Aziridine–Metathesis based Approaches to Alkaloid Synthesis

A Thesis presented by

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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

&

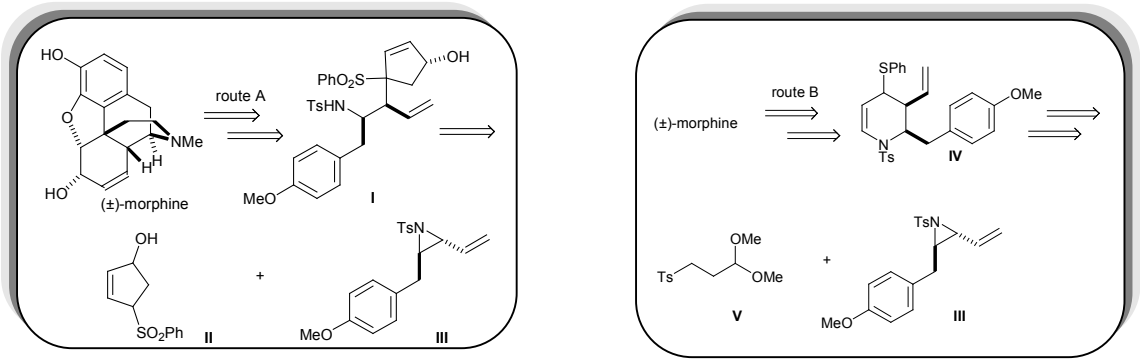
For Bill Armstrong on the occasion of his 80th birthday

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-SO_2Ph 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.

Contents

Acknowledgements

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Abbreviations

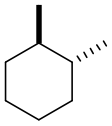
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
ADDP	1,1'-(azodicarbonyl)dipiperidine
(aq.)	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
CI	chemical ionisation
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublet of doublets
diast.	diastereomer
dr	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

Et_2O	diethyl ether
EtOAc	ethyl acetate
Et_3N	triethylamine
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
IBX	*o*-iodoxybenzoic acid
Lit.	literature
KHMDS	potassium hexamethyldisilazide
m	multiplet
maj.	major (spectroscopic; in reference to diastereoisomers)
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
min.	minor (spectroscopic; in reference to diastereoisomers)
MOM	methoxymethyl
mp	melting point
MS	mass spectrum
Ms	methanesulfonyl (mesyl)
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NADPH	reduced form of NADP
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Ns	nitrophenylsulfonyl
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
PTAB	phenyltrimethylammonium tribromide
q Ar	quaternary aromatic
q	quartet

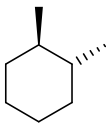
rt	room temperature
RRM	ring-rearrangement metathesis
SES	2-(trimethylsilyl)ethylsulfonyl
SM	starting material
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
Ts	*p*-toluenesulfonyl

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.



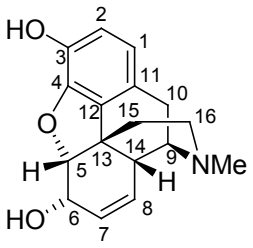
Racemate
Relative stereochemistry



Single enantiomer
Absolute stereochemistry

Morphine Numbering

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



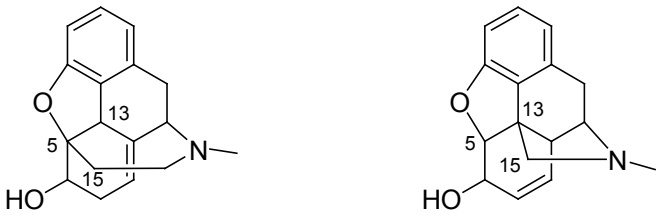
(–)-morphine

1. Introduction

1.1 Historical Aspects of Morphine

Morphine, the active principle of opium, was the first alkaloid discovered.[2,3] Its isolation from opium poppy, *Papaver somniferum*, was attempted by a number of scientists.[4] At the beginning of the 19th century Séguin in France and Sertürner in Germany both independently completed the isolation of morphine.[5] However, since Séguin's work was not published until 1814, the discovery of morphine is generally attributed to Sertürner in the year 1805.[2,4,5] Sertürner named the white crystalline powder morphinum, after Morpheus, the Greek god of dreams. He realised that morphinmum, 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.[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.[2,4,5] In 1847 Laurent correctly deduced the empirical formula of morphine as $C_{17}H_{19}NO_3$.[2,3] Further progress was made by Knorr and Hörlein whose conclusion was published in 1907 (**1** in Figure 1).[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).[2,3,4]



1 **2**

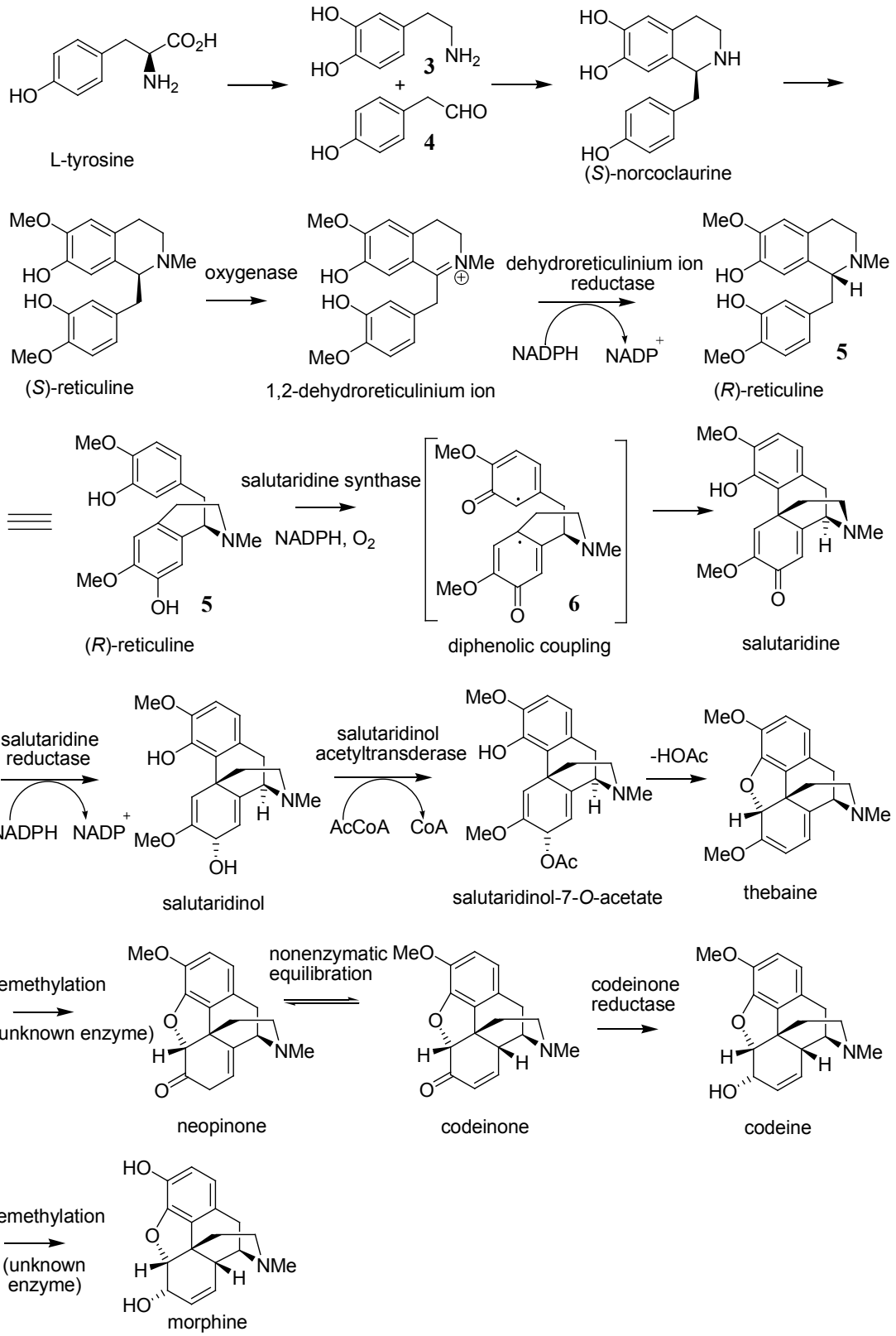
Figure 1

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, δ, κ and μ have been identified.[8] The expression of morphine's interaction with the μ 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 μ 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]


L-tyrosine
3
4
(S)-norcoclaurine
(S)-reticuline
oxygenase
1,2-dehydroreticulinium ion
dehydroreticulinium ion reductase
NADPH
NADP+
(R)-reticuline
5
salutaridine synthase
NADPH, O2
6
diphenolic coupling
salutaridine
salutaridine reductase
salutaridinol
salutaridinol acetyltransderase
AcCoA
CoA
salutaridinol-7-O-acetate
-HOAc
thebaine
demethylation
(unknown enzyme)
nonenzymatic equilibration
neopinone
codeinone
codeinone reductase
codeine
morphine

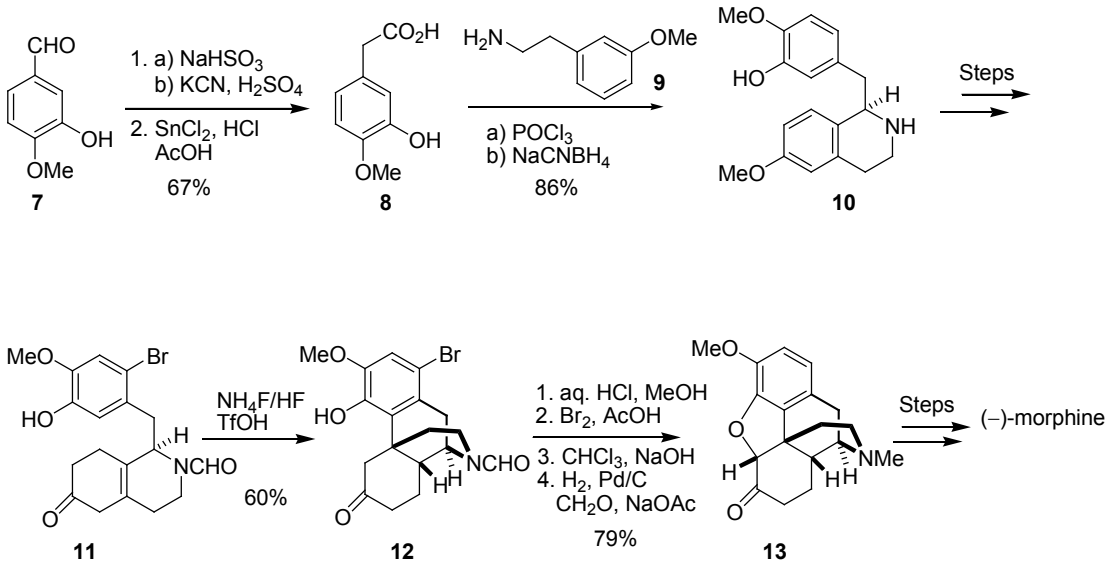
Scheme 2

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.[13,14,15] Since the first total synthesis was accomplished by Gates in 1952,[16] over 20 others have been published.[13,14,15]

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).[17] Homologation of benzaldehyde **7** gave acid **8**, which was coupled with amine **9** to give the corresponding amide. Subsequent Bischler–Napieralski reaction mediated by $POCl_3$ 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**.



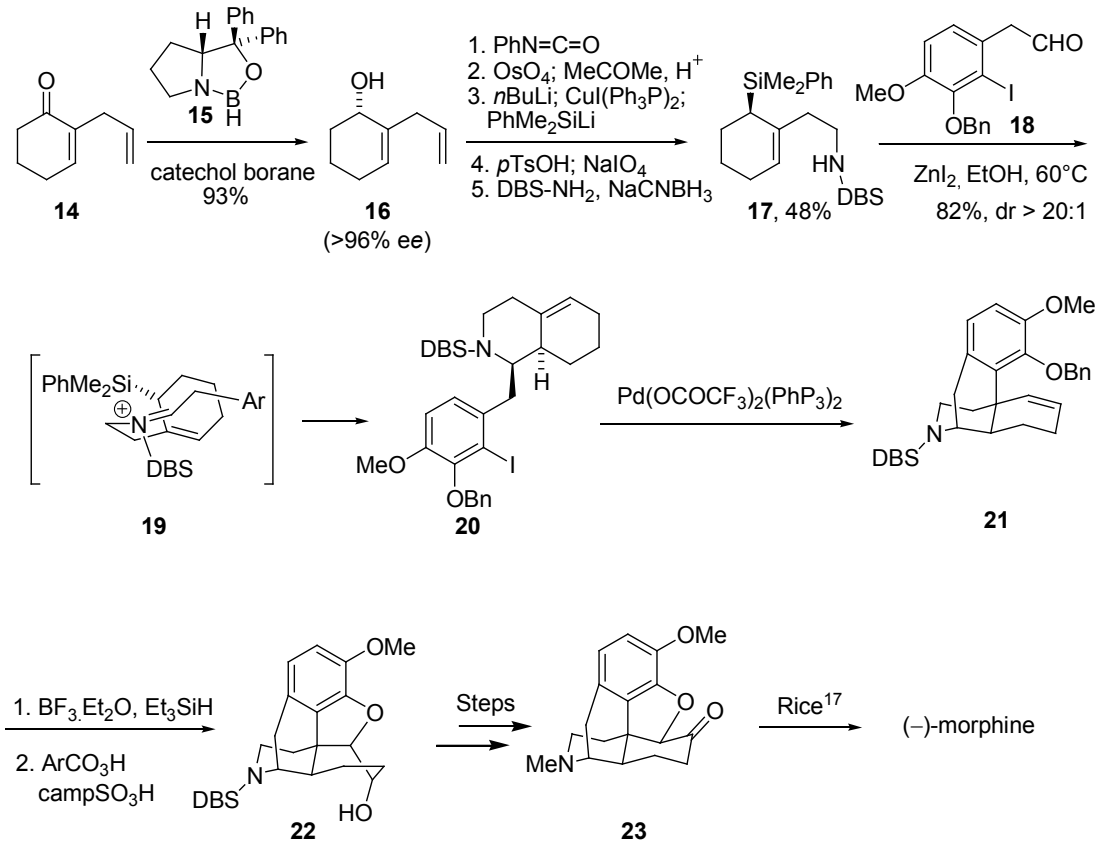
Scheme 3

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).[18] 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, S_N2' displacement of the carbamate, deprotection of the acetonide followed by cleavage of the resulting diol, and treatment of the resulting aldehyde with dibenzosuberylamine (DBS-NH_2). 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.

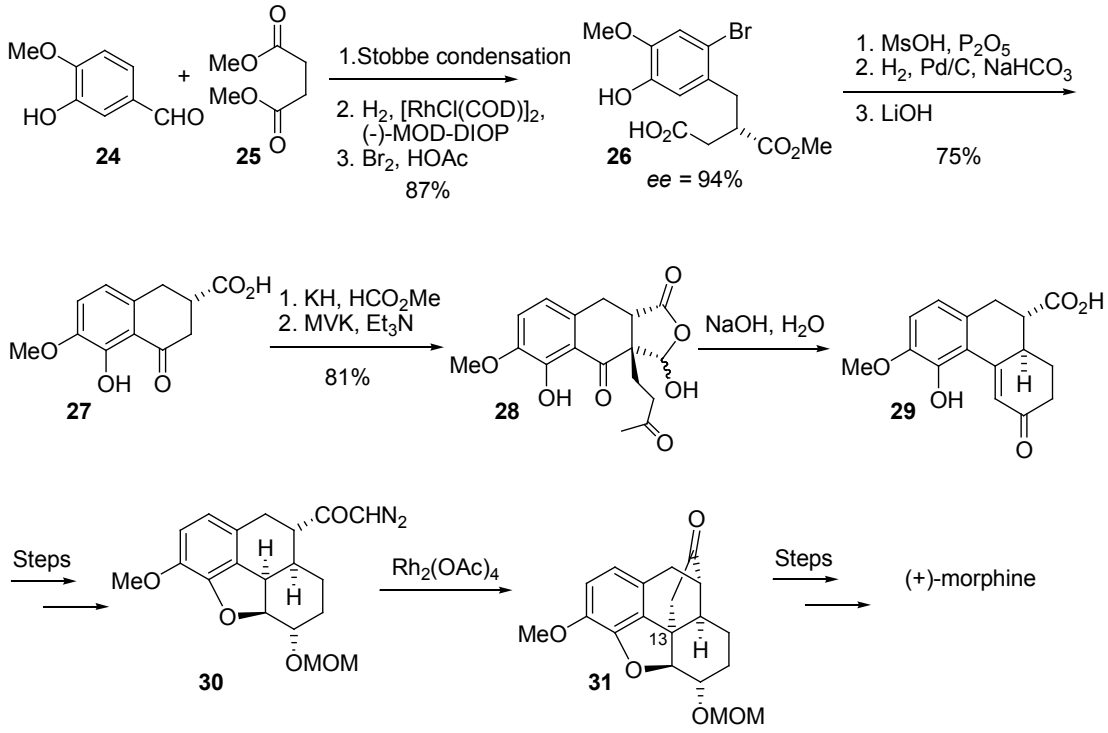


Scheme 4

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,[19] Mulzer[20] and White[21], both in the 1990s.

1.3.3 White's Approach to Morphine

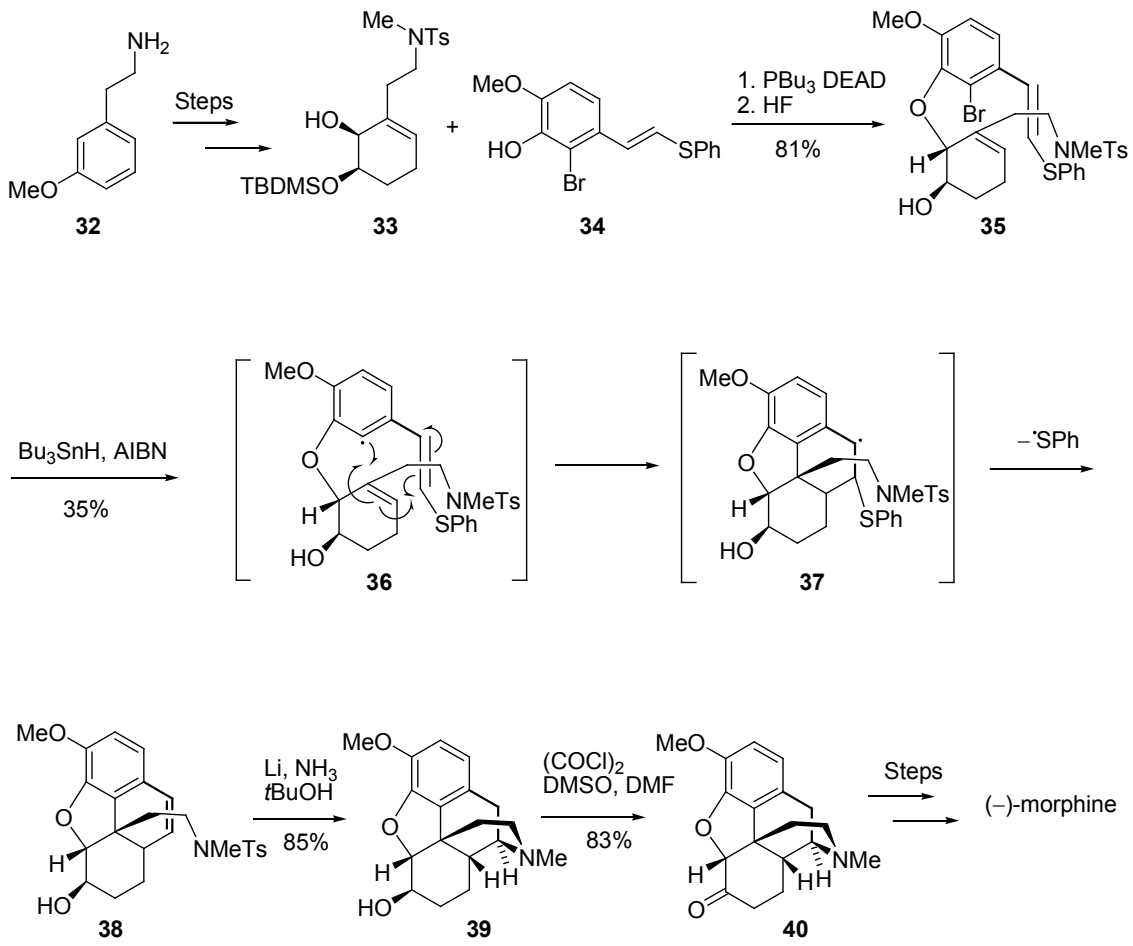
Due to the interest of the pharmacological properties of the unnatural enantiomer, White's synthesis focused on (+)-morphine (Scheme 5).[21] Stobbe condensation[22] of isovanillin **24** and dimethyl succinate **25**, followed by a chiral rhodium catalysed asymmetric hydrogenation[23] and bromination 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 (*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).[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_3SnH 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 (–)-morphine according to literature procedures.[17,25]



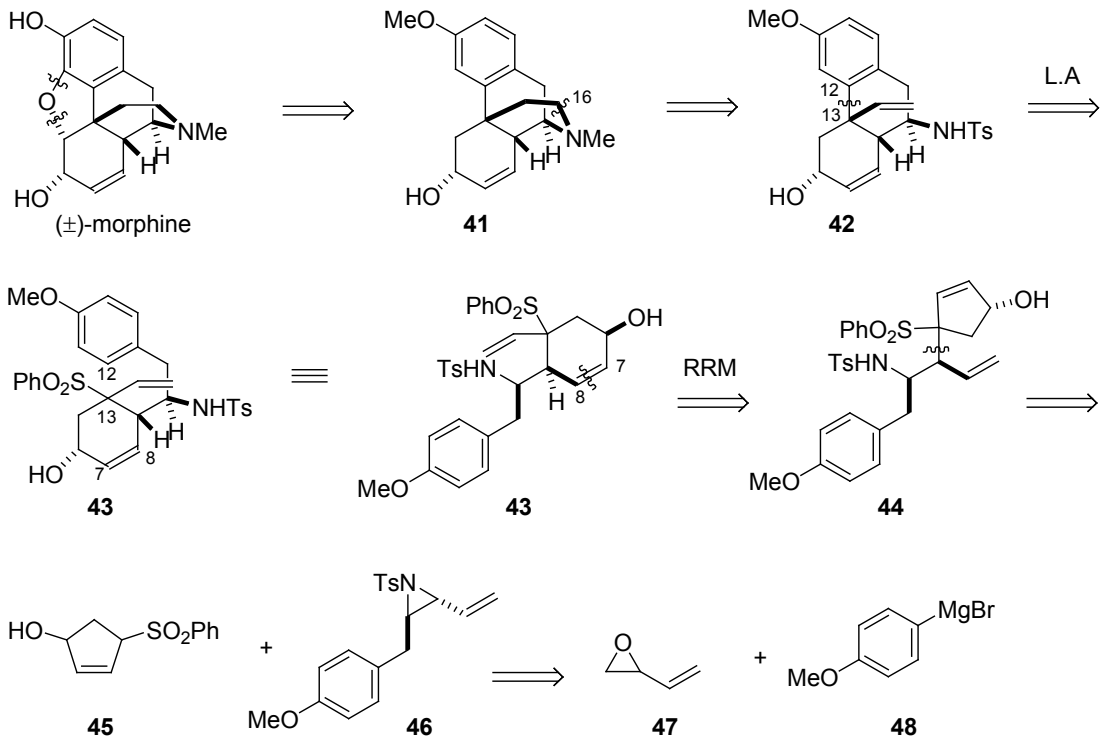
32 **33** **34** **35** **36** **37** **38** **39** **40**

Scheme 6

Morphine is currently produced mostly by extraction from the natural plant opium.[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.[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[27,28,29] and has been very active in exploring the synthesis of morphine in recent years. [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

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**.

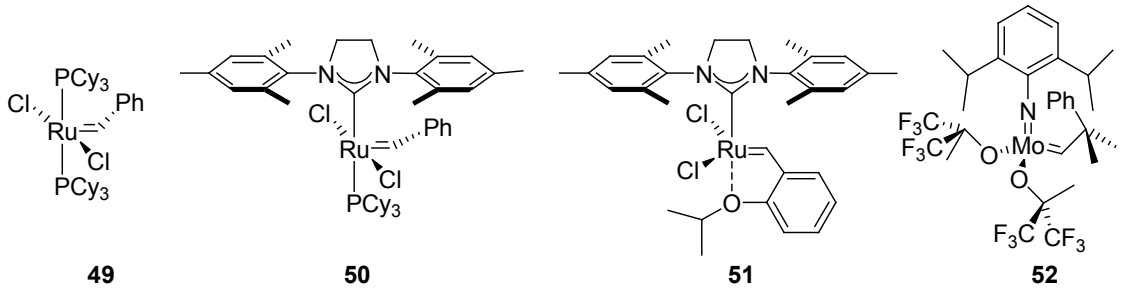
It was believed that the three-membered *N*-ring of aziridine **46** would undergo a regioselective ring-opening reaction when treated with the α-sulfonyl carbanion of **45**. The sulfonyl cyclopentene product **44** would then be subjected to metathesis conditions in an attempt to synthesise sulfonyl 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.[33] Its unique and easy way of forming and redistributing carbon–carbon bonds makes it one of the most powerful tools in organic chemistry.[33] Moreover, with increasingly robust catalysts being discovered (Figure 2), its impact will continue to expand.[34]



49 **50** **51** **52**

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.[33,35] 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. [36] 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).[34,36b, 37]

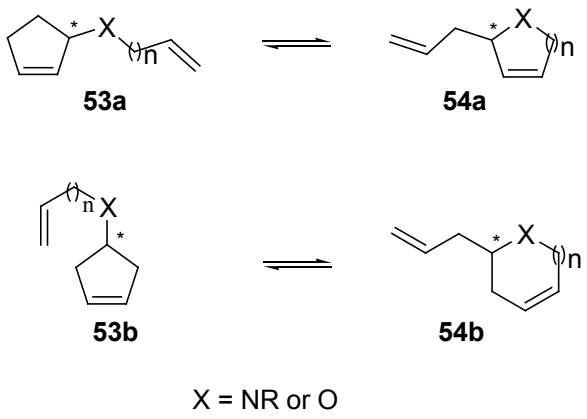
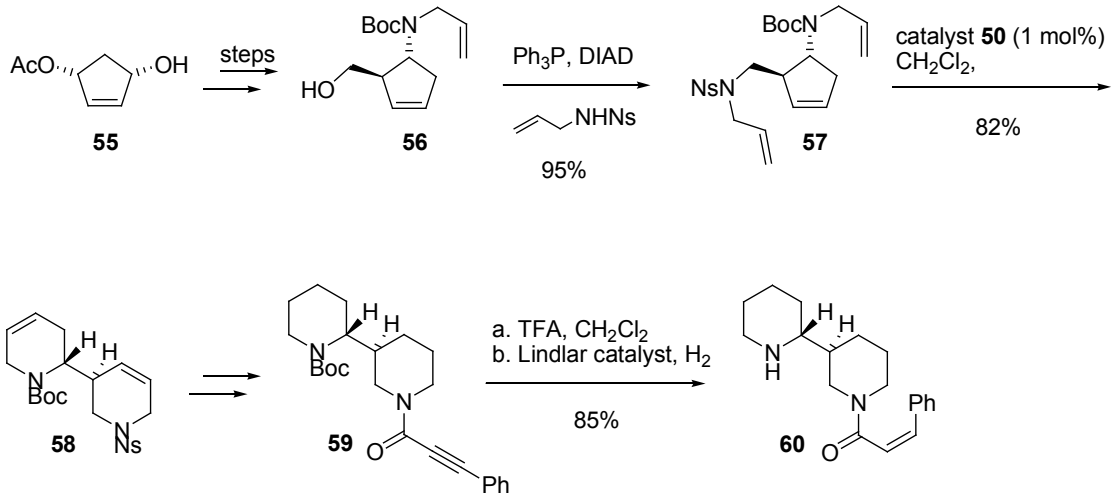


Figure 3

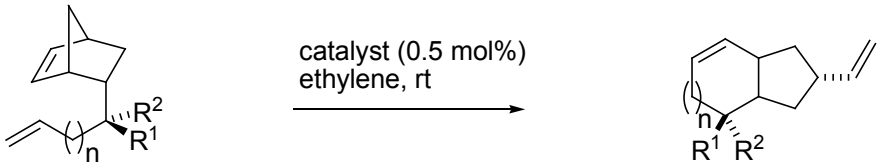
Blechert and Schaudt have successfully synthesised the first natural *cis*-cinnamoyl alkaloid (+)-astrophylline utilising RRM chemistry (Scheme 8).[38] The RRM reaction precursor **57** came from a Mitsunobu substitution of the alcohol of **56** with *N*-Ns allyl amine. Alcohol **56** derived from optically pure acetate **55**[39] 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**.



Scheme 8

1.5.2 RRM of Carbocycles to Carbocycles

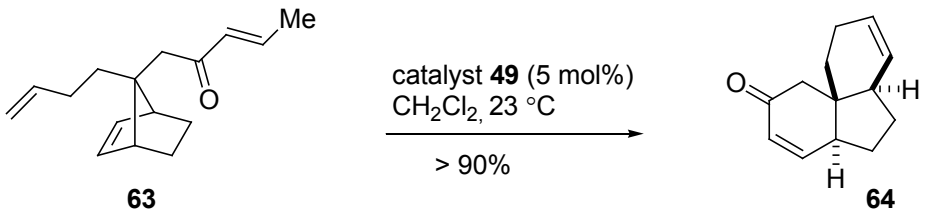
In contrast to the transformations described above, converting one carbocyle into another by RRM is more challenging, especially when the ring strain of the product is close to the starting material.[40] Norborenes are good substrates for RRM owing to their highly strained bridged bicyclic system.[41] Blechert and co-workers have reported the first application of RRM for the synthesis of [*X*.3.0] carbo-bicycles using olefin substituted norborenes **61a–d** (Scheme 9).[42] 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.



61a[a]	n = 0, R^1 = H, R^2 = OTBS	**62a** 80%
61b[a]	n = 1, R^1 = H, R^2 = OTBS	**62b** 88%
61c[a]	n = 2, R^1 = H, R^2 = OTBS	**62c** 75%
61d[b]	n = 3, R^1 = OTBS, R^2 = H	**62d** 83%

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

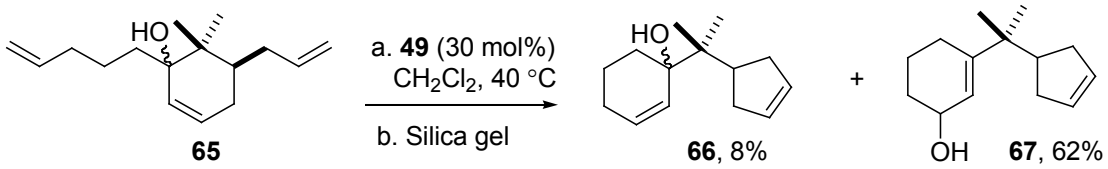
A highly efficient synthesis of fused tricyclic enones from norborene derivatives has been achieved by Holtsclaw and Koreeda using tether-directed RRM (Scheme 10).[41b] In the presence of catalyst **49**, norborene **63** underwent the desired rearrangement to give tricyclic compound **64** in an excellent yield.



63 **64**

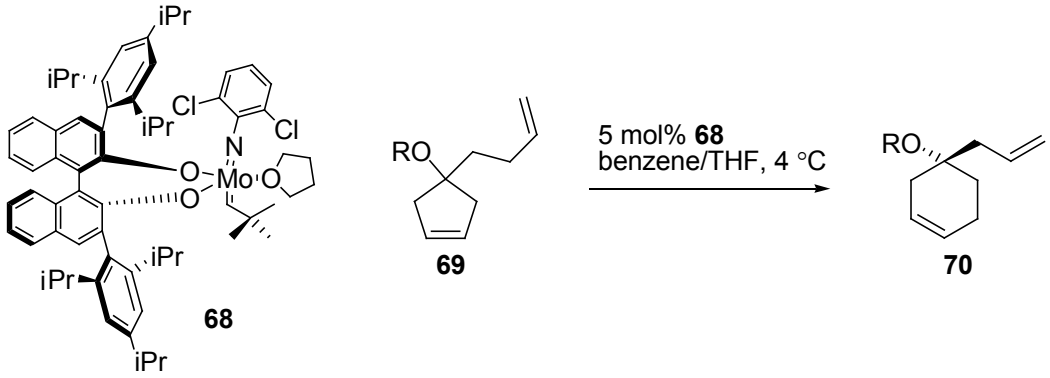
Scheme 10

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).[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

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**.[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.[45]



Scheme 12

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.[46] 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.[47] Aziridines have become important building blocks in synthetic chemistry, especially for nitrogen-containing bioactive natural compounds.[48]

The utility of aziridines is profoundly dependent on their ability to undergo nucleophilic ring-opening, both stereo- and regioselectively.[49] 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.[50]

Regarding the regiochemistry, the intrinsic properties of the aziridine and the nature of the incoming nucleophile can both affect the outcome.[51] 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, eg: 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.[46,49,50,52]

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**.

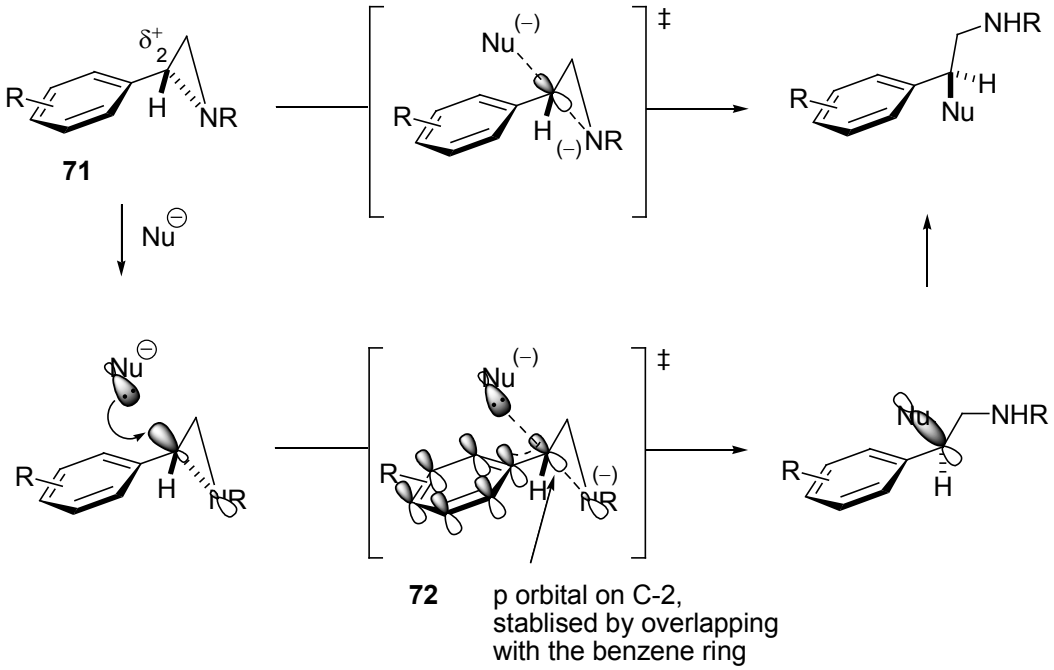


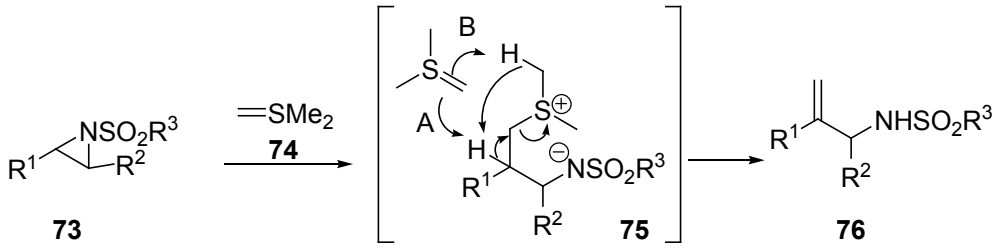
Figure 4 - nucleophilic ring-opening of 2-benzyl substituted aziridines

A comprehensive review on the subject of nucleophilic ring-opening of aziridines was offered by Hu,[53] together with many others.[48a,49,51] 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.

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 **73a–d** by **74** generated intermediates **75**, which could then undergo elimination to give the desired products **76a–d** through either path **A** or **B** with another equivalent of **74**.

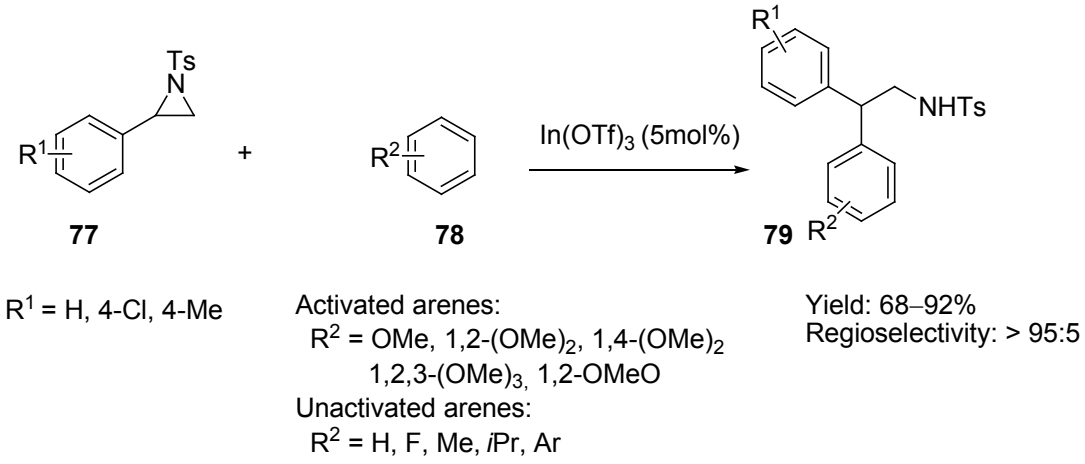
As shown in Scheme 13, both *N*-Ts and *N*-Bus (Bus = *tert*-butylsulfonyl) aziridines gave the corresponding allylic amines in good yields. With the exception of substrate **73b** that gave the other regioisomer in 12% yield, all others produced exclusively the expected compounds. Diene **76d** is also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



Entry	aziridine	product	yield(%)
1	NTs, OR^4; R^4 = H, TES **73a**	OR^4, NHTs **76a**	R^4 = H, 85; TES, 79
2	NBus **73b**	NHBus **76b**	81
3	NBus **73c**	NHBus **76c**	95
4	NTs **73d**	NHTs **76d**	75

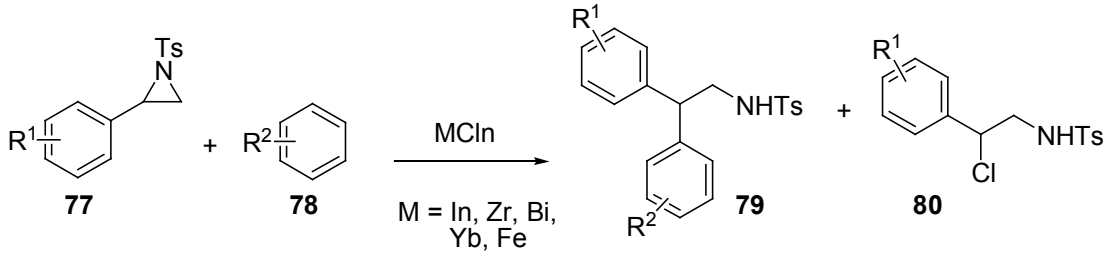
Scheme 13

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.[53] Yadav *et al.* examined the use of $In(OTf)_3$ as catalyst in the reaction of aryl aziridines **77** and arenes **78** (Scheme 14).[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% $Sc(OTf)_3$ and 10% $Yb(OTf)_3$ gave similar results for activated arenes but $In(OTf)_3$ was the only catalyst effective for unactivated arenes. Additionally, without the use of catalyst, no reaction was observed.



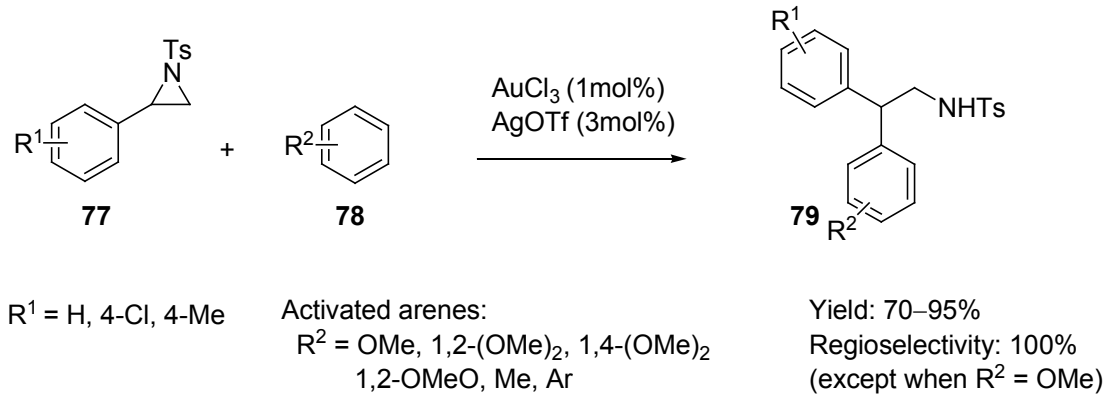
Scheme 14

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



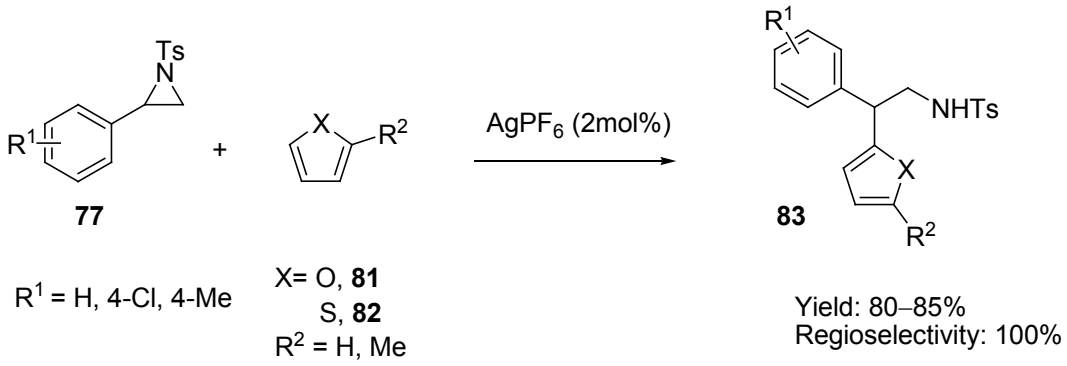
Scheme 15

This methodology was extended by Wu *et al.*[57] and Roy *et al.*[58] In the interest of applying gold and silver catalysts in organic synthesis, Wu and co-workers demonstrated that the combination use of $AuCl_3$ 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 = 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 –Cl, $–CF_3$ and $–NO_3$, complex, unidentified mixtures were obtained.



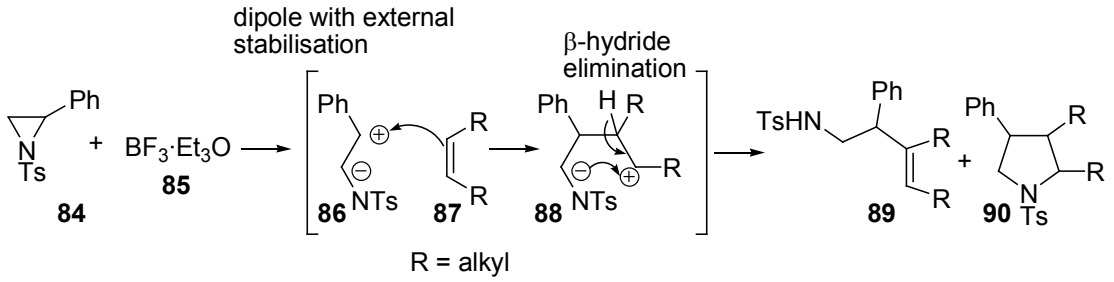
Scheme 16

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,[59] Roy *et al.* recently showed that in the presence of $AgPF_6$, furans **81** and thiophenes **82** are good nucleophiles for the regioselective ring-opening of aziridines **77** to yield exclusively **83** (Scheme 17).[58] The authors believed that the well-known binding ability of Ag(I) towards arenes[60] and aziridines[61] might contribute to such reactivity.



Scheme 17

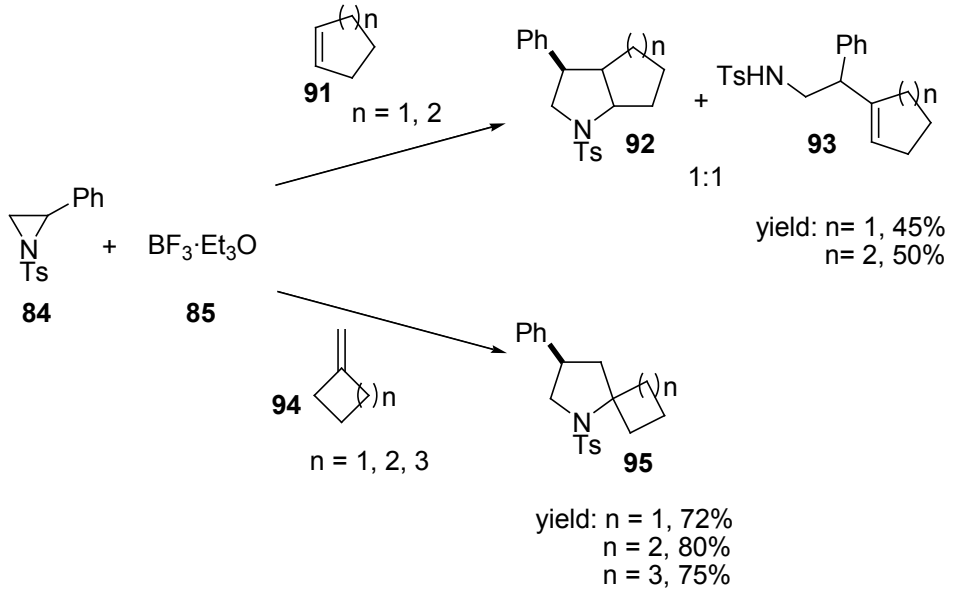
Aziridines have also been found to undergo ring-opening reactions with nonactivated alkenes in the presence of $BF_3{\cdot}Et_2O$. This remarkable work was published by Man and co-workers (Scheme 18).[62, 63] They described this process as a formal [3+2] cycloaddition involving a 1,3-dipole 2-phenyl aziridine precursor. Building on the success of reacting aziridine with allylsilanes,[62] they were able to extend this methodology to a variety of other alkenes.[63] 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 18

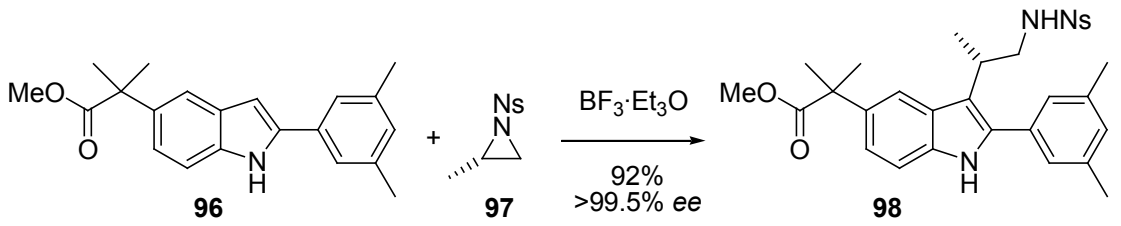
Results showed that the ratio of **89** and **90** depends on the stability of the carbocation of **88** (Scheme 19). When cyclopentene and cyclohexene **91** were used, a 1:1 mixture of **92** and **93** was observed. The yields of these two reactions were low, which was

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.



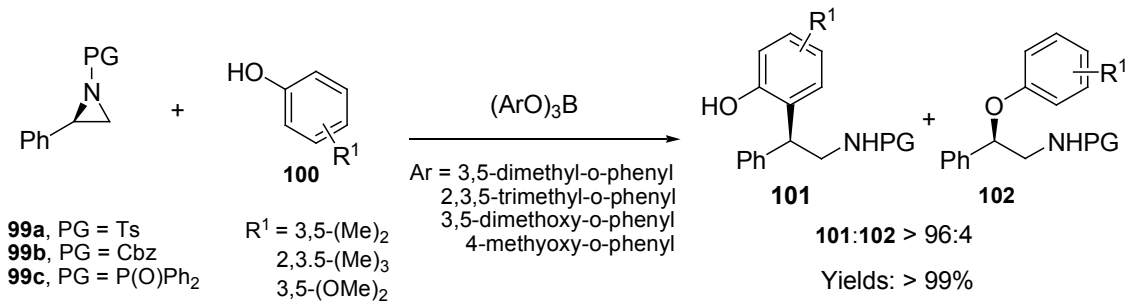
Scheme 19

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-1 is the unprecedented $BF_3{\cdot}Et_2O$-catalysed enantio- and regioselective reaction between 2-arylindole **96** and nosyl aziridine **97** (Scheme 20).[64] The use of $BF_3{\cdot}Et_2O$ 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.[65]



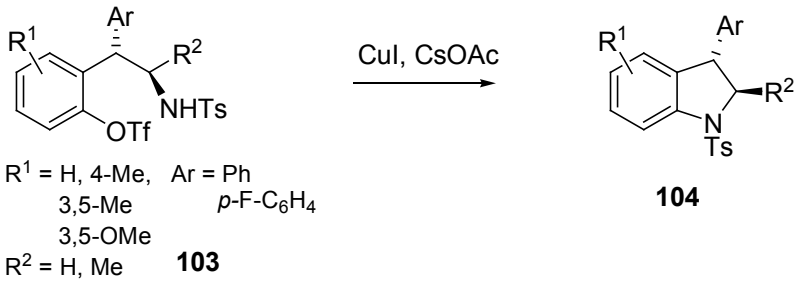
Scheme 20

Effective boron-based Lewis acids are not limited to just $BF_3{\cdot}Et_2O$. 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.[66] 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.



Scheme 21

Having successfully accessed aminophenol derivatives **101**, Pineschi also managed to convert them into aryl indolines **104** using intramolecular amination of aryltriflates **103** with CuI and CsOAc.

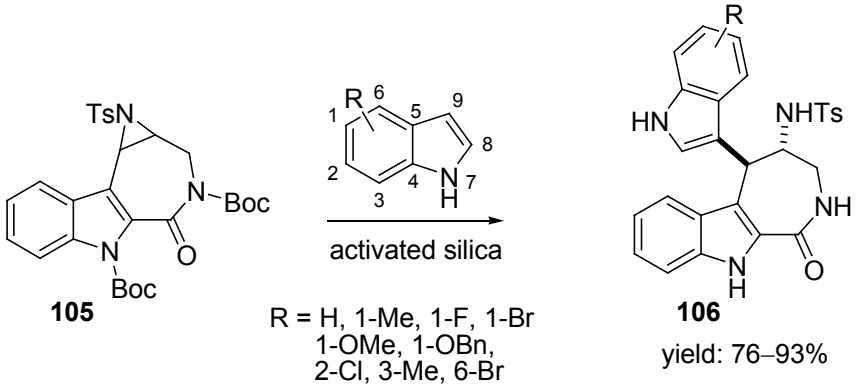


Scheme 22

Another group of substrates capable of directing regioselective attack on the benzylic carbon of the aziridine is α-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).[67] 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.



Scheme 23

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).

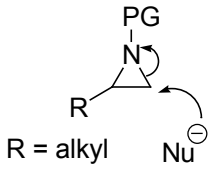
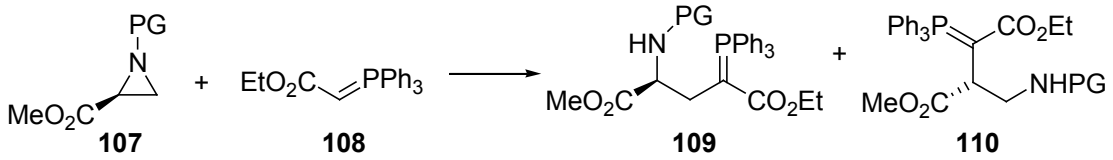


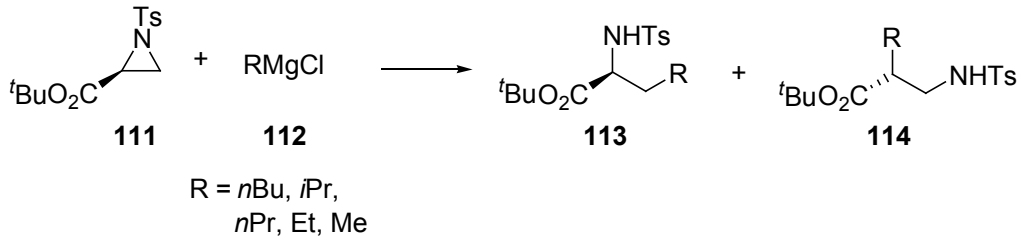
Figure 5

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).[68] 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, $-COC_6H_4NO_2$ 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 $-COCH_2C_6H_4NO_2$ or $-COCH_2Ph$, only **109** was isolated with yields of 30%.



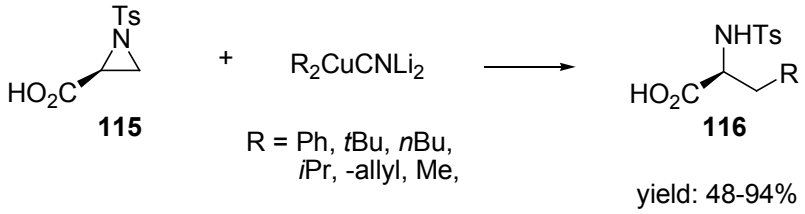
Scheme 24

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).[69] 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.

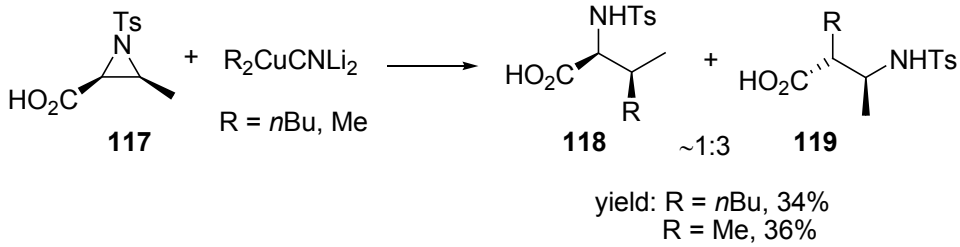


Scheme 25

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).[70] 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).



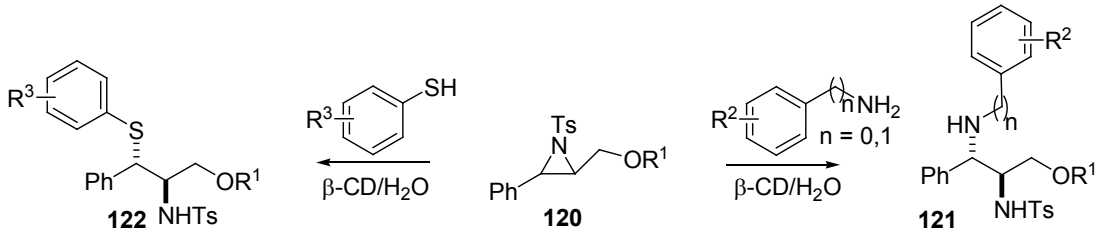
Scheme 26



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.[71] Diamines and amino sulfides are biologically and synthetically important classes of compounds in the pharmaceutical industry.[72] Rao *et al.* have devised an approach to synthesise these two groups of substrates (Scheme 28).[72] In the presence of β-cyclodextin (β-CD) in H_2O, 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.



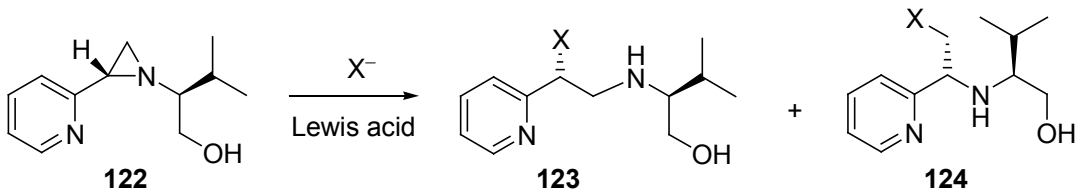
R^3 = H, 2-Me, 4-Br, 4-OMe
yield: 86–94%

R^1 = H, TBDMS

R^2 = H, 2-Me, 4-F
yield: 84–92%

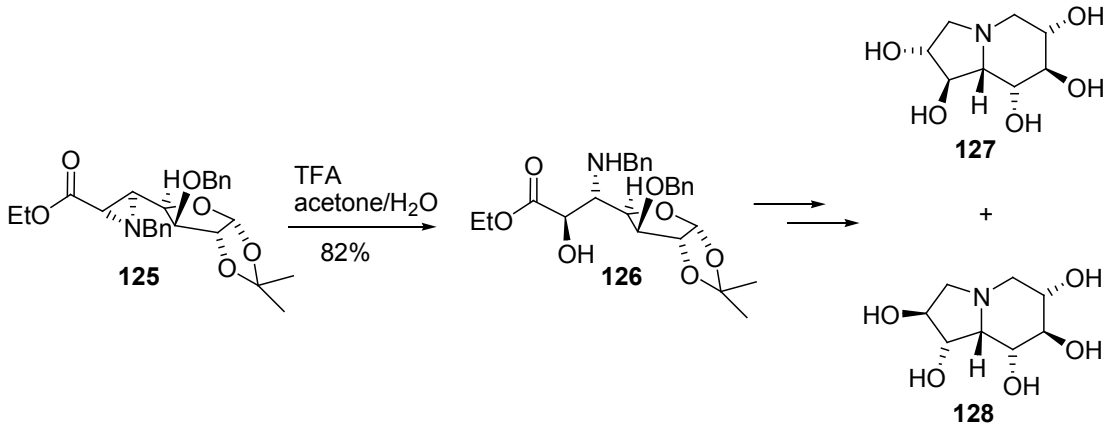
Scheme 28

Ring-opening of pyridyl-substituted aziridine with *N*-, *S*- and *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 chloromethyllithium to pyridineimine derived from (*S*)-valinol, aziridine **122** was allowed to react with a series of nucleophiles in the presence of Lewis acids. Except when NaN_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 H_2O to give **126**, promoted by TFA (Scheme 30).[73] Following a six-step sequence from **126**, compound **127** and **128** were prepared.

