# THE DECARBOXYLATIVE IRELAND-CLAISEN REARRANGEMENT: METHODOLOGY STUDIES AND APPROACHES TO THE TOTAL SYNTHESIS OF (-)-SUAVEOLINE

A Thesis Presented by

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***Abstract***

This thesis is divided into three sections.

*Section one* is a review of recent progress in the synthesis of macroline, sarpagine and ajmaline-related indole alkaloids. The review covers approximately the last ten years of published literature.

*Section two* is divided into two parts and discusses the results of research into the decarboxylative Ireland–Claisen rearrangement.
Part one gives the background to the project and discusses the mechanism of this rearrangement. The development of methodology for the synthesis of bifunctional rearrangement substrates is detailed. The competitive rearrangement of these bifunctional substrates is outlined and trends in reactivity are discussed. An account is given of the application of the decarboxylative Ireland–Claisen rearrangement to a cyclic malonate, which gave rise to a cyclopropane. Efforts towards a cyclic malonate substrate are detailed, including the use of carbon suboxide.
Part two concerns studies towards the total synthesis of (–)-suaveoline. The retrosynthetic analysis is explained and pertinent methodology introduced. The initial construction of a synthetically relevant rearrangement substrate is outlined. The reasons for the failure of this substrate to rearrange are discussed, as is the modified protecting group strategy that was adopted. Subsequent successful rearrangement and the synthesis of a key cyclopentenyl intermediate are described. Unsuccessful attempts to alkylate this cyclopentene are detailed and an alternative strategy is put forward. Novel methodology for the formation of pyridine-*N*-oxides is disclosed and attempts to apply this to the synthesis of suaveoline are discussed.

*Section three* is the experimental section, which gives detailed descriptions of the synthesis and spectroscopic characteristics of the compounds discussed in section two.

***Declaration***

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced.

Simon Eliot Lewis

***Contents***

## ***Acknowledgement***

First and foremost I would like to thank Professor Donald Craig for the opportunity to pursue my interest in synthetic chemistry in such a rewarding environment. His advice and boundless enthusiasm have been an inspiration. Thanks are due also to Mark Lansdell at Pfizer for being an ever-present source of helpful advice and second opinions.

I would also like to thank my co-workers for providing intellectual stimulation and entertainment in equal measure. I can not imagine that any other lab could be quite the same. Special mention must be afforded to Santiago Carballares, John Caldwell, Tanya Matthie, Fabienne Grellepois, Paolo Innocenti, Damien Bourgeois, Henrik Jensen, Chi Ming Cheung, Volker Rahn, Chris Hyland, Alan Stewart, Alan Braunton, Gavin Henry, Samuel Beligny, Barry Dillon, Dave Mountford, Alice Fleming, Federica Paina, Steve Johns, Sophie Gore, Darryl Thomas, Pengfei Lu, Barry Cottam-Howarth, Cassim Ashraff, Yunas Bhonoah, Paula Rzepa and Marcus Medley. They all made the Craig group into something I will never forget. Several other colleagues at Pfizer also helped out in my hours of need, especially Peter Wilson and Torren Peakman. At Novartis in Vienna, Hubert Gstach and Manfred Auer provided great encouragement in the early days and played no small part in shaping my future. All of the faculty at Imperial College have influenced this work in one form or another; in particular Prof. Charles Rees, whose advice should be listened to!

Finally I must extend my heartfelt thanks to my family and especially to my wife Alex, who has supported me so much throughout this endeavour. I could not have done it without her.

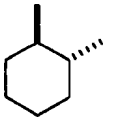
## ***Abbreviations***

| | |
|---|---|
| Ac | acetyl |
| AIBN | azobis(*iso*butyronitrile) |
| app | appears |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| bp | boiling point |
| br | broad |
| bu | butyl |
| BSA | bis(trimethylsilyl)acetamide |
| Bz | benzoyl |
| CI | chemical ionisation |
| Cbz | benzyloxycarbonyl |
| d | doublet |
| dd | doublet of doublets |
| ddd | doublet of doublet of doublets |
| ddq | doublet of doublet of quartets |
| dqd | doublet of quartets of doublets |
| dt | doublet of triplets |
| DBU | 1,8-diazobicyclo[5.4.0]undec-7-ene |
| DCC | *N,N'*-dicyclohexyl carbodiimide |
| dCr | decarboxylative Claisen rearrangement |
| DDQ | 2,3,5,6-dichlorodicyanoquinone |
| DIBAL-H | Di*iso*butylaluminium hydride |
| DIC | *N,N'*-di*iso*propyl carbodiimide |
| DMAP | 4-(*N,N*-dimethylamino)pyridine |
| DMDO | dimethyldioxirane |
| DMP | Dess–Martin Periodinane |
| DMSO | dimethyl sulfoxide |
| DMF | *N,N*-dimethylformamide |
| EDCI | 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide |
| equiv | equivalents |
| ESI | electrospray ionisation |
| Et | ethyl |
| FAB | fast atom bombardment |
| h | hours |

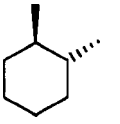
| | |
|---|---|
| HMDS | hexamethyldisilazide |
| HOSA | hydroxylamine-*O*-sulfonic acid |
| IBX | *o*-iodoxybenzoic acid |
| Im | imidazolyl |
| IMDA | intramolecular Diels–Alder reaction |
| LDA | lithium di*iso*propylamine |
| m | multiplet |
| min | minutes |
| mp | melting point |
| MOM | methoxymethyl |
| MS | mass spectrum |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NMR | nuclear magnetic resonance |
| Ns | nitrophenylsulfonyl |
| *p*-TSA | *para*-toluenesulfonic acid |
| py | pyridine |
| q | quartet |
| quint | quintet |
| RCM | ring-closing metathesis |
| s | singlet |
| SER | serine |
| $Sia_2BH$ | di*iso*amylborane |
| SM | starting material |
| t | triplet |
| td | triplet of doublets |
| tdd | triplet of doublet of doublets |
| tt | triplet of triplets |
| TBDMS | *tert*-butyldimethylsilyl |
| TBME | *tert*-butyl methyl ether |
| TFA | trifluoroacetic acid |
| TIPS | tri*iso*propylsilyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilane |
| TRP | tryptophan |
| Ts | toluene-4-sulfonyl |
| VAL | valine |

## ***Stereochemical Notation***

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



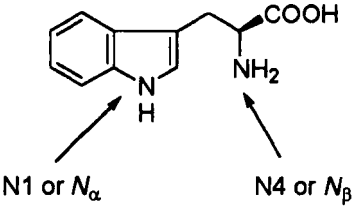
Racemate
Relative stereochemistry



Single enantiomer
Absolute stereochemistry

## ***Tryptophan Nitrogen Designation***

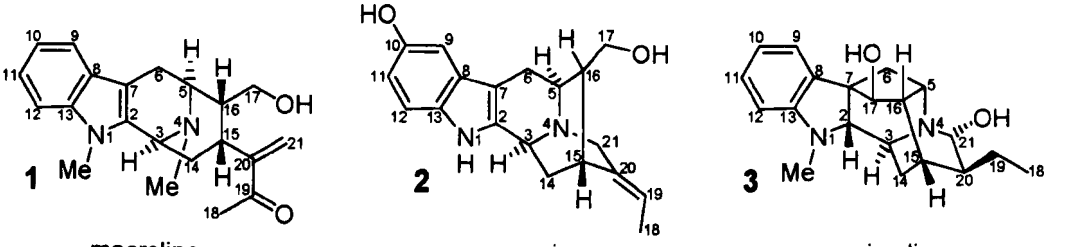
In the review section of this report, a biogenetic numbering system is adopted. The tryptophan nitrogens are designated N1 and N4. In the results and discussion and experimental sections of this report, the tryptophan nitrogens are designated $N_\alpha$ and $N_\beta$ to avoid ambiguity.



## *1. Review: Recent Advances in the Chemistry of Macroline, Sarpagine and Ajmaline-Related Indole Alkaloids*

### 1.1: Introduction and Scope

A huge variety of indole alkaloids are known,[2] many of which have submitted to total synthesis. This review concerns the chemistry of indole alkaloids related to macroline **1**, sarpagine **2** and ajmaline **3**. The structures of these three species are shown in scheme 1.




macroline sarpagine ajmaline

**Scheme 1:** *The three parent alkaloids under discussion*

The skeletal numbering shown is the biogenetic numbering proposed[3] by LeMen and Taylor and is used throughout this review where required. It may be seen that there is significant structural similarity between the three compounds. All possess an indole-annulated azabicyclo[3.3.1] structure and various efforts towards this structural motif are detailed below. Macroline-related alkaloids are defined as those having the same skeletal connectivity as macroline. They crucially do not possess an N4-C21 linkage. Sarpagine-related alkaloids are defined as those having the same skeletal connectivity as sarpagine, specifically with an N4-C21 linkage and the C16-(*R*) configuration shown. Ajmaline-related alkaloids are defined as those having the same skeletal connectivity as ajmaline, also with an N4-C21 linkage but with C16-(*S*) configuration epimeric to that of sarpagine as shown. Alkaloids with a quaternary C16 are known and are included herein. There also may or may not be a C7-C17 linkage, the quaternary C7 implied thus rendering the C2-C7 bond saturated. Additionally the compounds under consideration may or may not be N1- and N4-substituted and may or may not possess indole ring oxygenation. Also included in this review are bis(indole) alkaloids in which one or both of the subunits consist of a macroline/sarpagine/ajmaline indole base.

It must be noted that unlike ajmaline and sarpagine, macroline itself has not been isolated from natural sources. Many macroline-related alkaloids have, however, and it is believed that macroline is a likely biosynthetic precursor of various sarpagine alkaloids. One can envisage the relationship in a synthetic sense, with 1,2- or 1,4- addition of N4 to C19 or C21 respectively providing access to the sarpagan skeleton. Such a synthetic strategy has been employed in some of the total syntheses detailed herein. The reverse transformation may also be envisaged – quaternisation of N4, followed by Hofmann elimination (provided C20 has an appropriate hydrogen, e.g. in ajmaline) resulting in N4-C bond scission. This strategy has also been adopted in total synthesis, as will be seen, and interconversions of this nature are important in structural elucidation and stereochemical correlation.

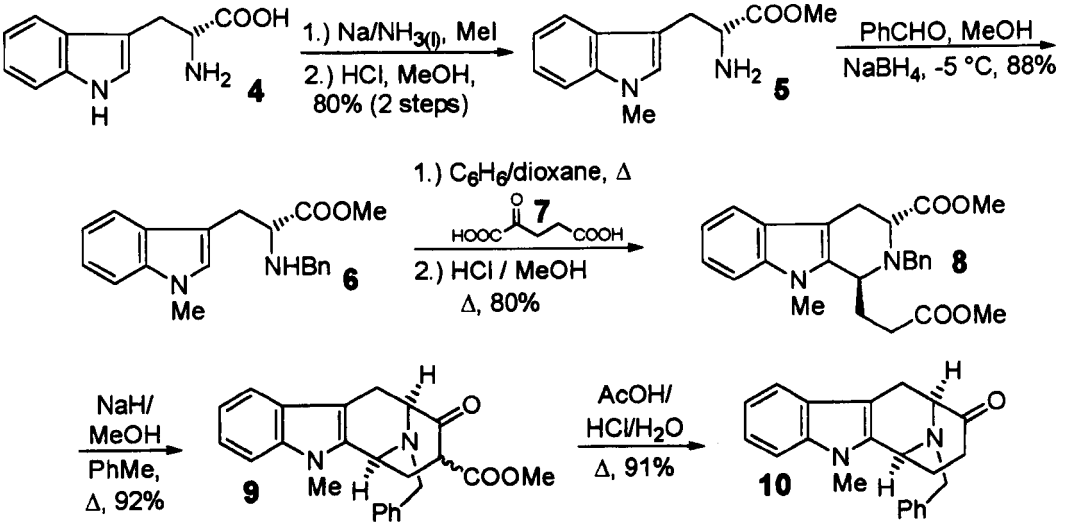
The field of macroline, sarpagine and ajmaline-related alkaloids was reviewed extensively by Cook[4] in 1993 and 1995 and again by Lounasmaa[5] in 1999 and 2001. As well as detailing reported synthetic endeavours relevant to the field, these reviews give a comprehensive account of the species from which these alkaloids have been isolated (mostly *Rauvolfia* and *Alstonia* species) and an overview of proposals for their biosyntheses. Only work reported subsequent to these prior reviews or not covered therein is included here.

## 1.2 Cook's Syntheses

Cook and co-workers have published extensively in the area of indole alkaloids and in the last decade have reported the partial and total syntheses of more than 40 macroline/sarpagine/ajmaline-related alkaloids, as well as bis(indole) alkaloids and related degradation products. These syntheses are detailed in this section and are grouped by the methodology used as opposed to the final targets in question.

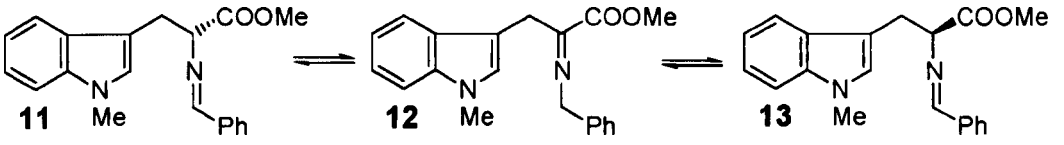
### *1.2.1: The Tetracyclic Ketone*

Fundamental to Cook's syntheses is the tetracyclic ketone intermediate **10**. Its synthesis has been reviewed before,[4,5] but will be detailed here also due to its relevance to the following sections. The overview of the synthesis is shown in scheme 2.



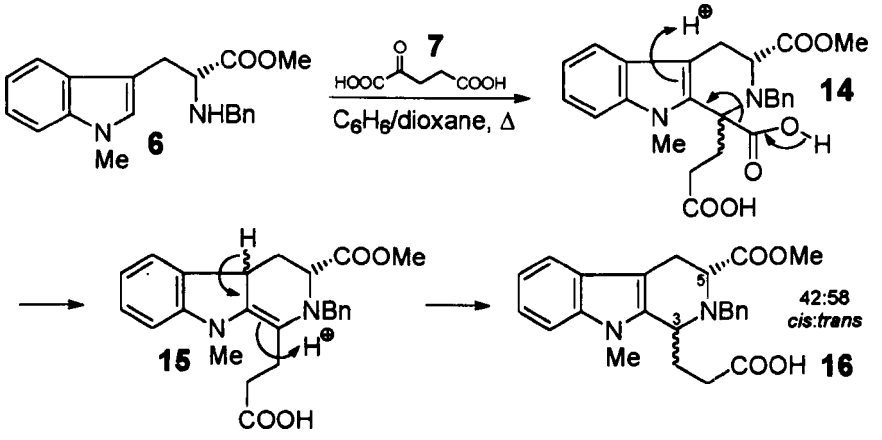

**Scheme 2:** *Cook's key tetracyclic ketone and its synthesis*

The synthesis outlined above, whilst only seven steps, has been the subject of extensive study and optimisation.[6] The individual steps merit consideration in detail. Starting from unnatural D-tryptophan, N1-methylation and esterification were routine. The reductive amination to protect N4, however, required careful control. After stirring **5** with benzaldehyde for 2 h at room temperature to form the imine, sodium borohydride was added at –5 °C and allowed to react for 3 h. Longer reaction times or higher reaction temperatures led to erosion of the *e.e.* by imine isomerisation (scheme 3).



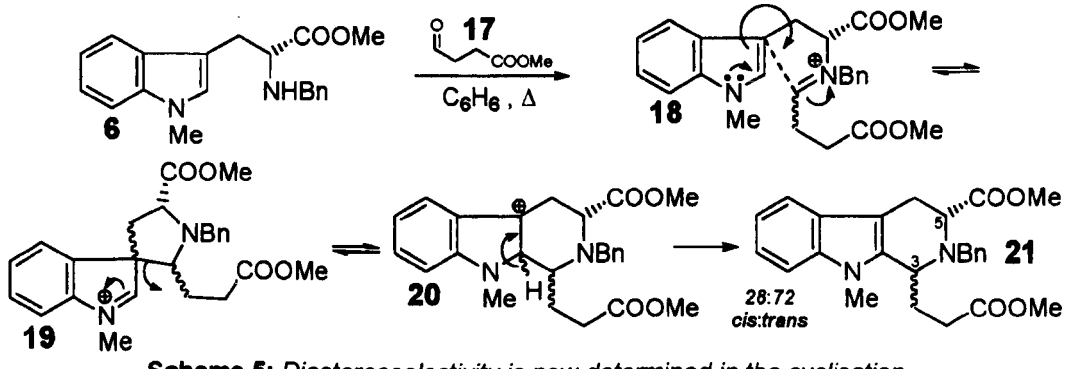

**Scheme 3:** *Care was needed to avoid racemisation*

The Pictet–Spengler condensation (and subsequent esterification) shown in scheme 2 is represented as affording solely the C3,C5-*trans* tetrahydro-β-carboline **8**. In fact a more complex series of events was occurring. As shown in scheme 4, the initial Pictet–Spengler cyclisation proceeded to give a diastereoisomeric mixture of tetrahydro-β-carboline diacids **14**. These underwent decarboxylation as shown and it was therefore the protonation upon rearrangement of intermediate **15** that determined the diastereoisomeric ratio in the product, not inherent selectivity in the Pictet–Spengler reaction.



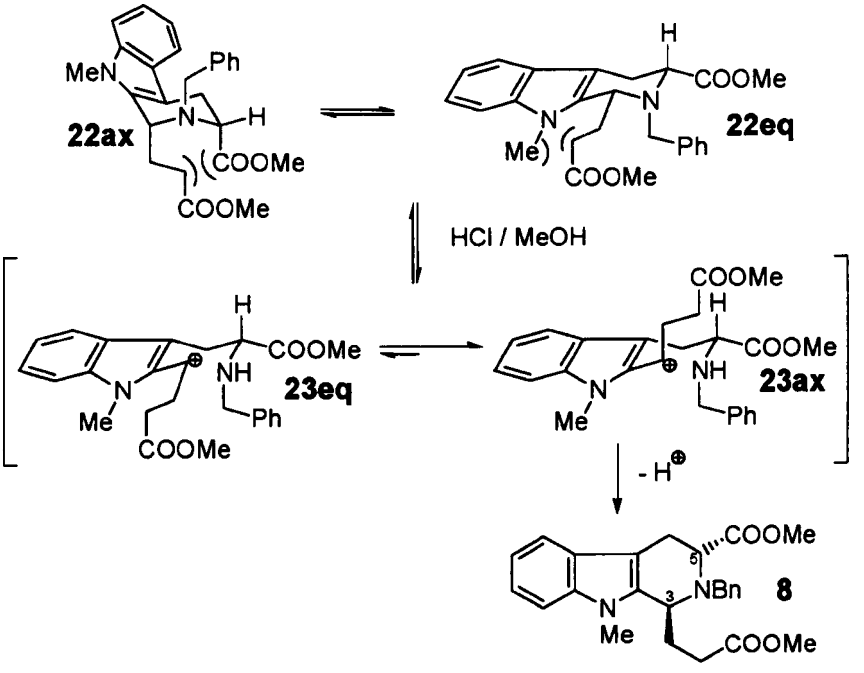

**Scheme 4:** *Diastereoselectivity is determined in the protonation step*

If the tetrahydro-β-carboline monoacid intermediates **16** were isolated, the diastereoisomeric ratio was found to be C3,C5-*cis*:*trans* 42:58. Alternatively, if methyl 3-formylpropionate **17** was used in place of 2-ketoglutaric acid **7**, the diastereoisomeric ratio in **21** was found to be C3,C5-*cis*:*trans* 28:72 (scheme 5). This enhanced diastereoisomeric ratio was observed due to the lack of a post-cyclative decarboxylation step; in this instance the ratio is a true representation of the inherent selectivity of the Pictet–Spengler cyclisation.



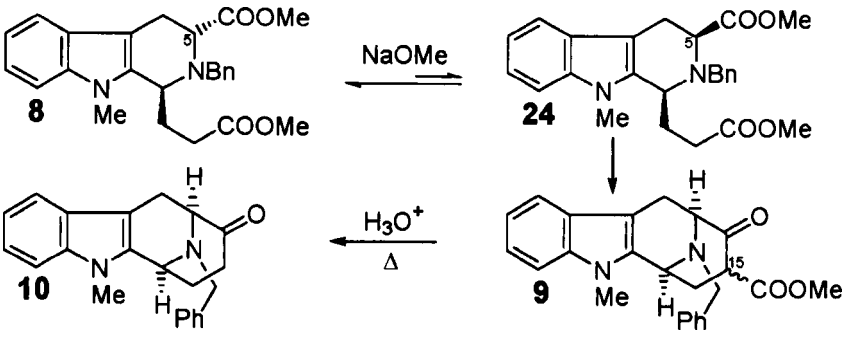

**Scheme 5:** *Diastereoselectivity is now determined in the cyclisation*

Whilst use of methyl 3-formylpropionate **17** increased the diastereoselectivity, total selectivity was desired in order that tedious chromatography might be avoided and the sequence might be executed on a large scale. This was achieved by acid-catalysed isomerisation of the C3,C5-*cis* isomer to the more stable C3,C5-*trans* isomer, simply by treating the diastereoisomeric mixture **16** or **21** with methanolic HCl (in the case of **16** this also effected esterification). Rather than a C2-C3 bond cleavage, the isomerisation is thought to proceed *via* a C3-N4 bond cleavage and stabilised C3 cation formation (scheme 6).



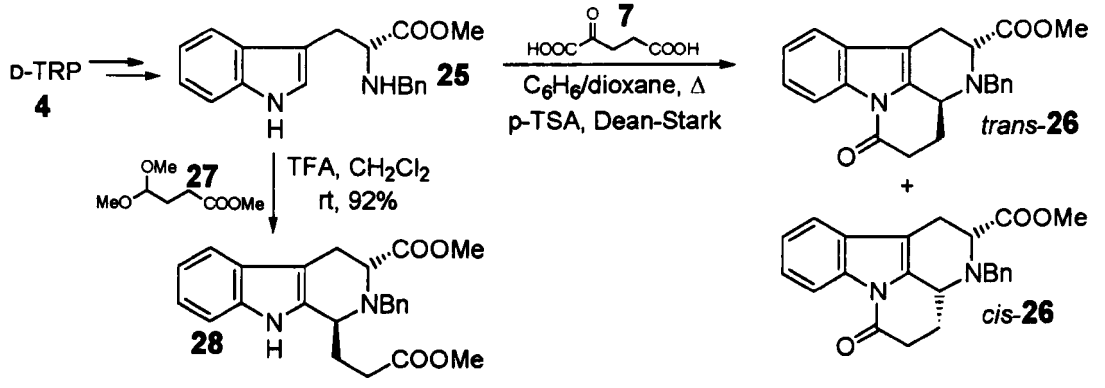

**Scheme 6:** *Acid-induced epimerisation to the 3,5-*trans *tetrahydro-β-carboline*

With pure **8** in hand, Dieckmann cyclisation to the tetracyclic system **9** was effected with sodium methoxide. The C3,C5-*trans*-configured tetrahydro-β-carboline **8** is unable to attain a conformation suitable for cyclisation, so base-induced epimerisation of C5 must occur prior to cyclisation. Whilst the *cis* tetrahydro-β-carboline **24** is the less stable diastereoisomer (as established in scheme 6), the small amount formed is irreversibly transformed to the tetracycle, the equilibrium then replenishes the amount of **24** present and so all material is eventually transformed to tetracycle **9** (scheme 7). The epimerisation prior to Dieckmann cyclisation is the reason Cook's synthesis commences with the unnatural amino acid antipode. This (incorrect) initial C5 configuration induces the correct C3 configuration which in turn induces complete epimerisation at C5 to the correct configuration.



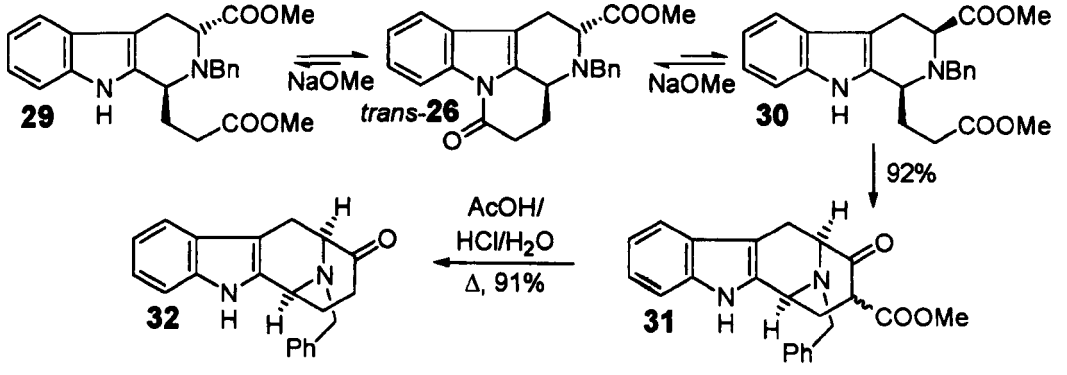

**Scheme 7:** *C5 epimerisation occurs prior to Dieckmann cyclisation*

The uncontrolled configuration of C15 in **9** is of no consequence as acid-induced decarboxylation leads to key tetracycle **10** (7 steps from D-tryptophan, 47% overall yield). Cook's group have routinely performed this synthetic sequence on a 100 gram scale. As not all macroline/sarpagine/ajmaline alkaloids are N1-substituted, the tetracyclic ketone **32** has also been prepared[7] with a free N1-H. The synthesis was complicated by unwanted lactam formation as shown in scheme 8.




**Scheme 8:** *Undesired lactam formation precluded use of ketoglutaric acid*

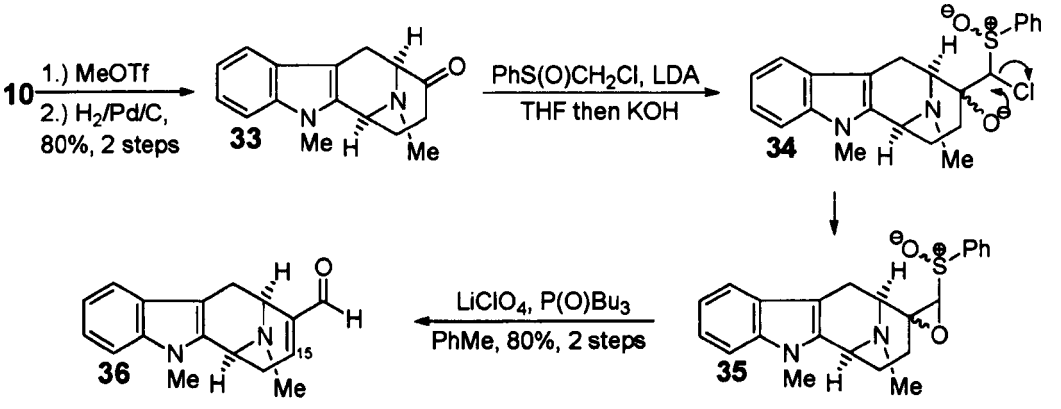
Acid/methanol-induced transformation of *cis*-**26** to **28** did not occur, likely because the lactam moiety would destabilise the α-aryl cation intermediate. The reaction occurred as desired in the absence of a free carboxyl group to give **28**. Upon exposure to base, **28** initially formed *trans*-**26**, but eventually gave the desired Dieckmann product **31**. Decarboxylation as before gave **32**.




**Scheme 9:** *Dieckmann cyclisation proceeded via the lactam*

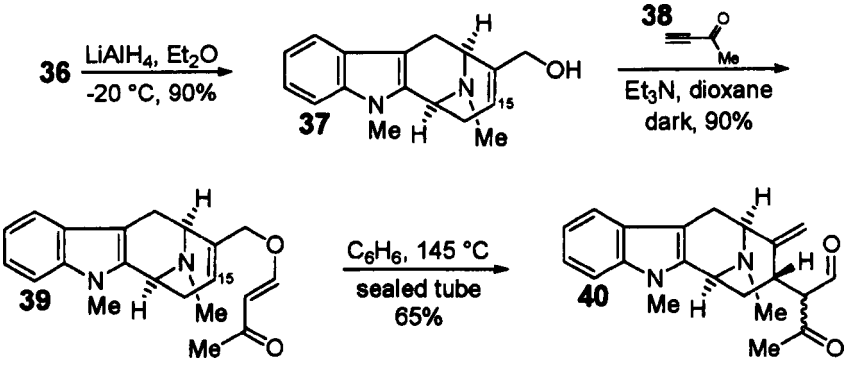
## *1.2.2: α,β-Unsaturated Aldehyde Formation and Claisen Rearrangement – Alstonerine, Anhydromacrosalhine-methine and Macrocarpamine*

The tetracyclic ketone **10** was elaborated by Cook's group in the first total synthesis of (–)-alstonerine[8] as shown in scheme 10. Exchange of the N4-benzyl group for methyl was followed by elaboration of the ketone to the α,β-unsaturated aldehyde[9] **36** *via* the intermediate epoxide **35**.



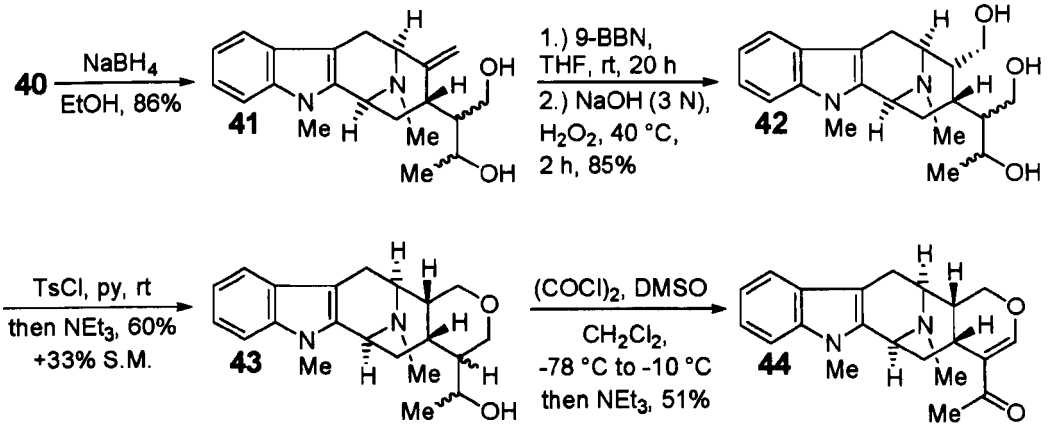

**Scheme 10:** *Transformation of tetracyclic ketone to α,β-unsaturated aldehyde*

Extensive studies had shown that intermolecular addition to the C15 position of **36** was not a facile process, so an intramolecular strategy was used. Reduction of **36** to **37** and formation of vinylogous ester **39** permitted C15 functionalisation *via* a Claisen rearrangement to give **40** (scheme 11).



