tr>
<tr>
<td>(61b)</td>
<td>(62b)</td>
<td>88%</td>
</tr>
<tr>
<td>(61c)</td>
<td>(62c)</td>
<td>75%</td>
</tr>
<tr>
<td>(61d)</td>
<td>(62d)</td>
<td>83%</td>
</tr>
</tbody>
</table>

**Scheme 9** [a] catalyst 49 used; [b] catalyst 52 used

A highly efficient synthesis of fused tricyclic enones from norborne derivatives has been achieved by Holtsclaw and Koreeda using tether-directed RRM (Scheme 10). In the presence of catalyst 49, norborne \(63\) underwent the desired rearrangement to give tricyclic compound \(64\) in an excellent yield.

![Scheme 10](image)
The rearrangement of cyclohexenes under metathesis conditions is rarely reported. However, Mehta and Nandakumar have successfully applied this strategy in a domino process (Scheme 11).\textsuperscript{43} By using 30 mol% of catalyst 49, they were able to convert cyclohexenyl diene 65 into a mixture of tertiary alcohol 66 as the major product and secondary alcohol 67. After purification by silica gel column chromatography, 66 almost completely rearranged to the more stable 67.

![Scheme 11](image)

Ring-rearrangement metathesis process can also be carried out stereoselectively. Hoveyda, Schrock and co-workers have successfully converted achiral homoallylic cyclopentene 69 into cyclohexene 70 using chiral molybdenum based catalysts 68.\textsuperscript{44} Depending on the reaction conditions the ee of the desired product can reach up to 96% in a reaction yield of 94%. This ring shuffling encouragingly proved the feasibility of interconversion from cyclopentenes to cyclohexenes where the ring strains are very similar.\textsuperscript{45}

![Scheme 12](image)
1.6 Regioselective Ring-opening of Aziridines

The aziridine functionality, or alternatively recognised as azaethylene or ethylenimine unit, is one of the most important three-membered ring moieties in organic synthesis. Structurally, aziridines are analogous to epoxides with the nitrogen group replacing the oxygen. The chemistry of aziridines has been increasingly researched over the last few decades and their application has been greatly broadened. Aziridines have become important building blocks in synthetic chemistry, especially for nitrogen-containing bioactive natural compounds.

The utility of aziridines is profoundly dependent on their ability to undergo nucleophilic ring-opening, both stereo- and regioselectively. It is widely accepted that aziridines with nitrogen bearing electron-withdrawing substituents, such as sulfonyl, sulfinyl, phosphoryl, phosphinyl and carbonyl, are more reactive towards ring-opening than their nitrogen unsubstituted counterparts.

Regarding the regiochemistry, the intrinsic properties of the aziridine and the nature of the incoming nucleophile can both affect the outcome. In general, 1,2-disubstituted aziridines mirror that of similarly substituted epoxides, in that they suffer attack at the less substituted 3-position. This regioselectivity may be changed when the two C–N bonds are polarised unsymmetrically and there is significant positive charge development at the 2-carbon atom, e.g. 2-benzyl substituted aziridines in acidic media. When both carbon atoms are substituted, competing steric and electronic effects may be such that the regioselectivity of nucleophilic ring-opening is eroded, though many examples of selective reactions are documented.

2-Phenyl substituents are powerful directing groups for regioselective ring-opening of aziridines by both carbon and hetero nucleophiles. Two possible mechanisms may be proposed as outlined in Figure 4. Firstly, as above mentioned, there is a partial positive character developed on the C-2 induced by the electron withdrawing phenyl group, as shown in structure 71. Secondly, the resulting C-2 p orbital of the nucleophilic ring-opening transition state is stabilised through overlapping with the aromatic system of the phenyl ring, as depicted in structure 72.
A comprehensive review on the subject of nucleophilic ring-opening of aziridines was offered by Hu, together with many others. The following review intends to give an overview of regioselective ring-opening of aziridines organised by class of nucleophile, focused mainly on reports from the year 2000 onwards.

**Figure 4 - nucleophilic ring-opening of 2-benzyl substituted aziridines**
1.6.1 Carbon Nucleophiles

Hodgson and co-workers have established a general process to access allylic N-sulfonylamines by regio-controlled opening of 2,3-disubstituted N-sulfonylaziridines with dimethylsulfonium methylide 74\(^{54}\) (Scheme 13).\(^{55}\) Initial attack on the benzylic or allylic carbon of the aziridines 73\(_a\)–\(_d\) by 74 generated intermediates 75, which could then undergo elimination to give the desired products 76\(_a\)–\(_d\) through either path A or B with another equivalent of 74.

As shown in Scheme 13, both N-Ts and N-Bus (Bus = tert-butylsulfonyl) aziridines gave the corresponding allylic amines in good yields. With the exception of substrate 73\(_b\) that gave the other regioisomer in 12% yield, all others produced exclusively the expected compounds. Diene 76\(_d\) is also potentially useful for cycloaddition chemistry.\(^{55}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>aziridine</th>
<th>product</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73(_a)</td>
<td>76(_a)</td>
<td>R(_4) = H, 85 TES, 79</td>
</tr>
<tr>
<td>2</td>
<td>73(_b)</td>
<td>76(_b)</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>73(_c)</td>
<td>76(_c)</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>73(_d)</td>
<td>76(_d)</td>
<td>75</td>
</tr>
</tbody>
</table>

Scheme 13
The use of Lewis acids, such as Cu, Zn, B, Sc, In, Bi, Ce, Au and Ag in promoting aziridine ring-opening has attracted much attention.\textsuperscript{53} Yadav \textit{et al.} examined the use of In(OTf)\textsubscript{3} as catalyst in the reaction of aryl aziridines 77 and arenes 78 (Scheme 14).\textsuperscript{56} This was the first report on regioselective aziridine ring-opening with arenes. Despite the fact that there is no substitution on C-3, nucleophilic additions almost exclusively occur on C-2. With short reaction times of 1–2 hours for activated arenes, and slightly longer for unactivated arenes (4–6.5 hours), β-diaryl amines 79 were prepared in high yields and excellent regioselectivity. In addition, they also investigated other metal triflates and found that 5% Sc(OTf)\textsubscript{3} and 10% Yb(OTf)\textsubscript{3} gave similar results for activated arenes but In(OTf)\textsubscript{3} was the only catalyst effective for unactivated arenes. Additionally, without the use of catalyst, no reaction was observed.

![Scheme 14](image)

Interestingly, when metal halide catalysts were used, a mixture of β-diaryl amines and β-chloro amines 80 were obtained (Scheme 15).

![Scheme 15](image)
This methodology was extended by Wu et al.\textsuperscript{57} and Roy et al.\textsuperscript{58} In the interest of applying gold and silver catalysts in organic synthesis, Wu and co-workers demonstrated that the combination use of AuCl\textsubscript{3} and AgOTf had similar results as that of Yadav (Scheme 16), whereas poor yields were resulted when only one of them was used. Except when $R^2 = \text{OMe}$ obtained with a selectivity of 5.2:1, all other reactions gave 100% regioselectivity. However, when switching $R^2$ to electron withdrawing groups such as $-\text{Cl}$, $-\text{CF}_3$ and $-\text{NO}_3$, complex, unidentified mixtures were obtained.

![Reaction Scheme](image)

**Scheme 16**

This type of process is not restricted to arenes. Heteroarenes are also susceptible to Lewis acid mediated nucleophilic addition to aziridines. In addition to Yadav’s earlier work,\textsuperscript{59} Roy et al. recently showed that in the presence of AgPF\textsubscript{6}, furans 81 and thiophenes 82 are good nucleophiles for the regioselective ring-opening of aziridines 77 to yield exclusively 83 (Scheme 17).\textsuperscript{58} The authors believed that the well-known binding ability of Ag(I) towards arenes\textsuperscript{60} and aziridines\textsuperscript{61} might contribute to such reactivity.
Aziridines have also been found to undergo ring-opening reactions with nonactivated alkenes in the presence of BF$_3$·Et$_2$O. This remarkable work was published by Man and co-workers (Scheme 18). They described this process as a formal [3+2] cycloaddition involving a 1,3-dipole 2-phenyl aziridine precursor. Building on the success of reacting aziridine with allylsilanes, they were able to extend this methodology to a variety of other alkenes. They suggested that the reaction occurred via a rather unusual zwitterionic 1,3-dipole, as depicted in intermediate 86, stabilised externally by the aromatic ring and the tosyl group. It is so electron deficient that it can react with nonactivated alkenes to generate 88. Intermediated 88 can then undergo either β-hydride elimination to give 89 or nucleophilic attack of the nitrogen anion on the carbocation to afford pyrrolidine 90.

Scheme 17

Scheme 18

Results showed that the ratio of 89 and 90 depends on the stability of the carbocation of 88 (Scheme 19). When cyclopentene and cyclohexene 91 were used, a 1:1 mixture of 92 and 93 was observed. The yields of these two reactions were low, which was
probably also due to the stability of the carbocation. This hypothesis was supported by the outcome of the reactions using geminal disubstituted alkenes 94, in which more stable tertially carbocations were formed. As shown in Scheme 19, only the cyclised products 95 were prepared in good yields.

![Scheme 19](image)

Boron trifluoride etherate 85 is an excellent Lewis acid for mediating regioselective aziridine ring-openings. A key step in Farr’s synthesis of the GnRH antagonist GnRH-I is the unprecedented BF$_3$·Et$_2$O-catalysed enantio- and regioselective reaction between 2-arylindole 96 and nosyl aziridine 97 (Scheme 20). The use of BF$_3$·Et$_2$O resulted from the screening of a series of Lewis acids. Indole 96 was prepared in a nine-step sequence starting from 4-nitrophenyl acetic acid, involving a palladium-catalysed coupling of iodo aniline with phenyl acetylene followed by a 5-endo-dig indole formation triggered by CuI. Aziridine 97 could be obtained in a one-step transformation by treating L-alaninol with 2.1 equivalents of nosyl chloride in the presence of triethylamine. As illustrated in Scheme 20, the reaction of 96 with 97 gave a very good yield of 98, with perfect regio- and enantioselectivity. The stereochemistry of 98 was determined by direct comparison with that previously prepared by Walsh.
Effective boron-based Lewis acids are not limited to just BF$_3$·Et$_2$O. Pineschi et al. adopted the use of electron-rich aryl borates to achieve highly chemo-, stereo- and regioselective carbon–carbon bond formations from aziridines 99 and phenols 100 (Scheme 21) with retention of configuration at the C-2 of the aziridines.

When Ar is phenyl, a 1:1 mixture of C- and O-alkylated products 101 and product 102 was obtained. Interestingly, the amount of C-alkylated product was dramatically increased when Ar was more electron rich, with a ratio of >95:5 over their O-alkylated counterparts. Changing the protecting groups of the aziridine had very little effect on the outcome. During all these transformations, no alternative regioisomer was observed.

Having successfully accessed aminophenol derivatives 101, Pineschi also managed to convert them into aryl indolines 104 using intramolecular amination of aryl triflates 103 with CuI and CsOAc.
Another group of substrates capable of directing regioselective attack on the benzylic carbon of the aziridine is $\alpha$-indole aziridines. Tse et al. have developed a very efficient method of furnishing highly functionalised bisindoles 106 from 105 on a solid support under solvent free conditions (Scheme 23). The advantage of employing activated silica as the solid support was not only enhanced regioselectivity but also it cleaved the two $N$-Boc groups whereas clay (Montmorillonite K-10) gave both regioisomers and neutral alumina only yielded a small amount of the deprotected products.

Many functionalities on the indole nucleophile including halides, alkoxy groups and esters, were tolerated under these conditions. However, 1-nitroindole only gave a poor yield of less than 20% and 1,2-dimethylindole yielded a substantial amount of the undesired regioisomer.

In addition to indole carbon nucleophiles, others such as $N$-, $O$- and $H$-nucleophiles also gave similar results.
In addition to investigations of regioselective nucleophilic additions at the aziridine C-2 centre, interest in C-3 attack has also been aroused. Unsurprisingly, when R are alkyl groups, ring-opening on the 3-carbon is favoured due to steric factors (Figure 5).

![Figure 5](image)

However, this limits the synthetic utility of the ring-opening product, considering the difficulties of further functionalising the R group α to the resulting amine. Introduction of other functionalities will complicate the electronic effect, as a result, both C-3 and C-2 attacks are possible due to steric and electronic reasons. For example, when using 2-carboxylate ester aziridines in the course of the study to provide new amino acids, Baldwin et al. observed some interesting regioselectivities (Scheme 24). When carbonyl stabilised reagent 108 was used to react with aziridine 107 and the protecting group of the nitrogen was either of the strongly electron withdrawing groups, –COC₆H₄NO₂ and –Ts, both isomers 109 and 110 were obtained with the C-3–N-1 cleavage product 109 favoured. Whereas when the protecting group was –COCH₂C₆H₄NO₂ or –COCH₂Ph, only 109 was isolated with yields of 30%.

![Scheme 24](image)

They also tested organolithium and Grignard reagents, such as 112, in the reactions with aziridine 111 and found that nucleophilic attacks on both carbons took place (Scheme 25). The ratio between products 113 and 114 is affected by the size of the nucleophile. When R is methyl, compound 114 was obtained as the major isomer at a ratio of 4:1. However, when R is isopropyl, only compound 113 was observed.
To overcome this problem, Young and co-workers examined the reaction of 2-carboxylic acid aziridine 115 with a variety of organocuprate nucleophiles, where completely regioselective C-3 attack was achieved to furnish α-amino acids 116 (Scheme 26). Nevertheless, the reaction of 3-methyl substituted aziridine 117 gave a ~1:3 mixture of isomers 118 and 119 with the β-amino acid as the preferred product (Scheme 27).

Scheme 26

Scheme 27
1.6.2 Heteroatom Nucleophiles

2-Phenyl aziridines are also often used to effect regioselective attack by heteroatom nucleophiles, similar to carbon nucleophiles, on the benzylic carbon.\textsuperscript{71} Diamines and amino sulfides are biologically and synthetically important classes of compounds in the pharmaceutical industry.\textsuperscript{72} Rao et al. have devised an approach to synthesise these two groups of substrates (Scheme 28).\textsuperscript{72} In the presence of β-cyclodextrin (β-CD) in H\textsubscript{2}O, the reaction of hydroxy phenylaziridine 120 and amines/sulfides yielded only single regioisomers 121 and 122. β-Cyclodextins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme28.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 28}

Ring-opening of pyridyl-substituted aziridine with \textit{N}-, \textit{S}- and \textit{O}-nucleophiles was tested by Savoia et al. (Scheme 29). Intriguingly, in contrast to phenyl-substituted aziridines, it did not produce good selectivity. Prepared by addition of chloromethyl锂thium to pyridineimine derived from (\textit{S})-valinol, aziridine 122 was allowed to react with a series of nucleophiles in the presence of Lewis acids. Except when NaN\textsubscript{3} was used which gave 100% C-2 addition isomer 123, all other reagents gave mixtures of 123 and 124 with ratios varied from 96:4–40:60.
Scheme 29

Nucleophilic addition of heteroatoms to carboxylate aziridines is of particular interest due to the ease of accessing the precursor natural or unnatural amino acids, which are themselves useful building blocks for synthesis. In their work towards indolizidine alkaloid syntheses, the Dhavale group developed an efficient approach for the synthesis of pentahydroxylated indolizidine derivatives by using regioselective ring-opening of aziridine 125 with H₂O to give 126, promoted by TFA (Scheme 30). Following a six-step sequence from 126, compound 127 and 128 were prepared.

Scheme 30

The importance of fluorinated compounds has been well documented. This class of substrates has attracted increasing attention in recent years, especially in the pharmaceutical industry. The introduction of fluorine atoms into organic molecules often results in profound changes in their chemical and biological properties. One
important family is fluorine-substituted amino acids. Many methods for their preparation have been reported. However, few methodologies for the synthesis of fluorinated diamino acid have been developed.

Bonnet-Delpon et al. have achieved the synthesis of fluoro-alkyl α,β-diamino acids by ring-opening of 2-carboxy-3-trifluoromethyl aziridines 129 and 131 with nitrogen nucleophiles (Schemes 31, 32). 2,3-cis-Aziridines 129 were prepared form CF₃-imines reacting with ethyl diazoacetate in the presence of a sub-stoichiometric amount of BF₃·Et₂O. When treated with amines or NaN₃, ring-opening products 130 were obtained with complete stereo- and regioselectivity without Lewis acid catalysis (Scheme 31). 2,3-trans-Aziridine 131 was synthesised by bromination of (E)-ethyl 4,4,4-trifluorobut-2-enoate followed by aminative cyclisation with tosylamine. Regioselective nucleophilic attack of 131 was accomplished with benzylamine 132 to give the α,β-diamino ester 133 (Scheme 32). The stereochemistry of 133 was determined by X-ray crystallography.

Scheme 31

Scheme 32
Bonnet-Delpon believed that the regioselectivity of these reactions was due to the strongly electronegative nature of the fluorine atoms, resulting in electrostatic repulsion between the trifluoromethyl group and the incoming nucleophiles. Additionally, it may also be explained by the theory that the \(-\text{CF}_3\) substituent is less able than the \(-\text{COOEt}\) group to stabilise the p orbital of the transition state on the adjacent carbon in an S_N2 process.

The Joullié group has reported a thorough investigation of ring-opening reactions of highly substituted alkynyl aziridines with oxygen nucleophiles (Schemes 33, 34).  

Remarkably, addition of phenol nucleophiles 134 occurred exclusively on the more substituted C-2 of both aziridine carboxamide 135 and aziridine ester 137. The yields of products 136 were low, typically around 50%. It was found that, under these conditions, the sulfonamide anion intermediate further reacted with the terminal alkyne undergoing a 5-endo-dig cyclisation to give the corresponding pyrroles. This was avoided when stronger base TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene or 2,3,4,6,7,8-hexahydro-1Hpyrimido[1,2-a]pyrimidine) was used in the absence of copper catalyst. When these optimised conditions were later applied to the reactions of 137, the yields of products 138 were dramatically increased.
To probe the mechanism of these reactions, aziridine 139 was used to investigate whether the regioselectivity was dictated by the alkynyl substituent (Scheme 35), as literature precedent suggested that alkynyl aziridine ring-opening processes could occur through an allene carbenoid intermediate. However, as shown in Scheme 35, with absence of the C2 alkynyl group, aziridine 139 underwent a regio-controlled nucleophilic addition with phenol at the more hindered C2 to give 140. This unanticipated result prompted the authors to carry out computational studies which showed that, in both alkyl and alkynyl aziridines, the C2–N bond was longer than the C3–N bond. Additionally there was a partially positive charge on C2. Further X-ray analysis of aziridine 141 (Figure 5) confirmed that C2–N bond length was 1.552 Å, longer than 1.496 Å of the C3–N, implying that it was indeed the weaker bond. Furthermore, the ethynyl–C2–methyl bond angle is greater than that of a normal tetrahedral carbon making it more susceptible towards nucleophilic attacks.

![Scheme 35](image)

**Figure 5**

Halides are another good class of nucleophiles in the reactions with aziridines. Righi et al. found that N-Boc-alkenyl aziridines 142 underwent regioselective ring-opening with lithium halides when catalysed by Amberlyst-15 (Scheme 36). With various R substituents, only single regioisomers 143 were observed. Interestingly, when purified by silica gel column chromatography, the bromo- and iodo-products underwent intramolecular S_N2 reactions to give oxazolidinones 144, whereas no conversion occurred on the chloro-derivatives.
Nevertheless, when aziridine 145 was used, with a methyl group replacing the carboxylate group of 143, the reactions gave a complex mixture of products (Scheme 37).
1.6.3 via Aziridinium Ion

Aziridinium ion chemistry has gained increasing interest from synthetic chemists. They are useful intermediates in facilitating aziridine ring-opening processes and proved to be valuable for the synthesis of chiral diamines. A general strategy in forming aziridinium ions such as 148, as shown in path A in Scheme 38, relies on an intramolecular SN2 reaction of hydroxyamine 146. Subsequent regioselective attack of 148 with amine 147 will give C2 and/or C3 addition adducts 149 and/or 150. The regioselectivity depends on the R1 and R5 substituents, or sometimes the nucleophiles.

![Scheme 38](image)

However, as illustrated in path B, direct intermolecular SN2 reaction of 146 with amine 147 can occur under the same conditions. This gives diamine 151, which is diastereomeric to 149. Since the difficulties in differentiating between 149 and 150 by common analytical techniques, such as NMR, questions arise whether the aziridinium intermediates have indeed been formed during the reaction.
The O’Brien group has probed the evidence of the aziridinium ion formation using a novel deuterium substitution approach. During their investigation for the synthesis of 1,2-chiral diamines, they observed that varying the R group of 152 affected the regioselectivity (Scheme 39). When R = Me, Bn or iPr, 153a–c were favoured against 154a–c. Whereas when R = Ph, 154d was synthesised with an excellent regioselectivity. They argued that the formation of 154d must have proceeded via an aziridinium ion intermediate whereas it was not conclusive for the formations of 153a–c since direct S_N2 substitution on 152a–c with MeNH_2 would also give 153a–c.

![Scheme 39](image)

<table>
<thead>
<tr>
<th>starting material</th>
<th>R</th>
<th>yield(%)</th>
<th>153a-d:154a-d</th>
</tr>
</thead>
<tbody>
<tr>
<td>152a</td>
<td>Me</td>
<td>78</td>
<td>70:30</td>
</tr>
<tr>
<td>152b</td>
<td>Bn</td>
<td>70</td>
<td>94:6</td>
</tr>
<tr>
<td>152c</td>
<td>iPr</td>
<td>62</td>
<td>93:7</td>
</tr>
<tr>
<td>152d</td>
<td>Ph</td>
<td>78</td>
<td>2:98</td>
</tr>
</tbody>
</table>

To clear this ambiguity, they decided to prepare the deuterated adduct syn-155 by incorporating a deuterium atom onto the α-hydroxy carbon of 152b and determine the mechanism of nucleophilic addition of NH_2Me by analysing the stereochemistry of the products. As depicted in Scheme 40, compound syn-155 was prepared via a Swern oxidation of 152b followed by reduction with sodium borodeuteride. Subsequent methanesulfonate formation with MsCl followed by treatment with MeNH_2 gave a 94:6 C1/C2 addition regioisomeric mixture with C1 addition products 156 as the major isomer. Further experimental and NMR analyses revealed that 156 consisted of an 85:15 diastereomeric mixture of syn-156 and anti-156. The retention of the C1 stereocentre of syn-156 indicated that this process went through an aziridinium ion intermediate whereas the C1 inversion conformation of anti-156 came from a direct S_N2 process.
Ha et al. have reported a novel synthesis of oxazolidinones via aziridinium ion species (Scheme 41). Acylation of the nucleophilic nitrogen of carboxylate aziridines 157 gave aziridinium ions 158, which were more reactive and regioselectively attacked by the resulting chloride anion to give chlorides 159. Chloro-substituted intermediates 159 were then converted into oxazolidinone 160 through intramolecular S_N2 reactions. The formation of the aziridinium intermediate was also evidenced by the isolation of compound 159 when the reaction was performed in toluene instead of acetonitrile. Furthermore, when 159 was heated under reflux in acetonitrile, it gave oxazolidinone 160 in excellent yield.
In addition to carboxylate aziridines, Ha also investigated vinylaziridines 162 and 164, prepared from aldehyde 161 via Horner-Wadsworth-Emmons reaction and Wittig reaction respectively (Scheme 42). When exposed to standard conditions, oxazolidinones 163 and 165 were isolated in good yields and excellent regioselectivity.
Wang and co-workers extended this methodology to the synthesis of 1,4-benzodiazepine derivatives 170 (Scheme 43). This process began with N-benzylation of aziridines 166 with benzyl bromides 167 followed by a highly regioselective ring-opening of the aziridinium intermediates 168 by the resulting bromide anion to generate bromoesters 169. The regioselectivity was ca. 10:1, as determined by 1H-NMR, in favour of attack on the more substituted carbon adjacent to the ester group. Although compounds 169 could be isolated by silica gel column chromatography, they were used in a one-pot process by addition of triethylamine under reflux to furnish the desired products 170. The overall yield was respectable, typically around 50–60%, with the exception of where R is 3-Cl and Ar is phenyl giving a yield of 25%. This tandem method provides an efficient way of preparing 1,4-benzodiazepines with easy availability of starting materials and simple procedure.

Scheme 43
1.7 Conclusion

The current Craig group retrosynthetic approach to morphine was proposed (Scheme 7), together with examples of some classical total syntheses of morphine. Our strategy includes two key steps: 1) an unprecedented RRM of allyl cyclopentene 44 to vinyl cyclohexene 43; 2) regioselective ring-opening of vinyl aziridine 46 with anionic sulfone 45. The RRM step was considered to be challenging since the relatively similar ring-strain of the starting material and the desired product. Some reported examples were provided to prove the feasibility of this transformation. A brief review in the area of nucleophilic regioselective ring-opening of aziridines was presented. It demonstrates the unique value of this methodology in constructing carbon–carbon bonds stereo- and regioselectively and incorporating nitrogen into molecules. The foregoing discussion shows that, in general, phenyl substituents are particularly effective for directing regioselective attack, both for carbon and heteroatom nucleophiles. Some interesting results with carboxylate-substituted aziridines have been observed where the control elements are less obvious. Additionally, the presence of Lewis acids proved to be essential in some cases and their effects were fascinating. Finally, aziridinium rings have significant potential in directing regio-controlled attack, which allows rapid formation of a variety of heterocycles.
2. Results and Discussion

Application of aziridine chemistry in natural products synthesis:
Previous results from the Craig group

The Craig group is actively involved in the application of aziridine chemistry directed towards natural product synthesis. Previous research has successfully accomplished the synthesis of (±)-lepadiformine 179 via two key reactions: aziridine ring-opening and 5-endo-trig pyrrolidine formation mediated by a phenylsulfonyl group, as shown in Scheme 44. The natural form (−)-lepadiformine, a decahydro-1H-pyrrolo[1,2-j]quinoline isolated in 1994 by Biard et al. from the tunicate Clavelina lepadiformis92, has moderate in vitro cytotoxic activity towards various tumor cell lines, including nonsmall-cell lung carcinoma (NSCLCN6), and is also a cardiac-K⁺-channel blocker.93

N-SES Protected aziridine 174 was prepared from N-cyclohexylidenecyclohexanamine 171 and 2-(2-bromoethyl)-1,3-dioxolane 172 in a four-step sequence. Alkylation of the lithium enolate of 171 with 172 gave ketone 173, as described by Minor and Overman.95 Epoxidation of 173 with dimethylsulfoxonium methyliide, prepared from Me₃S(O)I and NaH in situ, yielded a single epoxide, which reacted with SESNH₂ to give the corresponding amino alcohol. Subjection of this amino alcohol to modified Mitsunobu conditions [1,1’-(azodicarbonyl)dipiperidine (ADDP), Me₃P] furnished 174 with inversion of configuration at the tertiary alcohol stereocentre. Completely regioselective attack at the less hindered site of the aziridine of 174 was achieved by treatment with lithiated PhSO₂Me, giving 175 in 97% yield. Exposure of the dianion of 175 to BnOCH₂CHO followed by quenching with PhCOCl furnished pyrrolidine 176. This process proceeds through a 5-endo-trig cyclisation of the resulting E-vinylc sulfone intermediate.

The tetracyclic intermediate 177 contains the tricyclic skeleton of lepadiformine 179, which was constructed by deprotection of the benzyl and SES group of 176 followed by cleavage of the acetal triggering aminal formation. Reaction of 177 with hex-1-ylnylmagnesium bromide in an S₈1-like substitution gave alkyne 178, which was transformed into 179 in another seven steps.
Scheme 44

A modified approach to the previously established route\(^9\) in the group that has achieved the pentacyclic framework of \((-\)-alstonerine\(^9\) 187, a macroline-related alkaloid, was also investigated, as outlined in Scheme 45.\(^9\) This involves the synthesis and ring-opening reaction of the 1,2,3-trisubstituted indole hydroxymethyl-substituted aziridine 184.

Mono-protection of diol 180 followed by aziridination gave cis-aziridine 181. This substrate was then converted to cis-aziridine 184 in a four-step sequence involving: NaH-mediated aza-Payne rearrangement to yield the epoxide 182,\(^9\) BF\(_3\)-OEt\(_2\)-assisted ring-opening of 182 by 1-methylindole and cyclisation of amino alcohol 183 under Mitsunobu conditions followed by silyl deprotection. Reaction of O-lithio-aziridine 184 with lithiated tosyl acetal 185 gave a 1:1 mixture of adducts 186 in 83\% yield, with none of the alternative regioisomers observed. However, in an attempt to convert 186 into the corresponding tetrahydropyridine by treatment with Lewis acids such as
BF$_3$·Et$_2$O and TMSI, a Pictet–Spengler reaction occurred involving the indole C2. Current effort is focused on the use of alternative nucleophiles for ring-opening of 184.

Scheme 45
2.1 Previous Approaches to Morphine Synthesis

The approach to morphine synthesis shown in Scheme 46 has been investigated previously in the group.\textsuperscript{31} In this route, a key step was the preparation of acetal tosamide 191, by reaction of acetal 185 and 2,3-\textit{trans}-vinylaziridine 46. Aziridine 46 may in principle react at either of the aziridine ring carbon atoms, or in an $S_{N}2'$ sense at the terminal alkene carbon atom, as depicted in Figure 6. Additionally, it has acidic benzylic protons whose removal could trigger styrene formation through eliminative ring-opening.

![Scheme 46](image)

![Figure 6](image)
Despite all these possible side-reactions, lithio-185 was combined with aziridine 46 with complete chemo- and regio-selectivity to give acetal tosamide 191 in an excellent yield (Scheme 47). When treated with the Lewis acid BF$_3$·Et$_2$O, 191 cyclised to yield N-tosyl tetrahydropyridines 190.

**Scheme 47**

It was also discovered that under the same conditions the reaction of aziridine 46 with a more hindered nucleophile sulfone 192 gave allyl tosamide 193, the product of an $S_{N}2'$ addition at the terminal olefin, in a poor yield of 28% (Scheme 48).

**Scheme 48**

Intriguingly, when the 2,3-\emph{cis}-benzyl vinyl aziridine 194 was treated with lithio-192, the desired products 195 were obtained with once again complete chemo- and regio-selectivity, albeit in a low yield of 50% (Scheme 49).

**Scheme 49**
With tetrahydropyridine 191 in hand, its C-4 alkylation was investigated in an attempt to access the next key intermediate 189. However, after extensive experimentation, no direct alkylations were realised, although carboxylation was achieved when lithio-191 was treated with methyl chloroformate, giving 196 (Scheme 50).

Scheme 50


2.2 Investigation of the Current Retrosynthesis of Morphine

2.2.1 Synthesis of 2-(4-Methoxybenzyl)-1-tosyl-3-vinylaziridine 46

The work presented herein follows the current proposed retrosynthetic route to morphine synthesis, as previously described in Scheme 7, and its modifications as appropriate.

![Scheme 7]

At the outset of the new work described in this thesis, the synthesis of key vinylaziridine 46 was re-investigated. Two methods were available before the commencement of the project, both developed by former group members, Hyland\textsuperscript{30} and Carballares.\textsuperscript{31}

Initially the shorter approach uncovered by Hyland was examined. As depicted in Scheme 51, aziridine 46 was prepared stereoselectively in a four-step sequence starting from butadiene monoxide 47. Conjugate addition of (4-methoxyphenyl)magnesium bromide 48 to the terminal olefinic position of 47 was achieved in the presence of sub-
stoichiometric CuCN. The resulting allyl alcohol 197 was exposed to Sharpless aziridination conditions to produce hydroxylaziridine 198 with the desired 2,3-trans configuration, together with 8% of the 2,3-cis isomer. No alternative reactions for the synthesis of 198 were carried out using another common aziridination procedure with PhI=NTs and Cu(OTf)$_2$ since it was found by Hyland that only starting material and tosylamide were recovered.

Scheme 51

The proposed pathway for this bromine-catalysed aziridination process is shown in Figure 7. Initial addition of Br$^+$ to trans-olefin 199 gave bromonium ion 200 which reacts with TsNCl$^-$ to give $\beta$-bromo-N-chloro-N-toluene sulfonamide 201. Attack of Br$^-$ on the Cl–N group generates substrate 203 and Br$^-$ resource species entering the catalytic cycle. Intermediate 203 undergoes an intramolecular substitution of Br with NTs yields aziridine 204.
The subsequent oxidation of alcohol 198 was achieved using IBX to give the corresponding aldehyde in typically above 95% yields. However, the final Wittig olefination step was problematic. It was poor yielding and not reproducible. This was believed to be due to the instability of the aldehyde as decomposition was observed when it was passed through a silica gel column. Steric hindrance from the $N$-Ts group may also contribute to this outcome.

Although this approach gave access to aziridine 46, low yields rendered it impractical. As a result, the longer but more robust route of Carballares was adopted as shown in Scheme 52. Epoxidation of allyl alcohol 197, prepared as described previously in Scheme 51, yielded hydroxy epoxide 205, which was converted into vinyl epoxide 206 after oxidation and Wittig olefination. Microwave assisted ammonolysis of 206 gave amino alcohol 207 together with its regioisomer in a 10:1 ratio. This transformation could also be performed by conventional methods. However, a reaction time of 12 days was required to obtain similar results. Subsequent tosylation of 207 followed by Mitsunobu cyclisation of tosamide 208 furnished aziridine 46.
This method gave an overall yield of 52% compared to 11% for the route shown in Scheme 51. Furthermore, it gave good consistency when scaling up. It is noteworthy that only four column chromatography purifications were necessary as substrates 197, 205 and 207 could be used crude.

Scheme 52

2.2.2 Synthesis of 4-(Phenylsulfonyl)cyclopent-2-enol 45

Having successfully synthesised aziridine 46, the focus shifted to the synthesis of another key intermediate, 4-(phenylsulfonyl)cyclopent-2-enol 45 (Scheme 53). It has previously been prepared from epoxide 210 via a palladium(0) π-allyl addition process with two equivalents of PhSO₂Na. This method employed 0.5 mol% Pd(acac)₂ in THF to give 57% yield after five hours.³²

Encouraged by this report, cyclopentadiene monoxide 210 was prepared from cyclopentadiene 209 following a literature described procedure.¹⁰³ In an attempt to
improve the reaction yield, an alternative epoxidising reagent m-CPBA was tested. However, both TLC profiles and crude NMRs suggested that undesired by-products were produced and the expected compound was synthesised only in a very small amount. Nevertheless, with sufficient quantity of this substrate in hand, the synthesis of sulfone 45 was investigated. Disappointingly, when the literature conditions were repeated only a trace amount of sulfone 45 was isolated. Therefore other conditions were investigated (Table 1).

![Scheme 53](image)

By increasing the loading of the catalyst Pd(acac)$_2$ to 5 mol% and reaction time to four days, the yield of this reaction was improved to 37% (Entry 1). Interestingly, when switching the solvent from THF to DMF, no reaction occurred after six hours (Entry 2). When Pd(PPh$_3$)$_4$ was used in THF (Entry 3), no product was detected despite the fact that all the starting material of 210 had been consumed. Finally, when Pd$_2$(dba)$_3$ was employed in DMF, the highest yield of 42% was obtained (Entry 4) compared to 20% in THF. This was likely to be because the solubility of PhSO$_2$Na salt is much greater in DMF than THF.

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>catalyst (mol %)</th>
<th>time</th>
<th>temp. (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>Pd(acac)$_2$ (0.5→5)</td>
<td>4 days</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Pd(acac)$_2$ (5)</td>
<td>6 h</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>Pd(PPh$_3$)$_4$ (5)</td>
<td>2 days</td>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Pd$_2$(dba)$_3$ (5)</td>
<td>6 h</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>Pd$_2$(dba)$_3$ (5)</td>
<td>6 h</td>
<td>90</td>
<td>42</td>
</tr>
</tbody>
</table>

**Table 1**
Although cyclopentenyl sulfone 45 could be made via this route, low yields hindered its practicality. In order to overcome this unsatisfactory outcome, alternative methods were considered. There are many examples of synthesising cyclopentenes using RCM chemistry. It was expected that compound 45 could be derived from RCM of diene precursor 211 (Scheme 54). Diene 211 was anticipated to come from a regioselective ring-opening of epoxide 47 on C3 by lithiated allyl sulfone 212 that in turn could be prepared from inexpensive starting materials allyl bromide 213 and PhSO₂Na.

\[
\begin{align*}
\text{PhO}_2\text{S} & \xrightarrow{\text{RCM}} \text{PhO}_2\text{S} \quad \text{OH} & \quad \text{211} \\
\text{211} & \quad \Rightarrow 3 \quad \text{O} & \quad 2 \quad \text{212} & \quad \text{SO}_2\text{Ph} \\
& \xrightarrow{} \quad \text{213} & \quad + \quad \text{PhSO}_2\text{Na}
\end{align*}
\]

Scheme 54

As planned, allyl sulfone 212 was obtained after an S_N2 reaction of allyl bromide 213 and sodium phenylsulfinate (Scheme 55). The low yield of this step was likely due to the quality of reagent 213. Surprisingly, the subsequent ring-opening of epoxide 47 by lithiated anion of 212 resulted in olefin migrated products 216 and 217 with a 1.7:1 ratio according to ^1H NMR analysis of the crude mixture.

\[
\begin{align*}
\text{213} & \quad \text{Br} & \quad + \quad \text{PhSO}_2\text{Na} & \quad \xrightarrow{i} & \quad 70\% & \quad \text{212} \\
\text{212} & \quad \xrightarrow{ii} & \quad \text{PhO}_2\text{S} & \quad \text{OH} & \quad \text{216, 29\%} \\
\text{PhO}_2\text{S} & \quad \text{OH} & \quad \text{217, 17\%}
\end{align*}
\]

\[i) \text{DMF, rt, 4 h; ii) a) nBuLi (1.2 equiv), Et}_2\text{O, -20 °C-rt, 45 min; b) butadiene monoxide 47 (1.0 equiv), -20 °C-rt, 2.5 h}\]

Scheme 55
These results are probably due to the relative lack of stability of intermediates 214 and 215, induced by the strong electron withdrawing ability of the β-sulfonyl and the products being more stable α-sulfonyl tri-substituted olefins. The geometry of the double bonds was not proved. However, we believed that the E isomers were favoured because this process was considered to be driven by thermodynamic effect. Similar results were also reported by Cheng et al.\textsuperscript{105}

According to this hypothesis, it was speculated that the migration could be prevented if the β-sulfonyl olefin was stabilised by being more substituted such as 218 and/or having an electron withdrawing substituent such as 219 (Scheme 56). More importantly, the subsequent RCM would give the same product.

![Scheme 56](image)

Work by Hoveyda et al. has shown that RCM of diene 220 gave the corresponding cyclopentenol 221 in excellent yields (Scheme 57).\textsuperscript{106}

![Scheme 57](image)

Encouraged by this, prenyl sulfone 223 was prepared from prenyl bromide 222 and PhSO₂Na similar to that previously described in Scheme 55 (Scheme 58).\textsuperscript{104} Pleasingly, when butadiene monoxide 47 was treated with lithio-223, the expected products 224 and 225 were synthesised, both with dr >100:1. However, the regioselectivity of this reaction was poor. It gave 36% yield of the desired diene 224, less than that of the undesired diene 225 42%. Therefore RCM was not carried out at this point and the
stereochemical relationship between the phenylsulfonyl and hydroxyl substituents was not investigated.

\[
\begin{align*}
\text{PhSO}_2\text{Na} & \quad \text{PhSO}_2\text{Ph} \\
\text{222} & \quad \text{223} \\
+ & \quad \rightarrow \\
\text{i} & \quad \text{92\%} \\
\text{92\%} & \quad \rightarrow \\
\text{ii} & \quad \text{224, 36\%} \\
\text{225, 42\%} & \quad \\
\end{align*}
\]

i) DMF, rt, 6 h; ii) a) nBuLi (1.2 equiv), THF/TMEDA (1:1), –78-20 °C, 45 min; b) butadiene monoxide 47 (1.2 equiv), –78 °C, 1 h 45 min

![Scheme 58](image)

As depicted in Scheme 56, in line with the theory of having a more substituted double bond, introduction of an electron-withdrawing group such as phenyl was also expected to have a similar stabilising effect. Therefore, cinnamyl sulfone 227 was prepared from cinnamyl bromide 226 and PhSO₂Na. Indeed, when butadiene monoxide 47 was treated with lithio-227, the expected products 228 and 229 were obtained in around 3.5:1 ratio according to ¹H NMR analysis of the crude mixture. A number of conditions were tested in attempts to improve the yield and regioselectivity of this reaction, such as utilising co-solvent TMEDA, varying the reaction concentrations and temperatures. It was found that the yields for 228 and 229 were typically 55%–62% and 15–18% respectively. Compounds 228 were obtained as a 3:1 diastereomeric mixture, favouring the 3-phenylsulfonyl-5-hydroxyl-syn isomer, as determined later on in the RCM step. These two diastereoisomers were inseparable by column chromatography. However, a fraction of the syn isomer was isolated by slow recrystallisation.
With dienes 228 in hand, the subsequent RCM reactions were investigated. As had been hoped, when mixture 228 was treated with catalyst 50 in parallel with the small amount of 3,5-syn-228 isolated, they underwent facile ring-closing reactions to furnish 45 and 1,4-syn-45 in excellent yields and short reaction times (Scheme 60). Intriguingly, the reaction of 3,5-syn-228 was completed in just one minute, as monitored by TLC, whereas ten minutes were required for mixture 228. It is noteworthy that higher reaction temperature was crucial for these reactions. At room temperature the reaction proceeded very slowly and did not reach completion. Finally, the stereochemistry of syn-228 was determined by comparison of its RCM product syn-45 with that previously prepared via the palladium π-allyl nucleophilic addition strategy as illustrated in Scheme 53.

Scheme 59

Scheme 60

61
Due to difficulties in separating regioisomers 228 and 229 on large scales, a two-step experiment was devised by using the crude isomeric mixture for the subsequent RCM step. An overall yield of 54% for 45 was obtained when the reaction was carried out with 45 grams of cinnamyl sulfone 227.

In parallel with the investigation of the RCM of 228, its hydroxy-protected counterpart 230 was also subjected to metathesis conditions (Scheme 61). Protection of alcohol 228 with TBDMSI under standard conditions cleanly afforded 230. Interestingly, RCM of 230 demanded higher catalyst loadings and longer reaction times compared to 228. 5 mol% Catalyst 50 and 16 hours were required in order to obtain 231 in 79% yield.

$$\begin{align*}
\text{PhO}_2\text{S} & \quad \text{OH} \\
\text{Ph} & \quad \text{228} \\
\text{PhO}_2\text{S} & \quad \text{OTBDMS} \\
\text{Ph} & \quad \text{230} \\
\text{PhO}_2\text{S} & \quad \text{OTBDMS} \\
\text{231}
\end{align*}$$

i) TBDMSI (1.8 equiv), Et$_3$N (3.0 equiv), DMAP (7.5 mol%), CH$_2$Cl$_2$, 40 °C, 24 h; ii) catalyst 50 (5 mol%), CH$_2$Cl$_2$, 40 °C, 16 h

Scheme 61

Overall, a satisfactory route to access cyclopentenyl sulfone 45 was discovered. Cinnamyl sulfone 227 was the ideal starting material. It first of all precluded the double bond from migrating. Secondly it gave a regioselectivity of 3.5:1 in favour of the desired product. The explanation of the regioselectivity is believed to be that the steric hindrance of the phenyl group enhances the difficulties of attacking the more hindered C2 position of the epoxide.
2.2.3 Investigation of the Reactivity of Cyclopentenyl Sulfone 45

Having developed an efficient route to large quantities of cyclopentenyl sulfone 45, it was considered to be beneficial to investigate the reactivity of 45 prior to the reaction with aziridine 46. This section details the investigation of the stability of 45, α-SO₂Ph alkylation and RRM of its derivatives.

2.2.3.1 Stability Test of 45

The stability of 45 was considered to be crucial for subsequent transformations in the planned synthetic sequence. A major concern was that an elimination reaction would occur when 45 was treated with base, generating a more stable sulfonylecyclopentadiene 232 (Figure 8).

\[
\text{OHPhO} \quad \text{elimination} \quad \text{PhO}_2\text{S} \quad \text{PhO}_2\text{S} \quad \text{OH}
\]

\[
\begin{align*}
45 & \quad \rightarrow \quad 232
\end{align*}
\]

Figure 8

Therefore, a simple deprotonation experiment was carried out in which compound 45 was exposed to two equivalents of nBuLi in THF at –78 °C (Scheme 62). The resulting solution was warmed to 0 °C over a period of two hours. After stirring at that temperature for one hour followed by two hours at room temperature, the reaction was quenched with a 1M solution of AcOH in THF. Gratifyingly 100% of 45 as 1:1 diastereomixture were recovered.

\[
\begin{align*}
\text{PhO}_2\text{S} & \quad \text{OH} \quad 45, \text{ dr } = 3.5:1 \\
\text{1a. } & n\text{BuLi (2.0 equiv), THF} \quad -78^\circ \text{C } \rightarrow \text{ rt} \\
\text{1b. } & \text{AcOH, THF} \\
\text{PhO}_2\text{S} & \quad \text{OH} \quad 45, \text{ dr } = 1:1, \text{ 100%}
\end{align*}
\]

Scheme 62
2.2.3.2 α-SO₂Ph Alkylation of 45

As set out in the retrosynthetic route, our plan to access cyclohexene 43 entailed subjection to RRM of the cyclopentene-containing ring-opening adduct 44 (Scheme 63). This kind of RRM is unprecedented. In order to understand the RRM reactivity of this type of allyl cyclopentene moiety, it was considered to be useful to synthesise analogous cyclopentenes 234 in order to find out whether RRM would lead to cyclohexenes 235. The plan for synthesis of 234 involved treatment of lithio-45 with allylic bromides 233.