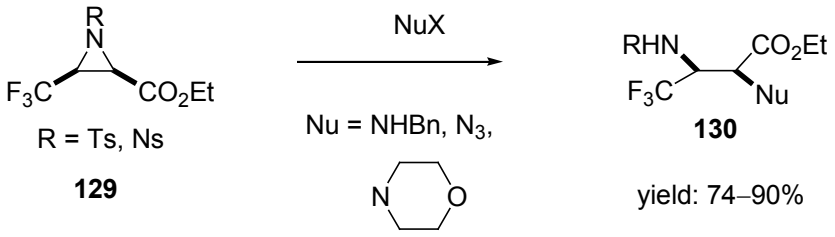


Scheme 30

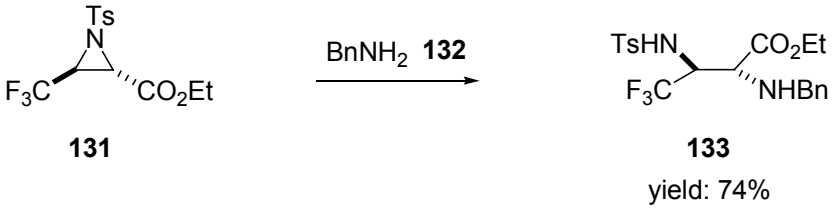
The importance of fluorinated compounds has been well documented.[74] This class of substrates has attracted increasing attention in recent years, especially in the pharmaceutical industry.[74,75] The introduction of fluorine atoms into organic molecules often results in profound changes in their chemical and biological properties.[75] One

important family is fluorine-substituted amino acids.[76] Many methods for their preparation have been reported.[75,76] However, few methodologies for the synthesis of fluorinated diamino acid have been developed.[77]

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).[78] 2,3-*cis*-Aziridines **129** were prepared form CF_3-imines reacting with ethyl diazoacetate in the presence of a sub-stoichiometric amount of $BF_3{\cdot}Et_2O$.[79] When treated with amines or NaN_3, 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.[80] 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.



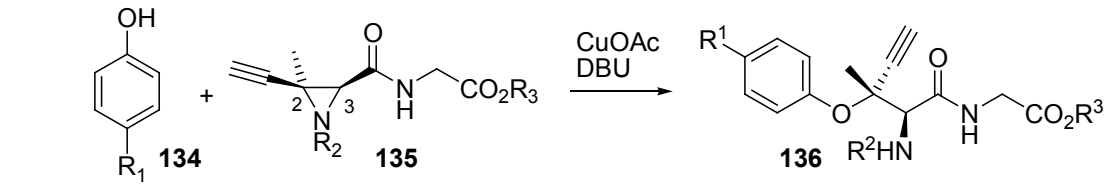
Scheme 31



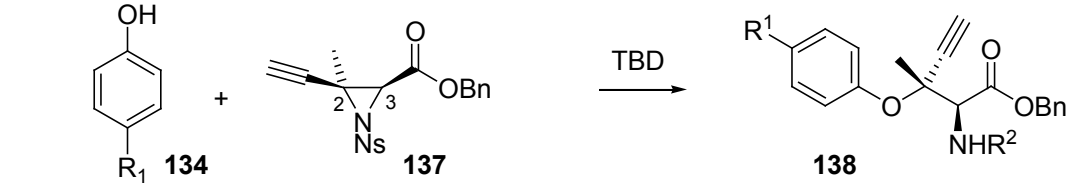
Scheme 32

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 $–CF_3$ substituent is less able than the –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).[81] 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.

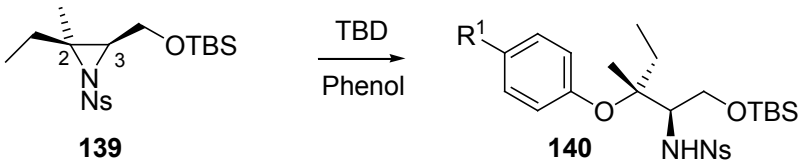


Scheme 33



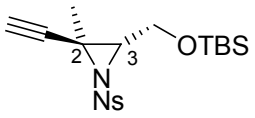
Scheme 34

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.[82] 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 that 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.



139 **140**

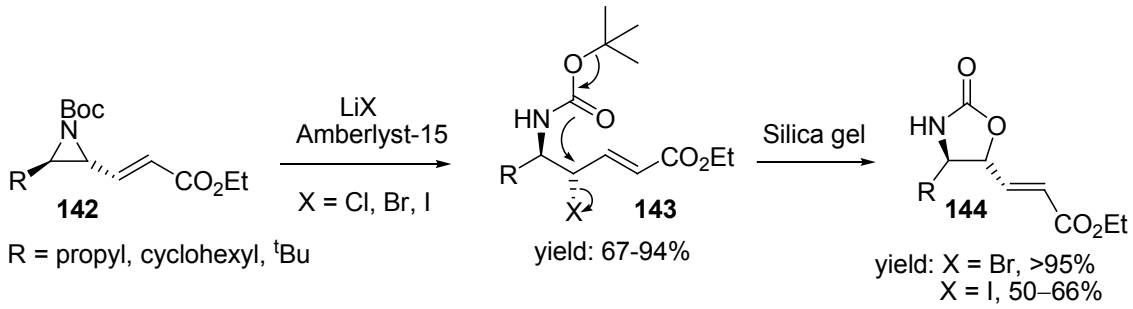
Scheme 35



141

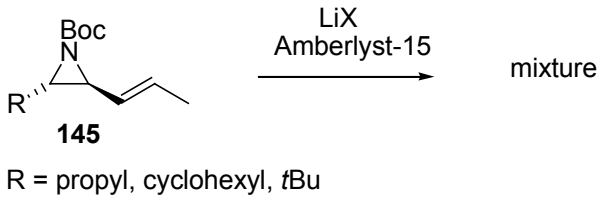
Figure 5

Halides are another good class of nucleophiles in the reactions with aziridines.[83] Righi *et al.* found that *N*-Boc-alkenyl aziridines **142** underwent regioselective ring-opening with lithium halides when catalysed by Amberlyst-15 (Scheme 36).[84] 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.



Scheme 36

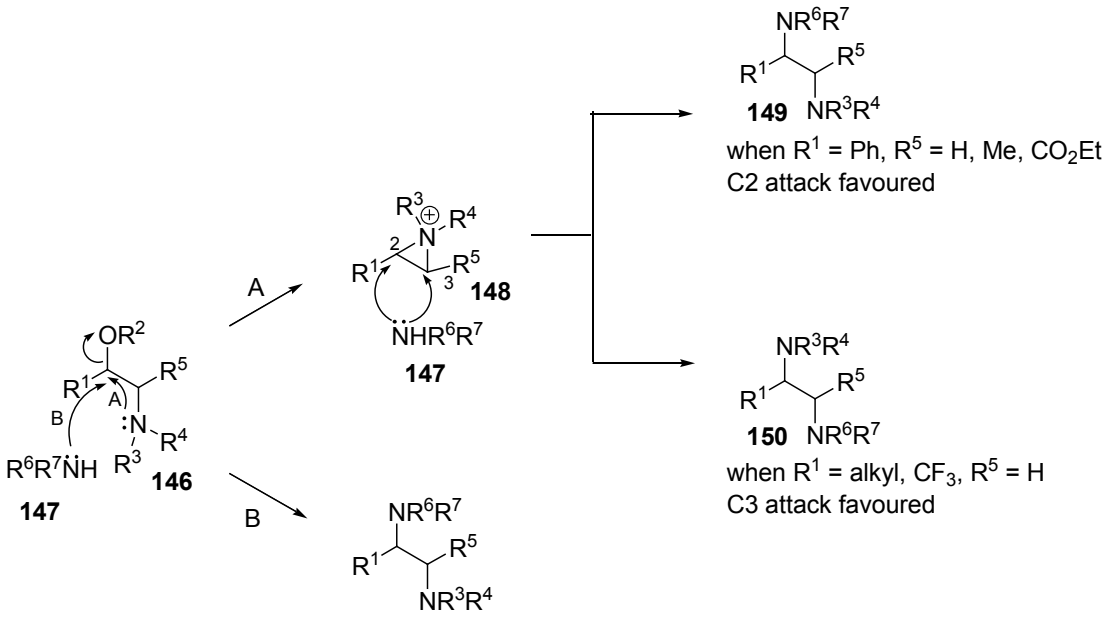
Nevertheless, when aziridine **145** was used, with a methyl group replacing the carboxylate group of **143**, the reactions gave a complex mixture of products (Scheme 37).



Scheme 37

1.6.3 *via* Aziridinium Ion

Aziridinium ion chemistry has gained increasing interest from synthetic chemists.[85] They are useful intermediates in facilitating aziridine ring-opening processes and proved to be valuable for the synthesis of chiral diamines.[85] A general strategy in forming aziridinium ions such as **148**, as shown in path A in Scheme 38, relies on an intramolecular S_N2 reaction of hydroxyamine **146**.[85,86] 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 R^1 and R^5 substituents, or sometimes the nucleophiles.[85,86,87]

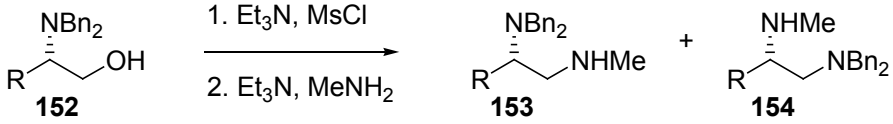


151, diastereomer of **149**

Scheme 38

However, as illustrated in path B, direct intermolecular S_N2 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.

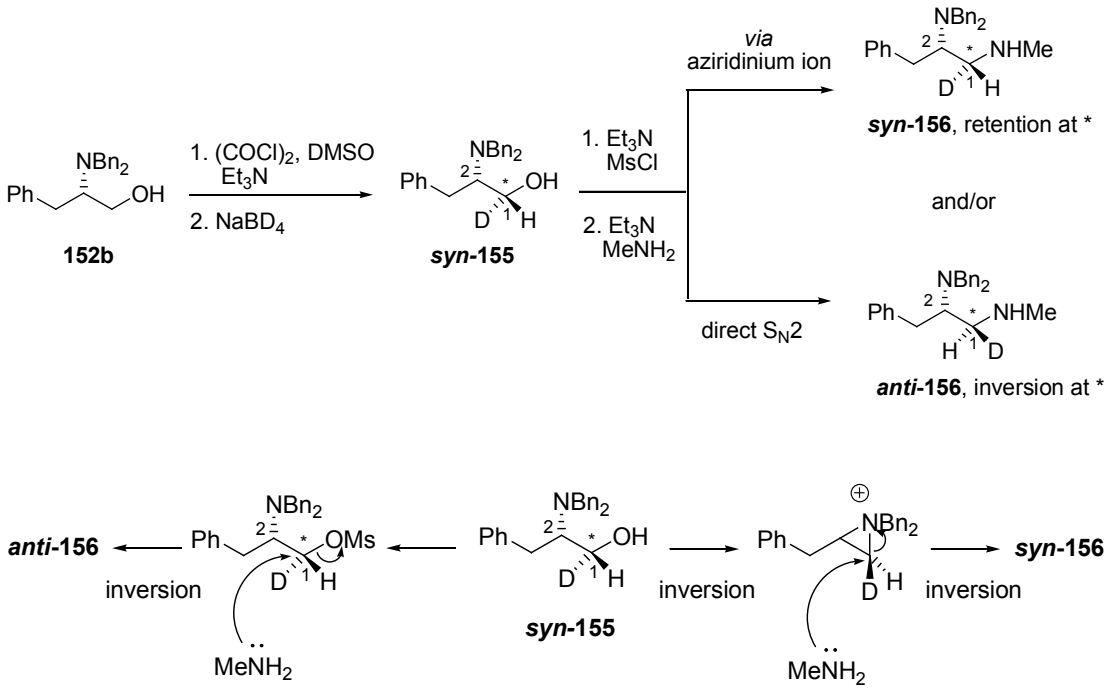
The O'Brien group has probed the evidence of the aziridinium ion formation using a novel deuterium substitution approach.[88] During their investigation for the synthesis of 1,2-chiral diamines, they observed that varying the R group of **152** affected the regioselectivity (Scheme 39). When R = Me, Bn or *i*Pr, **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**.



starting material	R	yield(%)	**153a-d:154a-d**
152a	Me	78	70:30
152b	Bn	70	94:6
152c	*i*Pr	62	93:7
152d	Ph	78	2:98

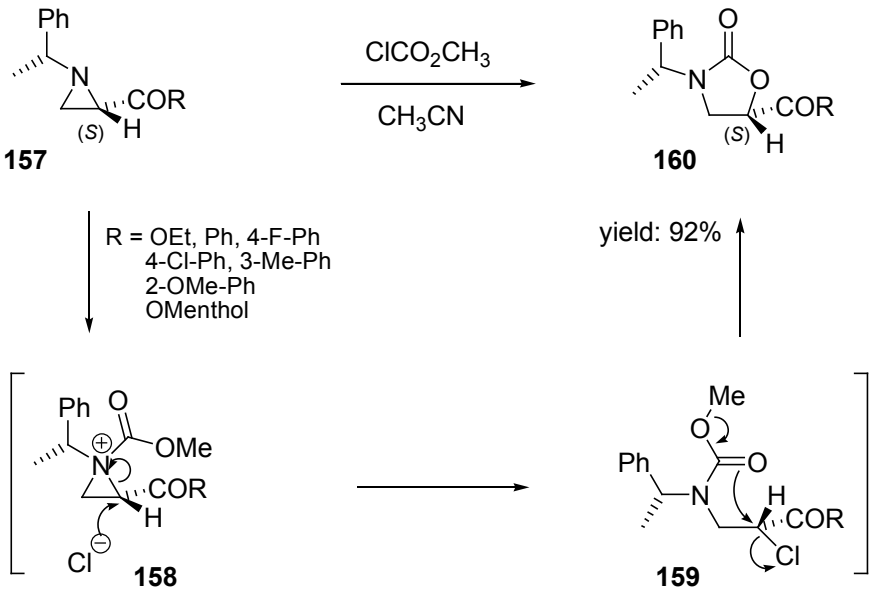
Scheme 39

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.



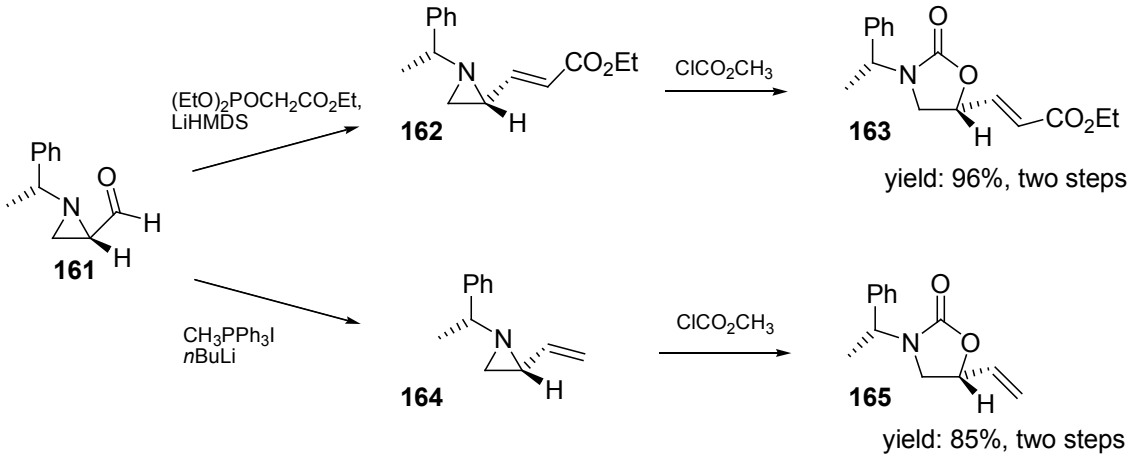
Scheme 40

Ha *et al.* have reported a novel synthesis of oxazolidinones *via* aziridinium ion species (Scheme 41).[89] 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.



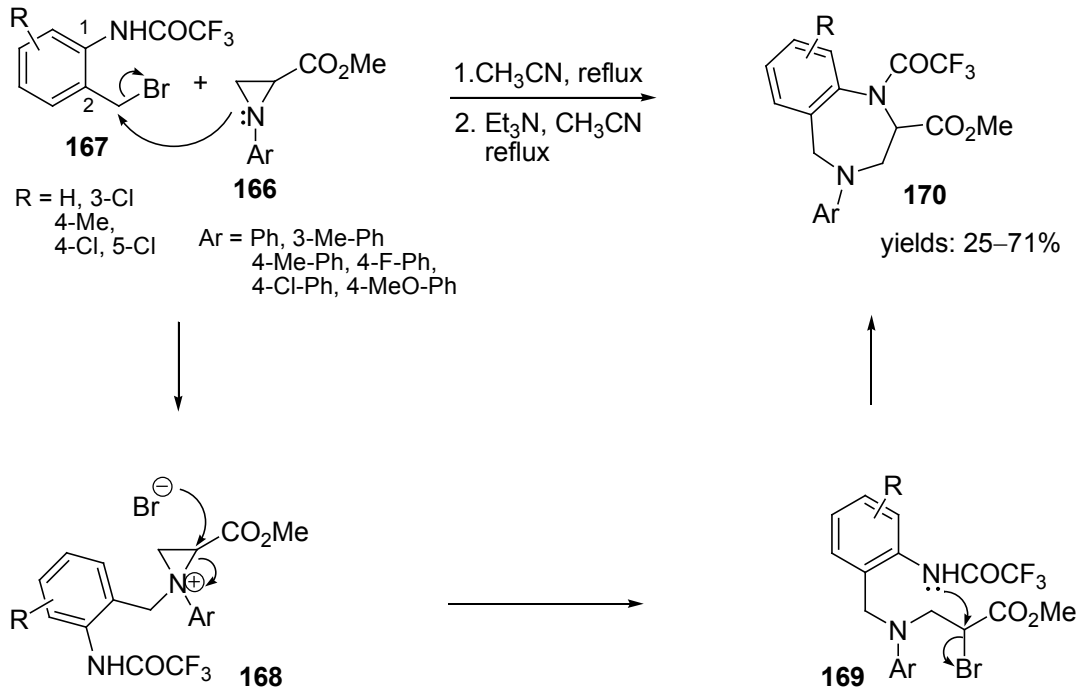
Scheme 41

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.



Scheme 42

Wang and co-workers extended this methodology to the synthesis of 1,4-benzodiazepine derivatives **170** (Scheme 43).[90] 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 ^{1}H-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.

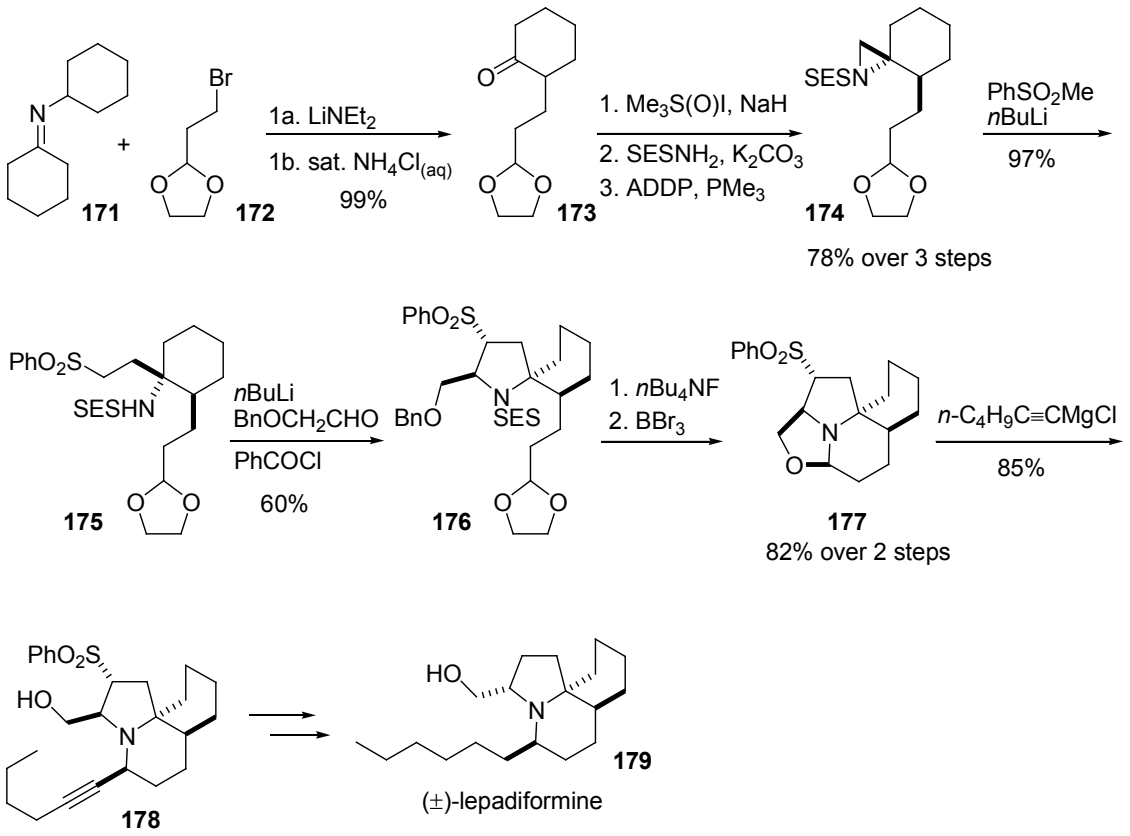
2. Results and Discussion

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.[91] The natural form (–)-lepadiformine, a decahydro-1*H*-pyrrolo[1,2-*j*]quinoline isolated in 1994 by Biard *et al.* from the tunicate *Clavelina lepadiformis*[92], has moderate in vitro cytotoxic activity towards varioustumor 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**[94], as described by Minor and Overman.[95] Epoxidation of **173** with dimethylsulfoxonium methylide, prepared from $Me_3S(O)I$ and NaH *in situ*, yielded a single epoxide, which reacted with $SESNH_2$ to give the corresponding amino alcohol. Subjection of this amino alcohol to modified Mitsunobu conditions [1,1'-(azodicarbonyl)dipiperidine (ADDP), Me_3P] 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 $PhSO_2Me$, giving **175** in 97% yield. Exposure of the dianion of **175** to $BnOCH_2CHO$ followed by quenching with PhCOCl furnished pyrrolidine **176**. This process proceeds through a 5-*endo-trig* cyclisation of the resulting *E*-vinylic 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-ynylmagnesium bromide in an S_N1-like substitution gave alkyne **178**, which was transformed into **179** in another seven steps.

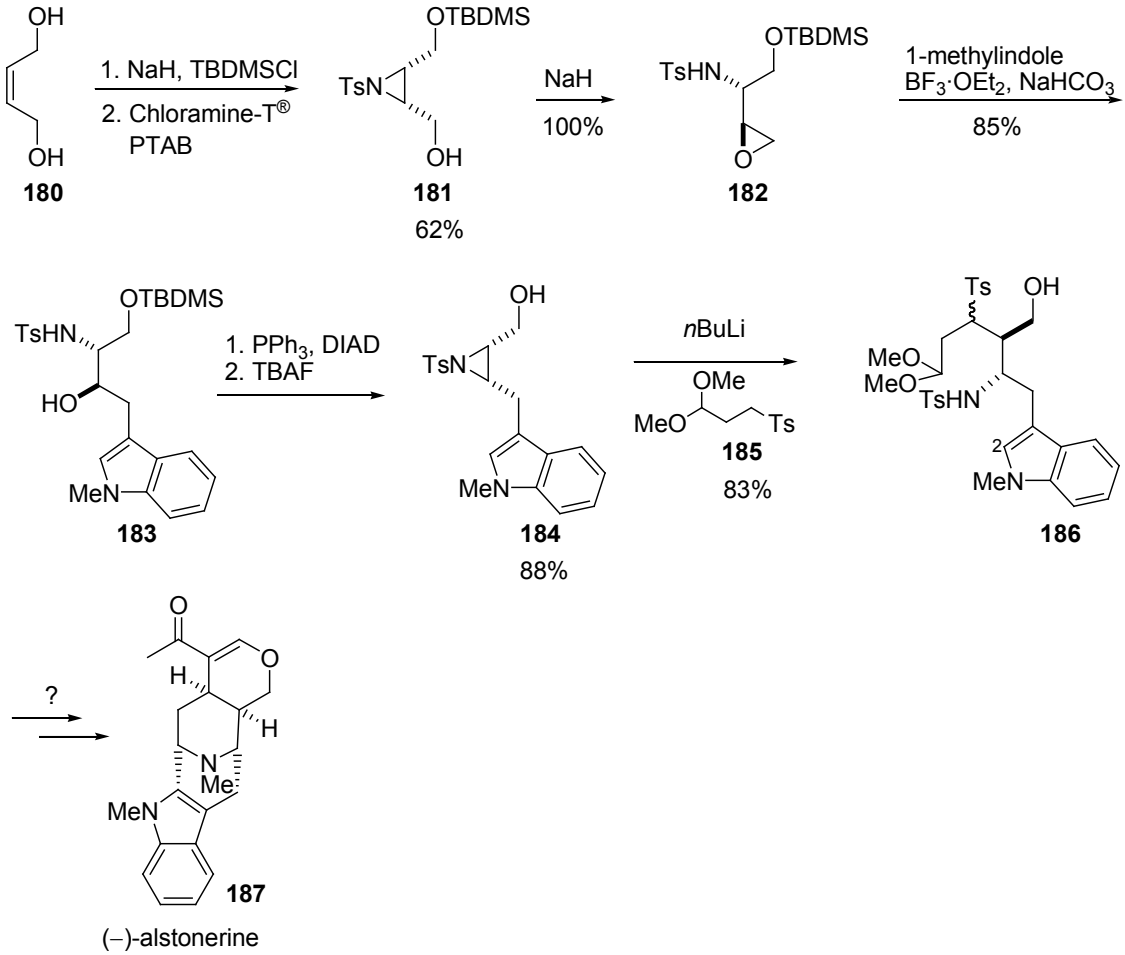


Scheme 44

A modified approach to the previously established route[96] in the group that has achieved the pentacyclic framework of (–)-alstonerine[97] **187**, a macroline-related alkaloid, was also investigated, as outlined in Scheme 45.[98] This involves the synthesis and ring-opening reaction of the 1,2,3-trisubstituted indole hydroxyl-methyl-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**;[99] $BF_3{\cdot}OEt_2$-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

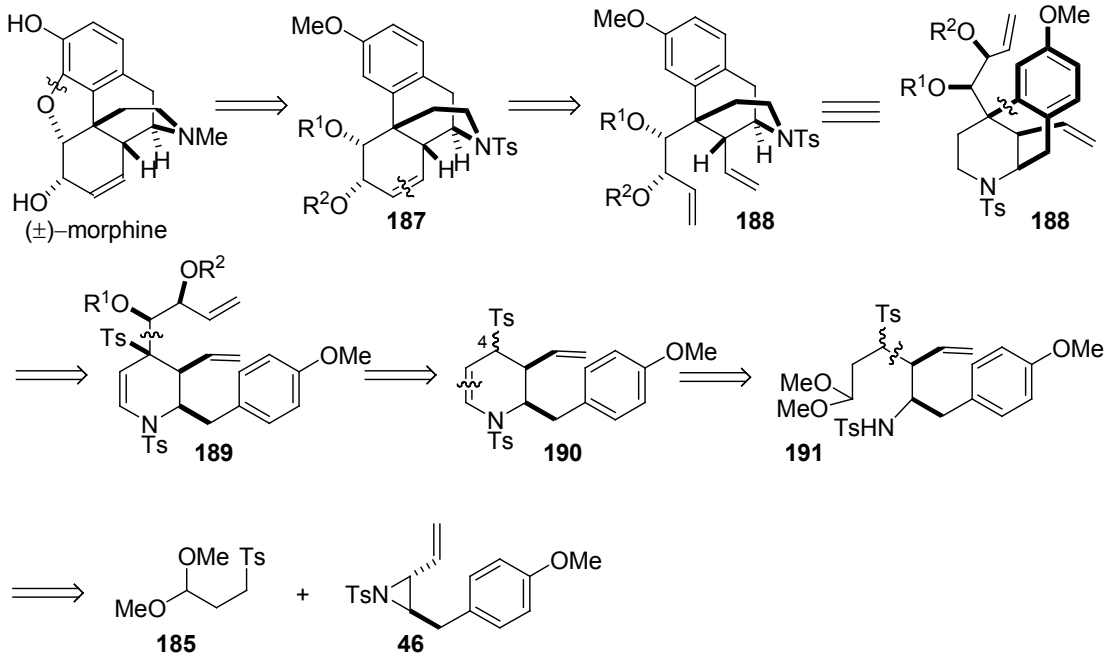
$BF_3{\cdot}Et_2O$ and TMSI, a Pictet–Spengler reaction occurred involving the indole C2. Current effort is focused on the use of alternative nucleophiles for ring-opening of **184**.



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.[31] In this route, a key step was the preparation of acetal tosamide **191**, by reaction of acetal **185** and 2,3-*trans*-vinylaziridine **46**. Aziridine **46** may in principle react at either of the aziridine ring carbon atoms, or in an S_N2' 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

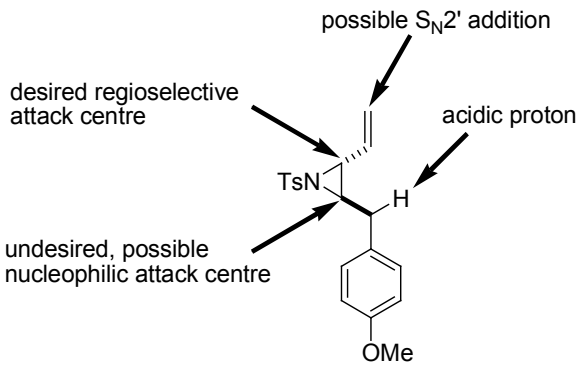
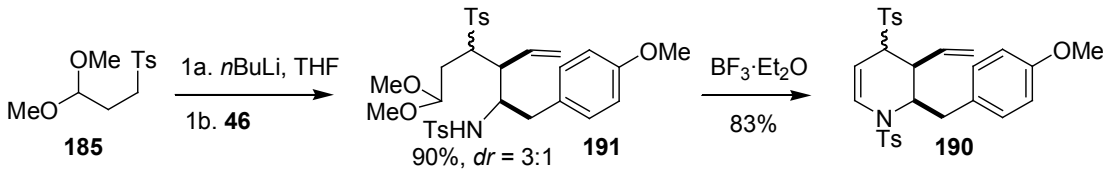


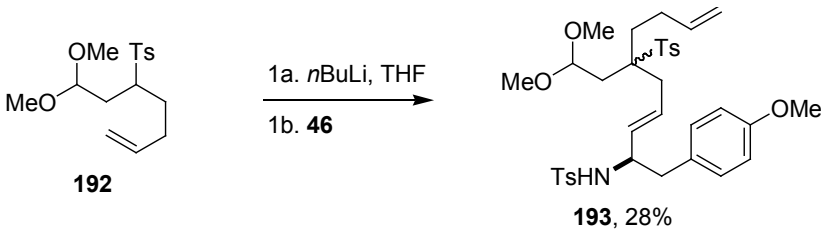
Figure 6

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 $BF_3{\cdot}Et_2O$, **191** cyclised to yield *N*-tosyl tetrahydropyridines **190**.



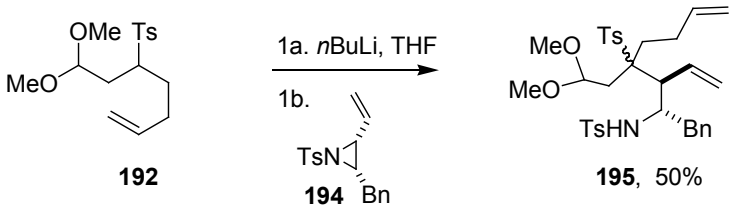
Scheme 47

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_N2' addition at the terminal olefin, in a poor yield of 28% (Scheme 48).



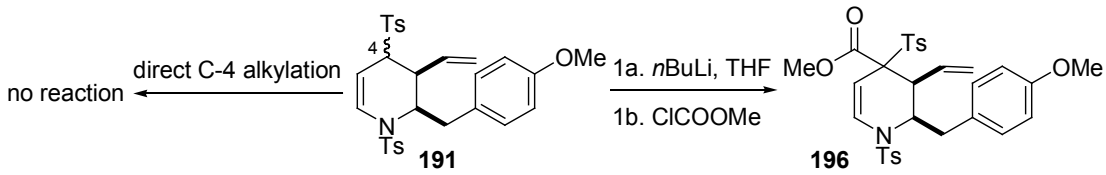
Scheme 48

Intriguingly, when the 2,3-*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).

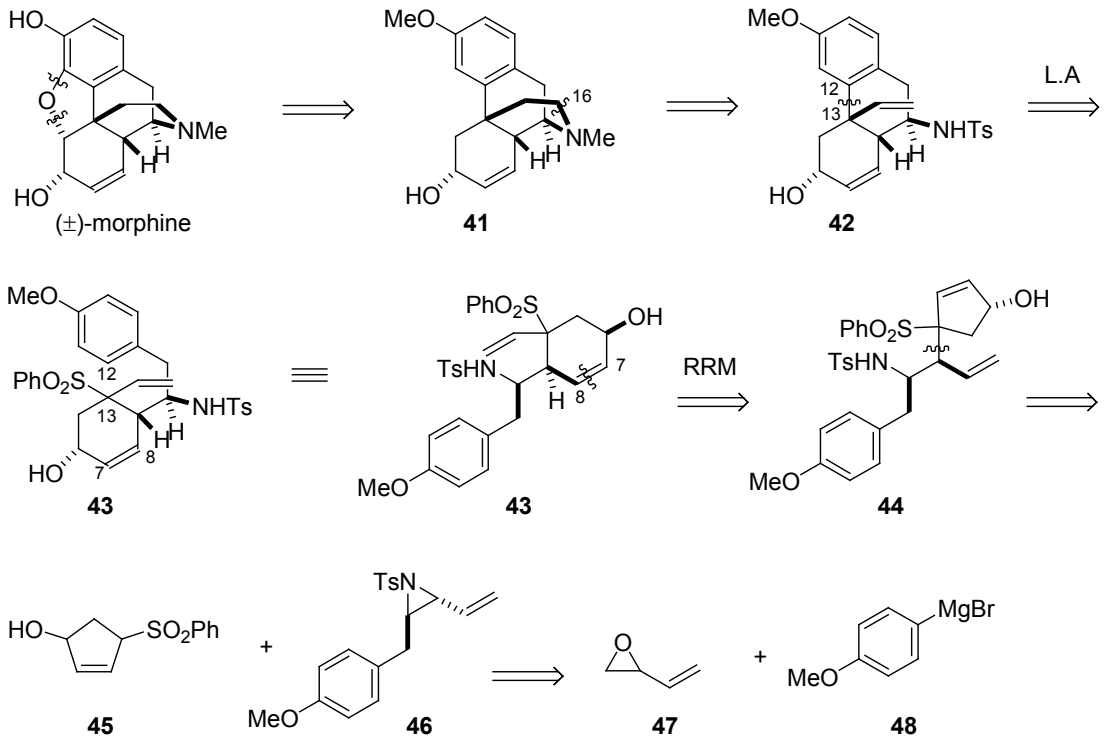


Scheme 50

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.

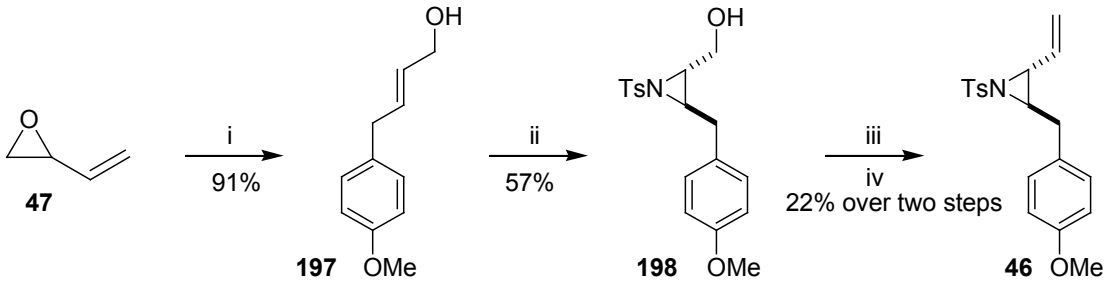


Scheme 7

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[30] and Carballares.[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[100] 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 $Cu(OTf)_2$[101] since it was found by Hyland that only starting material and tosylamide were recovered.



i) (4-methoxyphenyl)magnesium bromide **48** (1.2 equiv), CuCN (0.1 equiv), THF, –78 °C-rt, 3 h; ii) anhydrous chloramine-T® (1.1 equiv), $PhNMe_3Br_3$ (0.1 equiv), dry MeCN, rt, 20 h; iii) IBX (1.1 equiv), DMSO, rt, 22 h; iv) Ph_3PCH_3Br (1.1 equiv), KHMDS (1.1 equiv), THF

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 *β*-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**.

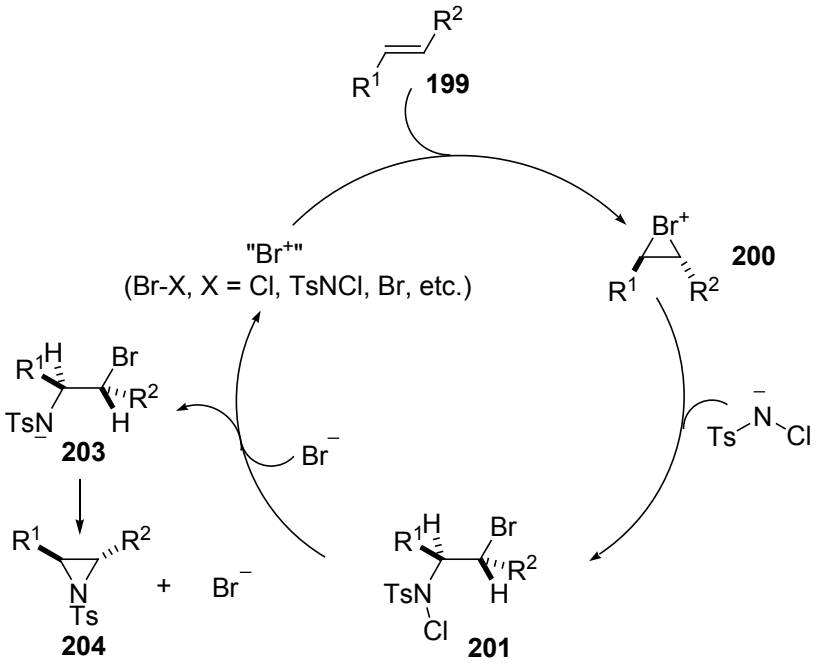
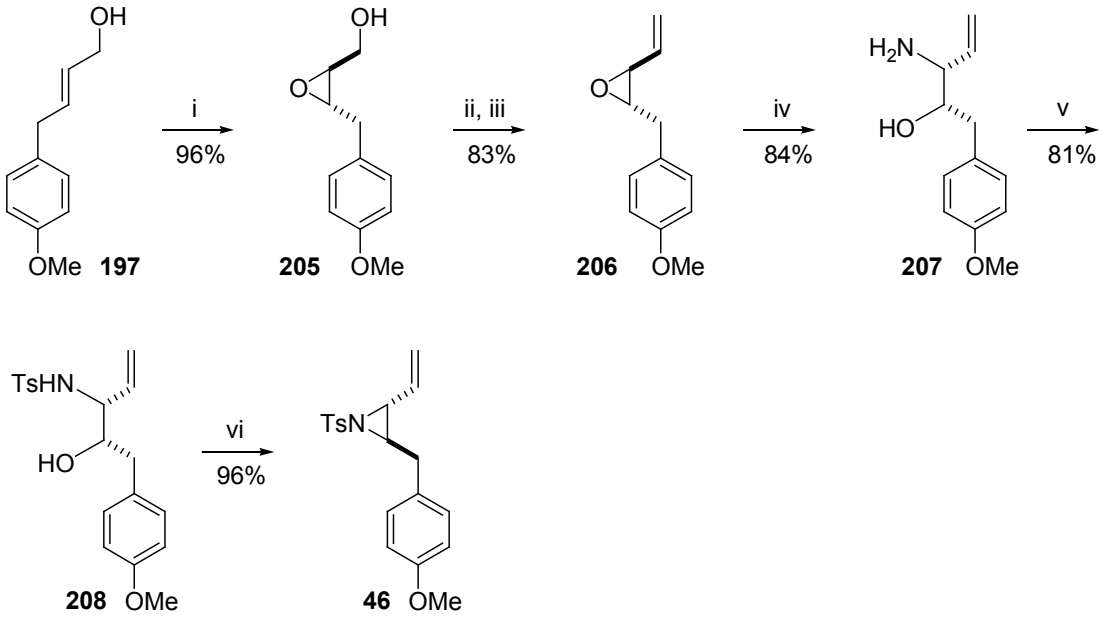


Figure 7

The subsequent oxidation of alcohol **198** was achieved using IBX to give the corresponding aldehyde in typically above 95% yields.[102] 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.



i) *m*-CPBA (1.3 equiv), CH_2Cl_2, –78 °C-rt, 4 h, 96%; ii) $(COCl)_2$ (1.2 equiv), DMSO (2.4 equiv), Et_3N (5.0 equiv), CH_2Cl_2, –78 °C-rt, 1h, 85%; iii) Ph_3PCH_3Br (2.0 equiv), KHMDS (2.0 equiv), THF, –20 °C, 1.5 h, 83% over two steps; iv) NH_4OH (28% NH_3), microwave, 110 °C, 35 min, 84%; v) TsCl (1.5 equiv), DMAP (0.12 equiv), Et_3N (3.1 equiv), CH_2Cl_2, –5-0 °C, 3 h, 81%; vi) DIAD (2.0 equiv), PPh_3 (2.6 equiv), THF, –25 °C then –5 °C, 13 h, 96%

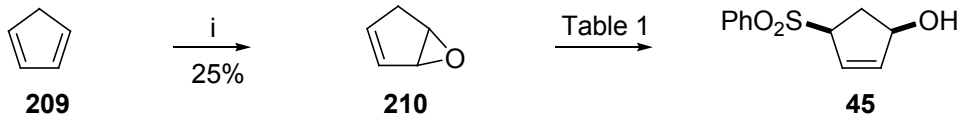
Scheme 52

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 $PhSO_2Na$. 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).



209 **210** **45**

i) CH_3COOOH (1.0 equiv), Na_2CO_3 (3.97 equiv), NaOAc (0.04 equiv), CH_2Cl_2, 20 °C

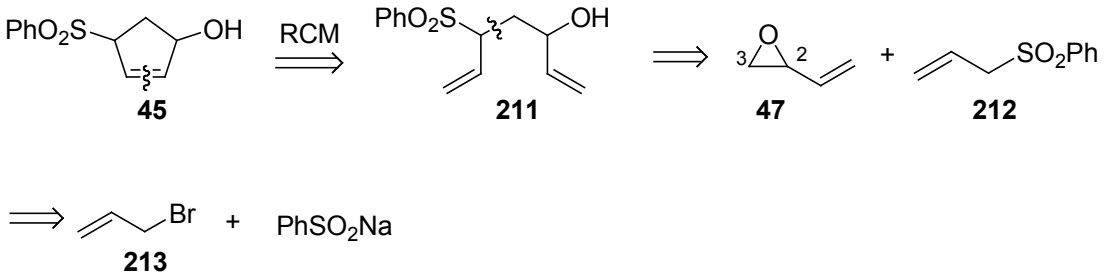
Scheme 53

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 $PhSO_2Na$ salt is much greater in DMF than THF.

Entry	solvent	catalyst (mol %)	time	temp. (°C)	yield (%)
1	THF	$Pd(acac)_2$ (0.5→5)	4 days	60	37
2	DMF	$Pd(acac)_2$ (5)	6 h	60	–
3	THF	$Pd(PPh_3)_4$ (5)	2 days	90	–
4	THF	$Pd_2(dba)_3$ (5)	6 h	60	20
5	DMF	$Pd_2(dba)_3$ (5)	6 h	90	42

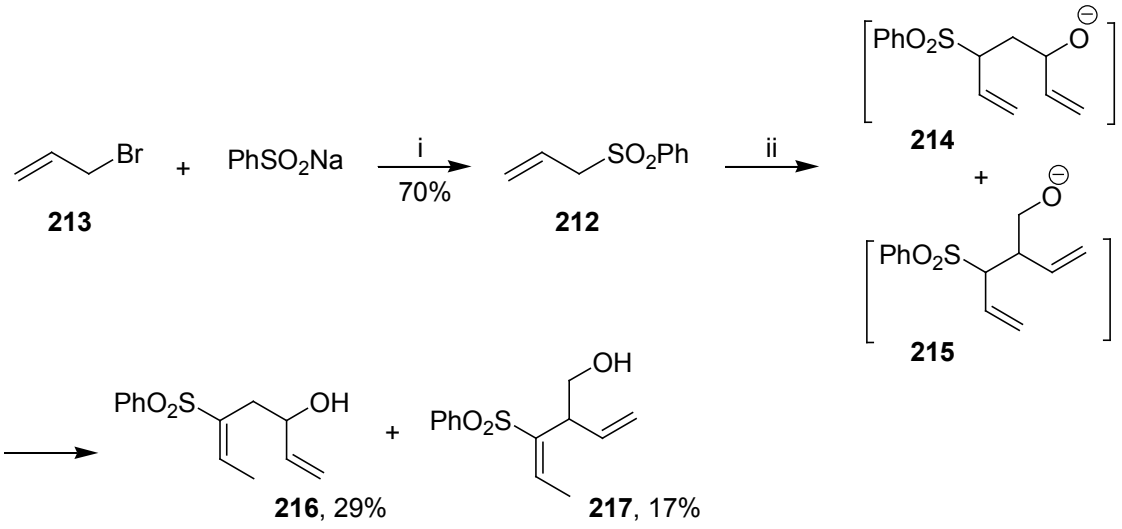
Table 1

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.[33a,34] 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 $PhSO_2Na$.



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**[104] resulted in olefin migrated products **216** and **217** with a 1.7:1 ratio according to ^1H NMR analysis of the crude mixture.

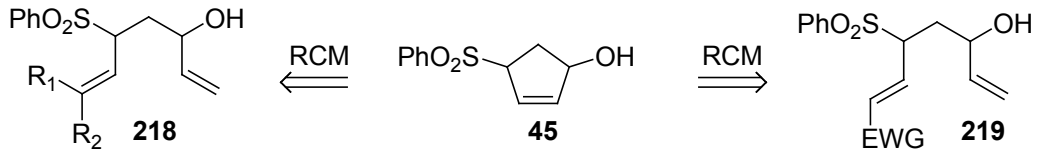


i) DMF, rt, 4 h; ii) a) *n*BuLi (1.2 equiv), Et_2O, –20 °C-rt, 45 min; b) butadiene monoxide **47** (1.0 equiv), –20 °C-rt, 2.5 h

Scheme 55

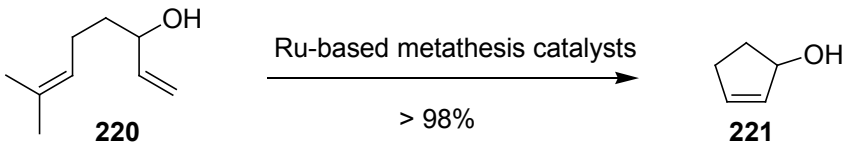
These results are probably due to the relative lack of stability of intermediates **214** and **215**, induced by the strong electron withdrawing ability of the β-sulfone and the products being more stable α-sulfonyl *tri*-substituted olefins. The geometry of the double bonds was not proved. However, 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.*[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

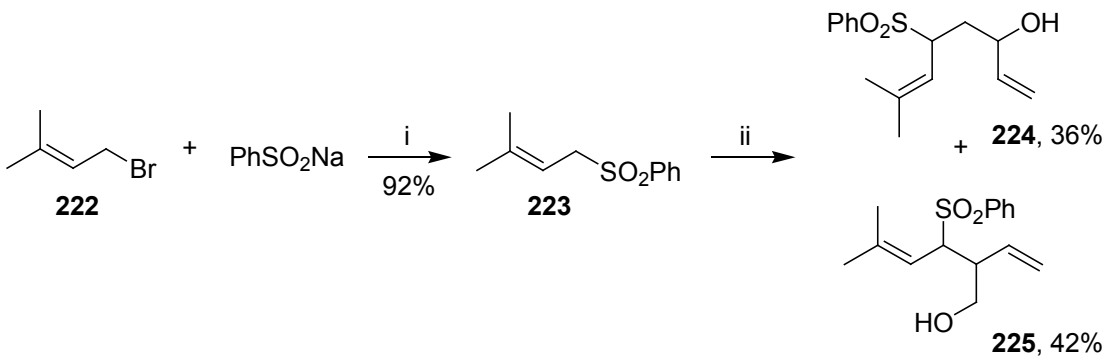
Work by Hoveyda *et al.* has shown that RCM of diene **220** gave the corresponding cyclopentenol **221** in excellent yields (Scheme 57).[106]



Scheme 57

Encouraged by this, prenyl sulfone **223** was prepared from prenyl bromide **222** and $PhSO_2Na$ similar to that previously described in Scheme 55 (Scheme 58).[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

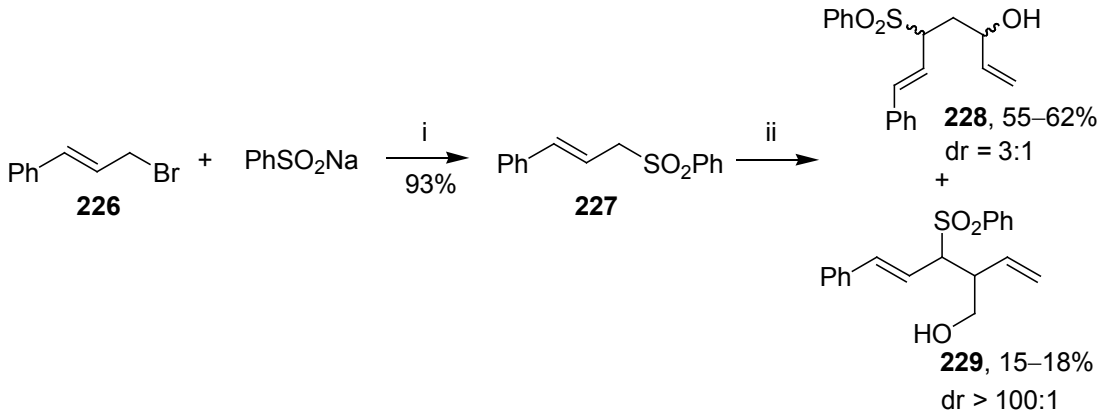
stereochemical relationship between the phenylsulfonyl and hydroxyl substituents was not investigated.



i) DMF, rt, 6 h; ii) a) *n*BuLi (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

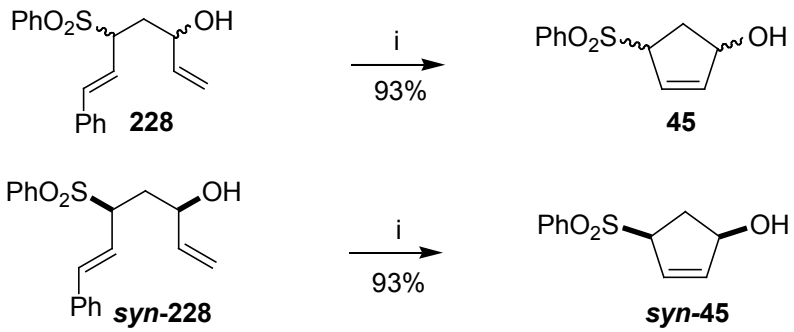
As depicted in Scheme 56, in line with the theory of having a more substituted double bond, introduction of an electron-withdrawing group such as phenyl was also expected to have a similar stabilising effect. Therefore, cinnamyl sulfone **227** was prepared from cinnamyl bromide **226** and $PhSO_2Na$.[107] 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.



i) DMF, rt, 2 h; ii) a) *n*BuLi (1.05 equiv), THF, –20-0 °C, 45 min; b) butadiene monoxide **47** (1.1 equiv), –20 °C- rt, 1 h 45 min

Scheme 59

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.

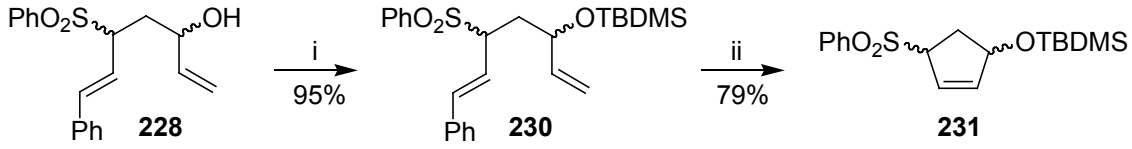


i) Catalyst **50** (1 mol%), CH_2Cl_2, 40 °C, 10 min for **228**; 1 min for 3,5-***syn*-228**

Scheme 60

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 TBDMSCl 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.



i) TBDMSCl (1.8 equiv), Et_3N (3.0 equiv), DMAP (7.5 mol%), CH_2Cl_2, 40 °C, 24 h; ii) catalyst **50** (5 mol%), CH_2Cl_2, 40 °C, 16 h

Scheme 61

Overall, a satisfactory route to access cyclopentenyl sulfone **45** was discovered. Cinnamylsulfone **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-SO_2Ph 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 sulfonylcyclopentadiene **232** (Figure 8).

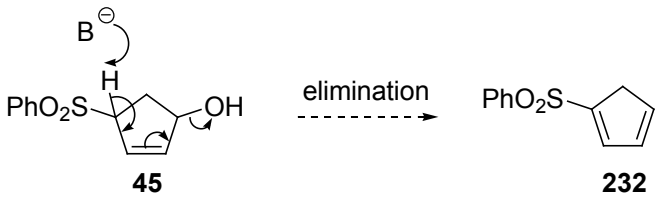
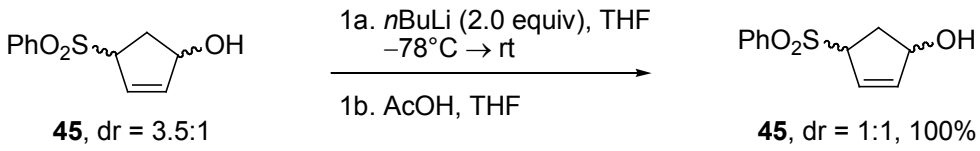


Figure 8

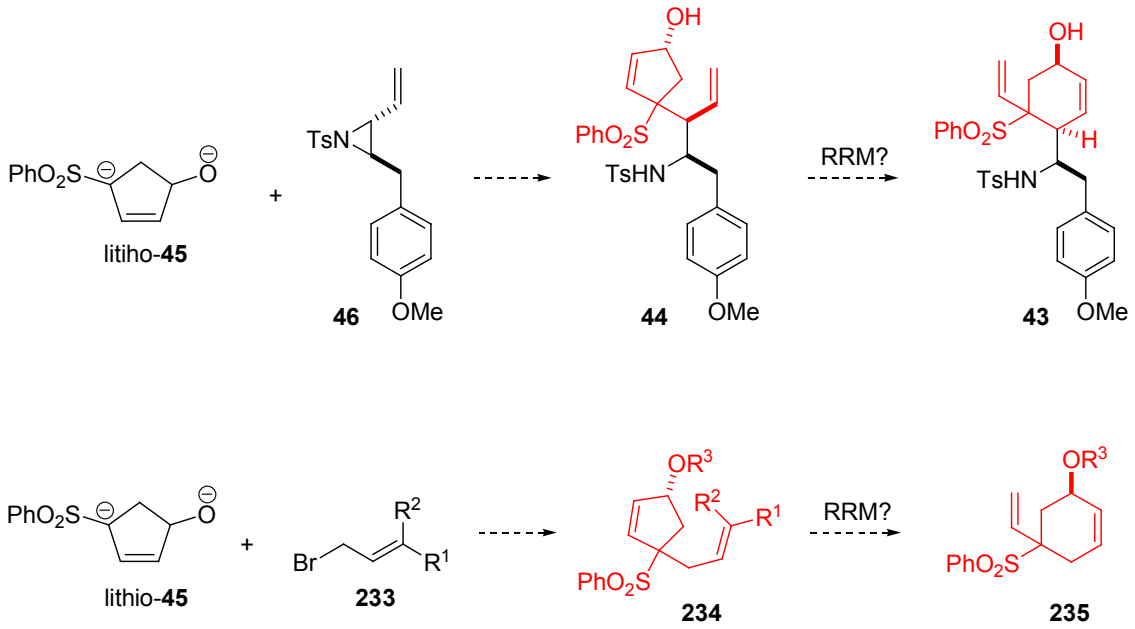
Therefore, a simple deprotonation experiment was carried out in which compound **45** was exposed to two equivalents of *n*BuLi in THF at –78 °C (Scheme 62). The resulting solution was warmed to 0 °C over a period of two hours. After stirring at that temperature for one hour followed by two hours at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



Scheme 62

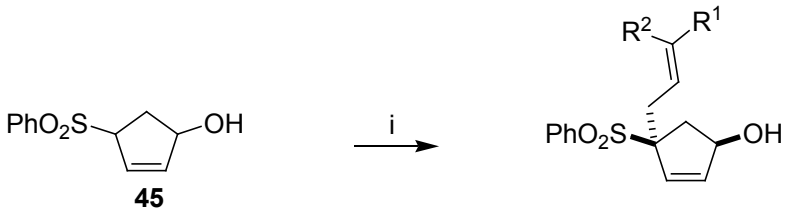
2.2.3.2 α-SO_2Ph Alkylation of 45

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).



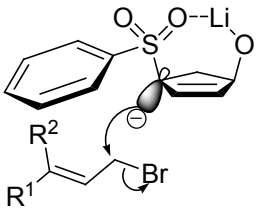
234a: R^1 = H, R^2 =H; 61%
234b: R^1 = Me, R^2 =H; 67%
234c: R^1 = Ph, R^2 =H; 49%
234d: R^1 = Me, R^2 =Me; 40%

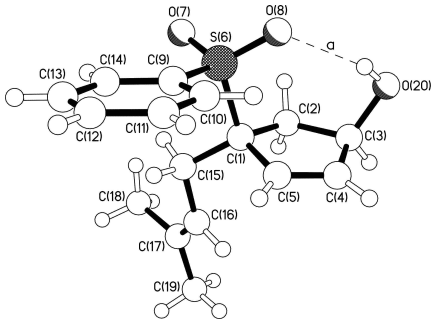
i) a) *n*BuLi (2.1 equiv), THF, –78 °C, 30 min; b) $R^1R^2C{=}CHCH_2Br$ **233** (1.0 equiv), THF, –78 °C-rt, 1.5-2.5 h

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-*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.[108] As illustrated in Figure 9, the lithium cation coordinates with the oxy-anion and the proximal oxygen of the $PhSO_2$ group.[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 –OH and the $–SO_2$ groups (Appendix I).