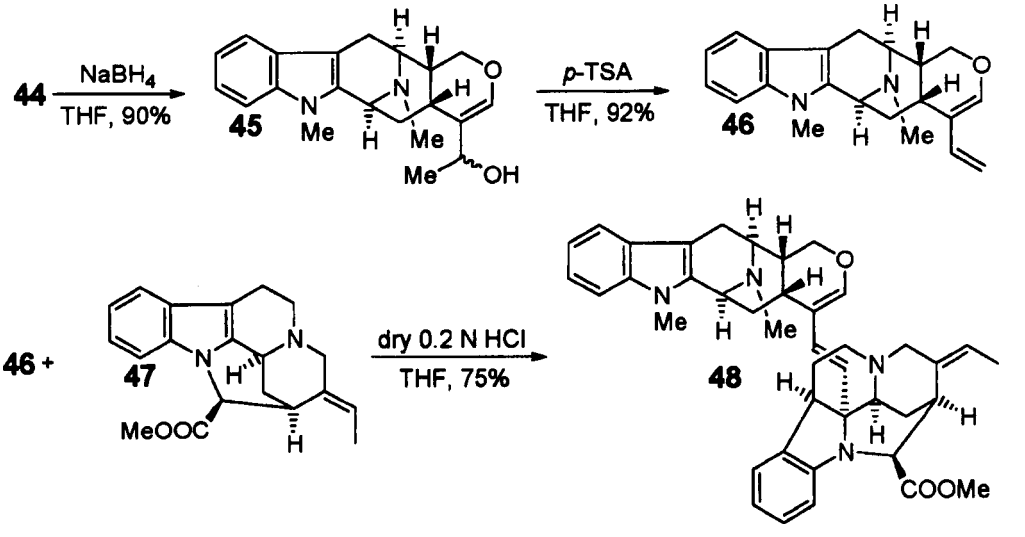

**Scheme 11:** *A Claisen rearrangement was used to functionalise C15*

Carbonyl reduction and hydroboration gave triol **42**, then selective toluene-4-sulfonylation of a primary alcohol and cyclisation gave **43**. A modified Swern oxidation[10] regenerated the vinylogous ester functionality and so led to (–)-alstonerine **44** (along with 31% dihydroalstonerine) in 8% overall yield from tetracyclic ketone **10** (not considering recycling of material) or 4% overall yield from D-tryptophan.




**Scheme 12:** *Completion of Cook's synthesis of (-)-alstonerine*

The strategy detailed above for the synthesis of (–)-alstonerine **44** was later extended by Cook *et al.* for the synthesis[11,12] of (–)-anhydromacrosalhine-methine **46**. Whilst not a natural product, this indole base constitutes the indole unit of the macroline-related bis(indole) alkaloid (–)-macrocarpamine **48**. Reduction of (–)-alstonerine **44** gave secondary alcohol **45**, which underwent acid-induced elimination to give (–)-anhydromacrosalhine-methine **46**. Coupling of **46** with a natural sample of pleiocarpamine **47** (scheme 13) completed the partial synthesis of (–)-macrocarpamine **48** (2% overall yield from D-tryptophan).

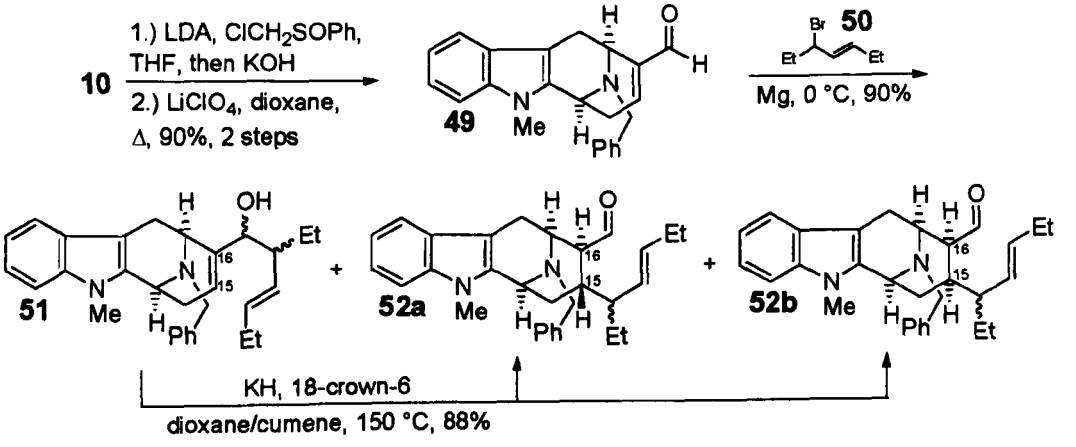



**Scheme 13:** *Partial synthesis of (-)-macrocarpamine from anhydromacrosalhine-methine*

*1.2.3 Ajmaline and Alkaloid G*

1.2.3.1: First-generation syntheses – 1,4-addition, oxyanion-Cope rearrangement and selective oxidations

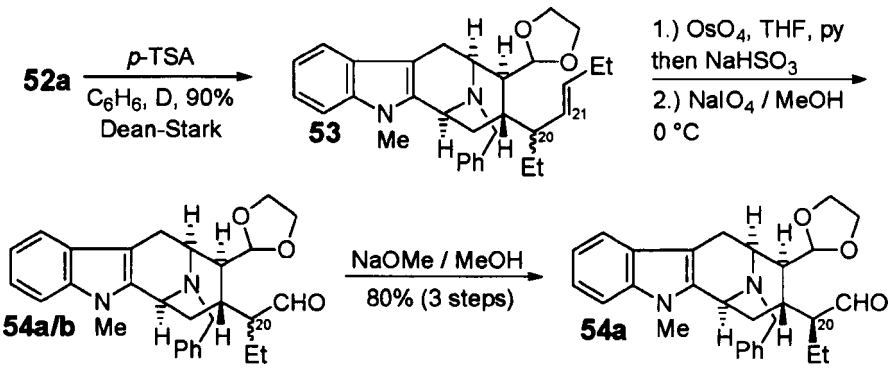
Cook and co-workers employed the tetracyclic ketone **10** in the first total synthesis of (–)-ajmaline.[13,14] Ketone **10** was elaborated into α,β-unsaturated aldehyde **49** as before, although the reaction was found to proceed in the absence of the phosphine oxide (also the N4-benzyl group was still in place). As mentioned in section 1.2.2, C15 functionalisation had been found to be difficult, but it transpired that successful organometallic addition was possible by use of a Barbier–Grignard process. A *pseudo*-symmetric allyl bromide was used to circumvent ambiguity regarding α- versus γ- addition. A mixture of 1,2- and 1,4-addition products resulted as shown, but in an elegant resolution to this problem, Cook was able to transform the undesired 1,2-addition product **51** into the 1,4-addition product **52** by means of an oxyanion-Cope rearrangement (scheme 14).




**Scheme 14:** *Undesired 1,2-addition product may be transformed into desired 1,4-addition product*

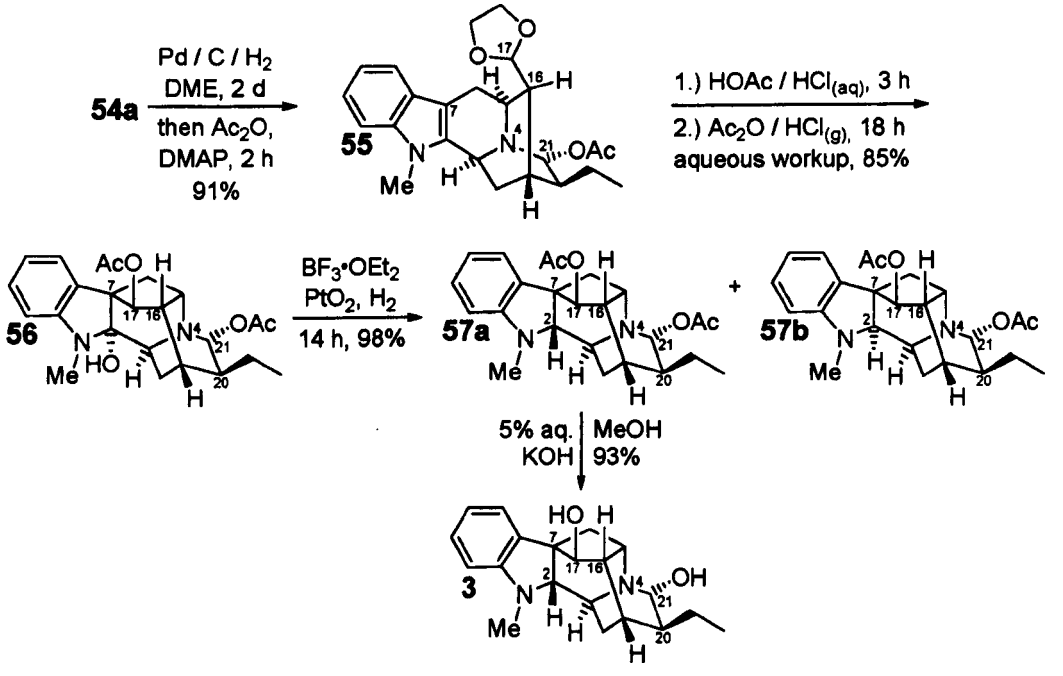
From the initial Barbier–Grignard reaction, **51** and **52** were formed in a ratio of 51:49. Of this, 1,4-addition product **52** was formed in a ratio of **52a**:**52b** 3:1, where **52a** was the desired isomer having (*S*)-C15. When **51** underwent oxyanion-Cope rearrangement, **52a** and **52b** were isolated in a ratio of 3:2. Subsequent elaboration of **52a** was by ethylidene acetal protection of the aldehyde and oxidative cleavage of the olefin. In order to effect chemoselective cleavage in the presence of the oxidatively-sensitive indole, a stoichiometric osmylation was required, with subsequent periodate cleavage of the resultant diol. At this point in the sequence it was possible to epimerise C20 via the aldehyde enolate, giving a 1:1 epimeric mixture, separable by

chromatography. With recycling of the undesired epimer **54b**, greater than 80% conversion from **53** was possible (scheme 15).



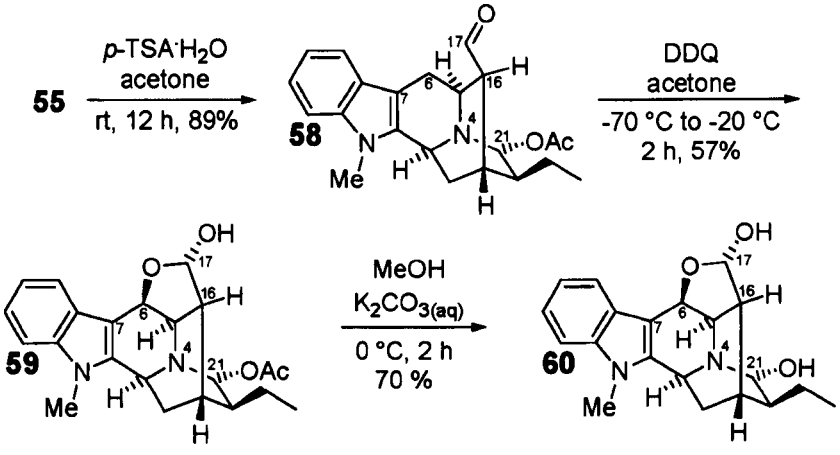

**Scheme 15:** *Chemoselective olefin cleavage renders C20 epimerisation possible*

N4-deprotection allowed formation of the *O*-acetyl aminal **55**. Treatment with $HCl_{(aq)}$ / AcOH, then $Ac_2O$ / $HCl_{(g)}$ effected the final cyclisation to the ajmalan skeleton by electrophilic addition to C7. The resultant C2 hemiaminal **56** was reduced under Lewis acidic conditions to furnish a C2-epimeric mixture, **57a**:**57b** 2:3. The epimer having the correct C2 configuration, **57a**, underwent base-mediated hydrolysis to afford (–)-ajmaline **3** (scheme 16) in 11% from tetracyclic ketone **10** (5% from D-tryptophan). Whilst formation of only 40% of the desired C2 epimer in the penultimate step is not ideal, Cook notes that 2-*epi*-diacetyl ajmaline **57b** is the thermodynamic product and many reagent systems provide solely **57b**.




**Scheme 16:** *Completion of Cook's first synthesis of (-)-ajmaline*

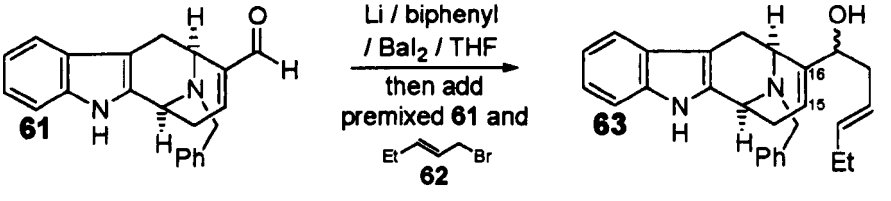
Hydrolysis of acetal **55** gave **58**, which had previously been converted into alkaloid G by Stöckigt and co-workers[15] (scheme 17), employing a DDQ oxidation to functionalise the C6 position. Cook's report therefore constitutes a formal synthesis of alkaloid G **60** in 10 steps and 12% yield from tetracyclic ketone **10** (17 steps from D-tryptophan, 6% overall yield).




**Scheme 17:** *Formal synthesis of Alkaloid G (Stöckigt's route)*

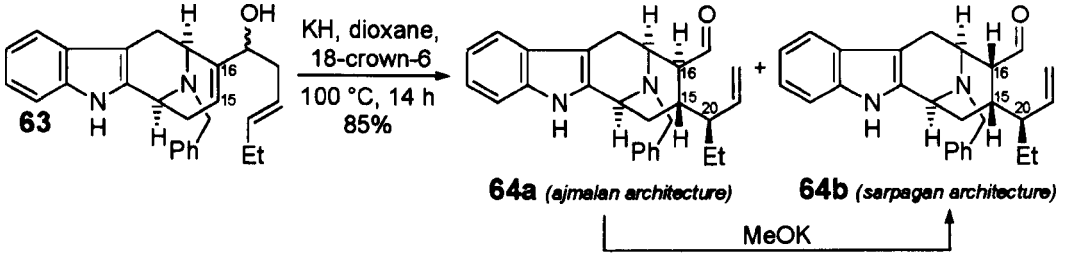
## 1.2.3.2: Second generation syntheses – organobarium chemistry and kinetic enolate quenching

Shortly after the reports summarised in section 1.2.3.1, Cook's group published improved syntheses of (–)-ajmaline[16] and alkaloid G.[16,17] The improvements address the issue of stereocontrol in the organometallic addition and oxyanion-Cope steps. Using methodology due to Yamamoto,[18] Cook and co-workers treated N1-unsubstituted α,β-unsaturated aldehyde **61** with an organobarium reagent derived from (*E*)-pent-2-enyl bromide. This addition took place solely via α-addition of the metallate, hence the need for a *pseudo*-symmetric alkenyl halide was removed. Additionally, only 1,2-addition was observed, giving **63** as the sole product (scheme 18).



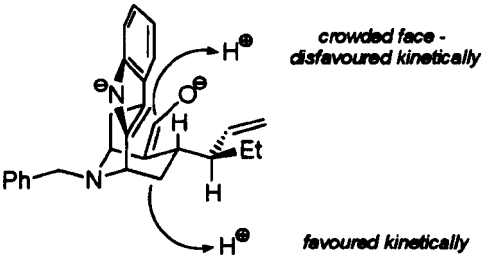

**Scheme 18:** *Barium chemistry allowed total regioselectivity in the addition*

Oxyanion-Cope rearrangement of **63** took place as before; in this instance, however, near total selectivity for the desired configurations was observed at C15 *and* C20 (*c.f.* selectivity of 3:2 in section 1.2.3.1). As regards selectivity at C16, in the first instance the selectivity was 1:4 **64a**:**64b** for undesired sarpagan (*R*)-C16 configuration. Upon prolonged exposure of (*S*)-C16 **64a** to base, epimerisation to mostly (*R*)-C16 **64b** was observed, implying **64b** was the thermodynamic product (scheme 19).




**Scheme 19:** *Two of three stereocentres were controlled in the first instance*

The 3D structure (scheme 20) of the enolate resulting from the oxyanion-Cope rearrangement suggested that the α-face might be less hindered and as such **64a** might be the kinetic product. After optimisation, it was found that quenching the oxyanion-Cope rearrangement with 1 N trifluoroacetic acid at low temperature favoured formation of **64a**. After the rearrangement had gone to completion, THF was added, allowing the reaction mixture to be cooled below the melting point of dioxane. At –100 °C in dioxane:THF, addition of 1 N trifluoroacetic acid in THF afforded **64a**:**64b** in a ratio 43:1.



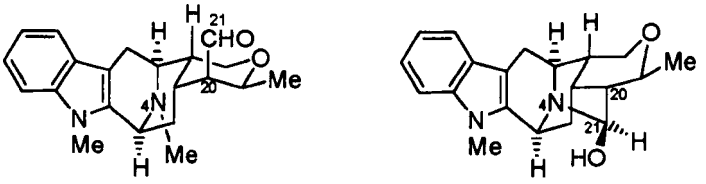

**Scheme 20:** *Protonation of the α-face leads to the kinetic product*

The ability to vary reaction conditions to favour either **64a** or **64b** permits stereospecific entry to either the macroline/sarpagine (C16 β-H) series or the ajmaline (C16 α-H) series. Aldehyde **64a** was protected as the ethylidene acetal, then N1-methylated to converge on the (–)-ajmaline synthesis detailed in section 1.2.3.1. The second generation synthesis was thus completed in 9% overall yield from D-tryptophan methyl ester, an appreciable improvement. In completing the second generation synthesis of alkaloid G, Cook's

laboratory reports a significant improvement to the DDQ-mediated α-aryl oxidation step – performing the reaction in wet THF leads to a yield of 94% **42** (one diastereoisomer only). The improved alkaloid G synthesis was therefore completed in 25% overall yield from D-tryptophan methyl ester.

### *1.2.4 Selenium Chemistry and an Unusual Pyrolytic Rearrangement – Talpinine, Talcarpine, Alstonerine and Anhydromacrosalhine-methine*

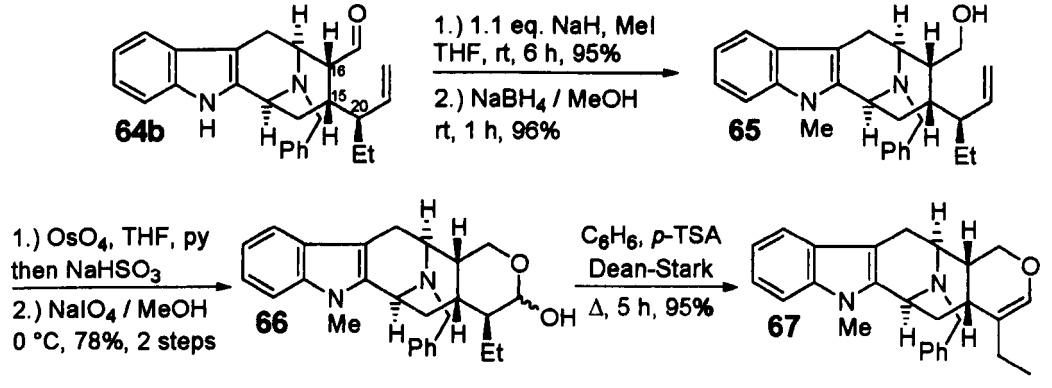
Cook *et al.* have reported syntheses[19,20] of the two structurally-related macroline/sarpagine alkaloids (–)-talcarpine **65** and (–)-talpinine **66**. They employ much of the methodology used for the synthesis of (–)-ajmaline and alkaloid G. It may be seen (scheme 21) that **65** and **66** are epimeric at C20 and that **66** lacks the N4-methyl group but has a hemiaminal moiety containing a C21-N4 linkage.



(-)-talcarpine **65** (-)-talpinine **66**

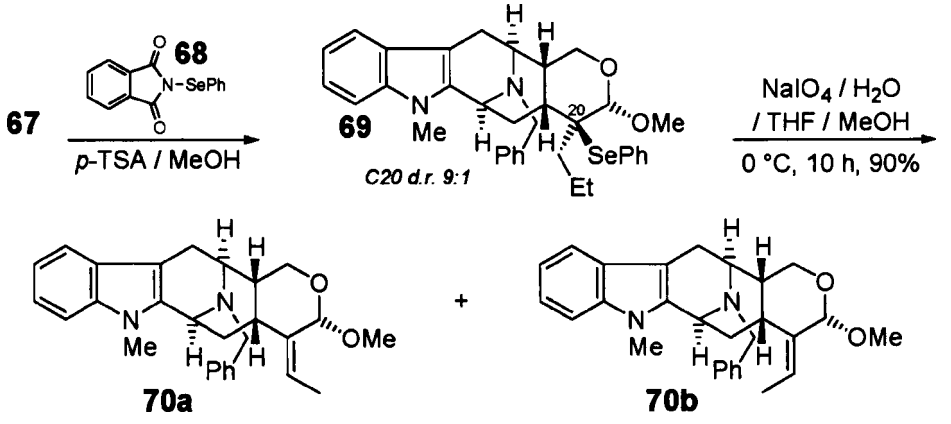
**Scheme 21:** *Talpinine and talcarpine are differentially N4-substituted C20 epimers*

The synthetic sequence was executed as per section 1.2.3.2, again from the N1-unsubstituted α,β-unsaturated aldehyde **61**. As the sarpagan configuration (C16 β-H) was required in this instance, the enolate deriving from oxyanion-Cope rearrangement was quenched under thermodynamic conditions, simply by adding MeOH to the reaction mixture and stirring at room temperature for 2 h to give **64b**. After N1-methylation, the aldehyde moiety was reduced and oxidative olefin cleavage (as previously) this time afforded a diastereoisomeric mixture of lactols **66**, which were then dehydrated (scheme 22).



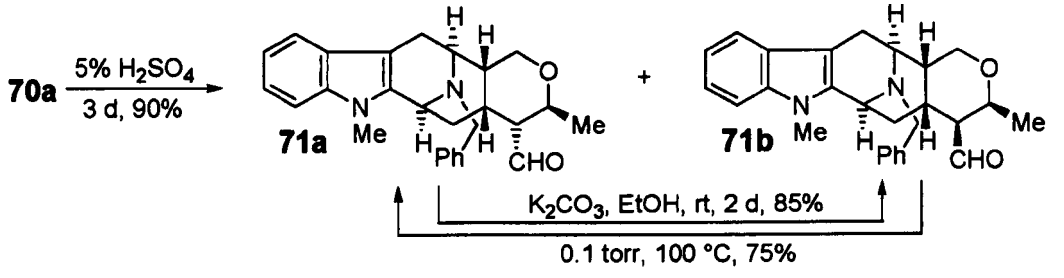

**Scheme 22:** *C20 stereochemistry is lost in dehydration*

Addition of a phenylselenenyl[21] and a methoxy group across the enol ether was followed by selenium oxidation and elimination with rearrangement to afford a mixture of exocyclic olefin geometries (scheme 23) in a ratio **70a**:**70b** 4:1 (where **70a** is the desired isomer).



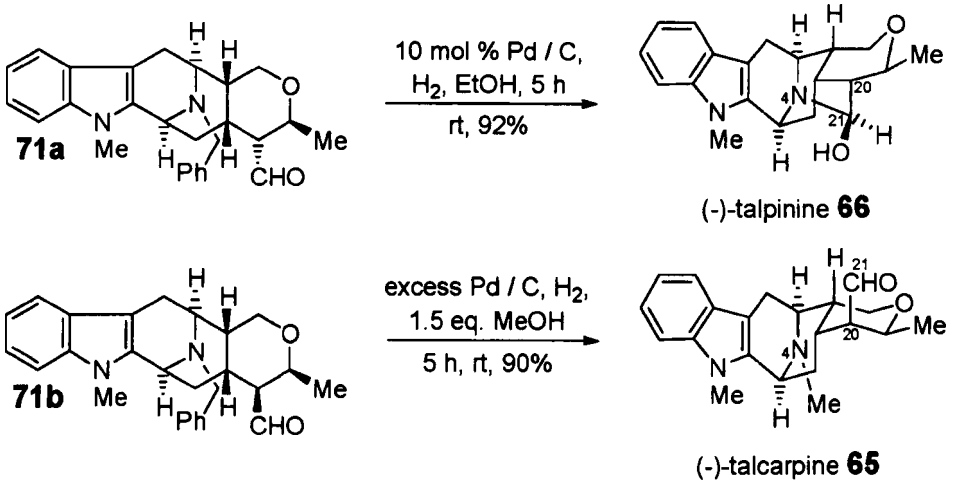

**Scheme 23:** *Selenoxide elimination led to a 4:1 geometric ratio*

The desired isomer **70a** was treated with 5% $H_2SO_4$ for 3 days, which induced acetal opening, C15-C20 bond rotation and Michael addition to generate saturated C20-aldehydes as a C20 epimeric mixture, 3:5 **71a**:**71b**. Aldehyde **71a** (with (*R*)-C20) is the precursor of talpinine and similarly **71b** (with (*S*)-C20) is the precursor of talcarpine. The two epimeric precursors may in fact be interconverted (scheme 24).



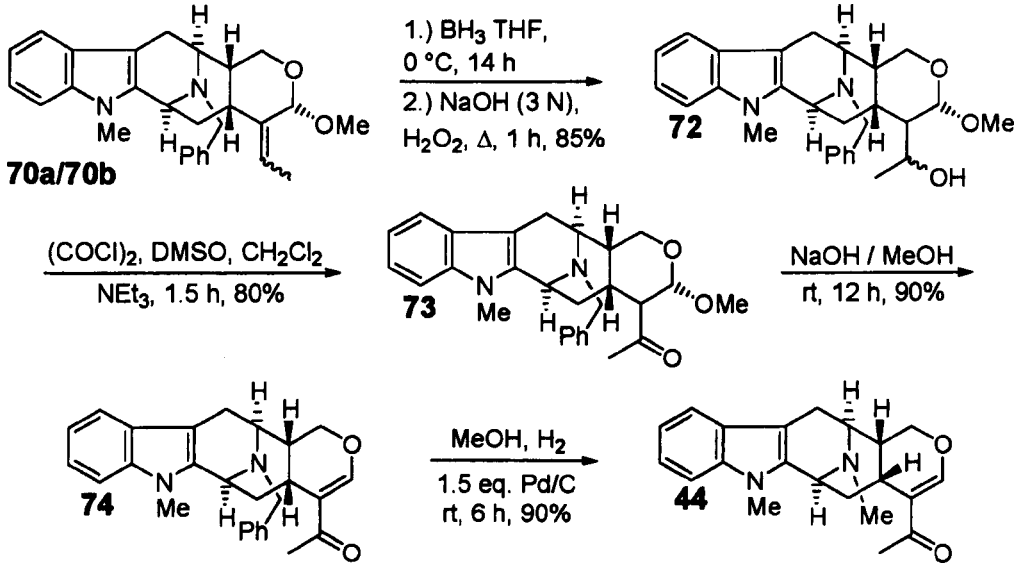

**Scheme 24:** *Final product precursors may be interconverted*

Conversion of **71a** to **71b** is simply base-induced epimerisation to the thermodynamic product. The pyrolytic conversion[22] of **71b** to **71a** is not fully understood mechanistically. Conversion of **71a** to talpinine (10% from D-tryptophan, scheme 25) was effected simply by N4-debenzylation (with spontaneous hemiaminal formation). Conversion of **71b** to talcarpine (10% from D-tryptophan, scheme 25) was effected by N4-debenzylation with concomitant N4-methylation, a transformation used by Cook in multiple total syntheses, speculated to involve *in-situ* formaldehyde formation.



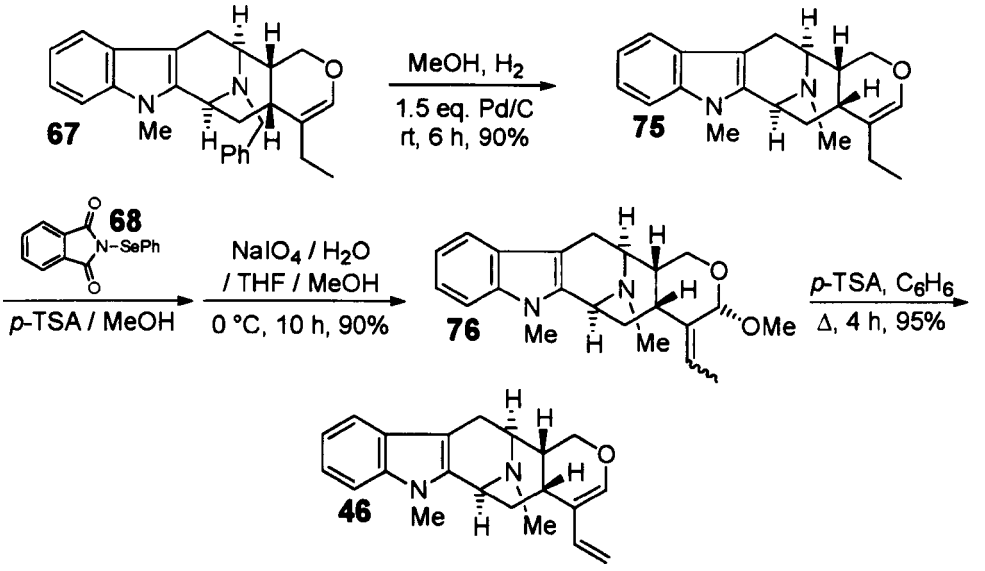

**Scheme 25:** *Conversion to talpinine and talcarpine*

The methodology detailed above has also been employed in second-generation syntheses[20] of anhydromacrosalhine-methine and alstonerine. The geometric mixture of olefins (**70a** and **70b**) was subjected to hydroboration, normal Swern oxidation, elimination of the elements of methanol and N4-debenzylation/methylation to furnish (–)-alstonerine **44** (scheme 26) in an improved 12% overall yield from D-tryptophan (*c.f.* section 1.2.2).