Scheme 63

Alkylations of cyclopentene 45 proved to be facile. When lithio-45 was treated with allylic bromides 233, 1-allyl-1-phenylsulfonyl cyclopentenes 234a–d were obtained (Scheme 64).
Remarkably, with the exception of 234a obtained with a 10:1 dr, these transformations gave complete diastereoselectivities favouring the 1-phenylsulfonyl-4-hydroxy-\textit{cis} isomers as depicted in Scheme 64. This was determined by the X-ray crystallographic structure of 234d (Appendix I).

This fascinating selectivity may be attributed to the chelating effect between lithium and oxygen atoms.\textsuperscript{108} As illustrated in Figure 9, the lithium cation coordinates with the oxy-anion and the proximal oxygen of the PhSO\textsubscript{2} group.\textsuperscript{108} This configuration leaves only the least hindered opposite face for the electrophiles to approach. This explanation is supported by X-ray crystallographic analysis of 234d, which shows a distinctive intramolecular H-bond between the \textendash OH and the \textendash SO\textsubscript{2} groups (Appendix I).
The yields of these reactions might be explained by steric effects. When the size of the electrophiles increased, the yields decreased. This was most marked by that the yields dropped from 61% for allyl bromide to 40% for prenyl bromide.

2.2.3.3 Investigation of RRM of 234a–d

Having acquired substrates 234a–d, their RRM reactivity was investigated. As previously mentioned, RRM of this kind is unprecedented. Two possible mechanisms may be proposed (Schemes 65, 66).

Mechanism 1 begins with an initially attack of the catalyst on the side chain olefin of 234 to give 236 followed by the interaction with the cyclic double bond in an attempt to undergo an intramolecular ring-opening of the cyclopentene (Scheme 65). However, as the Ru atom has to be bonded to the unsaturated cyclic carbon $\beta$ to the sulfone, as depicted in intermediate 237, ring strain impedes its viability.

Scheme 65

In mechanism 2, cyclopentene 234 is opened by the catalyst, generating intermediate 238 that then undergoes a ring-closing metathesis involving the side chain olefin (Scheme 66). Expulsion of LnRu=CHR$^1$R$^2$ 240 from 239 yields the expected cyclohexene 235. The regenerated ruthenium carbene species 240 is ready to initiate
another reaction cycle. This pathway avoids the ring strain seen in mechanism 1 and would therefore be the suitable mechanism for these reactions.

Scheme 66

Additionally, since RRM reactions were rationalised to be thermodynamically driven\textsuperscript{109} to ascertain whether cyclohexene was favoured, the following experiments were carried out (Scheme 67). Triene \textbf{241} was prepared from \textbf{228} via an S\textsubscript{N}2 reaction with allyl bromide. Treatment of \textbf{241} with catalyst \textbf{50} in dilute CH\textsubscript{2}Cl\textsubscript{2} afforded cyclohexene \textbf{242} as the only product isolated.
i) nBuLi (2.1 equiv), CH$_2$=CHCH$_2$Br (1.0 equiv), THF, $-78\,^\circ$C-rt, 1 h; ii) catalyst 50 (3 mol%), CH$_2$Cl$_2$, rt, 24 h

Scheme 67

Encouraged by this outcome, compounds 234a–c were subjected to metathesis conditions. Unexpectedly cyclopentenones 243a–c were isolated (Scheme 68). The yields of these ketones were directly proportional to the loadings of the catalyst. It was therefore rationalised that the ruthenium catalyst acted as an oxidant in a non-catalytic manner, thus incompatible with the hydroxyl group of these substrates.

Scheme 68

The structures of 243a–c were determined by their $^1$H NMR and IR spectra. All IR spectra of products 243a–c showed absorptions at $\sim$1726 cm$^{-1}$ for the cyclic $\alpha$,\$-unsaturated ketones. Figure 10 compares the key differences of the $^1$H NMR spectra of the starting material 234a and the product 243a. Olefinic H–2 of 243a is significantly more downfield than that of 234a. $\alpha$-Hydroxyl H–4 of 234a is not observed in 243a and cyclic olefinic H–3 changed from a dd in 234a to a d in 243a.
Figure 10
In light of the above results, attention was turned towards the investigation of the RRM of hydroxy-protected derivative 244, synthesised by protection of compound 234a with TBDMSCl (Scheme 69). When 244 was treated with catalyst 50, however, 10% of the dimerised adduct 245 and 3% of compound 234c were isolated, together with recovered SM. Compound 234c was believed to come from a cross metathesis between 244 and catalyst 50. Similar results were obtained using TES as an alternative protecting group.

\[
i) \text{TBDMS} \text{Cl (1.8 equiv), Et}_3\text{N (2.5 equiv), DMAP (15 mol%), CH}_2\text{Cl}_2, 40 \, ^\circ\text{C, 24 h; ii) catalyst 50 (10 mol%), CH}_2\text{Cl}_2, 40 \, ^\circ\text{C, 20 h}}
\]

Scheme 69

2.2.3.4 Attempt at Relay RRM Mediated by Dihydrofuran

The above experiments indicate the inability of the catalyst to access the cyclic alkene. According to this rationale, an alternative strategy was designed to facilitate the ring-opening of the cyclopentene by an allyl ether side chain (Scheme 70). Initial RRM of 246 involves the allyl ether side chain alkene and the cyclic alkene forming the dihydrofuran of 247 ready to undergo a second metathesis to give 248.
The feasibility of RRM of cyclopentenes bearing allyl ether side chains has been demonstrated by Grubbs et al.\textsuperscript{110} and Hoveyda et al.\textsuperscript{111} (Scheme 71). They showed that when treated with catalyst 49, cyclopentenyl allyl ethers 249, 251, 253, and 254 were converted to their corresponding dihydrofurans 250, 253, and 255. Grubbs proposed that mechanisms of initial attack of the catalyst at the acyclic olefin or the cyclic olefin were both possible.
In addition, Hoveyda et al. investigated the reaction equilibrium between cyclohexenyl allyl ether 256 and dihydrofuran 257 (Scheme 72). They showed that under the metathesis conditions as shown in Scheme 72, 256 was only poorly converted to 257 in 24% yield. They argued that the inefficiency was due to the relatively strain-free cyclohexene. In contrast, exposure of 257 under the same conditions led to a ca. 2:1 mixture of 256/257.

![Scheme 72](image)

Encouraged by these precedents, allyl ether 246 was prepared by O-allylation of 234d with allyl bromide (Scheme 73). The choice of 234d was in hope to increase the chemoselectivity of the initial metathesis on the allyl ether olefin. However, subjection of 246 to metathesis conditions led to alkene migrated adducts 258 with a 2:1 ratio of E/Z isomers.

![Scheme 73](image)

Many explanations have been proposed for Ru-based metathesis catalyses induced alkene isomerisations, such as metal-based hydride, π-allyl, or other pathways. Although the exact mechanism is unknown, Grubbs and co-workers have shown that ruthenium hydride species, formed from the decomposition of the ruthenium metathesis
catalysts, could cause migration of olefins.\textsuperscript{114} Additionally, they managed to suppress this type of unwanted transformation by deploying benzoquinone based additives.\textsuperscript{115}

Many people also take advantage of this methodology for their syntheses.\textsuperscript{113c,116} For example, Schmidt and co-workers have synthesised various 6-deoxy glycols by adopting a tandem process of RCM followed by isomerisation of the newly formed alkene.\textsuperscript{117}

Comparing the structural similarities of 246 (Scheme 73) and 249 (Scheme 71), these results seemed to indicate that the highly encumbered nature of the cyclic olefin of 246, primarily caused by the 1-SO$_2$Ph substituent, was deleterious to its reactivity. Additionally, the electron-withdrawing effect from the sulfone might further decrease its reactivity.

2.2.4 Attempted Synthesis of Aziridine Ring-opening Product 44

In light of the above results, it was considered to be necessary to change the original proposal, in which reaction of aziridine 46 and sulfone 45 was followed by a RRM of the product 44 (Scheme 6). Compound 44 would then undergo a cationic induced desulfonylative cyclisation\textsuperscript{31} to give 42. It was now believed that removal of the PhSO$_2$ group of 44 prior to RRM was essential. This would reveal the less hindered and more electron rich cyclic alkene of 259, which would be subjected to metathesis conditions to furnish 42 (Scheme 74).
Attention was focused on the synthesis of substrate 44, by reaction of regioselective ring-opening of vinyl aziridine 46 with sulfone 45 (Scheme 75). However, after testing various conditions including the use of excessive sulfone 45 and different bases, none of the desired product was observed (Table 2). Other methods were also tested, including deploying co-solvents TMEDA or DMPU, raising reaction temperatures to 60 °C, microwave irradiation and utilising Lewis acid additives such as Zn(OTf)$_2$. However, only starting materials were recovered in most cases. It was reasoned that the sterically congested $\alpha$-sulfonyl carbanion centre of 45 and the insufficient electrophilicity of 46 both contributed to the outcome.
To overcome this problem, the analogous hydroxyaziridine 198 was deployed to react with sulfone 45 in an attempt to synthesise adduct 260, which would then be converted to 44 by oxidation of the primary alcohol followed by olefination (Scheme 76). However, after trying similar reaction conditions, no desired product was isolated. Instead, when the reaction temperature was increased to ambient temperature, O-lithiated aziridine 198 underwent an aza-Payne rearrangement118 to give epoxide 261 (Scheme 76).

**Table 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comp. 45 (equiv)</th>
<th>Base (equiv)</th>
<th>Comp. 46 (equiv)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>nBuLi (2.1)</td>
<td>1.0</td>
<td>SMs</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>KH (2.2)</td>
<td>1.0</td>
<td>SMs + unidentified new product</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>nBuLi (1.0) + KH (1.0)</td>
<td>1.0</td>
<td>SMs + unidentified new product</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>nBuLi (4.4)</td>
<td>1.0</td>
<td>SMs</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>nBuLi (10.0)</td>
<td>1.0</td>
<td>SM(45) + unidentified new products</td>
</tr>
</tbody>
</table>

![Scheme 76](image-url)
2.2.5 Revised Route for Morphine Synthesis

Direct introduction of the cyclopentene moiety onto the vinylaziridine 46 or hydroxyaziridine 198 proved to be difficult. To overcome this problem, two revised approaches to morphine synthesis were proposed (Schemes 77, 78). Route A aimed at the synthesis of alkene 262 (Scheme 77), which would then be converted into morphine in a manner similar to that described in the initial retrosynthesis. Alkene 262 would be prepared from alcohol 263 by oxidation and olefination. The cyclopentene ring of 263 could be constructed by RCM of diene 264, which derived from C-α-SO₂Ph alkylation of tosamide 265 with β,γ-unsaturated aldehyde 266. Tosamide 265 would be synthesised by reaction of allylsulfone 212 and hydroxyaziridine 198.

Revised Route A:

![Scheme 77](image-url)
Route B diverged from route A by beginning with the reaction of allylsulfone \(212\) and vinylaziridine \(46\) to give tosamide \(269\). C-\(\alpha\)-SO\(_2\)Ph Alkylation of \(269\) with \(\beta,\gamma\)-unsaturated aldehyde \(266\) would give triene \(268\). Subjection of \(268\) to RCM should yield cyclohexene \(267\), which would then be converted into morphine along lines similar to those described in the initial retrosynthesis.

Revised Route B:

\[
\begin{align*}
\text{\(\text{HO} \text{O} \text{NMe} \text{H} \text{HO} \text{TsHN} \text{OR} 1 \text{H PhO} 2 \text{S H MeO} \text{NHTs H R 1 O H PhO} 2 \text{S H R 3 O R 3} \)} & \rightarrow \text{\(\text{O} \text{OR} 1 \text{R} 2 \)} \\
\text{aziridine ring opening} & \rightarrow \text{\(\text{MeO} \text{PhO} 2 \text{S PhN} \text{R} \text{O 1} \text{R} 1 \text{R} 2 \)}
\end{align*}
\]

Scheme 78

2.2.5.1 Regioselective Ring-opening of Aziridines 198 and 46

Both routes A and B required aziridine ring-opening reactions, and subsequent C-\(\alpha\)-SO\(_2\)Ph alkylations of \(265\) and \(269\) with aldehyde \(266\). Therefore the syntheses of \(265\) and \(269\) were first investigated. Intriguingly, reaction of lithio-\(212\) and \(O\)-lithiated aziridine \(198\) gave disulfone \(271\) in 25% yield with no desired product tosamide \(265\) isolated (Scheme 79). Disulfone \(271\) was believed to come from a self-coupling reaction of allyl sulfone \(212\) with possible vinyl sulfone intermediate \(270\). Such process has been reported by Bauld and co-workers.\(^{119}\)
This result indicates that isomerisation of the allylsulfone is such a rapid process. As previously described, the reaction of lithio-212 with butadiene monoxide 47 resulted in migration of the terminal olefins of the allyl sulfone intermediates to give vinyl sulfones 216 and 217 (Scheme 55). The experiment reported in Scheme 79 suggests that when 212 reacts with a less reactive electrophile such as hydroxylaziridine 198, self-coupling is preferred.

To overcome this problem, a similar strategy as aforementioned in Scheme 59 was adopted employing cinnamylsulfone 227\textsuperscript{120}. More importantly, the subsequent RCM step would give the same product 263. As shown in Scheme 80, reaction of lithio-227 with $O$-lithiated 198 gave a 10:1 mixture of diastereoisomers of tosamide 272, according to $^1$H NMR analysis, as single regioisomer in 52% yield. No aza-Payne rearrangement or olefin isomerisation side products were detected. Treatment of the major isomer with paraformaldehyde under acidic conditions gave $N$-tosyl aminal 273,\textsuperscript{121} whose identity was established by X-ray crystallographic analysis (Appendix II).
i) nBuLi (1.1 equiv) added to 198, THF, –78 °C, 5 min, then PhCH₂CH₂LiSO₂Ph (generated from 227 + nBuLi, THF), –78 °C, rt: 52%; ii) (HCHO)₉ (1.3 equiv), p-TsOH·H₂O (0.065 equiv), benzene, 90 °C, 6 h

Scheme 80

The unprotected hydroxyl group of 198 was considered to be crucial for the regioselectivity, supported by previous observations in the group (Scheme 81). Reaction of O-MOM protected aziridine 184 with lithio-185 gave a mixture of regioisomers, whereas a single regioisomer 186 was obtained after the reaction of lithio-185 with O-lithiated 184.

Scheme 81
The observed regioselectivity for hydroxyl aziridines 198 and 184 may be explained by that the lithiated oxygen moiety in 198 and 184 interacts in an attractive sense with lithiated 227 and 185 respectively, directing ring-opening to the proximal aziridine carbons.122

Following the successful ring-opening of aziridine 198, lithio-227 was reacted with vinylaziridine 46.123 Pleasingly, this reaction gave a single regioisomers 274 as a 10:1 diastereomeric mixture according to 1H NMR analysis. The configuration of the major isomer as shown in Scheme 82 was determined by X-ray crystallographic analysis (Appendix III). Intriguingly, this reaction exhibited the opposite diastereoselectivity to that of the hydroxyaziridine counterpart 198. A major unidentified by-product (38% yield by weight) was also isolated from this reaction. It was believed to be derived from an S_N2' addition of the sulfone at the terminal olefin of 46. It is also noteworthy that, in order for this transformation to reach completion, higher reaction concentrations and use of co-solvent TMEDA were essential.

![Scheme 82](image)

The observed regioselectivity in the above reaction may be attributed to the strong directing effect of the vinyl group, primarily through selective weakening of the allylic C–N bond of the aziridine by π_C=C–σ*_{C–N} overlap, as illustrated in Figure 11 and analogous to that depicted in Figure 3.
2.2.5.2 Attempted Alkylation of Sulfones 273 and 274

With aziridine ring-opening derivatives 273 and 274 in hand, focus shifted towards the preparation of the alkylation reagent $\beta,\gamma$-unsaturated aldehydes 266. The synthesis of aldehyde 266a was accomplished in a three-step sequence beginning with the protection of 3-butene-1,2-diol 275 with benzaldehyde 276 to yield a 1:1 diastereomeric mixture of acetals 277 (Scheme 83). Regioselective deprotection of 277 was achieved by treatment with excessive DIBAL-H giving a 4:1 mixture of regioisomeric alcohols 278 and 279. Finally oxidation of primary alcohol 278 with IBX gave the desired aldehyde 266a. However, attempted purification of 266a by silica gel column chromatography induced an isomerisation to give $\alpha,\beta$-unsaturated aldehyde 280. Therefore substrate 266a was used crude in subsequent reactions.

\[\text{HO-CH=CH-CH}_2\text{OH} + \text{PhCHO} \xrightarrow{i) p\text{-TsOH-H}_2\text{O} (0.02 \text{ equiv), toluene, reflux, 5 h; ii) DIBAL (3.0 \text{ equiv), CH}_2\text{Cl}_2, -78 \degree\text{C-rt, 16 h; iii) IBX (1.3 \text{ equiv), EtOAc, 80 \degree\text{C, 2 h}}}} \xrightarrow{275} \xrightarrow{276} \xrightarrow{277} \xrightarrow{278} \xrightarrow{279} \xrightarrow{86\% \text{ iii}} \xrightarrow{280} \xrightarrow{\text{silica gel}} \xrightarrow{266a}\]

Scheme 83
Unfortunately, treatment of aldehyde 266a with lithio-273 and lithio-274 resulted in isomerisation of 266a to 280 (Scheme 84). A similar outcome was observed in a test reaction with lithiated cinnamyl sulfone 227.

Scheme 84

In light of these results, it was anticipated that introduction of a γ-phenyl substituent to the aldehyde 266a would stabilise the double bond and prevent it from migrating. Therefore, attention was turned towards the synthesis of γ-phenyl-β,γ-unsaturated aldehyde 266b (Scheme 85). Acetals 282 were synthesised via a cross metathesis\textsuperscript{127} of acetals 277 and styrene 281. Subsequent deprotection of 282 gave 1:4 separated regioisomeric alcohols 283 and 284. Oxidation of alcohol 284 with Dess–Martin periodinate (DMP)\textsuperscript{128} proceeded smoothly at ambient temperature gave aldehyde 266b.

Scheme 85

\textsuperscript{i}) catalyst 50 (0.03 equiv), styrene 281 (2.0 equiv) CH\textsubscript{2}Cl\textsubscript{2}, reflux, 16 h; \textsuperscript{ii}) DIBAL (3.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}, – 78 °C-rt, 16 h; \textsuperscript{iii}) Dess–Martin periodinate (1.15 equiv), CH\textsubscript{2}Cl\textsubscript{2}, rt, 2 h
Acetals 282 were also synthesised by cross-metathesis of diol 275 with styrene 281 followed by protection of the resulting diol 285 with benzaldehyde 276 (Scheme 86).

\[
\begin{align*}
\text{HO-CH}_2\text{OH} + \text{C}_6\text{H}_5\text{C} = & \quad \text{HO-CH}_2\text{CH} = \text{C} = \text{C} = \text{CHPh} \\
i) & \quad \text{Catalyst 50 (0.01 equiv), styrene 281 (2.9 equiv), CH}_2\text{Cl}_2, \text{reflux, 16 h}; \\
\text{ii) } & \quad \text{p-TsOH·H}_2\text{O (0.05 equiv), benzaldehyde 276 (1.1 equiv), toluene, reflux, 5 h}
\end{align*}
\]

Scheme 86

With aldehyde 266b in hand, alkylations of lithio-227, 273 and 274 were investigated. Disappointingly, all of these reactions gave the isomerisation product, α,β-unsaturated aldehyde 286 (Figure 12).

The highly conjugating tendency of β,γ-unsaturated aldehydes suggested that double bond introduction at a later stage was necessary. It was envisaged that the double bond could be masked by a 2-phenyl-1,3-dioxane moiety as found in 289 (Scheme 87). Compound 289 was expected to derive from alkylation of 274 with aldehyde 290129,130,131,132. Regioselective deprotection of the acetal of 289 should give the corresponding primary alcohol, which could then be converted to a leaving group. Finally compound 288 would be subjected to E2 elimination to reveal the desired alkene in 287.
Thus, aldehyde 290 was prepared via a literature procedure (Scheme 88). Reduction of (S)-malic acid 291 with borane and trimethoxy borate gave optically pure 1,2,4-triol 292. Subsequent regioselective protection of 292 followed by DMP oxidation of the resulting alcohol 293 yielded aldehyde 290 in good overall yield. This aldehyde was prepared freshly and used crude in subsequent reactions since attempted purification by column chromatography resulted in material of inferior quality.

Unfortunately, when aldehyde 290 was treated with lithio-274, only starting materials were recovered (Scheme 89). This unexpected result prompted us to carry out test reactions of lithio-274 with other electrophiles such as benzaldehyde, benzoyl chloride and iodomethane, no desired products were detected. It was concluded that both the
poor nucleophilicity and highly hindered nature of the $\alpha$-SO$_2$Ph carbanion of 274 rendered it unsuitable for the proposed reaction with 290.

Scheme 89
2.2.6 Alkylation of Sulfide Stabilised Carbanions Approach to Morphine Synthesis

In light of the above conclusion, it was proposed that the problems could be overcome by adopting the sulfide analogue of sulfone 274. It was believed that the α-SPh carbanion has the advantages of being less hindered and more nucleophilic than the α-SO₂Ph carbanion. This section details the synthesis of sulfide nucleophiles prepared from regioselective ring-opening of vinyl aziridine 46 by appropriate sulfides, and investigation of their alkylation reactions in an approach to morphine synthesis.

2.2.6.1 Ring-opening of Vinyl Aziridine 46 with Allyl Phenyl Sulfide

The first sulfide investigated in aziridine ring-opening reactions was allyl phenyl sulfide 294. A major concern for 294 is that its delocalised anion can undergo both α- and γ-addition to give the corresponding α- and γ-adducts, as depicted in Scheme 90. The ratio between the two regioisomers depends on a number of factors such as: the base/the counter cation, the electrophile and additives used. It has been reported that HMPA is an excellent additive to enhance α-attack.

Despite this concern, the reaction of vinyl aziridine 46 with lithio-294, prepared from PhSH and allyl bromide, gave only the α-addition adducts (Scheme 91). Interestingly, when the reaction temperature was warmed up to 20 °C, migration of the β-alkene occurred to give the unwanted α,β-unsaturated sulfides 295 as a 5:1 olefin isomeric mixture according to 1H NMR analysis. This was avoided when the temperature was kept at −78 °C, in which case the desired β,γ-unsaturated sulfide 296 was synthesised. Later experiments showed that sulfide 296 was the only product
obtained when the reaction temperatures were kept below 0 °C. Similar phenomena were observed by Enholm and co-workers in the reaction of lithio-294 with ethylene oxide.136

Scheme 91

With sulfide 296 in hand, the subsequent C-α-SPh alkylation of lithio-296 with aldehyde 290 was investigated. Disappointingly, no reaction occurred. A number of other electrophiles were tested, such as benzaldehyde, benzoyl chloride, 1-iodo-3-butene and iodomethane, but no expected products were detected. Instead, the reaction of lithio-296 with MeI gave the N-methylated adduct 297 (Scheme 92),137 whose major isomer was assigned by X-ray crystallographic analysis (Appendix IV). The yield of 297 was increased to 82% when tBuOK was used as the base.

Scheme 92
2.2.6.2 Synthesis of Thiophenyl Tetrahydropyridine 299

Although the alkylation of the α-sulfide carbanion of 296 was not successful, the ring-opening reaction of aziridine 46 by the anion of allyl phenyl sulfide 290 demonstrated the superior reactivity of the sulfide anion compared to its sulfone counterpart, evidenced by the higher yield, significantly shorter reaction time and lower reaction temperature. In light of this observation, it was decided to re-visit a route previously pursued in the group, as described in Scheme 46. This approach was hindered by the reactivity of the C-4 centre of the tosyl tetrahydropyridine 190, as indicated by unsuccessful direct alkylation, and the low yield of the Lewis acid-mediated desulfonylative cation-assisted cyclisation shown in Scheme 93.

![Scheme 93](image)

It was now hoped that the reactivity of the C-4 centre could be improved by employing the thiophenyl-substituted tetrahydropyridine analogue 299 (Scheme 94). The alkylation derivative 300 would then be subjected to a cation-mediated cyclisation similar to that of tosyl tetrahydropyridine 190 to give diene 188. If diene 188 could be made via this route, the later-stage chemistry would remain the same, as described in Scheme 46. Following this plan, focus shifted to the synthesis of tetrahydropyridine 299.
2.2.6.2.1 Attempted approach via acetal

It was anticipated that thiophenyl-substituted tetrahydropyridine 299 could be accessed via a route similar to that used for tosyl-substituted analogue 190 as shown in Scheme 47. Therefore, aldehyde 303\(^{138}\) was made by conjugate addition of thiophenol 302 to acrolein 301 (Scheme 95). Acetal protection of 303 with trimethyl orthoformate yielded 304.\(^{139}\) Unexpectedly, the subsequent aziridine opening reaction gave acetal tosamide 305 in only 18% yield. This was believed to be caused by the instability of the lithiated anion of 304, since the by-product 308 was also isolated (Figure 13), indicating the generation of significant amounts of thiophenolate anion. The attempt of tetrahydropyridine formation by exposing 305 to Lewis acidic conditions resulted in a Pictet–Spengler type reaction giving 307 via 306. This was thought to be due to the lower electron-withdrawing ability of the thiophenyl substituent of intermediate 306 compared to the sulfone analogue.
2.2.6.2.2 Attempted approach via $\gamma$-lactam

This unexpected result indicated the need for alternative approaches for the synthesis of thiophenyl-substituted tetrahydropyridine. It was proposed that the route shown in Scheme 96 via $\gamma$-lactam 310 would provide the desired tetrahydropyridine 314. Ring-opening of aziridine 46 by sulfide ester 309 followed by lactamisation in one step would give $\gamma$-lactam 310. Subsequent alkylation of the $\alpha$-SPh carbanion, reduction of $\gamma$-lactam 311 and protection of the resulting alcohol would give 312. Ozonolysis of diene 312 should furnished C4 alkylated tetrahydropyridine 314 via tosamide aldehyde 313.
However, in an attempt to form $\gamma$-lactam 310 from the reaction of KH deprotonated sulfide ester 309 with aziridine 46, tosamide esters 315 were obtained (Scheme 97). The production of 315 suffered from poor reproducibility and low yielding. These were again likely due to the lack of stability of the anion of 309 as by-product 308 was also isolated. A series of other conditions were tested but no $\gamma$-lactam 310 was detected (Table 3).

\[ \text{Scheme 96} \]

\[ \text{Scheme 97} \]

i) KH (1.0 equiv), DMF, 0 °C, 20 min, then aziridine 46 in DMF added, 60 °C, 16 h
<table>
<thead>
<tr>
<th>Entry</th>
<th>base</th>
<th>solvent</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$BuLi</td>
<td>THF</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>tBuOK</td>
<td>DMSO</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>tBuOK/18-crown-6</td>
<td>THF</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>KH</td>
<td>toluene</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>KHMDS/18-crown-6</td>
<td>toluene</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>DMF</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>toluene</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3

2.2.6.2.3 Attempted approach via propargylic sulfide

Two alternative approaches for the synthesis of tetrahydropyridine 299 from propargyl sulfide aziridine ring-opening product 317 were also proposed, as outlined in Scheme 98. The reaction of propargylic sulfide 316 with aziridine 46 should give alkynyl tosamide 317. Path A converts substrate 317 into Z-vinyl halide 318, which will be subjected to an intramolecular N-vinylation mediated by appropriate transition metals to give 299. Path B involves a direct 6-endo-dig cyclisation of 317 to afford 299.

![Scheme 98](image-url)
Ullmann–Goldberg-type reactions mediated by copper reagents are valuable for construction of \( sp^2 \)-C–N bonds from amines and aryl or vinyl bromides.\(^\text{141}\) However, intramolecular \( N \)-vinylation under these conditions have rarely been reported, especially for small rings. Joyeau \textit{et al.}\(^\text{142}\) in 1989 and Li \textit{et al.}\(^\text{143}\) in 2006 have published their independent work for intramolecular enamide/enamine formations using modified Ullmann–Goldberg conditions. Joyeau \textit{et al.} treated the azetidinone 319 with copper powder at 110 °C in DMF to produce carbacephem 320 (Scheme 99).\(^\text{142}\) The yield of this reaction, albeit low (20–30%), depended on the amount of \( Z \) isomer contained in the starting material mixture, which was considered to be the reactive isomer.

![Scheme 99](image)

Li \textit{et al.} have demonstrated the high efficiency of 4-\textit{exo-trig} cyclisation of \( N \)-tosyl-3-halo-3-butenylamines 321 to yield 2-alkylideneazetidines 322 in the presence of stoichiometric amount of CuI and TMEDA (Scheme 100).\(^\text{143}\) The reaction times were typically under two hours.

![Scheme 100](image)

Another method for \( sp^2 \)-C–N bond formations is Buchwald–Hartwig palladium-catalysed cross coupling.\(^\text{144}\) It has been wildly adopted for the synthesis of aryl amines from amines and aryl halides.\(^\text{144,145}\) Intramolecular enamine/enamide formation between
a vinyl halide and an amine, however, is less well documented.\textsuperscript{146} One example is from Mori and co-workers who successfully applied this methodology to the synthesis of 3-ethoxycarbonyl-1β-methylcarbapenem \textit{324} (Scheme 101).\textsuperscript{147} They found that DPEphos was the optimum ligand for this reaction and better yield was obtained when vinyl iodide \textit{323} was used instead of the corresponding vinyl bromide.

![Scheme 101](image)

Encouraged by these precedents, the synthesis of tetrahydropyridine \textit{299} was explored. Propargylic sulfide \textit{316} was prepared from a biphasic reaction of propargylic bromide \textit{325} and thiophenol \textit{302} as described by Bäckwell \textit{et al.} (Scheme 102).\textsuperscript{148} It was subsequently doubly deprotonated\textsuperscript{149} and combined with aziridine \textit{46} to give a mixture of alkynyl tosamide \textit{317} with a 3:1 dr. Iodination of the terminal alkynes of \textit{317} was accomplished by treatment with NIS in the presence of AgNO\textsubscript{3} to yield alkynyl iodides \textit{326}. Following \textit{syn}-reduction with diimine, generated from dipotassium azodicarboxylate\textsuperscript{150b,151,152} (PADA) \textit{328}, and acetic acid,\textsuperscript{153} \textit{Z}-vinyl iodides \textit{327} were formed. The geometry of the double bond was assigned by \textsuperscript{1}H NMR analysis, where the \textit{Z}-alkene protons have a \textit{J} value of 7.5 Hz. An alternative reducing agent, 2-nitrophenylsulfonylhydrazide\textsuperscript{154} (2-NBSH), was also tested for the preparation of \textit{327} and gave similar results. Both of these two reagents were easy to prepare from cheap starting materials.\textsuperscript{151,152,154}

A number of conditions were investigated for the formation of tetrahydropyridine \textit{295} from \textit{327} with palladium and copper catalysts (Table 4). Unfortunately, no desired product was detected. Only starting material was recovered.
i) NaOH (1.7 equiv), nBu₃NBr (0.15 equiv), H₂O, benzene, 0 °C, 3 h; ii) a) nBuLi (2.4 equiv), 1.5 h, b) aziridine 46 (1.0 equiv), THF, −78-0 °C, 3.5 h, dr = 3:1; iii) NIS (1.22 equiv), AgNO₃ (0.5 equiv), DMF, rt, 16 h; iv) potassium azodicarboxylate 328 (5.1 equiv), AcOH (15.0 equiv), dioxane/iPrOH (0.3 mL), 18 h

Scheme 102

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>catalyst/ligand</th>
<th>base</th>
<th>temp. (°C)</th>
</tr>
</thead>
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<tr>
<td>1</td>
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<td>Pd(acac)₂/BINAP</td>
<td>Cs₂CO₃</td>
<td>rt</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>Pd(db)₃/P₄Bu₃</td>
<td>Cs₂CO₃</td>
<td>rt</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>Pd(db)₃/BINAP</td>
<td>Cs₂CO₃</td>
<td>rt–60</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>Pd₂(OAc)₂/PPh₃</td>
<td>Et₃N</td>
<td>rt</td>
</tr>
<tr>
<td>5</td>
<td>DMSO/PhH</td>
<td>CuI</td>
<td>Cs₂CO₃</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 4

Path B

This disappointing outcome led us to investigate path B of Scheme 98, 6-endo-dig cyclisation of alkynyl tosamide 317. Whilst 6-endo-dig cyclisation between a terminal alkyne and an amine or tosamide is unprecedented, reported literature indicated that, in general, the selectivity between 5-exo-dig and 6-endo-dig cyclisation can be markedly dependent on the reaction conditions. Work by Georg and co-workers has uncovered
a remarkably simple protocol for preparing enaminones via 6-endo-dig ring closures (Scheme 103).\textsuperscript{156}

Amino–ynones 329 were prepared from the corresponding N-Boc protected β-amino acids via Weinreb amide formation and subsequent addition of the appropriate alkynyl magnesium bromide. N-Boc Deprotection of 329 under acidic conditions followed by treatment of the crude with methanol and K$_2$CO$_3$ gave enaminones 332 in only 15 minutes (Scheme 103). This process is thought to go through either intermediate 330 with a conjugated π-orbital or 331 with the filled σ-orbital stabilised by the carbonyl group.

![Scheme 103](image)

Encouraged by this facile ring-closure process alkynyl tosamide 317 was exposed to similar cyclisation conditions (Scheme 104). When heated to 50 °C, 100% conversion was observed. However, only 5-exo-dig cyclised product pyrroles 335 were isolated in almost quantitative yield. Interestingly, when pyrroles 335 were left in a NMR tube with deuterated chloroform for two days, complete isomerisation occurred to give dihydropyrrole 336. This was thought be induced by the trace amounts of acid in the solvent.
Many transition metals are reported to be capable of activating triple bonds for cyclisation reactions, such as: Pd\textsuperscript{157}, Rh\textsuperscript{155}, Au\textsuperscript{158}, Ir\textsuperscript{159} and Cu\textsuperscript{160}. Therefore, our focus was shifted towards cyclisation mediated by organometallic catalysis. Disappointingly, after evaluating the cyclisation of \textbf{317} under a number of conditions, either no reaction occurred or only the 5-\textit{exo-dig} ring-closure adduct was formed (Table 5). For example, compounds \textbf{335} were isolated when \textbf{317} was exposed to the conditions described by Luo \textit{et al.}\textsuperscript{157b} (Entry 2). These workers had synthesised a range of 2-alkyldenetetrahydrofurans and pyrans by treatment of alkyl or aryl acetylenic alcohols with \textit{n}BuLi in THF, followed by addition of a solution of Pd(OAc)\textsubscript{2} and PPh\textsubscript{3} in THF and one equivalent of an organic halide. Modifying their conditions by employing DMF as a co-solvent only resulted in higher yields of \textbf{335} (Entry 3). When the reaction was attempted without prior deprotonation with \textit{n}BuLi, only starting materials were recovered (Entries 1 and 4). Surprisingly, substrate \textbf{317} decomposed when treated with sub-stoichiometric Cul (Entries 5 and 6). Many iridium catalysts were reported to be effective reagents to induce 6-\textit{endo-dig} reactions selectively over 5-\textit{exo-dig}.\textsuperscript{159} However when iridium catalyst \textbf{336} (Figure 14) was used, no reaction was observed (Entry 7).
<table>
<thead>
<tr>
<th>Entry</th>
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<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$, THF, 50 °C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>nBuLi, THF, PPh$_3$ $-78$ °C - rt</td>
<td>SM + 335 (3%)</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>nBuLi, THF/DMF, PPh$_3$ $-78$ °C - rt</td>
<td>SM + 335 (15%)</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$</td>
<td>PPh$_3$, toluene, 40 °C</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>DMF, 70 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>DMF, rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>[Ir]</td>
<td>CH$_2$Cl$_2$, 40 °C</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 5

2.3.6.2.4 Approach via an unexpected enal

In order to reverse the selectivity to favour 6-endo-dig cyclisation of alkynyl tosamides 317, it was considered that activation of the terminal carbon of the alkyne was required. It was proposed that this could be achieved by exposure of the corresponding sulfoxide of 317 to organometallic catalysts (Scheme 105). Initial coordination between the metal and the oxygen of the sulfoxide of 337 would direct the interaction of the metal with the alkyne.
Following this plan, the synthesis of sulfoxide 337 was carried out. Intriguingly, when alkynyl tosamide 317 was treated with mCPBA, enal 339 was isolated (Scheme 106).

A mechanism for this process is proposed in Scheme 107. Oxidation of 317 yields the sulfoxide intermediate 337, which undergoes [2,3]-sigmatropic rearrangement to give the unstable allenylsulfinate intermediate 340. Following hydrolysis of the enol ether group in 340, product 339 is formed. In an attempt to improve the yield of this reaction, many other oxidants were tested, including IBX, DMP, NaIO₄, Oxone® and DMDO. However, no reaction was observed with the exception of Oxone®, which gave a small amount of 339 as evidence by ¹H NMR analysis of the crude product.
To take advantage of this unexpected outcome, enal 339 was used for the synthesis of tetrahydropyridine 299, as shown in Scheme 108. 1,4-Addition of PhSH to enal 339 triggered a spontaneous cyclisation of the tosamide nitrogen and the resulting aldehyde to give thiophenyl-substituted piperidinol 341. Subsequent syn-elimination of H$_2$O from 341 was effected by converting the alcohol to the corresponding mesylate with MsCl in the presence of excessive Et$_3$N. This sequence was also performed in a one-pot process from enal 339 giving similar yields.

\[
\begin{array}{c}
\text{PhSH (3.0 equiv), Et$_3$N (5.0 equiv), CH$_2$Cl$_2$, 0 °C – rt, 16 h; ii) MsCl (10.0 equiv), Et$_3$N (5.0 equiv), CH$_2$Cl$_2$, –20 °C, 2 h}
\end{array}
\]
2.2.6.2.5 Approach via tosyl tetrahydropyridine 190

Although the above approach gave access to tetrahydropyridine 299, it was impractical due to overall low yields. It was proposed that 299 could be constructed by treatment of tosyl tetrahydropyridine 190 with (Me)₂AlSPh\textsuperscript{162}. Therefore, 190 was prepared as previously described in Scheme 47. Aziridine 46 was combined with lithiated tosylacetal 185 followed by cyclisation of the resultant acetal tosamide 191 under Lewis acidic conditions (Scheme 109). When 190 was exposed to (Me)₂AlSPh in CH₂Cl₂, generated \textit{in situ} from AlMe₃ and PhSH,\textsuperscript{162} thiophenyl-substituted tetrahydropyridine 299 was obtained in good yield.

![Scheme 109](image)

The unprecedented aluminium-mediated conversion of 190 into 299 was also applicable to the syntheses of other sulfides such as 342 and 343, by treatment of 190 with (Me)₂AlSPy\textsuperscript{163} and (Me)₂AlSMe\textsuperscript{164} respectively (Scheme 110). Reagent (Me)₂AlSPy was prepared in a similar manner to that of (Me)₂AlSPh whereas (Me)₂AlSMe was prepared from AlMe₃ and sulfur powder. Interestingly, in the reaction of 190 with (Me)₂AlSMe, C6 attack was favoured to give 344 as the major isomer. These results seemed to suggest that sterically bulky sulfide groups such as –SPh and –SPy favour C4 addition, whereas small sulfide groups such as –SMe favour C6 attack. When substrate 342 was treated with AgOTf, the elimination triene adduct 345 was isolated.
i) (Me)_2AlSPy (5.0 equiv) [prepared from AlMe_3 (5.0 equiv) and pyridine-2-thiol (5.0 equiv) in CH_2Cl_2, rt, 45 min] added to **190** in CH_2Cl_2, rt, 16 h, dr = 2.5:1. ii) **190** in toluene added to (Me)_2AlSMe (4.0 equiv) [prepared from AlMe_3 (4.0 equiv) and sulfur powder (5.0 equiv) in toluene under reflux, 2 h, then to rt], rt, 16 h, dr = 2:1 for **331**, 1.2:1 for **223**. iii) AgOTf (1.5 equiv), 4 Å molecular sieves, CH_2Cl_2, –40 °C, 2 h

**Scheme 110**

**2.2.6.3 Attempted Alkylation of Tetrahydropyridine 299**

Having developed an efficient route for the synthesis of the thiophenyl tetrahydropyridine 299, attention was turned towards its subsequent C4 alkylation in attempts to prepare diene 300 as described in Scheme 94. Compound 299 was treated with nBuLi followed by an electrophile. Disappointingly, after examining a range of electrophiles as shown in Scheme 111, no alkylated products were observed. Lactaldehyde 346\(^{165}\) was prepared from ethyl-L-lactate 347 after alcohol protection with TBDPSCI to give ester 348\(^{166}\) followed by a DIBAL-H reduction (Scheme 112).
Scheme 111

\[
\begin{align*}
E^+ &= \text{OTBDPS} : 346 \\
& \quad : \text{MeOCl} ; \\
& \quad : \text{Mel} \\
\end{align*}
\]

\[\text{Scheme 111}\]

\[
\begin{align*}
\text{EtO} & \quad \text{OH} \quad \xrightarrow{i} \quad 98\% \\
347 & \quad \text{EtO} \quad \text{OTBDPS} \quad \xrightarrow{\text{ii}} \quad 87\% \\
348 & \quad 346 \\
\end{align*}
\]

i) TBDPSCI (1.8 equiv), DMAP (0.15 equiv), Et₃N (2.5 equiv), CH₂Cl₂, 50 °C, 16 h; ii) DIBAL-H (1.15 equiv), CH₂Cl₂, −78 °C, 1.5 h

Scheme 112

In addition to alkylation, C4 α-sulfide halogenations of 299 were also investigated with NIS\textsuperscript{167}, NBS\textsuperscript{168}, NCS\textsuperscript{169} and SO₂Cl\textsubscript{2}\textsuperscript{170} in attempts to synthesise halides 349 (Scheme 113). However, no desired products were observed. Furthermore, attempted cyclisation of 299 to give compound 350 mediated by Pummerer rearrangement induced by MeSSMe₂BF₄ (DMTSF)\textsuperscript{171} gave only recovered starting materials.

Scheme 113
2.2.7 Alternative Strategies for C4 Alkylation

The failure of attempts to effect C4 alkylation of tetrahydropyridine 299 led us to consider alternative strategies. It was considered that sulfide- or sulfone-substituted unsaturated lactam 354 might be a suitable precursor for C4 alkylation via conjugate addition (Scheme 114). It was envisaged that 354 could be derived from allyl sulfone/sulfide 351 and aziridine 46. Reaction of 351 and 46 would give 352, which would be subjected to cyclisation to give lactam 353. Oxidation of 353 would give unsaturated lactam 354. Subsequent 1,4-addition followed by desulfurative cyclisation of 355 would give 356, which could ultimately lead to morphine.

\[
\begin{align*}
\text{OMe} & \quad \text{S(O)}_n\text{Ar}' \\
\text{MeO} & \quad \text{S(O)}_n\text{Ar}'
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \quad \text{S(O)}_n\text{Ar}' \\
\text{MeO} & \quad \text{S(O)}_n\text{Ar}'
\end{align*}
\]

\[
\begin{align*}
\text{S(O)}_n\text{Ar}' & \quad \text{Nu} \\
\text{O}Me & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{S(O)}_n\text{Ar}' & \quad \text{Nu} \\
\text{O}Me & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{S(O)}_n\text{Ar}' & \quad \text{Nu} \\
\text{O}Me & \quad \text{O}
\end{align*}
\]

Scheme 114

2.2.7.1 Attempted Synthesis of Allyl Sulfone 351

Following the above proposal, focus shifted to the preparation of allyl sulfone 351, which was anticipated to be accessed via isomerisation of vinyl sulfone 358. Two routes were examined for the synthesis of 358 (Schemes 115, 116). The first approach involved the synthesis of \(\alpha,\beta\)-unsaturated acetal 357\(^{172}\), which was synthesised by protection of acrolein 301 with \((\text{CH}_3\text{O})_3\text{CH}\) (Scheme 115). Subjection of 357 to either cross-metathesis with vinylsulfone 212\(^{173}\) or selenosulfonation with \(\text{PhSeSO}_2\text{Tol}\) 359\(^{174}\) followed by oxidation–elimination with \(\text{H}_2\text{O}_2\) resulted in no desired product.
In the second approach, bromination of 301 with Br₂ gave dibromide 360, which was treated with PhSO₂Na in DMF to give sulfonyl acrolein 361 (Scheme 116). 175 Subsequent acetal protection of 361 furnished vinyl sulfone 358a. Disappointingly, no desired product 351 was detected when 358a was treated with either Et₃N or DBU or tBuOK in tBuOH despite the fact that all starting materials were consumed. It was speculated that this was due to the instability of compound 351. This was supported by the work of Tasaki et al. who demonstrated that vinyl sulfones 362 underwent facile isomerisations to give allyl sulfones 363 (Scheme 117). 176 However, no products were isolated when similar conditions were applied to acetal vinyl sulfones 364 and 365 although all the starting materials were consumed. They reasoned that this was caused by the instability of the desired products.

