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Selectivity in the Synthesis of Cyclic Sulfonamides

Application in the Synthesis of Natural Products

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Selectivity in the Synthesis of Cyclic Sulfonamides

Application in the Synthesis of Natural Products

Doctoral Thesis accepted by
the University College Dublin, Ireland

Springer

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"Synthesis of (+)-Perillyl Alcohol from (+)-Limonene" Geoghegan, K.; Evans, P. *Tetrahedron Lett.* **2014**, *55*, 1431–1433. (**Chapter 5**)

Supervisor's Foreword

In the area of organic chemistry one major challenge we are being asked to address is to assemble potentially useful molecules in ways which generate molecular complexity in sequences that are as efficient as possible. Kimberly Geoghegan's doctoral thesis describes our efforts associated with this challenge for the preparation of amino containing compounds incorporating an aromatic ring. This type of structural motif (frequently encountered in natural products) is of interest since, based on similarity to the neurotransmitters dopamine and serotonin (5-HT), it represents a useful template to search for central nervous system activity. In relation to this we have developed a sequence which combines the temporary protection of an otherwise basic and nucleophilic nitrogen atom as its aryl sulfonamide derivative. The aromatic ring portion of this sulfonamide unit is then united with an alkene originating from the amine portion of the skeleton using the intramolecular Heck olefination reaction. The product of this two-step operation is a cyclic sulfonamide (also known as a sultam) and due to the nature of the Heck reaction it incorporates a new alkene. As Chap. 2 in this thesis details, we have uncovered an interesting regioselectivity in the latter reaction and have studied this for a series of substrates that are unbiased in terms of the size of the newly formed ring. This investigation demonstrated that the outcome of the Heck process is controlled by the substitution pattern of the alkene and very high levels of selectivity, in relation to the new carbon–carbon bond, are typically observed which do not seem to be sensitive to alkene polarisation. DFT calculations were performed by our collaborator (Prof. Ibon Alkorta) to attempt to shed light on the reaction sequence, the results of which are presented. Chapter 3 describes the development of a method to turn-over the selectivity observed in the intramolecular Heck reaction that relies on the activation of the new alkene as a bromonium, or an iodonium ion. Akin to the types of rearrangements prevalent in terpene chemistry, results suggest that this activation triggers a 1,2-carbon bond shift and that the intermediate carbocation can then undergo either interception with a nucleophile, or loss of a proton. This outcome depends on the reaction conditions and the particular substrate employed. Apart from halo-functionalization described, the newly formed Heck adduct alkene,

unsurprisingly, can also be converted into the corresponding alkane. One way to do this is to use a heterogeneous palladium source in the presence of hydrogen gas. The fact that the intramolecular Heck reaction was also performed using the same transition metal made us wonder whether both these processes could be performed sequentially using the same palladium source in the same reaction vessel. This type of reaction has recently been reported by others and Chap. 4 describes our results in transferring this one-pot Heck olefination–hydrogenation sequence to our sulfonamide substrates. Additionally, the transfer of this chemistry, which overall represents a means of performing a reductive Heck reaction, to intermolecular examples is also described. Finally, in Chap. 5, we explain how all these ideas and findings are brought together and combined with the reductive removal of the temporary amino-protecting and conformationally organising sulfonyl group (from the cyclic sulfonamide scaffold) in order to produce a variety of aryl-substituted amines. Particularly, the synthesis of the *Sceletium* alkaloids: mesembrane, mesembranol and mesembrine are detailed.

Work building on areas contained within this volume is underway. For example, we are preparing alternative substrates in order to challenge the regioselectivity found in the intramolecular Heck reaction. We are investigating the reasons for the partial aromatic methoxy-cleavage encountered during the sulfonyl tether removal and are attempting to design reaction conditions that either circumvent this or that completely lose the ether substituent. In addition, we aim to use a conceptually similar temporary templating effect with units other than the sulfonyl group.

Dublin, May 2014 Dr. Paul Evans

Contents

Abbreviations

δ	Chemical shift in ppm downfield from TMS
°C	Degrees Celsius
Δ	Heat
))))	Ultrasound sonication
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
atm.	Atmosphere
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bp	Boiling point
brsm	Based on recovered starting material
Bu	Butyl
ca.	Circa
Cbz	Carbobenzyloxycarbonyl
$CDCl_3$	Deuterated chloroform
c-Hex	Cyclohexane
COSY	Correlation spectroscopy
d	Doublet (spectral)
dba	Dibenzylidene acetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
dd	Doublet of doublets (spectral)
dep.	Deposition
DIB	(Diacetoxyiodo) benzene
DFT	Density function theory
DIBAL	Diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide

DMP	Dess–Martin periodinane
DMSO	Dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
equiv.	Equivalents
g	Gram(s)
h	Hour(s)
HFIP	Hexafluoroisopropanol
HRMS	High resolution mass spectroscopy
Hz	Hertz
i	Iso
IR	Infrared (spectroscopy)
J	Coupling constant
LDA	Lithium diisopropylamine
Li-naph	Lithium-naphthalenide
M	Molar
m	Multiplet (spectral)
m-CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Mega Hertz
min.	Minute(s)
mL	Millilitres
mmol	Millimoles
Mp	Melting point
MVK	Methyl vinyl ketone
MW	Microwave
Na-naph	Sodium-naphthalenide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nuc	Nucleophile
o-tol	*Ortho*-toluene
p	Para
PDC	Pyridinium dichromate
Ph	Phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	Parts per million
p-Ts	*p*-toluenesulfonyl
Pyr	Pyridine
q	Quartet (spectral)
quant.	Quantitative

RCM	Ring-closing metathesis
R_f	Retention factor
rt	Room temperature
s (br)	Broad singlet (spectral)
s	Singlet (spectral)
SSRI	Selective serotonin re-uptake inhibitor
t	Triplet (spectral)
t	Tert
TBS	*t*-butyldimethylsilyl
Tf	Trifluoromethane sulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
Ts	Tosyl
TS	Transition state

Chapter 1
Introduction

1.1 Alkaloids

Alkaloids are a class of naturally occurring organic compounds that possess a basic nitrogen atom within their structural motif. Apart from their abundance in the natural world they find uses as pharmaceuticals and are used for inspiration for structural targets. Naturally occurring alkaloids can often be isolated from natural sources relatively easily via simple acid-base extraction. However, the quantities obtained are often minute. These compounds can be complex in structure and have posed synthetic challenges for organic chemists for decades. In many cases the synthetic chemist can provide samples of the natural product for more detailed biological evaluation and are in a unique position to alter structure—preparing isomers and structural analogues, for example (Fig. 1.1).

1.2 *Sceletium* Alkaloids

Mesembrine **1** is a naturally occurring alkaloid isolated from the *Sceletium* plant species, which are found in the southern regions of Africa [1, 2]. Historically, these plants have been used to make a concoction known as *Channa*, or *Kougoed*, which literally means "to chew". Early reports have linked the effects of *Kougoed* to those displayed by cannabis and cocaine [2], and more recent studies have demonstrated that this naturally occurring alkaloid behaves as a selective serotonin re-uptake inhibitor (SSRI) [3, 4].

Mesembrine **1**, $[\alpha]_D$ −55 (MeOH) [1], is the major alkaloid found in *S. namaquense*, but has also been isolated from other related plants such as *S. tortuosum* and *S. expansum*. Mesembrine **1** was first isolated in 1914 by Zwicky and co-workers, who assigned **1** the chemical formula $C_{16}H_{19}NO_4$. This was later reassigned $C_{17}H_{23}NO_3$, on the basis of combustion analysis, additionally, the

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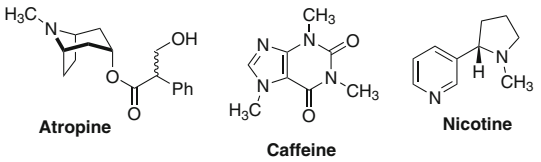


Fig. 1.1 Examples of alkaloids

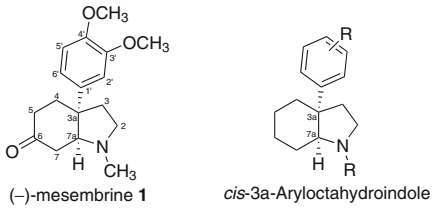


Fig. 1.2 (−)-mesembrine

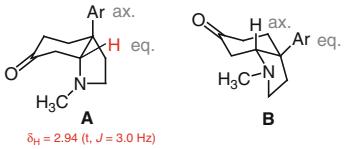


Fig. 1.3 Conformers of mesembrine

presence of the ketone functional group was confirmed by infrared (IR) spectroscopy.

Through degradation studies, the structure of the alkaloid **1** was elucidated as *N*-methyl-3a-(3′,4′-dimethoxyphenyl)-6-oxo-*cis*-octahydroindole by Popelak et al. (Fig. 1.2). The presence of the *cis*-ring structure allows two conformers of **1** to exist in the ground state (A and B, Fig. 1.3).

Extensive NMR studies showed that the proton at C-7a of mesembrine appeared as a triplet at 2.94 ppm with a coupling constant of 3.0 Hz, indicating that an equatorial position was preferentially adopted by this proton and therefore the aryl group is axial.

There have been a number of bases isolated from the *Sceletium* family, and these have been categorised, based on ring-structure, into four groups named after their parent compounds (Fig. 1.4) [5].

The mesembrine subgroup is the largest class of these alkaloids. Mesembrine **1** was the first alkaloid of its group to be fully characterised. It should be noted that the name ‘mesembrine’ does not follow systematic contemporary chemical nomenclature, which is based on mesembrane **2** being the basic ring structure for these type of alkaloids (Fig. 1.5).

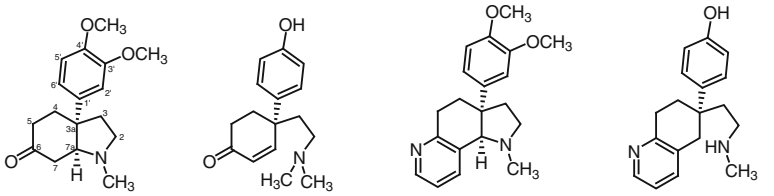


Fig. 1.4 *Sceletium* alkaloids

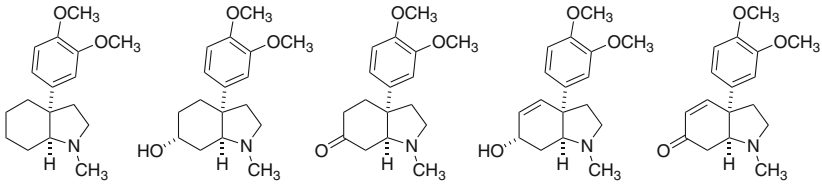


Fig. 1.5 Mesembrine alkaloids

Based on this system **1** should be named mesembranone and indeed this name has also been used [6], however, due to the substantial literature existing for this alkaloid, mesembrine was adopted.

The biosynthetic pathway for the mesembrine alkaloids was established through a combination of radiolabelling experiments and degradation studies, which identified phenylalanine, tyrosine and methionine as the amino acids that constitute the structural units of these alkaloids (Fig. 1.6) [1].

Mesembrine contains the *cis*-3a-aryloctahydroindole nucleus (shown in Fig. 1.7) and has been a popular synthetic target for several decades [7–22]. The main challenge in the synthesis of these alkaloids is the controlled construction of the

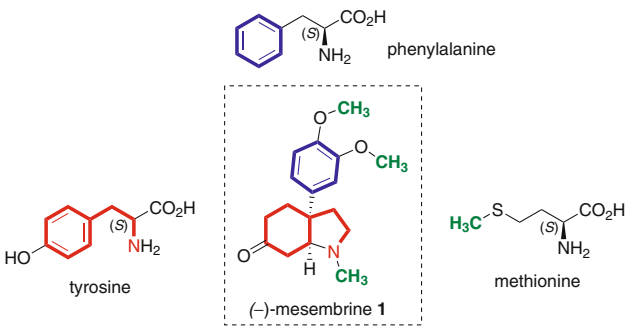


Fig. 1.6 Biosynthesis of (−)-mesembrine

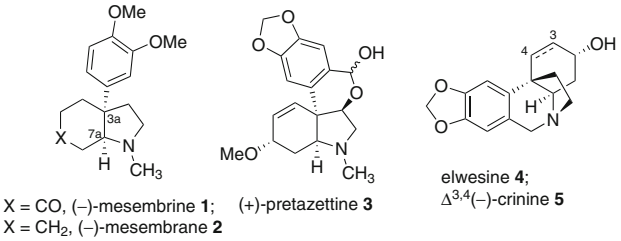


Fig. 1.7 *cis*-Aryloctahydroindole containing alkaloids

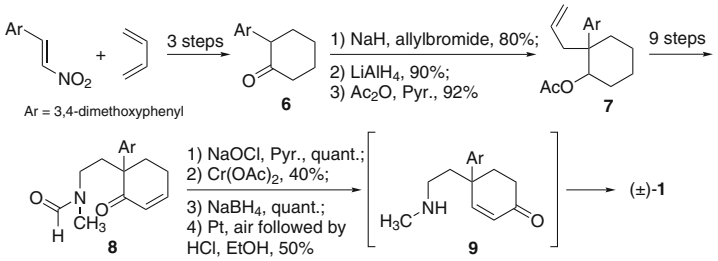
sterically hindered, benzylic, quaternary stereogenic centre [23–26]. The *Sceletium* alkaloids are closely structurally related to the *Amaryllidaceae* alkaloids, such as pretazettine (**3**) and the crinane-type alkaloids (**4** and **5**) (Fig. 1.7), where the *cis*-3a-aryloctahydroindole framework is embedded within these structures [1, 27, 28].

In the following sections, a review featuring notable syntheses of mesembrine **1** are presented.

1.3 The First Total Synthesis of Mesembrine

The first synthesis of mesembrine **1** was carried out in a 20 step linear sequence published in 1965 by Shamma and Rodriguez (Scheme 1.1) [7].

The synthesis begins by the conversion of nitrostyrene and butadiene, in 3 steps, into α-aryl ketone **6**. Subsequent mono-alkylation of **6** proceeded regioselectively at the more substituted carbon, thereby generating the quaternary carbon-centre necessary for the synthesis of the natural product. Ketone reduction, followed by acetylation produced compound **7** (66 % yield from **6**). Intermediate **7** was then converted in 9 steps into ketoamide **8**, which underwent epoxidation upon treatment with sodium hypochlorite and pyridine. The epoxide (not shown) underwent reduction followed by a platinum-catalysed oxidation and an acid mediated elimination reaction yielding enone **9**, which cyclised to give (±)-mesembrine (20 % yield from **8**).



Scheme 1.1 Shamma and Rodriguez synthesis of (±)-mesembrine

1.4 Annulation of Endocyclic Enamine

In 1968, Stevens and Wentland reported a thermal rearrangement of a cyclopropyl imine as their key step to access (±)-mesembrine **1** (Scheme 1.2) [8].

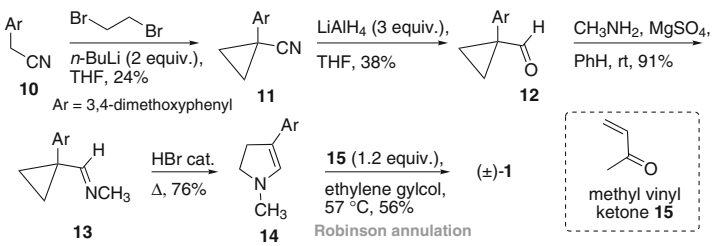
Cyclopropane **11** was directly accessed via a bis-alkylation reaction of the lithium salt of **10** with ethylene bromide in a low 24 % yield. Nitrile reduction to aldehyde **12** was effected using an excess of $LiAlH_4$ in THF (38 %), which in the presence of methylamine in refluxing benzene, afforded imine **13** in 91 % isolated yield. The rearrangement of cyclopropyl imine **13** was effected by refluxing the imine in the presence of catalytic amounts of hydrobromic acid which generated enamine **14** in 56 % yield. To complete the synthesis of the natural product, Robinson-type annulation of enamine **14** with methyl vinyl ketone **15** in ethylene glycol produced (±)-mesembrine (**1**) in 56 % isolated yield. It is in this step that the requisite quaternary carbon centre is formed, along with the fusion of the 5-membered heterocycle with the C-4 unit of **15** to give the octahydroindole skeleton.

Simultaneously, an almost identical route to this alkaloid was published by Keely and Tahk [29]. Another three groups target the synthesis of **1** and use the Robinson annulation strategy to complete the synthesis of the alkaloid [10, 30, 31].

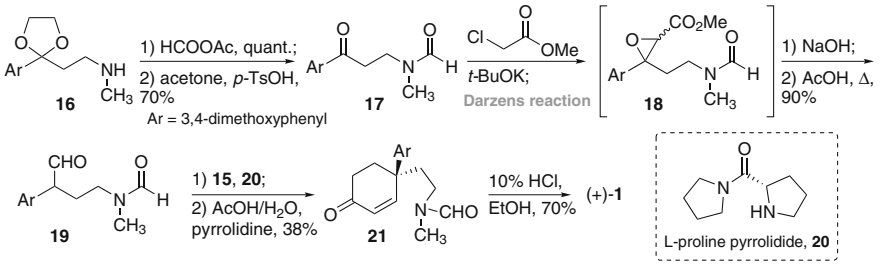
1.5 First Asymmetric Synthesis of Mesembrine

In 1971, the first asymmetric synthesis of mesembrine **1** was reported by Yamada, which utilised amino acid derived organocatalyst **20** in the synthetic process to access the unnatural enantiomer ((+)−**1**) (Scheme 1.3).

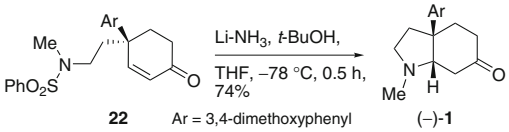
The key intermediate for this synthesis **16** was prepared in a total of 8 steps from bromoveratrole. As depicted in Scheme 1.3, *N*-formylation followed by acetal deprotection gave ketone **17**. A Darzens-based homologation strategy was performed using methyl 2-chloroacetate and potassium *t*-butoxide and ketone **17** furnishing α,β-epoxy ester **18**. Saponification followed by decarboxylation/epoxide fragmentation yielded aldehyde **19** in 90 % isolated yield from **18**. An asymmetric



Scheme 1.2 Stevens and Wentland synthesis of (±)-mesembrine



Scheme 1.3 Yamada synthesis of (+)-mesembrine



Scheme 1.4 Cyclisation under dissolved metal conditions

Robinson annulation reaction of **19** with methyl vinyl ketone **15** was carried out using L-proline pyrrolidine **20**, which gave optically active cyclohexenone **21**, $[\alpha]_D$ +12.7 (c = 1.48, MeOH), in 38 % yield. With the essential chiral quaternary centre set, the synthesis was completed by the treatment of **21** with ethanolic hydrochloric acid to afford (+)−**1** (70 % yield, $[\alpha]_D$ +16.1 (MeOH). No ee value was reported for synthetic (+)−**1** by the authors.

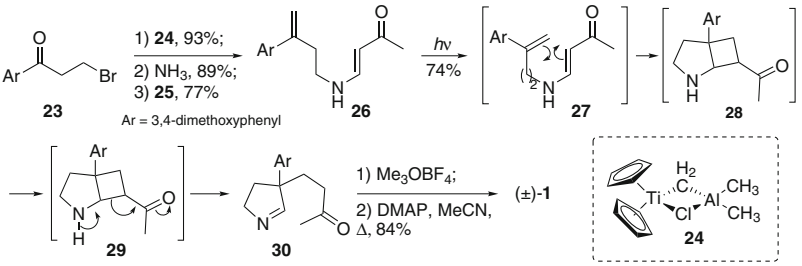
The preparation of similar chiral cyclohexenones leading towards asymmetric syntheses of mesembrine are prevalent in the literature (see also Sect. 1.7) [17, 18, 32–36]. A notable example, with regards to our studies, is the synthesis by Langlois et al. where detosylation of **22** under Birch-type conditions, followed by cyclisation, furnish the synthesis of (−)−**1** (Scheme 1.4).

Under these conditions it is appreciated that both enones [20] and aromatic functional groups are readily reduced, which were not observed in the above example.

1.6 Photocycloaddition of Vinylogous Amides

In 1988, Winkler et al. reported a new method for the formation of nitrogen-containing ring systems via an intramolecular photocycloaddition of vinylogous amides. This strategy was applied to the synthesis of racemic mesembrine **1** (Scheme 1.5) [11].

As outlined above, a methenylation reaction of **23** with the Tebbe reagent **24** gave styryl bromide (not shown) in 93 % yield. This material was treated with ammonia and was then further alkylated with 4-chloro-3-buten-2-one **25** yielding photosubstrate **26** in 77 % yield. Irradiation of a 0.026 M solution of **26** in MeCN



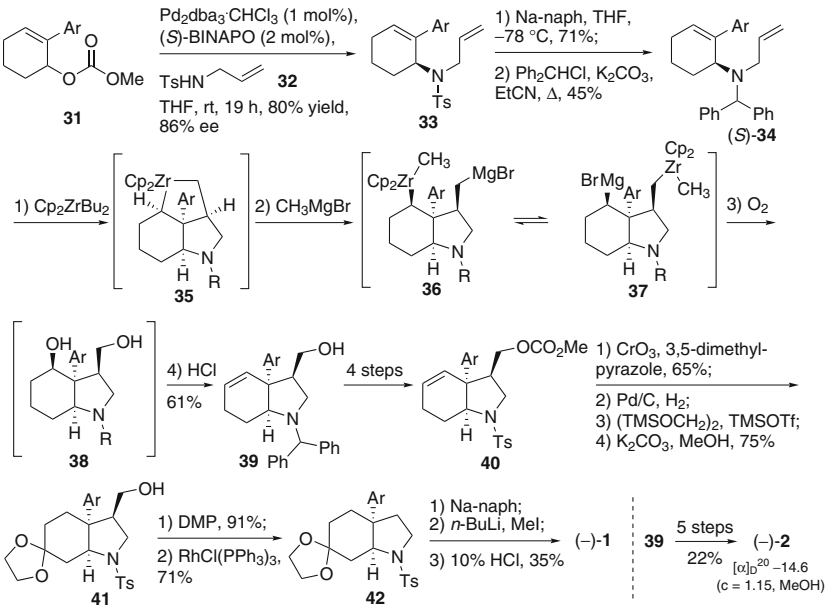
Scheme 1.5 Winkler synthesis of (±)−**1**

with a mercury lamp led to **27** via a [2 + 2]-cycloaddition reaction. This intermediate then undergoes a *retro*-Mannich reaction (**28** → **29**) facilitating the formation of ketoimine **30** in 74 % yield containing the requisite quaternary carbon centre. Methylation with trimethyloxonium tetrafluoroborate, followed by cyclisation in refluxing MeCN in the presence of 4-dimethylaminopyridine (DMAP) produced mesembrine **1** in 84 % yield.

1.7 Zirconium-Promoted Cyclisation

In this report, Mori et al. present the total syntheses of both racemic and (−)-mesembrine **1** and (−)-mesembrane **2**. There are two keys steps in this synthesis; a palladium-catalysed enantioselective allylic substitution reaction, and a zirconium-promoted cyclisation to access the hexahydroindole core of these *Sceletium* alkaloids (Scheme 1.6) [13, 37].

Allylic carbonate **31** was treated with a mixture of Pd(0), (*S*)-BINAPO and *N*-tosylallylamine **32** in THF to give (*S*)-**33** in 80 % isolated yield and 86 % ee. Detosylation was effected with sodium naphthalenide, and the free amine (not shown) was converted into diene **34**. Recrystallisation of this material from methanol gave **34** with an increased ee of 99 % with 79 % recovered material. The key cyclisation cascade proceeded by adding diene **34** to a THF solution of Cp_2ZrBu_2 at −78 °C (**34** → **35**). Zirconocycle **35** was then treated with methylmagnesium bromide which promotes a transmetalation reaction, which equilibrating between intermediates **36** and **37**, are then trapped as the diol **38** upon treatment with O_2, and isolated as alcohol **39** after hydrolysis in 61 % isolated yield. The large substituent on the nitrogen atom was found to be necessary for the success of this cyclisation reaction. From this intermediate both (−)-mesembrine **1** and (−)-mesembrane **2** (see Fig. 1.7) can be accessed. For the synthesis of (−)−**1**, a chromium-catalysed allylic oxidation of **40** (synthesised in 4 steps from **39**) gave the corresponding enone (not shown) in 65 % yield, which was subjected to hydrogenation and ketalization to furnish **41**. DMP oxidation of the primary alcohol, and subsequent rhodium-catalysed deformylation gave ketal **42**, which was converted into (−)-mesembrine **1**, $[\alpha]_D$ −53.0 (c = 0.24, MeOH) in 3 steps in 35 % overall yield.

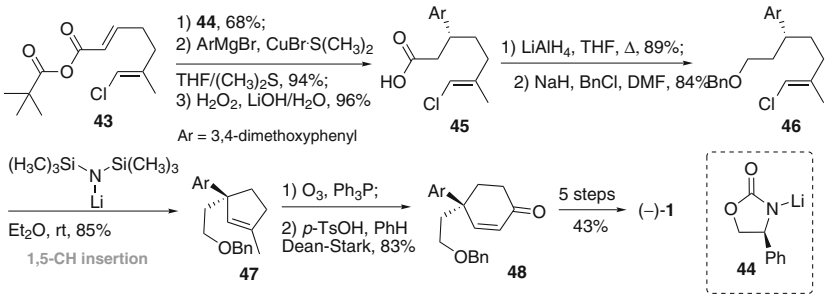


Scheme 1.6 Mori's synthesis of (−)-mesembrine **1** and (−)-mesembrane **2**

1.8 C–H Insertion Construction of Quaternary Carbon Centres

Taber and Neubert presented an intramolecular alkylidene C-H insertion strategy for the enantioselective construction of quaternary centres and applied this to the synthesis of (−)−**1** (Scheme 1.7) [15].

As outlined above, the mixed pivalic acid anhydride **43** reacted with the lithium salt of oxazolidinone **44** (68 %) and the resultant heterocycle (not shown) then underwent a diastereoselective conjugate addition reaction with a Grignard reagent



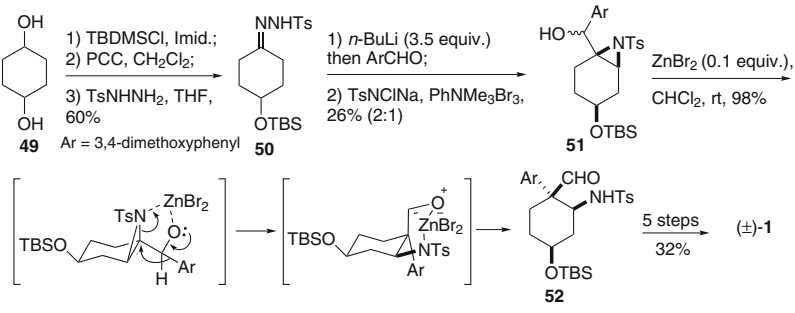
Scheme 1.7 Taber's enantioselective synthesis of (−)-mesembrine

in 94 % yield. Hydrolysis of the oxazolidinone amide furnished acid **45** in 96 % yield with a tertiary chiral centre present. Acid reduction to the free alcohol followed by Williamson ether formation gave adduct **46**. In the presence of lithium hexamethyldisilazide (LiHMDS) at rt for 17 h produced cyclopentene **47** in 85 % yield. The authors state that this reaction proceeds with complete retention of stereochemistry (set in **46** → **47**). With the requisite all carbon-centre set an ozonolysis reaction of the double bond, followed by an acid-catalysed intramolecular Aldol condensation reaction furnished the chiral cyclohexenone **48** in 83 % yield. This material was converted in 5 steps to (−)−**1**, $[\alpha]_D$ −59.3 (c = 3.0, MeOH) in 43 % overall yield from **48**.

1.9 Stereocontrolled $ZnBr_2$-Catalysed Rearrangement of 2,3-Aziridino Alcohols

Tu et al. reported a Zinc-catalysed rearrangement of 2,3-aziridino alcohols to generate quaternary carbon centres and applied this strategy to the synthesis of *rac*-**1** (Scheme 1.8) [16].

Commercially available diol **49** was converted in 3 steps into hydrazone **50** in 60 % overall yield. A Shapiro reaction with 3,4-dimethoxybenzaldehyde and **50** produced an allylic alcohol (not shown), and subsequent aziridination gave **51** in 26 % yield, in a 2:1 mixture of isomers. The key rearrangement reaction was effected by treating a dichloromethane solution of **51** with catalytic amounts of $ZnBr_2$. This produced **52**, with an all carbon centre as a single diastereoisomer in 98 % yield. It is proposed that the Lewis basic oxygen and nitrogen atoms coordinate to the Lewis acidic $ZnBr_2$, allowing the system to adopt a conformer (as shown above in Scheme 1.8) which rearranges placing the aromatic moiety in an equatorial position. From **52** the synthesis of (±)−**1** was completed in 5 steps in 32 % overall yield.



Scheme 1.8 Tu's racemic synthesis of mesembrine **1**

1.10 Oxy-Cope/Alkylation Sequence for the Formation of Quaternary Carbon Centres

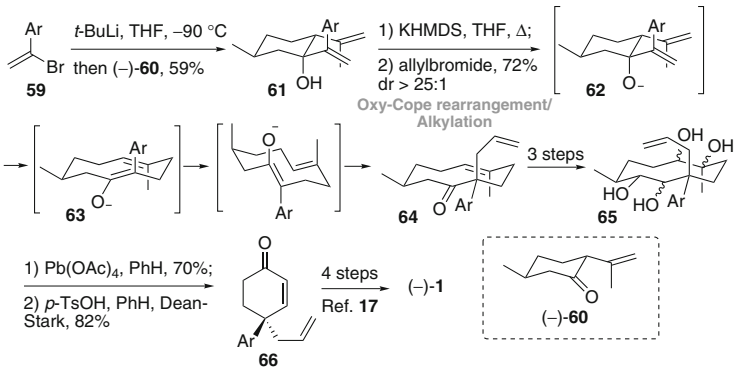
Barriault and co-workers demonstrated an elegant use of an oxy-Cope/alkylation sequence to diastereoselectively access quaternary centres, and applied this to a formal synthesis of (−)−**1** (Scheme 1.9) [19]. Chiral terpene (−)-isopugelone **60** was condensed with the lithium salt of **59** producing tertiary alcohol **61** in 59 % yield. The absolute stereochemistry of **61** was assigned by nOe studies. The treatment of this material with potassium hexamethyldisilazide (KHMDS) generated alkoxide **62** which gave the corresponding *E*-enolate **63**. Ring-inversion followed by face selective alkylation with allylbromide furnished ketone **64** (72 % yield, dr > 25:1) with the requisite quaternary centre found in the natural product **1**.

Oxidative cleavage of tetraol **65**, accessed in three steps from **64**, in the presence of $Pb(OAc)_4$ followed by an acid-catalysed intramolecular aldol condensation reaction yielded enantiopure enone **66** in 57 % overall yield from **65**. This intermediate has been shown to access (−)−**1** by Taber et al. [17].

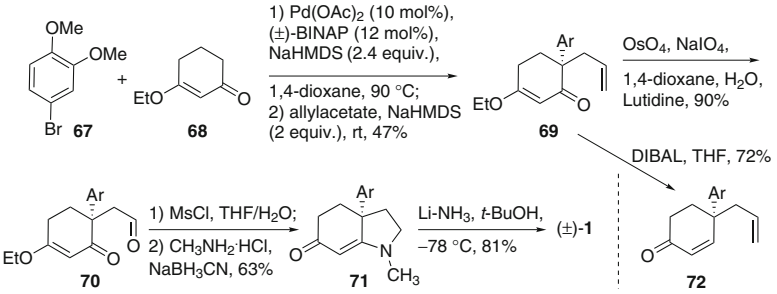
1.11 Palladium-Catalysed Sequential Arylation and Alkylation

In 2009, Zhang et al. employed a palladium-catalysed sequential arylation-alkylation of functionalised ketone **68** in their synthesis of (±)−**1** (Scheme 1.10) [38].

The palladium-mediated arylation-alkylation was conducted by treatment of ketone **68** with bromoveratrole **67**, utilising sodium hexamethyldisilazide (NaHMDS) as a base. Once the arylation reaction is complete, the addition of allylacetate and additional base to the cooled reaction mixture produced **69** in 47 % yield. Diisobutylaluminium hydride (DIBAL-H) reduction of **72** furnishes a known



Scheme 1.9 Barriault's Oxy-Cope rearrangement/alkylation sequence



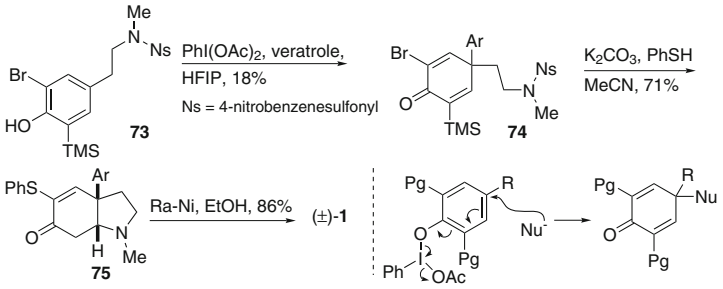
Scheme 1.10 Zhang's synthesis of (±)−**1**

mesembrane precursor **72** [17]. Alternatively, to complete the synthesis of mesembrine, oxidative cleavage of **69** produced aldehyde **70** (90 %) which, upon reductive amination, gave enone **71** in 63 % over 2 steps. Birch-type reduction converted vinylogous amide **71** to *rac*-**1** (81 %).

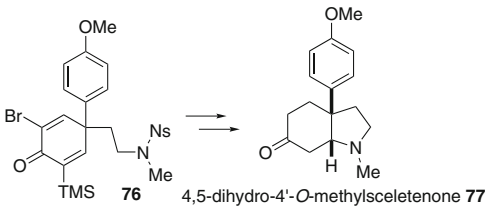
1.12 Aromatic Ring Umpolung

An aromatic ring umpolung method to generate quaternary centres has been utilised as a key step in the synthesis of (±)−**1** by Canesi et al. (Scheme 1.11) [22, 39].

The substrate **73** was designed to block the usually reactive *ortho* positions of the aromatic ring. Thus, when phenol **73** was treated with (diacetoxyiodo)benzene (DIB) in the presence of hexafluoroisopropanol (solvent), the nucleophile, veratrole, regioselectively added to the *para*-position of **73**, producing dieneone **74**, with an all carbon centre, in a low 18 % yield. Interestingly, when anisole was employed a higher yield of 42 % for compound **76** was observed. This material was carried through to access 4,5-dihydro-4′-*O*-methylsceletenone **77** (Scheme 1.12). To complete the synthesis of mesembrine **1** compound **74** was converted into **75**



Scheme 1.11 Canesi's synthesis of *rac*-**1**



Scheme 1.12 Synthesis of **77**

(71 %) which underwent desulfurisation and alkene reduction with Raney-nickel in ethanol to give (±)−**1** in 86 % yield.

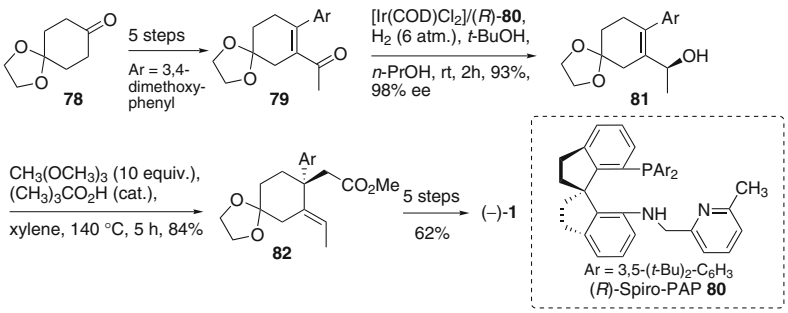
Enones of the type **74** have been used by other groups to access mesembrine [5, 30, 40–42].

1.13 Asymmetric Hydrogenation Approach

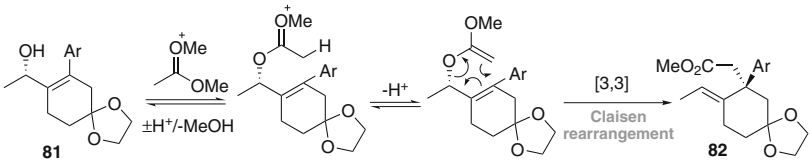
More recently, Zhou laboratories have reported an asymmetric hydrogenation as a key step in the enantioselective synthesis of (−)−**1** (Scheme 1.13) [21].

Methyl ketone **79**, prepared in 5 steps from commercially available **78**, was converted into chiral allylic alcohol (*S*)-**81** using [Ir(COD)Cl_2]/(*R*)-**80** in 93 % yield with 98 % ee. A Johnson-Claisen rearrangement reaction of **81** produced **82** in 84 % yield, with complete retention of stereochemistry (see Scheme 1.14).

This step must also be considered a key step in the synthesis, generating the necessary chiral quaternary centre found in the natural product. Natural mesembrine **1**, $[\alpha]_D$ −61.6 (c = 0.25, MeOH), was accessed in 5 steps from acetal **82** in 62 % overall yield.



Scheme 1.13 Asymmetric hydrogenation in the synthesis of (−)−**1**

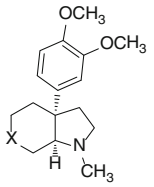


Scheme 1.14 Johnson-Claisen rearrangement

The syntheses described above focus on the formation of the all carbon quaternary centre present in mesembrine and are only a few examples chosen from the a significant selection present in the literature. They were chosen to give a flavour of the different strategies reported for the assembly of this small natural product.

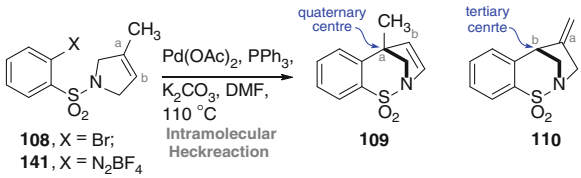
1.14 Aim

The main goal of this study was to investigate a novel route towards the natural product mesembrine **1**.



X = CO, (–)-mesembrine **1**;
X = CH_2, (–)-mesembrane **2**

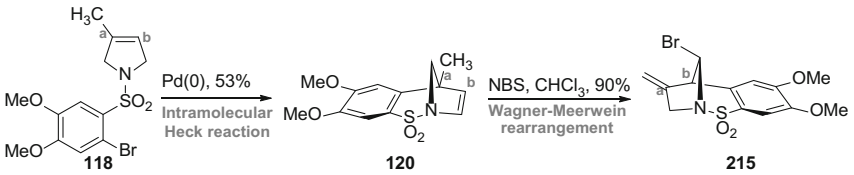
During these studies, it was found that the intramolecular Heck reaction of the unsymmetrical alkene **108** proceeds with high regioselectivity and leads preferentially to the formation of **109**, which contains a quaternary all-carbon-centre. Chapter Two describes studies aimed at probing the origin for this selectivity indicated that under a range of conditions there is an underlying propensity for the formation of a carbon-carbon bond at the most substituted carbon. However, by using diazonium salt **140** the alternate regioisomer **110** was observed preferentially, albeit in a low yield.



108, X = Br;
141, X = N_2BF_4

109 **110**

As discussed in Chapter Three the products of our Heck reaction (e.g. **120**) can be converted into their regioisomeric partners (e.g. **215**) through a bromonium ion mediated Wagner-Meerwein-type rearrangement.



A one-pot Heck olefination-hydrogenation protocol was also established during our research and is discussed in Chapter Four. In Chapter Five, the syntheses of the naturally occurring alkaloids (±)-mesembrane **2** and (+)-mesembrine **1** are described.

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Chapter 2
Regioselectivity in the Heck (Mizoroki-Heck) Reaction

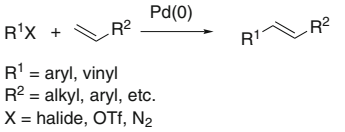
2.1 General Introduction

The alkenylation, or arylation of olefinic compounds in the presence of catalytic amounts of Pd(0) to give substituted olefins is referred to as the Heck (Mizoroki-Heck) reaction [1, 2]. This is a powerful tool used for the construction of carbon-carbon bonds, that often might otherwise be difficult to assemble [3–8]. Complex molecular structures [9–12], including those bearing asymmetric stereogenic centres [13] can be rapidly prepared and in addition, the reaction conditions used for this process can tolerate a wide range of functional groups. The active palladium catalyst can be generated in situ from air-stable precatalysts (e.g. $Pd(OAc)_2$), and reactions are usually carried out at elevated temperatures, in the presence of base (bulky amines or inorganic salts) and monodentate or bidentate phosphine ligands. One significant limitation of the reaction is that substrates cannot contain a β-hydrogen. However, recent reports suggest conditions that can circumvent this constraint, albeit for a limited range of substrates (Scheme 2.1) [14, 15].

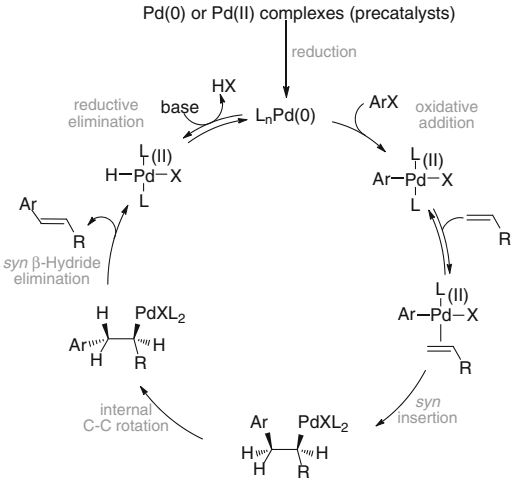
The precise mechanism of the Heck reaction is not fully understood, with the exact mechanistic pathways depending on reaction conditions and substrates employed [16–20]. However, Scheme 2.2 shows a simplified sequence of events for the catalytic cycle of the Heck reaction. This cycle begins by the formation of a homogenous palladium(0) complex as the catalytically active species (generated in situ by the reduction of Pd(II) salts (e.g. $Pd(OAc)_2$), or by employing a Pd(0)-precatalyst (e.g. $Pd(PPh_3)_4$).

The first step of the catalytic cycle is insertion of Pd(0) into the ArX bond, a step referred to as oxidative addition. The rate of oxidative addition of aryl halides depends on the nature of X: ArI > ArBr ≫ ArCl. Alkene association can then occur via dissociation of a ligand (L), followed by *syn*-insertion (also referred to as carbopalladation) which leads to a σ-alkyl-palladium(II) halide. The nature of alkene substitution, or regioselectivity, is dictated by this step. An internal C–C bond rotation brings an sp^3-bonded β-hydrogen *syn* to the palladium atom, which

K. Geoghegan, *Selectivity in the Synthesis of Cyclic Sulfonamides*,
Springer Theses, DOI 10.1007/978-3-319-10338-9_2



Scheme 2.1 Arylation/alkenylation of substituted olefins

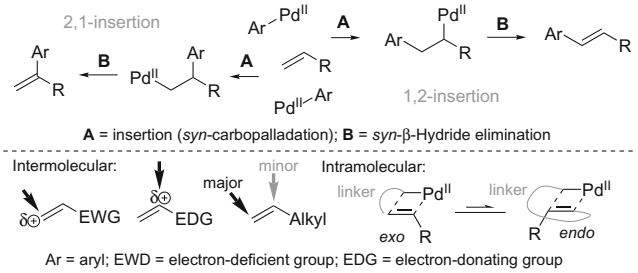


Scheme 2.2 A general representation of the catalytic cycle for a homogenous Pd(0) species in the Mizoroki-Heck reaction

then undergoes a β-hydride elimination reaction. This process can be reversible, which may lead to alkene isomerisation of the initially formed Heck products. Alkene dissociation, followed by base induced reductive elimination regenerates the active palladium(0) complex.

The carbopalladation step, which governs the regiochemical outcome of the newly formed carbon-carbon bond, is of interest. By design, stereogenic C–C bonds can be accessed with ease. Also the selectivity observed (stereo- and regio-selectivity) can shed light on the mechanism of the overall process. In a typical cross-coupling reaction of an aryl halide and an alkene (Scheme 2.3), it is thought that the carbopalladation event (insertion reaction, step A) is irreversible, and therefore the regiochemical outcome is dictated by this step.

There are several factors that affect the regioselective outcome of the Heck reaction. The electronic features of the alkene play a significant role. Typically, carbon-carbon bond formation occurs preferentially at the most electron-deficient carbon (indicated by arrow in Scheme 2.3) [1, 21, 22]. Steric effects will dominate with alkenes where bond polarisation is not as dramatic, for example aliphatic alkenes, leading to a mixture of regioisomeric products. For intramolecular examples, ring-size of the newly formed cycle is an additional factor in the regiochemical outcome of the reaction. The nature of the reaction conditions and



Scheme 2.3 Regioselectivity in the inter- and intramolecular Heck reaction

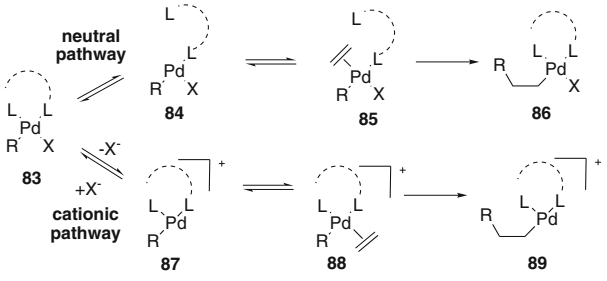
(*pseudo*) halide of the Heck precursor being employed also seem to be important, since these influence the identity, in terms of ligands and charge on the palladium atom of the active catalyst and thereby can affect the regiochemical outcome of the reaction.

2.2 Intermolecular Heck Reaction

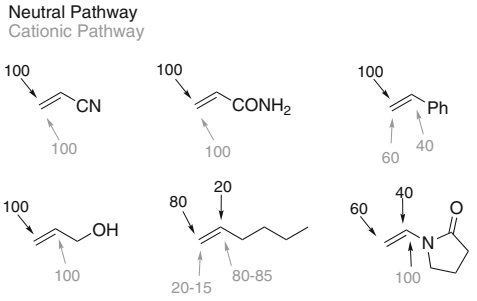
In a report by Cabri et al. two reaction pathways are proposed for the alkene coordination-insertion event (Scheme 2.4) [21].

In the neutral pathway olefin association to intermediate **83** can proceed via dissociation of one neutral ligand, generating neutral complex **84**. This pathway can be accessed by evoking halides such as I, Br and Cl, in the presence of phosphine ligands. In contrast, a cationic pathway involves dissociation of an anionic ligand (counterion) to give the cationic complex **87**. The use of triflates and halide scavengers (e.g. Ag and Tl salts when X is a halide) are thought to lead to this pathway. By accessing either pathway, differences in regioselectivity can be observed depending on the alkene substituent (Scheme 2.5).

These observations provide experimental evidence that the regiochemistry is related to the coordination-carbopalladation event.



Scheme 2.4 The alkene coordination-insertion process



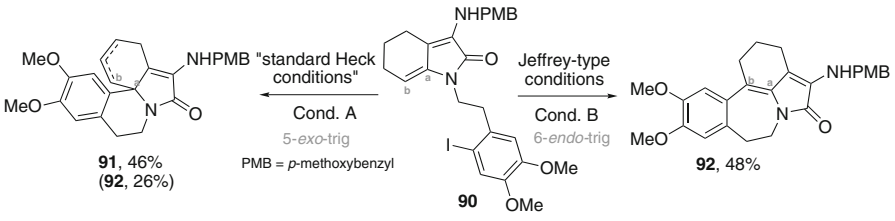
Scheme 2.5 Regioselectivity observed during arylation insertion process

2.3 Intramolecular Heck Reaction

The intramolecular Heck reaction is an efficient method for the construction of cyclic compounds containing an *endo*- or *exo*-cyclic double bond. A feature of this reaction is that sterically hindered tertiary [23] and quaternary [24] carbon stereocentres can be assembled. However, unlike the intermolecular Heck reaction, there are no general methods for turning over the regioselectivity in intramolecular reactions. While there are a few literature examples [25, 26] that probe this idea, the examples used are substrate specific and are not very general for synthetic applications.

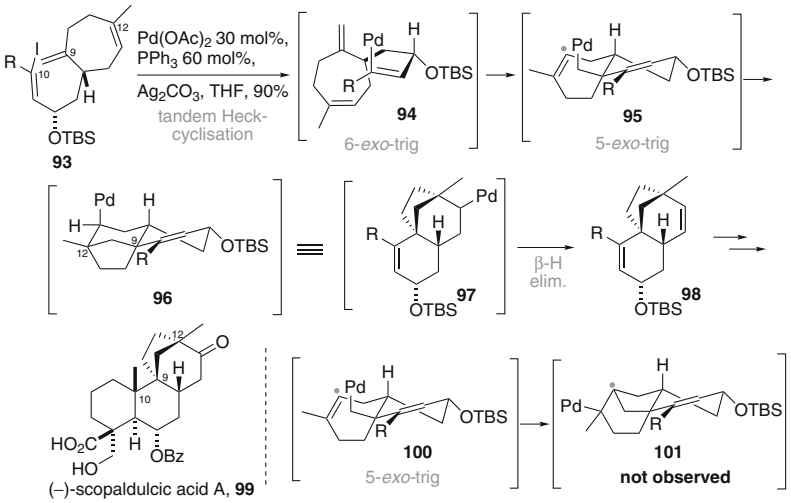
Generally, regioselectivity is governed by ring-size of the newly formed cycle (see Scheme 2.3) [4–7, 20, 27]. In one example, Rigby et al. showed that for a particular class of compound (**90**), they could obtain *exo*-adduct **91** as the major product under standard Heck conditions, and then reversed regioselectivity to obtain compound **92** solely, when Jeffrey-type conditions were employed ('ligand-free' conditions) (Scheme 2.6) [25].

A classic example of the intramolecular Heck reaction in action is Overman's synthesis of (−)-scopadulcic acid, whereby a tandem double Heck cyclisation (6-*exo*-trig followed by a 5-*exo*-trig) rapidly accesses the carbon skeleton found in the natural product **99** (Scheme 2.7) [28].



Cond. A: $Pd(OAc)_2$ (10 mol%), $P(o\text{-tol})_3$ (20 mol%), Et_3N (2 equiv.), $MeCN/H_2O$ (10:1), 80 °C
Cond. B: $Pd(OAc)_2$ (10 mol%), $n\text{-}Bu_4NCl$ (2 equiv.), KOAc (5.5 equiv.), DMF, 100 °C

Scheme 2.6 Rigby's example of 5-*exo* and 6-*endo*, reagent controlled intramolecular Heck reaction



Scheme 2.7 Overman's example of an intramolecular tandem Heck reaction

Following the initial 6-*exo*-trig cyclisation (**93** → **94**), a subsequent cyclisation onto the trisubstituted alkene yields **96**. However, this alkene is unbiased in terms of ring-size and insertion to either carbon of the alkene would proceed via a 5-*exo*-trig cyclisation. Carbopalladation at the least substituted carbon (labelled with a grey dot in **95**) would also proceed via an 5-exo-*trig* cyclisation, leading to intermediate **100**.

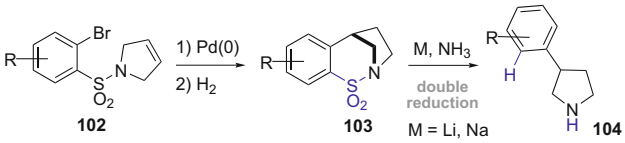
To date, what is lacking are examples where substrates are unbiased in terms of the ring-size of the new cycle formed (i.e. **95** → **96** or **101**). If substrates of this type could be designed, more information about the alkene-insertion event could be obtained.

2.4 Regioselectivity in the Intramolecular Heck Reaction of Sulfonamides

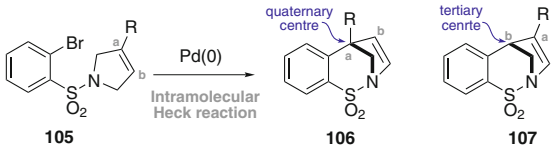
For several years, the Evans group have been interested in utilising a novel double reduction reaction of cyclic sulfonamides (of type **103**) in the preparation of substituted nitrogen-containing heterocycles (**104**) [29, 30]. An intramolecular Heck reaction of symmetrical alkenes of type **102**, followed by alkene hydrogenation, gave access to these substrates (**102** → **103**) (Scheme 2.8) [29].

Aryl-insertion (carbopalladation) to either alkenyl carbon atoms in **102** would proceed via a 6-*exo*-trig mode of cyclisation to provide, after hydrogenation, compound **103**.

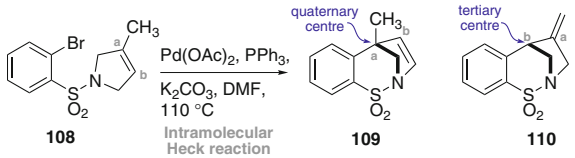
Replacing a hydrogen atom for an R-group on the alkene of **102** would generate an unsymmetrical alkene, e.g. **105**, where the carbon atoms are no longer chemically



Scheme 2.8 Evans' synthesis of aryl-substituted pyrrolidines



Scheme 2.9 Intramolecular Heck reaction of unsymmetrical sulfonamides

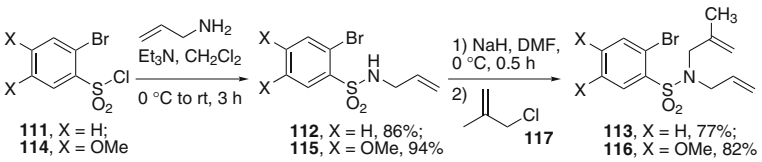


Scheme 2.10 Intramolecular Heck reaction of unsymmetrical sulfonamide **108**

equivalent (Scheme 2.9). Notably, the system is still unbiased in terms of ring-size; following an intramolecular Heck cyclisation of **105** could give **106** and/or its regioisomer **107**.