**Scheme 26:** *Second generation synthesis of (-)-alstonerine*

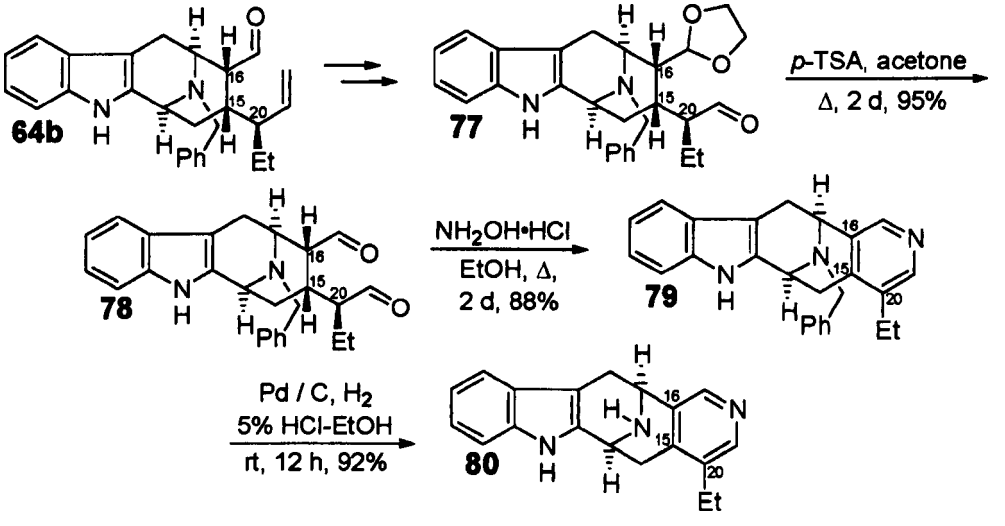
Anhydromacrosalhine-methine **46** was synthesised from **67** (scheme 27), by N4-debenzylation/methylation at an earlier stage, then selenium introduction, oxidation and elimination as before, followed by acid-induced elimination to the vinylogous enol ether product **46** (14% from D-tryptophan, *c.f.* section 1.2.2).




**Scheme 27:** *Second generation synthesis of (-)-anhydromacrosalhine-methine*

## *1.2.5 Pyridine Formation – Norsuaveoline (and Suaveoline)*

Cook's laboratory has also reported the synthesis of the pyridyl macroline alkaloid norsuaveoline.[14,23] From the N1-unsubstituted tetracyclic ketone **32**, the synthesis proceeded as per the ajmaline synthesis in section 1.2.3.2. Cook and co-workers opted to use the sarpagan C16-configured oxyanion-Cope product, although in this instance the configurations of C15, C16 and C20 are of less concern since all are ultimately incorporated into the pyridine ring. Ethylidene acetal formation and oxidative olefin cleavage were executed as before. In this case, however, the acetal was deprotected to furnish a 1,5-dialdehyde **78**. This was treated with ethanolic hydroxylamine hydrochloride to access the pyridine ring directly; N4-debenzylation afforded norsuaveoline **80** in 28% yield from D-tryptophan methyl ester (scheme 28).

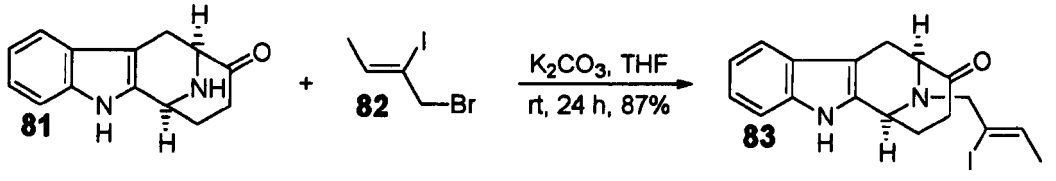



**Scheme 28:** *Cook's synthesis of norsuaveoline*

Cook has also reported a synthesis of (–)-suaveoline (the N4-methyl analogue), which is outside the scope of this review as it was published in 1993. Bailey[24] and Ohba[25] have published syntheses within the scope of this review. All these syntheses are detailed in section 2.2.2 of the results and discussion.

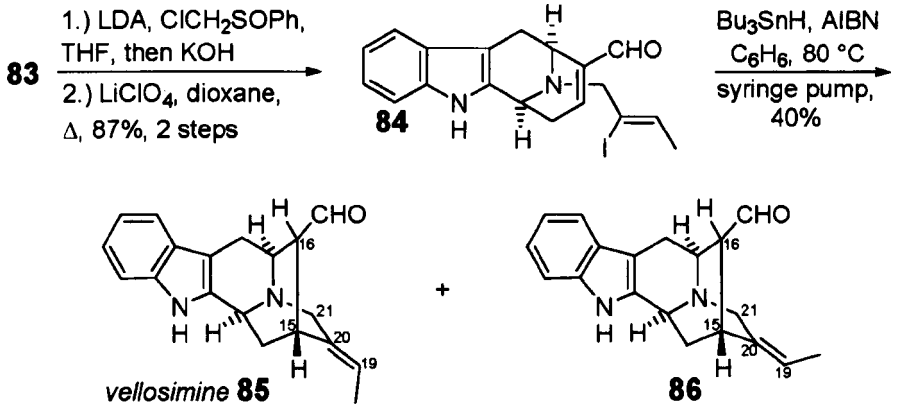
### *1.2.6 Palladium Sarpagan Methodology – ent-Affinisine, 16-epi-Affinisine, Alkaloid Q3, Dehydro-16-epi-affinisine, Koumidine, 16-epi-N-Methylpericyclivine, N-Methylvellosimine, Normacusine B, 16-epi-Normacusine B, Panarine and Vellosimine*

For the synthesis of alkaloids possessing the sarpagan skeleton, a key question is how to construct the skeleton such that the C19-C20 olefin geometry is controlled. Cook attempted to address this problem in various ways and met with success when he employed a palladium-mediated cyclisation. The key reaction may be illustrated with the example of Cook's total synthesis of (+)-vellosimine **85**.[26,27] The iodoalkene **82** (which had previously been employed by other workers[28]) was reacted with the N1-unsubstituted, N4-debenzylated tetracyclic ketone **81** to give **83** (scheme 29).



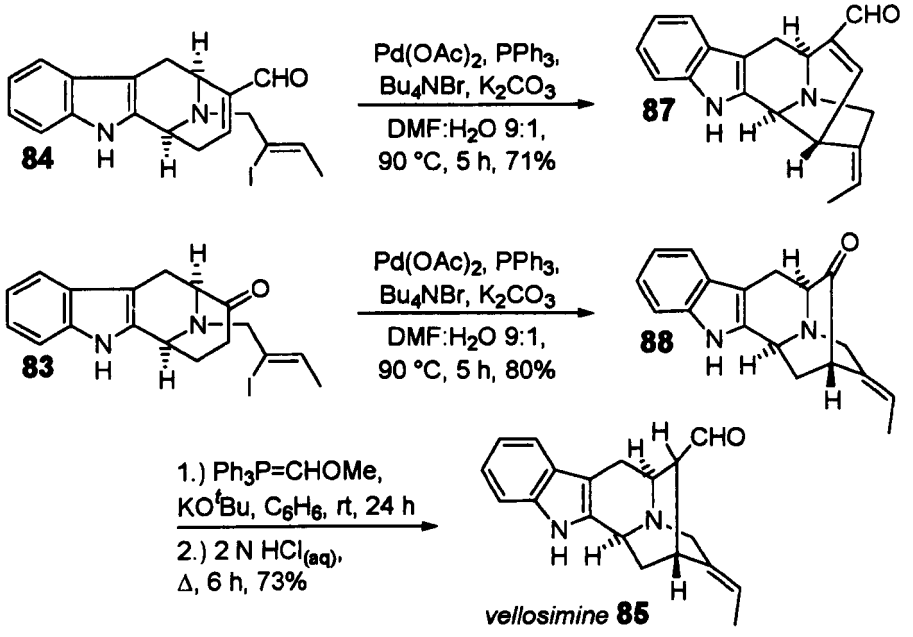

**Scheme 29:** *Introduction of iodoalkenyl fragment*

Ketone **83** was elaborated to the corresponding α,β-unsaturated aldehyde **84** as previously. One can envisage that transmetallation and Michael addition would give access to the sarpagan skeleton, but in fact no such reaction was successful. Instead, it was found that a radical-mediated coupling allowed C15-C20 bond formation. This occurred with scrambling of the C19-C20 olefin geometry, however, and the desired (+)-vellosimine **85** was the minor product in a ratio **85**:**86** 1:3 (scheme 30).



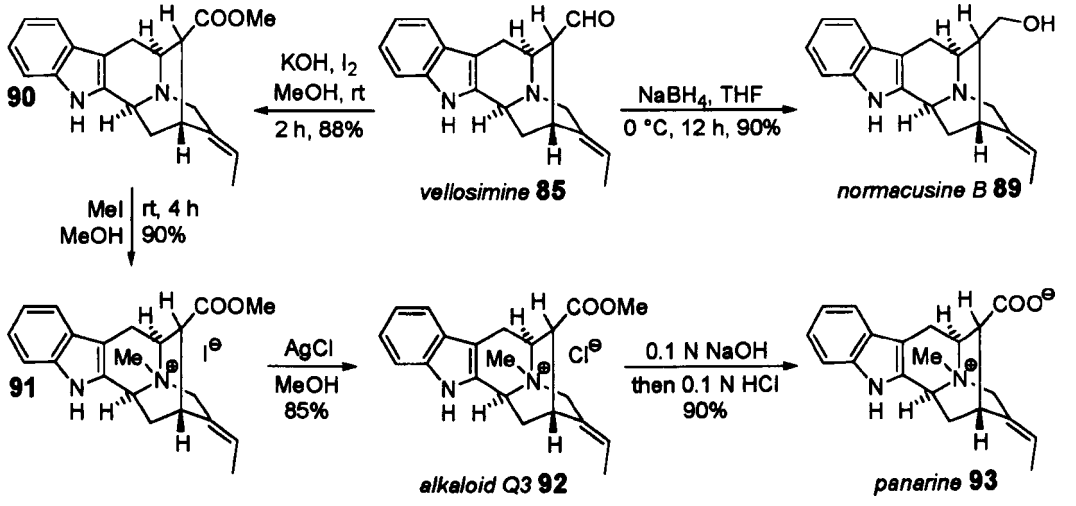

**Scheme 30:** *Synthesis of (+)-vellosimine via a radical pathway scrambled olefin geometry*

In light of the failure of both metallate and radical methods, the desired stereospecific cyclisation of **84** was attempted under conditions of $Pd^0$ catalysis. The unexpected product **87** was isolated (as a single geometric isomer), presumably arising from the enolate of **84**. Such a cyclisation had been previously observed in other systems.[29] By inference from this result, it followed that **83** might undergo cyclisation to the desired vellosimine skeleton. Ketone **83** did indeed give **88** stereospecifically under the same conditions. This was transformed into (+)-vellosimine **85** *via* a masked aldehyde which was unmasked and epimerised to the more stable C16 sarpagan configuration (scheme 31). The first total synthesis of this sarpagine alkaloid was therefore completed in 27% overall yield from D-tryptophan methyl ester.



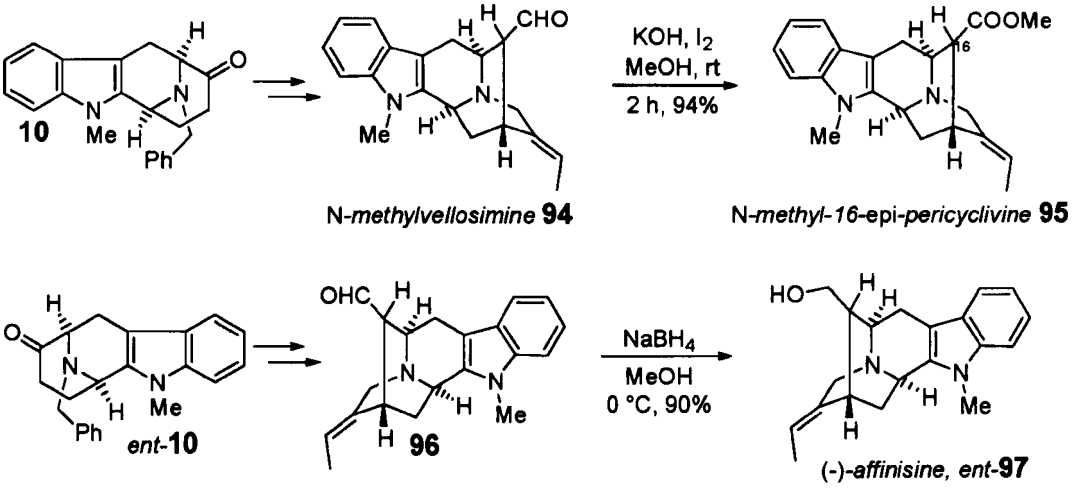

**Scheme 31:** *Stereospecific synthesis of (+)-vellosimine via palladium catalysed cyclisation*

Several more sarpagine alkaloids[27,30] were in turn synthesised from (+)-vellosimine **85** (scheme 32). Reduction of the aldehyde in **85** gave (+)-normacusine B **89** (24% from D-tryptophan methyl ester). Conversely, oxidation of the aldehyde in **85** and esterification gave **90**, quaternisation of which with methyl iodide and subsequent anion exchange gave (–)-alkaloid Q3 **92** (18% from D-tryptophan methyl ester). Ester hydrolysis of **92** and neutralisation gave zwitterionic (–)-panarine **93** (16% from D-tryptophan methyl ester).



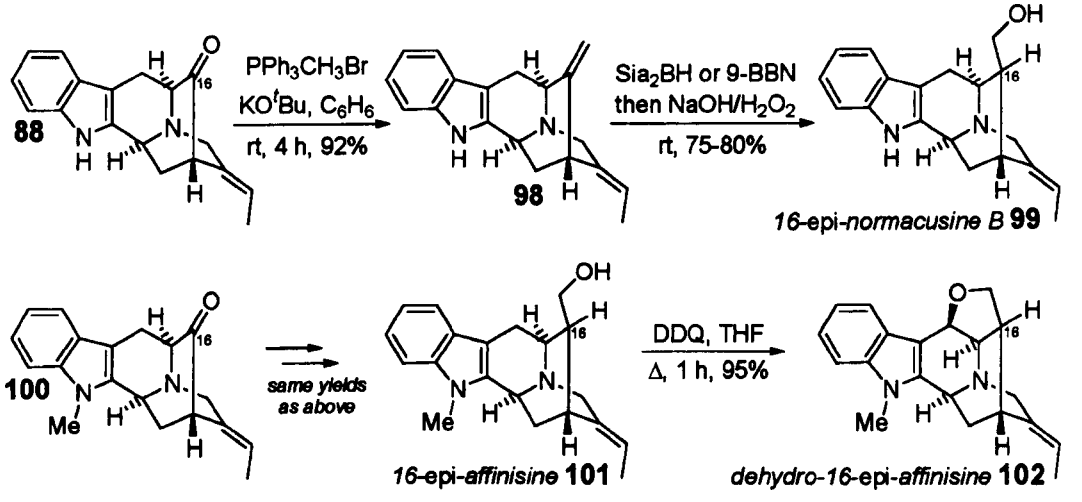

**Scheme 32:** *(+)-Vellosimine served as an intermediate for the synthesis of other alkaloids*

The same synthetic sequence used to prepare (+)-vellosimine was applied to the N1-methyl tetracyclic ketone **10** to produce (+)-*N*-methylvellosimine[27] **94** (29% overall yield from D-tryptophan, scheme 33). Oxidation and esterification provided (+)-*N*-methyl-16-*epi*-pericyclivine[27] **95** (27% overall yield from D-tryptophan). Reduction of the aldehyde in **94** provided (+)-affinisine[27] **97** (26% overall yield from D-tryptophan). Also, Cook's group executed the entire synthetic sequence from L-tryptophan, thus providing *ent*-**97** (–)-affinisine,[31] the enantiomer of the natural product (scheme 33). This *ent*-affinisine was required for the synthesis of "mismatched" unnatural bis(indole) alkaloids, to probe their biological activities and SAR. As LeQuesne had previously reported[32] partial syntheses of macroline **1** and alstonerine **44** from affinisine, Cook's work constitutes formal syntheses of the antipodes of these alkaloids also.



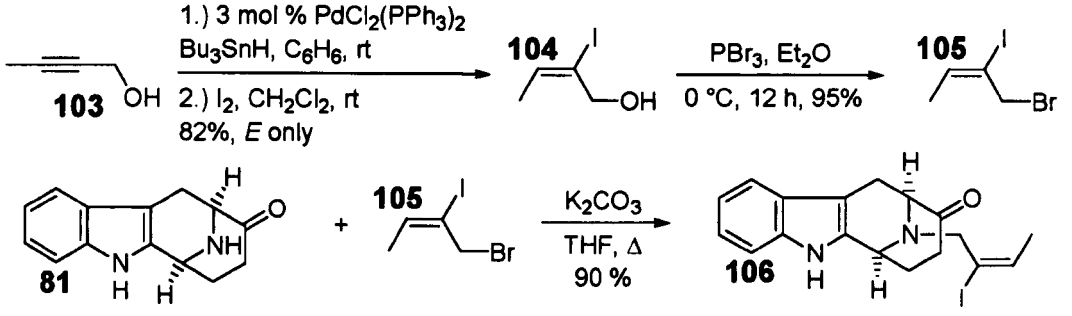

**Scheme 33:** N-*Methyl sarpagine alkaloids synthesised by Cook*

A slightly different approach was used to access sarpagine alkaloids possessing the opposite configuration at C16 (ajmaline configuration). From sarpagan C16 ketone **88**, Wittig methylenation and selective hydroboration of the disubstituted olefin from the less hindered face gave 16-*epi*-normacusine B[17,33] **99** (26% from D-tryptophan methyl ester). In the N1-methyl series, from sarpagan C16 ketone **100**, the same Wittig methylenation and selective hydroboration gave 16-*epi*-affinisine[17,33] **101** (25% from D-tryptophan methyl ester). DDQ-mediated α-aryl oxidation gave dehydro-16-*epi*-affinisine[17,33] **102** (24% from D-tryptophan methyl ester), as shown in scheme 34.



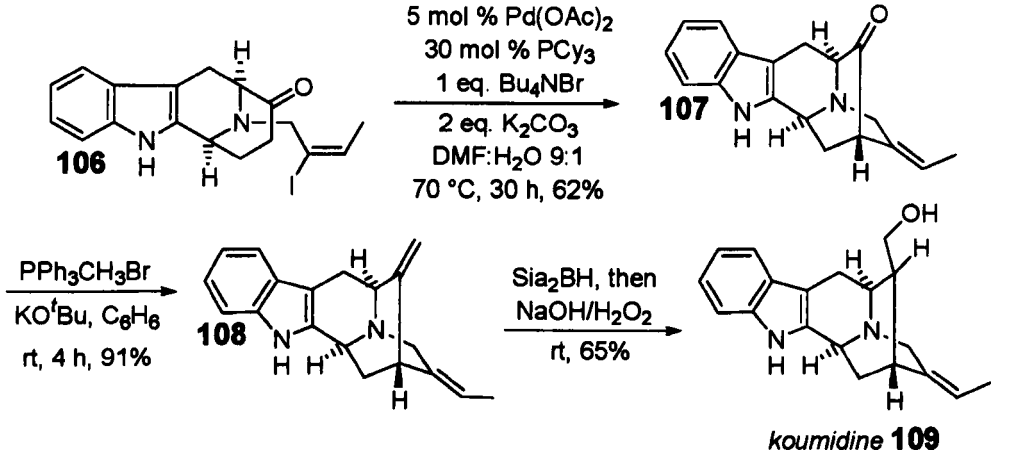

**Scheme 34:** *16-Epimeric* N-*methyl sarpagine alkaloids synthesised by Cook*

Cook employed a modified version of the palladium-mediated coupling in the synthesis of (–)-koumidine **109**, which differs from the various species shown above in that the geometry of the C19-C20 olefin is (*Z*). To access this alternative geometry,[34] the alternate iodoalkene **105** was synthesised as shown in scheme 35 and coupled to N1-unsubstituted tetracyclic ketone **81**.




**Scheme 35:** *Opposite olefin geometry is required for (-)-koumidine*

The palladium-mediated cyclisation was less facile than in previous examples with the opposite (*E*) olefin geometry – despite much optimisation, on reaction of **106** significant amounts of dealkylated product **81** were isolated along with the desired **107**. Completion of the synthesis (scheme 36) was *via* selective hydroboration as for the other C-16-*epi* alkaloids detailed previously.

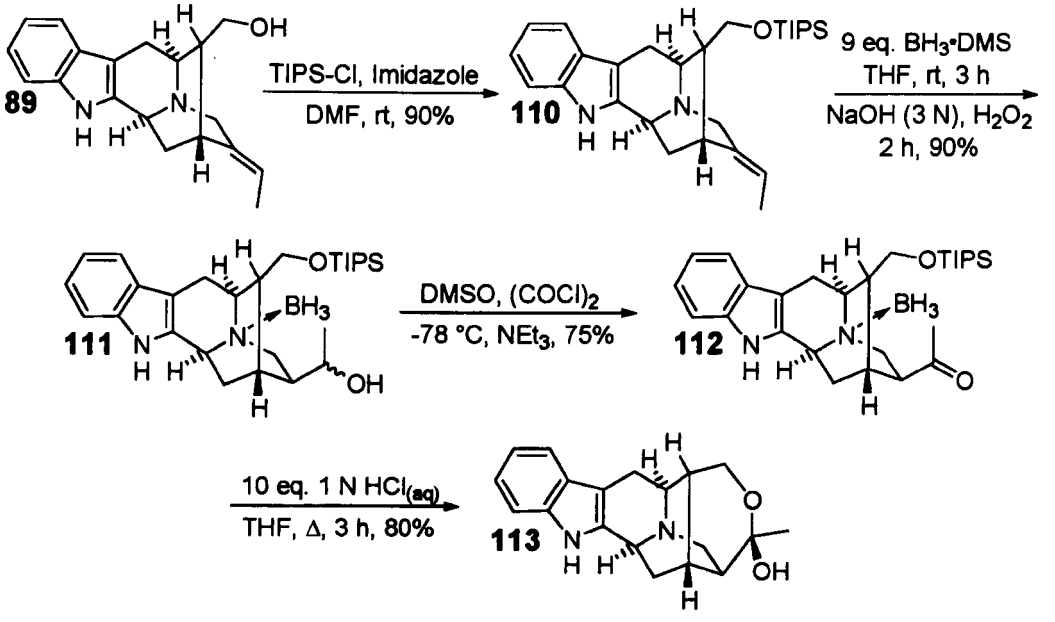



**Scheme 36:** *Final steps in the synthesis of (-)-koumidine*

## *1.2.7 Selective Hydroboration – Trinervine*

The sarpagine alkaloid trinervine **113**, a cyclic hemiacetal, was synthesised from (+)-normacusine B **89**, the synthesis of which is detailed in section 1.2.6. Silylation of the alcohol was followed by attempts at selective hydroboration of

the trisubstituted C19-C20 olefin (scheme 37). Surprisingly, the initial selectivity (at 0 °C) for secondary hydroxyl product **111** over the tertiary regioisomer was only 7:3. It was postulated that this may be due to complexation of the first equivalent of borane to N4, thus altering the electronic characteristics of the olefin. A detailed optimisation study was carried out[35] – use of bulky hydroborating agents resulted in no reaction, but increased selectivity was observed by using R=TIPS at room temperature, furnishing the desired regioisomer in a ratio 25:1. This was oxidised in turn to the ketone and upon deprotection of the hydroxyl group (and cleavage of the borane adduct), spontaneous cyclisation gave trinervine **113** (20% from tetracyclic ketone **32**).



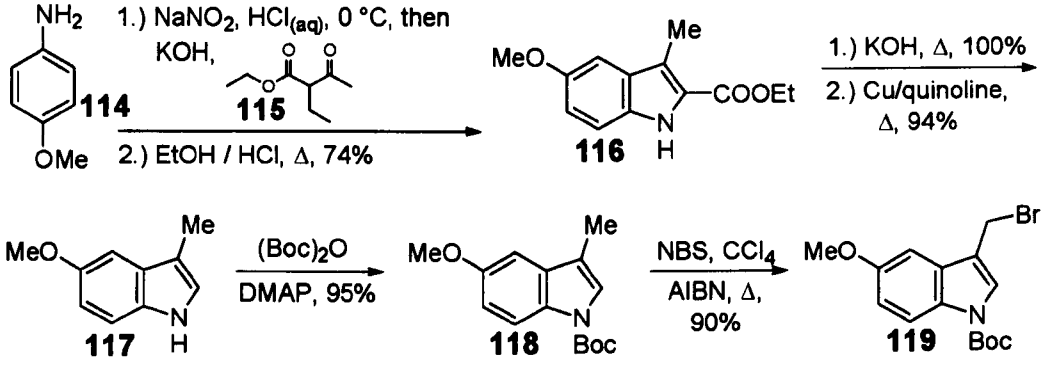

**Scheme 37:** *Synthesis of trinervine from normacusine B*

## *1.2.8 Indole Oxygenation*

As alluded to in the introduction, many macroline/sarpagine/ajmaline alkaloids possess indole ring oxygenation. Cook has synthesised many of these; key to these syntheses has been the optimisation of routes to the relevant oxygenated tryptophan derivatives. Cook has successfully introduced oxygenation in the C10-, C11- and C12-positions. In each instance the Schöllkopf chiral auxiliary[36] was used to introduce the correct amino acid stereochemistry. The precise details vary depending on ring substitution pattern, however, and so will be discussed individually.

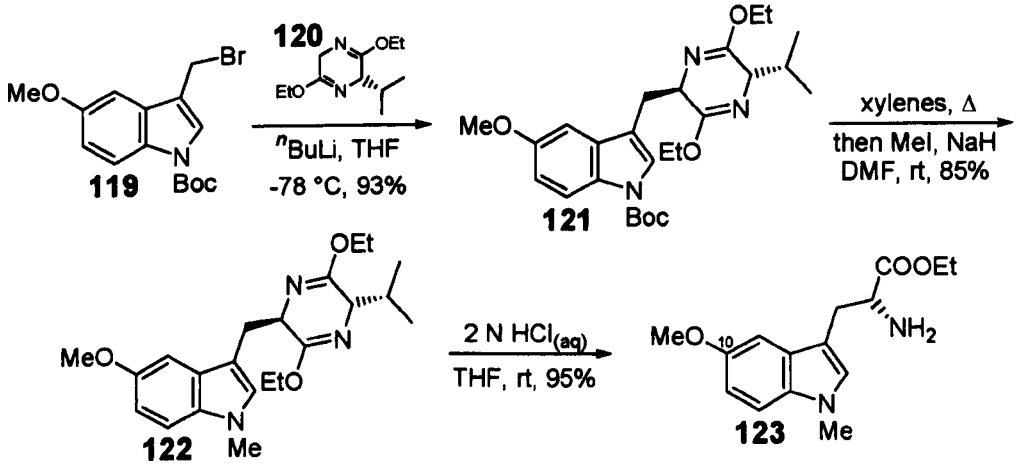
1.2.8.1 C10 Oxygenation – Majvinine, 10-Methoxyaffinisine, *N*-Methyl sarpagine and Macralstonidine

*p*-Anisidine was employed as a starting material for a synthesis[37,38] that Cook's laboratory has executed on a >600 gram scale (scheme 38). Fischer indole formation *via* a Japp–Klingemann azo-ester intermediate[39] gave trisubstituted indole **116**. C2-decarboxylation was followed by N1-protection, either with a Boc group or as a sulfonamide (only the Boc series is considered here). Optimisation of brominating conditions[38] was required to access the desired α-aryl brominated product **119** and avoid indolyl C2-bromination.



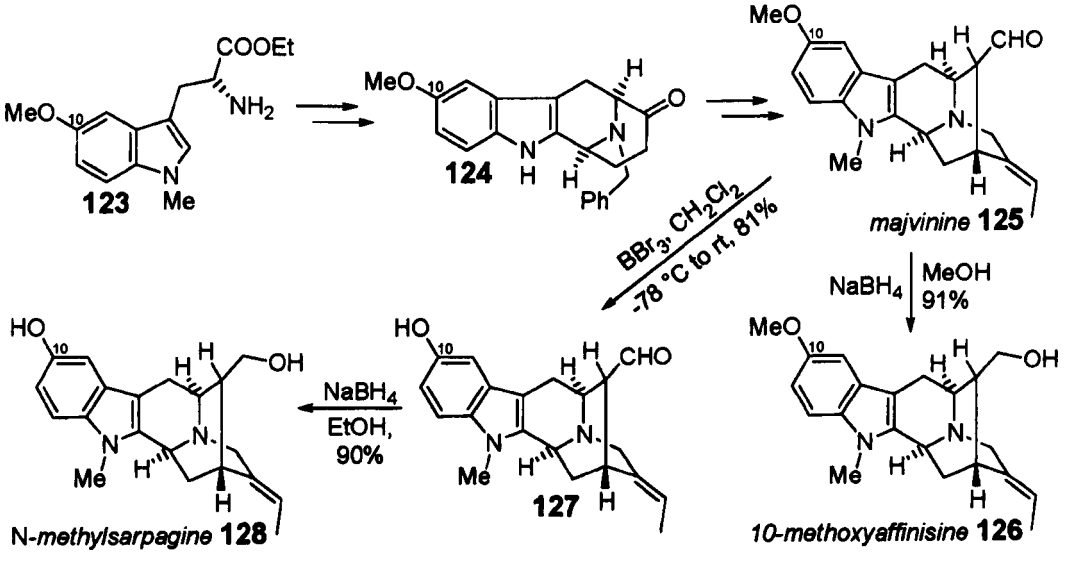

**Scheme 38:** *Synthesis of bromomethyl indole fragment*

Cook has studied the effect of the leaving group and other parameters on the diastereoselectivity of reaction with Schöllkopf auxiliaries.[40] Bromide **119** was coupled with the Schöllkopf auxiliary derived from L-valine to give **121** as a single diastereoisomer. The Boc group was cleaved thermolytically, followed by N1-methylation in one pot. The auxiliary was removed under conditions of acidic hydrolysis to furnish the C10-methoxy analogue of D-tryptophan ethyl ester **123** (scheme 39).