Scheme 116
2.2.7.2 Synthesis of Lactam 353

The above results meant that alternative synthesis of lactam 353 was required. It was expected that a one-step cyclisation–oxidation of acetal tosamide 191 would provide the desire product. Indeed, when 191 was exposed to Jones oxidation conditions, lactam 353 was obtained, albeit in low yield (Scheme 118). In an attempt to improve the yield by employing other acidic oxidising reagents such as PCC and PDC, only starting materials were recovered. The identity of 353 was firmly established by X-ray crystallographic analysis (Appendix V).

Although the exact mechanism of this transformation is unknown, two possible pathways are proposed, as outlined in Scheme 119. Both pathways starts from deprotection–cyclisation of 191 to give hemi-aminal intermediate 366. In path A, hemi-aminal 366 converts into piperidinium 367 under acidic conditions. Subsequent interception of the oxygen of the HCrO$_4$– ion to 367 generates chromate ester 368, which suffers elimination of the Cr(IV) HCrO$_3$ to give the observed compound 353 and Cr(IV) H$_2$CrO$_3$. This Cr(IV) substrate reacts with a Cr(VI) species to yield two Cr(V)

Scheme 118
molecules, and can oxidise 367 in a similar manner, and which are ultimately reduced to Cr(III). In pathway B, hemi-aminal 366 reacts with Cr(VI) CrO$_3$ to give chromate ester intermediate 369, which decomposes by elimination of Cr(IV) MeOCrO$_2$H to yield 353. Similarly, these Cr(IV) species will convert into Cr(III).

Scheme 119

It was believed that piperidinium intermediate 367 could be generated by treatment with TFA, since double bond reduction of the tetrahydropyridine of compound 190 has been achieved previously by group members with TFA and reductant Et$_3$SiH (Scheme 120). Therefore, other potential oxidants were used in combination with TFA, such as: DMSO, N-hydroxy succinamide, Dess–Martin periodinate, IBX, PCC and NMO. However no desired product was detected under any of these conditions.
2.2.7.3 Tosyl Elimination of Lactam 353

The final phase of research was devoted to the investigation of 4-tosyl elimination of lactam 353 by exposure to basic conditions. This was expected to give unsaturated lactam 373 (Scheme 121). Intriguingly, when compounds 353 were treated with DBU, a 2.7:1 olefin isomeric mixture of dienone 371 were isolated in quantitative yield. Whereas when the weaker base Et₃N was used, dienone 372 was obtained in 28% yield together with 63% 371. The conversion of lactam 353 to dienone 371 was believed to go via intermediate 373.

i) DBU (1.67 equiv), CH₂Cl₂, rt, 20 h; ii) Et₃N (0.1 equiv), CH₂Cl₂, rt, 16 h

Scheme 121

In an attempt to trap the elimination intermediate 373 with cuprate 374, generated from allylmagnesium bromide and CuCN, a 2:1 isomeric mixture of alcohols 375 was
isolated (Scheme 122). Further study is needed to determine the mechanism for this remarkable result.

\[
\text{Scheme 122}
\]

i) \(\text{CH}_2=\text{CHCH}_2\text{CuMgBr} \ 374\) (generated from \(\text{CH}_2=\text{CHCH}_2\text{MgBr} \ \text{2.0 equiv} \) and \(\text{CuCN} \ \text{2.0 equiv}\), \(\text{Et}_3\text{N} \ \text{(0.3 equiv)}\), THF, rt, 16 h, aqueous work-up
2.3 Future Work

In addition to further optimisation of the reaction to afford lactam 353, the remaining chemistry as described in Scheme 114 will need to be pursued. Oxidation of 353 to give α,β-unsaturated lactam 354 is key to the success of this route. Although Saegusa–Ito palladium-catalysed oxidation\(^{178}\) can give access to α,β-unsaturated ketone from silyl enol ether, generated from the corresponding ketone, oxidation to give a α,β-unsaturated lactam or amide is foreseen to be challenging. Subsequently, it will be interesting to see if compound 354 is susceptible to 1,4-addition to give 355. Lewis acid mediated cationic-cyclisation of 355 to give 356 will then be investigated.

Alternatively, it is envisaged that intermediate 356 could also be constructed by a route shown in Scheme 123. Aryl iodide 377 should be derived from aziridine 376 similar to the synthesis 354. Nucleophilic addition–elimination of compound 377 will give 378, which will be subjected to an intramolecular reductive Heck cyclisation\(^{179}\) to furnish 379.

![Scheme 123](image-url)
2.4 Conclusion

During the investigation of the initial retrosynthetic plan (Scheme 7), an extremely short and robust synthesis of 4-(phenylsulfonyl)cyclopent-2-enol 45 has been developed by application of RCM chemistry. However, attempts of incorporating 45 into vinylaziridine 46 were not realised after intensive studies. Therefore alternative strategies of morphine synthesis were explored. During these investigations, it was observed that functionally diverse sulfone- or sulfide-stabilised carbanionic species react with vinylaziridine 46 with complete regioselectivity. Furthermore, analogous sulfones and sulfides have exhibited markedly different reactivities under the same reaction conditions. For example, poor yields resulted when thiophenyl acetal 304 (Scheme 95) and thiophenyl methyl ester 309 (Scheme 97) were used. On the contrary, their sulfone counterparts gave good yields.

A practical synthesis of highly substituted \( N \)-tosyl thiophenyl-substituted tetrahydropyridine 299 was developed through a \( \text{Me}_2\text{AlSPh} \) mediated \( \text{trans} \)-sulfurisation from tosyl-substituted tetrahydropyridine 190. Extensive studies into C-4 alkylation of 299 led to the proposal of nucleophilic 1,4-addition of the \( N \)-tosyl \( \alpha,\beta \)-unsaturated \( \delta \)-lactam 354, which is foreseen to derive from oxidation of \( \delta \)-lactam 353 (Scheme 114). The synthesis of 353 was achieved by an unusual cyclisation–oxidation of acetal tosamide 191 under Jones oxidation conditions. Future endeavours will focus on the synthesis of 354 and its subsequent alkylations, towards a total synthesis of morphine.
3. Experimental

General Laboratory Procedure

Unless otherwise stated, all reactions were carried out under nitrogen; Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 5000 FTIR spectrometer and on a Perkin-Elmer Spectrum RX FT-IR System. Proton magnetic resonance (\(^1\)H NMR) and carbon magnetic resonance (\(^{13}\)C NMR) spectra were recorded in CDCl\(_3\) unless otherwise stated on a Jeol GSX-270, a Bruker DRX-300, a Bruker AV-400 or a Bruker AV-500 spectrometer. Chemical shifts are in part per million (ppm) and are referenced relative to the residual proton-containing solvent (\(^1\)H NMR: 7.26 ppm for CDCl\(_3\); \(^{13}\)C NMR: 77.0 ppm for CDCl\(_3\)). The following abbreviations are used to indicate the multiplicities: s, singlet; b, broad signal; d, doublet; t, triplet; m, multiplet. Mass spectra (Cl) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratory of the London Metropolitan University. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium-backed Merck Kiesegel 60 F\(_{254}\) plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Flash chromatography was performed using BDH (40-63 µm) silica gel unless otherwise stated. Standard solvents were distilled under nitrogen prior to use: Et\(_2\)O and THF from sodium-benzophenone ketyl; DMSO, CH\(_2\)Cl\(_2\) and DMPU from CaH\(_2\); toluene from sodium, TMEDA from sodium or CaH\(_2\). All other solvents were reagent-grade. Petrol refers to the fraction with bp\(_{760}\) 40–60 °C. All liquid reagents except HCl and Me\(_2\)S were distilled prior to use. All other reagents were purchased from Aldrich, Fluka, Acros, Alfa Aesar Lancaster and used as such unless otherwise stated. Microwave reactions were performed using a Biotage Initiator instrument.
(E)-4-(4-Methoxyphenyl)but-2-en-1-ol\textsuperscript{30,31} 197

![Chemical structure](image)

To a solution of butadiene monoxide 47 (5.00 g, 71.4 mmol, 1.0 equiv) and CuCN (639 mg, 7.14 mmol, 0.1 equiv) in THF (130 mL) at −78 °C a freshly prepared solution of (4-methoxyphenyl)magnesium bromide 48 (17 mL of a ca. 0.5 M solution in THF, 8.40 mmol, 0.1 equiv) in THF (17 mL) was added dropwise. After 15 min the solution was warmed to −20 °C then re-cooled to −78 °C for 20 min and a further amount of (4-methoxyphenyl)magnesium bromide 48 (153 mL of a ca. 0.5 M solution in THF, 76.6 mmol, 1.1 equiv) added. After 45 min, the resulting solution was warmed to rt. After 1 h sat. NH\textsubscript{4}Cl\textsubscript{(aq.)} (13 mL) and NH\textsubscript{3} (10 mL of a 17% aqueous solution) were added. After 15 min the solution was diluted with sat. NH\textsubscript{4}Cl\textsubscript{(aq.)} (53 mL), H\textsubscript{2}O (36 mL) and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave the alcohol 197 (11.6 g, 91%) as a colourless oil; R\textsubscript{f} 0.30 (20% EtOAc–petrol); \(\nu\)\textsubscript{max} (film) 3357, 3029, 3002, 2952, 1670, 1610, 1583, 1463, 1463, 1440, 1299, 1176, 1108, 1089, 1035, 998, 971, 817 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (270 MHz) 7.08 (2H, d, \(J 8.0\) Hz, meta ArOMe), 6.28 (2H, d, \(J 8.0\) Hz, ortho ArOMe), 5.85-5.68 (2H, m, CH=CH), 4.10 (2H, d, \(J 5.0\) Hz, CH\textsubscript{2}OH), 3.79 (3H, s, OMe), 3.35 (2H, d, \(J 6.0\) Hz, CH\textsubscript{2}Ar); \(\delta\)\textsubscript{C} (67.5 MHz) [158.1, 132.2 (q Ar)], [132.1, 130.0 (ortho & meta ArOMe)], [114.0, 113.9 (CH=CH)], 63.6 (OMe), 55.4 (CH\textsubscript{2}OH), 37.8 (CH\textsubscript{2}ArOMe); \(m/z\) (Cl) 196 [M+NH\textsubscript{4}]\textsuperscript{+}, 179 [M+H]\textsuperscript{+}, 161; data in agreement with that previously reported.\textsuperscript{30,31}
To a mixture of allylic alcohol 197 (4.10 g, 23.0 mmol, 1.0 equiv) and anhydrous Chloramine-T® (5.76 g, 25.3 mmol, 1.1 equiv) MeCN (115 mL) at rt was added phenyltrimethylammonium tribromide (0.860 g, 2.30 mmol, 0.1 equiv). After 20 h the suspension was concentrated to ca. 40 mL and filtered through a short pad of silica gel with Et₂O. Concentration under reduced pressure and column chromatography (25%→35% EtOAc–petrol) gave the hydroxyaziridine 198 (4.60 g, 57%) as a white solid; mp 71-72 °C; Rf 0.32 (40% EtOAc–petrol); v_max (film) 3511, 2935, 1612, 1514, 1443, 1304, 1248, 1157, 1088, 1034, 976, 943, 816, 710 cm⁻¹; δ_H (270 MHz) 7.65 (2H, d, J 8.0 Hz, ortho Ts), 7.22 (2H, d, J 8.0 Hz, meta Ts), 6.89 (2H, d, J 8.0 Hz, meta ArOMe), 6.67 (2H, d, J 8.0 Hz, ortho ArOMe), 4.12-3.89 (2H, m, CH₂OH), 3.73 (3H, s, OMe), 3.19-3.03 (2H, m, CHCH₂OH), 2.90 (1H, dd, J 16.5, 13.0 Hz, CHHArOMe), 2.63 (1H, dd, J 16.5, 13.0 Hz, CHHArOMe), 2.43 (3H, s, Me of Ts); δ_C (125 MHz) 158.4, 144.1, 136.9, 129.9, 129.6, 129.5, 127.4, 113.9, 60.8, 55.2, 51.7, 47.1, 35.8, 21.6; m/z (CI) 365 [M+NH₄]^+, 348 [M+H]^+, 189; data in agreement with that previously reported.³⁰
(2R*,3R*)-2-(4-Methoxybenzyl)-1-tosyl-3-vinylaziridine\textsuperscript{30} 46

To a solution of hydroxyaziridine 198 (4.54 g, 13.1 mmol, 1.0 equiv) in DMSO (140 mL) at rt was added IBX (4.06 g, 14.5 mmol, 1.1 equiv). After 22 h the reaction was diluted with Et\textsubscript{2}O (400 mL), washed with sat. NaHCO\textsubscript{3(aq.)} (4 × 100 mL), H\textsubscript{2}O (4 × 100 mL) and extracted with Et\textsubscript{2}O (3 × 100 mL). The combined organic layers were washed with brine (4 × 50 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduced pressure and drying under high vacuum for 1 h gave the corresponding crude aldehyde (4.14 g).

To a suspension of Ph\textsubscript{3}PCH\textsubscript{3}Br (5.20 g, 14.3 mmol, 1.1 equiv) in THF (104 mL) at −20 °C was added KHMDMS (28.6 mL of a 0.5 M solution in toluene, 14.3 mmol, 1.1 equiv). After 15 min the suspension was warmed to rt for 45 min and re-cooled to −20 °C and the solution of aldehyde (4.14 g, 11.9 mmol, 0.9 equiv) in THF (7.5 mL) added. After 45 min the solution was warmed to rt. After 35 min the solution was quenched with brine (300 mL) and extracted with Et\textsubscript{2}O (3 × 100 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduced pressure and column chromatography (25% EtOAc–petrol) gave vinylaziridine 46 (1.00 g, 22%) as a gum; R\textsubscript{f} 0.72 (25% EtOAc–petrol); v\textsubscript{max} (film) 3061, 3030, 2996, 2955, 2837, 1611, 1598, 1585, 1512, 1462, 1440, 1398, 1323, 1302, 1247, 1178, 1116, 1089, 989, 928, 906, 814 cm\textsuperscript{-1}; δ\textsubscript{H} (270 MHz) 7.65 (2H, d, J 8.0 Hz, ortho Ts), 7.20 (2H, d, J 8.0 Hz, meta Ts), 6.90 (2H, d, J 8.0 Hz, meta ArOMe), 6.67 (2H, d, J 8.0 Hz, ortho ArOMe), 6.67 (2H, d, J 8.0 Hz, ortho ArOMe), 6.11-6.04 (1H, m, CH=CH\textsubscript{2}), 5.50 (1H, d, J 16.5 Hz, cis CH=CH/H), 5.35 (1H, d, J 12.0 Hz, trans CH=CH/H), 3.77 (3H, s, OMe), 3.27-3.14 (2H, m, CHNCH), 2.90 (1H, dd, J 14.5, 5.0 Hz, CHHArOMe), 2.69 (1H, dd, J 14.5 Hz, 6.5 Hz, CHHArOMe), 2.42 (3H, s, Me of Ts); δ\textsubscript{C} (125 MHz) [158.4 , 143.8, 137.1 (q Ar)], 131.8 (CH=CH\textsubscript{2}), [129.7, 129.4 (4C, Ar)], 129.4 (q Ar), [127.4 (2C, Ar)], 122.0 (CH=CH\textsubscript{2}), [114.0, 113.9 (Ar)], 60.4 (OMe),
[(2R*,3R*)-3-(4-Methoxybenzyl)oxiran-2-yl]methanol \( ^{31} \) 205

To a solution of allylic alcohol 197 (21.0 g, 118 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (170 mL) at –20 °C was added m-CPBA [–26.5 g (45.7 g of a mixture of ~58% with water), 153 mmol, 1.3 equiv]. The suspension was warmed to rt over 2h. After another 1 h, it was re-cooled to –20 °C and 10% Na\(_2\)SO\(_3\)\(_{(aq.)}\) (10 mL) added. It was then warmed to rt and a further amount of 10% Na\(_2\)SO\(_3\)\(_{(aq.)}\) (290 mL) added. After 1 h, it was diluted with H\(_2\)O (200 mL) and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (4 × 100 mL). The combined organic layers were washed with 10% NaHCO\(_3\)(aq.) (2 × 100 mL), sat. NaHCO\(_3\)(aq.) (3 × 100 mL), brine (3 × 150 mL) and dried (Na\(_2\)SO\(_4\)). Concentration under reduced pressure cleanly gave the crude epoxide 205 (22.0 g, 96%) as an oil; R\(_f\) 0.24 (50% EtOAc–petrol); \( \nu\)\(_{\text{max}}\) (film) 3415, 2993, 2931, 2836, 1612, 1583, 1513, 1463, 1442, 1301, 1247, 1180, 1081, 1033 cm\(^{-1}\); \( \delta\)\(_{\text{H}}\) (400 MHz) 7.16 (2H, d, \( J\) 8.5 Hz, meta MeOAr), 6.87 (2H, d, \( J\) 8.5 Hz, ortho MeOAr), 3.93 (1H, dd, \( J\) 12.5, 2.5 Hz, CHHOOH), 3.80 (3H, s, OMe), 3.65 (1H, dd, \( J\) 12.5, 4.5 Hz, CHHOOH), 3.20 (1H, ddd, \( J\) 8.5, 5.5, 3.0 Hz, CHCH\(_2\)OH), 3.00 (1H, ddd, \( J\) 4.5, 4.5, 3.0 Hz, ArCH\(_2\)CH), 2.86 (1H, dd, \( J\) 12.0, 6.5 Hz, ArCHHCH), 2.84 (1H, dd, \( J\) 12.0, 6.5 Hz, ArCHHCH); \( \delta\)\(_{\text{C}}\) (125 MHz) 158.4 (Ar ipso to MeO), 130.0 (meta MeOAr), 128.9 (para MeOAr), 114.3 (ortho MeOAr), 61.6 (MeO), 58.4 (CH\(_2\)OH), 56.2 (CHCH\(_2\)OH), 55.3 (ArCH\(_2\)CH), 36.9 (ArCH\(_2\)); \( m/z\) (CI) 212 [M+NH\(_4\)]\(^{+}\), 195 [M+H]\(^{+}\), 177, 121; data in agreement with that previously reported.\(^{31}\)
To a solution of (COCl) \textsubscript{2} (1.05 mL, 12.1 mmol, 1.20 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) at –78 °C was added a solution of DMSO (1.72 mL, 24.2 mmol, 2.4 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (7 mL) dropwise. After 5 min, a solution of hydroxyl epoxide 205 (1.96 g, 10.1 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (23 mL) was added. After 25 min, Et\textsubscript{3}N (7.0 mL, 50.5 mmol, 5.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (7 mL) was added slowly. After 10 min it was warmed to rt over 15 min and sat. NaHCO\textsubscript{3(aq.)} (15 mL) added. The aqueous phase was extracted with Et\textsubscript{2}O (3 × 50 mL). The combined organic layers were washed with H\textsubscript{2}O (2 × 50 mL), brine (2 × 50 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduce pressure and column chromatography (20→40% EtOAc–petrol) gave aldehyde 380 (1.74 g, 85%) as an oil; R\textsubscript{f} 0.35 (40% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3000, 2956, 2913, 1836, 2738, 1725, 1612, 1514, 1464, 1440, 1301, 1249, 1180, 1143, 1112, 1033 cm\textsuperscript{-1}; \( \delta_H \) (270 MHz) 8.90 (1H, d, J 6.5 Hz, CHO), 7.13 (2H, d, J 8.5 Hz, meta ArOMe), 6.84 (2H, d, J 8.5 Hz, ortho ArOMe), 3.77 (3H, s, OMe), 3.42 (1H, dt, J 5.0, 1.5 Hz, CHCH\textsubscript{2}Ar), 3.14 (1H, dd, J 6.5, 1.5 Hz, CHCHO), 2.96 (1H, dd, J 15.5, 5.0 Hz, CHHAr), 2.88 (1H, dd, J 15.0, 5.5 Hz, CHHAr); \( \delta_C \) (67.5 MHz) 198.3 (CHO), 158.8 (q ArOMe), 130.2 (3\textdegree), 127.5 (q ArOMe), 114.2 (3\textdegree), [58.4, 57.0 (CHCH)], 55.3 (OMe), 36.4 (CH\textsubscript{2}Ar); m/z (Cl) 210 [M+NH\textsubscript{4}]\textsuperscript{+}, 193 [M+H]\textsuperscript{+}, 175, 163, 147, 138, 121, 71, 52 (Found: [M+H]\textsuperscript{+}, 193.0862. C\textsubscript{11}H\textsubscript{12}O\textsubscript{3} requires [M+H]\textsuperscript{+}, 193.0865); data in agreement with that previously reported.\textsuperscript{31}
To a mixture of Ph₃PCH₂Br (43.6 g, 121.9 mmol, 2.0 equiv) in THF (140 mL) at –20 °C was added KHMDS (243.8 mL of a 0.5 M solution in toluene, 121.9 mmol, 2.0 equiv). After 30 min, it was warmed to rt then re-cooled to –20 °C after 30 min and aldehyde 308 (11.7 g, 60.9 mmol, 1.0 equiv) in THF (30 mL) was added slowly. After 1 h at that temperature the reaction was quenched with brine (400 mL) was poured in and the aqueous phase extracted with Et₂O (3 × 200 mL). The combined organic layers were washed with H₂O (3 × 150 mL), brine (4 × 150 mL) and dried (Na₂SO₄). Concentration under reduced pressure gave a the brown liquid, which was cooled down to give P(O)PPh₃ precipitate that was filtered. Column chromatography of the filtrate gave vinyl epoxide 206 (11.1 g, 96%) as an oil; Rf 0.55 (10% EtOAc–petrol); νₘₐₓ (film) 2992, 2949, 2913, 2844, 1611, 1583, 1512, 1461, 1445, 1246, 1034, 923, 806 cm⁻¹; δₜ (400 MHz) 7.18 (2H, d, J 8.5 Hz, meta MeOAr), 6.88 (2H, d, J 8.5 Hz, ortho MeOAr), 5.58 (1H, ddd, J 17.0, 10.0, 7.5 Hz, CH=CH₂), 5.47 (1H, dd, J 17.0, 1.5 Hz, cis CH=CH₂), 5.25 (1H, dd, J 10.0, 1.5 Hz, trans CH=CH₂), 3.82 (3H, s, MeO), 3.18 (1H, dd, J 7.5, 2.0 Hz, CHCH=CH₂), 3.06 (1H, ddd, J 5.5, 5.5, 2.0 Hz, ArCH₂CH₂), 2.89 (1H, dd, J 10.0, 5.5 Hz, ArCHH₂), 2.87 (1H, dd, J 10.0, 5.5 Hz, ArCHH); δC (125 MHz) 158.4 (ipso MeOAr), 135.5 (CH=CH₂), 130.0 (meta MeOAr), 128.9 (para MeOAr), 119.3 (CH=CH₂), 114.3 (ortho MeOAr), 60.6 (MeO), [58.4, 55.3 (CHOCH)], 37.4 (ArCH₂); m/z (CI) 208 [M+NH₄]⁺, 192, 173, 161, 147, 134, 121, 107; data in agreement with that previously reported.³¹
The mixture of vinyl epoxide 206 (2.00 g, 10.4 mmol, 1.0 equiv) and NH₄OH (17 mL of a 28% A.C.S. reagent, 251 mmol, 24.1 equiv) was irradiated under microwave at 110 °C for 35 min. Water (20 mL) was added to the reaction mixture, extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (Na₂SO₄). Concentration under reduced pressure cleanly gave crude hydroxyamine 207 (1.8 g, 84%) as an oil; Rf 0.17 (15% EtOAc–petrol); νmax (film) 3355, 3289, 3099, 3031, 2935, 1612, 1582, 1511, 1463, 1442, 1423, 1299, 1246, 1178, 1108, 1035 cm⁻¹; δH (400 MHz) 7.16 (2H, d, J 8.5 Hz, meta MeOAr), 6.87 (2H, d, J 8.5 Hz, ortho MeOAr), 6.03-5.94 (1H, m, CH=CH₂), 6.29-5.25 (2H, m, CH=CH₂), 3.83-3.78 (4H, m, MeO & CHOH), 3.45 (1H, dd, J 7.0, 3.0 Hz, CHNH₂), 2.74 (1H, dd, J 14.0, 4.5 Hz, ArCHH), 2.65 (1H, dd, J 14.0, 8.5 Hz, ArCHH), 1.77 [2H, s (br), NH₂]; δC (125 MHz) 158.2 (Ar para to MeO), 138.2 (CH=CH₂), 130.6 (Ar ipso to MeO), 130.4 (Ar meta to MeO), 116.7 (CH=CH₂), 114.0 (Ar ortho to MeO), 75.3 (CHOH), 58.0 (CHNH₂), 38.4 (ArCH₂); m/z (CI) 208 [M+H]+, 189, 168, 150, 135, 123, 121, 109; data in agreement with that previously reported.³¹
**N-[(3S*,4R*)-4-Hydroxy-5-(4-methoxyphenyl)pent-1-en-3-yl]-4-methylbenzenesulfonamide**

To a solution of hydroxylamine **207** (7.10 g, 34.3 mmol, 1.0 equiv), DMAP (503 mg, 4.1 mmol, 0.12 equiv) and TsCl (13.0 g, 68.2 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (61 mL) at 0 °C was added Et$_3$N. After 3 h at that temperature, the resulting solution was diluted with CH$_2$Cl$_2$ (200 mL), washed with 10% NaHCO$_3$(aq.) (130 mL) and the aqueous phase extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried (Mg$_2$SO$_4$). Concentration under reduced pressure and column chromatography (35–60% EtOAc–petrol) gave tosamide **208** (10.1 g, 81%) as a gum; R$_f$ 0.3 (30% EtOAc–petrol); $v$$_{max}$ (film) 3447, 3356, 3291, 1511, 1322, 1288, 1153, 1077, 1025, 813, 675 cm$^{-1}$; $\delta$$_H$ (400 MHz) 7.70 (2H, d, J 8.0 Hz, *ortho* Ts), 7.28 (2H, d, J 8.0 Hz, *meta* Ts), 7.05 (2H, d, J 8.5 Hz, *meta* ArOMe), 6.85 (2H, d, J 8.5 Hz, *ortho* ArOMe), 6.74 (1H, ddd, J 17.5, 10.5, 7.5 Hz, CH=CH$_2$), 6.19-5.08 (2H, m, CH=CH$_2$), 3.86-3.79 (5H, m, OMe, CHNHTs & CHOH), 2.67 (1H, dd, J 14.0, 4.5 Hz, ArCHH), 2.58 (1H, dd, J 14.0, 9.0 Hz, CHHAr), 2.65 (1H, dd, J 14.0, 8.5 Hz, CHHAr), 2.44 (3H, s, Me of Ts), 1.88 (1H, d, J 4.5 Hz, NHTs); $\delta$$_C$ (100 MHz) [158.2, 143.4, 137.7 (q Ar)], 132.5 (CH=CH$_2$), [130.2, 129.6, (ArH)], 129.1 (q ArOMe), 127.2 (ArH), 119.4 (CH=CH$_2$), 114.2 (ArH), 74.7 (CHOH), 59.9 (CHNH$_2$), 55.3 (OMe), 39.0 (CH$_2$Ar), 21.6 (Me of Ts); m/z (Cl) 379 [M+NH$_4$]$^+$, 362 [M+H]$^+$, 344, 300, 251, 228, 227, 207, 189, 150, 148, 140, 134, 122, 120, 109; data in agreement with that previously report.$^{31}$
(2R*,3R*)-2-(4-Methoxybenzyl)-1-tosyl-3-vinylaziridine\textsuperscript{31} 46

\[
\begin{align*}
\text{TsHN} & \quad \text{TsN} \\
\text{HO} & \quad \text{OMe} \\
\end{align*}
\]

To a solution of tosamide 208 (7.20 g, 19.9 mmol, 1.0 equiv) and PPh\textsubscript{3} (13.6 g, 51.9 mmol, 2.6 equiv) in THF (200 mL) at –15 °C was added DIAD (8.1 g, 39.9 mmol, 2.0 equiv) dropwise. The solution was warmed to –5 °C. After 14 h at that temperature, the solvent was removed under reduced pressure. The liquid was cooled down and the resulting solid was filtered off. The filtrate was purified by column chromatography (25% EtOAc–petrol) to give vinylaziridine 46 (6.4 g, 94%); data identical to that previously reported.\textsuperscript{31}

(1R*,5S*)-6-Oxabicyclo[3.1.0]hex-3-ene\textsuperscript{103}

\[
\begin{align*}
\text{209} & \quad \rightarrow \\
\text{210} & \\
\end{align*}
\]

To a mixture of anhydrous sodium carbonate (65.0 g, 613 mmol, 4.0 equiv) and cyclopentadiene 209 (10.2 g, 154 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (169 mL) at 0 °C was added dropwise the solution of peracetic acid (28.8 mL of a 40 wt% solution in dilute acetic acid, 154 mmol, 1.0 equiv) and sodium acetate trihydrate (0.80 g, 5.9 mmol, 0.04 equiv) over 20 min with vigorous stirring. After 10 min the mixture was stirred in a water bath at 20 °C until a negative result was obtained from starch-iodide paper test then filtered. Concentration under reduced pressure and distillation under vacuum (46 mmHg) gave the epoxide 210 (3.20 g, 25%) as a colourless liquid; R\textsubscript{f} 0.60 (90% EtOAc–petrol); \(\nu\)\textsubscript{max} (film) 3492, 3459, 3401, 2958, 2922, 2873, 2105, 1837, 1463,
1361, 1182, 1122, 1072, 1041 cm\(^{-1}\); \(\delta_{\text{H}}\) (270 MHz) 6.15-5.93 (2H, m, CH=CH), 3.92-3.80 (2H, m, CHOCH), 2.63-2.59 (1H, m, CH/CHOCH), 2.41-2.32 (1H, m, CH/CHOCH); \(\delta_{\text{C}}\) (125 MHz) [138.5, 131.3 (CH=CH)], [59.2, 56.9 (CHOCH)], 35.6 (CH\(_2\)); m/z (Cl) 100 [M+NH\(_4\)]\(^+\), 83 [M+H]\(^+\), 71, 56; data in agreement with that previously reported.\(^{103}\)

\((1R^*,4S^*)\)-4-(Phenylsulfonyl)cyclopent-2-enol\(^{32}\) 45

Method 1: Pd(acac)\(_2\) in THF preparation

To a mixture of epoxide 210 (50.0 mg, 0.76 mmol, 1.0 equiv) and sodium benzenesulfinate (313 mg, 1.91 mmol, 2.5 equiv) in THF (2.5 mL) was added a solution of Pd(acac)\(_2\) (1.2 mg, 0.004 mmol, 0.005 equiv) in THF (1 mL). The mixture was heated to 60 °C. After 16 h a further amount of Pd(acac)\(_2\) (11.0 mg, 0.04 mmol, 0.05 equiv) in THF (1 mL) was added. After 3 days the mixture was quenched with sat. NH\(_4\)Cl\(_{\text{(aq)}}\) (0.5 mL). After 15 min the solution was diluted with sat. NH\(_4\)Cl\(_{\text{(aq)}}\) (1 mL), H\(_2\)O (10 mL) and the mixture extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 10 mL). The combined organic layers were washed with brine (2 \(\times\) 5 mL) and dried (MgSO\(_4\)). Concentration under reduced pressure and column chromatography (40% EtOAc–petrol) gave the \((1R^*,4S^*)\)-4-(phenylsulfonyl)cyclopent-2-enol 45 (63 mg, 37%) as a colourless oil; R\(_f\) 0.52 (80% EtOAc–petrol); \(v_{\text{max}}\) (film) 3428, 3000, 2985, 2956, 2921, 2850, 2815, 2802, 2782, 1910, 1884, 1658, 1641, 1552, 1303, 1145, 1083, 989 cm\(^{-1}\); \(\delta_{\text{H}}\) (270 MHz) 7.90 (2H, d, J 7.0 Hz, ortho PhSO\(_2\)), 7.67 (1H, t, J 7.0 Hz, para PhSO\(_2\)), 7.57 (2H, t, J 7.0 Hz, meta PhSO\(_2\)), 6.36-6.35 (1H, m, CH=CHCHOH), 5.74-5.73 (1H, m, CH=CHCHOH), 4.72-4.70 (1H, m, CH/SO\(_2\)Ph), 4.16-4.01 (1H, m, CHOHN), 2.26-2.21 (2H, m, CH\(_2\)); \(\delta_{\text{C}}\) (125 MHz) 142.5 (ipso PhSO\(_2\)), 137.7 (ortho PhSO\(_2\)), 134.2 (para PhSO\(_2\)), [129.4, 128.8 (CH=CH)], 126.3 (meta PhSO\(_2\)), 74.9 (CHSO\(_2\)Ph), 70.2 (CHOHN), 34.3 (CH\(_2\)); m/z (Cl) 242 [M+NH\(_4\)]\(^+\), 225 [M+H]\(^+\), 208 [M-OH]\(^+\); data in agreement with that previously reported.\(^{32}\)
Method 2: Pd$_2$(dba)$_3$ in DMF preparation

To a solution of Pd$_2$(dba)$_3$ (36.7 mg, 0.04 mmol, 0.05 equiv) in DMF (1 mL) at rt was added a solution of epoxide 210 (65.7 mg, 0.8 mmol, 1.0 equiv) in DMF (1 mL) and a suspension of sodium benzenesulfinate (263 mg, 1.6 mmol, 2.0 equiv) in DMF (2 mL). The resulting solution was heated to 90 °C. After 6 h the solution was quenched with sat. NH$_4$Cl(aq.) (0.5 mL). After 15 min the solution was diluted with sat. NH$_4$Cl(aq.) (1 mL) and H$_2$O (10 mL) then extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine (4 \times 5 mL) and dried (MgSO$_4$). Concentration under reduced pressure and column chromatography (30% EtOAc–petrol) gave the compound 45 (75.3 mg, 42%); data identical to that of method 1 preparation.

5-(Phenylsulfonyl)hepta-1,5-dien-3-ol 216 and 3-(phenylsulfonyl)-2-vinylpent-3-en-1-ol 217

![Chemical reaction diagram](image)

To a solution of allylic sulfone 212 (1.00 g, 5.5 mmol, 1.0 equiv) in Et$_2$O (27 mL) at −20 °C was added nBuLi (2.30 mL of a 2.8 M solution in hexanes, 6.60 mmol, 1.2 equiv) dropwise over 20 min. After 15 min the suspension was warmed for 30 min then re-cooled to −20 °C. Butadiene monoxide 47 (440 µL, 5.5 mmol, 1.0 equiv) was added. After 30 min the reaction was warmed to rt for 2 h then sat. NH$_4$Cl(aq.) (1.0 mL) added. After 5 min the mixture was diluted with sat. NH$_4$Cl(aq.) (4 mL), H$_2$O (30 mL) and extracted with Et$_2$O (3 \times 30 mL). The combined organic layers were washed with brine (2 \times 15 mL) and dried (MgSO$_4$). Concentration under reduced pressure and column chromatography (20%→30% EtOAc–petrol) gave 5-(phenylsulfonyl)hepta-1,5-dien-3-ol 216 (407 mg, 29%) and 3-(phenylsulfonyl)-2-vinylpent-3-en-1-ol 217 (232 mg, 17%) both as colourless gums.
Data for 216: Rf 0.37 (40% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3501, 3069, 2984, 2924, 1704, 1643, 1584, 1477, 1300, 1148, 1132, 1083, 1033, 1022, 996, 926, 762, 737, 693 cm\(^{-1}\); \( \delta_{\text{H}} \) (270 MHz) 7.86-7.79 (2H, m, ortho PhSO\(_2\)), 7.65-7.45 (3H, m, para & meta PhSO\(_2\)), 7.12 (1H, q, J 7.0 Hz, CH=CSO\(_2\)Ph), 5.86-5.72 (1H, m, CH\(_2\)=CHCHOH), 5.21 (1H, d, J 18.0 Hz, cis CHH=CH), 5.07 (1H, d, J 11.0 Hz, trans CHH=CH), 4.12-4.30 (1H, m, CHOH), 2.44-2.38 (2H, m, CH\(_2\)CHOH), 1.89 (3H, d, J 7.0 Hz, Me), 1.20 (1H, br s, OH); \( \delta_{\text{C}} \) (125 MHz) 140.5 (ipsoO PhSO\(_2\)), 139.6 (CH=CSO\(_2\)Ph), 138.6 (para PhSO\(_2\)), 133.4 (CH=CSO\(_2\)Ph), 129.4 (CH\(_2\)=CH), 129.2 (ortho PhSO\(_2\)), 115.3 (CH\(_2\)=CH), 71.6 (CHOH), 33.9 (CH\(_2\)CHOH), 14.7 (Me); m/z (Cl) 522 [M+NH\(_4\)]\(^+\), 270 [M+NH\(_4\)]\(^+\), 253 [M+H]\(^+\), 235 [M-OH]\(^+\), 216, 69, 52 (Found: [M+NH\(_4\)]\(^+\), 270.1157. C\(_{13}\)H\(_{16}\)O\(_3\)S requires [M+NH\(_4\)]\(^+\), 270.1164) (Found: C, 61.78; H, 6.32. C\(_{13}\)H\(_{16}\)O\(_3\)S requires C, 61.88; H, 6.39%).

Data for 217: Rf 0.23 (40% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3502, 3065, 2951, 2936, 2882, 1640, 1584, 1476, 1446, 1416, 1376, 1289, 1200, 1149, 1084, 1070, 1045, 996, 926, 894, 837, 762, 721, 689, 612 cm\(^{-1}\); \( \delta_{\text{H}} \) (500 MHz) 7.90-7.87 (2H, m, ortho PhSO\(_2\)), 7.64 (1H, m, para PhSO\(_2\)), 7.56-7.53 (2H, m, meta PhSO\(_2\)), 7.16 (1H, q, J 7.0 Hz, CH=CSO\(_2\)Ph), 5.71-5.64 (1H, m, CH\(_2\)=CH), 4.96 (1H, dd, J 10.0, 1.5 Hz, trans CHH=CH), 4.79 (1H, dd, J 17.0, 1.5 Hz, cis CHH=CH), 3.79 (2H, d, J 7.5 Hz, CH\(_2\)OH), 3.53 (1H, dt, J 14.5, 7.5 Hz, CHCH\(_2\)OH), 1.95 (3H, d, J 7.0 Hz, CH\(_3\)), 1.28-1.18 (1H, m, OH); \( \delta_{\text{C}} \) (125 MHz) 140.8 (ipso PhSO\(_2\)), 139.9 (CH=CSO\(_2\)Ph), 139.3 (para PhSO\(_2\)), 133.8 (CH=CSO\(_2\)Ph), 133.4 (CH\(_2\)=CH), 129.1 (ortho PhSO\(_2\)), 128.2 (meta PhSO\(_2\)), 117.4 (CH\(_2\)=CH), 64.5 (CH\(_2\)OH), 45.2 (CHCH\(_2\)), 15.1 (Me); m/z (Cl) 270 [M+NH\(_4\)]\(^+\), 253 [M+H]\(^+\), 235 [M-OH]\(^+\), 132, 52 (Found: [M+NH\(_4\)]\(^+\), 270.1160. C\(_{13}\)H\(_{16}\)O\(_3\)S requires [M+NH\(_4\)]\(^+\), 270.1164) (Found: C, 61.89; H, 6.37. C\(_{13}\)H\(_{16}\)O\(_3\)S requires C, 61.88; H 6.39%).
To a solution of sodium benzenesulfinate (4.92 g, 30.0 mmol, 1.0 equiv) in DMF (20 mL) at 70 °C was added prenyl bromide 222 (3.46 mL, 30.0 mmol, 1.0 equiv) then cooled to rt. After 6 h H_{2}O (30 mL) was poured into the yellow suspension and the mixture extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (4 × 50 mL) and dried (MgSO_{4}). Concentration under reduced pressure and recrystallisation (Et_{2}O–petrol) gave the sulfone 223 (5.80 g, 92%) as a white crystalline solid; mp 49-50 °C (lit. mp 50-51 °C); R_f 0.76 (40% Et_{2}O–petrol); ν_{max} (film) 2976, 2933, 2914, 1447, 1374, 1304, 1245, 1150, 1133, 1105, 1085, 774, 745, 689 cm\(^{-1}\); δ_H (270 MHz) 7.84 (2H, d, J = 8.5 Hz, ortho PhSO\(_{2}\)), 7.60 (1H, t, J = 8.0 Hz, para PhSO\(_{2}\)), 7.54 (2H, dd, J = 8.5, 8.0 Hz, meta PhSO\(_{2}\)), 5.17 (1H, t, J = 9.0 Hz, CH=CH), 3.76 (2H, d, J = 9.0 Hz, CH\(_{2}\)), 1.69 (3H, s, CH\(_{3}\)CCH\(_{3}\)), 1.28 (3H, s, CH\(_{3}\)CCH\(_{3}\)); δ_C (125 MHz) 143.0 (ipso PhSO\(_{2}\)), 138.7 (para PhSO\(_{2}\)), 133.5 (C=CH), 128.9 (ortho PhSO\(_{2}\)), 128.5 (meta PhSO\(_{2}\)), 110.4 (C=CH), 56.2 (CH\(_{2}\)SO\(_{2}\)Ph), [25.8, 17.7 (2 × Me)]; m/z (CI) 228 [M+NH\(_{4}\)]\(^{+}\), 211 [M+H]\(^{+}\); data in agreement with that previously reported.\(^{104}\)
7-Methyl-5-(phenylsulfonyl)octa-1,6-dien-3-ol 224 and 5-methyl-3-(phenylsulfonyl)-2-vinylhex-4-en-1-ol 225

\[
\begin{align*}
\text{PhO}_2\text{S} & \quad + \quad \text{O}=\text{CH} \quad \text{PhO}_2\text{S} \\
\text{223} & \quad \text{47} & \quad \text{224} \quad \text{225}
\end{align*}
\]

To a solution of prenyl sulfone 223 (1.05 g, 5.0 mmol, 1.0 equiv) in THF/TMEDA (1:1, 25 mL) at −78 °C was added nBuLi (2.50 mL of a 2.4 M solution in hexanes, 6.0 mmol, 1.2 equiv). After 15 min the solution was warmed to −20 °C for 30 then re-cooled to −78 °C and butadiene monoxide 47 (483 µL, 6.0 mmol, 1.2 equiv) added. After 15 min the suspension was warmed to −20 °C then to rt after 30 min. After 1 h the reaction was quenched with sat. NH₄Cl (aq.) (15 mL), diluted with H₂O (50 mL) and extracted with Et₂O (3 × 60 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (15% EtOAc–petrol) gave 7-methyl-5-(phenylsulfonyl)octa-1,6-dien-3-ol 224 (476 mg, 36%) and 5-methyl-3-(phenylsulfonyl)-2-vinylhex-4-en-1-ol 225 (550 mg, 42%) both as colourless gums.

Data for 224: Rf 0.48 (40% EtOAc–petrol); νmax (film) 3492, 3065, 2978, 2926, 2876, 1667, 1644, 1446, 1299, 1145, 1083, 1069, 1052, 996, 924, 744, 718, 689 cm⁻¹; δH (270 MHz) 7.82 (2H, d, J 7.5 Hz, ortho PhSO₂), 7.60 (1H, t, J 7.0 Hz, para PhSO₂), 7.51 (2H, dd, J 7.5, 7.0 Hz, meta PhSO₂), 5.88 (1H, ddd, J 14.0, 9.5, 5.0 Hz, CH=CH₂), 5.20 (1H, dd, J 14.0, 7.5 Hz, cis CHH=CH), 5.12 (1H, dd, J 9.5, 7.5 Hz, trans CHH=CH), 4.98 (1H, d, J 10.5 Hz, C=CH), 4.13-4.05 (2H, m, PhSO₂CH & CHOH), 2.24 (1H, ddd, J 6.5, 6.0, 2.5 Hz, CHHCHOH), 1.83 (1H, ddd, J 6.5, 6.0, 2.5 Hz, CHHCHOH), 1.65 (3H, s, CH₃CCH₃), 1.48 (1H, d, J 7.0 Hz, OH), 1.15 (3H, s, CH₃CCH₃); δC (101 MHz) 143.1 (ipso PhSO₂), 140.4 (C=CH), 137.9 (para PhSO₂), 133.4 (CH₂=CH), 129.1 (ortho PhSO₂), 128.7 (meta PhSO₂), 116.6 (C=CH), 115.1 (CH₂=CH), 69.6 (CHSO₂Ph), 61.9 (CHOH), 34.5 (CH₂), [25.9, 17.9 (2 × Me)]; m/z (CI) 298 [M+NH₄]⁺, 281 [M+H]⁺, 264, 263 [M-OH]⁺, 160, 121, 83 (Found: [M+NH₄]⁺, 298.1472. C₁₅H₂₀O₃S requires
[M+NH₄]⁺, 298.1477) (Found: C, 64.29; H, 7.13. C₁₅H₂₀O₃S requires C, 64.26; H, 7.19%).