Preliminary results concerning this sequence, obtained by Erasmus student Nicolas Méral, where R = Me (**108**), showed that in the Heck reaction there is a high preference for the formation of the more sterically hindered compound **109** (Scheme 2.10). Carbon-carbon bond formation occurred at the most substituted carbon of the system (position a) in excellent yield. Only trace amounts of material attributed to its regioisomer **110** could be detected (obtained after insertion at position *b*).

To try to understand the unusual regioselectivity observed and to further probe the scope of the reaction shown above, synthetic sequence **108** → **109** was repeated. Two series of dihydropyrrole Heck precursors were synthesised, within which the substituents on the aromatic moiety were varied (Scheme 2.11). Sulfonamides **112** and **115** were prepared in high yields using commercially available allylamine, the appropriate sulfonyl chloride **111**, or **114** (prepared from bromoveratrole **67**) [29] and triethylamine as a base. Subsequent *N*-alkylation of sulfonamides **112** and **115** with 3-chloro-2-methylpropene **117**, utilising NaH in DMF, furnished diallyl compounds **113** and **116** in 77 and 82 % isolated yields, respectively.

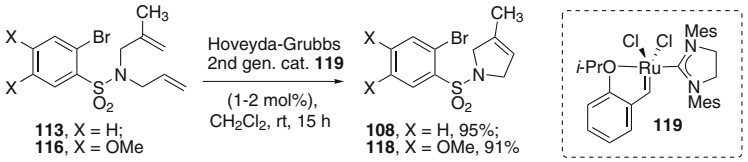


Scheme 2.11 Preparation of diallyl compounds **113/116**

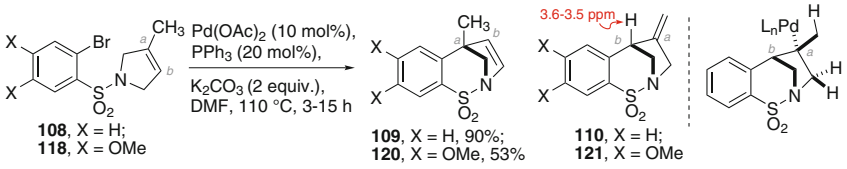
A ring-closing metathesis (RCM) reaction of **113** and **116** in the presence of catalytic amounts of the Hoveyda-Grubbs second generation catalyst [31] **119** in dichloromethane (0.05 M solution) at room temperature generated dihydropyrrole Heck precursors **108** (95 %) and **118** (91 %). No cross-metathesis products were isolated. This reaction is complete within a few hours with a catalyst loading of 10–15 mol%. However, catalyst loadings can be decreased to as low as 1–2 mol%, and, as a consequence, a longer reaction time is required (Scheme 2.12).

When Heck precursors **108** and **118** were submitted to standard Heck conditions ($Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 equiv.), DMF, 110 °C) the formation of cyclic sulfonamides **109** and **120**, possessing a quaternary all-carbon centre were observed in 90 and 53 % yields respectively (Scheme 2.13). The protons of the newly formed alkene present in **109** and **120** were observed as two doublets at approximately 6.4 and 6.3 ppm in the proton NMR spectra. Trace amounts of material corresponding to the regioisomeric products **110** and **121** (*exo*-cyclic alkene observed) could be detected in the ^1H NMR spectra of the crude reaction mixture (<5 %).

The Heck reaction of **108** can be also be performed with a lower catalyst loading of 1 mol% $Pd(OAc)_2$/2 mol% PPh_3 providing **109** in 84 % yield. Microwave irradiation [20] was briefly investigated as an alternative to standard conductive



Scheme 2.12 Ring-closing metathesis of **113/116**



Scheme 2.13 Regioselectivity in the intramolecular Heck reaction of sulfonamides **108/118**

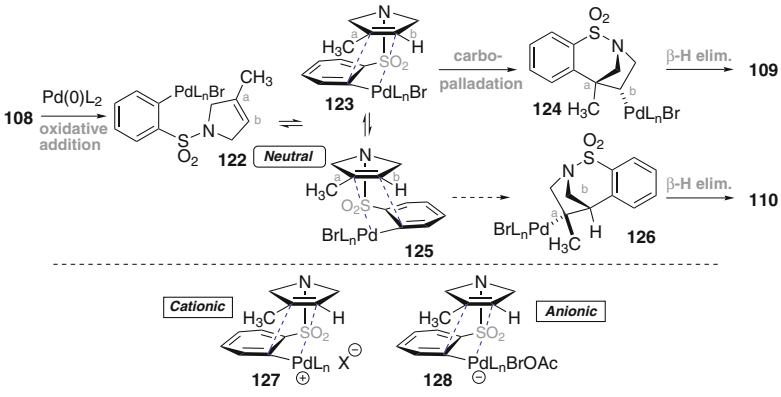
heating. Irradiation at 300 W at 125 °C for 25 min under otherwise identical reaction conditions gave an isolated yield of 62 and 68 % of **109** and **120** respectively.

Since both isomer **109/120** and **110/121** possess the same ring size and these reactions were carried out at elevated temperatures, the selectivity observed implies that there is an underlying preference for the formation of the quaternary isomer over the tertiary isomer.

Based on the generally accepted homogeneous pathway, which involves a coordinatively unsaturated palladium(0) species as the entity that undergoes oxidative addition with **108**, the formation of a neutral palladium(II) species (**122**) can be envisaged (Scheme 2.14).

Ligand dissociation, followed by alkene association could generate a complex of the type **123/125**. Carbopalladation (insertion step) may occur via conformer **123** or **125** to give intermediates **124** or **126**, respectively. Since carbopalladation is considered irreversible [18, 32], selectivity at this stage dictates the formation of **109**, which occurs following β-hydride elimination. Two alternatives to the neutral pathway have also been proposed. If X is a leaving group with weaker ligand donor properties, for example a triflate group, then a cationic reaction intermediate of type **127** is observed [21, 33]. This is of particular significance when employing bidentate ligands, chiefly exploited in the area of asymmetric synthesis [13]. Jutand and Amatore [16, 17] have proposed that under the conditions $[Pd(OAc)_2/3(PPh_3)]$ the identity of the palladium(0) species is the anionic complex $[Pd(OAc)(PPh_3)_2]^-$, which results in intermediates such as **128** undergoing carbopalladation. In addition to the homogeneous reaction intermediates, investigations into the high turnover numbers of some palladacycles (e.g. Herrmann-Beller palladacycle **130**) have suggested that nano-particulate colloidal palladium(0) may actually be the active catalyst [34, 35].

It is apparent that the choice of reaction conditions employed and the type of reaction substrate chosen influence the type of palladium(0) complex (**123/125**, **127** or **128**) that

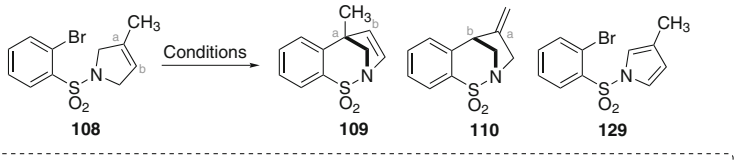


Scheme 2.14 Plausible reaction pathways for the regioselective carbopalladation

is undergoing carbopalladation (the regiochemical-establishing event). Based on this it was felt that the identity of the catalytically active palladium species participating in the initial oxidative addition step, and subsequent carbopalladation, might govern the regiochemical outcome of the reaction. Therefore, we initially aimed to uncover any effect the choice of reaction conditions would have on the regiochemical outcome of the cyclisation of **108** (Table 2.1).

As indicated in entry 1, when a palladium(0) source was used directly, there was no significant difference in the yield or regioselectivity to that observed in Scheme 2.10. A protocol by Danishefsky et al. [36] applying Pd/C as the catalyst gave only recovered starting material (entry 2). The use of palladacycle **130** also showed no dramatic difference in the regiochemical outcome (entry 3). A feature of catalyst **130** is extremely low loadings are often effective at higher temperatures (130 °C and above), and in fact result in a faster reaction [37–40]. However, in our hands, poor conversions were encountered for lower loadings of **130** (1–0.01 mol% at 130 °C). Replacement of K_2CO_3 with homogeneous amine bases (Et_3N and proton sponge **131**) proved detrimental to the isolated yields of **109** (entries 4 and 5).

Table 2.1 Intramolecular Heck reaction of **108**



Entry	Conditions	Product(s)[a] (% yield, ratio)
1	[$Pd(PPh_3)_4$] (10 mol%), K_2CO_3, DMF, 110 °C	**109** (72)
2	Pd/C 10% w/w (10 mol%), Et_3N, MeCN, 80 °C	**108** (85)
3	Herrmann-Beller cat. **130** (10 mol%), K_2CO_3, DMF, 110 °C	**109** (69)
4	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Et_3N, DMF, 110 °C	**109** (69)
5	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), proton sponge **131**, DMF, 110 °C	**109** (34)
6	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Ag_2CO_3, DMF, 110 °C	**109** (24), **108** (35), **129** (6)
7	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3, *n*-Bu_4NHSO_4, DMF-H_2O (9:1), 110 °C	**109** (83)
8	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3, PhMe, 110 °C	**109**/**110** (59, 85:15)[b]
9	$Pd(OAc)_2$ (10 mol%), P(*o*-tol)$_3$ (20 mol%), Et_3N, DMF, 110 °C	**109** (10), **108** (75)
10	$Pd(OAc)_2$ (10 mol%), PMe_3 (1M soln in THF, 20 mol%), K_2CO_3, DMF, 110 °C	**109** (56)
11	$Pd(OAc)_2$ (10 mol%), dppp **134** (20 mol%), K_2CO_3, DMF, 60 °C	**109** (88)
12	$Pd(OAc)_2$ (10 mol%), K_2CO_3, DMF, 110 °C	**109**/**110** (72; 88:12)[b]
13	$Pd(OAc)_2$ (10 mol%), (*R*)-BINAP **132** (20 mol%), K_2CO_3, DMF, 110 °C	**109**/**110** (91, 88:12)[b], 0% ee
14	[$Pd(dba)_2$] (10 mol%), (*R*)-BINAP **132** (23 mol%), PMP **133**, DMF, 110 °C[c]	**109** (41), 16% ee

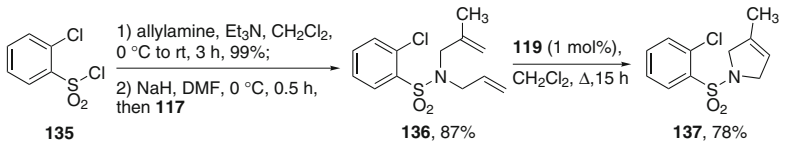
[a] Isolated yields after purification by column chromatography
[b] Ratio determined by ^{1}H NMR spectroscopy
[c] Reaction was conducted following three freeze-pump-thaw cycles

However, again regioisomer **110** was not detected in the reaction mixture. Thallium and silver salts [41] are often used as halide scavengers in these types of Heck processes generating cationic intermediates of the type **127**. As indicated in entry 6, the inclusion of Ag_2CO_3 led to an inefficient Heck process from which **109** was isolated in a low yield (24 %). The remaining mass balance was attributed to recovered starting material (35 %) and the isolation of pyrrole **129** (6 %), which is probably the product of a silver(I) mediated oxidation [42] of the dihydropyrrole ring.

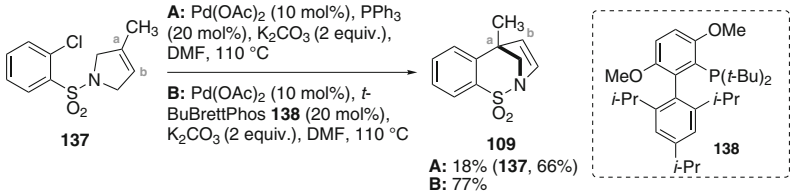
Conditions employed successfully to influence regioselectivity in intramolecular Heck reactions reported by Genêt et al. [43] and Evans et al. [26] (*n*-Bu_4NHSO_4, DMF/H_2O mixture) afforded no change in regiochemistry, yielding only compound **109** in 83 % yield (entry 7). Heck-type processes are usually performed in polar solvents, and under some reaction conditions, these solvents have been shown to stabilise the catalytically active intermediate [20]. Replacing DMF with toluene (chosen for its low dielectric constant) gave a chromatographically inseparable mixture of **109** and its regioisomer **110** in 59 % yield, in a 85:15 ratio (entry 8). Compound **109** was separated from **110** by recrystallisation. Characteristic shifts for the *exo*-cyclic methylene unit in **110** were observed as two doublets at 5.21 and 4.96 ppm, each with a ^2J-coupling constant value of 1.5 Hz (see Fig. 2.2). Applying electron-rich phosphine ligands, P(*o*-tol)$_3$ [44] and PMe_3 (entries 9 and 10), gave low to moderate yields for the formation of **109**. Bidentate phosphine ligand 1,3-bis (diphenylphosphino)propane (dppp) **134** gave only **109** in 88 % isolated yield (entry 11).

This survey of reaction conditions suggests that either there is an underlying preference for the formation of the quaternary isomer **109** (possibly via conformer **123** rather than **125**), or, that irrespective of the conditions employed, the same type of palladium species is responsible for the formation of **109** in each case. In relation to the latter, it has been suggested [34, 35] that for some examples the active catalyst is in fact nanoparticulate palladium(0) clusters, as opposed to the discrete, homogenous phosphine-bound monomeric species. Possible support for this argument was uncovered when ligand-free conditions (entry 12) gave a mixture of **109** and **110** in 72 % isolated yield in a ratio of 88:12. Asymmetric bidentate phosphine ligand (*R*)-BINAP **132** was studied since any enantioselectivity detected would be indicative of a step where the ligand is directly involved in the induction of asymmetry (i.e. directly bound to the metal centre). Replacing PPh_3 with (*R*)-**132** gave a racemic mixture of **109** and **110** in 91 % isolated yield in a ratio of 88:12 (entry 13). However, the use of conditions developed by Overman et al. [45]. yielded compound **109** (41 %) with a low enantiomeric excess (ee) of 16 % (entry 10), suggesting that a phosphine-bound arylpalladium(II) species is involved, at least in some part, in a process that converts **108**–**109**. The enantiomers of **109** were resolved by high-performance liquid chromatography (HPLC).

After an extensive study of a range of reaction conditions to convert bromide **108**, the less reactive chloride **137** was synthesised in order to investigate how the rate of oxidative addition might impact on the overall reaction (Scheme 2.14).



Scheme 2.15 Synthesis of dihydropyrrole **137**



Scheme 2.16 Cyclisation of aryl chloride **137**

The chloro-Heck precursor **137** was prepared using commercially available 2-chlorobenzene sulfonyl chloride as shown previously in Scheme 2.15.

Under identical conditions that furnished **109** from bromide **108** in 90 % yield (conditions **A** in Scheme 2.16), the use of chloride **137** gave **138** in a low 18 % yield. While it is appreciated that aryl chlorides are slow to undergo oxidative addition, it was reasoned that the electron-withdrawing effect of the *ortho*-sulfonamide functional group in **137** would assist with this process. Nevertheless, the use of electron-rich phosphine ligand *t*-BuBrettPhos **139** [46] gave **138** in 77 % yield (conditions **B**).

The reaction of halides **108/137** under a range of conditions gave exclusively, or in high selectivity, the quaternary regioisomer, even in examples with conditions thought to evoke a cationic pathway of type **127** (entries 5 and 6). It is well appreciated that the use of leaving groups triflates and nitrogen (diazonium salts) evoke a cationic palladium(0) species in the catalytic cycle of the Heck reaction. With this in mind, the Heck precursors **108/137** were modified to incorporate *pseudo*-halides (triflate and nitrogen groups, **139** and **140**). These labile leaving groups should not coordinate the intermediate arylpalladium(II) species (Fig. 2.1).

Aryl- and vinyl-triflates are routinely used as precursors for asymmetric Heck reactions. One classic example is the asymmetric construction of *cis*-decalin rings of type **142** by Shibasaki et al. in their synthesis of (+)-vernolepin [47]. The palladium catalysed arylation of olefins using arenediazonium salts is frequently referred to as the Matsuda-Heck reaction. Attractive features of this reaction are that aryldiazonium salts have a high reactivity at room temperature, and they do not require phosphine ligands to stabilise the active palladium species. This reaction has been employed in an intermolecular sense as the key step in Correia's racemic synthesis of the antidepressant paroxetine (Scheme 2.17) [48, 49].

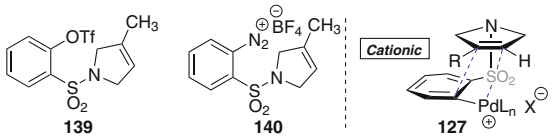
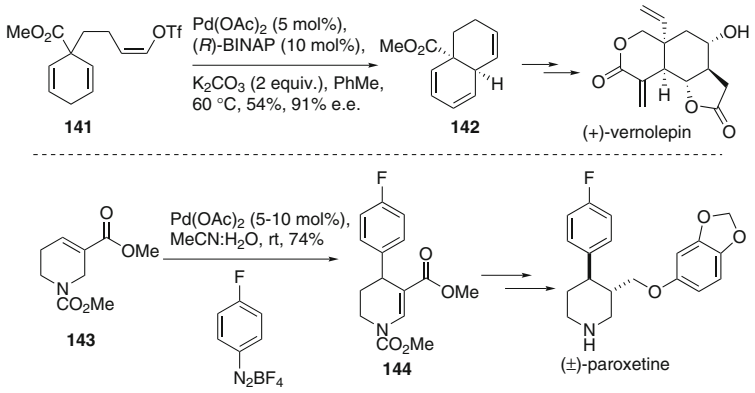


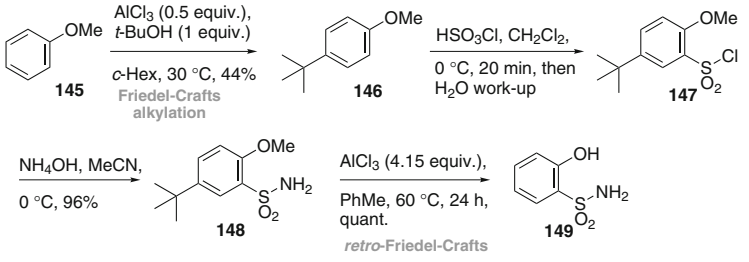
Fig. 2.1 Aryl triflate **139** and aryl diazonium salt **140**



Scheme 2.17 Examples of aryltriflates and aryldiazonium salts in total synthesis

Our first target, linked to the goal of probing how a cationic arylpalladium(II) species would participate in the intramolecular Heck reaction, was to synthesise the aryltriflate **139**. Our initial attempt towards this compound, was to use a Friedel-Crafts alkylation followed by a *retro*-Friedel-Crafts strategy [50] to access the required phenol functional group, is outlined in Scheme 2.18. This strategy allows us to perform electrophilic aromatic substitution at the *ortho*-positions by first blocking the *para*-position.

The reaction of anisole with *t*-butanol in the presence of Lewis acid $AlCl_3$ afforded the 1,4-disubstituted benzene **146** in a moderate 44 % isolated yield. Treatment of this material with chlorosulfonic acid, after water work-up, gave the

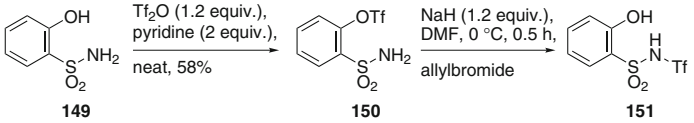


Scheme 2.18 Synthesis of 2-hydroxybenzene sulfonamide **149**

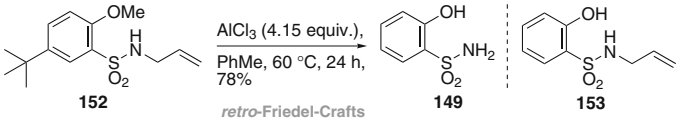
crude sulfonyl chloride **147** (one isomer detected in the ^{1}H NMR spectra), which was treated with excess ammonium hydroxide in MeCN to furnish sulfonamide **148** in an excellent 96 % isolated yield. A *retro*-Friedel-Crafts reaction, with $AlCl_3$ in refluxing toluene, cleaved both the *t*-butyl blocking group and the methyl ether, to afford 2-hydroxybenzene sulfonamide **149** [50] in quantitative yield. Conversion of phenol **149** to triflate **150** went smoothly (58 %). However, attempts to alkylate the nitrogen atom in compound **150** gave **151** as the sole product, resulting from migration of the triflate group (Scheme 2.19).

It was hoped that by pre-installing the allyl group (**152**) we could isolate the desired *N*-allyl sulfonamide **153** after the *retro* Friedel-Crafts reaction. However, only **149** was isolated resulting from cleavage of both alkyl groups and the nitrogen allyl group (Scheme 2.20).

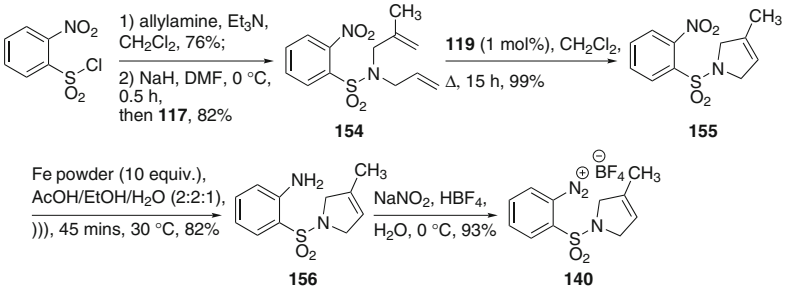
This route was then abandoned when it was realised, during our preparation of aryldiazonium salt **140** (Scheme 2.21), that the desired phenol **157** could be accessed from **140** via a Sandmeyer-type reaction.



Scheme 2.19 Attempts to alkylate sulfonamide **150**



Scheme 2.20 Attempts to access **153**



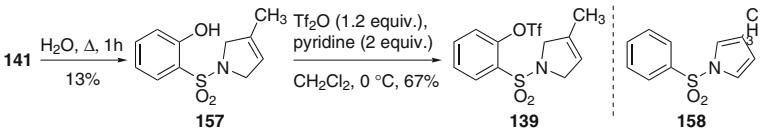
Scheme 2.21 Synthesis of tetrafluoroborate salt **140**

Commercially available 2-nitrobenzenesulfonyl chloride was converted into dihydropyrrole **155** over 3 steps using the standard chemistry we have developed to access these types of compounds. A chemoselective reduction of the nitro group was effected using Fe-AcOH in an ethanol/water mixture which gave **156** in 82 % isolated yield [51–53]. Diazonium-ion formation was achieved under typical conditions [48], obtaining salt **140**, after precipitation from cold ether/acetone, as a brown fluffy solid in 93 % yield. This material now serves two purposes for our studies; it can be used to access the requisite phenol for the preparation of aryltriflate **139**, and it can itself be used as a substrate in a Matsuda-Heck reaction.

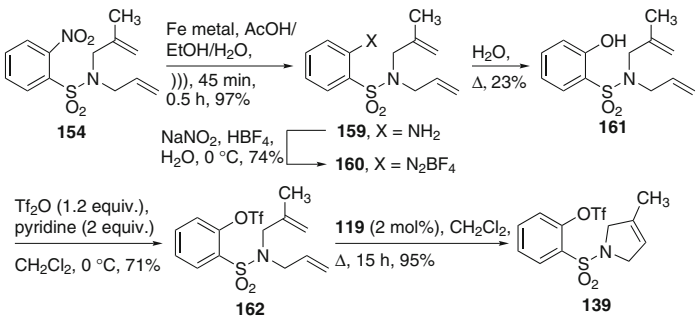
Heating **140** in water (either at pH 4 or 7) generated phenol **157** in poor yields of 10–20 %. *N*-sulfonylpyrrole **158** was always formed as a side product, along with coloured material that could not be characterised. Attempts to obtain higher yields for the hydrolysis of **140** to access the phenol were unsuccessful. Following a literature procedure [54], the use of Cu(II) salts gave only pyrrole **158** [55]. However, with sufficient material in hand, the synthesis of aryltriflate **139** was realised using triflic anhydride (Tf_2O) in neat pyridine in 67 % from phenol **157** (Scheme 2.22).

Unsatisfied with the poor yield obtained for the formation of phenol **157**, and to avoid the competing pyrrole formation reaction, it was reasoned that the unwanted oxidation, presumably favoured by aromaticity, would be avoided if the acyclic diazonium salt **140** was used instead (Scheme 2.23).

Nitro reduction of **154** cleanly gave aniline **159** in an excellent 97 % isolated yield, which was then converted to the diazonium salt **160** (74 %). Hydrolysis of **160** gave phenol **161** in low yields of 20–25 %. Nevertheless, the reaction was reproducible and thus provided sufficient material for our synthetic purposes.

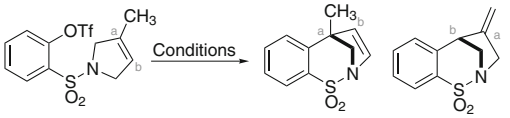


Scheme 2.22 Synthesis of aryltriflate **139**



Scheme 2.23 Alternative route to **139**

Table 2.2 Intramolecular Heck reaction of aryltriflate **139**



139 **109** **110**

Entry	Conditions	Product(s)[a] (% yield; ratio)
1	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3, DMF, 110 °C	**109** (15), **157** (55)
2	$[Pd(PPh_3)_4]$ (10 mol%), Et_3N, THF, 110 °C	**109** (14), **139** (50)
3	$[Pd(dba)_2]$ (5 mol%), (*R*)-BINAP **132** (11 mol%), PMP **133**, DMF, 110 °C	**109** (93), 17% ee

[a] Isolated yields after purification by column chromatography
[b] Ratio determined by ^{1}H NMR spectroscopy

Phenol **161** was converted into triflate **162** (71 %) and a ring-closing metathesis reaction provided **139** in 95 %.

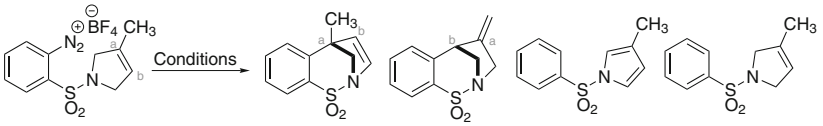
Cyclisation of **139** under our standard Heck conditions (Table 2.2, entry 1) provided quaternary regioisomer **109** in a low 15 % yield. However, phenol **157** was isolated as the major product (55 % yield).

We reasoned that this was due to the presence of water in the reaction conditions, a process presumably facilitated by the *ortho* electron-withdrawing sulfonyl moiety. A literature procedure for the cross-coupling of enoltriflates [56] gave poor conversion for the reaction, affording **109** and starting material **139** in 14 % and 50 % isolated yield respectively (in entry 2). In contrast, conditions developed by Overman et al. [23, 45]. (palladium(0)-BINAP) gave compound **109** in an excellent 94 % isolated yield, albeit with a low e.e. Interestingly, this result (entry 3) is almost identical in terms of yield and enantioselectivity observed with bromide **108** in Table 2.1, entry 14. In conclusion, unexpectedly employing triflate **139** in the Heck reaction in order to evoke a cationic reaction pathway (Scheme 2.14) did not alter the regiochemical outcome observed in Scheme 2.13.

Correia et al. recently reported the first example of a series of intramolecular Matsuda-Heck reactions [57]. With this report in mind, the Heck reaction was attempted on tetrafluoroborate **140**. Thus, treatment of tetrafluoroborate salt **140** with a palladium(0) source ($[Pd(dba)_2]$ or $[Pd(PPh_3)_4]$) in the presence of K_2CO_3 in acetonitrile at room temperature led to the isolation of **109** in low yields, in a process which was accompanied by the formation of pyrrole **158**, and dihydropyrrole **163** [55] as side products (Table 2.3, entries 1 and 2).

Switching the reaction conditions to sodium acetate in dichloromethane [58] led to reduced pyrrole formation, albeit compound **109** was isolated in a low 28 % yield (entry 3). No material attributable to regioisomer **110** was detected in entries 1–3. However, an interesting result was observed in entry 4 when base-free ligand-free conditions [59] were applied; a chromatographically inseparable mixture of **109** and **110** was isolated in 26 % yield. Analysis of the ^{1}H NMR spectra showed that for the first time we observed the formation of regioisomer **110** preferentially over the

Table 2.3 Intramolecular Heck reaction of **140**



140 **109** **110** **163** **158**

Entry	Conditions	Product(s)[a] (% yield; ratio)
1	$[Pd(dba)_2]$ (10 mol%), K_2CO_3, MeCN, rt	**109** (18), **158** (49), **163** (18)
2	$[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3, MeCN, rt	**109** (27), **158** (27), **163** (3)
3	$[Pd(dba)_2]$ (10 mol%), NaOAc, CH_2Cl_2, rt	**109** (28), **158** (10)
4	$Pd(OAc)_2$ (10 mol%), MeOH, 50 °C	**109/110** (26, 20:80)[b], **158** (37)

[a] Isolated yields after purification by column chromatography
[b] Ratio determined by ^{1}H NMR spectroscopy

formation of **109** in a 80:20 ratio. The formation of pyrrole **158** (37 %) was still a complication. Recrystallisation of the mixture of regioisomers from cyclohexane gave predominantly **110**, which allowed unambiguous assignment (see Fig. 2.2) and confirmation of the minor side-product encountered in Table 2.1 (entries **12** and **13**).

In summary, studies conducted towards altering the regiochemical outcome of the Heck reaction through condition screening and changing the aryl-leaving group indicated a high preference for the formation of the quaternary isomer **109**.

It was then felt that changing the alkenyl substituent on the dihydropyrrole ring might be instructive. Based on this, sulfonamides **164** and **165** were considered for their steric and electronic effect on the alkene (Scheme 2.24).

It was previously highlighted (Scheme 2.5) that the Heck arylation of styrenes generally occurs regioselectively at the least substituted carbon (labelled with a grey dot in compound **164**). While arylation of alkyl-substituted olefins produce a mixture of regioisomers, where sterics are thought to dictate regioselectivity, it seemed appropriate to investigate compound **164**.

Retrosynthetically, these compounds can be accessed by alkylating the common starting material in our sulfonamide synthesis (**112**) with electrophiles of the type **166/167**. These alkylating reagents are not commercially available. Thus α-bromo ketones **169** and **173** were prepared, using a literature procedure [60] (Scheme 2.25).

Alkylation of **112** with the appropriate electrophile, **169/173**, provided ketones **170** (65 %) and **174** (79 %). Analysis of the carbon NMR spectra data showed signals at 193 ppm (for compound **170**) and at 209 ppm (for compound **174**), characteristic for the ketone functional group. Conversion of the carbonyl functional group into a methylene unit was then attempted. Reaction of **170** under standard Wittig conditions, or with the highly reactive Tebbe reagent **176** [61, 62] was successful. However, synthetically useful quantities of **171** were not easily obtained. Interestingly, under the same set of conditions no reaction was observed for the *t*-butyl compound **174**, possibly due to the steric hinderance of the *t*-butyl group.

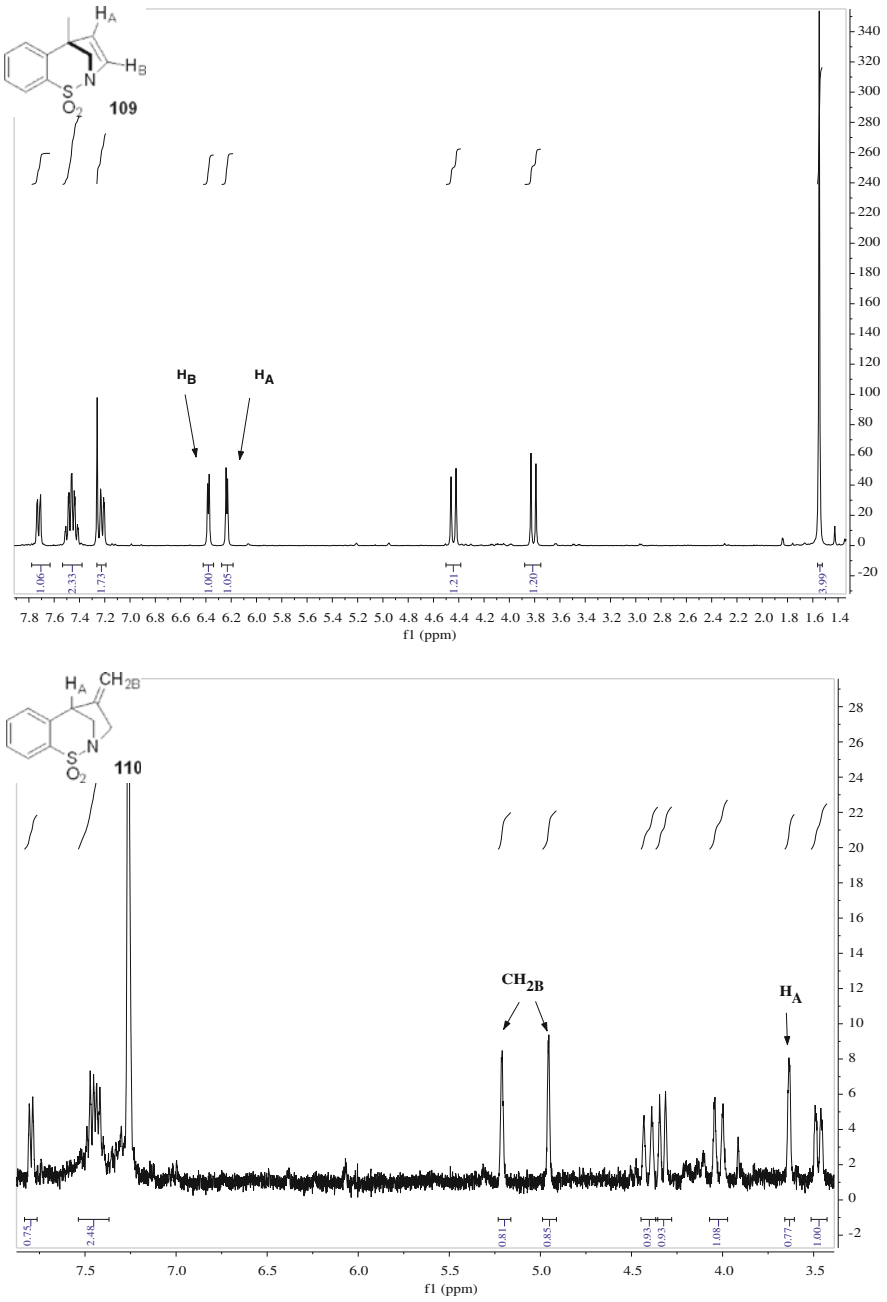
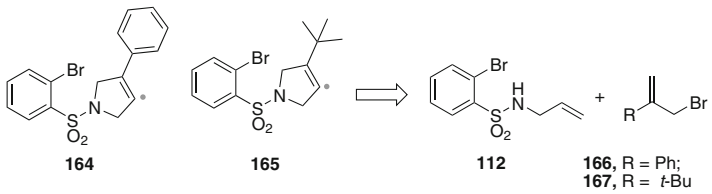
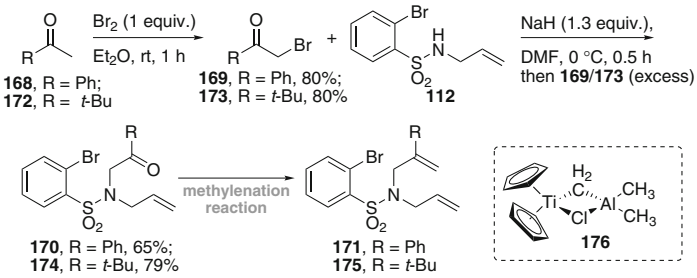


Fig. 2.2 ^{1}H NMR spectra of regioisomers **109** (*top*) and **110** (*bottom*)



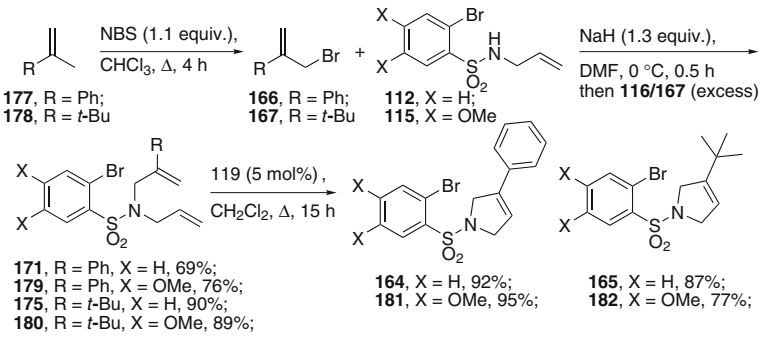
Scheme 2.24 Retrosynthetic analysis of compounds **164/165**



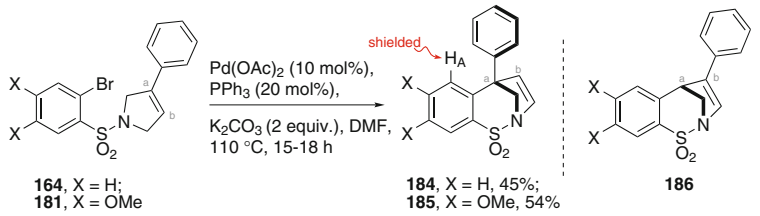
Scheme 2.25 Methylenation of ketones **170/174**

Direct access to electrophiles **166/167** was realised via allylic bromination (Wohl-Ziegler reaction) of commercially available olefins **177/178** with *N*-bromosuccinimide (NBS) **183** in refluxing chloroform [30, 63, 64] (Scheme 2.26). These alkylating agents were used without further purification and under our standard sulfonamide-alkylation conditions, using *N*-allyl sulfonamides **112** and (electron-rich) **115**, diallyl compounds **117/179/175/180** were obtained in moderate to high yields.

In terms of relating this sequence to that depicted in Scheme 2.12 (where R = Me), a higher loading (5 mol%) of ruthenium catalyst **119** in refluxing CH_2Cl_2 was required to obtain the desired Heck precursors **164/181/165/182** in high yields.



Scheme 2.26 Preparation of sulfonamides **164/181/165/182**



Scheme 2.27 Intramolecular Heck reaction of **164/181**

Firstly, the intramolecular Heck reactions of styrene-derivatives **164/181** were studied under our standard Heck conditions (Scheme 2.27).

The Heck reaction of both compounds **164** and **181** provided quaternary isomers **184** (45 %) and **185** (54 %), respectively, with traces of starting material also detected in the proton spectrum of the crude reaction mixture. None of the regioisomeric product **186** was isolated. Formation of the alkene was confirmed by ^{1}H NMR analysis by the presence of characteristic doublets in the alkene region. Interestingly, the aromatic proton, H_A, was found to be shielded by the adjacent phenyl ring and is observed in the ^{1}H NMR spectra as a singlet at 6.65 ppm for compound **184**, and at 6.11 ppm for compound **185**. The origin of this effect can be seen in the X-ray crystal structure of **184** (Fig. 2.3).

Next, the Heck reaction of **165** and **182** was considered and in both cases material for the tertiary regioisomers **188** and **190** was detected in the proton NMR spectra, along with quaternary isomers **187** and **189**. Fortunately, these regioisomers proved separable by column chromatography, allowing access to material for characterisation purposes (Scheme 2.28).

Pyrrole **191** formation, accompanied by halogen-proton exchange, was also observed during the cyclisation of **165**. Diagnostic shifts in the ^{1}H NMR spectra for the tertiary carbon (labelled H_A) were seen at 3.28 ppm for both **188** and **190**.

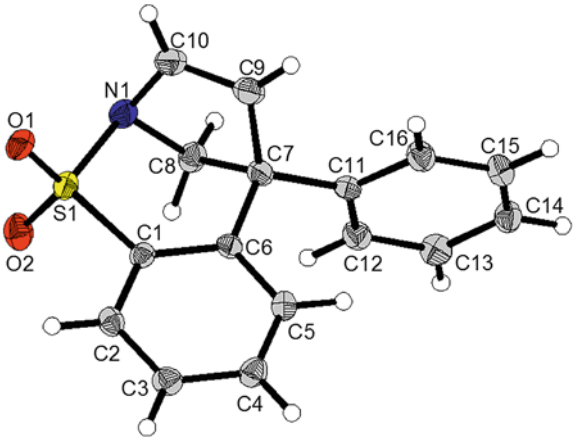
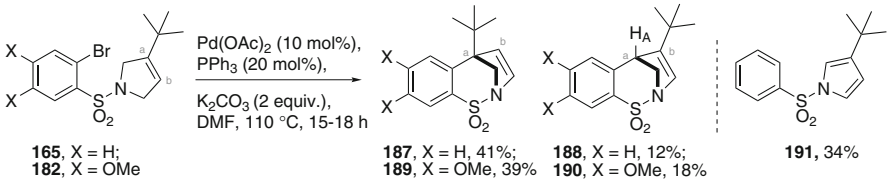


Fig. 2.3 X-ray crystal structure of **184**



Scheme 2.28 Intramolecular Heck reaction of **165/182**

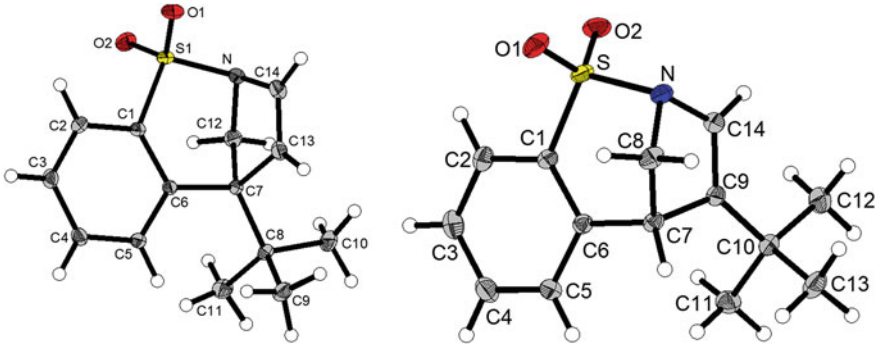


Fig. 2.4 X-ray crystal structures of **187** (*left*) and **188** (*right*)

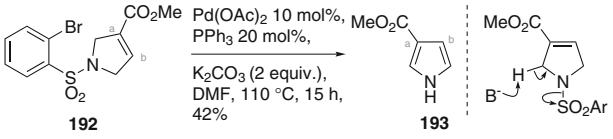
Structural confirmation of the regioisomers formed was achieved by X-ray crystallography (Fig. 2.4).

It should be noted that, following several attempts, the outcome observed from the Heck reaction of **165/182** is reproducible in terms of the ratio of products obtained.

Having obtained a sample of methyl ester **192** (previously prepared in the Evans group) its Heck cyclisation was attempted (Scheme 2.29).

Unfortunately, in this case no products for the Heck cyclisation were detected. Instead pyrrole **193**, most likely resulting from a base-catalysed sulfinate elimination reaction followed by isomerisation [65], was isolated as the sole product (43 %).

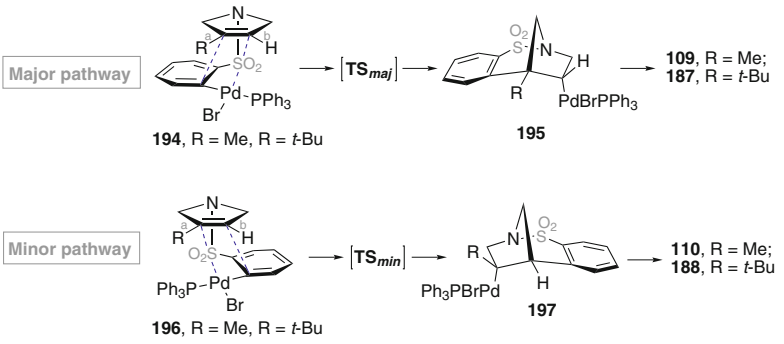
The investigation into the use of alternative alkenyl substituents in order to alter the regioselectivity demonstrated, yet again, an underlying preference for the



Scheme 2.29 Formation of pyrrole **193**

formation of the quaternary isomer, observed either as the sole product (**109/184/185**), or as the major isomer (**187/189**).

Mechanistic details of Heck reactions have been successfully interrogated computationally using density functional theory (DFT) methods [66]. Based on these precedents, we felt that a similar study might provide a basis for the regioselectivity that is experimentally observed. DFT studies were performed using the classic neutral Heck reaction pathway for the methyl and *t*-butyl substituents. These calculations were performed by our collaborators, Prof. Isabel Rozas (Trinity College Dublin, Ireland) and Prof. Ibon Alkorta (Instituto de Quimica Medica (IQM-CSIC), Spain). Calculations were performed on the likely chemical species involved in the regiochemistry setting event. Following a step-wise procedure, starting with simple computational methods up to the highest level readily considered, the Heck reaction of **108** and **165** (R = Me and *t*-Bu) was studied. Results were obtained using a B3LYP DFT function with the 6-31G* basis set for all the atoms, except for palladium, which used the pseudopotential LANL2DZ(d), and bromine that is described by LANL2DZ. This consideration enabled the characterisation of the possible complexes involved in the regiochemical setting sequence. Scheme 2.30 describes possible intermediates in the major pathway (based on experimental results) and in the corresponding minor pathway. Both conformations of the square planar alkene-complex were investigated where R = methyl and where R = *t*-butyl. Since regioselectivity is governed by the alkene-insertion event (carbopalladation), only the possible intermediates after the oxidative addition step were only considered.



E_{rel} (kJmol^{-1})

	Major pathway			Minor pathway			Products			
	194	**TS_{maj}**	**195**	**196**	**TS_{min}**	**197**	**109**	**110**	**187**	**188**
R = Me	0.0	73.7	27.6	27.8	86.8	-1.4	0.0	-19.0	-	-
R = *t*-Bu	8.8	95.1	73.1	0.0	114.1	40.5	-	-	0.0	-48.2

Scheme 2.30 DFT calculations performed for the regiochemistry-establishing sequence in which R = Me or *t*-Bu

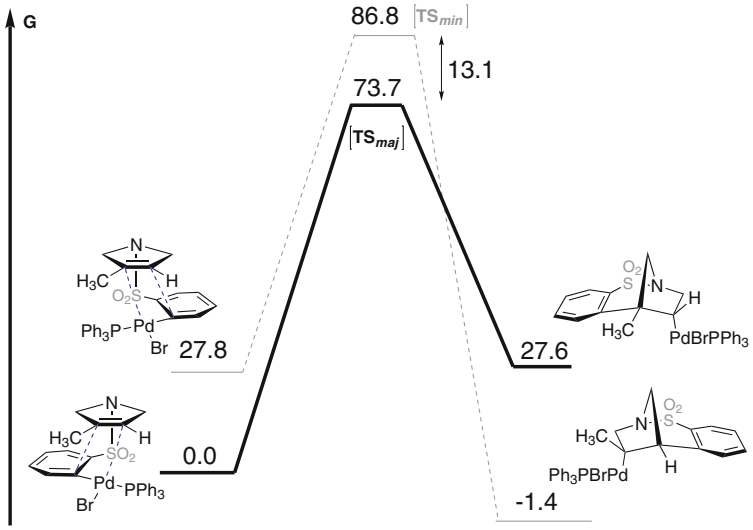


Fig. 2.5 Possible reaction pathways for the intramolecular Heck reaction of **108**, with free energies in kJmol^{-1}

A comparison of the possible final Heck products **109/187** and **110/188**, for both Me and *t*-Bu substituents, found that the experimentally observed *minor* product, the tertiary regioisomer, was more stable by 19 and 48.1 kJmol^{-1} for R = Me and *t*-Bu, respectively (Scheme 2.30). Next, the relative energies associated with the square planar carbopalladated intermediates **194** versus **196** (again for both R = Me and *t*-Bu) were calculated and were found to vary on the identity of the R-substituent.

The energies associated with the transition states in the pathway towards the carbopalladated intermediates **195** and **197** were considered for both the major pathway (based on experimental results) and the minor pathway. For both substituents (R = Me and *t*-Bu), the transition state associated with the major pathway (TS_{maj}) was found to be the most stable. The energy difference between the pathways (13.1 and 19 kJmol^{-1} for R = Me and *t*-Bu, respectively) was lower than expected, considering the overriding preference for the formation of the quaternary isomer (Fig. 2.5).

From these results it can be concluded that the key step in the formation of the major-pathway product depends mostly on the stability of the TS, despite the stability of the final products (which favours formation of products through the minor pathway).

In summary, this DFT study provides corroborative evidence for the experimental study and indicates that the reason for the counter-intuitive regiochemical outcome is kinetic. Product selection occurs because the transition state associated with formation of the quaternary centre is lower in energy. However, based on the relatively low difference in energies between the competing transition states, it

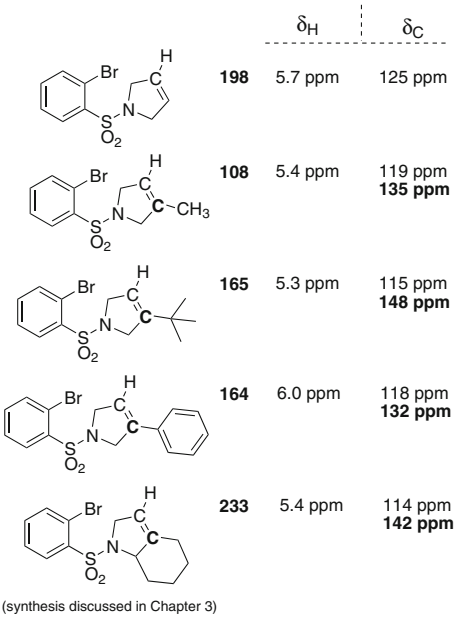


Fig. 2.6 Chemical shifts for Heck precursors **198**, **108**, **165**, **164** and **233**

would appear that for a reaction performed at elevated temperatures, DFT can only partly address the origin of selectivity.

The ^{1}H and ^{13}C NMR chemical shifts of the methine functional group and the alkenyl carbon of the participating Heck precursors have been summarised in Fig. 2.6. All protons contain a similar chemical shift except for the styrene derivative, whose proton is slightly deshielded by the adjacent phenyl ring, appearing at 6.0 ppm in the ^{1}H NMR spectrum. The same trend is observed in the carbon chemical shifts. In comparison, the substituted alkenyl carbon (in bold) for all compounds have a higher chemical shift in the carbon spectrum, downfield from the neighbouring C–H which is not undergoing C–C bond formation, suggesting that the alkenyl carbon is more electropositive than the methine group.

An interesting substrate to attempt our intramolecular Heck cyclisation would be the trimethylsilyl-derivative **199** (Fig. 2.7), where the TMS-substituent should have a stronger influence on the electronics of the alkene, and consequently might have a different outcome in our intramolecular Heck reaction.

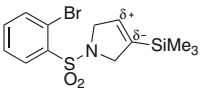


Fig. 2.7 TMS-substituted Heck precursor **199**

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Chapter 3
Wagner-Meerwein Rearrangement of Cyclic Sulfonamides

3.1 Introduction

In 2006, Paquette et al. reported that the treatment of sulfonamide **200** with bromine in chlorinated solvents (CCl_4, $CHCl_3$, CH_2Cl_2) gave a mixture of dibromides **201**, which, under basic conditions, underwent dehydrobromination, to give vinyl bromide **202** exclusively (Scheme 3.1) [1].

Optimal conditions for the formation of the cis-dibromide, over the trans-dibromide, were found to be by either the treatment of **200** with neat bromine at rt (99 %), or in PhMe at −78 °C (75 %). The latter set of reaction conditions were uncovered as part of a study conducted by Evans et al. concerning the functionalisation of vinyl bromides of type **202**, to access substituted nitrogen heterocycles [2]. The analogous functionalisation of electron-rich sulfonamide **203** could also be effected with bromine in PhMe yielding the desired cis-dibromide **204** in 78 % isolated yield (Table 3.1, entry 1).

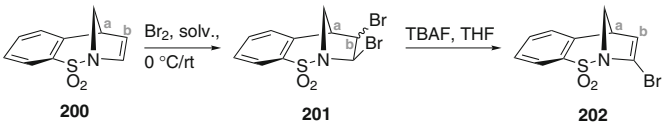
Interestingly, when the reaction was carried out in chloroform, the rearranged product **205** was isolated in 42 % yield (entry 2), whose identity was characterised by X-ray crystallography. As depicted in entry 3, a higher yield of 87 % for **205** could be realised when 10 equivalents of bromine was used. None of the rearranged product was observed when **200** was subjected to identical conditions.

A bromomethanolysis reaction was conducted to shed light on the possible reaction intermediates (Scheme 3.2).

The reaction gave a mixture of **206** and **207** in 58 and 37 % isolated yields respectively. Based on these isolated reaction products, a possible mechanistic pathway was proposed (Scheme 3.3).