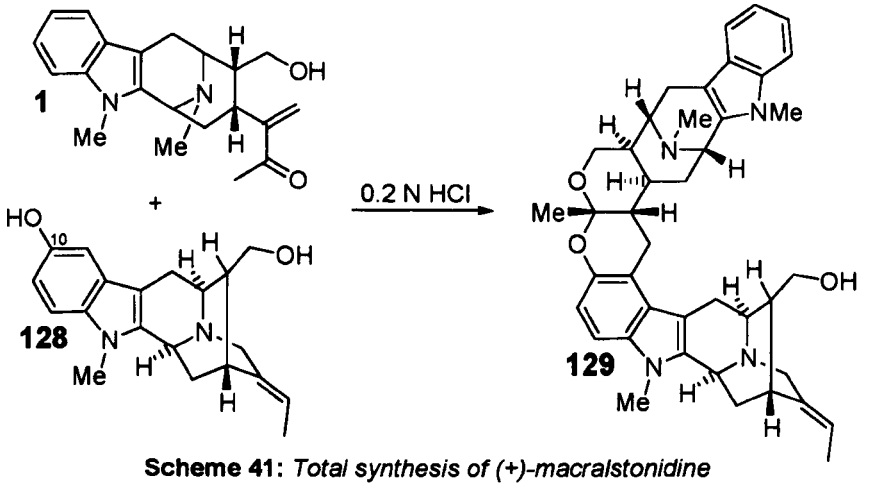

**Scheme 39:** *10-Methoxy analogue of D-tryptophan ethyl ester*

The ring-oxygenated amino acid **123** was amenable to the chemistry developed by Cook and co-workers detailed in sections 1.2.1 to 1.2.7. Thus, synthesis of C10-methoxy tetracyclic ketone **124** was high-yielding (although it was necessary to avoid harshly acidic conditions in the Pictet–Spengler and C3-isomerisation steps, otherwise decomposition of the indole occurred). The conversion of **124** to the sarpagan skeleton *via* the palladium enolate methodology described previously was similarly high-yielding (scheme 40). Synthesis of (+)-majvinine **125** (28% yield from C10-methoxy D-tryptophan ethyl ester analogue **123**) was executed as per *N*-methylvellosimine **94** (majvinine is simply the C10-methoxy analogue of **94**). Reduction of the aldehyde moiety in **125** gave (+)-10-methoyxaffinisine **126** (25% yield from **123**). For the synthesis of (+)-*N*-methylsarpagine **128**, a C10-hydroxy moiety was required as opposed to C10-methoxy. Therefore (+)-majvinine **125** was demethylated with boron tribromide prior to reduction to (+)-*N*-methylsarpagine **128** (20% yield from **123**).




**Scheme 40:** *C10-Methoxy alkaloids synthesised by Cook and co-workers*

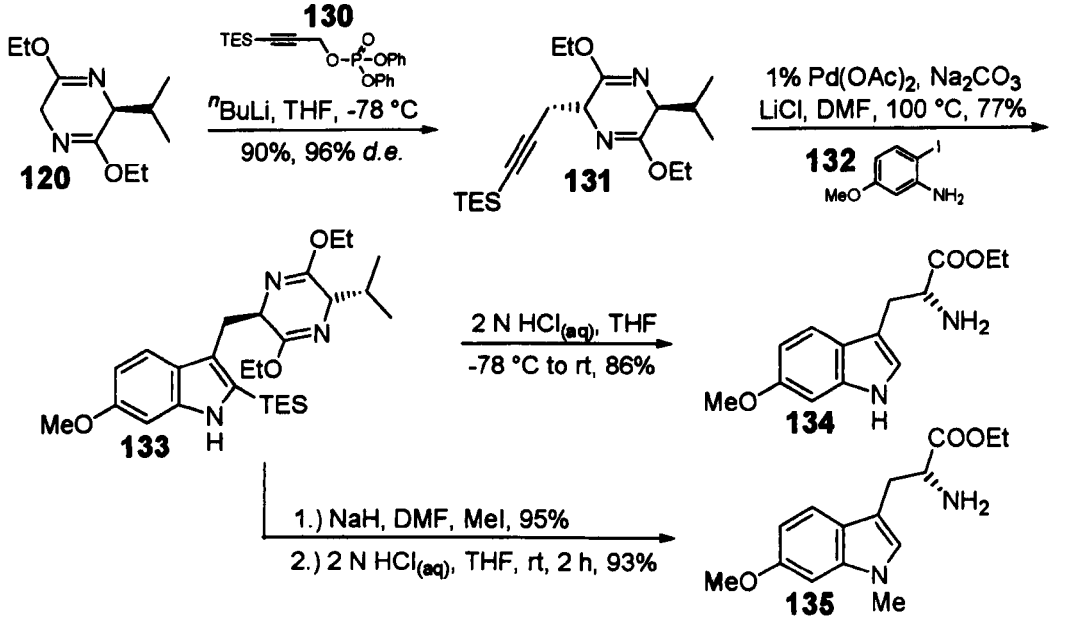
Cook also reported the first total synthesis of the bis(indole) alkaloid (+)-macralstonidine **129**, from the coupling[32b] of synthetic *N*-methylsarpagine **128** with synthetic macroline **1** (scheme 41)




**Scheme 41:** *Total synthesis of (+)-macralstonidine*

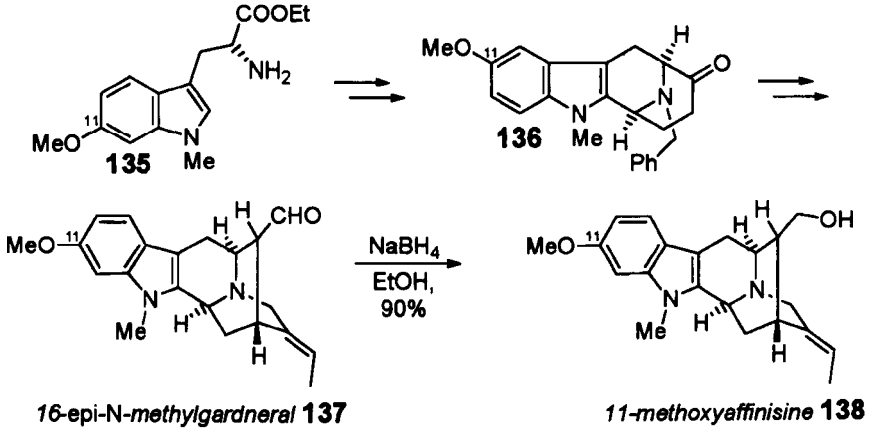
## 1.2.8.2 C11 Oxygenation – Gardnerine, Gardnutine, 11-Methoxyaffinisine and 16-*epi*-*N*-Methylgardneral

Synthesis of a C11-oxygenated tryptophan analogue would have been subject to regiochemical ambiguity if attempted *via* a Fischer indole formation. Cook and co-workers accessed this series[41] by means of a Larock heteroannulation.[42] The order of events is reversed from that in section 1.2.8.1, in that reaction with the Schöllkopf auxiliary occurs prior to indole formation (scheme 42). The formation of **131** in high *d.e.* is due in part to the choice of phosphonate leaving group.[40] The Larock heteroannulation has been carried out on a 300 g scale.



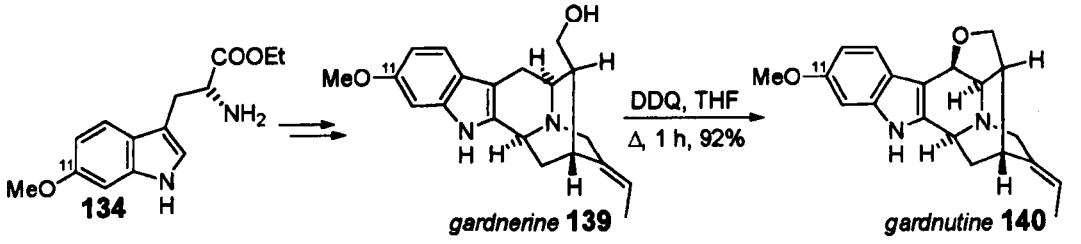

**Scheme 42:** *11-Methoxy analogues of D-tryptophan ethyl ester*

Both N1-methyl and N1-unsubstituted amino acids are easily accessible by this method. Once again, Cook's previously developed methodology was viable with these C11-oxygenated amino acids (scheme 43): (+)-16-*epi*-*N*-methylgardneral **137** was synthesised (35% from C11-methoxy, N1-methyl D-tryptophan ethyl ester **135**) as per *N*-methylvellosimine **94** (section 1.2.6, **137** is simply the C11-methoxy analogue of **94**). Reduction of **137** gave 11-methoxyaffinisine **138** (32% from **91**). Note that **137** and **138** have not been isolated from a natural source to date; they are precursors of natural products discussed in section 1.2.11 and 1.2.12.




**Scheme 43:** *C11-Methoxy indole bases*

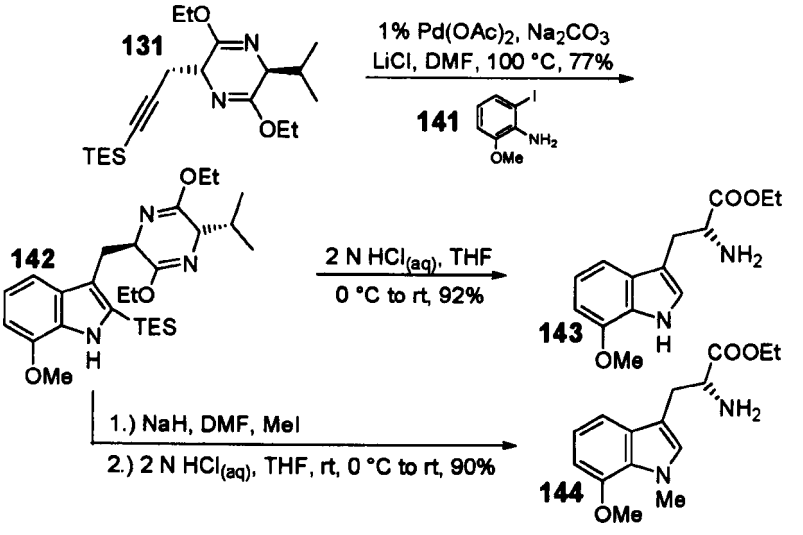
(–)-Gardnerine **139** and (+)-gardnutine **140** are N1-unsubstituted C11-methoxy sarpagine alkaloids synthesised from C11-methoxy D-tryptophan ethyl ester **134** by Cook and co-workers[43] in a manner analogous to that for 16-*epi*-normacusine B **99** (section 1.2.6, **139** is simply the 11-methoxy analogue of **99**). (–)-Gardnerine **139** was synthesised in 20% overall yield from **134**. (+)-Gardnutine **140** was synthesised from **139** by DDQ-mediated α-aryl oxidation (18% overall yield from **134**).




**Scheme 44:** *C11-Methoxy sarpagine alkaloids*

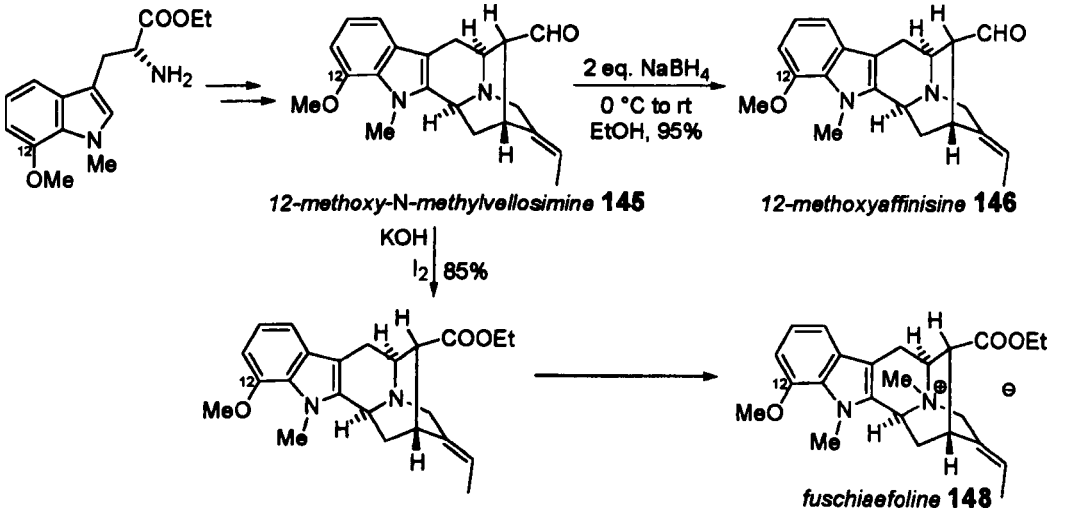
## 1.2.8.3 C12 Oxygenation – Fuchsiaefoline, 12-Methoxyaffinisine and 12-Methoxy-*N*-methylvellosimine

The required C12-methoxy amino acids were prepared by the same process used for the C11-methoxy series (namely a Larock heteroannulation), employing a regioisomeric iodoanisidine (scheme 45).




**Scheme 45:** *12-Methoxy analogues of D-tryptophan ethyl ester*

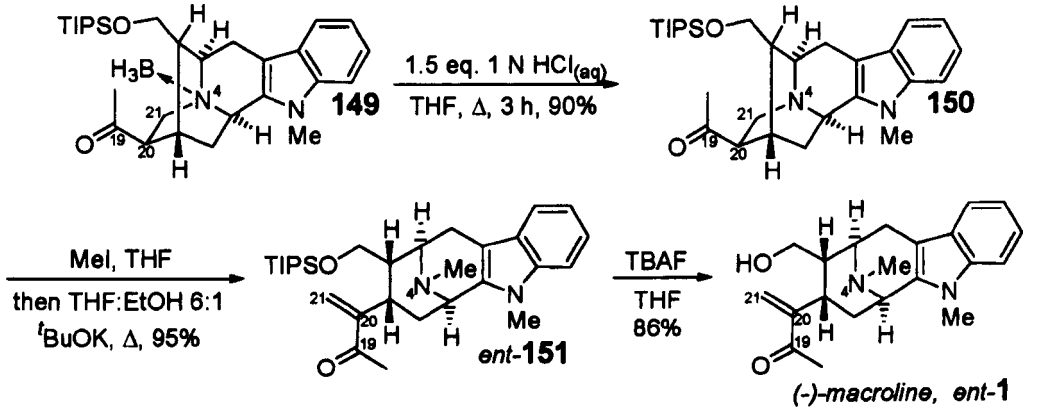
The C12-methoxy amino acids were compatible with Cook's previously developed methodology, thus permitting the synthesis of (+)-12-methoxy-*N*-methylvellosimine **145** (overall yield 40% from **144**) and (+)-12-methoxyaffinisine **146** (overall yield 38% from **144**) as per the unsubstituted analogues **85** and **97**. The quaternary alkaloid (–)-fuschiaefoline **148** was synthesised (27% overall yield from **144**) in two steps from **145** (scheme 46).




**Scheme 46:** *C12-Methoxy sarpagine alkaloids*

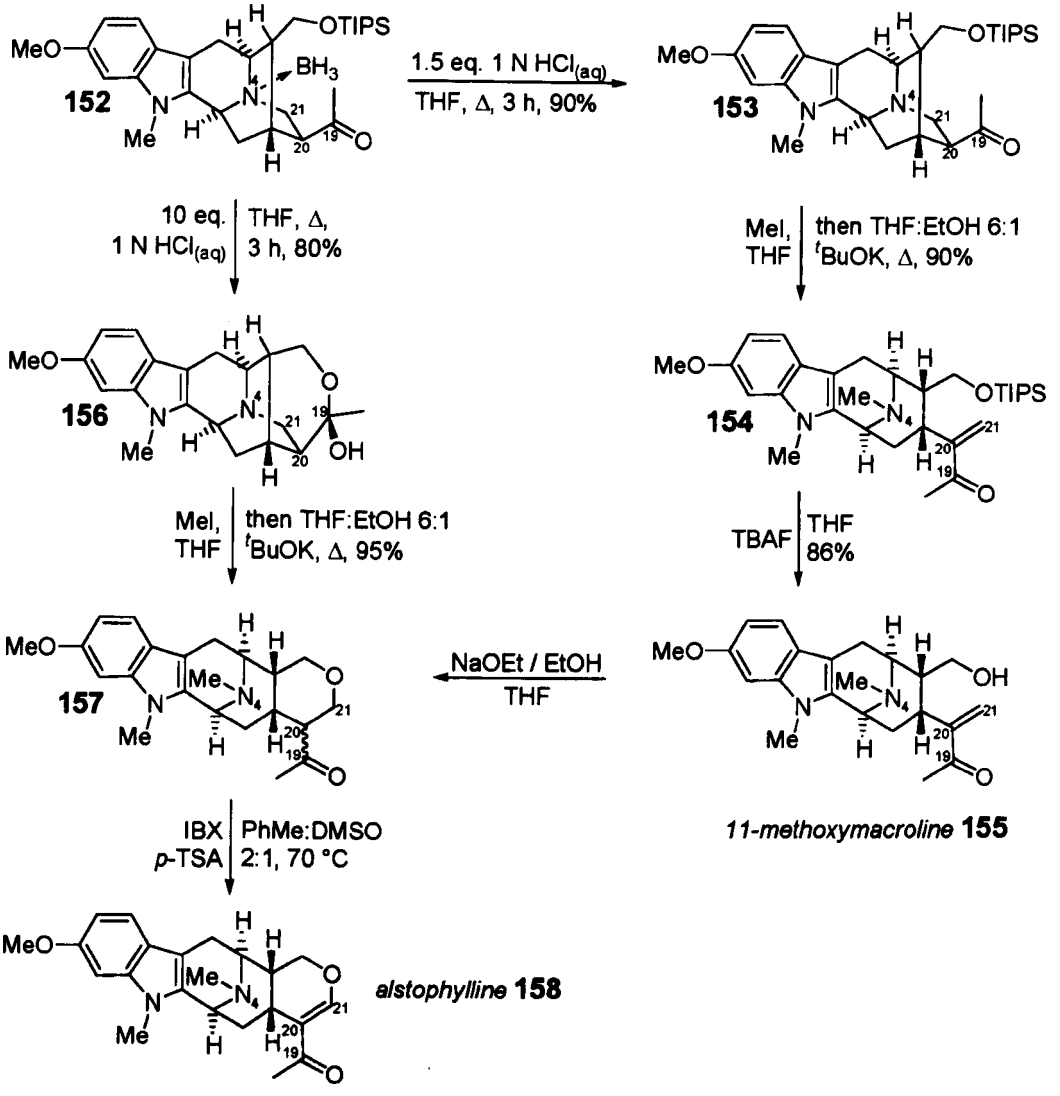
*1.2.9 Hofmann Elimination – Alstophylline, 6-Oxoalstophylline, ent-Macroline, 11-Methoxymacroline, Macralstonine*

As mentioned in the introduction, the macroline skeleton may be accessed by Hofmann elimination of the sarpagine skeleton, a transformation used by Cook to synthesise many macroline alkaloids. For example,[44] starting from L-tryptophan, Cook *et al.* synthesised **149**, the enantiomer of the C19-oxo borane adduct from the synthesis of trinervine (section 1.2.7). Whereas in the trinervine synthesis *ent*-**149** was treated with excess acid to effect both dative bond scission and desilylation, in this instance **149** was treated with a small excess of acid, removing the borane but leaving the silyl group intact to give **150**. N4 was quaternised with methyl iodide, then under basic conditions Hofmann elimination occurred with regiospecific N4-C21 bond scission to give *O*-silylated macroline derivative *ent*-**151**. This was stable upon storage, or could be deprotected to give reactive (–)-macroline, *ent*-**1**, 12% overall yield from L-tryptophan methyl ester (intended for use in the synthesis of mismatched bis(indole) alkaloid analogues).



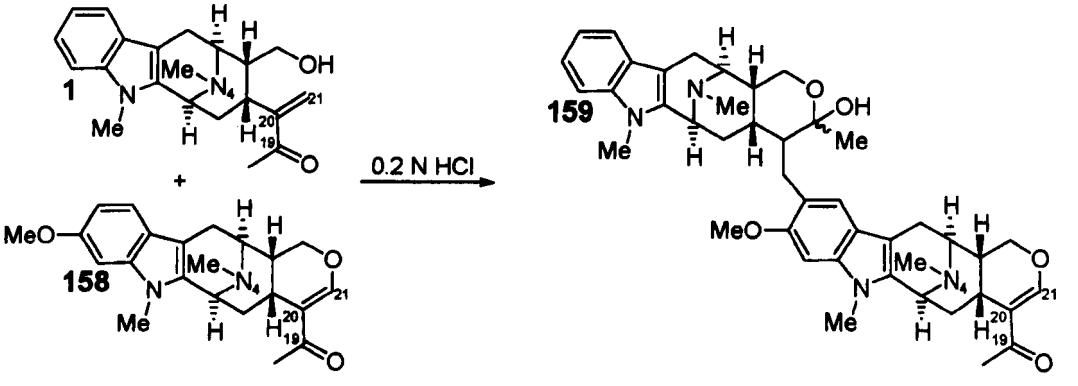

**Scheme 47:** *Synthesis of* ent-*macroline and a stable precursor*

11-Methoxymacroline **155** was synthesised[41] by an entirely analogous route from the (naturally configured) 11-methoxy amino acid ester **134** (detailed in section 1.2.8.2) in 14% overall yield. (–)-Alstophylline **158** (the 11-methoxy analogue of alstonerine **44**) was also synthesised by this route[41] – in this case two possible pathways were available, only one of which utilised 11-methoxymacroline **155** as an intermediate (scheme 48). The final step in the synthesis of (–)-alstophylline **158** is an IBX-mediated oxidation. Note that yields are not quoted for all steps (preliminary communication).




**Scheme 48:** *Synthesis of alstophylline by two possible pathways*

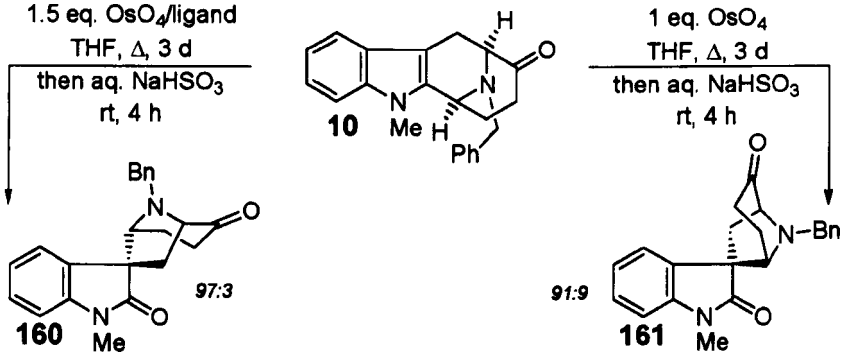
The bis(indole) alkaloid macralstonine **159** was synthesised by the protocol of LeQuesne and Cook[45] from macroline and alstophylline monomer units (scheme 49).




**Scheme 49:** *Synthesis of macralstonine*

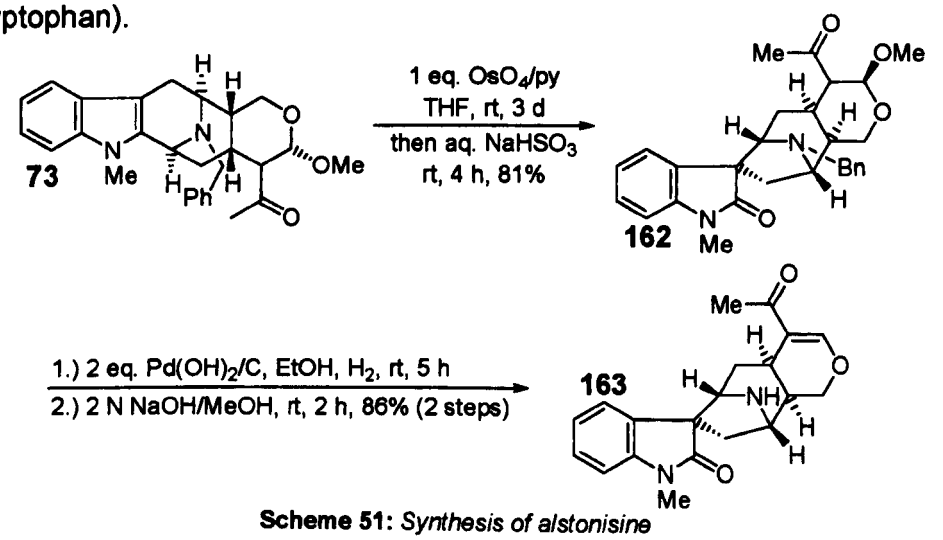
## *1.2.10 Diastereospecific Oxindole Formation – Alstonisine*

Brief consideration will be given to Cook's synthesis of the macroline-related oxindole (+)-alstonisine **163**. Oxindoles may be formed from the corresponding indoles by C2-C7 oxidation, with rearrangement to the C7-spirocyclic skeleton in the case of tetrahydro-β-carbolines. Model studies performed by Cook[46] on the tetracyclic ketone **10** (scheme 50) led to the discovery that if osmium tetroxide were used as oxidant, a particular diastereoisomer could be favoured by the presence or absence of a Sharpless ligand (quinuclidine, DHQ-CLB, DHQD-CLB, $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ were used).




**Scheme 50:** *Model studies on oxindole formation with the tetracyclic ketone*

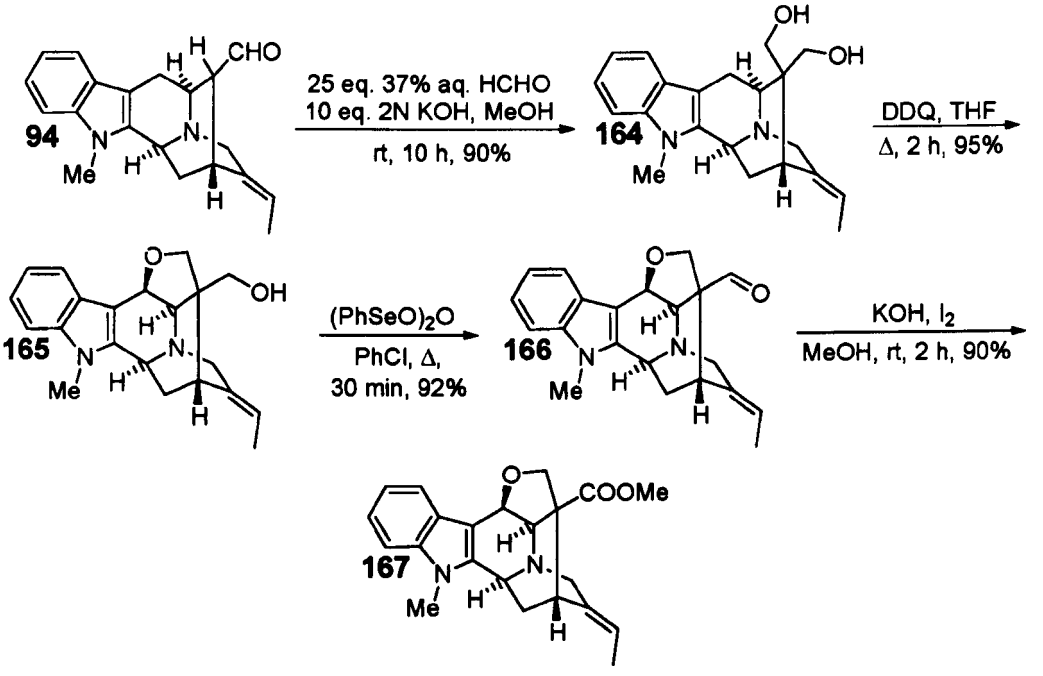
Cook applied the findings from the model studies to the synthesis[47] of (+)-alstonisine. Acetal **73** (a late-stage intermediate from the second generation synthesis of (–)-alstonerine, detailed in section 1.2.4) was oxidised diastereoselectively to furnish oxindole **162** as the sole diastereoisomer. Cook proposes that coordination of the N4 lone-pair to the osmium enhances the selectivity. N4-Debenzylation was followed by elimination to form the vinylogous ester product (+)-alstonisine **163** (12% overall yield from D-tryptophan).