X–ray structure of 234d

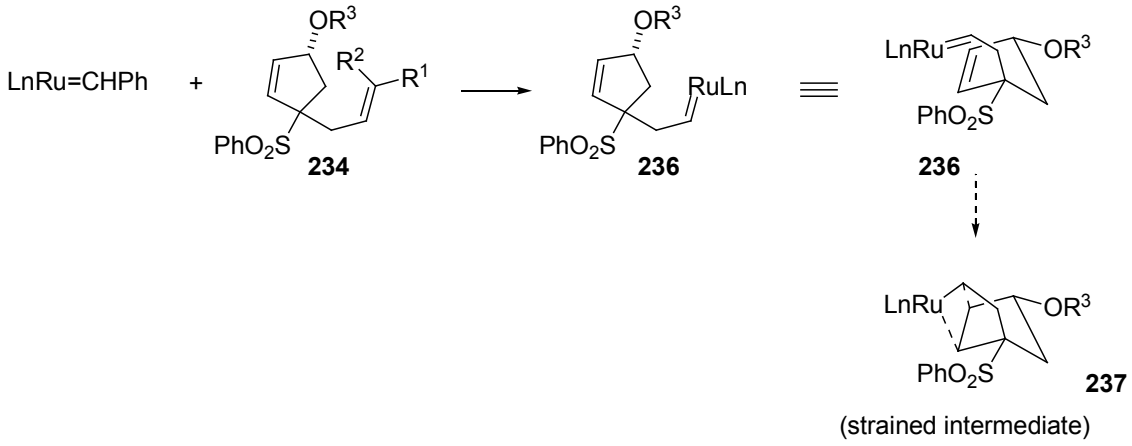
Figure 9

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).

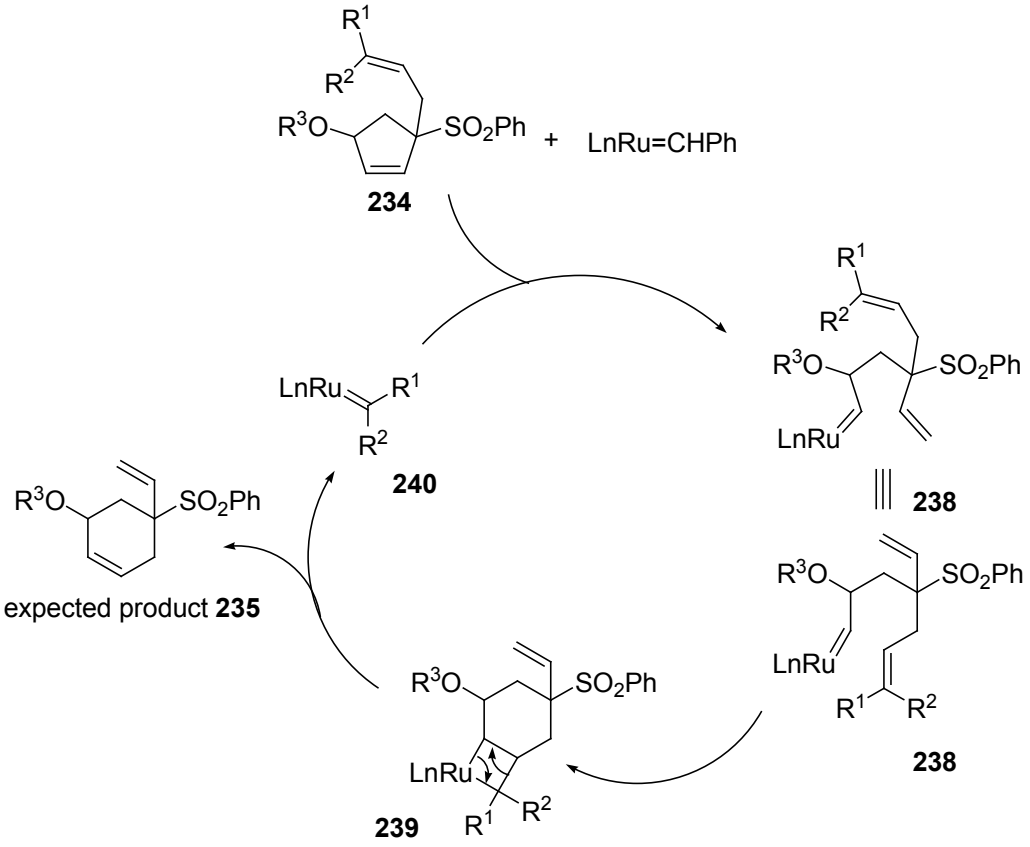
Mechanism 1 begins with an initially attack of the catalyst on the side chain olefin of **234** to give **236** followed by the interaction with the cyclic double bond in an attempt to undergo an intramolecular ring-opening of the cyclopentene (Scheme 65). However, as the Ru atom has to be bonded to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



Scheme 65

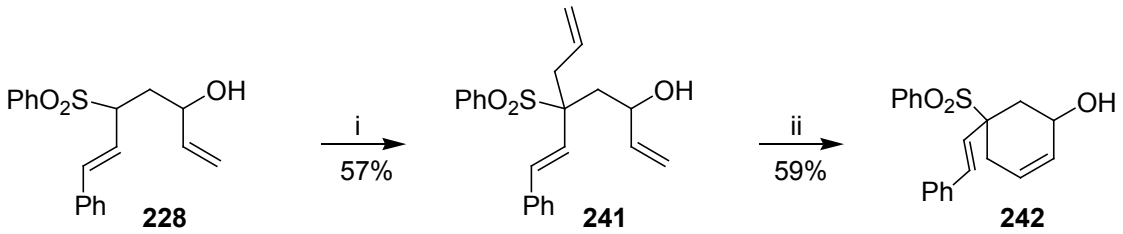
In mechanism 2, cyclopentene **234** is opened by the catalyst, generating intermediate **238** that then undergoes a ring-closing metathesis involving the side chain olefin (Scheme 66). Expulsion of $LnRu{=}CHR^1R^2$ **240** from **239** yields the expected cyclohexene **235**. The regenerated ruthenium 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

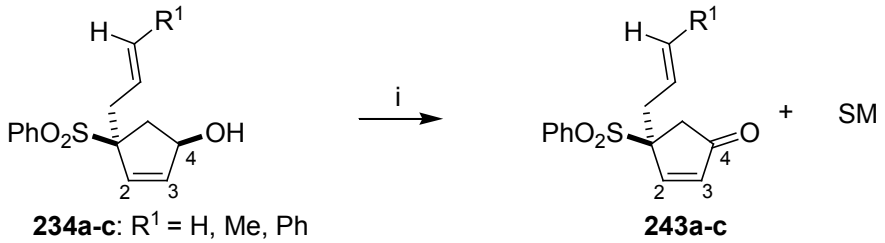
Additionally, since RRM reactions were rationalised to be thermodynamically driven,[109] to ascertain whether cyclohexene was favoured, the following experiments were carried out (Scheme 67). Triene **241** was prepared from **228** *via* an S_N2 reaction with allyl bromide. Treatment of **241** with catalyst **50** in dilute CH_2Cl_2 afforded cyclohexene **242** as the only product isolated.



i) *n*BnLi (2.1 equiv), CH_2=$CHCH_2Br$ (1.0 equiv), THF, –78 °C-rt, 1 h; ii) catalyst **50** (3 mol%), CH_2Cl_2, rt, 24 h

Scheme 67

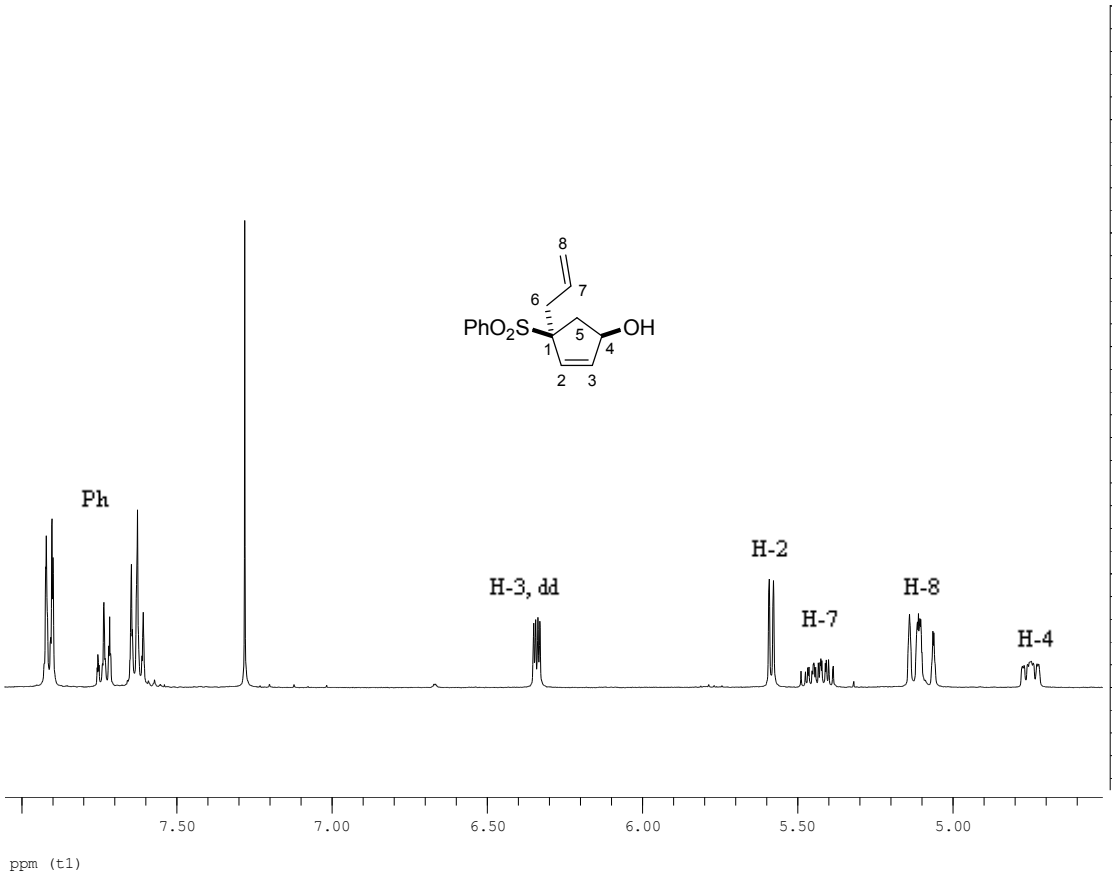
Encouraged by this outcome, compounds **234a–c** were subjected to metathesis conditions. Unexpectedly cyclopentenones **243a–c** were isolated (Scheme 68). The yields of these ketones were directly proportional to the loadings of the catalyst. It was therefore rationalised that the ruthenium catalyst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



i) catalyst **50** (5 mol%), CH_2Cl_2, rt, 24 h

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 ~1726 cm^{-1} for the cyclic α,β-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**. α-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**.


8
7
6
PhO2S
OH
5
1
4
2
3
Ph
H-3, dd
H-2
H-7
H-8
H-4
7.50
7.00
6.50
6.00
5.50
5.00
ppm (t1)

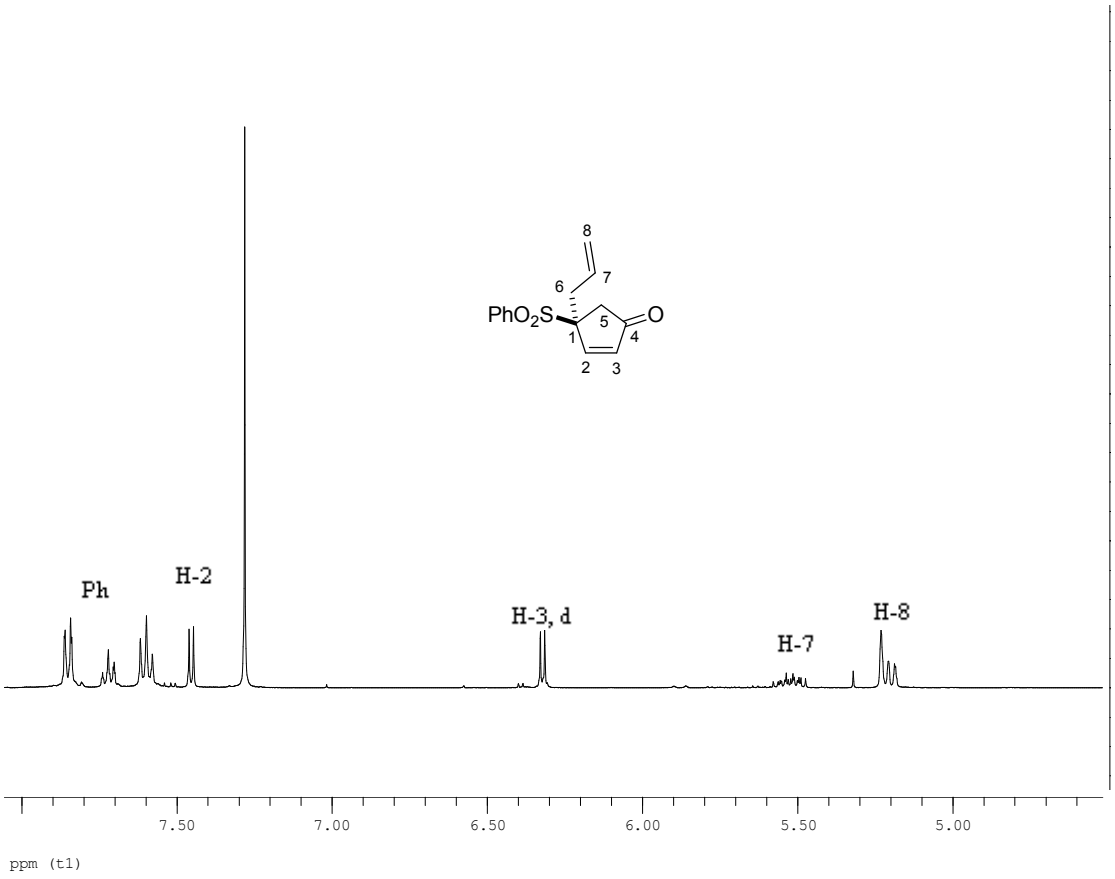
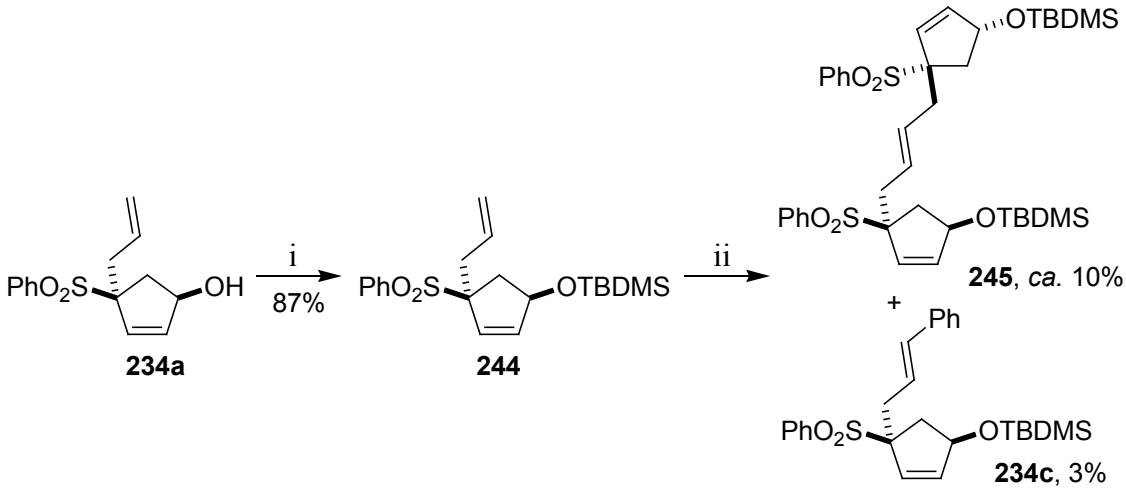

8
7
6
PhO2S
O
5
1
4
2
3
Ph
H-2
H-3, d
H-7
H-8
7.50
7.00
6.50
6.00
5.50
5.00
ppm (t1)

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.

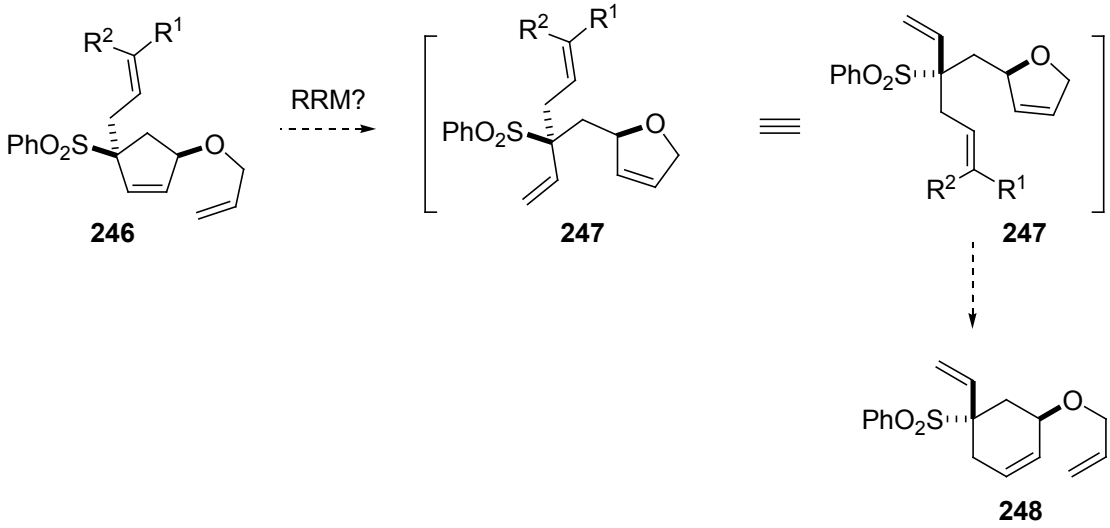


i) TBDMSCl (1.8 equiv), Et_3N (2.5 equiv), DMAP (15 mol%), CH_2Cl_2, 40 °C, 24 h; ii) catalyst **50** (10 mol%), CH_2Cl_2, 40 °C, 20 h

Scheme 69

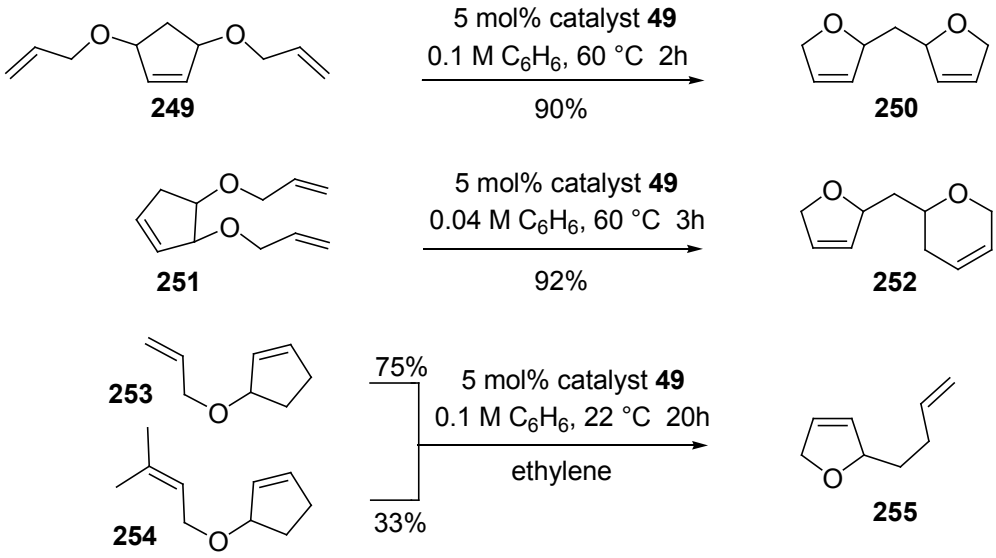
2.2.3.4 Attempt at Relay RRM Mediated by Dihydrofuran

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**.



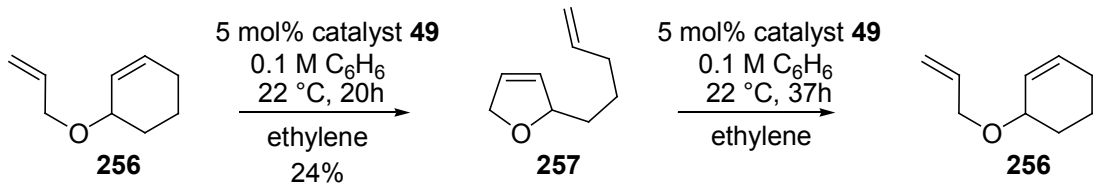
Scheme 70

The feasibility of RRM of cyclopentenes bearing allyl ether side chains has been demonstrated by Grubbs *et al*.[110] and Hoveyda *et al*.[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.



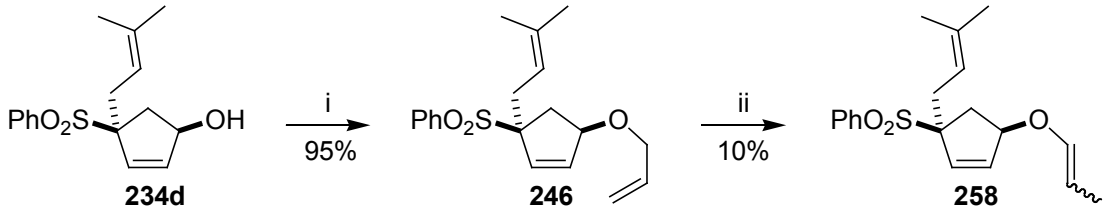
Scheme 71

In addition, Hoveyda *et al*. investigated the reaction equilibrium between cyclohexenyl allyl ether **256** and dihydrofuran **257** (Scheme 72).[111] 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

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.



i) NaH (1.1 equiv), CH_2=$CHCH_2Br$ (1.7 equiv), DMF, 0 °C-rt, 16 h; ii) catalyst **50** (0.07 equiv), toluene, rt, 16 h

Scheme 73

Many explanations have been proposed for Ru-based metathesis catalyses induced alkene isomerisations, such as metal-based hydride, π-allyl, or other pathways.[112,113] Although the exact mechanism is unknown, Grubbs and co-workers have shown that ruthenium hydride species, formed from the decomposition of the ruthenium metathesis

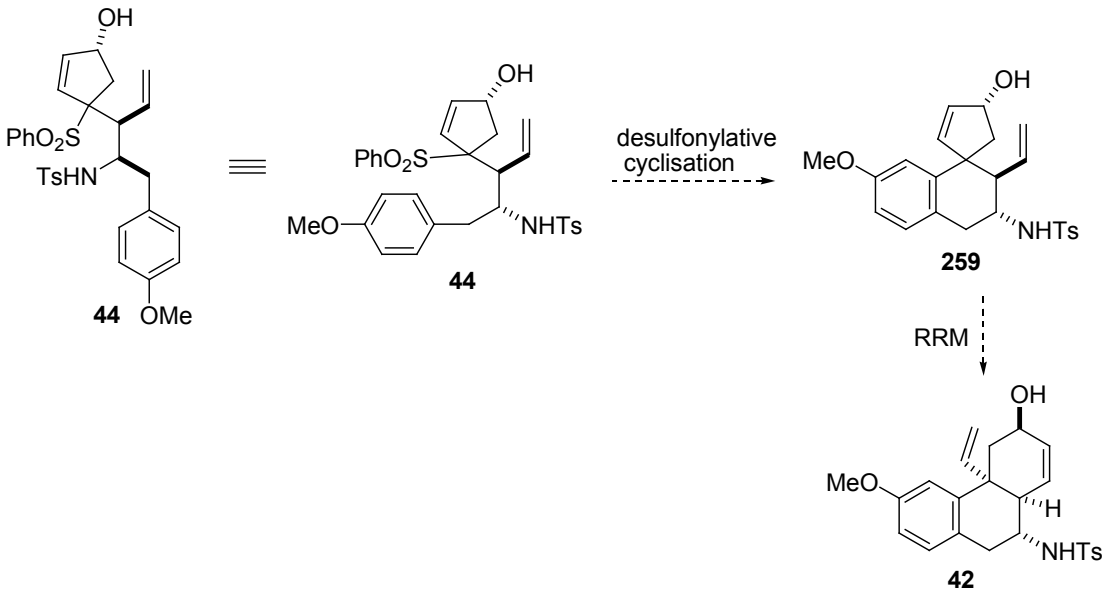
catalysts, could cause migration of olefins.[114] Additionally, they managed to suppress this type of unwanted transformation by deploying benzoquinone based additives.[115]

Many people also take advantage of this methodology for their syntheses.[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.[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_2Ph substituent, was deleterious to its reactivity. Additionally, the electron-withdrawing effect from the sulfone might further decrease its reactivity.

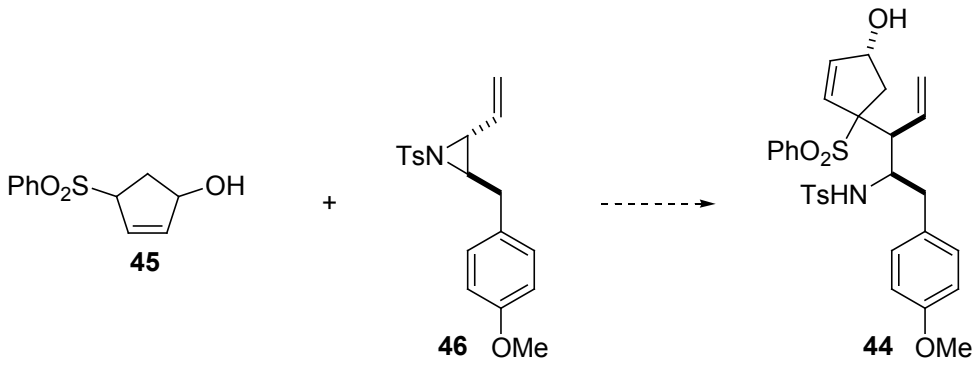
2.2.4 Attempted Synthesis of Aziridine Ring-opening Product 44

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[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).



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 α-sulfonyl carbanion centre of **45** and the insufficient electrophilicity of **46** both contributed to the outcome.

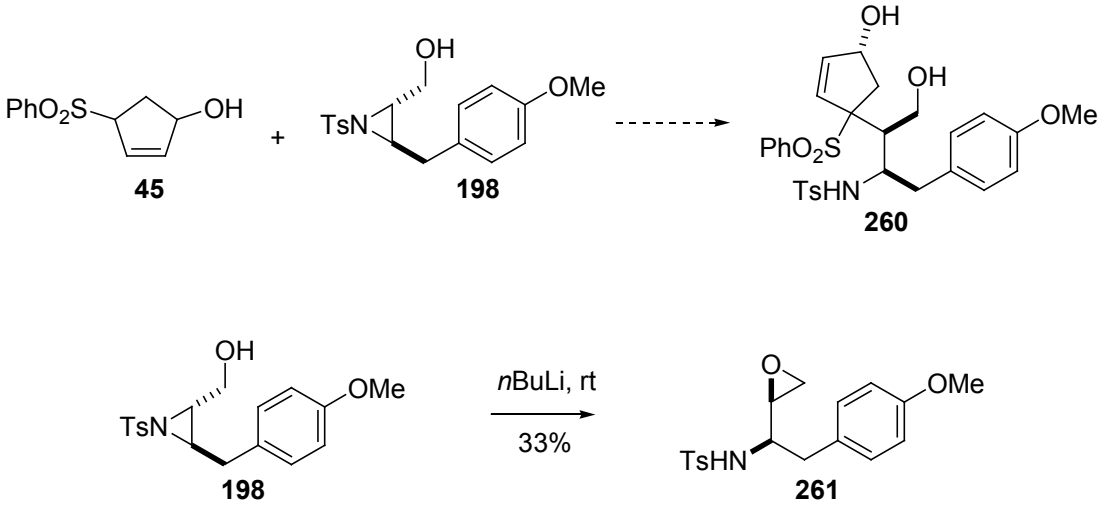


Scheme 75

Entry	Comp. **45** (equiv)	Base (equiv)	Comp. **46** (equiv)	result
1	1.0	*n*BuLi (2.1)	1.0	SMs
2	1.0	KH (2.2)	1.0	SMs + unidentified new product
3	1.0	*n*BuLi (1.0) + KH (1.0)	1.0	SMs + unidentified new product
4	2.2	*n*BuLi (4.4)	1.0	SMs
5	5.0	*n*BuLi (10.0)	1.0	SM(**45**) + unidentified new products

Table 2

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 rearrangement[118] to give epoxide **261** (Scheme 76).

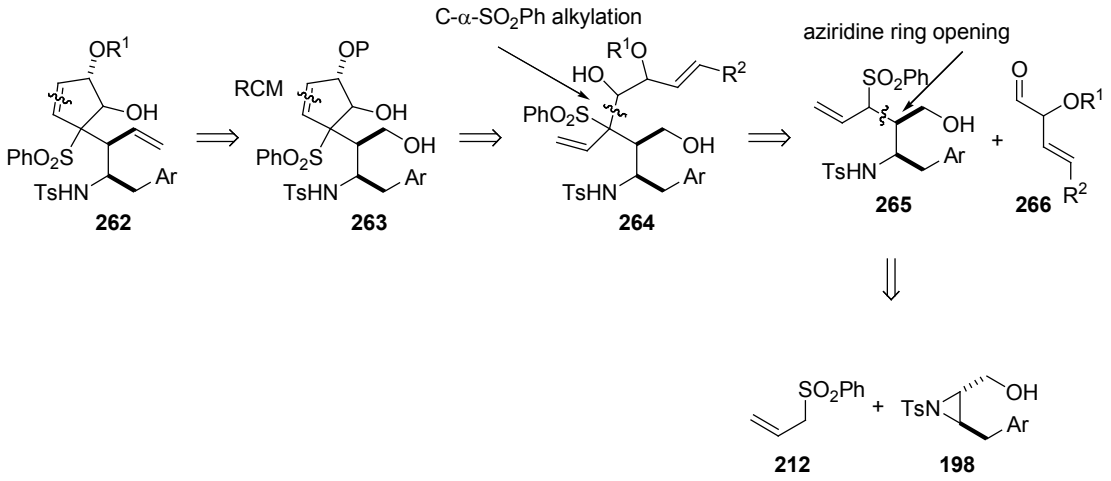


Scheme 76

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-SO_2Ph alkylation of tosamide **265** with β,γ-unsaturated aldehyde **266**. Tosamide **265** would be synthesised by reaction of allylsulfone **212** and hydroxyaziridine **198**.

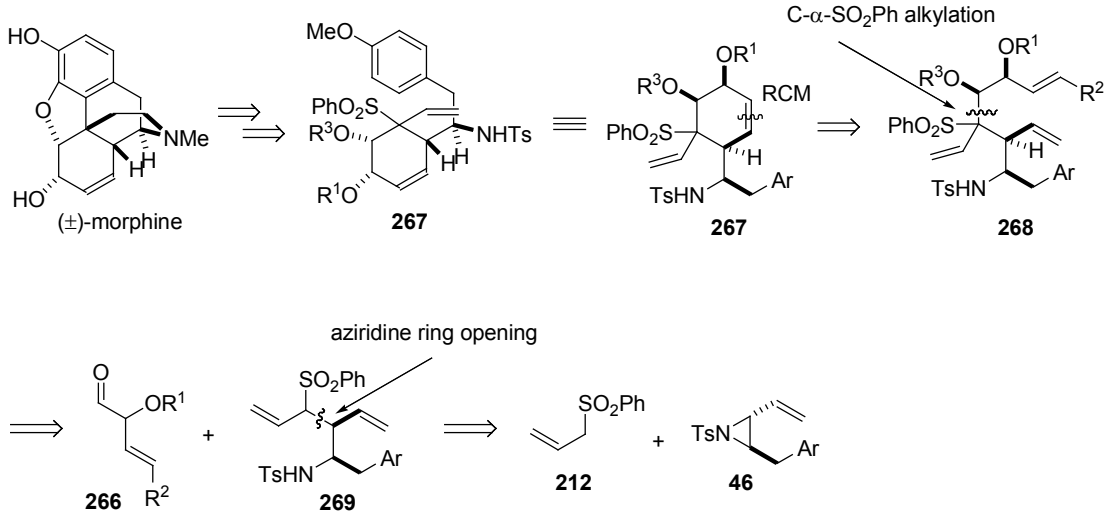
Revised Route A:



Scheme 77

Route B diverged from route A by beginning with the reaction of allylsulfone **212** and vinylaziridine **46** to give tosamide **269**. C-α-SO_2Ph Alkylation of **269** with β,γ-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.

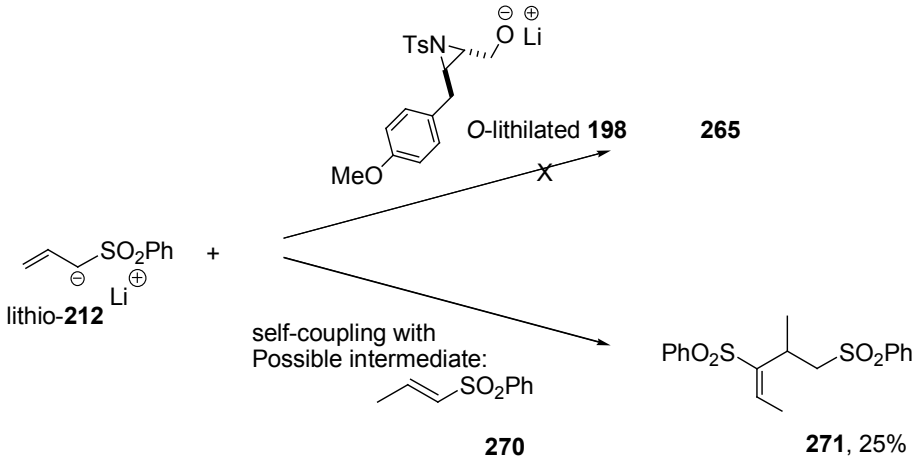
Revised Route B:



Scheme 78

2.2.5.1 Regioselective Ring-opening of Aziridines 198 and 46

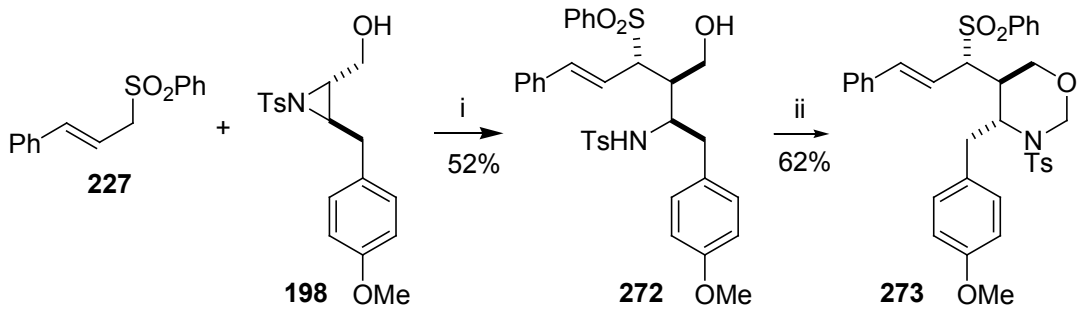
Both routes A and B required aziridine ring-opening reactions, and subsequent C-α-SO_2Ph alkylations of **265** and **269** with aldehyde **266**. Therefore the syntheses of **265** and **269** were first investigated. Intriguingly, reaction of lithio-**212** and *O*-lithiated aziridine **198** gave 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]



Scheme 79

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.

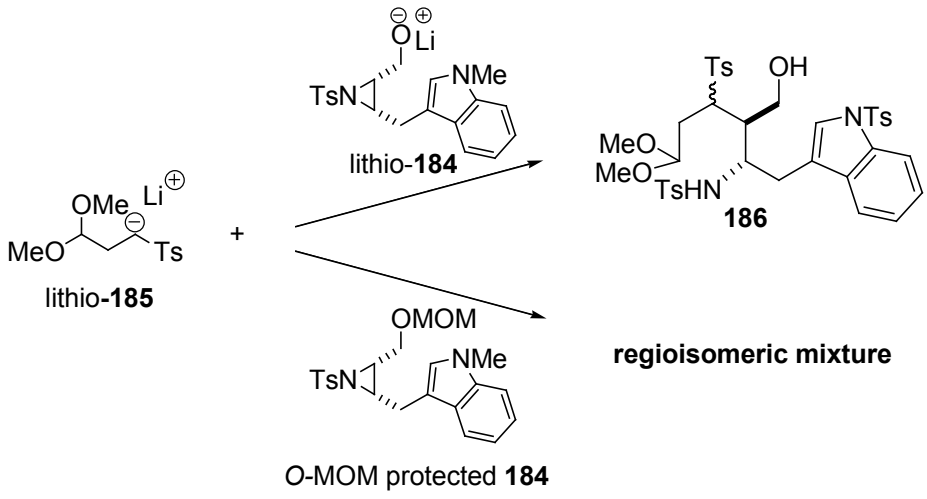
To overcome this problem, a similar strategy as aforementioned in Scheme 59 was adopted employing cinnamylsulfone **227**[120]. More importantly, the subsequent RCM step would give the same product **263**. As shown in Scheme 80, reaction of lithio-**227** with *O*-lithiated **198** gave a 10:1 mixture 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**,[121] whose identity was established by X-ray crystallographic analysis (Appendix II).



i) *n*BuLi (1.1 equiv) added to **198**, THF, –78 °C, 5 min, then PhCH:CHCHLiSO$_2$Ph (generated from **227** + *n*BuLi, THF), –78 °C-rt: 52%;; ii) (HCHO)$_n$ (1.3 equiv), *p*-TsOH·H$_2$O (0.065 equiv), benzene, 90 °C, 6 h

Scheme 80

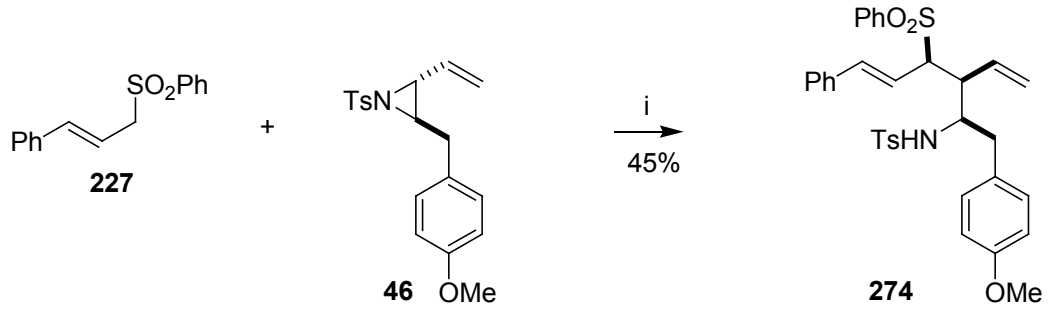
The unprotected hydroxyl group of **198** was considered to be crucial for the regioselectivity, supported by previous observations in the group (Scheme 81).[98] Reaction of *O*-MOM protected aziridine **184** with lithio-**185** gave a mixture of regioisomers, whereas a single regioisomer **186** was 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 ^{1}H 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.



i) vinylaziridine **46** (0.7 equiv) in THF added to PhCH:CHCHLiSO$_2$Ph [generated from **227** + *n*BuLi (1.1equiv), THF/TMEDA, –20 °C-rt, 0.5 h], 0 °C-rt, 16 h

Scheme 82

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 $\pi_{C=C}$–σ^*_{C-N} overlap, as illustrated in Figure 11 and analogous to that depicted in Figure 3.

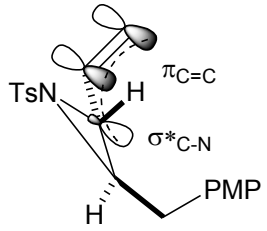
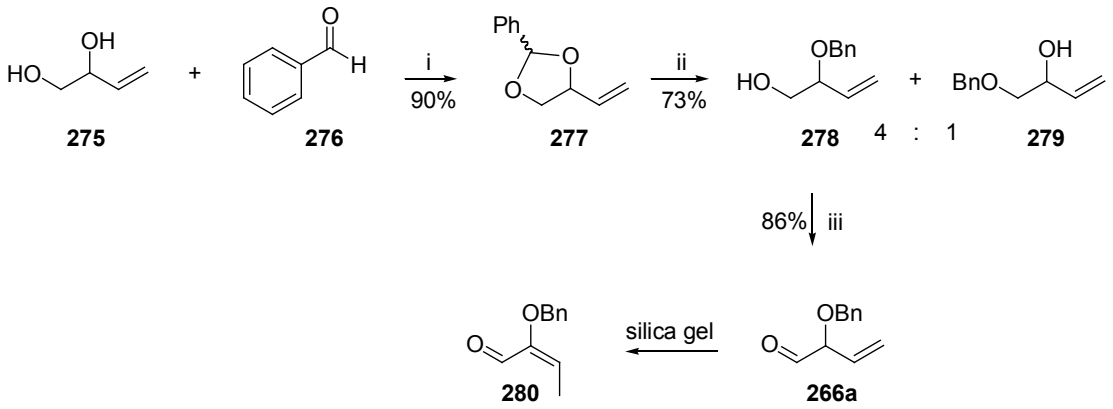


Figure 11

2.2.5.2 Attempted Alkylation of Sulfones 273 and 274

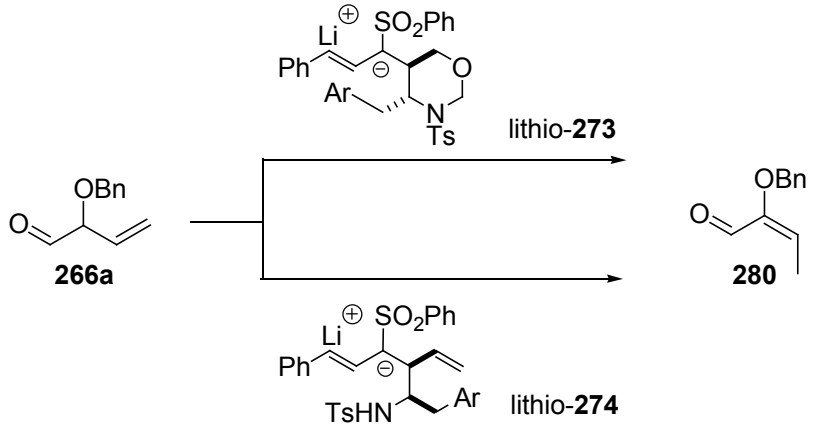
With aziridine ring-opening derivatives **273** and **274** in hand, focus shifted towards the preparation of the alkylating reagent β,γ-unsaturated aldehydes **266**. The synthesis of aldehyde **266a** was accomplished in a three-step sequence beginning with the protection of 3-butene-1,2-diol **275** with benzaldehyde **276** to yield a 1:1 diastereomeric mixture of acetals **277** (Scheme 83).[124] Regioselective deprotection of **277** was achieved by treatment with excessive DIBAL-H giving a 4:1 mixture of regioisomeric alcohols **278** and **279**.[125] Finally oxidation of primary alcohol **278** with IBX gave the desired aldehyde **266a**.[126] However, attempted purification of **266a** by silica gel column chromatography induced an isomerisation to give α,β-unsaturated aldehyde **280**. Therefore substrate **266a** was used crude in subsequent reactions.



i) *p*-TsOH·H_2O (0.02 equiv), toluene, reflux, 5 h; ii) DIBAL (3.0 equiv), CH_2Cl_2, –78 ºC-rt, 16 h; iii) IBX (1.3 equiv), EtOAc, 80 ºC, 2 h

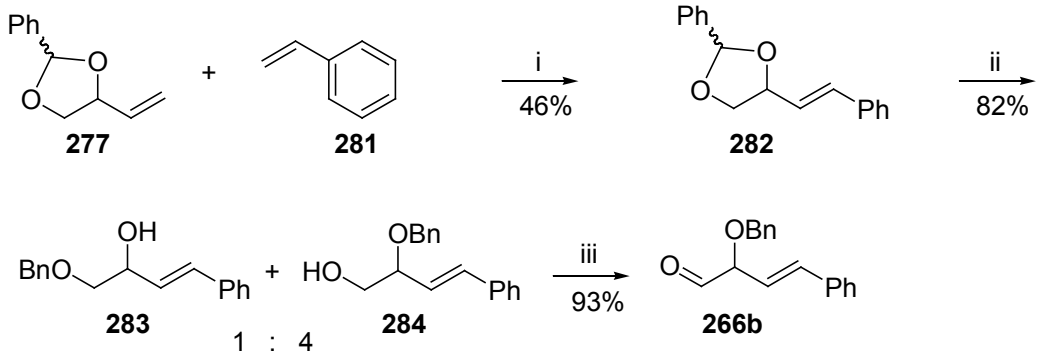
Scheme 83

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

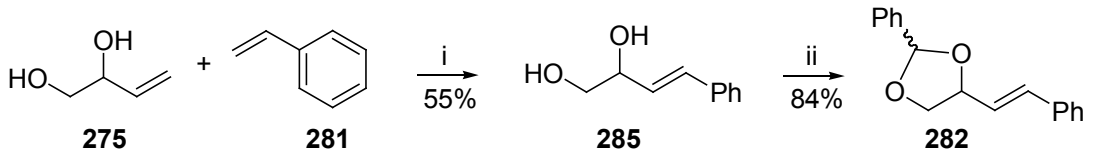
In light of these results, it was anticipated that introduction of a γ-phenyl substituent to the aldehyde **266a** would stabilise the double bond and prevent it from migrating. Therefore, attention was turned towards the synthesis of γ-phenyl-β,γ-unsaturated aldehyde **266b** (Scheme 85). Acetals **282** were synthesised *via* a cross metathesis[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)[128] proceeded smoothly at ambient temperature gave aldehyde **266b**.



i) catalyst **50** (0.03 equiv), styrene **281** (2.0 equiv) CH_2Cl_2, reflux, 16 h; ii) DIBAL (3.0 equiv), CH_2Cl_2, –78 ºC-rt, 16 h; iii) Dess-Martin periodinane (1.15 equiv), CH_2Cl_2, rt, 2 h

Scheme 85

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).

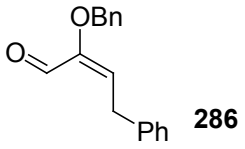


275 **281** **285** **282**

i) catalyst **50** (0.01 equiv), styrene **281** (2.9 equiv), CH_2Cl_2, reflux, 16 h; ii) *p*-TsOH·H_2O (0.05 equiv), benzaldehyde **276** (1.1 equiv), toluene, reflux, 5 h

Scheme 86

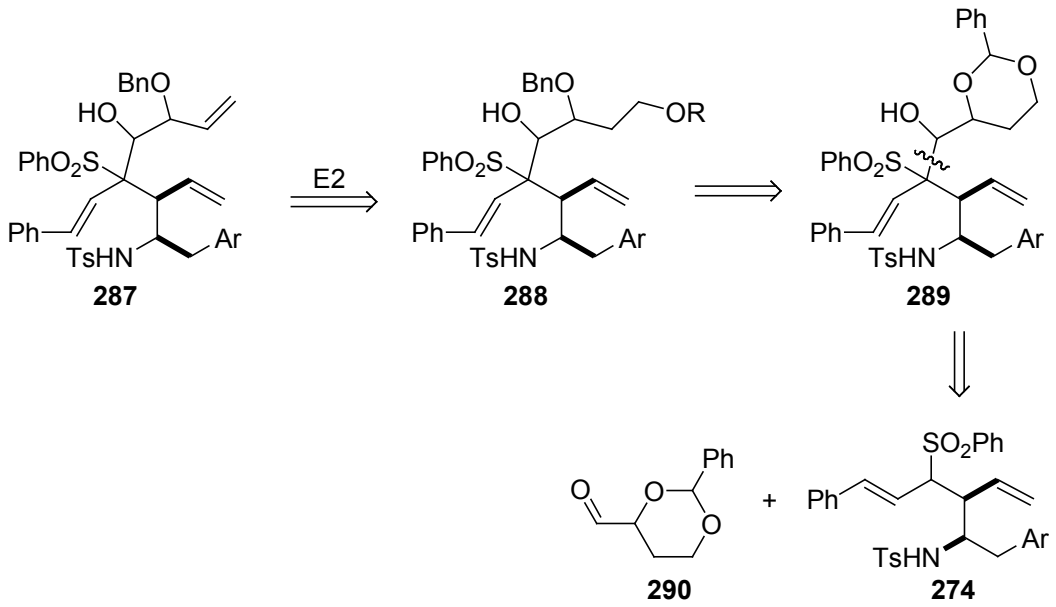
With aldehyde **266b** in hand, alkylations of lithio-**227**, **273** and **274** were investigated. Disappointingly, all of these reactions gave the isomerisation product, α,β-unsaturated aldehyde **286** (Figure 12).



286

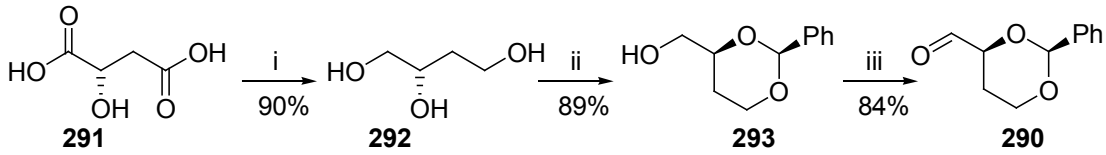
Figure 12

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 **290**[129,130,131,132]. 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**.



Scheme 87

Thus, aldehyde **290** was prepared *via* a literature procedure (Scheme 88).[129,131] 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.

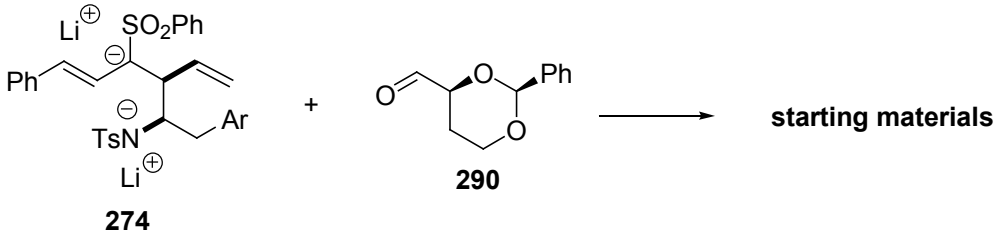


i) $BH_3{\cdot}SMe_2$ (3.1 equiv), $B(OMe)_3$ (3.3 equiv), THF, 0 ºC-rt, 16 h; ii) $PhCH(OMe)_2$ (1.07 equiv), (*R*)-(–)-CSA (0.05 equiv), CH_2Cl_2 rt, 16 h; iii) Dess-Martin periodinane (1.28 equiv), CH_2Cl_2, rt, 2 h

Scheme 88

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 α-SO_2Ph carbanion of **274** rendered it unsuitable for the proposed reaction with **290**.



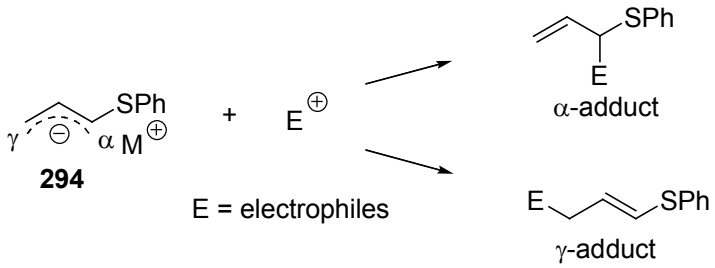
Scheme 89

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-SO_2Ph 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

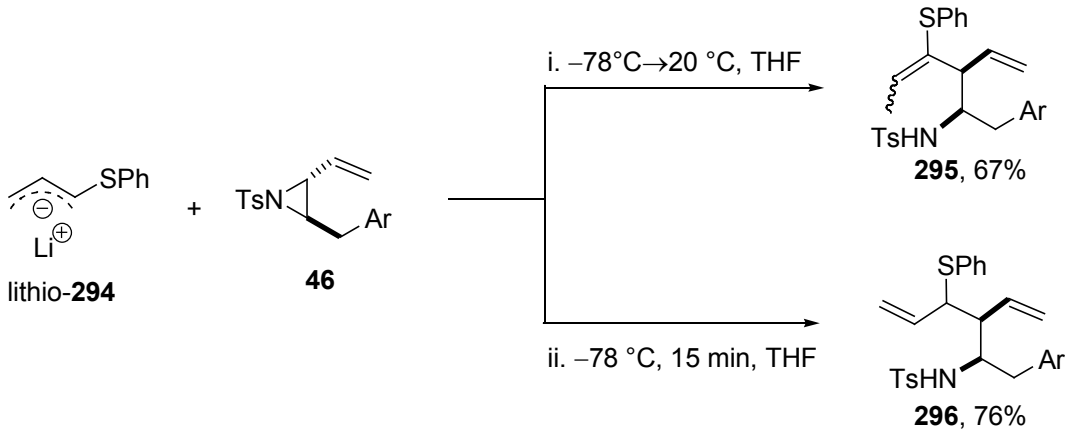
The first sulfide investigated in aziridine ring-opening reactions was allyl phenyl sulfide **294**. A major concern for **294** is that its delocalised anion can undergo both α- and γ-addition to give the corresponding α- and γ-adducts,[133,134] as depicted in Scheme 90. The ratio between the two regioisomers depends on a number of factors such as: the base/the counter cation, the electrophile and additives used.[133,134] It has been reported that HMPA is an excellent additive to enhance α-attack.[135]



Scheme 90

Despite this concern, the reaction of vinyl aziridine **46** with lithio-**294**, prepared from PhSH and allyl bromide,[134] gave only the α-addition adducts (Scheme 91). Interestingly, when the reaction temperature was warmed up to 20 ºC, 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 ºC, in which case the desired β,γ-unsaturated sulfide **296** was synthesised. Later experiments showed that sulfide **296** was the only product

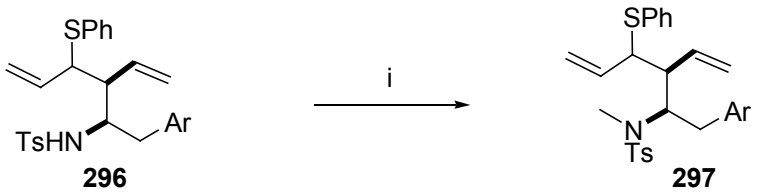
obtained when the reaction temperatures were kept below 0 ºC. Similar phenomena were observed by Enholm and co-workers in the reaction of lithio-**294** with ethylene oxide.[136]



i) $CH_2CHCHLiSPh$ generated from **294** + *n*BuLi, THF, –78-0 ºC, 30 min, then aziridine **46** in THF added, 20 ºC, 16 h; ii) $CH_2CHCHLiSPh$ generated from **294** + *n*BuLi, THF, –78-0 ºC, 30 min, recooled to –78 ºC, then aziridine **46** in THF added, –78 ºC, 15 min, dr = 5:1

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 *t*BuOK was used as the base.

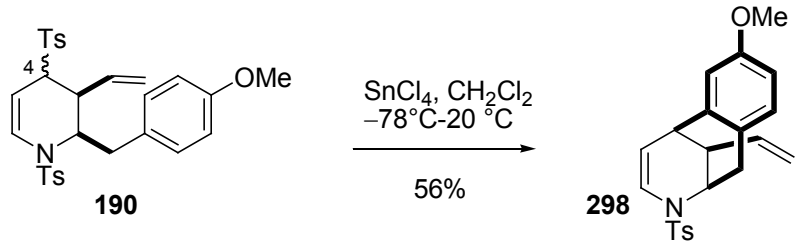


i) *n*BuLi (2.0 equiv), –78 ºC, 30 min, then MeI, 0.5 h, 53% or *t*BuOK (1.0 equiv), *t*BuOH, MeI, 4 h, 82%

Scheme 92

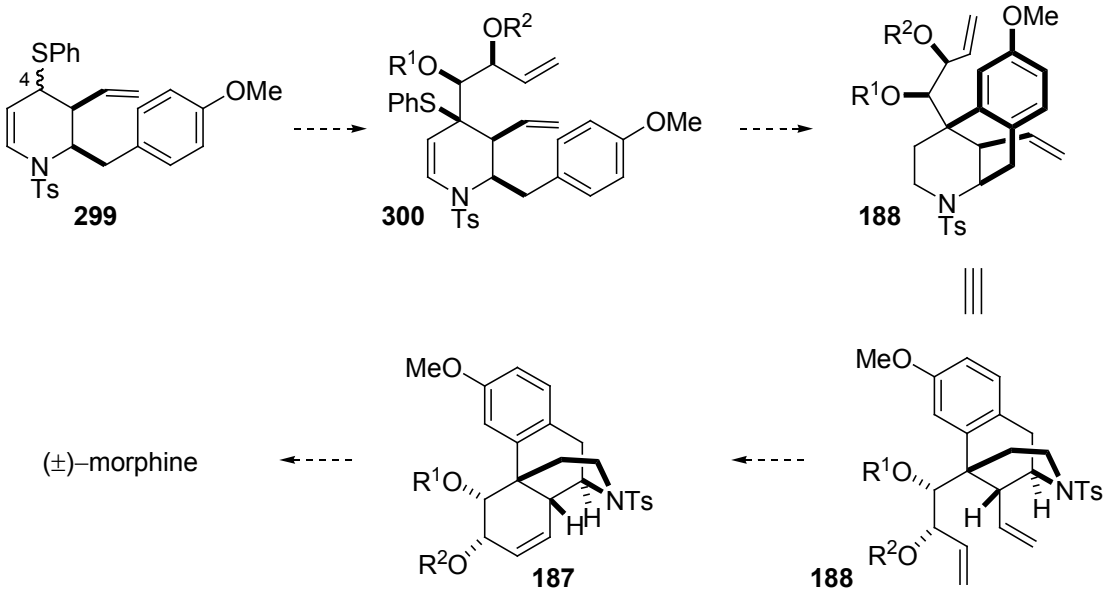
2.2.6.2 Synthesis of Thiophenyl Tetrahydropyridine 299

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

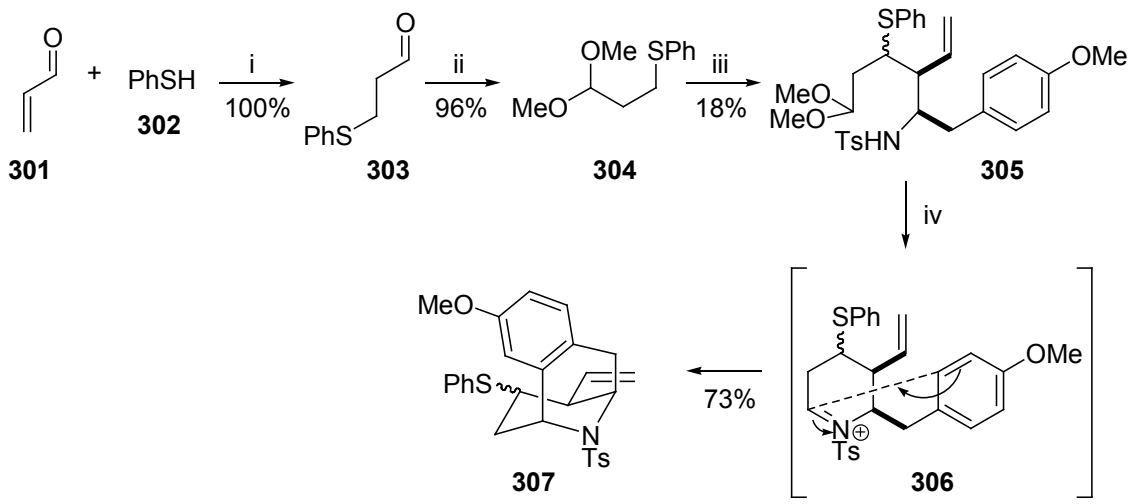
It was now hoped that the reactivity of the C-4 centre could be improved by employing the thiophenyl-substituted tetrahydropyridine analogue **299** (Scheme 94). The alkylation derivative **300** would then be subjected to a cation-mediated cyclisation similar to that of tosyl tetrahydropyridine **190** 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**.