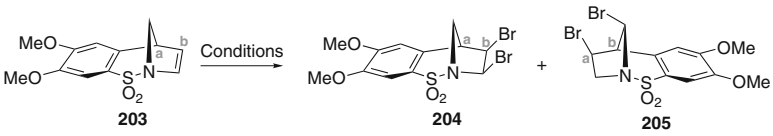
The authors proposed two possible competing pathways, both commencing after bromonium ion formation, which occurs on the most accessible convex face of alkene **203**. Path A (blue) could proceed via an S_N1-type process whereby the resulting carbocation is intercepted by a nucleophile, X^- (X = Br, OMe), from the least hindered top face of the cation, affording cis-product **204/206**. Alternatively,

K. Geoghegan, *Selectivity in the Synthesis of Cyclic Sulfonamides*,
Springer Theses, DOI 10.1007/978-3-319-10338-9_3

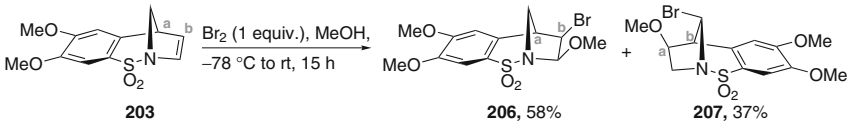


Scheme 3.1 Alkene functionalisation

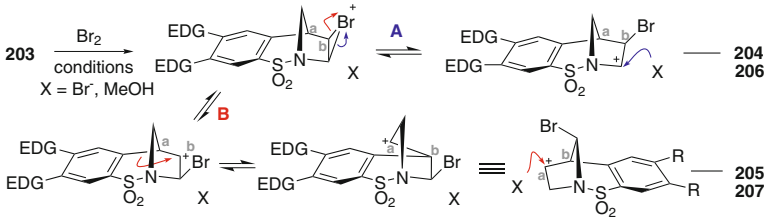
Table 3.1 Bromination of alkene **203**



Entry	Conditions	Product(s)
1	Br_2 (1 equiv.), PhMe, –78 °C to rt, 15 h	**204**, 78%
2	Br_2 (1 equiv.), $CHCl_3$, –78 °C to rt, 15 h	**205**, 42%
3	Br_2 (10 equiv.), $CHCl_3$, –78 °C to rt, 15 h	**205**, 87%



Scheme 3.2 A bromomethanolysis reaction of **203**



Scheme 3.3 Possible pathway for the formation of **204/206** and **205/207**

Path B (red), upon bromonium ion opening, aryl bond migration (which is aligned with the empty p-orbital of the cation, see Fig. 3.1) can occur from carbon *a* to carbon *b*. This is presumably facilitated by the +M-group on the aromatic ring. Subsequent nucleophilic attack, again, from the top face of the resulting carbocation could give rearranged compound **205/207**. The transformation of **203** to **205/207** is

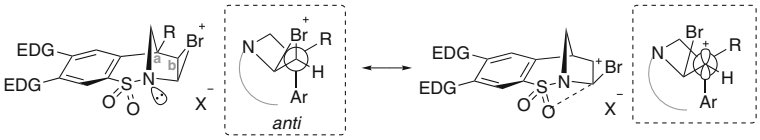
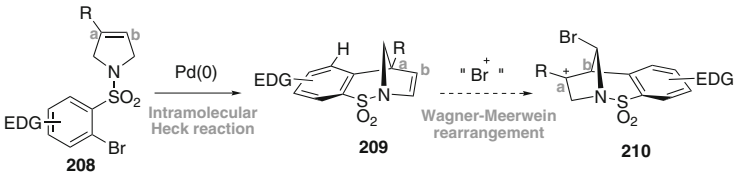


Fig. 3.1 Newman projection



Scheme 3.4 Wagner-Meerwein rearrangement of **208**

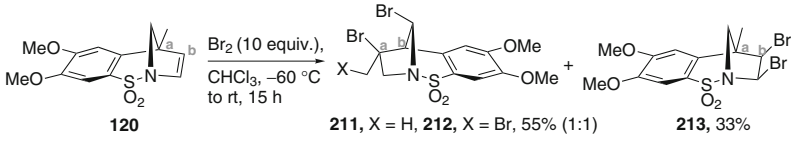
an example of a Wagner-Meerwein type rearrangement and can be viewed as 'reversing' the regioselectivity originally set during the intramolecular Heck reaction of these types of compounds. It should be noted that the lone pair on the nitrogen atom is orthogonal to the C-Br bond (bisects the two oxygen atoms) and based on this is thought not to participate mesomerically in the reaction (Fig. 3.1) [3]. In contrast, although not precedented, it's possible that an oxygen atom from the adjacent sulfone can serve in a similar manner.

With this in mind, and considering our efforts in trying to overturn the regioselectivity in the intramolecular Heck reaction of a range of trisubstituted alkenes (for example **208** → **209**, described in Chap. 2), it was speculated that a bromonium ion triggered Wagner-Meerwein rearrangement [4, 5] would formally give access to the isomeric series of compounds of the type **210** (Scheme 3.4).

3.2 Bromonium Ion Mediated Migration of Bicyclic Compounds

With alkene **120** in hand, conditions detailed in Table 3.1 (**203** → **205**) were employed (Scheme 3.5).

This reaction provided three major compounds; a chromatographically inseparable mixture of **211/212** (1:1) and cis-1, 2-dibromide **213** in 55 and 33 % isolated



Scheme 3.5 Bromination of **120**

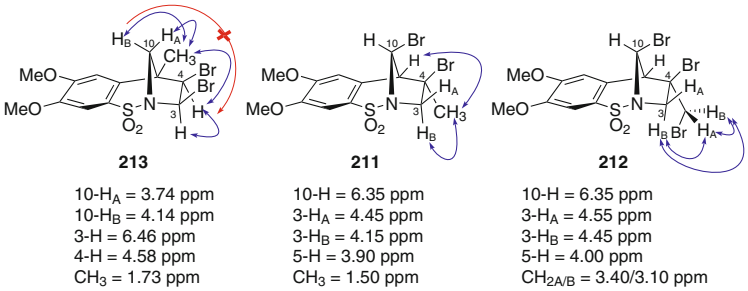


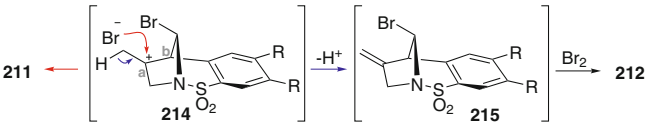
Fig. 3.2 NOe studies of compounds **211**–**213**

yield respectively. Relative stereochemistry of the three compounds was assigned using COSY and nOe NMR studies, represented in Fig. 3.2.

The cis-relationship between the two bromine atoms of compound **213** was reasoned due to a strong correlation between protons 3-H and 4-H, which could be observed in the 2-D nOe spectrum (Fig. 3.2). More evidence to support this was the absence of a correlation between protons 3-H and 4-H with the bridgehead protons 10-H_A/10-H_B, suggesting the stereochemistry of compound **213** might resemble that depicted in Fig. 3.2. With regards to compounds **211** and **212**, a strong correlation could be seen between one of the methylene protons (labelled 3-H_A/3-H_B) and the respective flanking groups, i.e. methyl group (**211**) or –CH_2Br group (**212**). Based on analogous compounds previously made in Evans' laboratories, the chemical shifts for the two protons adjacent to the nitrogen atom (labelled 3-H_A/3-H_B for compounds **211** and **212**) could be inferred. Based on the deduction that 3-H_B is slightly more shielded than 3-H_A and therefore resonates at a lower frequency than 3-H_A in the proton spectrum, the stereochemistry suggested for compounds **211** and **212** are depicted in Fig. 3.2. Indeed, it is 3-H_B that correlates with the –CH_3/–CH_2Br groups.

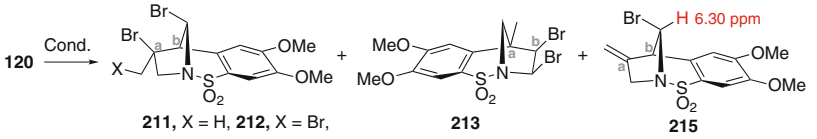
1,2-Dibromide **211** formation is consistent with a diastereoselective interception of a tertiary cation of the type **214** (Scheme 3.6) with a bromide anion. It was reasoned that tribromide **212** formation arises from a subsequent bromination of alkene **215**, not observed in this reaction, which itself may form on loss of a proton from the same tertiary carbocation.

In an attempt to influence the product outcome (i.e. to form only **211** or **212**, and inhibit the formation of **213**) variations were made to the reaction conditions (Table 3.2).



Scheme 3.6 Possible intermediates yielding **211** and **212**

Table 3.2 Bromination of alkene **120**



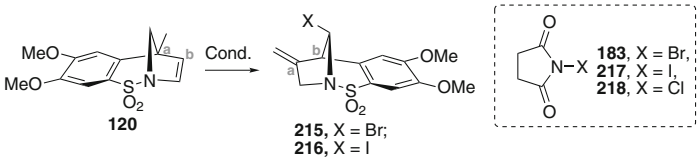
Entry	Conditions	Product(s) (% yield, ratio)
1	Br_2 (10 equiv.), CH_2Cl_2, –78 °C to rt, 15 h	**211:212** (44, 1:1), **213** (49)
2	Br_2 (10 equiv.), MeCN, –45 °C to rt, 15 h	**211:212** (7, 1:1.2), **213** (5)
3	Br_2 (10 equiv.), AgOAc (1 equiv.), $CHCl_3$, –60 °C to rt, 15 h	**211:212** (25, 1:1.2), **213** (49)
4	Br_2 (1.4 equiv.), $CHCl_3$, –60 °C to rt, 15 h	**211:212** (50, 1:1), **213** (45)
5	Br_2 (0.55 equiv.), $CHCl_3$, –60 °C to rt, 15 h	**213** (3), **215** (50)

As shown in entry 1, reducing the polarity of the solvent did not change the ratio of di- and tri-bromide (**211/212**) formation. When the reaction was performed in acetonitrile, a solvent with a high dielectric constant value, it proved detrimental to the overall yield of the process (entry 2). Interestingly, when the reaction was performed in the polar, aprotic solvent propylene carbonate (not listed above), trace material (<5 %) was observed for the formation of only tri-bromide **212**. It was then felt that the use of a basic silver salt might diminish the rate of the bromide interception of carbocation **214** versus alkene formation, and consequently, more tribromide **213** would be formed. As depicted in entry 3, the use of Ag(I) salt gave a mixture of **211** and **212** in approximately the same ratio observed in Scheme 3.5. A reduction in bromine concentration of the reaction (in chloroform) gave similar results compared to using 10 equivalents (entry 4). However, when 0.55 equivalents of bromine were used in the reaction, a trace amount of cis-dibromide **213** was isolated along with the rearranged alkene **215** (50 %) (entry 5). The methylene functional group could be detected by proton NMR spectroscopy, and was characterised by singlets resonating at 5.35 and 5.11 ppm, along with the bridgehead proton at 6.30 ppm. The isolation of alkene **215** indicates that a proton loss from the presumed cation **214** is indeed feasible (Scheme 3.6), and as long as the alkene is guarded from further bromination it can be isolated.

With this in mind, we felt it appropriate to use *N*-bromosuccinimde (NBS) **183** as our source of bromine, as it is known that NBS promotes the release of low concentrations of bromine in solution (Table 3.3).

No reaction was observed when the reaction was carried out with a slight excess of NBS in chloroform at room temperature. However, heating the reaction mixture to reflux in chloroform led to the isolation of alkene **215** in 66 % yield along with 35 % recovered starting material (entry 1). Switching the reaction vessel for a Pyrex sealable tube, and holding the oil bath temperature at 80 °C overnight afforded alkene **215** in an excellent 90 % isolated yield (entry 2). The iodo-compound **216** could be accessed in 82 % yield under identical conditions, employing *N*-iodosuccinimide

Table 3.3 *N*-halosuccinimides in the Wagner-Meerwein rearrangement



120 **215**, X = Br; **216**, X = I

Entry	Conditions	Product(s) (% yield)
1	NBS **183** (1.1 equiv.), $CHCl_3$, reflux, 15 h	**120** (35), **215** (66)
2[a]	NBS **183** (1.1 equiv.), $CHCl_3$, 80 °C, 15 h	**215** (90)
3[a]	NIS **217** (1.25 equiv.), $CHCl_3$, 80 °C, 15 h	**216** (82)
4[a]	NCS **218** (1.5 equiv.), $CHCl_3$, 80 °C, 15 h	**120** (95)

[a] Reactions were performed in a sealed tube

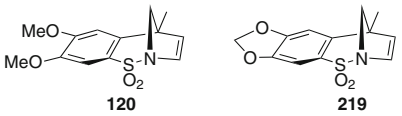
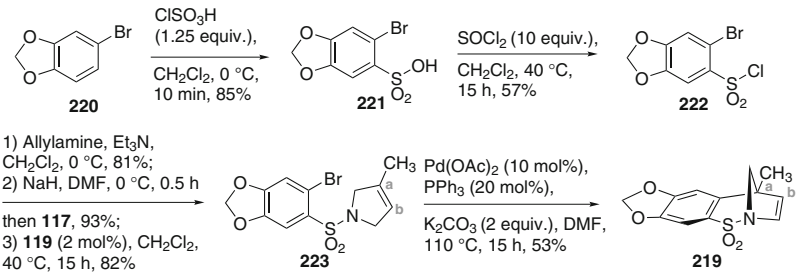


Fig. 3.3 Alkenes **120** and **219**

217 (NIS) (entry 3). However, the use of *N*-chlorosuccinimide failed to give any reaction products (entry 4).

We were interested in the methylenedioxy analogues of **219**, and had a particular interest in their behaviour during our double reduction studies towards pyrrolidine synthesis (Chap. 5). Additionally, since the Wagner rearrangement of **120** is evidently facilitated by the presence of the electron-donating methoxy groups on the aromatic portion; we wanted to examine whether the dioxolane derivative **219** would also undergo the rearrangement (Fig. 3.3).

To investigate if this was indeed feasible, the synthesis of alkene **219** was next considered (Scheme 3.7).

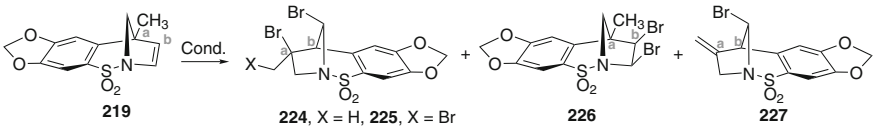


Scheme 3.7 Synthesis of cyclic sulfonamide **219**

Initial attempts to convert commercially available 1-bromo-3,4-(methylenedioxy)benzene **220** directly into sulfonyl chloride **222** using chlorosulfonic acid resulted in decomposition. In comparison, 4-bromoveratrole **67** can be directly converted into its respective sulfonyl chloride **114**. We reasoned that the acid-sensitive methylenedioxy functional group could not survive the necessary aqueous work-up step, which generates HCl and probably converts the in situ formed sulfonic acid **221** into the corresponding sulfonyl chloride **222**. Therefore, a modified 2-step process was adopted to access sulfonyl chloride **222**. The treatment of **220** at 0 °C in dichloromethane, with a slight excess of chlorosulfonic acid, resulted in the precipitation of sulfonic acid **221**. High yields up to 85 % were obtained for this reaction when the mixture was filtered strictly 5 min after the complete addition of the chlorosulfonic acid. At this stage we could confirm by ^{1}H NMR spectroscopy that we had isolated one regioisomer, in contrast to the synthesis of dimethoxy-substituted sulfonyl chloride **114**. Thionyl chloride then mediated the conversion of the sulfonic acid to the requisite sulfonyl chloride **222** in 57 % isolated yield. A large excess of thionyl chloride in refluxing dichloromethane was required for this transformation. With sufficient material of **222** in hand it was straightforward to access the Heck product **219** in four steps using our chemistry described in Chap. 2. The conversion of **223** to **219** can also be effected by microwave irradiation at 300 W, 125 °C for 25 min affording **219** in 68 %, which is slightly higher compared to the traditional method (53 %).

Having optimised conditions for the rearrangement of **120** (Tables 3.2 and 3.3, entry **2** and **3**), we then applied them to the methylenedioxy alkene **219** (Table 3.4). Treatment of a chloroform solution of **219** with bromine (10 equiv.) at −60 °C gave a chromatographically inseparable mixture of rearranged products **224** and **225** (1:3) and 1,2-dibromide **226** in 32 and 38 % isolated yield, respectively (entry 1). It is interesting to note that significantly smaller quantities of dibromide **224** are observed in this example compared to the dimethoxy analogue **120**. In entry 2, these use of NBS **183** led to the isolation of alkene **227** (42 %) and recovered starting material (22 %).

Table 3.4 Bromination of **219**



219 **224**, X = H, **225**, X = Br **226** **227**

Entry	Conditions	Product(s) (% yield, ratio)
1	Br_2 (10 equiv.), $CHCl_3$, –60 °C to rt, 15h	**224**:**225** (32, 1:3), **226** (38)
2[a]	NBS **183** (10 equiv.), $CHCl_3$, 80 °C, 15 h	**219** (22), **227** (42)

[a] Reactions were performed in a sealed tube

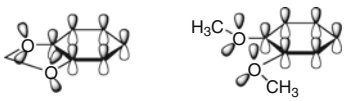
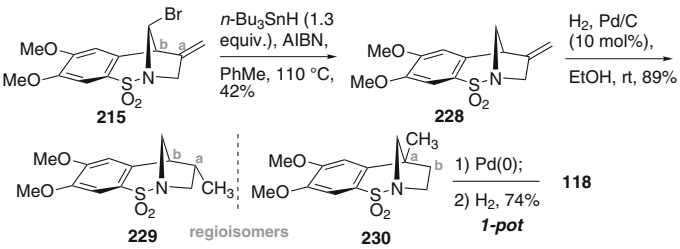


Fig. 3.4 Stereoelectronic effects of methylenedioxy and dimethoxy substituted aromatic systems



Scheme 3.8 Accessing regioisomer **229** from **215**

The difference in reactivity of **120** and **217** could be associated with the stereoelectronic factors of the +M group on the aromatic moiety (Fig. 3.4) [6]. It can be reasoned that the rigid structure of the methylenedioxy compound prohibits good overlap between the oxygen lone pairs of electrons and the π-system of the aromatic ring. In contrast, the methoxy functional groups can freely rotate and allow complete alignment of the oxygen lone pairs with the aromatic π-system.

Overall, we have developed conditions as a means of accessing the regioisomeric material, albeit, brominated (or iodinated), from our intramolecular Heck reaction. To illustrate this, compound **215** was converted into tertiary regioisomer **229** (Scheme 3.8).

Debromination of compound **215** using tributyltin hydride and azobisisobutyronitrile (AIBN) in refluxing toluene led to the formation of alkene **228**. However, this reaction was not clean and the crude product obtained was contaminated with material attributed to quaternary regioisomer **120**. It was reasoned that the formation of the latter could arise following a fragmentation of the secondary radical intermediate in a process involving aryl bond migration and generation of a primary radical. Nevertheless, the desired alkene **228** could be isolated after careful purification in 42 % yield. A diastereoselective alkene hydrogenation with Pd/C under an atmosphere of hydrogen gave alkane **229** (89 %), the regioisomer of **230**, which is itself synthesised from Heck precursor **118** in a one-pot Heck-hydrogenation sequence (described in Chap. 4). Based on the success of the bicyclic compounds **120** and **219**, we turned our attention to the rearrangement of tricycles **241** and **242** (Scheme 3.11).

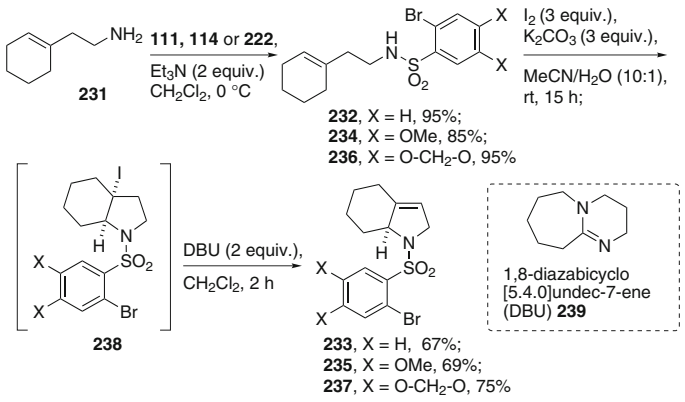
3.3 Bromonium Ion Migration of Tricyclic Compounds

Sulfonamides **232**, **234** and **236** were generated from amine **231** and the appropriate sulfonyl chloride (**111**, **114** or **222**) in high yields (Scheme 3.9). The synthesis of the unsubstituted analogue **232** was carried out for our studies described in Chap. 4.

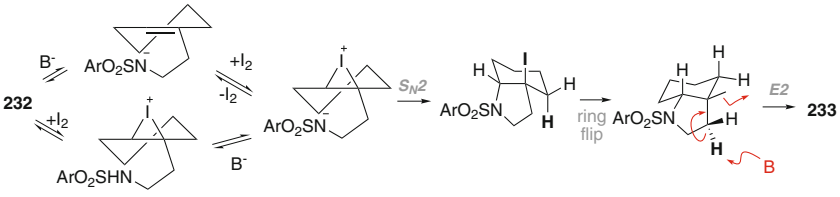
Following a protocol reported by Knight et al. [7] the exposure of **232/234/236** to a mixture of I_2/K_2CO_3 in $MeCN/H_2O$ (10:1) facilitated an amino-cyclisation. The formation of the intermediate iodide **238** could be monitored by ^1H NMR analysis, which, after work-up, was treated with DBU **239** in dichloromethane facilitating a regioselective dehydroiodination step, yielding racemic dihydropyrroles **233** (67 %), **235** (69 %) and **237** (75 %). A possible explanation for the regioselective base mediated dehydroiodination step is depicted in Scheme 3.10.

Once the amino-cyclisation occurs via an intramolecular S_N2 like reaction of the iodonium ion, the system will adopt the more stable conformation, where the tertiary iodide occupies the equatorial position. Anti-elimination (E_2) with the antiperiplanar proton which is part of the 5-membered heterocyclic ring will give **233/235/237**.

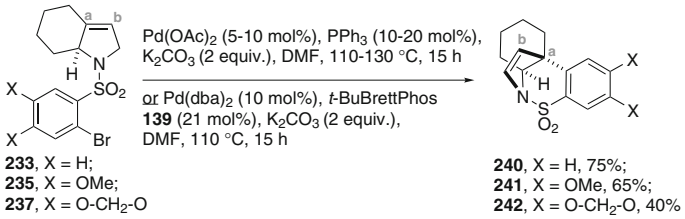
With dihydropyrroles **233**, **235** and **237** in hand, the intramolecular Heck cyclisation was attempted (Scheme 3.11). Pleasingly, under our standard Heck conditions, cyclic sulfonamides **240** and **241** were isolated as the sole products in 75



Scheme 3.9 Synthesis of Heck precursors **233**, **235** and **237**



Scheme 3.10 Knight's amino-cylisation-elimination protocol[115]



Scheme 3.11 Intramolecular Heck cyclisation of **240**, **241** and **242**

and 65 % isolated yields, respectively. However, a poor yield was obtained for the formation of dioxolane **242** under these standard Heck conditions and after some experimentation it was found that optimum yields of 40 % could be achieved using a Pd(0) source and electron-rich phosphine **139** (along with 50 % recovered starting material, **237**).

Two features of this cyclisation are noteworthy. Firstly, as seen in the examples discussed in Chap. 2, the regiochemical outcome of this Heck reaction is selective for the formation of a quaternary centre from an unbiased system, in terms of the size of the newly formed ring. Carbon-carbon bond formation at either carbon *a*, or *b* in **233/235/237** would both proceed via a 6-*exo-trig* mode of cyclisation. Secondly, using this process, the installation of the quaternary aryl bond was achieved in a diastereoselective manner, governed by the stereogenic carbon centre (adjacent to the nitrogen atom), i.e. one diastereomer was isolated for all three compounds (**240**, **241** and **242**). This can be seen in the X-ray crystallographic structure of compound **241** (Fig. 3.5).

With electron-rich analogues **241** and **242** in hand, the bromonium ion mediated Wagner-Meerwein rearrangement was attempted (Scheme 3.12).

A chloroform solution of **241** was treated with bromine (10 equiv.) at −60 °C which reached room temperature over a 15 h period to generate a mixture of three compounds. After purification by column chromatography and analysis by ^{1}H and

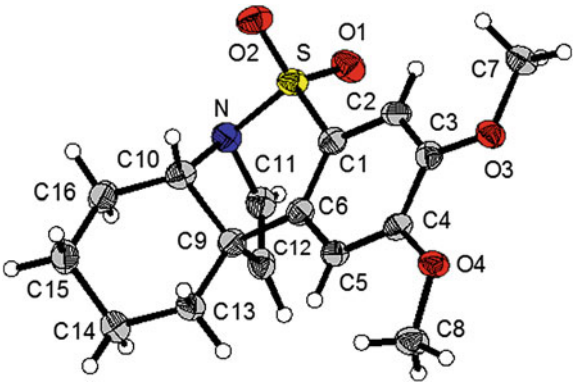
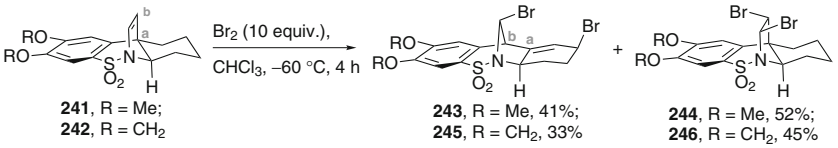


Fig. 3.5 X-ray crystal structure of sulfonamide **241**



Scheme 3.12 Wagner-Meerwein rearrangement of **241** and **242**

[13]C NMR spectroscopy, the major compound proved to be the rearranged compound **243** (41 %). NOe experiments were used to correlate the characteristic methine proton adjacent to the nitrogen atom around the cyclohexenyl ring to the cis-allylic methine proton (Fig. 3.6). The minor compound isolated from this reaction was an inseparable mixture of trans-1,2-dibromide 2**44** and an impurity that resembled **243** (epimeric at the allylic bromide). The stereochemistry for trans-**244** was verified by nOe studies. No reaction was observed when **241** was treated with excess NBS **183** in refluxing chloroform. The treatment of methylenedioxy **242** under identical conditions gave rearranged product **245** and trans-**246** in 33 and 45 % isolated yields, respectively. The structure of **245** was confirmed by X-ray crystallography (Fig. 3.6) (Fig. 3.7).

Pleasingly, on doubling the concentration of bromine (20 equiv.) and holding the reaction at −60 °C for 1.5 h, synthetically useful quantities of **243** (77 %) were observed, while, under the same conditions, compound **245** was isolated in an improved but still moderate 40 % yield (Scheme 3.13).

With regards to dibromides **243** and **245**, there are two aspects to be noted. Firstly, the newly formed trisubstituted alkene is reluctant to participate in further 1,2-dibromination (unlike alkene **215**). Secondly, the newly formed alkene rapidly undergoes an allylic bromination reaction diastereoselectively. Although allylic

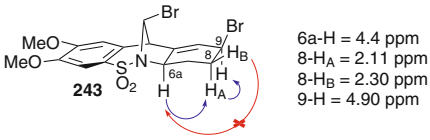


Fig. 3.6 NOe analysis of **245**

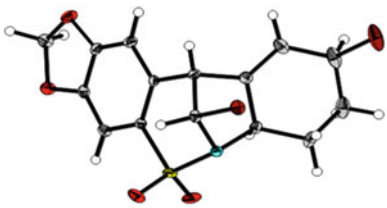
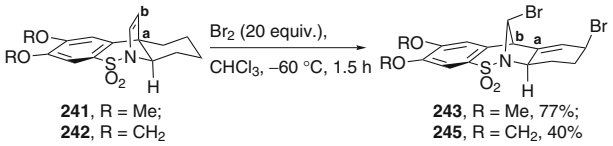


Fig. 3.7 X-ray crystal structure of **245**



Scheme 3.13 Effects of increased bromine concentration in the Wagner-Meerwein rearrangement

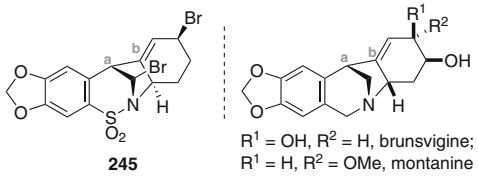


Fig. 3.8 Structure of some montanine alkaloids

bromination has been reported to proceed at diffusion controlled rates for cyclohexene at low bromine concentration and on irradiation with a Sun lamp, [8] under these reaction conditions their reproducible formation was not expected.

In summary, we have been able to take the products of our Heck reaction, quaternary isomers **120**, **219**, **241** and **242**, and convert them into their regioisomeric partners through a bromonium ion mediated Wagner-Meerwein rearrangement. In terms of a potential application, the tricyclic core of **245** is found in a variety of naturally occurring alkaloids, and, in particular, could be applied to synthesis of the montanine alkaloids (Fig. 3.8) [9, 10].

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Chapter 4
An Investigation into the One-Pot Heck Olefination-Hydrogenation Reaction

4.1 Introduction

A major objective in synthetic organic chemistry is the development of new methodologies for the transformation of simple precursors into more complex molecules. Taking inspiration from nature, where multi-enzymatic systems carry out two or more transformations to access structurally intricate molecules, one-pot procedures involving multiple catalytic events, i.e. multi-task, or cascade/tandem/domino processes, are being sought by synthetic chemists. The term 'one-pot' refers to several chemical transformations occurring in one reaction vessel, with a single work up at the end of the reaction (Scheme 4.1). The advantages of these 'one-pot' procedures, over a two-pot 'stop-go' process, include improved atom economy, savings in time and cost. And that they are typically more straightforward to perform and are environmentally friendly.

The use of multi-task or tandem processes have been developed particularly in the area of transition-metal catalysis, where another major advantage is catalyst efficiency [1, 2]. This is appropriately termed as "tandem catalysis", and has been defined by Fogg and dos Santos as "coupled catalyses in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes" [3]. In the report the authors outline the three classes of tandem catalysis; orthogonal, auto- and assisted-catalysis.

Orthogonal tandem catalysis involves two or more functionally different, non-interfering catalysts present in the reaction vessel from the outset of the reaction, which transform the substrate, sequentially, into product (Scheme 4.2).

Grigg et al. developed a RCM-Heck tandem process to access cyclic sulfonamides of the type **200** [4, 5]. Both catalysts are present at the start of the reaction. The ruthenium catalyst employed is the Grubbs 1st generation catalyst, **248**, which performs an initial RCM leading to the formation of dihydropyrrole Heck precursor **247**. The scene is then set for a subsequent Pd-mediated intramolecular Heck cyclisation to give the final cyclic sulfonamide product **200** in 65 % overall yield.

K. Geoghegan, *Selectivity in the Synthesis of Cyclic Sulfonamides*,
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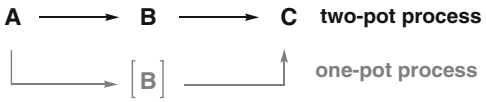
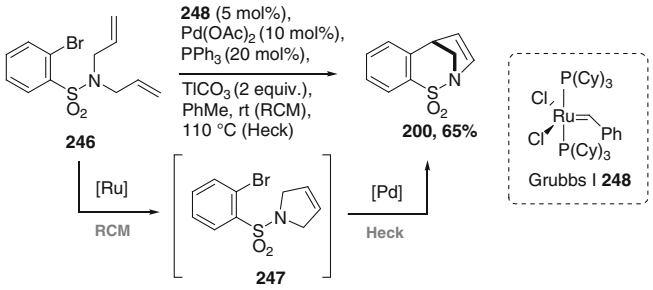
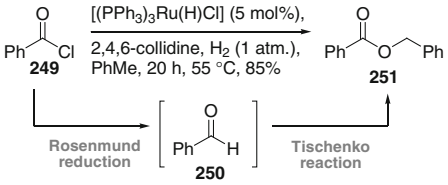


Scheme 4.1 Two-pot versus one-pot transformation



Scheme 4.2 Grigg's example of an orthogonal tandem process



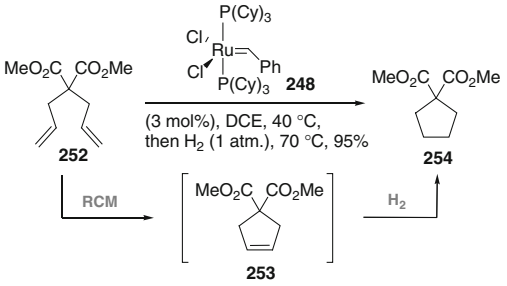
Scheme 4.3 Grushin and Apler's example of an auto-tandem reaction for ester synthesis

Another subclass, auto-tandem catalysis, describes a reaction in which a single catalyst carries out two or more fundamentally different chemical transformations in a single reactor. All reagents are present in the vessel at the start of the reaction. An example of auto-tandem catalysis is demonstrated in Scheme 4.3.

Grushin and Apler carry out a sequential Rosenmund reaction of acid chloride **249** to aldehyde **250**, which acts as a substrate for a Ru-catalysed Tischenko reaction to provide ester **251**, in a single reaction vessel [6].

Assisted-tandem reactions are similar to auto-assisted tandem reactions, where a single catalyst is responsible for carrying out two or more distinct chemical transformations. However, a change in reaction conditions is required to trigger a shift in the role of the catalyst (Scheme 4.4).

In 2001, Grubbs et al. reported a ruthenium-catalysed RCM-hydrogenation protocol for the formation of cyclic alkanes [7]. In Scheme 4.4, ruthenium catalyst **248** performs a RCM reaction (at 40 °C) to furnish cyclic alkene **253**. Without isolating the compound, the reaction atmosphere is then swapped to hydrogen and the reaction temperature is increased to 70 °C. This change in reaction conditions



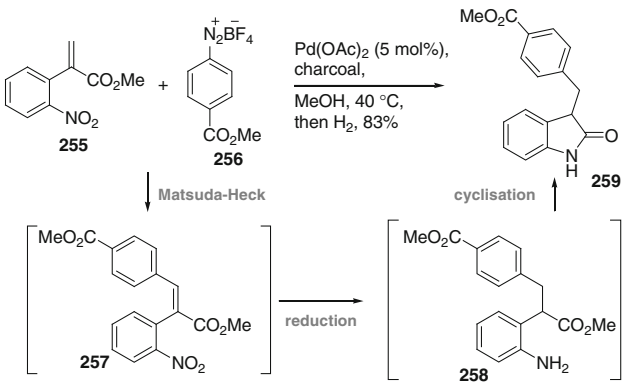
Scheme 4.4 RCM-hydrogenation cascade

alters the role of the catalyst, promoting the Ru-catalysed hydrogenation of the in situ alkene, yielding alkane **254** in 95 % yield, in one-pot.

Another example of this assisted-tandem catalysis is demonstrated by Felpin et al. who reported a palladium-catalysed Heck-Reduction-Cyclisation (HRC) protocol towards the synthesis of oxindoles of the type **259** (Scheme 4.5) [8, 9].

A Matsuda-Heck reaction in the presence of a Pd(II) precatalyst provides intermediate **257**. Swapping the atmosphere to hydrogen effects both alkene hydrogen and nitro-reduction to give the aniline **258**, which cyclises to give oxindole **259** in 83 % yield. The inclusion of charcoal as a support was necessary for the success of this HRC protocol. Another feature of this sequence is the recovery of the Pd(0)/C supported catalyst by a simple filtration, which could not be reused for further HRC reactions but displayed high reactivity as a catalyst for hydrogenation reactions.

In contrast to the orthogonal and auto- tandem processes, the successive transformations do not proceed spontaneously during assisted-tandem protocols. The initial reaction must be monitored to completion before advancing onto the next transformation to avoid any premature reactions occurring.

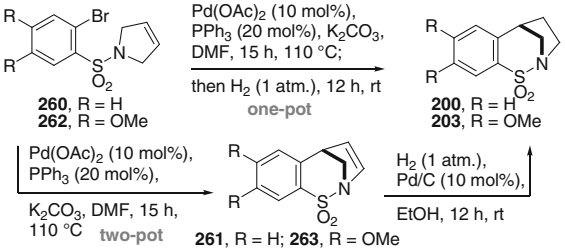


Scheme 4.5 HRC cascade

4.2 Intramolecular Heck-Hydrogenation Sequence

In relation to the Matsuda-Heck-hydrogenation sequence shown in Scheme 4.5, it was felt that a similar palladium assisted-tandem sequence could be utilised for our purposes. As previously mentioned in Sect. 2.4, we have been interested in the preparation of saturated cyclic sulfonamides of the type **200** (Scheme 4.6) to study their behaviour under dissolved metal conditions (described in Chap. 5). It was envisaged that the palladium catalyst used to synthesise our cyclic sulfonamide compounds through an intramolecular Heck reaction, could also be used to effect alkene hydrogenation in 'one-pot'. A previous report by Kelleher showed that indeed saturated cyclic sulfonamides **200/203** can be accessed in a 'one-pot' Heck-hydrogenation fashion from the requisite symmetrical dihydropyrrole **260/262** (Scheme 4.6) [10].

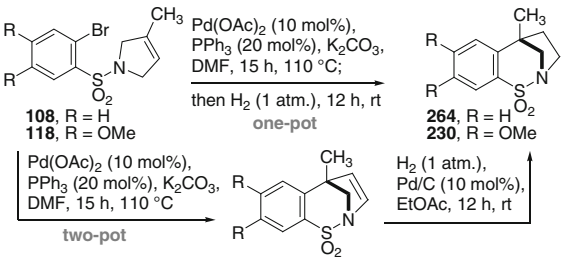
Based on this precedence, unsymmetrical dihydropyrroles **108** and **118** were considered for the 'one-pot' Heck-hydrogenation process (Scheme 4.7).



Compound	one-pot	two-pot[a]
200	61%	81%
203	52%	48%

[a] Yield over two steps

Scheme 4.6 Formation of saturated sultams



Compound	one-pot	two-pot[a]
264	67%	76%
230	58%	35%

[a] Yield over two steps

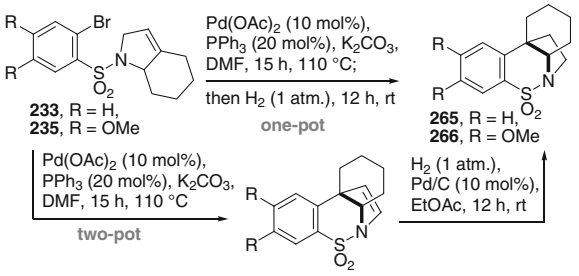
Scheme 4.7 Synthesis of saturated sultams

Firstly, benzo-annulated sulfonamides **108** and **118** were prepared using our standard Heck conditions (described in Chap. 2). Subsequent hydrogenation of the Heck products **109** and **120** was then effected by Pd/C under an atmosphere of hydrogen (1 atm.) affording saturated sultams **264** (quantitative yield) and **230** (60 %). With yields for the two-step process available and authentic material for the saturated cyclic sulfonamides **264** and **230**, the assisted-tandem reaction sequence was next attempted. Again, compounds **108** and **118** were subjected to our standard Heck olefination conditions. These reactions could be monitored by thin layer chromatography (TLC) or left to react overnight. Once starting material consumption was confirmed by TLC, the reaction mixture was cooled to rt before swapping the atmosphere from N_2 to H_2 and the reaction mixture continued to stir at rt overnight. Upon work-up and purification by column chromatography, alkane products **264** and **230** were isolated in 67 and 58 % overall yield, starting from dihydropyrroles **108** and **118**. The assisted-tandem reaction utilises the Pd(0) species generated from the initial Heck reaction to effect hydrogenation, i.e. the role of the catalyst has been shifted due to the addition of hydrogen to the system.

Based on the success of the tandem Heck olefination-hydrogenation protocol on the trisubstituted dihydropyrrole Heck precursors, we were also able to extend this methodology to hexahydroindoles **233** and **235** (Scheme 4.8).

The hexahydroindoles **233** and **235** proved to be suitable substrates for the one-pot procedure, with the isolation of saturated sultams **265** and **260** in 62 and 43 % yield respectively.

On the whole, the success of the intramolecular examples above indicate that this is a reliable process to access saturated sultams, and, generally, the yields observed for the simpler one-pot method were comparable to the traditional two-pot procedure.



Compound	one-pot	two-pot[a]
265	62%	75%
266	43%	81%

[a] Yield over two steps

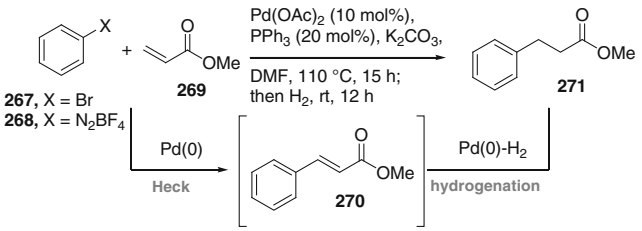
Scheme 4.8 Synthesis of tricyclic compounds **265/266**

4.3 Intermolecular Heck-Hydrogenation Sequence with Bromobenzene

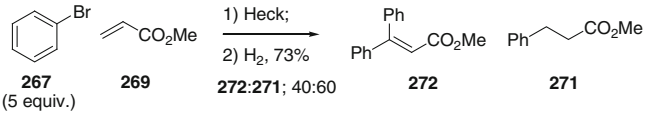
Building on these examples, we were interested in studying the scope and generality of this useful Heck olefination-hydrogenation sequence. We set out by investigating the intermolecular Heck reaction of bromobenzene **267** with a wide range of alkene components. Initially, the one-pot Heck-hydrogenation protocol of bromobenzene **267** and methyl acrylate **269** was attempted (Scheme 4.9).

The conditions used to effect a one-pot intramolecular Heck-reaction (Schs. 4.6, 4.7 and 4.8) provided methyl ester **271** in 73 % isolated yield. Due to problems with volatility, the alkene component methyl acrylate was used in excess (5 equiv.). If the Heck process was conducted at 60 °C lower yields were obtained for the alkane product **271**, similarly, omission of the catalyst ligand PPh_3 had detrimental effects to the yield of the reaction (24 %). The use of 'ligand free' conditions ($Pd(OAc)_2$ (5 mol%), Et_4NBr (1 equiv.), NaOAc (2.5 equiv.), MeCN, rt), the so-called Jeffrey conditions, furnished **271** in a low 43 % overall yield [11]. By switching bromobenzene to phenyl diazonium tetrafluoroborate **268**, an intramolecular Matsuda-Heck reaction followed by alkene hydrogenation proceeded in one-pot, furnished **271** in excellent yield (92 %) [12, 13]. However, in our hands, this process was less reliable than the reaction of **267**: the alkene hydrogenation was capricious and for reasons that remain unknown, did not always proceed efficiently (leading to **270** being isolated).

We also wondered if trisubstituted alkenes could be formed and reduced under the conditions outlined above (Scheme 4.10). The treatment of **269** with an excess of **267** (5 equiv.) under standard Heck conditions facilitated the formation of trisubstituted alkene **272**, but subsequent hydrogenation led only to the isolation of a

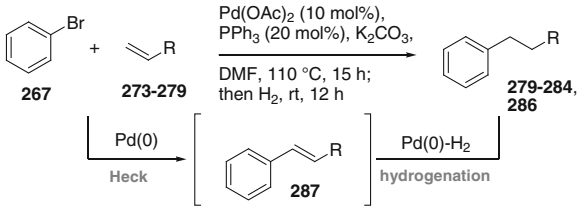


Scheme 4.9 One-Pot intermolecular Heck-hydrogenation sequence with **267** and methyl acrylate



Scheme 4.10 Trisubstituted alkenes in the Heck-hydrogenation process

Table 4.1 One-pot intermolecular Heck-hydrogenation with bromobenzene varying the alkene component



Entry	Alkene	Product	Yield (%)[a]
1	CO_2n-Bu **273**	Ph CO_2n-Bu **279**	79
2	SO_2Ph **274**	Ph SO_2Ph **280**	51[b]
3	CN **275**	Ph CN **281**	43
4	COMe **15**	Ph COMe **282**	15 (62)[c]
5	Ph **276**	Ph Ph **283**	49
6	*n*-Bu **277**	Ph *n*-Bu + Ph *n*-Bu **284** **285**	24 (84)[c]
7	O **278**	Ph O **286**	55 (77)[c]

[a] Isolated yields after purification by column chromatography
[b] Alkane:Alkene = 4:1
[c] Heck reaction performed under nitrogen in a sealed tube

mixture of **272** and **271** (40:60), indicating that trisubstituted alkenes of the type **272** are not readily reduced under the reaction conditions.

Based on the success of the intermolecular one-pot Heck-hydrogenation sequence, described in Scheme 4.9, we investigated the reaction of bromobenzene **267** with a range of electron-poor (**273**-**276**, **15**) and electron-rich (**277** and **278**) alkene components (Table 4.1).

The reaction with *n*-butyl acrylate **273** proceeded smoothly, affording **279** in an excellent 79 % yield (entry 1). Phenyl vinyl sulfone **274** underwent the Heck olefination reaction efficiently, however, the hydrogenation step proved sluggish, resulting in a mixture of product **280** and intermediate alkene **287** (R = SO_2Ph) (4:1) in approximately 50 % yield (entry 2). Increasing the hydrogen pressure (5 atm.) did not alter this ratio. The reaction with acrylonitrile **275** (entry 3) afforded **281** in a moderate 43 % yield. It is worthwhile to mention that under these mild conditions in the absence of a Brønsted acid, no nitrile reduction was observed [14]. Initial yields for the formation of the sweet smelling ketone **282** were poor, probably due to the volatility of methyl vinyl ketone **15** when the reaction was carried out in a traditional

round-bottomed flask. This was circumvented by performing the reaction in a Pyrex sealable tube, isolating **282** in 62 % yield (entry 4). In entry 5, undistilled styrene **276** gave **283** in a moderate yield of 43 %, although this figure was somewhat diminished by difficulties associated with the purification of the nonpolar compound by column chromatography. The use of terminal alkene **277** provided a mixture of regioisomers **284** and **285** (linear:branched, 9:1). Again, improved yields were observed if the reaction was carried out in a Pyrex sealable tube (84 %, entry 6). The reaction of heterocycle dihydrofuran **278** furnished **286** in 55 % isolated yield, and increased yields were obtained if the reaction was carried out in a sealed tube (77 %) (entry 7). No benzylic reduction took place under these conditions.

4.4 Intermolecular Heck-Hydrogenation Sequence with Methyl Acrylate

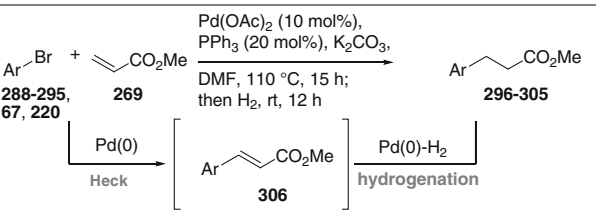
Next, we screened a range of alternative aryl- and vinyl-bromide components (**288**-**295**, **67**, **220**) with methyl acrylate **269** to investigate their behaviour under the intermolecular one-pot Heck-hydrogenation conditions employed in Table 4.2. As shown in entry 1, the reaction of 1-bromonaphthalene **288** with **269** under our one-pot conditions gave **296** in 79 % isolated yield. However, the use of 1-bromo-4-nitrobenzene gave a mixture of product **297** and intermediate alkene (4:1) in 59 % isolated yield (entry 2). In both cases the nitro-group was reduced, revealing the aniline moiety after the initial Heck reaction [15]. Conducting the hydrogenation under increased pressure (5 atm.) led to a slight improvement in the overall yield, but no change in the ratio of products was observed.

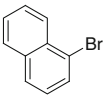
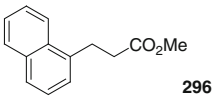
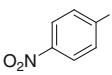
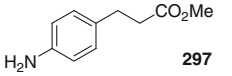
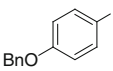
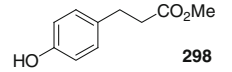
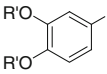
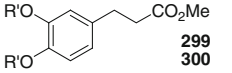
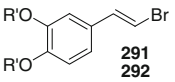
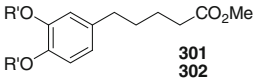
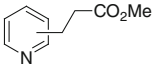
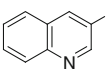
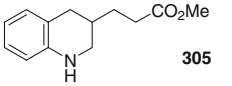
It was hoped that the same approach could be used with compound **290**, where the intermediate **307** would, after the hydrogenolysis step, give phenol **298**, which could ultimately be used to access raspberry ketone **308** (Scheme 4.11).

Unfortunately, only bromide **289** was recovered from this reaction sequence (entry 3). Next, electron-rich bromoveratrole **67** was chosen in the hope that, we could access **299**, which is an analogue of the pungent component of ginger, zingerone **309** (Scheme 4.12).

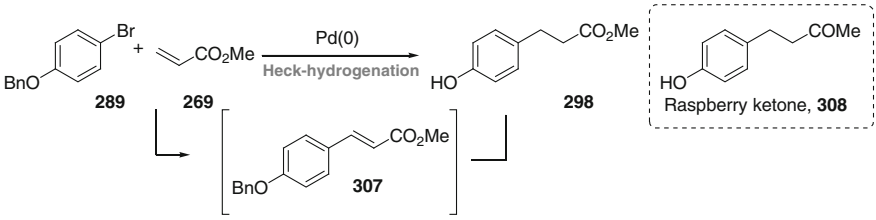
Unfortunately, the initial intermolecular Heck reaction did not proceed efficiently, with only trace amounts of the desired material isolated. However, the dioxolane analogue **220** gave adduct **300**, albeit in a low 25 % isolated yield (entry 4). Presumably, this outcome reflects the disturbance of the mesomeric communication of the 4-oxygen sustitutent with the *ipso*-bromide carbon atom due to the presence of the dioxolane ring. As indicated in entry 5, bromostyrenes **291** and **292** worked well in the one-pot procedure, furnishing 5-aryl esters **301** and **302** in 64 and 83 % isolated yields respectively. At this point we were interested to find out if heteroaromatic compounds with Lewis basic functionality would participate in this process. As depicted in entry 6, the reaction of 2-bromopyridine **293** gave 2,2′-bipyridine as the sole product [16]. In contrast, 3-bromopyridine **294** led to

Table 4.2 One-pot intermolecular Heck-hydrogenation with bromobenzene varying the brom component

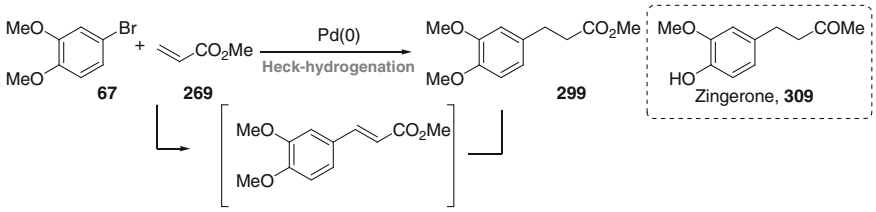


Entry	Bromide	Product	Yield (%)[a]
1	 **288**	 **296**	79
2	 **289**	 **297**	59[b] (67)[b,c]
3	 **290**	 **298**	0
4	 **67** **220**	 **299** **300**	**299**, R = Me; trace; **300**, R = CH_2; 25
5	 **291** **292**	 **301** **302**	**301**, R = Me; 64 **302**, R = CH_2; 83
6	 **(2)-293** **(3)-294**	 **(2)-303** **(3)-304**	**(2)-303**, 0[d] **(3)-304**, 92
7	 **295**	 **305**	35

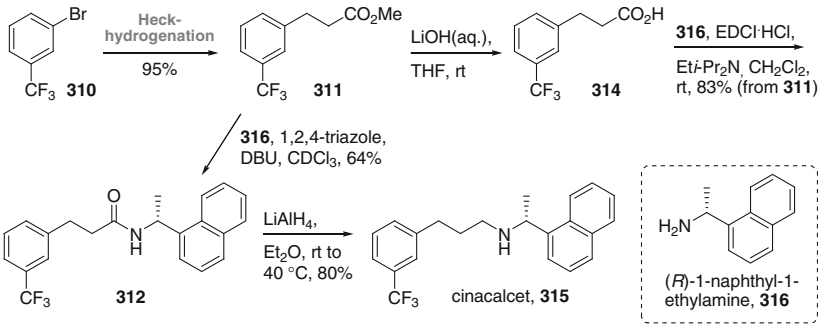
[a] Isolated yields after purification by column chromatography
[b] Alkane:Alkene = 4:1
[c] Hydrogenationperformed under 5 atm. pressure
[d] 2,2-bipyridine isolated



Scheme 4.11 Attempts to access phenol **298** via Heck-hydrogenation/debenzylation sequence



Scheme 4.12 Attempts to access **299** via Heck-hydrogenation sequence



Scheme 4.13 Synthesis of (*R*)-cinacalcet featuring a one-pot Heck-hydrogenation approach

isolation of **304** in an excellent 92 % yield. Based on this success the use of 3-bromo-quinoline **295** was investigated (entry 7), and in this case a mixture of compounds were formed, the major isolable compound being tetrahydroquinoline **305** (35 %).

Finally, the utility of the one-pot Heck olefination-hydrogenation method was demonstrated in a short synthesis of the calcimimetic drug cinacalcet **315** (Scheme 4.13) [17, 18]. Cinacalcet, sold under the trade name Sensipar and Mimpara, is used clinically to treat hyperparathyroidism (excessive parathyroid hormone production) in patients suffering with renal disease and parathyroid carcinoma.

The coupling of 1-bromo-3-(trifluoromethyl)benzene **310** and methyl acrylate **269** under our one-pot Heck-hydrogenation conditions ($Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 equiv.), DMF, 110 °C, 15 h then H_2 (1 atm.), rt, 15 h) gave methyl ester **311** in an excellent 95 % yield. In relation to this sequence, it was found that a catalyst loading of 1 mol% palladium was sufficient for a successful Heck reaction, but proved inefficient for the transfer of hydrogen, leading to a mixture of Heck adduct alkene (not shown) and alkane (**311**). The requisite amide **312** could be accessed either in a one-pot, or a two-pot fashion. First, a direct aminolysis reaction of methyl ester **311**, catalysed by 1,2,4-triazole, in the presence chiral amine **316**, furnished amide **312** in 64 % isolated yield [19]. Alternatively, saponification of methyl ester **311** to the carboxylic acid **314** with aqueous LiOH in THF, followed by carbodiimide-coupling of **316**, provided amide **312** in 83 % yield. Although the

latter sequence requires an additional step to access the amide, it was higher yielding than the one-pot procedure. Amide **312** underwent smooth reduction to amine **315** with an excess of $LiAlH_4$ in refluxing diethyl ether, yielding synthetic cinacalcet **315** (80 %) with data identical to those reported in the literature [17, 18].