**Scheme 51:** *Synthesis of alstonisine*

### *1.2.11 Tollens Reaction – Dehydrovoachalotine, 11-Methoxy-17-epi-vincamajine and Vincamajinine*

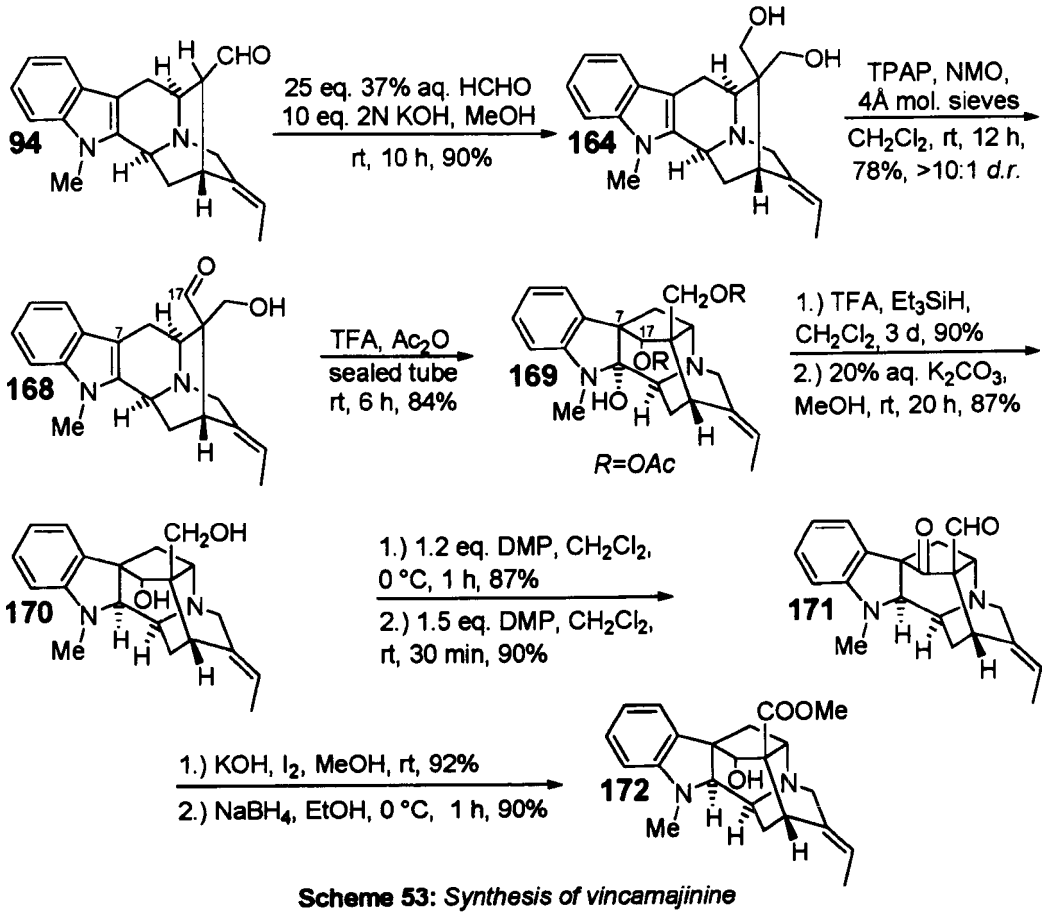
Various sarpagine/ajmaline-related alkaloids are known which have a quaternary C16 motif. To access this substitution pattern from tertiary C16 species such as those dealt with in sections 1.2.6-1.2.8, Cook *et al.* employed the Tollens reaction. For example, in the synthesis[48,49] of (+)-dehydrovoachalotine **167**, *N*-methylvellosimine **94** was transformed into the 1,3-diol **164** in a yield of up to 90% after optimisation (scheme 52). DDQ-mediated α-aryl oxidation was high-yielding as before, but oxidation of the neopentyl hydroxyl group proved problematic; eventually it was found that a selenium-mediated oxidation furnished the aldehyde, which in turn could be oxidised to (+)-dehydrovoachalotine **167** (21% overall yield from D-tryptophan).




**Scheme 52:** *Synthesis of dehydrovoachalotine*

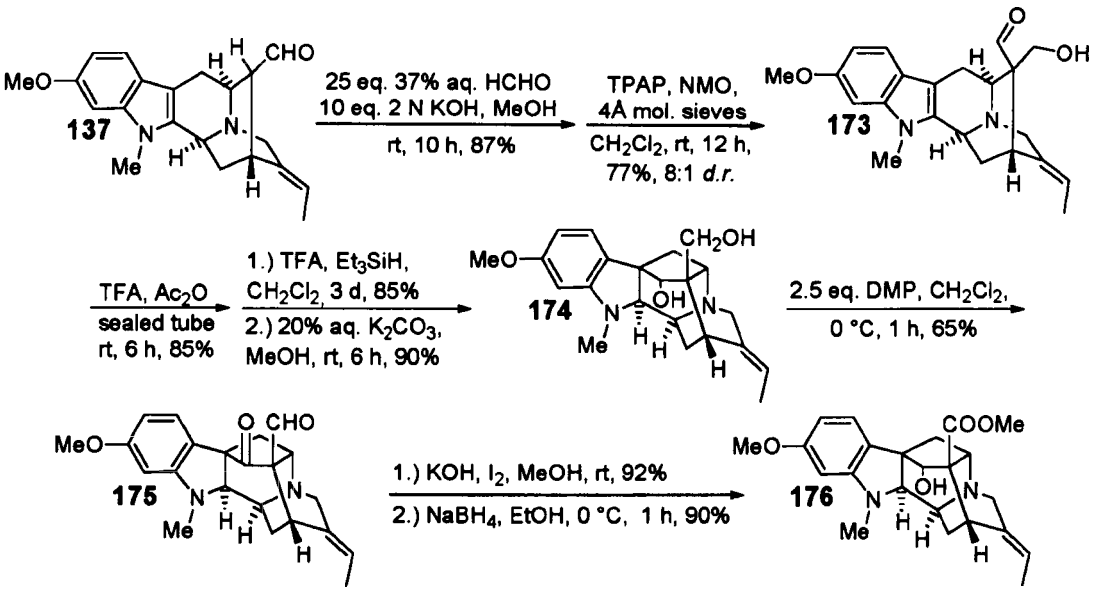
The Tollens reaction was also used by Cook and co-workers in their syntheses[49,50] of (–)-vincamajinine **172**, and (–)-11-methoxy-17-*epi*-vincamajine **176**. The synthesis of **172** (scheme 53) also commenced with the transformation of *N*-methylvellosimine into the 1,3-diol **164**. To enable cyclisation to the ajmaline skeleton, a selective oxidation to a β-hydroxyaldehyde was needed. In the event, TPAP was able to selectively oxidise the less hindered hydroxymethyl group with diastereoselectivity >10:1.

Treatment of **168** with trifluoroacetic acid and acetic anhydride in a sealed tube effected the C7-C17 cyclisation, then the unwanted C2-hydroxyl was reduced. Completion of the synthesis of **172** required several sequential oxidations and reductions – all attempts to combine these steps resulted in a dramatic drop in yield. (–)-Vincamajinine **172** was obtained in 12% overall yield from D-tryptophan methyl ester.




**Scheme 53:** *Synthesis of vincamajinine*

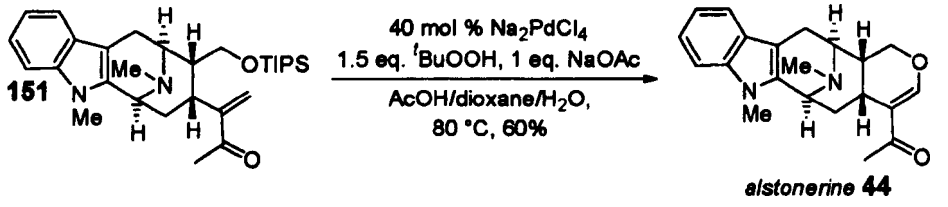
The synthesis of (–)-11-methoxy-17-*epi*-vincamajine **176** (scheme 54) was broadly similar to that of **172**, except that a ring-oxygenated precursor (*N*-methyl-16-*epi*-gardneral **137**) was employed. The Tollens reaction has been shown to be compatible with both C10 and C11 oxygenation.[48] (–)-11-Methoxy-17-*epi*-vincamajine **176** was obtained in an overall yield of 8% from 10-methoxy D-tryptophan ethyl ester **123**. Cook has also prepared[49] related compounds such as quebranchidine diol, epimeric at C17.




**Scheme 54:** *Synthesis of 11-methoxy-17-epi-vincamajine*

## *1.2.12 Modified Wacker Oxidation – Alstophylline, 6-Oxoalstophylline, Alstonerine and Macralstonine*

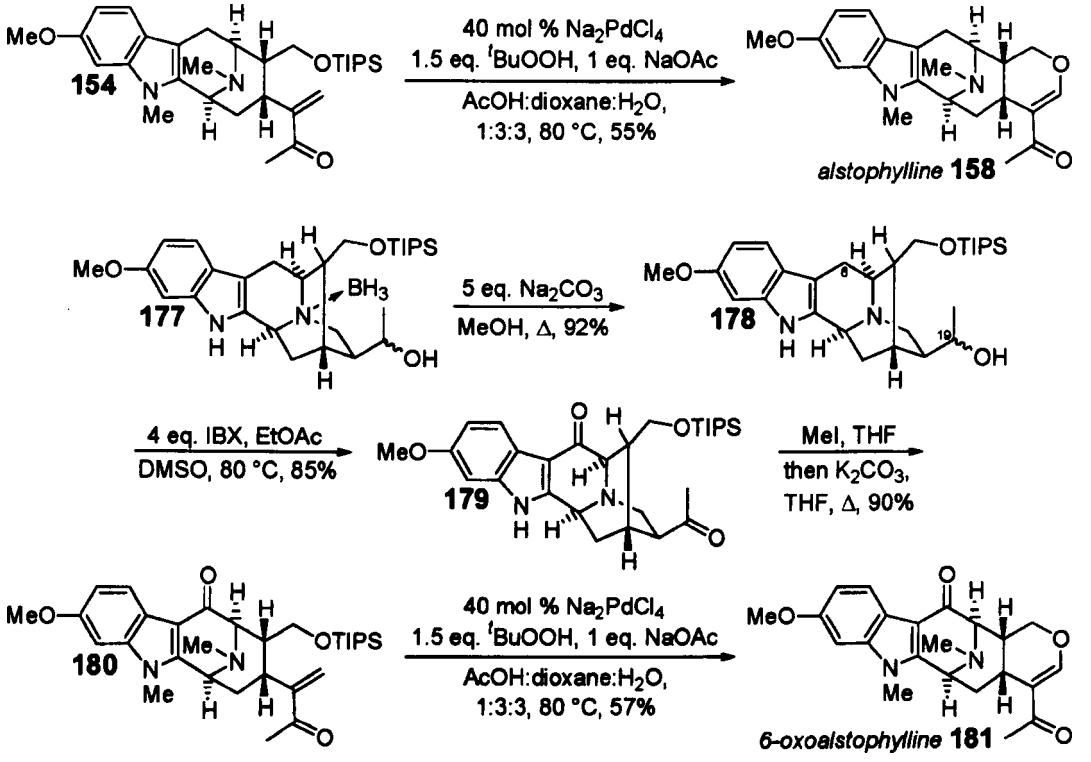
Cook has recently reported[51] the use of a modified Wacker protocol[52] to improve on the previous syntheses of the above-named alkaloids. For example, in the third generation synthesis of (–)-alstonerine, silylated macroline equivalent **151** (described in section 1.2.9) undergoes deprotection and oxidative cyclisation directly to (–)-alstonerine **44** in a palladium-catalysed process employing $^t$BuOOH as oxidant (scheme 55). The yield of 60% is the result of optimisation work.




**Scheme 55:** *Third generation synthesis of alstonerine*

(–)-Alstonerine **44** was synthesised in 9% overall yield from D-tryptophan methyl ester. In a second generation synthesis of (–)-alstophylline **158** (scheme 56) the same protocol was applied to the corresponding 11-methoxymacroline equivalent, affording **158** directly in 55% yield. (–)-Alstophylline **158** was obtained in 9% overall yield from 11-methoxy amino

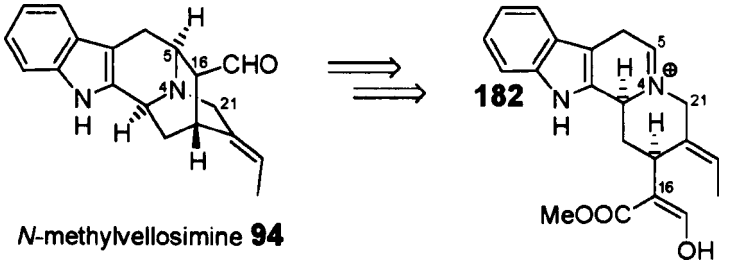
acid ester **135**. This improved synthesis of (–)-alstophylline also constituted a second generation synthesis of macralstonine **159** (*c.f.* section 1.2.9). Finally, to effect the first total synthesis of (+)-6-oxoalstophylline **181**, silylated sarpagan borane adduct **177** underwent N4-B bond scission and was then oxidised[53] with excess IBX to effect not only C19 but also C6 ketone formation. Tertiary amine **179** underwent Hofmann elimination as expected and the modified Wacker protocol furnished (+)-6-oxoalstophylline in 10% overall yield from 11-methoxy amino acid ester **135**. The mechanism of the modified Wacker oxidation has not yet been fully elucidated.




**Scheme 56:** *Syntheses of alstophylline and 6-oxoalstophylline by modified Wacker procedure*

## 1.3 Martin's Biomimetic Synthesis of (+)-*N*-Methylvellosimine

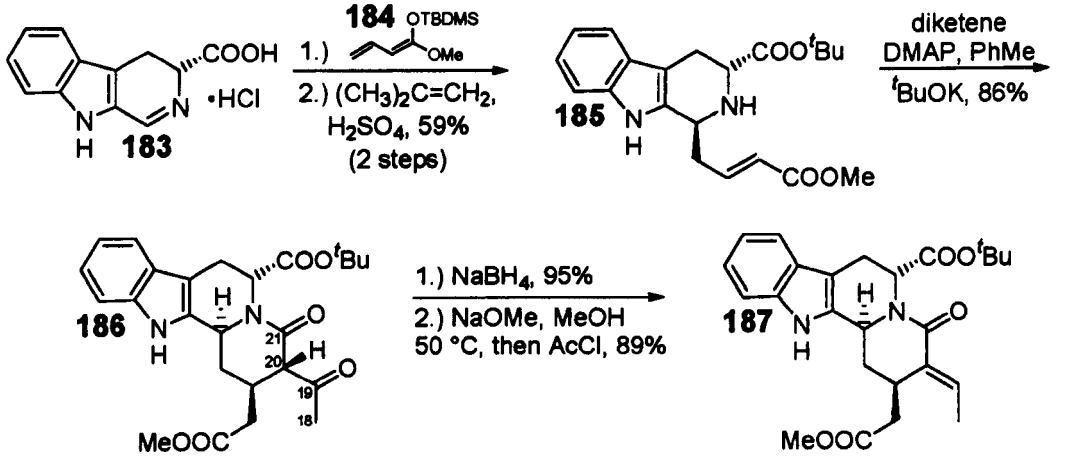
Martin *et al.* have reported[54] an enantiospecific total synthesis of *N*-methylvellosimine **94**, which differs fundamentally from that of Cook in that formation of the C5-C16 bond is the final C-C bond-forming event (scheme 57).




*N*-methylvellosimine **94**

**Scheme 57:** *Proposed key intramolecular Mannich reaction*

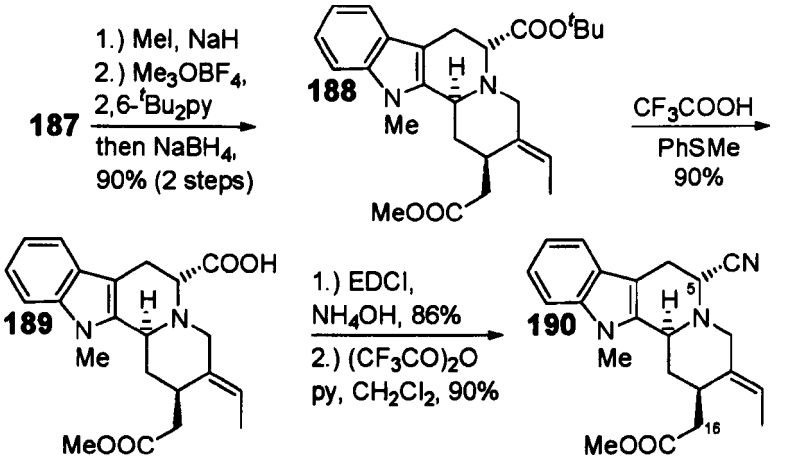
That such a reaction might occur in the biosynthesis of **94** was first proposed by van Tamelen,[55] a proposition supported by the subsequent report[56] of a biogenetic-type synthesis of ajmaline involving just such a transformation. Later Lounasmaa *et al.* attempted the cyclisation of similar iminium ions, but with no success.[57] This led him to propose an alternative biosynthetic pathway for formation of the sarpagan skeleton, with C5-C16 bond formation as the *penultimate* skeletal bond-forming transformation and N4-C21 bond formation as the final cyclisation. Partly to discern which pathway was most likely to operate, Martin and co-workers undertook the synthesis outlined below.




**Scheme 58:** *Formation of tetracyclic skeleton in Martin's synthesis of* N*-methylvellosimine*

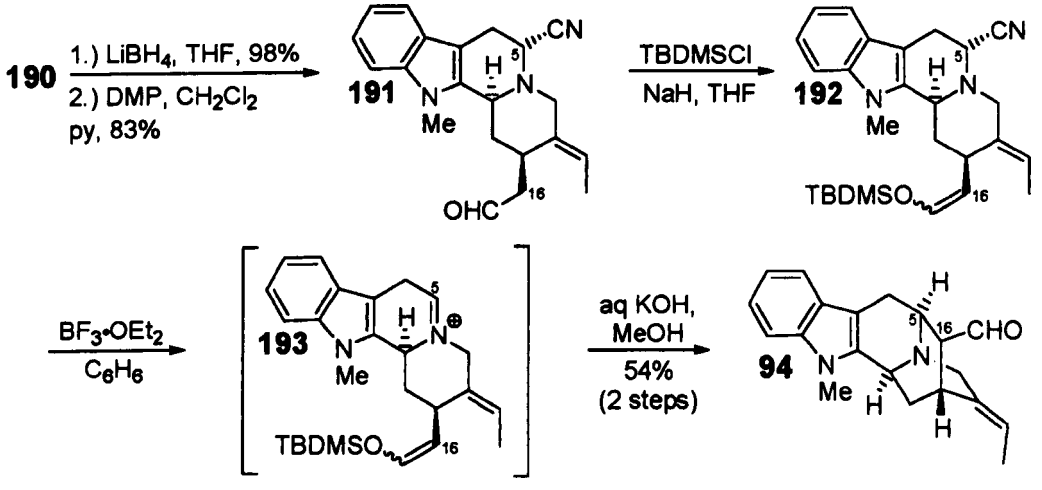
Martin's synthesis (scheme 58) commenced with the vinylogous Mannich reaction of dihydro-β-carboline **183** (derived from D-tryptophan and formic acid in 60% yield) with silyl ketene acetal **184** to give tetrahydro-ß-carboline **185**

with total diastereoselectivity. Introduction of the 4-carbon C18-21 fragment with diketene (and concomitant cyclising Michael addition) gave tetracycle **186**. Stepwise borohydride reduction and elimination gave trisubstituted olefin **187** as a single geometric isomer. Amide reduction, N1-methylation and selective ester hydrolysis gave the potential iminium precursor **189**. It was decided to employ an α-aminonitrile as the actual iminium precursor as these were known to furnish the corresponding iminium ions under mild conditions. α-Aminonitrile **190** was thus synthesised by introduction of an amide at the C5 position and its subsequent dehydration (scheme 59).




**Scheme 59:** *Formation of iminium precursor in Martin's synthesis of* N-*methylvellosimine*

α-Aminonitrile **190** was subjected to imine-generating conditions, but no C5-C16 cyclisation was observed. This was taken to mean that the ester was insufficiently activating and so it was converted into aldehyde **191**. This also was inert to cyclisation, but upon formation of the corresponding silyl enol ether **192** and treatment with $BF_3{\cdot}OEt_2$, cyclisation to the sarpagan skeleton was observed.

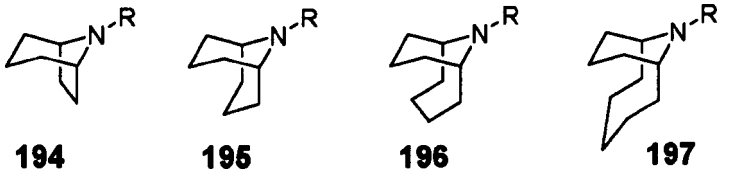



**Scheme 60:** *Successful cyclisation in Martin's synthesis of* N-*methylvellosimine*

The target was obtained as an epimeric mixture (7:3 (+)-*N*-methylvellosimine: (+)-16-*epi*-*N*-methylvellosimine). As the desired natural epimer is the more thermodynamically stable, conversion to pure **94** was achieved by exposure of the mixture to aqueous KOH in MeOH. This elegant synthesis (15 steps from D-tryptophan, 7% overall yield) provides significant evidence for the feasibility of van Tamelen's original biogenetic pathway. Furthermore, it points to the possibility that the total synthesis of other sarpagine/ajmaline alkaloids might be viable *via* such an iminium-induced cyclisation.

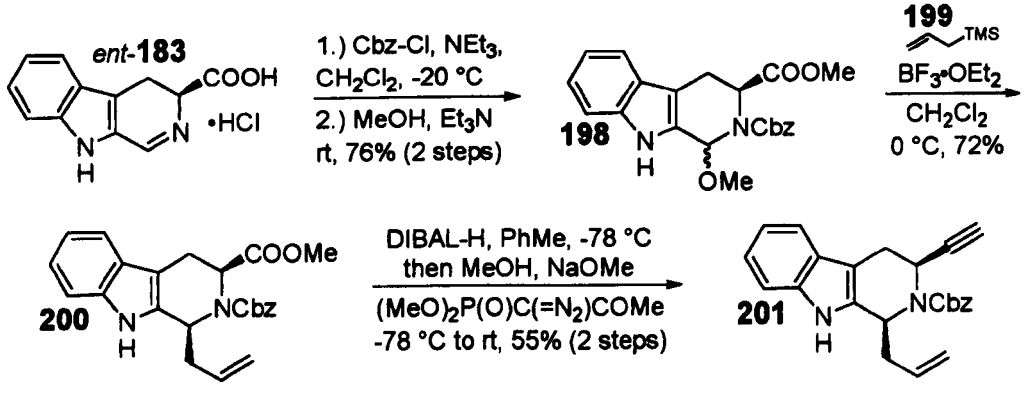
## 1.4 Martin's Olefin Metathesis Route to Azabicyclo[3.3.1]nonenes

Martin *et al.* have conducted an extensive study[58] on olefin metathesis as a method of accessing various azabicyclo[m.n.1] structures (m = 3-5, n = 2-3, with the nitrogen in the 1-atom bridge). Such structural motifs are common in alkaloids (scheme 61).




**Scheme 61:** *Azabicyclo[m.n.1] structures*

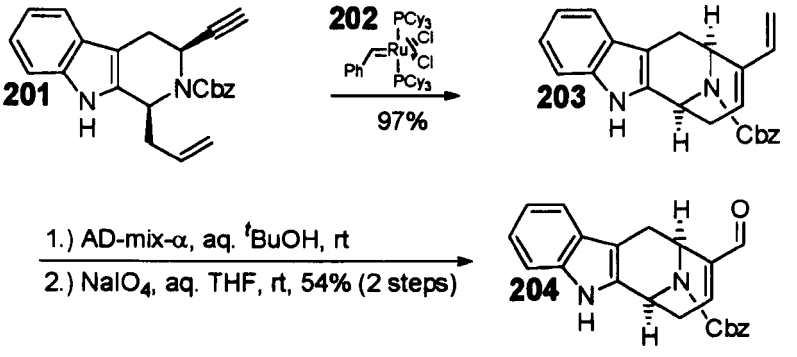
An indole-annulated azabicyclo[3.3.1] structure constitutes the tetracyclic skeleton of the macroline/sarpagine/ajmaline alkaloids and Martin and co-workers have been able to access this skeleton as shown in scheme 62.




**Scheme 62:** *Formation of enyne metathesis substrate*

Starting this time from L-tryptophan, the dihydro-β-carboline *ent*-**183** (accessed in 63% yield) was *N*-protected before aminal formation with *in situ*

esterification. This diastereoisomeric mixture was treated with allyltrimethylsilane **199** and boron trifluoride etherate to afford C3,C5-*cis* tetrahydro-β-carboline **200** in a 5.5:1 diastereoisomeric ratio. The ester was then selectively reduced and the aldehyde reacted with the diazophosphonate shown to afford the alkyne in a one-pot procedure. This alkyne **201** underwent enyne metathesis (scheme 63) with Grubbs' 1st generation catalyst **202** to give tetracyclic diene **203** in essentially quantitative yield. The monosubstituted olefin of this diene was then selectively cleaved with AD-mix and $NaIO_4$ to give α,β-unsaturated aldehyde **204**.

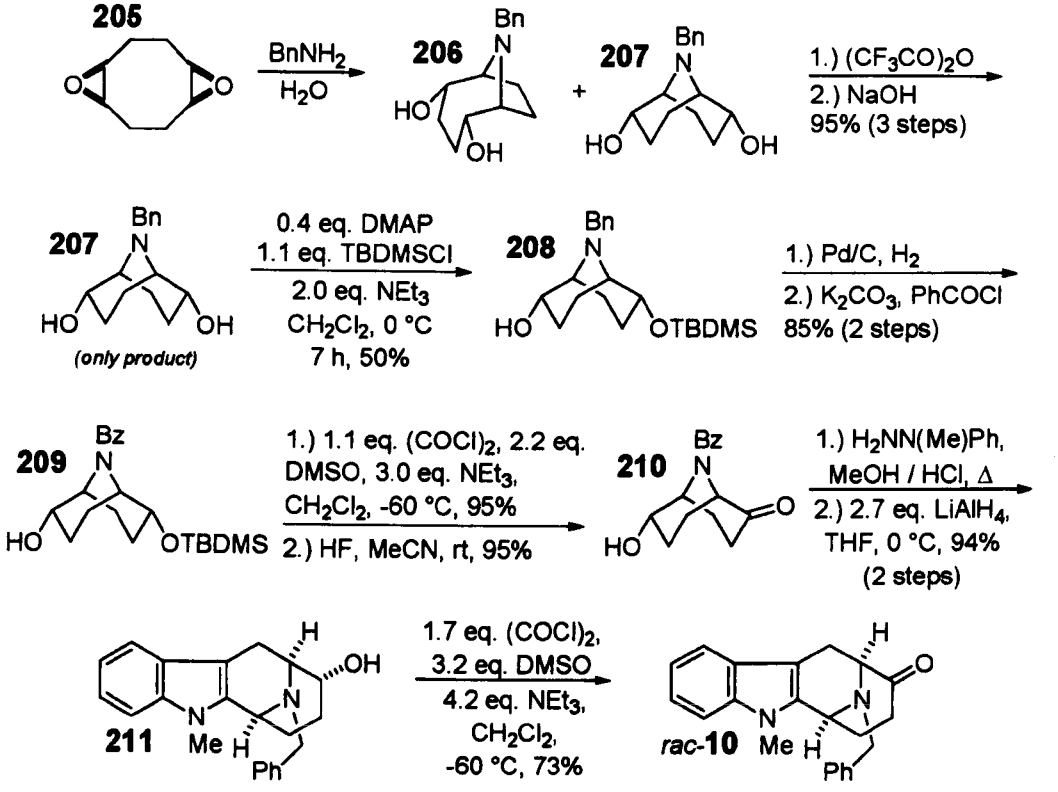



**Scheme 63:** *Formation of α,β-unsaturated aldehyde*

The α,β-unsaturated aldehyde **204** (9 steps from L-tryptophan, 10% overall yield) is a differentially protected form of an advanced intermediate reported by Cook in the enantiospecific syntheses of macroline/sarpagine/ajmaline alkaloids, as detailed in section 1.2. As such this report from Martin constitutes a useful alternative approach to these natural products, starting as it does from L-tryptophan (approximately ⅓ the cost of D-tryptophan, Cook's starting material).

## 1.5 Rassat's Synthesis of the Tetracyclic Ketone

In 2000, Rassat and co-workers reported[59] a synthesis of Cook's tetracyclic ketone intermediate **10** (summarized in scheme 64). The crucial strategic difference in this approach is that formation of the [3.3.1]bicyclic skeleton occurs prior to the introduction of an indole.

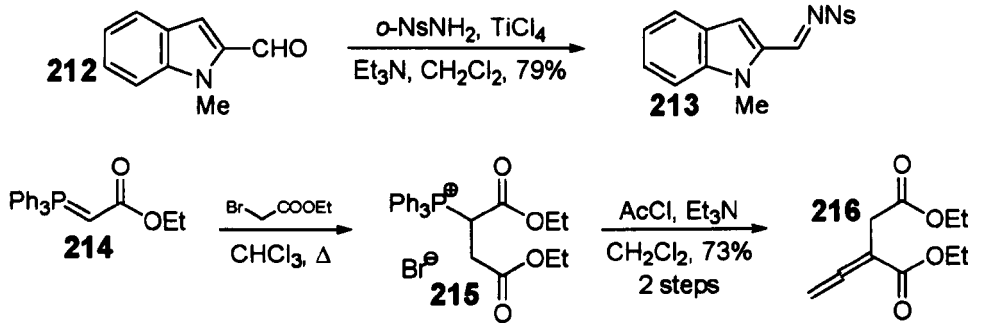



**Scheme 64:** *Rassat's route to Cook's intermediate* ***rac*-10**

Transannular cyclisation of the bis(epoxide) starting material **205** with benzylamine led to a regioisomeric mixture of bicyclic structures. The unwanted [4.2.1]bicycle **206** may be converted to the desired [3.3.1]bicycle **207** under conditions of trifluoroacetate formation and subsequent hydrolysis. Selective monoprotection of the resultant diol was followed by a protecting group swap. Oxidation to the ketone and deprotection of the other hydroxyl functionality led to the precursor **210** for Fischer indole synthesis of the tetracyclic core. This was effected in good yield with *N*-methyl-*N*-phenylhydrazine in acidic methanol at reflux overnight. Reduction regenerates the original *N*-benzyl protecting group and oxidation affords the racemate of Cook's intermediate **10** in 11 steps and 25% overall yield.