Data for 225: Rf 0.41 (40% EtOAc–petrol); νmax (film) 3497, 2978, 2937, 2915, 1446, 1377, 1301, 1175, 1143, 1083, 1069, 1049, 995, 927, 777, 745, 795, 689 cm⁻¹; δH (270 MHz) 7.78 (2H, d, J 8.5 Hz, ortho PhSO₂), 7.55 (1H, t, J 7.0 Hz, para PhSO₂), 7.51 (2H, dd, J 8.5, 7.0 Hz, meta PhSO₂), 5.79-5.73 (1H, m, CH₂=CH), 5.21-5.11 (2H, m, CH₂=CH), 4.95 (1H, d, J 11.5 Hz, C=CH), 4.23-4.21 (1H, m, PhSO₂CH), 3.84-3.44 (2H, m, CH₂OH), 2.39-2.33 (1H, m, CHCH₂OH), 1.60 (3H, s, CH₃CCH₃), 1.15 (1H, m, OH), 1.11 (3H, s, CH₃CCH₃); δC (100 MHz) 142.8 (ipso PhSO₂), 141.9 (C=CH), 137.9 (para PhSO₂), 134.0 (CH₂=CH), 129.1 (ortho PhSO₂), 128.7 (meta PhSO₂), 117.3 (C=CH), 116.4 (CH₂=CH), 70.9 (CHSO₂Ph), 61.7 (CH₂OH), 30.3 (CHCH₂OH), [25.7, 18.0 (2 × Me)]; m/z (CI) 298 [M+NH₄]⁺, 281 [M+H]⁺, 264, 263 [M-OH]⁺, 160, 121, 109, 83 (Found: [M+NH₄]⁺, 298.1471. C₁₅H₂₀O₃S requires [M+NH₄]⁺, 298.1477) (Found: C, 64.37; H, 7.16; C₁₅H₂₀O₃S requires C, 64.26; H, 7.19%).
Cinnamylsulfonylbenzene\textsuperscript{107} \textit{227}

\[
\text{Ph} = \overset{\text{Br}}{\text{C}} = \overset{\text{Br}}{\text{C}} + \text{PhSO}_2\text{Na} \rightarrow \text{Ph} = \overset{\text{SO}_2\text{Ph}}{\text{C}} = \overset{\text{SO}_2\text{Ph}}{\text{C}}
\]

To a solution of sodium benzenesulfinate (10.0 g, 60.9 mmol, 1.0 equiv) in DMF (20 mL) at 80 °C was added cinnamyl bromide \textit{226} (12.0 g, 60.9 mmol, 1.0 equiv) then cooled to rt. After 2 h the suspension was diluted with H\textsubscript{2}O (150 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (3 × 40 mL) and dried (MgSO\textsubscript{4}). Concentration under reduced pressure and recrystallisation (EtOAc–petrol) gave cinnamylphenylsulfone \textit{227} (14.7 g 93\%) as a white crystalline solid; mp 50-51 °C (EtOAc–petrol) (lit.\textsuperscript{107} mp 50-51 °C); R\textsubscript{f} 0.62 (30% EtOAc–petrol); \(\nu\)\textsubscript{max} (film) 2974, 1445, 1403, 1317, 1237, 1160, 1135, 1084, 1058, 998, 982, 759, 697 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (270 MHz) 7.87 (2H, d, J 7.0 Hz, ortho PhSO\textsubscript{2}), 7.64 (1H, t, J 7.0 Hz, para PhSO\textsubscript{2}), 7.54 (2H, t, J 7.0 Hz, meta PhSO\textsubscript{2}), 7.30-7.25 (5H, m, PhCH), 6.36 (1H, d, J 16.0 Hz, \(\text{CH}=\text{CHCH}\_2\)), 6.05 (1H, dt, J 16.0, 8.0 Hz, \(\text{CH}=\text{CHCH}\_2\)), 3.94 (2H, d, J 8.0 Hz, CH\_2SO\textsubscript{2}Ph); \(\delta\)\textsubscript{C} (125 MHz) 139.2 (ipso PhSO\textsubscript{2}), 138.5 (ortho PhSO\textsubscript{2}), 135.8 (ipso PhCH=CH), 133.7 (PhCH=CH), 130.8 (para PhCH=CH), [129.1, 128.8, 126.6 (ortho & meta PhCH & PhSO\textsubscript{2}), 115.2 (PhCH=CH)), 60.5 (CH\_2SO\textsubscript{2}); \(m/z\) (Cl) 276 [M+NH\textsubscript{4}\textsuperscript{+}], 269, 229, 175, 160; data in agreement with that previously reported.\textsuperscript{107}
(3R*,5S*,E)-7- Phenyl-5-(phenylsulfonyl)hepta-1,6-dien-3-ol  3,5-syn-228,  (E)-7-phenyl-5-(phenylsulfonyl)hepta-1,6-dien-3-ol  228 and  (E)-5-phenyl-3-(phenylsulfonyl)2vinylpent-4-en-1-ol  229

To a solution of cinnamylsulfone  227 (2.10 g, 8.0 mmol, 1.0 equiv) in THF (40 ml) at –78 °C was added nBuLi (4.54 mL of a 2.3 M solution in hexanes, 10.4 mmol, 1.3 equiv) dropwise over 10 min. After 15 min the solution was warmed to –20 °C for 30 min then re-cooled to –78 °C and butadiene monoxide (677 µL, 8.4 mmol, 1.05 equiv) added. The reaction was warmed to rt over a period of 1 h. After 3 h the reaction was quenched with sat. NH₄Clₐq.) (10 mL) then diluted with water (50 mL) and extracted with Et₂O (3 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried (MgSO₄). Concentration under reduced pressure and recrystallisation (Et₂O–petrol) gave (3R*,5S*,E)-7-phenyl-5-(phenylsulfonyl)hepta-1,6-dien-3-ol  3,5-syn-228 (534 mg, 20%) as a white solid, further column chromatography (20% EtOAc–petrol) gave (E)-7-phenyl-5-(phenylsulfonyl)hepta-1,6-die-3-ol  228 (923 mg, 35%) as a yellow solid and (E)-5-phenyl-3-(phenylsulfonyl)-2-vinylpent-4-en-1-ol  229 (394 mg, 15%) as a gum.

Data for  3,5-syn-228: mp 114-116 °C (Et₂O–petrol); Rf 0.40 (40% EtOAc–petrol);  vₘₐₓ (film) 3461, 2955, 2923, 2886, 2773, 1446, 1297, 1143, 1083, 1072, 996, 971, 734, 688 cm⁻¹;  δH (270 MHz) 7.83 (2H, d, J 8.0 Hz, ortho PhSO₂), 7.60 (1H, t, J 8.0 Hz, para PhSO₂), 7.54 (2H, t, J 8.0 Hz, meta PhSO₂), 7.26-7.24 (5H, m, PhCH), 6.30 (1H, d, J 16.0 Hz, PhCH=CH), 5.99-5.82 (2H, m, PhCH=CH & CH₂=CH), 5.23 (1H, dd, J 16.0, 5.5 Hz, cis CHH=CH), 5.13 (1H, dd, J 10.5, 5.5 Hz, trans CHH=CH), 4.13-4.03 (2H, m, CHSO₂Ph & CHO), 2.33 (1H, ddd, J 20.5, 11.0, 3.0 Hz, CHHCHOH), 1.96 (1H, ddd, J 20.5, 11.0, 3.0 Hz, CHHCHOH), 1.55-1.52 (1H, d, J 3.5 Hz, OH);  δC (101 MHz) 140.1 (ipso PhSO₂), [138.7, 137.5, 135.7 (ipso PhCH & ortho, para PhSO₂)], 133.7 (PhCH=CH), [129.1, 128.9, 128.7 (meta PhSO₂ & ortho, para PhCH)], 128.5 (PhCH=CH), 126.6 (meta PhCH), 120.5 (CH₂=CH), 115.5 (CH₂=CH), 69.4

Data for 229: Rₑ 0.34 (40% EtOAc–petrol); ν_max (film) 3493, 3055, 2975, 2954, 2930, 2878, 1447, 1302, 1144, 1083, 1060, 732, 689 cm⁻¹; δ_H (270 MHz) 7.82 (2H, d, J 8.5 Hz, ortho PhSO₂), 7.55 (1H, t, J 8.0 Hz, para PhSO₂), 7.42 (2H, dd, J 8.5, 8.0 Hz, meta PhSO₂), 7.24-7.12 (5H, m, PhCH=CH) 6.09 (1H, d, J 16.0 Hz, PhCH=CH), 6.07 (1H, dd, J 16.0, 8.5 Hz, PhCH=CH), 5.27 (1H, dd, J 10.0, 1.0 Hz, trans CHH=CH), 5.25 (1H, dd, J 15.5, 1.0 Hz, cis CHH=CH), 3.59 (1H, dd, J 11.0, 8.5 Hz, CHSO₂Ph), 3.34-3.26 (1H, m, CHCH₂OH), 1.24-1.19 (1H, m, OH); δ_C (101 MHz) 139.1 (ipso PhSO₂), 138.1 (para PhSO₂), 135.7 (ipso PhCH), 133.6 (PhCH=CH), [129.0, 128.8, 128.6, 128.3 (ortho, meta PhSO₂ & ortho, para PhCH)], 128.3 (PhCH=CH), 126.6 (meta PhCH), 119.5 (CH₂=CH), 118.6 (CH₂=CH), 69.2 (PhSO₂CH), 63.3 (CH₂OH), 44.6 (CH); m/z (CI) 346 [M+NH₄]⁺, 329 [M+H]⁺, 206, 204, 287, 177, 169, 160, 157, 52 (Found: [M+NH₄]⁺, 346.1479. C₁₉H₂₆O₃S requires [M+NH₄]⁺, 346.1477) (Found: C, 69.58; H, 6.12. C₁₉H₂₆O₃S requires C, 69.48; H, 6.14%).

(1R*,4S*)-4-(Phenylsulfonyl)cyclopent-2-enol cis-45

To a solution of 3,5-syn-228 (400 mg, 1.20 mmol, 1.0) in CH₂Cl₂ (15 mL) at 40 °C was added catalyst 50 (31.1 mg, 0.04 mmol, 0.03 equiv) in CH₂Cl₂ (2 mL). After 10 min concentration under reduced pressure and column chromatography (15%→50% EtOAc–petrol) gave cyclopentenylsulfone cis-45 (255 mg, 93%); data identical to that previously reported.¹³
To a solution of compound 228 (311 mg, 0.95 mmol, 1.0 equiv), DMAP (8.7 mg, 0.07 mmol, 0.08 equiv) and TBDMSCl (258 mg, 1.7 mmol, 1.8 equiv) in CH₂Cl₂ (1 mL) at 40 ºC was added Et₃N (397 µL, 2.85 mmol, 3.0 equiv) dropwise. After 24 h the brown suspension was quenched with sat. NH₄Cl (aq.) (2 mL), diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with sat. NaHCO₃ (aq.) (5 mL), brine (3 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (40% ether–petrol) gave tert-butyldimethyl[(3R*,5S*,E), (3S*,5S*,E)-7-phenyl-5-(phenylsulfonyl)hepta-1,6-dien-3-yloxy]silane 230 (400 mg, 95%) as a colourless oil; Rf 0.67 (40% Et₂O–petrol); νmax (film) 2953, 2929, 2902, 2856, 1470, 1447, 1360, 1316, 1305, 1254, 1083, 1028, 988, 968, 943, 906, 873, 836, 819, 777, 753, 734, 705 cm⁻¹; δH (270 MHz) 7.83–7.79 (2 × 2H, m, ortho PhSO₂, 2 × diast.), 7.61–7.45 (2 × 3H, m, para & meta PhSO₂, 2 × diast.), 7.30–7.19 (2 × 5H, m, PhCH=CH, 2 × diast.), 6.25 (1H, d, J 18.5 Hz, CH=CHPh, diast. of PhSO₂ syn to OTBDMS), 6.15 (1H, d, J 18.5, CH=CHPh, diast. of PhSO₂ anti to OTBDMS), 5.92–5.60 (2 × 2H, m, PhCH=CH & CH₂=CH, 2 × diast.), 5.13–5.02 (2 × 2H, m, CH₂=CH, 2 × diast.), 4.23–3.77 (2 × 2H, m, PhSO₂CHCH₂CHOH, 2 × diast.), [2.40–2.28, 2.02–1.77 (2 × 2H, m, CHCH₂CH, 2 × diast.)], 0.91 (9H, s, tBu, diast. of PhSO₂ anti to OTBDMS), 0.86 (9H, s, tBu, diast. of PhSO₂ syn to OTBDMS), {0.12, 0.06, 0.02, -0.02, -0.04 [2 × 6H, m, Si(CH₃)₂, 2 × diast.]}; δC (101 MHz) 140.9, 140.2, 138.7, 137.9, 137.6, 137.4, 135.8, 133.6, 129.2, 129.1, 128.8, 128.6, 128.4, 126.6, 126.5, 121.5, 120.8, 115.6, 115.3, 71.8, 70.9, 66.2, 65.9, [35.9, 35.6 (2 × C, CHCH₂CH, 2 × diast.)], 25.8, 25.7, 25.6, [18.1, 18.0 (2 × C, SiC(CH₃)₃, 2 × diast.), {−3.6, −3.8, −4.4, −4.8 [2 × 2C, Si(CH₃)₂, 2 × diast.]}; m/z (CI) 460 [M+NH₄]⁺, 443 [M+H]⁺, 312, 311, 301, 298, 171; 169, 132 (Found: [M+H]⁺, 443.2057. C₂₂H₃₄O₃SSi requires [M+H]⁺, 443.2076) (Found: C, 67.96; H, 7.68. C₂₂H₃₄O₃SSi requires C, 67.83; H, 7.74%).
tert-Butyldimethyl[(1R*,4S*), (1S*,4S*)-4-(phenylsulfonyl)cyclopent-2-enyl oxy]silane 213

To a solution of diene 230 (350 mg, 0.79 mmol, 1.0 equiv) in CH₂Cl₂ (13 mL) at 40°C was added a solution of catalyst 50 (20 mg, 0.024 mmol, 0.03 equiv) in CH₂Cl₂ (2 mL). After 2 h another solution of Grubbs II (13.4 mg, 0.016 mmol, 0.02 equiv) in DCM (1 mL) was added. After 16 h concentrated under reduced pressure and column chromatography (5% EtOAc–petrol) gave tert-butyldimethyl[(1R*,4S*), (1S*,4S*)-4-(phenylsulfonyl)cyclopent-2-enyloxy]silane 231 (211 mg, 79%); Rf (10% EtOAc–petrol); ν max (film) 2953, 2935, 2882, 2856, 1725, 1470, 1447, 1367, 1307, 1256, 1179, 1148, 1083, 897, 837, 778, 755, 718, 689 cm⁻¹; δH (270 MHz) 7.85 (2 × 2H, d, J 7.5 Hz, ortho PhSO₂, 2 × diast.), 7.61 (2 × 1H, t, J 7.0 Hz, para PhSO₂, 2 × diast.), 7.56 (2H, dd, J 7.5, 7.0 Hz, meta PhSO₂, 2 × diast.), [6.06-6.04, 5.93-5.91 (2H, m, CH=CH, diast. of PhSO₂ syn to OTBDMS)]; [5.84-5.82, 5.74-5.71 (2H, m, CH=CH, diast. of PhSO₂ anti to OTBDMS)], 4.80-4.76 (2H, m, PhSO₂CH₂CH₂CHOTBDMS, 1 × diast.), [4.38-4.35, 4.15-4.11 (2H, m, PhSO₂CH₂CH₂CHOTBDMS, 1 × diast.)), 2.70-2.52 (2H, m, CH₂, diast. of PhSO₂ syn with OTBDMS), 2.02-1.88 (2H, m, CH₂, diast. of PhSO₂ anti to OTBDMS), 0.87 (9H, s, tBu, diast. of PhSO₂ anti to OTBDMS), 0.79 (9H, s, tBu, diast. of PhSO₂ cis to OTBDMS), {0.00, −0.03, −0.05 [2 × 6H, s, Si(CH₃)₂, 2 × diast.]}; δC (125 MHz) [143.3, 141.4 (2 × ipso PhSO₂, 2 × diast.), 136.5 (para PhSO₂, 1 × diast.), [133.8, 133.7 (2 × CH=CHCHSO₂Ph, 2 × diast.), 129.6 (para PhSO₂, 1 × diast.), [129.4, 129.1 (2 × ortho PhSO₂, 2 × diast.).], [129.0, 128.9 (2 × meta PhSO₂, 2 × diast.), [125.6, 125.4 (2 × CH=CHCHSO₂Ph, 2 × diast.), [76.4, 70.2, 71.4, 70.2 (2 × CHSO₂Ph & CHOTBDMS, 2 × diast.), [35.5, 34.4 (2 × CH₂CHOTBDMS, 2 × diast.), [25.8, 25.7, 25.6 (2 × (CH₃)₂CSi, 2 × diast.], [18.1, 18.0 (2 × (CH₃)₂CSi, 2 × diast.], [−4.8, −4.7 (2 × (CH₃)₂Si, 2 × diast.)] m/z (CI) 356 [M+NH₄]+, 339 [M+H]+, 321, 281, 242, 240, 224, 197 [M-PhSO₂]+; (Found: [M+H]+, 339.1439. C₁₇H₂₈O₃SSi requires [M+H]+, 339.1450) (Found: C, 60.23; H, 7.73. C₁₇H₂₈O₃SSi requires C, 60.31; H, 7.74%).
(E)-5-(Phenylsulfonyl)-5-styrylocta-1,7-dien-3-ol 241

![Chemical structure]

To a solution of diene 228 (405 mg, 1.23 mmol, 1.0 equiv) in THF (2.5 mL) at –78 °C was added nBuLi (1.05 mL of a 2.45 M solution in hexanes, 2.58 mmol, 2.1 equiv). After 20 min the solution was warmed to –20 °C for 20 min then re-cooled to –78 °C and allyl bromide (107 µL, 1.23 mmol, 1.0 equiv) added to this deep red solution. After 15 min it was warmed to 0 °C for 15 min then to rt. After 30 min the reaction was quenched with sat. NH₄Cl (aq.) (1.1 mL), diluted with H₂O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (30% EtOAc–petrol) gave 2:1 diastereomeric mixture of (E)-5-(phenylsulfonyl)-5-styrylocta-1,7-dien-3-ol 241 (260 mg, 57%) as a colourless gum; Rf 0.24 (30% EtOAc–petrol); vmax (film) 3505, 3463, 3063, 3026, 2978, 2922, 1640, 1493, 1445, 1300, 1146, 1083, 1017, 923, 760, 740, 680 cm⁻¹; δH (400 MHz) [7.84, 7.78 (2 × 2H, 2 × d, 2 × J 7.5 Hz, ortho PhSO₂, 2 × diast.)], 7.67-7.61 (2 × 1H, m, para PhSO₂, 2 × diast.), 7.55-7.46 (2 × 2H, m, meta PhSO₂, 2 × diast.), 7.37-7.21 (2 × 5H, m, PhCH, 2 × diast.), 6.34 (1H, d, J 16.5 Hz, PhCH=CH, major diast.), 6.25 (1H, d, J 16.5 Hz, PhCH=CH, major diast.), 6.15-6.03 (1H, m, CH₂=CHCH₂, minor diast.), 5.95 (1H, dd, J 10.0, 6.5 Hz, CHH=CHCHOH, minor diast.), 5.92 (1H, dd, J 10.0, 6.5 Hz, CHH=CHCHOH, minor diast.), 5.82 (1H, dd, J 10.0, 4.5 Hz, CHH=CHCHOH, major diast.), 5.78 (1H, dd, J 10.0, 6.0 Hz, CHH=CHCHOH, major diast.), 5.72-5.58 (1H, m, CH₂=CHCH₂, major diast.), [5.33-4.99 (2H, m, PhCH=CHC, minor diast.) & (2 × 3H, m, CH₂=CHCH₂, 2 × diast.)], 4.63 (1H, br s, OH, major diast.), 4.36 (1H, br s, OH, min. OH), 4.28 (1H, q, J 6.20 Hz, CHOH, major diast.), 3.76 (1H, m, CHOH, major diast.), 3.06 (1H, dd, J 15.0, 6.5 Hz, CHHCH=CH₂, minor diast.), 2.78 (1H, dd, J 15.0, 6.5 Hz, CHHCH=CH₂, minor diast.), 2.65-2.46 (4H, m, CH₂CH=CH₂ & CH₂CHOH, major diast.), 2.38 (1H, dd, J 14.0, 2.0 Hz, CHHCHOH, minor diast.), 2.22 (1H, dd, J 14.0, 8.5 Hz, CHHCHOH, minor diast.); δC (125 MHz) 147.0, 141.4, 140.8, 139.6, 139.1, 137.6,
135.2, 134.9, 134.6, 133.8, 133.5, 132.4, 130.9, 129.2, 128.9, 128.8, 128.5, 128.1, 127.5, 127.4, 127.1, 126.7, 126.6, 119.7, 117.7, 115.4, 114.7, 71.5, 69.7, 69.2, 44.5, 44.4, 41.1, 40.9, 38.1, 35.9, 34.7, 17.5; m/z (Cl) 386 [M+NH₄]⁺, 368, 351, 330, 244, 227, 171, 160, 52 (Found: [M+NH₄]⁺, 386.1788. C_{22}H_{24}O_{3}S requires [M+NH₄]⁺, 386.1782).

(E)-5-(Phenylsulfonyl)-5-styrylcyclohex-2-enol 242

![Chemical structure](image)

To a solution triene 241 (100 mg) in CH₂Cl₂ (12.6 mL) at rt was added a solution of catalyst 50 (6.90 mg) in CH₂Cl₂. After 24 h, concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave a 2:1 diastereomixture (E)-5-(phenylsulfonyl)-5-styrylcyclohex-2-enol 242 (54.0 mg, 59%) as a gum; Rₚ 0.17 (30% EtOAc–petrol); δH (400 MHz) 7.87 (2H, d, J 7.5 Hz, ortho PhSO₂, minor diast.), 7.81 (2H, d, J 7.5 Hz, ortho PhSO₂, major diast.), 7.67-7.20 (2 × 8H, m, para & meta PhSO₂ and PhCH, 2 × diast.), 6.31 (1H, d, J 16.5 Hz, PhCH=CH, major diast.), 6.05 (1H, d, J 16.5 Hz, PhCH=CH, major diast.), [5.81-5.65 (2 × 2H, m, CH=CHCHOH, 2 × diast.) & (2H, m, PhCH=CH, minor diast.)], 5.60-5.54 (1H, m, CHOH, minor diast.), 4.78-4.74 (1H, m, OH, minor diast.), 4.22-4.19 (1H, m, OH, major diast.), 3.99-3.94 (1H, m, CHOH, major diast.), 2.99-2.61 (2 × 2H, m, CH₂CH=CH₂, 2 × diast.), 2.35-2.11 (2H, 2 × 2H, , CH₂CHOH, 2 × diast.).
To a solution of cinnamylsulfone 227 (45.0 g, 174.2 mmol, 1.0 equiv) in THF (360 ml) at −78 °C was added nBuLi (60.0 mL of a 2.45 M solution in hexanes, 149 mmol, 0.86 equiv) dropwise. It was warmed to −30 °C for 15 min then re-cooled to −78 °C. Another amount of nBuLi (10.5 mL of a 2.45 M solution in hexanes, 26.0 mmol, 0.14 equiv) was added dropwise. After 15 min the solution was warmed to −20 °C for 30 min then re-cooled to −78 °C and butadiene monoxide (14.7 mL, 182.9 mmol, 1.05 equiv) added. The reaction was warmed to rt over a period of 2 h. After 3 h the reaction was quenched with sat. NH₄Cl (aq.) (200 mL) then diluted with water (300 mL) and extracted with Et₂O (3 × 150 mL). The combined organic layers were washed with brine (3 × 100 mL) and dried (MgSO₄). Concentration under reduced pressure and drying under high vacuum for 16 h gave 55g of a crude mixture of 228 and its regioisomer 229 as a gum. This crude mixture was then dissolved in CH₂Cl₂ (1.5 L). To the resulting solution was added catalyst 50 (750 mg). The solution was then heated under reflux. After 30 min, the reaction was cooled to rt. Concentration under reduced pressure and column chromatography (35→45% EtOAc–petrol) gave a 2:1 diastereomixture of 45 (21.0 g, 93.6 mmol, 54%); δH (400 MHz) 7.95-7.88 (2 × 2H, m, ortho PhSO₂, 2 × diast.), 7.67 (2 × 3H, m, para & meta PhSO₂, 2 × diast.), 6.36-6.35 (1H, m, CH=CHOH, major diast.), 6.20-6.18 (1H, app. dt, J 5.5, 2.0 Hz, CH=CHOH, minor diast.), 5.85-5.87 (1H, m, CH=CHOH, minor diast.), 5.74-5.73 (1H, m, CH=CHOH, major diast.), 4.83-4.87 (1H, m, CHSO₂Ph, minor diast.), 4.72-4.70 (1H, m, CHSO₂Ph, major diast.), 4.41-4.44 (1H, m, CHOH, minor diast.), 4.16-4.01 (1H, m, CHOH, major diast.), 2.79-2.72 (2H, m, CH₂, minor diast.), 2.26-2.21 (2H, m, CH₂, major diast.).
(1R*,4S*)-4-Allyl-4-(phenylsulfonyl)cyclopent-2-enol 234a

![Chemical structure](image)

To a solution of cyclopentenol 45 (837 mg, 3.74 mmol, 1.0 equiv) in THF (15 mL) at –78 °C was added nBuLi (3.31 mL of a 2.45 M solution in hexanes, 7.85 mmol, 2.1 equiv). After 15 min the reaction was warmed to –20 °C for 15 min then to 0 °C. After 15 min it was re-cooled to –78 °C and allyl bromide (326 µL, 3.74 mmol, 1.0 equiv) added. After 15 min the reaction was warmed to 0 °C for 0.5 h then to rt. After 2 h the reaction was quenched with sat. NH₄Cl(aq.) (3.5 mL), diluted with H₂O (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 15 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave (1R*,4S*)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enol 234a (603 mg, 61%) as a white crystalline solid; mp 56-58 °C; Rf 0.19 (30% EtOAc–petrol); v_max (film) 3490, 3416, 3209, 3069, 2978, 1445, 1299, 1142, 1082, 1052, 1019, 732, 691 cm⁻¹; δ_H (400 MHz) 7.91 (2H, d, J 8.0 Hz, ortho PhSO₂), 7.74 (1H, t, J 7.0 Hz, para PhSO₂), 7.63 (2H, dd, J 8.0, 7.0 Hz, meta PhSO₂), 6.34 (1H, dd, J 5.5, 2.5 Hz, CH=CHCH), 5.58 (1H, d, J 5.5 Hz, CH=CHCH), 5.49–5.39 (1H, m, CH=CH₂), 5.14–5.06 (2H, m, CH=CH₂), 4.75 (1H, ddd, J 12.0, 7.0, 2.5 Hz, CHO), 3.17 (1H, d, J 12.0 Hz, CHO), [2.67–2.62, 2.52–2.47 (2H, m, CH₂CHOH)], 2.42–2.26 (2H, m, CH₂CHOH); δ_C (125 MHz) 142.2 (ipso PhSO₂), 135.6 (para PhSO₂), [130.9, 130.7 (CH=CH)], [130.4, 129.2 (ortho & meta PhSO₂), [128.0, 120.5 (CH=CH₂)], 79.0 (CSO₂Ph), 75.7 (CHOH), [37.3, 37.0 (2 × CH₂)]; m/z (CI) 282 [M+NH₄]⁺, 265 [M+H]⁺, 264, 247, 105 (Found: [M+NH₄]⁺, 282.1154. C₁₄H₁₆O₃S requires [M+NH₄]⁺, 282.1164) (Found: C, 63.69; H, 6.10. C₁₄H₁₆O₃S requires C, 63.61; H, 6.10%).
(1R*,4S*)-4-[\(\textit{E}\)-But-2-enyl]-4-(phenylsulfonyl)cyclopent-2-enol 234b

\[
\begin{align*}
\text{PhO}_2\text{S} & \quad \text{OH} \\
45 & \quad + \\
\text{Br} & \quad \rightarrow \\
\text{PhO}_2\text{S} & \quad \text{OH}
\end{align*}
\]

To a solution of cyclopentenol 45 (300 mg, 1.34 mmol, 1.0 equiv) in THF (2.7 mL) at rt was added \(n\)BuLi (1.15 mL of 2.45 M solution in hexanes, 2.82 mmol, 1.01 equiv). After 20 min to the dark red solution was added 4-bromo-2-butene (136 µL, 1.35 mmol, 1.01 equiv). After 1.5 h the reaction was quenched with sat. NH\(\text{4Cl(aq.)}\) (1.2 mL), diluted with H\(\text{2O}\) (5 mL) and extracted with EtOAc (3 \(\times\) 10 mL). The combined organic layers were washed with brine (2 \(\times\) 5 mL) and dried (MgSO\(\text{4}\)). Concentration under reduced pressure and column chromatography (30% EtOAc–petrol) gave (1R*,4S*)-4-[\(\textit{E}\)-but-2-enyl]-4-(phenylsulfonyl)cyclopent-2-enol 234b (250 mg, 67%) as a white solid; mp 64–66 °C; \(R_f\) 0.22 (30% EtOAc–petrol); \(\nu_{\text{max}}\) (film) 3493, 3063, 3026, 2942, 2922, 2884, 2855, 1445, 1299, 1287, 1140, 1083, 1071, 1050, 969, 793, 756, 691 cm\(^{-1}\); \(\delta_H\) (400 MHz) 7.90 (2H, d, \(J\ 8.0\ Hz\), ortho PhSO\(\text{2}\)), 7.73 (1H, t, \(J\ 7.0\ Hz\), para PhSO\(\text{2}\)), 7.63 (2H, dd, \(J\ 8.0,\ 7.0\ Hz\), meta PhSO\(\text{2}\)), 6.33 (1H, dd, \(J\ 5.5,\ 3.0\ Hz\), CH=CHCHOH), 5.57 (1H, d, \(J\ 5.5\ Hz\), CH=CHCHOH), 5.55–5.45 (1H, m, CH\(\text{2}\)CH=CH), 5.08–5.00 (1H, m, CH\(\text{2}\)CH=CH), 4.78–4.73 (1H, m, CHOH), 3.23 (1H, d, \(J\ 12.0\ Hz\), OH), 2.71–2.20 (4H, m, 2 \(\times\) CH\(\text{2}\)), 1.63 (3H, d, \(J\ 6.5\ Hz\), Me); \(\delta_C\) (125 MHz) 142.0 (ipso PhSO\(\text{2}\)), 135.8 (para PhSO\(\text{2}\)), 134.1, 131.3, 130.9, 123.1 (2 \(\times\) CH=CH)), [130.4, 129.1 (ortho & meta PhSO\(\text{2}\)]), 79.0 (CO\(\text{2}\)Ph), 75.6 (CHOH), [37.3, 35.8 (CH\(\text{2}\)CH=CHCH\(\text{2}\)), 18.0 (CH\(\text{2}\)CHOH); \(m/z\) (CI) 296 [M+NH\(\text{4}\)]\(^{+}\), 278 M\(^{+}\), 261, 119 (Found: [M+NH\(\text{4}\)]\(^{+}\), 296.1314. C\(\text{15}\)H\(\text{18}\)O\(\text{3}\)S requires [M+NH\(\text{4}\)]\(^{+}\), 296.1320) (Found: C, 64.79; H, 6.60. C\(\text{15}\)H\(\text{18}\)O\(\text{3}\)S requires C, 64.72; H, 6.52%).
(1R*,4S*)-4-Cinnamyl-4-(phenylsulfonyl)cyclopent-2-enol 234c

To a solution of cyclopentenol 45 (110 mg, 0.49 mmol, 1.0 equiv) in THF (3.4 mL) at –78 °C was added nBuLi (0.4 mL of a 2.45 M solution in hexanes, 0.98 mmol, 2.1 equiv). After 15 min the reaction was warmed to –20 °C for 15 min then to 0 °C. After 15 min the solution was re-cooled to –78 °C and cinnamyl bromide (96 mg, 0.49 mmol, 1.0 equiv) added. After 15 min the reaction was warmed to 0 °C for 0.5 h then to rt. After 2 h the reaction was quenched with sat. NH₄Cl(aq.) (1 mL), diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (20% Et₂O–petrol) gave (1R*,4S*)-4-cinnamyl-4-(phenylsulfonyl)cyclopent-2-enol 234c (80 mg, 49%) as a colourless gum; Rf 0.57 (40% EtOAc–petrol); νmax (film) 3488, 3428, 3060, 3027, 2924, 2852, 2359, 1737, 1498, 1445, 1299, 1288, 1192, 1135, 1082, 1052, 998, 969, 733, 679 cm⁻¹; δH (400 MHz) 7.92 (2H, d, J 7.0 Hz, ortho PhSO₂), 7.71 (1H, t, J 7.0 Hz, para PhSO₂), 7.63 (2H, t, J 7.0 Hz, meta PhSO₂), 7.29-7.17 (5H, m, PhCH=CH), 6.39 (1H, d, J 15.5 Hz, PhCH=CH), 6.34 (1H, dd, J 5.5, 2.5 Hz, CH=CHCH), 5.78 (1H, ddd, J 15.5, 9.0, 6.0 Hz, CH=CHCH₂), 5.64 (1H, d, J 5.5 Hz, CH=CHCH), 4.75-4.70 (1H, m, CHOH), 3.19 (1H d, J 12.0 Hz, OH), 2.79 (1H, dd, J 14.0, 6.0 Hz, CHHCH=CH), 2.64 (1H, dd, J 14.0, 9.0 Hz, CHHCH=CH), 2.44-2.29 (2H, m, CHzCHOH); δC (125 MHz) 142.4 (ipso PhSO₂), 136.4 (para PhSO₂), [135.3, 134.2, 130.6 (ipso, para PhCH & CH=CHCHOH)], [130.4, 129.2, 128.6 (ortho, meta PhSO₂ & ortho PhCH)], 127.8 (PhCH=CH), 126.2 (meta PhCH), 122.1 (PhCH=CH), 78.9 (CSO₂Ph), 75.7 (CHOH), [37.5, 36.3 (2 × CH₂)]; m/z (CI) 358 [M+NH₄]⁺, 340, 323, 198, 181, 160 (Found: [M+NH₄]⁺ 358.1469. C₂₀H₂₀O₃S requires [M+NH₄]⁺, 358.1477) (Found: C, 70.47; H, 5.98. C₂₀H₂₀O₃S requires C, 70.58; H, 5.92%).
(1R*,4S*)-4-(3-Methylbut-2-enyl)-4-(phenylsulfonfonyl)cyclopent-2-enol 234d

To a solution of cyclopentenol 45 (837 mg, 3.74 mmol, 1.0 equiv) in THF (15 mL) at –78 °C was added nBuLi (3.31 mL of a 2.45 M solution in hexanes, 7.85 mmol, 2.1 equiv). After 15 min the reaction was warmed to –20 °C for 15 min then to 0 °C. After 15 min it was re-cooled to –78 °C and prenyl bromide (411 µL, 3.74 mmol, 1.0 equiv) added. After 15 min the reaction was warmed to 0 °C for 0.5 h then to rt. After 2 h the reaction was quenched with sat. NH₄Cl (aq.) (3.5 mL), diluted with H₂O (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 15 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (25% EtOAc-petrol) followed by recrystallisation (EtOAc-petrol) gave (1R*,4S*)-4-(3-methylbut-2-enyl)-4-(phenylsulfonfonyl)cyclopent-2-enol 234d (440 mg, 40%) as a colourless crystalline solid; mp 70-72 °C (EtOAc-petrol); Rf 0.16 (25% EtOAc-petrol); vₘₐₓ (film) 3507, 2966, 2934, 1445, 1405, 1298, 1285, 1267, 1138, 1054, 1025, 690 cm⁻¹; δₗₜ (400 MHz) 7.91 (2H, d, J 7.5 Hz, ortho PhSO₂), 7.72 (1H, t, J 7.0 Hz, para PhSO₂), 7.61 (2H, dd, J 7.5, 7.0 Hz, meta PhSO₂), 6.32 (1H, dd, J 5.5, 2.5 Hz, CH=CHCH), 5.54 (1H, d, J 5.5 Hz, CH=CHCH), 4.77-4.72 (2H, m, C=CHCH₂ & CHOH), 3.22 (1H, d, J 12.0 Hz, OH), 2.58 (1H, dd, J 14.0, 8.5 Hz, C=CHCHH), 2.46 (1H, dd, J 14.0, 6.0 Hz, C=CHCHH), 2.41 (1H, dd, J 15.5, 6.0 Hz, CHHCHOH), 2.21 (1H, dd, J 15.5, 7.0 Hz, CHHCHOH), 1.66 (3H, s, Me), 1.54 (3H, s, Me); δₗ ≤ (125 MHz) 141.9 (ipso PhSO₂), 136.8 (para PhSO₂), [135.5, 134.1 (CH=CH)], 131.0 (C=CH), [130.4, 129.0 (ortho & meta PhSO₂)], 111.3 (C=CH), 79.4 (CSO₂Ph), 75.8 (CHOH), [37.4, 30.9 (CH₃CH₃)], 25.9 (C=CHCH₂), 18.0 (CH₂CHOH); m/z (CI) 310 [M+NH₄]+, 293 [M+H]+, 292 M+, 133, 52 (Found: [M+NH₄]+, 310.1479. C₁₆H₂₀O₃S requires [M+NH₄]+, 310.1477) (Found: C, 65.71; H, 6.90. C₁₆H₂₀O₃S requires C, 65.72; H, 6.89%).
(E)-(1-Phenylhepta-1,6-dien-3-ylsulfonyl)benzene 381

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\begin{align*}
\text{Ph} & \quad \text{SO}_2\text{Ph} \\
\text{227} & \quad \text{+} \\
\text{PhO}_2\text{S} & \quad \text{381}
\end{align*}
\]

To a solution of cinnamylsulfone 227 (657 mg, 2.54 mmol, 1.0 equiv) in THF (12 mL) at −78 °C was added nBuLi (1.14 mL of a 2.45 M solution in hexanes, 2.80 mmol, 1.0 equiv). After 15 min the solution was warmed to −20 °C for 15 min then to 0 °C. After 15 min it was re-cooled to −78 °C and butenyl bromide (310 µL, 3.05 mmol, 1.2 equiv) added. After 15 min it was gradually warmed to rt over 1 h. After 1 h the reaction was quenched with sat. NH₄Cl (aq.) (2.2 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (8% EtOAc–petrol) gave (E)-(1-phenylhepta-1,6-dien-3-ylsulfonyl)benzene 381 (660 mg, 83%) as a colourless gum; Rₐ 0.28 (15% EtOAc–petrol); νₘₐₓ (film) 3062, 3027, 2932, 1640, 1494, 1446, 1304, 1145, 1084, 996, 969, 734, 689 cm⁻¹; δ_H (400 MHz) 7.86 (2H, d, J 7.5 Hz, ortho PhSO₂), 7.64 (1H, t, J 7.5 Hz, para PhSO₂), 7.53 (2H, t, J 7.5 Hz, meta PhSO₂), 7.34-7.27 (5H, m, PhCH=CH), 6.27 (1H, d, J 16.0 Hz, PhCH=CH), 5.92 (1H, dd, J 16.0, 9.0 Hz, PhCH=CH), 5.82-5.72 (1H, m, CH₂=CH), 5.06-5.02 (2H, m, CH₂=CH), 3.71 (1H, ddd, J 11.0, 9.0, 3.0 Hz, CHSO₂Ph), 2.39-2.37 (2H, m, CH₂CH=CH₂), 2.08 (1H, dt, J 15.0, 9.0 Hz, CH/HCHSO₂Ph), 1.95-1.85 (1H, m, CH/HCHSO₂Ph); δ_C (125 MHz) 138.2 (ipso PhSO₂), 137.3 (ipso PhCH=CH), 136.3 (para PhSO₂), 135.6 (para PhCH=CH), 133.5 (PhCH=CH), [129.0, 128.7, 128.5, 128.3 (ortho & meta PhSO₂ & PhCH=CH)], 126.4 (PhCH=CH), [120.8, 116.1 (CH₂=CH)], 68.6 (PhSO₂CH₂), 30.2 (CH₂=CHCH₂), 26.1 (CHCH₂); m/z (CI) 330 [M+NH₄]⁺, 188, 171, 160 (Found: [M+NH₄]⁺, 330.1523. C₁₉H₂₀O₂S requires [M+NH₄]⁺, 330.1528) (Found: C, 73.11; H, 6.41. C₁₉H₂₀O₂S requires C, 73.04; H, 6.45%).
[(1R*,4S*)-4- Allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy][(tert-butyl)
dimethylsilane 244

To a solution of cyclopentenol 234a (137 mg, 0.52 mmol, 1.0 equiv), TBDMSCl (141
mg, 0.94 mmol, 1.8 equiv) and DMAP (9.5 mg, 0.08 mmol, 0.15 equiv) in CH₂Cl₂ (1.0
mL) at rt was added Et₃N (181 µL, 1.3 mmol, 2.5 equiv) dropwise. The solution was
heated under reflux for 24 h then quenched with sat. NH₄Cl (aq.) (0.8 mL), diluted with
H₂O (5 mL) and extracted with CH₂Cl₂ (3 × 7 mL). The combined organic layers were
washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced
pressure and column chromatography (10% EtOAc–petrol) gave [(1R*,4S*)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy][(tert-butyl)dimethylsilane 244 (170 mg, 87%) as a
colourless oil; Rf 0.57 (10% EtOAc–petrol); νmax (film) 2953, 2929, 2855, 1446, 1303,
1146, 1088, 716 cm⁻¹; δ₁H (400 MHz) 7.87 (2H, d, J 8.0 Hz, ortho PhSO₂), 7.63 (1H, t, J
7.5 Hz, para PhSO₂), 7.53 (2H, dd, J 8.0, 7.5 Hz, meta PhSO₂), 5.83 (1H, dd, J 5.5, 2.0
Hz, CH=CHCH), 5.78 (1H, d, J 5.5 Hz, CH=CHCH), 5.61–5.51 (1H, m, CH₂CH=CH₂),
5.19–5.14 (2H, m, CH=CH₂), 4.68–4.65 (1H, m, CHOTBDMS), 2.81 (1H, dd, J 14.0,
5.5 Hz, CHHCH=CH₂), 2.70 (1H, dd, J 14.0, 7.0 Hz, CHHCH=CH₂), 2.33 (1H, dd, J
14.5, 7.5 Hz, CH/CHOTBDMS), 2.12 (1H, dd, J 14.5, 4.5 Hz, CHHCHOTBDMS),
0.77 (9H, s, ³Bu of TBDMS), -0.04 (3H, s, CCH₃CH₃Si), -0.07 (3H, s, CCH₃CH₃Si); δ₁C
(125 MHz) 140.7, 133.6, 131.4, 130.5, 130.0, 128.8, 128.5, 120.1, 77.9, 76.3, 39.8, 36.4,
25.7, 17.9, -4.8; m/z (Cl) 396 [M+NH₄]⁺, 379 [M+H]⁺, 264, 105 (Found: [M+H]⁺,
To a solution of cyclopentenol 234a (137 mg, 0.52 mmol, 1.0 equiv), TESCl (141 mg, 0.94 mmol, 1.8 equiv) and DMAP (9.5 mg, 0.08 mmol, 0.15 equiv) in CH$_2$Cl$_2$ (1.0 mL) at rt was added Et$_3$N (181 µL, 1.3 mmol, 2.5 equiv) dropwise. After 16 h the reaction was quenched with sat. NH$_4$Cl (aq.) (0.7 mL), then diluted with H$_2$O (5 mL) and extracted with CH$_2$Cl$_2$ (3 × 7 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na$_2$SO$_4$). Concentration under reduced pressure and column chromatography (5% EtOAc-petrol) gave [(1R*,4S*)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy]triethylsilane 382 (185 mg, 92%) as a colourless oil; R$_f$ 0.17 (5% EtOAc–petrol); $v$$_{max}$ (film) 2954, 2911, 2866, 1367, 1303, 1147, 1090, 1033, 749, 714, 689 cm$^{-1}$; $\delta$$_H$ (400 MHz) 7.88 (2H, d, J 8.0 Hz, ortho PhSO$_2$), 7.65 (1H, t, J 7.5 Hz, para PhSO$_2$), 7.54 (2H, dd, J 8.0, 7.5 Hz, meta PhSO$_2$), 5.86 (1H, dd, J 5.5, 2.0 Hz, CH=CH), 5.78 (1H, d, J 5.5 Hz, CH=CH), 5.61–5.51 (1H, m, CH=CH$_2$), 5.20–5.15 (2H, m, CH=CH$_2$), 4.69–4.65 (1H, m, CHOTES), 2.81 (1H, dd, J 13.5, 6.0 Hz, CHHCH=CH$_2$), 2.70 (1H, dd, J 13.5, 9.0 Hz, CHHCH=CH$_2$), 2.32 (1H, dd, J 14.5, 7.5 Hz, CHHCHOTES), 2.15 (1H, dd, J 14.5, 4.5 Hz, CHHCHOTES), 0.86 [9H, t, J 8.0 Hz, (CH$_3$CH$_2$)$_3$Si], 0.48 [6H, q, J 8.0 Hz, (CH$_3$CH$_2$)$_3$Si]; $\delta$$_C$ (125 MHz) 140.8 (ipso PhSO$_2$), 135.4 (para PhSO$_2$), [133.7, 131.5 (CH=CH)], [130.5, 130.1, 128.6, 120.2 (ortho & meta PhSO$_2$, C=CH$_2$)], 77.9 (CSO$_2$Ph), 76.0 (CHOH), 39.1 (CH$_2$CH=CH$_2$), 36.5 (CH$_2$CHOTES), 36.4, 6.7 [Si(CH$_2$CH$_3$)$_3$]; m/z (CI) 396 [M+NH$_4$]$^+$, 379 [M+H]$^+$, 282, 264, 247 [M-OTES]$^+$, 105 (Found: [M+H]$^+$, 3791754. C$_{20}$H$_{30}$O$_3$SSi requires [M+H]$^+$, 379.1763) (Found: C, 63.40; H, 7.92. C$_{20}$H$_{30}$O$_3$SSi requires C, 63.45; H, 7.99%).
To a flask containing NaH (25.0 mg of a 60% in mineral oil, 0.64 mmol, 1.2 equiv) under N₂ was added petrol (1 mL). The suspension was stirred vigorously then allowed to settle. The petrol was removed by syringe. This process was repeated twice. The remaining petrol was dried by flushing N₂. To this flask at 0 °C was slowly added a solution of cyclopentenol 234a (137 mg, 0.5 mmol, 1.0 equiv) and allyl bromide (86 µL, 0.9 mmol, 1.8 equiv) in DMF (2 mL). Upon addition the yellow solution was warmed to rt. After 16 h the reaction was quenched with sat. NaHCO₃(aq.) (0.5 mL) then diluted with H₂O (10 mL) and extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave [(1S*,4R*)-1-allyl-4-(allyloxy)cyclopent-2-enylsulfonyl]benzene 383 (110 mg, 70%) as a colourless oil; Rf 0.50 (25% EtOAc–petrol); ν_max (film) 3071, 2980, 2920, 2850, 1445, 1360, 1301, 1086, 1038, 997, 923, 756, 716, 690 cm⁻¹; δ_H (400 MHz) 7.88 (2H, d, J 7.0 Hz, ortho PhSO₂), 7.66 (1H, t, J 7.0 Hz, para PhSO₂), 6.04 (1H, dd, J 5.5, 2.0 Hz, CH=CHCH), 5.87 (1H, d, J 5.5 Hz, CH=CHCH), 5.75 (1H, ddt, J 22.5, 10.5, 5.5 Hz, CH₂=CHCH₂OCH), 5.59-5.49 (1H, m, CH₂=CHCH₂C), 5.19-5.11 (4H, m, 2 × CH₂=CHCH₂), 4.46-4.44 (1H, m, CHOCH₂), 3.79 (1H, dd, J 7.0, 5.5 Hz, OCHH), 3.75 (1H, dd, J 7.0, 6.0 Hz, OCHH), 2.81 (1H, dd, J 13.5, 6.0 Hz, CHCH), 2.70 (1H, dd, J 13.5, 9.0 Hz, CHHC), 2.28 (2H, d, J 5.5 Hz, CH₂CHO); δ_C (125 MHz) 138.2 (ipsos PhSO₂), 135.4 (paras PhSO₂), [134.7, 133.8 (CH=CH)], [131.9, 131.3 (CH₂=CHCH₂OCH)], [130.5, 128.7 ( orthos & metas PhSO₂)], [120.3, 116.9 (CH₂=CH)], 82.6 (CPhSO₂), 77.9 (CHOCH₂), 69.6 (OCH₂CH=CH₂), 36.7 (CH₂CH=CH₂), 35.4 (CH₂CHOCH₂); m/z (CI) 322 [M+NH₄]⁺, 305 [M+H]⁺, 282, 264, 163, 105 (Found: [M+H]⁺, 305.1219. C₁₇H₂₀O₃S requires [M+H]⁺, 305.1211) (Found: C, 67.14; H, 6.69. C₁₇H₂₀O₃S requires C, 67.08; H, 6.62%).
[(1S*,4R*)-4-(Allyloxy)-1-(3-methylbut-2-enyl)cyclopent-2-enyisulfonyl]benzene

\[ 246 \]