In summary, we have demonstrated that using standard conditions for the Heck reaction, the same catalyst can also be used to effect hydrogenation of the Heck adduct in one-pot. The use of a single catalyst to carry out two distinct transformations has been shown to work efficiently for both intra- and intermolecular examples. In some cases it was found that a higher catalyst loading is required for the hydrogenation step. The one-pot Heck-hydrogenation sequence was also successfully applied to a short synthesis of (*R*)-cinacalcet **315**.

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Chapter 5
Double Reduction of Cyclic Aromatic Sulfonamides

5.1 Introduction

Sulfonamides are routinely employed as nitrogen protecting groups in organic synthesis. They are often crystalline, chemically robust, and, most importantly, the basicity/nucleophilicity of the nitrogen atom is reduced dramatically due to the presence of the electron-withdrawing sulfonyl moiety. Unlike their carbamate or amide analogues, there are no spectroscopic problems associated with rotamers when employing sulfonamides as protecting group. A variety of reductive methods exist for the cleavage of sulfonamides, for example, sodium- [1, 2] and lithium [3] -naphthalenide, Li-NH_3 [4, 5], Na-NH_3 [6], Mg-MeOH [7], Raney-Ni [8, 9] and SmI_2 [10].

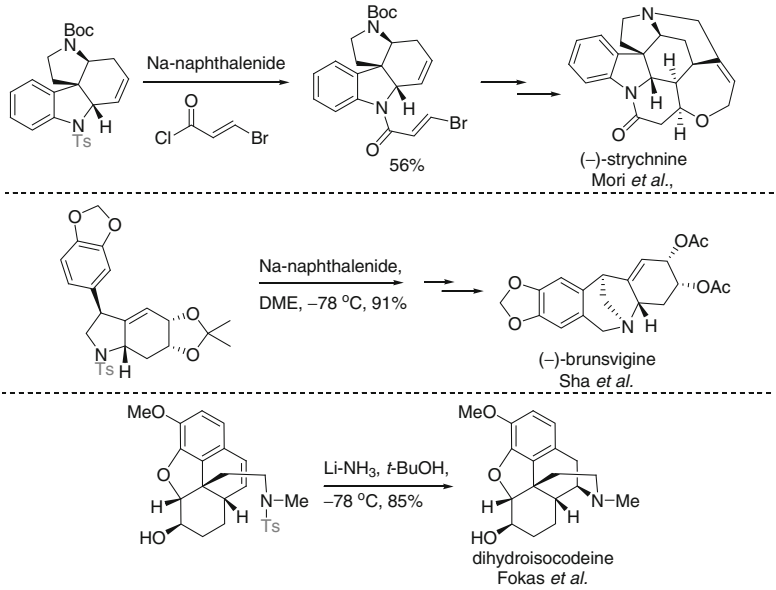
Scheme 5.1 illustrates selected examples highlighting the use of sulfonamide protecting groups in total syntheses [1, 2, 4]. In this regard, the fate of the sulfonyl moiety is as a rule discounted. Early reports by Kovacs [11] and Closson [12] provided some insight into the possible fate of the sulfonyl functional group. Both studies reported the isolation of toluene as a by-product from the reductive cleavage of a variety of *N*-tosyl protected amines, where both the nitrogen-sulfur and carbon-sulfur bonds have been cleaved (Scheme 5.2).

In 2005, Evans et al. reported that the treatment of cyclic sulfonamides (of the type **103**) under standard detosylation conditions, sodium or lithium-ammonia at −78 °C, led to the isolation of 3-aryl pyrrolidines of the type **104** (Scheme 5.3) [5, 13].

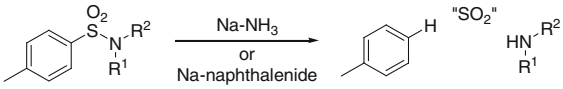
These products arise from a process whereby both the carbon-nitrogen and carbon-sulfur bonds are cleaved, and is termed a 'double reduction' reaction. This process, using the sulfonyl moiety as a nitrogen protecting group and as a *disposable tether*, has been extended to access a number of aryl-substituted pyrrolidines, some examples of which are enantiomerically pure (see Fig. 5.1).

Based on this precedence, the double reduction of quaternary compound **264** (for the preparation of compound **264**, see Chap. 4, Sect. 4.2) was attempted (Scheme 5.4).

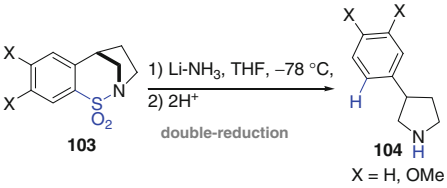
K. Geoghegan, *Selectivity in the Synthesis of Cyclic Sulfonamides*,
Springer Theses, DOI 10.1007/978-3-319-10338-9_5



Scheme 5.1 Examples of sulfonamides as protecting groups in total synthesis



Scheme 5.2 Toluene detection from detosylation of sulfonamides



Scheme 5.3 Double reduction of cyclic sulfonamides of the type **103**

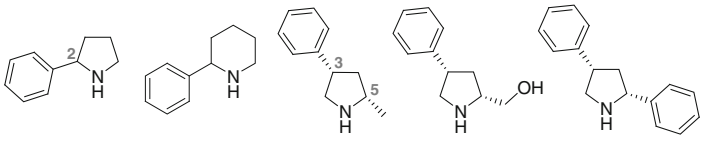
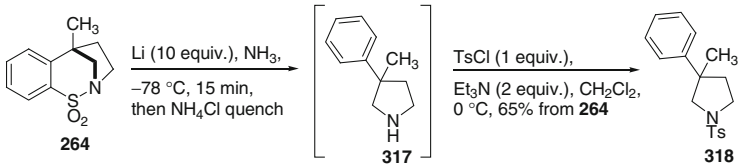
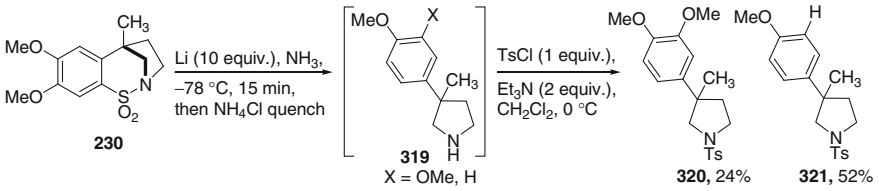


Fig. 5.1 Aryl-substituted pyrrolidines



Scheme 5.4 Double reduction of cyclic sulfonamide **264**



Scheme 5.5 Double reduction of cyclic sulfonamide **230**

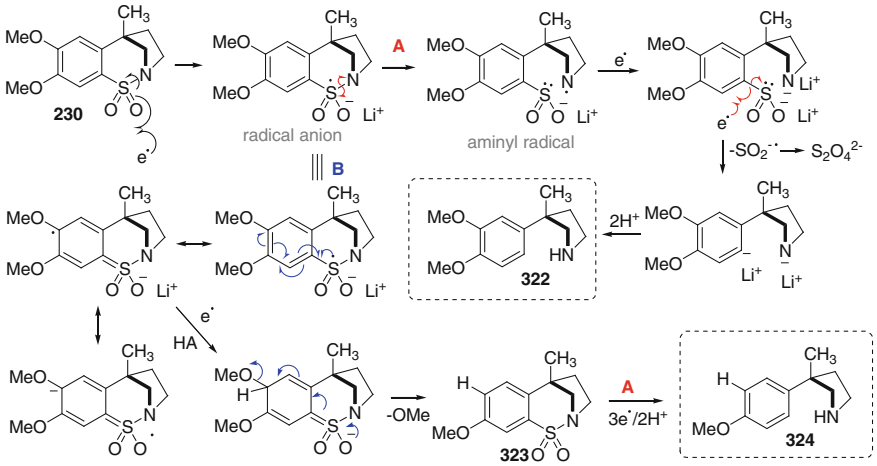
Pleasingly, under standard reductive conditions used in Scheme 5.3, compound **264** was converted, in two steps, into 3-methyl-3-phenyl-1-tosylpyrrolidine **318** in 65 % yield (from **64**). The formation of the intermediate secondary amine **317** was detected by mass spectrometry, which was subsequently converted into the *N*-tosyl amide **318** for characterisation purposes. A double reduction reaction was then successfully extended to the electron-rich aromatic system **230** (Scheme 5.5).

Treatment of **230** with Li-NH_3 followed by *N*-tosylation, afforded a chromatographically separable mixture of the expected substituted pyrrolidine **320** and mono-methoxy **321** (in a ratio of 33:67). The latter product arises from regioselective methoxy cleavage during the double reduction sequence. This regioselective ether cleavage was also observed during the double reduction of compound **200** (Scheme 2.8) and has been documented in the literature [14, 15]. Based on product outcome in Scheme 5.5, a possible reaction mechanism is proposed in Scheme 5.6.

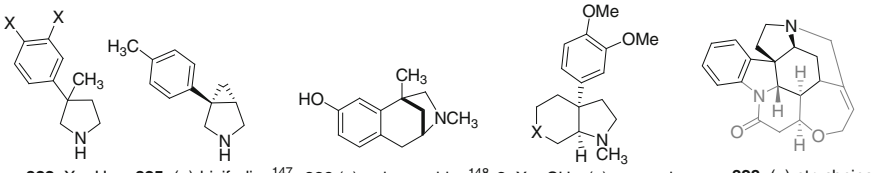
It could be envisaged that the initially formed radical anion could proceed via Path A, which leads to the desired dimethoxy-compound **322**. Alternatively, this radical could be resonance-stabilised into the aromatic functional group (Path B), which would lead to cleavage of the methoxy group *para* to the sulfonyl-group affording **323** which then could continue to compound **324**. However, associated with this proposal it should be noted that the addition of a Brønsted acid (*t*-BuOH) to the reaction did not alter the ratio of products formed.

5.2 Total Synthesis of (±)-Mesembrane

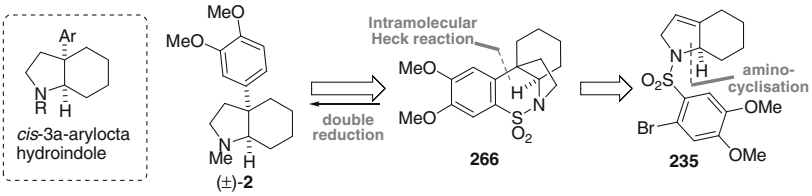
The pyrrolidine products **322**–**324** possess a quaternary carbon centre within its structure, and such motifs can also be observed in some natural product [2] and pharmaceutical scaffolds [16, 17] (Scheme 5.7).



Scheme 5.6 Possible competing pathways for the formation of **322** and **324**



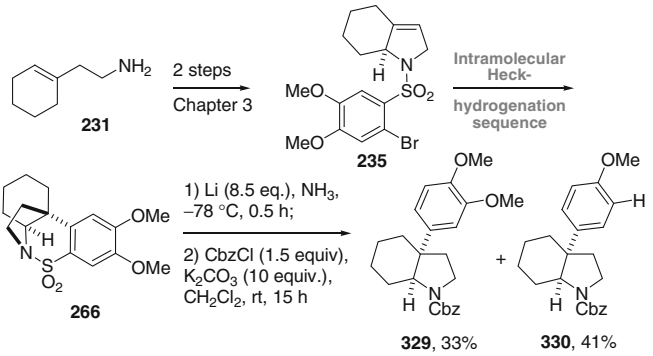
Scheme 5.7 3-Arylpyrrolidine containing alkaloids



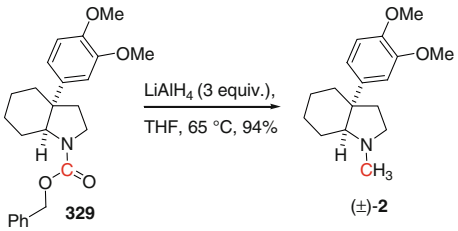
Scheme 5.8 Retrosynthetic analysis of mesembrane **2**

In particular, it was felt that we could access the *cis*-3a-aryloctahydroindole framework observed in the naturally occurring alkaloids mesembrane **2** and mesembrine **1**, utilising a combination of a double reduction reaction and a regioselective intramolecular Heck reaction on the appropriate sulfonamide (Scheme 5.8).

As depicted in Scheme 5.8, we intend to install the double bond in **235** using a sequential amino-cyclisation/elimination strategy which was used in Chap. 3. Based



Scheme 5.9 Double reduction of **266**



Scheme 5.10 Completion of the total synthesis of (±)−**2**

on the unusual regioselectivity uncovered in our intramolecular Heck reaction (Chap. 2), cyclic sulfonamide **266** could be accessed, and a double reduction reaction of this compound would furnish the *cis*-3a-aryloctahydroindole skeleton of the natural product **2**.

The electron-rich aromatic sulfonamide **266** was carried through to pursue the synthesis of racemic mesembrane **2** (for the preparation of **266**, see Chap. 4).

The treatment of **266** with lithium metal in NH_3 in THF, followed by carbamate formation, gave compounds **329** and **330** in 33 and 41 % isolated yields (Scheme 5.9). Fortunately, these carbobenzyloxy derivatives proved separable by column chromatography. Again, product **330** arises from a regioselective methoxy cleavage during the double reduction sequence (see Scheme 5.5). An alternative means to achieve the double reduction of cyclic sulfonamide **266** was briefly investigated. The use of sodium- or lithium-naphthalenide did provide compound **329**, albeit in a low isolated yield of 20–25 %. Interestingly, under aprotic conditions formation of the mono-methoxy compound **330** was not detected.

With sufficient amounts of **329** in hand the total synthesis of (±)-mesembrane **2** was completed (Scheme 5.10).

Apart from facilitating the separation of **329** and **330**, we used the Cbz-protecting group in our synthesis to strategically reveal a methyl group on the nitrogen atom [18]. Thus, when compound **329** was treated with lithium aluminium

hydride in refluxing THF the synthesis of (±)-mesembrane **2** was achieved in 94 % isolated yield, with data matching those reported in the literature [19].

In summary, a total synthesis of (±)−**2** was achieved utilising a regio- and diastereoselective Heck cyclisation and a double reduction reaction as our key steps. During this synthesis the sulfonamide functional group and the benzyl carbamate groups were both used in strategic bond formation reactions, which therefore did not require non-productive, additional deprotection steps.

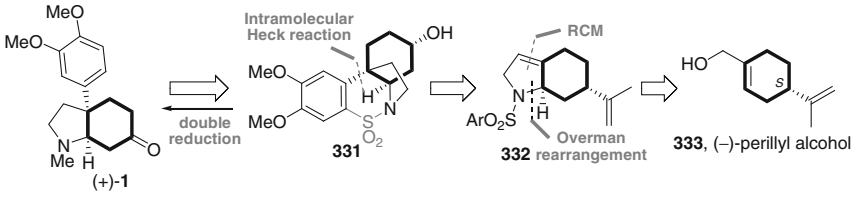
5.3 Total Synthesis of (−)-Mesembrine

Having completed the synthesis of racemic mesembrane **2**, we considered utilising the same synthetic strategy for the asymmetric synthesis of this group of alkaloids, in specific targeting the synthesis of mesembrine **1** (Scheme 5.11).

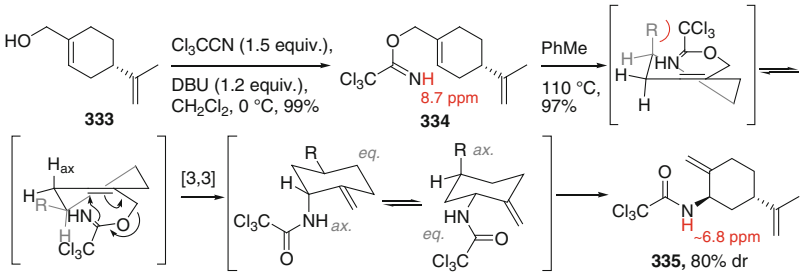
We anticipated that a double reduction reaction of **331** would give access to the naturally occurring alkaloid **1**. Cyclic sulfonamide **331** would be the product of a diastereo- and regioselective intramolecular Heck reaction performed on trisubstituted alkene **332**. It was envisaged that **332** could be synthesised as a single enantiomer from the monoterpenoid (*S*)-perillyl alcohol **333**. This terpene would constitute both the source of asymmetry, the cyclohexyl ring and, in addition, the isopropenyl group could be further elaborated to provide the ketone functional group incorporated into the natural product.

As outlined in Scheme 5.11, the starting point of the synthesis was conversion of the commercially available (*S*)-perillyl alcohol **333** into the corresponding trichloroacetimidate **334** (Scheme 5.12) [20].

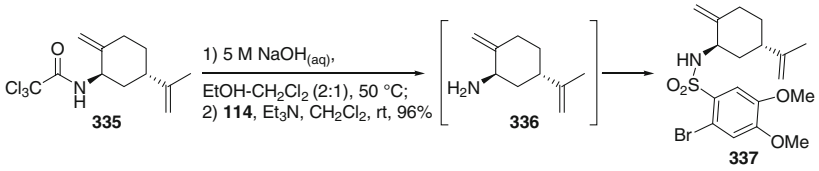
An Overman rearrangement [21, 22] of imidate **334** could be performed by refluxing in dry toluene for 5 days, which gave trichloroacetamide **335** in 97 % yield after purification. Trichloroacetamide **335** was isolated as an inseparable mixture of diastereoisomers in a 9:1 ratio (determined from the ^{1}H NMR spectra of the crude product); the major diastereomer contained the correct stereochemistry for (+)-mesembrine (unnatural enantiomer). Presumably, the diastereoselectivity observed in this [3, 3]-sigmatropic rearrangement arises from a *pseudo*-axial carbon-nitrogen bond formation from a conformer in which the isopropenyl substituent occupies a *pseudo*-equatorial position. The acetamide mixture was cleaved under basic conditions (ethanolic aqueous NaOH) [23] to access a mixture of



Scheme 5.11 Retrosynthetic analysis of (+)-mesembrine **1**



Scheme 5.12 Overman rearrangement of **334**



Scheme 5.13 Sulfonamide formation

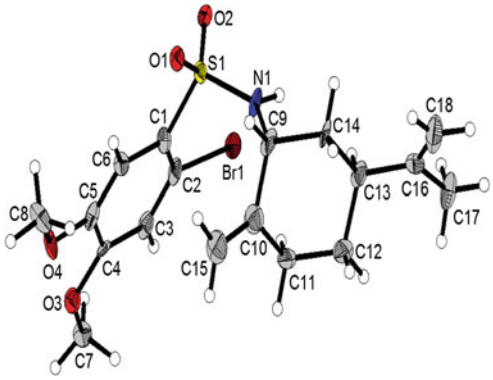
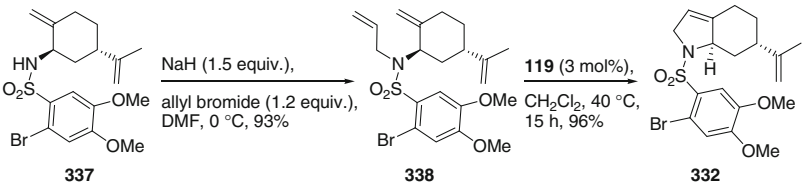


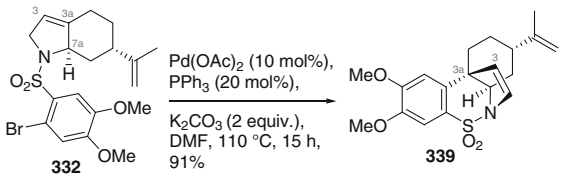
Fig. 5.2 X-ray crystal structure of sulfonamide **337**

diastereomeric primary amines, which, due to volatility, were directly converted into the corresponding sulfonamides with 2-bromo-4,5-dimethoxybenzenesulfonyl chloride **114** (Scheme 5.13).

Optimum yields for this reaction were realised when an excess of amine **336** (*ca.* 1.3 equiv.) was used. At this point chromatographic separation of the two diastereoisomers was possible and the major crystalline sulfonamide **337** was isolated (96 % in two steps from **335**, based on **114**). X-ray crystallography indicated that the diastereoisomer necessary for the synthesis of (+)−**1**, had indeed been obtained (Fig. 5.2).



Scheme 5.14 Synthesis of Heck precursor **332**



Scheme 5.15 Regio- and diastereoselective Heck-Mizoroki reaction of **332**

Subsequent alkylation of sulfonamide **337** with allyl bromide, followed by a ring-closing metathesis (RCM) reaction in the presence of catalytic amounts of Hoveyda-Grubbs 2nd generation catalyst **119**, efficiently generated the desired Heck precursor **332** in near quantitative yield. No products arising from a competitive reaction with the isopropenyl olefin were detected (Scheme 5.14).

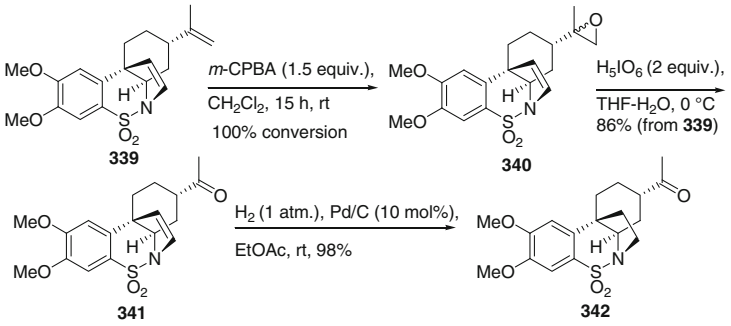
With alkene **332** in hand the planned intramolecular Heck-Mizoroki cyclisation was attempted (Scheme 5.15).

Pleasingly, using our standard conditions gave access to cyclic sulfonamide **339** in 91 % isolated yield. Again the carbon-carbon bond formation event occurred at the most substituted carbon, 3a, and also in a diastereoselective manner, governed by the stereogenic carbon-7a set by the Overman rearrangement.

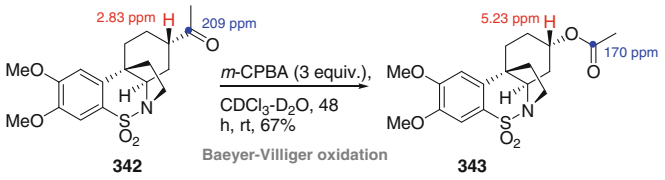
After serving as a non-participating bystander in the RCM and Heck process our next challenge was to convert the *exo*-cyclic alkene in **339** into a functional group that would ultimately become the carbonyl functional group present in the target natural products (+)−**1** and (+)−**327** (Scheme 5.16).

Based on previous studies conducted within the group, a chemoselective epoxidation of the *exo*-cyclic alkene could be effected by using slight excess of *meta*-chloroperbenzoic acid (*m*-CPBA), with the *endo*-cyclic alkene remaining unchanged [24]. The epoxide **340** was formed as a mixture of diastereoisomers, which was not as issue since it was directly converted to the methyl ketone **341** on treatment with periodic acid (H_5IO_6) in a THF-H_2O mixture. (86 % from **339**) [25]. Subsequent hydrogenation of the *endo*-cyclic double bond yielded the saturated cyclic sulfonamide **342** in near quantitative yield.

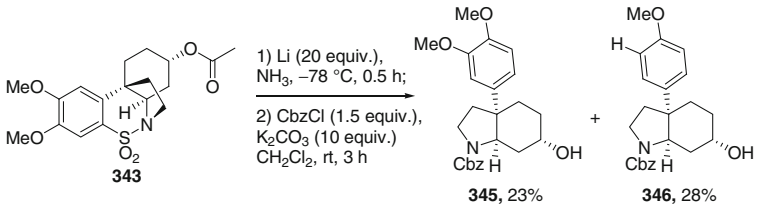
Having successfully converted the isopropenyl group into ketone 341, a Baeyer-Villiger oxidation reaction [26, 27] was used to install the requisite oxygen atom at C-6 (Scheme 5.17). Although this reaction proved sluggish, after some optimisation,



Scheme 5.16 Synthesis of ketone **342**



Scheme 5.17 Baeyer-Villiger oxidation of **342**

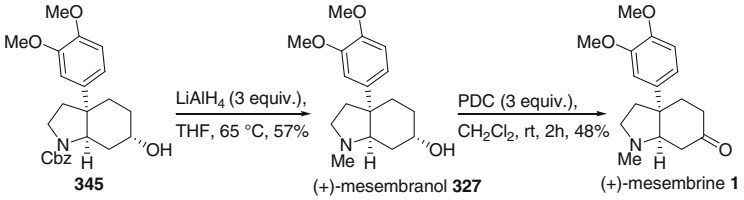


Scheme 5.18 Double reduction of **343**

acetate **343** was obtained in 67 % yield when 3 equivalents of *m*-CPBA were used in a deuterated solvent mixture ($CDCl_3$-D_2O; 1:1), which enabled monitoring of the reaction progress by ^1H NMR spectroscopy.

Based on our earlier work on the double reduction reaction we anticipated partial loss of the *para*-methoxy-group to the sulfonyl moiety (Scheme 5.5). Thus, when we subjected sulfonamide **343** to lithium (20 equivalents) in liquid ammonia, we isolated a 1:1 mixture of mono- and di-methoxy substituted amino alcohols (Scheme 5.18). During this reaction, in addition to the reductive sulfonyl excision, ammonia also facilitated a deacetylation process to reveal the secondary alcohol.

The crude mixture of amino alcohols were converted to their respective carbamate derivatives using benzyl chloroformate (CbzCl) in CH_2Cl_2 with potassium carbonate. Carbamates **345** (28 %) and **346** (23 %) proved readily separable by

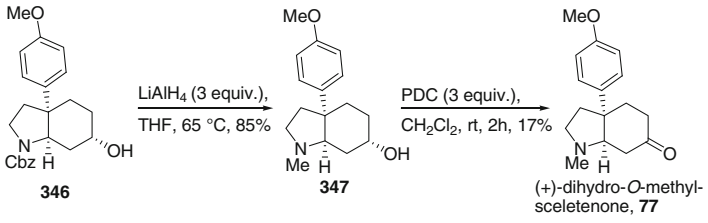


Scheme 5.19 Completing the synthesis of (+)-mesembranol and (+)-mesembrine

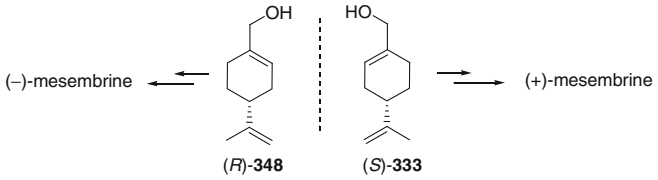
flash column chromatography. The carbamate moiety is a strategy used to aid the separation of **345** and **346** and to install the required methyl group onto the nitrogen atom found in the natural product (Scheme 5.19).

Thus, when compound **345** was treated with lithium aluminium hydride the *N*-methyl-amino alcohol **327** was obtained in moderate yield. This amino alcohol **327** is in fact the enantiomer of the naturally occurring alkaloid mesembranol **327** [28], which is also a known intermediate [29] on route to the target molecule mesembrine. To complete the synthesis of (+)−**1** an oxidation of the secondary alcohol in (+)−**327** was carried out. In our hands, despite numerous attempts and several different conditions (Swern oxidation and Dess-Martin periodinane), the optimum conditions proved to be pyridinium dichromate (PDC) in anhydrous CH_2Cl_2, which gave (+)−**1** in 48 % with data consistent to that reported in the literature [30]. Starting material consumption could be observed from the ^{1}H NMR spectra by the disappearance of the proton at C6 (at 4.03 ppm) and present in the ^{13}C NMR spectra was a peak at 211.6 ppm, indicative of a ketone carbonyl functional group. Infrared spectroscopy also suggested the formation of a ketone functional group with a signal at 1,709 cm^{-1}. It is also worth noting that a Wolff-Kishner reduction of mesembrine (**1**) has been reported to generate mesembrane (**2**) [31].

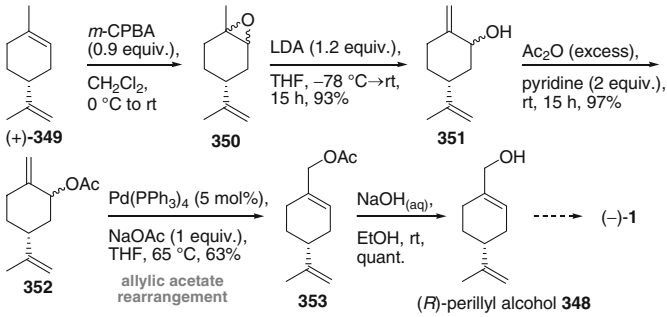
Although the reduction in yield associated with the partial methoxy cleavage was detrimental in relation to the synthesis of (+)−**1** (Scheme 5.18), the mono-methoxy side product is synthetically useful since other alkaloids belonging to the *Sceletium* family (for example, (+)-dihydro-*O*-methylsceletenone **77**), possess this type of aromatic substitution (Scheme 5.20) [32–35].



Scheme 5.20 Completing the synthesis of (+)−**77**



Scheme 5.21 Synthesis of both enantiomers of mesembrine



Scheme 5.22 Synthesis of (*R*)-perillyl alcohol **348**

Therefore, under identical conditions that furnished (+)−**1** from **345**, **77** was synthesised in 2 steps from carbamate **346**. It has to be noted that the poor yield for the oxidation of **347** → **77** reflects the difficulties associated with performing this reaction on small scale.

In conclusion, we have reported the stereoselective total synthesis of (+)−**1** and (+)−**327** from inexpensive (*S*)-perillyl alcohol **333**. The partial methoxy cleavage observed during the double reduction enables access of mono-methoxy members of the *Sceletium* alkaloid family. Based on the route developed, the natural enantiomer of mesembrine would be accessible using non-commercially available (*R*)-(+)-perillyl alcohol **348** (Scheme 5.21).

Scheme 5.22 depicts our efforts towards the synthesis of (*R*)-perillyl alcohol **348**, which, based on the work described above, would furnish the natural enantiomer of mesembrine (**1**). Starting from inexpensive (*R*)-(+)-limonene **349**, e*ndo*-cyclic epoxide **350** may be prepared using 1 equiv. of *meta*-chloroperbenzoic acid (*m*-CPBA) [36]. Epoxide **350** is, in fact, also commercially available as a mixture of *cis*- and *trans*-diastereoisomers. This material was treated with LDA [37] in THF at −78 °C and following work-up, the allylic alcohol **351** was isolated in an excellent 93 % yield. Acetylation of the epimeric alcohol **351** in neat acetic anhydride and pyridine furnished acetate **352** in near quantitative yield.

A literature procedure concerning the conversion of **352** to **353** using bromotrimethylsilane (TMS-Br) was investigated [38]. However, in our hands none of the hoped for primary bromide could be isolated. We therefore considered use of π-allyl transition metal chemistry to isomerise the epimeric allylic acetoxy-functionality in

352 to the less-sterically encumbered, primary isomer, **353**. Although the use of acetoxy groups as nucleophiles in π-allyl palladium chemistry does not feature frequently in the literature, there are several reported examples for allylic acetate rearrangements available [39–43]. Our initial attempts using a literature procedure by Trost et al. [39]. ($[Pd(PPh_3)_4]$ (5 mol%) in refluxing THF) failed to give any desired product **353**. Performing the reaction under identical conditions but in a Pyrex sealable tube gave trace amounts of isomerised acetate **353** (<5 %) along with recovered starting material. The addition of sodium acetate (NaOAc) [42, 43] to the reaction mixture led to the isolation of primary acetate **353**. However, differences in isolated yields were observed when varying the equivalents of sodium acetate used; 1 equiv. gave 63 % yield for **353**, whereas an excess of 1.3 equiv. or 3 equiv. gave slightly smaller amounts of **353** in 59 and 30 % isolated yields respectively. Basic hydrolysis of **353** gave perillyl alcohol (**348**) in quantitative yield. Comparison between the specific rotation of commercial (*S*)−**333** and synthetic (*R*)−**348** demonstrated approximately equal and opposite values.

Based on this work (Scheme 5.22) and the chemistry reported previously in Sect. 5.3 a formal synthesis of the natural enantiomer (−)-mesembrine **1** using the synthesised (*R*)-perillyl alcohol **348** has therefore been accomplished.

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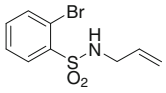
Chapter 6
Experimental

6.1 General Directions

Reactions with anhydrous solvents were carried out under an atmosphere of nitrogen. Glassware was either dried in an oven or by heat-gun before use, assembled hot and cooled to room temperature under a stream of N_2. Anhydrous THF was freshly distilled from sodium-benzophenone prior to use, anhydrous CH_2Cl_2 was freshly distilled from CaH_2, anhydrous DMF, Toluene (PhMe) and MeCN were purchased from Sigma Aldrich. Reagents from Acros, Fluka or Sigma Aldrich were used without further purification. *n*-Butyllithium reagents were titrated prior to use. Thin layer chromatography (TLC) was carried out on Merck silica gel aluminium sheets (60 F254). UV light and a mixture of 1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10 % NaOH in 200 mL water were used as a visualising stain. Merck silica gel (60, 0.040–0.063) was used for flash column chromatography. NMR spectra were recorded on a Varian 300, 400, 500, or 600 MHz spectrometer and calibrated using trimethylsilane (TMS). IR spectra were recorded on a Varian 3100 FT-IR spectrometer. High Resolution Mass Spectra (HRMS) were recorded using a Waters Corp, Micromass LCT, Electrospray Ionisation (ESI) spectrometer. Melting points were determined in an open capillary on a Gallenkamp melting point apparatus and are uncorrected. Sealed tubes used in this study were purchased from Sigma Aldrich.

6.2 Experimental



***N*-Allyl-2-bromobenzenesulfonamide 112:** [1] A mixture of 2-bromobenzene sulfonyl chloride **111** (1.5 g, 5.9 mmol, 1 equiv.) and allylamine (0.53 mL, 7.04 mmol,

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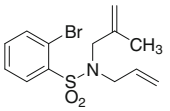
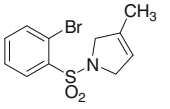
Springer Theses, DOI 10.1007/978-3-319-10338-9_6

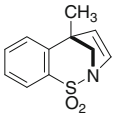
1.2 equiv.) in CH_2Cl_2 (15 mL) was treated with Et_3N (1.02 mL, 7.34 mmol, 1.25 equiv.) in a dropwise fashion at 0 °C. Stirring was continued for 2 h and the reaction gradually warmed to room temperature. 1 M HCl (15 mL) was added and the layers were partitioned. The organic layer was washed with H_2O, brine and dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded the *title compound* **112** (1.39 g, 86 %) as a colourless solid. Mp 66–68 °C; R_f = 0.4 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3316, 3087, 2988, 2922, 2855, 1647, 1575, 1448, 1427, 1332, 1253, 1163, 1127, 1103, 1020 cm^{-1}; HRMS (ESI): calcd for $[(C_9H_{10}NO_2\ ^{79}BrS + H)]^+$ 275.9694, found 275.9695; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.14 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.74 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.39–7.51 (m, 2H, ArH), 5.64–5.77 (m, 1H, CH), 5.08–5.21 (m, 3H, CH_2, NH), 3.57 (t, *J* = 6.0 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9 (C), 135.0 (CH), 133.7 (CH), 132.5 (CH), 131.6 (CH), 127.8 (CH), 119.7 (C), 118.2 (CH_2), 45.9 (CH_2) ppm. NMR data matched that in the literature.



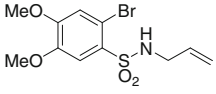
***N*-Allyl-*N*-2-methylallyl-2-bromobenzenesulfonamide 113:** *N*-Allyl-2-bromobenzenesulfonamide **112** (1.48 g, 5.4 mmol, 1 equiv.) was dissolved in DMF (20 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 257 mg, 6.43 mmol, 1.2 equiv.) was added and the mixture was stirred for a 0.5 h. 3-Chloro-2-methylprop-1-ene **117** (0.8 mL, 8.04 mmol, 1.5 equiv.) was added in a dropwise fashion. Stirring was continued for 2 h during which period room temperature was reached. EtOAc (20 mL) and H_2O (20 mL) were added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 × 20 mL) and the combined organic extracts were dried ($MgSO_4$). The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 5:1) which gave the *title compound* **113** (1.29 g, 77 %) as a viscous colourless oil. R_f = 0.5 (*c*-Hex/EtOAc, 5:1); IR (NaCl, dep. from CH_2Cl_2) 3082, 2976, 2919, 2851, 1575, 1446, 1434, 1342, 1280, 1255, 1160, 1125, 1102, 1078, 1027 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{16}NO_2\ ^{79}BrS + H)]^+$ 330.0163, found 330.0179; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.17 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.73 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.44 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.37 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 5.49–5.63 (m, 1H, CH), 5.07-5.14 (m, 2H, CH_2), 4.93 (s, 1H, CH_2), 4.90 (s, 1H, CH_2), 3.91 (s, 2H, CH_2), 3.86 (d, *J* = 7.0 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.7 (C), 139.5 (C), 135.3 (CH), 133.3 (CH), 132.2 (CH), 131.9 (CH), 127.3 (CH), 120.3 (C), 119.2 (CH_2), 114.7 (CH_2), 52.8 (CH_2), 48.4 (CH_2), 19.5 (CH_3) ppm.



1-(2-Bromobenzenesulfonyl)-2,5-dihydro-3-methyl-1*H*-pyrrole 108: Under N_2, a degassed solution of **113** (1.2 g, 3.7 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) was treated with the Hoveyda-Grubbs 2nd gen. catalyst **119** (44 mg, 0.183 mmol, 2 mol %). Stirring was continued at rt for 15 h and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 5:1) gave **108** (1.05 g, 95 %) as a light brown solid. R_f = 0.3 (*c*-Hex/EtOAc, 5:1), Mp 29-31 °C; IR (NaCl, dep. from CH_2Cl_2) 3075, 2918, 2858, 1631, 1574, 1431, 1334, 1256, 1165, 1130, 1107, 1088, 1023 cm^{-1}; HRMS (ESI): calcd for $[(C_{11}H_{12}NO_2\ ^{79}BrS + H)]^+$ 301.9850, found 301.9863; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.75 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.44 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.38 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 5.34–5.38 (m, 1H, CH), 4.21–4.26 (m, 2H, CH_2), 4.11–4.15 (m, 2H, CH_2), 1.74 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7 (C), 135.7 (CH), 134.9 (C), 133.4 (CH), 131.5 (CH), 127.5 (CH), 120.4 (C), 118.9 (CH), 57.7 (CH_2), 55.2 (CH_2), 14.1 (CH_3) ppm.

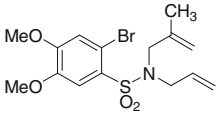


1-Methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 109: Under N_2, a mixture of **108** (100 mg, 0.33 mmol, 1 equiv.), $Pd(OAc)_2$ (7.5 mg, 0.033 mmol, 10 mol%), PPh_3 (17.5 mg, 0.066 mmol, 20 mol%) and K_2CO_3 (90 mg, 0.66 mmol, 2 equiv.) in anhydrous DMF (10 mL) was heated to 110 °C for 3.5 h. The reaction mixture was cooled and EtOAc (15 mL) and H_2O (15 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 3:1) affording the Heck product **109** (65 mg, 90 %) as a colourless solid. Mp 128–134 °C; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 2935, 2883, 1840, 1723, 1591, 1463, 1439, 1386, 1329, 1277, 1243, 1207, 1166, 1112, 1053, 1027 cm^{-1}; HRMS (EI): calcd for $[C_{11}H_{11}NO_2\ ^{79}BrS]^+$ 221.0511, found 221.0520; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.49 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.44 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 7.22 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 6.38 (d, *J* = 4.0, 1H, CH), 6.23 (d, *J* = 4.0 Hz, 1H, CH), 4.45 (d, *J* = 12.0 Hz, 1H, CH_2), 3.81 (d, *J* = 12.0 Hz, 1H, CH_2), 1.47 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.6 (C), 139.5 (CH), 132.5 (CH), 132.4 (C), 130.7 (CH), 128.7 (CH), 126.3 (CH), 121.8 (CH), 67.5 (CH_2), 43.9 (C), 16.0 (CH_3) ppm.

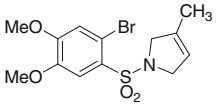


***N*-Allyl-2-bromo-4,5-dimethoxybenzenesulfonamide 115:** A mixture of 2-bromo-4,5-dimethoxybenzene-1-sulfonyl chloride **114** (1.00 g, 3.2 mmol, 1 equiv.) and allylamine (0.29 mL, 3.8 mmol, 1.2 equiv.) was treated with Et_3N

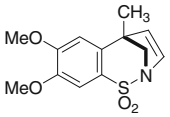
(0.5 mL, 3.96 mmol, 1.25 equiv.) in CH_2Cl_2 (10 mL) in a dropwise fashion at 0 °C. Stirring was continued for 2 h and the reaction gradually warmed to room temperature. 1 M HCl (15 mL) was added and the layers were partitioned. The organic layer was washed with H_2O, brine and dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded the *title compound* **115** (1.16 g, 94 %) as a light brown solid. Mp 60–64 °C; R_f = 0.3 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3098, 1609, 1330, 1170, 1143, 924, 874, 582 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (s, 1H, ArH), 7.07 (s, 1H, ArH), 5.77-5.64 (m, 1H, CH), 5.21–5.16 (m, 2H, CH_2, NH), 5.09 (d, *J* = 10 Hz, 1H, CH_2), 3.87 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.48 (t, *J* = 6.5 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5 (C), 148.1 (C), 132.7 (CH), 130.6 (C), 118.2 (CH_2), 117.1 (CH), 114.0 (CH), 111.2 (C), 56.6 (CH_3), 56.5 (CH_3), 46.0 (CH_2) ppm.



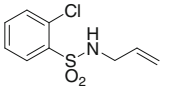
***N*-Allyl-2-bromo-4,5-dimethoxy-*N*-(2-methylallyl)benzenesulfonamide 116:** *N*-Allyl-2-bromo-4,5-dimethoxybenzenesulfonamide **115** (845 mg, 2.51 mmol, 1 equiv.) was dissolved in DMF (15 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 178 mg, 3.1 mmol, 1.78 equiv.) was added and the mixture was stirred for a 0.5 h. 3-Chloro-2-methylprop-1-ene **117** (0.32 mL, 3.14 mmol, 1.25 equiv.) was added in a dropwise fashion. Stirring was continued for 2 h during which period room temperature was reached. Et_2O (20 mL) and H_2O (20 mL) were added and the phases were separated. The aqueous phase was further extracted with Et_2O (2 × 20 mL). The combined ethereal extracts were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 1:1) which gave *title compound* **116** (800 mg, 82 %) as a colourless solid. Mp 76–80 °C; R_f = 0.5 (*c*-Hex/EtOAc, 1:1); IR (NaCl, dep. from CH_2Cl_2) 3043, 2935, 1360, 1153, 920, 590 cm^{-1}; HRMS (ESI): calcd for $[(C_{15}H_{20}NO_4\ ^{79}BrS + Na)]^+$ 412.0194, found 412.0201; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H, ArH), 7.13 (s, 1H, ArH), 5.58 (ddt, *J* = 17.0, 11.0, 6.5 Hz, 1H, CH), 5.15 (d, *J* = 4.0 Hz, 1H, CH_2), 5.12 (d, *J* = 11.0 Hz, 1H, CH_2), 4.93 (s, 1H, CH_2), 4.92 (s, 1H, CH_2), 3.93 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 3.84 (d, *J* = 6.5 Hz, 2H, CH_2), 1.65 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3 (C), 147.9 (C), 140.2 (C), 132.4 (CH), 131.6 (C), 119.5 (CH_2), 117.5 (CH), 114.9 (CH, CH_2), 112.1 (C), 56.6 (CH_3), 56.7 (CH_3), 53.2 (CH_2), 48.8 (CH_2), 19.9 (CH_3) ppm.



1-(2-Bromo-4,5-dimethoxyphenylsulfonyl)-3-methyl-2,5-dihydro-1*H*-pyrrole 118: Under N_2, a degassed solution of **116** (750 mg, 1.92 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (12 mg, 0.0192 mmol, 1 mol%). Stirring was continued at room temperature for 5 h and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 1:1) gave **118** (695 g, 91 %) as a white solid. Mp 70–74 °C; R_f = 0.4 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3064, 3007, 2937, 1360, 1160, 871, 791, 679, 600 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{16}NO_4{}^{79}BrS + H)]^+$ 362.0062, found 362.0077; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H, ArH), 7.16 (s, 1H, ArH), 5.36 (s, 1H, CH), 4.21 (d, *J* = 2.0 Hz, 2H, CH_2), 4.10 (s, 2H, CH_2), 3.93 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 1.74 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.2 (C), 147.9 (C), 135.0 (C), 130.2 (C), 119.0 (CH), 117.7 (CH), 114.4 (CH), 111.9 (C), 57.7 (CH_2), 56.6 (CH_3), 56.5 (CH_3), 55.2 (CH_2), 14.3 (CH_3) ppm.

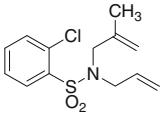


4,5-Dimethoxy-1-methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 120: Under N_2, a mixture of **118** (100 mg, 0.28 mmol, 1 equiv.), $Pd(OAc)_2$ (6 mg, 0.028 mmol, 10 mol%), PPh_3 (13 mg, 0.056 mmol, 20 mol%) and K_2CO_3 (77 mg, 0.56 mmol, 2 equiv.) in anhydrous DMF (5 mL) was heated to 110 °C for 2.5 h. The reaction mixture was cooled and Et_2O (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with Et_2O (2 × 10 mL) and the combined ethereal extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by recrystallisation from *c*-Hex affording the Heck product **120** (41 mg, 53 %) as a colourless solid. Mp 204–208 °C; R_f = 0.2 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3030, 2948, 1324, 1153, 1118, 732 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{15}NO_4S + H)]^+$ 281.0722, found 281.0710; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16 (s, 1H, ArH), 6.67 (s, 1H, ArH), 6.37 (d, *J* = 4.0 Hz, 1H, CH), 6.25 (d, *J* = 4.0 Hz, 1H, CH), 4.40 (d, *J* = 12.0 Hz, 1H, CH_2), 3.92 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.77 (d, *J* = 12.0 Hz, 1H, CH_2), 1.53 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.2 (C), 149.8 (C), 140.8 (CH), 136.4 (C), 133.7 (CH), 124.5 (C), 109.6 (CH), 106.0 (CH), 69.1 (CH_2), 56.4 (CH_3), 56.3 (CH_3), 44.9 (C), 17.4 (CH_3) ppm.

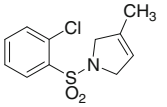


***N*-Allyl-2-chlorobenzenesulfonamide:** A mixture of 2-chlorobenzenesulfonyl chloride **135** (0.65 mL, 4.7 mmol, 1 equiv.) and allylamine (0.38 mL, 52.0 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) was treated with Et_3N (1.31 mL, 9.4 mmol, 2 equiv.)

in a dropwise fashion at 0 °C. Stirring was continued for 15 h and the reaction gradually warmed to room temperature. The organic layer was washed with 1 M HCl (20 mL), the layers separated and the organic layer was dried ($MgSO_4$). Filtration followed by solvent removal in vacuo afforded the *title compound* (1.09 g, 99 %) as a colourless solid. Mp 58–60 °C; R_f = 0.2 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3312, 3089, 1577, 1330, 1162, 835, 666 cm^{-1}; HRMS (ESI): calcd for $[(C_9H_{10}NO_2\ ^{35}ClS + H)]^+$ 232.0199, found 232.0203; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13–8.07 (m, 1H, ArH), 7.57–7.49 (m, 2H, ArH), 7.45–7.39 (m, 1H, ArH), 5.70 (ddt, *J* = 16.0, 10.5, 6.0 Hz, 1H, CH), 5.18 (dd, *J* = 17.0, 1.0 Hz, 2H, NH, CH_2), 5.09 (dd, *J* = 10.0, 1.0 Hz, 1H, CH_2), 3.59 (t, *J* = 6.0 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.5 (C), 133.9 (CH), 132.7 (CH), 131.7 (CH), 131.5 (CH), 127.4 (CH), 118.2 (C, CH_2), 46.0 (CH_2) ppm.

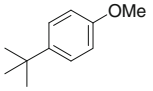


***N*-Allyl-2-chloro-*N*-(2-methylallyl)benzenesulfonamide 136:** *N*-Allyl-2-chloro-benzenesulfonamide (200 mg, 0.87 mmol, 1 equiv.) was dissolved in DMF (2 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 45 mg, 1.13 mmol, 1.2 equiv.) was added and the mixture was stirred for a 0.5 h. 3-Chloro-2-methyl-1-ene **117** (0.1 mL, 1.04 mmol, 1.2 equiv.) was added in a dropwise fashion. Stirring was continued for 17 h during which period room temperature was reached. EtOAc (10 mL) and (H_2O 10 mL) were added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 3:1) which gave the *title compound* **136** (216 mg, 87 %) as a light yellow oil. R_f = 0.8 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{13}H_{16}NO_2\ ^{35}ClS + Na)]^+$ 308.0488, found 308.0500; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.54–7.44 (m, 2H, ArH), 7.42–7.35 (m, 1H, ArH), 5.54 (m, 1H, CH), 5.10 (ddd, *J* = 11.0, 6.0, 1.0 Hz, 2H, CH_2), 4.91 (d, *J* = 9.0 Hz, 2H, CH_2), 3.90 (s, 2H, CH_2), 3.84 (s, 1H, CH_2), 3.82 (s, 1H, CH_2), 1.63 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.9 (C), 138.3 (C), 133.6 (CH), 132.2 (CH), 132.1 (C), 132.0 (CH), 131.9 (CH), 127.0 (CH), 119.4 (CH_2), 114.9 (CH_2), 52.7 (CH_2), 48.7 (CH_2), 19.7 (CH_3) ppm.

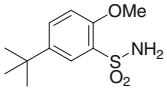


1-(2-Chlorophenylsulfonyl)-3-methyl-2,5-dihydro-1*H*-pyrrole 137: Under N_2, a degassed solution of compound **136** (200 mg, 0.70 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (4.3 mg, 0.007 mmol, 1 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure.

Purification by flash column chromatography (*c*-Hex/EtOAc, 4:1) gave **137** (141 mg, 78 %) as a pale green oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3105, 1600, 1337, 1169 1134, 750 cm^{-1}; HRMS (ESI): calcd for $[(C_{11}H_{12}NO2\ ^{35}ClS + H)]^+$ 258.0356, found: 258.0345; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.48 (td, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.39 (td, *J* = 8.0, 1.5 Hz, 1H, ArH), 5.36 (dd, *J* = 3.5, 2.0 Hz, 1H, CH), 4.23 (ddd, *J* = 6.5, 4.5, 2.0 Hz, 2H, CH_2), 4.16–4.09 (m, 2H, CH_2), 1.74 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.1 (C), 135.1 (C), 133.5 (CH), 132.2 (C), 132.0 (CH), 131.6 (CH), 127.0 (CH), 119.1 (CH), 57.7 (CH_2), 55.2 (CH_2), 14.3 (CH_3) ppm.

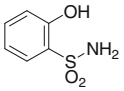


1-(*tert*-Butyl)-4-methoxybenzene 146:[92] A solution of anisole (6 mL, 0.056 mol, 1 equiv.) in *c*-Hex (100 mL) was treated to *t*-BuOH (5.3 mL, 0.056 mol, 1 equiv.) and $AlCl_3$ (3.7 g, 0.028 mol, 0.05 equiv.). Stirring was continued for 3 h at 30 °C. The reaction mixture was added cautiously to ice (*ca.* 300 mL), and, once melted, was extracted with *c*-Hex (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$. Filtration, followed by solvent removal afforded the crude product, which, after vacuum distillation, yielded **146** (4.1 g, 45 %) as a brown liquid. Bp = 222 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.27 (m, 2H, ArH), 6.93–6.79 (m, 2H, ArH), 3.76-3.75 (m, 3H, CH_3), 1.26 (s, 9H, CH_3) ppm. NMR data matched that in the literature.

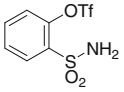


5-(*tert*-Butyl)-2-methoxybenzenesulfonamide 148: A solution of **146** (1 g, 0.01 mol, 1 equiv.) in CH_2Cl_2 (100 mL) was treated dropwise with a solution of HSO_3Cl (10 mL) in CH_2Cl_2 (2 mL) at 0 °C. Stirring was continued for 20 min before cautiously adding to ice (*ca.* 60 mL). Once melted, the reaction mixture was extracted with CH_2Cl_2 (2 × 60 mL), dried ($MgSO_4$), filtered and reduced under pressure to yield the crude 5-(*tert*-butyl)-2-methoxybenzene-1-sulfonyl chloride **147** [^1H NMR ($CDCl_3$, 300 MHz): δ 7.95–7.92 (m, 1H, ArH), 7.77–7.72 (m, 1H, ArH), 7.13 (d, *J* = 8.5 Hz, 1H, ArH), 4.03 (m, 3H, CH_3), 1.34 (s, 9H, CH_3)]. A solution of the crude chloride **147** in MeCN (60 mL) was treated dropwise to an aqueous solution of NH_4OH (2 M, *ca.* 30 mL) at 0 °C. Stirring was continued for 15 h, during which period room temperature was reached. The reaction mixture was carefully added to ice (*ca.* 50 mL) and carefully neutralised with conc. HCl. The brown precipitate was filtered, redissolved in CH_2Cl_2 (30 mL), dried ($MgSO_4$), filtered and reduced under pressure to afford the *title compound* **148** (1.4 g, 96 %) as a yellow solid. Mp 123–125 °C; HRMS (ESI): calcd for $[(C_{11}H_{17}NO_3S + Na)]^+$ 266.0827, found 266.0829; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* = 2.5 Hz, 1H, ArH), 7.55 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 6.98 (d, *J* = 8.5 Hz, 1H, ArH), 5.05

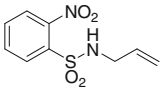
(s, 2H, NH_2), 4.00 (s, 3H, CH_3), 1.31 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7 (C), 144.2 (C), 131.3 (C), 129.5 (CH), 125.4 (CH), 112.1 (CH), 56.7 (CH_3), 34.6 (C), 31.4 (CH_3) ppm. NMR data matched that in the literature.