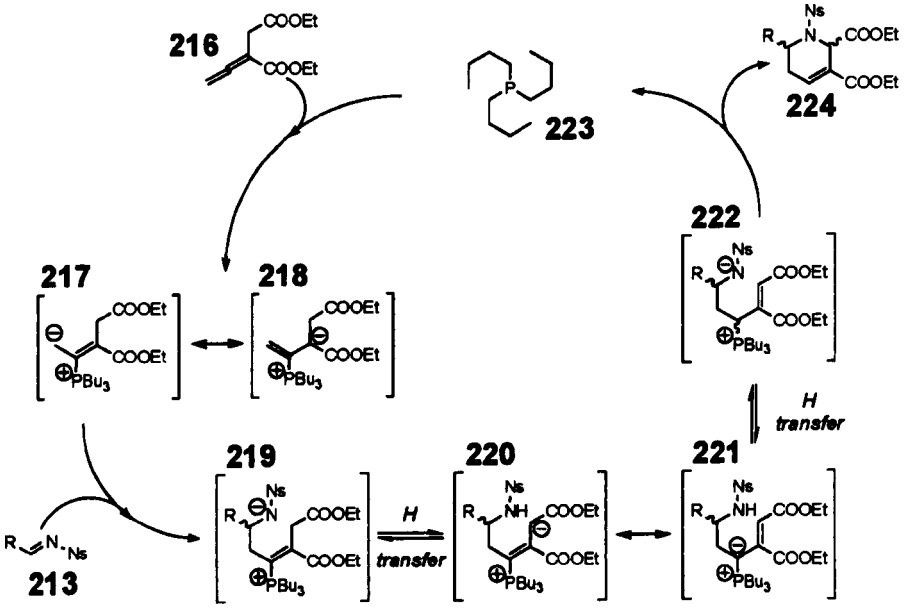
## 1.6 Kwon's Formal Syntheses of (±)-Alstonerine and (±)-Macroline

Kwon and co-workers' formal syntheses[60] arose from their interest in phosphine-catalysed [4+2] annulations.[61] This key reaction occurred between an indolyl imine dienophile **213** and a diene synthetic equivalent, the allenyl diester **216**. The synthesis of these two coupling partners is shown in scheme 65.




**Scheme 65:** *Formation of cyclisation precursors*

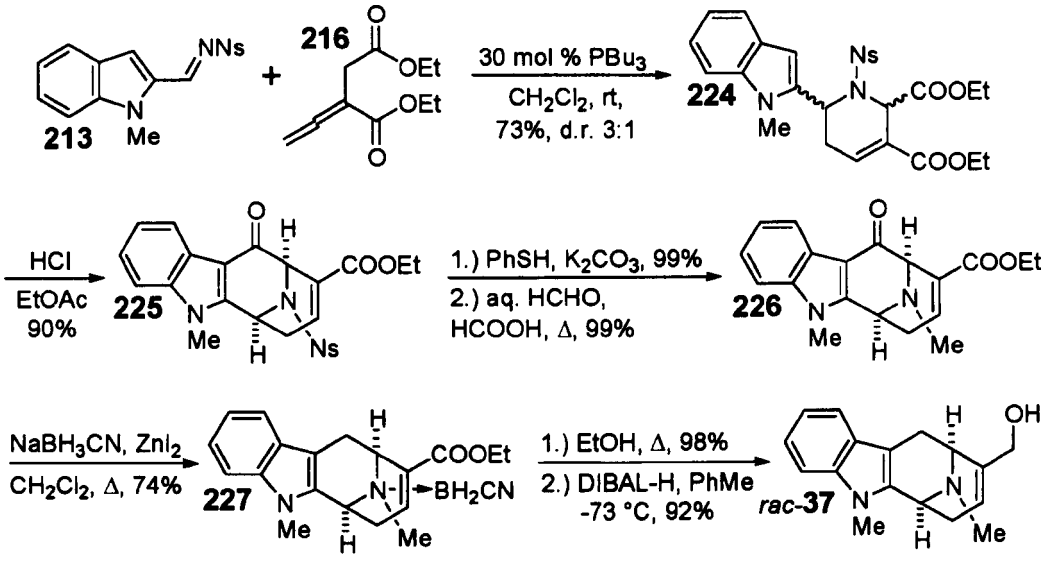
The cyclisation of **213** and **216** proceeded in 73% yield to give **224** as a 3:1 mixture of diastereoisomers. The proposed mechanism is shown in scheme 66.




**Scheme 66:** *Proposed mechanistic cycle for phosphine-catalysed annulation*

Under acidic conditions the [4+2] product **224** underwent an intramolecular Friedel–Crafts acylation (scheme 67) to give the tetracyclic macroline skeleton **225**. Thiolate-mediated N4-deprotection and subsequent Eschweiler–Clarke

N4-methylation both proceeded in essentially quantitative yield. $NaBH_4$ and $ZnI_2$ effected benzylic ketone reduction (along with formation of the N4-borane adduct shown; this was removed by heating to reflux in EtOH). DIBAL-H ester reduction gave tetracyclic allyl alcohol *rac*-**23**.

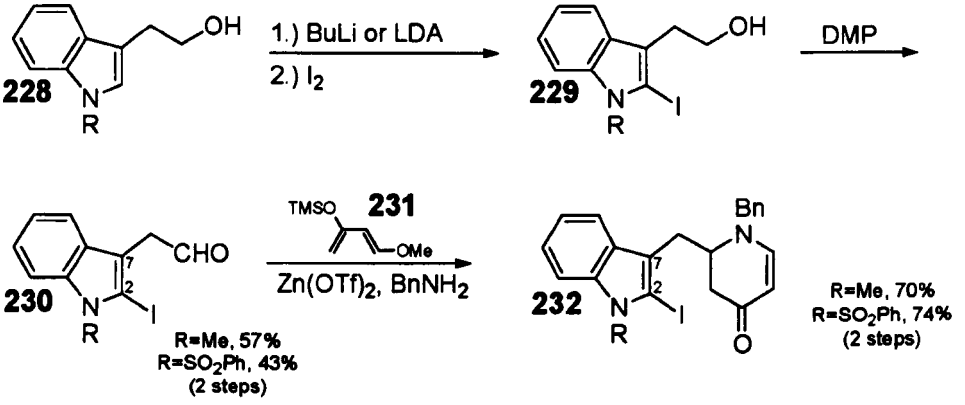



**Scheme 67:** *Synthesis of tetracyclic allyl alcohol*

*Racemic* alcohol *rac*-**37** (10 steps, 31% overall yield, longest linear sequence) is an advanced intermediate in Cook's syntheses of alstonerine **44** and macroline **1** (see sections 1.2.2 and 1.2.9).

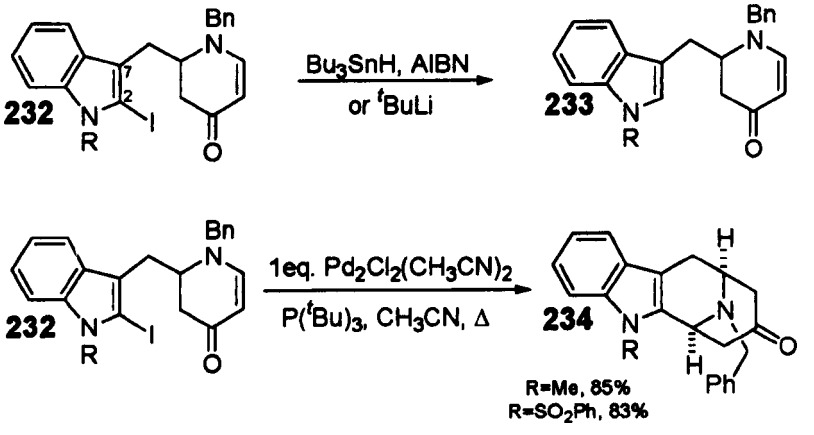
## 1.7 Kuethe's Aza-Diels–Alder / Intramolecular Heck Approach

Kuethe and co-workers[62] have also adopted a [4+2] annulation strategy for construction of the tetracyclic macroline core. Adapting the work of Waldmann,[63] they employed Danishefsky's diene **231** with an imine **230** whose connectivity was different to that used by Martin, in that it was derived from an indole substituted at the C7-position, not the C2-position. The cyclisation is shown in scheme 68.




**Scheme 68:** *Aza-Diels-Alder reaction to give dihydropyridone Heck substrates*

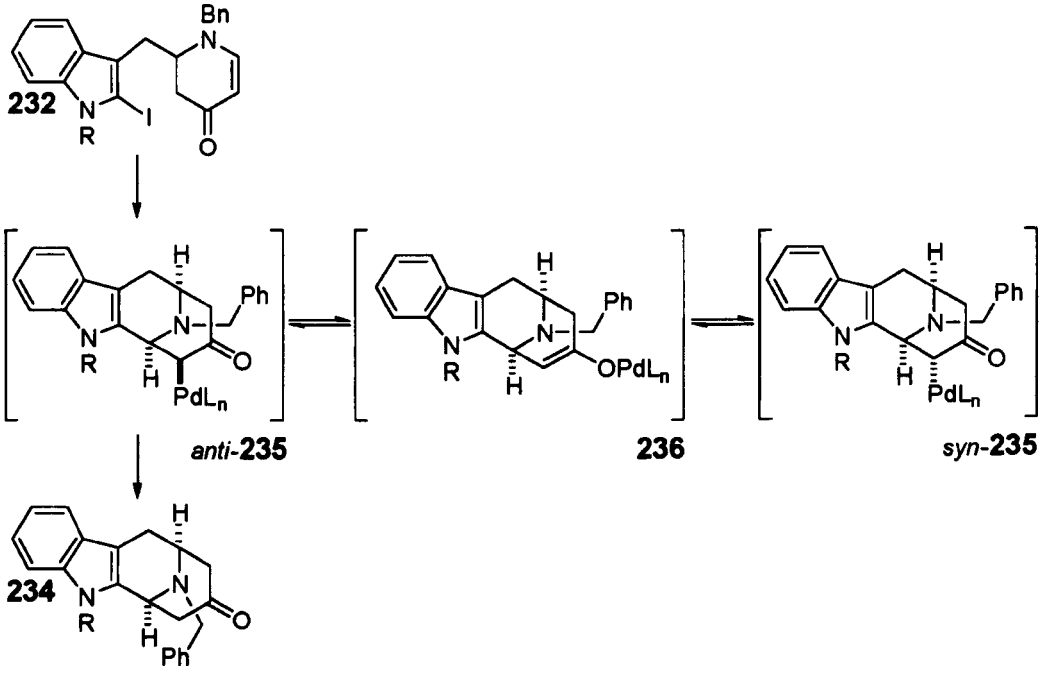
Kuethe's group then attempted the synthesis of the desired tetracyclic system under conditions of both transmetallation and radical initiation. In both instances, however, the substrate **232** was simply deiodinated at the indolyl 2-position. The desired cyclisation was eventually effected by use of palladium.




**Scheme 69:** *Successful and unsuccessful cyclisations*

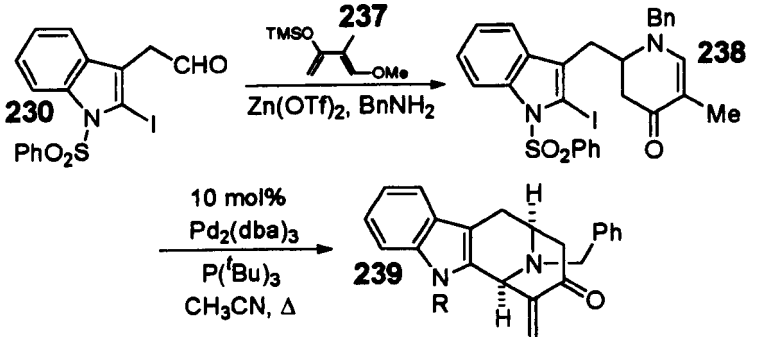
The reaction required stoichiometric amounts of Pd(II); rapid deposition of palladium black was observed during the course of the reaction. The inability

of the reaction to go to completion under catalytic Heck conditions is presumed to arise from the lack of an appropriate β-hydrogen for elimination. The proposed intermediate *anti*-**235** (scheme 70) has no β-hydrogen for *syn* elimination. Whilst isomerisation *via* a palladium enolate **236** is feasible,[64] *syn* elimination still does not occur, presumably since it would entail formation of a high-energy anti-Bredt bridgehead olefin.



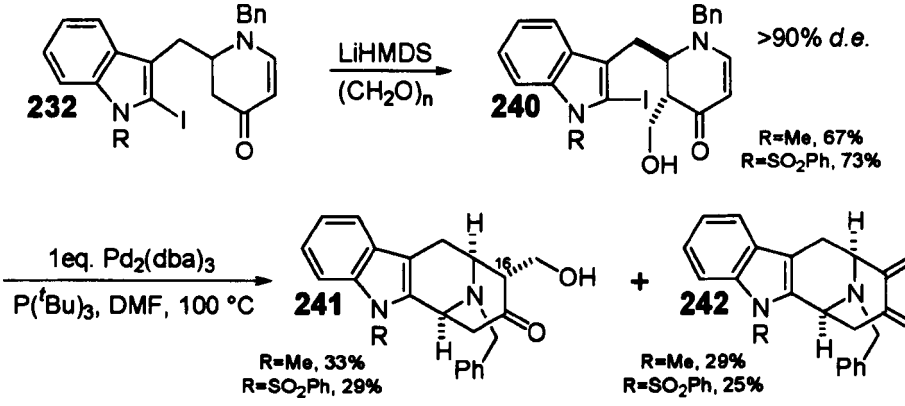

**Scheme 70:** *Lack of a suitable β-hydrogen impedes catalytic reaction*

Attempts at performing the catalytic Heck reaction under reductive conditions led only to isolation of the deiodinated by-products **233**. When a modified Heck substrate **238** that contained additional β-hydrogens was prepared, this smoothly underwent cyclisation with 10 mol% $Pd^0$ (scheme 71).



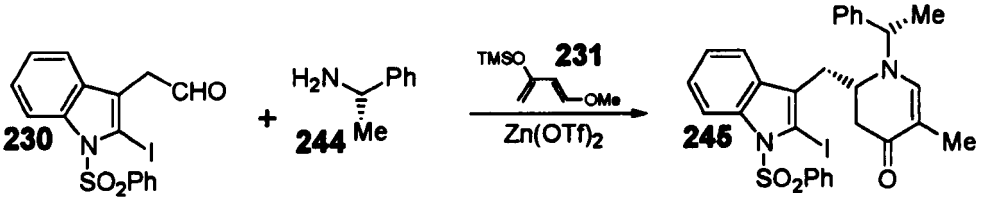

**Scheme 71:** *Catalytic Heck cyclisation is viable when additional β-hydrogens are present*

Many ajmaline/sarpagine alkaloids possess a hydroxymethyl group at the C16 position. In order to introduce such a moiety, **232** was hydroxymethylated prior to palladium cyclisation as before to give **241**. Notably, appreciable amounts of α,β-unsaturated ketone **242** were isolated also. This is proposed to arise by elimination from the palladium enolate of type **236**. Whilst the use of stoichiometric amounts of palladium has obvious disadvantages, this entry to the tetracyclic macroline skeleton is novel and reasonably succinct (e.g. *N*-methyl-**241**, 5 steps, 9% yield).



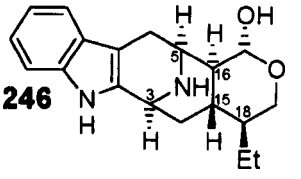

**Scheme 72:** *Presence of a hydroxymethyl group led to significant elimination*

Efforts are currently underway to induce asymmetry[65] in the aza-Diels–Alder cyclisation by use of a chiral amine for imine formation. For example use of (*S*)-α-methylbenzylamine **244** gave rise to dihydropyridone **245** in a diastereoisomeric ratio of 92:8 (scheme 73).




**Scheme 73:** *Asymmetric induction by use of chiral auxiliary / protecting group*

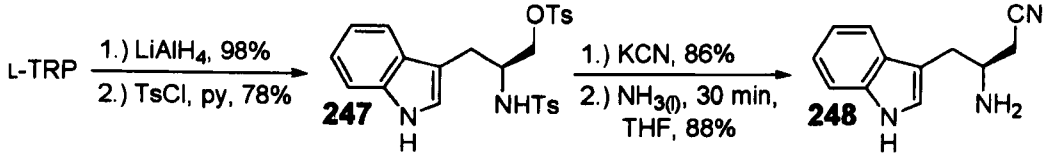
## 1.8 Bailey's Synthesis of (–)-Raumacline




**Scheme 74:** *(-)-Raumacline*

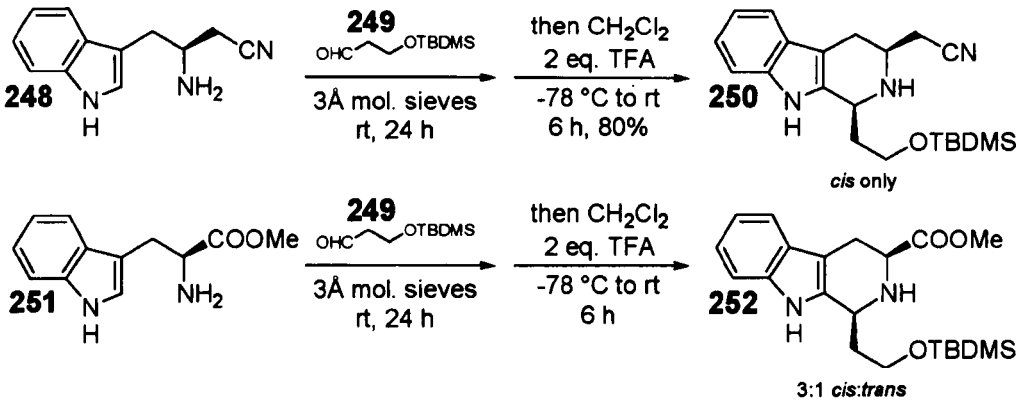
Like Cook, Bailey and co-workers have made extensive study of the Pictet–Spengler reaction and have utilised it in previously-reported syntheses of ajmaline and suaveoline[24] among others. Unlike Cook, Bailey's syntheses have as their core strategy the use of C3,C5-*cis* specific Pictet–Spengler reactions. This permits use of L-tryptophan to access various tetrahydro-β-carbolines having the correct configuration at C-3 and C-5. In contrast, Cook employs L-tryptophan in C3,C5-*trans* specific Pictet–Spengler reactions, followed by selective total epimerisation at C-5.

Bailey *et al.* employed cyanomethyltryptamine **248** as their Pictet–Spengler substrate.[66] It may be synthesised in 4 steps from the amino acid starting material on a large scale with no need for chromatography – the cyanosulfonamide made from **247** may be purified by crystallisation and the subsequent reductive desulfonylation has been optimised to provide pure **248**.



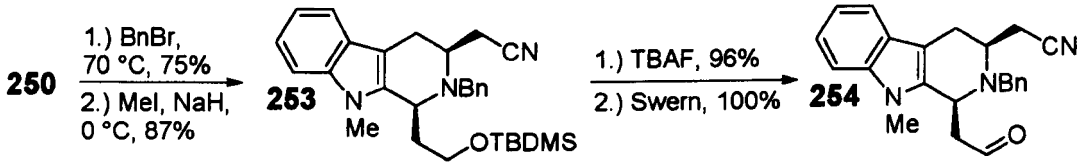

**Scheme 75:** *Synthesis of cyanomethyltryptamine in 4 steps*

Pictet–Spengler cyclisation of **248** with a protected β-hydroxyaldehyde **249** gave C3,C5-*cis* tetrahydro-β-carboline **250** entirely stereoselectively. The factors that influence the selectivity had previously been studied[67] and it had been shown that in general, only for reactions of aryl aldehydes with tryptophan allyl ester was total C3,C5-*cis* selectivity observed. A C-3 aryl substituent would not have been synthetically useful in the context of raumacline, however. A two-carbon masked aldehyde equivalent was required at the C-3 position, and the use of the silylated alcohol in conjunction with the cyanomethyl group is both synthetically useful and *cis*-specific. Such a choice of substituents likely arose from extensive optimisation; for example cyclisation of the same aldehyde **249** with L-tryptophan methyl ester **251** gave **252** with only 3:1 *cis*-selectivity (scheme 76).



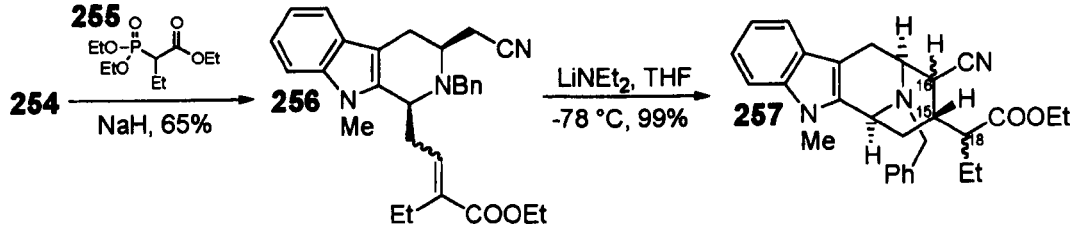

**Scheme 76:** *Specific choice of indolyl amine and aldehyde is necessary for selecvitiy*

Once formed, tetrahydro-β-carboline **250** was N4-benzylated and N1-methylated without complication. It is probably significant that the Pictet–Spengler reaction was performed on the N1,N4-unsubstituted system; Cook has observed that an N4-benzyl substituent (or any bulky substituent) enhances C3,C5-*trans* selectivity in the cyclisation. Hydroxyl deprotection and oxidation were routine.



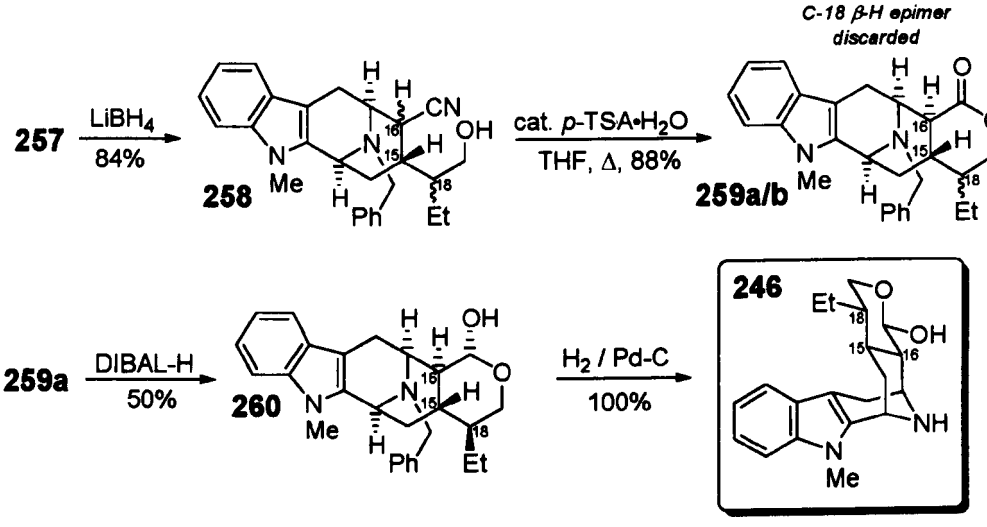

**Scheme 77:** *Alkylation preceded the revealing of the aldehyde*

Horner–Wadsworth–Emmons reaction furnished **256** (5:3 *E*:*Z*), the substrate for intramolecular Michael cyclisation to the tetracycle. This was induced with $LiNEt_2$, giving **257** as an inseparable mixture of diastereoisomers. C-15 was found to have entirely β-H configuration as desired and C-16 was found to be 4:1 α-H:β-H. No selectivity was observed at C-18 (1:1 α-H:β-H). Bailey makes no comment relating the C-18 stereochemistry to olefin geometry or otherwise.




**Scheme 78:** *Access to tetracyclic skeleton: total stereocontrol shown at C-15 only*

Heating the diastereoisomeric mixture **258** to reflux with catalytic toluene-4-sulfonic acid hydrate in THF gave a mixture of two lactones **259a/b**, diastereoisomeric at C-18. Gratifyingly both C-16 epimers had been transformed only into (16*S*) lactones **259a/b**. Presumably the (16*R*) epimer of **258** had initially cyclised to the *cis*-decalin before base-induced epimerisation to the *trans*-decalin structure. That the *trans*-decalin would be the lower-energy configuration may be seen from the predicted 3D structure of (–)-raumacline (scheme 79), where the all-equatorial conformation is visible. The C-18 epimeric lactones were separated by chromatography and the isomer having the correct (18*S*) configuration (**259a**) underwent DIBAL reduction to introduce the lactol **260** (correctly configured) and hydrogenolytic debenzylation to afford (–)-raumacline **246** (scheme 79).

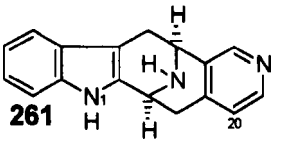



**Scheme 79:** *Final approach to (-)-raumacline*

The difficulty in exerting control over the C-18 stereochemistry is regrettable, but nevertheless, in this synthesis of (–)-raumacline (15 steps from L-tryptophan, 7% overall yield) five of the six stereocentres have been effectively controlled, a notable achievement and a significant improvement on previous approaches.

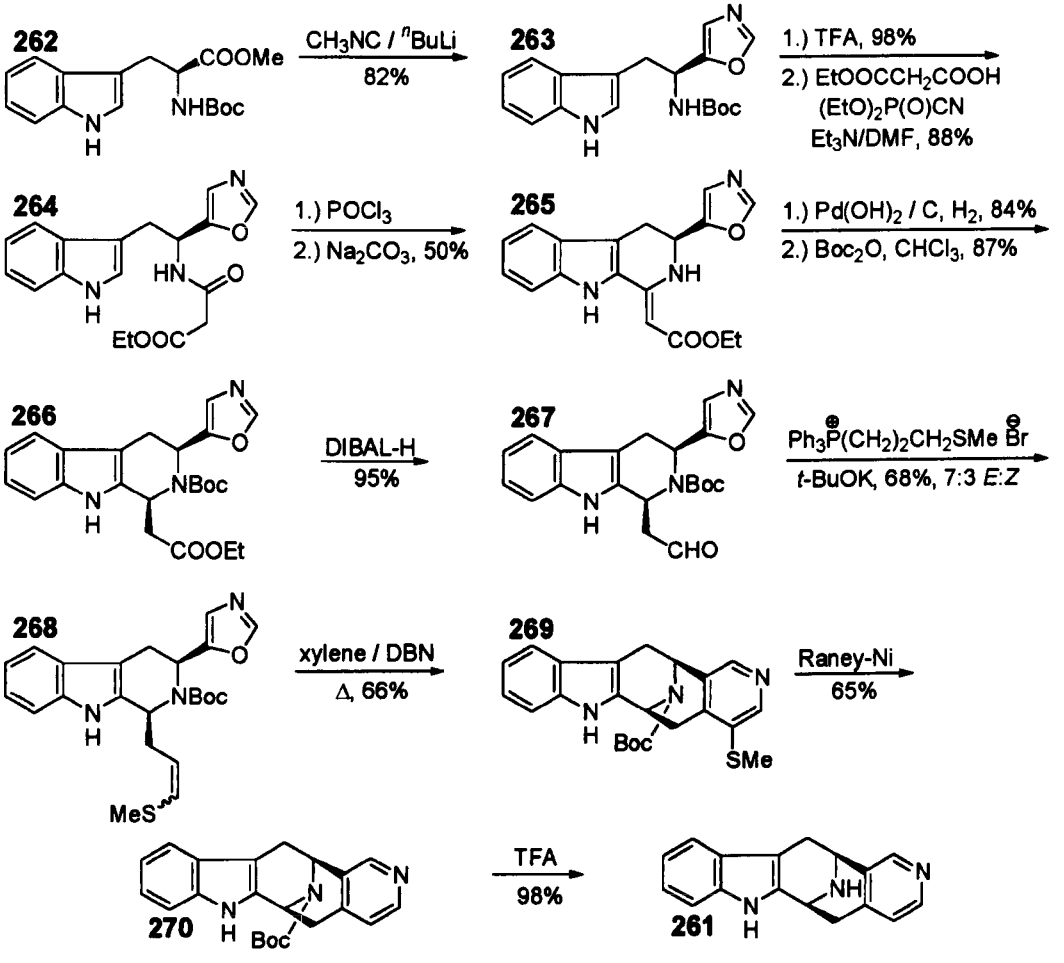
## 1.9 Ohba's Synthesis of 1-Demethyl-20-deethylsuaveoline

In 1996, Batista *et al.* isolated sellowiine, a macroline-related alkaloid, from the leaves of *Rauvolfia sellowii*.[68] For this natural product they proposed the structure 1-demethyl-20-deethylsuaveoline **261** (scheme 80). Ohba and co-workers, having a long-standing interest in oxazole–olefin Diels–Alder reactions, were able to achieve a total synthesis of this structure (scheme 81).[69]



**261**

**Scheme 80:** *Proposed structure for sellowiine*




**Scheme 81:** *Ohba's route to 1-demethyl-20-deethylsuaveoline*

Oxazole formation from N4-Boc-protected L-tryptophan methyl ester **262** occurred without erosion of *e.e.* according to their previously reported methodology.[70] Temporary removal of the protecting group was necessary for *N*-acylation, Bischler–Napieralski reaction[71] (6 days in neat $POCl_3$)[72] and stereospecific hydrogenation. Upon reintroduction of the Boc group to give

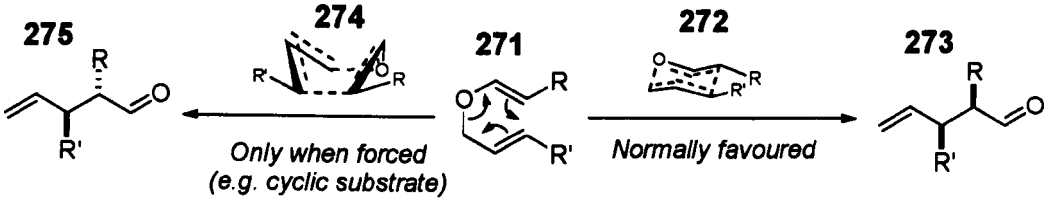
**266**, a chemoselective ester to aldehyde reduction was effected followed by Wittig reaction to introduce a vinyl sulfide side-chain (it was found that a terminal olefin was not able to undergo the intramolecular Diels–Alder reaction). Thus the removable thiomethyl group was used instead, and the IMDA reaction of **268** was found to work best by heating in xylene at reflux, with addition of 1,5-diazabicyclo[4.3.0]non-5-ene (suggested simply to be a scavenger for $H_2O$). Removal of the thiomethyl group from **269** by reduction with Raney-nickel and trifluoroacetic acid-induced N4-deprotection gave 1-demethyl-20-deethylsuaveoline **261** (7% yield, 11 steps from N4-Boc L-tryptophan methyl ester). The spectroscopic data recorded by Ohba and co-workers for **261** did not correlate with those reported for sellowiine by Batista; the chemistry of sellowiine remains incomplete, therefore.