To a flask containing NaH (54.0 mg of a 60% in mineral oil, 1.25 mmol, 1.1 equiv, washed by petrol as described above) at 0 °C was slowly added a solution of cyclopentenol \[ 234d \] (365 mg, 1.25 mmol, 1.0 equiv) and allyl bromide (179 µL, 2.06 mmol, 1.7 equiv) in DMF (3 mL). Upon addition the yellow solution was warmed to rt. After 16 h the reaction was quenched with sat. NaHCO\(_3\) (aq.) (1 mL) then diluted with H\(_2\)O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (MgSO\(_4\)). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave \([(1S*,4R*)-4-(allyloxy)-1-(3-methylbut-2-enyl)cyclopent-2-enylsulfonyl]benzene \[ 246 \] (395 mg, 95%) as a colourless gum; \( R_f \) 0.55 (25% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3065, 2978, 2915, 2857, 1446, 1361, 1301, 1146, 1086, 1046, 924, 756, 690, 606 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.89 (2H, d, \( J 7.5 \) Hz, \textit{ortho} PhSO\(_2\)), 7.65 (1H, t, \( J 7.5 \) Hz, \textit{para} PhSO\(_2\)), 7.55 (2H, dd, \( J 7.5, 7.5 \) Hz, \textit{meta} PhSO\(_2\)), 6.03 (1H, dd, \( J 5.5, 2.0 \) Hz, CH=CHCH), 5.84 (1H, d, \( J 5.5 \) Hz, CH=CHCH), 5.75 (1H, ddt, \( J 22.5, 10.5, 5.5 \) Hz, CH\(_2\)=CHCH\(_2\)OCH), 5.16-5.11 (1H, m, CH\(_2\)=CHCH\(_2\)OCH), 4.86 (1H, app t, \( J 7.5 \) Hz, CH=C(CH\(_3\))\(_2\)), 4.45-4.42 (1H, m, CHOCH\(_2\)), 3.80-3.71 (2H, m, OCH\(_2\)), 2.79 (1H, dd, \( J 14.0, 8.5 \) Hz, CHHC), 2.64 (1H, dd, \( J 14.0, 6.0 \) Hz, CHHC), 2.26-2.16 (2H, m, CH\(_2\)CHO), 1.70 (3H, s, CH\(_3\)), 1.63 (3H, s, CH\(_3\)); \( \delta_C \) (100 MHz) 137.8 (ipso PhSO\(_2\)), 136.6 [CH=C(CH\(_3\))\(_2\)], 135.5 (para PhSO\(_2\)), [134.7, 133.7 (CH=CH)], [132.2 (CH=CHCH\(_2\)OCH)], [130.5, 128.6 (ortho & meta PhSO\(_2\))], 116.8 [CH=C(CH\(_3\))\(_2\)], 116.6 (CH\(_2\)=CH), 78.6 (CHOCH\(_2\)), 69.4 (OCH\(_2\)CH=CH\(_2\)), 35.4 [CH\(_2\)CH=C(CH\(_3\))\(_2\)], 30.4 (CH\(_2\)CHOCH\(_2\)), [26.0, 18.1 (2 × CH\(_3\))].
To a solution of allyl ether 246 (80.0 mg, 0.241 mmol, 1.0 equiv) in toluene (5 mL) at rt in an environment of ethylene was added a solution of catalyst 50 (14.3 mg, 0.0168 mmol, 0.07 equiv) in toluene (1 mL). After 16 h, concentration under reduced pressure and column chromatography (15% EtOAc–petrol) gave a 2:1 mixture of E/Z isomers of [(1S*,4R*)-1-(3-methylbut-2-enyl)-4-(prop-1-enyloxy)cyclopent-2-enylsulfonyl]benzene 258 (8 mg, 10%) as a gum; Rf 0.35 (20% EtOAc–petrol); v_max (film) 3061, 2968, 2919, 1668, 1445, 1368, 1301, 1147, 1122, 768, 753 690, 606 cm⁻¹; δ_H (400 MHz) 7.90-7.86 (2 × 2H, m, ortho PhSO₂), 7.67-7.64 (2 × 1H, m, para PhSO₂, 2 × isomers), 7.58-7.54 (2 × 2H, m, meta PhSO₂, 2 × isomers), 5.99-5.97 (2 × 1H, m, CH=CHCH, both isomers), 5.92-5.8 (2 × 1H, m, CH=CHCH, 2 × isomers), 5.83 (1H, dd, J 12.5, 1.5 Hz, CH=CHOCH, _E_ isomer), 5.69 (1H, dd, J 6.5, 1.5 Hz, CH=CHOCH, _Z_ isomer), 4.87-4.84 [2 × 1H, m, CH=CHOCH, 2 × isomers], 4.70-4.62 (2 × 1H, m, CHOCH₂, 2 × isomers), 4.61-4.57 (1H, m, CH=CHOCH, _E_ isomer), 4.35-4.27 (1H, m, CH=CHOCH, _Z_ isomer), 2.84-2.76 (2 × 1H, dd, J 14.0, 8.5 Hz, CH/H/CH=C, 2 × isomers), 2.71-2.64 (2 × 1H, m, CH/H/CH=C, 2 × isomers), 2.30-2.19 (2 × 2H, m, CH₂CHO, 2 × isomers), 1.70 (2 × 3H, s, CH₃, 2 × isomers), 1.64 (2 × 3H, s, CH₃, 2 × isomers), 1.49 (3H, dd, J 7.0, 1.5 Hz, CH₃CH=CH, _E_ isomer), 1.37 (3H, dd, J 7.0, 1.5 Hz, CH₃CH=CH, _Z_ isomer); δ_C (100 MHz) 203.1, 141.9, 138.7, 138.2, 136.8, 135.9, 134.1, 133.6, 131.6, 131.4, 131.0, 130.4, 130.4, 129.0, 126.7, 126.7, 116.6, 116.3, 102.7, 102.6, 75.7, 37.4, 36.7, 30.9, 27.0, 26.1, 25.9, 18.1, 18.0, 9.1, 6.0.
**N-[(R*)-2-(4-Methoxyphenyl)-1-[(R*)-oxiran-2-yl]ethyl]-4-methylbenzene Sulfonamide 261**

To a solution of hydroxyaziridine 198 (110 mg, 0.32 mmol, 1.0 equiv) in THF (1.0 mL) at −78 °C was added nBuLi (182 µL of a 2.28 M solution in hexanes, 0.42 mmol, 1.3 equiv). The resulting solution was warmed to rt over a period of 1.5 h then heated to 40 °C. After 1 h the reaction was quenched sat. NH₄Cl (aq.) (0.6 mL) then diluted with H₂O (6 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography gave N-[(R*)-2-(4-methoxyphenyl)-1-[(R*)-oxiran-2-yl]ethyl]-4-methylbenzenesulfonamide 261 (36 mg, 33%) as a brown gum; Rₕ 0.43 (40% EtOAc–petrol); ν max (film) 3271, 2954, 2922, 2858, 1611, 1513, 1453, 1329, 1304, 1247, 1160, 1117, 1092, 1058, 1050, 840, 813, 665 cm⁻¹; δ_H (400 MHz) 7.51 (2H, d, J 8.5 Hz, ortho Ts), 7.19 (2H, d, J 8.0 Hz, meta Ts), 6.93 (2H, d, J 8.0 Hz, meta PhOMe), 6.73 (2H, d, J 8.5 Hz, ortho PhOMe), 4.64 (1H, d, J 6.5 Hz, NH), 3.80 (3H, s, OMe), 3.06 (1H, ddd, 12.0, 7.5, 4.8 Hz, CHOCH₂), 2.93-2.88 (2H, m, CH/NHTs & CHHOCH), 2.78-2.67 (3H, m, CHHOCH & CH₂Ar), 2.43 (3H, s, Me of Ts); δ_C (125 MHz) [158.7, 143.4, 136.9 (q Ar)], 130.3 (ortho Ts), 129.6 (meta Ts), 127.3 (q ArOMe), 126.9 (meta ArOMe), 114.2 (ortho ArOMe), 66.3 (OMe), [55.2, 53.5 (CHCH₂O)], 47.7 (CHNHTs), 37.3 (CH₂ of Ts), 21.5 (CH₂ArOMe); m/z (CI) 365 [M+NH₄]⁺, 348 [M+H]⁺, 246, 189 [TsNH+H+NH₄]⁺ (Found: [M+NH₄]⁺, 365.1539. C₁₈H₂₁NO₄S requires [M+NH₄]⁺, 365.1535) (Found: C, 62.38; H, 6.16; N, 4.06. C₁₈H₂₁NO₄S requires C, 62.23; H, 6.09; N, 4.03%).
(E)-(2-Methylnpent-3-ene-1,3-diy)bis(phenylsulfone) 271

Preparation of solution 1: To a solution of allyl sulfone 212 (68.3 mg, 0.375 mmol, 1.3 equiv) in THF (1.0 mL) at −78 °C was added nBuLi (171 µL of a 2.19 M solution in hexanes, 1.87 mmol, 1.3 equiv). After 15 min it was warmed to −20 °C for 15 min then re-cooled to −78 °C.

Preparation of solution 2: To a solution of hydroxyaziridine 198 (100 mg, 0.288 mmol, 1.0 equiv) in THF (1 mL) at −78 °C was added nBuLi (132 µL of a 2.19 M solution in hexanes, 0.288 mmol, 1.0 equiv). After 5 min solution 1 was added via cannula. The resulting solution was warmed to 10 °C over a period of 3 h then to rt. After 1 h 40 min, the reaction was quenched with sat. NH₄Cl(aq.) (3 mL), then diluted with H₂O (10 mL) and EtOAc (8 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave disulfone 271 (34.0 mg, 50% as to the input of allyl sulfone) as a colourless gum; Rf 0.31 (40% EtOAc–petrol); νmax (film) 3062, 2981, 2923, 1612, 1512, 1446, 1301, 1149, 1086, 841, 707, 689 cm⁻¹; δH (400 MHz) [7.86 (2H, d, J 7.5 Hz), 7.76 (2H, d, J 7.5 Hz), 2 × ortho PhSO₂], 7.70 (1H, t, J 7.5 Hz, 1 × para PhSO₂), 7.63-7.49 (5H, m, 2 × meta PhSO₂ & 1 × para PhSO₂), 6.96 (1H, q, J 7.5 Hz, CH₃CH=C), 3.48-3.42 (1H, m, CH₂CH₂CH₃), 3.39-3.37 (2H, m, CH₂SO₂Ph), 1.94 (3H, d, J 7.5 Hz, CH₃CH=C), 1.24 (3H, d, J 7.0 Hz, CH₃CHCH₂); δC (100 MHz) [144.1, 140.3 (2 × ipso Ph)], 139.6 (CH=C), 139.4 (CH=C), [133.9, 133.3 (2 × para Ph)], [129.7, 129.6, 127.9, 127.8 (2 × ortho Ph & 2 × meta Ph)], 60.3 (CH₂SO₂Ph), 27.8 (CH), 18.7 (CH₃CH=C), 14.6 (CH₃CHCH₂); m/z (CI) 382 [M+NH₄]⁺, 365 [M+H]⁺, 348, 223 (Found (ESI): [M+Na]⁺, 387.0710. C₁₈H₂₀O₄S₂ requires [M+Na]⁺, 387.0701).
Preparation of solution 1: To a solution of cinnamyl sulfone 227 (484 mg, 1.87 mmol, 1.3 equiv) in THF (3.5 mL) at −20 °C was added nBuLi (821 μL of a 2.3 M solution in hexanes, 1.87 mmol, 1.3 equiv). After 5 min it was warmed to 0 °C for 30 min then re-cooled to −20 °C.

Preparation of solution 2: To a solution of hydroxyaziridine 198 (500 mg, 1.44 mmol, 1.0 equiv) in THF (2 mL) at −78 °C was added nBuLi (632 μL of a 2.3 M solution in hexanes, 1.44 mmol, 1.0 equiv). After 10 min solution 1 was added via cannula. The resulting solution was warmed to 8 °C over a period of 2.5 h then to 25 °C. After 1 h the reaction was quenched with sat. NH₄Clₐq. (4 mL), then diluted with H₂O (15 mL) and extraction with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (10% EtOAc–petrol) gave a 10:1 diastereomixture of N-[(2R*,3R*,4S*,E)-3-(hydroxymethyl)-1-(4-methoxyphenyl)-6-phenyl-4-(phenylsulfonyl)hex-5-en-2-yl]-4-methylbenzenesulfonamide 272 (453 mg, 52%) as a colourless gum; Rₚ 0.19 (43% EtOAc–petrol); vₚₚ (film) 3582, 3298, 2954, 2932, 1513, 1447, 1318, 1301, 1247, 1154, 1035, 735, 690 cm⁻¹; δₜ (400 MHz) 7.72 (2H, d, J 8.0 Hz, ortho Ts), 7.71 (2H, d, J 6.5 Hz, ortho PhSO₂), 7.58 (1H, t, J 7.0 Hz, para PhSO₂), 7.44 (2H, dd, J 7.0, 6.5 Hz, meta PhSO₂), 7.29-7.28 (3H, m, ortho & para Ph), 7.21 (2H, d, J 8.0 Hz, meta Ts), 6.93–6.91 (2H, m, meta PhSO₂), 6.89 (2H, d, J 8.6 Hz, meta MeOAr), 6.76 (2H, d, J 8.6 Hz, ortho MeOAr), 6.24 (1H, d, J 16.0 Hz, PhCH=CH, diagnostic signal of the minor diast.), 5.71 (1H, d, J 16.0 Hz, PhCH=CH), 5.18 (1H, dd, J 16.0, 9.5 Hz, PhCH=CH), 4.57-4.54 (1H, m, NH), 4.29-4.24 (1H, m, TsNHCH), 3.98
(1H, t, J 9.5 Hz, PhSO₂CH), 3.81 (3H, s, OMe), 3.72-3.59 (2H, m, CH₂OH), 2.87 (1H, dd, J 14.0, 4.5 Hz, MeOArCH), 2.73 (1H, dd, J 14.0, 11.0 Hz, MeOArCHH), 2.45-2.40 (1H, m, CHCH₂OH) 2.37 (3H, s, Me of Ts); δC (125 MHz) 171.2, 158.4, 143.0, 139.7, 138.8, 137.8, 135.5, 133.9, 129.9, 129.7, 129.6, 129.1, 128.9, 128.8, 128.5, 126.9, 126.7, 126.5, 120.1, 114.2, 113.9, 67.4, 58.9, 56.9, 55.2, 53.5, 40.3, 39.4, 21.5; m/z (ESI) 628.1789 [M+Na]⁺, 606.1971 [M+H]⁺, 464.1922, 304.1042, 241.1812, 196.0183 (Found: [M+H]⁺, 606.1971. C₃₃H₃₅NO₆S₂ requires [M+H]⁺, 606.1984) (Found: C, 65.48; H, 5.87; N, 2.39. C₃₃H₃₅NO₆S₂ requires C, 65.43; H, 5.82; N, 2.31%).

(4R*,5R*)-4-(4-Methoxybenzyl)-5-[((S*,E)-3-phenyl-1-(phenylsulfonyl)allyl)-3-tosyl-1,3-oxazinane 273

The suspension of hydroxyl tosamide 272 (496 mg, 0.82 mmol, 1.0 equiv), paraformaldehyde (32 mg, 1.06 mmol, 1.3 equiv) and p-TsOH·H₂O (10.0 mg, 0.05 mmol, 0.064 equiv) in benzene (2 mL) was heated to reflux for 16 h. The dark mixture was filtered through a short pat of cotton wool. The filtrate was extracted with EtOAc (5 mL). The organic layer was washed with brine (3 × 3 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (15→25% EtOAc-petrol) gave (4R*,5R*)-4-(4-methoxybenzyl)-5-[(S*,E)-3-phenyl-1-(phenylsulfonyl)allyl]-3-tosyl-1,3-oxazinane 273 (316 mg, 62%) as a solid; mp 136-138 °C (CH₂Cl₂-methanol); Rf 0.31 (40% EtOAc–petrol); νmax (film) 2928, 1621, 1513, 1447, 1341, 1304, 1248, 1178, 1146, 1084, 1034, 970, 816, 734, 693 cm⁻¹; δH (400 MHz) 7.65 (2H, d, J 7.5 Hz, ortho PhSO₂), 7.59 (2H, d, J 8.0 Hz, ortho Ts), 7.53 (1H, dd, J 7.5, 7.5 Hz, para PhSO₂), 7.39 (2H, dd, J 7.5, 7.5 Hz, meta PhSO₂), 7.29-7.27
(3H, m, ortho & para PhCH=CH), 7.21 (2H, d, J 8.5 Hz, meta Ts), 6.95 (2H, d, J 8.5 Hz, meta MeOAr), 6.91-6.89 (2H, m, meta PhCH=CH), 6.78 (2H, d, J 8.5 Hz, ortho MeOAr), 5.62 (1H, d, J 16.0 Hz, PhCH=CH), 5.49 (1H, d, J 10.5 Hz, NToCPhH), 5.14-5.05 (2H, m, PhCH=CH & CHCHOHCH₃), 4.76 (1H, d, J 10.5 Hz, NToCPhH), 4.13-4.05 (2H, m, CHCHOHCH₃ & CHNtos), 3.96 (1H, dd, J 10.5, 10.0 Hz, CHSO₂Ph), 3.82 (3H, s, OMe), 3.06 (1H, dd, J 13.5, 11.0 Hz, MeOArCHH), 2.82 (1H, dd, J 13.5, 4.5 Hz, MeOArCHH), 2.39 (3H, s, CH₃ of Ts), 2.20-2.18 (1H, m, CH₂O); δC (125 MHz) 158.6, 143.6, 139.6, 138.6, 137.8, 135.6, 133.4, 130.2, 129.7, 129.1, 128.8, 128.7, 128.6, 128.5, 127.3, 126.5, 126.0, 114.3, 74.1, 66.9, 64.3, 55.4, 55.3, 36.2, 34.6, 21.5; m/z (ESI) 640.1835 [M+Na]⁺, 618.1989 [M+H]⁺, 476.1903, 182.9854, 154.9901 (Found: [M+Na]⁺, 640.1835. C₃₄H₃₅NO₆S₂ requires [M+Na]⁺, 640.1804) (Found: C, 66.00; H, 5.68; N, 2.28. C₃₄H₃₅NO₆S₂ requires C, 66.10; H, 5.71; N, 2.27%).

N-[(2R*,3S*,4R*,E)-1-(4-Methoxyphenyl)-6-phenyl-4-(phenylsulfonyl)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 274

![Chemical Structure](image)

To a mixture of cinnamyl sulfone 227 (1.58 g, 6.12 mmol, 1.4 equiv) in THF (5.0 mL)/TMEDA (1.7 mL) at −20 °C was added nBuLi (570 µL of a 11.5 M solution in hexanes, 6.56 mmol, 1.5 equiv). The mixture became a red solution. It was warmed to 0 °C for 15 min then to rt. After 15 min the reaction was re-cooled to 0 °C and vinylaziridine 46 (1.51 g, 4.39 mmol, 1.0 equiv) in THF (0.9 mL) added. After 16 h the reaction was quenched with sat. NH₄Cl(aq.) (10 mL) then diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography gave N-[(2R*,3S*,4R*,E)-1-(4-Methoxyphenyl)-6-phenyl-4-
(phenylsulfonyl)-3-vinylhex-5-en-2-ylf-4-methylbenzenesulfonamide 274 (1.20 g, 45%) as a yellow solid; mp 120-122 °C (EtOAc–petrol); Rf 0.46 (30% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3260, 2954, 2952, 1611, 1512, 1446, 1302, 1247, 1147, 1032, 926, 735 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz) 7.85 (2H, d, \( J = 7.5 \) Hz, ortho PhSO\(_2\)), 7.76 (2H, d, \( J = 8.5 \) Hz, ortho Ts), 7.58 (1H, t, \( J = 7.5 \) Hz, para PhSO\(_2\)), 7.46 (2H, t, \( J = 7.5 \) Hz, meta PhSO\(_2\)), 7.27-7.15 (5H, m, PhCH=CH), 6.88 (2H, d, \( J = 8.5 \) Hz, meta MeOAr), 6.71 (2H, d, \( J = 8.5 \) Hz, ortho MeOAr), 6.0 (1H, d, \( J = 16.0 \) Hz, PhCH=CH), 6.75 (1H, dd, \( J = 16.0 \), 10.5 Hz, PhCH=CH), 5.51 (1H, dt, \( J = 17.0 \), 10.5, 7.0 Hz, CH=CH\(_2\)), 5.29 (1H, dd, \( J = 10.5 \), 1.5 Hz, trans CH=CH\(_2\)), 5.16 (1H, dd, \( J = 17.0 \), 1.5 Hz, cis CH=CH\(_2\)), 4.63-4.58 (2H, m, CHSO\(_2\)Ph & TsNHCH), 4.32 (1H, d, \( J = 9.5 \) Hz, NH), 3.81 (3H, s, MeO), 3.11 (1H, dt, \( J = 10.5 \), 10.0, 1.5 Hz, CH=CH\(_2\)), 2.79 (1H, dd, \( J = 14.0 \), 4.5 Hz, MeOArCHH, diagnostic signal of the minor diast) 2.60 (1H, dt, \( J = 14.0 \), 8.5 Hz, MeOArCHH), 2.45 (3H, s, Me of Ts), 2.33 (1H, dd, \( J = 14.0 \), 6.5 Hz, MeOArCHH); \( \delta_{\text{C}} \) (125 MHz) 158.4, 143.6, 137.6, 136.7, 135.9, 133.5, 132.6, 130.2, 129.8, 129.3, 128.7, 128.6, 128.2, 128.1, 127.3, 126.5, 121.3, 113.9, 67.4, 56.4, 55.2, 44.5, 39.4, 21.6; \( m/z \) (ESI) 624.1842 \([\text{M+Na}]^+\), 602.2050 \([\text{M+H}]^+\), 539.1342, 304.1051 (Found: \([\text{M+H}]^+\), 602.2050. \( \text{C}_{34}\text{H}_{35}\text{NO}_{5}\text{S}_2 \) requires \([\text{M+H}]^+\), 602.2035) (Found: C, 67.84; H, 6.00; N, 2.44. \( \text{C}_{34}\text{H}_{35}\text{NO}_{5}\text{S}_2 \) requires C, 67.86; H, 5.86; N, 2.33%).

2-Phenyl-4-vinyl-1,3-dioxolane\(^{124} \) 277

\[
\text{HO} \quad \text{OH} \quad + \quad \text{O} \quad \text{CHO} \quad \xrightarrow{} \quad \text{Ph} \quad \text{O} \quad \text{O} \quad \text{Ph} \quad \text{O} \quad \text{O} \quad \text{Ph}
\]

The solution of 3-butene-1,2-diol 275 (7.00 g, 79.5 mmol, 1.0 equiv), benzaldehyde 276 (8.43 g, 79.5 mmol, 1.0 equiv) and \( p \)-TsOH-H\(_2\)O (303 mg, 1.59 mmol, 0.02 equiv) in toluene (100 mL) was heated under reflux azeotropically. After 5 h, the reaction mixture was concentrated to ~40 mL and filtered though a short pad of cotton wool. Concentration of the filtrate under reduced pressure and column chromatography (5→12% EtOAc–petrol) gave a 1:1 diastereomixture of 2-phenyl-4-vinyl-1,3-dioxolane 277 (12.6 g, 90%) as an oil; Rf 0.67 (10% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3067, 2986, 2879,
2-(Benzyloxy)but-3-en-1-ol 278 & 1-(benzyloxy)but-3-en-2-ol 279

To a solution of dioxolane 277 (2.40 g, 13.6 mmol, 1.0 equiv) in CH₂Cl₂ (68 mL) at −78 °C was added DIBAL (27.2 mL of a 1.5 M solution in toluene, 40.8 mmol, 3.0 equiv) dropwise. The solution was warmed to rt slowly. After 12 h, the resulting solution was re-cooled to −78 °C and quenched with sat. Na/K tartrateₐq.) (14 mL). After 15 min, it was warmed to rt for 30 min. Water (50 mL) was added and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (15% EtOAc–petrol) gave a 4:1 regioisomeric mixture of 2-(benzyloxy)but-3-en-1-ol 278 and 1-(benzyloxy)but-3-en-2-ol 279 (1.77 g, 73%) as an oil; Rf 0.24 (15% EtOAc–petrol); νmax (film) 3382, 2916, 2880, 2853, 1719, 1686, 1598, 1449, 1399, 1274, 1215, 1178, 1120, 1027, 816, 759, 714, 560 cm⁻¹; δH (400 MHz) 7.41-7.33 (m, 2 × Ph, 2 × regio.) 5.91-5.75 (m, 2 × CH=CH₂, 2 × regio.), 5.43-5.37 (m, CH=CH₂, major regio.), 5.24-5.22 (m, CH=CH₂, minor regio.), 4.71 (d, J 11.5 Hz, PhCHH, major regio.), 4.61 (s, PhCHH, minor regio.), 4.43 (d, J 11.5 Hz, PhCHH, major regio.), 3.98 (dd, J 12.5, 6.5 Hz, CHCH=CH₂, major regio.), 3.64-3.63 (m,
$\text{CH}_2\text{OH}$, major regio.), 3.57 (dd, $J$ 9.5, 3.5 Hz, $\text{CHOH}$, minor regio.), 3.41 (dd, $J$ 9.5, 8.0 Hz, $\text{CH}_2\text{OBn}$); $\delta_C$ (125 MHz) 138.1, 137.8, 136.6, 135.1, 128.5, 127.9, 126.9, 119.4, 116.5, 81.1, 74.0, 73.4, 71.5, 70.5, 65.3; $m/z$ (CI) 196 [M+NH$_4^+$], 178 [M$^+$], 161, 108 (Found: [M+NH$_4^+$], 196.1331. C$_{11}$H$_{14}$O$_2$ requires [M+NH$_4^+$], 196.1338).

2-(Benzyloxy)but-3-enal 266a & (E)-2-(benzyloxy)but-2-enal 280

The suspension of a regioisomeric mixture of alcohols 278 and 279 (51.0 mg, 0.29 mmol, 1.0 equiv) and IBX (105 mg, 0.38 mmol, 1.3 equiv) in EtOAc (3 mL) was heated to reflux. After 2.5 h, the resulting mixture was cooled to rt and filtered. The filtrate was concentrated under reduced pressure to give 2-(benzyloxy)but-3-enal 266a (44.1 mg, 86%) as an oil. After column chromatography 266a isomerised to give (E)-2-(benzyloxy)but-2-enal 280 as an oil.

Data for 266a: $R_f$ 0.58 (20% EtOAc–petrol); $\delta_H$ (400 MHz) 9.58 (1H, d, $J$ 1.5 Hz, CHO), 7.39-7.26 (5H, m, Ph), 5.80 (1H, ddd, $J$ 17.0, 10.5, 6.5 Hz, CH=CH$_2$), 5.55-5.48 (2H, m, CH=CH$_2$), 4.72 (1H, d, $J$ 12.0 Hz, PhCH=H), 4.61 (1H, d, $J$ 12.0 Hz, PhCH=H), 4.32 (1H, dd, $J$ 6.5, 1.5 Hz, BnOCH$_2$); $\delta_C$ (100 MHz) 199.6 (CHO), 137.1 (ipso Ph), 130.7 (3º), 128.6 (meta or ortho Ph), 128.1 (3º), 128.0 (meta or ortho Ph), 120.9 (CH=CH$_2$), 84.7 (BnOCH), 71.4 (PhCH$_2$).

Data for 280: $R_f$ 0.63 (20% EtOAc–petrol); $\delta_H$ (400 MHz) 9.26 (1H, s, CHO), 7.42-7.34 (5H, m, Ph), 6.11 (1H, q, $J$ 7.0 Hz, CH=C), 5.09 (2H, s, PhCH$_2$), 1.84 (3H, d, $J$ 7.0 Hz, CH$_3$); $\delta_C$ (100 MHz) 189.2 (CHO), 154.8 (BnOC), 137.2 (ipso Ph), 136.9 (3º), 128.4 (meta or ortho Ph), 128.2 (3º), 127.8 (3º), 72.9 (PhCH$_2$), 12.0 (CH$_3$).
(E)-4-Phenylbut-3-ene-1,2-diol 285

\[
\begin{align*}
&\text{HO} \quad \text{OH} \\
&\quad \downarrow \\
&\text{HO} \quad \text{OH} \\
&\quad \downarrow \\
&\text{OH} \quad \text{OH} \\
&\quad \downarrow \\
&\text{OH} \quad \text{OH} \\
&\quad \downarrow
\end{align*}
\]

To a solution of catalyst 50 (210 mg, 0.247 mmol, 0.01 equiv) in CH\(_2\)Cl\(_2\) (110 mL) at rt was added styrene (6.65 g, 63.8 mmol, 2.9 equiv) and diol 275 (1.95 g, 22.0 mmol, 1.0 equiv). The resulting solution was heated to reflux. After 16 h, concentration under reduced pressure and column chromatography (5→30% EtOAc–petrol) gave (E)-4-phenylbut-3-ene-1,2-diol 285 (1.99 g, 55%) as a gum; R\(_f\) 0.29 (10% EtOAc–petrol); \(v_{\text{max}}\) (film) 3302, 2973, 1448, 1053, 1018, 987, 971, 745, 690 cm\(^{-1}\); \(\delta\)\(_H\) (400 MHz) 7.45-7.29 (5H, m, Ph), 6.73 (1H, d, \(J = 16.0\) Hz, Ph\(CH=CH\)), 6.24 (1H, dd, \(J = 16.0, 6.5\) Hz, Ph\(CH=CH\)), 4.98-4.96 (1H, m, CH\(_2\)\(CH\)), 3.81-3.78 (1H, m, CH\(HH\)), 3.67-3.62 (1H, m, CH\(HH\)), 2.27 (1H, d, \(J = 3.5\) Hz, OH), 2.01 (1H, t, \(J = 5.5\) Hz, OH); \(\delta\)\(_C\) (100 MHz) 136.3 (ipso Ph), 132.3 (3º), 128.6 (meta or ortho Ph), 127.9 (3º), 127.7 (3º), 126.6 (meta or ortho Ph), 73.2 (CHOH), 66.5 (CH\(_2\)OH); \(m/z\) (CI) 182 [M+\(\text{NH}_4\)\(^+\)], 164, 147, 129, 52 (Found: [M+\(\text{NH}_4\)\(^+\)], 182.1185. C\(_{10}\)H\(_{12}\)O\(_2\) requires [M+\(\text{NH}_4\)\(^+\)], 182.1181).

(2R\(^*\))-2-Phenyl-4-styryl-1,3-dioxolane & (2S\(^*\))-2-phenyl-4-styryl-1,3-dioxolane 282

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

To a solution of catalyst 50 (127 mg, 0.15 mmol, 0.03 equiv) in CH\(_2\)Cl\(_2\) (25 mL) at rt was added styrene (1.05 g, 10.1 mmol, 2.0 equiv) and dioxolane 277 (825 mg, 4.7 mmol, 1.0 equiv). The resulting solution was heated to 40 °C. After 14 h concentration under reduced pressure and column chromatography (5→15% EtOAc–petrol) gave a 1:1 diastereomixture of 282 (544 mg, 46%) as a gum;
Data for one diastereomer: \( R_f \) 0.22 (10% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3030, 2987, 2880, 1718, 1596, 1493, 1450, 1400, 1273, 1091, 1068, 967, 750, 698 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.56-7.27 (10H, m, 2 × Ph), 6.75 (1H, d, \( J = 16.0 \) Hz, PhCH\( =CH \)), 6.28 (1H, dd, \( J = 16.0, 7.5 \) Hz, PhCH=CH\( H \)), 6.08 (1H, s, PhCH\( H \)), 4.85 (1H, ddd, \( J = 7.5, 7.5, 7.5 \) Hz, CHCH=CH\( H \)), 4.04 (1H, dd, \( J = 8.5, 7.5 \) Hz, CHHCH\( H \)), 3.83 (1H, dd, \( J = 8.5, 7.5 \) Hz, CHHCH\( H \)); \( \delta_C \) (125 MHz) 136.2, 133.5, 129.2, 128.6, 128.4, 128.1, 126.7, 126.4, 126.2, 103.9, 80.9, 70.7.

Data for the other diastereomer: \( R_f \) 0.19 (10% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3030, 2879, 1720, 1599, 1494, 1450, 1400, 1272, 1219, 1092, 1068, 967, 750, 695 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.59-7.27 (10H, m, 2 × Ph), 6.73 (1H, d, \( J = 16.0 \) Hz, PhCH=CH\( H \)), 6.28 (1H, dd, \( J = 16.0, 7.5 \) Hz, PhCH=CH\( H \)), 5.96 (1H, s, PhCH\( H \)), 4.85 (1H, ddd, \( J = 7.0, 7.0, 7.0 \) Hz, CHCH=CH\( H \)), 4.26 (1H, dd, \( J = 8.0, 7.0 \) Hz, CHHCH\( H \)), 3.83 (1H, dd, \( J = 8.0, 7.0 \) Hz, CHHCH\( H \)); \( \delta_C \) (125 MHz) 137.6, 136.2, 133.8, 129.4, 128.6, 128.4, 128.1, 126.6, 126.4, 104.5, 78.3, 70.2; \( m/z \) (CI) 270 [M+NH\(_4\)]\(^+\), 251, 164, 147 (Found: [M+NH\(_4\)]\(^+\), 253.1216. C\(_{17}\)H\(_{16}\)O\(_2\) requires [M+NH\(_4\)]\(^+\), 253.1229) (Found: C, 80.72; H, 6.32. C\(_{17}\)H\(_{16}\)O\(_2\) requires C, 80.93; H, 6.39%).

**\( (E)\)-1-(Benzyloxy)-4-phenylbut-3-en-2-ol 283 and \( (E)\)-2-(benzyloxy)-4-phenylbut-3-en-1-ol 284**

To a solution of a 1:1 diastereomixture of dioxolane 282 (260 mg, 1.0 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (2 mL) at –78 °C was added DIBAL (3.1 mL of a 1 M solution in CH\(_2\)Cl\(_2\), 3.1 mmol, 3.0 equiv). The solution was warmed to rt slowly then stirred at that temperature for 12 h. The resulting solution was re-cooled to –78 °C, sat. Na/K tartrate\(_{\text{aq.}}\) (3 mL) was added slowly. After 10 min it was warmed to rt. After 30 min H\(_2\)O (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (MgSO\(_4\)).
Concentration under reduced pressure and column chromatography (E)-1-(benzyloxy)-4-phenylbut-3-en-2-ol 283 (41 mg, 16%) and (E)-2-(benzyloxy)-4-phenylbut-3-en-1-ol 284 (167 mg, 66%).

Data for 283: Rf 0.42 (25% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3424, 3062, 3029, 2864, 1495, 1435, 1392, 1206, 1071, 932, 747, 697 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz) 7.42-7.26 (10H, m, 2 × Ph), 6.73 (1H, d, J 15.5 Hz, PhCH=CH), 6.22 (1H, dd, J 16.0, 6.0 Hz, PhCH=CH), 4.69 (1H, d, J 11.5 Hz, BnOCH\(\text{H}\)), 4.44 (1H, d, J 11.5 Hz, BnOCH\(\text{H}\)), 3.99 (1H, app dd, J 12.5, 6.0 Hz, CHO\(\text{H}\)), 3.66-3.64 (2H, m, CH\(_2\)OBn); \( \delta_{\text{C}} \) (100 MHz) 136.1, 134.5, 128.7, 128.6, 128.2, 127.9, 127.8, 126.6, 126.1, 80.8 (CHOH), 70.6 (CH\(_2\)OBn), 65.6 (PhCH\(_2\)); \( m/z \) (Cl) 254 [M+NH\(_4\)-H\(_2\)O]+, 236, 219 (Found: [M+NH\(_4\)-H\(_2\)O]+, 254.1556. C\(_{17}\)H\(_{18}\)O\(_2\) requires [M+NH\(_4\)-H\(_2\)O]+, 254.1545).

Data for 284: Rf 0.36 (25% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3331, 3029, 2872, 1495, 1435, 1208, 1019, 734, 696 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz) 7.45-7.29 (10H, m, Ph of Bn & PhCH=CH), 6.70 (1H, d, J 16.0 Hz, PhCH=CH), 6.16 (1H, dd, J 16.0, 8.0 Hz, PhCH=CH), 4.73 (1H, d, J 11.5 Hz, OCH\(\text{H}\)Ph), 4.48 (1H, d, J 11.5 Hz, OCH\(\text{H}\)Ph), 4.18-4.13 (1H, m, CHO\(\text{Bn}\)), 3.72-3.71 (2H, m, CH\(_2\)OH); \( \delta_{\text{C}} \) (125 MHz) 138.1 (ipso Ph), 136.1 (ipso Ph), 134.5 (\(^{3}\)o), [128.7, 128.5 (meta or ortho Ph)], 128.1 (\(^{3}\)o), 127.9 (meta or ortho Ph), 127.8 (\(^{3}\)o), 126.6 (meta or ortho Ph), 126.1 (\(^{3}\)o), 80.8 (CHOH), 70.6 (CH\(_2\)OBn), 65.6 (PhCH\(_2\)); \( m/z \) (Cl) 254 [M+NH\(_4\)-H\(_2\)O]+ (Found: C, 80.19; H, 7.21. C\(_{17}\)H\(_{18}\)O\(_2\) requires C, 80.28; H, 7.13%).
(E)-2-(Benzyloxy)-4-phenylbut-3-enal 266b & (E)-2-(benzyloxy)-4-phenylbut-2-enal 286

To a solution of Dess–Martin periodinatate (495 mg, 1.17 mmol, 1.5 equiv) in CH₂Cl₂ (3.5 mL) at rt was added a solution of alcohol 284 (270 mg, 1.01 mmol, 1.0 equiv) in CH₂Cl₂ (1.5 mL). After 2.5 h, Et₂O (6 mL) was added to the solution, followed by a solution of sat. NaHCO₃(aq.) dissolving Na₂S₂O₃ (1.5 g). After 3 min, the mixture was further diluted with Et₂O (10 mL). The organic phase was separated, washed with sat. NaHCO₃(aq.) (6 mL), H₂O (10 mL), brine (2 × 8 mL) and dried (Na₂SO₄). Concentration under reduced pressure and drying under high vacuum cleanly gave crude (E)-2-(benzyloxy)-4-phenylbut-3-enal 266b (250 mg, 93%); Rf 0.42 (13% EtOAc–petrol); δH (400 MHz) 9.64 (1H, s, CHO), 7.44-7.31 (10H, m, 2 × Ph), 6.81 (1H, d, J 16.0 Hz, PhCH=CH), 6.12 (1H, dd, J 16.0, 7.0 Hz, PhCH=CH₂), 4.77 (1H, d, J 12.0 Hz, PhCHH), 4.67 (1H, d, J 12.0 Hz, PhCH₂H), 4.49 (1H, dt, J 7.0, 1.5 Hz, CHOObn). When enal 266b was treated with anionic nucleophiles, it isomerised to (E)-2-(benzyloxy)-4-phenylbut-2-enal 286; δH (400 MHz) 9.29 (1H, s, CHO), 7.44-7.07 (10H, m, 2 × Ph), 6.15 (1H, t, J 7.5 Hz, CH=COBn), 5.17 (2H, s, PhCH₂O), 3.60 (2H, d, J 7.5 Hz, PhCH₂CH).