2-Hydroxybenzenesulfonamide 149: [2] Under N_2, a solution of **148** (800 mg, 3.29 mmol, 1 equiv.) in anhydrous PhMe (15 mL) was treated to anhydrous $AlCl_3$ (1.82 g, 13.66 mmol, 4.15 equiv.) and the reaction heated to 60 °C for 24 h. Once cooled, the reaction mixture was poured onto ice-water (60 mL). NaCl (*ca.* 4 g) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and reduced under pressure to give a crude product. Purification by column chromatography (*c*-Hex/EtOAc, 1:1) gave **149** (560 mg, 98 %) as a pale yellow solid. Mp = 119-121 °C; R_f = 0.2 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3105, 1600, 1337, 1169 1134, 750 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 10.61 (s, 1H, OH), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.39 (m, 1H, ArH), 7.00–6.81 (m, 4H, ArH, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5 (C), 133.3 (CH), 129.4 (C), 127.4 (CH), 118.4 (CH), 117.0 (CH) ppm. NMR data matched that in the literature.

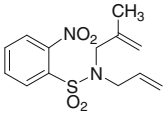


2-Sulfamoylphenyl trifluoromethanesulfonate 150: A solution of **149** (300 mg, 1.73 mmol, 1 equiv.) in pyridine (3 mL) was treated to Tf_2O (0.35 mL, 2.08 mmol, 1.2 equiv.) at 0 °C. Stirring was maintained at this temperature for 40 min and then rt for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and the layers were separated. The ethereal layer was washed with 1 M HCl, sodium bicarbonate and dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 5:1 → 1:1) which gave the *title compound* **150** (252 mg, 58 %) as a colourless solid. Mp 131–133 °C; R_f = 0.2 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3377, 3271, 1436, 1340, 1215, 1204, 1159, 1134, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.88–7.76 (m, 3H, ArH, NH_2), 7.69 (td, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.57 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8 (C), 136.5 (CH), 134.6 (CH), 129.3 (CH), 122.7 (q, *J* = 2.0 Hz, C), 117.9 (q, *J* = 321 Hz, C) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.4 ppm.

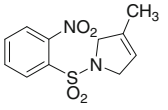


***N*-Allyl-2-nitrobenzenesulfonamide:** A mixture of 2-nitrobenzenesulfonyl chloride (1.00 g, 4.5 mmol, 1 equiv.) and allylamine (0.38 mL, 4.9 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) was treated with Et_3N (1.25 mL, 9.04 mmol, 2 equiv.) in a

dropwise fashion at 0 °C. Stirring was continued for 5 h and the reaction gradually warmed to room temperature. The organic layer was washed with H_2O (3 × 50 mL) and dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded the *title compound* (830 mg, 76 %) as a colourless solid. Mp 48–50 °C; R_f = 0.1 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_9H_{10}N_2O_4S + H)]^+$ 243.0440, found 243.0446; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15–8.09 (m, 1H, ArH), 7.89–7.84 (m, 1H, ArH), 7.79–7.73 (m, 2H, ArH), 5.74 (ddt, *J* = 16.0, 11.0, 6.0 Hz, 1H, CH), 5.21 (dd, *J* = 17.0, 1.0 Hz, 1H, CH_2), 5.10 (dd, *J* = 11.0, 1.0 Hz, 1H, CH_2), 3.77 (t, *J* = 6.0 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.0 (C), 133.7 (C, CH), 132.9 (CH), 132.6 (CH), 131.1 (CH), 125.4 (CH), 118.1 (CH_2), 46.3 (CH_2) ppm.

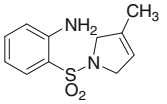


***N*-Allyl-*N*-(2-methylallyl)-2-nitrobenzenesulfonamide 154:** *N*-Allyl-2-nitrobenzenesulfonamide (810 mg, 3.35 mmol, 1 equiv.) was dissolved in DMF (5 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 174 mg, 4.35 mmol, 1.2 equiv.) was added and the mixture was stirred for a 0.5 h. 3-Chloro-2-methyl-1-ene **117** (0.39 mL, 4.02 mmol, 1.2 equiv.) was added in a dropwise fashion. Stirring was continued for 5 h during which period room temperature was reached. EtOAc (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. The crude product, obtained after solvent removal and filtration, was purified by column chromatography (*c*-Hex/EtOAc, 3:1) which gave the *title compound* **154** (820 mg, 82 %) as a light brown oil. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 2917, 1542, 1644, 1350, 1172 cm^{-1}; HRMS (EI): calcd for $[(C_{13}H_{16}N_2O_4S)]^+$ 296.0831, found: 296.0836; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (m, 1H, ArH), 7.73–7.61 (m, 3H, ArH), 5.63–5.52 (m, 1H, CH), 5.17–5.09 (m, 2H, CH_2), 4.93 (s, 1H, CH_2), 4.88 (s, 1H, CH_2), 3.91 (d, *J* = 7.0 Hz, 4H, CH_2), 1.63 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.9 (C), 146.4 (C), 139.5 (CH), 134.1 (C), 131.9 (CH), 131.8 (CH), 131.1 (CH), 124.3 (CH), 119.6 (CH_2), 115.0 (CH_2), 52.8 (CH_2), 48.9 (CH_2), 19.7 (CH_3) ppm.

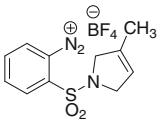


3-Methyl-1-(2-nitrophenylsulfonyl)-2,5-dihydro-1*H*-pyrrole 155: Under N_2, a degassed solution of compound **154** (800 mg, 2.7 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (17 mg, 0.027 mmol, 1.0 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 4:1) gave **155**

(716 mg, 99 %) as a pale brown solid. Mp 68-70 °C; R_f = 0.2 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 3059, 3010, 2933, 1584, 1360, 1328, 1152 cm^{-1}; HRMS (ESI): calcd for $[(C_{11}H_{12}N_2O_4S + Na)]^+$ 291.0415, found 291.0421; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96–7.91 (m, 1H, ArH), 7.72–7.66 (m, 2H, ArH), 7.63–7.58 (m, 1H, ArH), 5.35 (m, 1H, CH), 4.26–4.18 (m, 2H, CH_2), 4.16–4.10 (m, 2H, CH_2), 1.72 (d, *J* = 1.5 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.4 (C), 134.9 (C), 133.6 (CH), 132.0 (C), 131.8 (CH), 130.2 (CH), 124.2 (CH), 118.9 (CH), 57.7 (CH_2), 55.3 (CH_2), 14.1 (CH_3) ppm.

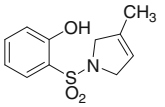


2-(3-Methyl-2,5-dihydro-1*H*-pyrrol-1-ylsulfonyl)aniline 156: To a suspension of **155** (500 mg, 1.87 mmol, 1 equiv.) in a mixture of glacial acetic acid (4 mL), EtOH (4 mL) and H_2O (2 mL) was added iron powder (522 mg, 9.35 mmol, 5 equiv.). The resulting suspension was exposed to ultrasonic irradiation for 45 min at 30 °C with TLC monitoring the completion of the reaction. The reaction mixture was filtered to remove the iron residue which was washed with EtOAc (30 mL). The filtrate was basified with 2 M KOH (30 mL) and further extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, reduced in vacuo and purified by flash column chromatography (*c*-Hex/EtOAc, 1:1) to afford the aniline **156** (366 mg, 82 %) as a brown solid. Mp 44–46 °C; R_f = 0.5 (*c*-Hex/EtOAc, 2:1); HRMS (ESI): calcd for $[(C_{11}H_{14}N_2O_4S + H)]^+$ 239.0854, found 239.0845; IR (NaCl, dep. from CH_2Cl_2) 3436, 1646, 1374, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (dd, *J* = 8.5, 1.5 Hz, 1H, ArH), 7.31–7.25 (m, 1H, ArH), 6.77–6.70 (m, 2H, ArH), 5.28 (s, 1H, CH), 5.00 (s (br), 2H, NH_2), 4.14 (dd, *J* = 4.0, 2.0 Hz, 2H, CH_2), 4.04 (d, *J* = 1.0 Hz, 2H, CH_2), 1.68 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4 (C), 135.2 (C), 134.1 (CH), 130.1 (CH), 119.8 (C), 119.2 (CH), 117.8 (CH), 117.2 (CH), 57.5 (CH_2), 55.0 (CH_2), 14.2 (CH_3) ppm.

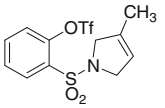


Dihydropyrrole tetrafluorborate salt 140: To a solution of aniline **156** (300 mg, 1,26 mmol, 1 equiv.) dissolved in HBF_4 50 % w/w (0.925 mL) and H_2O (0.63 mL) was added dropwise an aqueous solution of $NaNO_2$ (307 mg in 0.945 mL H_2O) at 0 °C. The resulting suspension was allowed to stir for 45 min. The solution was then filtered and the flask rinsed with ice-cold Et_2O. The crude diazonium salt was dissolved in minimal acetone (*ca.* 1 mL) and re-precipitated with ice-cold Et_2O (50 mL). The suspension was filtered and the solid allowed to dry in the air to afford the tetrafluorborate salt **140** (400 mg, 93 %) as a light brown solid. ^1H NMR (400 MHz, acetone-d_6): δ 9.16 (d, *J* = 7.5 Hz, 1H, ArH), 8.63–8.53 (m, 2H, ArH), 8.41–8.35 (m, 1H, ArH), 5.45 (dd, *J* = 3.0, 1.5 Hz, 1H, CH), 4.37–4.33 (m, 2H, CH_2),

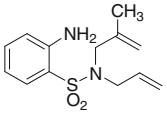
4.30 (dd, J = 3.0, 1.5 Hz, 2H, CH_2), 1.72 (s, 3H, CH_3) ppm. Compound stored in a brown jar in the freezer.



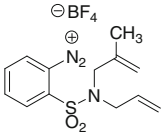
2-(3-Methyl-2,5-dihydro-1*H*-pyrrol-1-ylsulfonyl)phenol 157: A solution of diazonium **140** (200 mg, 0.56 mmol) dissolved in H_2O (20 mL) was heated to reflux for 1 h. Once the solution was cooled to room temperature the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, reduced in vacuo and purified by flash column chromatography (*c*-Hex/EtOAc, 6:1 → 2:1) to afford the phenol **157** (17 mg, 13 %) as a viscous orange oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{11}H_{13}NO_3S + H)]^+$ 240.0694, found 240.0686; IR (NaCl, dep. from CH_2Cl_2) 3644, 3582, 3072, 2922, 2855, 1604, 1328, 1140, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.92 (s, 1H, OH), 7.62 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 7.50-7.44 (m, 1H, ArH), 7.05 (d, J = 8.5 Hz, 1H, ArH), 7.02–6.96 (m, 1H, CH, ArH), 5.29 (d, J = 1.5 Hz, 1H, CH), 4.14–4.09 (m, 2H, CH_2), 4.01 (s, 2H, CH_2), 1.69 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7 (C), 135.3 (CH), 135.1 (C), 128.6 (CH), 120.7 (C), 120.5 (CH), 119.1 (CH), 110.2 (CH), 57.6 (CH_2), 55.2 (CH_2), 14.2 (CH_3) ppm.



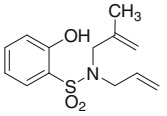
2-(3-Methyl-2,5-dihydro-1*H*-pyrrol-1-ylsulfonyl)phenyl trifluoromethane-sulfonate 139: Under N_2, a solution of phenol **157** (67 mg, 0.28 mmol, 1 equiv.) and pyridine (0.04 mL, 0.56 mmol, 2 equiv.) dissolved in anhydrous CH_2Cl_2 (10 mL) was treated with, dropwise, a solution of triflic anhydride (0.06 mL, 0.34 mmol, 1.2 equiv.) in anhydrous CH_2Cl_2 (1 mL) at 0 °C. The resulting suspension was stirred for 15 h, during which period room temperature was reached. The organic layer was washed with H_2O (3 × 10 mL), dried over $MgSO_4$ and reduced under pressure. The crude residue was purified by flash column chromatography (*c*-Hex/EtOAc, 7:1 → 2:1) to afford the *title compound* **139** (70 mg, 67%) as a colourless oil. R_f = 0.2 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 1429, 1209, 1172, 1135, 1101 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{12}NO_5S_2F_3 + Na)]^+$ 394.0007, found 394.0008; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 7.66 (td, J = 8.0, 2.0 Hz, 1H, ArH), 7.54–7.46 (m, 2H, ArH), 5.33 (d, J = 1.5 Hz, 1H, CH), 4.22–4.14 (m, 2H, CH_2), 4.09 (d, J = 2.0 Hz, 2H, CH_2), 1.72 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4 (C), 135.5 (C), 135.1 (CH), 132.3 (C), 131.7 (CH), 128.4 (CH), 122.8 (q, J = 2.0 Hz, CH), 119.1 (CH), 118.7 (q, J = 319 Hz, C), 56.8 (CH_2), 54.7 (CH_2), 14.0 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.55 (CF_3) ppm.



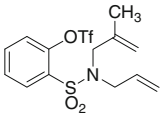
***N*-Allyl-2-amino-*N*-(2-methylallyl)benzenesulfonamide 159:** To a suspension of compound **154** (1.0 g, 3.4 mmol, 1 equiv.) in a mixture of glacial acetic acid (8 mL), EtOH (8 mL) and H_2O (4 mL) was added iron powder (960 mg, 17.2 mmol, 5 equiv.). The resulting suspension was exposed to ultrasonic irradiation for 45 min at 30 °C with TLC monitoring the completion of the reaction. The reaction mixture was filtered to remove the iron residue and the flask rinsed with EtOAc (50 mL). The filtrate was washed with 2 M KOH (50 mL) and further extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, reduced in vacuo and purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) to afford the aniline **159** (870 mg, 97 %) as a yellow oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{13}H_{18}N_2O_2S + Na)]^+$ 289.0987, found: 289.0987; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 1.5 Hz, 1H, ArH), 7.30–7.24 (m, 1H, ArH), 6.77–6.67 (m, 2H, ArH), 5.62 (m, 1H, CH), 5.15–5.07 (m, 2H, NH_2), 5.00 (s, 2H, CH_2), 4.88 (s, 1H, CH_2), 4.86 (s, 1H, CH_2), 3.80 (d, *J* = 6.5 Hz, 2H, CH_2), 3.75 (s, 2H, CH_2), 1.65 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6 (C), 139.0 (C), 132.9 (CH), 131.6 (CH), 129.0 (CH), 120.7 (C), 118.0 (CH_2), 116.6 (CH), 116.3 (CH), 113.4 (CH_2), 51.5 (CH_2), 47.9 (CH_2), 18.6 (CH_3) ppm.



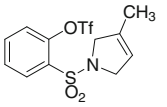
Diallyl tetrafluoroborate salt 160: A solution of diallyl aniline **159** (960 mg, 3.61 mmol, 1 equiv.) dissolved in HBF_4 50 % w/w (2.74 mL) and H_2O (1.8 mL) was treated dropwise an aqueous solution of $NaNO_2$ (890 mg in 2.74 mL H_2O) at 0 °C. The resulting suspension was allowed to stir for 1 h. The solution was then filtered and the flask rinsed with ice-cold Et_2O. The crude diazonium salt was dissolved in minimal acetone (*ca.* 10 mL) and product precipitated with ice-cold Et_2O (100 mL). The suspension was filtered and the solid allowed to dry in the air affording tetrafluorborate salt **160** (960 mg, 74 %) as a brown solid. ^{1}H NMR (300 MHz, acetone- d_6): δ 9.18 (d, *J* = 8.5 Hz, 1H, ArH), 8.63 (m, 2H, ArH), 8.40 (dd, *J* = 12.0, 5.0 Hz, 1H, ArH), 5.76 (dd, *J* = 17.0, 10.5 Hz, 1H, CH), 5.26 (m, 2H, CH_2), 5.03 (s, 1H, CH_2), 5.01 (s, 1H, CH_2), 4.11 (m, 4H, CH_2), 1.74 (s, 3H, CH_3) ppm. Compound stored in a brown jar in the freezer.



***N*-Allyl-2-hydroxy-*N*-(2-methylallyl)benzenesulfonamide 161:** A solution of tetrafluoroborate **160** (700 mg, 1.92 mmol) dissolved in H_2O (20 mL) was heated to reflux for 1 h. The mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced in vacuo. Purification by flash column chromatography (*c*-Hex/EtOAc, 8:1 → 6:1) gave phenol **161** (116 mg, 23 %) as a viscous yellow oil. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3703, 3611, 3015, 2946, 2881, 1600, 1348, 1129, 799 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{17}NO_3S + Na)]^+$ 290.0827, found: 290.0833; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.92 (s, 1H, OH), 7.57 (d, *J* = 8.0 Hz, 1H, ArH), 7.45 (t, *J* = 8.0 Hz, 1H, ArH), 7.05–6.93 (m, 2H, ArH), 5.57 (ddt, *J* = 16.0, 10.0, 7.0 Hz, 1H, CH), 5.18–5.09 (m, 2H, CH_2), 4.94 (s, 1H, CH_2), 4.87 (s, 1H, CH_2), 3.81 (d, *J* = 7.0 Hz, 2H, CH_2), 3.75 (s, 2H, CH_2), 1.67 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4 (C), 139.6 (C), 135.2 (CH), 131.8 (CH), 128.4 (CH), 123.3 (C), 120.5 (CH), 119.9 (CH), 119.1 (CH_2), 115.2 (CH_2), 52.9 (CH_2), 49.5 (CH_2), 19.8 (CH_3) ppm.

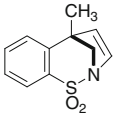


2-(*N*-Allyl-*N*-(2-methylallyl)sulfamoyl)phenyl trifluoromethanesulfonate 162: Under N_2, a solution of phenol **161** (116 mg, 0.43 mmol, 1 equiv.) in neat pyridine (1 mL) was treated dropwise with a solution of triflic anhydride (0.15 mL, 0.86 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (1 mL) at 0 °C. The resulting suspension was stirred for 15 h, during which period room temperature was reached. The organic layer was washed with H_2O (3 × 10 mL), dried over $MgSO_4$ and reduced under pressure. The crude residue was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) to afford the *title compound* **162** (121 mg, 71%) as a light yellow oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3089, 2922, 2854, 1464, 1431, 1353, 1213, 1164, 1137 cm^{-1}; HRMS (ESI): calcd for $[(C_{14}H_{16}F_3NO_5S_2 + Na)]^+$ 422.0320, found 422.0326; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.65 (td, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.52–7.44 (m, 2H, ArH), 5.49 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, CH), 5.08 (dd, *J* = 20.0, 5.0 Hz, 2H, CH_2), 4.92 (s, 1H, CH_2), 4.84 (s, 1H, CH_2), 3.86 (m, 4H, CH_2), 1.63 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.1 (C), 139.6 (C), 134.6 (CH), 134.1 (C), 131.9 (CH), 131.8 (CH), 128.4 (CH), 122.4 (q, *J* = 2.0 Hz, CH), 119.7 (CH_2), 118.7 (q, *J* = 321 Hz, C), 115.0 (CH_2), 52.8 (CH_2), 48.9 (CH_2), 19.7 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.28 ppm.

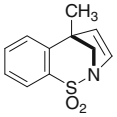


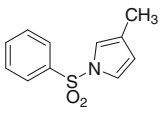
2-(3-Methyl-2,5-dihydro-1*H*-pyrrol-1-ylsulfonyl)phenyl trifluoromethane sulfonate 139: Under N_2, a degassed solution of compound **162** (120 mg, 0.3 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was treated with the Hoveyda-Grubbs 2nd

gen. catalyst **119** (3.7 mg, 0.006 mmol, 2.0 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 9:1 → 6:1) gave the *title compound* **139** (105 mg, 95 %) as a viscous brown oil. Data as above.

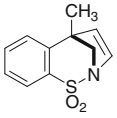


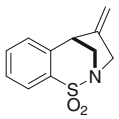
1-Methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 109: Under N_2, a solution of **139** (60 mg, 0.16 mmol, 1 equiv.) dissolved in anhydrous THF (1 mL) was degassed under a steady stream of nitrogen (*ca.* 0.5 h). To this solution was added $Pd(PPh_3)_4$ (10 mg, 0.008 mmol, 5 mol%), Et_3N (0.045 mL, 0.32 mmol, 2 equiv.) and 4Å molecular sieves, and the mixture was heated to 100 °C for 15 h. The reaction vessel was cooled and Et_2O (15 mL) and H_2O (15 mL) were added. The resultant aqueous layer was further extracted with Et_2O (2 × 15 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 3:1 → 2:1) affording the Heck product **109** (5 mg, 14 %) as a colourless solid, with data as above, and compound **139** (30 mg, 50 %) as a colourless oil.

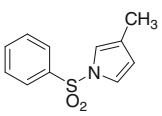




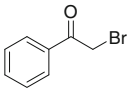
1-Methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 109 and 3-methyl-*N*-benzenesulfonylpyrrole 163: A solution of $Pd(dba)_2$ (3.4 mg, 0.0059 mmol, 4 mol%) and NaOAc (21 mg, 0.252 mmol, 1.7 equiv.) dissolved in anhydrous CH_2Cl_2 (1 mL) was treated to tetrafluoroborate salt **140** (50 mg, 0.15 mmol, 1 equiv.) and the resulting solution stirred at rt for 15 h. The reaction mixture was concentrated, and the residue dissolved in EtOAc (15 mL) and washed with water (15 mL). The organic portion was further extracted with EtOAc (2 × 15 mL) and the organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal in vacuo gave the crude material which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1 → 3:1) affording the Heck product **109** (9 mg, 28 %) as a colourless solid, with data as above, and pyrrole **163** (3 mg, 10 %). [3].



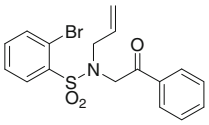




1-Methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 109, 11-methylene-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8,8-dioxide 110 and 3-methyl-*N*-benzenesulfonylpyrrole 163: A solution of Pd $(OAc)_2$ (10 mg, 0.045 mmol, 10 mol%) in MeOH (2 mL) were stirred for 1 h at 50 °C. Once the solution was cooled to room temperature tetrafluoroborate **140** (150 mg, 0.45 mmol, 1 equiv.) was added and the reaction stirred at 50 °C for 15 h. Once cooled, the reaction mixture was filtered through a plug of Celite eluting with EtOAc (15 mL). Solvent removal in vacuo gave the crude material which was purified by flash column chromatography (*c*-Hex/EtOAc, 9:1 → 4:1) affording an inseparable mixture of the Heck product **109** and regioisomer **110** (15 mg, 15%) in a 1:6 ratio and pyrrole **163** (37 mg, 37 %). Regioisomer **110** was recrystallised from the mixture using *c*-Hex. Data for **110**: light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 8.0 Hz, 1H, ArH), 7.50–7.38 (m, 2H, ArH), 7.29-7.25 (m, 1H, ArH), 5.21 (d, *J* = 1.5 Hz, 1H, CH_2), 4.96 (d, *J* = 1.5 Hz, 1H, CH_2), 4.45–4.37 (m, 1H, CH_2), 4.36–4.29 (m, 1H, CH_2), 4.06–3.98 (dt, *J* = 17.0, 2.0 Hz, 1H, CH_2), 3.63 (d, *J* = 3.0 Hz, 1H, CH), 3.47 (dd, *J* = 13.0, 3.0 Hz, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.7 (C), 139.4 (C), 133.8 (C), 133.1 (CH), 128.4 (CH), 126.9 (CH), 126.3 (CH), 107.0 (CH_2), 57.4 (CH_2), 52.2 (CH_2), 47.3 (CH) ppm.

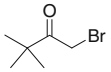


2-Bromo-1-phenylethanone 169: [4] A solution of acetophenone **168** (0.97 mL, 8.32 mmol, 1 equiv.) in Et_2O (3 mL) at was treated with Br_2 (0.42 mL, 8.32 mmol, 1 equiv.) in a dropwise fashion over 1 h at rt. Stirring was continued for 0.5 h and the reaction quenched with aq. Na_2SO_3 sat. soln (5 mL) was added and the phases were separated. The organic phase was further washed with aq. Na_2SO_3 sat. soln (2 × 10 mL) and dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded the *title compound* **169** (1.2 g, 80 %) as a dark green solid. Data consistent with literature.[103] R_f = 0.8 (*c*-Hex/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00-7.94 (m, 2H, ArH), 7.65–7.43 (m, 3H, ArH), 4.46 (s, 2H, CH_2) ppm. NMR data matched that in the literature.

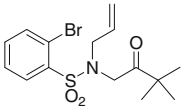


***N*-Allyl-2-bromo-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide 170:** *N*-Allyl-2-bromobenzenesulfonamide **112** (150 mg, 0.54 mmol, 1 equiv.) was dissolved in DMF (6 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 27 mg, 0.702 mmol, 1.3 equiv.) was added and the mixture was stirred for a 0.5 h. Bromide **169** (183 mg, 0.702 mmol, 1.3 equiv.) was added in a dropwise fashion. Stirring was continued for 15 h during which period room temperature was reached. A solution of aq. Na_2SO_3 sat. soln (10 mL) was added and the phases were separated.

The organic phase was further washed with aq. Na_2SO_3 sat. soln (2 × 10 mL), dried over $MgSO_4$. The crude product, obtained after solvent removal and filtration afforded *the title compound* **170** (138 mg, 65 %) as a colourless solid. Mp 102–106 °C; R_f = 0.3 (*c*-Hex/EtOAc, 5:1); HRMS (ESI): calcd for $[(C_{17}H_{17}NO_3\ ^{79}BrS + H)]^+$ 394.0113, found 394.0132; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, *J* = 8.0 Hz, 1H, ArH), 7.91 (d, *J* = 8.0 Hz, 2H, ArH), 7.75 (d, *J* = 8.0 Hz, 1H, ArH), 7.61-7.56 (m, 1H, ArH), 7.51–7.34 (m, 4H, ArH), 5.75–5.59 (m, 1H, CH), 5.19–5.06 (m, 2H, CH_2), 4.93 (s, 2H, CH_2), 4.04 (d, *J* = 7.0 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.7 (CO), 139.7 (C), 135.7 (CH), 134.9 (C), 133.9 (CH), 133.7 (CH), 132.4 (CH), 132.3 (CH), 128.9 (CH), 128.0 (CH), 127.7 (CH), 120.5 (C), 120.2 (CH_2), 52.4 (CH_2), 50.9 (CH_2) ppm.

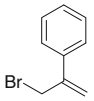


1-Bromo-3,3-dimethylbutan-2-one 173: [4] A solution of pinacolone **172** (1.2 mL, 9.42 mmol) in Et_2O (4 mL) was treated with Br_2 (0.48 mL, 9.42 mmol, 1 equiv.) in a dropwise fashion over 1 h at rt. Stirring was continued for 0.5 h and the reaction quenched with aq. Na_2SO_3 sat. soln (5 mL) was added and the phases were separated. The organic phase was further washed with aq. Na_2SO_3 sat. soln (2 × 10 mL) and dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded the *title compound* **173** (1.3 g, 80 %) as a brown liquid. Data consistent with literature.[103] R_f = 0.9 (*c*-Hex/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.23 (s, 2H, CH_2), 1.24 (s, 9H, CH_3) ppm. NMR data matched that in the literature.

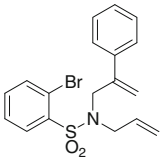


***N*-Allyl-2-bromo-*N*-(3,3-dimethyl-2-oxobutyl)benzenesulfonamide 174:** *N*-Allyl-2-bromobenzenesulfonamide **112** (150 mg, 0.54 mmol, 1 equiv.) was dissolved in DMF (6 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 27 mg, 0.702 mmol, 1.3 equiv.) was added and the mixture was stirred for a 0.5 h. Bromide **173** (137 mg, 0.702 mmol, 1.3 equiv.) was added in a dropwise fashion and stirring was continued for 15 h during which period room temperature was reached. An aq. Na_2SO_3 sat. soln (10 mL) was added and the phases were separated. The organic phase was further washed with aq. Na_2SO_3 sat. soln (2 × 10 mL), dried over $MgSO_4$. The crude product, obtained after solvent removal and filtration afforded the *title compound* **174** (159 mg, 79 %) as a colourless solid. R_f = 0.4 (*c*-Hex/EtOAc, 5:1); IR (NaCl, dep. from CH_2Cl_2) 2965, 2930, 2874, 2359, 1722, 1422, 1341, 1260, 1161, 1059, 1006, 935, 804, 758 cm^{-1}; HRMS (ESI): calcd for $[(C_{15}H_{20}NO_3\ ^{79}BrS + H)]^+$ 374.0426, found 374.0421; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.74 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.46–7.33 (m, 2H, ArH), 5.70–5.59 (m, 1H, CH), 5.19–5.07 (m, 2H, CH_2), 4.44 (s, 2H, CH_2), 3.94 (d, *J* = 7.0 Hz, 2H, CH_2), 1.13 (s, 9H, CH_3) ppm;

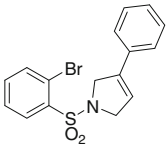
^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.3 (CO), 139.8 (C), 135.7 (CH), 133.6 (CH), 132.8 (CH), 132.2 (CH), 127.6 (CH), 120.6 (C), 119.9 (CH_2), 50.6 (CH_2), 50.5 (CH_2), 43.3 (C), 26.5 (CH_3) ppm.



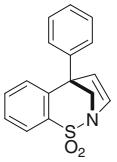
3-Bromo-2-phenylprop-1-ene 166: [5] This reaction was performed in a sealed tube as follows: A solution of α-methyl styrene **177** (5 mL, 38 mmol, 1 equiv.) and *N*-bromosuccinimide **183** (8.0 g, 44 mmol, 1.1 equiv.) in $CHCl_3$ (10 mL) was heated to 100 °C (oil bath temperature) for 4 h, until the NBS dissolved. On cooling to room temperature the insoluble succinimde was filtered, washed with $CHCl_3$ (2 × 10 mL) and the crude material was isolated as a brown liquid following solvent removal under reduced pressure. NMR data matched that in the literature.



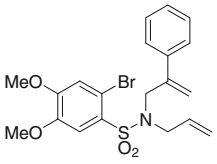
***N*-Allyl-*N*-2-phenylallyl-(2-bromobenzene)sulfonamide 171:** *N*-Allyl-2-bromobenzenesulfonamide **112** (70 mg, 0.25 mmol, 1 equiv.) was dissolved in DMF (1 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 15 mg, 0.325 mmol, 1.3 equiv.) was added and the mixture was stirred for 0.5 h. 3-Bromo-2-phenylprop-1-ene **166** (in excess, *ca*. 1 mL) was added in a dropwise fashion. Stirring was continued for 17 h during which period room temperature was reached. Et_2O (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous phase was further extracted with Et_2O (2 × 10 mL) and the combined ethereal extracts were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 5:1) which gave the *title compound* **171** (68 mg, 69 %) as a colourless solid. Mp 58–60 °C; R_f = 0.4 (*c*-Hex/EtOAc, 5:1); IR (NaCl, dep. from CH_2Cl_2) 3083, 3059, 1600, 1338, 1160, 911, 791, 759 cm^{-1}; HRMS (ESI): calcd for [($C_{18}H_{18}NO_2$ ^{79}BrS + H)]$^+$ 392.0320, found 392.0331; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.63 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.44–7.31 (m, 2H, ArH), 7.21 (m, 5H, ArH), 5.69–5.56 (m, 1H, CH), 5.39 (s, 1H, CH_2), 5.28 (s, 1H, CH_2), 5.19–5.10 (m, 2H, CH_2), 4.38 (s, 2H, CH_2), 3.91 (d, *J* = 6.0 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0 (C), 139.7 (C), 138.9 (C), 135.7 (CH), 133.5 (CH), 132.5 (CH), 132.4 (CH), 128.4 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 120.9 (C), 119.6 (CH_2), 116.6 (CH_2), 50.7 (CH_2), 49.4 (CH_2) ppm.



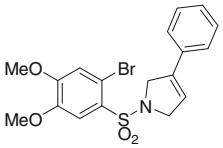
1-(2-Bromophenylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole 164: Under N_2, a degassed solution of compound **171** (120 mg, 0.306 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (10 mg, 0.015 mmol, 5.0 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 4:1) gave **164** (112 mg, 92 %) as a light green solid. Mp 58-62 °C; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.43 (dt, *J* = 26.5, 8.0 Hz, 2H, ArH), 7.32 (d, *J* = 14.0 Hz, 5H, ArH), 6.15–6.05 (m, 1H, CH), 4.67–4.63 (m, 2H, CH_2), 4.52–4.40 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.6 (C), 137.4 (C), 135.9 (CH), 133.7 (CH), 132.7 (C), 131.9 (CH), 128.9 (CH), 128.6 (CH), 127.7 (CH), 125.6 (CH), 120.6 (C), 118.9 (CH), 55.9 (CH_2), 55.1 (CH_2) ppm.



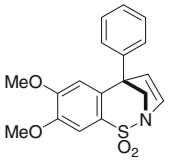
1-Phenyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 184: Under N_2, a degassed solution of compound **164** (90 mg, 0.247 mmol, 1 equiv.) in anhydrous DMF (2 mL) was treated with $Pd(OAc)_2$ (5 mg, 0.0219 mmol, 10 mol%), PPh_3 (11 mg, 0.0438 mmol, 20 mol%) and K_2CO_3 (61 mg, 0.438 mmol, 2 equiv.) and the solution heated to 110 °C for 18 h. The reaction mixture was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 3:1) affording the Heck product **184** (65 mg, 45 %) as a colourless solid. Mp 130–132 °C; R_f = 0.4 (*c*-Hex/EtOAc, 6:1); IR (NaCl, dep. from CH_2Cl_2) 3061, 2955, 2923, 2853, 1338, 1168 cm^{-1}; HRMS (ESI): calcd for [($C_{16}H_{13}NO_2$ ^{79}BrS + H)]$^+$ 284.0745, found 284.0738; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (dd, *J* = 8.0, 1H, ArH), 7.51–7.37 (m, 4H, ArH), 7.37–7.20 (m, 3H, ArH), 6.87 (d, *J* = 4.0 Hz, 1H, CH), 6.65 (d, *J* = 8.0 Hz, 1H, ArH), 6.54 (d, *J* = 4.0 Hz, 1H, CH), 4.88 (m, 1H, CH_2), 3.98 (d, *J* = 12.0 Hz, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7 (C), 137.6 (C), 137.2 (CH), 134.6 (CH), 133.3 (C), 131.6 (CH), 130.1 (CH), 129.5 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 125.9 (CH), 67.9 (CH_2), 55.8 (C) ppm.



***N*-Allyl-2-bromo-4,5-dimethoxy-*N*-(2-phenylallyl)benzenesulfonamide 179:** *N*-Allyl-2-bromo-4,5-dimethoxybenzenesulfonamide **115** (150 mg, 0.45 mmol, 1 equiv.) was dissolved in DMF (2 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 24 mg, 0.59 mmol, 1.3 equiv.) was added and the mixture was stirred for a 0.5 h. 3-Bromo-2-phenylprop-1-ene **166** (in excess, *ca*. 1 mL) was added in a dropwise fashion. Stirring was continued for 17 h during which period room temperature was reached. Et_2O (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous phase was further extracted with Et_2O (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 5:1) which gave the *title compound* **179** (155 mg, 76 %) as a pale yellow oil. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{20}H_{22}NO_4\ ^{79}BrS + Na)]^+$ 474.0351, found 474.0343; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H, ArH), 7.25–7.23 (m, 5H, ArH), 7.02 (s, 1H, ArH), 5.67-5.65 (m, 1H, CH), 5.41 (s, 1H, CH_2), 5.30 (s, 1H, CH_2), 5.22–5.11 (m, 2H, CH_2), 4.37 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 3.90 (s, 5H, CH_2, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.2 (C), 147.8 (C), 142.9 (C), 138.9 (C), 132.6 (CH), 131.3 (C), 128.4 (CH), 127.9 (CH), 126.5 (CH), 119.5 (CH_2), 117.6 (CH), 116.5 (CH_2), 114.8 (CH), 112.4 (C), 56.6 (CH_3), 56.5 (CH_3), 50.7 (CH_2), 49.4 (CH_2) ppm.

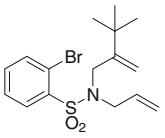


1-(2-Bromo-4,5-dimethoxyphenylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole 181: Under N_2, a degassed solution of **179** (145 mg, 0.321 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (10 mg, 0.016 mmol, 5 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 3:1) gave **181** (129 mg, 95 %) as a light brown oil. R_f = 0.2 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 3059, 3010, 2968, 2933, 1360, 1152, 602 cm^{-1}; HRMS (ESI): calcd for $[(C_{18}H_{18}NO_4\ ^{79}BrS + H)]^+$ 424.0218, found 424.0239; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (s, 1H, ArH), 7.40–7.26 (m, 5H, ArH), 7.16 (s, 1H, ArH), 6.11 (s, 1H, CH), 4.61 (s, 2H, CH_2), 4.44 (s, 2H, CH_2), 3.92 (s, 6H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4 (C), 147.9 (C), 137.4 (C), 132.7 (C), 130.0 (C), 128.8 (CH), 128.5 (CH), 125.5 (CH), 118.9 (CH), 117.7 (CH), 114.6 (CH), 112.1 (C), 56.6 (CH_3), 56.5 (CH_3), 55.7 (CH_2), 54.9 (CH_2) ppm.



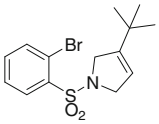
4,5-Dimethoxy-1-phenyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 185: Under N_2, a degassed solution of compound **181** (87 mg, 0.21 mmol, 1 equiv.) in anhydrous DMF (1.75 mL), was treated with $Pd(OAc)_2$ (5 mg, 0.021 mmol, 10 mol%), PPh_3 (11 mg, 0.042 mmol, 20 mol%) and K_2CO_3 (58 mg, 0.428 mmol, 2 equiv.) and the solution heated to 110 °C for 18 h. The reaction mixture was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 5:1) affording the Heck product **185** (39 mg, 54 %) as a yellow solid. Mp 150–152 °C; R_f = 0.5 (*c*-Hex/EtOAc, 1:1); IR (NaCl, dep. from CH_2Cl_2) 3102, 3059, 3004, 2935, 2847, 1597, 1333, 1148 cm^{-1}; HRMS (ESI): calcd for $[(C_{18}H_{17}NO_4\ ^{79}BrS + Na)]^+$ 366.0776, found 366.0784; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.28 (m, 5H, ArH), 7.18 (s, 1H, ArH), 6.90 (d, *J* = 4.0 Hz, 1H, CH), 6.53 (d, *J* = 4.0 Hz, 1H, CH), 6.11 (s, 1H, ArH), 4.83 (d, *J* = 12.0 Hz, 1H, CH_2), 3.95 (d, *J* = 12.0 Hz, 1H, CH_2), 3.90 (s, 3H, CH_3), 3.60 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9 (C), 150.0 (C), 137.7 (C), 137.5 (CH), 137.2 (CH), 134.5 (CH), 129.4 (CH), 128.5 (CH), 127.7 (C), 124.0 (C), 109.2 (CH), 108.9 (CH), 68.3 (CH_2), 56.5 (CH_3), 56.0 (CH_3), 54.9 (C) ppm.

2-(Bromomethyl)-3,3-dimethylbut-1-ene 167: [5] This reaction was performed in a sealed tube as follows; a solution of 2,3,3-trimethylbut-1-ene **178** (5 mL, 40 mmol, 1 equiv.) and *N*-bromosuccinimide **183** (7.8 g, 44 mmol, 1.1 equiv.) in $CHCl_3$ (10 mL) was heated to 100 °C (oil bath temperature) for 4 h, until the NBS dissolved. On cooling to room temperature the insoluble succinimde was filtered, washed with $CHCl_3$ (3 × 10 mL) and the crude material was isolated as a brown liquid following solvent removal under reduced pressure. NMR data matched that in the literature.[106]

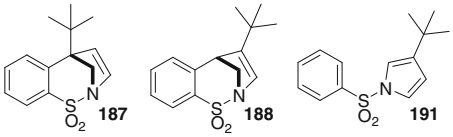


***N*-Allyl-2-bromo-*N*-(3,3-dimethyl-2-methylenebutyl)benzenesulfonamide 175:** *N*-Allyl-2-bromobenzenesulfonamide **112** (225 mg, 0.905 mmol, 1 equiv.) was dissolved in DMF (4 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 47 mg, 1.18 mmol, 1.3 equiv.) was added and the mixture was stirred for 0.5 h. 2-(Bromomethyl)-3,3-dimethylbut-1-ene **167** (in excess, *ca.* 2 mL of the crude material) was added in a dropwise fashion. Stirring was continued for 17 h during which period room temperature was reached. Et_2O (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous phase was further

extracted with Et_2O (2 × 10 mL) and the combined ethereal extracts were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) which gave the *title compound* **175** (302 mg, 90 %) as a colourless oil. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 2965, 2931, 1642, 1341, 1161, 919, 761, 575 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{22}NO_2\ ^{79}BrS + H)]^+$ 372.0633, found 372.0620; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.43 (td, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.37 (td, *J* = 8.0, 2.0 Hz, 1H, ArH), 5.53 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, CH), 5.12–5.04 (m, 2H, CH_2), 5.00 (d, *J* = 7.0 Hz, 2H, CH_2), 4.09 (s, 2H, CH_2), 3.88 (d, *J* = 6.5 Hz, 2H, CH_2), 1.05 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7 (C), 140.0 (C), 135.7 (CH), 133.5 (CH), 132.6 (CH), 132.5 (CH), 127.7 (CH), 120.5 (C), 119.6 (CH_2), 108.2 (CH_2), 49.3 (CH_2), 48.3 (CH_2), 35.3 (C), 29.2 (CH_3) ppm.



1-(2-Bromophenylsulfonyl)-3-*tert*-butyl-2,5-dihydro-1*H*-pyrrole 165: Under N_2, a degassed solution of compound **175** (100 mg, 0.27 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (8 mg, 0.0135 mmol, 5 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 9:1) gave **165** (81 mg, 87 %) as a colourless solid. Mp 62–64 °C; R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 2962, 2925, 2869, 1338, 919, 575 cm^{-1}; (EI): calcd for $[(C_{14}H_{18}NO_2\ ^{79}BrS)]^+$ 343.0242, found: 343.0227; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.41 (m, 2H, ArH), 5.34 (s, 1H, CH), 4.29 (s, 2H, CH_2), 4.21 (s, 2H, CH_2), 1.08 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.7 (C), 138.2 (C), 135.9 (CH), 133.5 (CH), 131.6 (CH), 127.6 (CH), 120.6 (C), 115.6 (CH), 55.2 (CH_2), 54.3 (CH_2), 31.0 (C), 29.1 (CH_3) ppm.



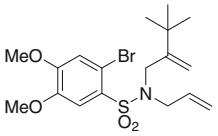
1-*tert*-Butyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 187, 11-*tert*-butyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 188 and 3-*tert*-butyl-*N*-benzenesulfonylpyrrole 191: Under N_2, a degassed solution of compound **165** (170 mg, 0.49 mmol, 1 equiv.) in anhydrous DMF (4 mL), was treated with $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol%), PPh_3 (26 mg, 0.098 mmol, 20 mol%) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv.) and the

solution heated to 110 °C for 18 h. The reaction mixture was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 15:1) affording products **187** (51 mg, 41 %) as a colourless solid, **188** (16 mg, 12%) and pyrrole **191** (45 mg, 34 %).

Data for **187**. Mp 164-168 °C; R_f = 0.4 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3112, 2965, 2935, 1330, 1165 cm^{-1}; HRMS (EI): calcd for $[(C_{14}H_{17}NO_2S)]^+$ 264.1058, found 264.1058; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.45 (td, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.38 (td, *J* = 8.0, 1.5 Hz, 1H, ArH), 6.43 (d, *J* = 4.0 Hz, 1H, CH), 6.36 (d, *J* = 4.0 Hz, 1H, CH), 4.36 (d, *J* = 12.0 Hz, 1H, CH_2), 4.21 (d, *J* = 12.0 Hz, 1H, CH_2), 1.28 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.1 (C), 137.3 (CH), 134.9 (C), 133.5 (CH), 130.8 (CH), 129.4 (CH), 128.6 (CH), 125.9 (CH), 63.6 (CH_2), 56.7 (C), 32.8 (C), 28.9 (CH_3) ppm.

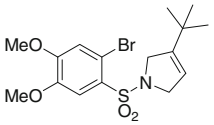
Data for **188**: colourless solid; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); Mp 72–74 °C; IR (NaCl, dep. from CH_2Cl_2) 3086, 2967, 1642, 1336, 1156 cm^{-1}; HRMS (EI): calcd for $[(C_{14}H_{17}NO_2S)]^+$ 263.0980, found: 263.0988; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76–7.71 (m, 1H, ArH), 7.48–7.41 (m, 1H, ArH), 7.39–7.33 (m, 1H, ArH), 7.20 (d, *J* = 8.0 Hz, 1H, ArH), 6.10 (s, 1H, CH), 4.42 (d, *J* = 12.0 Hz, 1H, CH_2), 4.16–4.07 (m, 1H, CH_2), 3.28 (d, *J* = 4.0 Hz, 1H, CH), 1.07 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6 (C), 140.9 (C), 135.6 (C), 131.2 (CH), 129.7 (CH), 127.6 (CH), 127.1 (CH), 125.6 (CH), 64.8 (CH_2), 43.6 (CH), 33.2 (C), 29.1 (CH_3) ppm.

Data for pyrrole **191**. light brown waxy solid; R_f = 0.5 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3139, 3066, 1584, 1368, 1161 cm^{-1}; HRMS (EI): calcd for $[(C_{14}H_{17}NO_2S)]^+$ 263.0980, found 263.0976; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, *J* = 7.5 Hz, 2H, CH), 7.59 (t, *J* = 7.5 Hz, 1H, CH), 7.50 (t, *J* = 8.0 Hz, 2H, CH), 7.07 (s, 1H, CH), 6.89 (s, 1H, CH), 6.25 (s, 1H, CH), 1.18 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.8 (C), 139.5 (CH), 133.7 (CH), 129.4 (CH), 126.8 (C), 121.1 (CH), 115.2 (CH), 112.9 (CH), 31.0 (C), 27.0 (CH_3) ppm.

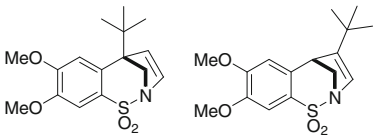


***N*-Allyl-2-bromo-*N*-(3,3-dimethyl-2-methylenebutyl)-4,5-dimethoxybenzene sulfonamide 180:** Compound **115** (100 mg, 0.297 mmol, 1 equiv.) was dissolved in DMF (2 mL) and cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 16 mg, 0.39 mmol, 1.3 equiv.) was added and the mixture was stirred for a 0.5 h. 2-(Bromomethyl)-3,3-dimethylbut-1-ene **167** (in excess, *ca.* 2 mL of the crude material) was added in a dropwise fashion. Stirring was continued for 17 h during which period room temperature was reached. Et_2O (10 mL) and H_2O (10 mL) were

added and the phases were separated. The aqueous phase was further extracted with Et_2O (2 × 10 mL) and the combined ethereal extracts were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) which gave the *title compound* **180** (83 mg, 89 %) as a colourless oil. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{18}H_{26}NO_4\ ^{79}BrS + Na)]^+$ 454.0664, found 454.0668; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H, ArH), 7.14 (s, 1H, ArH), 5.62–5.49 (m, 1H, CH), 5.10 (dd, *J* = 13.5, 7.5 Hz, 2H, CH_2), 5.02 (d, *J* = 10.5 Hz, 2H, CH_2), 4.15–4.04 (m, 2H, CH_2), 3.93 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 3.85 (d, *J* = 6.5 Hz, 2H, CH_2), 1.06 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.2 (C), 150.7 (C), 147.8 (C), 132.6 (CH), 131.7 (C), 119.5 (CH_2), 117.5 (CH_2), 114.8 (CH), 111.9 (C), 108.1 (CH), 56.5 (CH_3), 56.4 (CH_3), 49.2 (CH_2), 48.2 (CH_2), 35.2 (C), 29.1 (CH_3) ppm.



1-(2-Bromo-4,5-dimethoxyphenylsulfonyl)-3-*tert*-butyl-2,5-dihydro-1*H*-pyrrole 182: Under N_2, a degassed solution of compound **180** (100 mg, 0.23 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (7 mg, 0.0115 mmol, 5 mol%). Stirring was continued at reflux for 15 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 7:1) gave **182** (72 mg, 77 %) as a colourless solid. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 2949, 2922, 2849, 1365, 1094, 1060, 678 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{22}NO_4\ ^{79}BrS + H)]^+$ 404.0531, found 404.0516; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59 (s, 1H, ArH), 7.15 (s, 1H, ArH), 5.35–5.30 (m, 1H, CH), 4.29–4.23 (m, 2H, CH_2), 4.21–4.15 (m, 2H, CH_2), 3.93 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 1.08 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3 (C), 148.7 (C), 147.9 (C), 130.3 (C), 117.7 (CH), 115.6 (CH), 114.5 (C), 112.0 (CH), 56.7 (CH_3), 56.6 (CH_3), 55.1 (CH_2), 54.2 (CH_2), 32.5 (C), 29.2 (CH_3) ppm.

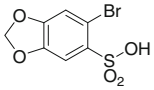


1-*tert*-Butyl-4,5-dimethoxy-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 189 and 11-*tert*-butyl-4,5-dimethoxy-8-thia-9-azatricyclo [7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide 190: Under N_2, a solution of compound **182** (75 mg, 0.19 mmol, 1 equiv.), $Pd(OAc)_2$ (5 mg, 0.019 mmol, 10 mol %), PPh_3 (10 mg, 0.038 mmol, 20 mol%) and K_2CO_3 (53 mg, 0.38 mmol, 2 equiv.) in anhydrous DMF (2 mL) was heated to 110 °C for 18 h. The reaction mixture was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer

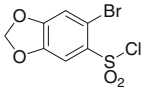
was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) affording products **189** (24 mg, 39 %) and **190** (11 mg, 18%).

Data for **189**. colourless solid; Mp 158-160 °C; R_f = 0.2 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2961, 2393, 1508, 1331, 1172 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{21}NO_4S + Na)]^+$ 346.1089, found 346.1100; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 2H, ArH), 6.44 (d, *J* = 4.0 Hz, 1H, CH), 6.34 (d, *J* = 4.0 Hz, 1H, CH), 4.33 (d, *J* = 12.0 Hz, 1H, CH_2), 4.17 (d, *J* = 12.0 Hz, 1H, CH_2), 3.90 (s, 6H, CH_3), 1.29 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.9 (C), 149.4 (C), 137.5 (CH), 137.4 (C), 135.6 (C), 126.1 (CH), 121.3 (C), 110.4 (CH), 109.7 (CH), 64.1 (CH_2), 56.4 (C), 32.7 (C), 28.9 (CH_3) ppm.

Data for **190**. colourless solid; Mp 138-140 °C; R_f = 0.1 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2957, 2918, 2849, 1500, 1333, 1136 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{21}NO_4S + H)]^+$ 324.1270, found 324.1282; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.09 (s, 1H, CH), 4.38 (d, *J* = 11.5 Hz, 1H, CH_2), 4.08 (dd, *J* = 11.5, 4.0 Hz, 1H, CH), 3.89 (s, 6H, CH_3), 3.18 (d, *J* = 4.0 Hz, 1H, CH), 1.09 (s, 9H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9 (C), 160.9 (C), 150.8 (C), 149.8 (C), 134.4 (C), 125.6 (CH), 109.9 (CH), 109.5 (CH), 65.2 (CH_2), 56.4 (CH_3), 43.4 (CH), 31.8 (C), 29.2 (CH_3) ppm.

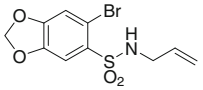


6-Bromobenzo[*d*] [1, 3] dioxole-5-sulfonic acid 221: A solution of 5-bromobenzo [*d*] [1, 3] dioxole **220** (1 mL, 8.3 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was treated with a solution of HSO_3Cl (0.7 mL, 10.4 mmol, 1.25 equiv.) in CH_2Cl_2 (5 mL) dropwise over 5 min. The reaction mixture was then filtered under suction and washed repeatedly with CH_2Cl_2 (3 × 20 mL) to afford 6-bromobenzo[*d*] [1, 3] dioxole-5-sulfonic acid **221** (1.97 g, 85%) as a grey solid. Mp 87–89 °C; IR (NaCl, dep. from CH_2Cl_2) 1613, 1503, 1485, 1372, 1337, 1251, 1174, 1038, 938 cm^{-1}; HRMS (ES-): calcd for $[(C_7H_4O_5S\ ^{79}Br)]^-$ 278.8963, found 278.8964; ^1H NMR (DMSO, 400 MHz): δ 7.38 (s, 1H, ArH), 7.12 (s, 1H, ArH), 6.06 (s, 2H, CH_2), 4.77 (OH) ppm; ^{13}C NMR (DMSO, 100 MHz): δ 148.0 (C), 145.9 (C), 140.9 (C), 113.4 (CH), 110.7 (C), 109.0 (CH), 102.1 (CH_2) ppm.