## 2.1 – Methodology Studies on the Decarboxylative Claisen Rearrangement

### 2.1.1 – Background

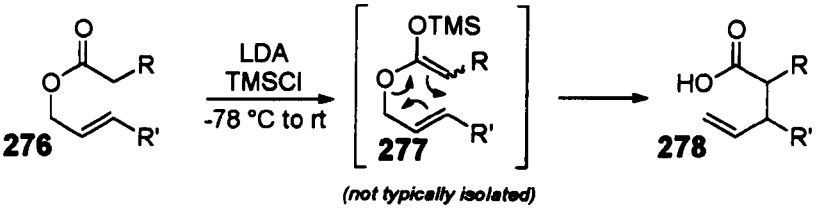
#### *2.1.1.1 – Historical background*

It is nearly a century since Ludwig Claisen reported[73] the rearrangement with which his name has since become synonymous (scheme 82). The ability of this reaction to reliably deliver the γ,δ-unsaturated carbonyl products (**273** or **275**) in a predictable stereodefined manner has seen it employed with great frequency in synthesis.[74]




**Scheme 82:** *Outline of the Claisen rearrangement*

Several variants of the Claisen rearrangement have subsequently been reported, of which arguably the most synthetically versatile is due to Ireland.[75] In this transformation, the reactive moiety is a silyl ketene acetal **277**, typically prepared *in situ* from the corresponding allyl ester **276** (scheme 83).

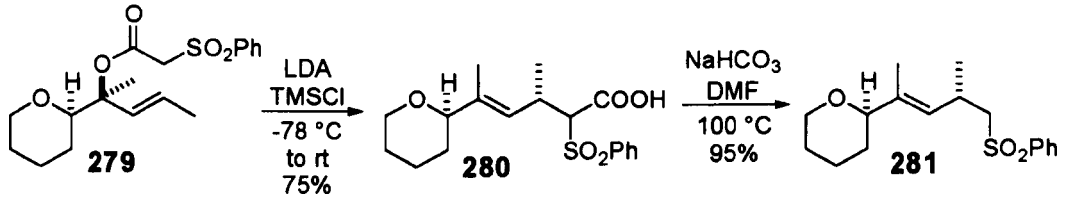



**Scheme 83:** *Outline of Ireland's variant of the Claisen rearrangement*

The ubiquity of this transformation in the literature of the last three decades[76] derives in part from the high levels of stereoselectivity achievable in this transformation. For example, Ireland has reported[77] conditions for the selective formation of silyl ketene acetals of either geometry, which in turn determines the C2-C3 relative configuration in the product. Additionally, the ease of access to the substrates, the mild reaction conditions and the tolerance of a wide variety of substrate functionality all contribute to the great utility of this process.

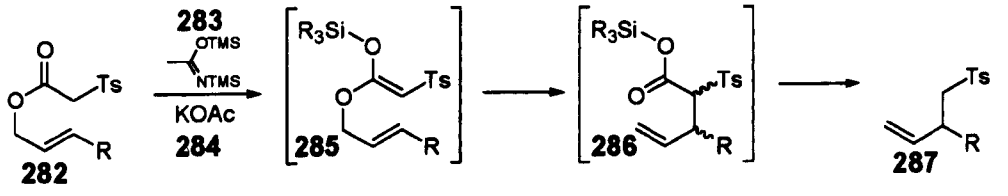
*2.1.1.2 – Prior work within the Craig group*

In 2000, a co-worker in the Craig group, Damien Bourgeois, undertook an investigation into possible stereochemical induction in the Ireland–Claisen rearrangement due to stereocentre(s) exocyclic to the pericyclic array. In its primary aim, this project met with limited success. However, some serendipitous discoveries arose from the work. In 1991, Davidson and co-workers reported[78] the Ireland–Claisen rearrangement of a substrate **279** comprising an α-phenylsulfonylacetate ester of a highly substituted allyl alcohol. In the subsequent step they effected decarboxylation under mildly basic conditions (scheme 84).




**Scheme 84:** *Davidson's α-sulfonyl Ireland-Claisen rearrangement*

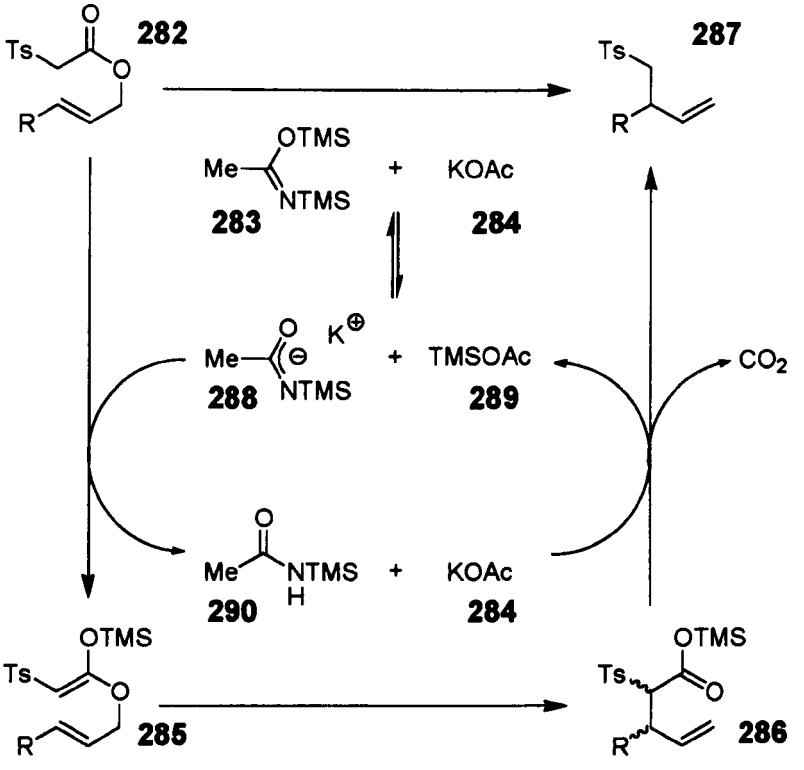
α-Sulfonyl acetates were also being employed in the Craig group study, so Bourgeois sought to employ Davidson's conditions to effect the rearrangements (merely use of LDA and TMS-Cl, as originally reported by Ireland). However, no rearrangement was ever observed for our (structurally distinct) toluene-4-sulfonylacetates **282**. Other reagent systems were employed and it was observed that use of *N,O*-bis(trimethylsilyl)acetamide **283** (BSA) as the silylating agent and potassium acetate **284** as base led to Ireland–Claisen rearrangement *with concomitant decarboxylation* (scheme 85).




**Scheme 85:** *Decarboxylative Ireland-Claisen rearrangement*

The reaction was repeated for a variety of allyl alcohols and was shown to be tolerant of a variety of olefinic substitution patterns and pendent functionality. The outcomes of these studies on this decarboxylative Claisen rearrangement (or "dCr") have been reported.[79] A highly significant observation followed soon after, with the recognition that the reaction may be induced with sub-

stoichiometric quantities of both base and silylating agent.[80] Yields obtained were comparable to those in the stoichiometric cases. To our knowledge, this is the first example of a ketene acetal formation-Claisen rearrangement sequence which utilises sub-stoichiometric amounts of base and silylating agent. As such the mechanism of the reaction was of considerable interest. Two co-workers, David Mountford and Fabienne Grellepois, performed extensive studies, as a result of which the mechanistic cycle shown in scheme 86 has been proposed.

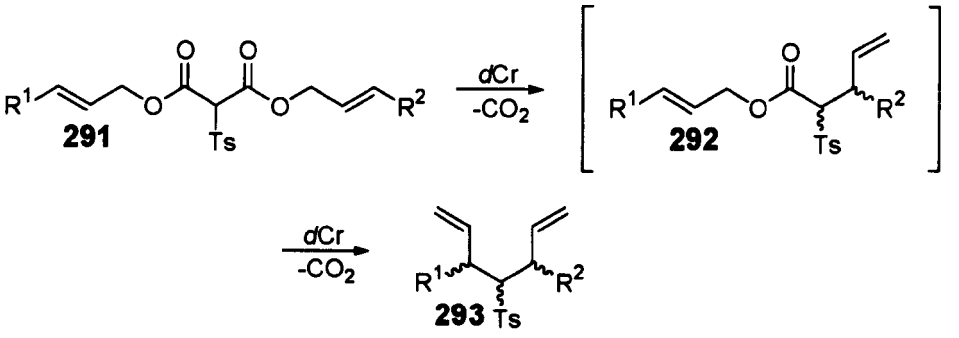



**Scheme 86:** *Proposed mechanistic cycle for the dCr*

A pre-equilibrium between the reagents generates the active species *in situ*, namely trimethylsilyl acetate **289** and the conjugate base of trimethylsilyl acetamide **288**. It is this anion **288** which effects deprotonation of substrate **282**, the resultant enolate being silylated by TMSOAc **289**, the effective silyl "shuttle". [3,3]-Sigmatropic rearrangement of **285** ensues, affording a silyl ester **286**. The acetate anion **284** then acts in a nucleophilic capacity, abstracting the silyl group with extrusion of carbon dioxide. The resultant α-sulfonyl anion abstracts a proton from (trimethylsilyl)acetamide **290** (or the starting material **282**) to furnish the product **287**; in so doing the active species are regenerated.

*2.1.1.3 – Rationale for the current work*

We wished to investigate whether we could expand the scope of the dCr to encompass bifunctional substrates, *i.e.* 2-(toluene-4-sulfonyl)malonates **291**. It was hoped these would undergo two dCr reactions in one pot to give access to 4-(toluene-4-sulfonyl)-1,6-heptadienyl species **293** as shown in scheme 87.




**Scheme 87:** *Proposed one-pot dual dCr cascade*

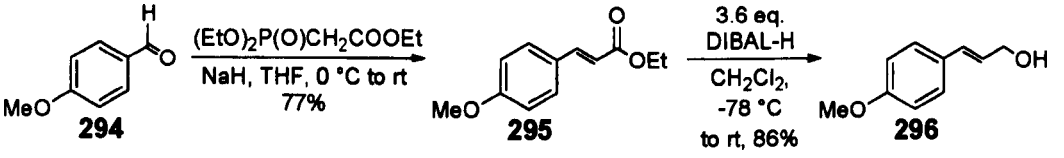
Such species, it seemed to us, may be of appreciable synthetic value. They would likely be substrates for facile ring-closing metathesis and the resultant 3-cyclopentenes would potentially be versatile intermediates for the synthesis of natural products (this is discussed in section 2.2). In addition, one could imagine accessing cyclopentadienyl compounds from such intermediates. The question of what diastereoselectivity (if any) might arise in the reaction was also of interest.

Before the viability of the proposed dual-dCr cascade could be determined, a reliable route to the substrates had to be established, as literature precedent[81] for the synthesis of such 2-(toluene-4-sulfonyl)malonyl di-esters **291** was scant. This author's immediate predecessor, Jörg Kley, was able to synthesise three symmetrical ($R^1 = R^2$) 2-(toluene-4-sulfonyl)malonyl bis(allyl) esters **291** (albeit in poor yield) and show that they did indeed undergo the desired dual-dCr reaction upon treatment with several equivalents of BSA in toluene or *o*-xylene at reflux.

## 2.1.2 – Synthesis of Bis(allyl) 2-(toluene-4-sulfonyl)malonates

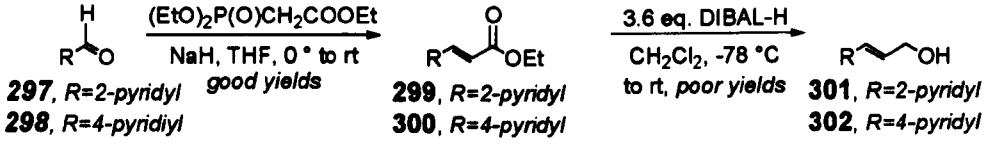
### *2.1.2.1 – Synthesis of allyl alcohols*

The three 2-(toluene-4-sulfonyl)malonyl di-esters synthesised prior to the commencement of the current work incorporated commercially-available allyl moieties (allyl alcohol, cinnamyl alcohol, (*E*)-pent-2-en-1-ol). In addition to these side-chains, we wished to investigate the properties of a wide variety of other side-chains, not all of which were commercially available. For example, electron-poor *p*-nitrocinnamyl alcohol was readily commercially available, whereas the electron-rich *p*-methoxycinnamyl alcohol **296** was not. This was synthesised in two steps[82,83] from *p*-anisaldehyde **294** (scheme 88).



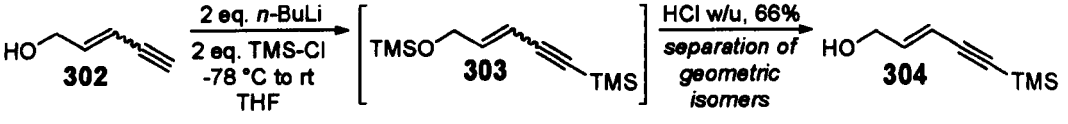

**Scheme 88:** *Synthesis of* p-*methoxycinnamyl alcohol*

A similar attempt to prepare allyl alcohols substituted with a 2- or 4-pyridyl aromatic moiety was less successful – the corresponding aldehydes furnished the α,β-unsaturated esters[84,85] **299** and **300** in good yields, but in our hands the DIBAL-mediated reductions gave impure products[86,87] in low yield.




**Scheme 89:** *Synthesis of pyridyl allyl alcohols was problematic*

We were also keen to explore the behaviour of conjugated non-aryl side-chains. A dienyl alcohol, (*E*,*E*)-hexa-2,4-dien-1-ol **302**, was commercially available, as was a terminal enynyl alcohol; the acetylene was capped with silicon to avoid possible problems arising from acetylenic proton acidity (scheme 90). Whilst the starting material was an inseparable mixture of geometric isomers, fortuitously it consisted predominantly of the desired (*E*)-isomer; furthermore the silylated products were separable by

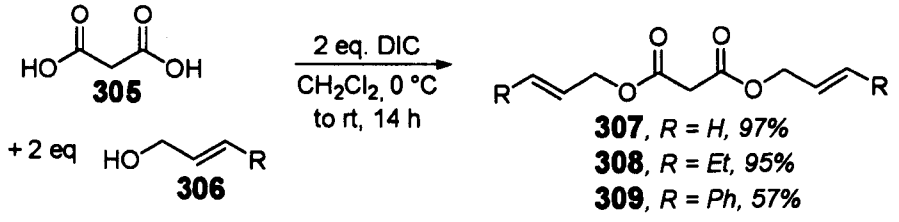



**Scheme 90:** *Synthesis of enynyl alcohol*

chromatography.

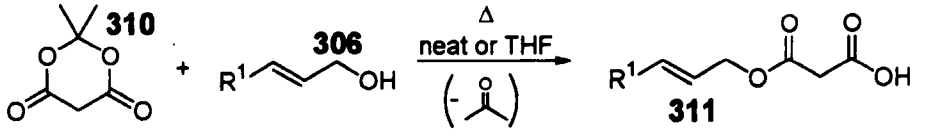
### *2.1.2.2* – Synthesis of 2-(toluene-4-sulfonyl)malonates by direct sulfonylation

With an array of allyl alcohols at our disposal, we turned our attention to synthesis of the dual-dCr substrates. As stated previously, Kley had had some limited success accessing 2-(toluene-4-sulfonyl)malonates **291**. This was by way of direct *C*-sulfonylation of the corresponding malonates **314**. We set about reproducing these results with a view to improving on them. In order to do so we needed to synthesise the diallyl malonates **314** for sulfonylation. If a symmetrical malonate were required, esterification of malonic acid with the requisite alcohol was trivial (scheme 91).



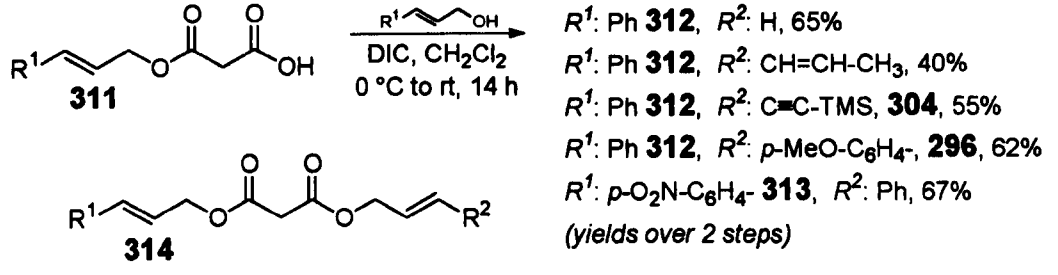

**Scheme 91:** *No unexpected complications arose in the synthesis of diallyl malonates*

Alternatively, if non-symmetrical di-esters were required, it was found that Meldrum's acid **310** provided the most convenient starting material for sequential esterification. Firstly, the mono-ester **311** was synthesised with loss of acetone (scheme 92). These reactions were often performed neat under heating, with the appearance of acetone in the reflux condenser a qualitative visual indicator of reaction progression.



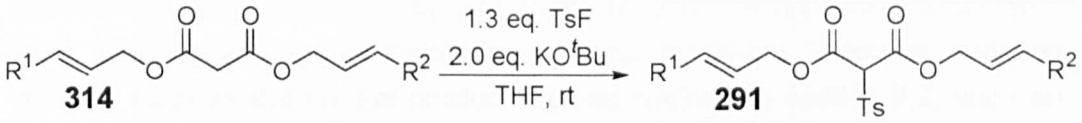

**Scheme 92:** *Synthesis of malonyl monoesters from Meldrum's acid*

The resultant mono-esters **311** were used immediately without purification in the second esterification step, which was also carbodiimide-mediated (scheme 93).




**Scheme 93:** *Access to unsymmetrical malonates*

With a variety of symmetrical and unsymmetrical malonates in hand, we sought to effect their 2-sulfonylation. This was to be carried out by formation of the malonyl anion and treatment with a suitable sulfonylating agent. Kley had used potassium *tert*-butoxide in THF followed by introduction of toluene-4-sulfonyl fluoride. We applied the same conditions to the substrates in our possession (scheme 94). Yields are given in table 1.




**Scheme 94:** *Synthesis of 2-(toluene-4-sulfonyl)malonates by direct sulfonylation with toluene-4-sulfonyl fluoride*

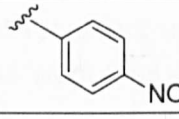
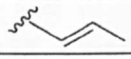
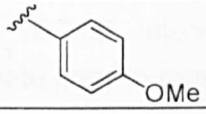
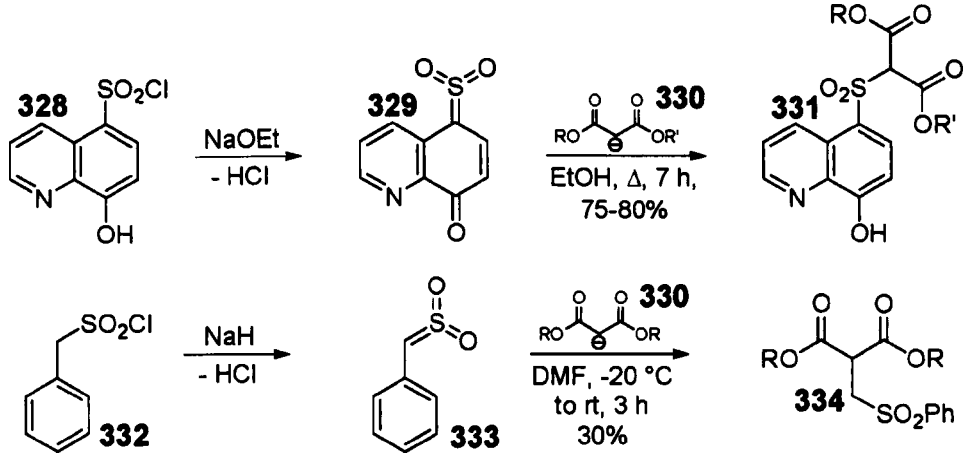
| $R_1$ | $R_2$ | Starting Material | Product | Yield |
|---|---|---|---|---|
| Ph | Ph | **309** | **320** | 8% |
| H | H | **307** | **321** | 9% |
| Et | Et | **308** | **322** | 13% |
| Ph | H | **315** | **323** | 22% |
| Ph |  | **316** | **324** | 0% *(decomposition)* |
| Ph |  | **317** | **325** | 9% |
| Ph |  | **318** | **326** | 0% |
| Ph |  | **319** | **327** | 4% |

**Table 1:** *Yields of 2-(toluene-4-sulfonyl)malonate formation by direct sulfonylation with toluene-4-sulfonyl fluoride*

Yields were broadly reproducible, but low. It was speculated this might be due to partial *O*-sulfonylation. Large amounts of unreacted starting material were typically recovered, as one would expect if this hypothesis is correct – *O*-sulfonylated product would be hydrolysed during workup. Attempts were made to systematically vary the reaction conditions, but yields remained low. Additionally, the reaction scope was slightly limited, as in the case of the *p*-nitrocinnamyl-containing substrate **316** spectacular decomposition was observed upon addition of the base – within seconds the contents of the flask were transformed from a colourless solution to a black solid.

It should be pointed out that subsequent to this work being carried out, co-workers (Fabienne Grellepois and Federica Paina) experienced greater success in the use of toluene-4-sulfonyl fluoride in direct sulfonylation. They found[88] that upon use of a two-fold excess of malonate and base in DMSO at high concentration (2.0 M), good yields of product (with respect to toluene-4-sulfonyl fluoride) were obtained. The utility of this approach is diminished somewhat by the requirement of such an excess of malonate with respect to toluene-4-sulfonyl fluoride (and incomplete recovery of unreacted malonate). In a scenario where the malonate is by far the more "valuable" reaction partner, such as the natural product studies outlined in section 2.2, such an approach is not appropriate.

The low yields of sulfonylated product produced with toluene-4-sulfonyl fluoride led us to apply alternative sulfonylation conditions. Kley had found that use of toluene-4-sulfonyl chloride effected chlorination as opposed to the desired sulfonylation. (The resulting 2-chloromalonates could be transformed to the desired product by displacement with sodium *p*-tolylsulfinate, but neither reaction was particularly high-yielding, the overall yield being no better than that for direct use of toluene-4-sulfonyl fluoride). It must be noted that since this work was carried out, two reports have come to our attention[89] of successful use of malonate 2-sulfonylation with different sulfonyl chlorides (**328** and **332**, scheme 95). These results were investigated[90] by a co-worker, Henrik Jensen, who concluded that in these cases a different mechanism was operating. The sulfonyl chlorides in question are able to eliminate the elements of HCl under the basic conditions, forming a reactive sulfene intermediate prior to reaction with the malonyl anion.

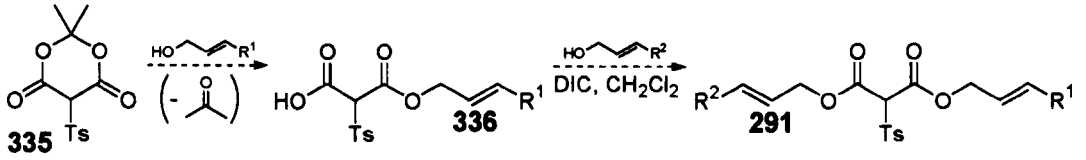



**Scheme 95:** *Successful sulfonylations with other sulfonyl chlorides, thought to proceed by a different mechanism*

We were hopeful that use of toluene-4-sulfonic anhydride would circumvent the chemoselectivity issue. Contrary to literature reports[81d] however, in our hands no reaction with this reagent was observed, for these substrates and this sulfonic anhydride at least. At this point we did not further investigate direct sulfonylation of malonates. Instead we changed strategic bearing and probed the viability of having the sulfone present prior to formation of the malonate.

### *2.1.2.3 – Attempted synthesis of (toluene-4-sulfonyl)-Meldrum's acid*

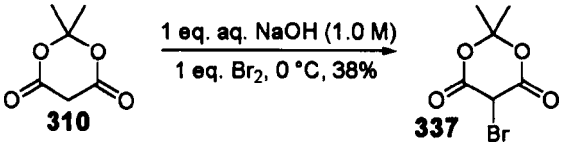
We hoped the 2-(toluene-4-sulfonyl)malonyl di-esters **291** might be accessible by sequential side chain introduction to (toluene-4-sulfonyl)-Meldrum's acid **335** (as a synthetic equivalent for the malonate fragment), scheme 96.




**Scheme 96:** *Proposed use of (toluene-4-sulfonyl)-Meldrum's acid*

As a starting material, **335** would be highly desirable, as this more convergent route could reduce dCr substrate synthesis to two straightforward reactions. However, toluene-4-sulfonylated Meldrum's acid **335** is not a commercial compound, or indeed a reported compound. Attempts to synthesise it by exposing deprotonated Meldrum's acid to sulfonylating agents such as toluene-4-sulfonyl chloride, toluene-4-sulfonyl fluoride or toluene-4-sulfonic anhydride were entirely unsuccessful.

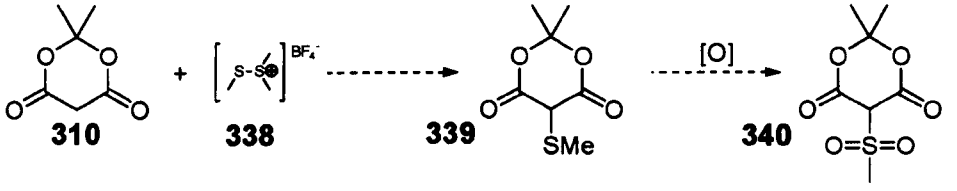
Rather than accessing the desired product by electrophilic substitution, it was decided to try to derivatise Meldrum's acid at the desired site of substitution. If a suitable leaving group were introduced, it could in turn be displaced by *p*-tolylsulfinate or similar. We first attempted the synthesis of chloro-Meldrum's acid.[91] A general precedent exists[92] for the chlorination of open-chain malonate di-esters. *N*-Chlorosuccinimide was employed as the source of electrophilic chlorine with various bases (DBU and LHMDS in THF, NaOH in $H_2O$), yet none of the reactions was successful. It was decided instead to synthesise bromo-Meldrum's acid **337** (scheme 97).




**Scheme 97:** *Synthesis of bromo-Meldrum's acid*

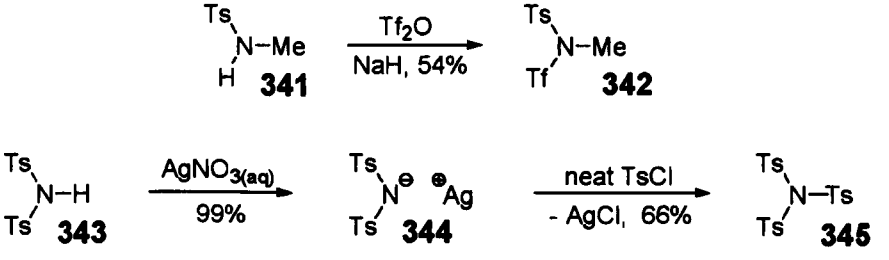
Recrystallisation from toluene affords **337** in pure form, which may be stored without degradation for several weeks under an inert atmosphere at 4 °C, contrary to earlier reports of its instability.[93] Attempts to introduce a phenylsulfonyl moiety directly by use of sodium phenylsulfinate and catalytic tetra-*n*-butylammonium iodide were unsuccessful. It was reasoned that a softer nucleophile such as phenyl (or *p*-tolyl) sulfide anion would displace the bromide with greater ease; this could then be oxidised to the desired sulfone with peracid, etc. Unfortunately use of sodium phenylthiolate was similarly unsuccessful.

We returned to the idea of directly sulfonylating deprotonated Meldrum's acid **310**, attempting reaction with dimethyl(methylthio)sulfonium tetrafluoroborate **338** (scheme 98). Upon formation of methylthio-Meldrum's acid **339**, oxidation to the corresponding sulfone (methylsulfonyl-Meldrum's acid **340**) should be facile. The reaction was attempted in both the presence and absence of base; the desired product was not detected in either case.




**Scheme 98:** *Proposed utilisation of sulfonium electrophile*

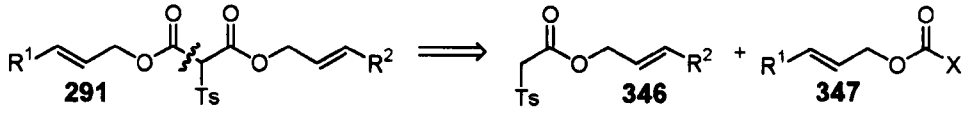
A colleague drew our attention to the species **342**. Initially reported as a methylating agent, it had also been observed to effect sulfonylation. Sulfonamide **342** was duly prepared, but this would-be sulfonylating reagent could be improved upon, as there is an inherent ambiguity as to which substituent may be transferred. A reagent such as **345** would not be subject to such ambiguity. We prepared[94] **345** also, but it proved to be highly insoluble, rendering attempts at sulfonylation difficult. No desired product was ever detected when Meldrum's acid was treated with various bases and either **342** or **345**.




**Scheme 99:** *Synthesis of potential nitrogen-based sulfonylating agents*

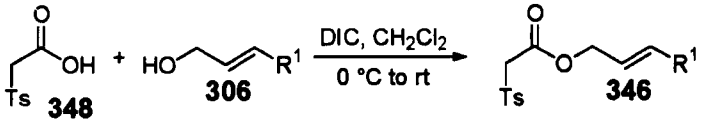
*2.1.2.4 – Synthesis of 2-(toluene-4-sulfonyl)malonates by carboxylation*

In view of the failure to prepare (toluene-4-sulfonyl)-Meldrum's acid **335**, the need persisted to improve on the direct sulfonylation methodology (section 2.1.2.2). One may disconnect the target 2-(toluene-4-sulfonyl)malonate di-esters **291** across one of the central C–C bonds (scheme 100), the required synthons being an ester **346** derived from (toluene-4-sulfonyl)acetic acid **348** (commercially available) and a carbonate or equivalent **347**.