Scheme 94

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.



i) Et_3N (0.1 equiv), CH_2Cl_2, 0 °C, 30 min; ii) $(MeO)_3CH$ (2.0 equiv), *p*-$TsOH{\cdot}H_2O$ (0.03 equiv), MeOH, 50 °C, 16 h; iii) *n*BuLi (1.0 equiv), THF/TMEDA, –78 °C, 40 min, then aziridine **46** in THF, rt, 16 h, dr = 5:1; iv) $BF_3{\cdot}Et_2O$ (15.0 equiv), CH_2Cl_2; –78 °C-rt, 16 h

Scheme 95

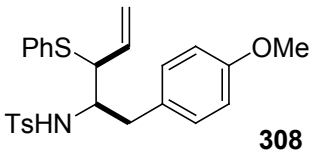
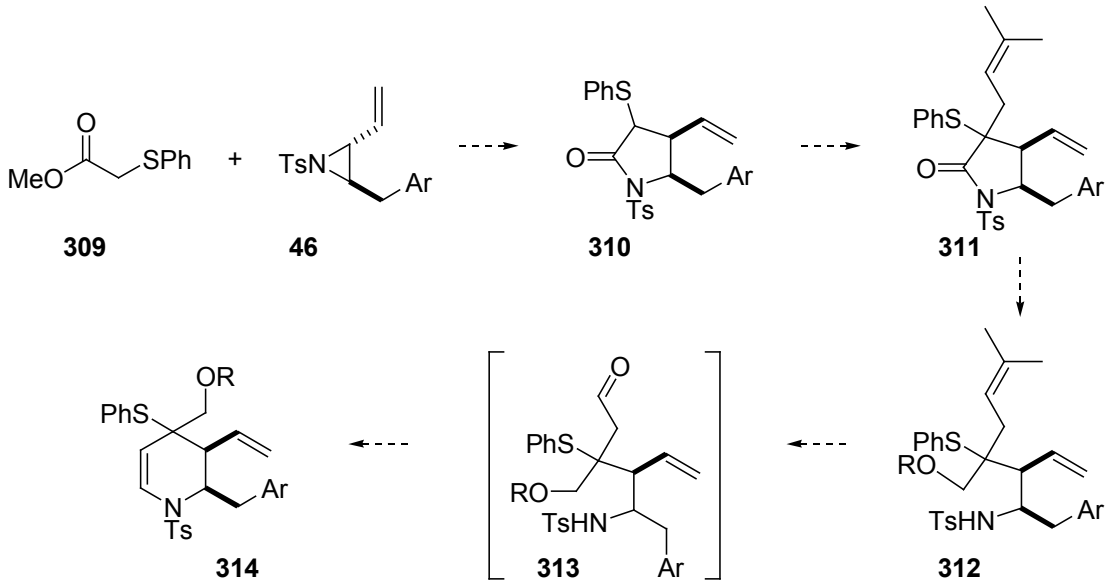


Figure 13

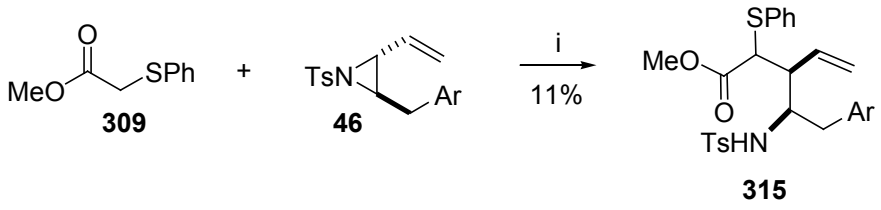
2.2.6.2.2 Attempted approach *via* γ-lactam

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* γ-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 γ-lactam **310**. Subsequent alkylation of the α-SPh carbanion, reduction of γ-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**.



Scheme 96

However, in an attempt to form γ-lactam **310** from the reaction of KH deprotonated sulfide ester **309**[140] 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 γ-lactam **310** was detected (Table 3).



i) KH (1.0 equiv), DMF, 0 °C, 20 min, then aziridine **46** in DMF added, 60 °C, 16 h

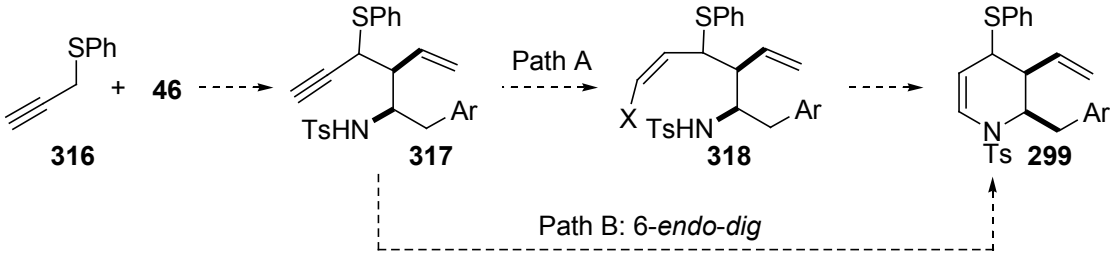
Scheme 97

Entry	base	solvent	yield(%)
1	*n*BuLi	THF	–
2	*t*BuO K	DMSO	–
3	*t*BuO K/18-crown-6	THF	–
4	KH	toluene	–
5	KHMDS/18-crown-6	toluene	–
6	NaH	DMF	5
7	DBU	toluene	–

Table 3

2.2.6.2.3 Attempted approach *via* propargylic sulfide

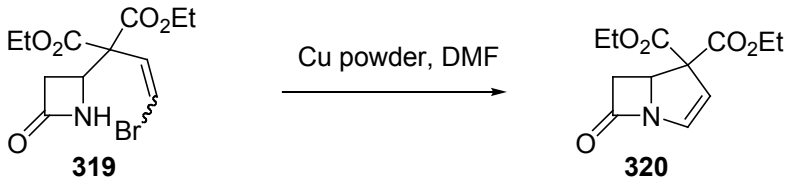
Two alternative approaches for the synthesis of tetrahydropyridine **299** from propargyl sulfide aziridine ring-opening product **317** were also proposed, as outlined in Scheme 98. The reaction of propargylic sulfide **316** with aziridine **46** should give alkynyl tosamide **317**. Path A converts 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

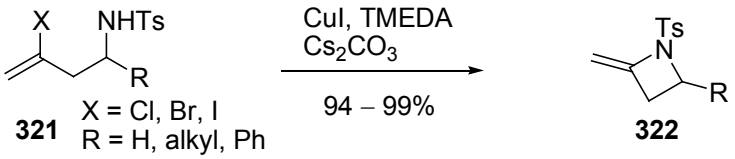
Path A

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.[141] However, intramolecular *N*-vinylations under these conditions have rarely been reported, especially for small rings. Joyeau *et at.*[142] in 1989 and Li *et al.*[143] in 2006 have published their independent work for intramolecular enamide/enamine formations using modified Ullmann–Goldberg conditions. Joyeau *et al*. treated the azetidinone **319** with copper powder at 110 °C in DMF to produce carbacephem **320** (Scheme 99).[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

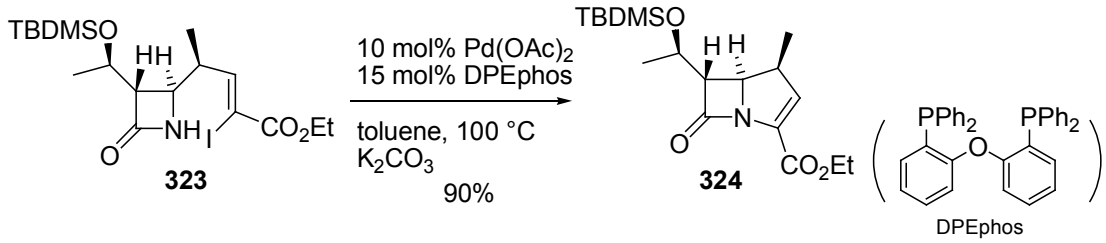
Li *et al*. have demonstrated the high efficiency of 4-*exo*-*trig* cyclisation of *N*-tosyl-3-halo-3-butenylamines **321** to yield 2-alkylideneazetidines **322** in the presence of stoichiometric amount of CuI and TMEDA (Scheme 100).[143] The reaction times were typically under two hours.



Scheme 100

Another method for sp^2-C–N bond formations is Buchwald–Hartwig palladium-catalysed cross coupling.[144] It has been wildly adopted for the synthesis of aryl amines from amines and aryl halides.[144,145] Intramolecular enamine/enamide formation between

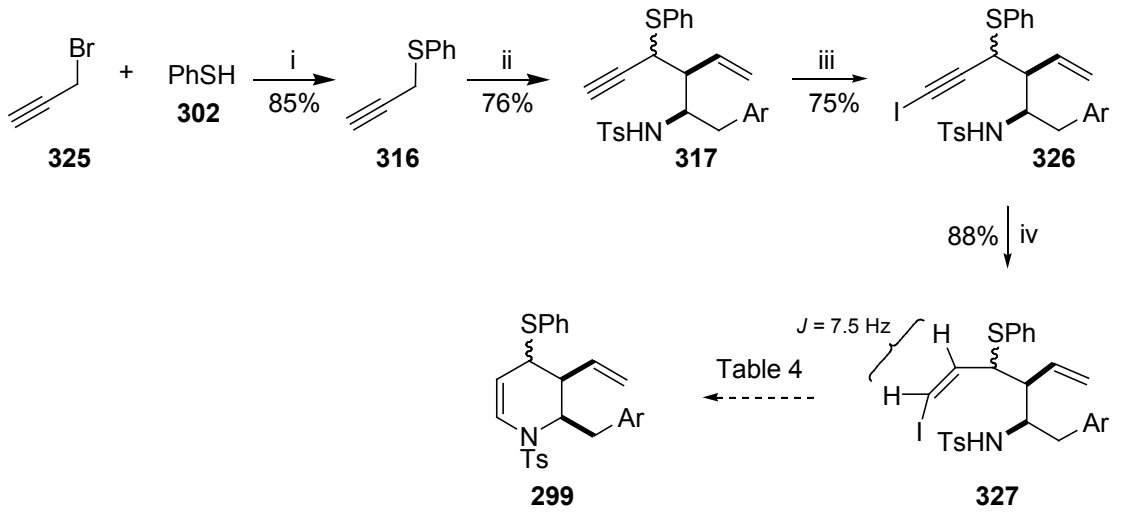
a vinyl halide and an amine, however, is less well documented.[146] One example is from Mori and co-workers who successfully applied this methodology to the synthesis of 3-ethoxycarbonyl-1β-methylcarbapenem **324** (Scheme 101).[147] They found that DPEphos was the optimum ligand for this reaction and better yield was obtained when vinyl iodide **323** was used instead of the corresponding vinyl bromide.



Scheme 101

Encouraged by these precedents, the synthesis of tetrahydropyridine **299** was explored. Propargylic sulfide **316** was prepared from a biphasic reaction of propargylic bromide **325** and thiophenol **302** as described by Bäckwell *et al.* (Scheme 102).[148] It was subsequently doubly deprotonated[149] and combined with aziridine **46** to give a mixture of alkynyl tosamide **317** with a 3:1 dr. Iodination of the terminal alkynes of **317** was accomplished by treatment with NIS in the presence of $AgNO_3$[150] to yield alkynyl iodides **326**. Following *syn*-reduction with diimine, generated from dipotassium azodicarboxylate[150b,151,152] (PADA) **328**, and acetic acid,[153] *Z*-vinyl iodides **327** were formed. The geometry of the double bond was assigned by ^{1}H NMR analysis, where the *Z*-alkene protons have a *J* value of 7.5 Hz. An alternative reducing agent, 2-nitrophenylsulfonylhydrazide[154] (2-NBSH), was also tested for the preparation of **327** and gave similar results. Both of these two reagents were easy to prepare from cheap starting materials.[151,152,154]

A number of conditions were investigated for the formation of tetrahydropyridine **295** from **327** with palladium and copper catalysts (Table 4). Unfortunately, no desired product was detected. Only starting material was recovered.



i) NaOH (1.7 equiv), nBu$_4$NBr (0.15 equiv), H_2O, 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), $AgNO_3$ (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

Entry	solvent	catalyst/ligand	base	temp. (°C)
1	PhMe	$Pd(acac)_2$/BINAP	Cs_2CO_3	rt
2	PhMe	$Pd(dba)_3$/P^{n}Bu$_3$	Cs_2CO_3	rt
3	PhMe	$Pd(dba)_3$/BINAP	Cs_2CO_3	rt–60
4	DMF	$Pd_2(OAc)_2$/PPh_3	Et_3N	rt
5	DMSO/PhH	CuI	Cs_2CO_3	60

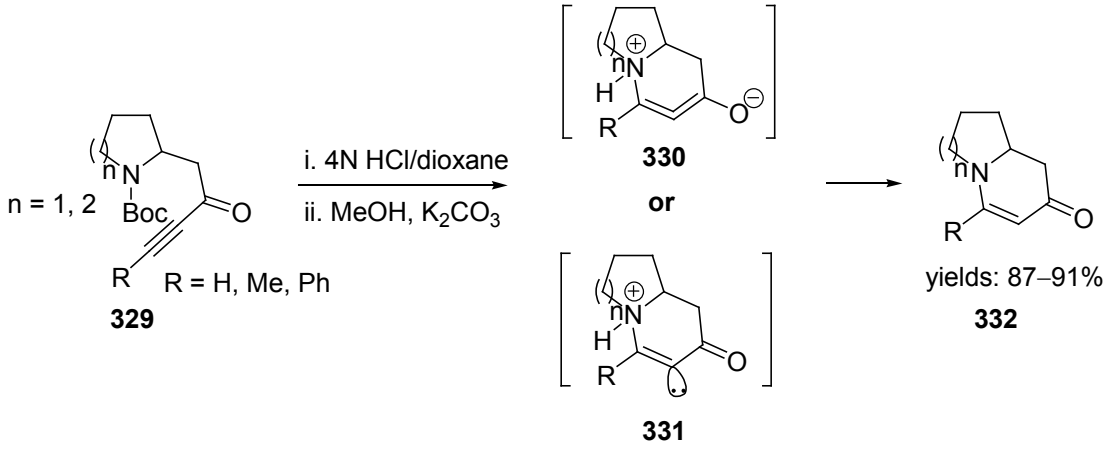
Table 4

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.[155] Work by Georg and co-workers has uncovered

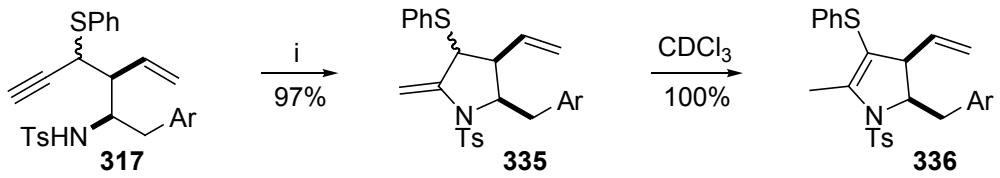
a remarkably simple protocol for preparing enaminones *via* 6-*endo-dig* ring closures (Scheme 103).[156]

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_2CO_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

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.



i) K_2CO_3, MeOH, 50 °C, 16 h

Scheme 104

Many transition metals are reported to be capable of activating triple bonds for cyclisation reactions, such as: Pd[157], Rh[155], Au[158], Ir[159] and Cu[160]. Therefore, our focus was shifted towards cyclisation mediated by organometallic catalysis. Disappointingly, after evaluating the cyclisation of **317** under a number of conditions, either no reaction occurred or only the 5-*exo-dig* ring-closure adduct was formed (Table 5). For example, compounds **335** were isolated when **317** was exposed to the conditions described by Luo *et al*.[157b] (Entry 2). These workers had synthesised a range of 2-alkylidenetetrahydrofurans and pyrans by treatment of alkyl or aryl acetylenic alcohols with *n*BuLi in THF, followed by addition of a solution of $Pd(OAc)_2$ and PPh_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 **335** (Entry 3). When the reaction was attempted without prior deprotonation with *n*BuLi, only starting materials were recovered (Entries 1 and 4). Surprisingly, substrate **317** decomposed when treated with sub-stoichiometric CuI (Entries 5 and 6). Many iridium catalysts were reported to be effective reagents to induce 6-*endo-dig* reactions selectively over 5-*exo-dig*.[159] However when iridium catalyst **336** (Figure 14) was used, no reaction was observed (Entry 7).

Entry	catalyst	conditions	result
1	$Pd(OAc)_2$	PPh_3, THF, 50 °C	SM
2	$Pd(OAc)_2$	*n*BuLi, THF, PPh_3 −78 °C - rt	SM + **335** (3%)
3	$Pd(OAc)_2$	*n*BuLi, THF/DMF, PPh_3 −78 °C - rt	SM + **335** (15%)
4	$PdCl_2$	PPh_3, toluene, 40 °C	SM
5	CuI	DMF, 70 °C	decomposition
6	CuI	DMF, rt	decomposition
7	[Ir]	CH_2Cl_2, 40 °C	SM

Table 5

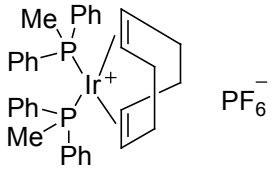
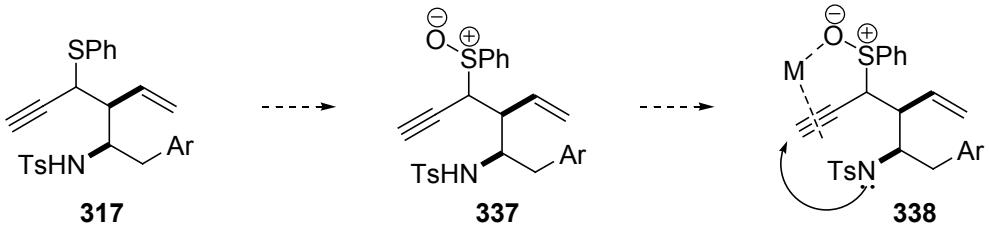


Figure 14

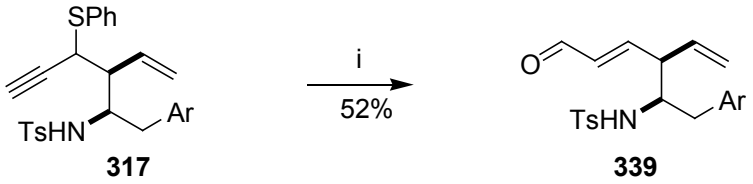
2.3.6.2.4 Approach *via* an unexpected enal

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.



Scheme 105

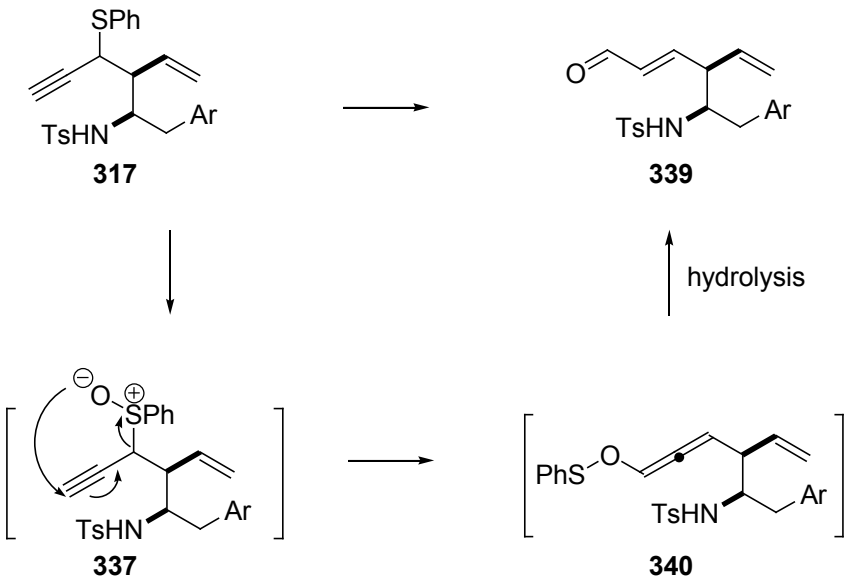
Following this plan, the synthesis of sulfoxide **337** was carried out. Intriguingly, when alkynyl tosamide **317** was treated with mCPBA, enal **339** was isolated (Scheme 106).



i) mCPBA (1.1 equiv), CH_2Cl_2, rt, 16 h

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**.[161] 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, $NaIO_4$, Oxone® and DMDO. However, no reaction was observed with the exception of Oxone®, which gave a small amount of **339** as evidence by ^{1}H NMR analysis of the crude product.



Scheme 107

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_2O from **341** was effected by converting the alcohol to the corresponding mesylate with MsCl in the presence of excessive Et_3N. This sequence was also performed in a one-pot process from enal **339** giving similar yields.

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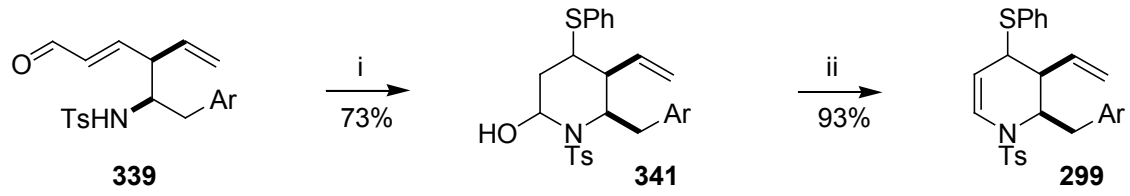
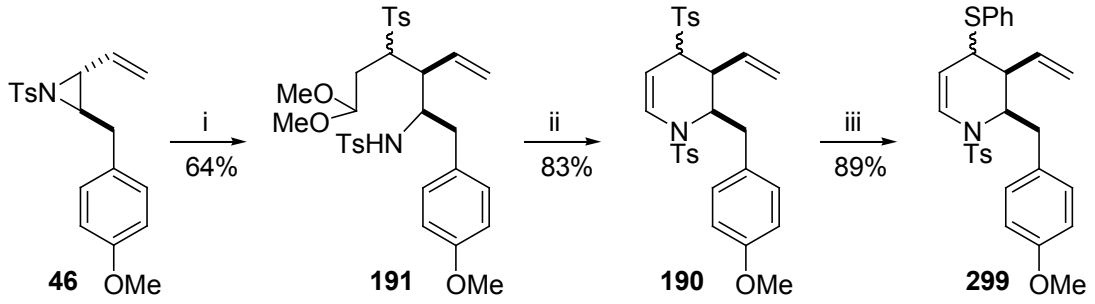


i) PhSH (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C – rt, 16 h; ii) MsCl (10.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, –20 °C, 2 h

Scheme 108

2.2.6.2.5 Approach *via* tosyl tetrahydropyridine 190

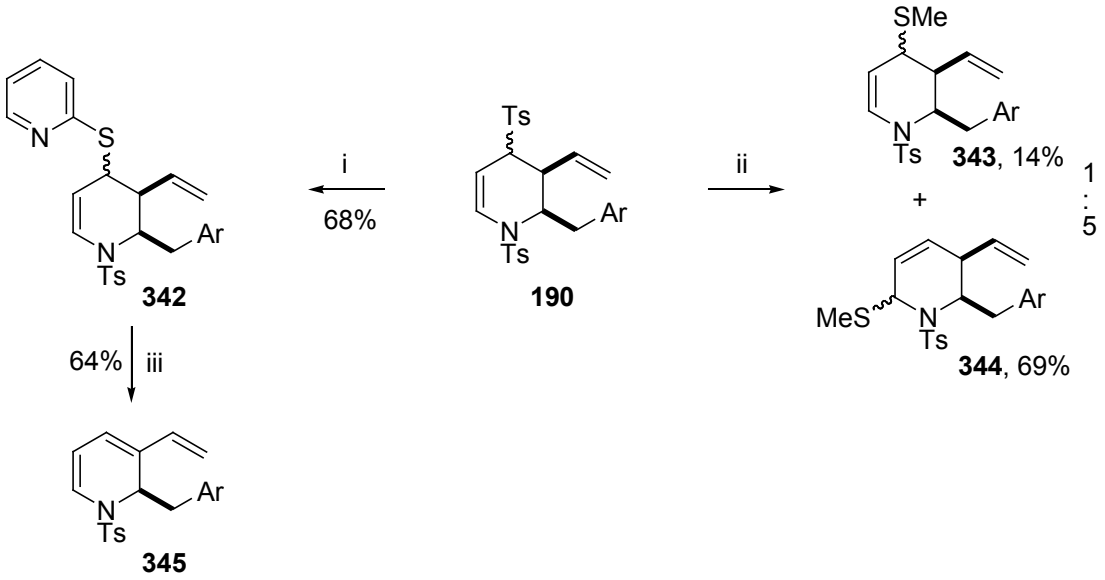
Although the above approach gave access to tetrahydropyridine **299**, it was impractical due to overall low yields. It was proposed that **299** could be constructed by treatment of tosyl tetrahydropyridine **190** with $(Me)_2AlSPh$[162]. Therefore, **190** was prepared as previously described in Scheme 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 CH_2Cl_2, generated *in situ* from $AlMe_3$ and PhSH,[162] thiophenyl-substituted tetrahydropyridine **299** was obtained in good yield.



i) $(MeO)_2CHCH_2CHLiTs$(1.5 equiv) [generated from $(MeO)_2CHCH_2CH_2Ts$ **185** and *n*BuLi (1.5 equiv)], THF, –78-–30 °C, 40 min then added to **46** (1.0 equiv), THF, –30 °C-rt, 16 h, dr = 3:1; ii) $BF_3{\cdot}Et_2O$ (10.0 equiv), CH_2Cl_2, –78 °C for 30 min then –55 °C for 16 h; iii) $AlMe_3$ (4.5 equiv), PhSH (4.5 equiv), CH_2Cl_2, rt, 1 h

Scheme 109

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 $(Me)_2AlSPy$[163] and $(Me)_2AlSMe$[164] respectively (Scheme 110). Reagent $(Me)_2AlSPy$ was prepared in a similar manner to that of $(Me)_2AlSPh$ whereas $(Me)_2AlSMe$ was prepared from $AlMe_3$ 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.

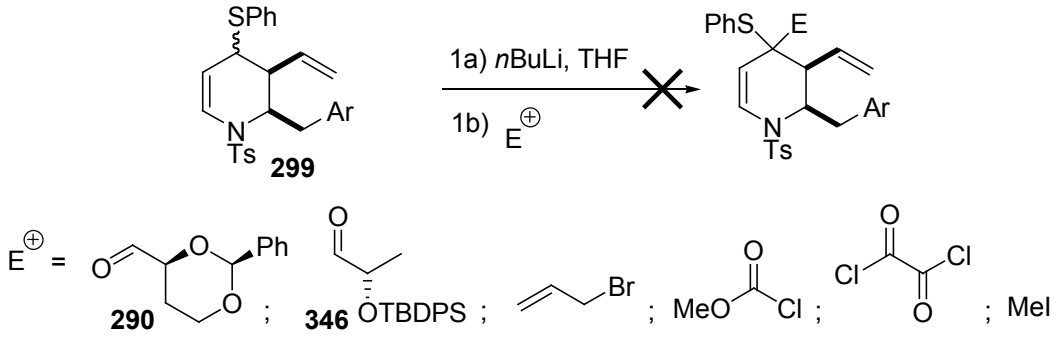


i) $(Me)_2AlSPy$ (5.0 equiv) [prepared from $AlMe_3$ (5.0 equiv)and pyridine-2-thiol (5.0 equiv)in CH_2Cl_2, rt, 45 min) added to **190** in CH_2Cl_2, rt, 16 h, dr = 2.5:1. ii)) **190** in toluene added to $(Me)_2AlSMe$ (4.0 equiv) [prepared from $AlMe_3$ (4.o equiv)and sulfur powder (5.0 equiv) in toluene under reflux, 2 h, then to rt], rt, 16 h, dr = 2:1for **331**, 1.2:1 for **223**. iii) AgOTf (1.5 equiv), 4 Å molecular sieves, CH_2Cl_2, –40 °C, 2 h

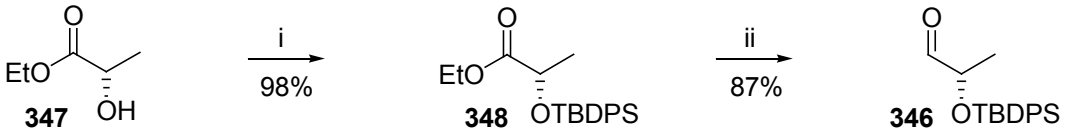
Scheme 110

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 *n*BuLi 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 TBDPSCl to give ester **348**[166] followed by a DIBAL-H reduction (Scheme 112).



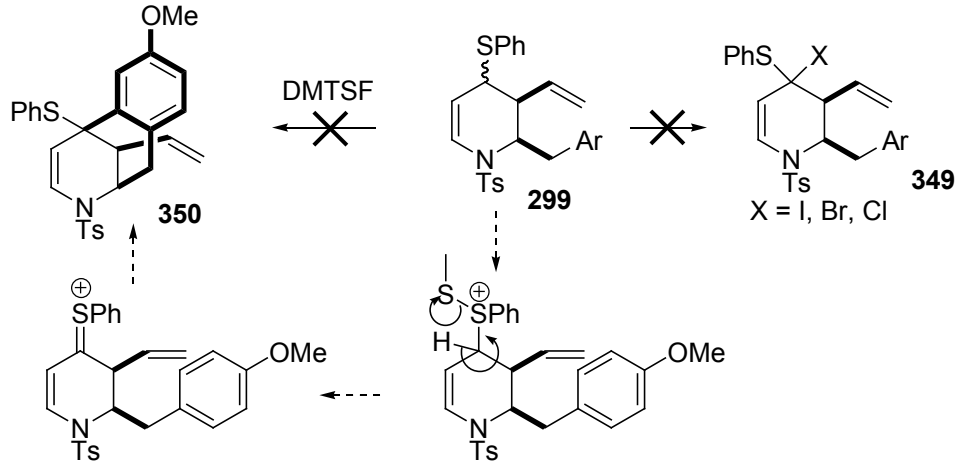
Scheme 111



i) TBDPSCl (1.8 equiv), DMAP (0.15 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 50 °C, 16 h; ii) DIBAL-H (1.15 equiv), CH_2Cl_2, –78 °C, 1.5 h

Scheme 112

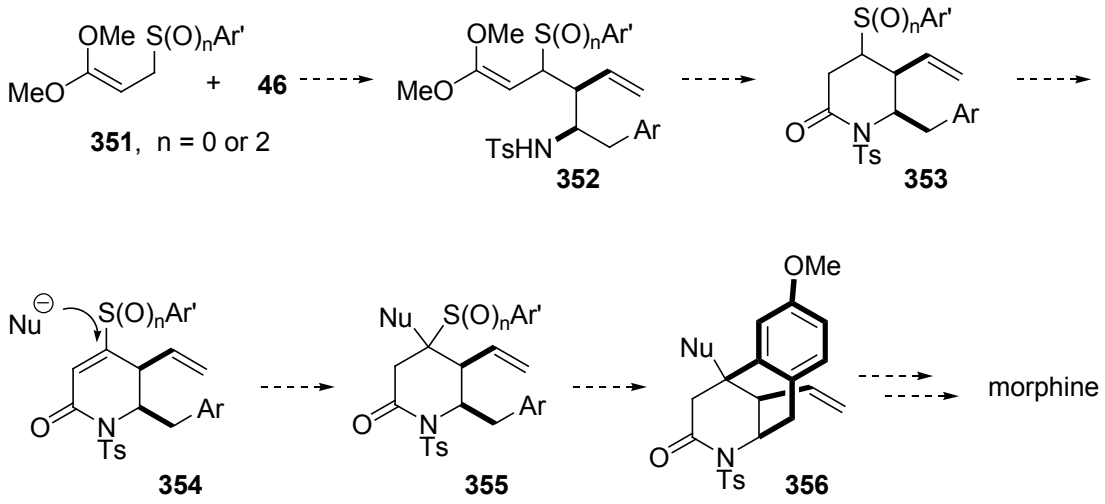
In addition to alkylation, C4 α-sulfide halogenations of **299** were also investigated with NIS[167], NBS[168], NCS[169] and SO_2Cl_2[170] in attempts to synthesise halides **349** (Scheme 113). However, no desired products were observed. Furthermore, attempted cyclisation of **299** to give compound **350** mediated by Pummerer rearrangement induced by $MeSSMe_2BF_4$ (DMTSF)[171] gave only recovered starting materials.



Scheme 113

2.2.7 Alternative Strategies for C4 Alkylation

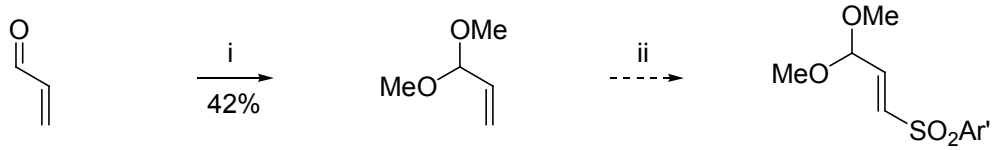
The failure of attempts to effect C4 alkylation of tetrahydropyridine **299** led us to consider alternative strategies. It was considered that sulfide- or sulfone-substituted unsaturated lactam **354** might be a suitable precursor for C4 alkylation *via* conjugate addition (Scheme 114). It was envisaged 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.



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 α,β-unsaturated acetal **357**[172], which was synthesised by protection of acrolein **301** with $(CH_3O)_3CH$ (Scheme 115). Subjection of **357** to either cross-metathesis with vinylsulfone **212**[173] or selenosulfonation with $PhSeSO_2Tol$ **359**[174] followed by oxidation–elimination with H_2O_2 resulted in no desired product.

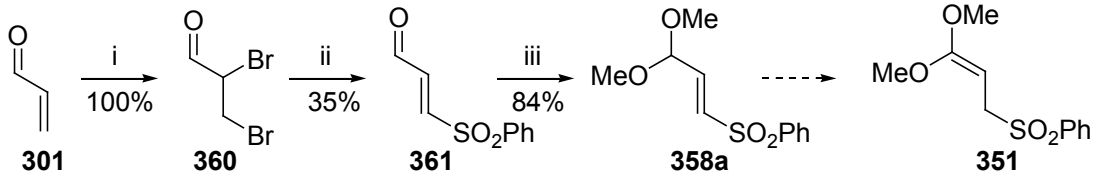


301 **357** **358a: Ar = Ph** **358 b: Ar = Tol**

i) $CH(CH_3O)_3$ (1.33 equiv), NH_4NO_3 (0.05 equiv), MeOH, rt, 16 h; ii) catalyst **50** (0.05 equiv), CH_2=$CHSO_2Ph$ **212** or $PhSeSO_2Tol$ **359** *hv*, CCl_4, 2.5 h, H_2O_2, 2 h

Scheme 115

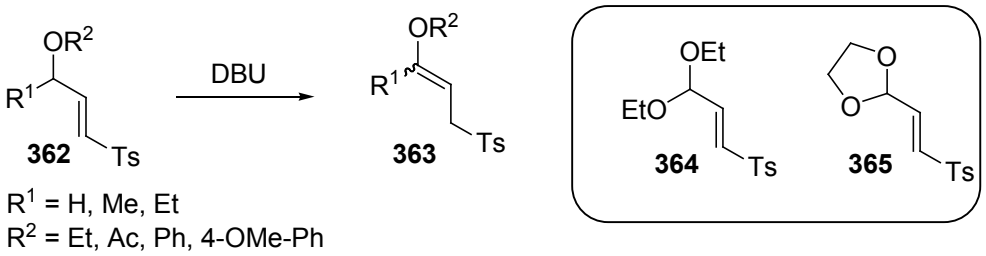
In the second approach, bromination of **301** with Br_2 gave dibromide **360**, which was treated with $PhSO_2Na$ in DMF to give sulfonyl acrolein **361** (Scheme 116).[175] Subsequent acetal protection of **361** furnished vinyl sulfone **358a**. Disappointingly, no desired product **351** was detected when **358a** was treated with either Et_3N or DBU or *t*BuOK in *t*BuOH despite the fact that all smarting 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.



301 **360** **361** **358a** **351**

i) Br_2 (1.0 equiv), CCl_4, 0°C, 4 h; ii) $PhSO_2Na$ (1.5 equiv), DMF, rt, 30 h; iii) $(CH_3O)_3CH$ (2.0 equiv), NH_4NO_3 (0.05 equiv), MeOH, rt, 96 h

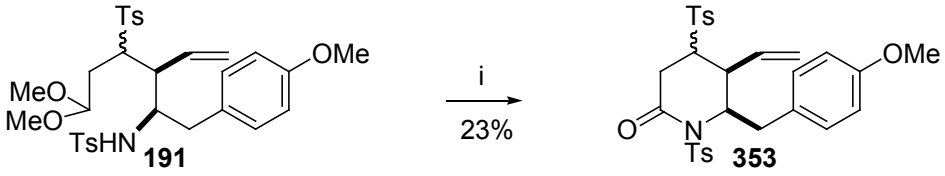
Scheme 116



Scheme 117

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,[177] 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).

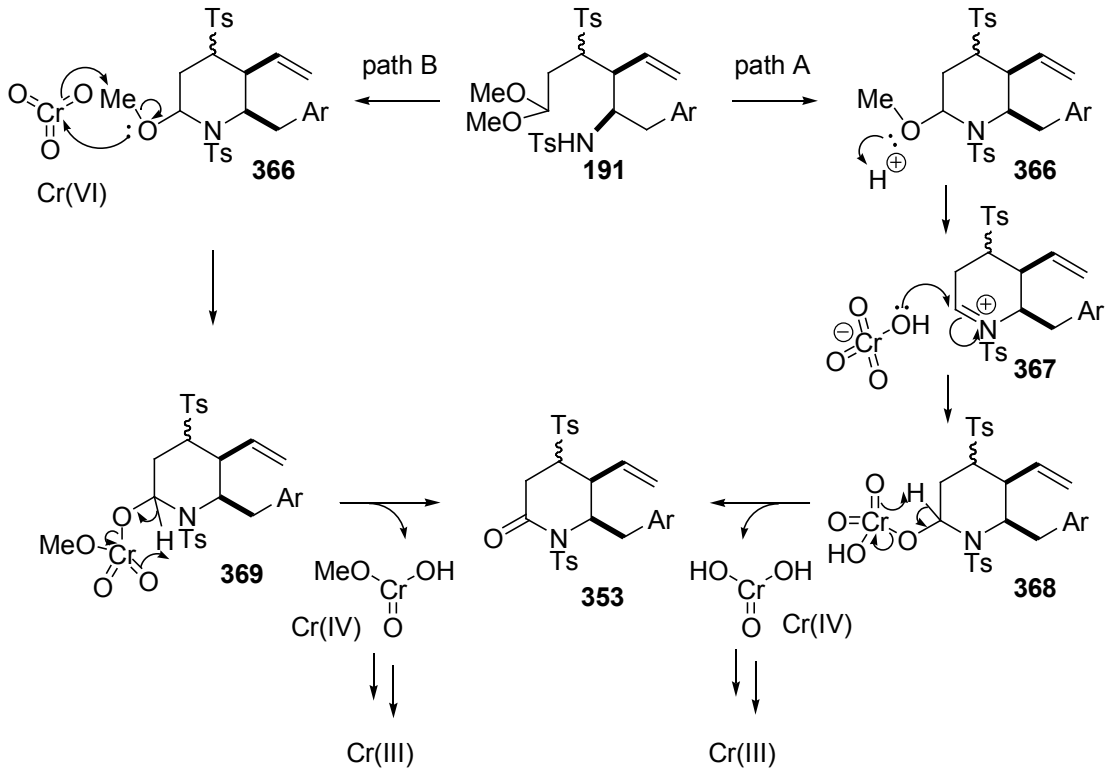


i) CrO_3 (5.0 equiv), H_2SO_4 (11.0 equiv), H_2O, acetone

Scheme 118

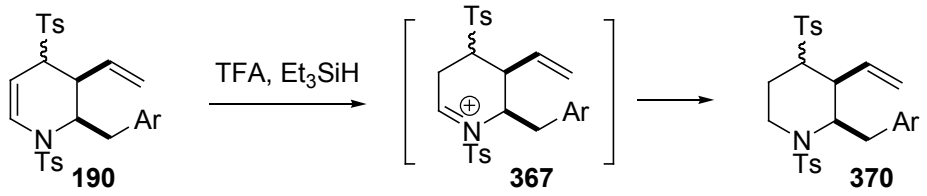
Although the exact mechanism of this transformation is unknown, two possible pathways are proposed, as outlined in Scheme 119.[177] Both pathways starts from deprotection–cyclisation of **191** to give hemi-aminal intermediate **366**. In path A, hemi-aminal **366** converts into piperidinium **367** 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_2CrO_3. This Cr(IV) substrate reacts with a Cr(VI) species to yield two Cr(V)

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) $MeOCrO_2H$ to yield **353**. Similarly, these Cr(IV) species will convert into Cr(III).



Scheme 119

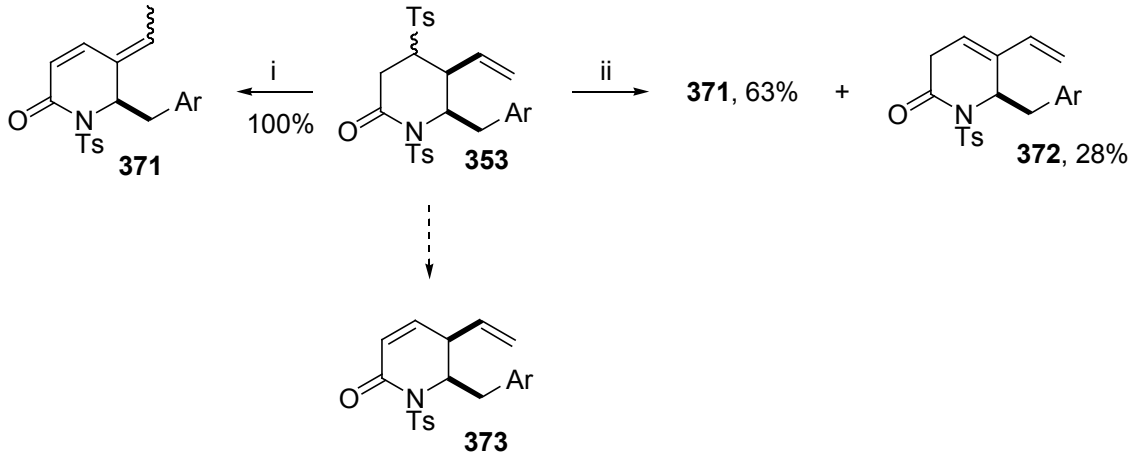
It was believed that piperidinium intermediate **367** could be generated by treatment with TFA, since double bond reduction of the tetrahydropyridine of compound **190** has been achieved previously by group members with TFA and reductant Et_3SiH (Scheme 120).[31] Therefore, other potential oxidants 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.



Scheme 120

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 Et_3N 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**.

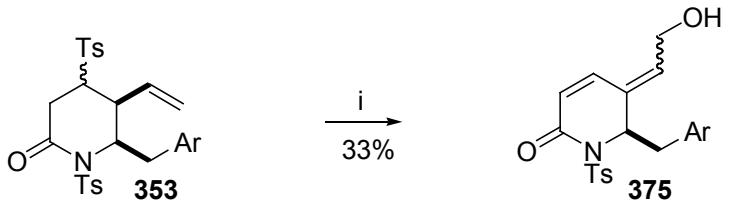


i) DBU (1.67 equiv), CH_2Cl_2, rt, 20 h; ii) Et_3N (0.1 equiv), CH_2Cl_2, rt, 16 h

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.



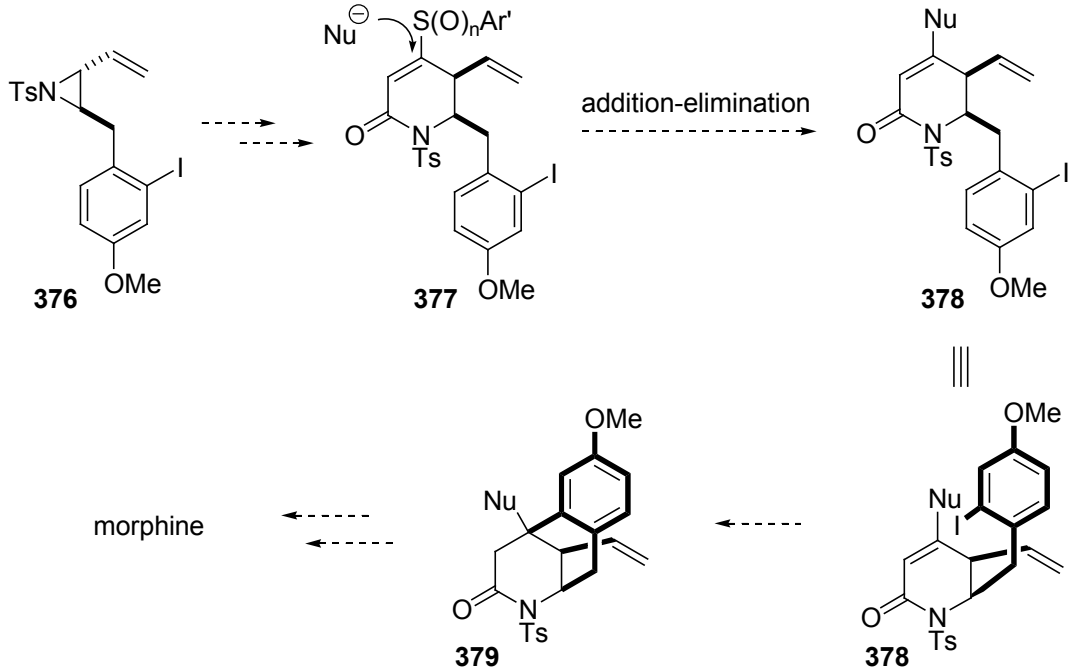
i) CH_2=$CHCH_2CuMgBr$ **374** (generated from CH_2=$CHCH_2MgBr$ 2.0 equiv and CuCN 2.0 equiv), Et_3N (0.3 equiv), THF, rt, 16 h, aqueous work-up

Scheme 122

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

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.

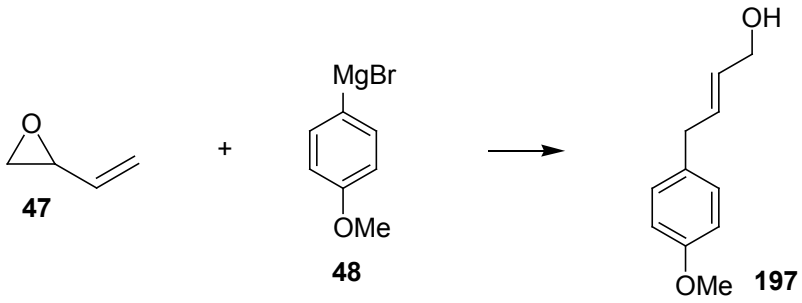
A practical synthesis of highly substituted *N*-tosyl thiophenyl-substituted tetrahydropyridine **299** was developed through a Me_2AlSPh mediated *trans*-sulfurisation from tosyl-substituted tetrahydropyridine **190**. Extensive studies into C-4 alkylation of **299** led to the proposal of nucleophilic 1,4-addition of the *N*-tosyl α,β-unsaturated δ-lactam **354**, which is foreseen to derive from oxidation of δ-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

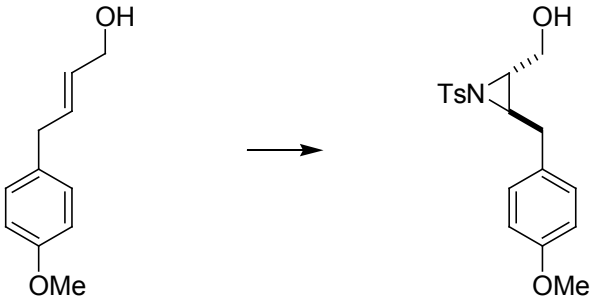
Unless otherwise stated, all reactions were carried out under nitrogen; Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 5000 FTIR spectrometer and on a Perkin-Elmer Spectrum RX FT-IR System. Proton magnetic 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, bs, broad signal; d, doublet; t, triplet; m, multiplet. Mass spectra (CI) 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_2O and THF from sodium-benzophenone ketyl; DMSO, CH_2Cl_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_2S 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[30,31] **197**



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. $NH_4Cl_{(aq.)}$ (13 mL) and NH_3 (10 mL of a 17% aqueous solution) were added. After 15 min the solution was diluted with sat. $NH_4Cl_{(aq.)}$ (53 mL), H_2O (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_2SO_4). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave the alcohol **197** (11.6 g, 91%) as a colourless oil; R_f 0.30 (20% EtOAc–petrol); ν_{max} (film) 3357, 3029, 3002, 2952, 1670, 1610, 1583, 1463, 1463, 1440, 1299, 1176, 1108, 1089, 1035, 998, 971, 817 cm^{-1}; δ_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_2OH), 3.79 (3H, s, OMe), 3.35 (2H, d, *J* 6.0 Hz, CH_2Ar); δ_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_2OH), 37.8 (*C*H_2ArOMe); *m*/*z* (CI) 196 $[M+NH_4]^+$, 179 $[M+H]^+$, 161; data in agreement with that previously reported.[30,31]

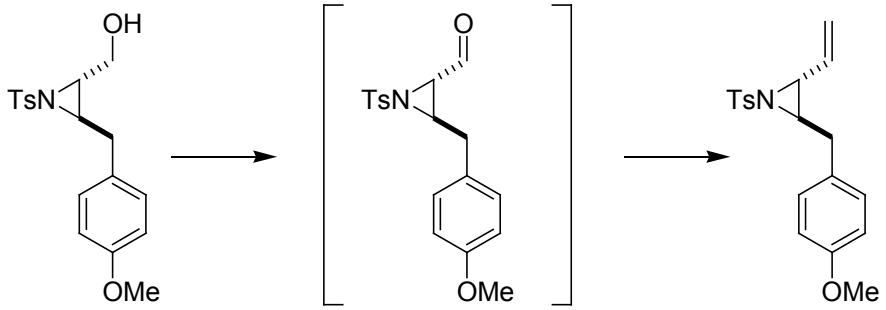
[(2*S,3*R**)-3-(4-Methoxybenzyl)-1-tosylaziridin-2-yl]methanol[30] 198**



197 **198**

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 Et_2O. 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; R_f 0.32 (40% EtOAc–petrol); ν_{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, C*H*$_2$OH), 3.73 (3H, s, OMe), 3.19-3.03 (2H, m, C*H*C*H*CH$_2$OH), 2.90 (1H, dd, *J* 16.5, 13.0 Hz, C*H*HArOMe), 2.63 (1H, dd, *J* 16.5, 13.0 Hz, CH*H*ArOMe), 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 $[M+NH_4]^+$, 348 $[M+H]^+$, 189; data in agreement with that previously reported.[30]

(2*R,3*R**)-2-(4-Methoxybenzyl)-1-tosyl-3-vinylaziridine[30] 46**



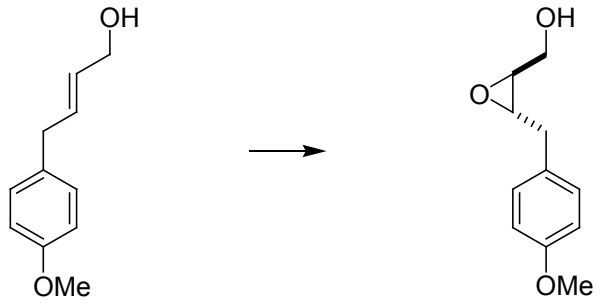
198 **46**

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_2O (400 mL), washed with sat. $NaHCO_{3(aq.)}$ (4 × 100 mL), H_2O (4 × 100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (4 × 50 mL) and dried (Na_2SO_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_3PCH_3Br (5.20 g, 14.3 mmol, 1.1 equiv) in THF (104 mL) at –20 °C was added KHMDS (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_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (25% EtOAc–petrol) gave vinylaziridine **46** (1.00 g, 22%) as a gum; R_f 0.72 (25% EtOAc–petrol); ν_{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^{-1}; δ_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), 6.11-6.04 (1H, m, C*H*=CH_2), 5.50 (1H, d, *J* 16.5 Hz, *cis* CH=C*H*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, C*H*HArOMe), 2.69 (1H, dd, *J* 14.5 Hz, 6.5 Hz, CH*H*ArOMe), 2.42 (3H, s, Me of Ts); δ_C (125 MHz) [158.4 , 143.8, 137.1 (q Ar)], 131.8 (*C*H=CH_2), [129.7, 129.4 (4C, Ar)], 129.4 (q Ar), [127.4 (2C, Ar)], 122.0 (CH=*C*H_2), [114.0, 113.9 (Ar)], 60.4 (OMe),

[55.2, 51.5 (*C*HN*C*H)], 36.0 (*C*H_2ArOMe), 21.6 (Me of Ts); *m/z* (CI) 344 $[M+NH_4]^+$, 196, 173, 163, 121; data in agreement with that previously reported.[30]

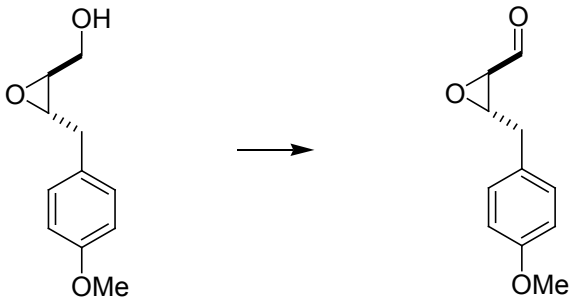
[(2*R,3*R**)-3-(4-Methoxybenzyl)oxiran-2-yl]methanol[31] 205**



197 **205**

To a solution of allylic alcohol **197** (21.0 g, 118 mmol, 1.0 equiv) in CH_2Cl_2 (170 mL) at –20 ºC 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 ºC and 10% $Na_2SO_{3(aq.)}$ (10 mL) added. It was then warmed to rt and a further amount of 10% $Na_2SO_{3(aq.)}$ (290 mL) added. After 1 h, it was diluted with H_2O (200 mL) and the aqueous phase extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with 10% $Na_2CO_{3(aq.)}$ (2 × 100 mL), sat. $NaHCO_{3(aq.)}$ (3 × 100 mL), brine (3 × 150 mL) and dried (Na_2SO_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); ν_{max} (film) 3415, 2993, 2931, 2836, 1612, 1583, 1513, 1463, 1442, 1301, 1247, 1180, 1081, 1033 cm^{-1}; δ_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, C*H*HOH), 3.80 (3H, s, OMe), 3.65 (1H, dd, *J* 12.5, 4.5 Hz, CH*H*OH), 3.20 (1H, ddd, *J* 8.5, 5.5, 3.0 Hz, C*H*CH_2OH), 3.00 (1H, ddd, *J* 4.5, 4.5, 3.0 Hz, ArCH_2C*H*), 2.86 (1H, dd, *J* 12.0, 6.5 Hz, ArC*H*HCH), 2.84 (1H, dd, *J* 12.0, 6.5 Hz, ArCH*H*CH); δ_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_2OH), 56.2 (*C*HCH_2OH), 55.3 (ArCH_2*C*H), 36.9 (Ar*C*H_2); *m*/*z* (CI) 212 $[M+NH_4]^+$, 195 $[M+H]^+$, 177, 121; data in agreement with that previously reported.[31]

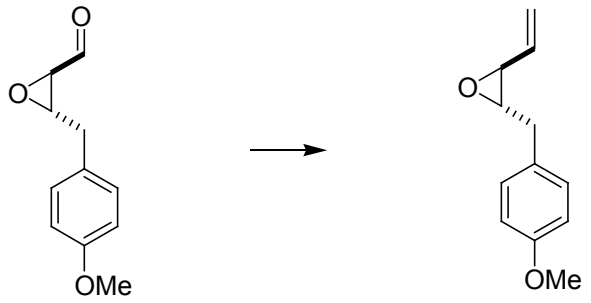
(2*S,3*R**)-3-(4-Methoxybenzyl)oxirane-2-carbaldehyde[31] 380**



205 **380**

To a solution of $(COCl)_2$ (1.05 mL, 12.1 mmol, 1.20 equiv) in CH_2Cl_2 (15 mL) at –78 ºC was added a solution of DMSO (1.72 mL, 24.2 mmol, 2.4 equiv) in CH_2Cl_2 (7 mL) dropwise. After 5 min, a solution of hydroxyl epoxide **205** (1.96 g, 10.1 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) was added. After 25 min, Et_3N (7.0 mL, 50.5 mmol, 5.0 equiv) in CH_2Cl_2 (7 mL) was added slowly. After 10 min it was warmed to rt over 15 min and sat. $NaHCO_{3(aq.)}$ (15 mL) added. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL), brine (2 × 50 mL) and dried (Na_2SO_4). Concentration under reduce pressure and column chromatography (20→40% EtOAc–petrol) gave aldehyde **380** (1.74 g, 85%) as an oil; R_f 0.35 (40% EtOAc–petrol); ν_{max} (film) 3000, 2956, 2913, 1836, 2738, 1725, 1612, 1514, 1464, 1440, 1301, 1249, 1180, 1143, 1112, 1033 cm^{-1}; δ_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, C*H*CH_2Ar), 3.14 (1H, dd, *J* 6.5, 1.5 Hz, C*H*CHO), 2.96 (1H, dd, *J* 15.5, 5.0 Hz, C*H*HAr), 2.88 (1H, dd, *J* 15.0, 5.5 Hz, CH*H*Ar); δ_C (67.5 MHz) 198.3 (CHO), 158.8 (q ArOMe), 130.2 (3º), 127.5 (q ArOMe), 114.2 (3º), [58.4, 57.0 (*C*H*C*H)], 55.3 (OMe), 36.4 (*C*H_2Ar); *m/z* (CI) 210 $[M+NH_4]^+$, 193 $[M+H]^+$, 175, 163, 147, 138, 121, 71, 52 (Found: $[M+H]^+$, 193.0862. $C_{11}H_{12}O_3$ requires $[M+H]^+$, 193.0865); data in agreement with that previously reported.[31]

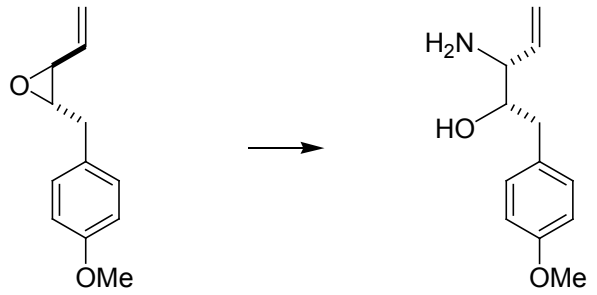
(2*R,3*R**)-2-(4-Methoxybenzyl)-3-vinyloxirane[31] 206**