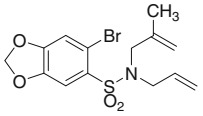


6-Bromobenzo[*d*] [1, 3] dioxole-5-sulfonyl chloride 222: A mixture of sulfonic acid **221** (1.07 g, 3.8 mmol, 1 equiv.) and $SOCl_2$ (2.76 mL, 38.1 mmol, 10 equiv.) in CH_2Cl_2 (40 mL) was heated to reflux for 15 h. The reaction mixture was cooled, filtered and the filtrate washed with $NaHCO_3$ aq. sat. soln. (20 mL). The aqueous layer was re-extracted with CH_2Cl_2 (20 mL). The combined organic layers were

washed with brine, dried over $MgSO_4$ and reduced under pressure to give sulfonyl chloride **222** (643 mg, 57 %) as a pale brown solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); Mp 54–56 °C; IR (NaCl, dep. from CH_2Cl_2) 3056, 2984, 2917, 1608, 1507, 1476, 1384, 1251, 1180 cm^{-1}; HRMS (ESI): calcd for $[(C_7H_4O_4S\ ^{79}Br\ ^{35}Cl + Na)]^+$ 320.8594; found 320.8624; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H, ArH), 7.23 (s, 1H, ArH), 6.16 (s, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6 (C), 147.6 (C), 136.6 (C), 115.7 (CH), 115.1 (C), 110.6 (CH), 103.8 (CH_2) ppm.

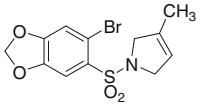


***N*-Allyl-6-bromobenzo[*d*] [1, 3] dioxole-5-sulfonamide:** A solution of **222** (1.0 g. 3.3 mmol, 1 equiv.) and allylamine (0.34 mL, 4.30 mmol, 1.3 equiv.) in CH_2Cl_2 (50 mL) was treated with Et_3N (0.6 mL, 4.30 mmol, 1.3 equiv.) in a dropwise fashion at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. 1 M HCl (20 mL) was added to the reaction mixture and the layers separated. The organic layer was washed successively with $NaHCO_3$ aq. sat. soln. (30 mL), H_2O (20 mL) and brine and was dried over $MgSO_4$. Filtration followed by solvent removal under pressure afforded *N*-allyl sulfonamide (862 mg, 81 %) as a pale yellow solid. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); Mp 101–104 °C; IR (NaCl, dep. from CH_2Cl_2) 2921, 2853, 1505, 1475, 1329, 1243, 1167, 1034, 924 cm^{-1}; HRMS (ESI): calcd for $[(C_{10}H_{10}NO_4S\ ^{79}Br + H)]^+$ 319.9592, found 319.9599; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.58 (s, 1H, ArH), 7.13 (s, 1H, ArH), 6.10 (s, 2H, CH_2), 5.74–5.63 (m, 1H, CH), 5.25–5.06 (m, 3H, CH_2, NH), 3.54 (t, J = 6.0, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.6 (C), 147.7 (C), 132.9 (CH), 132.5 (C), 118.5 (CH_2), 114.7 (CH), 112.8 (C), 111.7 (CH), 102.6 (CH_2), 45.9 (CH_2) ppm.

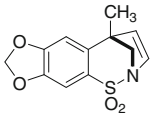


***N*-Allyl-6-bromo-*N*-(2-methylallyl)benzo[*d*] [1, 3] dioxole-5-sulfonamide:** *N*-Allyl-6-bromobenzo[*d*] [1, 3] dioxole-5-sulfonamide (400 mg, 1.25 mmol, 1 equiv.) was dissolved in DMF (5 mL) and cooled to 0 °C. Sodium hydride (60 %w/w in mineral oil, 75 mg, 1.89 mmol, 1.5 equiv.) was added and the mixture was stirred for 0.5 h. 3-Chloro-2-methylprop-1-ene **117** (0.16 mL, 1.63 mmol, 1.3 equiv.) was added in a dropwise fashion. Stirring was continued for 15 h during which time room temperature was reached. EtOAc (10 mL) and H_2O (10 mL) were added and the phases separated. The aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1 → 3:1) which gave the diallyl compound (430 mg, 93 %) as a colourless solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); Mp 39–40 °C; IR (NaCl, dep. from CH_2Cl_2) 3081, 2981, 2916, 1505, 1475, 1369, 1329, 1243,

1164, 1143, 1033, 925 cm^{-1}; HRMS (ESI): calcd for $[(C_{14}H_{17}NO_4S^{79}Br + H)]^+$ 374.0062, found 374.0069; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H, ArH), 7.12 (s, 1H, ArH), 6.09 (s, 2H, CH_2), 5.63-5.53 (m, 1H, CH), 5.19–5.10 (m, 2H, CH_2), 4.95–4.86 (m, 2H, CH_2), 3.88 (s, 2H, CH_2), 3.83 (d, J = 6.5 Hz, 2H, CH_2), 1.65 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5 (C), 147.3 (C), 140.1 (C), 133.2 (C), 132.3 (CH), 119.5 (CH_2), 115.0 (CH_2), 114.9 (CH), 113.5 (C), 112.4 (CH), 103.1 (CH_2), 53.2 (CH_2), 48.8 (CH_2), 19.9 (CH_3) ppm.

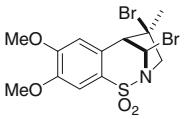


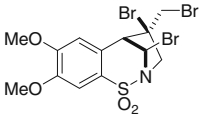
1-((6-Bromobenzo[*d*] [1, 3] dioxol-5-yl)sulfonyl)-3-methyl-2,5-dihydro-1*H*-pyrrole 223: Under N_2, a degassed solution of diallyl compound (430 mg, 1.15 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (50 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (14 mg, 0.023 mmol, 2 mol%). Stirring was continued at 40 °C for 15 h. Once cooled, the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 3:1) gave **223** (324 mg, 82 %) as a white solid. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); Mp 71–73 °C; IR (NaCl, dep. from CH_2Cl_2) 2918, 1483, 1331, 1260, 1164, 1136, 1036, 936, 737 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{12}NO_4S\ ^{79}Br + H)]^+$ 345.9749, found 345.9751; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1H, ArH), 7.15 (s, 1H, ArH), 6.09 (s, 2H, CH_2), 5.36-5.34 (m, 1H, CH), 4.22-4.18 (m, 2H, CH_2), 4.15–4.04 (m, 2H, CH_2), 1.73 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 151.5 (C), 147.4 (C), 135.0 (C), 132.0 (C), 119.1 (CH), 115.2 (CH), 113.4 (C), 111.7 (CH), 103.1 (CH_2), 57.8 (CH_2), 55.3 (CH_2), 14.3 (CH_3) ppm.



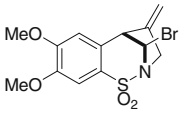
5-Methyl-5*H*-2,5-methano [1, 3] dioxolo[4′,5′:4,5]benzo[1,2-*f*] [1, 2] thiazepine 1,1-dioxide 219: Under N_2, a solution of **223** (100 mg, 0.29 mmol, 1 equiv.) in anhydrous DMF (3 mL) was degassed under a steady stream of nitrogen (*ca.* 0.5 h). To this solution was added $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 10 mol%), PPh_3 (15 mg, 0.058 mmol, 20 mol%) and K_2CO_3 (80 mg, 0.58 mmol, 2 equiv.) and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1) affording the Heck product **219** (72 mg, 80 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); Mp 130–132 °C; IR (NaCl, dep. from CH_2Cl_2) 3055, 2915, 2859, 1610, 1504, 1475, 1368, 1330, 1243, 1168, 1148, 1094, 1034, 922, 664 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{11}NO_4S + H)]^+$ 266.0487, found 266.0475; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 1H, ArH), 6.71 (s, 1H, ArH),

6.34 (d, J = 4.0 Hz, 1H, CH), 6.22 (d, J = 4.0 Hz, 1H, CH), 6.01-6.00 (m, 2H, CH_2), 4.36 (d, J = 12.0 Hz, 1H, CH_2), 3.74 (d, J = 12.0 Hz, 1H, CH_2), 1.49 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1 (C), 148.1 (C), 140.7 (CH), 138.2 (C), 133.8 (CH), 125.8 (C), 107.6 (CH), 103.9 (CH), 102.1 (CH_2), 68.9 (CH_2), 45.2 (C), 17.7 (CH_3) ppm.



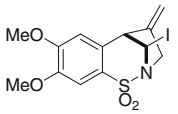


(4*R,5*S**,10*S**)-4,10-Dibromo-7,8-dimethoxy-4-methyl-4,5-dihydro-3*H*-2,5-methanobenzo-[*f*] [1, 2] thiazepine 1,1-dioxide 211 and (4*R**,5*S**,10*S**)-4,10-dibromo-4-(bromomethyl)-7,8-dimethoxy-4,5-dihydro-3*H*-2,5-methanobenzo [*f*] [1, 2] thiazepine 1,1-dioxide 212:** A solution of alkene **120** (40 mg, 0.142 mmol, 1 equiv.) in $CHCl_3$ (0.8 mL) was treated with bromine (0.7 mL, 1.42 mmol, 10 equiv.) at −60 °C (dry ice-acetone cold bath) and allowed to stir for 15 h. Once room temperature was reached, the reaction was quenched with aq. $Na_2S_2O_3$ sat. soln. (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 5:1) affording compounds **211** and **212** (37 mg, 55 %) as a chromatographically inseparable mixture (**211**:**212**; 1:1). R_f = 0.5 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3010, 2960, 2937, 2849, 1598, 1509, 1464, 1347, 1271, 1154 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{15}NO_4S\ ^{79}Br_2 + H)]^+$ 439.9167, found 439.9146 (**211**); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (s, 1H, ArH), 7.19 (s,1H, ArH), 6.94 (s, 1H, ArH), 6.67 (s, 1H, ArH), 6.36 (s, 1H, CH), 6.35 (s, 1H, CH), 4.58 (d, J = 15.5 Hz, 1H, CH_2), 4.49 (d, J = 15.0 Hz, 1H, CH_2), 4.38–4.35 (m, 1H, CH_2), 4.33-4.31 (m, 1H, CH_2), 4.18-4.14 (m, 1H, CH_2), 4.12-4.11 (m, 1H, CH_2), 4.05 (s, 1H, CH), 3.97-3.92 (m, 13H, 4 × OCH_3, CH), 3.41 (d, J = 11.5 Hz, 1H, CH_2), 3.04 (d, J = 11.5 Hz, 1H, CH_2), 1.48 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8 (C), 152.1 (C), 150.9 (C), 150.4 (C), 128.4 (C), 126.9 (C), 126.7 (C), 126.3 (C), 112.6 (CH), 110.5 (CH), 107.4 (2 × CH), 65.8 (C), 65.6 (C), 65.5 (CH), 64.0 (CH, CH_2), 62.8 (CH), 61.7 (CH_2), 60.7 (C), 56.7 (CH_3), 43.3 (CH_2), 33.6 (CH_3) ppm. Further elution gave (3*R**,4,*R**,5*S**)-3,4-dibromo-7,8-dimethoxy-5-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*] [1, 2] thiazepine 1,1-dioxide **213** (21 mg, 33%) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 2:1); HRMS (ESI): calcd for $[(C_{13}H_{15}NO_4S\ ^{79}Br_2 + Na)]^+$ 461.8981, found 461.8988.



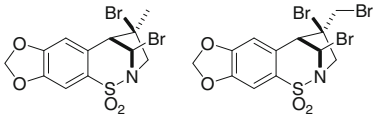
(5*S,10*S**)-10-Bromo-7,8-dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo-[*f*] [1, 2] thiazepine 1,1-dioxide 215**: A mixture of **120** (40 mg, 0.14 mmol, 1 equiv.) and *N*-bromosuccinimide **183** (27 mg, 0.154 mmol, 1.1 equiv.) in $CHCl_3$ (0.8 mL, 0.178 M) were heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O (10 mL) and brine (10 mL) and dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title* compound **215** (45 mg, 90 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); M.p. 48–50 °C; IR (NaCl, dep. from CH_2Cl_2) 3063, 2938, 2848, 1704, 1599, 1511, 1343, 1268, 1173, 1151, 1047, 1047, 916, 753 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{14}NO_4S\,^{79}Br + H)]^+$ 359.9905, found 359.9918; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.30 (s, 1H, CH), 5.35 (s (br), 1H, CH_2), 5.11 (s (br), 1H, CH_2), 4.43–4.25 (m, 2H, CH_2), 3.93 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.87 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2(C), 149.9 (C), 144.6 (C), 130.6 (C), 125.6 (C), 109.4 (CH_2), 108.3 (CH), 107.5 (CH), 67.3 (CH), 57.7 (CH), 56.5 (2 × CH_3), 50.1 (CH_2) ppm; Found C, 43.20; H, 3.62; N, 3.71 %, $C_{13}H_{14}NO_4BrS$ requires C, 43.35; H, 3.92; N, 3.89 %.

Method using Bromine: A solution of alkene **120** (30 mg, 0.107 mmol, 1 equiv.) in $CHCl_3$ (0.6 mL) was treated with Br_2 (3.0 μL, 0.058 mmol, 0.55 equiv.) at −60 °C (dry ice-acetone cold bath) and allowed to stir for 15 h. Once room temperature was reached, the reaction was quenched with $Na_2S_2O_3$ aq. sat. soln. (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title compound* **215** (19 mg, 50 %) as a colourless solid with data as above.

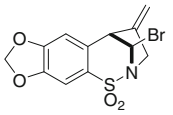


(5*S,10*S**)-10-Iodo-7,8-dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo [*f*] [1, 2] thiazepine 1,1-dioxide 216:** A mixture of **120** (40 mg, 0.14 mmol, 1 equiv.) and *N*-iodosuccinimide **217** (39 mg, 0.18 mmol, 1.25 equiv.) in $CHCl_3$ (0.8 mL, 0.178 M) were heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title* compound **216** (47 mg, 82 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); M.p. 174-176 °C; IR (NaCl, dep. from CH_2Cl_2) 2882, 1598, 1508, 1463, 1339, 1267, 1219, 1150, 1046, 1011, 912,

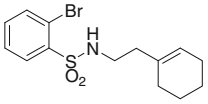
746, 639 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{14}NO_4SI + Na)]^+$ 429.9599; found; 429.9586; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 1H, ArH), 6.61 (s, 1H, CH), 6.60 (s, 1H, ArH), 5.34–5.33 (m, 1H, CH_2), 5.13 (s, 1H, CH_2), 4.42–4.29 (m, 2H, CH_2), 3.95-3.89 (m, 7H, CH, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8 (C), 149.9 (C) 145.5 (C), 130.8 (C), 125.6 (C), 109.0 (CH_2), 107.9 (CH), 107.7 (CH), 59.8 (CH), 56.4 (2 × CH_3), 50.4 (CH), 42.4 (CH) ppm.



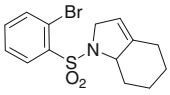
(4*R,5*S**,11*S**)-4,11-dibromo-4-methyl-4,5-dihydro-3*H*-2,5-methano [1, 3] dioxolo-[4′,5′:4,5]benzo[1,2-*f*] [1, 2] thiazepine 1,1-dioxide 224 and (4*R**,5*S**,11*S**)-4,11-Dibromo-4-(bromomethyl)-4,5-dihydro-3*H*-2,5-methano [1, 3]-dioxolo[4′,5′:4,5]benzo[1,2-*f*] [1, 2] thiazepine 1,1-dioxide 225:** A solution of alkene **219** (30 mg, 0.094 mmol, 1 equiv.) in $CHCl_3$ (1 mL) was treated with bromine (0.05 mL, 0.94 mmol, 10 equiv.) at −60 °C (dry ice-acetone cold bath) and allowed to stir for 15 h. Once room temperature was reached, the reaction was quenched with aq. $Na_2S_2O_3$ aq. sat. soln. (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) affording compounds affording compounds **224** and **225** (15 mg, 32 %) as a chromatographically inseparable mixture (**224**:**225**; 1:3). R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3053, 2921, 2855, 1504, 1483, 1347, 1251, 1175, 1036, 931 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{11}NO_4S\ ^{79}Br_2 + H)]^+$ 423.8854, found 423.8835 (**224**); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20 (s, 1H, ArH), 7.18 (s,1H, ArH), 6.89 (s, 1H, ArH), 6.70 (s, 1H, ArH), 6.34 (d, 1H, *J* = 1.0 Hz, CH), 6.35 (d, 1H, *J* = 1.0 Hz, CH), 6.13-6.11 (m, 4H, CH_2), 4.54 (d, *J* = 15.0 Hz, 1H, CH_2), 4.48 (d, *J* = 15.0 Hz, 1H, CH_2), 4.38–4.34 (m, 1H, CH_2), 4.17-4.14 (m, 1H, CH_2), 4.12-4.11 (m, 1H, CH_2), 4.01 (s, 1H, CH), 3.88 (s, CH), 3.36 (d, *J* = 11.5 Hz, 1H, CH_2), 3.14 (d, *J* = 11.5 Hz, 1H, CH_2), 1.51 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5 (C), 149.9 (C), 128.5 (C), 127.4 (C), 110.0 (CH), 108.4 (CH), 105.6 (2 × CH), 103.0 (CH_2), 102.8 (CH_2), 65.9 (C), 65.2 (CH), 64.9 (CH), 63.9 (CH), 63.7 (CH_2), 62.9 (CH), 61.5 (CH_2), 60.1 (C), 42.3 (CH_2), 33.5 (CH_3) ppm. Further elution gave (3*R**,4*R**,5*S**)-3,4-dibromo-5-methyl-4,5-dihydro-3*H*-2,5-methano [1, 3] dioxolo[4′,5′:4,5]benzo[1,2-*f*] [1, 2] thiazepine 1,1-dioxide **226** (15 mg, 38 %) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); HRMS (ESI): calcd for $[(C_{12}H_{11}NO_4S\ ^{79}Br_2 + H)]^+$ 423.8854, found 423.8844.



(5*S,11*S**)-11-Bromo-4-methylene-4,5-dihydro-3*H*-2,5-methano [1, 3]-dioxolo [4′,5′:4,5]-benzo[1,2-*f*] [1, 2] thiazepine 1,1-dioxide 227:** A mixture of **219** (40 mg, 0.15 mmol, 1 equiv.) and *N*-bromosuccinimide **183** (269 mg, 1.51 mmol, 10 equiv.) in $CHCl_3$ (0.85 mL, 0.178 M) were heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. Filtration, followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title* compound **227** (22 mg, 42 %) as a light brown solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); M.p. 211–213 °C; IR (NaCl, dep. from CH_2Cl_2) 2918, 1614, 1504, 1481, 1342, 1246, 1159, 1120, 1036, 916, 668 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{10}NO_4S\ ^{79}Br + H)]^+$ 343.9583; found 343.9592; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.16 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.29 (s, 1H, CH), 6.06 (d, *J* = 1.5 Hz, 1H, CH_2), 6.05 (d, *J* = 1.5 Hz, 1H, CH_2), 5.33–5.31 (m, 1H, CH_2), 5.12 (s (br), 1H, CH_2), 4.43–4.25 (m, 2H, CH_2), 3.83 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.8 (C), 148.5 (C), 144.4 (C), 132.3 (C), 127.1 (C), 109.2 (CH_2), 106.2 (CH), 105.6 (CH), 102.6 (CH), 66.9 (CH_2), 57.9 (CH), 49.9 (CH_2) ppm.

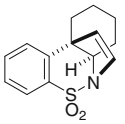


2-Bromo-*N*-(2-cyclohex-1-enylethyl)-benzenesulfonamide 232: To a solution of 2-bromobenzene-sulfonyl chloride **111** (1 g, 15.94 mmol, 1 equiv.) and triethylamine (2.2 mL, 15.6 mmol, 2 equiv.) in CH_2Cl_2 (15 mL) was added 2-cyclohex-1-enylethylamine **231** (1.6 mL, 12.00 mmol, 1.5 equiv.) at 0 °C in a dropwise fashion. The mixture was stirred for 16 h during which period room temperature was reached. The solution was poured into 1 M HCl solution (30 mL) and extracted with Et_2O (3 × 30 mL). Combined organic extracts were dried over $MgSO_4$, filtered and solvent removal in vacuo afforded **232** (1.25 g, 95 % yield) as a white solid. R_f = 0.4 (*c*-Hex/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.73 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.50–7.38 (m, 2H, ArH), 5.44 (s (br), 1H, CH), 5.14 (t (br), *J* = 5.0 Hz, 1H, NH), 2.97 (dd, *J* = 13.0, 6.0 Hz, 2H, CH_2), 2.10 (t, *J* = 6.0 Hz, 2H, CH_2), 1.97 (d, *J* = 1.0 Hz, 2H, CH_2), 1.75 (s (br), 2H, CH_2), 1.63–1.46 (m, 4H, CH_2) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 138.8 (C), 135.1(C), 133.7 (CH), 133.4 (CH), 131.8 (CH), 127.9 (CH), 125.1 (CH), 119.8 (C), 40.8(CH_2), 37.4 (CH_2), 27.6 (CH_2), 25.3 (CH_2), 22.8 (CH_2), 22.3 (CH_2) ppm.

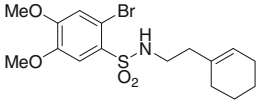


1-(2-Bromobenzenesulfonyl)-2,4,5,6,7,7a-hexahydro-1*H*-indole 233: A solution of **232** (1.2 g, 3.5 mmol, 1 equiv.) in MeCN:H_2O (10:1) (3.3 mL) was treated with powdered K_2CO_3 (1.5 g, 10.5 mmol, 3 equiv.) the mixture was stirred for 0.5 h at

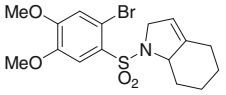
room temperature. Solid I_2 (2.6 g, 10.5 mmol, 3 equiv.) was then added and the mixture stirred for 18 h. A saturated solution of Na_2SO_3 (50 mL) was added and the combined mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and filtration and solvent removal in vacuo afforded the crude iodide. The crude material was directly dissolved in CH_2Cl_2 (20 mL) and treated at room temperature with DBU **239** (1.06 ml, 7.00 mmol, 2 equiv.). Stirring was maintained for 24 h before a 1 M solution of HCl (15 mL) was added. The resultant aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were dried over $MgSO_4$, filtered and the solvent removed under removal in vacuo afforded the alkene **233** (720 mg, 65 %) as a viscous brown oil. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. fromCH_2Cl_2) 2931, 2851, 1447, 1345, 1329, 1165, 1128, 1105, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.74 (m, 1H, ArH), 7.40 (m, 2H, ArH), 5.29 (d, *J* = 4.0 Hz, 2H, CH, CH_2), 4.39–4.23 (m, 3H, CH, CH_2), 2.55–2.42 (m, 1H, CH_2), 2.18 (m, 1H, CH_2), 1.95 (m, 2H, CH_2), 1.77 (d, *J* = 12.0 Hz, 3H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.0 (C), 135.9 (C), 133.4 (CH), 131.2 (CH), 127.7 (CH), 120.8 (CH), 114.2 (CH), 110.2 (C), 66.8 (CH), 55.4 (CH_2), 35.4 (CH_2), 28.6 (CH_2), 26.7 (CH_2), 23.9 (CH_2) ppm.



Heck Product 240: Under N_2, a mixture of above **233** compound (550 mg, 1.61 mmol, 1 equiv.), $Pd(OAc)_2$ (36 mg, 0.16 mmol, 10 mol%), PPh_3 (84 mg, 0.32 mmol, 20 mol%) and K_2CO_3 (455 mg, 3.22 mmol, 2 equiv.) in DMF (10 mL) was heated to 110 °C for 18 h. The reaction mixture was cooled and Et_2O (20 mL) and H_2O (20 mL) were added. The resultant aqueous layer was further extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 3:1) affording the Heck product **240** (361 mg, 85 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.79–7.65 (m, 1H, ArH), 7.56–7.36 (m, 2H, ArH), 7.22-7.19 (m, 1H, ArH), 6.23 (d, *J* = 4.0 Hz, 1H, CH), 6.12 (d, *J* = 4.0 Hz, 1H, CH), 4.55-4.50 (m, 1H, CH), 2.45 (d, *J* = 14.0 Hz, 1H, CH_2), 2.21–2.08 (m, 1H, CH_2), 1.93–1.59 (m, 4H, CH_2), 1.32–1.19 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1 (C), 138.1 (C), 134.2 (CH), 132.8 (CH), 131.7 (CH), 129.5 (CH), 127.5 (CH), 122.3 (CH), 72.2 (CH), 48.5 (C), 28.2 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 21.7 (CH_2) ppm.

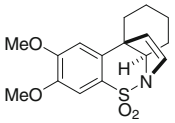


2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-4,5-dimethoxybenzenesulfonamide 234: A mixture of sulfonyl chloride **114** (2.0 g, 6.4 mmol, 1 equiv.) and 2-cyclohex-1-enyethylamine **231** (1.5 mL, 8.32 mmol, 1.3 equiv.) in CH_2Cl_2 (60 mL) was treated with Et_3N (1.78 mL, 12.8 mmol,2 equiv.) in a dropwise fashion at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. 1 M HCl (10 mL) was added to the reaction mixture and the layers separated. The organic layer was washed successively with an aq. $NaHCO_3$ sat. soln. (40 mL), H_2O (40 mL), brine and dried over $MgSO_4$. Filtration followed by solvent removal under pressure afforded the crude product. Purification through a plug of silica (*c*-Hex/EtOAc, 2:1) afforded the *title compound* **234** (2.2 g, 85 %) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 1:1); Mp = 69 °C; IR (NaCl, dep. from CH_2Cl_2) 3318, 3111, 3089, 3057, 2999, 2928, 2839, 1585, 1503, 1360, 1159 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{22}NO_4S\ ^{79}Br + H)]^+$ 404.0531, found 404.0515; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (s, 1H, ArH), 7.12 (s, 1H, ArH), 5.46 (s (br), 1H, CH), 5.05 (t, *J* = 6.0 Hz, 1H, NH), 3.93 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 2.93 (q, *J* = 6.0 Hz, 2H, CH_2), 2.11 (t, *J* = 6.0 Hz, 2H, CH_2), 1.99 (s (br), 2H, CH_2), 1.76 (s (br), 2H, CH_2), 1.50–1.61 (m, 4H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.2 (C), 148.0 (C), 133.3 (C), 130.2 (C), 125.0 (CH), 116.9 (CH), 114.0 (CH), 110.9 (C), 56.5 (CH_3), 56.4 (CH_3), 40.6 (CH_2), 37.1 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 22.2 (CH_2) ppm.

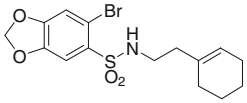


1-((2-Bromo-4,5-dimethoxyphenyl)sulfonyl)-2,4,5,6,7,7a-hexahydro-1*H*-indole 235: A solution of **234** (2.7 g, 6.7 mmol, 1 equiv.) in distilled MeCN (15 mL) was treated with powdered K_2CO_3 (2.8 g, 20.1 mmol, 3 equiv.). The mixture was stirred for 1 h at room temperature. Finely ground I_2 (5.1 g, 20.1 mmol, 3 equiv.) was added in one shot and the reaction stirred for 15 h. An aq. Na_2SO_3 sat. soln. (20 mL) was added and the combined mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered and reduced under pressure to afford the crude iodide. The crude material was directly dissolved in CH_2Cl_2 (30 mL) and treated with DBU **239** (2 mL, 13.4 mmol, 2 equiv.) at room temperature. Stirring was maintained for 2 h before 1 M HCl (25 mL) was added and the layers were separated. The resulting aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 4:1) gave **235** (1.9 g, 69 %) as a viscous yellow oil. R_f = 0.2 (*c*-Hex/EtOAc, 4:1); IR (NaCl, dep. from CH_2Cl_2) 3133, 3090, 3062, 2935, 2858, 1585, 1503, 1438, 1360, 1323, 1261, 1158, 1117, 1023 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{20}NO_4S\ ^{79}Br + H)]^+$ 402.0375, found 402.0359; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (s, 1H, ArH), 7.16 (s, 1H, ArH), 5.26 (s (br), 1H, CH), 4.35-4.28 (m, 2H, CH, CH_2), 4.24–4.19 (m, 1H, CH_2), 3.92 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.51–2.45 (m, 1H, CH_2), 2.14-2.19 (m, 1H, CH_2), 2.00–1.96 (m, 1H, CH_2),1.79–1.61 (m, 2H, CH_2), 1.34-1.18 (m, 3H, CH_2) ppm; ^{13}C NMR ($CDCl_3$,

125 MHz): δ 152.2 (C), 147.9 (C), 141.9 (C), 131.1 (C), 117.7 (CH), 114. (2 × CH), 112.2 (C), 66.4 (CH), 56.5 (CH_3), 56.4 (CH_3), 55.2 (CH_2), 35.3 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 23.9 (CH_2) ppm.

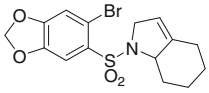


(6*S,10a*R**)-2,3-Dimethoxy-7,8,9,10-tetrahydro-6a*H*-6,10a-ethenodibenzo[*c*,*e*] [1, 2] thiazine 5,5-dioxide 241:** Under N_2, a solution of **235** (150 mg, 0.34 mmol, 1 equiv.) in anhydrous DMF (3 mL) was degassed under a steady stream of nitrogen (*ca.* 0.5 h). To this solution was added $Pd(OAc)_2$ (7 mg, 0.017 mmol, 10 mol%), PPh_3 (9 mg, 0.03 mmol, 20 mol%) and K_2CO_3 (103 mg, 0.74 mmol, 2 equiv.) and the mixture was heated to 130 °C for 15 h. The reaction vessel was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1) affording the Heck product **241** (57 mg, 65 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); Mp 130–132 °C; IR (NaCl, dep. from CH_2Cl_2) 3088, 3008, 2937, 2859, 1599, 1568, 1505, 1451, 1332, 1268, 1152, 1054 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{19}NO_4S + H)]^+$ 322.1113, found 322.1100; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (s, 1H, ArH), 7.16 (s, 1 H, ArH), 5.26 (s (br), 1H, CH). 4.35-4.28 (m, 2H, CH, CH_2), 4.24–4.19 (m, 1H, CH_2), 3.92 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.51–2.45 (m, 1H, CH_2), 2.19-2.14 (m, 1H, CH_2), 2.00–1.92 (m, 1H, CH_2), 1.79-1.61(m, 2H, CH_2), 1.34-1.18 (m, 3H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2 (C), 147.9 (C), 141.9 (C), 131.1 (C), 117.7 (C), 114.1(2 × CH), 112.2 (C), 66.4 (CH), 56.5 (CH_3), 56.4 (CH_3), 55.2 (CH_2), 35.3 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 23.9 (CH_2) ppm.

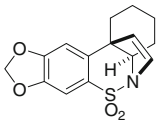


6-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)benzo[*d*] [1, 3] dioxole-5-sulfonamide 236: A mixture of sulfonyl chloride **222** (600 mg, 2.02 mmol, 1 equiv.) and 2-cyclohex-1-enyethylamine **231** (0.37 mL, 2.42 mmol, 1.2 equiv.) in CH_2Cl_2 (15 mL) was treated with Et_3N (0.34 mL, 2.42 mmol, 1.2 equiv.) in a dropwise fashion at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. 1 M HCl (10 mL) was added to the reaction mixture and the layers separated. The organic layer was washed successively with $NaHCO_3$ aq. sat. soln. (10 mL), H_2O (10 mL) and brine and was dried over $MgSO_4$. Filtration followed by solvent removal under pressure afforded the crude product. Purification through a plug of silica (*c*-Hex/EtOAc, 2:1) afforded the *title compound* **236** (743 mg, 95 %) as a brown viscous oil. R_f = 0.2 (*c*-Hex/EtOAc, 4:1); IR (NaCl, dep. from CH_2Cl_2) 2925, 1504, 1475, 1369, 1329, 1243, 1167, 1136, 1034, 653 cm^{-1}; HRMS (ESI): calcd for

$[(C_{15}H_{18}NO_4S\ ^{79}Br + H)]^+$ 388.0218, found 388.0218; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (s, 1H, ArH), 7.13 (s, 1H, ArH), 6.10 (s, 2H, CH_2), 5.47 (s (br), 1H, CH), 5.06 (t, J = 6.0 Hz, 1H, NH), 2.94 (q, J = 6.0 Hz, 2H, CH_2), 2.11 (t, J = 6.0 Hz, 2H, CH_2), 1.99 (s (br), 2H, CH_2), 1.76 (s (br), 2H, CH_2), 1.67–1.48 (m, 4H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5 (C), 147.4 (C), 133.3 (C), 131.9 (C), 125.1 (CH), 114.4 (CH), 112.2 (C), 111.6 (CH), 102.9 (CH_2), 40.6 (CH_2), 37.1 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 22.2 (CH_2) ppm.

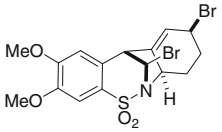


1-((6-Bromobenzo[*d*] [1, 3] dioxol-5-yl)sulfonyl)-2,4,5,6,7,7a-hexahydro-1*H*-indole 237: A solution of **236** (1.0 g, 2.6 mmol, 1 equiv.) in distilled MeCN (20 mL) was treated with powdered K_2CO_3 (1.31 g, 9.48 mmol, 3.6 equiv.). The mixture was stirred for 1 h at room temperature. Finely ground I_2 (907 mg, 9.48 mmol, 3.6 equiv.) was added in one shot and the reaction stirred for 4 h. Na_2SO_3 aq. sat. soln. (50 mL) was added and the combined mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered and reduced under pressure to afford the crude iodide. The crude material was directly dissolved in CH_2Cl_2 (30 mL) and treated with DBU **239** (0.77 mL, 5.16 mmol, 2 equiv.) at room temperature. Stirring was maintained for 2 h before 1 M HCl (15 mL) was added and the layers were separated. The resulting aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 4:1) gave **237** (750 mg, 75 %) as a viscous brown oil. R_f = 0.5 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2933, 2853, 1610, 1505, 1475, 1368, 1327, 1242, 1166, 1142, 1082, 1034, 922, 671 cm^{-1}; HRMS (ESI): calcd for $[(C_{15}H_{16}NO_4S\ ^{79}Br + Na)]^+$ 407.9876, found 407.9880; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H, ArH), 7.14 (s, 1H, ArH), 6.08 (s, 2H, CH_2), 5.26 (s (br), 1H, CH), 4.31–4.25 (m, 2H, CH_2), 4.22–4.18 (m, 1H, CH), 2.50–2.44 (m, 1H, CH_2), 2.20–2.16 (m, 1H, CH_2), 2.00–1.96 (m, 1H, CH_2),1.79-1.70 (m, 2H, CH_2), 1.32-1.19 (m, 3H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4 (C), 147.8 (C), 142.1 (C), 132.8 (C), 115.2 (CH), 114.3 (CH), 113.6 (C), 111.3 (CH), 102.9 (CH_2), 66.5 (CH), 55.5 (CH_2), 35.6 (CH_2), 28.6 (CH_2), 26.5 (CH_2), 24.0 (CH_2) ppm.



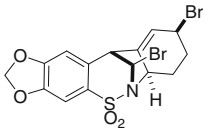
2,3,4,4a-Tetrahydro-1*H*-5,11b-etheno [1, 3] dioxolo[4′,5′:4,5]benzo[1,2-e]benzo [*c*] [1, 2] -thiazine 6,6-dioxide 242: Under N_2, a premixed solution (1 h at 50 °C) of $Pd(dba)_2$ (8 mg, 0.014 mmol, 10 mol%) and *t*-BuBrett-Phos **139** (13 mg, 0.03 mmol, 21 mol%) in anhydrous DMF (2 mL) was treated with a solution of **237** (53 mg, 0.14 mmol, 1 equiv.) in anhydrous DMF (0.5 mL) and K_2CO_3 (39 mg,

0.28 mmol, 2 equiv.) and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1 → 1:1) affording the Heck product **242** (17 mg, 40, 80 % brsm) as a brown viscous oil. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2932, 1609, 1504, 1482, 1346, 1249, 1176, 1161, 1036, 944, 757, 673 cm^{-1}; HRMS (ESI): calcd for $[(C_{15}H_{15}NO_4S + H)]^+$ 306.0800, found 306.0809; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 1H, ArH), 6.70 (s, 1H, ArH), 6.20 (d, *J* = 3.5 Hz, 1H, CH), 6.12 (d, *J* = 3.5 Hz, 1H, CH), 6.00 (d, *J* = 4.5 Hz, 2H, CH_2), 4.46-4.42 (m, 1H, CH), 2.36 (d, *J* = 13.5 Hz, 1H, CH_2), 2.16-2.10 (m, 1H, CH_2), 1.88–1.49 (m, 4H, CH_2), 1.42–1.09 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1 (C), 147.8 (C), 140.8 (C), 138.3 (CH), 132.8 (CH), 126.4 (C), 107.4 (CH), 103.4 (CH), 102.1 (CH_2), 72.4 (CH), 48.6 (C), 28.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.7 (CH_2) ppm.

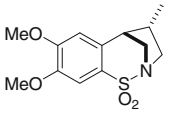


(6a*R,9*S**,11*S**,12*S**)-9,12-Dibromo-2,3-dimethoxy-7,8,9,11-tetrahydro-6a*H*-6,11-methanodibenzo[*c*,*f*] [1, 2] thiazepine 5,5-dioxide 243**: A solution of **241** (18 mg, 0.056 mmol, 1 equiv.) in $CHCl_3$ (0.8 mL, 0.178 M) was treated with Br_2 (57 μL, 1.12 mmol, 20 equiv.) at −60 °C (dry ice-acetone cold bath) and allowed to stir at this temperature for 1.5 h (reaction monitored by TLC). Once room temperature was reached the reaction was quenched with $Na_2S_2O_3$ aq. sat. soln. (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title compound* 2**43** (21 mg, 77 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); Mp 181–183 °C; IR (NaCl, dep. from CH_2Cl_2) 2932, 1609, 1504, 1482, 1346, 1249, 1176, 1161, 1036, 944, 757, 673 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{17}NO_4S\ ^{79}Br_2 + H)]^+$ 477.9323, found; 477.9332; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.35 (s, 1H, CH), 6.17 (s, 1H, CH), 4.90 (s, 1H, CH), 4.38–4.32 (m, 1H, CH), 3.92 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 3.86 (s (br), 1H, CH), 2.46–2.39 (m, 2H, CH_2), 2.33-2.26 (m, 1H, CH_2), 2.18–2.08 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2 (C), 150.6 (C), 140.2 (C), 128.2 (C), 126.1 (C), 125.1 (CH), 109.6 (CH), 108.0 (CH), 66.8 (CH), 59.3 (CH), 56.6 (CH_3), 56.5 (CH_3), 56.1 (CH), 46.4 (CH), 32.3 (CH_2), 24.3 (CH_2) ppm. Initial elution gave (6*R**,10a*R**,11*R**,12*R**)-11,12-dibromo-2,3-dimethoxy-7,8,9,10-tetrahydro-6a*H*-6,10a-ethanodibenzo[*c*,*e*] [1, 2] thiazine 5,5-

dioxide **244** (3 mg, 11 %) as a white solid. R_f = 0.6 (*c*-Hex/EtOAc, 2:1); HRMS (ESI): calcd for $[(C_{16}H_{19}NO_4S\ ^{79}Br_2 + Na)]^+$ 501.9294, found; 501.9314.

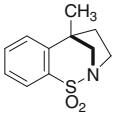


(6a*R,9*S**,11*S**,13*S**)-9,13-Dibromo-7,8,9,11-tetrahydro-6a*H*-6,11-methano-[1, 3] -dioxolo-[4′,5′:4,5]benzo[1,2-*f*]benzo[*c*] [1, 2] thiazepine 5,5-dioxide 245:** A solution of **242** (20 mg, 0.066 mmol, 1 equiv.) in $CHCl_3$ (0.35 mL, 0.178 M) was treated with Br_2 (64 μL, 1.24 mmol, 20 equiv.) at −60 °C (dry ice-acetone cold bath) and allowed to stir at this temperature for 1.5 h. Once room temperature was reached the reaction was quenched with $Na_2S_2O_3$ aq. sat. soln. (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) affording the *title compound* **245** (12 mg, 40 %) as a colourless solid. R_f = 0.4 (*c*-Hex/EtOAc, 2:1); Mp 172-175 °C; IR (NaCl, dep. from CH_2Cl_2) 2960, 2923, 1609, 1504, 1481, 1342, 1249, 1178, 1160, 1036, 944, 821, 756 cm^{-1}; HRMS (ESI): calcd for $[(C_{15}H_{13}NO_4S\ ^{79}Br_2 + Na)]^+$ 483.8824, found 483.8841; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s,1H, ArH), 6.65 (s, 1H, ArH), 6.34 (s, 1H, CH), 6.14 (s, 1H, CH), 6.07-6.05 (m, 2H, CH_2), 4.09 (s (br), 1H, CH), 4.38-4.31 (m, 1H, CH), 3.82 (s, 1H, CH), 2.48-2.38 (m, 2H, CH_2), 2.32–2.26 (m, 1H, CH_2), 2.17-2.08 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.9 (C), 148.7 (C), 139.9 (C), 129.9 (C), 127.7 (C), 125.7 (CH), 107.7 (CH), 106.2 (CH), 102.3 (CH_2), 66.4 (CH), 59.2 (CH), 56.8 (CH), 48.5 (CH), 32.5 (CH_2), 24.1 (CH_2) ppm. Initially eluting was (5*R**,11b*R**,12*R**,13*R**)-12,13-dibromo-2,3,4,4a-tetrahydro-1*H*-5,11b-ethano [1, 3] -dioxolo-[4′,5′:4,5]benzo [1,2-*e*]benzo[*c*] [1, 2] thiazine 6,6-dioxide **246** (5 mg, 16 %) as a colourless solid. R_f = 0.5 (*c*-Hex/EtOAc, 2:1); HRMS (ESI): calcd for $[(C_{15}H_{15}NO_4S\ ^{79}Br_2 + Na)]^+$ 485.8981, found 485.8992.



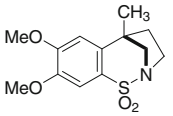
(4*S,5*S**)-7,8-Dimethoxy-4-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*] [1, 2] - thiazepine 1,1-dioxide 229:** A solution of **215** (100 mg, 0.28 mmol, 1 equiv.) in anhydrous toluene (6 mL) was treated with *n*-Bu_3SnH (0.097 mL, 0.363 mmol, 1.3 equiv.) and AIBN (cat.). The reaction mixture was heated to reflux for 15 h (oil bath temperature 110 °C). Once cooled, Et_2O (50 mL) and 2 % KF solution (100 mL) were added and the reaction mixture stirred for 2 h, after which the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined ethereal layers dried ($MgSO_4$). Filtration followed by solvent removal gave the crude material, which was purified by column chromatography (*c*-Hex/EtOAc,

4:1) to afford the debrominated compound (33 mg, 42 %) as a brown viscous oil. [7,8-Dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo[*f*] [1, 2] thiazepine 1,1-dioxide **228**: R_f = 0.3 (*c*-Hex/EtOAc, 2:1); HRMS (ESI): calcd for $[(C_{13}H_{15}NO_4S + H)]^+$ 282.0800; found 282.0812; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s, 1H, ArH), 6.65 (s, 1H, ArH), 5.19 (s, 1H, CH_2), 4.93 (s, 1H, CH_2), 4.29 (dd, *J* = 12.5 Hz, 2.5 Hz, 1H, CH_2), 4.02–3.97 (m, 1H, CH_2), 3.93 (s, 3H, CH_3), 3.90 (s, 4H, CH_3, CH_2), 3.53–3.51 (m, 1H, CH), 3.44 (dd, *J* = 12.5, 3.0 Hz, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5 (C), 149.9 (C), 148.3 (C), 132.6 (C), 125.7 (C), 108.7 (CH), 108.1 (CH), 106.7 (CH_2), 57.6 (CH_2), 56.4 (CH_3), 56.3 (CH_3), 52.3 (CH_2), 47.1 (CH) ppm]. A mixture of the alkene **228** (18 mg, 0.064 mmol, 1.0 equiv.) and 20 % w/w Pd/C (1.4 mg, 0.013 mmol) in EtOH:EtOAc (1:1, 10 mL) was stirred under an atmosphere of hydrogen (1 atm) for 15 h. The mixture was filtered through Celite (washed with EtOAc, 3 × 20 mL) and solvent removal afforded the alkane compound **229** (16 mg, 89 %) as a colourless viscous oil. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2958, 2924, 2853, 1602, 1509, 1463, 1322, 1264, 1146 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{17}NO_4S + Na)]^+$ 306.0776; found 306.0768; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (s, 1H, Ar), 6.56 (s, 1H, Ar), 4.26 (dd, *J* = 12.5, 1.5 Hz, 1H, CH_2), 3.90 (s, 6H, CH_3), 3.66 (dd, *J* = 13.5, 9.5 Hz, 1H, CH_2), 3.34 (dd, *J* = 1.5, 3.0 Hz, 1H, CH_2), 3.26-3.22 (m, 1H, CH_2), 2.94-2.92 (m, 1H, CH), 2.69-2.60 (m, 1H, CH), 0.78 (d, *J* = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7 (C), 149.1 (C), 129.9 (C), 127.3 (C), 111.2 (CH), 108.2 (CH), 58.2 (CH_2), 56.3 (2 × CH_3), 54.0 (CH_2), 44.6 (CH), 38.9 (CH), 16.4 (CH_3) ppm.

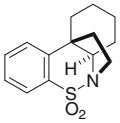


1-Methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide 264: General procedure for one-pot Heck-hydrogenation sequence. Under N_2, a solution of **108** (370 mg, 1.23 mmol, 1 equiv.), $Pd(OAc)_2$ (27 mg, 0.120 mmol, 10 mol%), PPh_3 (64 mg, 0.244 mmol, 20 mol%) and K_2CO_3 (373 mg, 2.70 mmol, 2.2 equiv.) in anhydrous DMF (8 mL) was heated at 110 ºC (oil bath temperature), where the reaction was monitored by TLC. Once cooled to room temperature, the mixture was stirred under an atmosphere of H_2 for 15 h. EtOAc (10 mL) and H_2O (10 mL) were added and the layers partitioned. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$). Filtration followed by solvent removal under pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc, 3:1) to afford **264** (177 mg, 65 %) as a colourless solid. Mp 186–188 °C; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3064, 2963, 2881, 1464, 1331, 1166, 1058 cm^{-1}; HRMS (ESI): calcd for $[(C_{11}H_{13}NO_2S + H)]^+$ 224.0745, found 224.0744; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 8.0 Hz, 1H, ArH), 7.52 (t, *J* = 8.0 Hz, 1H, ArH), 7.47–7.31 (m, 2H, ArH), 4.18 (d, *J* = 13.0 Hz, 1H, CH_2), 3.93–3.80 (m, 1H, CH_2), 3.66–3.55 (m, 1H, CH_2), 3.09 (d, *J* = 13.0 Hz, 1H, CH_2),

2.00–1.94 (m, 2H, CH_2), 1.58 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6 (C), 135.2 (C), 132.9 (CH), 128.3 (CH), 126.6 (CH), 124.6 (CH), 63.1 (CH_2), 48.1 (CH_2), 42.2 (C), 40.4 (CH_2), 16.0 (CH_3) ppm.

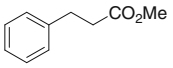


4,5-Dimethoxy-1-methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide 230: Under N_2, a solution of **118** (100 mg, 0.28 mmol, 1 equiv.), Pd $(OAc)_2$ (6 mg, 0.027 mmol, 10 mol%), PPh_3 (15 mg, 0.057 mmol, 20 mol%) and K_2CO_3 (77 mg, 0.56 mmol, 2 equiv.) in anhydrous DMF (2.3 mL) was heated at 110 ºC for 18 h. Once cooled, the mixture was stirred under an atmosphere of H_2 for 15 h. EtOAc (10 mL) and H_2O (10 mL) were added and the layers partitioned. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$). Filtration followed by solvent removal under pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1) to afford **230** (79 mg, 58 %) as a colourless solid. Mp 192–196 °C; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 2939, 1507, 1462, 1326, 1270, 1150, 1041 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{17}NO_4S + H)]^+$ 284.0957, found 284.0963; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24 (s, 1H, ArH), 6.77 (s, 1H, ArH), 4.15 (d, *J* = 13.5 Hz, 1H, CH_2), 3.93 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 3.89–3.79 (m, 1H, CH_2), 3.65–3.54 (m, 1H, CH_2), 3.06 (d, *J* = 13.5 Hz, 1H, CH_2), 1.97–1.92 (m, 2H, CH_2), 1.57 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4 (C), 148.8 (C), 137.1 (C), 126.5 (C), 108.1 (CH), 106.9 (CH), 63.4 (CH_2), 56.4 (CH_3), 56.3 (CH_3), 48.3 (CH_2), 42.0 (C), 40.3 (CH_2), 20.3 (CH_3) ppm.



(4a*R,10a*S**)-4a,10-ethano-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-azaphenanth-rene 9,9-dioxide 265**: Under N_2, a solution of **233** (250 mg, 0.73 mmol, 1 equiv.), $Pd(OAc)_2$ (16 mg, 0.071 mmol, 10 mol%), PPh_3 (40 mg, 0.153 mmol, 20 mol%) and K_2CO_3 (207 mg, 1.50 mmol, 2 equiv.) in anhydrous DMF (6 mL) was heated at 110 °C for 15 h. Once cooled, the mixture was stirred under an atmosphere of H_2 for 15 h. EtOAc (10 mL) and H_2O (10 mL) were added and the layers partitioned. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$). Filtration followed by solvent removal under pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc, 4:1) to afford **265** (119 mg, 62 %) as a colourless solid. Mp 138–140 °C; R_f = 0.3 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 3086, 2935, 2883, 1840, 1723, 1591, 1463, 1439, 1386, 1329, 1277,

1243, 1207, 1166, 1112, 1053, 1027 cm^{-1}; HRMS (ESI): calcd for $[(C_{14}H_{17}NO_2S + H)]^+$ 264.1058, found 264.1066; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, *J* = 8.0 Hz, 1H, ArH), 7.51 (t, *J* = 8.0 Hz, 1H, ArH), 7.43–7.31 (m, 2H, ArH), 4.10 (dd, *J* = 12.0, 6.0 Hz, 1H, CH), 3.89-3.81 (m, 1H, CH_2), 3.66–3.59 (m, 1H, CH_2), 2.58–2.27 (m, 2H, CH_2), 2.03–1.48 (m, 4H, CH_2), 1.47–1.19 (m, 4H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.3 (C), 135.7 (C), 132.8 (CH), 127.9 (CH), 126.6 (CH), 124.0 (CH), 67.4 (CH), 45.7 (CH_2), 44.9 (C), 33.4 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 23.8 (CH_2), 21.4 (CH_2) ppm.



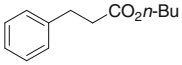
3-Phenylpropionic acid methyl ester (methyl dihydrocinnamate) 271: According to the general procedure above; a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), methyl acrylate **269** (0.3 mL, 3.19 mmol, 5 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) afforded **271** (76 mg, 73 %) as a yellow oil, [6] following purification by flash column chromatography (*c*-Hex/EtOAc, 6:1). R_f = 0.3 (*c*-Hex/EtOAc, 6:1); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.23 (m, 3H, ArH), 7.23–7.16 (m, 2H, ArH), 3.67 (s, 3H, CH_3), 2.96 (t, *J* = 8.0 Hz, 2H, CH_2), 2.63 (t, *J* = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (CO), 140.7 (CH), 128.7 (CH), 128.5 (CH), 126.5 (CH), 51.7 (CH_3), 35.9 (CH_2), 31.2 (CH_2) ppm. NMR data matched that in the literature.

"Phosphine free" procedure: A mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), methyl acrylate **269** (58 μL, 0.64 mmol, 1 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) afforded **271** (25 mg, 24 %) following standard work-up and purification by flash column chromatography with data as above.

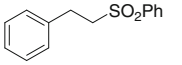
"Jeffery conditions": $Pd(OAc)_2$ (7 mg, 0.031 mmol, 5 mol%), *n*-Bu_4NBr (205 mg, 0.64 mmol, 1 equiv.) and NaOAc (131 mg, 1.60 mmol, 2.5 equiv.) were sequentially added to a degassed (bubbled with a N_2 stream *ca*. 30 min) solution of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.) and methyl acrylate **269** (0.058 μL, 0.64 mmol, 1 equiv.) in anhydrous DMF (0.6 mL). The mixture was then heated at 50 °C for 15 h. Once cooled, the mixture was stirred under an atmosphere of H_2 for 15 h. EtOAc (10 mL) and H_2O (10 mL) were added and the layers partitioned. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$). Filtration followed by solvent removal in vacuo yielded the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) affording **271** (45 mg, 43 %) with data as above.