(S)-Butane-1,2,4-triol 292

To a solution of (S)-malic acid 291 (2.00 g, 14.9 mmol, 1.0 equiv) in THF (30 mL) at 0 °C were added BH₃·SMe₂ (44.0 mL, 46.4 mmol, 3.1 equiv) and B(OMe)₃ (5.50 mL, 49.1 mmol, 3.3 equiv). It was then warmed to rt. After 16 h, methanol (12 mL) was added slowly. Concentration under reduced pressure and column chromatography
(5→15% MeOH–CH₂Cl₂) gave triol 292 as a colourless oil (1.42 g, 90%). Rₜ 0.22 (15% MeOH–CH₂Cl₂); νₘₐₓ (film) 3355, 2941, 1422, 1059, 987, 872 cm⁻¹; δₜ (400 MHz, [d₆]DMSO) 4.48 (1H, t, J 5.5 Hz, CHO𝐻), 4.51-4.46 (2H, m, 𝐶𝐻₂OHCHO𝐻), 3.56-3.48 (3H, m, 𝐌𝐻), 3.26 (2H, qt, J 11.0, 5.5 Hz, 𝐶𝐻₂𝐶𝐻₂𝑂𝐻), 2.53-2.50 (2H, m, 𝐶𝐻₂𝐶𝐻₂𝑂𝐻); δ (100 MHz) 69.2, 66.6, 58.5, 37.2; m/z (CI) 210, 124 [M+NH₄]⁺, 107 [M+H]⁺, data in agreement with that previously reported.¹³⁰,¹³²

\[ \text{[(2S,4S)-2-Phenyl-1,3-dioxan-4-yl]methanol}^{130,132} 293 \]

A solution of triol 292 (900 mg, 8.49 mmol, 1.0 equiv), benzaldehyde dimethylacetal (1.38 g, 9.08 mmol, 1.07 equiv) and (R)-(−)-CSA (99.0 mg, 0.427 mmol, 0.05 equiv) in CH₂Cl₂ (13 mL) was stirred at rt. After 16 h, the solution was re-cooled to −5 °C and Et₃N (125 µL) added dropwise. Concentration under reduced pressure and column chromatography (30% EtOAc–petrol) gave the alcohol 293 (1.46 g, 89%) % as a colourless oil; Rₜ 0.09 (20% EtOAc–petrol); νₘₐₓ (film) 3424, 2924, 2861, 1454, 1399, 1364, 1313, 1240, 1215, 1141, 1104, 1066, 1025, 758, 699 cm⁻¹; δₜ (400 MHz) 7.53-7.51 (2H, m, ortho PhS), 7.42-7.37 (3H, m, meta & ortho PhS), 5.58 (1H, s, CHPH), 4.35-4.32 (1H, m, CHOCHPH), 4.08-3.98 (2H, m, 𝐶𝐻₂𝑂𝐻), 2.02-1.91 (1H, m, 𝐶𝐻₂𝐶𝐻𝐶𝐻𝐻), 1.50-1.47 (1H, m, 𝐶𝐻₂𝐶𝐻𝐶𝐻𝐻); δ (101 MHz) 138.3 (ipso Ph), 129.0 (para Ph), [128.3, 126.1 (meta & ortho Ph)], 101.3 (CHPh), 77.4, 66.6, 65.8, 26.8; m/z (CI) 212 [M+NH₄]⁺, 195 [M+H]⁺, 163; data in agreement with that previously reported.¹³⁰,¹³²
(2S,4S)-2-Phenyl-1,3-dioxane-4-carbaldehyde\textsuperscript{130,132} \text{290}

\[
\begin{array}{c}\text{293} \quad \text{290}\end{array}
\]

To a solution of alcohol \text{293} (150 mg, 0.772 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL) at 0 °C was added a mixture of Dess–Martin periodinane (418 mg, 0.987 mmol, 1.28 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL). The resulting suspension was warmed to rt. After 1 h, the mixture was diluted with Et\textsubscript{2}O (3 mL) and washed with a solution of sat. NaHCO\textsubscript{3(aq.)} (5mL) dissolving Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}·5H\textsubscript{2}O (2.5 g). After 5 min, the organic phase was separated and the aqueous phase extracted with Et\textsubscript{2}O (5 mL). The combined organic layers were washed with sat. NaHCO\textsubscript{3(aq.)} (5mL), H\textsubscript{2}O (8 mL), brine (8 mL) and dried (MgSO\textsubscript{4}). Concentration under reduced pressure cleanly gave crude aldehyde \text{290} (120 mg, 84%) as a colourless oil; R\text{f} 0.21 (20% EtOAc–petrol); \(\delta\text{H} (400\text{ MHz}) \) 9.78 (1H, s, CHO), 7.60-7.28 (5H, m, Ph), 5.61 (1H, s, C\text{H}Ph), 4.44-4.36 (1H, m, CH\textsubscript{2}CH\textsubscript{2}), 4.11-4.01 (2H, m, CH\textsubscript{2}O), 2.07-1.80 (2H, m, CH\textsubscript{2}CH\textsubscript{2}O); \(\delta\text{C} (101\text{ MHz}) \) 200.1 (CHO), 137.5 (ipso Ph), 129.0 (para Ph), [128.1, 126.3 (meta & ortho Ph)], 101.0 (C\text{Ph}), 80.1, 66.0, 25.8; m/z (CI) 210 [M+NH\textsubscript{4}]\textsuperscript{+}, 193 [M+H]\textsuperscript{+}; data in agreement with that previously reported.\textsuperscript{130,132}

\textbf{Allyl(phenyl)sulfane}\textsuperscript{135} \text{294}

\[
\begin{array}{c}\text{294}\end{array}
\]

To a flask containing NaH (1.09 g of a 60% wt% dispersion in mineral oil, 27.2 mmol, 1.0 equiv) at 0 °C was added EtOH (40 mL). To this resulting solution were added thiophenol (3.00 g, 27.2 mmol, 1.0 equiv) and allyl bromide (3.62 g, 29.9 mmol, 1.0 equiv). The resulting mixture was stirred at rt for 16 h then filtered. H\textsubscript{2}O (100 mL) was added to the filtrate and the aqueous phase extracted with Et\textsubscript{2}O (3 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL) and dried (MgSO\textsubscript{4}). Concentration under reduced pressure cleanly gave crude product \text{294} (3.50 g, 86%) as
a colourless oil; \( \nu_{\text{max}} \) (film) 3070, 3059, 2919, 2916, 1948, 1852, 1636, 1583, 1480, 1438, 1228, 1089, 1025, 987, 919, 737, 690 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.38-7.36 (2H, m, \textit{ortho} Ph), 7.32-7.28 (2H, m, \textit{meta} Ph), 7.22-7.19 (1H, m, \textit{para} Ph), 5.90 (1H, ddt, \( J \text{ 17.0, 7.0, 7.0 Hz, } CH=CH_2 \)), 5.18-5.14 (1H, m, \textit{cis} \( CH/H=CH \)), 5.11-5.08 (1H, m, \textit{trans} \( CH/H=CH \)), 5.57 (2H, d, \( J 7.0 \text{ Hz, } CH_2 \)); \( \delta_C \) (125 MHz) 137.5 (ipso PhS), 133.6 (para PhS), [129.8, 128.8 (\textit{ortho} & \textit{meta} PhS)], 126.2 (\( CH=CH_2 \)), 117.7 (\( CH=CH_2 \)), 37.2 (\( CH_2 \)); \textit{m/z} (Cl) 184, 166, 149, 52; data in agreement with that previously reported. \(^{135}\)

\[N-[(2R*,3S*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-4-en-2-yl]-4-methylbenzenesulfonamide 295\]

\[
\begin{align*}
N- & [(2R*,3S*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-4-en-2-yl]-4-methylbenzenesulfonamide 295
\end{align*}
\]

To a solution of allyl sulfide 294 (81.4 mg, 0.542 mmol, 1.4 equiv) in THF (0.3 ml) at \(-78 \text{ °C}\) was added \( n \text{BuLi} \) (62 \( \mu \text{L} \) of a 9.4 M solution in hexanes, 0.581 mmol, 1.5 equiv). After 15 min, it was warmed to \(-30 \text{ °C}\) then to 0 °C. After 15 min, it was re-cooled to \(-20 \text{ °C}\) then a solution of aziridine 46 (100 mg, 0.387 mmol, 1.0 equiv) in THF (0.2 ml) was added. The resulting solution was warmed to rt. After 16 h the solution was quenched with sat. \( \text{NH}_4\text{Cl}_{\text{aq.}} \) (2 mL), diluted with \( H_2O \) (5 mL) and the aqueous phase extracted with EtOAc (2 \( \times \) 5 ml). The combined organic layers were washed with brine (2 \( \times \) 5 ml) and dried (Na\(_2\)SO\(_4\)). Concentration under reduced pressure and column chromatography (5→15% EtOAc–petrol) gave a 5:1 olefin isomeric mixture of \( N-[(2R*,3S*)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-4-en-2-yl]-4-methylbenzenesulfonamide 295 \) (97.0 mg, 67%) as a solid; data for the major isomer: \( R_f \) 0.33% (15% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3287, 1612, 1513, 1439, 1326, 1247, 1158, 1093, 1036, 813, 741, 690, 663 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.66 (2H, d, \( J 8.5 \text{ Hz, } ortho \text{ Ts} \)), 7.30 (2H, d, \( J 8.5 \text{ Hz, } meta \text{ Ts} \)), 7.25 (2H, d, \( J 8.0 \text{ Hz, } ortho \text{ PhS} \)), 7.13-7.09 (1H, m,
para PhS), 6.98-6.96 (2H, m, meta PhS), 6.85 (2H, d, J 8.5 Hz, meta ArOMe), 6.63 (2H, d, J 8.5 Hz, ortho ArOMe), 6.03 (1H, q, J 6.5 Hz, CH$_3$CH=C), 5.85 (1H, app. dt, J 16.0, 9.5 Hz, CH$_2$=CH, diagnostic signal of the minor isomer), 5.75 (1H, ddd, J 17.0, 10.0, 8.5 Hz, CH$_2$=CH), 5.16 (1H, dd, J 10.0, 1.5 Hz, trans CHH=CH), 4.91 (1H, dd, J 17.0, 1.5 Hz, cis CHH=CH), 4.44 (1H, d, J 8.0 Hz, NH), 3.80-3.78 (4H, m, OMe & NCH), 2.85-2.81 (1H, m, CHCH=CH$_2$), 2.74 (1H, dd, J 14.0, 5.0 Hz, CHH), 2.63-2.58 (1H, m, CHH), 2.43 (3H, s, Me of Ts), 1.79 (3H, d, J 6.5 Hz, CH$_3$CH=C); δ$_C$ (125 MHz) [158.0, 143.1, 137.5 (q Ar)], [134.9, 134.8, 133.8 (CH=C & para PhS)], [129.9, 129.6 (q Ar)], [130.1, 129.5, 128.9, 128.7, 127.2 (ortho & meta Ar)], 125.8 (CH=CH$_2$), 119.2 (CH=CH$_2$), 113.6 (ortho or meta Ar), 56.9, 55.1, 52.1, 38.5, 21.5, 15.9; m/z (ESI) 516 [M+Na]$^+$, 494 [M+H]$^+$, 304, 214 (Found: [M+Na]$^+$, 516.1642. C$_{28}$H$_{31}$NO$_3$S$_2$ requires [M+Na]$^+$, 516.1643).

$N$-[(2R$^*$,3S$^*$)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 296

![Chemical structure](image)

To a solution of allyl sulfide 294 (241 mg, 1.60 mmol, 1.1 equiv) in THF (1.0 mL) at −78 °C was added $n$BuLi (988 µL of a 1.62 M solution in hexanes, 1.60 mmol, 1.1 equiv). After 25 min, the reaction vessel was put into a 0 °C bath for 5 min then recooled to −78 °C. To the resulting solution was added a solution of aziridine 46 (500 mg, 1.46 mmol, 1.0 equiv) in THF (0.8 mL) at −78 °C. After 20 min, the reaction was quenched with a solution of AcOH (96 mg) in THF (865 mg) then warmed to rt. This solution was further diluted with H$_2$O (10 mL) and the aqueous phase extracted with EtOAc (3 × 15 ml). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na$_2$SO$_4$). Concentration under reduced pressure and column chromatography
(15% EtOAc–petrol) gave a 5:1 diastereomixture of N-[(2R*,3S*)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 296 (547 mg, 76%) as a gum; data for major diastereomer: Rf 0.33 (15% EtOAc–petrol); νmax (film) 3280, 1612, 1513, 1440, 1325, 1247, 1158, 1093, 1035, 923 cm⁻¹; δH (500 MHz) 7.79 (2H, d, J 8.5 Hz, ortho Ts, diagnostic signal of the minor diast.), 7.73 (2H, d, J 8.5 Hz, ortho Ts), 7.33-7.19 (7H, m, meta Ts and PhS), 6.88 (2H, d, J 8.5 Hz, meta ArOMe), 6.77 (2H, d, J 8.5 Hz, ortho ArOMe), 5.74 (1H, ddd, J 15.5, 10.0, 8.5 Hz, CH₂=CHCHCHN), 5.40 (1H, dd, J 10.0, 1.5 Hz, trans CHH=CHCHCHN), 5.29-5.17 (2H, m, CH₂=CHCHS & cis CHH=CHCHCHN), 4.89 (1H, dd, J 10.0, 1.0 Hz, trans CHH=CHCHS), 4.65 (1H, dd, J 17.0, 1.0 Hz, cis CHH=CHCHS), 4.34 (1H, m, NH), 3.83-3.76 (4H, m, OMe & NCH), 2.62-2.49 (2H, m, CH₃CHN), 2.44 (3H, s, Me of Ts), 2.22-2.17 (1H, m, CHCHN); δC (125 MHz) [158.3, 143.5, 137.7 (q Ar)], [136.7, 134.4, 134.2 (meta PhS & CH=CH₂ & CH=CH₂)], [133.1, 130.2, 129.7 (meta & ortho Ar)], [128.9, 128.8 (q Ar)], [128.6, 127.1 (meta & ortho Ar)], [120.9, 117.9 (CH=CH₂ & CH=CH₂)], 113.9 (meta or ortho Ar), 56.0, 55.2, 53.0, 48.6, 39.1, 21.6; m/z (ESI) 516 [M+Na]+, 494 [M+H]+, 384, 304 (Found: [M+Na]+, 516.1646. C₂₈H₃₁NO₅S₂ requires [M+Na]+, 516.1643).

N-[(2R*,3S*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-N,N,4-
dimethylbenzenesulfonamide 297

![Diagram](image)

To a diastereomixture of sulfide 296 (207 mg, 0.42 mmol, 1.0 equiv), Mel (168 µL, 2.69 mmol, 6.4 equiv) and tBuOK (48.0 mg, 0.42 mmol, 1.0 equiv) at rt was added tBuOH (0.6 mL). The suspension was heated to 70 °C. After 4 h, it was concentrated under reduced pressure. Then, H₂O (5 mL) was added to the crude mixture and
extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→20% EtOAc–petrol) gave N-[(2R*,3S*)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-N,4-dimethylbenzenesulfonamide 297 (173 mg, 82%) as a gum; data for major diastereomer only: Rₜ 0.62 (25% EtOAc–petrol); vₘₐₓ (film) 3072, 2933, 2835, 1720, 1612, 1513, 1439, 1333, 1303, 1247, 1157, 1088, 1035, 932, 815, 740, 655 cm⁻¹ (400 MHz) 7.46 (2H, d, J 8.5 Hz, ortho Ts), 7.35-7.17 (7H, m, meta Ts and PhS), 6.96 (2H, d, J 8.5 Hz, meta ArMe), 6.74 (2H, d, J 8.5 Hz, ortho ArOMe), 5.91-5.81 (1H, m, CH₂=CHCHCHN), 5.40 (1H, td, J 17.0, 9.5 Hz, CH₂=CHCHS), 5.32-4.82 (4H, m, CH₂=CHCHCHN & CH₂=CHCHS), 3.87-3.81 (5H, m, OMe & NCH & CHS), 3.83 (3H, s, OMe, diagnostic signal of minor diast.), 2.76-2.73 (5H, m, NMe & CH₂Ar), 2.43-2.37 (4H, m, Me of Ts & CHCHN); δC (125 MHz) [158.4, 142.7 (q Ar)], 137.6 (CH=CH₂), 136.7 (q Ar), 135.6 (CH=CH₂), 134.7 (q Ar), [132.8, 130.3 (3° Ar)], 130.1 (q Ar), [129.5, 128.6, 127.1 (3° Ar), [118.9, 116.4 (2 × CH=CH₂)], 113.8 (3° Ar)], 59.8 (OMe), [55.2, 54.3 (MeNMe)], 51.9 (CHSPh), 35.9 (CH₂ArOMe), 30.2 (CHCHS), 21.5 (Me of Ts); m/z (ESI) 530 [M+Na]⁺, 508 [M+H]⁺, 465, 318 (Found: [M+Na]⁺, 530.1816. C₈₀H₃₃NO₃S₂ requires [M+Na]⁺, 530.1800) (Found: C, 68.65; H, 6.67; N, 2.71. C₂₉H₃₃NO₃S₂ requires C, 68.60; H, 6.55; N, 2.76%).

5-(Phenylthio)hepta-1,6-dien-3-ol 384

![Diagram]

To a solution of allyl sulfide 294 (300 mg, 2.0 mmol, 1.0 equiv) in THF (1 mL) at –78 °C was added nBuLi (230 µL of a 8.7 M solution in hexanes, 2.0 mmol, 1.0 equiv). After 20 min, the reaction vessel was put in a 0 °C bath for 10 min then re-cooled to –78 °C. Butadiene monoxide 47 (154 mg, 2.2 mmol, 1.1 equiv) was added. After 15 min, AcOH (120 mg) in THF (1 mL) was added and the solution warmed to rt. Concentration under reduced pressure and column chromatography (10% EtOAc–petrol) gave diene 384 (82 mg, 19%) as a colourless oil; Rₜ 0.59 (20% EtOAc–petrol);
δ\textsubscript{H} (400 MHz) 7.40-7.42 (2H, m, ortho Ph, 2 × dias.), 7.33-7.26 (3H, m, para & meta Ph), 5.95-5.68 (2H, m, CH\textsubscript{2}=CH & CH\textsubscript{2}=CH, 2 × dias.), [5.33-5.28, 5.19-5.15, 5.04-4.89 (4H, m, CH\textsubscript{2}=CH & CH\textsubscript{2}=CH, 2 × dias.)], 4.49-4.23 (1H, m, CHO\textsubscript{H}), 3.89-3.78 (1H, m, CHPh), 1.99-1.76 (2H, m, CH\textsubscript{2}, 2 × dias.); δ\textsubscript{C} (125 MHz) [140.6, 140.4, 138.7, 138.2, 133.1, 132.9, 128.7, 127.4, 127.3, 116.4, 115.6, 115.4, 115.1 (Ph & 2 × CH\textsubscript{2}=CH, 2 × dias.)], [70.8 70.7 (CHOH, 2 × dias.), [48.9, 48.8 (CH\textsubscript{2}Ph, 2 × dias.)], [41.0, 40.9 (CH\textsubscript{2}, 2 × dias.)]; m/z (Cl) 238 [M+NH\textsubscript{4}]\textsuperscript{+}, 221 [M+H]\textsuperscript{+}, 203, 149 (Found: [M+H]\textsuperscript{+}, 221.1007. C\textsubscript{13}H\textsubscript{16}OS requires [M+H]\textsuperscript{+}, 221.1007).

3-(Phenylthio)propanal\textsuperscript{138} 303

\[
\begin{align*}
\text{301} & \quad \text{PhSH} \quad \text{302} \quad \text{303}
\end{align*}
\]

To a solution of thiophenol 302 (2.20 g, 20.0 mmol, 1.0 equiv) and Et\textsubscript{3}N (0.28 mL, 2.0 mmol, 0.1 equiv) and CH\textsubscript{2}Cl\textsubscript{2} (20 mL) at 0 °C was added acrylaldehyde 301 (2.67 mL, 40 mmol, 2.0 equiv). After 30 min, concentration under reduced pressure and dried under high vacuum gave aldehyde 303 (3.32 g, 100%) as a colourless oil; R\textsubscript{f} 0.59 (50% EtOAc–petrol); δ\textsubscript{H} (400 MHz) 9.79 (1H, s, CHO), 7.39-7.25 (5H, m, Ph), 3.21 (2H, t, J 7.0 Hz, CH\textsubscript{2}CHO), 2.80 (2H, t, J 7.0 Hz, PhSCH\textsubscript{2}); δ\textsubscript{C} (125 MHz) 200.3 (CHO), 135.1 (ipso PhS), 130.0 (ortho PhS), 129.1 (meta PhS), 126.7 (para PhS), 43.3 (CH\textsubscript{2}CHO), 26.4 (CH\textsubscript{2}PhS); m/z (Cl) 184 [M+NH\textsubscript{4}]\textsuperscript{+}, 166, 52; data in agreement with that previously reported.\textsuperscript{138}
(3,3)-Dimethoxypropyl)(phenyl)sulfane\textsuperscript{139} 304

\[
\begin{array}{c}
\text{PhS} \\
\text{PhS} \\
\text{303} \\
\end{array}
\quad \rightarrow \\
\begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{304} \\
\end{array}
\]

The solution of aldehyde 303 (2.90 g, 17.5 mmol, 1.0 equiv), CH(MeO)\textsubscript{3} (3.71 g, 34.9 mmol, 2.0 equiv), p-TsOH⋅H\textsubscript{2}O (100 mg, 0.526 mmol, 0.03 equiv) and MeOH (35 mL) was heated to 50 °C. After 16 h, the resulting solution was concentrated under reduced pressure. Then, EtOH (15 mL) was added to the crude, washed with sat. NaHCO\textsubscript{3(aq.)} (3 × 30 mL), H\textsubscript{2}O (3 × 10 mL), brine (2 × 15 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduced pressure and column chromatography (5% EtOAc–petrol with 1% Et\textsubscript{3}N) gave acetal 304 (3.90 g, 96%) as a colourless oil; R\textsubscript{f} 0.51 (23% Et\textsubscript{2}O–petrol); \( \nu \text{max} \) (film) 3057, 2933, 2830, 1944, 1870, 1724, 1686, 1583, 1400, 1438, 1382, 1366, 1281, 1192, 1160, 1123, 1073 cm\textsuperscript{-1}; \( \delta \text{H} \) (400 MHz) 7.38-7.19 (5H, m, Ph), 4.53 (1H, t, J 5.0 Hz, CH), 3.35 (6H, s, OMe), 2.99 (2H, t, J 7.0 Hz, \text{CH}_{2}\text{Ph}), 1.96 (2H, dt, J 7.0, 5.0 Hz, \text{CH}_{2}\text{CH}); \( \delta \text{C} \) (125 MHz) 136.2 (ipso PhS), 129.2 (ortho PhS), 128.9 (meta PhS), 125.9 (para PhS), 103.2 (CH), 53.2 (OMe), 32.3 (CH\textsubscript{2}PhS), 28.8 (CH\textsubscript{2}CH); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.\textsuperscript{139}
To a solution of acetal 304 (403 mg, 1.90 mmol, 1.3 equiv) in THF (0.7 mL) at −78 °C was added nBuLi (905 µL of a 2.1 M solution in hexanes, 1.90 mmol, 1.3 equiv). After 20 min, it was warmed to 0 °C. After 20 min it was re-cooled to −78 °C, then a solution of vinylaziridine 46 (500 mg, 1.46 mmol, 1.0 equiv) in THF (0.7 mL) was added. The resulting solution was allowed to warm to rt slowly. After 16 h, the reaction was quenched with sat. NaHCO₃(aq.) (10 mL) and the aqueous phase extracted with EtOAc (3 × 7 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (10%→25% EtOAc–petrol) gave a 5:1 diastereomixture of N-[(2R*,3S*)-6,6-Dimethoxy-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhexan-2-yl]-4-methylbenzenesulfonamide 305 (100 mg, 12%) as a gum; data for major diastereomer:

Rf 0.21 (25% EtOAc–petrol); νmax (film) 3277, 2938, 2833, 1161, 1583, 1513, 1439, 1324, 1302, 1248, 1178, 1157, 1124 cm⁻¹; δ_H (400 MHz) 7.69 (2H, d, J 8.0 Hz, ortho Ts), 7.65–7.14 (7H, m, SPh & meta Ts), 6.95 (2H, d, J 8.5 Hz, meta ArOMe), 6.73 (2H, d, J 8.5 Hz, ortho ArOMe), 5.58 (1H, app. dt, J 17.0, 10.0 Hz, CH=CH₂, diagnostic signal of the minor diast.), 5.47 (1H, app. dt, J 17.0, 10.0 Hz, CH=CH₂), 5.18 (1H, dd, J 10.0, 1.5 Hz, trans CH=CHH), 5.01 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH), 4.54 [1H, t, J 5.5 Hz, CH(OMe)₂], 4.42 (1H, d, J 7.5 Hz, NH), 3.92-3.89 (1H, m, CHN), 3.79 (3H, s, ArOMe), 3.54 (1H, dt, J 7.0, 4.0 Hz, CHS), 3.25 (3H, s, MeOCHOMe), 3.23 (3H, s, MeOCHOMe), 2.76 (1H, dd, J 14.0, 6.0 Hz, CHHArOMe), 2.55 (1H, dd, J 14.0, 4.5 Hz, CHHArOMe), 2.44 (3H, s, Me of Ts), 2.30-2.25 (1H, m, CHCH=CH₂), 1.85 (2H, dd, J 7.0, 5.5 Hz, CH₂CHS); δ_C (100.7 MHz) [158.3, 143.2, 137.6, 135.6 (q Ar)], 134.9 (3º Ar), [131.4, 130.9, 129.6, 128.9 (3º Ar), 128.1 (q Ar), 127.2 (3º Ar), 126.9
To a solution of tosamide 305 (16.0 mg, 0.029 mmol, 1.0 equiv) in CH₂Cl₂ (0.6 mL) at −78 °C was added BF₃·Et₂O (0.06 mL, 0.44 mmol, 15.0 equiv). The solution was warmed to rt slowly. After 16 h, sat. NaHCO₃ (aq.) (1.0 mL) was added. The mixture was extracted with CH₂Cl₂ (2 × 2 mL). The combined organic layers were washed with brine and dried (Na₂SO₄). Concentration under reduced pressure and purified by prep–TLC to obtain the major diastereomer of pyridine 307 (10.0 mg, 73%) as a gum; Rf 0.74 (30% EtOAc–petrol); δH (400 MHz) 7.50 (2H, d, J 8.5 Hz, ortho Ts), 7.26–7.23 (5H, m, SPh), 7.05 (2H, d, J 8.5 Hz, meta Ts), 6.75 (1H, d, J 8.5 Hz, meta ArOMe), 6.67 (1H, dd, J 8.5, 2.5 Hz, ortho MeOAr), 6.50 (1H, d, J 2.5 Hz, ortho MeOAr), 5.76 (1H, ddd, J 17.0, 10.5, 8.5 Hz, CH=CH₂), 5.34-5.27 (2H, m, CH=CH₂), 5.07 (1H, m, ArCHN), 4.29-4.27 (1H, m, CHCHN), 3.79 (3H, s, OMe), 2.91-2.84 (1H, m, CHSPh), 2.69-2.56 (3H, m, CH₂ArOMe & CHCH=CH), 2.33 (3H, s, Me of Ts), 2.07-2.00 (2H, m, CH₃CHS); δC (100.7 MHz) [157.9, 143.0 (q Ar)], 137.7 (3⁰), [137.2, 135.9 (q Ar)], 133.6 (3⁰), 131.8 (q Ar), [129.1, 129.0 (3⁰)], 128.8 (3⁰), 127.7 (3⁰), 126.9 (3⁰), 125.5 (q Ar), 119.2 (CH=CH₂), 113.5, 110.5, 55.4 (OMe), [53.8, 53.6 (CHCHN)], 50.1 (PhSCH), 41.1 (CHCH=CH₂), 40.4 (CH₂ArOMe), 25.4 (CH₂CHS), 21.4 (Me of Ts);
m/z (EI) 491 [M]+, 382, 314, 227, 160, 91 (Found: [M]+, 491.1583. C_{28}H_{29}NO_{3}S_{2} requires [M]+, 491.1589).

**Methyl 2-(phenylthio)acetate**

\[ \text{O} \quad \text{Br} \quad + \quad \text{PhSH} \quad \rightarrow \quad \text{O} \quad \text{SPh} \]

To a solution of methyl bromoacetate (8.30 g, 54.4 mmol, 2.0 equiv) and thiophenol 302 (3.00 g, 27.2, 1.0 equiv) in MeOH (7 mL) at 40 °C was added NaOMe (2.20 g, 40.8 mmol, 1.5 equiv). After 2 h, the resulting mixture was cooled to rt and filtered. The filtrate was concentrated under reduced pressure. Distillation under high vacuum gave sulfide ester 309 (9.61 g, 97%) as a colourless oil; R_f 0.47 (15% Et_2O–petrol); \( \nu_{\text{max}} \) (film) 3058, 3002, 2952, 2842, 1743, 1583, 1482, 1437, 1407, 1279, 1194, 1153, 1009, 894, 741, 690 cm^{-1}; \( \delta_H \) (400 MHz) 7.43 (2H, d, J 7.5 Hz, meta Ph), 7.35-7.26 (3H, m, ortho & para Ph), 3.75 (3H, s, CH_3), 3.68 (2H, s, CH_2); \( \delta_C \) (125 MHz) 170.2 (COO), 135.0 (ipso Ph), [129.8, 129.1 (meta & ortho Ph)], 126.9 (para Ph), 52.5 (SCH_2CO), 36.4 (CH_3O); m/z (CI) 279, 217, 200 [M+NH_4]^+, 182 [M+ NH_4–H_2O]^+, 140, 123, 52; data in agreement with that previously reported. \(^{140}\)
(S*)-Methyl 3-[(R*)-2-(4-methoxyphenyl)-1-(4-methylphenylsulfonamido)ethyl]-2-(phenylthio)pent-4-enoate 315

A solution of sulfide ester 309 (64.0 mg, 0.35 mmol, 1.3 equiv) in DMF (0.2 mL) was added dropwise to KH (27 mg, from a 35% mixture in oil washed with petrol three times, 0.673 mmol, 2.6 equiv) at 0°C. After 30 min, a solution of aziridine 46 in DMF (0.8 mL) was added. After 2 h at that temperature, the reaction mixture was heated to 60 °C. After 16 h, the reaction was quenched with MeOH (2 mL). The resulting mixture was concentrated under reduced pressure to remove the excess MeOH, then diluted with EtOAc (3 mL) and brine (5 mL). The organic phase was separated and aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (MgSO₄). Concentration under reduced pressure and column chromatography (10 → 25% EtOAc–petrol) gave a separated 3:1 diastereomeric of (S*)-methyl 3-[(R*)-2-(4-methoxyphenyl)-1-(4-methylphenylsulfonamido)ethyl]-2-(phenylthio)pent-4-enoate 315 (93.0 mg, 68%) as gums;

Data for minor diastereomer: 22 mg, 16%; Rf 0.73 (40% EtOAc–petrol); νmax (film) 3522, 3275, 3061, 2988, 2958, 2836, 1728, 1612, 1584, 1513, 1438, 1326, 1248, 1159, 1091, 1036, 998, 928, 814, 738, 665 cm⁻¹; δH (400 MHz) 7.55 (2H, d, J 8.0 Hz, ortho Ts), 7.38-7.36 (2H, m, meta SPh), 7.27-7.25 (3H, m, ortho & para SPh), 7.17 (2H, d, J 8.0 Hz, meta Ts), 6.81 (2H, d, J 8.5 Hz, meta ArOMe), 6.67 (2H, d, J 8.5 Hz, ortho ArOMe), 5.66 (1H, td, J 17.0, 10.0 Hz, CH=CH₂), 5.40 (1H, dd, J 10.0, 1.5 Hz, trans CH=CHH), 5.14 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH), 4.57 (1H, d, J 8.5 Hz, NH), 3.96 (1H, d, J 11.0 Hz, CHSPh), 3.77 (3H, s, CH₃OOC), 3.70 (1H, m, NCH), 3.64 (3H, s, CH₃OAr), 2.66 (1H, ddd, J 11.5, 11.5, 2.0 Hz, CHCH=CH₂), 2.55 (1H, dd, J 14.0, 8.5 Hz, CHHArOMe), 2.42-2.37 (4H, m, Me of Ts & CHHArOMe); δC (125 MHz) 171.9
(COO), [158.3, 143.2, 137.3 (q Ar)], [133.2, 133.0 (3°)], 132.9 (q Ar), [130.1, 129.9, 128.8 (3°)], 128.4(q Ar), [127.9, 126.9 (3°)], 121.7 (CH=CH2), 113.8 (3°), 55.3, 55.1, 52.1, 51.2, 47.0, 39.2 (CH2), 21.5; m/z (ESI) 548.1555 [M+Na]+, 526.1734 [M+H]+, 469.3163, 208.0410 (Found: [M+Na]+, 526.1734. C28H31O3S2 requires [M+Na]+, 526.1722).

Data for major diastereomer: 71 mg, 52%; Rf 0.65 (40% EtOAc–petrol); νmax (film) 3510, 3273, 3060, 2837,1732, 1612, 1513, 1439, 1326, 1248, 1159, 1048, 1035, 931, 815, 737, 664 cm⁻¹; δH (400 MHz) 7.78 (2H, d, J 8.0 Hz, ortho Ts), 7.29-7.19 (7H, SPh & meta Ts), 6.87 (2H, d, J 8.5 Hz, meta ArOMe), 6.76 (2H, d, J 8.5 Hz, ortho ArOMe), 5.70 (1H, td, J 17.0, 10.0 Hz, CH=CH2), 5.29 (1H, dd, J 10.5, 1.0 Hz, trans CH=CHH), 5.14 (1H, dd, J 17.0, 1.0 Hz, cis CH=CHH), 4.81 (1H, d, J 9.0 Hz, NH), 4.27-4.21 (1H, m, NCH), 3.99 (1H, d, J 11.0 Hz, CHPh), 3.80 (3H, s, CH3OOC), 3.48 (3H, s, CH3OAr), 2.51-2.39 (6H, m, CHCH=CH2 & CH2ArOMe & Me of Ts); δC (125 MHz) 171.7 (COO), [158.4, 143.5, 137.3 (q Ar)], [133.5, 132.6 (3°)], 131.9 (q Ar), [130.1, 129.7 (3°)], 129.4 (q Ar), [128.7, 128.1, 127.2 (3°)], 121.8 (CH=CH2), 114.1 (3°), 55.2, 54.6, 52.0, 51.7, 45.6, 39.2 (CH2), 21.5; m/z (ESI) 548.1540 [M+Na]+, 526.1730 [M+H]+, 494.1479, 344.1046 (Found: [M+Na]+, 526.1730. C28H31O3S2 requires [M+Na]+, 526.1722).

Phenyl(prop-2-ynyl)sulfane

To a solution of sodium hydroxide (5.72 g, 143 mmol, 1.7 equiv) in H2O (70 mL) at rt was added thiophenol 302 (9.26 g, 84.1 mmol, 1.0 equiv). After 40 min, it was cooled to 0 °C and a solution of propargylic bromide 325 (15.0 g, 126 mmol, 1.5 equiv) in benzene (100 mL) added dropwise followed by tetra-nbutylammonia bromide (4.19 g, 13.0 mmol, 0.15 equiv). After 2.5 h vigorously stirring, the reaction was diluted with H2O (50 mL). The organic phase was separated, washed with H2O (2 × 20 mL), brine (2 × 30 mL) and dried (MgSO4). Concentration under reduced pressure and distillation (105 °C at 7 mmHg) gave propargylic sulfide 316 (10.7 g, 85%) as a colourless oil; Rf
0.42 (100% petrol); \( \nu_{\text{max}} \) (film) 3292, 3058, 3019, 2947, 2914, 2118, 1949, 1878, 1670, 1585, 1480, 1438, 1407, 1299, 1233, 1086, 1025, 740, 689, 643 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz) 7.48 (2H, d, \( J \) 7.5 Hz, ortho SPh), 7.38-7.26 (3H, m, meta & para SPh), 3.64 (2H, d, \( J \) 2.5 Hz, CH\(_2\)), 2.27 (1H, t, \( J \) 2.5 Hz, CH); \( \delta_{\text{C}} \) (125 MHz) 135.0 (q Ph), 130.0 (ortho Ph), 129.0 (meta Ph), 127.0 (para Ph), 79.9 (CHC), 71 (CHC), 22.6 (CH\(_2\)); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.\(^{148}\)

\[ \text{N-}[(2R^*,3S^*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 317] \]

To a solution of propargylic sulfide 316 (1.25 g, 8.4 mmol, 1.2 equiv) in THF (9 mL) at −78 °C was added \( n \)BuLi (6.72 mL of a 2.5 M solution in hexanes, 16.8 mmol, 2.4 equiv) dropwise. It was warmed to −30 °C over a period of 1.5 h then re-cooled to −78 °C. A solution of aziridine 46 (2.30 g, 6.7 mmol, 1.0 equiv) in THF (5.0 mL) was added via cannula. The resulting red solution was warmed to 5 °C over a period of 3 h then to rt. After 30 min, it was cooled to 0 °C, quenched with sat. \( \text{NH}_4\text{Cl(aq.)} \) (19 mL) then diluted with \( \text{H}_2\text{O} \) (10 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (\( \text{Na}_2\text{SO}_4 \)). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave a 3:1 diastereomeric mixture of \( \text{N-}[(2R^*,3S^*)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 317 \) (2.50 g, 76%) as a solid; \( R_f \) 0.42 (25% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3285, 2925, 1731, 1612, 1512, 1439, 1326, 1303, 1248, 1158, 1081, 1034, 927, 815, 742, 691, 663 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz) 7.78 (2H, d, \( J \) 8.0 Hz, ortho Ts, minor...
diast.), 7.73 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.36-7.21 (2 × 7H, m, SPh & meta Ts, 2 × diast.), 6.98 (2H, d, J 8.5 Hz, meta ArOMe, minor diast.), 6.89 (2H, d, J 8.5 Hz, meta ArOMe, major diast.), 6.78-6.72 (2 × 2H, m, ortho ArOMe, 2 × diast.), 5.73-5.61 (2 × 1H, m, CH=CH₂, 2 × diast.), 5.44-5.38 (2 × 1H, m, trans CH=CHH, 2 × diast.), 5.15 (1H, dd, J 17.0, 1.0 Hz, cis CH=CHH, major diast.), 5.13 (1H, dd, J 17.0, 1.0 Hz, cis CH=CHH, minor diast.), 4.69-4.59 (2 × 1H, m, NH, 2 × diast.), 4.14-3.91 (2 × 2H, m, NCH & CHSPh, 2 × diast.), 3.82 (3H, s, Me of ArOMe, minor diast.), 3.79 (3H, s, Me of ArOMe, major diast.), 2.79-2.52 (2 × 3H, m, CHCH=CH₂ & CH₂ArOMe, 2 × diast.), 2.44 (3H, s, Me of Ts, minor diast.), 2.41 (3H, s, Me of Ts, major diast.), 2.37 (1H, d, J 2.0 Hz, CHCCHSPh, major diast.), 2.32 (1H, d, J 2.5 Hz, CHCCHSPh, minor diast.); δC (125 MHz) [158.5, 158.3, 143.6, 143.4 (q Ar, 2 × diast.)], 137.5, 134.2, 133.6, 133.3, 133.2, 132.9, 132.2, 130.1, 130.4, 130.1, 129.7, 129.6, 129.5, 128.9, 128.7, 128.2, 127.4, 127.3, 126.9, [121.6, 121.4 (CH=CH₂, 2 × diast.)], 114.1, 113.9, 89.6, 82.8, 74.6, 73.6, 56.8, 56.4, 55.8, 55.2, 51.6, 49.6, 40.4, 39.8, 39.7, 39.6, 21.9, 21.6; m/z (ESI) 514.1473 [M+Na]^+, 492.1661 [M+H]^+ (Found: [M+H]^+, 492.1661. C_{28}H_{29}NO_{3}S_{2} requires [M+H]^+, 492.1667).

**N-[(2R*,3S*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-N,4-dimethylbenzenesulfonamide 384**

![Diagram](image_url)

To a mixture of tosamides 317 (100 mg, 0.204 mmol, 1.0 equiv), tBuOK (23.0 mg, 0.204 mmol, 1.0 equiv) and MeI (17 µL, 1.23 mmol, 6.0 equiv) at rt was added tBuOH (1.0 mL). After 16 h, the reaction mixture was heated to 60 °C. After 1.5 h, concentration under reduced pressure, the crude product was diluted with H₂O (5 mL), extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine.
(2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→20% EtOAc–petrol) gave a 2:1 diastereomeric mixture of N-[(2R*,3S*)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-N,4-dimethylbenzenesulfonamide 384 (70 mg, 68%) as a solid; Rₗ 0.43 (25% EtOAc–petrol); νmax (film) 3286, 2924, 1611, 1513, 1439, 1334, 1304, 1247, 1157, 1088, 1034, 931, 815 cm⁻¹; δH (400 MHz) 7.52-7.46 (2 × 4H, m, ortho Ts & meta SPh, 2 × diast.), 7.37-7.27 (2 × 5H, m, ortho & para SPh & meta Ts, 2 × diast.), 6.98-6.93 (2 × 2H, m, meta ArOMe, 2 × diast.), 6.76-6.72 (2 × 2H, m, ortho ArOMe, 2 × diast.), 5.93-5.78 (2 × 1H, m, CH=CH₂, 2 × diast.), 5.28 (1H, dd, J 10.0, 1.5 Hz, trans CH=CHH, major diast.), 5.25 (1H, dd, J 11.0, 1.5 Hz, trans CH=CHH, minor diast.), 5.19 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH, major diast.), 5.18 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH, minor diast.), 4.74 (1H, q, J 7.5 Hz, NCH, major diast.), 4.68 (1H, q, J 7.5 Hz, NCH, minor diast.), 4.15 (1H, dd, J 7.5, 2.5 Hz, CHSPh, major diast.), 4.06 (1H, dd, J 5.5, 2.5 Hz, CHSPh, minor diast.), 3.81 (3H, s, OMe, minor diast.), 3.79 (3H, s, OMe, major diast.), 2.83-2.73 (2 × 4H, m, NMe & CHCH=CH₂, 2 × diast.), 2.58-2.37 (2 × 6H, m, Me of Ts & CH₂ArOMe & CHCHSPh, 2 × diast.); δC (100 MHz) [158.5, 158.4, 142.9, 142.8, 136.8, 136.4 (q Ar, 2 × diast.), 135.0, 134.7, [134.1, 133.7 (q Ar, 2 × diast.)], 132.9, 132.0, 130.2, 130.1, 129.5, 129.4, 128.8, 127.8, 127.4, 127.2, [119.6, 119.6 (2 × CH=CH₂, 2 × diast.),] 114.1, 114.0, 113.9, 83.1, 81.1, 74.8, 73.2, 65.9, 60.3, 59.8, 55.2, 51.3, 50.7, 41.0, 40.7, 35.9, 35.6, 30.7, 30.1, 22.0, 21.5; m/z (ESI) 528.1654 [M+NH₄]⁺, 506.1837 [M+H]⁺, 318.1166, 224.0127, 196.0175 (Found: [M+H]⁺, 506.1824. C₂₀H₃₁NO₃S₂ requires [M+H]⁺, 506.1824).
To a solution of diastereomers (68.0 mg, 0.138 mmol, 1.0 equiv) in MeOH (6 mL) at rt was added K$_2$CO$_3$ (227 mg, 1.60 mmol, 11.6 equiv). The mixture was then heated to 50 °C. After 16 h, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure. Water (5 mL) was added and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na$_2$SO$_4$). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave a 3:1 mixture of 335 and 336 (68.0 mg, 100%) as a gum. Upon standing in CDCl$_3$ in an NMR tube for 48 h, 335 isomerised to 336 (68.0 mg, 100%) as a gum; $R_f$ 0.76 (25% EtOAc–petrol); $\nu_{\text{max}}$ (film) 2925, 1612, 1582, 1512, 1439, 1354, 1247, 1167, 1089, 1035, 815 cm$^{-1}$; $\delta_H$ (400 MHz) 7.67 (2H, $d$, J 8.5 Hz ortho O Ts), 7.34 (2H, $d$, J 8.5 Hz meta O Ts), 7.17 (2H, $d$, J 8.5 Hz meta ArOMe), 7.08-7.07 (3H, m, ortho & para SPh), 6.84 (2H, $d$, J 8.5 Hz ortho ArOMe), 6.74-6.72 (3H, m, meta SPh), 5.60 (1H, $dt$, J 17.0, 10.0 Hz, $CH=CH_2$), 5.00 (1H, $dd$, J 10.0, 1.5 Hz, trans CH=CHH), 4.74 (1H, $ddd$, J 17.0, 1.5, 1.0 Hz, cis CH=CHH), 4.51 (1H, $dd$, J 6.0, 1.5 Hz, CHNTs), 3.80 (3H, s, OMe), 3.30 (1H, $dt$, J 10.0, 1.5 Hz, $CHCH=CH_2$), 2.91 (2H, $d$, J 6.0 Hz, $CH_2$ArOMe), 2.49 (3H s, Me of Ts), 2.25 (3H, d, J 2.5 Hz, CH$_3$CNTs); $\delta_C$ (100 MHz) 158.1, 145.4, 143.9, 136.2, 135.0 (4°), 133.7 (CH=CH$_2$), 130.9, 129.9, 128.6, 127.5, 127.3 (3° Ar), 125.6 (3°), 120.0 (CH=CH$_2$), 118.6 (4°), 113.8, 113.4, 67.1 (CHNTs), 55.2 (OMe), 51.8 (CHCH=CH$_2$), 36.4 (CH$_2$ArOMe), 21.7 (Me of Ts), 15.2 (CH$_3$CNTs); $m/z$ (ESI) 514.1487 [M+Na]$^+$, 492.1678 [M+H]$^+$, 337.1508 (Found: [M+Na]$^+$, 514.1495; [M+H]$^+$, 492.1678. C$_{28}$H$_{20}$NO$_3$S$_2$ requires [M+Na]$^+$, 514.1487; [M+H]$^+$, 492.1667).
N-[(2R*,3R*,E)-1-(4-Methoxyphenyl)-6-oxo-3-vinylhex-4-en-2-yl]-4-methyl-
Benzenesulfonamide 339

To a solution of tosamides 317 (1.47 g, 2.99 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) at rt
was added a solution of mCPBA (1.07 g of a 53% mixture of m-chlorobenzoic acid and
H₂O, 3.29 mmol, 1.1 equiv) in CH₂Cl₂ (5 mL). After 16 h, concentration under reduced
pressure and column chromatography (20% EtOAc–petrol) gave N-[(2R*,3R*,E)-1-(4-
methoxyphenyl)-6-oxo-3-vinylhex-4-en-2-yl]-4-methylbenzen-
sulfonamide 339 (622 mg, 52%) as a gum; R_f 0.21 (25% EtOAc–petrol); νmax (film)
3275, 2923, 1687, 1612, 1513, 1442, 1324, 1303, 1248, 1158, 1093, 1034, 814 cm⁻¹; δ_H
(400 MHz) 9.37 (1H, d, J 8.0 Hz, CHO), 7.60 (2H, d, J 8.0 Hz, ortho Ts), 7.23 (2H, d, J
8.0 Hz, meta Ts), 6.89 (2H, d, J 8.5 Hz, meta ArOMe), 6.75-6.69 (3H, m, ortho ArOMe
& CHOCH=CH), 6.03 (1H, ddd, J 16.0, 8.0, 1.5 Hz, CHOCH=CH), 5.77 (1H, ddd, J
17.0, 10.5, 8.0 Hz, CH=CH₂), 5.37 (1H, d, J 10.5 Hz, trans CH=CHH), 5.21 (1H, d, J
17.0 Hz, cis CH=CHH), 4.43 (1H, d, J 8.0 Hz, NH), 3.80 (3H, s, OMe), 3.59-3.53 (1H,
m, NCH), 3.28-3.24 (1H, m, CHCH=CH₂), 2.73 (1H, dd, J 14.0, 7.5 Hz, CHHArOMe),
2.54 (1H, dd, J 14.0, 7.0 Hz, CHHArOMe), 2.44 (3H, s, Me of Ts); δ_C (125 MHz) 193.4
(CHO), 158.6 (q Ar), 155.7, [143.6, 139.9 (q Ar)], 134.1, 132.9, 129.9, 129.6, 128.2 (q
Ar), 128.1, 121.3 (CH=CH₂), 114.1, 58.5, 55.1, 48.9, 37.9 (CH₂), 21.5, 15.3; m/z (ESI)
(Found: [M+H]⁺, 400.1585. C₂₂H₂₅NO₄S requires [M+H]⁺, 400.1583) (Found: C, 66.20;
H, 6.30; N, 3.50. C₂₂H₂₃NO₄S requires C, 66.14; H, 6.31; N, 3.51%).
To a solution of enal 339 (244 mg, 0.561 mmol, 1.0 equiv) in CH₂Cl₂ (2.3 mL) at 0 °C was added thiophenol (173 µL, 1.68 mmol, 3.0 equiv) and Et₃N (391 µL, 2.80 mmol, 5.0 equiv). The solution was then warmed to rt gradually. After 16 h, TLC showed complete conversion of enal to piperidinol 341. The mixture was cooled to −20 °C followed by addition of Et₃N (391 µL, 2.80 mmol, 5.0 equiv) and mesylchloride (434 µL, 5.61 mmol, 10.0 equiv). After 2 h, concentration under reduced pressure and column chromatography (5% EtOAc–petrol) gave a 2:1 diastereomeric mixture of \((2R^*,3S^*)\)-2-(4-methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 299 (182 mg, 66%) as a solid; Rf 0.47 (18% EtOAc–petrol); \(\nu_{\text{max}}\) (film) 2930, 1721, 1640, 1612, 1512, 1440, 1353, 1302, 1247, 1165, 1091, 1035, 991, 927, 815, 749, 675 cm⁻¹; \(\delta_H\) (400 MHz) 7.57 (2H, d, J 8.5 Hz, ortho Ts, minor diast.), 7.48 (2H, d, J 8.5 Hz, ortho Ts, major diast.), 7.41-7.24 [(2 × 5H, m, SPh, 2 × diast.) & (2H, meta Ts, minor diast.)], 7.19 (2H, d, J 8.5 Hz, meta Ts, major diast.), 7.14 (2H, d, J 8.5 Hz, meta ArOMe, minor diast.), 7.08 (2H, d, J 8.5 Hz, meta ArOMe, major diast.), 6.88-6.82 (2 × 2H, d, J 8.5 Hz, ortho ArOMe, 2 × diast.), 6.65-6.12 (2 × 1H, m, CH=CHNTs, 2 × diast.), 5.70 (1H, ddd, J 17.5, 10.5, 8.0 Hz, CH=CH₂ major diast.), 5.49-5.43 (1H, m, CH=CH₂ minor diast.), 5.28-5.22 [(2 × 1H, m, CH=CHNTs, 2 × diast.) & (1H, m, trans CH=CHH, major diast.)], 5.16 (1H, dd, J 10.5, 1.5 Hz, trans CH=CHH, minor diast.), 4.99-4.92 (2 × 1H, m, cis CH=CHH, 2 × diast.), 4.09-4.03 (2 × 1H, m, NTsCHCH₂, 2 × diast.), 3.83 (3H, s, OMe, minor diast.), 3.82 (3H, s, OMe, major diast.), 3.55-3.48 (2 × 1H, m, CHSPh, 2 × diast.), [2.98-2.85 & 2.78-2.65 (2 × 2H, m, CH₂ArOMe, 2 × diast.), 2.44 (3H, s, Me of Ts, major diast.), 2.43 (3H, s, Me of Ts, minor diast.), 1.73-1.68 (2 × 1H, m, CHCH=CH₂, 2 × diast.); \(\delta_C\) (125 MHz) (major
diast.) [158.3, 143.4 (q Ar)], 137.4, 135.7 (q Ar), 133.7 (3° Ar), 132.0 (q Ar), [130.6, 129.7 (3° Ar)], 129.6 (q Ar), 128.7 (3° Ar), 127.7, 126.8 (3° Ar), 124.2, 118.7 (CH=CH₂), 113.6 (3° Ar), 112.1, 60.9, 55.1, 43.9, 42.9, 32.4 (CH₂ArOMe), 21.6; m/z (ESI) 555.1768, 530.1248, 514.1501 [M+Na]⁺, 509.1948, 492.1668 [M+H]⁺, 382.1476 (Found: [M+H]⁺, 514.1668. C₂₈H₂₉NO₅S₂ requires [M+H]⁺, 492.1667).