308 **206**

To a mixture of Ph_3PCH_3Br (43.6 g, 121.9 mmol, 2.0 equiv) in THF (140 mL) at –20 ºC 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 ºC 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 Et_2O (3 × 200 mL). The combined organic layers were washed with H_2O (3 × 150 mL), brine (4 × 150 mL) and dried (Na_2SO_4). Concentration under reduced pressure gave a the brown liquid, which was cooled down to give $P(O)PPh_3$ precipitate that was filtered. Column chromatography of the filtrate gave vinyl epoxide **206** (11.1 g, 96%) as an oil; R_f 0.55 (10% EtOAc–petrol); ν_{max} (film) 2992, 2949, 2913, 2844, 1611, 1583, 1512, 1461, 1445, 1246, 1034, 923, 806 cm^{-1}; δ_H (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, C*H*=CH_2), 5.47 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=C*H*H), 5.25 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=CH*H*), 3.82 (3H, s, MeO), 3.18 (1H, dd, *J* 7.5, 2.0 Hz, C*H*CH=CH_2), 3.06 (1H, ddd, *J* 5.5, 5.5, 2.0 Hz, $ArCH_2CH$), 2.89 (1H, dd, *J* 10.0, 5.5 Hz, ArC*H*H), 2.87 (1H, dd, *J* 10.0, 5.5 Hz, ArCH*H*); δ_C (125 MHz) 158.4 (*ipso* MeOAr), 135.5 (*C*H=CH_2), 130.0 (*meta* MeOAr), 128.9 (*para* MeOAr), 119.3 (CH=*C*H_2), 114.3 (*ortho* MeOAr), 60.6 (MeO), [58.4, 55.3 (*C*HO*C*H)], 37.4 (Ar*C*H_2); *m/z* (CI) 208 $[M+NH_4]^+$, 192, 173, 161, 147, 134, 121, 107; data in agreement with that previously reported.[31]

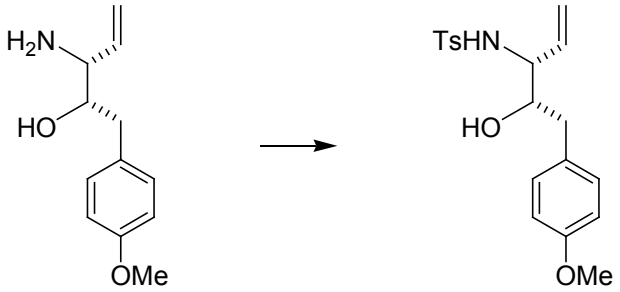
(2*R,3*S**)-3-Amino-1-(4-methoxyphenyl)pent-4-en-2-ol**[31] **207**



206 **207**

The mixture of vinyl epoxide **206** (2.00 g, 10.4 mmol, 1.0 equiv) and NH_4OH (17 mL of a 28% A.C.S. reagent, 251 mmol, 24.1 equiv) was irradiated under microwave at 110 ºC 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 (Na_2SO_4). Concentration under reduced pressure cleanly gave crude hydroxyamine **207** (1.8 g, 84%) as an oil; R_f 0.17 (15% EtOAc–petrol); ν_{max} (film) 3355, 3289, 3099, 3031, 2935, 1612, 1582, 1511, 1463, 1442, 1423, 1299, 1246, 1178, 1108, 1035 cm^{-1}; δ_H (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, C*H*=CH_2), 6.29-5.25 (2H, m, CH=CH_2), 3.83-3.78 (4H, m, *Me*O & C*H*OH), 3.45 (1H, dd, *J* 7.0, 3.0 Hz, C*H*NH_2), 2.74 (1H, dd, *J* 14.0, 4.5 Hz, ArC*H*H), 2.65 (1H, dd, *J* 14.0, 8.5 Hz, ArCH*H*), 1.77 [2H, s (br), NH_2]; δ_C (125 MHz) 158.2 (Ar *para* to MeO), 138.2 (*C*H=CH_2), 130.6 (Ar *ipso* to MeO), 130.4 (Ar *meta* to MeO), 116.7 (CH=*C*H_2), 114.0 (Ar *ortho* to MeO), 75.3 (*C*HOH), 58.0 (*C*HNH_2), 38.4 (Ar*C*H_2); *m/z* (CI) 208 $[M+H]^+$, 189, 168, 150, 135, 123, 121, 109; data in agreement with that previously reported.[31]

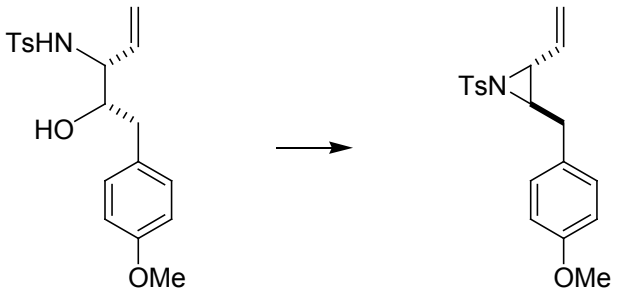
***N*-[(3*S**,4*R**)-4-Hydroxy-5-(4-methoxyphenyl)pent-1-en-3-yl]-4-methylbenzenesulfonamide[31] 208**



207 **208**

To a solution of hydroxyamine **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_2Cl_2 (61 mL) at 0 ºC was added Et_3N. After 3 h at that temperature, the resulting solution was diluted with CH_2Cl_2 (200 mL), washed with 10% $NaHCO_{3(aq.)}$ (130 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried (Mg_2SO_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); ν_{max} (film) 3447, 3356, 3291, 1511, 1322, 1288, 1153, 1077, 1025, 813, 675 cm^{-1}; δ_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, C*H*=CH_2), 6.19-5.08 (2H, m, CH=CH_2), 3.86-3.79 (5H, m, O*Me*, C*H*NHTs & C*H*OH), 2.67 (1H, dd, *J* 14.0, 4.5 Hz, ArC*H*H), 2.58 (1H, dd, *J* 14.0, 9.0 Hz, CH*H*Ar), 2.65 (1H, dd, *J* 14.0, 8.5 Hz, CH*H*Ar), 2.44 (3H, s, Me of Ts), 1.88 (1H, d, *J* 4.5 Hz, N*H*Ts); δ_C (100 MHz) [158.2, 143.4, 137.7 (q Ar)], 132.5 (*C*H=CH_2), [130.2, 129.6, (ArH)], 129.1 (q ArOMe), 127.2 (ArH), 119.4 (CH=*C*H_2), 114.2 (ArH), 74.7 (*C*HOH), 59.9 (*C*HNH_2), 55.3 (OMe), 39.0 (*C*H_2Ar), 21.6 (Me of Ts); *m/z* (CI) 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]

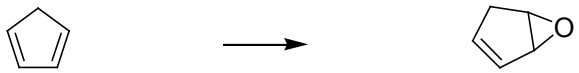
(2*R,3*R**)-2-(4-Methoxybenzyl)-1-tosyl-3-vinylaziridine**[31] **46**



208 **46**

To a solution of tosamide **208** (7.20 g, 19.9 mmol, 1.0 equiv) and PPh_3 (13.6 g, 51.9 mmol, 2.6 equiv) in THF (200 mL) at –15 ºC was added DIAD (8.1 g, 39.9 mmol, 2.0 equiv) dropwise. The solution was warmed to –5 ºC. 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.[31]

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

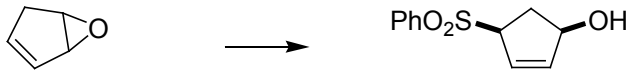


209 **210**

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_2Cl_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_f 0.60 (90% EtOAc–petrol); ν_{max} (film) 3492, 3459, 3401, 2958, 2922, 2873, 2105, 1837, 1463,

1361, 1182, 1122, 1072, 1041 cm^{-1}; δ_H (270 MHz) 6.15-5.93 (2H, m, CH=CH), 3.92-3.80 (2H, m, CHOCH), 2.63-2.59 (1H, m, C*H*HCHOCH), 2.41-2.32 (1H, m, CH*H*CHOCH); δ_C (125 MHz) [138.5, 131.3 (CH=CH)], [59.2, 56.9 (*C*HO*C*H)], 35.6 (CH_2); *m/z* (CI) 100 $[M+NH_4]^+$, 83 $[M+H]^+$, 71, 56; data in agreement with that previously reported.[103]

(1*R,4*S**)-4-(Phenylsulfonyl)cyclopent-2-enol[32] 45**



210 **45**

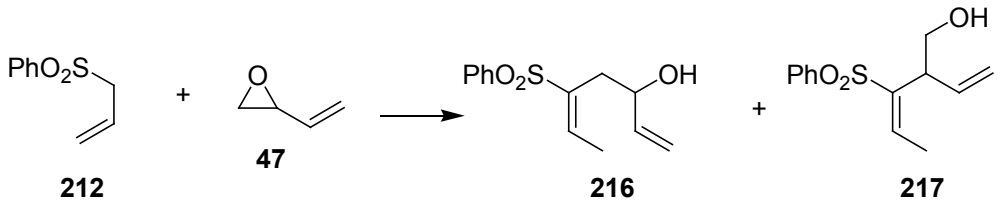
Method 1: $Pd(acac)_2$ in THF preparation

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. $NH_4Cl_{(aq.)}$ (0.5 mL). After 15 min the solution was diluted with sat. $NH_4Cl_{(aq.)}$ (1 mL), H_2O (10 mL) and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (40% EtOAc–petrol) gave the (1*R**,4*S**)-4-(phenylsulfonyl)cyclopent-2-enol **45** (63 mg, 37%) as a colourless oil; R_f 0.52 (80% EtOAc–petrol); ν_{max} (film) 3428, 3000, 2985, 2956, 2921, 2850, 2815, 2802, 2782, 1910, 1884, 1658, 1641, 1552, 1303, 1145, 1083, 989 cm^{-1}; δ_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, C*H*=CHCHOH), 5.74-5.73 (1H, m, CH=C*H*CHOH), 4.72-4.70 (1H, m, C*H*SO_2Ph), 4.16-4.01 (1H, m, C*H*OH), 2.26-2.21 (2H, m, CH_2); δ_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 ($CHSO_2Ph$), 70.2 (CHOH), 34.3 (CH_2); *m/z* (CI) 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. $NH_4Cl_{(aq.)}$ (0.5 mL). After 15 min the solution was diluted with sat. $NH_4Cl_{(aq.)}$ (1 mL) and H_2O (10 mL) then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (4 × 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

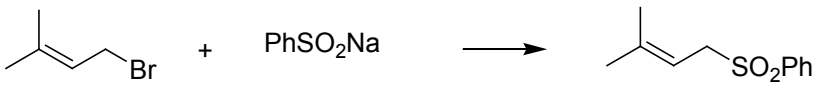


To a solution of allylic sulfone **212** (1.00 g, 5.5 mmol, 1.0 equiv) in Et_2O (27 mL) at –20 °C was added *n*BuLi (2.30 mL of a 2.8 M solution in hexanes, 6.60 mmol, 1.2 equiv) dropwise over 20 min. After 15 min the suspension was warmed for 30 min then re-cooled to –20 °C. Butadiene monoxide **47** (440 μL, 5.5 mmol, 1.0 equiv) was added. After 30 min the reaction was warmed to rt for 2 h then sat. $NH_4Cl_{(aq.)}$ (1.0 mL) added. After 5 min the mixture was diluted with sat. $NH_4Cl_{(aq.)}$ (4 mL), H_2O (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (2 × 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**: R_f 0.37 (40% EtOAc–petrol); ν_{max} (film) 3501, 3069, 2984, 2924, 1704, 1643, 1584, 1477, 1300, 1148, 1132, 1083, 1033, 1022, 996, 926, 762, 737, 693 cm^{-1}; δ_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, C*H*=CSO_2Ph), 5.86-5.72 (1H, m, CH_2=C*H*CHOH), 5.21 (1H, d, *J* 18.0 Hz, *cis* C*H*H=CH), 5.07 (1H, d, *J* 11.0 Hz, *trans* CH*H*=CH), 4.12-4.30 (1H, m, C*H*OH), 2.44-2.38 (2H, m, CH_2CHOH), 1.89 (3H, d, *J* 7.0 Hz, Me), 1.20 (1H, br s, OH); δ_C (125 MHz) 140.5 (*ipso* $PhSO_2$), 139.6 (CH=*C*SO_2Ph), 138.6 (*para* $PhSO_2$), 133.4 (*C*H=CSO_2Ph), 129.4 (CH_2=*C*H), 129.2 (*ortho* $PhSO_2$)], 128.1 (*meta* $PhSO_2$), 115.3 (*C*H_2=CH), 71.6 (CHOH), 33.9 (*C*H_2CHOH), 14.7 (Me); *m*/*z* (CI) 522 $[2M+NH_4]^+$, 270 $[M+NH_4]^+$, 253 $[M+H]^+$, 235 $[M-OH]^+$, 216, 69, 52 (Found: $[M+NH_4]^+$, 270.1157. $C_{13}H_{16}O_3S$ requires $[M+NH_4]^+$, 270.1164) (Found: C, 61.78; H, 6.32. $C_{13}H_{16}O_3S$ requires C, 61.88; H, 6.39%).

Data for **217**: R_f 0.23 (40% EtOAc–petrol); ν_{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}; δ_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, C*H*=CSO_2Ph), 5.71-5.64 (1H, m, CH_2=C*H*), 4.96 (1H, dd, *J* 10.0, 1.5 Hz, *trans* C*H*H=CH), 4.79 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH*H*=CH), 3.79 (2H, d, *J* 7.5 Hz, C*H*$_2$OH), 3.53 (1H, dt, *J* 14.5, 7.5 Hz, C*H*CH_2OH), 1.95 (3H, d, *J* 7.0 Hz, CH_3), 1.28-1.18 (1H, m, OH); δ_C (125 MHz) 140.8 (*ipso* $PhSO_2$), 139.9 (CH=*C*SO_2Ph), 139.3 (*para* $PhSO_2$), 133.8 (*C*H=CSO_2Ph), 133.4 (CH_2=*C*H), 129.1 (*ortho* $PhSO_2$), 128.2 (*meta* $PhSO_2$), 117.4 (*C*H_2=CH), 64.5 (CH_2OH), 45.2 (*C*HCH_2), 15.1 (Me); *m*/*z* (CI) 270 $[M+NH_4]^+$, 253 $[M+H]^+$, 235 $[M-OH]^+$, 132, 52 (Found: $[M+NH_4]^+$, 270.1160. $C_{13}H_{16}O_3S$ requires $[M+NH_4]^+$, 270.1164) (Found: C, 61.89; H, 6.37. $C_{13}H_{16}O_3S$ requires C, 61.88; H 6.39%).

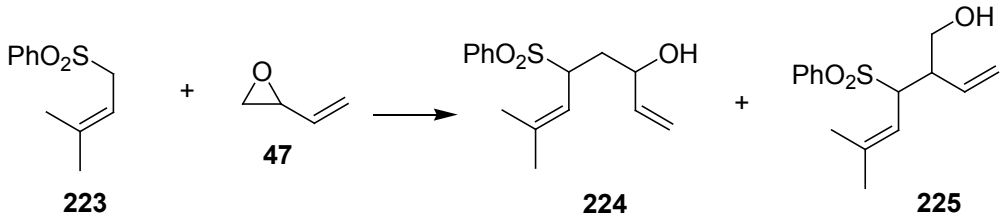
(3-Methylbut-2-enylsulfonyl)benzene[104] **223**



222 **223**

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_2O (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 recrystalisation (Et_2O–petrol) gave the sulfone **223** (5.80 g, 92%) as a white crystalline solid; mp 49-50 ºC (lit. mp 50-51 ºC); R_f 0.76 (40% Et_2O–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=C), 3.76 (2H, d, *J* 9.0 Hz, CH_2), 1.69 (3H, s, CH_3CCH_3), 1.28 (3H, s, CH_3CCH_3); δ_C (125 MHz) 143.0 (*ipso* $PhSO_2$), 138.7 (*para* $PhSO_2$), 133.5 (C=*C*H), 128.9 (*ortho* $PhSO_2$), 128.5 (*meta* $PhSO_2$), 110.4 (*C*=CH), 56.2 (CH_2SO_2Ph), [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



223 **224** **225**

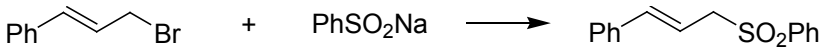
To a solution of prenyl sulfone **223** (1.05 g, 5.0 mmol, 1.0 equiv) in THF/TMEDA (1:1, 25 mL) at –78 °C was added *n*BuLi (2.50 mL of a 2.4 M solution in hexanes, 6.0 mmol, 1.2 equiv). After 15 min the solution was warmed to –20 °C for 30 then re-cooled to –78 °C and butadiene monoxide **47** (483 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. $NH_4Cl_{(aq.)}$ (15 mL), diluted with H_2O (50 mL) and extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried ($MgSO_4$). 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**: R_f 0.48 (40% EtOAc–petrol); ν_{max} (film) 3492, 3065, 2978, 2926, 2876, 1667, 1644, 1446, 1299, 1145, 1083, 1069, 1052, 996, 924, 744, 718, 689 cm^{-1}; δ_H (270 MHz) 7.82 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$), 7.60 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.51 (2H, dd, *J* 7.5, 7.0 Hz, *meta* $PhSO_2$), 5.88 (1H, ddd, *J* 14.0, 9.5, 5.0 Hz, C*H* =CH_2), 5.20 (1H, dd, *J* 14.0, 7.5 Hz, *cis* C*H*H=CH), 5.12 (1H, dd, *J* 9.5, 7.5 Hz, *trans* CH*H*=CH), 4.98 (1H, d, *J* 10.5 Hz, C=CH), 4.13-4.05 (2H, m, $PhSO_2CH$ & C*H*OH), 2.24 (1H, ddd, *J* 6.5, 6.0, 2.5 Hz, C*H*HCHOH), 1.83 (1H, ddd, *J* 6.5, 6.0, 2.5 Hz, CH*H*CHOH), 1.65 (3H, s, CH_3CCH_3), 1.48 (1H, d, *J* 7.0 Hz, OH), 1.15 (3H, s, CH_3CCH_3); δ_C (101 MHz) 143.1 (*ipso* $PhSO_2$), 140.4 (*C*=CH), 137.9 (*para* $PhSO_2$), 133.4 (CH_2=*C*H), 129.1 (*ortho* $PhSO_2$), 128.7 (*meta* $PhSO_2$), 116.6 (C=*C*H), 115.1 (*C*H_2=CH), 69.6 (*C*HSO_2Ph), 61.9 (CHOH), 34.5 (CH_2), [25.9, 17.9 (2 × Me)]; *m*/*z* (CI) 298 $[M+NH_4]^+$, 281 $[M+H]^+$, 264, 263 [M-OH] $^+$, 160, 121, 83 (Found: $[M+NH_4]^+$, 298.1472. $C_{15}H_{20}O_3S$ requires

$[M+NH_4]^+$, 298.1477) (Found: C, 64.29; H, 7.13. $C_{15}H_{20}O_3S$ requires C, 64.26; H, 7.19%).

Data for **225**: R_f 0.41 (40% EtOAc–petrol); ν_{max} (film) 3497, 2978, 2937, 2915, 1446, 1377, 1301, 1175, 1143, 1083, 1069, 1049, 995, 927, 777, 745, 795, 689 cm^{-1}; δ_H (270 MHz) 7.78 (2H, d, *J* 8.5 Hz, *ortho* $PhSO_2$), 7.55 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.51 (2H, dd, *J* 8.5, 7.0 Hz, *meta* $PhSO_2$), 5.79-5.73 (1H, m, CH_2=C*H*), 5.21-5.11 (2H, m, CH_2=CH), 4.95 (1H, d, *J* 11.5 Hz, C=CH), 4.23-4.21 (1H, m, $PhSO_2$C*H*), 3.84-3.44 (2H, m, CH_2OH), 2.39-2.33 (1H, m, C*H*CH_2OH), 1.60 (3H, s, C$H_3$$CCH_3$), 1.15 (1H, m, OH), 1.11 (3H, s, CH_3CCH_3); δ_C (100 MHz) 142.8 (*ipso* $PhSO_2$), 141.9 (*C*=CH), 137.9 (*para* $PhSO_2$), 134.0 (CH_2=*C*H), 129.1 (*ortho* $PhSO_2$), 128.7 (*meta* $PhSO_2$), 117.3 (C=*C*H), 116.4 (*C*H_2=CH), 70.9 (*C*HSO_2Ph), 61.7 (*C*H_2OH), 30.3 (*C*HCH_2OH), [25.7, 18.0 (2 × Me)]; *m*/*z* (CI) 298 $[M+NH_4]^+$, 281 $[M+H]^+$, 264, 263 $[M-OH]^+$, 160, 121, 109, 83 (Found: $[M+NH_4]^+$, 298.1471. $C_{15}H_{20}O_3S$ requires $[M+NH_4]^+$, 298.1477) (Found: C, 64.37; H, 7.16; $C_{15}H_{20}O_3S$ requires C, 64.26; H, 7.19%).

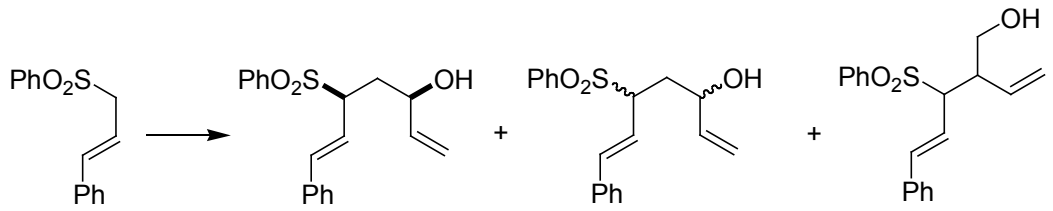
Cinnamylsulfonylbenzene[107] **227**



226 **227**

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 **226** (12.0 g, 60.9 mmol, 1.0 equiv) then cooled to rt. After 2 h the suspension was diluted with H_2O (150 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (3 × 40 mL) and dried ($MgSO_4$). Concentration under reduced pressure and recrystalisation (EtOAc–petrol) gave cinnamylphenylsulfone **227** (14.7 g 93%) as a white crystalline solid; mp 50-51 ºC (EtOAc–petrol) (lit.[107] mp 50-51 ºC); R_f 0.62 (30% EtOAc–petrol); ν_{max} (film) 2974, 1445, 1403, 1317, 1237, 1160, 1135, 1084, 1058, 998, 982, 759, 697 cm^{-1}; δ_H (270 MHz) 7.87 (2H, d, *J* 7.0 Hz, *ortho* $PhSO_2$), 7.64 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.54 (2H, t, *J* 7.0 Hz, *meta* $PhSO_2$), 7.30-7.25 (5H, m, *Ph*CH), 6.36 (1H, d, *J* 16.0 Hz, C*H*=CHCH_2), 6.05 (1H, dt, *J* 16.0, 8.0 Hz, CH=C*H*CH_2), 3.94 (2H, d, *J* 8.0 Hz, CH_2SO_2Ph); δ_C (125 MHz) 139.2 (*ipso* $PhSO_2$), 138.5 (*ortho* $PhSO_2$), 135.8 (*ipso* PhCH=CH), 133.7 (Ph*C*H=CH), 130.8 (*para* PhCH=CH), [129.1, 128.8, 126.6 (*ortho* & *meta* PhCH & $PhSO_2$), 115.2 (PhCH=*C*H), 60.5 (*C*H_2SO_2); *m*/*z* (CI) 276 $[M+NH_4]^+$, 269, 229, 175, 160; data in agreement with that previously reported.[107]

(3*R,5*S**,*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**



227 **3,5-*syn*-228** **228** **229**

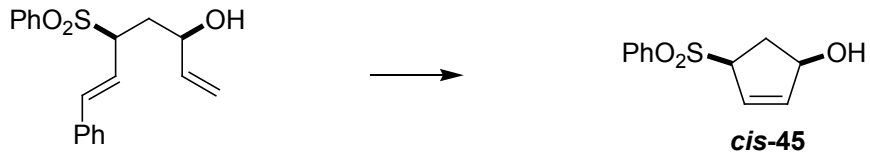
To a solution of cinnamylsulfone **227** (2.10 g, 8.0 mmol, 1.0 equiv) in THF (40 ml) at –78 °C was added *n*BuLi (4.54 mL of a 2.3 M solution in hexanes, 10.4 mmol, 1.3 equiv) dropwise over 10 min. After 15 min the solution was warmed to –20 °C for 30 min then re-cooled to –78 °C and butadiene monoxide (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. $NH_4Cl_{(aq.)}$ (10 mL) then diluted with water (50 mL) and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and recrystalisation (Et_2O–petrol) gave *(3*R**,5*S**,*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 ºC (Et_2O–petrol); R_f 0.40 (40% EtOAc–petrol); ν_{max} (film) 3461, 2955, 2923, 2886, 2773, 1446, 1297, 1143, 1083, 1072, 996, 971, 734, 688 cm^{-1}; δ_H (270 MHz) 7.83 (2H, d, *J* 8.0 Hz, *ortho* $PhSO_2$), 7.60 (1H, t, *J* 8.0 Hz, *para* $PhSO_2$), 7.54 (2H, t, *J* 8.0 Hz, *meta* $PhSO_2$), 7.26-7.24 (5H, m, *Ph*CH), 6.30 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 5.99-5.82 (2H, m, PhCH=C*H* & CH_2=C*H*), 5.23 (1H, dd, *J* 16.0, 5.5 Hz, *cis* C*H*H=CH), 5.13 (1H, dd, *J* 10.5, 5.5 Hz, *trans* CH*H*=CH), 4.13-4.03 (2H, m, C*H*SO_2Ph & C*H*OH), 2.33 (1H, ddd, *J* 20.5, 11.0, 3.0 Hz, CH*H*CHOH), 1.96 (1H, ddd, *J* 20.5, 11.0, 3.0 Hz, C*H*HCHOH), 1.55-1.52 (1H, d, *J* 3.5 Hz, OH); δ_C (101 MHz) 140.1 (*ipso* $PhSO_2$), [138.7, 137.5, 135.7 (*ipso* PhCH & *ortho*, *para* $PhSO_2$)], 133.7 (PhCH=*C*H), [129.1, 128.9, 128.7 (*meta* $PhSO_2$ & *ortho, para* PhCH)], 128.5 (Ph*C*H=CH), 126.6 (*meta* PhCH), 120.5 (CH_2=*C*H), 115.5 (*C*H_2=CH), 69.4

($PhSO_2CH$), 66.4 (*C*HOH), 34.4 (CH_2); *m*/*z* (CI) 346 $[M+NH_4]^+$, 333, 332, 329 $[M+H]^+$, 297, 276, 206, 204, 175, 160, 134, 132, 131, 52 (Found: $[M+NH_4]^+$, 346.1480. $C_{19}H_{20}O_3S$ requires $[M+NH_4]^+$, 346.1477) (Found: C, 69.49; H, 6.19. $C_{19}H_{20}O_3S$ requires C, 69.48; H, 6.14%).

Data for **229**: R_f 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* $PhSO_2$), 7.55 (1H, t, *J* 8.0 Hz, *para* $PhSO_2$), 7.42 (2H, dd, *J* 8.5, 8.0 Hz, *meta* $PhSO_2$), 7.24-7.12 (5H, m, *Ph*CH=CH) 6.09 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.07 (1H, dd, *J* 16.0, 8.5 Hz, PhCH=C*H*), 5.27 (1H, dd, *J* 10.0, 1.0 Hz, *trans* C*H*H=CH), 5.25 (1H, dd, *J* 15.5, 1.0 Hz, *cis* CH*H*=CH), [4.14-4.00, 3.88-3.69 (2H, m, CH_2OH)], 3.59 (1H, dd, *J* 11.0, 8.5 Hz, C*H*SO_2Ph), 3.34-3.26 (1H, m, C*H*CH_2OH), 1.24-1.19 (1H, m, OH); δ_C (101 MHz) 139.1 (*ipso* $PhSO_2$), 138.1 (*para* $PhSO_2$), 135.7 (*ipso* PhCH), 133.6 (PhCH=*C*H), [129.0, 128.8, 128.6, 128.3 (*ortho*, *meta* $PhSO_2$ & *ortho*, *para* PhCH)], 128.3 (Ph*C*H=CH), 126.6 (*meta* PhCH), 119.5 (CH_2=*C*H), 118.6 (*C*H_2=CH), 69.2 ($PhSO_2CH$), 63.3 (CH_2OH), 44.6 (CH); *m*/*z* (CI) 346 $[M+NH_4]^+$, 329 $[M+H]^+$, 206, 204, 287, 177, 169, 160, 157, 52 (Found: $[M+NH_4]^+$, 346.1479. $C_{19}H_{20}O_3S$ requires $[M+NH_4]^+$, 346.1477) (Found: C, 69.58; H, 6.12. $C_{19}H_{20}O_3S$ requires C, 69.48; H, 6.14%).

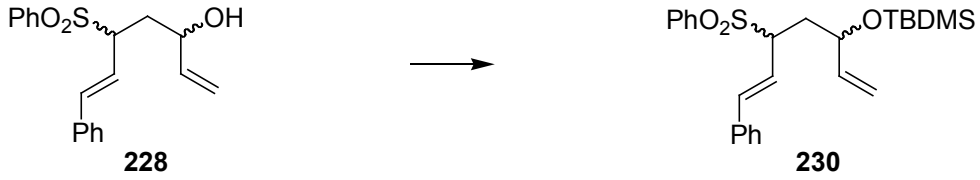
(1*R,4*S**)-4-(Phenylsulfonyl)cyclopent-2-enol**[32] ***cis*-45**



3,5-*syn*-228 ***cis*-45**

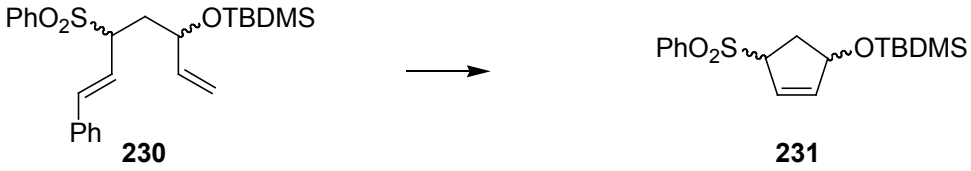
To a solution of **3,5-*syn*-228** (400 mg, 1.20 mmol, 1.0) in CH_2Cl_2 (15 mL) at 40 °C was added catalyst **50** (31.1 mg, 0.04 mmol, 0.03 equiv) in CH_2Cl_2 (2 mL). After 10 min concentration under reduced pressure and column chromatography (15%→50% EtOAc–petrol) gave cyclopentenylsulfone ***cis*-45** (255 mg, 93%); data identical to that previously reported.[32]

***tert*-Butyldimethyl[(3*R**,5*S**,*E*), (3*S**,5*S**,*E*)-7-phenyl-5-(phenylsulfonyl) hepta-1,6-dien-3-yloxy]silane 230**



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 CH_2Cl_2 (1 mL) at 40 °C was added Et_3N (397 µL, 2.85 mmol, 3.0 equiv) dropwise. After 24 h the brown suspension was quenched with sat. $NH_4Cl_{(aq.)}$ (2 mL), diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq.)}$ (5 mL), brine (3 × 5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (40% ether–petrol) gave *tert-butyldimethyl[(3*R**,5*S**,*E*), (3*S**,5*S**,*E*)-7-phenyl-5-(phenylsulfonyl)hepta-1,6-dien-3-yloxy]silane* **230** (400 mg, 95%) as a colourless oil; R_f 0.67 (40% Et_2O–petrol); ν_{max} (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}; δ_H (270 MHz) 7.83-7.79 (2 × 2H, m, *ortho* $PhSO_2$, 2 × diast.), 7.61-7.45 (2 × 3H, m, *para & meta* $PhSO_2$, 2 × diast.), 7.30-7.19 (2 × 5H, m, *Ph*CH=CH, 2 × diast.), 6.25 (1H, d, *J* 18.5 Hz, CH=C*H*Ph, diast. of $PhSO_2$ *syn* to OTBDMS), 6.15 (1H, d, *J* 18.5, CH=C*H*Ph, diast. of $PhSO_2$ *anti* to OTBDMS), 5.92-5.60 (2 × 2H, m, PhCH=C*H* & CH_2=C*H*, 2 × diast.), 5.13-5.02 (2 × 2H, m, C*H*$_2$=CH, 2 × diast.), 4.23-3.77 (2 × 2H, m, $PhSO_2CHCH_2CHOH$, 2 × diast.), [2.40–2.28, 2.02–1.77 (2 × 2H, m, CHC*H*$_2$CH, 2 × diast.)], 0.91 (9H, s, *t*Bu, diast. of $PhSO_2$ *anti* to OTBDMS), 0.86 (9H, s, *t*Bu, diast. of $PhSO_2$ *syn* to OTBDMS), {0.12, 0.06, 0.02, -0.02, -0.04 [2 × 6H, m, Si(CH$_3$)$_2$, 2 × diast.]}; δ_C (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, CH*C*H$_2$CH, 2 × diast.)], 25.8, 25.7, 25.6, [18.1, 18.0 (2 × C, Si*C*(CH$_3$)$_3$, 2 × diast.], {-3.6, -3.8, -4.4, -4.8 [2 × 2C, Si(CH$_3$)$_2$, 2 × diast.]}; *m/z* (CI) 460 $[M+NH_4]^+$, 443 $[M+H]^+$, 312, 311, 301, 298, 171; 169, 132 (Found: $[M+H]^+$, 443.2057. $C_{25}H_{34}O_3SSi$ requires $[M+H]^+$, 443.2076) (Found: C, 67.96; H, 7.68. $C_{25}H_{34}O_3SSi$ requires C, 67.83; H, 7.74%).

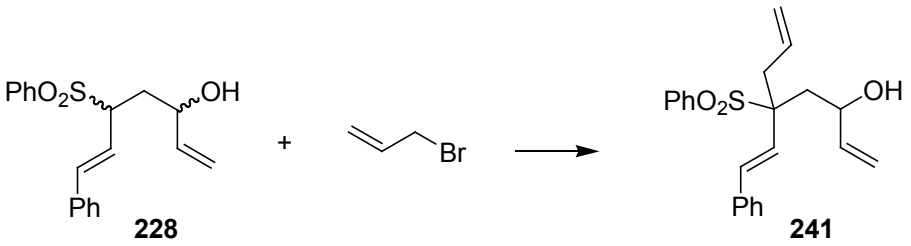
***tert*-Butyldimethyl[(1*R**,4*S**), (1*S**,4*S**)-4-(phenylsulfonyl)cyclopent-2-enyl oxy]silane 213**



230 **231**

To a solution of diene **230** (350 mg, 0.79 mmol, 1.0 equiv) in CH_2Cl_2 (13 mL) at 40ºC was added a solution of catalyst **50** (20 mg, 0.024 mmol, 0.03 equiv) in CH_2Cl_2 (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[(1*R**,4*S**), (1*S**,4*S**)-4-(phenylsulfonyl)cyclopent-2-enyloxy]silane* **231** (211 mg, 79%); R_f (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}; δ_H (270 MHz) 7.85 (2 × 2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$, 2 × diast.), 7.61 (2 × 1H, t, *J* 7.0 Hz, *para* $PhSO_2$, 2 × diast.), 7.56 (2H, dd, *J* 7.5, 7.0 Hz, *meta* $PhSO_2$, 2 × diast.), [6.06-6.04, 5.93-5.91 (2H, m, CH=CH, diast. of $PhSO_2$ *syn* to OTBDMS)], [5.84-5.82, 5.74-5.71 (2H, m, CH=CH, diast. of $PhSO_2$ *anti* to OTBDMS)], 4.80-4.76 (2H, m, $PhSO_2C\mathit{H}CH_2C\mathit{H}$OTBDMS, 1 × diast.), [4.38-4.35, 4.15-4.11 (2H, m, $PhSO_2C\mathit{H}CH_2C\mathit{H}$OTBDMS, 1 × diast.)], 2.70-2.52 (2H, m, CH_2, diast. of $PhSO_2$ *syn* with OTBDMS), 2.02-1.88 (2H, m, CH_2, diast. of $PhSO_2$ *anti* to OTBDMS), 0.87 (9H, s, *t*Bu, diast. of $PhSO_2$ *anti* to OTBDMS), 0.79 (9H, s, *t*Bu, diast. of $PhSO_2$ *cis* to OTBDMS, {0.00, –0.03, –0.05 [2 × 6H, s, $Si(CH_3)_2$, 2 × diast.]}; δ_C (125 MHz) [143.3, 141.4 (2 × *ipso* $PhSO_2$, 2 × diast.)], 136.5 (*para* $PhSO_2$, 1 × diast.), [133.8, 133.7 (2 × CH=CHCHSO_2Ph, 2 × diast.)], 129.6 (*para* $PhSO_2$, 1 × diast.), [129.4, 129.1 (2 × *ortho* $PhSO_2$, 2 × diast.)], [129.0, 128.9 (2 × *meta* $PhSO_2$, 2 × diast.)], [125.6, 125.4 (2 × CH=CHCHSO_2Ph, 2 × diast.)], [76.4, 70.2, 71.4, 70.2 (2 × CHSO_2Ph & CHOTBDMS, 2 × diast.)], [35.5, 34.4 (2 × CH$_2$CHOTBDMS, 2 × diast.)], {25.8, 25.7, 25.6 [2 × (CH$_3$)$_3$CSi, , 2 × diast.]}, {18.1, 18.0 [2 × (CH_3)$_3C$Si, , 2 × diast.]}, {-4.8, -4.7 [2 × (CH_3)$_2$Si, 2 × diast.]} *m*/*z* (CI) 356 $[M+NH_4]^+$, 339 $[M+H]^+$, 321, 281, 242, 240, 224, 197 $[M-PhSO_2]^+$; (Found: $[M+H]^+$, 339.1439. $C_{17}H_{26}O_3SSi$ requires $[M+H]^+$, 339.1450) (Found: C, 60.23; H, 7.73. $C_{17}H_{26}O_3SSi$ requires C, 60.31; H, 7.74%).

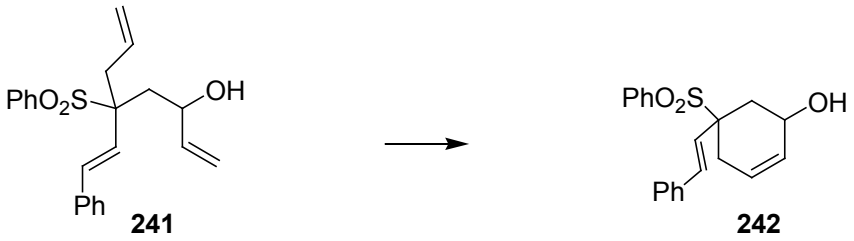
(*E*)-5-(Phenylsulfonyl)-5-styrylocta-1,7-dien-3-ol 241



To a solution of diene **228** (405 mg, 1.23 mmol, 1.0 equiv) in THF (2.5 mL) at –78 °C was added *n*BuLi (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. $NH_4Cl_{(aq.)}$ (1.1 mL), diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried ($MgSO_4$). 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; R_f 0.24 (30% EtOAc–petrol); ν_{max} (film) 3505, 3463, 3063, 3026, 2978, 2922, 1640, 1493, 1445, 1300, 1146, 1083, 1017, 923, 760, 740, 680 cm^{-1}; δ_H (400 MHz) [7.84, 7.78 (2 × 2H, 2 × d, 2 × *J* 7.5 Hz, *ortho* $PhSO_2$, 2 × diast.)], 7.67-7.61 (2 × 1H, m, *para* $PhSO_2$, 2 × diast.), 7.55-7.46 (2 × 2H, m, *meta* $PhSO_2$, 2 × diast.), 7.37-7.21 (2 × 5H, m, *Ph*CH, 2 × diast.), 6.34 (1H, d, *J* 16.5 Hz, PhC*H*=CH, *major* diast.), 6.25 (1H, d, *J* 16.5 Hz, PhCH=C*H*, *maj*or diast.), 6.15-6.03 (1H, m, CH_2=C*H*CH_2, *minor* diast.), 5.95 (1H, dd, *J* 10.0, 6.5 Hz, C*H*H=CHCHOH, *minor* diast.), 5.92 (1H, dd, *J* 10.0, 6.5 Hz, CH*H*=CHCHOH, *minor* diast.), 5.82 (1H, dd, *J* 10.0, 4.5 Hz, C*H*H=CHCHOH, *major* diast.), 5.78 (1H, dd, *J* 10.0, 6.0 Hz, CH*H*=CHCHOH, *major* diast.), 5.72-5.58 (1H, m, CH_2=C*H*CH_2, *major* diast.), [5.33-4.99 (2H, m, PhC*H*=C*H*C, *minor* diast.) & (2 × 3H, m, CH_2=C*H*CH_2, 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, C*H*OH, *major* diast.), 3.76 (1H, m, C*H*OH, *major.* diast.), 3.06 (1H, dd, *J* 15.0, 6.5 Hz, C*H*HCH=CH_2, *minor* diast.), 2.78 (1H, dd, *J* 15.0, 6.5 Hz, CH*H*CH=CH_2, *minor* diast.), 2.65-2.46 (4H, m, CH_2CH=CH_2 & CH_2CHOH, *major* diast.), 2.38 (1H, dd, *J* 14.0, 2.0 Hz, C*H*HCHOH, *minor* diast.), 2.22 (1H, dd, *J* 14.0, 8.5 Hz, CH*H*CHOH, *minor* diast.); δ_C (125 MHz) 147.0, 141.4, 140.8, 139.6, 139.1, 137.6,

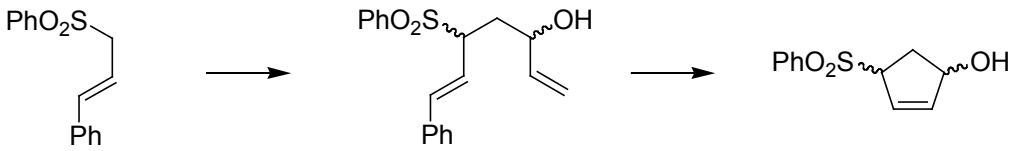
135.2, 134.9, 134.6, 133.8, 133.5, 132.4, 130.9, 129.2, 128.9, 128.8, 128.5, 128.1, 127.5, 127.4, 127.1, 126.7, 126.6, 119.7, 117.7, 115.4, 114.7, 71.5, 69.7, 69.2, 44.5, 44.4, 41.1, 40.9, 38.1, 35.9, 34.7, 17.5; *m/z* (CI) 386 $[M+NH_4]^+$, 368, 351, 330, 244, 227, 171, 160, 52 (Found: $[M+NH_4]^+$, 386.1788. $C_{22}H_{24}O_3S$ requires $[M+NH_4]^+$, 386.1782).

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



To a solution triene **241** (100 mg) in CH_2Cl_2 (12.6 mL) at rt was added a solution of catalyst **50** (6.90 mg) in CH_2Cl_2. 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; R_f 0.17 (30% EtOAc–petrol); δ_H (400 MHz) 7.87 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$, minor diast.), 7.81 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$, *major* diast.), 7.67-7.20 (2 × 8H, m, *para* & *meta* $PhSO_2$ and *Ph*CH, 2 × diast.), 6.31 (1H, d, *J* 16.5 Hz, PhC*H*=CH, *major* diast.), 6.05 (1H, d, *J* 16.5 Hz, PhCH=C*H*, *major* diast.), [5.81-5.65 (2 × 2H, m, C*H*=C*H*CHOH, 2 × diast.) & (2H, m, PhC*H*=C*H*, *minor* diast.)], 5.60-5.54 (1H, m, C*H*OH, *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, C*H*OH, *major* diast.), 2.99-2.61 (2 × 2H, m, CH_2CH=CH_2, 2 × diast.), 2.35-2.11 (2H, 2 × 2H, , CH_2CHOH, 2 × diast.).

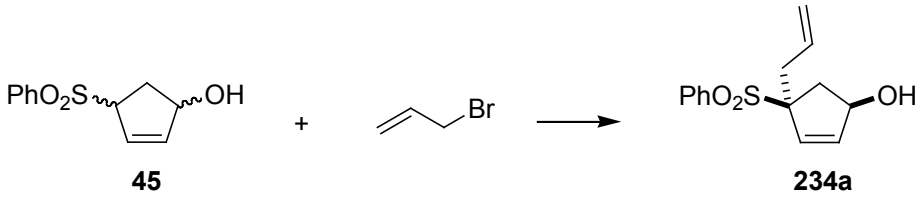
4-(Phenylsulfonyl)cyclopent-2-enol 45



227 **228** **45**

To a solution of cinnamylsulfone **227** (45.0 g, 174.2 mmol, 1.0 equiv) in THF (360 ml) at –78 °C was added *n*BuLi (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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (200 mL) then diluted with water (300 mL) and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (3 × 100 mL) and dried ($MgSO_4$). 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 CH_2Cl_2 (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** (21.0g, 93.6mmol, 54%); δ_H (400 MHz) 7.95-7.88 (2 × 2H, m, *ortho* $PhSO_2$, 2 × diast.), 7.67 (2 × 3H, m, *para* & *meta* $PhSO_2$, 2 × diast.), 6.36-6.35 (1H, m, C*H*=CHCHOH, *major* diast.), 6.20-6.18 (1H, app. dt, *J* 5.5, 2.0 Hz, C*H*=CHCHOH, *minor* diast.), 5.85-5.87 (1H, m, CH=C*H*CHOH, *minor* diast.), 5.74-5.73 (1H, m, CH=C*H*CHOH, *major* diast.), 4.83-4.87 (1H, m, C*H*SO_2Ph, *minor* diast.), 4.72-4.70 (1H, m, C*H*SO_2Ph, *major* diast.), 4.41-4.44 (1H, m, C*H*OH, *minor* diast.), 4.16-4.01 (1H, m, C*H*OH, *major* diast.), 2.79-2.72 (2H, m, CH_2, *minor* diast.), 2.26-2.21 (2H, m, CH_2, *major* diast.).

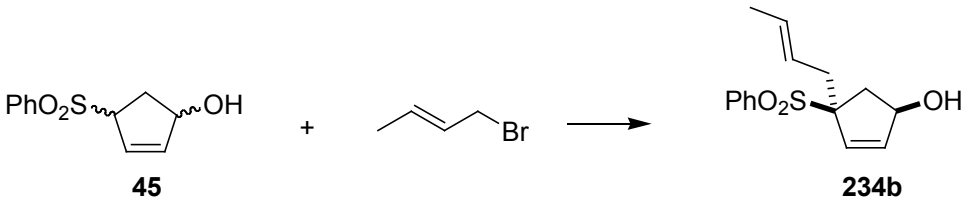
(1*R,4*S**)-4-Allyl-4-(phenylsulfonyl)cyclopent-2-enol 234a**



45 **234a**

To a solution of cyclopentenol **45** (837 mg, 3.74 mmol, 1.0 equiv) in THF (15 mL) at –78 °C was added *n*BuLi (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. $NH_4Cl_{(aq.)}$ (3.5 mL), diluted with H_2O (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave *(1*R**,4*S**)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enol* **234a** (603 mg, 61%) as a white crystalline solid; mp 56-58 ºC; R_f 0.19 (30% EtOAc–petrol); ν_{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* $PhSO_2$), 7.74 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.63 (2H, dd, *J* 8.0, 7.0 Hz, *meta* $PhSO_2$), 6.34 (1H, dd, *J* 5.5, 2.5 Hz, CH=C*H*CH), 5.58 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 5.49–5.39 (1H, m, C*H*=CH_2), 5.14–5.06 (2H, m, CH=CH_2), 4.75 (1H, ddd, *J* 12.0 , 7.0, 2.5 Hz, C*H*OH), 3.17 (1H, d, *J* 12.0 Hz, CHO*H*), [2.67–2.62, 2.52–2.47 (2H, m, CH_2CH=CH_2)], 2.42–2.26 (2H, m, CH_2CHOH); δ_C (125 MHz) 142.2 (*ipso* $PhSO_2$), 135.6 (*para* $PhSO_2$), [130.9, 130.7 (CH=CH)], [130.4, 129.2 (*ortho & meta* $PhSO_2$)], [128.0, 120.5 (CH=CH_2)], 79.0 (*C*SO_2Ph), 75.7 (CHOH), [37.3, 37.0 (2 × CH_2)]; *m*/*z* (CI) 282 $[M+NH_4]^+$, 265 $[M+H]^+$, 264, 247, 105 (Found: $[M+NH_4]^+$, 282.1154. $C_{14}H_{16}O_3S$ requires $[M+NH_4]^+$, 282.1164) (Found: C, 63.69; H, 6.10. $C_{14}H_{16}O_3S$ requires C, 63.61; H, 6.10%).

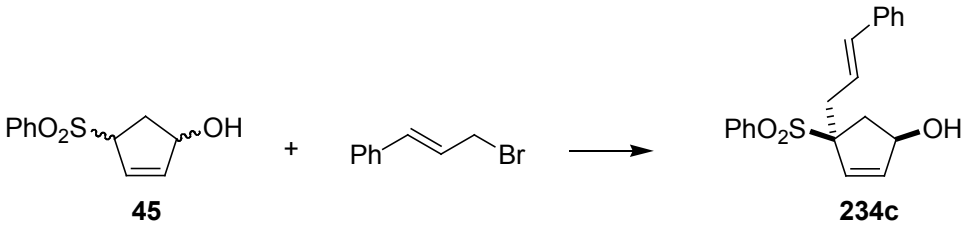
(1*R,4*S**)-4-[(*E*)-But-2-enyl]-4-(phenylsulfonyl)cyclopent-2-enol 234b**



45 **234b**

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. $NH_4Cl_{(aq.)}$ (1.2 mL), diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (30% EtOAc–petrol) gave *(1*R**,4*S**)-4-[(*E*)-but-2-enyl]-4-(phenylsulfonyl)cyclopent-2-enol* **234b** (250 mg, 67%) as a white solid; mp 64–66 ºC; R_f 0.22 (30% EtOAc–petrol); ν_{max} (film) 3493, 3063, 3026, 2942, 2922, 2884, 2855, 1445, 1299, 1287, 1140, 1083, 1071, 1050, 969, 793, 756, 691 cm^{-1}; δ_H (400 MHz) 7.90 (2H, d, *J* 8.0 Hz, *ortho* $PhSO_2$), 7.73 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.63 (2H, dd, *J* 8.0, 7.0 Hz, *meta* $PhSO_2$), 6.33 (1H, dd, *J* 5.5, 3.0 Hz, CH=C*H*CHOH), 5.57 (1H, d, *J* 5.5 Hz, C*H*=CHCHOH), 5.55-5.45 (1H, m, CH_2CH=CH), 5.08-5.00 (1H, m, CH_3CH=CH), 4.78-4.73 (1H, m, C*H*OH), 3.23 (1H, d, *J* 12.0 Hz, OH), 2.71–2.20 (4H, m, 2 × CH_2), 1.63 (3H, d, *J* 6.5 Hz, Me); δ_C (125 MHz) 142.0 (*ipso* $PhSO_2$), 135.8 (*para* $PhSO_2$), [134.1, 131.3, 130.9, 123.1 (2 × CH=CH)], [130.4, 129.1 (*ortho & meta* $PhSO_2$)], 79.0 (*C*SO_2Ph), 75.6 (*C*HOH), [37.3, 35.8 (*C*H_3CH=CH*C*H_2)], 18.0 (*C*H_2CHOH); *m*/*z* (CI) 296 $[M+NH_4]^+$, 278 M^+, 261, 119 (Found: $[M+NH_4]^+$, 296.1314. $C_{15}H_{18}O_3S$ requires $[M+NH_4]^+$, 296.1320) (Found: C, 64.79; H, 6.60. $C_{15}H_{18}O_3S$ requires C, 64.72; H, 6.52%).

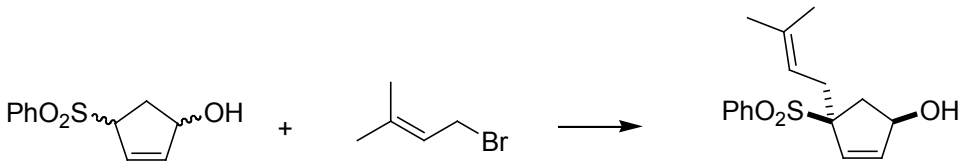
(1*R,4*S**)-4-Cinnamyl-4-(phenylsulfonyl)cyclopent-2-enol 234c**



45 **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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (1 mL), diluted with H_2O (5 mL) and 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 (20% Et_2O–petrol) gave *(1*R**,4*S**)-4-cinnamyl-4-(phenylsulfonyl)cyclopent-2-enol* **234c** (80 mg, 49%) as a colourless gum; R_f 0.57 (40% EtOAc–petrol); ν_{max} (film) 3488, 3428, 3060, 3027, 2924, 2852, 2359, 1737, 1498, 1445, 1299, 1288, 1192, 1135, 1082, 1052, 998, 969, 733, 679 cm^{-1}; δ_H (400 MHz) 7.92 (2H, d, *J* 7.0 Hz, *ortho* $PhSO_2$), 7.71 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.63 (2H, t, *J* 7.0 Hz, *meta* $PhSO_2$), 7.29-7.17 (5H, m, *Ph*CH=CH), 6.39 (1H, d, *J* 15.5 Hz, PhC*H*=CH), 6.34 (1H, dd, *J* 5.5, 2.5 Hz, CH=C*H*CH), 5.78 (1H, ddd, *J* 15.5, 9.0, 6.0 Hz, CH=C*H*CH_2), 5.64 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 4.75-4.70 (1H, m, C*H*OH), 3.19 (1H d, *J* 12.0 Hz, OH), 2.79 (1H, dd, *J* 14.0, 6.0 Hz, C*H*HCH=CH), 2.64 (1H, dd, *J* 14.0, 9.0 Hz, CH*H*CH=CH), 2.44-2.29 (2H, m, CH_2CHOH); δ_C (125 MHz) 142.4 (*ipso* $PhSO_2$), 136.4 (*para* $PhSO_2$), [135.3, 134.2, 130.6 (*ipso*, *para* PhCH & *C*H=*C*HCHOH)], [130.4, 129.2, 128.6 (*ortho*, *meta* $PhSO_2$ & *ortho* PhCH)], 127.8 (Ph*C*H=CH), 126.2 (*meta* PhCH), 122.1 (PhCH=*C*H), 78.9 (*C*SO_2Ph), 75.7 (CHOH), [37.5, 36.3 (2 × CH_2)]; *m*/*z* (CI) 358 $[M+NH_4]^+$, 340, 323, 198, 181, 160 (Found: $[M+NH_4]^+$, 358.1469. $C_{20}H_{20}O_3S$ requires $[M+NH_4]^+$, 358.1477) (Found: C, 70.47; H, 5.98. $C_{20}H_{20}O_3S$ requires C, 70.58; H, 5.92%).

(1*R,4*S**)-4-(3-Methylbut-2-enyl)-4-(phenylsulfonyl)cyclopent-2-enol 234d**



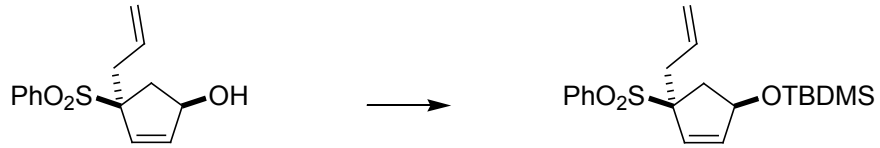
45 **234d**

To a solution of cyclopentenol **45** (837 mg, 3.74 mmol, 1.0 equiv) in THF (15 mL) at –78 °C was added *n*BuLi (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. $NH_4Cl_{(aq.)}$ (3.5 mL), diluted with H_2O (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (25% EtOAc-petrol) followed by recrystalisation (EtOAc-petrol) gave *(1*R**,4*S**)-4-(3-methylbut-2-enyl)-4-(phenylsulfonyl)cyclopent-2-enol* **234d** (440 mg, 40%) as a colourless crystalline solid; mp 70-72 ºC (EtOAc-petrol); R_f 0.16 (25% EtOAc–petrol); ν_{max} (film) 3507, 2966, 2934, 1445, 1405, 1298, 1285, 1267, 1138, 1054, 1025, 690 cm^{-1}; δ_H (400 MHz) 7.91 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$), 7.72 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.61 (2H, dd, *J* 7.5, 7.0 Hz, *meta* $PhSO_2$), 6.32 (1H, dd, *J* 5.5, 2.5 Hz, CH=C*H*CH), 5.54 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 4.77-4.72 (2H, m, C=C*H*CH_2 & C*H*OH), 3.22 (1H, d, *J* 12.0 Hz, OH), 2.58 (1H, dd, *J* 14.0, 8.5 Hz, C=CHC*H*H), 2.46 (1H, dd, *J* 14.0*,* 6.0 Hz, C=CHCH*H*), 2.41 (1H, dd, *J* 15.5, 6.0 Hz, C*H*HCHOH), 2.21 (1H, dd, *J* 15.5, 7.0 Hz, CH*H*CHOH), 1.66 (3H, s, Me), 1.54 (3H, s, Me); δ_C (125 MHz) 141.9 (*ipso* $PhSO_2$), 136.8 (*para* $PhSO_2$), [135.5, 134.1 (CH=CH)], 131.0 (C=*C*H), [130.4, 129.0 (*ortho & meta* $PhSO_2$)], 111.3 (*C*=CH), 79.4 (*C*SO_2Ph), 75.8 (*C*HOH), [37.4, 30.9 (*C*H_3C*C*H_3)], 25.9 (C=CH*C*H_2), 18.0 (*C*H_2CHOH); *m*/*z* (CI) 310 $[M+NH_4]^+$, 293 $[M+H]^+$, 292 M^+, 133, 52 (Found: $[M+NH_4]^+$, 310.1479. $C_{16}H_{20}O_3S$ requires $[M+NH_4]^+$, 310.1477) (Found: C, 65.71; H, 6.90. $C_{16}H_{20}O_3S$ requires C, 65.72; H, 6.89%).