Matsuda-Heck reaction: NaOAc (270 mg, 3.30 mmol, 1.7 equiv.) and benzenediazonium tetrafluoroborate [7] **268** (380 mg, 1.98 mmol, 1 equiv.) were added sequentially to a degassed (bubbled with a N_2 stream *ca*. 10 min) solution of methyl acrylate **269** (0.62 mL, 6.93 mmol, 3.5 equiv.) in acetonitrile* (7.5 mL). At room temperature $Pd(OAc)_2$ (20 mg, 0.089 mmol, 5 mol%) was added to the mixture and stirring was maintained for 15 h (after approximately 30 min gas evolution was

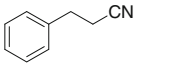
observed and the orange solution became black). The nitrogen atmosphere was then swapped with hydrogen (balloon *ca*. 1 atm.) and stirring was continued for 15 h at room temperature. H_2O (15 mL) and Et_2O (15 mL) were added and the resultant aqueous layer was further extracted with ether (2 × 15 mL). The combined ethereal extracts were dried over $MgSO_4$. Filtration followed by solvent removal in vacuo afforded **271** (298 mg, 92 %) with data as above. *HPLC grade without further drying or distillation.



***n*-Butyl 3-phenylpropanoate (*n*-butyl dihydrocinnamate) 279:** According to the general procedure above; a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), *n*-butyl acrylate **273** (0.09 mL, 0.64 mmol, 1 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) afforded **279**[6] (104 mg, 79 %) as a white solid following purification by flash column chromatography (*c*-Hex). R_f = 0.7 (*c*-Hex/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.22 (m, 2H, ArH), 7.23–7.14 (m, 3H, ArH), 4.07 (t, *J* = 7.0 Hz, 2H, CH_2), 2.95 (t, *J* = 8.0 Hz, 2H, CH_2), 2.61 (t, *J* = 8.0 Hz, 2H, CH_2), 1.67–1.49 (m, 2H, CH_2), 1.40–1.24 (m, 2H, CH_2), 0.91 (t, *J* = 7.5 Hz, 3H, CH_3). NMR data matched that in the literature.

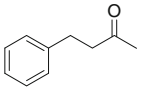


1-Phenylsulfonyl-2-phenylethane 280 According to the general procedure described above; a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), phenyl vinyl sulfone **274** (107 mg, 0.64 mmol, 1 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) afforded an inseparable mixture (4:1) of **280** and the alkene Heck adduct, (*E*)-1-phenylsulfonyl-2-phenylethene (80 mg, 51 %) following purification by flash column chromatography (*c*-Hex/EtOAc, 4:1). [8] R_f = 0.2 (*c*-Hex/EtOAc, 4:1); HRMS (ESI): calcd for $[(C_{14}H_{14}O_2S + Na)]^+$ 269.0612, found 269.0602; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.90 (m, 2H, ArH), 7.66 (m,1H, ArH), 7.56 (m, 2H, ArH), 7.26 (m, 2H), 7.22–7.16 (m, 1H, ArH), 7.10 (d, *J* = 7.0 Hz, 2H, ArH), 3.39–3.32 (m, 2H, CH_2), 3.08–3.01 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 139.3 (C), 137.6 (C), 133.8 (CH), 129.5 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 57.7 (CH_2), 28.9 (CH_2) ppm. NMR data matched that in the literature.

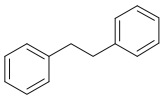


3-Phenylpropanenitrile (dihydrocinnamonitrile) 281: According to the general procedure a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), acrylonitrile **275** (46 mg, 0.87 mmol, 1.4 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol,

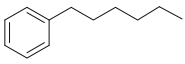
10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) gave **281** (36 mg, 43 %) as a colourless oil [9] following purification by flash column chromatography (*c*-Hex/EtOAc, 4:1). R_f = 0.3 (*c*-Hex/EtOAc, 4:1); HRMS (EI): calcd for $[C_9H_9N]^+$ 131.0735, found 131.0735; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.0 Hz, 2H, ArH), 7.30–7.21 (m, 3H, ArH), 2.96 (t, *J* = 7.0 Hz, 2H, CH_2), 2.62 (t, *J* = 7.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2 (C), 129.0 (CH), 128.4 (CH), 127.4 (CH), 119.2 (C), 31.8 (CH_2), 19.5 (CH_2) ppm. NMR data matched that in the literature.



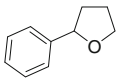
4-Phenylbutan-2-one 282: Due to alkene volatility this reaction was performed in a sealed tube. A mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), methyl vinyl ketone **15** (0.5 mL, 6.37 mmol, 10 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) were mixed and sealed in a screw capped thick walled glass reaction vessel. The tube was immersed in an oil bath (110 °C) for 15 h. Upon cooling hydrogen was introduced (balloon, *ca.* 1 atm.) and stirring continued for 15 h. Following standard work-up (as above) purification flash column chromatography (*c*-Hex/EtOAc, 4:1) afforded **282** (59 mg, 62 %) as a pale orange oil. [10] R_f = 0.4 (*c*-Hex/EtOAc, 4:1); HRMS (EI): calcd for $[C_{10}H_{12}O]^+$ 148.0888, found 148.0887; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.23 (m, 2H, ArH), 7.11–7.08 (m, 3H, ArH), 2.88 (t, *J* = 8.0 Hz, 2H, CH_2), 2.74 (t, *J* = 8.0 Hz, 2H, CH_2), 2.12 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9 (CO), 141.1 (C), 128.5 (CH), 128.3 (CH), 126.1 (CH), 45.2 (CH_2), 30.1 (CH_3), 29.8 (CH_2) ppm. NMR data matched that in the literature.



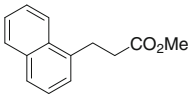
1,2-Diphenylethane 283: According to the general procedure; a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), styrene* **276** (0.07 mL, 0.64 mmol, 1 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) followed by purification flash column chromatography (*c*-Hex) afforded **283** (57 mg, 49 %) as a white solid. [11] Mp 45-47 °C (45–49 °C); [12] R_f = 0.4 (*c*-Hex); HRMS (EI): calcd for $[C_{14}H_{20}O_4]^+$ 182.1096, found 182.1098; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.15 (m, 10H, ArH), 2.92 (s, 4H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9 (C), 128.6 (CH), 128.5 (CH), 126.1 (CH), 38.1 (CH_2) ppm. *Used as supplied, *i.e.* not distilled. NMR data matched that in the literature.



1-Hexylbenzene 284: Due to alkene volatility this reaction was performed in a sealed tube as follows; a mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), hex-1-ene **277** (0.40 mL, 3.20 mmol, 5 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL). Purification flash column chromatography (*c*-Hex) afforded **284** (87 mg, 84 %) as a colourless oil. [13] $R_f = 0.6$ (*c*-Hex); HRMS (EI): calcd for $[C_{12}H_{18}]^+$ 162.1409, found 162.1408; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.11 (m, 5H, ArH), 2.72–2.50 (m, 2H, CH_2); 1.68–1.49 (m, 2H, CH_2), 1.35–1.23 (m, 4H, CH_2), 0.89 (t, J = 6.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1 (C), 128.5 (CH), 128.4 (CH), 125.7 (CH), 36.2 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3) ppm. NMR data matched that in the literature.

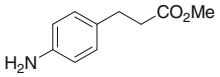


2-Phenyltetrahydrofuran 286: Due to alkene volatility this reaction was performed in a sealed tube. A mixture of bromobenzene **267** (0.07 mL, 0.64 mmol, 1 equiv.), 2,3-dihydrofuran **278** (0.24 mL, 3.20 mmol, 5 equiv.), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol%), PPh_3 (33 mg, 0.126 mmol, 20 mol%) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv.) in anhydrous DMF (5 mL) followed by purification flash column chromatography (*c*-Hex/EtOAc, 6:1) afforded **286** (52 mg, 55 %) as a light brown oil. [14, 15] $R_f = 0.6$ (*c*-Hex/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.19 (m, 5H, ArH), 4.88 (t, J = 7.0 Hz, 1H, CH), 4.09 (dd, J = 15.0, 7.0 Hz, 1H, CH_2), 3.93 (dd, J = 15.0, 7.0 Hz, 1H, CH_2), 2.31 (td, J = 13.0, 7.0 Hz, 1H, CH_2), 2.04–1.93 (m, 2H, CH_2), 1.80 (ddd, J = 16.0, 12.0, 8.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C), 128.7 (CH), 127.2 (CH), 125.7 (CH), 80.8 (CH), 68.8 (CH_2), 34.7 (CH_2), 26.1 (CH_2) ppm. NMR data matched that in the literature.

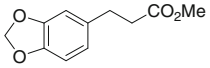


Methyl 3-(1-naphthyl)propanoate **296**: According to the general procedure a mixture of 1-bromonaphthalene **288** (100 mg, 0.48 mmol, 1 equiv.), methyl acrylate **269** (0.22 mL, 2.40 mmol, 5 equiv.), $Pd(OAc)_2$ (10 mg, 0.046 mmol, 10 mol%), PPh_3 (25 mg, 0.095 mmol, 20 mol%) and K_2CO_3 (133 mg, 0.96 mmol, 2 equiv.) in anhydrous DMF (4 mL) afforded **296** (81 mg, 79 %) as a yellow oil. $R_f = 0.4$ (*c*-Hex/EtOAc, 9:1); IR (NaCl, dep. from CH_2Cl_2) 3047, 2950, 1737, 1435, 1167, 777 cm^{-1}; HRMS (ESI): calcd for $[(C_{14}H_{14}O_2 + Na)]^+$ 237.0891, found 237.0900; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 1H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 7.72 (d, J = 8.0 Hz, 1H, ArH), 7.55–7.43 (m, 2H, ArH), 7.41–7.30 (m, 2H, ArH), 3.68 (s, 3H, CH_3), 3.45–3.37 (m, 2H, CH_2), 2.79–2.71 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6 (CO), 136.6 (C), 133.9 (CH), 131.7

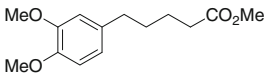
(CH), 128.9 (CH), 127.3 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 125.7 (CH), 123.5 (CH), 51.8 (CH_3), 35.1 (CH_2), 28.3 (CH_2) ppm.



Methyl 3-(4-aminophenyl)propanoate 297: According to the general procedure above a mixture of 1-bromo-4-nitrobenzene **289** (100 mg, 0.49 mmol, 1 equiv.), methyl acrylate **269** (0.22 mL, 2.45 mmol, 5 equiv.), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol%), PPh_3 (25 mg, 0.095 mmol, 20 mol%) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv.) in anhydrous DMF (4 mL) afforded a mixture (4:1) of **297** and the alkene Heck product 3-(4-aminophenyl)-acrylic acid methyl ester (52 mg, 59 %) as a brown solid. [16] R_f = 0.2 (*c*-Hex/EtOAc, 5:1); HRMS (ESI): calcd for $[(C_{10}H_{14}O_2N + H)]^+$ 180.1025, found 180.1023; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00–6.94 (m, 2H, ArH), 6.63–6.58 (m, 2H, ArH), 3.65 (s, 3H, CH_3), 2.83 (t, *J* = 8.0 Hz, 2H, CH_2), 2.56 (t, *J* = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7 (CO), 144.8 (C), 130.0 (C), 129.2 (CH), 115.4 (CH), 51.63 (CH_3), 36.3 (CH_2), 30.3 (CH_2) ppm. NMR data matched that in the literature.

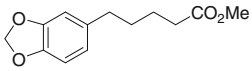


Methyl 3-(3,4-methylenedioxyphenyl)propionate 300: According to the general procedure; a mixture of 1-bromo-3,4-(methylenedioxy)benzene **220** (60 μL, 0.50 mmol, 1 equiv.), methyl acrylate **269** (0.22 mL, 2.50 mmol, 5 equiv.), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol%), PPh_3 (26 mg, 0.099 mmol, 20 mol%) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv.) in anhydrous DMF (4 mL) afforded **300** (25 mg, 25 %) as a yellow oil. [17] R_f = 0.4 (*c*-Hex/EtOAc, 9:1); HRMS (EI): calcd for $[C_{11}H_{12}O_4]^+$ 208.0736, found 208.0741; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76–6.60 (m, 3H, ArH), 5.92 (s, 2H, CH_2), 3.67 (s, 3H, CH_3), 2.87 (t, *J* = 8.0 Hz, 2H, CH_2), 2.58 (t, *J* = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4 (CO), 147.8 (C), 145.1 (C), 134.4 (CH), 121.2 (C), 108.9 (CH), 108.4 (CH), 100.9 (CH_2), 51.8 (CH_3), 36.2 (CH_2), 30.8 (CH_2) ppm. NMR data matched that in the literature.

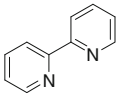


Methyl 5-(3,4-dimethoxyphenyl)pentanoate 301: According to the general procedure; a mixture of (E)-4-(2-bromovinyl)-1,2-dimethoxybenzene **291** (40 mg, 0.165 mmol, 1 equiv.), methyl acrylate **269** (74 μL, 0.825 mmol, 5 equiv.), $Pd(OAc)_2$ (4 mg, 0.018 mmol, 11 mol%), PPh_3 (9 mg, 0.034 mmol, 21 mol%) and K_2CO_3 (46 mg, 0.33 mmol, 2 equiv.) in anhydrous DMF (1.4 mL) afforded **301**

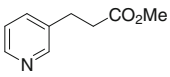
(35 mg, 83 %) as a yellow oil. R_f = 0.3 (*c*-Hex/EtOAc, 4:1); IR (NaCl, dep. from CH_2Cl_2) 3051, 2929, 1734, 1515, 1439, 1260, 1155, 1027, 801 cm^{-1}; HRMS (ESI): calcd for $[(C_{14}H_{20}O_4 + Na)]^+$ 275.1259, found 275.1259; ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.0 Hz, 1H, ArH), 6.71 (d, *J* = 8.0 Hz, 1H, ArH), 6.70 (s, 1H, ArH), 3.87 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 2.58 (t, *J* = 7.0 Hz, 2H, CH_2), 2.34 (t, *J* = 7.0 Hz, 2H, CH_2), 1.73-1.57 (m, 4H, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2 (CO), 148.9 (C), 147.3 (C), 134.9 (C), 120.3 (CH), 111.9 (CH), 111.4 (CH), 56.1 (CH_3), 55.9 (CH_3), 51.6 (CH_3), 35.3 (CH_2), 34.1 (CH_2), 31.2 (CH_2), 24.7 (CH_2) ppm.



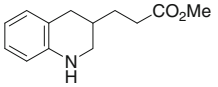
Methyl 5-(3,4-(methylenedioxy)phenyl)pentanoate 302: According to the general procedure described a mixture of (*E*)-5-(2-bromovinyl)benzo[d] [1, 3] dioxole **292** (100 mg, 0.44 mmol, 1 equiv.), methyl acrylate **269** (0.20 mL, 2.20 mmol, 5 equiv.), $Pd(OAc)_2$ (9 mg, 0.040 mmol, 10 mol%), PPh_3 (23 mg, 0.088 mmol, 20 mol%) and K_2CO_3 (121 mg, 0.88 mmol, 2 equiv.) in anhydrous DMF (4 mL) afforded **302** (86 mg, 83 %) as a yellow oil. [18] R_f = 0.4 (*c*-Hex/EtOAc, 9:1); HRMS (ESI): calcd for $[(C_{13}H_{16}O_4 + Na)]^+$ 259.0946, found 259.0956; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74–6.57 (m, 3H, ArH), 5.91 (s, 2H, CH_2), 3.66 (s, 3H, CH_3), 2.54 (t, *J* = 7.0 Hz, 2H, CH_2), 2.32 (t, *J* = 7.0 Hz, 2H, CH_2), 1.79–1.44 (m, 4H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (CO), 147.7 (C), 145.7 (C), 136.1 (C), 121.2 (CH), 108.9 (CH), 108.2 (CH), 100.9 (CH_2), 51.6 (CH_3), 35.4 (CH_2), 34.1 (CH_2), 31.3 (CH_2), 24.6 (CH_2) ppm. NMR data matched that in the literature.



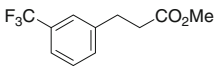
Bipyridyl: This reaction was performed in a sealed tube as follows; a mixture of 2-bromopyridine **(2)-293** (50 μL, 0.53 mmol, 1 equiv.), methyl acrylate **269** (0.24 mL, 2.65 mmol, 5 equiv.), $Pd(OAc)_2$ (12 mg, 0.053 mmol, 10 mol%), PPh_3 (27 mg, 0.103 mmol, 20 mol%) and K_2CO_3 (146 mg, 1.06 mmol, 2 equiv.) in anhydrous DMF (5 mL) after standard work-up and purification by flash column chromatography (*c*-Hex/EtOAc, 1:2) afforded the *title compound* (21 mg, 61 %) as a colourless oil. [19] R_f = 0.2 (*c*-Hex/EtOAc, 1:2); HRMS (ESI): calcd for $[(C_{10}H_8N_2 + H)]^+$ 157.0766, found 157.0763; ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 2H, CH), 8.41 (d, *J* = 8.0 Hz, 2H, CH), 7.81 (td, *J* = 8.0, 1.0 Hz, 2H, CH), 7.36–7.22 (m, 2H, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4 (C), 149.3 (CH), 137.0 (CH), 123.9 (CH), 121.3 (CH) ppm. NMR data matched that in the literature.



Methyl 3-(pyridin-3-yl)propanoate (3)-304: This reaction was performed in a sealed tube as follows; a mixture of 3-bromopyridine **(3)-294** (50 μL, 0.53 mmol, 1 equiv.), methyl acrylate **269** (0.24 mL, 2.65 mmol, 5 equiv.), $Pd(OAc)_2$ (12 mg, 0.053 mmol, 10 mol%), PPh_3 (27 mg, 0.103 mmol, 20 mol%) and K_2CO_3 (146 mg, 1.06 mmol, 2 equiv.) in anhydrous DMF (5 mL) afforded **(3)-304** (73 mg, 84 %) as a colourless oil following purification by flash column chromatography (*c*-Hex → *c*-Hex/EtOAc, 1:3). [20] R_f = 0.4 (*c*-Hex/EtOAc, 1:2); HRMS (ESI): calcd for $[(C_9H_{11}NO_2 + H)]^+$ 166.0868, found 166.0866; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (s, 2H, ArH), 7.53 (d, *J* = 8.0 Hz, 1H, ArH), 7.22 (dd, *J* = 7.0, 5.0 Hz, 1H, ArH), 3.67 (s, 3H, CH_3), 2.96 (t, *J* = 8.0 Hz, 2H, CH_2), 2.65 (t, *J* = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7 (CO), 149.8 (CH), 147.8 (CH), 135.9 (CH), 135.8 (C), 123.4 (CH), 51.7 (CH_3), 35.2 (CH_2), 28.1 (CH_2) ppm. NMR data matched that in the literature.

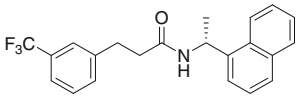


Methyl 3-(1,2,3,4-tetrahydroquinolin-3-yl)propanoate 305: This reaction was performed in a sealed tube as follows; according to the general procedure above; a mixture of 3-bromoquinoline **295** (65 μL, 0.48 mmol, 1 equiv.), methyl acrylate **269** (0.22 mL, 2.40 mmol, 5 equiv.), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol%), PPh_3 (26 mg, 0.099 mmol, 20 mol%) and K_2CO_3 (138 mg, 1.00 mmol, 2 equiv.) in anhydrous DMF (4 mL) afforded **305** (37 mg, 35 %) as a colourless oil. R_f = 0.5 (*c*-Hex); IR (NaCl, dep. from CH_2Cl_2) 3028, 2924, 1735, 1430, 1179, 712 cm^{-1}; HRMS (ESI): calcd for $[(C_{13}H_{17}NO_4 + H)]^+$ 220.1338, found 220.1335; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (m, 2H, ArH), 6.60 (t, *J* = 7.0 Hz, 1H, ArH), 6.47 (d, *J* = 8.0 Hz, 1H, ArH), 3.67 (s, 3H, CH_3), 3.32 (m, 1H, CH), 2.96 (dd, *J* = 11.0, 9.0 Hz, 1H, CH_2), 2.90–2.78 (m, 1H, CH_2), 2.45 (m, 4H, CH_2), 1.95 (s (br), 1H, NH), 1.81–1.59 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1 (CO), 144.4 (C), 129.8 (CH), 127.0 (CH), 120.6 (C), 117.4 (CH), 114.1 (CH), 51.7 (CH_3), 46.9 (CH), 33.4 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 28.8 (CH_2) ppm.



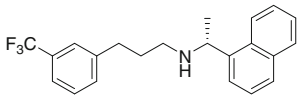
Methyl 3-(3-(trifluoromethyl)phenyl)propanoate 311: This reaction was performed in a sealed tube as follows; according to the general procedure above a mixture of 3-bromobenzotrifluoride **310** (0.12 mL, 0.89 mmol, 1 equiv.), methyl acrylate **269** (0.40 mL, 4.45 mmol, 5 equiv.), $Pd(OAc)_2$ (20 mg, 0.09 mmol, 10 mol %), PPh_3 (47 mg, 0.18 mmol, 20 mol%) and K_2CO_3 (248 mg, 1.80 mmol, 2 equiv.) in anhydrous DMF (7 mL) afforded **311** (198 mg, 95 %) as a yellow colourless oil. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 3053, 2955, 2849, 1740, 1430, 1331, 1164, 1124, 702 cm^{-1}; HRMS (EI): calcd $[(C_{11}H_{11}O_2F_3)]^+$ 232.0711, found 232.0700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.42 (m, 2H, ArH), 7.41–7.33 (m, 2H, ArH), 3.65 (s, 3H, CH_3), 3.00 (t, *J* = 8.0 Hz, 2H, CH_2),

2.63 (t, J = 8.0 Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (CO), 141.6 (CH), 131.9 (d, J = 1.0 Hz, CH), 131.0 (q, J = 34.0 Hz, C), 129.1 (CH), 125.2 (q, J = 4.0 Hz, CH), 124.3 (q, J = 270.0 Hz, C), 123.3 (q, J = 4.0 Hz, CH), 51.7 (CH_3), 35.4 (CH_2), 30.8 (CH_2) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.79 ppm.

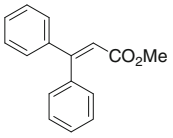


(*R*)-*N*-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propanamide 312: A solution of **311** (625 mg, 2.71 mmol, 1 equiv.) dissolved in $CDCl_3$ (1 mL) (*R*)-1-(1-naphthyl)ethylamine **316** (0.48 mL, 3.00 mmol, 1.1 equiv.), 1,2,4-triazole (69 mg, 1.00 mmol, 37 mol%) and DBU **139** (80 μL, 0.54 mmol, 20 mol%) was heated to reflux for 24 h. Once cooled, the crude material was flushed through a plug of silica and recrystallisation (*c*-Hex) afforded **312** (645 mg, 64 %) as a white solid. Mp 90–92 °C (*c*-Hex); R_f = 0.3 (*c*-Hex/EtOAc, 3:1); $[\alpha]_D$ = + 9.5 (*c* = 0.1, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 3292, 3065, 2973, 2929, 1638, 1329, 1163, 1122 cm^{-1}; HRMS (ESI): calcd for $[(C_{22}H_{20}NOF_3 + H)]^+$ 371.1575, found 372.1587; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–8.00 (m, 1H, ArH), 7.85 (dd, J = 6.0, 4.0 Hz, 1H, ArH), 7.78 (dd, J = 6.0, 4.0 Hz, 1H, ArH), 7.50 (p, J = 6.0 Hz, 2H, ArH), 7.47–7.38 (m, 4H, ArH), 7.33 (q, J = 8.0 Hz, 2H, ArH), 5.96–5.86 (m, 1H, CH), 5.61–5.51 (m, 1H, NH), 3.12–2.95 (m, 2H, CH_2), 2.46 (td, J = 7.0, 3.0 Hz, 2H, CH_2), 1.60 (m, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (CO), 141.9 (C), 138.3 (C), 134.1 (C), 132.0 (q, J = 1.0 Hz, CH), 131.2 (C), 130.9 (q, J = 32.0 Hz, C), 128.9 (q, J = 6.5 Hz, CH), 128.5 (CH), 126.7 (CH), 125.9 (2 × CH), 125.3 (CH), 125.1 (q, J = 4.0 Hz, CH), 124.2 (q, J = 270.0 Hz, C), 123.4 (CH), 123.2 (q, J = 4.0 Hz, CH), 122.6 (C), 44.8 (CH), 38.0 (CH_2), 31.4 (CH_2), 20.7 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.64 ppm.

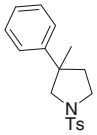
Hydrolysis-amide coupling: At room temperature a solution of methyl ester **311** (40 mg, 0.17 mmol, 1 equiv.) in THF (3 mL) was treated with a solution of $LiOH{\cdot}H_2O$ (22 mg, 0.52 mmol, 3 equiv.) in H_2O (2 mL). Stirring was continued for 48 h before Et_2O (5 mL) and 1 M HCl (5 mL) were added. The resultant aqueous layer was further extracted Et_2O (2 × 5 mL) and the combined ethereal extracts were dried over $MgSO_4$. Filtration and solvent removal under reduced pressure afforded the crude carboxylic acid **314**. The crude material was dissolved in anhydrous CH_2Cl_2 (2 mL) and treated with EDCI·HCl (36 mg, 0.19 mmol, 1.1 equiv.), (*R*)-(+)-1-(1-naphthyl)ethylamine **316** (30 μL, 0.19 mmol, 1.1 equiv.) and DIPEA (34 μL, 0.19 mmol, 1.1 equiv.) at rt under N_2. Stirring was continued for 15 h before CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The organic layer was dried over $MgSO_4$ to afford the crude material. Recrystallisation (*c*-Hex) gave **312** (52 mg, 83 %) as a white solid with data consistent with above.



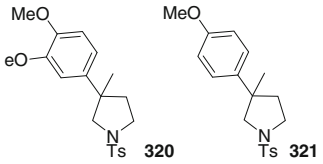
(*R*)-*N*-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine (Sensipar) 315: A slurry lithium aluminium hydride (106 mg, 2.79 mmol, 10 equiv.) in Et_2O (10 mL) was treated with a solution of **312** (100 mg, 0.27 mmol, 1 equiv.) in Et_2O (10 mL). The reaction mixture was heated to reflux for 5 h. On cooling the reaction mixture was added to ice and extracted with Et_2O (3 × 50 mL) and the combined ethereal extracts were dried over $MgSO_4$. Filtration followed by solvent removal in vacuo yielded the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 1:2) affording **315** (77 mg, 80 %) as a yellow oil. [21] R_f = 0.2 (*c*-Hex/EtOAc, 1:2); $[\alpha]_D$ = + 10 (*c* = 0.1, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 3339, 3049, 2958, 2927, 2856, 1450, 1330, 1163, 1124, 1073 cm^{-1}; HRMS (ESI): calcd for $[(C_{22}H_{22}NF_3 + H)]^+$ 358.1783, found 358.1795; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H, ArH), 7.86 (d, *J* = 8.0 Hz, 1H, ArH), 7.73 (d, *J* = 8.0 Hz, 1H, ArH), 7.63 (d, *J* = 7.0 Hz, 1H, ArH), 7.53–7.38 (m, 5H, ArH), 7.36–7.25 (m, 2H, ArH), 4.61 (q, *J* = 7.0 Hz, 1H, CH), 2.77–2.53 (m, 4H, CH_2), 1.82 (p, *J* = 7.0 Hz, 2H, CH_2), 1.48 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1 (C), 141.3 (C), 134.0 (C), 131.8 (q, *J* = 1.0 Hz, CH), 131.3 (C), 130.6 (q, *J* = 32.0 Hz, C), 129.0 (CH), 128.6 (CH), 127.2 (CH), 125.7 (2 × CH), 125.6 (CH), 125.3 (CH), 125.0 (q, *J* = 4.0 Hz, CH), 124.3 (q, *J* = 270.0 Hz, C), 122.9 (CH), 122.7 (CH), 122.6 (q, *J* = 3.0 Hz, CH), 53.8 (CH), 47.2 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 23.6 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.55 ppm. NMR data matched that in the literature.



Methyl 3,3-diphenylacrylate 272: This reaction was performed in a sealed tube as follows; according to the general procedure above a mixture of bromobenzene **267** (0.6 mL, 5.80 mmol, 5 equiv.), methyl acrylate **269** (0.10 mL, 1.16 mmol, 1 equiv.), $Pd(OAc)_2$ (29 mg, 0.13 mmol, 10 mol%), PPh_3 (63 mg, 0.24 mmol, 20 mol%) and K_2CO_3 (331 mg, 2.40 mmol, 2 equiv.) in anhydrous DMF (9 mL). On cooling the mixture was stirred under a H_2 atmosphere for 15 h which afforded, following standard work-up and column chromatography (*c*-Hex/EtOAc, 6:1), an inseparable mixture of **272** and **271** (161 mg, 73 %; **272**:**271**; 40:60) as a pale yellow oil. NMR spectroscopic analysis indicated identity of **272**. [22, 23] R_f = 0.3 (*c*-Hex/EtOAc, 6:1); HRMS (ESI): calcd for $[(C_{16}H_{14}O_2)]^+$ 238.0994, found 238.0993; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H, ArH), 7.22–7.13 (m, 5H, ArH), 6.36 (s, 1H, CH), 3.58 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (CO), 157.1 (C), 140.7 (C), 138.9 (C), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.4 (CH), 117.0 (CH), 51.3 (CH_3) ppm. NMR data matched that in the literature.



3-Methyl-3-phenyl-1-tosylpyrrolidine 318: Under N_2, small pieces of Li (80 mg, 12.74 mmol, 20 equiv.) were added to NH_3 (*ca.* 75 mL) at –78 ºC. The mixture was stirred for 1 h before a solution of **264** (150 mg, 0.637 mmol, 1 equiv.) in THF (5 mL + 5 mL to wash flask) was added in a dropwise fashion. Stirring was continued for 0.5 h at –78 ºC before addition of solid NH_4Cl (*ca.* 2.0 g). The NH_3 was allowed to evaporate on warming to room temperature and the residue was taken up in CH_2Cl_2 (15 mL). A solution of 1 M solution of NaOH solution (until pH 12) was added and the resultant aqueous layer was further extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure, to afford the crude amine. A solution of the crude amine (107 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.18 mL, 1.34 mmol, 2 equiv.) and *p*-TsCl (127 mg, 0.67 mmol, 1 equiv.) at 0 ºC. Stirring was continued for 15 h and the reaction gradually warmed to room temperature. Silica (*ca.* 2.0 g) was added to the reaction mixture and solvent removal under pressure. Purification by flash chromatography gave the *title compound* **318** (129 mg, 65 %) as a colourless oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); IR (NaCl, dep. from CH_2Cl_2) 2965, 2876, 1597, 1496, 1445, 1343, 1158, 1095, 701, 663 cm^{-1}; HRMS (EI): calcd for $[(C_{18}H_{22}NO_2S + H)]^+$ 316.1371, found 316.1366; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 2H, ArH), 7.32–7.24 (m, 4H, ArH), 7.22-7.20 (m, 1H, ArH), 7.14 (d, *J* = 7.0 Hz, 2H, ArH), 3.55–3.37 (m, 4H, CH_2), 2.41 (s, 3H CH_3), 2.10–1.96 (m, 2H, CH_2), 1.20 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4 (C), 143.4 (C), 134.0 (C), 129.6 (CH), 128.4 (CH), 127.4 (CH), 126.5 (CH), 125.3 (CH), 58.9 (CH_2), 46.5 (CH_2), 45.9 (C), 37.6 (CH_2), 27.7 (CH_3), 21.4 (CH_3) ppm.

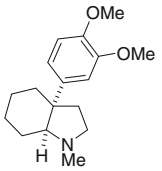


3-(3,4-Dimethoxyphenyl)-3-methyl-1-tosylpyrrolidine 320 and 3-(4-methoxyphenyl)-3-methyl-1-tosylpyrrolidine 321 Under N_2, small pieces of Li (35 mg, 5.0 mmol, 10 equiv.) were added to NH_3 (*ca.* 75 mL) at –78 ºC. The mixture was stirred for 1 h before a solution of **230** (140 mg, 0.5 mmol, 1 equiv.) in THF (5 mL + 5 mL to wash flask) was added in a dropwise fashion. Stirring was continued for 0.5 h at –78 ºC before addition of solid NH_4Cl (*ca.* 2.0 g). The NH_3 was allowed to evaporate on warming to room temperature and the residue was dissolved in CH_2Cl_2 (25 mL). A solution of 1 M solution of NaOH solution (until pH 12) was added and the resultant aqueous layer was further extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$. A solution of the crude amine (109 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.13 mL, 1.00 mmol, 2 equiv.) and *p*-TsCl (95 mg, 0.5 mmol, 1 equiv.) at 0 ºC. Stirring was continued for 15 h and the reaction gradually warmed to room temperature. Silica (*ca.* 2.0 g) was added to the reaction mixture and

solvent removal under pressure. Purification by flash chromatography gave 3-(3,4-Dimethoxyphenyl)-3-methyl-1-tosylpyrrolidine **320** (44 mg, 24 %) as a colourless solid and 3-(4-methoxyphenyl)-3-methyl-1-tosylpyrrolidine **321** (90 mg, 52 %) as a colourless solid.

Data for **320:** Mp 94–98 °C; R_f = 0.4 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2960, 2917, 1520, 1464, 1340, 1255, 1158, 1094, 1027, 807, 663 cm^{-1}; HRMS (EI): calcd for $[(C_{20}H_{26}NO_4S + H)]^+$ 376.1583, found 376.1590; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, *J* = 8.0 Hz, 2H, ArH), 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 6.76 (d, *J* = 8.0 Hz, 1H, ArH), 6.68 (d, *J* = 9.0 Hz, 2H, ArH), 3.84 (s, 6H, CH_3), 3.51–3.39 (m, 4H, CH_2), 2.42 (s, 3H, CH_3), 2.12–1.90 (m, 2H, CH_2), 1.19 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1 (C), 147.8 (C), 143.5 (C), 139.2 (C), 134.5 (C), 129.8 (CH), 127.5 (CH), 117.6 (CH), 111.3 (CH), 109.5 (CH), 59.4 (CH_2), 56.1 (CH_3), 46.7 (CH_2), 45.9 (C), 37.9 (CH_2), 29.8 (CH_2), 27.8 (CH_3), 21.6 (CH_3) ppm.

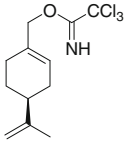
Data for **321:** Mp 102–108 °C; R_f = 0.6 (*c*-Hex/EtOAc, 2:1); IR (NaCl, dep. from CH_2Cl_2) 2924, 2854, 1737, 1516, 1340, 1289, 1249, 1158, 1033, 810, 622 cm^{-1}; HRMS (EI): calcd for $[(C_{19}H_{24}NO_3S + H)]^+$ 346.1477, found 346.1478; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.0 Hz, 2H, ArH), 7.29 (d, *J* = 8.0 Hz, 2H, ArH), 7.06 (d, *J* = 9.0 Hz, 2H, ArH), 6.80 (d, *J* = 9.0 Hz, 2H, ArH), 3.77 (s, 3H, CH_3), 3.53–3.33 (m, 4H, CH_2), 2.42 (s, 3H, CH_3), 2.09–1.89 (m, 2H, CH_2), 1.18 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2 (C), 143.4 (C), 138.6 (C), 134.4 (C), 129.8 (CH), 127.5 (CH), 126.7 (CH), 113.9 (CH), 59.4 (CH_2), 55.4 (CH_3), 46.8 (CH_2), 45.6 (C), 38.0 (CH_2), 27.8 (CH_3), 21.6 (CH_3) ppm.



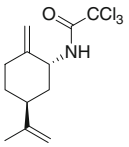
(±)-(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindole (mesembrane) 2: Under N_2, small pieces of Li (15 mg, 2.143 mmol, 8.6 equiv.) were added to NH_3 (75 mL) at –78 ºC. The mixture was stirred for 45 min before a solution of **266** (80 mg, 0.248 mmol, 1 equiv.) in THF (15 mL + 5 mL to wash flask) was added in a dropwise fashion. Stirring was continued for 15 min at –78 ºC before addition of solid NH_4Cl (*ca.* 2 g). The NH_3 was allowed to evaporate on warming to room temperature and the residue was dissolved in CH_2Cl_2 (25 mL). A solution of 1 M NaOH solution (25 mL) was added and the resultant aqueous layer was further extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure afforded a 1:1 mixture of 3a-(4-methoxyphenyl)octahydroindole and 3a-(3,4-dimethoxyphenyl)octahydroindole (72 mg) [3a-(4-methoxyphenyl)octahydroindole: HRMS (ESI): calcd for $[(C_{15}H_{21}NO + H)]^+$ 232.1701, found 232.1692; 3a-(3,4-dimethoxyphenyl)octahydroindole: HRMS (ESI): calcd for $[(C_{16}H_{23}NO_2 + H)]^+$ 262.1807, found 262.1805]. This mixture was taken up in CH_2Cl_2 (3 mL) and powdered K_2CO_3

(343 mg, 2.482 mmol, 10 equiv.) was added followed by benzyl chloroformate (63 mg, 0.369 mmol, 1.5 equiv.). Stirring was continued at room temperature for 4 h before addition of silica (*ca.* 2 g) and solvent removal under reduced pressure. Purification by flash column chromatography gave **330** (47 mg, 52 %). R_f = 0.2 (*c*-Hex/EtOAc, 4:1); HRMS (ESI): calcd for $[(C_{23}H_{27}NO_3 + H)]^+$ 366.2069, found 366.2077. Further elution gave **329** (23 mg, 33 %). R_f = 0.1 (*c*-Hex/EtOAc, 4:1). Under N_2, **329** (32 mg, 0.081 mmol, 1 equiv.) in THF (5 mL) was treated with $LiAlH_4$ (10 mg, 0.263 mmol, 3.25 equiv.). The reaction mixture was heated to reflux for 2 h. On cooling EtOAc (20 mL) was gradually added followed by 1 M NaOH solution (20 mL). The resultant aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Following filtration and solvent removal column chromatography ($CHCl_3$/MeOH, 19:1, 1% Et_3N) afforded the title compound **2** (21 mg, 94 %) as a colourless oil with data in accord to that reported. R_f = 0.1 ($CHCl_3$/MeOH, 19:1, 1% Et_3N); IR (NaCl, dep. from CH_2Cl_2) 3054, 2929, 2852, 1516, 1456, 1253 cm^{-1}; HRMS (ESI): calcd for $[(C_{17}H_{25}NO_2 + H)]^+$ 276.1964, found 276.1971; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.91 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 6.88 (d, *J* = 2.0 Hz, 1H, ArH), 6.81 (d, *J* = 8.0 Hz, 1H, ArH), 3.89 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.34–3.39 (m, 1H, CH_2), 2.60 (s(br), 1H, CH), 2.39 (s, 3H, CH_3), 2.33-2.40 (m, 1H, CH_2), 1.89-1.97 (m, 3H, CH_2), 1.81–1.88 (m, 2H, CH_2), 1.58-1.69 (m, 2H, CH_2), 1.50 (d, *J* = 12.0 Hz, 1H, CH_2), 1.39–1.42 (m, 1H, CH_2), 1.14-1.19 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.8 (C), 147.0 (C), 139.8 (C), 118.8 (CH), 110.9 (CH), 110.8 (CH), 69.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 54.3 (CH_2), 47.6 (C), 40.8 (CH_2, CH_3), 35.7 (CH_2), 23.6 (CH_2), 22.7 (CH_2), 20.4 (CH_2) ppm.

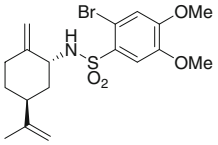
Lithium Naphthalenide Method: Under nitrogen a solution of naphthalene (138 mg, 1.07 mmol, 7 equiv.) in THF (10 mL) was treated with small pieces of lithium metal (7.5 mg, 1.07 mmol, 7 equiv.) and sonicated for 0.5 h at rt. The reaction mixture was cooled to −78 °C and treated with a solution of **266** (49 mg, 0.15 mmol, 1 equiv.) in THF (10 mL). After 10 min the reaction was warmed to rt (*ca.* 30 min). NH_4Cl sat. (20 mL) was added and the mixture extracted with CH_2Cl_2 (20 mL) and washed with 1 M NaOH solution (3 × 20 mL). The organic layer was dried over $MgSO_4$ before filtration and evaporation under reduced pressure. The crude product was dissolved in CH_2Cl_2 (10 mL) and treated with K_2CO_3 (149 mg, 1.08 mmol, 7.2 equiv.) and benzyl chloroformate (0.2 mL, 1.40 mmol, 9.3 equiv.). Stirring was maintained for 4 h at rt. Water (20 mL) and CH_2Cl_2 (20 mL) were added and the resultant aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by silica gel chromatography (*c*-Hex/EtOAc, 4:1) afforded the product **329** (13 mg, 22 %) with data as those above.



(*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl 2,2,2-trichloroacetimidate 334: A solution of **333** (1.04 mL, 6.58 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (30 mL) was cooled to 0 °C. DBU **239** (1.17 mL, 7.9 mmol, 1.2 equiv.) and trichloroacetonitrile (0.98 mL, 9.87 mmol, 1.5 equiv.) were added sequentially. Stirring was continued for 2 h during which period room temperature was reached. The reaction mixture was then filtered through a plug of silica washing with CH_2Cl_2, and the filtrate concentrated in vacuo to give the imidate **334** (1.92 g, 99 %) as an orange liquid. The thus obtained imidate **334** was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H, NH), 5.89–5.81 (m, 1H, CH), 4.77–4.69 (m, 2H, CH_2), 4.68 (s, 2H, CH_2), 2.24–2.19 (m, 1H, CH), 2.20–2.13 (m, 3H, CH_2), 2.06–1.97 (m, 1H, CH_2), 1.87 (m, 1H, CH_2), 1.74 (s, 3H, CH_3), 1.58–1.46 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (C), 149.7 (C), 132.4 (C), 126.2 (CH), 108.9 (CH_2), 91.8 (C), 73.3 (CH_2), 40.9 (CH), 30.6 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 20.9 (CH_3) ppm.

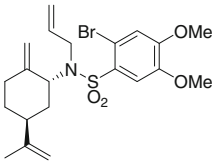


2,2,2-Trichloro-*N*-((1*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)acetamide 335: Under N_2, a solution of imidate **334** (1.9 g, 6.4 mmol) in anhydrous toluene (60 mL) was heated to reflux for 7 days (oil bath temperature 130 °C). Once cooled, the mixture was concentrated under pressure to give a brown oil, which was flushed through a pad of silica (*c*-Hex/EtOAc, 3:1) to afford acetamide **335** (1.85 g, 97, 80 % d.e.) as a golden yellow liquid. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20}$ = + 40.3 (*c* = 2.0, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 3435, 3369, 3083, 2939, 2858, 1708, 1645, 1504, 893, 821 cm^{-1}; HRMS (ESI): calcd for $[(C_{12}H_{17}NO^{35}Cl_3 + H)]^+$ 296.0376, found 296.0365; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.85–6.72 (m, 1H, NH), 4.97 (s, 1H, CH_2), 4.89 (s, 1H, CH_2), 4.78 (s, 1H, CH_2), 4.76 (s, 1H, CH_2), 4.55 (dt, *J* = 8.0, 4.5 Hz, 1H, CH), 2.35 (dt, *J* = 14.0, 4.5 Hz, 1H, CH_2), 2.25–2.19 (m, 2H, CH,CH_2), 2.03 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.72 (s, 4H, CH_2,CH_3), 1.47 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6 (CO), 147.5 (C), 144.6 (C), 111.9 (CH_2), 110.1 (CH_2), 92.9 (C), 53.5 (CH), 39.4 (CH), 36.1 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 21.1 (CH_3) ppm.



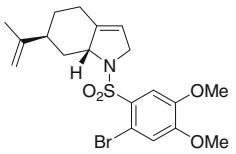
2-Bromo-4,5-dimethoxy-*N*-((1*R*,5S)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl) benzene sulfonamide 337: A solution of **335** (2.20 g, 7.5 mmol,) in EtOH-CH_2Cl_2 (2:1, 12 mL) was treated with 5 M NaOH (5 mL) and the reaction heated to 50 °C for 15 h. Once cooled, CH_2Cl_2 (20 mL) added and the organic layer washed with brine,

dried ($MgSO_4$) and filtered. The crude amine-CH_2Cl_2 solution was treated with 2-bromo-4,5-dimethoxybenzene-1-sulfonyl chloride **114** (1.78 g, 5.64 mmol, 0.76 equiv.) and Et_3N (0.9 mL, 6.77 mmol, 1.2 equiv.) at 0 °C. Stirring was continued for 5 h and the reaction gradually warmed to room temperature. The reaction mixture was washed once with H_2O and the organic layer dried over $MgSO_4$. The crude product, obtained after solvent removal and filtration, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) which gave the *title compound* **337** (2.30 g, 96 %, based on **114**) as a light yellow solid. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); Mp 100–102 °C; $[\alpha]_D^{20}$ = + 62.5 (*c* = 2.0, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 3081, 2937, 1464, 1360, 1331, 1161, 1132, 690 cm^{-1}; HRMS (ESI): calcd for $[(C_{18}H_{24}NO_4S\ ^{79}Br + Na)]^+$ 452.0507, found 452.0515; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 1H, ArH), 7.09 (s, 1H, ArH), 5.34 (d, *J* = 6.0 Hz, 1H, NH), 4.71–4.64 (m, 1H, CH_2), 4.65–4.57 (m, 2H, CH_2), 4.53 (s, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.89 (s, 4H, CH_3, CH), 2.28 (tt, *J* = 12.0, 3.0 Hz, 1H, CH), 2.19-2.09 (m, 2H, CH_2), 1.93 (dq, *J* = 13.5, 3.0 Hz, 1H, CH_2), 1.83–1.74 (m, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.50–1.41 (m, 1H, CH_2), 1.25 (td, *J* = 12.0, 5.0 Hz, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3 (C), 148.3 (C), 147.9 (C), 145.2 (C), 131.2 (C), 116.9 (CH), 114.2 (CH), 111.6 (CH), 111.5 (CH_2), 109.6 (CH_2), 56.6 (CH), 56.5 (CH_3), 56.4 (CH_3), 38.9 (CH), 37.9 (CH_2), 32.2 (CH_2), 30.4 (CH_2), 20.9 (CH_3) ppm.

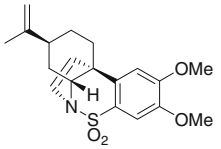


***N*-Allyl-2-bromo-4,5-dimethoxy-*N*-((1*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl) cyclohexyl)benzene sulfonamide 338:** A solution of **337** (150 mg, 0.35 mmol) dissolved in DMF (4 mL) was cooled to 0 °C. Sodium hydride (60 % w/w in mineral oil, 22 mg, 0.525 mmol, 1.5 equiv.) was added and the mixture stirred for 0.5 h. Allyl bromide (0.04 mL, 0.42 mmol, 1.2 equiv.) was added in a dropwise fashion. Stirring was continued for 15 h during which period room temperature was reached. EtOAc (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic layers dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) to yield the *title compound* **338** (152 mg, 93 %) a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); Mp 78–80 °C; $[\alpha]_D^{20}$ = −8.8 (*c* = 0.8, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2846, 1584, 1503, 1437, 1360, 1330, 1158, 1116, 598 cm^{-1}; HRMS (ESI): calcd for $[(C_{21}H_{28}NO_4S\ ^{79}Br + H)]^+$ 470.1001, found 470.0986; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H, ArH), 7.08 (s, 1H, ArH), 5.87 (ddt, *J* = 16.5, 10.5, 6.0 Hz, 1H, CH), 5.18 (d, *J* = 17.0 Hz, 1H, CH_2), 5.09 (d, *J* = 11.0 Hz, 1H, CH_2), 4.84 (s, 1H, CH_2), 4.81–4.76 (m, 2H, CH_2), 4.72 (s, 1H, CH_2), 4.51 (dd, *J* = 8.5, 4.5 Hz, 1H, CH), 4.19 (ddt, *J* = 17.0, 6.0, 1.5 Hz, 1H, CH_2), 4.03 (ddt, *J* = 17.0, 6.0, 1.5 Hz, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 2.24-2.18 (m, 1H, CH), 2.10–2.04 (m, 2H, CH_2), 2.02–1.95 (m, 2H, CH_2), 1.64 (s, 3H, CH_3),

1.60–1.57 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1 (C), 147.7 (C), 146.7 (C), 145.9 (C), 135.9 (CH), 132.5 (C), 117.3 (CH_2), 117.2 (CH), 114.9 (CH), 112.3 (C), 110.8 (CH), 110.6 (CH), 58.6 (CH), 56.6 (CH_3), 56.5 (CH_3), 48.9 (CH_2), 39.5 (CH), 35.3 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 21.9 (CH_3) ppm.

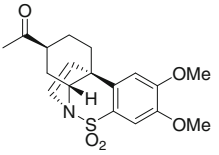


(6*S*,7a*R*)-1-(2-Bromo-4,5-dimethoxyphenylsulfonyl)-6-(prop-1-en-2-yl)-2,4,5,6, 7,7a-hexahydro-1*H*-indole 332: Under N_2, a degassed solution of **338** (500 mg, 1.06 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was treated with Hoveyda-Grubbs 2nd gen. catalyst **119** (20 mg, 0.0321 mmol, 3.0 mol%). Stirring was continued at 40 °C for 15 h. Once cooled, the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 6:1) gave **332** (450 mg, 96 %) as a viscous oil. $R_f = 0.4$ (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20} = +1.6$ ($c = 1.1$, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2872, 1585, 1503, 1465, 1439, 1360, 1330, 1158, 1116 cm^{-1}; HRMS (ESI): calcd for $[(C_{19}H_{24}NO_4S^{79}Br + H)]^+$ 442.0688, found 442.0706; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (s, 1H, ArH), 7.13 (s, 1H, ArH), 5.23 (s, 1H, CH), 4.89 (s, 1H, CH_2), 4.81 (s, 1H, CH_2), 4.48–4.42 (m, 1H, CH), 4.31 (m, 1H, CH_2), 4.21–4.15 (m, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.45–2.44 (m, 1H, CH_2), 2.41 (s, 1H, CH), 2.29 (m, 1H, CH_2), 2.19– 2.12 (m, 1H, CH_2), 2.09–2.04 (m, 1H, CH_2), 1.71 (s, 3H, CH_3), 1.52–1.42 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0 (C), 147.7 (C), 144.9 (C), 141.9 (C), 130.8 (C), 117.6 (CH), 113.9 (CH), 113.5 (CH), 112.1 (C), 111.4 (CH_2), 62.8 (CH), 56.4 (CH_3), 56.3 (CH_3), 55.0 (CH_2), 38.5 (CH), 36.8 (CH_2), 28.3 (CH_2), 24.3 (CH_2), 22.6 (CH_3) ppm.

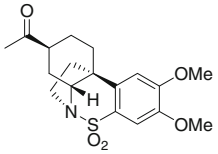


(2*S*,4a*R*,10a*S*)-6,7-Dimethoxy-4a,10-etheno-2,3,4,4a,10,10a-hexahydro-1*H*-2-isopropenyl-9-thia-10-aza-phenanthrene 9,9-dioxide 339: Under N_2, a solution of **332** (105 mg, 0.24 mmol, 1 equiv.) dissolved in DMF (2 mL) was degassed under a steady stream of nitrogen (*ca.* 0.5 h). To this solution was added $Pd(OAc)_2$ (6 mg, 0.024 mmol, 10 mol%), PPh_3 (12 mg, 0.048 mmol, 20 mol%) and K_2CO_3 (66 mg, 0.48 mmol, 2 equiv.) and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash

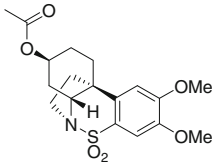
column chromatography (*c*-Hex/EtOAc, 6:1 → 4:1) affording the Heck product **339** (79 mg, 91 %) as a colourless solid. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); Mp 63–66 °C; $[\alpha]_D^{20}$ = + 10 (*c* = 0.5, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2920, 1562, 1470, 1361, 1334, 1146 cm^{-1}; HRMS (ESI): calcd for $[(C_{19}H_{23}NO_4S + Na)]^+$ 384.1245, found 384.1245; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.23 (d, *J* = 3.5 Hz, 1H, CH), 6.16 (d, *J* = 3.5 Hz, 1H, CH), 4.94 (s, 1H, CH_2), 4.90 (s, 1H, CH_2), 4.74 (dd, *J* = 11.0, 6.0 Hz, 1H, CH), 3.90 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.48 (s, 1H, CH), 2.46–2.39 (m, 1H, CH_2), 2.16–2.12 (m, 2H, CH_2), 2.11–2.05 (m, 1H, CH_2), 1.98–1.90 (m, 1H, CH_2), 1.75 (s, 3H, CH_3), 1.69–1.65 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.1 (C), 149.6 (C), 144.5 (C), 138.7 (C), 138.3 (CH), 132.5 (CH), 125.1 (C), 112.6 (CH_2), 109.4 (CH), 105.3 (CH), 69.7 (CH), 56.4 (CH_3), 56.3 (CH_3), 48.4 (C), 37.3 (CH), 29.4 (CH_2), 23.2 (CH_2), 22.8 (CH_2), 22.5 (CH_3) ppm.