(2R*,3S*)-2-(4-Methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinylpiperidine 385

To a solution of tetrahydropyridines 299 (70.0 mg, 0.143 mmol, 1.0 equiv) in CH₂Cl₂ (0.5 mL) at rt were added Et₃SiH (36.5 mg, 0.314 mmol, 2.2 equiv) and TFA (36.0 mg, 0.314 mmol, 2.2 equiv). After 16 h, further amounts of Et₃SiH (36.5 mg, 0.314 mmol, 2.2 equiv) and TFA (36.0 mg, 0.314 mmol, 2.2 equiv) were added. After 3 h, concentration under reduced pressure and column chromatography (8% EtOAc–petrol) gave (2R*,3S*)-2-(4-methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinylpiperidines 385 (54 mg, 77%) as a gum; data for major diastereomer only: Rf 0.44 (18% EtOAc–petrol); νmax (film) 2926, 1725, 1677, 1611, 1512, 1440, 1320, 1247, 1154, 1093, 1034, 814 cm⁻¹; δH (400 MHz) 7.45-7.41 (3H, m, SPh), 7.33-7.31 (2H, m, SPh), 7.18 (2H, d, J 8.0 Hz, ortho Ts), 7.03 (2H, d, J 8.0 Hz, meta Ts), 6.96 (2H, d, J 8.5 Hz, meta ArOMe), 6.73 (2H, d, J 8.5 Hz, ortho ArOMe), 5.87 (1H, ddd, J 18.5, 9.5, 9.5 Hz, CH=CH₂), 5.68-5.59 (1H, m, CH=CH₂, diagnostic signal of the minor diast.), 5.35-5.31 (2H, m, CH=CH₂), 4.38 (1H, ddd, J 11.0, 4.5 Hz, NTsCH), 3.81 (3H, s, OMe), 3.69-3.64 (1H, m, CHSPh), 3.34-3.25 (1H, m, CHHNTs), 3.13-3.05 (1H, m, CHHNTs), 2.88 (1H, dd, J 14.0, 4.0 Hz, CHHArOMe), 2.74 (1H, dd, J 14.0, 11.5 Hz, CHHArOMe), 2.61-2.54 (1H, m, CHCH=CH₂), 2.38 (3H, s, Me of Ts), 1.71-1.54 (2H, m, CH₂CHSPh); δC (125 MHz) [158.3, 142.6, 137.9, 137.5 (q Ar)], 134.1 (3° Ar), [132.7, 130.1 (q Ar), [129.9,
129.3, 128.9 (3° Ar), 127.8 (CH=CH₂), 127.1 (3° Ar), 118.6 (CH=CH₂), 113.8 (3° Ar), 60.8 (OMe), 55.2 (CHNTs), 49.5, 44.9, 40.2, 32.8, 30.7, 29.7, 21.5; m/z (ESI) 516.1662 [M+Na]⁺, 494.1827 [M+H]⁺, 406.1471, 384.1657 (Found: [M+H]⁺, 494.1827. C₂₈H₃₁NO₃S₂ requires [M+H]⁺, 494.1824).

(S)-Ethyl 2-((tert-butyldiphenylsilyloxy)propanoate¹⁶⁶ 348

![Chemical Structure](image)

To a solution of ethyl-L-lactate 347 (250 mg, 2.12 mmol, 1.0 equiv) and DMAP (38.9 mg, 0.318 mmol, 0.15 equiv) in CH₂Cl₂ at 0 °C was added TBDPSCl (1.05 g, 3.81 mmol, 1.8 equiv) followed by Et₃N (697 mg, 5.30 mmol, 2.5 equiv). The cloudy suspension was warmed to rt then heated to 50 °C. After 16 h, the reaction was quenched with sat. NH₄Cl(aq.) (1 mL) then diluted with sat. NaHCO₃(aq.) (4 mL). After 5 min, the mixture was further diluted with H₂O (3 mL) and the aqueous phase extracted with Et₂O (3 × 8 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→15% Et₂O–petrol) gave ester 348 (739 mg, 98%) as a colourless liquid; Rf 0.63 (5% EtOAc–petrol); [α]D²⁰−41.5 (c 2.0, CHCl₃); [Lit.¹⁶⁶a [α]D²⁰−41.1 (c 2.0, CHCl₃)]; νmax (film) 3071, 3050, 2932, 2894, 2858, 1753, 1734, 1589, 1473, 1428, 1372, 1273, 1195, 1137, 1111, 1060, 1023, 974, 822, 739, 702, 611 cm⁻¹; δH (400 MHz) 7.72-7.67 (4H, m, ortho Ph), 7.45-7.36 (6H, m, meta & para Ph), 4.29 (1H, q, J 7.0 Hz, CHOTBDPS), 4.04 (1H, dq, J 7.0, 1.0 Hz, CH₂), 1.39 (3H, d, J 7.0 Hz, CH₃CH), 1.17 (3H, d, J 7.0 Hz, CH₃CH₂), 1.12 (9H, s, tBu); δC (125 MHz) 173.7 (COO), 135.8, 133.6, 129.7, 127.6, 68.9 (CHOTBDPS), 60.6 (CH₂), 26.8 (Me of tBu), 21.3, 19.3, 14.1; data in agreement with that previously reported.¹⁶⁶
(S)-2-(tert-Butyldiphenylsilyloxy)propanal\textsuperscript{165} \textit{346}

\[
\begin{align*}
\text{OEt} & \quad \rightarrow \quad \text{OH} \\
\text{OTBDPS} & \quad \text{OTBDPS}
\end{align*}
\]

To a solution of ester \textit{348} (100 mg, 0.28 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} at \(-78 \, ^\circ\text{C}\) was added DIBAL-H (322 µL of a 1.0 M solution in CH\textsubscript{2}Cl\textsubscript{2}, 0.322 mmol, 1.15 equiv) dropwise. After 50 min, MeOH (0.07 mL) was added to the solution, then Et\textsubscript{2}O (1.2 mL) slowly, followed by Na/K tartrate (0.9 mL), Et\textsubscript{2}O (2.2 mL). After 5 min, the mixture was warmed to rt. After 90 min, brine (2 mL) was added to the mixture. The organic layer was then separated and dried (Na\textsubscript{2}SO\textsubscript{4}). Following concentration under reduce pressure, the crude product was azotroped with toluene three times. Further drying under high vacuum cleanly gave aldehyde \textit{346} (76 mg, 87\%) as a colourless liquid; R\textsubscript{f} 0.31 (25\% EtOAc–petrol); [\textgreek{a}]\textsubscript{D}\textsuperscript{20} –10.2 (c 1.2, ethanol); \{Lit.\textsuperscript{166b} [\textgreek{a}]\textsubscript{D}\textsuperscript{20} –10.2 (c 1.2, ethanol)\}; \textgreek{d}\textsubscript{H} (400 MHz) 9.67 (1H, d, J 1.0 Hz, CHO), 7.69-7.66 (4H, m, \textit{ortho} Ph), 7.49-7.39 (6H, m, \textit{meta} & \textit{para} Ph), 4.12 (1H, dq, J 7.0, 1.0 Hz, CH\textsubscript{OTBDPS}), 1.25 (3H, d, J 7.0 Hz, CH\textsubscript{3}CH), 1.14 (9H, s, tBu); \textgreek{d}\textsubscript{C} (125 MHz) 203.9 (CHO), 135.7, 132.9, 130.0, 127.8, 74.4 (CH\textsubscript{OTBDPS}), 26.9 (Me of tBu), 19.2, 18.4; data in agreement with that previously reported.\textsuperscript{165}
**N-[(2R*,3S*)-6-Iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 326**

To a solution of tosamides 317 (118 mg, 0.240 mmol, 1.0 equiv) in DMF (0.9 mL) at rt was added NIS (60.0 mg, 0.27 mmol, 1.22 equiv) and AgNO₃ (20.1 mg, 0.12 mmol, 0.5 equiv). After 16 h, the yellow mixture was quenched with sat. NH₄Cl (aq.) (0.8 mL), diluted with H₂O (2 mL) and Et₂O (5 mL). The organic phase was separated and the aqueous phase was extracted with Et₂O (3 × 8 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave 2:1 diastereomeric mixture of **N-[(2R*,3S*)-6-iido-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 326** (111 mg, 75%) as a solid; Rf 0.41 (25% EtOAc–petrol); νmax (film) 3274, 2931, 1710, 1611, 1513, 1439, 1325, 1303, 1248, 1158, 1092, 1035, 927, 814 cm⁻¹; δH (400 MHz) 7.80 (2H, d, J 8.0 Hz, ortho Ts of minor diast.), 7.75 (2H, d, J 8.0 Hz, ortho Ts of major diast.), 7.42-7.14 (2 × 7H, m, SPh & meta Ts, 2 × diast.), 6.89 (2H, d, J 8.5 Hz, meta ArOMe of minor diast.), 6.86 (2H, d, J 8.5 Hz, meta ArOMe of major diast.), 6.79-6.75 (2 × 2H, m, ortho ArOMe, 2 × diast.), 5.68-5.45 (2 × 1H, m, CH=CH₂), 5.40 (1H, dd, J 10.5, 1.5 Hz, trans CH=CHH, major diast.), 5.34 (1H, dd, J 10.5, 1.5 Hz, trans CH=CHH, minor diast.), 5.16-5.09 (2 × 1H, m, cis CH=CH/H, 2 × diast.), 4.60-4.56 (2 × 1H, m, NH, 2 × diast.), 4.06-4.97 (2 × 2H, m, CHNHTs & CHSPh, 2 × diast.), 3.83 (3H, s, OMe, minor diast.), 3.82 (3H, s, OMe, major diast.), 2.71-2.54 (2 × 2H, m, CH₂ArOMe, 2 × diast.), 2.46 (3H, s, Me of Ts, minor diast.), 2.44 (3H, s, Me of Ts, major diast.), 2.30-2.21 (2 × 1H, m, CHCH=CH₂, 2 × diast.); δC (100 MHz) [158.4, 158.3, 143.6, 143.5, 137.1, 136.9 (q Ar, 2 × diast.)], 134.9, 133.8, 133.3, 133.1, 132.7, 131.7, 130.4, 130.1, 130.0, 129.8, 129.7, 129.5, 129.4, 127.6, 127.5, 127.4, 127.2, 127.1, 121.7, 121.6, 114.1, 113.8, 92.8
(C–I, major diast.), 91.9 (C–I, minor diast.), 67.2 (CCHSPh, minor diast.), 65.9 (CCHSPh, major diast.), 56.3, 55.6, 55.2, 55.2, 49.5, 48.6, 42.2, 41.9, 39.7, 38.7, 21.6, 21.6; m/z (ESI) 681.0728, 656.0203, 640.0463 [M+Na]+, 618.0645 [M+H]+ (Found: [M+Na]+, 640.0463; [M+H]+, 618.0645. C_{28}H_{28}INO_{3}S_{2} requires [M+Na]+, 640.0453; [M+H]+, 618.0634).

\[ \text{N-}[\text{2R}^*,\text{3S}^*,\text{Z}]-\text{6-Iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 327} \]

\[
\begin{align*}
\text{326} & \quad \text{TsHN} \\
\text{327} & \quad \text{TsHN}
\end{align*}
\]

To a mixture of alkynl iodide 326 (70.0 mg, 0.113 mmol, 1.0 equiv) and dipotassium azodicarboxylate (42.0 mg, 0.216 mmol, 1.9 equiv) in dioxane (1.5 mL) and iPrOH (1.0 mL) at rt was added a solution of AcOH (34.0 mg, 0.565 mmol, 5.0 equiv) in iPrOH (0.3 mL) dropwise over 15 min. After 1 h, potassium azodicarboxylate (35.0 mg, 0.180 mmol, 1.6 equiv) was added followed by another solution of AcOH (34.0 mg, 0.565 mmol, 5.0 equiv) in iPrOH (0.3 mL). This procedure was repeated after 1 h. The mixture was stirred for 16 h and was then quenched with 1 M HCl (0.7 mL) and diluted with Et₂O (15 mL) and H₂O (20 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (10% EtOAc–petrol) gave a 2:1 diastereomeric mixture of N-\[\text{[2R}^*,\text{3S}^*,\text{Z}]-\text{6-Iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 327} \] (62.0 mg, 88%) as a solid; Rf 0.61 (25% EtOAc–petrol); ν\text{max} (film) 3059, 2957, 1654, 1654, 1512, 1465, 1337, 1247, 1159, 1094, 1037, 904, 812 cm\(^{-1}\); δ\text{H} (400 MHz) 7.87 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 7.64 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.59 (2H, d, J 8.0 Hz, meta Ts, minor diast.), 7.41 (2H, d, J
8.0 Hz, *meta* Ts, major diast.), 7.33-7.15 (2 × 3H, m, SPh, 2 × diast.), 6.99 (2H, d, J 8.5 Hz, *meta* ArOMe, minor diast.), 6.96 (2H, d, J 8.5 Hz, *meta* ArOMe, major diast.), 6.89-6.82 (2 × 2H, m, SPh, 2 × diast.), 6.72 (2H, d, J 8.5 Hz, *ortho* ArOMe, major diast.), 6.68 (2H, d, J 8.5 Hz, *ortho* ArOMe, minor diast.), 6.27 (1H, d, J 7.5 Hz, ICH=CH, major diast.), 6.23 (1H, d, J 7.5 Hz, ICH=CH, minor diast.), 6.19-6.13 (2 × 1H, m, ICH=CH, 2 × diast.), 5.75-5.64 (1H, m, CH=CH₂ major diast.), 5.54 (1H, ddd, J 17.0, 10.0, 8.5 Hz, CH=CH₂ minor diast.), 5.30 (1H, dd, J 10.0, 1.5 Hz, *trans* CH=CH₂, major diast.), 5.28 (1H, dd, J 10.0, 1.5 Hz, *trans* CH=CH₂, minor diast.), 5.15 (1H, dd, J 17.0, 1.0 Hz, *cis* CH=CH₂, major diast.), 5.06 (1H, dd, J 17.0, 1.0 Hz, *cis* CH=CH₂, minor diast.), 4.45 (1H, d, J 10.0 Hz, NH, minor diast.), 4.33 (1H, d, J 8.5 Hz, NH, major diast.), 4.15-3.99 (2 × 1H, m, NTsCH, 2 × diast.), 3.84-3.78 (2 × 4H, m, OMe & CHSPh, 2 × diast.), 2.81-2.53 (2 × 2H, m, CH₂ArOMe, 2 × diast.), 2.44-2.43 (2 × 3H, m, Me of Ts, 2 × diast.), 2.33-2.28 (1H, m, CHCH=CH₂, major diast.), 2.01-1.97 (1H, m, CHCH=CH₂, minor diast.); δC (100 MHz) 158.4, 158.4, 143.5, 143.2, 140.4, 140.3, 137.6, 137.6, 135.5, 134.9, 134.6, 134.4, 133.8, 130.5, 130.4, 130.0, 129.8, 129.6, 128.8, 128.7, 128.6, 128.1, 127.8, 127.4, 127.1, 127.1, 121.1, 120.7, 114.1, 113.9, [83.7, 83.6 CH=CHI, 2 × diast.], 56.9, 55.9, 55.2, 55.2, 49.8, 48.0, 46.0, 39.2, 37.6, 23.7, 21.6, 21.6; *m/z* (ESI) 683.0884, 658.0369, 642.0631 [M+Na]⁺, 620.0798 [M+H]⁺, 518.1794 (Found: [M+Na]⁺, 642.0631; [M+H]⁺, 620.0790. C₂₈H₃₀INO₃S₂ requires [M+Na]⁺, 642.0610; [M+H]⁺, 620.0798).
To a solution of acetal 185 (3.25 g, 12.6 mmol, 1.5 equiv) in THF (36 mL) at −78 °C was added nBuLi (5.50 mL of a 2.29 M solution in hexanes, 12.6 mmol, 1.5 equiv). The resulting red solution was warmed to −30 °C over 40 min. A solution of vinylaziridine 46 (2.90 g, 8.4 mmol, 1.0 equiv) in THF (3.5 mL) was added via cannula. The solution was warmed to rt gradually. After 16 h, the reaction was quenched with sat. NaHCO₃ (aq.) (60 mL) and diluted with H₂O (50 mL) and EtOAc (20 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (25→40% EtOAc–petrol) gave a 2:1 diastereomeric mixture of *N*-(2R*,3S*)-6,6-dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methylbenzenesulfonamide 191 (3.20 g, 63.4%) as a solid; *R*₇ 0.32 (40% EtOAc–petrol); νₘₐₓ (film) 3273, 2937, 1602, 1512, 1447, 1294, 1248, 1156, 1083, 928, 816, 664 cm⁻¹; δ_H (400 MHz) 7.76-7.21 (2 × 2H, m, ortho Ts, 2 × diast.), 7.52 (2 × 2H, m, ortho Ts, 2 × diast.), 7.30-7.23 (4 × 2H, m, meta Ts, 2 × diast.), 7.03 (2H, d, J 8.5 Hz, meta ArOMe, minor diast.), 6.84 (2H, d, J 8.5 Hz, meta ArOMe, major diast.), 6.78 (2H, d, J 8.5 Hz, ortho ArOMe, minor diast.), 6.71 (2H, d, J 8.5 Hz, ortho ArOMe, major diast.), 5.78 (1H, dt, J 17.0, 10.0 Hz, CH=CH₂, minor diast.), 5.66 (1H, dt, J 17.0, 10.0 Hz, CH=CH₂, major diast.), 5.34 (1H, dd, J 10.0, 1.5 Hz, trans CH=CHH, major diast.), 5.24 (1H, dd, J 10.0, 1.5 Hz, trans CH=CHH, minor diast.), 5.04 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH, minor diast.), 4.98 (1H, dd, J 17.0, 1.5 Hz, cis CH=CHH, minor diast.), 4.97 (1H, d, J 7.5 Hz, NH, minor diast.), 4.77 (1H, d, J 7.5 Hz, NH, major diast.), 4.26 [1H, t, J 5.5 Hz, CH(OMe)₂, major diast.], 4.18-4.13 (2H, m, CH(OMe)₂ & CHN, minor diast.), 3.99-3.93 (1H, dq, J 7.5,
3.0 Hz, CHN, major diast.), 3.82 (3H, s, Me of ArOMe, minor diast.), 3.81 (3H, s, Me of ArOMe, major diast.), 3.65 (1H, dt, 11.0, 6.0 Hz, CHTs, major diast.), 3.47-3.43 (1H, m, CHTs, minor diast.), 3.33 [3H, s, CH(OMe)₂, major diast.], 3.29 [3H, s, CH(OMe)₂, major diast.], 3.16 [3H, s, CH(OMe)₂, minor diast.], 3.08 [3H, s, CH(OMe)₂, minor diast.], 2.86 (1H, dd, J 14.0, 4.5 Hz, CHHArOMe, minor diast.), 2.81-2.71 (2 × 1H, m, CHCH=CH₂ of major diast. & CHHArOMe of minor diast.), 2.67-2.61 (1H, m, CHCH=CH₂, minor diast.), [2.56, 2.54 (2 × 3H, 2 × s, 2 × Me of 2 × Ts, minor diast.]), [2.46, 2.44 (2 × 3H, 2 × s, 2 × Me of 2 × Ts, major diast.]), 2.07-1.95 (3 × 1H, m, CH₂CHTs of minor diast. & CHHArOMe of major diast.), 1.85 (1H, dt, J 15.0, 6.0 Hz, CHHArOMe, major diast.), 1.59-1.56 (2H, m, CH₂CHTs, major diast.); δC (100 MHz) [158.4, 158.3, 144.6, 144.5, 143.4, 143.3, 137.7, 136.8, 135.9, 134.4 (q Ar, 2 × diast.)), [133.1, 132.5 (CH=CH₂, 2 × diast.)), [130.8, 130.3, 129.8, 129.7, 129.7, 129.6 (3°, 2 × diast.)), 129.2 (q Ar, minor diast.), 129.1 (3°, major diast.), 128.7 (q Ar, major diast.), 128.6 (3°, minor diast.), 127.4 (3°, major diast.), 127.3 (3°, minor diast.), 122.4 (CH=CH₂, major diast.), 121.4 (CH=CH₂, minor diast.), [113.9, 113.8 (3°, 2 × diast.)), 103.6 [CH(OMe)₂, major diast.], 102.2 [CH(OMe)₂, minor diast.], [61.8, 58.9, 57.6, 55.9 (CHT & CHNT, 2 × diast.)), [55.2, 55.1, 54.9, 54.3, 53.7, 52.7 (OMe, 2 × diast.)), [47.5, 44.9 (CHCH=CH₂)], 38.8 (2 × CH₂ArOMe, 2 × diast.)), [30.8, 30.5 (2 × CH₂CHTs, 2 × diast.)), [21.7, 21.6 (2 × 2Me of Ts, 2 × diast.)); m/z (ESI) 624.2070 [M+Na]⁺, 570.1986, 538.1744, 382.1457 (Found: [M+Na]⁺, 624.2070. C₃₁H₃₉NNaO₇S₂ requires [M+Na]⁺, 624.2070).
$N$-[(2$R$,3$S$)-6,6-Dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methyl-$N$-(3-methylbut-2-enyl)benzenesulfonamide 386

To a solution of diastereomixture of tosamides 191 (175 mg, 0.29 mmol, 1.0 equiv) in THF (0.4 mL) at $-78^\circ$C was added $n$BuLi (236 µL of a 2.47 M solution in hexanes, 0.582 mmol, 2.0 equiv). The solution was warmed to rt over 1 h and then prenyl bromide (101 µL, 0.873 mmol, 3.0 equiv) was added. After 20 h, the reaction was quenched with sat. NaHCO$_3$(aq.) then diluted with H$_2$O (5 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 $\times$ 10 mL). The combined organic layers were washed with brine (2 $\times$ 5 mL) and dried (Na$_2$SO$_4$). Concentration under reduced pressure and column chromatography (20$\rightarrow$40% EtOAc-petrol) gave N-[(2$R$,3$S$)-6,6-dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methyl-$N$-(3-methylbut-2-enyl)benzenesulfonamide 386 (44.0 mg, 23%) as a gum with a dr $> 100:1$; $R_f$ 0.62 (40% EtOAc–petrol); $\nu_{\text{max}}$ (film) 2933, 1601, 1512, 1447, 1380, 1303, 1248, 1150, 1086, 926, 816, 729 cm$^{-1}$; $\delta_H$ (400 MHz) 7.70 (2H, d, $J$ 8.0 Hz, ortho Ts), 7.33 (2H, d, $J$ 8.0 Hz, meta Ts), 7.19 (2H, d, $J$ 7.5 Hz, ortho Ts), 7.03-6.98 (4H, m, meta ArOMe & meta Ts), 6.75 (2H, d, $J$ 8.5 Hz, ortho ArOMe), 5.89 (1H, dt, $J$ 17.0, 10.0 Hz, CH=$\text{CHH}$), 5.31 (1H, dd, $J$ 10.0, 1.5 Hz, trans CH=$\text{CHH}$), 5.18 (1H, dd, $J$ 17.0, 1.0 Hz, cis CH=$\text{CHH}$), 5.09-4.95 [1H, m, (CH$_3$)$_2$=CHH], 4.49-4.69 [2H, m, CHN & CH(OMe)$_2$], 3.94 (1H, dd, $J$ 16.0, 7.0 Hz, CHHNN), 3.83 (3H, s, ArOMe), 3.57 (1H, dd, $J$ 16.0, 4.0 Hz, CHHN), 3.45 (1H, dt, $J$ 6.0, 2.0 Hz, CHTs), 3.33 (3H, s, OMe), 3.28 (3H, s, OMe), 3.18-3.13 (1H, m, CHCH=CH$_2$), 2.84 (1H, dd, $J$ 14.5, 4.5Hz, CHHArOMe), 2.49-2.45 (4H, m, Me of Ts & CHHArOMe), 2.34 (3H, s, Me of Ts), 2.24-2.17 (1H, m, CHHCHTs), 2.12-2.07 (1H, m, CHHCHTs), 1.66 (3H, s, CH$_3$CCH$_3$), 1.63 (3H, s, CH$_3$CCH$_3$); $\delta_C$ (100 MHz) [158.4, 144.7, 142.7, 138.5 (q Ar)], [135.3, 134.1 (q)], 133.5 (CH=CH$_2$), 130.4 (3°), 130.1 (q), [129.8, 129.0, 128.9, 127.2 (3°)],
121.7 (CH₃CCH₃), 121.5 (CH=CH₂), 113.8 (3°), 101.9 [CH(OMe)₂], 62.1 (CHN), 61.3 (CHT), 55.2 (ArOMe), 55.0 (MeOCHOMe), 51.8 (MeOCHOMe), 45.4 (CHCH=CH₂), 42.3 (CH₂N), 36.5 (CH₂ArOMe), 29.5 (CH₂CHT), 25.7 (CH₃CCH₃), [21.7, 21.4 (2 × Me of 2 × Ts)], 17.8 (CH₃CCH₃); m/z (ESI) 692.2662 [M+Na]⁺, 638.2621, 304.1006 (Found: [M+Na]⁺, 692.2662. C₃₆H₄₇NO₇S₂ requires [M+Na]⁺, 692.2692).

(2R*,3S*)-2-(4-Methoxybenzyl)-1,4-ditosyl-3-vinyl-1,2,3,4-tetrahydropyridine 190

![Chemical structure of (2R*,3S*)-2-(4-Methoxybenzyl)-1,4-ditosyl-3-vinyl-1,2,3,4-tetrahydropyridine 190](attachment:image)

To a solution of diastereomeric mixture of tosamide 191 (3.10 g, 5.16 mmol, 1.0 equiv) in CH₂Cl₂ (55 mL) at −78 °C was added BF₃·Et₂O (6.53 mL, 51.6 mmol, 10.0 equiv) dropwise. After 30 min, the reaction was warmed to −55 °C. After 16 h, the reaction was quenched with sat. NaHCO₃(aq.) (55 mL). The resulting mixture was warmed to rt gradually then stirred for 15 min. The organic phase was separated and the aqueous phase extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave a 2:1 diastereomeric mixture of (2R*,3S*)-2-(4-methoxybenzyl)-1,4-ditosyl-3-vinyl-1,2,3,4-tetrahydropyridine 190 (2.31 g, 83%) as a solid; Rf 0.60 (40% EtOAc–petrol); νmax (film) 2922, 1640, 1512, 1461, 1317, 1248, 1164, 1087, 1034, 814, 671 cm⁻¹; δH (400 MHz) 7.75 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.57 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.54 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 7.40 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 7.34 (2H, d, J 8.0 Hz, meta Ts, major diast.), 7.29-7.27 (2 × 2H, m, meta Ts, 2 × diast.), 7.13 (2H, d, J 8.0 Hz, meta Ts, minor diast.), 7.03 (2H, d, J 8.5 Hz, meta ArOMe, major diast.), 7.00 (2H, d, J 8.5 Hz, meta ArOMe, minor diast.), 6.94 (1H, dd, J 8.5, 2.5 Hz, NTsCH=CH, major diast.), 6.89-6.87 (1H, m, NTsCH=CH, minor diast.), 6.83 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 6.68 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 5.20-5.16 (2H, m, ortho Ts, 2 × diast.), 3.84-3.79 (3H, s, OMe), 2.24-2.05 (4H, m, ArOMe), 1.19-1.06 (6H, m, HMe).
8.5 Hz, ortho ArOMe, major diast.), 6.82 (2H, d, J 8.5 Hz, ortho ArOMe, minor diast.), 6.20 (1H, ddd, J 17.0, 10.0, 8.5 Hz, CH=CH₂, major diast.), 5.76 (1H, ddd, J 17.0, 10.0, 8.5 Hz, CH=CH₂, minor diast.), 5.36 (1H, dd, J 8.0, 2.5 Hz, NTsCH=CH, minor diast.), 5.25 (1H, dd, J 10.0, 2.5 Hz, trans CH=CH/H, major diast.), 5.14 (1H, d, J 10.0 Hz, trans CH=CH/H, minor diast.), 5.07 (1H, dd, J 17.0, 1.0 Hz, cis CH=CH₂, major diast.), 4.93 (1H, dd, J 8.5, 3.5 Hz, NTsCH=CH, major diast.), 4.73 (1H, d, J 17.0 Hz, cis CH=CH₂, minor diast.), 3.92-3.88 (2 × 1H, m, NTsCHCH₂, 2 × diast.), 3.82 (3H, s, OMe, major diast.), 3.81 (3H, s, OMe, minor diast.), 3.74-3.71 (2 × 1H, m, CHSPh, 2 × diast.), 3.24 (1H, dd, J 14.5, 7.5 Hz, CHHArOMe, major diast.), 2.96 (1H, dd, J 14.5, 6.5 Hz, CHHArOMe, major diast.), 2.75 (1H, dd, J 14.0, 4.5 Hz, CHHArOMe, minor diast.), 2.63-2.58 (2 × 1H, m, CHHArOMe of minor diast. & CHCH=CH₂ of major diast.), 2.52 (3H, s, Me of Ts, minor diast.), 2.47 (3H, s, Me of Ts, major diast.), 2.44 (3H, s, Me of Ts, major diast.), 2.43 (3H, s, Me of Ts, minor diast.), 1.82-1.77 (1H, m, CHCH=CH₂, minor diast.); δc (100 MHz) 158.4, 158.2, 144.7, 144.4, 143.7, 136.7, 136.4, 135.9, 135.3, 133.4, 132.9, 130.5, 130.4, 130.1, 129.9, 129.8, 129.7, 129.6, 129.4, 129.4, 128.8, 128.6, 127.3, 126.9, 126.8, 120.1, 118.1, 117.4, 114.2, 113.8, 113.7, 63.3, 62.1, 60.9, 60.5, 55.2, 55.1, 43.9, 40.9, 34.3, 32.5, 21.8, 21.6, 21.6, 21.6; m/z (ESI) 601.1808, 576.1287, 560.1536 [M+Na]⁺, 538.1725 [M+H]⁺, 382.1481, 318.0590 (Found: [M+Na]⁺, 560.1536; [M+H]⁺, 538.1725. C_{29}H_{31}NO_{5}S_{2} requires [M+Na]⁺, 560.1541; [M+H]⁺, 538.1722).
To a solution of 2:1 diastereomixture of tetrahydropyridines 190 (150 mg, 0.28 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) at −78 °C was added SnCl₄ (86 µL, 0.73 mmol, 2.6 equiv) dropwise. It was warmed to −20 °C over a period of 2 h then to 0 °C. After 1 h, the resulting red solution was quenched with sat. NaHCO₃(aq.) (15 mL). After 5 min, it was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave 8-methoxy-3-(toluene-4-sulfonyl)-11-vinyl-1,2,3,6-tetrahydro-2,6-methano[1]benzo[d]azocine 298 (60.0 mg, 56%) as a gum; Rf 0.72 (20% EtOAc–petrol); υ_max (film) 3067, 2917, 2835, 1642, 1610, 1503, 1395, 1363, 1341, 1304, 1248, 1167, 1092, 1051, 986, 711, 680 cm⁻¹; δH (400 MHz) 7.74 (2H, d, J 8.0 Hz, ortho Ts), 7.35 (2H, d, J 8.0 Hz, meta Ts), 7.00 (1H, d, J 8.5 Hz, CHCHCOMe), 6.70-6.66 (2H, m, CHCHCOMe & NCH=CH), 6.59 (1H, d, J 2.5 Hz, CCHCOMe), 5.55 (1H, ddd, J 17.5, 10.5, 7.5 Hz, CH=CHH), 5.31 (1H, dd, J 7.5, 7.0 Hz, NCH=CH), 4.99-4.92 (2H, m, CH=CH₂), 4.30 (1H, m, NCHCH₂), 3.78 (3H, s, OMe), 3.22 (1H, dd, J 18.5, 6.0 Hz, CHHArOMe), 3.11-3.10 (1H, m, NCH=CHCH), 2.98 (1H, d, J 18.5 Hz, CHHArOMe), 2.47 (3H, s, Me of Ts), 2.14-2.12 (1H, m, CHCH=CH₂); δC (100 MHz) [157.8, 143.8, 139.4 (q Ar)], 136.7 (3°), 136.4 (q Ar), 130.2 (3°), [129.9, 126.9 (ortho & meta Ts)], 124.6 (q Ar), 123.1 (3°), 117.4 (CH=CH₂), [113.3, 113.0, 111.9 (3°)], 55.3 (OMe), 52.8 (NCHCH₂), [39.5, 37.1 (CH₂=CHCHCH)], 33.8 (CH₂ArOMe), 21.7 (Me of Ts); m/z (ESI) 382.1483 [M+H]⁺, 292.6040, 226.1265 (Found: [M+H]⁺, 382.1483. C₂₂H₂₃NO₃S requires [M+H]⁺, 382.1477); data in agreement with that previously reported.³¹
(2R*,3S*)-2-(4-Methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 299

To a solution of PhSH (924 mg, 8.38 mmol, 4.5 equiv) in CH₂Cl₂ at rt was added AlMe₃ (4.20 mL of a 3 M solution in hexanes, 8.38 mmol, 4.5 equiv). After 30 min, the resulting solution was added to a solution of tetrahydropyridines 190 in CH₂Cl₂ via cannula. After 1 h, the solution was cooled to 0 °C and sat. Na/K tartrateₐq, (15 mL) added dropwise, followed by H₂O (10 mL) and EtOAc (10 mL). The organic phase was separated and aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Purification by column chromatography (5→10% EtOAc–petrol) followed by recrystallisation gave a 2:1 diastereomixture of (2R*,3S*)-2-(4-methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 299 (810 mg, 89%) as a solid; data in agreement with that previously reported.
(2R*,3S*)-2-(4-Methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 343 and (2R*,3R*)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine 344

To a mixture of sulfur powder (27.0 mg, 0.842 mmol, 4.5 equiv) in toluene (1.3 mL) at rt was added AlMe₃ (373 µL of a 2 M solution in hexanes, 0.745 mmol, 4.0 equiv). The mixture was heated to reflux for 2 h then cooled to rt. To the resulting mixture was added via cannula a solution of 2:1 diastereomixture of tetrahydropyridines 190 (100 mg, 0.186 mmol, 1.0 equiv) in toluene (0.6 mL). After 16 h, it was quenched with H₂O (5 mL), diluted with sat. Na/K tartrate(aq.) (5 mL) and EtOAc (5 mL). After stirring for 5 min, the organic phase was separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave a 1.2:1 diastereomeric mixture of (2R*,3S*)-2-(4-methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 343 (11.1 mg, 14%) as a gum and a 2:1 diastereomeric mixture of (2R*,3R*)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine 344 (55.1 mg, 69%) as a gum.

Data for 1.2:1 diastereomixture of (2R*,3R*)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine 343: Rₖ 0.76 (30% EtOAc–petrol); vₘₐₓ (film) 3035, 2922, 2837 1609, 1512 1442, 1339, 1247, 1159, 1094, 1036, 914, 816 cm⁻¹; δₜₜ (400 MHz) 7.60 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.55 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 7.28-7.19 (2 × 4H, m, meta Ts & meta ArOMe, 2 × diast.), 6.87 (2H, d, J 8.5 Hz, ortho ArOMe, major diast.), 6.77 (2H, d, J 8.5 Hz, ortho ArOMe, minor diast.), 5.89-5.63 (2 × 3H, m, CH=CH₂ & CH=CH₂, 2 × diast.), 5.19-5.02 (2 × 2H, m, CH=CH₂, 2 × diast.), 4.57-4.52 (1H, m, NCHSMe, minor diast.), 4.39-4.34 (1H, m,
NCHSMe, major diast.), 3.83 (3H, s, OMe, minor diast.), 3.81 (3H, s, OMe, major diast.), 3.51-3.44 (1H, m, NCHCH₂, major diast.), 3.22 (1H, dd, J 15.0, 10.0 Hz, CHHArOMe, major diast.), 3.09 (1H, dd, J 14.5, 9.0 Hz, CHHArOMe, minor diast.), 2.76-2.68 (2 × 1H, m, CHHArOMe, 2 × diast. & 1H, m, NCHCH₂, minor diast.), 2.44-2.39 (2 × 4H, m, Me of Ts & CHCH=CH₂, 2 × diast.), 2.14 (3H, s, SMe, major diast.), 1.66 (3H, s, SMe, minor diast.); δC (100 MHz) 158.2, 157.8, 143.6, 143.4, 137.3, 136.9, 134.8, 130.9, 130.8, 130.6, 130.5, 130.2, 129.6, 129.4, 129.3, 128.1, 127.7, 127.3, 125.3, 124.8, 118.4, 117.1, 113.8, 113.3, 64.0, 59.8, 58.8, 57.7, 57.1, 56.5, 55.3, 55.2, 43.8, 40.2, 35.2, 32.5, 21.5, 15.5; m/z (ESI) 425.1346 [M+Na]⁺, 382.1488 [M+H]⁺, 318.0591, 253.5798, 227.1316 (Found: [M+Na]⁺, 452.1346. C₂₃H₂₇NO₃S₂ requires [M+Na]⁺, 452.1330). Data for 2:1 diastereomixture of (2R*,3S*)-2-(4-methoxy benzyl)-4-[(methylthio)1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 344: Rf 0.71 (30% EtOAc–petrol); vmax (film) 3034, 2920, 2835, 1636, 1611, 1598, 1584, 1513, 1464, 1440, 1420, 1347, 1303, 1247, 1161, 1092, 1036, 913, 814 cm⁻¹; δH (400 MHz) 7.61 (2H, d, J 8.0 Hz, ortho Ts, major diast.), 7.57 (2H, d, J 8.0 Hz, ortho Ts, minor diast.), 7.30-7.26 (2 × 2H, m, meta Ts, 2 × diast.), 7.12-7.09 (2 × 2H, m, meta ArOMe, 2 × diast.), 6.87-6.84 (2 × 2H, m, ortho ArOMe, 2 × diast.), 6.69 (1H, d, J 8.0 Hz, NCH=CH, major diast.), 6.62 (1H, d, J 8.0 Hz, NCH=CH, minor diast.), 6.18 (1H, ddd, J 17.5, 10.0, 8.0 Hz, CH=CHH, minor diast.), 5.66 (1H, ddd, J 17.5, 10.0, 8.0 Hz, CH=CHH, major diast.), 5.47 (1H, dd, J 8.0, 4.5 Hz, NCH=CH, minor diast.), 5.28-5.15 (2 × 1H, m, CH=CHH, 2 × diast. & 1H, m, NCH=CH, major diast.), 5.01-4.94 (2 × 1H, m, CH=CHH, 2 × diast.), 4.14-4.07 (2 × 1H, m, NCHCH₂, 2 × diast.), 3.83 (2 × 3H, s, OMe, 2 × diast.), 3.14-3.11 (1H, m, CHSMe, major diast.), 3.03-3.00 (1H, m, CHSMe, minor diast.), 2.92 (1H, dd, J 14.0, 4.0 Hz, CHHArOMe, minor diast.), 2.84 (1H, dd, J 14.0, 10.0 Hz, CHHArOMe, minor diast.), 2.72 (1H, dd, J 14.0, 4.0 Hz, CHHArOMe, major diast.), 2.65 (1H, dd, J 14.0, 10.0 Hz, CHHArOMe, major diast.), 2.43 (3H, s, Me of Ts, major diast.), 2.25-2.20 (1H, m, CHCH=CH₂, minor diast.), 2.18 (3H, s, Me of Ts, minor diast.), 1.77-1.72 (1H, m, CHCH=CH₂, major diast.), 1.59 (3H, s, SMe, minor diast.), 1.56 (3H, s, SMe, major diast.); δC (100 MHz) 158.3, 158.1, 143.8, 143.6, 137.6, 136.5, 136.1, 135.6, 130.7, 130.5, 129.7, 129.6, 127.1, 127.0, 125.5, 125.4, 123.2, 118.4, 117.9, 113.7, 113.6, 113.1, 60.8, 60.1, 55.2, 45.7, 44.3, 42.6, 39.5, 33.8, 32.1, 31.8, 29.7, 21.5, 18.4, 9.7; m/z
(Found: [M+Na]⁺, 452.1334. C_{23}H_{27}NO_{3}S_{2} requires [M+Na]⁺, 452.1330).