(*E*)-(1-Phenylhepta-1,6-dien-3-ylsulfonyl)benzene 381

To a solution of cinnamylsulfone **227** (657 mg, 2.54 mmol, 1.0 equiv) in THF (12 mL) at –78 °C was added *n*BuLi (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 ºC 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. $NH_4Cl_{(aq.)}$ (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 ($MgSO_4$). 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; R_f 0.28 (15% EtOAc–petrol); ν_{max} (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* $PhSO_2$), 7.64 (1H, t, *J* 7.5 Hz, *para* $PhSO_2$), 7.53 (2H, t, *J* 7.5 Hz, *meta* $PhSO_2$), 7.34-7.27 (5H, m, *Ph*CH=CH), 6.27 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 5.92 (1H, dd, *J* 16.0, 9.0 Hz, PhCH=C*H*), 5.82-5.72 (1H, m, CH_2=C*H*), 5.06-5.02 (2H, m, CH_2=CH), 3.71 (1H, ddd, *J* 11.0, 9.0, 3.0 Hz, C*H*SO_2Ph), 2.39-2.37 (2H, m, CH_2CH=CH_2), 2.08 (1H, dt, *J* 15.0, 9.0 Hz, C*H*HCHSO_2Ph), 1.95-1.85 (1H, m, CH*H*CHSO_2Ph); δ_C (125 MHz) 138.2 (*ipso* $PhSO_2$), 137.3 (*ipso* PhCH=CH), 136.3 (*para* $PhSO_2$), 135.6 (*para* PhCH=CH), 133.5 (Ph*C*H=CH), [129.0, 128.7, 128.5, 128.3 (*ortho* & *meta* $PhSO_2$ & PhCH=CH)], 126.4 (PhCH=*C*H), [120.8, 116.1 (*C*H_2=*C*H)], 68.6 ($PhSO_2$*C*H), 30.2 (CH_2=CH*C*H_2), 26.1 (CH*C*H_2); *m*/*z* (CI) 330 $[M+NH_4]^+$, 188, 171, 160 (Found: $[M+NH_4]^+$, 330.1523. $C_{19}H_{20}O_2S$ requires $[M+NH_4]^+$, 330.1528) (Found: C, 73.11; H, 6.41. $C_{19}H_{20}O_2S$ requires C, 73.04; H, 6.45%).

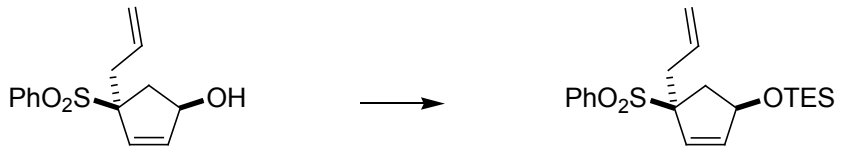
[(1*R,4*S**)-4-Allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy](*tert*-butyl) dimethylsilane 244**



234a **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 CH_2Cl_2 (1.0 mL) at rt was added Et_3N (181 µL, 1.3 mmol, 2.5 equiv) dropwise. The solution was heated under reflux for 24 h then quenched with sat. $NH_4Cl_{(aq.)}$ (0.8 mL), diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (10% EtOAc-petrol) gave *[(1*R**,4*S**)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy](*tert-*butyl)dimethylsilane* **244** (170 mg, 87%) as a colourless oil; R_f 0.57 (10% EtOAc–petrol); ν_{max} (film) 2953, 2929, 2855, 1446, 1303, 1146, 1088, 716 cm^{-1}; δ_H (400 MHz) 7.87 (2H, d, *J* 8.0 Hz, *ortho* $PhSO_2$), 7.63 (1H, t, *J* 7.5 Hz, *para* $PhSO_2$), 7.53 (2H, dd, *J* 8.0, 7.5 Hz, *meta* $PhSO_2$), 5.83 (1H, dd, *J* 5.5, 2.0 Hz, CH=C*H*CH), 5.78 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 5.61–5.51 (1H, m, CH_2CH=CH_2), 5.19-5.14 (2H, m, CH=CH_2), 4.68-4.65 (1H, m, C*H*OTBDMS), 2.81 (1H, dd, *J* 14.0, 5.5 Hz, C*H*HCH=CH_2), 2.70 (1H, dd, *J* 14.0, 7.0 Hz, CH*H*CH=CH_2), 2.33 (1H, dd, *J* 14.5, 7.5 Hz, CH*H*CHOTBDMS), 2.12 (1H, dd, *J* 14.5, 4.5 Hz, C*H*HCHOTBDMS), 0.77 (9H, s, ^{t}Bu of TBDMS), -0.04 (3H, s, CC$H_3$$CH_3$Si), -0.07 (3H, s, CCH_3CH_3Si); δ_C (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* (CI) 396 $[M+NH_4]^+$, 379 $[M+H]^+$, 264, 105 (Found: $[M+H]^+$, 379.1778. $C_{20}H_{30}O_3SSi$ requires $[M+NH_4]^+$, 379.1763).

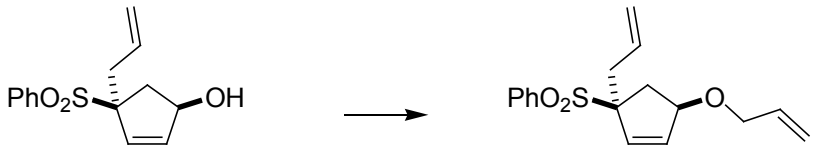
[(1*R,4*S**)-4-Allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy]triethylsilane 382**



234a **382**

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_2Cl_2 (1.0 mL) at rt was added Et_3N (181 μL, 1.3 mmol, 2.5 equiv) dropwise. After 16 h the reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (0.7 mL), then diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5% EtOAc-petrol) gave *[(1*R**,4*S**)-4-allyl-4-(phenylsulfonyl)cyclopent-2-enyloxy]triethylsilane* **382** (185 mg, 92%) as a colourless oil; R_f 0.17 (5% EtOAc–petrol); ν_{max} (film) 2954, 2911, 2866, 1367, 1303, 1147, 1090, 1033, 749, 714, 689 cm^{-1}; δ_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=C*H*), 5.78 (1H, d, *J* 5.5 Hz, C*H*=CH), 5.61-5.51 (1H, m, C*H*=CH_2), 5.20-5.15 (2H, m, CH=CH_2), 4.69-4.65 (1H, m, C*H*OTES), 2.81 (1H, dd, *J* 13.5, 6.0 Hz, C*H*HCH=CH_2), 2.70 (1H, dd, *J* 13.5, 9.0 Hz, CH*H*CH=CH_2), 2.32 (1H, dd, *J* 14.5, 7.5 Hz, CH*H*CHOTES), 2.15 (1H, dd, *J* 14.5, 4.5 Hz, C*H*HCHOTES), 0.86 [9H, t, *J* 8.0 Hz, (CH_3CH_2)$_3$Si], 0.48 [6H, q, *J* 8.0 Hz, (CH_3CH_2)$_3$Si]; δ_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 (*C*SO_2Ph), 76.0 (*C*HOH), 39.1 (*C*H_2CH=CH_2), 36.5 (*C*H_2CHOTES), {6.7, 4.6 [Si(CH_2CH_3)$_3$]}; *m/z* (CI) 396 $[M+NH_4]^+$, 379 $[M+H]^+$, 282, 264, 247 $[M\text{-OTES}]^+$, 105 (Found: $[M+H]^+$, 3791754. $C_{20}H_{30}O_3SSi$ requires $[M+H]^+$, 379.1763) (Found: C, 63.40; H, 7.92. $C_{20}H_{30}O_3SSi$ requires C, 63.45; H, 7.99%).

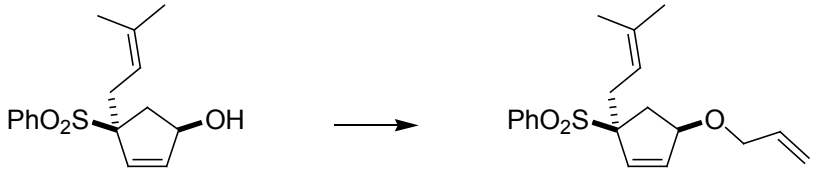
[(1*S,4*R**)-1-Allyl-4-(allyloxy)cyclopent-2-enylsulfonyl]benzene 383**



234a **383**

To a flask containing NaH (25.0 mg of a 60% in mineral oil, 0.64 mmol, 1.2 equiv) under N_2 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 N_2. 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. $NaHCO_{3(aq.)}$ (0.5 mL) then diluted with H_2O (10 mL) and extracted with EtOAc (3 × 8 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 *[(1*S**,4*R**)-1-allyl-4-(allyloxy)cyclopent-2-enylsulfonyl]benzene* **383** (110 mg, 70%) as a colourless oil; R_f 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* $PhSO_2$), 7.66 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.54 (2H, dd, *J* 7.0, 7.0 Hz, *meta* $PhSO_2$), 6.04 (1H, dd, *J* 5.5, 2.0 Hz, CH=C*H*CH), 5.87 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 5.75 (1H, ddt, *J* 22.5, 10.5, 5.5 Hz, CH_2=C*H*CH_2OCH), 5.59-5.49 (1H, m, CH_2=C*H*CH_2C), 5.19-5.11 (4H, m, 2 × C*H*$_2$=CHCH_2), 4.46-4.44 (1H, m, C*H*OCH_2), 3.79 (1H, dd, *J* 7.0, 5.5 Hz, OC*H*H), 3.75 (1H, dd, *J* 7.0, 6.0 Hz, OCH*H*), 2.81 (1H, dd, *J* 13.5, 6.0 Hz, C*H*HC), 2.70 (1H, dd, *J* 13.5, 9.0 Hz, CH*H*C), 2.28 (2H, d, *J* 5.5 Hz, C*H*$_2$CHO); δ_C (125 MHz) 138.2 (*ipso* $PhSO_2$), 135.4 (*para* $PhSO_2$), [134.7, 133.8 (CH=CH)], [131.9, 131.3 (*C*H_2=*C*HCH_2OCH)], [130.5, 128.7 (*ortho & meta* $PhSO_2$)], [120.3, 116.9 (CH_2=CH)], 82.6 (C$PhSO_2$), 77.9 (*C*HOCH_2), 69.6 (O*C*H_2CH=CH_2), 36.7 (*C*H_2CH=CH_2), 35.4 (*C*H_2CHOCH_2); *m*/*z* (CI) 322 $[M+NH_4]^+$, 305 $[M+H]^+$, 282, 264, 163, 105 (Found: $[M+H]^+$, 305.1219. $C_{17}H_{20}O_3S$ requires $[M+H]^+$, 305.1211) (Found: C, 67.14; H, 6.69. $C_{17}H_{20}O_3S$ requires C, 67.08; H, 6.62%).

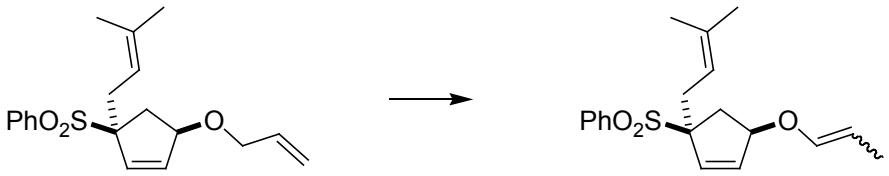
[(1*S,4*R**)-4-(Allyloxy)-1-(3-methylbut-2-enyl)cyclopent-2-enylsulfonyl]benzene 246**



234d **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_2O (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 *[(1*S**,4*R**)-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); ν_{max} (film) 3065, 2978, 2915, 2857, 1446, 1361, 1301, 1146,1086, 1046, 924, 756, 690, 606 cm^{-1}; δ_H (400 MHz) 7.89 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$), 7.65 (1H, t, *J* 7.5 Hz, *para* $PhSO_2$), 7.55 (2H, dd, *J* 7.5, 7.5 Hz, *meta* $PhSO_2$), 6.03 (1H, dd, *J* 5.5, 2.0 Hz, CH=C*H*CH), 5.84 (1H, d, *J* 5.5 Hz, C*H*=CHCH), 5.75 (1H, ddt, *J* 22.5, 10.5, 5.5 Hz, CH_2=C*H*CH_2OCH), 5.16-5.11 (1H, m, C*H*$_2$=CHCH$_2$OCH), 4.86 [1H, app t, *J* 7.5 Hz, C*H*=C(CH3)$_2$], 4.45-4.42 (1H, m, C*H*OCH_2), 3.80-3.71 (2H, m, OCH_2), 2.79 (1H, dd, *J* 14.0, 8.5 Hz, C*H*HC), 2.64 (1H, dd, *J* 14.0, 6.0 Hz, CH*H*C), 2.26-2.16 (2H, m, C*H*$_2$CHO), 1.70 (3H, s, CH_3), 1.63 (3H, s, CH_3); δ_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_2=*C*CH_2OCH)], [130.5, 128.6 (*ortho & meta* $PhSO_2$)], 116.8 [*C*H=C$(CH_3)_2$], 116.6 (*C*H_2=CH), 78.6 (*C*$HOCH_2$), 69.4 (O*C*H_2CH=CH_2), 35.4 [*C*H_2CH=C$(CH_3)_2$], 30.4 (*C*$H_2$$CHOCH_2$), [26.0, 18.1 (2 × CH_3)].

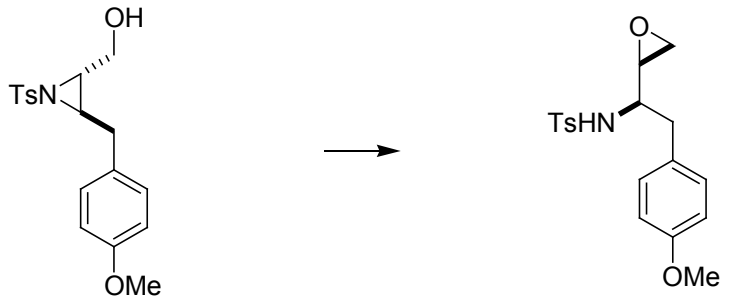
[(1*S,4*R**)-1-(3-Methylbut-2-enyl)-4-(prop-1-enyloxy)cyclopent-2-enylsulfonyl]benzene 258**



246 **258**

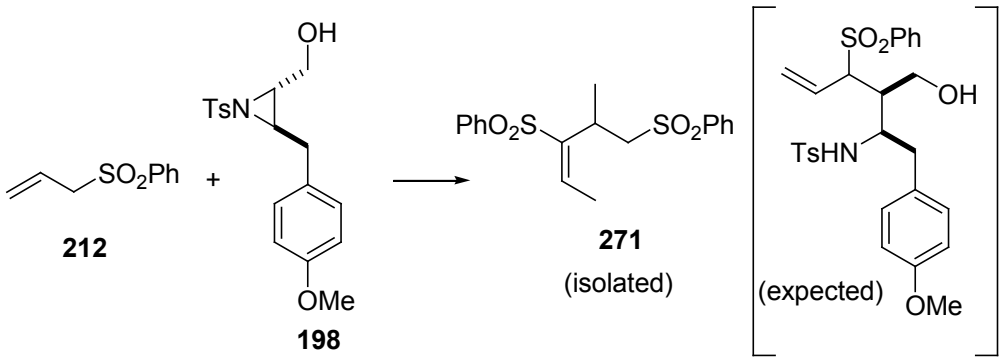
To a solution of allyl ether **246** (80.0 mg, 0.241 mmol, 1.0 equiv) in toluene (5 mL) at rt in a environment of ethylene was added a solution of catalyst 50 (14.3 mg, 0.0168 mmol, 0.07 equiv) in toluene (1 mL). After 16 h, concentration under reduced pressure and column chromatography (15% EtOAc–petrol) gave a 2:1 mixture of *E*/*Z* isomers of *[(1S*,4R*)-1-(3-mmethylbut-2-enyl)-4-(prop-1-enyloxy)cyclopent-2-enylsulfonyl]benzene* **258** (8 mg, 10%) as a gum; R_f 0.35 (20% EtOAc–petrol); ν_{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* $PhSO_2$), 7.67-7.64 (2 × 1H, m, *para* $PhSO_2$, 2 × isomers), 7.58-7.54 (2 × 2H, m, *meta* $PhSO_2$, 2 × isomers), 5.99-5.97 (2 × 1H, m, CH=C*H*CH, both isomers), 5.92-5.8 (2 × 1H, m, C*H*=CHCH, 2 × isomers), 5.83 (1H, dd, *J* 12.5, 1.5 Hz, CH=C*H*OCH, *E* isomer), 5.69 (1H, dd, *J* 6.5, 1.5 Hz, CH=C*H*OCH, *Z* isomer), 4.87-4.84 [2 × 1H, m, C*H*=CHOCH, 2 × isomers], 4.70-4.62 (2 × 1H, m, C*H*OCH_2, 2 × isomers), 4.61-4.57 (1H, m, CH=CHOC*H*, *E* isomer), 4.35-4.27 (1H, m, , CH=CHOC*H*, *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, C*H*HCH=C, 2 × isomers), 2.30-2.19 (2 × 2H, m, CH_2CHO, 2 × isomers), 1.70 (2 × 3H, s, CH_3, 2 × isomers), 1.64 (2 × 3H, s, CH_3, 2 × isomers), 1.49 (3H, dd, *J* 7.0, 1.5 Hz, CH_3CH=CH, *E* isomer), 1.37 (3H, dd, *J* 7.0, 1.5 Hz, CH_3CH=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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (0.6 mL) then diluted with H_2O (6 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried ($MgSO_4$). 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; R_f 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, $CHOCH_2$), 2.93-2.88 (2H, m, C*H*NHTs & C*H*HOCH), 2.78-2.67 (3H, m, CH*H*OCH & CH_2Ar), 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 ($CHCH_2O$)], 47.7 (CHNHTs), 37.3 (CH_2 of Ts), 21.5 (*C*H_2ArOMe); *m*/*z* (CI) 365 $[M+NH_4]^+$, 348 $[M+H]^+$, 246, 189 $[TsNH+H+NH_4]^+$ (Found: $[M+NH_4]^+$, 365.1539. $C_{18}H_{21}NO_4S$ requires $[M+NH_4]^+$, 365.1535) (Found: C, 62.38; H, 6.16; N, 4.06. $C_{18}H_{21}NO_4S$ requires C, 62.23; H, 6.09; N, 4.03%).

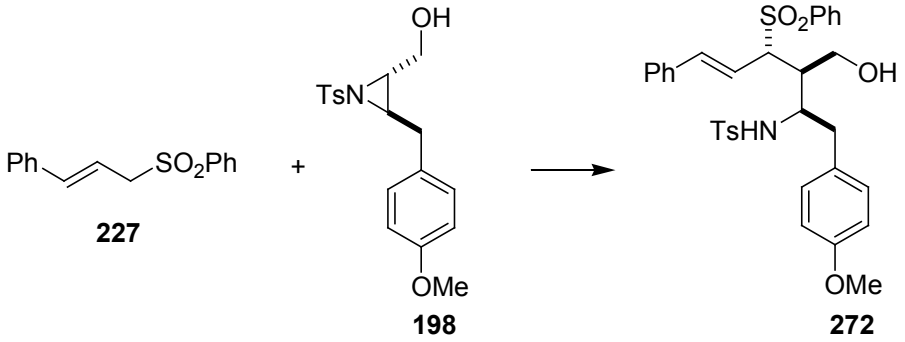
(*E*)-(2-Methylpent-3-ene-1,3-diyl)bis(phenylsulfone) 271



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 *n*BuLi (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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (3 mL), then diluted with H_2O (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 (Na_2SO_4). 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; R_f 0.31 (40% EtOAc–petrol); ν_{max} (film) 3062, 2981, 2923, 1612, 1512, 1446, 1301, 1149, 1086, 841, 707, 689 cm^{-1}; δ_H (400 MHz) [7.86 (2H, d, *J* 7.5 Hz), 7.76 (2H, d, *J* 7.5 Hz), 2 × *ortho* $PhSO_2$], 7.70 (1H, t, *J* 7.5 Hz, 1 × *para* $PhSO_2$), 7.63-7.49 (5H, m, 2 × *meta* $PhSO_2$ & 1 × *para* $PhSO_2$), 6.96 (1H, q, *J* 7.5 Hz, CH_3CH=C), 3.48-3.42 (1H, m, CH_2CHCH_3), 3.39-3.37 (2H, m, CH_2SO_2Ph), 1.94 (3H, d, *J* 7.5 Hz, CH_3CH=C), 1.24 (3H, d, *J* 7.0 Hz, CH_3CHCH_2); δ_C (100 MHz) [144.1, 140.3 (2 × *ipso* Ph)], 139.6 (*C*H=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 (CH_2SO_2Ph), 27.8 (CH), 18.7 (CH_3CH=C), 14.6 (CH_3CHCH_2); *m*/*z* (CI) 382 $[M+NH_4]^+$, 365 $[M+H]^+$, 348, 223 (Found (ESI): $[M+Na]^+$, 387.0710. $C_{18}H_{20}O_4S_2$ requires $[M+Na]^+$, 387.0701).

***N*-[(2*R**,3*R**,4*S**,*E*)-3-(Hydroxymethyl)-1-(4-methoxyphenyl)-6-phenyl-4-(phenylsulfonyl)hex-5-en-2-yl]-4-methylbenzenesulfonamide 272**

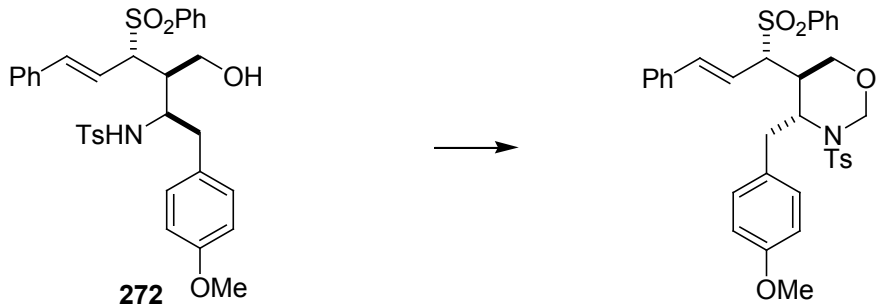


Preparation of solution 1: To a solution of cinnamyl sulfone **227** (484 mg, 1.87 mmol, 1.3 equiv) in THF (3.5 mL) at –20 °C was added *n*BuLi (821 μL of a 2.3 M solution in hexanes, 1.87 mmol, 1.3 equiv). After 5 min it was warmed to 0 °C for 30 min then re-cooled to –20 °C.

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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (4 mL), then diluted with H_2O (15 mL) and extraction with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (10% EtOAc–petrol) gave a 10:1 diastereomixture of *N-[(2*R**,3*R**,4*S**,*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; R_f 0.19 (43% EtOAc–petrol); ν_{max} (film) 3582, 3298, 2954, 2932, 1513, 1447, 1318, 1301, 1247, 1154, 1035, 735, 690 cm^{-1}; δ_H (400 MHz) 7.72 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.71 (2H, d, *J* 6.5 Hz, *ortho* $PhSO_2$), 7.58 (1H, t, *J* 7.0 Hz, *para* $PhSO_2$), 7.44 (2H, dd, *J* 7.0, 6.5 Hz, *meta* $PhSO_2$), 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* $PhSO_2$), 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, PhC*H*=CH, diagnostic signal of the minor diast.)5.71 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 5.18 (1H, dd, *J* 16.0, 9.5 Hz, PhCH=C*H*), 4.57-4.54 (1H, m, NH), 4.29-4.24 (1H, m, TsNHC*H*), 3.98

(1H, t, *J* 9.5 Hz, $PhSO_2CH$), 3.81 (3H, s, OMe), 3.72-3.59 (2H, m, CH_2OH), 2.87 (1H, dd, *J* 14.0, 4.5 Hz, MeOArC*H*H), 2.73 (1H, dd, *J* 14.0, 11.0 Hz, MeOArCH*H*), 2.45-2.40 (1H, m, $CHCH_2OH$)2.37 (3H, s, Me of Ts); δ_C (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. $C_{33}H_{35}NO_6S_2$ requires $[M+H]^+$, 606.1984) (Found: C, 65.48; H, 5.87; N, 2.39. $C_{33}H_{35}NO_6S_2$ requires C, 65.43; H, 5.82; N, 2.31%).

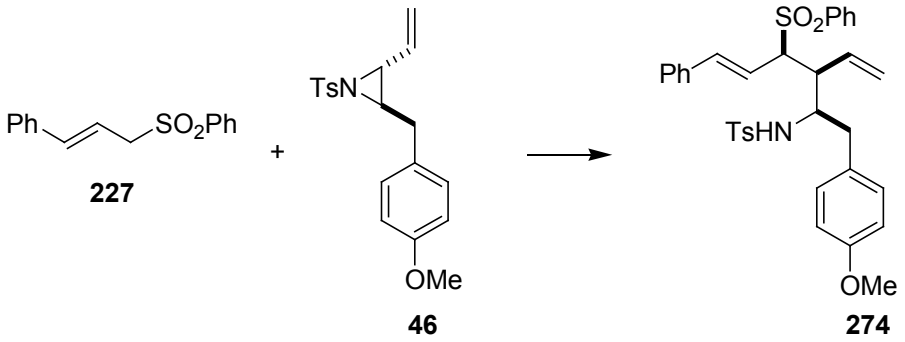
(4*R,5*R**)-4-(4-Methoxybenzyl)-5-[(*S**,E)-3-phenyl-1-(phenylsulfonyl)allyl]-3-tosyl-1,3-oxazinane 273**



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*-$TsOH{\cdot}H_2O$ (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (15→25% EtOAc-petrol) gave *(4*R**,5*R**)-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 (CH_2Cl_2-methanol); R_f 0.31 (40% EtOAc–petrol); ν_{max} (film) 2928, 1621, 1513, 1447, 1341, 1304, 1248, 1178, 1146, 1084, 1034, 970, 816, 734, 693 cm^{-1}; δ_H (400 MHz) 7.65 (2H, d, *J* 7.5 Hz, *ortho* $PhSO_2$), 7.59 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.53 (1H, dd, *J* 7.5, 7.5 Hz, *para* $PhSO_2$), 7.39 (2H, dd, *J* 7.5, 7.5 Hz, *meta* $PhSO_2$), 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, PhC*H*=CH), 5.49 (1H, d, *J* 10.5 Hz, NTsC*H*HO), 5.14-5.05 (2H, m, PhCH=C*H* & CHC*H*HOCH$_2$), 4.76 (1H, d, *J* 10.5 Hz, NTsCH*H*O), 4.13-4.05 (2H, m, CHCH*H*OCH$_2$ & C*H*NTs), 3.96 (1H, dd, *J* 10.5, 10.0 Hz, C*H*SO$_2$Ph), 3.82 (3H, s, OMe), 3.06 (1H, dd, *J* 13.5, 11.0 Hz, MeOArC*H*H), 2.82 (1H, dd, *J* 13.5, 4.5 Hz, MeOArCH*H*), 2.39 (3H, s, CH$_3$ of Ts), 2.20-2.18 (1H, m, C*H*CH$_2$O); δ_C (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, 120.68, 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. $C_{34}H_{35}NO_6S_2$ requires [M+Na]$^+$, 640.1804) (Found: C, 66.00; H, 5.68; N, 2.28. $C_{34}H_{35}NO_6S_2$ requires C, 66.10; H, 5.71; N, 2.27%).

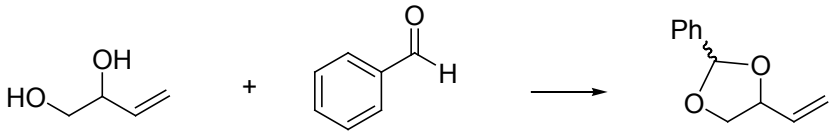
_N_-[(2_R_*,3_S_*,4_R_*,E)-1-(4-Methoxyphenyl)-6-phenyl-4-(phenylsulfonyl)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 274



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 *n*BuLi (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. $NH_4Cl_{(aq.)}$ (10 mL) then diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography gave N-*[(2*R**,3*S**,4*R**,*E*)-1-(4-Methoxyphenyl)-6-phenyl-4-*

(phenylsulfonyl)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide **274** (1.20 g, 45%) as a yellow solid; mp 120-122 °C (EtOAc–petrol); R_f 0.46 (30% EtOAc–petrol); ν_{max} (film) 3260, 2954, 2952, 1611, 1512, 1446, 1302, 1247, 1147, 1032, 926, 735 cm^{-1}; δ_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, *Ph*CH=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, PhC*H*=CH), 6.75 (1H, dd, *J* 16.0, 10.5 Hz, PhCH=C*H*), 5.51 (1H, ddd, *J* 17.0, 10.5, 7.0 Hz, C*H*=CH_2), 5.29 (1H, dd, *J* 10.5, 1.5 Hz, *trans* CH=C*H*H), 5.16 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*), 4.63-4.58 (2H, m, C*H*SO_2Ph & TsNHC*H*), 4.32 (1H, d, *J* 9.5 Hz, NH), 3.81 (3H, s, MeO), 3.11 (1H, ddd, 10.5, 10.0, 1.5 Hz, C*H*CH=CH_2), 2.79 (1H, dd, *J* 14.0, 4.5 Hz, MeOArC*H*H, diagnostic signal of the minor diast.)2.60 (1H, dd, *J* 14.0, 8.5 Hz, MeOArC*H*H), 2.45 (3H, s, Me of Ts), 2.33 (1H, dd, *J* 14.0, 6.5 Hz, MeOArCH*H*); δ_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 $[M+Na]^+$, 602.2050 $[M+H]^+$, 539.1342, 304.1051 (Found: $[M+H]^+$, 602.2050. $C_{34}H_{35}NO_5S_2$ requires $[M+H]^+$, 602.2035) (Found: C, 67.84; H, 6.00; N, 2.44. $C_{34}H_{35}NO_5S_2$ requires C, 67.86; H, 5.86; N, 2.33%).

2-Phenyl-4-vinyl-1,3-dioxolane[124] **277**

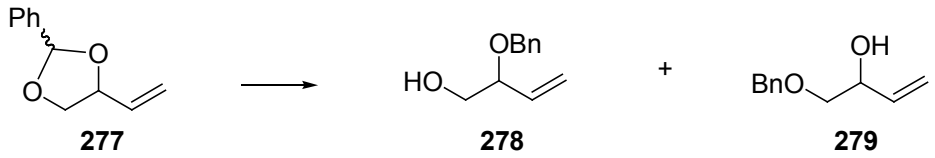


275 **276** **277**

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_2O (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; R_f 0.67 (10% EtOAc–petrol); ν_{max} (film) 3067, 2986, 2879,

1702, 1458, 1397, 1311, 1291, 1220, 1204, 1091, 1068, 1027, 988, 759, 698 cm^{-1}; δ_H (400 MHz) 7.55-7.41 (2 × 5H, m, Ph, 2 × diast.), 6.01 (1H, s, PhC*H*, 1 × dias.), 6.00-5.92 (2 × 1H, m, C*H*=CH_2, 2 × dias.), 5.91 (1H, s, PhC*H*, 1 × dias.), 5.44 (2H, dd, *J* 17.0, 1.0 Hz, CH=CH_2, 1 × dias.), 5.31 (2H, dd, *J* 10.5, 5.0 Hz, CH=CH_2, 1 × dias.), 4.72-4.66 (2 × 1H, m, C*H*CH=CH_2, 2 × dias.), 4.35 (1H, dd, *J* 8.5, 6.5 Hz, C*H*HCH, 1 × dias.), 4.20 (1H, dd, *J* 8.5, 7.5 Hz, CH*H*CH, 1 × dias.), 3.82 (1H, dd, *J* 7.5, 7.0 Hz, C*H*HCH, 1 × dias.), 3.75 (1H, dd, *J* 8.0, 7.5 Hz, CH*H*CH, 1 × dias.); δ_C (125 MHz) 138.0, 137.6, 135.5, 135.3, 129.4, 129.2, 128.4, 127.7, 126.9, 126.7, 126.4, 118.6, 118.2, 104.4, 103.8, 78.4, 70.5, 70.0; *m/z* (CI) 194 $[M+NH_4]^+$, 177 $[M+H]^+$, 170, 164, 106, 52; data in agreement with that previously reported.[124]

2-(Benzyloxy)but-3-en-1-ol 278 & 1-(benzyloxy)but-3-en-2-ol 279

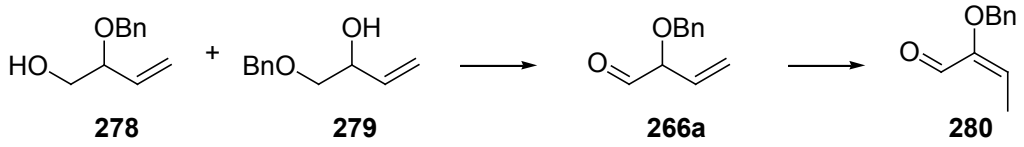


277 **278** **279**

To a solution of dioxolane **277** (2.40 g, 13.6 mmol, 1.0 equiv) in CH_2Cl_2 (68 mL) at –78 ºC 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 ºC and quenched with sat. Na/K tartrate$_{(aq.)}$ (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 ($MgSO_4$). 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; R_f 0.24 (15% EtOAc–petrol); ν_{max} (film) 3382, 2916, 2880, 2853, 1719, 1686, 1598, 1449, 1399, 1274, 1215, 1178, 1120, 1027, 816, 759, 714, 560 cm^{-1}; δ_H (400 MHz) 7.41-7.33 (m, 2 × Ph, 2 × regio.) 5.91-5.75 (m, 2 × C*H*=CH_2, 2 × regio.), 5.43-5.37 (m, CH=CH_2, major regio.), 5.24-5.22 (m, CH=CH_2, minor regio.), 4.71 (d, *J* 11.5 Hz, PhC*H*H, major regio.), 4.61 (s, PhC*HH*, minor regio.), 4.43 (d, *J* 11.5 Hz, PhCH*H*, major regio.), 3.98 (dd, *J* 12.5, 6.5 Hz, C*H*CH=CH_2, major regio.), 3.64-3.63 (m,

CH_2OH, major regio.), 3.57 (dd, *J* 9.5, 3.5 Hz, C*H*OH, minor regio.), 3.41 (dd, *J* 9.5, 8.0 Hz, CH_2OBn); δ_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



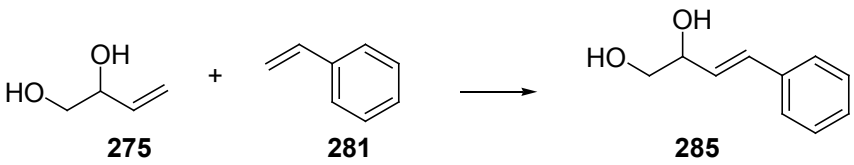
278 **279** **266a** **280**

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); δ_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, C*H*=CH_2), 5.55-5.48 (2H, m, CH=CH_2), 4.72 (1H, d, *J* 12.0 Hz, PhC*H*H), 4.61 (1H, d, *J* 12.0 Hz, PhCH*H*), 4.32 (1H, dd, *J* 6.5, 1.5 Hz, BnOC*H*); δ_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=*C*H_2), 84.7 (BnO*C*H), 71.4 (Ph*C*H_2).

Data for **280**: R_f 0.63 (20% EtOAc–petrol); δ_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); δ_C (100 MHz) 189.2 (CHO), 154.8 (BnO*C*), 137.2 (*ipso* Ph), 136.9 (3º), 128.4 (*meta* or *ortho* Ph), 128.2 (3º), 127.8 (3º), 72.9 (Ph*C*H_2), 12.0 (CH_3).

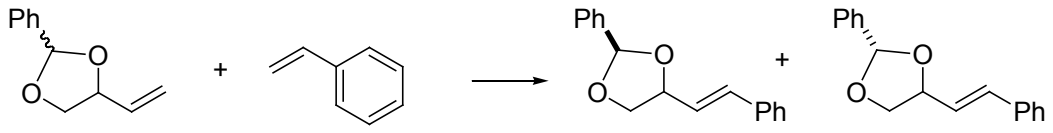
(*E*)-4-Phenylbut-3-ene-1,2-diol 285



275 **281** **285**

To a solution of catalyst **50** (210 mg, 0.247 mmol, 0.01 equiv) in CH_2Cl_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); ν_{max} (film) 3302, 2973, 1448, 1053, 1018, 987, 971, 745, 690 cm^{-1}; δ_H (400 MHz) 7.45-7.29 (5H, m, Ph), 6.73 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.24 (1H, dd, *J* 16.0, 6.5 Hz, PhCH=C*H*), 4.98-4.96 (1H, m, CH_2CH), 3.81-3.78 (1H, m, C*H*HCH), 3.67-3.62 (1H, m, CH*H*CH), 2.27 (1H, d, *J* 3.5 Hz, OH), 2.01 (1H, t, *J* 5.5 Hz, OH); δ_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_2OH); *m*/*z* (CI) 182 $[M+NH_4]^+$, 164, 147, 129, 52 (Found: $[M+NH_4]^+$, 182.1185. $C_{10}H_{12}O_2$ requires $[M+NH_4]^+$, 182.1181).

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



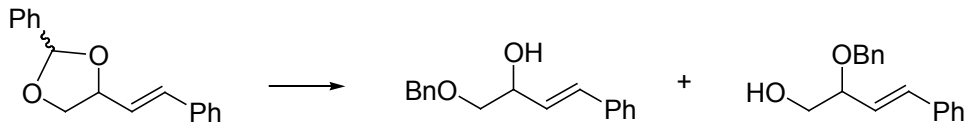
277 **281** **282**

To a solution of catalyst **50** (127 mg, 0.15 mmol, 0.03 equiv) in CH_2Cl_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 ºC. 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); ν_{max} (film) 3030, 2987, 2880, 1718, 1596, 1493, 1450, 1400, 1273, 1091, 1068, 967, 750, 698 cm^{-1}; δ_H (400 MHz) 7.56-7.27 (10H, m, 2 × Ph), 6.75 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.28 (1H, dd, *J* 16.0, 7.5 Hz, PhCH=C*H*), 6.08 (1H, s, PhC*H*), 4.85 (1H, ddd, *J* 7.5, 7.5, 7.5 Hz, C*H*CH=CH_2), 4.04 (1H, dd, *J* 8.5, 7.5 Hz, C*H*HCH), 3.83 (1H, dd, *J* 8.5, 7.5 Hz, C*H*HCH); δ_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); ν_{max} (film) 3030, 2879, 1720, 1599, 1494, 1450, 1400, 1272, 1219, 1092, 1068, 967, 750, 695 cm^{-1}; δ_H (400 MHz) 7.59-7.27 (10H, m, 2 × Ph), 6.73 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.28 (1H, dd, *J* 16.0, 7.5 Hz, PhCH=C*H*), 5.96 (1H, s, PhC*H*), 4.85 (1H, ddd, *J* 7.0, 7.0, 7.0 Hz, C*H*CH=CH_2), 4.26 (1H, dd, *J* 8.0, 7.0 Hz, CH*H*CH), 3.83 (1H, dd, *J* 8.0, 7.0 Hz, CH*H*CH); δ_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



282 **283** **284**

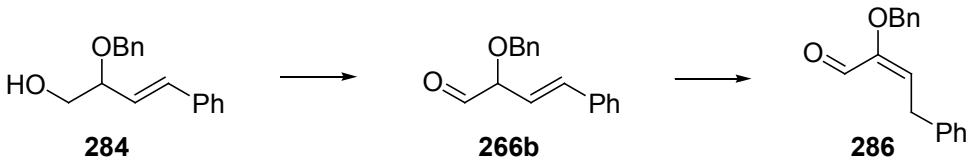
To a solution of a 1:1 diastereomixture of dioxolane **282** (260 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at –78 ºC was added DIBAL (3.1 mL of a 1 M solution in CH_2Cl_2, 3.1 mmol, 3.0 equiv). The solution was warmed to rt slowly then stirred at that temperature for 12 h. The resulting solution was re-cooled to –78 ºC, sat. Na/K $tartrate_{(aq.)}$ (3 mL) was added slowly. After 10 min it was warmed to rt. After 30 min H_2O (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**: R_f 0.42 (25% EtOAc–petrol); ν_{max} (film) 3424, 3062, 3029, 2864, 1495, 1435, 1392, 1206, 1071, 932, 747, 697 cm^{-1}; δ_H (400 MHz) 7.42-7.26 (10H, m, 2 × Ph), 6.73 (1H, d, *J* 15.5 Hz, PhC*H*=CH), 6.22 (1H, dd, *J* 16.0, 6.0 Hz, PhCH=C*H*), 4.69 (1H, d, *J* 11.5 Hz, BnOC*H*H), 4.44 (1H, d, *J* 11.5 Hz, BnOCH*H*), 3.99 (1H, app dd, *J* 12.5, 6.0 Hz, C*H*OH), 3.66-3.64 (2H, m, CH_2OBn); δ_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 (*C*H_2OBn), 65.6 (Ph*C*H_2); *m*/*z* (CI) 254 $[M+NH_4–H_2O]^+$, 236, 219 (Found: $[M+NH_4–H_2O]^+$, 254.1556. $C_{17}H_{18}O_2$ requires $[M+NH_4–H_2O]^+$, 254.1545).

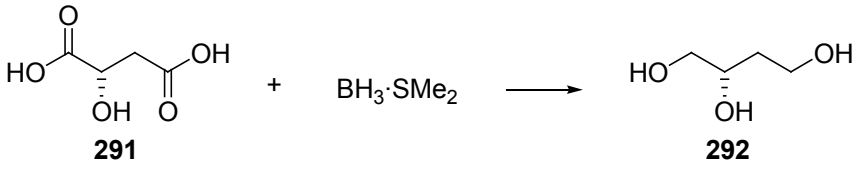
Data for **284**: R_f 0.36 (25% EtOAc–petrol); ν_{max} (film) 3331, 3029, 2872, 1495, 1435, 1208, 1019, 734, 696 cm^{-1}; δ_H (400 MHz) 7.45-7.29 (10H, m, *Ph* of Bn & *Ph*CH=CH), 6.70 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.16 (1H, dd, *J* 16.0, 8.0 Hz, PhCH=C*H*), 4.73 (1H, d, *J* 11.5 Hz, OC*H*HPh), 4.48 (1H, d, *J* 11.5 Hz, OCH*H*Ph), 4.18-4.13 (1H, m, C*H*OBn), 3.72-3.71 (2H, m, CH_2OH); δ_C (125 MHz) 138.1 (*ipso* Ph), 136.1 (*ipso* Ph), 134.5 (3º), [128.7, 128.5 (*meta* or *ortho* Ph)], 128.1 (3º), 127.9 (*meta* or *ortho* Ph), 127.8 (3º), 126.6 (*meta* or *ortho* Ph), 126.1 (3º), 80.8 (CHOH), 70.6 (*C*H_2OBn), 65.6 (Ph*C*H_2); *m*/*z* (CI) 254 $[M+NH_4–H_2O]^+$ (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 periodinate (495 mg, 1.17 mmol, 1.5 equiv) in CH_2Cl_2 (3.5 mL) at rt was added a solution of alcohol **284** (270 mg, 1.01 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL). After 2.5 h, Et_2O (6 mL) was added to the solution, followed by a solution of sat. $NaHCO_{3(aq.)}$ dissolving $Na_2S_2O_3$ (1.5 g). After 3 min, the mixture was further diluted with Et_2O (10 mL). The organic phase was separated, washed with sat. $NaHCO_{3(aq.)}$ (6 mL), H_2O (10 mL), brine (2 × 8 mL) and dried (Na_2SO_4). Concentration under reduced pressure and drying under high vacuum cleanly gave crude *(*E*)-2-(benzyloxy)-4-phenylbut-3-enal* **266b** (250 mg, 93%); R_f 0.42 (13% EtOAc–petrol); δ_H (400 MHz) 9.64 (1H, s, CHO), 7.44-7.31 (10H, m, 2 × Ph), 6.81 (1H, d, *J* 16.0 Hz, PhC*H*=CH), 6.12 (1H, dd, *J* 16.0, 7.0 Hz, PhCH=C*H*), 4.77 (1H, d, *J* 12.0 Hz, PhC*H*H), 4.67 (1H, d, *J* 12.0 Hz, PhCH*H*), 4.49 (1H, dt, *J* 7.0, 1.5 Hz, C*H*OBn). When enal **266b** was treated with anionic nucleophiles, it isomerised to *(*E*)-2-(benzyloxy)-4-phenylbut-2-enal* **286**; δ_H (400 MHz) 9.29 (1H, s, CHO), 7.44-7.07 (10H, m, 2 × Ph), 6.15 (1H, t, *J* 7.5 Hz, C*H*=COBn), 5.17 (2H, s, PhCH_2O), 3.60 (2H, d, *J* 7.5 Hz, PhCH_2CH).

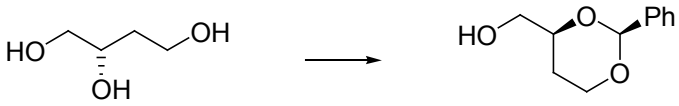
(*S*)-Butane-1,2,4-triol[130,132] **292**



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 $BH_3{\cdot}SMe_2$ (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–CH_2Cl_2) gave triol **292** as a colourless oil (1.42 g, 90%). R_f 0.22 (15% MeOH–CH_2Cl_2); ν_{max} (film) 3355, 2941, 1422, 1059, 987, 872 cm^{-1}; δ_H (400 MHz, [d_6]DMSO) 4.48 (1H, t, *J* 5.5 Hz, C*H*OH), 4.51-4.46 (2H, m, CH_2OHCHOH), 3.56-3.48 (3H, m, OH), 3.26 (2H, qt, *J* 11.0, 5.5 Hz, CH_2CH_2OH), 2.53-2.50 (2H, m, CH_2CH_2OH); δ_C (100 MHz) 69.2, 66.6, 58.5, 37.2; *m*/*z* (CI) 210, 124 $[M+NH_4]^+$, 107 $[M+H]^+$, data in agreement with that previously reported.[130,132]

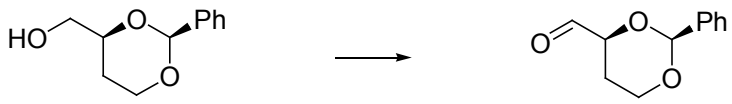
[(2*S*,4*S*)-2-Phenyl-1,3-dioxan-4-yl]methanol[130,132] **293**



292 **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 CH_2Cl_2 (13 mL) was stirred at rt. After 16 h, the solution was re-cooled to –5 °C and Et_3N (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; R_f 0.09 (20% EtOAc–petrol); ν_{max} (film) 3424, 2924, 2861, 1454, 1399, 1364, 1313, 1240, 1215, 1141, 1104, 1066, 1025, 758, 699 cm^{-1}; δ_H (400 MHz) 7.53-7.51 (2H, m, *ortho* PhS), 7.42-7.37 (3H, m, *meta* & *ortho* PhS), 5.58 (1H, s, C*H*Ph), 4.35-4.32 (1H, m, C*H*OCHPh), 4.08-3.98 (2H, m, CH_2OH), 2.02-1.91 (1H, m, CH_2CHC*H*H), 1.50-1.47 (1H, m, CH_2CHCH*H*); δ_C (101 MHz) 138.3 (*ipso* Ph), 129.0 (*para* Ph), [128.3, 126.1 (*meta* & *ortho* Ph)], 101.3 (*C*HPh), 77.4, 66.6, 65.8, 26.8; *m*/*z* (CI) 212 $[M+NH_4]^+$, 195 $[M+H]^+$, 163; data in agreement with that previously reported.[130,132]

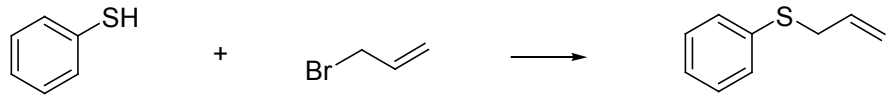
(2*S*,4*S*)-2-Phenyl-1,3-dioxane-4-carbaldehyde[130,132] **290**



293 **290**

To a solution of alcohol **293** (150 mg, 0.772 mmol, 1.0 equiv) in CH_2Cl_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_2Cl_2 (2.0 mL). The resulting suspension was warmed to rt. After 1 h, the mixture was diluted with Et_2O (3 mL) and washed with a solution of sat. $NaHCO_{3(aq.)}$ (5mL) dissolving $Na_2S_2O_3{\cdot}5H_2O$ (2.5 g). After 5 min, the organic phase was separated and the aqueous phase extracted with Et_2O (5 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq.)}$ (5mL), H_2O (8 mL), brine (8 mL) and dried ($MgSO_4$). Concentration under reduced pressure cleanly gave crude aldehyde **290** (120 mg, 84%) as a colourless oil; R_f 0.21 (20% EtOAc–petrol); δ_H (400 MHz) 9.78 (1H, s, CHO), 7.60-7.28 (5H, m, Ph), 5.61 (1H, s, C*H*Ph), 4.44-4.36 (1H, m, C*H*CH_2), 4.11-4.01 (2H, m, CH_2O), 2.07-1.80 (2H, m, CH_2CH_2O); δ_C (101 MHz) 200.1 (CHO), 137.5 (*ipso* Ph), 129.0 (*para* Ph), [128.1, 126.3 (*meta* & *ortho* Ph)], 101.0 (*C*HPh), 80.1, 66.0, 25.8; *m*/*z* (CI) 210 $[M+NH_4]^+$, 193 $[M+H]^+$; data in agreement with that previously reported.[130,132]

Allyl(phenyl)sulfane[135] **294**

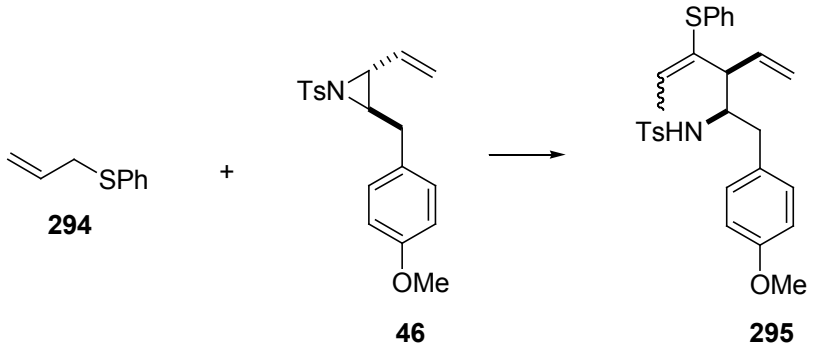


294

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_2O (100 mL) was added to the filtrate and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL) and dried ($MgSO_4$). Concentration under reduced pressure cleanly gave crude product **294** (3.50 g, 86%) as

a colourless oil; ν_{max} (film) 3070, 3059, 2007, 2919, 2916, 1948, 1852, 1636, 1583, 1480, 1438, 1228, 1089, 1025, 987, 919, 737, 690 cm^{-1}; δ_H (400 MHz) 7.38-7.36 (2H, m, *ortho* Ph), 7.32-7.28 (2H, m, *meta* Ph), 7.22-7.19 (1H, m, *para* Ph), 5.90 (1H, ddt, *J* 17.0, 7.0, 7.0 Hz, C*H*=CH_2), 5.18-5.14 (1H, m, *cis* C*H*H=CH), 5.11-5.08 (1H, m, *trans* CH*H*=CH), 5.57 (2H, d, *J* 7.0 Hz, CH_2); δ_C (125 MHz) 137.5 (*ipso* PhS), 133.6 (*para* PhS), [129.8, 128.8 (*ortho* & *meta* PhS)], 126.2 (*C*H=CH_2), 117.7 (CH=*C*H_2), 37.2 (CH_2); *m*/*z* (CI) 184, 166, 149, 52; data in agreement with that previously reported. [135]

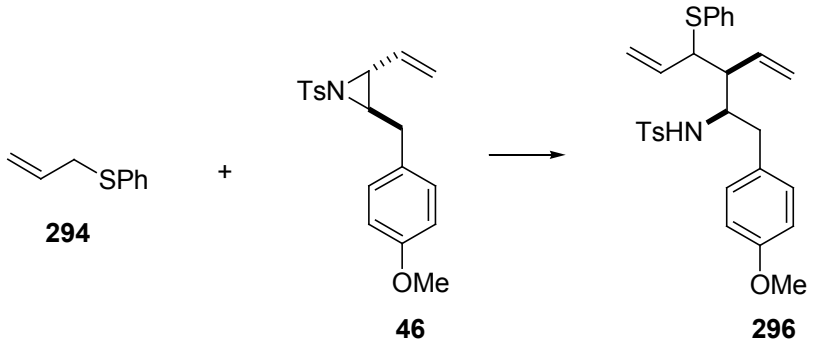
_N_-[(2_R_*,3_S_*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-4-en-2-yl]-4-methylbenzenesulfonamide 295



To a solution of allyl sulfide **294** (81.4 mg, 0.542 mmol, 1.4 equiv) in THF (0.3 ml) at –78 °C was added *n*BuLi (62 μL of a 9.4 M solution in hexanes, 0.581 mmol, 1.5 equiv). After 15 min, it was warmed to –30 °C then to 0 °C. After 15 min, it was re-cooled to –20 °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. $NH_4Cl_{(aq.)}$ (2 mL), diluted with H_2O (5 mL) and the aqueous phase extracted with EtOAc (2 × 5 ml). The combined organic layers were washed with brine (2 × 5 ml) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→15% EtOAc–petrol) gave a 5:1 olefin isomeric mixture of N-*[(2*R**,3*S**)-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); ν_{max} (film) 3287, 1612, 1513, 1439, 1326, 1247, 1158, 1093, 1036, 813, 741, 690, 663 cm^{-1}; δ_H (400 MHz) 7.66 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.30 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.25 (2H, d, *J* 8.0 Hz, *ortho* 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_3CH=C), 5.85 (1H, app. dt, *J* 16.0, 9.5 Hz, CH_2=C*H*, diagnostic signal of the minor isomer), 5.75 (1H, ddd, *J* 17.0, 10.0, 8.5 Hz, CH_2=C*H*), 5.16 (1H, dd, *J* 10.0, 1.5 Hz, *trans* C*H*H=CH), 4.91 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH*H*=CH), 4.44 (1H, d, *J* 8.0 Hz, NH), 3.80-3.78 (4H, m, OMe & NCH), 2.85-2.81 (1H, m, C*H*CH=CH_2), 2.74 (1H, dd, *J* 14.0, 5.0 Hz, CH*H*), 2.63-2.58 (1H, m, C*H*H), 2.43 (3H, s, Me of Ts), 1.79 (3H, d, *J* 6.5 Hz, CH_3CH=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 (*C*H=CH_2), 119.2 (CH=*C*H_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. $C_{28}H_{31}NO_3S_2$ requires $[M+Na]^+$, 516.1643).

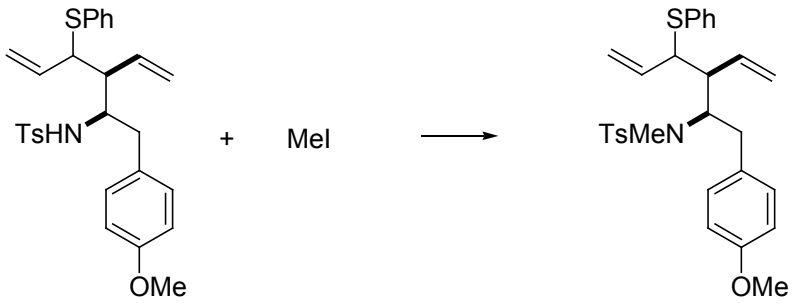
_N_-[(2_R_*,3_S_*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 296



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 re-cooled 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_2O (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_2SO_4). Concentration under reduced pressure and column chromatography

(15% EtOAc–petrol) gave a 5:1 diastereomixture of N-*[(2*R**,3*S**)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide* **296** (547 mg, 76%) as a gum; data for major diastereomer: R_f 0.33 (15% EtOAc–petrol); ν_{max} (film) 3280, 1612, 1513, 1440, 1325, 1247, 1158, 1093, 1035, 923 cm^{-1}; δ_H (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, CH_2=C*H*CHCHN), 5.40 (1H, dd, *J* 10.0, 1.5 Hz, *trans* C*H*H=CHCHCHN), 5.29-5.17 (2H, m, CH_2=C*H*CHS & *cis* CH*H*=CHCHCHN), 4.89 (1H, dd, *J* 10.0, 1.0 Hz, *trans* C*H*H=CHCHS), 4.65 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH*H*=CHCHS), 4.34 (1H, m, NH), 3.83-3.76 (4H, m, OMe & NCH), 2.62-2.49 (2H, m, CH_2CHN), 2.44 (3H, s, Me of Ts), 2.22-2.17 (1H, m, C*H*CHN); δ_C (125 MHz) [158.3, 143.5 137.7 (*q* Ar)], [136.7, 134.4, 134.2 (*para* PhS & *C*H=CH_2 & *C*H=CH_2)], [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=*C*H_2 & CH=*C*H_2)], 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. $C_{28}H_{31}NO_3S_2$ requires $[M+Na]^+$, 516.1643).

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

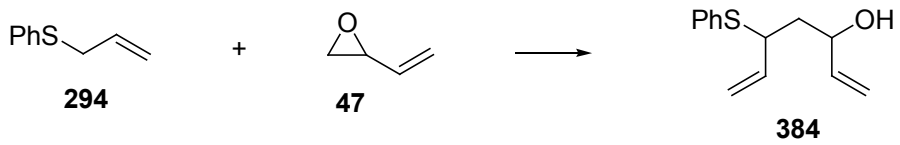


296 **297**

To a diastereomixture of sulfide **296** (207 mg, 0.42 mmol, 1.0 equiv), MeI (168 µL, 2.69 mmol, 6.4 equiv) and *t*BuOK (48.0 mg, 0.42 mmol, 1.0 equiv) at rt was added ^{t}BuOH (0.6 mL). The suspension was heated to 70 °C. After 4 h, it was concentrated under reduced pressure. Then, H_2O (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→20% EtOAc–petrol) gave N-*[(2*R**,3*S**)-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: R_f 0.62 (25% EtOAc–petrol); ν_{max} (film) 3072, 2933, 2835, 1720, 1612, 1513, 1439, 1333, 1303, 1247, 1157, 1088, 1035, 932, 815, 740, 655 cm^{-1} δ_H (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* ArOMe), 6.74 (2H, d, *J* 8.5 Hz, *ortho* ArOMe), 5.91-5.81 (1H, m, CH_2=C*H*CHCHN), 5.40 (1H, td, *J* 17.0, 9.5 Hz, CH_2=C*H*CHS), 5.32-4.82 (4H, m, CH_2=CHCHCHN & CH_2=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 & CH_2Ar), 2.43-2.37 (4H, m, Me of Ts & C*H*CHN); δ_C (125 MHz) [158.4, 142.7 (q Ar)], 137.6 (*C*H=CH_2), 136.7 (q Ar), 135.6 (*C*H=CH_2), 134.7 (q Ar), [132.8, 130.3 (3º Ar)], 130.1 (q Ar), [129.5, 128.6, 127.1 (3º Ar)], [118.9, 116.4 (2 × CH=*C*H_2)], 113.8 (3º Ar)], 59.8 (OMe), [55.2, 54.3 (MeNMe)], 51.9 (*C*HSPh), 35.9 (*C*H_2ArOMe), 30.2 (*C*HCHS), 21.5 (Me of Ts); *m*/*z* (ESI) 530 $[M+Na]^+$, 508 $[M+H]^+$, 465, 318 (Found: $[M+Na]^+$, 530.1816. $C_{29}H_{33}NO_3S_2$ requires $[M+Na]^+$, 530.1800) (Found: C, 68.65; H, 6.67; N, 2.71. $C_{29}H_{33}NO_3S_2$ requires C, 68.60; H, 6.55; N, 2.76%).