(2*S*,4a*R*,10a*S*)-2-Acetyl-6,7-dimethoxy-4a,10-etheno-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 341: A solution of **339** (296 mg, 0.819 mmol, 1 equiv.) dissolved in CH_2Cl_2 (10 mL) was treated with *m*-CPBA (77 % w/w, 275 mg, 1.23 mmol, 1.5 equiv.) at room temperature. After 15 h, sodium sulfite sat. (10 mL) and $NaHCO_3$ sat. (10 mL) were added and the reaction mixture allowed to stir for 0.5 h, after which the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL), dried over $MgSO_4$ and reduced under pressure to afford the crude epoxide. The crude epoxide **340** was dissolved in THF-H_2O (2:1, 12 mL) was treated to H_5IO_6 (446 mg, 1.64 mmol, 2 equiv.) at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. Et_2O (20 mL) and H_2O (15 mL) were added and the phases separated. The resultant aqueous layer was further extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1 → 1:2) affording the *title* compound **341** (255 mg, 86 %) as a white solid. R_f = 0.1 (*c*-Hex/EtOAc, 1:1); Mp 78–81 °C; $[\alpha]_D^{20}$ = −5.7 (*c* = 1.4, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2945, 2854, 1705, 1599, 1352, 1330, 1158, 1149 cm^{-1}; HRMS (ESI): calcd for $[(C_{18}H_{21}NO_5S + Na)]^+$ 386.1038, found 386.1039; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.11 (s, 1H, ArH), 6.58 (s, 1H, ArH), 6.18 (d, *J* = 3.5 Hz, 1H, CH), 6.13 (d, *J* = 3.5 Hz, 1H, CH), 4.82 (dd, *J* = 10.5, 6.5 Hz, 1H, CH), 3.86 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 2.82 (s, 1H, CH), 2.41 (dd, *J* = 14.0, 6.5 Hz, 1H, CH_2), 2.26–2.23 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.81–1.73 (m, 1H, CH_2), 1.72–1.65 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.1 (C), 151.0 (C), 149.6 (C), 138.2 (C), 137.7 (CH), 132.6 (CH), 125.0 (C), 109.3 (CH), 105.3 (CH), 69.5 (CH), 56.3 (CH_3), 56.2 (CH_3), 48.0 (C), 45.4 (CH), 28.1 (CH_3), 27.6 (CH_2), 23.7 (CH_2), 22.4 (CH_2) ppm.

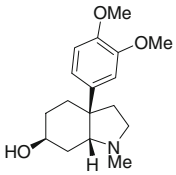


(2*S*,4a*R*,10a*S*)-2-Acetyl-6,7-dimethoxy-4a,10-ethano-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 342: A mixture of **341** (300 mg, 0.826 mmol, 1 equiv.) and 10 % w/w Pd/C (9 mg, 0.083 mmol) in EtOAc (20 mL) was stirred under an atmosphere of hydrogen (1 atm.) for 19 h. The mixture was filtered through Celite (washed with EtOAc 3 × 20 mL) and solvent removal under reduced pressure afforded the alkane compound **342** (295 mg, 98 %) as an oil. R_f = 0.1 (*c*-Hex/EtOAc, 1:1); $[\alpha]_D^{20}$ = -5.4 (*c* = 3.7, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2981, 1703, 1601, 1321, 1156 cm^{-1}; HRMS (EI): calcd for $[(C_{18}H_{23}NO_5S)]^+$ 365.1297, found 365.1306; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s, 1H, ArH), 6.69 (s, 1H, ArH), 4.28 (dd, *J* = 12.0, 5.5 Hz, 1H, CH), 3.92 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.87–3.81 (m, 1H, CH_2), 3.59 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1H, CH_2), 2.83 (s, 1H, CH), 2.36–2.39 (m, 3H, CH_2), 2.28–2.20 (m, 1H, CH_2), 2.18 (s, 3H, CH_3), 1.95–1.87 (m, 1H, CH_2), 1.82 (ddt, *J* = 18.5, 9.0, 4.5 Hz, 1H, CH_2), 1.70 (ddd, *J* = 13.0, 9.5, 4.0 Hz, 1H, CH_2), 1.64–1.55 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.6 (C), 152.4 (C), 148.7 (C), 139.4 (C), 126.9 (C), 108.0 (CH), 106.1 (CH), 64.3 (CH), 56.3 (CH_3), 56.2 (CH_3), 45.9 (CH_2), 45.7 (CH), 44.3 (C), 33.3 (CH_2), 28.1 (CH_3), 27.6 (CH_2), 25.4 (CH_2), 21.6 (CH_2) ppm.



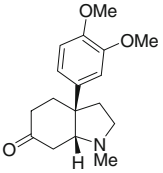
(2*S*,4a*R*,10a*S*)-2-Acetoxy-6,7-dimethoxy-4a,10-ethano-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 343: A of solution of ketone **342** (120 mg, 0.329 mmol, 1 equiv.) dissolved in $CDCl_3$-D_2O (2 mL, 1:1) was treated with *m*-CPBA 77 % pure (221 mg, 0.986 mmol, 3 equiv.) at room temperature. The reaction was periodically monitored by ^1H NMR until all starting material was consumed (approx. 48 h). An aq. $Na_2S_2O_3$ sat. soln (5 mL) and $NaHCO_3$ sat. (5 mL) were added and the reaction mixture allowed to stir for 0.5 h, after which the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), dried over $MgSO_4$ and reduced under pressure to afford the crude acetate which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1 → 1:2) affording the *title* compound **343** (125 mg, 67 %) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 1:2); Mp 110–113 °C; $[\alpha]_D^{20}$ = −28.6 (*c* = 1.8, $CHCl_3$); IR (NaCl, dep. from CH_2Cl_2) 2956, 2849, 1729, 1160, 1567, 1509, 1331, 1322, 1159, 1130 cm^{-1}; HRMS (ESI): calcd for $[(C_{18}H_{23}NO_6S + Na)]^+$ 404.1144, found 404.1137; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27 (s, 1H, ArH), 6.78 (s, 1H, ArH), 5.23 (s, 1H, CH), 4.39 (dd,

J = 12.0, 5.5 Hz, 1H, CH), 3.94 (s, 3H, CH_3), 3.92 (s, 3H, CH_3) 3.90–3.85 (m, 1H, CH_2), 3.65-3.58 (m, 1H, CH_2), 2.37-2.29 (m, 3H, CH_2), 2.18–2.13 (m, 1H, CH_2), 2.05 (s, 1H, CH_2), 2.03 (s, 3H, CH_3), 1.81–1.78 (m, 1H, CH_2), 1.77–1.73 (m, 1H, CH_2), 1.59–1.52 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4 (C), 152.5 (C), 148.8 (C), 139.1 (C), 126.9 (C), 108.03 (CH), 106.1 (CH), 68.4 (C), 63.9 (C), 56.4 (CH_3), 56.2 (CH_3), 45.9 (CH_2), 44.1 (C), 33.1 (CH_2), 30.7 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 21.4 (CH_3) ppm.

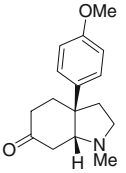


(+)-Mesembranol [(3a*R*,6*S*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydro-1*H*-indol-6-ol] 327: Under N_2, small pieces of Li (32 mg, 4.57 mmol, 20 equiv.) were added to NH_3 (*ca.* 75 mL) at –78 ºC. The mixture was stirred for 1 h before a solution of **343** (87 mg, 0.228 mmol, 1 equiv.) in THF (5 mL + 5 mL to wash flask) was added in a dropwise fashion. Stirring was continued for 0.5 h at –78 ºC before addition of solid NH_4Cl (*ca.* 2.0 g). The NH_3 was allowed to evaporate on warming to room temperature and the residue was dissolved in CH_2Cl_2 (15 mL). A solution of 1 M solution of NaOH solution (until pH 12) was added and the resultant aqueous layer was further extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure afforded compounds 3a-(3,4-dimethoxyphenyl)octahydroindol-6-ol (LRMS (ESI): calcd for $[(C_{16}H_{23}NO_3 + H)]^+$ found 278.17) and 3a-(4-methoxyphenyl)octahydroindol-6-ol (LRMS (ESI): calcd for $[(C_{15}H_{21}NO_2 + H)]^+$ found 247.16). The crude mixture was dissolved in CH_2Cl_2 (30 mL) and treated subsequently with benzyl chloroformate (0.05 mL, 0.342 mmol, 1.5 equiv.) and K_2CO_3 (315 mg, 2.28 mmol, 10 equiv.). Stirring was continued room temperature for 4 h before addition of H_2O (30 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined layers were dried over $MgSO_4$. Following filtration and solvent removal, column chromatography (*c*-Hex/EtOAc, 6:1 → 1:1) afforded **345** (22 mg, 23 %) and **346** (24 mg, 28 %); [(3a*R*,6*S*,7a*R*)-benzyl 3a-(3,4-dimethoxyphenyl)-6-hydroxyoctahydro-1*H*-indole-1-carboxylate **345**: HRMS (ESI): calcd for $[(C_{23}H_{27}NO_4 + Na)]^+$ 404.1838, found 404.1853; (3a*R*,6*S*,7a*R*)-benzyl 6-hydroxy-3a-(4-methoxyphenyl)octahydro-1*H*-indole-1-carboxylate **346**: HRMS (ESI): calcd for $[(C_{24}H_{29}NO_5 + Na)]^+$ 434.1943, found 434.2012]. Under N_2, a solution of **345** (52 mg, 0.127 mmol, 1 equiv.) dissolved in anhydrous THF (4 mL) was treated with $LiAlH_4$ (15 mg, 0.38 mmol, 3 equiv.). The reaction mixture was heated to reflux for 3 h. Once cooled, EtOAc (10 mL) was added followed 1 M NaOH (1 mL). H_2O (10 mL) was added and the phases separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic layers dried over $MgSO_4$, filtered and purified by column chromatography ($CHCl_3$/MeOH, 8:1) to afford the *title* compound **327** (9 mg, 57 %) as a light pink solid. R_f = 0.2 ($CHCl_3$/MeOH, 8:1); Mp

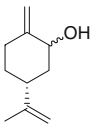
111-114 °C; $[\alpha]_D^{20} = +25.2$ ($c = 0.7$, $CHCl_3$) lit. −24 ($c = 0.2$, $CHCl_3$); [24] IR (NaCl, dep. from CH_2Cl_2) 3355, 1655, 1454, 1410 cm^{-1}; HRMS (ESI): calcd for $[(C_{17}H_{25}NO_3 + H)]^+$ 292.1913, found 292.1906; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.91–6.77 (m, 2H, ArH), 6.82–6.79 (m, 1H, ArH), 4.01 (m, 1H, CH), 3.88 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.30–3.23 (m, 1H, CH_2), 2.80 (s, 1H, CH), 2.38 (s, 3H, CH_3), 2.34-2.30 (m, 1H, CH_2), 2.21-2.16 (m, 1H, CH_2), 2.04 (dd, $J = 8.0$, 3.0 Hz, 2H, CH_2), 1.97–1.87 (m, 1H, CH_2), 1.86-1.82 (m, 1H, CH_2), 1.80–1.71 (m, 1H, CH_2), 1.59–1.49 (m, 1H, CH_2), 1.25–1.16 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 148.9 (C), 147.2 (C), 139.0 (C), 118.9 (CH), 111.0 (CH), 110.6 (CH), 70.2 (CH), 66.7 (CH), 56.1 (CH_3), 56.0 (CH_3), 54.4 (CH_2), 47.3 (C), 40.7 (CH_2), 40.2 (CH_2), 34.9 (CH_2), 33.1 (CH_2), 32.8 (CH_2) ppm.



(+)-Mesembrine [(3a*R*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-methylhexahydro-1*H*-indol-6(2H)-one] 1: Under N_2, a solution of **327** (6 mg, 0.02 mmol, 1 equiv.) dissolved in anhydrous CH_2Cl_2 (5 mL) was treated with PDC (23 mg, 0.062 mmol, 3 equiv.). The reaction mixture was allowed to stir at room temperature for 2 h. A solution of 0.1 M NaOH (2 mL) was added and the reaction allowed to stir for a further 2 h before the addition of CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (10 mL) and the phases separated. The organic layer was further extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers dried over $MgSO_4$, filtered and reduced under pressure. Purification by column chromatography ($CHCl_3$/Me_2CO, 6:1) afforded the *title* compound as a brown oil (6 mg, 48 %). $R_f = 0.2$ ($CHCl_3$/Me_2CO, 6:1); $[\alpha]_D^{20} = +43$ ($c = 0.8$, MeOH) (+28.2 ($c = 2.8$, $CHCl_3$)) lit. +53 ($c = 0.53$, MeOH), [25] lit. -61.6 ($c = 0.2$, MeOH); [24] IR (NaCl, dep. from CH_2Cl_2) 1709, 1653, 1456 cm^{-1}; HRMS (ESI): calcd for $[(C_{17}H_{23}NO_3 + H)]^+$ 290.1756, found 290.1766; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.95–6.87 (m, 2H, ArH), 6.84 (d, $J = 8.5$ Hz, 1H, ArH), 3.90 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.14-3.11 (m, 1H, CH_2), 2.96–2.92 (m, 1H, CH), 2.60 (s, 2H, CH_2), 2.49–2.37 (m, 2H, CH_2), 2.37–2.27 (m, 4H, CH_2, CH_3), 2.24–2.19 (m, 2H, CH_2), 2.15–2.09 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.6 (CO), 149.2 (C), 147.7 (C), 140.4 (C), 118.1 (CH), 111.2 (CH), 110.1 (CH), 70.5 (CH), 56.2 (CH_3), 56.1 (CH_3), 55.0 (CH_2), 47.7 (C), 46.7 (CH_2), 40.2 (CH_3), 39.0 (CH_2), 36.4 (CH_2), 35.4 (CH_2) ppm.

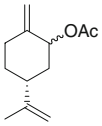


(3a*R*,7a*R*)-3a-(4-Methoxyphenyl)-1-methylhexahydro-1*H*-indol-6(2H)-one 77: Under N_2, a solution of **346** (95 mg, 0.25 mmol, 1 equiv.) dissolved in anhydrous THF (6 mL) was treated with $LiAlH_4$ (30 mg, 0.75 mmol, 3 equiv.). The reaction mixture was heated to reflux for 3 h. Once cooled, EtOAc (10 mL) was added followed 1 M NaOH (1 mL). H_2O (10 mL) was added and the phases separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL) and the combined organic layers dried over $MgSO_4$, filtered and purified by column chromatography ($CHCl_3$/MeOH, 8:1) to afford (3a*R*,6*S*,7a*R*)-3a-(4-Methoxyphenyl)-1-methyloctahydro-1*H*-indol-6-ol **347** (55 mg, 85 %) as a colourless solid. [R_f = 0.06 ($CHCl_3$/MeOH, 8:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.23 (m, 2H, ArH), 6.85–6.80 (m, 2H, ArH), 4.05–3.92 (m, 1H, CH_2), 3.77 (s, 3H, CH_3), 3.23 (m, 1H, CH_2), 2.76 (s(br), 1H, CH), 2.35 (s, 3H, CH_3), 2.31–2.24 (m, 1H, CH_2), 2.17–2.17 (m, 1H, CH_2), 2.06–1.96 (m, 2H, CH, CH_2), 1.96–1.64 (m, 3H, CH_2), 1.52-1.43 (m, 2H, CH_2), 1.24–1.09 (m, 1H, CH_2)]. Under N_2, a solution of **347** (55 mg, 0.21 mmol, 1 equiv.) dissolved in anhydrous CH_2Cl_2 (15 mL) was treated with PDC (119 mg, 0.316 mmol, 3 equiv.). The reaction mixture was allowed to stir at room temperature for 2 h. A solution of 0.1 M NaOH (2 mL) was added and the reaction allowed to stir for a further 2 h before the addition of CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (10 mL) and the phases separated. The organic layer was further extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers dried over $MgSO_4$, filtered and reduced under pressure. Purification by column chromatography ($CHCl_3$/Me_2CO, 6:1) afforded the *title* compound as a brown oil (9 mg, 19 %). [26] R_f = 0.2 ($CHCl_3$/Me_2CO, 6:1); $[\alpha]_D$ = + 48.9 (*c* = 0.9, MeOH); IR (NaCl, dep. from CH_2Cl_2) 1700, 1559 cm^{-1}; HRMS (ESI): calcd for $[(C_{16}H_{21}NO_2 + H)]^+$ 260.1651; found 260.1646; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (dd, *J* = 9.0 Hz, 2H, ArH), 6.90 (dd, *J* = 9.0 Hz, 2H, ArH), 3.81 (s, 3H, CH_3), 3.15–3.10 (m, 1H, CH_2), 2.95–2.93 (m, 1H, CH), 2.58 (s, 2H, CH_2), 2.48–2.39 (m, 2H, CH_2), 2.35–2.28 (m, 4H, CH_2, CH_3), 2.22–2.17 (m, 2H, CH_2), 2.12–2.07 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.7 (CO), 158.3 (C), 139.7 (C), 127.3 (CH), 113.9 (CH), 70.7 (CH), 55.4 (CH_3), 54.9 (CH_2), 47.3 (C), 40.6 (CH_2), 40.2 (CH_3), 9.0 (CH_2), 36.4 (CH_2), 35.4 (CH_2) ppm.

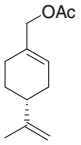


(*R*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexanol 351: Under N_2, a solution of *n*-butyllithium in hexane (6.47 mL, 16.0 mmol, 2.47 M, 1.2 equiv.) was added to a stirred solution of diisopropylamine (1.97 mL, 14.0 mmol, 1.1 equiv.) in anhydrous Et_2O (39 mL) at 0 °C. The reaction mixture stirred for 20 min before (*R*)-limonene oxide **350** (2.15 mL, 13.0 mmol, 1 equiv., a mixture of *cis* and *trans* isomers) in anhydrous Et_2O (8 mL) was added dropwise. Stirring was continued for 15 h during which period room temperature was reached. The reaction mixture was cooled to 0 °C and H_2O (40 mL) was added and the layers partitioned. The organic layer was

washed successively with 2 M HCl (40 mL), $NaHCO_3$ (40 mL), brine (40 mL) and dried ($MgSO_4$). Filtration followed by solvent removal gave alcohol **351** (2.22 g, 93 %) as a light yellow oil, [27, 28] which was used without purification. Data consistent with that reported in literature.

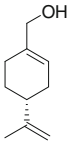


(*R*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl acetate 352: A mixture of alcohol **351** (1.02 g, 6.7 mmol, 1 equiv.), pyridine (1.08 mL, 13.4 mmol, 2 equiv.) and acetic anhydride (6 mL) was stirred for 15 h at room temperature. The solution was poured onto ice-water (*ca.* 50 mL) and extracted with Et_2O (2 × 20 mL). The combined ethereal extracts were washed successively with 1 M HCl (20 mL), brine (20 mL) and dried ($MgSO_4$). The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 5:1 → 4:1) which gave **352** (1.27 g, 97 %) as a light yellow oil. R_f = 0.5 (*c*-Hex/EtOAc, 6:1); IR (NaCl, dep. from CH_2Cl_2) 2965, 2938, 2861, 1762, 1645, 1590,,1373, 1240, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.37 (s, 1H, CH), 5.23–5.16 (m, 1H, CH), 4.91 (s, 1H, CH_2), 4.82 (s, 1H, CH_2), 4.73–4.68 (m, 2H, CH_2), 4.65 (s, 2H, CH_2), 2.45–2.15 (m, 5H, CH, CH_2), 2.07–1.95 (m, 6H, CH_2, CH_3), 2.01 (s, 3H, CH_3), 1.85–1.77 (m, 1H, CH_2), 1.68 (s, 3H, CH_3), 1.55–1.17 (m, 3H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (CO), 148.6 (C), 147.6 (C), 145.8 (C), 145.2 (C), 112.4 (CH), 109.3 (CH_2), 109.1 (CH_2), 104.7 (CH_2), 74.2 (CH), 73.4 (CH), 48.6 (CH), 38.9 (CH), 38.4 (CH_2), 36.9 (CH_2), 33.8 (CH_2), 32.4 (CH_2), 32.1 (C), 30.7 (CH_2), 21.4 (CH_3), 21.1 (C), 20.9 (CH_3) ppm. Mixture of diastereoisomers.



(*R*)-(4-(Prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl acetate 353: Under N_2, a mixture of acetate **352** (300 mg, 1.55 mmol, 1 equiv.), [$Pd(PPh_3)_4$] (90 mg, 0.078 mmol, 5 mol%), NaOAc (165 mg, 2.015 mmol, 1.3 equiv.) in anhydrous THF (3.2 mL) was heated in a sealed tube for 15 h (oil bath temperature 90 °C). Once cooled, Et_2O (10 mL) and H_2O (10 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined ethereal layers were washed with brine (10 mL) and dried ($MgSO_4$). The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 11:1) to yield (*R*)-perillyl acetate **353** (147 mg, 59 %) a light orange oil. R_f = 0.5 (*c*-Hex/EtOAc, 6:1); IR (NaCl, dep. from CH_2Cl_2) 2933, 1741, 1654, 1373, 1240, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.73 (s, 1H, CH), 4.73–4.70 (m, 2H, CH_2), 4.44 (s, 2H, CH_2), 2.19-2.14 (m, 3H, CH_2), 2.06 (s, 4H,

CH, CH_3), 1.99-1.92 (m, 1H, CH_2), 1.87–1.81 (m, 1H, CH_2), 1.53–1.45 (m, 1H, CH_2), 1.72 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9 (CO), 149.6 (C), 132.6 (C), 126.1 (CH), 108.8 (CH_2), 68.6 (CH_2), 40.9 (CH), 30.5 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 21.1 (CH_3), 20.7 (CH_3) ppm.



(*R*)-Perillyl alcohol [(*R*)-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methanol)] 348: A mixture of (*R*)-perillyl acetate **353** (53 mg, 0.0273 mmol, 1 equiv.) and 1 M NaOH (1 mL) in EtOH (4 mL) was heated to reflux for 1 h. Once cooled, the ethanol was removed under reduced pressure, and the residue was diluted with H_2O (10 mL) and acidified with 2 M HCl. The solution was extracted with Et_2O (20 mL), and the layers separated. The ethereal layer was washed successively with H_2O (10 mL), brine (10 mL) and dried ($MgSO_4$). The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1 → 3:1) which gave **348** (40 mg, 98 %) as a light orange oil. $R_f = 0.2$ (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20} = +0.223$ (*c* = 0.4, CH_2Cl_2) [(*S*)-perillyl alcohol: $[\alpha]_D^{20} = -0.371$ (*c* = 0.4, CH_2Cl_2)]; IR (NaCl, dep. from CH_2Cl_2) 2923, 1646, 1451, 1436, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.70 (s (br), 1H, CH), 4.78–4.67 (m, 2H, CH_2), 4.01 (s, 2H, CH_2), 2.23–2.03 (m, 4H, CH, CH_2), 1.99-1.89 (m, 1H, CH_2), 1.87–1.82 (m, 1H, CH_2), 1.74 (s, 3H, CH_3), 1.54–1.44 (m, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.9 (C), 137.4 (C), 122.6 (CH), 108.8 (CH_2), 67.4 (CH_2), 41.3 (CH), 30.6 (CH_2), 27.6 (CH_2), 26.3 (CH_2), 20.9 (CH_3) ppm.

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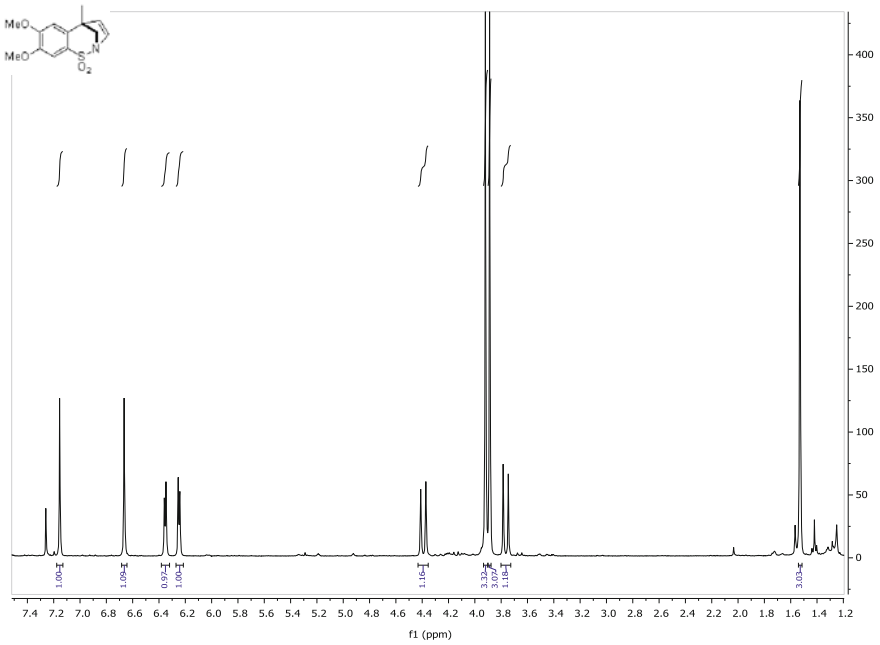
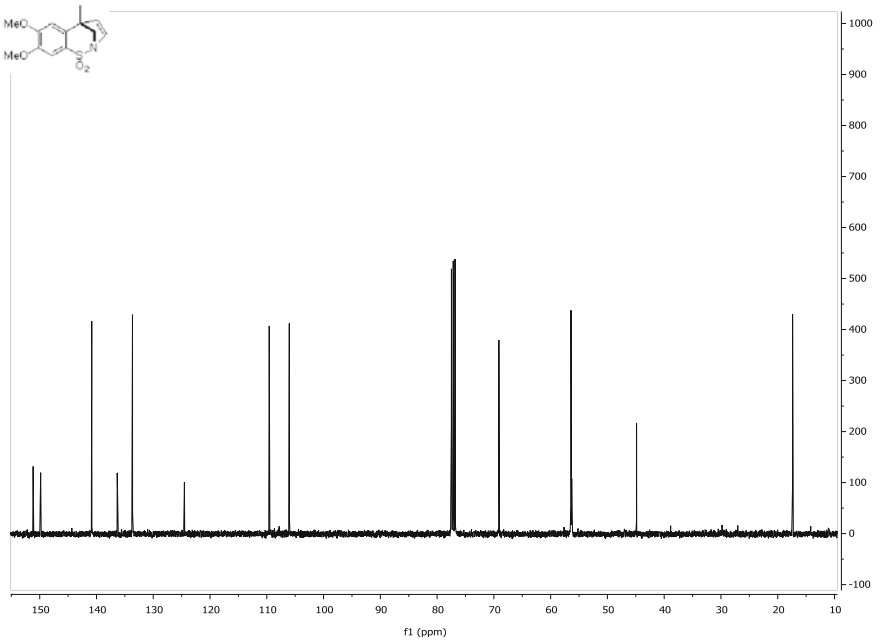
Appendix

Representative NMR Spectra

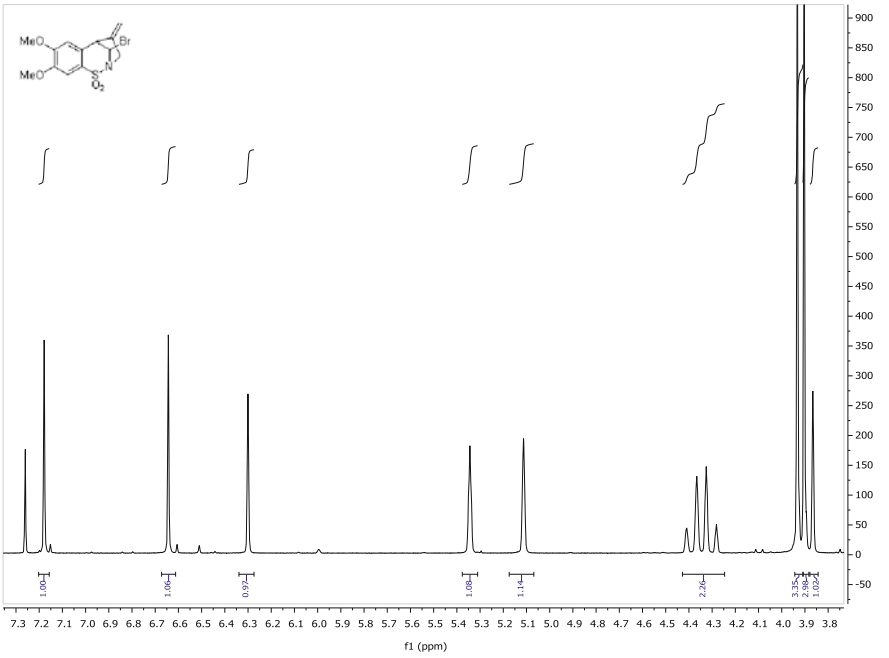
4,5-Dimethoxy-1-methyl-8-thia-9-azatricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8,8-dioxide **120** ($CDCl_3$):

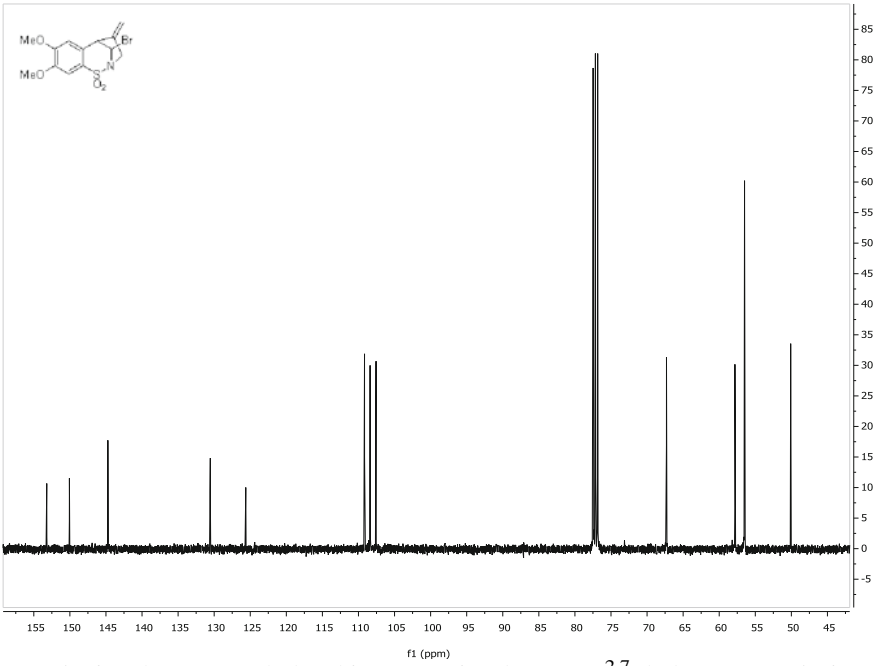


K. Geoghegan, *Selectivity in the Synthesis of Cyclic Sulfonamides*,
Springer Theses, DOI 10.1007/978-3-319-10338-9

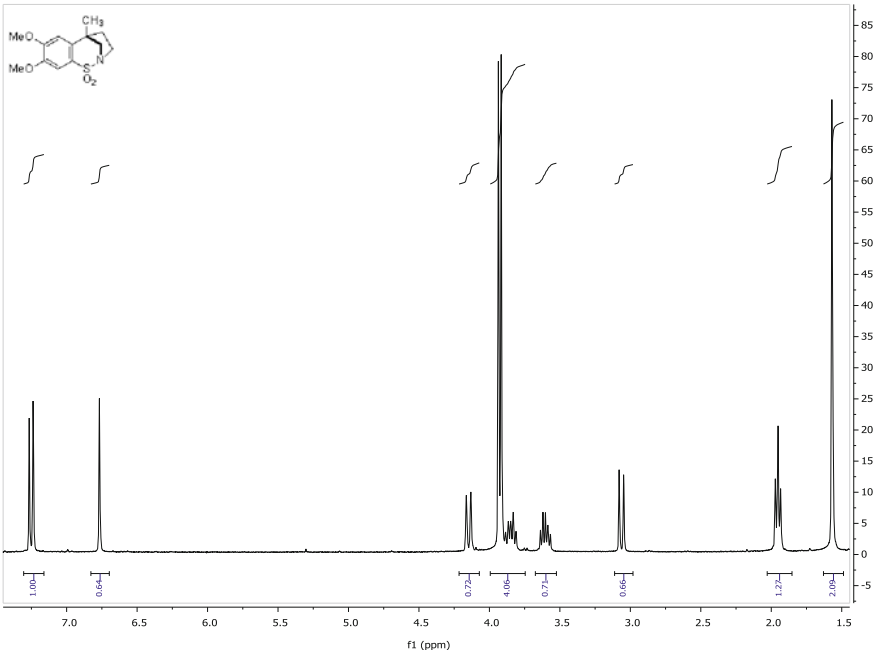


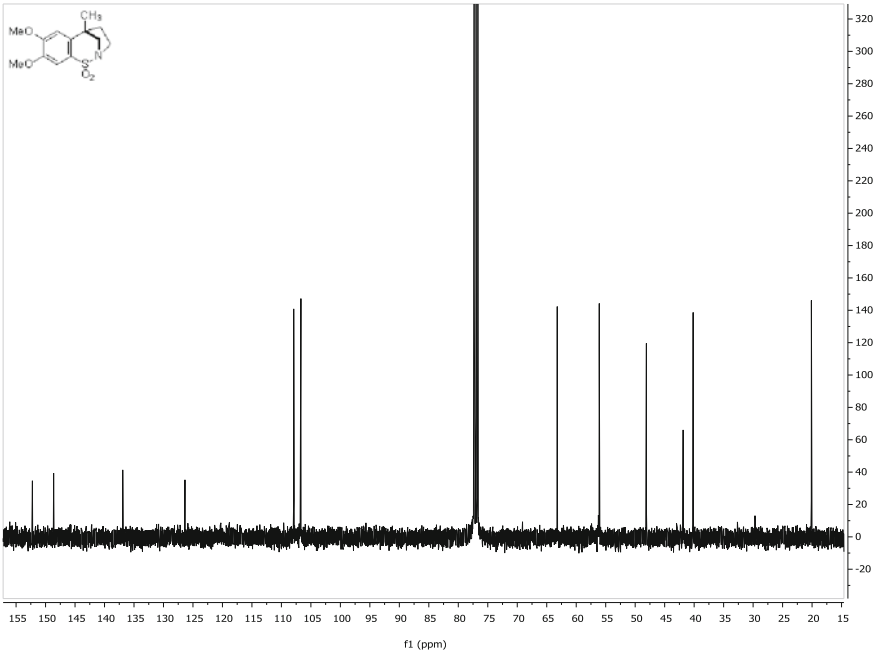
(2*S*,5*S*,10*S*)-10-bromo-7,8-dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2]thiazepine 1,1-dioxide **215** ($CDCl_3$):



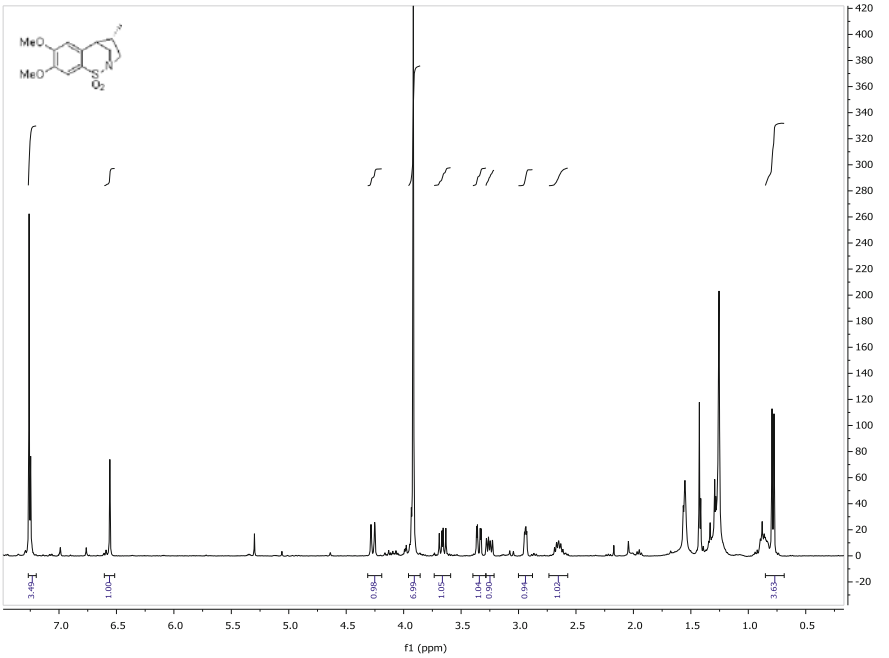


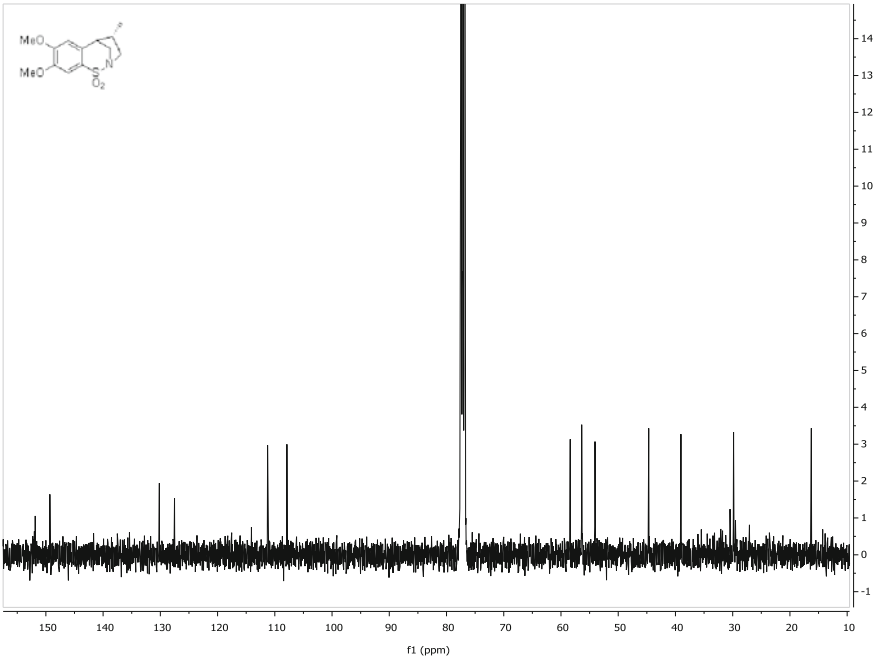
4,5-Dimethoxy-1-methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide **230** ($CDCl_3$):



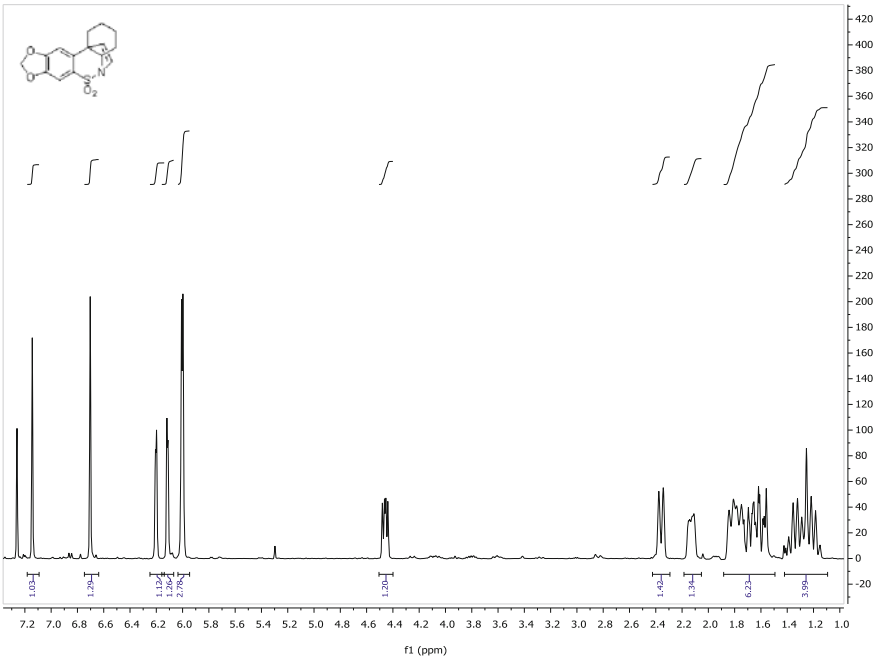


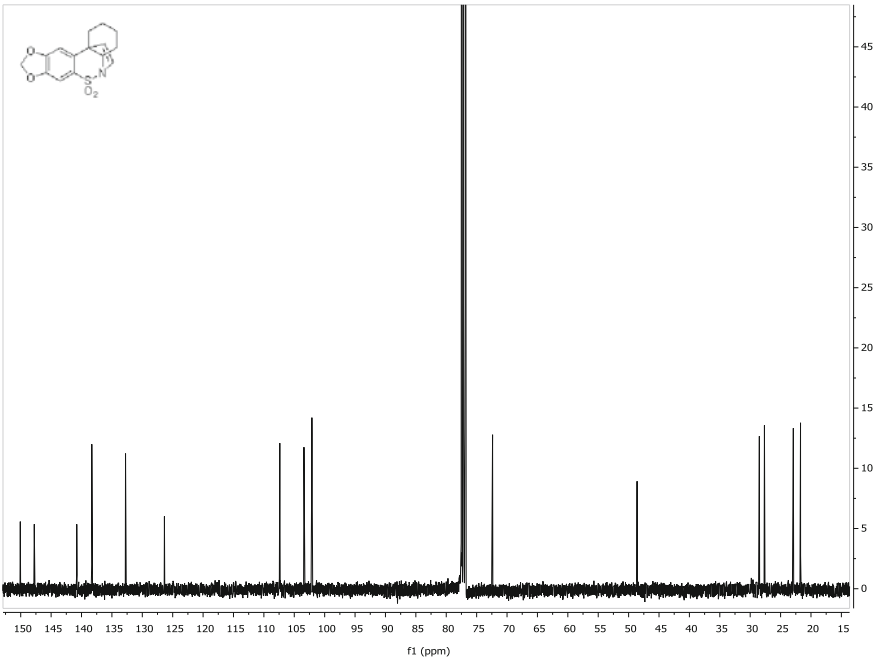
(2*S*,5*S*)-7,8-Dimethoxy-4-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2] thiazepine 1,1-dioxide **229** ($CDCl_3$):



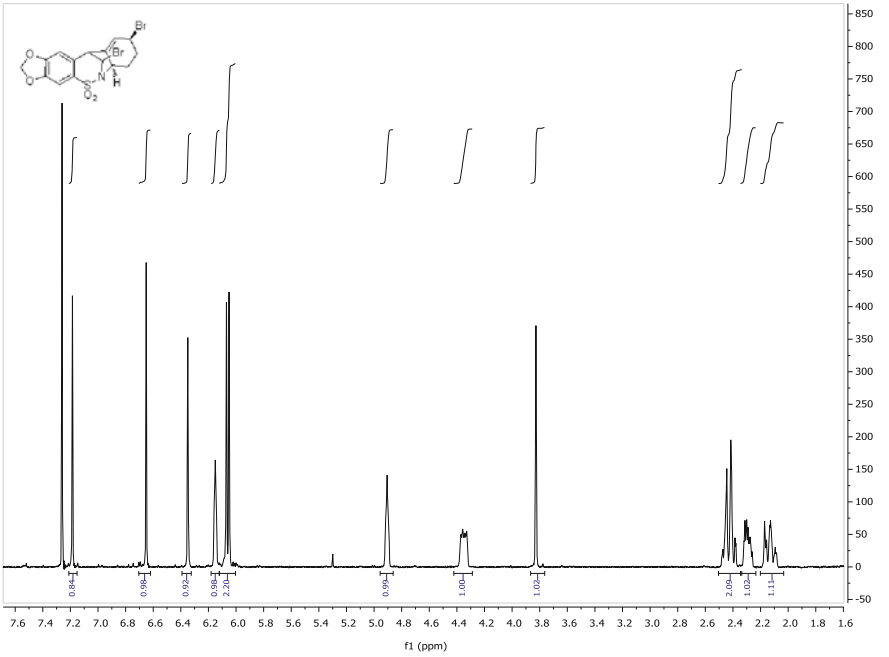


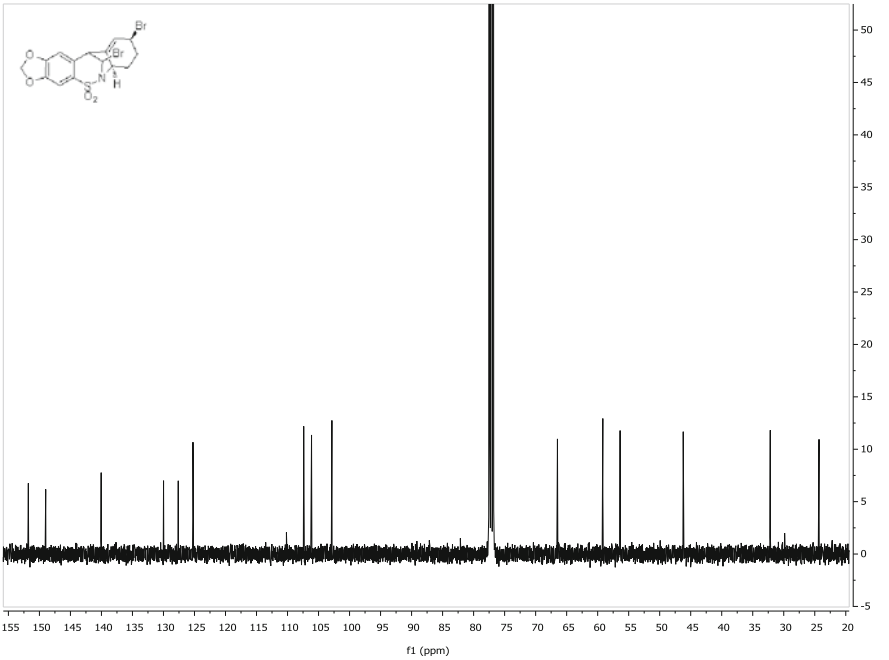
2,3,4,4a-Tetrahydro-1*H*-5,11b-etheno[1,3]dioxolo[4',5':4,5]benzo[1,2-e]benzo[*c*][1,2]-thiazine 6,6-dioxide **242** ($CDCl_3$):



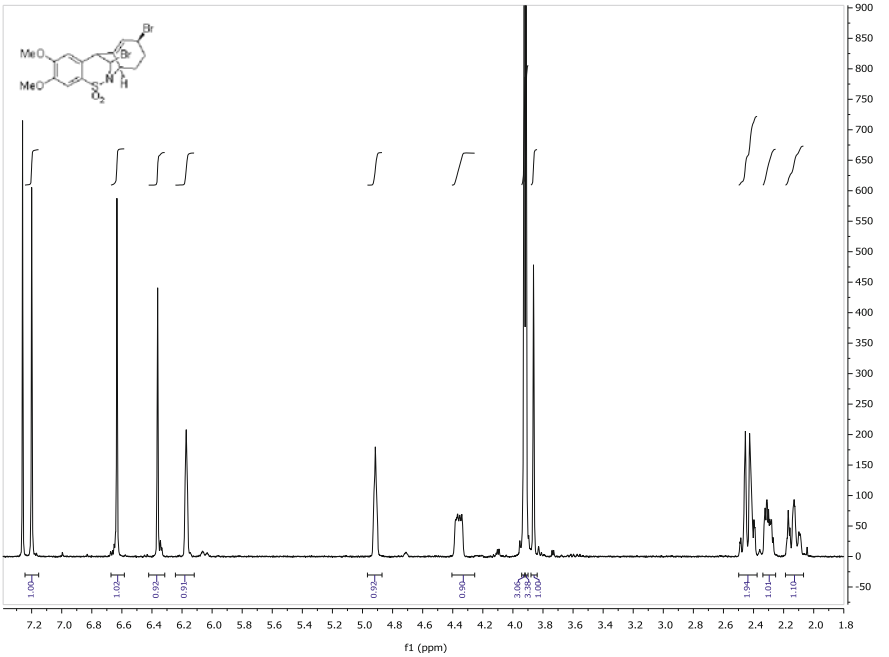


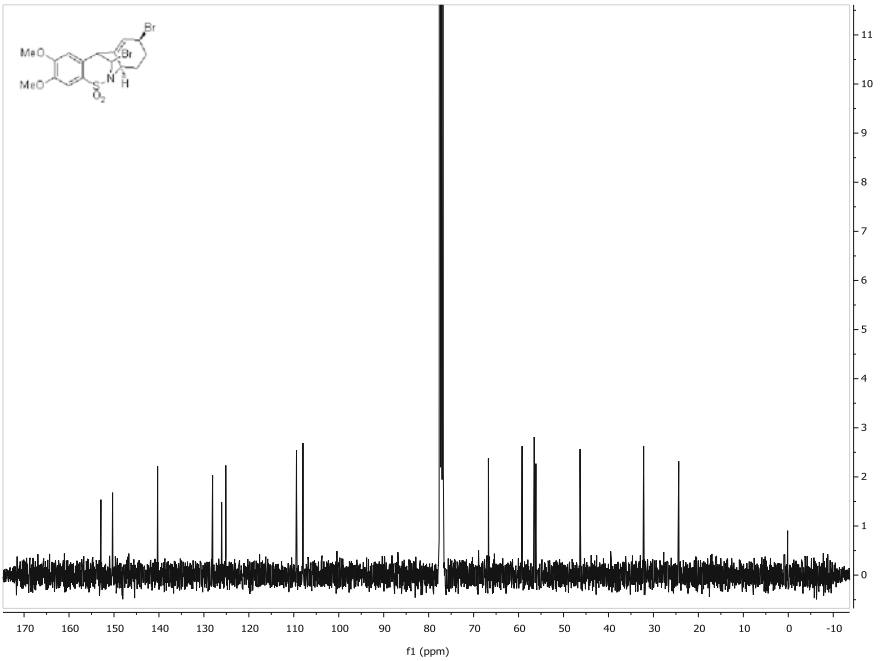
(6*S*,6a*R*,9*S*,11*S*,13*S*)-9,13-Dibromo-7,8,9,11-tetrahydro-6a*H*-6,11-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-*f*]benzo[*c*][1,2]thiazepine 5,5-dioxide **245** ($CDCl_3$):



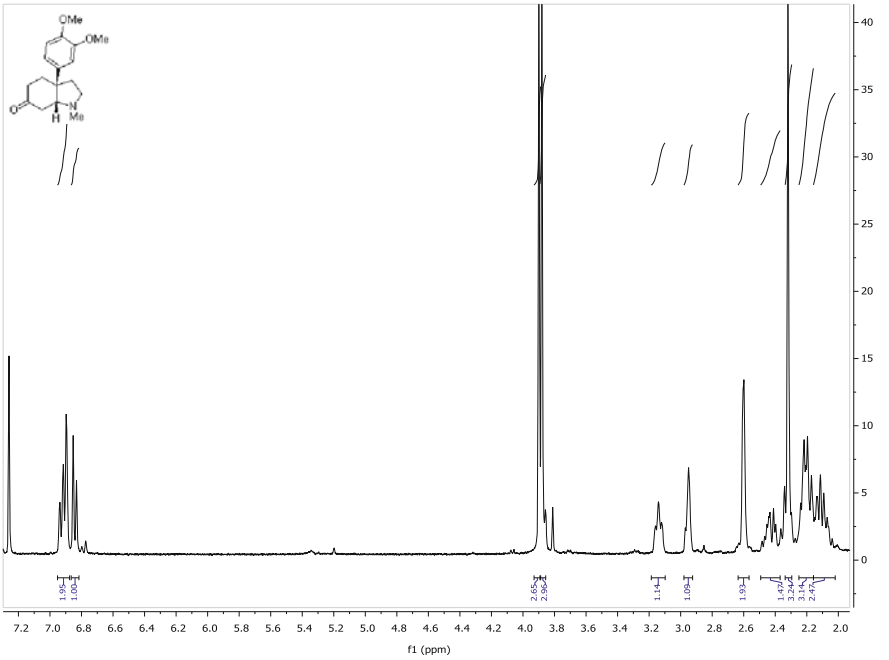


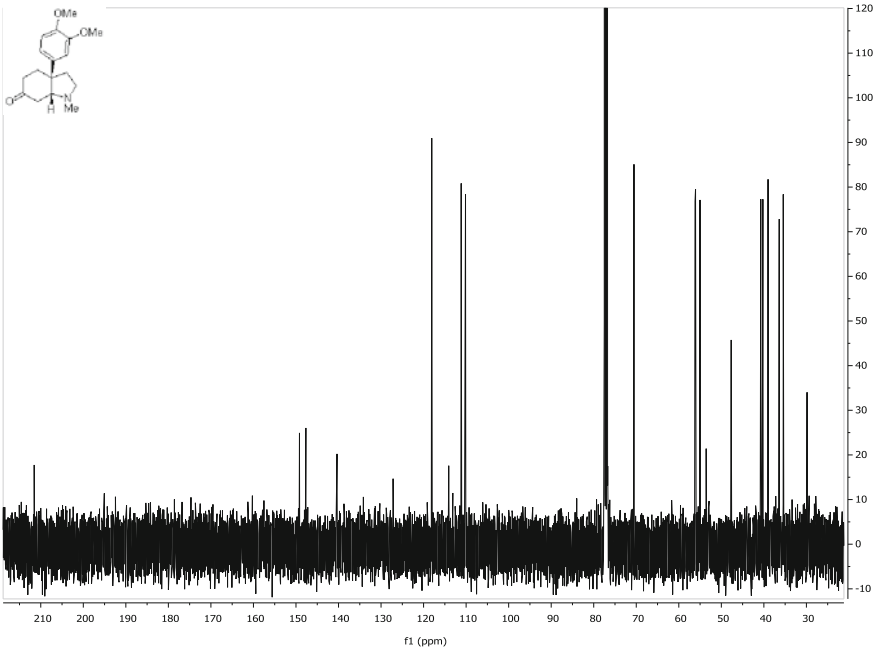
(6*S*,6a*R*,9*S*,11*S*,12*S*)-9,12-Dibromo-2,3-dimethoxy-7,8,9,11-tetrahydro-6a*H*-6,11-methanodibenzo-[*c*,*f*][1,2]thiazepine 5,5-dioxide **243** ($CDCl_3$):





(+)-mesembrine **1** ($CDCl_3$):

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