2-[(2R*,3S*)-2-(4-Methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ylthio]pyridine 342

![Chemical structure]

To a solution of 2-mercaptapyridine (207 mg, 1.86 mmol, 5.0 equiv) in CH$_2$Cl$_2$ (2 mL) at rt was added AlMe$_3$ (930 µL of a 2 M solution in hexane, 1.86 mmol, 5.0 equiv). After 45 min, it was added to a solution of a 2:1 diastereomixture of tetrahydropyridines 190 (200 mg, 0.372 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.7 mL) at rt. After 16 h, the reaction was quenched with sat. Na/K tartrate (aq.) and stirred for 5 min. The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Purification by column chromatography (5→10% EtOAc–petrol) followed by recrystallisation gave a 2.5:1 diastereomixture of 2-[(2R*,3S*)-2-(4-methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ylthio]pyridine 342 (125 mg, 68%) as a solid; $R_f$ 0.69 (30% EtOAc–petrol); $\nu_{\text{max}}$ (film) 3044, 2922, 2850, 1637, 1613, 1597, 1577, 1558, 1512, 1453, 1416, 1354, 1302, 1247, 1165, 1122, 1091, 1035, 986, 927, 891, 815, 760, 684 cm$^{-1}$; $\delta_H$ (400 MHz) 8.42 (1H, ddd, J 4.0, 1.5, 1.0 Hz, 2-pyH, minor diast.), 8.35 (1H, ddd, J 4.0, 1.5, 1.0 Hz, 2-pyH, major diast.), 7.61-7.57 (2 × 2H, m, ortho Ts, 2 × diast.), 7.48-7.43 (2 × 1 H, m, 6-pyH, 2 × diast.), 7.29-7.26 (2 × 2H, m, meta Ts, 2 × diast.), 7.16-7.09 (2 × 3H, m, meta ArOMe & 1-pyH, both diast.), 6.98-6.95 (2 × 1H, m, 5-pyH, 2 × diast.), 6.86-6.82 (2 × 2H, m, ortho ArOMe, 2 × diast.), 6.67 (1H, ddd, J 6.5, 1.5, 1.0 Hz, CH=CHNTs, major diast.), 6.60 (1H, ddd, J
6.5, 1.5, 1.0 Hz, minor diast.), 5.99 (1H, ddd, J 14.0, 8.5, 6.0 Hz, CH=CH₂, major diast.), 5.63 (1H, ddd, J 14.5, 8.5, 6.5 Hz, CH=CH₂, minor diast.), 5.46 (1H, dd, J 6.5, 4.0 Hz, CH=CHiative, major diast.), 5.38-5.36 (1H, dd, J 6.5, 2.0 Hz, CH=CHiative, minor diast.), 5.11-5.09 (1H, m, CH=CHiative, minor diast.), 5.06-5.04 (1H, m, CH=CHiative, major diast.), 4.97-4.92 (2 × 1H, m, CH=CHNTs, 2 × diast.), 4.83-4.81 (1H, m, CHNTs, major diast.), 4.62-4.59 (1H, m, CHNTs, minor diast.), [3.80, 3.79 (2 × 3H, 2 × s, OMe, 2 × diast.)], 2.88-2.76 (2 × 2H, m, CH₂ArOMe, 2 × diast.), [2.43, 2.42 (2 × 3H, 2 × s, Me of Ts, 2 × diast.)], 2.39-2.36 (1H, m, CHCH=CH₂, major diast.), 2.87-2.82 (1H, m, CHCH=CH₂, minor diast.); δC (100 MHz) 157.9, 157.9, 149.6, 149.4, 149.1, 143.7, 137.4, 137.1, 136.1, 135.9, 135.8, 130.8, 130.6, 130.5, 130.4, 129.8, 129.7, 129.7, 127.0, 126.9, 123.9, 123.6, 122.8, 122.6, 121.1, 119.7, 118.5, 117.5, 113.8, 113.6, 113.3, 60.9, 59.9, 55.1, 44.4, 38.6, 38.2, 33.7, 31.9, 29.7, 21.6; m/z (ESI) 531.1200, 515.1447, 493.1632 [M+Na]⁺, 382.1485, 221.0214 (Found: [M+Na]⁺, 493.1632. C₂₇H₂₈N₂O₃S₂ requires [M+Na]⁺, 493.1620).

(R*)-2-(4-Methoxybenzyl)-1-tosyl-3-vinyl-1,2-dihydropyridine

To a mixture of AgOTf (16.0 mg, 0.061 mmol, 1.5 equiv), 4 Å molecular sieves and CH₂Cl₂ (1.5 mL) in the dark at –40 °C was added a solution of a 2.5:1 diastereomixture of 2-[(2R*,3S*)-2-(4-methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ythio]pyridines 342 (20.0 mg, 0.041 mmol, 1.0 equiv) in CH₂Cl₂ (0.2 mL). After 2 h, the reaction was quenched with sat. NaHCO₃(aq.) (2 mL). After stirring for 2 min, it was diluted with H₂O (2 mL), CH₂Cl₂ (2 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined
organic layers were washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave (R*)-2-(4-methoxybenzyl)-1-tosyl-3-vinyl-1,2-dihydropyridine 345 (10.0 mg, 64%) as a gum; Rf 0.67 (20% EtOAc–petrol); δH (400 MHz) 7.55 (2H, d, J 8.0 Hz, ortho Ts), 7.19 (2H, d, J 8.0 Hz, meta Ts), 7.14 (2H, d, J 8.5 Hz, meta ArOMe), 6.85 (2H, d, J 8.5 Hz, ortho ArOMe), 6.57 (1H, d, J 6.5 Hz, NCH=CH), 6.13 (1H, dd, J 17.5, 11.0 Hz, CH=CHH), 5.73 (1H, d, J 5.5 Hz, NCH=CHCHCH), 5.59 (1H, dd, J 6.5, 5.5 Hz, NCH=CH), 5.14-5.08 (2H, m, CH=CH₂), 4.98 (1H, d, J 11.0 Hz, NCHCH₂), 3.82 (3H, s, OMe), 2.78-2.75 (2H, m, CH₂ArOMe), 2.38 (3H, s, Me of Ts); δC (100 MHz) [158.4, 143.5, 136.7 (q Ar)], 135.3 (3°), 131.3 (q), [130.9, 129.4 (ortho or meta Ar)], 128.8 (q), 126.2 (ortho or meta Ar), 124.4 (3°), 121.4 (CH=CH₂), 113.5 (ortho ArOMe), [112.5, 112.2 (3°)], [55.2, 54.8 (OMe & NCHCH₂)], 37.7 (CH₂ArOMe), 21.5 (Me of Ts); m/z (ESI) 404.1299 [M+Na]+, 398.1432, 382.1489 [M+H]+, 226.1230 (Found: [M+H]+, 382.1489. C₂₂H₂₃NO₃S requires [M+H]+, 382.1477).

3,3-Dimethoxyprop-1-ene[172] 357

To a solution of NH₄NO₃ (357 mg, 4.46 mmol, 0.05 equiv) in MeOH (3mL) at rt was added acryaldehyde 301 (5.00 g, 89.2 mmol, 1.0 equiv) and CH(CH₃)O₃ (12.6 g, 118.8 mmol, 1.33 equiv). After 16 h, the reaction mixture was filtered. Solid Na₂CO₃ (241 mg) was added to the filtrate. Distillation gave 3,3-dimethoxyprop-1-ene 357 (3.8 g, 42%) as a colourless liquid; bp: 88-89 °C; Rf 0.61 (15% EtOAc–petrol); δH (400 MHz) 5.83 (1H, dd, J 17.5, 10.5, 5.0 Hz, CH=CH₂), 5.43 (1H, dt, J 17.5, 1.0 Hz, CH=CHH), 5.35 (1H, dt, J 10.5, 1.0 Hz, CH=CHH), 4.79 [1H, dt, J 5.0, 1.0 Hz, CH(OMe)₂], 3.36 [6H, s, (OMe)₂]; δC (100 MHz) 134.5 (CH=CH₂), 118.9 (CH=CH₂), 103.1 [CH(OMe)₂], [52.7, 50.7 (OMe)₂]; compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported[172].
2,3-Dibromopropanal\textsuperscript{175} 360

![Chemical Structure](image)

To a solution of acrylaldehyde 301 (2.80 g, 50.0 mmol, 1.0 equiv) in CCl\textsubscript{4} (5 mL) at 0\textdegree C was added Br\textsubscript{2} (2.56 mL, 50.0 mmol, 1.0 equiv) dropwise. After 4 h, the reaction was quenched with sat. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3(aq.)} (25 mL). The organic layer was separated and the aqueous phase extracted with Et\textsubscript{2}O (3 × 15 mL). The combined organic layers were washed with H\textsubscript{2}O (20 mL), brine (3 × 15 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration cleanly gave crude dibromide 360 (10.7 g, 100\%) as an oil, used without further purification; R\textsubscript{f} 0.78 (43\% EtOAc–hexane); \(\nu_{\text{max}}\) (film) 3504, 2938, 1731, 1425, 1396, 1125 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (400 MHz) 9.40 (1H, d, J 2.5 Hz, CHO), 4.55 (1H, ddd, J 10.5, 4.5, 2.5 Hz, CH/BrCHO), 3.89 (1H, t, J 10.5 Hz, CH/HBr), 3.74 (1H, dd, J 10.5, 4.5 Hz, CH/HBr); \(\delta\)\textsubscript{C} (100 MHz) 189.0 (CHO), 48.9 (CHBrCHO), 26.8 (CH\textsubscript{2}Br); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.\textsuperscript{175}

\((E)-3-\text{(Phenylsulfonyl)}\text{acrylaldehyde}\textsuperscript{175} 361

![Chemical Structure](image)

To a solution of dibromide 360 (10.7 g, 50.0 mmol, 1.0 equiv) in DMF (28 mL) at rt was added PhSO\textsubscript{2}Na (12.3 g, 75.0 mmol, 1.5 equiv). After 30 h, the reaction was quenched with H\textsubscript{2}O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (4 × 50 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Concentration under reduced pressure and column chromatography (20→30\% EtOAc–petrol) gave \((E)-3-\text{(phenylsulfonyl)}\text{acrylaldehyde} 361 (3.40 g, 35\%) as a gum; R\textsubscript{f} 0.46 (43\% EtOAc–...
hexane); \( \nu_{\text{max}} \) (film) 3476, 3062, 2928, 2852, 1729, 1700, 1584, 1448, 1308, 1150, 1083, 964, 819, 753, 687 cm\(^{-1}\); \( \delta_H \) (400 MHz) 9.67 (1H, d, \( J \) 7.0 Hz, CHO), 7.88-7.86 (2H, m, \textit{ortho} SO\(_2\)Ph), 7.66-7.64 (1H, m, \textit{para} SO\(_2\)Ph), 7.57-7.54 (2H, m, \textit{meta} SO\(_2\)Ph), 7.31 (1H, d, \( J \) 15.5 Hz, CHSO\(_2\)Ph), 6.83 (1H, dd, \( J \) 15.5, 7.0 Hz, CHCHO); \( \delta_C \) (100 MHz) 190.3 (CHO), 147.9, 137.8, 136.2, 134.7, [129.8, 128.5 (\textit{ortho} & \textit{meta} Ph)]; \textit{m/z} (CI) 214 \([\text{M+NH}_4]^+\), 160, 125 (Found: \([\text{M+NH}_4]^+\), 214.0548. \( \text{C}_9\text{H}_8\text{O}_3\text{S} \) requires \([\text{M+NH}_4]^+\), 214.0538); data in agreement with that previously reported.\(^{175}\)

\( \text{(E)-(3,3)-Dimethoxyprop-1-enylsulfonyl)benzene 358a} \)

To a solution of \( \text{(E)-3-(phenylsulfonyl)acrylaldehyde 361} \) (2.00 g, 9.50 mmol, 1.0 equiv) in MeOH (1 mL) at rt was added a solution of NH\(_4\)NO\(_3\) (38.4 mg, 0.480 mmol, 0.05 equiv) and (CH\(_3\)O\(_3\)CH (2.02 g, 19.0 mmol, 2.0 equiv) in MeOH (1 mL). After 96 h, concentration under reduced pressure and column chromatography (15→20\% EtOAc–petrol with 1.5\% Et\(_3\)N) gave \( \text{(E)-(3,3-dimethoxyprop-1-enylsulfonyl)benzene 358a} \) (1.93 g, 84\%) as a crystalline solid; mp 59–61°C; \( R_f \) 0.56 (30\% EtOAc–petrol); \( \nu_{\text{max}} \) (film) 3058, 2939, 2834, 1448, 1359, 1332, 1277, 1172, 1150, 1061, 986, 822, 763, 688, 614 cm\(^{-1}\); \( \delta_H \) (400 MHz) 7.91 (2H, d, \( J \) 7.5 Hz, \textit{ortho} Ph), 7.65 (1H, t, \( J \) 7.5 Hz, \textit{para} Ph), 7.57 (2H, t, \( J \) 7.5 Hz, \textit{meta} Ph), 6.81 (1H, dd, \( J \) 15.0, 3.0 Hz, CH=CHSO\(_2\)Ph), 6.71 (1H, dd, \( J \) 15.0, 0.5 Hz, CH=CHSO\(_2\)Ph), 5.02 [1H, dd, \( J \) 3.0, 0.5 Hz, CH(OMe)], 3.32 [6H, s, CH(OMe)]; \( \delta_C \) (100 MHz) 140.6 (3\°), 139.8 (ipso Ph), [134.6, 133.7 (3\°)], [129.4, 127.9 (\textit{ortho} & \textit{meta} Ph)], 99.1 [CH(OMe)], 52.9 [CH(OMe)]; \textit{m/z} (CI) 260 \([\text{M+NH}_4]^+\), 101, 86 (Found: \([\text{M+NH}_4]^+\), 260.0961. \( \text{C}_{11}\text{H}_{14}\text{O}_3\text{S} \) requires \([\text{M+NH}_4]^+\), 260.0957).
(4S*,5S*,6R*)-6-(4-Methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one 353

![Chemical Structure](image)

To a solution of tosamides 191 (1.15 g, 1.90 mmol, 1.0 equiv) in acetonitrile (3.1 mL) at rt was added dropwise a solution of CrO₃ (950 mg, 9.50 mmol, 5.0 equiv) in H₂O (2.8 mL) and concentrated H₂SO₄ (1.58 mL, 30.5 mmol, 16.0 equiv). After 40 h, concentration under reduced pressure and column chromatography (30→40% EtOAc–petrol) gave a 20:1 diastereomixture of (4S*,5S*,6R*)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one 353 (242 mg, 23%) as a colourless solid; data for major diastereomer only: Rf 0.31 (35% EtOAc–petrol); δmax (film) 2963, 2934, 1709, 1598, 1509, 1355, 1295, 1251, 1148, 1089, 1030, 927, 816, 668, 550 cm⁻¹; δH (400 MHz) 7.76 (2H, d, J 8.5 Hz, ortho Ts), 7.57 (2H, d, J 8.5 Hz, ortho Ts), 7.33–7.28 (4H, m, 2 × meta Ts), 7.11 (2H, d, J 8.5 Hz, meta ArOMe), 6.85 (2H, d, J 8.5 Hz, ortho ArOMe), 5.90 (1H, ddd, J 17.0, 10.0, 8.5 Hz, CH=CH₂), 5.38–5.31 (2H, m, CH=CH₂), 4.89 (1H, app q, J 5.0 Hz, CHNTs), 3.82 (3H, s, OMe), 3.29 (1H, ddd, J 11.0, 8.5, 7.0 Hz, CHTs), 3.19 (1H, dd, J 15.0, 5.0 Hz, CHHarOMe), 3.05–2.99 (1H, m, CHCH=CH₂), 2.90 (1H, dd, J 15.0, 5.0 Hz, CHHarOMe), 2.60 (1H, dd, J 18.5, 7.0 Hz, COCHH), [2.46, 2.45 (2 × 3H, 2 × s, 2 × Me of Ts)], 2.22 (1H, dd, J 18.5, 8.5 Hz, COCHH); δC (100 MHz) 166.5 (CO), 159.1 (ipso Ts), [145.5, 145.1, 135.7 (4°)], 134.9 (3°), 133.6 (4°), [131.0, 129.9, 129.3 (meta or ortho Ar)], 129.0 (2 × meta or ortho Ar), 127.9 (4°), 119.9 (CH=CH₂), 114.4 (meta or ortho Ar), 61.5 (CHNTs), 58.4 (CHTs), 55.2 (OMe), 44.5 (CHCH=CH₂), [36.2, 32.6 (CH₂ArOMe & CH₂CO)], 21.7 (2 × Me of 2 × Ts); m/z (ESI) 576.1489 [M+Na]+, 554.1674 [M+H]+, 420.1237, 358.0995 (Found: [M+Na]+, 576.1489. C₂₉H₃₁NO₆S₂ requires [M+Na]+, 576.1490).
(R*)-5-Ethylidene-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 371

To a solution of (5S*,6R*)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one 353 (18.0 mg, 0.0325 mmol, 1.0 equiv) in CH₂Cl₂ (0.1 mL) at rt was added DBU (8 µL). After 20 h, the resulting solution was concentrated to half volume by flushing with N₂. The crude product was purified by prep-TLC (35% EtOAc–petrol) to give a 2.7:1 isomeric mixture of (R*)-5-ethylidene-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 371 (12.9 mg, 100%) as a solid; R₇ 0.72 (40% EtOAc–petrol); νmax (film) 2923, 1682, 1640, 1611, 1513, 1447, 1402, 1346, 1302, 1247, 1166, 1116, 1087, 1033, 1006, 912, 614, 680, 650, 608, 550 cm⁻¹; δH (400 MHz) 8.01-7.98 (2 × 2H, m, ortho Ts, 2 × isomers), 7.34-7.32 (2 × 2H, m, meta Ts, 2 × isomers), 7.06 (1 × 2H & 1 × 1H, m, meta ArOMe, major isomer CH=CHCO, minor isomer), 7.00 (2H, d, J 8.5 Hz, meta ArOMe, minor isomer), 6.83-6.79 (2 × 2H, m, ortho ArOMe, 2 × isomers), 6.61 (1H, d, J 9.5 Hz, CH=CHCO, major isomer), 5.90 (1H, t, J 7.5 Hz, C=CHCH₃, major isomer), 5.69-5.66 (2 × 1H, m, CHNTs, major isomer & CH=CHCO, minor isomer), 5.53 (1H, d, J 9.5 Hz, CH=CHCO, major isomer), 5.32 (1H, d, J 7.5 Hz, C=CHCH₃, minor isomer), 5.19 (1H, dd, J 9.0, 3.5 Hz, CHNTs, minor isomer), [3.82, 3.80 (2 × 3H, 2 × s, OMe, 2 × isomers), 3.14 (1H, dd, J 13.0, 3.5 Hz, CHHArOMe, major isomer), 2.95-2.90 (2 × 2H & 1 × 1H, m, CHHArOMe, 2 × isomers and CHHArOMe, minor isomer), 2.44 (2 × 3H, s, Me of Ts, 2 × isomers), 1.72 (3H, d, J 7.5 Hz, C=CHCH₃, minor isomer), 1.35 (3H, d, J 7.5 Hz, C=CHCH₃, major isomer); δC (100 MHz) 162.6, 158.7, 144.7, 143.2, 136.6, 135.8, 134.9, 132.7, 131.1, 130.9, 129.3, 129.0, 128.5, 127.9, 121.4, 119.5, 113.7, 63.2, 56.9, 55.3, 42.7, 41.6, 21.6, 14.1, 13.4; m/z (ESI) 817.2614, 461.1540, 420.1264 [M+Na]⁺, 398.1433 [M+H]⁺, 300.6002 (Found: [M+H]⁺, 398.1433. C₂₂H₂₃NO₄S requires [M+H]⁺, 398.1426).
(R*)-6-(4-Methoxybenzyl)-1-tosyl-5-vinyl-1,6-dihydropyridin-2(3H)-one 372

\[ \text{Ts} \quad \text{OMe} \quad \text{O} \quad \text{Ts} \quad \text{OMe} \]

\[ \text{O} \quad \text{Ts} \quad \text{Ts} \quad \text{O} \quad \text{OMe} \]

To a solution of (5S*,6R*)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one 353 (20.0 mg, 0.036 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.3 mL) at rt was added Et$_3$N (1 µL, 0.0072 mmol, 0.2 equiv). After 16 h, the solution was concentrated to ~0.1 mL by flushing with N$_2$. The crude was purified by prep-TLC (30% EtOAc–petrol) to give (R*)-6-(4-methoxybenzyl)-1-tosyl-5-vinyl-1,6-dihydropyridin-2(3H)-one 372 (4.0 mg, 28%) and 371 (9.0 mg, 63%) as a gum.

Data for 372: R$_f$ 0.66 (40% EtOAc–petrol); $\nu_{\text{max}}$ (film) 2920, 1698, 1513, 1351, 1251, 1169, 1046, 821, 674 cm$^{-1}$; $\delta_H$ (400 MHz) 7.93 (2H, d, J 8.5 Hz, ortho Ts), 7.30 (2H, d, J 8.5 Hz, meta Ts), 7.00 (2H, d, J 8.5 Hz, meta ArOMe), 6.75 (2H, d, J 8.5 Hz, ortho ArOMe), 6.34 (1H, dd, J 17.5, 11.0 Hz, CH=CH$_2$), 5.66-5.64 (1H, m, NTsCH), 5.58 (1H, dd, J 5.5, 2.0 Hz, C=CH), 5.42 (1H, d, J 17.5 Hz, CH=CHH), 5.28 (1H, d, J 11.0 Hz, CH=CHH), 3.79 (3H, s, OMe), 3.35 (1H, dd, J 14.0, 5.0 Hz, CHHArOMe), 3.04 (1H, dd, J 14.0, 2.5 Hz, CHHArOMe), 2.41-2.36 (5H, m, Me of Ts & CH$_2$CO); $\delta_C$ (100 MHz) 168.6 (CO), 158.9 (ipsO Ts), [144.9, 136.3 (4°)], 134.4 (3°), 134.2 (4°), [132.2, 129.2, 129.0 (ortho or meta Ar)], 126.4 (4°), 124.7 (3°), 113.8 (CH=CH$_2$), 113.5 (ortho or meta Ar), [57.4, 55.2 (NTsCH & OMe)], [39.6, 34.0 (CH$_2$CO & CH$_2$ArOMe)], 21.7 (Me of Ts); $m/z$ (ESI) 461.1503, 420.1251 [M+Na]$^+$, 398.1441 [M+H]$^+$, 300.6017 (Found: [M+Na]$^+$, 420.1251. C$_{22}$H$_{23}$NO$_4$S requires [M+Na]$^+$, 420.1245) (Found: C, 66.50; H, 5.77; N, 3.47. C$_{22}$H$_{23}$NO$_4$S requires C, 66.48; H, 5.83; N, 3.52%).
(R*)-5-(2-Hydroxyethylidene)-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 375

To a mixture of allylmagnesium bromide (0.18 mL of a 1 M solution in Et₂O, 0.18 mmol, 2.0 equiv) and CuCN (16.0 mg, 0.18 mmol, 2.0 equiv) in THF (0.3 mL) was added a solution (5S*,6R*)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one (50.0 mg, 0.090 mmol, 1.0 equiv) 353 in THF (0.3 mL), followed by Et₃N (4 µL, 0.027 mmol, 0.3 equiv). After 16 h, the reaction was diluted with sat. NH₄Cl(aq.) (2 mL) and THF (2 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure and purification by prep-TLC (55% EtOAc–petrol) gave separable isomers of (R*)-5-(2-hydroxyethylidene)-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 375 as gums.

Data for minor isomer: (4 mg, 11%); Rf 0.14 (40% EtOAc–petrol); v max (film) 3457, 2925, 1682, 1611, 1597, 1514, 1443, 1402, 1347, 1169, 1103, 1088, 1030, 914, 815, 730, 689 cm⁻¹; δH (400 MHz) 8.00 (2H, d, J 8.5 Hz, ortho Ts), 7.34 (2H, d, J 8.5 Hz, meta Ts), 7.10 (1H, d, J 10.0 Hz, CH=CHCO), 7.04 (2H, d, J 8.5 Hz, meta ArOMe), 6.84 (2H, d, J 8.5 Hz, ortho ArOMe), 5.74 (1H, d, J 10.0 Hz, CH=CHCO), 5.34 (1H, app. t, J 6.5 Hz, C=CH), 5.23 (1H, dd, J 9.0, 3.5 Hz, NTsCH), 4.24-4.18 (2H, m, CH₂OH), 3.81 (3H, s, OMe), 3.23 (1H, dd, J 13.0, 3.5 Hz, CHHArOMe), 2.95 (1H, dd, J 13.0, 9.0 Hz, CHHArOMe), 2.45 (3H, s, Me of Ts).
Data for **major isomer**: 8 mg, 22%; Rf 0.18 (40% EtOAc–petrol); νmax (film) 3455, 2924, 1682, 1611, 1596, 1513, 1442, 1402, 1347, 1166, 1107, 1086, 1031, 913, 815, 730, 686 cm⁻¹; δH (400 MHz) 8.01 (2H, d, J 8.5 Hz, *ortho* Ts), 7.34 (2H, d, J 8.5 Hz, *meta* Ts), 7.11 (2H, d, J 8.5 Hz, *meta* ArOMe), 6.87 (2H, d, J 8.5 Hz, *ortho* ArOMe), 6.77 (1H, d, J 9.5 Hz, CH=CHCO), 5.90 (1H, app. t, J 6.0 Hz, C=CH), 5.75 (1H, d, J 9.5 Hz, CH=CHCO), 5.63 (1H, dd, J 10.0, 3.5 Hz, NTsCH), 3.93-3.86 (1H, m, CHHOH), 3.82 (3H, s, OMe), 3.34-3.31 (1H, m, CHHOH), 3.24 (1H, dd, J 13.0, 3.5 Hz, CHHArOMe), 2.89 (1H, dd, J 13.0, 10.5 Hz, CHHArOMe), 2.45 (3H, s, Me of Ts); δC (100 MHz) 162.3 (CO), 158.9 (ipso Ts), 144.9, 142.3, 137.2, 136.9, 131.2 (ortho or meta Ar), 130.7, [129.4, 129.1 (ortho or meta Ar)], 127.8, 122.0, 113.9 (ortho or meta Ar), 58.8, 57.3, 55.3, 42.1, 21.7; m/z (ESI) 477.1458, 452.0938, 436.1154 [M+Na]+, 414.1374 [M+H]+, 308.5988 (Found: [M+H]+, 436.1154. C_{22}H_{23}NO_{5}S requires [M+H]+, 436.1175) (Found: C, 63.85; H, 5.50; N, 3.32. C_{22}H_{23}NO_{5}S requires C, 63.90; H, 5.61; N, 3.39%).
Appendices-Crystal Structures

Appendix I-compound 234d
Crystal data and structure refinement for 234d.

Identification code DC0602
Empirical formula C16 H20 O3 S
Formula weight 292.38
Temperature 173(2) K
Diffractometer, wavelength OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group Monoclinic, P2(1)/c
Unit cell dimensions
\[a = 17.906(4) \, \text{Å} \quad \alpha = 90^\circ\]
\[b = 6.3895(18) \, \text{Å} \quad \beta = 99.06(2)^\circ\]
\[c = 12.901(4) \, \text{Å} \quad \gamma = 90^\circ\]

Volume, Z 1457.6(7) Å³, 4
Density (calculated) 1.332 Mg/m³
Absorption coefficient 2.012 mm⁻¹
\(F(000)\) 624
Crystal colour / morphology Colourless blocky needles
Crystal size 0.31 x 0.12 x 0.06 mm³
\(\theta\) range for data collection 6.95 to 71.24°
Index ranges -21<=h<=21, -7<=k<=7, -15<=l<=15
Reflns collected / unique 33681 / 2800 [R(int) = 0.0316]
Reflns observed \([F>4\sigma(F)]\) 2359
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.06087 and 0.86647
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2800 / 1 / 188
Goodness-of-fit on F² 1.106
Final R indices \([F>4\sigma(F)]\) \(R1 = 0.0313, \, wR2 = 0.0910\)
R indices (all data) \(R1 = 0.0369, \, wR2 = 0.0929\)
Extinction coefficient 0.0011(4)
Largest diff. peak, hole 0.292, -0.328 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001
Bond lengths [Å] and angles [°] for 234d.

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Appendix II-Compound 273
Crystal data and structure refinement for 273.

Identification code: DC0606
Empirical formula: C34 H35 N O6 S2
Formula weight: 617.75
Temperature: 173(2) K
Diffractometer, wavelength: OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group: Orthorhombic, Pccn
Unit cell dimensions:
- a = 15.99710(10) Å, α = 90°
- b = 30.5236(2) Å, β = 90°
- c = 12.73420(10) Å, γ = 90°

Volume, Z: 6217.97(7) Å³, 8
Density (calculated): 1.320 Mg/m³
Absorption coefficient: 1.932 mm⁻¹
F(000): 2608
Crystal colour / morphology: Colourless tablets
Crystal size: 0.22 x 0.20 x 0.06 mm³
θ range for data collection: 2.90 to 71.05°
Index ranges: -19<=h<=19, -36<=k<=37, -15<=l<=15
Reflns collected / unique: 165242 / 6002 [R(int) = 0.0504]
Reflns observed [F>4σ(F)]: 4796
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 1.00000 and 0.76604
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 6002 / 0 / 390
Goodness-of-fit on F²: 1.071
Final R indices [F>4σ(F)]: R1 = 0.0375, wR2 = 0.1052
R indices (all data): R1 = 0.0469, wR2 = 0.1111
Largest diff. peak, hole: 0.631, -0.292 eÅ⁻³
Mean and maximum shift/error: 0.000 and 0.001
Bond lengths [Å] and angles [°] for 273.

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Appendix III-compound 274
Crystal data and structure refinement for 274.

Identification code DC0604
Empirical formula C34 H35 N O5 S2
Formula weight 601.75
Temperature 173(2) K
Diffractometer, wavelength OD Xcalibur 3, 0.71073 Å
Crystal system, space group Orthorhombic, Pbca
Unit cell dimensions $a = 16.4268(6)$ Å $\alpha = 90^\circ$
$b = 13.8616(6)$ Å $\beta = 90^\circ$
$c = 26.447(5)$ Å $\gamma = 90^\circ$
Volume, Z $6021.9(11)$ Å$^3$, 8
Density (calculated) 1.327 Mg/m$^3$
Absorption coefficient 0.220 mm$^{-1}$
F(000) 2544
Crystal colour / morphology Colourless tablets
Crystal size $0.39 \times 0.29 \times 0.15$ mm$^3$
$\theta$ range for data collection 3.85 to 28.54°
Index ranges $-21 \leq h \leq 21$, $-17 \leq k \leq 17$, $-35 \leq l \leq 34$
Reflns collected / unique 56392 / 7131 [$R$(int) = 0.0460]
Reflns observed [$F>4\sigma(F)$] 5759
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.09029 and 0.91578
Refinement method Full-matrix least-squares on $F^2$
Data / restraints / parameters 7131 / 7 / 385
Goodness-of-fit on $F^2$ 1.218
Final R indices [$F>4\sigma(F)$] $R1 = 0.0664$, $wR2 = 0.1400$
R indices (all data) $R1 = 0.0830$, $wR2 = 0.1444$
Largest diff. peak, hole 0.723, -0.436 eÅ$^{-3}$
Mean and maximum shift/error 0.000 and 0.000
Bond lengths [Å] and angles [°] for 274.

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C(13) - C(12) - C(11) 119.7 (3)
C(12) - C(13) - C(14) 121.0 (3)
C(15) - C(14) - C(13) 119.6 (3)
C(14) - C(15) - C(10) 119.1 (3)
C(17) - C(16) - C(6) 122.8 (3)
C(16) - C(17) - C(18) 126.6 (3)
C(23) - C(18) - C(19) 118.3 (3)
C(23) - C(18) - C(17) 123.0 (3)
C(19) - C(18) - C(17) 118.6 (3)
C(20) - C(19) - C(18) 120.4 (4)
C(21) - C(20) - C(19) 119.9 (4)
C(22) - C(21) - C(20) 119.9 (4)
C(21) - C(22) - C(23) 120.9 (4)
C(22) - C(23) - C(18) 120.5 (4)
C(25) - C(24) - C(29) 117.6 (3)
C(25) - C(24) - C(5) 121.7 (3)
C(29) - C(24) - C(5) 120.5 (3)
C(26) - C(25) - C(24) 122.1 (3)
C(25) - C(26) - C(27) 119.2 (3)
O(30) - C(27) - C(26) 124.4 (3)
O(30) - C(27) - C(28) 116.1 (3)
C(26) - C(27) - C(28) 119.5 (3)
C(29) - C(28) - C(27) 120.2 (3)
C(28) - C(29) - C(24) 121.4 (3)
C(27) - O(30) - C(31) 117.2 (3)
C(4) - N(32) - S(33) 124.65 (18)
O(35) - S(33) - O(34) 118.89 (12)
O(35) - S(33) - N(32) 108.38 (12)
O(34) - S(33) - N(32) 104.71 (12)
O(35) - S(33) - C(36) 107.62 (13)
O(34) - S(33) - C(36) 107.06 (13)
N(32) - S(33) - C(36) 110.02 (13)
C(37) - C(36) - C(41) 120.2 (3)
C(37) - C(36) - S(33) 120.3 (2)
C(41) - C(36) - S(33) 119.5 (2)
C(38) - C(37) - C(36) 119.3 (3)
C(39) - C(38) - C(37) 121.5 (3)
C(38) - C(39) - C(40) 118.8 (3)
C(38) - C(39) - C(42) 121.0 (4)
C(40) - C(39) - C(42) 120.2 (4)
C(41) - C(40) - C(39) 121.1 (3)
C(40) - C(41) - C(36) 119.0 (3)
Appendix IV-Compound 297
Crystal data and structure refinement for 297.

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<th><strong>Identification code</strong></th>
<th>DC0701</th>
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<td><strong>Formula weight</strong></td>
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<tr>
<td><strong>Temperature</strong></td>
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<td><strong>Diffractometer, wavelength</strong></td>
<td>OD Xcalibur PX Ultra, 1.54248 Å</td>
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<td><strong>Crystal system, space group</strong></td>
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<td><strong>Unit cell dimensions</strong></td>
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<td>b = 12.3842(2) Å</td>
<td>β = 90°</td>
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<tr>
<td>c = 28.0436(4) Å</td>
<td>γ = 90°</td>
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<td><strong>Density (calculated)</strong></td>
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<td><strong>Max. and min. transmission</strong></td>
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<td><strong>Data / restraints / parameters</strong></td>
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<td><strong>R indices (all data)</strong></td>
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<td><strong>Mean and maximum shift/error</strong></td>
<td>0.000 and 0.001</td>
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Bond lengths [Å] and angles [°] for 297.

- C(1)–C(2): 1.312(4) Å
- C(2)–C(3): 1.490(4) Å
- C(3)–C(4): 1.552(4) Å
- C(3)–S(7): 1.845(3) Å
- C(4)–C(5): 1.507(4) Å
- C(4)–C(14): 1.557(4) Å
- C(5)–C(6): 1.308(4) Å
- C(8)–C(9): 1.361(4) Å
- C(8)–C(13): 1.388(4) Å
- C(9)–C(10): 1.396(5) Å
- C(10)–C(11): 1.368(5) Å
- C(11)–C(12): 1.359(5) Å
- C(12)–C(13): 1.375(4) Å
- C(14)–N(15): 1.471(3) Å
- C(14)–C(27): 1.536(4) Å
- N(15)–C(26): 1.460(3) Å
- N(15)–S(16): 1.619(2) Å
- S(16)–O(18): 1.4357(18) Å
- S(16)–O(17): 1.4380(19) Å
- S(16)–C(19): 1.756(3) Å
- C(19)–C(20): 1.382(4) Å
- C(19)–C(24): 1.387(4) Å
- C(20)–C(21): 1.384(4) Å
- C(21)–C(22): 1.381(4) Å
- C(22)–C(23): 1.382(4) Å
- C(22)–C(25): 1.511(4) Å
- C(23)–C(24): 1.374(4) Å
- C(27)–C(28): 1.505(4) Å
- C(28)–C(33): 1.383(4) Å
- C(28)–C(29): 1.388(4) Å
- C(29)–C(30): 1.370(4) Å
- C(30)–C(31): 1.377(4) Å
- C(31)–C(32): 1.376(4) Å
- C(31)–O(34): 1.384(4) Å
- C(32)–C(33): 1.388(4) Å
- O(34)–C(35): 1.413(4) Å

Bond angles [°]:

- C(1)–C(2)–C(3): 124.7(3) °
- C(2)–C(3)–C(4): 112.3(3) °
- C(2)–C(3)–S(7): 109.3(2) °
- C(4)–C(3)–S(7): 109.3(2) °
- C(5)–C(4)–C(3): 112.8(2) °
- C(5)–C(4)–C(14): 110.3(2) °
- C(3)–C(4)–C(14): 112.9(2) °
- C(6)–C(5)–C(4): 124.3(3) °
- C(8)–S(7)–C(3): 101.29(14) °
- C(9)–C(8)–C(13): 119.2(3) °
- C(9)–C(8)–S(7): 120.2(3) °
- C(13)–C(8)–S(7): 120.6(3) °
- C(8)–C(9)–C(10): 120.6(4) °
- C(11)–C(10)–C(9): 119.3(4) °
- C(12)–C(11)–C(10): 120.4(4) °
- C(11)–C(12)–C(13): 120.5(4) °
- C(12)–C(13)–C(8): 120.0(3) °
- N(15)–C(14)–C(27): 110.7(2) °
- N(15)–C(14)–C(4): 110.1(2) °
- C(27)–C(14)–C(4): 112.6(3) °
- C(26)–N(15)–C(14): 119.8(2) °
C(26) - N(15) - S(16) 117.36(18)
C(14) - N(15) - S(16) 122.1(2)
O(18) - S(16) - O(17) 119.48(12)
O(18) - S(16) - N(15) 109.01(12)
O(17) - S(16) - N(15) 107.38(12)
O(18) - S(16) - C(19) 105.71(14)
O(17) - S(16) - C(19) 107.99(14)
N(15) - S(16) - C(19) 106.60(13)
C(20) - C(19) - C(24) 119.0(3)
C(20) - C(19) - S(16) 120.2(3)
C(24) - C(19) - S(16) 120.8(3)
C(19) - C(20) - C(21) 120.2(3)
C(22) - C(21) - C(20) 121.2(3)
C(21) - C(22) - C(23) 117.9(3)
C(21) - C(22) - C(25) 121.6(3)
C(23) - C(22) - C(25) 120.5(3)
C(24) - C(23) - C(22) 121.7(3)
C(23) - C(24) - C(19) 120.1(3)
C(28) - C(27) - C(14) 112.7(3)
C(33) - C(28) - C(29) 117.2(3)
C(33) - C(28) - C(27) 121.7(3)
C(29) - C(28) - C(27) 121.1(3)
C(30) - C(29) - C(28) 122.1(3)
C(29) - C(30) - C(31) 119.4(3)
C(32) - C(31) - C(30) 120.6(3)
C(32) - C(31) - O(34) 124.6(3)
C(30) - C(31) - O(34) 114.8(4)
C(31) - C(32) - C(33) 119.0(3)
C(28) - C(33) - C(32) 121.7(3)
C(31) - O(34) - C(35) 116.5(3)
Appendix V-Compound 253
Identification code  DC0806
Empirical formula  C29 H31 N O6 S2
Formula weight  553.67
Temperature  173(2) K
Diffractometer, wavelength  OD Xcalibur 3, 0.71073 Å
Crystal system, space group  Triclinic, P-1
Unit cell dimensions  
\[ a = 7.2944(2) \text{ Å} \]
\[ b = 14.0189(7) \text{ Å} \]
\[ c = 14.7590(7) \text{ Å} \]
\[ \alpha = 64.138(5)^\circ \]
\[ \beta = 84.419(3)^\circ \]
\[ \gamma = 85.889(3)^\circ \]
Volume, Z  1350.93(12) Å³, 2
Density (calculated)  1.361 Mg/m³
Absorption coefficient  0.242 mm⁻¹
F(000)  584
Crystal colour / morphology  Colourless needles
Crystal size  0.44 x 0.05 x 0.03 mm³
θ range for data collection  3.75 to 32.18°
Index ranges  -10<=h<=10, -20<=k<=20, -21<=l<=21
Reflns collected / unique  21735 / 8763 [R(int) = 0.0521]
Reflns observed [F>4σ(F)]  4478
Absorption correction  Semi-empirical from equivalents
Max. and min. transmission  1.00000 and 0.82846
Refinement method  Full-matrix least-squares on F²
Data / restraints / parameters  8763 / 0 / 345
Goodness-of-fit on F²  0.905
Final R indices [F>4σ(F)]  R1 = 0.0474, wR2 = 0.1049
R indices (all data)  R1 = 0.1057, wR2 = 0.1162
Largest diff. peak, hole  0.536, -0.353 eÅ⁻³
Mean and maximum shift/error  0.000 and 0.000
Bond lengths [Å] and angles [°] for 253.

N(1)–C(2) 1.396(2)  
N(1)–C(6) 1.489(2)  
N(1)–S(7) 1.6858(13)  
C(2)–O(2) 1.2085(19)  
C(2)–C(3) 1.503(2)  
C(3)–C(4) 1.527(2)  
C(4)–C(5) 1.556(2)  
C(4)–S(17) 1.7945(18)  
C(5)–C(27) 1.510(2)  
C(5)–C(6) 1.533(2)  
C(6)–C(29) 1.531(2)  
S(7)–O(8) 1.4292(13)  
S(7)–O(9) 1.4292(13)  
S(7)–C(10) 1.7566(18)  
C(10)–C(11) 1.386(2)  
C(10)–C(15) 1.391(2)  
C(11)–C(12) 1.385(3)  
C(12)–C(13) 1.391(3)  
C(13)–C(14) 1.390(3)  
C(13)–C(16) 1.502(3)  
C(14)–C(15) 1.376(3)  
S(17)–O(18) 1.4357(15)  
S(17)–O(19) 1.4376(15)  
S(17)–C(20) 1.7581(19)  
C(20)–C(25) 1.380(3)  
C(20)–C(21) 1.386(3)  
C(21)–C(22) 1.377(3)  
C(22)–C(23) 1.381(3)  
C(23)–C(24) 1.381(3)  
C(23)–C(26) 1.511(3)  
C(24)–C(25) 1.378(3)  
C(27)–C(28) 1.299(3)  
C(29)–C(30) 1.509(2)  
C(30)–C(35) 1.378(3)  
C(30)–C(31) 1.391(2)  
C(31)–C(32) 1.378(3)  
C(32)–C(33) 1.389(3)  
C(33)–O(36) 1.368(2)  
C(33)–C(34) 1.387(3)  
C(34)–C(35) 1.388(2)  
O(36)–C(37) 1.421(2)  
C(2)–N(1)–C(6) 119.66(13)  
C(2)–N(1)–S(7) 119.01(11)  
C(6)–N(1)–S(7) 120.63(11)  
O(2)–C(2)–N(1) 122.24(14)  
O(2)–C(2)–C(3) 123.23(15)  
N(1)–C(2)–C(3) 114.52(14)  
C(2)–C(3)–C(4) 115.23(14)  
C(3)–C(4)–C(5) 114.62(13)  
C(3)–C(4)–S(17) 107.53(12)  
C(5)–C(4)–S(17) 111.06(12)  
C(27)–C(5)–C(6) 110.97(15)  
C(27)–C(5)–C(4) 112.58(13)  
C(6)–C(5)–C(4) 111.27(14)  
N(1)–C(6)–C(29) 112.61(14)  
N(1)–C(6)–C(5) 108.59(13)  
C(29)–C(6)–C(5) 114.35(13)  
O(8)–S(7)–O(9) 118.96(8)
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<td>C(33) - O(36) - C(37)</td>
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References:

26 Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. 
39, 3012.
120, 2343. (b) Stragies, R.; Blechert, S. Tetrahedron 1999, 55, 8179.
41 Examples of RRM of norbornenes: (a) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. 
2004, 126, 10945.
46 (a) Mitsunobu, O. Comprehensive Organic Synthesis Trost, B. M.; Fleming, I.; Winterfeldt, E.; Eds, 
Zhou, P.; Fang, T.; Reddy, G. V.; Zhang Y. J. Org. Chem. 1999, 64, 7559. (c) Zwanenburg, B.; Holte, P. 

49 McCoull W.; Davis, F. A. Synthesis 2000, 1347.


Prati, F.; Forni, A.; Moretti, I.; Torre, G.; Rozhkov, V. V.; Makarov, K. N.; Chervin, I. I.; Kostyanovsky, R. G. J. Fluor. Chem. 1998, 89, 177.


References:


225


123 For reactions of lithio-227 with 1,2-di-, 1,2,2-tri-, and symmetrical 1,2,3-trisubstituted aziridines, see: Breternitz, H. J.; Schaumann, E. J. Chem. Soc., Perkin Trans. 1, 1999, 1927.