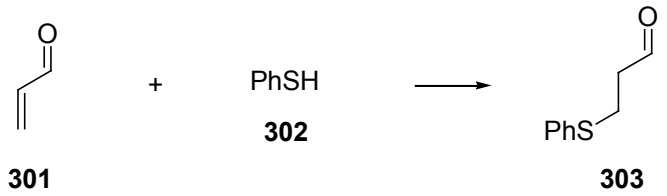
5-(Phenylthio)hepta-1,6-dien-3-ol 384



To a solution of allyl sulfide **294** (300 mg, 2.0 mmol, 1.0 equiv) in THF (1 mL) at –78 °C was added *n*BuLi (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; R_f 0.59 (20% EtOAc–petrol);

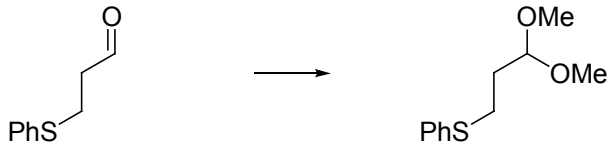
δ_H (400 MHz) 7.40-7.42 (2H, m, *ortho* Ph, 2 × dias.), 7.33-7.26 (3H, m, *para* & *meta* Ph), 5.95-5.68 (2H, m, CH_2=C*H* & CH_2=C*H*, 2 × dias.), [5.33-5.28, 5.19-5.15, 5.04-4.89 (4H, m, CH_2=CH & CH_2=CH, 2 × dias.)], 4.49-4.23 (1H, m, C*H*OH), 3.89-3.78 (1H, m, C*H*SPh), 1.99-1.76 (2H, m, CH_2, 2 × dias.); δ_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_2=CH, 2 × dias.)], [70.8 70.7 (CHOH, 2 × dias.), [48.9, 48.8 (*C*HSPh, 2 × dias.)], [41.0, 40.9 (CH_2, 2 × dias.)]; *m*/*z* (CI) 238 $[M+NH_4]^+$, 221 $[M+H]^+$, 203, 149 (Found: $[M+H]^+$, 221.1007. $C_{13}H_{16}OS$ requires $[M+H]^+$, 221.1007).

3-(Phenylthio)propanal[138] **303**



To a solution of thiolphenol **302** (2.20 g, 20.0 mmol, 1.0 equiv) and Et_3N (0.28 mL, 2.0 mmol, 0.1 equiv) and CH_2Cl_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_f 0.59 (50% EtOAc–petrol); δ_H (400 MHz) 9.79 (1H, s, CHO), 7.39-7.25 (5H, m, Ph), 3.21 (2H, t, *J* 7.0 Hz, CH_2CHO), 2.80 (2H, t, *J* 7.0 Hz, PhSCH_2); δ_C (125 MHz) 200.3 (CHO), 135.1 (*ipso* PhS), 130.0 (*ortho* PhS), 129.1 (*meta* PhS), 126.7 (*para* PhS), 43.3 (*C*H_2CHO), 26.4 (*C*H_2PhS); *m*/*z* (CI) 184 $[M+NH_4]^+$, 166, 52; data in agreement with that previously reported.[138]

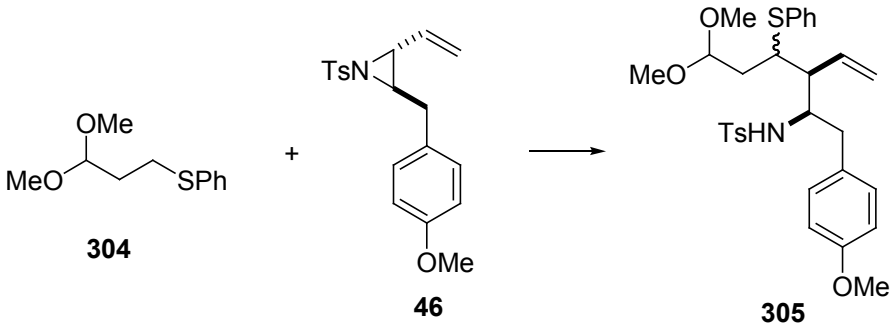
(3,3)-Dimethoxypropyl)(phenyl)sulfane[139] 304



303 **304**

The solution of aldehyde **303** (2.90 g, 17.5 mmol, 1.0 equiv), $CH(MeO)_3$ (3.71 g, 34.9 mmol, 2.0 equiv), *p*-TsOH·H_2O (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. $NaHCO_{3(aq.)}$ (3 × 30 mL), H_2O (3 × 10 mL), brine (2 × 15 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5% EtOAc–petrol with 1% Et_3N) gave acetal **304** (3.90 g, 96%) as a colourless oil; R_f 0.51 (23% Et_2O–petrol); ν_{max} (film) 3057, 2933, 2830, 1944, 1870, 1724, 1686, 1583, 1400, 1438, 1382, 1366, 1281, 1192, 1160, 1123, 1073 cm^{-1}; δ_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, CH_2SPh), 1.96 (2H, dt, *J* 7.0, 5.0 Hz, CH_2CH); δ_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 (*C*H_2PhS), 28.8 (*C*H_2CH); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.[139]

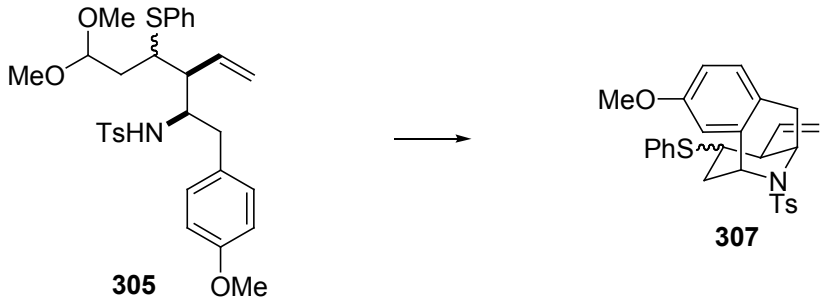
***N*-[(2*R**,3*S**)-6,6-Dimethoxy-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhexan-2-yl]-4-methylbenzenesulfonamide 305**



To a solution of acetal **304** (403 mg, 1.90 mmol, 1.3 equiv) in THF (0.7 mL) at –78 °C was added *n*BuLi (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 warmed to rt slowly. After 16 h, the reaction was quenched with sat. $NaHCO_{3(aq.)}$ (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (10%→25% EtOAc–petrol) gave a 5:1 diastereomixture of N-*[(2*R**,3*S**)-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: R_f 0.21 (25% EtOAc–petrol); ν_{max} (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, C*H*=CH_2, diagnostic signal of the minor diast.), 5.47 (1H, app. dt, *J* 17.0, 10.0 Hz, C*H*=CH_2), 5.18 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 5.01 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*), 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, ArO*Me*), 3.54 (1H, dt, *J* 7.0, 4.0 Hz, CHS), 3.25 (3H, s, *Me*OCHOMe), 3.23 (3H, s, MeOCHO*Me*), 2.76 (1H, dd, *J* 14.0, 6.0 Hz, C*H*HArOMe), 2.55 (1H, dd, *J* 14.0, 4.5 Hz, CH*H*ArOMe), 2.44 (3H, s, Me of Ts), 2.30-2.25 (1H, m, C*H*CH=CH_2), 1.85 (2H, dd, *J* 7.0, 5.5 Hz, CH_2CHS); 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

(*C*H=CH_2), 120.8 (CH=*C*H_2), 113.8 (3º Ar), 102.5 [*C*H$(OMe)_2$], 55.3 [CH$(O$*Me*$)_2$], 53.1 (ArO*Me*), 50.7 (CHN), 47.1 (*C*HSPh), [37.6, 37.4 (CH_2)], 23.9 (Me of Ts), 21.6 (*C*HCH=CH_2); *m*/*z* (ESI) 578 $[M+Na]^+$, 556 $[M+H]^+$, 554, 492 (Found: $[M+NH_4]^+$, 578.1995. $C_{30}H_{37}NO_5S_2$ requires $[M+NH_4]^+$. 578.2011) (Found: C, 65.00; H, 6.71; N, 2.58. $C_{30}H_{37}NO_5S_2$ requires C, 64.84; H, 6.71; N, 2.52%).

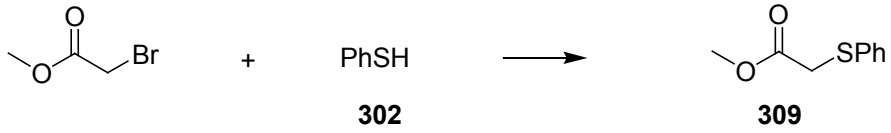
(2*S)-6,7-(3-Methoxyphenyl)-3-(phenylthio)-9-tosyl-2-vinyl-9-azabicyclo[3.3.1]non-6-ene 307**



To a solution of tosamide **305** (16.0 mg, 0.029 mmol, 1.0 equiv) in CH_2Cl_2 (0.6 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (0.06 mL, 0.44 mmol, 15.0 equiv). The solution was warmed to rt slowly. After 16 h, sat. $NaHCO_{3\,(aq.)}$ (1.0 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure and purified by prep–TLC to obtain the major diastereomer of pyridine **307** (10.0 mg, 73%) as a gum; R_f 0.74 (30% EtOAc–petrol); δ_H (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, C*H*=CH_2), 5.34-5.27 (2H, m, CH=CH_2), 5.07 (1H, m, ArC*H*N), 4.29-4.27 (1H, m, CHC*H*N), 3.79 (3H, s, OMe), 2.91-2.84 (1H, m, C*H*SPh), 2.69-2.56 (3H, m, CH_2ArOMe & C*H*CH=CH), 2.33 (3H, s, Me of Ts), 2.07-2.00 (2H, m, CH_2CHS); δ_C (100.7 MHz) [157.9, 143.0 (q Ar)], 137.7 (3º), [137.2, 135.9 (q Ar)], 133.6 (3º), 131.8 (q Ar), [129.1, 129.0 (3º)], 128.8 (3º), 127.7 (3º), 126.9 (3º), 125.5 (q Ar), 119.2 (CH=*C*H_2), 113.5, 110.5, 55.4 (OMe), [53.8, 53.6 (CHNCH)], 50.1 (PhS*C*H), 41.1 (*C*HCH=CH_2), 40.4 (*C*H_2ArOMe), 25.4 (*C*H_2CHS), 21.4 (Me of Ts);

m/z (EI) 491 $[M]^+$, 382, 314, 227, 160, 91 (Found: $[M]^+$, 491.1583. $C_{28}H_{29}NO_3S_2$ requires $[M]^+$, 491.1589).

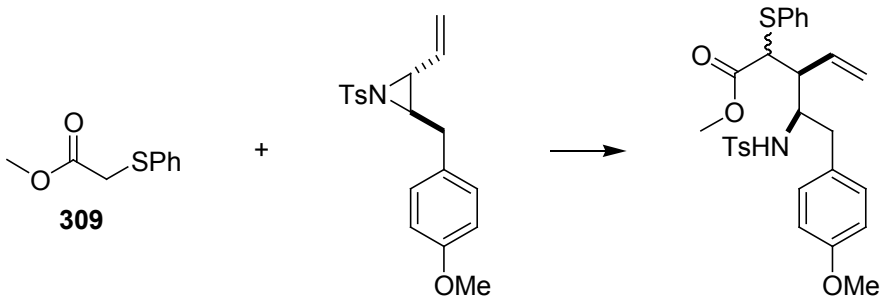
Methyl 2-(phenylthio)acetate[140] **309**



302 **309**

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); ν_{max} (film) 3058, 3002, 2952, 2842, 1743, 1583, 1482, 1437, 1407, 1279, 1194, 1153, 1009, 894, 741, 690 cm^{-1}; δ_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); δ_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**



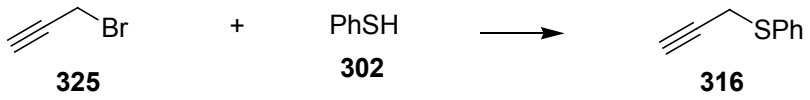
A solution of sulfide ester **309** (64.0 mg, 0.35 mmol, 1.3 equiv) in DMF (0.2 mL) was added dropwise to KH (27 mg, from a 35% mixture in oil washed with petrol three times, 0.673 mmol, 2.6 equiv) at 0°C. After 30 min, a solution of aziridine **46** in DMF (0.8 mL) was added. After 2 h at that temperature, 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 ($MgSO_4$). 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%; R_f 0.73 (40% EtOAc–petrol); ν_{max} (film) 3522, 3275, 3061, 2988, 2958, 2836, 1728, 1612, 1584, 1513, 1438, 1326, 1248, 1159, 1091, 1036, 998, 928, 814, 738, 665 cm^{-1}; δ_H (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, C*H*=CH_2), 5.40 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 5.14 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*), 4.57 (1H, d, *J* 8.5 Hz, NH), 3.96 (1H, d, *J* 11.0 Hz, C*H*SPh), 3.77 (3H, s, CH_3OOC), 3.70 (1H, m, NCH), 3.64 (3H, s, CH_3OAr), 2.66 (1H, ddd, *J* 11.5, 11.5, 2.0 Hz, C*H*CH=CH_2), 2.55 (1H, dd, *J* 14.0, 8.5 Hz, C*H*HArOMe), 2.42-2.37 (4H, m, Me of Ts & CH*H*ArOMe); δ_C (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=*C*H_2), 113.8 (3°), 55.3, 55.1, 52.1, 51.2, 47.0, 39.2 (CH_2), 21.5; *m*/*z* (ESI) 548.1555 $[M+Na]^+$, 526.1734 $[M+H]^+$, 469.3163, 208.0410 (Found: $[M+Na]^+$, 526.1734. $C_{28}H_{31}O_5S_2$ requires $[M+Na]^+$, 526.1722).

Data for **major diastereomer**: 71 mg, 52%; R_f 0.65 (40% EtOAc–petrol); ν_{max} (film) 3510, 3273, 3060, 2951, 2837,1732, 1612, 1513, 1439, 1326, 1248, 1159, 1048, 1035, 931, 815, 737, 664 cm^{-1}; δ_H (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, C*H*=CH_2), 5.29 (1H, dd, *J* 10.5, 1.0 Hz, *trans* CH=C*H*H), 5.14 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*), 4.81 (1H, d, *J* 9.0 Hz, NH), 4.27-4.21 (1H, m, NCH), 3.99 (1H, d, *J* 11.0 Hz, C*H*SPh), 3.80 (3H, s, CH_3OOC), 3.48 (3H, s, CH_3OAr), 2.51-2.39 (6H, m, C*H*CH=CH_2 & CH_2ArOMe & Me of Ts); δ_C (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=*C*H_2), 114.1 (3°), 55.2, 54.6, 52.0, 51.7, 45.6, 39.2 (CH_2), 21.5; *m*/*z* (ESI) 548.1540 $[M+Na]^+$, 526.1730 $[M+H]^+$, 494.1479, 344.1046 (Found: $[M+Na]^+$, 526.1730. $C_{28}H_{31}O_5S_2$ requires $[M+Na]^+$, 526.1722).

Phenyl(prop-2-ynyl)sulfane[148] **316**

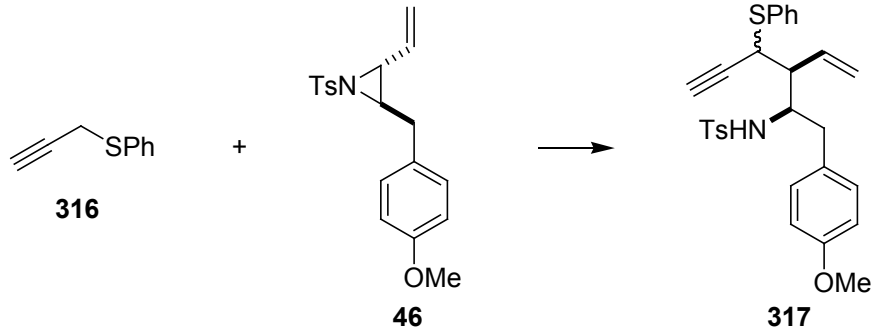


325 **302** **316**

To a solution of sodium hydroxide (5.72 g, 143 mmol, 1.7 equiv) in H_2O (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-n*butylammonia bromide (4.19 g, 13.0 mmol, 0.15 equiv). After 2.5 h vigorously stirring, the reaction was diluted with H_2O (50 mL). The organic phase was separated, washed with H_2O (2 × 20 mL), brine (2 × 30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and distillation (105 °C at 7 mmHg) gave propargylic sulfide **316** (10.7 g, 85%) as a colourless oil; R_f

0.42 (100% petrol); ν_{max} (film) 3292, 3058, 3019, 2947, 2914, 2118, 1949, 1878, 1670, 1585, 1480, 1438, 1407, 1299, 1233, 1086, 1025, 740, 689, 643 cm^{-1}; δ_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); δ_C (125 MHz) 135.0 (q Ph), 130.0 (*ortho* Ph), 129.0 (*meta* Ph), 127.0 (*para* Ph), 79.9 (CH*C*), 71 (*C*HC), 22.6 (CH_2); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.[148]

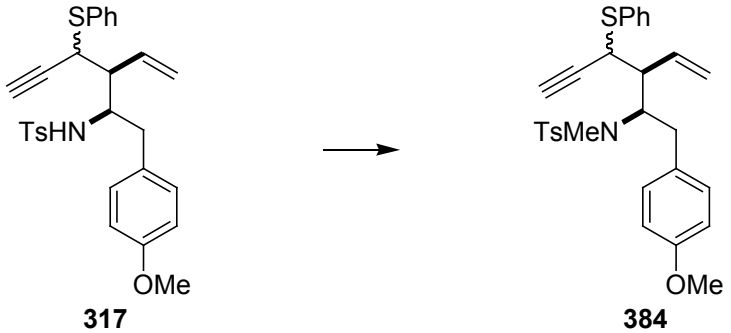
_N_-[(2_R_*,3_S_*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 317



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. $NH_4Cl_{(aq.)}$ (19 mL) then diluted with H_2O (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave a 3:1 diastereomeric mixture of *N-[(2*R**,3*S**)-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); ν_{max} (film) 3285, 2925, 1731, 1612, 1512, 1439, 1326, 1303, 1248, 1158, 1081, 1034, 927, 815, 742, 691, 663 cm^{-1}; δ_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, C*H*=CH_2, 2 × diast.), 5.44-5.38 (2 × 1H, m, *trans* CH=C*H*H, 2 × diast.), 5.15 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*, major diast.), 5.13 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*, 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, C*H*CH=CH_2 & CH_2ArOMe, 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, C*H*CCHSPh, major diast.), 2.32 (1H, d, *J* 2.5 Hz, C*H*CCHSPh, minor diast.); δ_C (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=*C*H_2, 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. $C_{28}H_{29}NO_3S_2$ requires $[M+H]^+$, 492.1667).

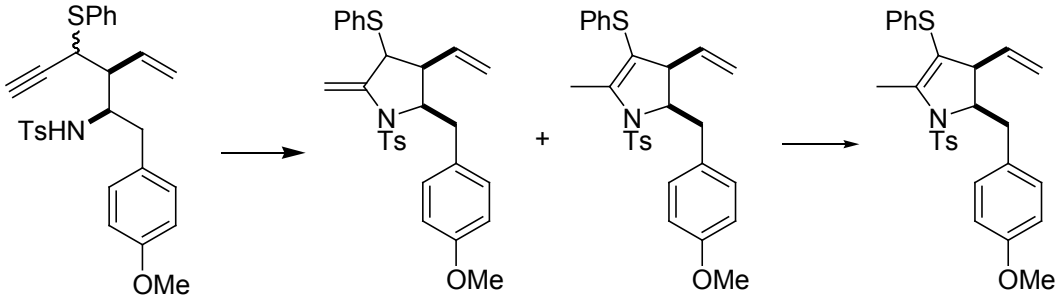
_N_-[(2_R_*,3_S_*)-1-(4-Methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-_N_,4-dimethylbenzenesulfonamide 384



To a mixture of tosamides **317** (100 mg, 0.204 mmol, 1.0 equiv), *t*BuOK (23.0 mg, 0.204 mmol, 1.0 equiv) and MeI (17 µL, 1.23 mmol, 6.0 equiv) at rt was added *t*BuOH (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 H_2O (5 mL), extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine

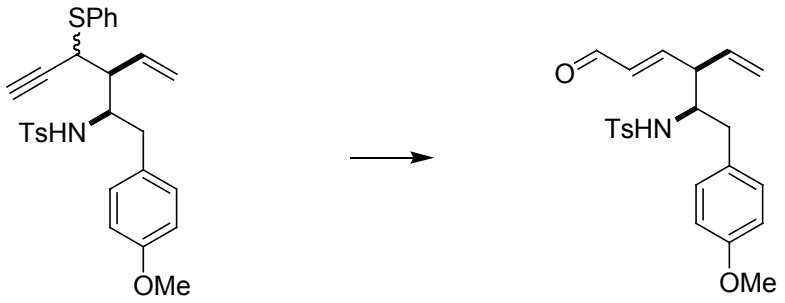
(2 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→20% EtOAc–petrol) gave a 2:1 diastereomeric mixture of *N-[(2*R**,3*S**)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-N,4-dimethylbenzenesulfonamide* **384** (70 mg, 68%) as a solid; R_f 0.43 (25% EtOAc–petrol); ν_{max} (film) 3286, 2924, 1611, 1513, 1439, 1334, 1304, 1247, 1157, 1088, 1034, 931, 815 cm^{-1}; δ_H (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, C*H*=CH_2, 2 × diast.), 5.28 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H, major diast.), 5.25 (1H, dd, *J* 11.0, 1.5 Hz, *trans* CH=C*H*H, minor diast.), 5.19 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*, major diast.), 5.18 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*, 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 & C*H*CH=CH_2, 2 × diast.), 2.58-2.37 (2 × 6H, m, Me of Ts & CH_2ArOMe & C*H*CCHSPh, 2 × diast.); δ_C (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=*C*H_2, 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 $[M+NH_4]^+$, 506.1837 $[M+H]^+$, 318.1166, 224.0127, 196.0175 (Found: $[M+H]^+$, 506.1824. $C_{29}H_{31}NO_3S_2$ requires $[M+H]^+$, 506.1824).

(2*R,3*S**)-2-(4-Methoxybenzyl)-5-methyl-4-(phenylthio)-1-tosyl-3-vinyl-2,3-dihydro-1H-pyrrole 336**



To a solution of diastereomers (68.0 mg, 0.138 mmol, 1.0 equiv) in MeOH (6 mL) at rt was added K_2CO_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_2SO_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); ν_{max} (film) 2925, 1612, 1582, 1512, 1439, 1354, 1247, 1167, 1089, 1035, 815 cm^{-1}; δ_H (400 MHz) 7.67 (2H, d, *J* 8.5 Hz *ortho* Ts), 7.34 (2H, d, *J* 8.5 Hz *meta* 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, C*H*=CH_2), 5.00 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 4.74 (1H, ddd, *J* 17.0, 1.5, 1.0 Hz, *cis* CH=CH*H*), 4.51 (1H, dd, *J* 6.0, 1.5 Hz, C*H*NTs), 3.80 (3H, s, OMe), 3.30 (1H, dt, *J* 10.0, 1.5 Hz, C*H*CH=CH_2), 2.91 (2H, d, *J* 6.0 Hz, CH_2ArOMe), 2.49 (3H s, Me of Ts), 2.25 (3H, d, *J* 2.5 Hz, CH_3CNTs); δ_C (100 MHz) [158.1, 145.4, 143.9, 136.2, 135.0 (4°)], 133.7 (*C*H=CH_2), 130.9, 129.9, 128.6, 127.5, 127.3 (3° Ar), 125.6 (3°), 120.0 (CH=*C*H_2), 118.6 (4°), 113.8, 113.4, 67.1 (*C*HNTs), 55.2 (OMe), 51.8 (*C*HCH=CH_2), 36.4 (*C*H_2ArOMe), 21.7 (Me of Ts), 15.2 (*C*H_3CNTs); *m*/*z* (ESI) 514.1487 $[M+Na]^+$, 492.1678 $[M+H]^+$, 337.1508 (Found: $[M+Na]^+$, 514.1495; $[M+H]^+$, 492.1678. $C_{28}H_{29}NO_3S_2$ requires $[M+Na]^+$, 514.1487; $[M+H]^+$, 492.1667).

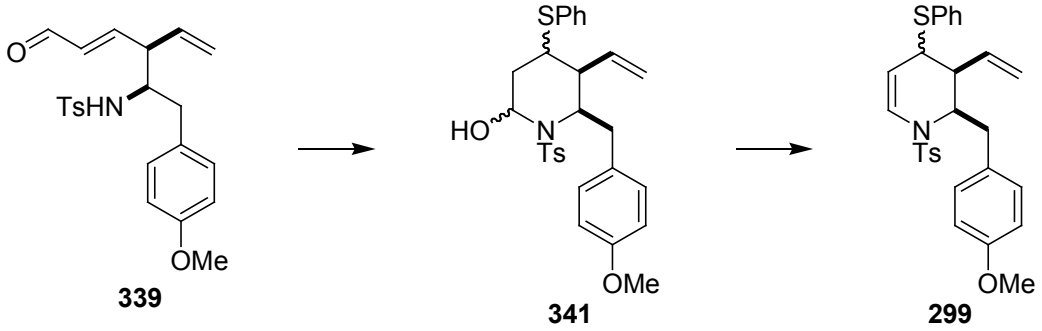
***N*-[(2*R**,3*R**,*E*)-1-(4-Methoxyphenyl)-6-oxo-3-vinylhex-4-en-2-yl)]-4-methyl-Benzenesulfonamide 339**



317 **339**

To a solution of tosamides **317** (1.47 g, 2.99 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at rt was added a solution of mCPBA (1.07 g of a 53% mixture of *m*-chlorobenzoic acid and H_2O, 3.29 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL). After 16 h, concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave N-*[(2*R**,3*R**,*E*)-1-(4-methoxyphenyl)-6-oxo-3-vinylhex-4-en-2-yl)]-4-methylbenzene-sulfonamide* **339** (622 mg, 52%) as a gum; R_f 0.21 (25% EtOAc–petrol); ν_{max} (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=C*H*), 6.03 (1H, ddd, *J* 16.0, 8.0, 1.5 Hz, CHOC*H*=CH), 5.77 (1H, ddd, *J* 17.0, 10.5, 8.0 Hz, C*H*=CH_2), 5.37 (1H, d, *J* 10.5 Hz, *trans* CH=C*H*H), 5.21 (1H, d, *J* 17.0 Hz, *cis* CH=CH*H*), 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, C*H*CH=CH_2), 2.73 (1H, dd, *J* 14.0, 7.5 Hz, C*H*HArOMe), 2.54 (1H, dd, *J* 14.0, 7.0 Hz, CH*H*ArOMe), 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=*C*H_2), 114.1, 58.5, 55.1, 48.9, 37.9 (CH_2), 21.5, 15.3; *m*/*z* (ESI) 422.1422 $[M+Na]^+$, 417.1865, 400.1585 $[M+H]^+$, 382.1478, 338.3427, 245.0269 (Found: $[M+H]^+$, 400.1585. $C_{22}H_{25}NO_4S$ requires $[M+H]^+$, 400.1583) (Found: C, 66.20; H, 6.30; N, 3.50. $C_{22}H_{25}NO_4S$ requires C, 66.14; H, 6.31; N, 3.51%).

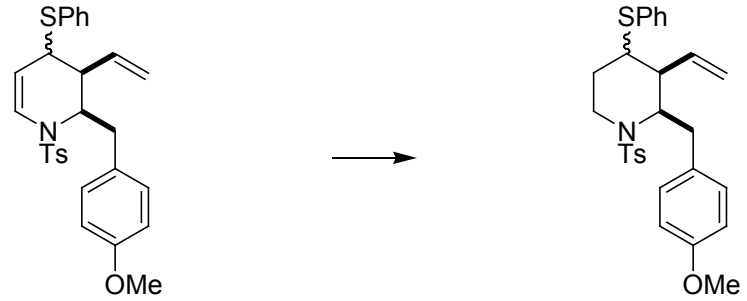
(2*R,3*S**)-2-(4-Methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 299**



To a solution of enal **339** (244 mg, 0.561 mmol, 1.0 equiv) in CH_2Cl_2 (2.3 mL) at 0 °C was added thiophenol (173 µL, 1.68 mmol, 3.0 equiv) and Et_3N (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 Et_3N (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; R_f 0.47 (18% EtOAc–petrol); ν_{max} (film) 2930, 1721, 1640, 1612, 1512, 1440, 1353, 1302, 1247, 1165, 1091, 1035, 991, 927, 815, 749, 675 cm^{-1}; δ_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=C*H*NTs, 2 × diast.), 5.70 (1H, ddd, *J* 17.5, 10.5, 8.0 Hz, C*H*=CH_2, major diast.), 5.49-5.43 (1H, m, C*H*=CH_2, minor diast.), 5.28-5.22 [(2 × 1H, m, CH=CHNTs, 2 × diast.) & (1H, m, *trans* CH=C*H*H, major diast.)], 5.16 (1H, dd, *J* 10.5, 1.5 Hz, *trans* CH=C*H*H, minor diast.), 4.99-4.92 (2 × 1H, m, *cis* CH=CH*H*, 2 × diast.), 4.09-4.03 (2 × 1H, m, $NTsCHCH_2$, 2 × diast.), 3.83 (3H, s, OMe, minor diast.), 3.82 (3H, s, OMe, major diast.), 3.55-3.48 (2 × 1H, m, C*H*SPh, 2 × diast.), [2.98-2.85 & 2.78-2.65 (2 × 2H, m, CH_2ArOMe, 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, C*H*CH=CH_2, 2 × diast.); δ_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=*C*H_2), 113.6 (3° Ar), 112.1, 60.9, 55.1, 43.9, 42.9, 32.4 (*C*H_2ArOMe), 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. $C_{28}H_{29}NO_3S_2$ requires $[M+H]^+$, 492.1667).

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

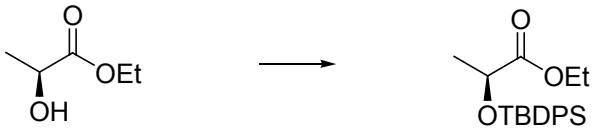


299 **385**

To a solution of tetrahydropyridines **299** (70.0 mg, 0.143 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at rt were added Et_3SiH (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 Et_3SiH (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: R_f 0.44 (18% EtOAc–petrol); ν_{max} (film) 2926, 1725, 1677, 1611, 1512, 1440, 1320, 1247, 1154, 1093, 1034, 814 cm^{-1}; δ_H (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, C*H*=CH_2), 5.68-5.59 (1H, m, C*H*=CH_2, diagnostic signal of the minor diast.), 5.35-5.31 (2H, m, CH=CH_2), 4.38 (1H, ddd, *J* 11.0, 4.5 Hz, NTsC*H*), 3.81 (3H, s, OMe), 3.69-3.64 (1H, m, C*H*SPh), 3.34-3.25 (1H, m, C*H*HNTs), 3.13-3.05 (1H, m, CH*H*NTs), 2.88 (1H, dd, *J* 14.0, 4.0 Hz, C*H*HArOMe), 2.74 (1H, dd, *J* 14.0, 11.5 Hz, CH*H*ArOMe), 2.61-2.54 (1H, m, C*H*CH=CH_2), 2.38 (3H, s, Me of Ts), 1.71-1.54 (2H, m, CH_2CHSPh); δ_C (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 (*C*H=CH_2), 127.1 (3° Ar), 118.6 (CH=*C*H_2), 113.8 (3° Ar), 60.8 (OMe), 55.2 (*C*HNTs), 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. $C_{28}H_{31}NO_3S_2$ requires $[M+H]^+$, 494.1824).

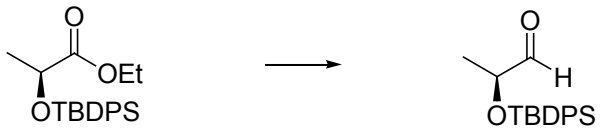
(*S*)-Ethyl 2-(*tert*-butyldiphenylsilyloxy)propanoate[166] 348



347 **348**

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 CH_2Cl_2 at 0 °C was added TBDPSCl (1.05 g, 3.81 mmol, 1.8 equiv) followed by Et_3N (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. $NH_4Cl_{(aq.)}$ (1 mL) then diluted with sat. $NaHCO_{3(aq.)}$ (4 mL). After 5 min, the mixture was further diluted with H_2O (3 mL) and the aqueous phase extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→15% Et_2O–petrol) gave ester **348** (739 mg, 98%) as a colourless liquid; R_f 0.63 (5% EtOAc–petrol); $[\alpha]_D^{22}$ –41.5 (*c* 2.0, $CHCl_3$); {Lit.[166a] $[\alpha]_D^{20}$ –41.1 (*c* 2.0, $CHCl_3$)}; ν_{max} (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}; δ_H (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, CH_2), 1.39 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 1.17 (3H, d, *J* 7.0 Hz, C*H*$_3$CH$_2$), 1.12 (9H, s, *t*Bu); δ_C (125 MHz) 173.7 (COO), 135.8, 133.6, 129.7, 127.6, 68.9 (*C*HOTBDPS), 60.6 (CH_2), 26.8 (Me of *t*Bu), 21.3, 19.3, 14.1; data in agreement with that previously reported.[166]

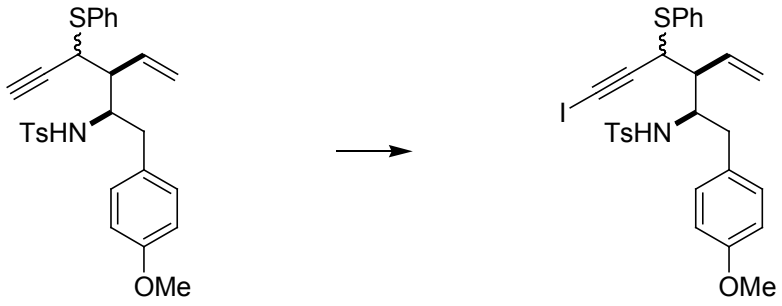
(*S*)-2-(*tert*-Butyldiphenylsilyloxy)propanal[165] 346



348 **346**

To a solution of ester **348** (100 mg, 0.28 mmol, 1.0 equiv) in CH_2Cl_2 at –78 °C was added DIBAL-H (322 μL of a 1.0 M solution in CH_2Cl_2, 0.322 mmol, 1.15 equiv) dropwise. After 50 min, MeOH (0.07 mL) was added to the solution, then Et_2O (1.2 mL) slowly, followed by Na/K tartrate (0.9 mL), Et_2O (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_2SO_4). Following concentration under reduce pressure, the crude product was azotroped with toluene three times. Further drying under high vacuum cleanly gave aldehyde **346** (76 mg, 87%) as a colourless liquid; R_f 0.31 (25% EtOAc–petrol); $[\alpha]_D^{20}$ –10.2 (*c* 1.2, ethanol); {Lit.[166b] $[\alpha]_D^{20}$ –10.2 (*c* 1.2, ethanol)}; δ_H (400 MHz) 9.67 (1H, d, *J* 1.0 Hz, CHO), 7.69-7.66 (4H, m, *ortho* Ph), 7.49-7.39 (6H, m, *meta* & *para* Ph), 4.12 (1H, dq, *J* 7.0, 1.0 Hz, C*H*OTBDPS), 1.25 (3H, d, *J* 7.0 Hz, CH_3CH), 1.14 (9H, s, *t*Bu); δ_C (125 MHz) 203.9 (CHO), 135.7, 132.9, 130.0, 127.8, 74.4 (*C*HOTBDPS), 26.9 (Me of *t*Bu), 19.2, 18.4; data in agreement with that previously reported.[165]

***N*-[(2*R**,3*S**)-6-Iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide 326**

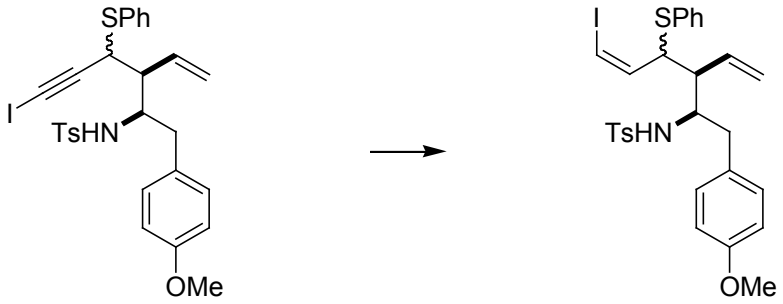


317 **326**

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 $AgNO_3$ (20.1 mg, 0.12 mmol, 0.5 equiv). After 16 h, the yellow mixture was quenched with sat. $NH_4Cl_{(aq.)}$ (0.8 mL), diluted with H_2O (2 mL) and Et_2O (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine (3 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave 2:1 diastereomeric mixture of N-*[(2*R**,3*S**)-6-iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-yn-2-yl]-4-methylbenzenesulfonamide* **326** (111 mg, 75%) as a solid; R_f 0.41 (25% EtOAc–petrol); ν_{max} (film) 3274, 2931, 1710, 1611, 1513, 1439, 1325, 1303, 1248, 1158, 1092, 1035, 927, 814 cm^{-1}; δ_H (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, C*H*=CH_2), 5.40 (1H, dd, *J* 10.5, 1.5 Hz, *trans* CH=C*H*H, major diast.), 5.34 (1H, dd, *J* 10.5, 1.5 Hz, *trans* CH=C*H*H, 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, C*H*NHTs & C*H*SPh, 2 × diast.), 3.83 (3H, s, OMe, minor diast.), 3.82 (3H, s, OMe, major diast.), 2.71-2.54 (2 × 2H, m, CH_2ArOMe, 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, C*H*CH=CH_2, 2 × diast.); δ_C (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 (*C*CHSPh, minor diast), 65.9 (*C*CHSPh, 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. $C_{28}H_{28}INO_3S_2$ requires $[M+Na]^+$, 640.0453; $[M+H]^+$, 618.0634).

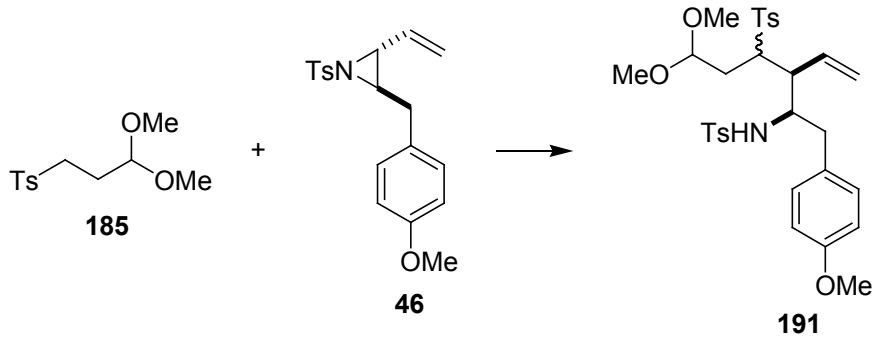
_N_-[(2_R_*,3_S_*,_Z_)-6-Iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide 327



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 *i*PrOH (1.0 mL) at rt was added a solution of AcOH (34.0 mg, 0.565 mmol, 5.0 equiv) in *i*PrOH (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 *i*PrOH (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 Et_2O (15 mL) and H_2O (20 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (10% EtOAc–petrol) gave a 2:1 diastereomeric mixture of *N-[(2*R**,3*S**,Z)-6-iodo-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-5-en-2-yl]-4-methylbenzenesulfonamide* **327** (62.0 mg, 88%) as a solid; R_f 0.61 (25% EtOAc–petrol); ν_{max} (film) 3059, 2957, 1654, 1654, 1512, 1465, 1337, 1247, 1159, 1094, 1037, 904, 812 cm^{-1}; δ_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, IC*H*=CH, major diast.), 6.23 (1H, d, *J* 7.5 Hz, IC*H*=CH, minor diast.), 6.19-6.13 (2 × 1H, m, ICH=C*H*, 2 × diast.), 5.75-5.64 (1H, m, C*H*=CH_2, major diast.), 5.54 (1H, ddd, *J* 17.0, 10.0, 8.5 Hz, C*H*=CH_2, minor diast.), 5.30 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H, major diast.), 5.28 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H, minor diast.), 5.15 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*, major diast.), 5.06 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*, 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, NTsC*H*, 2 × diast.), 3.84-3.78 (2 × 4H, m, OMe & C*H*SPh, 2 × diast.), 2.81-2.53 (2 × 2H, m, CH_2ArOMe, 2 × diast.), 2.44-2.43 (2 × 3H, m, Me of Ts, 2 × diast.), 2.33-2.28 (1H, m, C*H*CH=CH_2, major diast.), 2.01-1.97 (1H, m, C*H*CH=CH_2, minor diast.); δ_C (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=*C*HI, 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. $C_{28}H_{30}INO_3S_2$ requires $[M+Na]^+$, 642.0610; $[M+H]^+$, 620.0798).

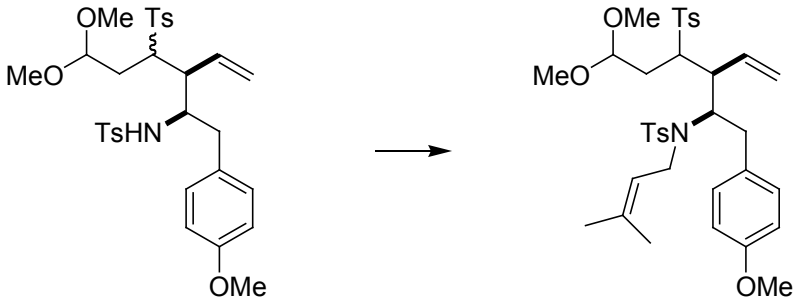
_N_-[(2_R_*,3_S_*)-6,6-Dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methylbenzenesulfonamide 191



To a solution of acetal **185** (3.25 g, 12.6 mmol, 1.5 equiv) in THF (36 mL) at –78 °C was added *n*BuLi (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. $NaHCO_{3(aq.)}$ (60 mL) and diluted with H_2O (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (25→40% EtOAc–petrol) gave a 2:1 diastereomeric mixture of *N*-[(2*R**,3*S**)-6,6-dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methylbenzenesulfonamide **191** (3.20 g, 63.4%) as a solid; R_f 0.32 (40% EtOAc–petrol); ν_{max} (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, C*H*=CH_2, minor diast.), 5.66 (1H, dt, *J* 17.0, 10.0 Hz, C*H*=CH_2, major diast.), 5.34 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H, major diast.), 5.24 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H, minor diast.), 5.04 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*, minor diast.), 4.98 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=C*H*H, 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, C*H*$(OMe)_2$, major diast.], 4.18-4.13 (2H, m, C*H*$(OMe)_2$ & 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, C*H*Ts, major diast.), 3.47-3.43 (1H, m, C*H*Ts, minor diast.), 3.33 [3H, s, CH(O*Me*)$_2$, major diast.], 3.29 [3H, s, CH(O*Me*)$_2$, major diast.], 3.16 [3H, s, CH(O*Me*)$_2$, minor diast.], 3.08 [3H, s, CH(O*Me*)$_2$, minor diast.], 2.86 (1H, dd, *J* 14.0, 4.5 Hz, C*H*HArOMe, minor diast.), 2.81-2.71 (2 × 1H, m, C*H*CH=CH$_2$ of major diast. & CH*H*ArOMe of minor diast.), 2.67-2.61 (1H, m, C*H*CH=CH$_2$, 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, C*H*$_2$CHTs of minor diast. & C*H*HArOMe of major diast.), 1.85 (1H, dt, *J* 15.0, 6.0 Hz, CH*H*ArOMe, major diast.), 1.59-1.56 (2H, m, C*H*$_2$CHTs, major diast.); δ_C (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 (*C*H=CH$_2$, 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=*C*H$_2$, major diast.), 121.4 (CH=*C*H$_2$, minor diast.), [113.9, 113.8 (3°, 2 × diast.)], 103.6 [*C*H(OMe)$_2$, major diast.], 102.2 [*C*H(OMe)$_2$, minor diast.], [61.8, 58.9, 57.6, 55.9 (*C*HTs & *C*HNTs, 2 × diast.)], [55.2, 55.1, 54.9, 54.3, 53.7, 52.7 (OMe, 2 × diast.)], [47.5, 44.9 (*C*HCH=CH$_2$)], 38.8 (2 × *C*H$_2$ArOMe, 2 × diast.), [30.8, 30.5 (2 × *C*H$_2$CHTs, 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. $C_{31}H_{39}NNaO_7S_2$ requires [M+Na]$^+$, 624.2070).

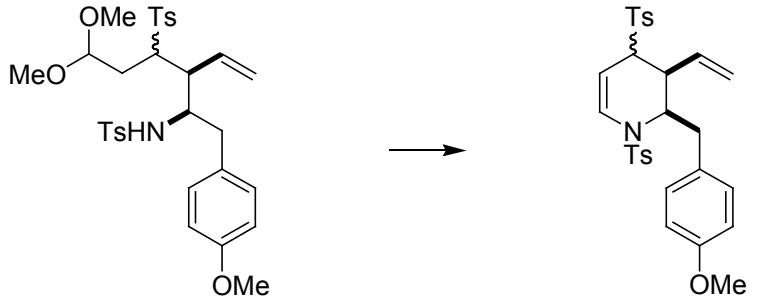
***N*-[(2*R**,3*S**)-6,6-Dimethoxy-1-(4-methoxyphenyl)-4-tosyl-3-vinylhexan-2-yl]-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide 386**



To a solution of diastereomixture of tosamides **191** (175 mg, 0.29 mmol, 1.0 equiv) in THF (0.4 mL) at –78°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_2O (5 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (20→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); ν_{max} (film) 2933, 1601, 1512, 1447, 1380, 1303, 1248, 1150, 1086, 926, 816, 729 cm^{-1}; δ_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, C*H*=CHH), 5.31 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 5.18 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*), 5.09-4.95 [1H, m, $(CH_3)_2$=C*H*)], 4.49-4.69 [2H, m, C*H*N & C*H*$(OMe)_2$], 3.94 (1H, dd, *J* 16.0, 7.0 Hz, C*H*HN), 3.83 (3H, s, ArOMe), 3.57 (1H, dd, *J* 16.0, 4.0 Hz, CH*H*N), 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, C*H*CH=CH_2), 2.84 (1H, dd, *J* 14.5, 4.5Hz, C*H*HArOMe), 2.49-2.45 (4H, m, Me of Ts & CH*H*ArOMe), 2.34 (3H, s, Me of Ts), 2.24-2.17 (1H, m, C*H*HCHTs), 2.12-2.07 (1H, m, CH*H*CHTs), 1.66 (3H, s, CH_3CCH_3), 1.63 (3H, s, CH_3CCH_3); δ_C (100 MHz) [158.4, 144.7, 142.7, 138.5 (q Ar)], [135.3, 134.1 (q)], 133.5 (*C*H=CH_2), 130.4 (3°), 130.1 (q), [129.8, 129.0, 128.9, 127.2 (3°)],

121.7 (CH_3CCH_3), 121.5 ($CH=CH_2$), 113.8 (3°), 101.9 [$CH(OMe)_2$], 62.1 (*C*HN), 61.3 (*C*HTs), 55.2 (ArO*Me*), 55.0 (*Me*OCHOMe), 51.8 (MeOCHO*Me*), 45.4 (*C*HCH=CH_2), 42.3 (CH_2N), 36.5 (CH_2ArOMe), 29.5 (CH_2CHTs), 25.7 (CH_3CCH_3), [21.7, 21.4 (2 × Me of 2 × Ts)], 17.8 (CH_3CCH_3); *m*/*z* (ESI) 692.2662 $[M+Na]^+$, 638.2621, 304.1006 (Found: $[M+Na]^+$, 692.2662. $C_{36}H_{47}NO_7S_2$ requires $[M+Na]^+$, 692.2692).

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

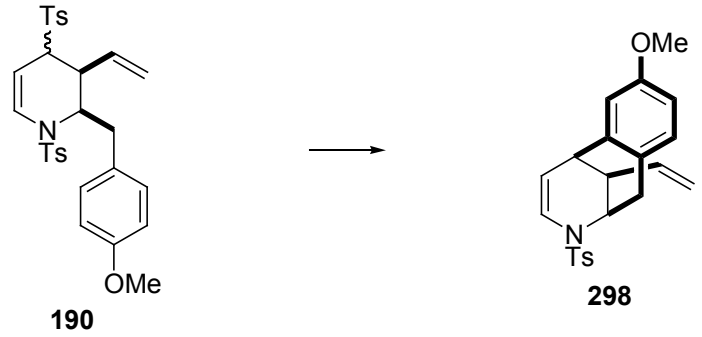


191 **190**

To a solution of diastereomeric mixture of tosamide **191** (3.10 g, 5.16 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (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. $NaHCO_{3(aq.)}$ (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 CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol) gave a 2:1 diastereomeric mixture of (2*R**,3*S**)-2-(4-methoxybenzyl)-1,4-ditosyl-3-vinyl-1,2,3,4-tetrahydropyridine **190** (2.31g, 83%) as a solid; R_f 0.60 (40% EtOAc–petrol); ν_{max} (film) 2922, 1640, 1512, 1461, 1317, 1248, 1164, 1087, 1034, 814, 671 cm^{-1}; δ_H (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, NTsC*H*=CH, major diast.), 6.89-6.87 (1H, m, NTsC*H*=CH, minor diast.), 6.83 (2H, d, *J*

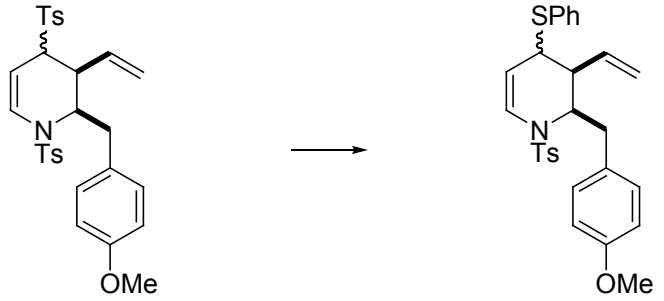
8.5 Hz, *ortho* ArOMe, major diast.), 6.82 (2H, d, *J* 8.5 Hz, *ortho* ArOMe, minor diast.), 6.20 (1H, ddd, *J* 17.0, 10.0, 8.5 Hz, C*H*=CH_2, major diast.), 5.76 (1H, ddd, *J* 17.0, 10.0, 8.5 Hz, C*H*=CH_2, minor diast.), 5.36 (1H, dd, *J* 8.0, 2.5 Hz, NTsCH=C*H*, minor diast.), 5.25 (1H, dd, *J* 10.0, 2.5 Hz, *trans* CH=C*H*H, major diast.), 5.14 (1H, d, *J* 10.0 Hz, *trans* CH=C*H*H, minor diast.), 5.07 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*, major diast.), 4.93 (1H, dd, *J* 8.5, 3.5 Hz, NTsCH=C*H*, major diast.), 4.73 (1H, d, *J* 17.0 Hz, *cis* CH=CH*H*, minor diast.), 3.92-3.88 (2 × 1H, m, NTsC*H*CH_2, 2 × diast.), 3.82 (3H, s, OMe, major diast.), 3.81 (3H, s, OMe, minor diast.), 3.74-3.71 (2 × 1H, m, C*H*SPh, 2 × diast.), 3.24 (1H, dd, *J* 14.5, 7.5 Hz, C*H*HArOMe, major diast.), 2.96 (1H, dd, *J* 14.5, 6.5 Hz, CH*H*ArOMe, major diast.), 2.75 (1H, dd, *J* 14.0, 4.5 Hz, C*H*HArOMe, minor diast.), 2.63-2.58 (2 × 1H, m, CH*H*ArOMe of minor diast. & C*H*CH=CH_2 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, C*H*CH=CH_2, minor diast.); δ_C (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. $C_{29}H_{31}NO_5S_2$ requires $[M+Na]^+$, 560.1541; $[M+H]^+$, 538.1722).

8-Methoxy-3-(toluene-4-sulfonyl)-11-vinyl-1,2,3,6-tetrahydro-2,6-methano-benzo[d]azocine[31] **298**



To a solution of 2:1 diastereomixture of tetrahydropyridines **190** (150 mg, 0.28 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at –78 °C was added $SnCl_4$ (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. $NaHCO_{3(aq.)}$ (15 mL). After 5 min, it was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). 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-benzo[d]azocine **298** (60.0 mg, 56%) as a gum; R_f 0.72 (20% EtOAc–petrol); ν_{max} (film) 3067, 2917, 2835, 1642, 1610, 1503, 1395, 1363, 1341, 1304, 1248, 1167, 1092, 1051, 986, 711, 680 cm^{-1}; δ_H (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, C*H*CHCOMe), 6.70-6.66 (2H, m, CHC*H*COMe & NC*H*=CH), 6.59 (1H, d, *J* 2.5 Hz, CC*H*COMe), 5.55 (1H, ddd, *J* 17.5, 10.5, 7.5 Hz, C*H*=CHH), 5.31 (1H, dd, *J* 7.5, 7.0 Hz, NCH=C*H*), 4.99-4.92 (2H, m, CH=CH_2), 4.30 (1H, m, NC*H*CH_2), 3.78 (3H, s, OMe), 3.22 (1H, dd, *J* 18.5, 6.0 Hz, C*H*HArOMe), 3.11-3.10 (1H, m, NCH=CHC*H*), 2.98 (1H, d, *J* 18.5 Hz, CH*H*ArOMe), 2.47 (3H, s, Me of Ts), 2.14-2.12 (1H, m, C*H*CH=CH_2); δ_C (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=*C*H_2), [113.3, 113.0, 111.9 (3°)], 55.3 (OMe), 52.8 (N*C*HCH_2), [39.5, 37.1 (CH_2=CH*C*H*C*H)], 33.8 (*C*H_2ArOMe), 21.7 (Me of Ts); *m*/*z* (ESI) 382.1483 $[M+H]^+$, 292.6040, 226.1265 (Found: $[M+H]^+$, 382.1483. $C_{22}H_{23}NO_3S$ requires $[M+H]^+$, 382.1477); data in agreement with that previously reported.[31]

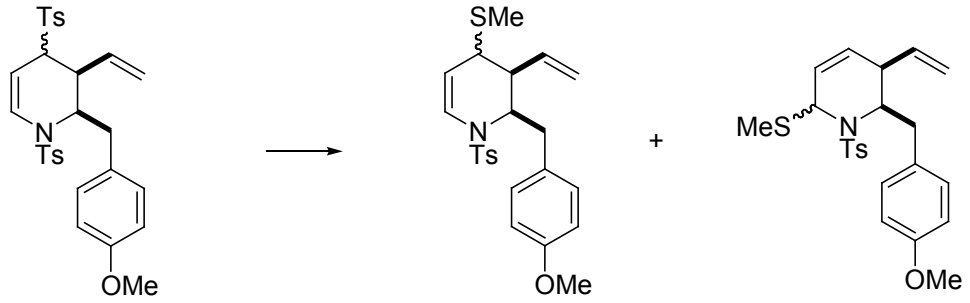
(2*R,3*S**)-2-(4-Methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 299**



190 **299**

To a solution of PhSH (924 mg, 8.38 mmol, 4.5 equiv) in CH_2Cl_2 at rt was added $AlMe_3$ (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 CH_2Cl_2 *via* cannula. After 1 h, the solution was cooled to 0 °C and sat. Na/K tartrate$_{(aq.)}$ (15 mL) added dropwise, followed by H_2O (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 (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5→10% EtOAc–petrol) followed by recrystallisation gave a 2:1 diastereomixture of (2*R**,3*S**)-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.

(2*R,3*S**)-2-(4-Methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine 343 and (2*R**,3*R**)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine 344**



190 **343** **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 $AlMe_3$ (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 H_2O (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 (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave a 1.2:1 diastereomeric mixture of *(2*R**,3*S**)-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 *(2*R**,3*R**)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine* **344** (55.1 mg, 69%) as a gum.

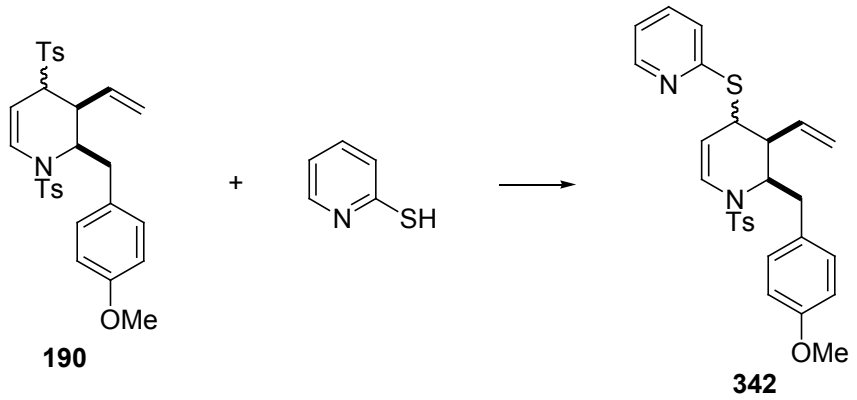
Data for 1.2:1 diastereomixture of (2*R**,3*R**)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine **343**: R_f 0.76 (30% EtOAc–petrol); ν_{max} (film) 3035, 2922, 2837 1609, 1512 1442, 1339, 1247, 1159, 1094, 1036, 914, 816 cm^{-1}; δ_H (400 MHz) 7.60 (2H, d, *J* 8.0 Hz, *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, C*H*=CH_2 & C*H*=C*H*, 2 × diast.), 5.19-5.02 (2 × 2H, m, CH=CH_2, 2 × diast.), 4.57-4.52 (1H, m, NC*H*SMe, minor diast.), 4.39-4.34 (1H, m,

NC*H*SMe, major diast.), 3.83 (3H, s, OMe, minor diast.), 3.81 (3H, s, OMe, major diast.), 3.51-3.44 (1H, m, NC*H*CH_2, major diast.), 3.22 (1H, dd, *J* 15.0, 10.0 Hz, C*H*HArOMe, major diast.), 3.09 (1H, dd, *J* 14.5, 9.0 Hz, C*H*HArOMe, minor diast.), 2.76-2.68 (2 × 1H, m, C*H*HArOMe, 2 × diast. & 1H, m, NC*H*CH_2, minor diast.), 2.44-2.39 (2 × 4H, m, Me of Ts & C*H*CH=CH_2, 2 × diast.), 2.14 (3H, s, SMe, major diast.), 1.66 (3H, s, SMe, minor diast.); δ_C (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. $C_{23}H_{27}NO_3S_2$ requires $[M+Na]^+$, 452.1330).

Data for 2:1 diastereomixture of (2*R**,3*S**)-2-(4-methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine **344**: R_f 0.71 (30% EtOAc–petrol); ν_{max} (film) 3034, 2920, 2835, 1636, 1611, 1598, 1584, 1513, 1464, 1440, 1420, 1347, 1303, 1247, 1161, 1092, 1036, 913, 814 cm^{-1}; δ_H (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, NC*H*=CH, major diast.), 6.62 (1H, d, *J* 8.0 Hz, NC*H*=CH, minor diast.), 6.18 (1H, ddd, *J* 17.5, 10.0, 8.0 Hz, C*H*=CHH, minor diast.), 5.66 (1H, ddd, *J* 17.5, 10.0, 8.0 Hz, C*H*=CHH, major diast.), 5.47 (1H, dd, *J* 8.0, 4.5 Hz, NCH=C*H*, minor diast.), 5.28-5.15 (2 × 1H, m, CH=C*H*H, 2 × diast. & 1H, m, NCH=C*H*, major diast.), 5.01-4.94 (2 × 1H, m, CH=CH*H*, 2 × diast), 4.14-4.07 (2 × 1H, m, NC*H*CH_2, 2 × diast), 3.83 (2 × 3H, s, OMe, 2 × diast), 3.14-3.11 (1H, m, C*H*SMe, major diast.), 3.03-3.00 (1H, m, C*H*SMe, minor diast.), 2.92 (1H, dd, *J* 14.0, 4.0 Hz, C*H*HArOMe, minor diast.), 2.84 (1H, dd, *J* 14.0, 10.0 Hz, CH*H*ArOMe, minor diast.), 2.72 (1H, dd, *J* 14.0, 4.0 Hz, C*H*HArOMe, major diast.), 2.65 (1H, dd, *J* 14.0, 10.0 Hz, CH*H*ArOMe, major diast.), 2.43 (3H, s, Me of Ts, major diast.), 2.25-2.20 (1H, m, C*H*CH=CH_2, minor diast.), 2.18 (3H, s, Me of Ts, minor diast.), 1.77-1.72 (1H, m, C*H*CH=CH_2, major diast.), 1.59 (3H, s, SMe, minor diast.), 1.56 (3H, s, SMe, major diast.); δ_C (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*

(ESI) 452.1334 $[M+Na]^+$, 447.1773, 430.1506 $[M+H]^+$, 382.1479, 242.1179, 227.1312 (Found: $[M+Na]^+$, 452.1334. $C_{23}H_{27}NO_3S_2$ requires $[M+Na]^+$, 452.1330).

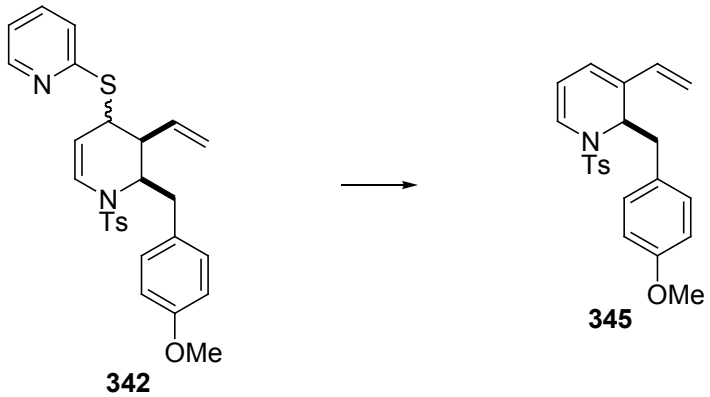
2-[(2*R,3*S**)-2-(4-Methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ylthio]pyridine 342**



To a solution of 2-mercaptapyridine (207 mg, 1.86 mmol, 5.0 equiv) in CH_2Cl_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_2Cl_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_2SO_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-[(2*R**,3*S**)-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); ν_{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}; δ_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=C*H*NTs, 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, C*H*=CH_2, major diast.), 5.63 (1H, ddd, *J* 14.5, 8.5, 6.5 Hz, C*H*=CH_2, minor diast.), 5.46 (1H, dd, *J* 6.5, 4.0 Hz, CH=C*H*H, major diast.), 5.38-5.36 (1H, dd, *J* 6.5, 2.0 Hz, CH=C*H*H, minor diast.), 5.11-5.09 (1H, m, CH=CH*H*, minor diast.), 5.06-5.04 (1H, m, CH=CH*H*, major diast.), 4.97-4.92 (2 × 1H, m, C*H*=CHNTs, 2 × diast.), 4.83-4.81 (1H, m, C*H*NTs, major diast.), 4.62-4.59 (1H, m, C*H*NTs, minor diast.), [3.80, 3.79 (2 × 3H, 2 × s, OMe, 2 × diast.)], 2.88-2.76 (2 × 2H, m, CH_2ArOMe, 2 × diast.), [2.43, 2.42 (2 × 3H, 2 × s, Me of Ts, 2 × diast.)], 2.39-2.36 (1H, m, C*H*CH=CH_2, major diast.), 2.87-2.82 (1H, m, C*H*CH=CH_2, minor diast.); δ_C (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. $C_{27}H_{28}N_2O_3S_2$ requires $[M+Na]^+$, 493.1620).

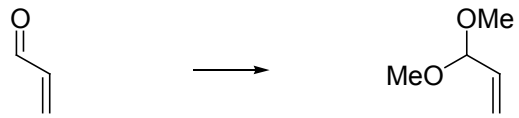
(*R)-2-(4-Methoxybenzyl)-1-tosyl-3-vinyl-1,2-dihydropyridine**



To a mixture of AgOTf (16.0 mg, 0.061 mmol, 1.5 equiv), 4 Å molecular sieves and CH_2Cl_2 (1.5 mL) in the dark at –40 °C was added a solution of a 2.5:1 diastereomixture of 2-[(2*R**,3*S**)-2-(4-methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ylthio]pyridines **342** (20.0 mg, 0.041 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL). After 2 h, the reaction was quenched with sat. $NaHCO_{3(aq.)}$ (2 mL). After stirring for 2 min, it was diluted with H_2O (2 mL), CH_2Cl_2 (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 (Na_2SO_4). 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; R_f 0.67 (20% EtOAc–petrol); δ_H (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, NC*H*=CH), 6.13 (1H, dd, *J* 17.5, 11.0 Hz, C*H*=CHH), 5.73 (1H, d, *J* 5.5 Hz, NCH=CHC*H*), 5.59 (1H, dd, *J* 6.5, 5.5 Hz, NCH=C*H*), 5.14-5.08 (2H, m, CH=CH_2), 4.98 (1H, d, *J* 11.0 Hz, NC*H*CH_2), 3.82 (3H, s, OMe), 2.78-2.75 (2H, m, CH_2ArOMe), 2.38 (3H, s, Me of Ts); δ_C (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=*C*H_2), 113.5 (*ortho* ArOMe), [112.5, 112.2 (3°)], [55.2, 54.8 (OMe & N*C*HCH_2)], 37.7 (*C*H_2ArOMe), 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. $C_{22}H_{23}NO_3S$ requires $[M+H]^+$, 382.1477).

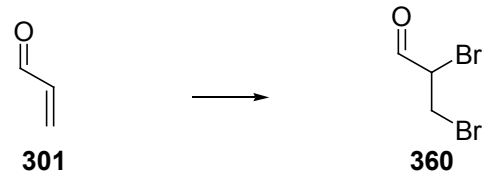
3,3-Dimethoxyprop-1-ene[172] **357**



301 **357**

To a solution of NH_4NO_3 (357 mg, 4.46 mmol, 0.05 equiv) in MeOH (3mL) at rt was added acrylaldehyde **301** (5.00 g, 89.2 mmol, 1.0 equiv) and $CH(CH_3O)_3$ (12.6 g, 118.8 mmol, 1.33 equiv). After 16 h, the reaction mixture was filtered. Solid Na_2CO_3 (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; R_f 0.61 (15% EtOAc–petrol); δ_H (400 MHz) 5.83 (1H, dd, *J* 17.5, 10.5, 5.0 Hz, C*H*=CH_2), 5.43 (1H, dt, *J* 17.5, 1.0 Hz, CH=C*H*H), 5.35 (1H, dt, *J* 10.5, 1.0 Hz, CH=CH*H*), 4.79 [1H, dt, *J* 5.0, 1.0 Hz, $CH(OMe)_2$], 3.36 [6H, s, $(OMe)_2$]; δ_C (100 MHz) 134.5 (*C*H=CH_2), 118.9 (CH=*C*H_2), 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]

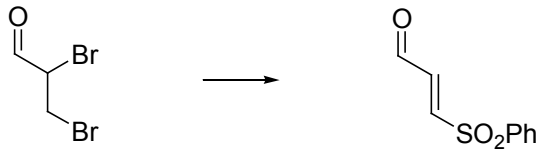
2,3-Dibromopropanal[175] **360**



301 **360**

To a solution of acrylaldehyde **301** (2.80 g, 50.0 mmol, 1.0 equiv) in CCl_4 (5mL) at 0°C was added Br_2 (2.56 mL, 50.0 mmol, 1.0 equiv) dropwise. After 4 h, the reaction was quenched with sat. $Na_2S_2O_{3(aq.)}$ (25 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (20 mL), brine (3 × 15 mL) and dried (Na_2SO_4). Concentration cleanly gave crude dibromide **360** (10.7 g, 100%) as an oil, used without further purification; R_f 0.78 (43% EtOAc–hexane); ν_{max} (film) 3504, 2938, 1731, 1425, 1396, 1125 cm^{-1}; δ_H (400 MHz) 9.40 (1H, d, *J* 2.5 Hz, CHO), 4.55 (1H, ddd, *J* 10.5, 4.5, 2.5 Hz, C*H*BrCHO), 3.89 (1H, t, *J* 10.5 Hz, C*H*HBr), 3.74 (1H, dd, *J* 10.5, 4.5 Hz, CH*H*Br); δ_C (100 MHz) 189.0 (CHO), 48.9 (*C*HBrCHO), 26.8 (CH_2Br); compound not suitable for CI and ESI mass spectroscopic technologies; data in agreement with that previously reported.[175]

(*E*)-3-(Phenylsulfonyl)acrylaldehyde[175] **361**

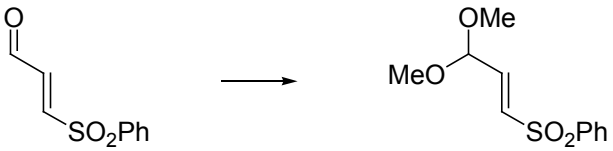


360 **361**

To a solution of dibromide **360** (10.7 g, 50.0 mmol, 1.0 equiv) in DMF (28 mL) at rt was added $PhSO_2Na$ (12.3 g, 75.0 mmol, 1.5 equiv). After 30 h, the reaction was quenched with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (4 × 50 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (20→30% EtOAc–petrol) gave (*E*)-3-(phenylsulfonyl)acrylaldehyde **361** (3.40 g, 35%) as a gum; R_f 0.46 (43% EtOAc–

hexane); ν_{max} (film) 3476, 3062, 2928, 2852, 1729, 1700, 1584, 1448, 1308, 1150, 1083, 964, 819, 753, 687 cm^{-1}; δ_H (400 MHz) 9.67 (1H, d, *J* 7.0 Hz, CHO), 7.88-7.86 (2H, m, *ortho* SO_2Ph), 7.66-7.64 (1H, m, *para* SO_2Ph), 7.57-7.54 (2H, m, *meta* SO_2Ph), 7.31 (1H, d, *J* 15.5 Hz, C*H*SO_2Ph), 6.83 (1H, dd, *J* 15.5, 7.0 Hz, C*H*CHO); δ_C (100 MHz) 190.3 (CHO), 147.9, 137.8, 136.2, 134.7, [129.8, 128.5 (*ortho* & *meta* Ph)]; *m*/*z* (CI) 214 $[M+NH_4]^+$, 160, 125 (Found: $[M+NH_4]^+$, 214.0548. $C_9H_8O_3S$ requires $[M+NH_4]^+$, 214.0538); data in agreement with that previously reported.[175]

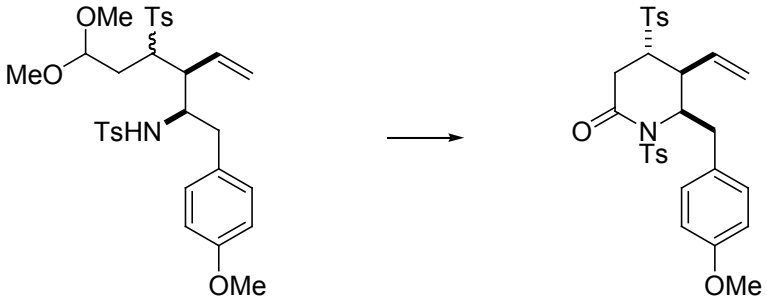
(*E*)-(3,3)-Dimethoxyprop-1-enylsulfonyl)benzene 358a



361 **358a**

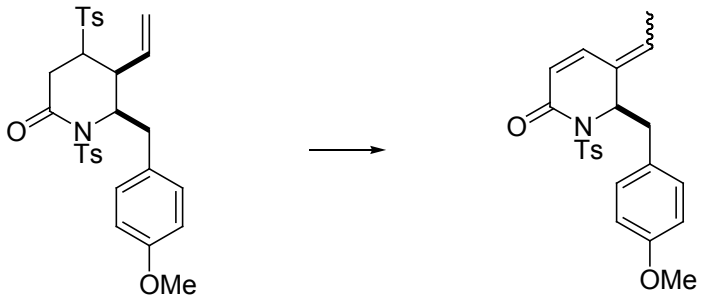
To a solution of (*E*)-3-(phenylsulfonyl)acrylaldehyde **361** (2.00 g, 9.50 mmol, 1.0 equiv) in MeOH (1 mL) at rt was added a solution of NH_4NO_3 (38.4 mg, 0.480 mmol, 0.05 equiv) and $(CH_3O)_3CH$ (2.02 g, 19.0 mmol, 2.0 equiv) in MeOH (1 mL). After 96 h, concentration under reduced pressure and column chromatography (15→20% EtOAc–petrol with 1.5% Et_3N) gave *(*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); ν_{max} (film) 3058, 2939, 2834, 1448, 1359, 1332, 1277, 1172, 1150, 1061, 986, 822, 763, 688, 614 cm^{-1}; δ_H (400 MHz) 7.91 (2H, d, *J* 7.5 Hz, *ortho* Ph), 7.65 (1H, t, *J* 7.5 Hz, *para* Ph), 7.57 (2H, t, *J* 7.5 Hz, *meta* Ph), 6.81 (1H, dd, *J* 15.0, 3.0 Hz, C*H*=CHSO_2Ph), 6.71 (1H, dd, *J* 15.0, 0.5 Hz, CH=C*H*SO_2Ph), 5.02 [1H, dd, *J* 3.0, 0.5 Hz, C*H*$(OMe)_2$], 3.32 [6H, s, CH(O*Me*)$_2$]; δ_C (100 MHz) 140.6 (3°), 139.8 (*ipso* Ph), [134.6, 133.7 (3°)], [129.4, 127.9 (*ortho* & *meta* Ph)], 99.1 [*C*H$(OMe)_2$], 52.9 [CH(O*Me*)$_2$]; *m*/*z* (CI) 260 $[M+NH_4]^+$, 101, 86 (Found: $[M+NH_4]^+$, 260.0961. $C_{11}H_{14}O_4S$ requires $[M+NH_4]^+$, 260.0957).

(4*S,5*S**,6*R**)-6-(4-Methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one 353**



To a solution of tosamides **191** (1.15g, 1.90 mmol, 1.0 equiv) in acetone (3.1 mL) at rt was added dropwise a solution of CrO_3 (950 mg, 9.50 mmol, 5.0 equiv) in H_2O (2.8 mL) and concentrated H_2SO_4 (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 *(4*S**,5*S**,6*R**)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one* **353** (242 mg, 23%) as a colourless solid; data for major diastereomer only: R_f 0.31 (35% EtOAc–petrol); ν_{max} (film) 2963, 2934, 1709, 1598, 1509, 1355, 1295, 1251, 1148, 1089, 1030, 927, 816, 668, 550 cm^{-1}; δ_H (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, C*H*=CH_2), 5.38-5.31 (2H, m, CH=CH_2), 4.89 (1H, app q, *J* 5.0 Hz, C*H*NTs), 3.82 (3H, s, OMe), 3.29 (1H, ddd, *J* 11.0, 8.5, 7.0 Hz, C*H*Ts), 3.19 (1H, dd, *J* 15.0, 5.0 Hz, C*H*HArOMe), 3.05-2.99 (1H, m, C*H*CH=CH_2), 2.90 (1H, dd, *J* 15.0, 5.0 Hz, CH*H*ArOMe), 2.60 (1H, dd, *J* 18.5, 7.0 Hz, COC*H*H), [2.46, 2.45 (2 × 3H, 2 × s, 2 × Me of Ts)], 2.22 (1H, dd, *J* 18.5, 8.5 Hz, COCH*H*); δ_C (100 MHz) 166.5 (CO), 159.1 (*ipso* Ts), [145.5, 145.1, 135.7 (4º)], 134.9 (3º), 133.6 (4º), [131.0, 129.9, 129.3 (*meta* or *ortho* Ar)], 129.0 (2 × *meta* or *ortho* Ar), , 127.9 (4º), 119.9 (CH=*C*H_2), 114.4 (*meta* or *ortho* Ar), 61.5 (*C*HNTs), 58.4 (*C*HTs), 55.2 (OMe), 44.5 (*C*HCH=CH_2), [36.2, 32.6 (*C*H_2ArOMe & *C*H_2CO)], 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. $C_{29}H_{31}NO_6S_2$ requires $[M+Na]^+$, 576.1490).

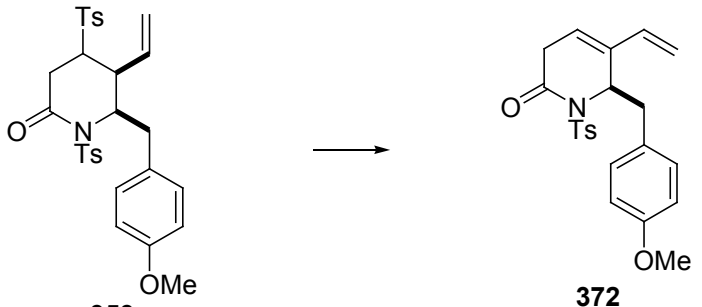
(*R)-5-Ethylidene-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 371**



353 **371**

To a solution of (5*S**,6*R**)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one **353** (18.0 mg, 0.0325 mmol, 1.0 equiv) in CH_2Cl_2 (0.1 mL) at rt was added DBU (8 μL). After 20 h, the resulting solution was concentrated to half volume by flushing with N_2. 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; R_f 0.72 (40% EtOAc–petrol); ν_{max} (film) 2923, 1682, 1640, 1611, 1513, 1447, 1402, 1346, 1302, 1247, 1166, 1116, 1087, 1033, 1006, 912, 614, 680, 650, 608, 550 cm^{-1}; δ_H (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 C*H*=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, C*H*=CHCO, major isomer), 5.90 (1H, t, *J* 7.5 Hz, C=C*H*CH_3, major isomer), 5.69-5.66 (2 × 1H, m, C*H*NTs, major isomer & CH=C*H*CO, minor isomer), 5.53 (1H, d, *J* 9.5 Hz, CH=C*H*CO, major isomer), 5.32 (1H, d, *J* 7.5 Hz, C=C*H*CH_3, minor isomer), 5.19 (1H, dd, *J* 9.0, 3.5 Hz, C*H*NTs, minor isomer), [3.82, 3.80 (2 × 3H, 2 × s, OMe, 2 × isomers), 3.14 (1H, dd, *J* 13.0, 3.5 Hz, C*H*HArOMe, major isomer), 2.95-2.90 (2 × 2H & 1 × 1H, m, CH*H*ArOMe, 2 × isomers and C*H*HArOMe, minor isomer), 2.44 (2 × 3H, s, Me of Ts, 2 × isomers), 1.72 (3H, d, *J* 7.5 Hz, C=CHCH_3, minor isomer), 1.35 (3H, d, *J* 7.5 Hz, C=CHCH_3, major isomer); δ_C (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. $C_{22}H_{23}NO_4S$ requires $[M+H]^+$, 398.1426).

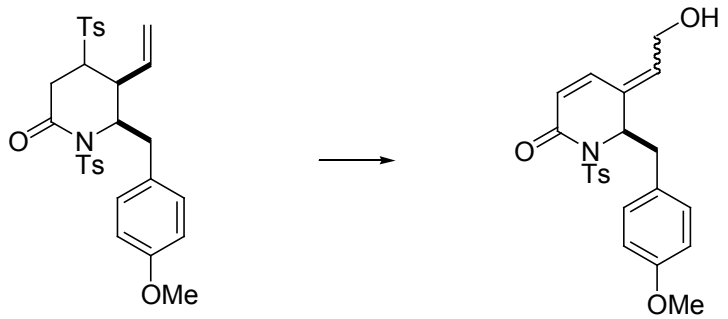
(*R)-6-(4-Methoxybenzyl)-1-tosyl-5-vinyl-1,6-dihydropyridin-2(3H)-one 372**



To a solution of (5*S**,6*R**)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one **353** (20.0 mg, 0.036 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) at rt was added Et_3N (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); ν_{max} (film) 2920, 1698, 1513, 1351, 1251, 1169, 1046, 821, 674 cm^{-1}; δ_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, C*H*=CH_2), 5.66-5.64 (1H, m, NTsC*H*), 5.58 (1H, dd, *J* 5.5, 2.0 Hz, C=CH), 5.42 (1H, d, *J* 17.5 Hz, CH=C*H*H), 5.28 (1H, d, *J* 11.0 Hz, CH=CH*H*), 3.79 (3H, s, OMe), 3.35 (1H, dd, *J* 14.0, 5.0 Hz, C*H*HArOMe), 3.04 (1H, dd, *J* 14.0, 2.5 Hz, CH*H*ArOMe), 2.41-2.36 (5H, m, Me of Ts & CH_2CO); δ_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=*C*H_2), 113.5 (*ortho* or *meta* Ar), [57.4, 55.2 (NTs*C*H & OMe)], [39.6, 34.0 (*C*H_2CO & *C*H_2ArOMe)], 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. $C_{22}H_{23}NO_4S$ requires $[M+Na]^+$, 420.1245) (Found: C, 66.50; H, 5.77; N, 3.47. $C_{22}H_{23}NO_4S$ 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**



353 **375**

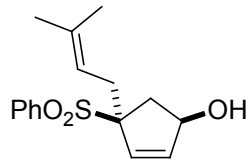
To a mixture of allylmagnezium bromide (0.18 mL of a 1 M solution in Et_2O, 0.18 mmol, 2.0 equiv) and CuCN (16.0 mg, 0.18 mmol, 2.0 equiv) in THF (0.3 mL) was added a solution (5*S**,6*R**)-6-(4-methoxybenzyl)-1,4-ditosyl-5-vinylpiperidin-2-one (50.0 mg, 0.090 mmol, 1.0 equiv) **353** in THF (0.3 mL), followed by Et_3N (4 μL, 0.027 mmol, 0.3 equiv). After 16 h, the reaction was diluted with sat. $NH_4Cl_{(aq.)}$ (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 (Na_2SO_4). 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.

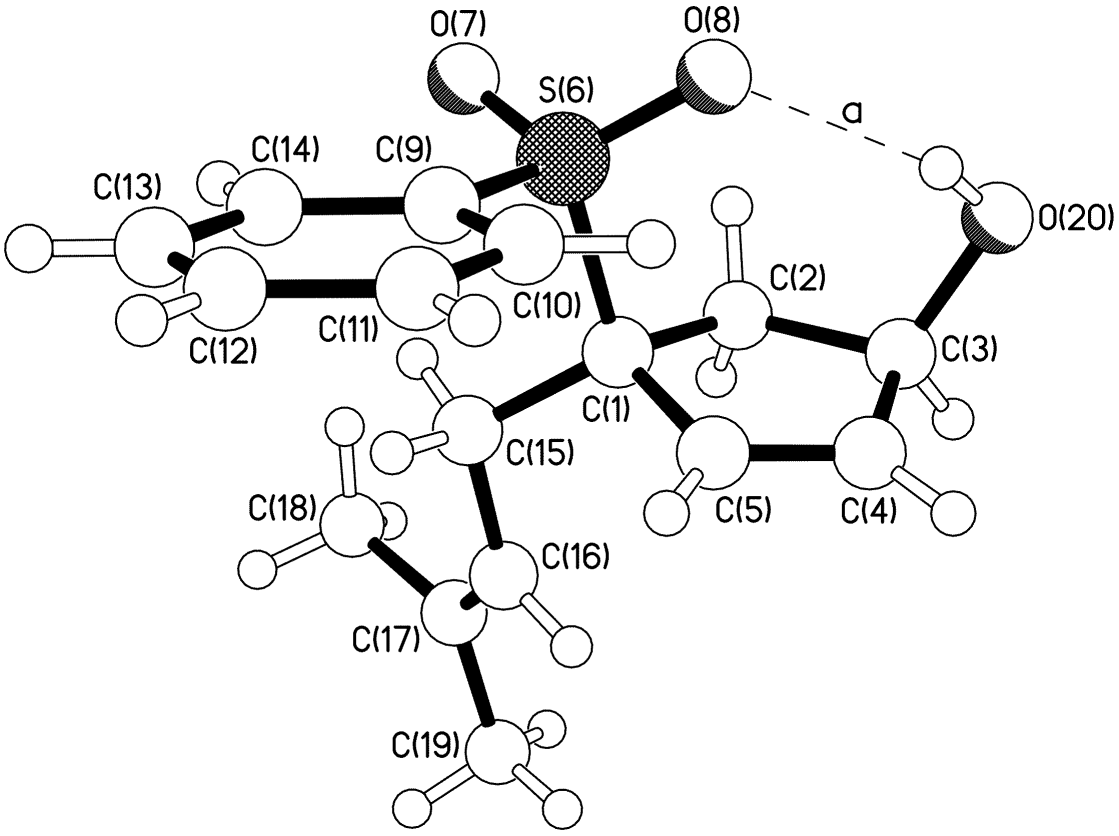
Data for **minor isomer**: (4 mg, 11%); R_f 0.14 (40% EtOAc–petrol); ν_{max} (film) 3457, 2925, 1682, 1611, 1597, 1514, 1443, 1402, 1347, 1169, 1103, 1088, 1030, 914, 815, 730, 689 cm^{-1}; δ_H (400 MHz) 8.00 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.34 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.10 (1H, d, *J* 10.0 Hz, C*H*=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=C*H*CO), 5.34 (1H, app. t, *J* 6.5 Hz, C=C*H*), 5.23 (1H, dd, *J* 9.0, 3.5 Hz, NTsC*H*), 4.24-4.18 (2H, m, CH_2OH), 3.81 (3H, s, OMe), 3.23 (1H, dd, *J* 13.0, 3.5 Hz, C*H*HArOMe), 2.95 (1H, dd, *J* 13.0, 9.0 Hz, CH*H*ArOMe), 2.45 (3H, s, Me of Ts).

Data for **major isomer**: 8 mg, 22%; R_f 0.18 (40% EtOAc–petrol); ν_{max} (film) 3455, 2924, 1682, 1611, 1596, 1513, 1442, 1402, 1347, 1166, 1107, 1086, 1031, 913, 815, 730, 686 cm^{-1}; δ_H (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, C*H*=CHCO), 5.90 (1H, app. t, *J* 6.0 Hz, C=C*H*), 5.75 (1H, d, *J* 9.5 Hz, CH=C*H*CO), 5.63 (1H, dd, *J* 10.0, 3.5 Hz, NTsC*H*), 3.93-3.86 (1H, m, C*H*HOH), 3.82 (3H, s, OMe), 3.34-3.31 (1H, m, CH*H*OH), 3.24 (1H, dd, *J* 13.0, 3.5 Hz, C*H*HArOMe), 2.89 (1H, dd, *J* 13.0, 10.5 Hz, CH*H*ArOMe), 2.45 (3H, s, Me of Ts); δ_C (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. $C_{22}H_{23}NO_5S$ requires $[M+H]^+$, 436.1175) (Found: C, 63.85; H, 5.50; N, 3.32. $C_{22}H_{23}NO_5S$ requires C, 63.90; H, 5.61; N, 3.39%).

Appendices-Crystal Structures

Appendix I-compound **234d**





Crystal data and structure refinement for **234d.**

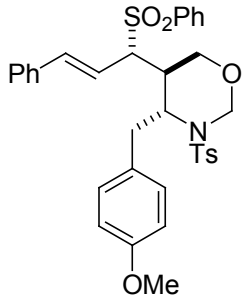
Identification code	DC0602
Empirical formula	C16 H20 O3 S
Formula weight	292.38
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 17.906(4) Å α = 90°
	b = 6.3895(18) Å β = 99.06(2)°
	c = 12.901(4) Å γ = 90°
Volume, Z	1457.6(7) $Å^3$, 4
Density (calculated)	1.332 Mg/m^3
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 mm^3
θ 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>4σ(F)]	2359
Absorption correction	Semi-empirical from equivalents
Max. and min. *trans*mission	1.06087 and 0.86647
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2800 / 1 / 188
Goodness-of-fit on F^2	1.106
Final R indices [F>4σ(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

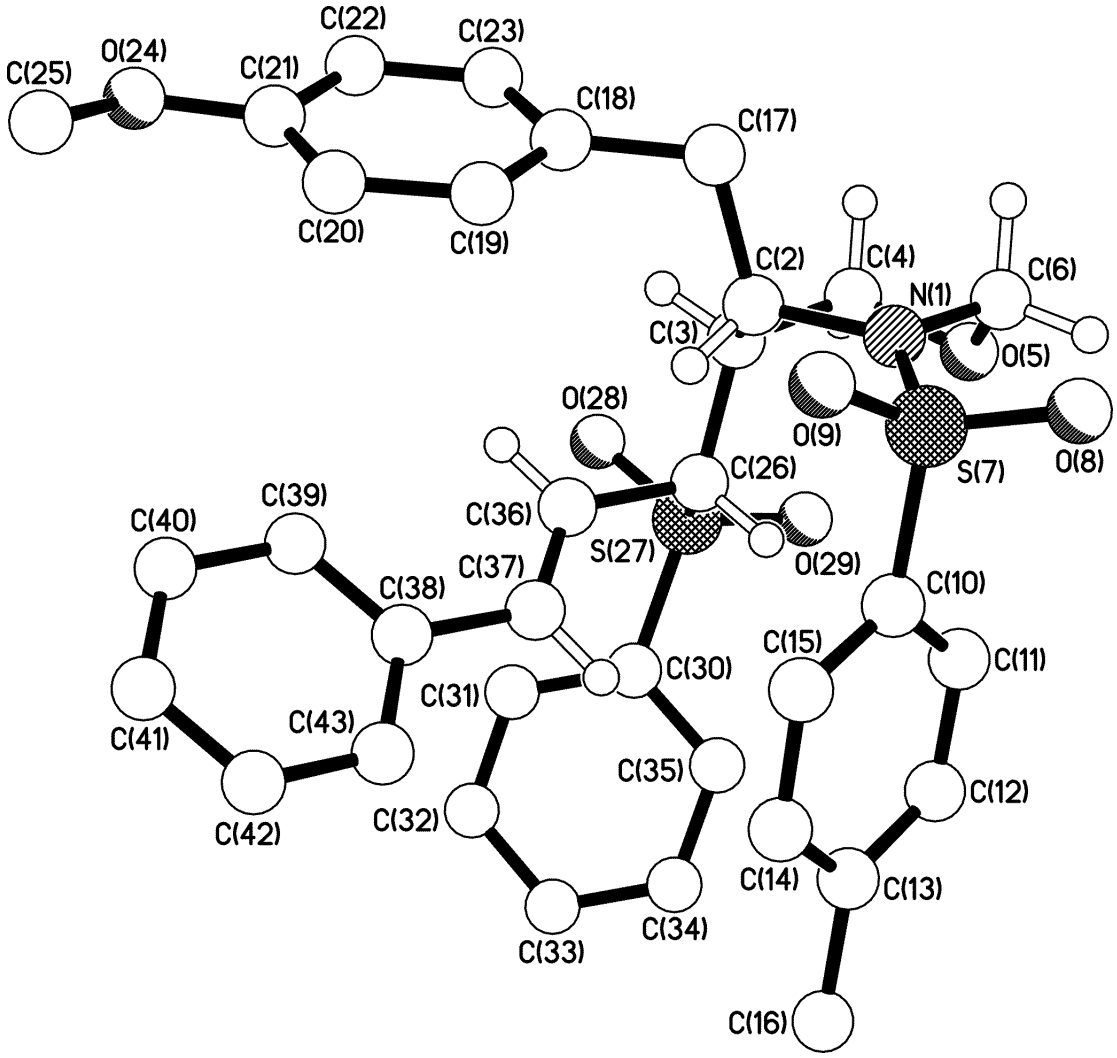
Bond lengths [Å] and angles [°] for **234d.**

C(1)-C(5)	1.5020(19)
C(1)-C(15)	1.5412(18)
C(1)-C(2)	1.5483(19)
C(1)-S(6)	1.8249(13)
C(2)-C(3)	1.540(2)
C(3)-O(20)	1.4305(18)
C(3)-C(4)	1.494(2)
C(4)-C(5)	1.319(2)
S(6)-O(7)	1.4359(12)
S(6)-O(8)	1.4454(11)
S(6)-C(9)	1.7609(14)
O(8)-O(20)	2.9949(18)
C(9)-C(10)	1.386(2)
C(9)-C(14)	1.391(2)
C(10)-C(11)	1.386(2)
C(11)-C(12)	1.381(2)
C(12)-C(13)	1.383(2)
C(13)-C(14)	1.388(2)
C(15)-C(16)	1.5001(19)
C(16)-C(17)	1.329(2)
C(17)-C(18)	1.499(2)
C(17)-C(19)	1.501(2)

C(5)-C(1)-C(15)	114.33(11)
C(5)-C(1)-C(2)	103.11(11)
C(15)-C(1)-C(2)	115.21(11)
C(5)-C(1)-S(6)	108.66(8)
C(15)-C(1)-S(6)	108.19(9)
C(2)-C(1)-S(6)	106.94(9)
C(3)-C(2)-C(1)	106.17(11)
O(20)-C(3)-C(4)	112.20(12)
O(20)-C(3)-C(2)	114.02(12)
C(4)-C(3)-C(2)	103.21(11)
C(5)-C(4)-C(3)	112.96(13)
C(4)-C(5)-C(1)	112.18(12)
O(7)-S(6)-O(8)	117.84(6)
O(7)-S(6)-C(9)	108.73(7)
O(8)-S(6)-C(9)	108.20(7)
O(7)-S(6)-C(1)	108.56(6)
O(8)-S(6)-C(1)	107.47(6)
C(9)-S(6)-C(1)	105.33(6)
C(10)-C(9)-C(14)	121.49(13)
C(10)-C(9)-S(6)	119.28(11)
C(14)-C(9)-S(6)	119.22(11)
C(9)-C(10)-C(11)	118.87(13)
C(12)-C(11)-C(10)	120.17(14)
C(11)-C(12)-C(13)	120.63(14)
C(12)-C(13)-C(14)	120.10(14)
C(13)-C(14)-C(9)	118.73(14)
C(16)-C(15)-C(1)	111.66(11)
C(17)-C(16)-C(15)	127.53(14)
C(16)-C(17)-C(18)	124.41(15)
C(16)-C(17)-C(19)	120.85(15)
C(18)-C(17)-C(19)	114.69(14)

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) $Å^3$, 8
Density (calculated)	1.320 Mg/m^3
Absorption coefficient	1.932 mm^{-1}
F(000)	2608
Crystal colour / morphology	Colourless tablets
Crystal size	0.22 x 0.20 x 0.06 mm^3
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. *trans*mission	1.00000 and 0.76604
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6002 / 0 / 390
Goodness-of-fit on F^2	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

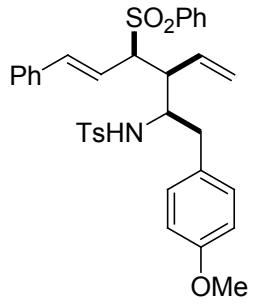
Bond lengths [Å] and angles [°] for **273**.

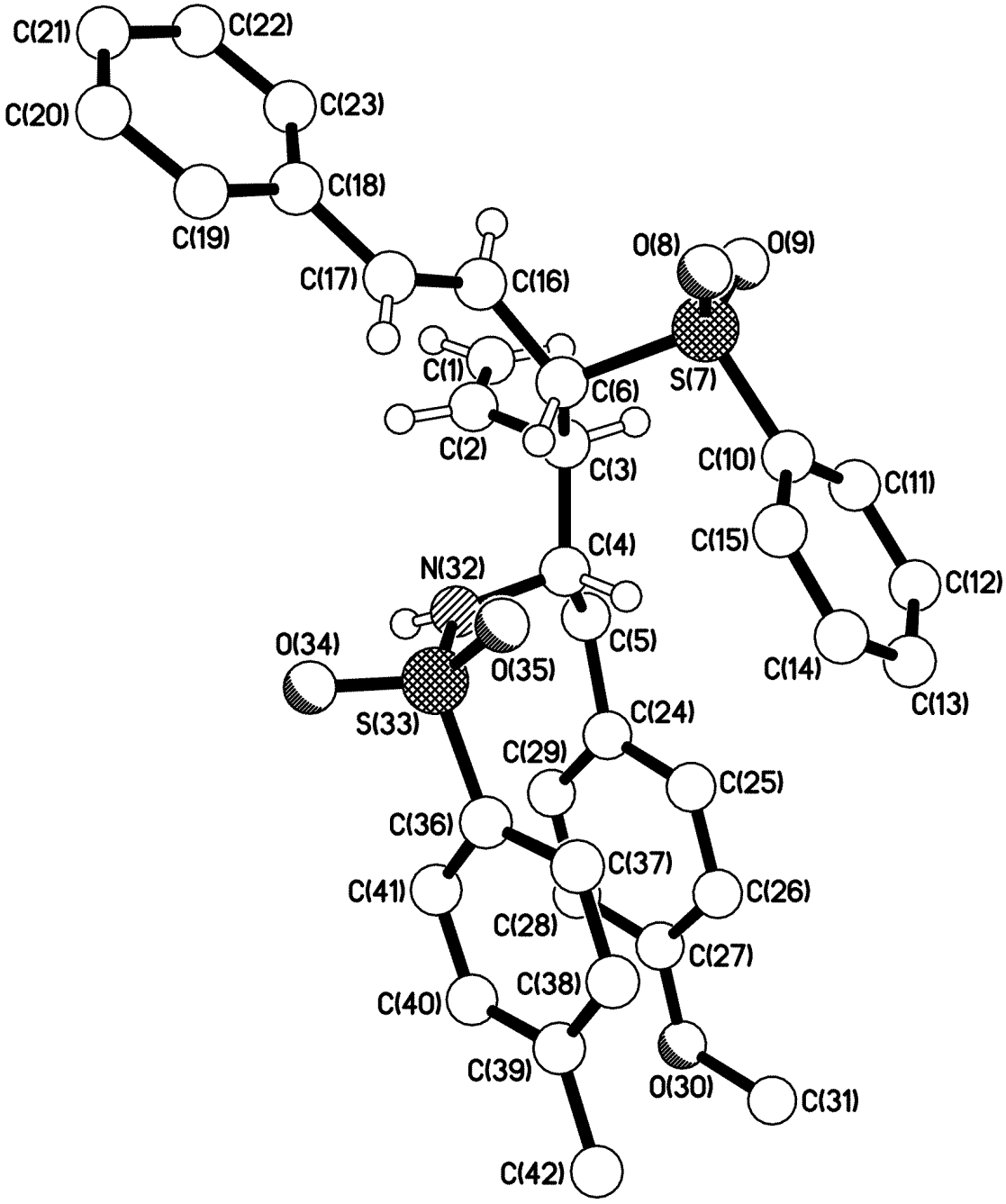
N(1)-C(6)	1.463(2)
N(1)-C(2)	1.475(2)
N(1)-S(7)	1.6183(15)
C(2)-C(17)	1.544(2)
C(2)-C(3)	1.550(2)
C(3)-C(4)	1.526(2)
C(3)-C(26)	1.545(2)
C(4)-O(5)	1.4326(19)
O(5)-C(6)	1.404(2)
S(7)-O(9)	1.4339(13)
S(7)-O(8)	1.4343(13)
S(7)-C(10)	1.7671(18)
C(10)-C(15)	1.385(2)
C(10)-C(11)	1.392(2)
C(11)-C(12)	1.380(3)
C(12)-C(13)	1.390(3)
C(13)-C(14)	1.387(3)
C(13)-C(16)	1.505(3)
C(14)-C(15)	1.386(3)
C(17)-C(18)	1.505(2)
C(18)-C(23)	1.383(3)
C(18)-C(19)	1.385(3)
C(19)-C(20)	1.397(3)
C(20)-C(21)	1.374(3)
C(21)-O(24)	1.379(2)
C(21)-C(22)	1.383(3)
C(22)-C(23)	1.386(3)
O(24)-C(25)	1.425(2)
C(26)-C(36)	1.520(2)
C(26)-S(27)	1.8167(16)
S(27)-O(28)	1.4378(12)
S(27)-O(29)	1.4382(12)
S(27)-C(30)	1.7630(18)
C(30)-C(31)	1.383(3)
C(30)-C(35)	1.385(2)
C(31)-C(32)	1.382(3)
C(32)-C(33)	1.387(3)
C(33)-C(34)	1.371(3)
C(34)-C(35)	1.387(3)
C(36)-C(37)	1.305(3)
C(37)-C(38)	1.480(2)
C(38)-C(43)	1.370(3)
C(38)-C(39)	1.393(3)
C(39)-C(40)	1.402(3)
C(40)-C(41)	1.370(3)
C(41)-C(42)	1.369(3)
C(42)-C(43)	1.379(3)

C(6)-N(1)-C(2)	117.75(14)
C(6)-N(1)-S(7)	122.21(11)
C(2)-N(1)-S(7)	119.78(11)
N(1)-C(2)-C(17)	111.61(14)
N(1)-C(2)-C(3)	110.08(13)
C(17)-C(2)-C(3)	112.91(14)
C(4)-C(3)-C(26)	116.02(13)
C(4)-C(3)-C(2)	109.84(13)
C(26)-C(3)-C(2)	109.27(13)
O(5)-C(4)-C(3)	111.09(13)
C(6)-O(5)-C(4)	108.82(13)

O(5)-C(6)-N(1)	110.46(13)
O(9)-S(7)-O(8)	119.22(8)
O(9)-S(7)-N(1)	107.86(7)
O(8)-S(7)-N(1)	106.48(8)
O(9)-S(7)-C(10)	106.97(8)
O(8)-S(7)-C(10)	107.77(8)
N(1)-S(7)-C(10)	108.13(8)
C(15)-C(10)-C(11)	120.55(17)
C(15)-C(10)-S(7)	119.89(13)
C(11)-C(10)-S(7)	119.53(14)
C(12)-C(11)-C(10)	119.17(17)
C(11)-C(12)-C(13)	121.57(17)
C(14)-C(13)-C(12)	118.01(18)
C(14)-C(13)-C(16)	120.57(18)
C(12)-C(13)-C(16)	121.42(18)
C(15)-C(14)-C(13)	121.71(18)
C(10)-C(15)-C(14)	118.98(16)
C(18)-C(17)-C(2)	110.66(14)
C(23)-C(18)-C(19)	116.96(17)
C(23)-C(18)-C(17)	123.10(17)
C(19)-C(18)-C(17)	119.94(16)
C(18)-C(19)-C(20)	121.92(17)
C(21)-C(20)-C(19)	119.53(18)
C(20)-C(21)-O(24)	123.80(17)
C(20)-C(21)-C(22)	119.82(18)
O(24)-C(21)-C(22)	116.38(16)
C(21)-C(22)-C(23)	119.57(17)
C(18)-C(23)-C(22)	122.20(18)
C(21)-O(24)-C(25)	116.85(15)
C(36)-C(26)-C(3)	108.56(13)
C(36)-C(26)-S(27)	108.01(11)
C(3)-C(26)-S(27)	111.36(11)
O(28)-S(27)-O(29)	118.39(8)
O(28)-S(27)-C(30)	109.43(8)
O(29)-S(27)-C(30)	107.42(8)
O(28)-S(27)-C(26)	107.47(8)
O(29)-S(27)-C(26)	109.44(8)
C(30)-S(27)-C(26)	103.72(8)
C(31)-C(30)-C(35)	121.69(17)
C(31)-C(30)-S(27)	119.73(13)
C(35)-C(30)-S(27)	118.56(14)
C(32)-C(31)-C(30)	118.81(18)
C(31)-C(32)-C(33)	120.1(2)
C(34)-C(33)-C(32)	120.45(19)
C(33)-C(34)-C(35)	120.43(19)
C(30)-C(35)-C(34)	118.53(18)
C(37)-C(36)-C(26)	124.98(17)
C(36)-C(37)-C(38)	126.15(18)
C(43)-C(38)-C(39)	118.67(19)
C(43)-C(38)-C(37)	118.60(18)
C(39)-C(38)-C(37)	122.7(2)
C(38)-C(39)-C(40)	120.4(2)
C(41)-C(40)-C(39)	119.4(2)
C(42)-C(41)-C(40)	120.0(2)
C(41)-C(42)-C(43)	120.7(2)
C(38)-C(43)-C(42)	120.8(2)

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 α = 90°
	b = 13.8616(6) Å β = 90°
	c = 26.447(5) Å γ = 90°
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 x 0.29 x 0.15 mm^3
θ range for data collection	3.85 to 28.54°
Index ranges	-21<=h<=21, -17<=k<=17, -35<=l<=34
Reflns collected / unique	56392 / 7131 [R(int) = 0.0460]
Reflns observed [F>4σ(F)]	5759
Absorption correction	Semi-empirical from equivalents
Max. and min. *trans*mission	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>4σ(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

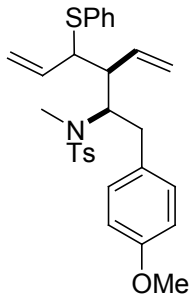
Bond lengths [Å] and angles [°] for **274**.

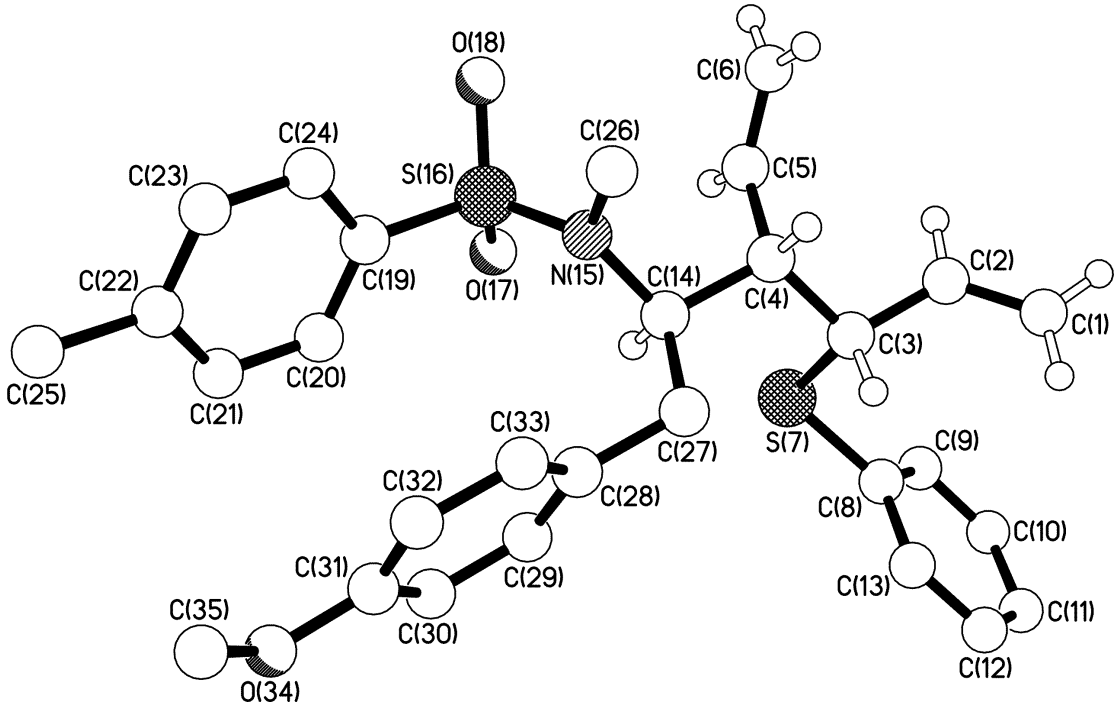
C(1)-C(2)	1.319(5)
C(2)-C(3)	1.497(4)
C(3)-C(4)	1.536(4)
C(3)-C(6)	1.548(4)
C(4)-N(32)	1.471(3)
C(4)-C(5)	1.511(4)
C(5)-C(24)	1.504(4)
C(6)-C(16)	1.484(4)
C(6)-S(7)	1.808(3)
S(7)-O(8)	1.424(2)
S(7)-O(9)	1.432(2)
S(7)-C(10)	1.753(3)
C(10)-C(11)	1.377(4)
C(10)-C(15)	1.385(4)
C(11)-C(12)	1.376(4)
C(12)-C(13)	1.372(5)
C(13)-C(14)	1.383(5)
C(14)-C(15)	1.372(4)
C(16)-C(17)	1.322(4)
C(17)-C(18)	1.461(4)
C(18)-C(23)	1.391(5)
C(18)-C(19)	1.392(5)
C(19)-C(20)	1.381(5)
C(20)-C(21)	1.378(6)
C(21)-C(22)	1.362(6)
C(22)-C(23)	1.367(5)
C(24)-C(25)	1.380(4)
C(24)-C(29)	1.384(4)
C(25)-C(26)	1.377(4)
C(26)-C(27)	1.381(4)
C(27)-O(30)	1.360(4)
C(27)-C(28)	1.384(4)
C(28)-C(29)	1.368(4)
O(30)-C(31)	1.419(5)
N(32)-S(33)	1.606(2)
S(33)-O(35)	1.429(2)
S(33)-O(34)	1.4346(19)
S(33)-C(36)	1.743(3)
C(36)-C(37)	1.385(4)
C(36)-C(41)	1.391(4)
C(37)-C(38)	1.373(5)
C(38)-C(39)	1.365(5)
C(39)-C(40)	1.390(5)
C(39)-C(42)	1.504(5)
C(40)-C(41)	1.370(5)

C(1)-C(2)-C(3)	123.1(4)
C(2)-C(3)-C(4)	110.4(2)
C(2)-C(3)-C(6)	111.5(3)
C(4)-C(3)-C(6)	112.8(2)
N(32)-C(4)-C(5)	110.3(2)
N(32)-C(4)-C(3)	109.9(2)
C(5)-C(4)-C(3)	109.8(2)
C(24)-C(5)-C(4)	117.3(2)
C(16)-C(6)-C(3)	114.5(2)
C(16)-C(6)-S(7)	107.91(19)
C(3)-C(6)-S(7)	110.01(19)
O(8)-S(7)-O(9)	118.56(14)
O(8)-S(7)-C(10)	108.62(14)

O(9)-S(7)-C(10)	108.79(14)
O(8)-S(7)-C(6)	108.10(14)
O(9)-S(7)-C(6)	108.97(13)
C(10)-S(7)-C(6)	102.64(13)
C(11)-C(10)-C(15)	121.3(3)
C(11)-C(10)-S(7)	120.3(2)
C(15)-C(10)-S(7)	118.4(2)
C(12)-C(11)-C(10)	119.2(3)
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**.

Identification code	DC0701
Empirical formula	C29 H33 N O3 S2
Formula weight	507.68
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 15.6552(2) Å α = 90°
	b = 12.3842(2) Å β = 90°
	c = 28.0436(4) Å γ = 90°
Volume, Z	5437.01(14) $Å^3$, 8
Density (calculated)	1.240 Mg/m^3
Absorption coefficient	2.009 mm^{-1}
F(000)	2160
Crystal colour / morphology	Colourless needles
Crystal size	0.28 x 0.05 x 0.02 mm^3
θ range for data collection	3.15 to 52.24°
Index ranges	-15<=h<=15, -10<=k<=12, -28<=l<=28
Reflns collected / unique	10559 / 3002 [R(int) = 0.0380]
Reflns observed [F>4σ(F)]	1958
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.61918
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3002 / 0 / 318
Goodness-of-fit on F^2	0.995
Final R indices [F>4σ(F)]	R1 = 0.0423, wR2 = 0.0761
R indices (all data)	R1 = 0.0854, wR2 = 0.0867
Largest diff. peak, hole	0.157, -0.198 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

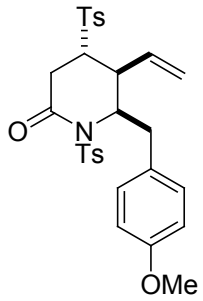
Bond lengths [Å] and angles [°] for **297**.

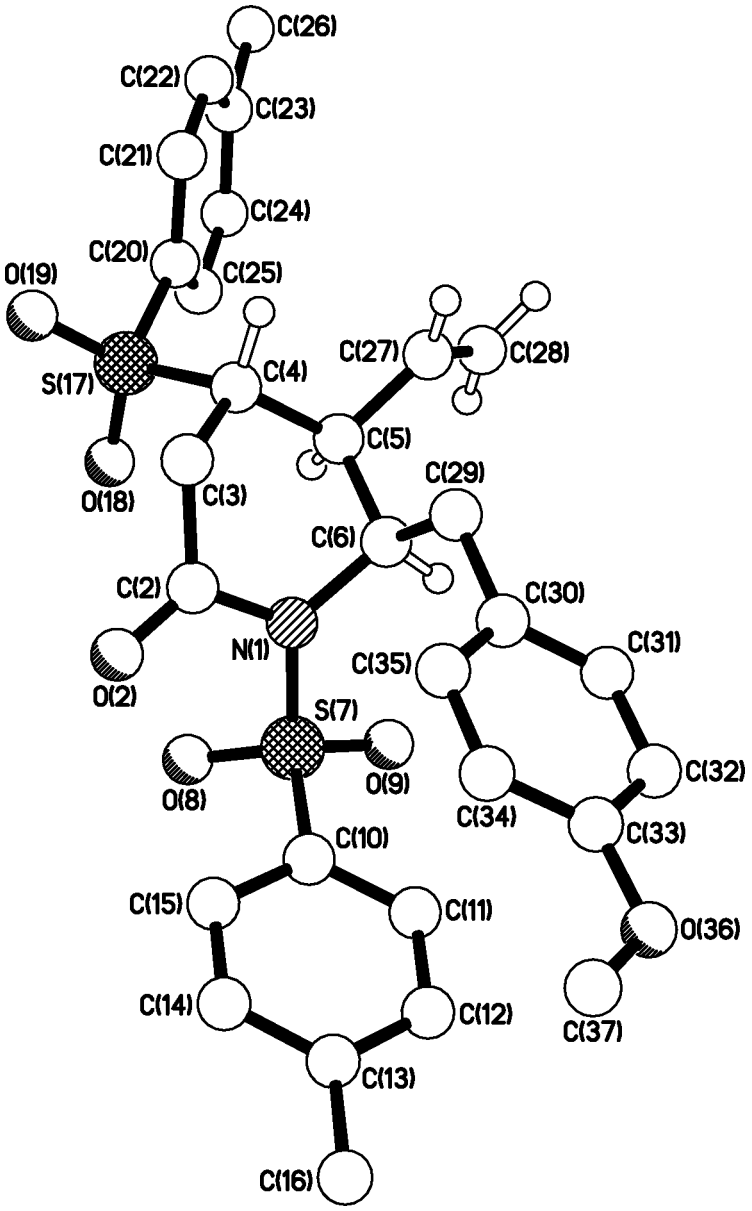
C(1)-C(2)	1.312(4)
C(2)-C(3)	1.490(4)
C(3)-C(4)	1.552(4)
C(3)-S(7)	1.845(3)
C(4)-C(5)	1.507(4)
C(4)-C(14)	1.557(4)
C(5)-C(6)	1.308(4)
S(7)-C(8)	1.768(3)
C(8)-C(9)	1.361(4)
C(8)-C(13)	1.388(4)
C(9)-C(10)	1.396(5)
C(10)-C(11)	1.368(5)
C(11)-C(12)	1.359(5)
C(12)-C(13)	1.375(4)
C(14)-N(15)	1.471(3)
C(14)-C(27)	1.536(4)
N(15)-C(26)	1.460(3)
N(15)-S(16)	1.619(2)
S(16)-O(18)	1.4357(18)
S(16)-O(17)	1.4380(19)
S(16)-C(19)	1.756(3)
C(19)-C(20)	1.382(4)
C(19)-C(24)	1.387(4)
C(20)-C(21)	1.384(4)
C(21)-C(22)	1.381(4)
C(22)-C(23)	1.382(4)
C(22)-C(25)	1.511(4)
C(23)-C(24)	1.374(4)
C(27)-C(28)	1.505(4)
C(28)-C(33)	1.383(4)
C(28)-C(29)	1.388(4)
C(29)-C(30)	1.370(4)
C(30)-C(31)	1.377(4)
C(31)-C(32)	1.376(4)
C(31)-O(34)	1.384(4)
C(32)-C(33)	1.388(4)
O(34)-C(35)	1.413(4)

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**





Crystal data and structure refinement for **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) Å α = 64.138(5)°
	b = 14.0189(7) Å β = 84.419(3)°
	c = 14.7590(7) Å γ = 85.889(3)°
Volume, Z	1350.93(12) $Å^3$, 2
Density (calculated)	1.361 Mg/m^3
Absorption coefficient	0.242 mm^{-1}
F(000)	584
Crystal colour / morphology	Colourless needles
Crystal size	0.44 x 0.05 x 0.03 mm^3
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 F^2
Data / restraints / parameters	8763 / 0 / 345
Goodness-of-fit on F^2	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)	1.539(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)

O(8)-S(7)-N(1)	107.19(7)
O(9)-S(7)-N(1)	104.78(7)
O(8)-S(7)-C(10)	108.48(8)
O(9)-S(7)-C(10)	108.20(8)
N(1)-S(7)-C(10)	108.86(7)
C(11)-C(10)-C(15)	120.15(17)
C(11)-C(10)-S(7)	119.31(14)
C(15)-C(10)-S(7)	120.22(13)
C(12)-C(11)-C(10)	119.28(18)
C(11)-C(12)-C(13)	121.33(17)
C(14)-C(13)-C(12)	118.29(18)
C(14)-C(13)-C(16)	120.08(18)
C(12)-C(13)-C(16)	121.63(18)
C(15)-C(14)-C(13)	121.18(18)
C(14)-C(15)-C(10)	119.77(16)
O(18)-S(17)-O(19)	118.69(10)
O(18)-S(17)-C(20)	109.11(9)
O(19)-S(17)-C(20)	107.10(9)
O(18)-S(17)-C(4)	108.26(8)
O(19)-S(17)-C(4)	107.13(9)
C(20)-S(17)-C(4)	105.84(8)
C(25)-C(20)-C(21)	120.36(19)
C(25)-C(20)-S(17)	120.54(15)
C(21)-C(20)-S(17)	118.97(15)
C(22)-C(21)-C(20)	119.0(2)
C(21)-C(22)-C(23)	121.6(2)
C(22)-C(23)-C(24)	118.3(2)
C(22)-C(23)-C(26)	121.0(2)
C(24)-C(23)-C(26)	120.7(2)
C(25)-C(24)-C(23)	121.2(2)
C(24)-C(25)-C(20)	119.45(19)
C(28)-C(27)-C(5)	125.0(2)
C(30)-C(29)-C(6)	115.15(13)
C(35)-C(30)-C(31)	117.82(17)
C(35)-C(30)-C(29)	120.98(16)
C(31)-C(30)-C(29)	121.20(17)
C(32)-C(31)-C(30)	121.30(18)
C(31)-C(32)-C(33)	120.00(17)
O(36)-C(33)-C(34)	124.06(18)
O(36)-C(33)-C(32)	116.26(16)
C(34)-C(33)-C(32)	119.68(17)
C(33)-C(34)-C(35)	119.10(18)
C(30)-C(35)-C(34)	122.10(17)
C(33)-O(36)-C(37)	117.31(15)

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