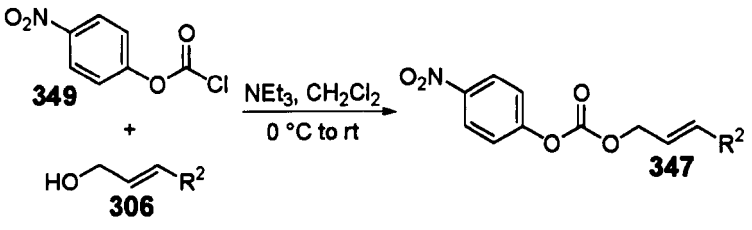



**Scheme 100:** *Alternative retrosynthetic analysis of 2-(toluene-4-sulfonyl)malonate diester*

The $R^1$ component was to be derived from the corresponding alcohol and one of several possible reagents, e.g. phosgene (X = Cl) or *p*-nitrophenyl chloroformate (X = *p*-nitrophenyl). Formation of the (toluene-4-sulfonyl)acetic acid ester enolate and addition of this to the $R^1$-containing species was envisaged, hopefully giving the desired compounds. Synthesis of a variety of (toluene-4-sulfonyl)acetic acid esters proved facile, as did the synthesis of a variety of *p*-nitrophenyl carbonates from *p*-nitrophenyl chloroformate.




**350**, R: Et, 91%
**351**, R: Ph, 71%
**352**, R: *p*-$NO_2$-$C_6H_4$-, 94%
**353**, R: H, 92%
**354**, R: CH=CH-Me, 87%
**355**, R: C≡C-$SiMe_3$, 65%
**356**, R: *p*-MeO-$C_6H_4$-, 76%

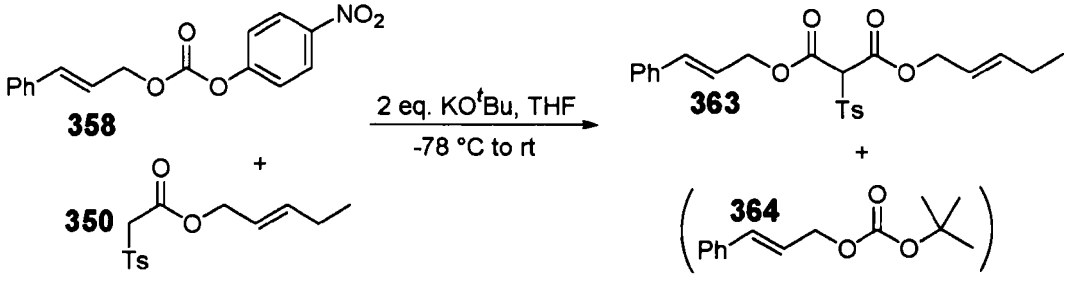



**357**, R: Et, 60%
**358**, R: Ph, 86%
**359**, R: *p*-$NO_2$-$C_6H_4$-, 41%
**360**, R: H, 91%
**361**, R: CH=CH-Me, 76%
**362**, R: C≡C-$SiMe_3$, 75%

**Scheme 101:** *Synthesis of (toluene-4-sulfonyl)acetates and* p*-nitrophenylcarbonates was routine*

The fragment union was initially attempted on a system wherein $R^1$ = Et and $R^2$ = Ph. Potassium *t*-butoxide (both solid and as a solution) was used and reactions were performed in THF at –78 °C. Two equivalents of base were employed since the 2-(toluene-4-sulfonyl)malonate product was more acidic

than the (toluene-4-sulfonyl)acetate starting material. Gratifyingly, the desired 2-(toluene-4-sulfonyl)malonate **363** was isolated in around 30% yield in the first instances.




**Scheme 102:** *First application of carboxylation methodology*

The enolate anion was typically preformed before being added via cannula to a solution of the carbonate, resulting in the appearance of a yellow colour. Once the reaction mixtures were allowed to warm to room temperature, large amounts of yellow material precipitated, characteristically indicative of formation of *p*-nitrophenolate salts. Co-elution of *p*-nitrophenol with the desired product was initially problematic, but could be reduced by acidifying the eluent with acetic acid. Additionally, whilst a mildly acidic aqueous workup was used in the first instances, this could be substituted with a mildly basic workup if needed, extracting the *p*-nitrophenolate into the aqueous phase. No appreciable diminution in yield was observed.

Variation of the reaction conditions was then undertaken. It was found to be necessary to pre-form the enolate anion – if the sulfonylacetate and carbonate components were mixed prior to introduction of the base little or no product was obtained. It was also ascertained that pre-forming the anion at –78 °C was unnecessary and that comparable yields could be obtained at 0 °C.

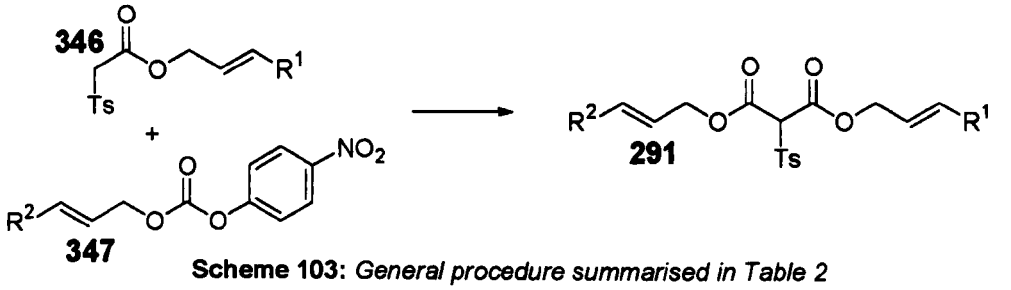
In each instance unreacted (toluene-4-sulfonyl)acetate was isolated along with desired product, the mass balance being essentially quantitative. Also visible by TLC was a spot which was assumed to correspond to unreacted carbonate. In fact, once isolated it transpired that the material was largely *t*-butyl cinnamyl carbonate **364**, the product of nucleophilic addition of the base. Potassium *tert*-butoxide had been chosen specifically as a hindered non-nucleophilic base, yet appreciable **364** was being formed. In light of this observation it was decided to employ an inherently non-nucleophilic strong base and for ease of handling sodium hydride was chosen. Concurrently it was decided to employ DMF as solvent. This was expected to completely solubilise all products and reactants, aiding reaction progression, whereas the

insolubility of *p*-nitrophenolate in THF was leading to material precipitating in quantities which may have retarded reaction.

Formation of the enolate anion with only one equivalent of NaH in DMF solution, followed by addition to a solution of the carbonate led to isolation of the desired product in precisely 50% yield, with quantitative recovery of unreacted starting materials. It was expected therefore that when a second equivalent of base was employed, the desired product would be isolated in greater yield. In the event, 56% yield was obtained under these conditions. When comparable conditions (2 equivalents NaH, DMF, 0 °C to room temperature) were applied to other substrates throughout the course of this work, isolated yields were typically around 50%, and as high as 71%. Unreacted starting materials were recovered and near quantitative mass balance was typical.

Attempts to improve on these yields by use of "heterobasic" systems were unsuccessful. Formation of the anion with one equivalent of NaH, addition to the carbonate **358** followed by addition of one equivalent of triethylamine led to a yield of 41%. Reactions were also undertaken whereby the enolate anion was preformed with one equivalent of NaH and a second equivalent of a different base was added before cannulation into the carbonate **358** solution. When the second base was DBU the reaction appears to have been actively retarded, the isolated yield of product **363** being only 21%. When the second base was potassium *t*-butoxide, the isolated yield of product **363** was 30%.

Further scope for forcing the reaction to completion was limited. The yields appeared constant with concentration and excess of carbonate (2 equivalents appearing sufficient). Also, DMF and sodium hydride are incompatible at elevated temperature. Nevertheless, a generally reproducible yield of 50% for this reaction represents a significant improvement on previously employed direct sulfonylation methodology (section 2.1.2.2). The conditions were applied for a range of (toluene-4-sulfonyl)acetates and carbonates, with the results summarized in table 2.




**Scheme 103:** *General procedure summarised in Table 2*

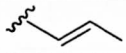
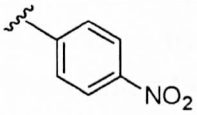
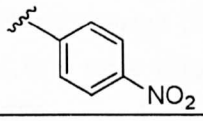
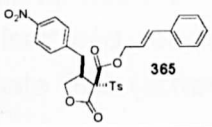
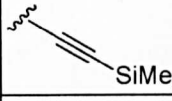
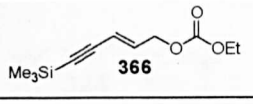
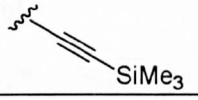
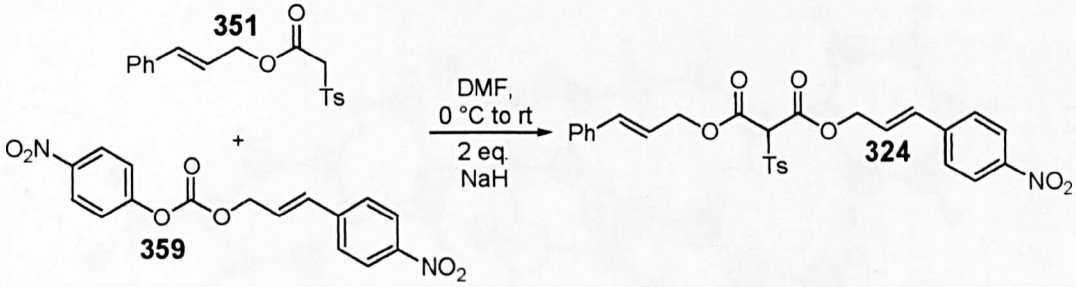
| $R^1$ (toluene-4-sulfonylacetates) | $R^2$ (*p*-nitrophenyl carbonate) | Yield of 2-(toluene-4-sulfonyl)malonate formation | Structure of any byproduct isolated |
|---|---|---|---|
| Ph | Ph | 26% (**320**) | - |
| H | Ph | 46% (**323**) | - |
| Et | Ph | 56% (**363**) | - |
|  | Ph | 30% (**325**) | - |
| Ph |  | 10% (**324**) | - |
|  | Ph | 23% (**324**), *also* *35% (**365**)* |  **365** |
| Ph |  | 2% (**326**), *also* *trace (**366**)* |  **366** |
|  | Ph | 28% (**326**) | - |

**Table 2:** *Carboxylation methodology was applied with various side-chains*

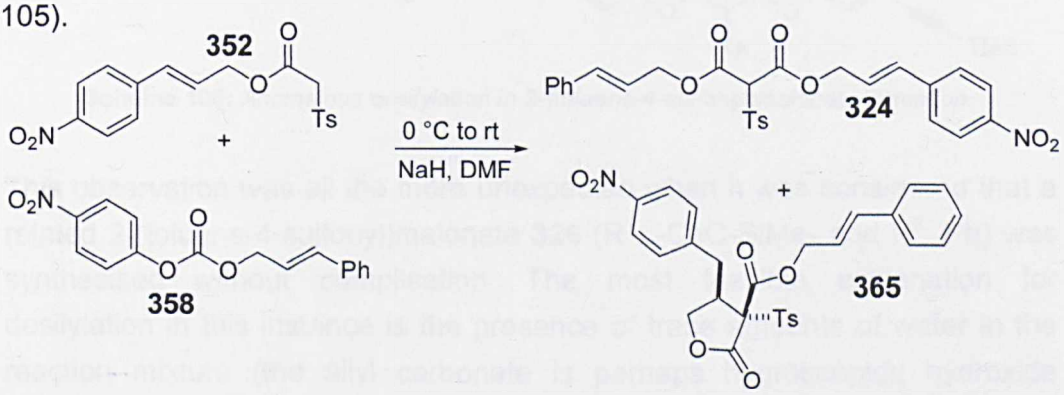
There are other advantages to this new carboxylation methodology. For each (unsymmetrical) 2-(toluene-4-sulfonyl)malonate product, there are two possible combinations of reactants that may be exploited. If a particular (toluene-4-sulfonyl)acetate / *p*-nitrophenyl carbonate combination is unsuccessful, more success may sometimes be had by simply exchanging the two allyl moieties, as exemplified above in table 2. Additionally, the carboxylation methodology allows the synthesis of compounds that were not accessible by the previous procedure.




**Scheme 104:** *Synthesis of previously inaccessible 2-(toluene-4-sulfonyl)malonate*

As detailed in section 2.1.2.2, efforts to synthesise the 2-(toluene-4-sulfonyl)malonate species **324**, (comprising of a *p*-nitrocinnamyl and a cinnamyl moiety) by direct sulfonylation were unsuccessful due to the

instability of the precursor under the basic conditions required (scheme 94, table 1). The synthesis of **324** was attempted using the new methodology. Of the two possible reactant combinations, the reaction of *p*-nitrocinnamyl *p*-nitrophenyl carbonate **359** and cinnamyl (toluene-4-sulfonyl)acetate **351** was carried out first. Synthesis of **359** proved problematic, as the product appeared highly hydrolytically labile and could not be isolated pure, only as a mixture contaminated with *p*-nitrocinnamyl alcohol and *p*-nitrophenol, these three species seeming to have a remarkable affinity for each other on silica. The coupling was attempted regardless and the desired product **324** was isolated in 10% yield (scheme 104). While not ideal, isolation of any material at all represents an improvement on the previous case. In light of the apparent instability of carbonate **359**, the inverse combination of reagents was tried. *p*-Nitrocinnamyl (toluene-4-sulfonyl)acetate **352** was synthesised and coupling of this was attempted with cinnamyl *p*-nitrophenyl carbonate **358** (scheme 105).




**Scheme 105:** *Unexpected lactone product*

In this case **324** was isolated in an improved yield of 23%. Also isolated in 34% yield was the lactone product **365**, presumably resulting from intramolecular Michael addition of the malonyl anion to the electron-poor *p*-nitrostyryl olefin. The structure and relative stereochemistry of **365** have been confirmed by X-ray crystallography (figure 1).

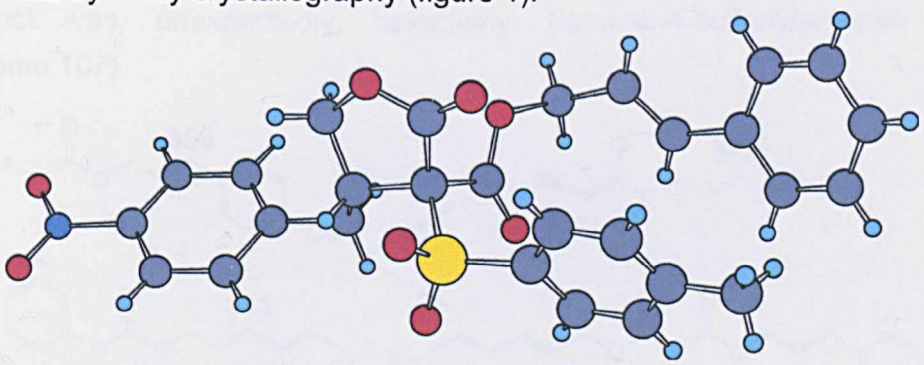
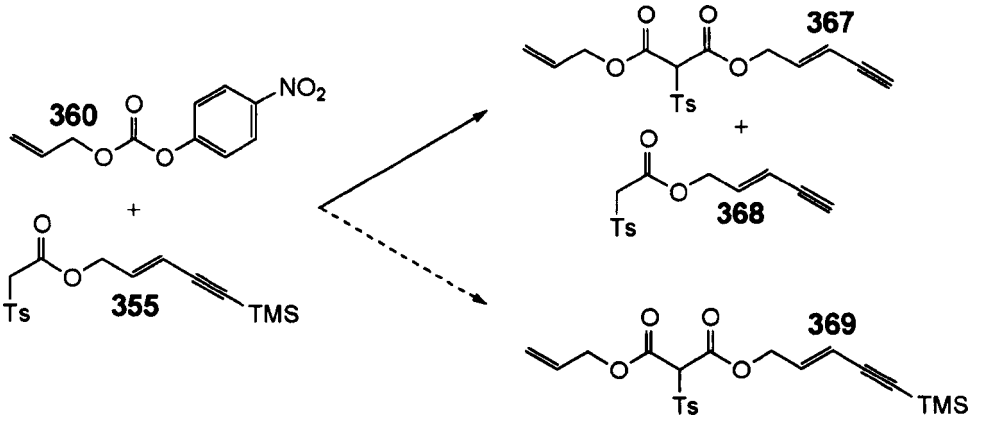


**Figure 1:** *X-ray crystal structure of lactone* **365**

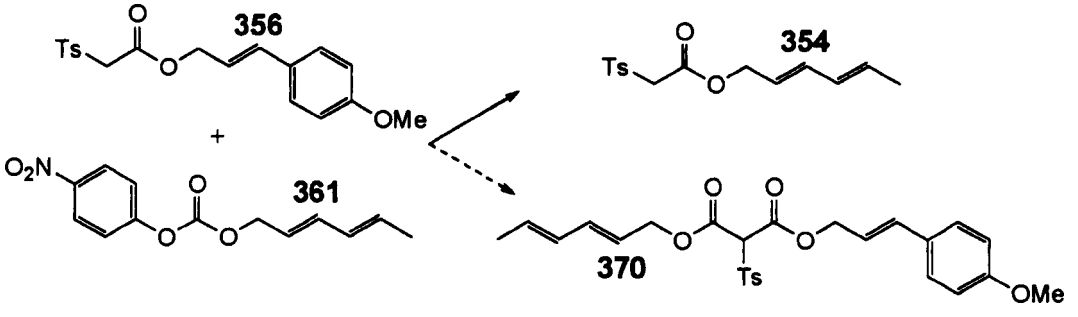
Anomalous reaction products been observed in other instances. In one case, the synthesis of 2-(toluene-4-sulfonyl)malonate **369** was attempted ($R^1$: -C≡C-$SiMe_3$ and $R^2$: H). To our consternation, both 2-(toluene-4-sulfonyl)malonate **367** and residual (toluene-4-sulfonyl)acetate **368** were isolated, both products of desilylation (scheme 106).




**Scheme 106:** *Anomalous desilylation in 2-(toluene-4-sulfonyl)malonate formation*

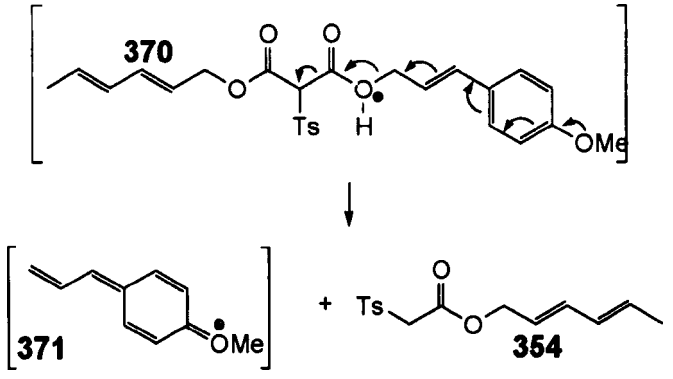
This observation was all the more unexpected when it was considered that a related 2-(toluene-4-sulfonyl)malonate **326** ($R^1$: -C≡C-$SiMe_3$ and $R^2$: Ph) was synthesised without complication. The most feasible explanation for desilylation in this instance is the presence of trace amounts of water in the reaction mixture (the allyl carbonate is perhaps hygroscopic); hydroxide formed *in situ* might effect desilylation. Both reactants were therefore thoroughly azeotropically dried from toluene and the reaction performed in a flame-dried flask. This time the desired product **369** was isolated exclusively.

Another elusive 2-(toluene-4-sulfonyl)malonate product was **370** ($R^1$: *p*-MeO-$C_6H_4$- and $R^2$: -CH=CH-$CH_3$). Upon its attempted formation, the only isolated product was, unexpectedly, hexadienyl (toluene-4-sulfonyl)acetate **354** (scheme 107).




**Scheme 107:** *Unexpected "transesterified" (toluene-4-sulfonyl)acetate product*

This formal transesterification was unlikely to have come about by carbonate hydrolysis and subsequent actual transesterification. Instead, this byproduct could arise via transient formation of the desired product and its subsequent fragmentation (possibly acid-catalysed), as shown in scheme 108. Note that the proposed mechanism might also result in the formation of *p*-methoxycinnamyl alcohol upon workup; none was in fact observed.

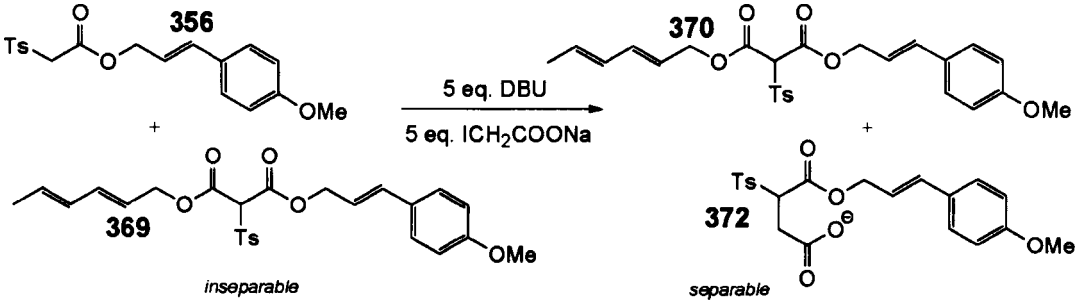



**Scheme 108:** *Possible product fragmentation pathway*

If such a fragmentation may be acid-assisted, then by inference exclusion of acid from the workup and purification procedure might allow isolation of the desired product. When the reaction was performed with a neutral workup and chromatography attempted with base-washed silica, spectroscopic evidence appeared to indicate the desired product had survived the purification procedure. The success was qualified, however, by the fact that the desired product co-eluted with the unreacted starting material **356**. (Toluene-4-sulfonyl)acetates and the corresponding 2-(toluene-4-sulfonyl)malonates have generally been found to have rather similar $R_f$ values. Usually use of a toluene-based eluent permits their separation, but in this case separation proved impossible in all eluent systems tried.

The failure to separate these two species led to our adopting a selective derivatisation strategy. We aimed to take advantage of the likely differing reactivity of the enolates of the two mixture components. We reasoned that the enolate of **356** would likely be both less stabilised and less hindered. In order to take advantage of this potential handle for selective derivatisation, we exposed the mixture to DBU and neopentyl iodide. We hoped only the starting material would be alkylated and thus rendered separable from the desired product. The selective alkylation did occur as desired, but the resultant two

mixture components were even closer in $R_f$ than before. We took this to indicate that rendering the unreacted (toluene-4-sulfonyl)acetate **356** *more* polar would instead be the preferred strategy. Thus treatment of the mixture with DBU and sodium iodoacetate selectively derivatised the starting material as the carboxylate; this was removed upon workup and/or chromatography to finally afford the desired product **370** in the pure form (scheme 109). The final yield of 16% was low, but sufficient for dCr reaction.

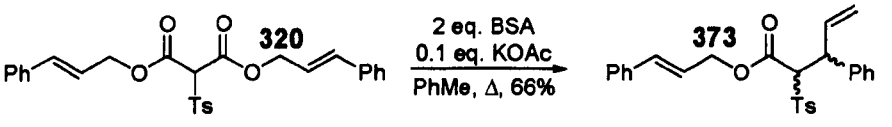



**Scheme 109:** *Selective derivatisation finally provided the pure desired product.*

## 2.1.3 – Decarboxylative Claisen Rearrangements of Bis(allyl) 2-(toluene-4-sulfonyl)malonates

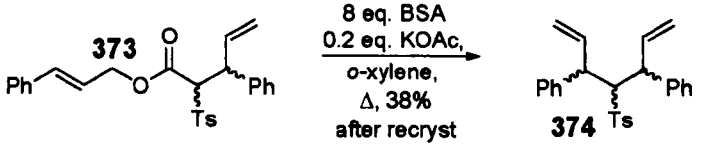
### *2.1.3.1 – Symmetrical 2-(toluene-4-sulfonyl)malonates*

The first dCr reaction attempted on a 2-(toluene-4-sulfonyl)malonate substrate was carried out in accordance with the conditions determined by previous co-workers (scheme 110).



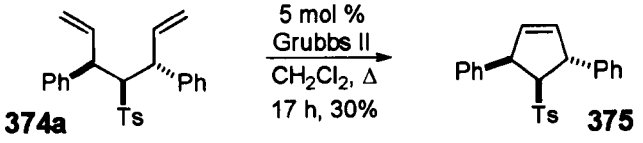

**Scheme 110:** *First dCr attempted on a 2-(toluene-4-sulfonyl)malonyl substrate*

As shown above, only single rearrangement was observed. It seemed that more forcing conditions would be required to effect the second rearrangement. Use of *o*-xylene at reflux and a greater excess of silylating agent gave the desired dual-dCr reaction product (scheme 111). The rationale for use of the excess of BSA was its hydrolytic lability, leading us to suspect reagent degradation over the period of the reaction.



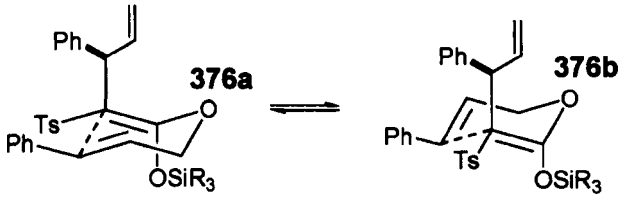

**Scheme 111:** *The second dCr requires more forcing conditions*

The desired dual-dCr product **374abc** was obtained as a mixture of the three possible diastereoisomers in the approximate ratio 3:1:1 (by integration of the tolyl methyl singlets in the $^1$H-NMR). This material was recrystallised from $Et_2O$, yielding a single diastereoisomer **374a**. This diastereoisomer was not assignable from its NMR spectrum. Instead, the relative configurations were assigned by inference from the spectrum of the ring-closed derivative **375**, in which the benzyl methine inequivalence was clearly evident (scheme 112).



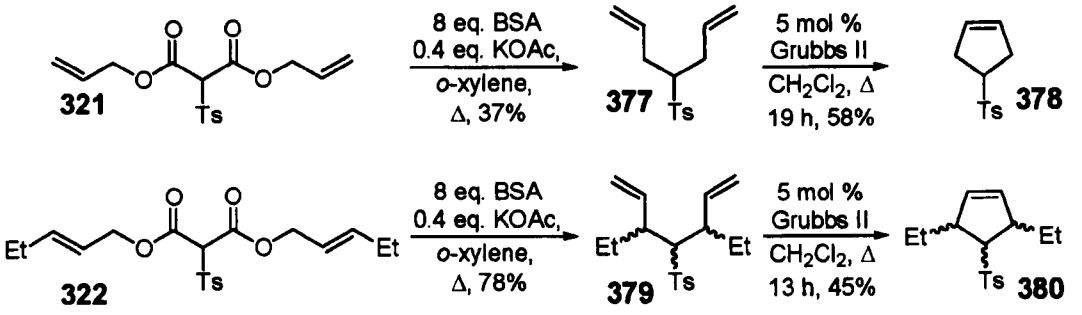

**Scheme 112:** *Ring-closing metathesis gave a more easily assignable derivative*

Noteworthy is the low level of diastereoselectivity in the product distribution, indicative of the two possible transition states being of similar energy. As shown in scheme 113, diastereoisomerism at the benzylic centre arises from the existence of two possible transition state conformers.




**Scheme 113:** *Possible transition state conformations*

The dual-dCr reaction was subsequently attempted with **320** in *o*-xylene, resulting in direct conversion to the di-rearranged product **374**. Having shown the reaction could be driven to completion with sufficiently forcing conditions, we subjected the two other symmetrical 2-(toluene-4-sulfonyl)malonates to identical conditions, obtaining the corresponding 4-(toluene-4-sulfonyl)-1,6-heptadienyl dual-dCr products. These also underwent ring-closing metathesis (scheme 114).



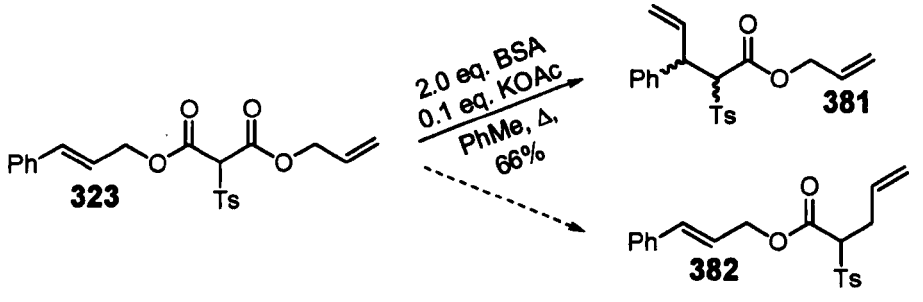

**Scheme 114:** *Dual dCr and RCM of other symmetrical 2-(toluene-4-sulfonyl)malonates*

In contrast to the diphenyl product **374**, neither selective recrystallisation nor diastereoisomeric assignment of diethyl product **379** was possible, although the overall diastereoisomeric ratio was nearly equivalent. For both the open-chain and cyclopentenyl products, the diastereoisomers had entirely coincident $R_f$ values in all eluents tried. This observation later proved to be general, the only exception being one instance during the studies on (–)-suaveoline (section 2.2) when chromatographic separation of diastereoisomers proved possible to a limited extent. Single and di-rearrangement products were always separable.

### *2.1.3.2 – Unsymmetrical 2-(toluene-4-sulfonyl)malonates*

The studies on the dual-dCr of symmetrical malonates had not only shown the dual-dCr cascade to be viable as a one-pot process but had also given rise to a potentially highly significant observation: that the first rearrangement appeared to be markedly more facile than the second.

Two intriguing questions arose from this. Firstly, was the possibility of isolating the singly rearranged intermediate common to all substrates? Secondly, in the case of unsymmetrical 2-(toluene-4-sulfonyl)malonates (those with inequivalent side chains, $R^1 \neq R^2$), would any regioselectivity be observed in this single rearrangement? To discern the answers, an unsymmetrical 2-(toluene-4-sulfonyl)malonate **323** ($R^1$: Ph, $R^2$: H) was subjected to the milder reaction conditions (toluene at reflux) which had induced single rearrangement in a symmetrical 2-(toluene-4-sulfonyl)malonate. The reaction yielded <u>exclusively</u> the product **381** in which the cinnamyl ester had rearranged in preference to the allyl ester (scheme 115).

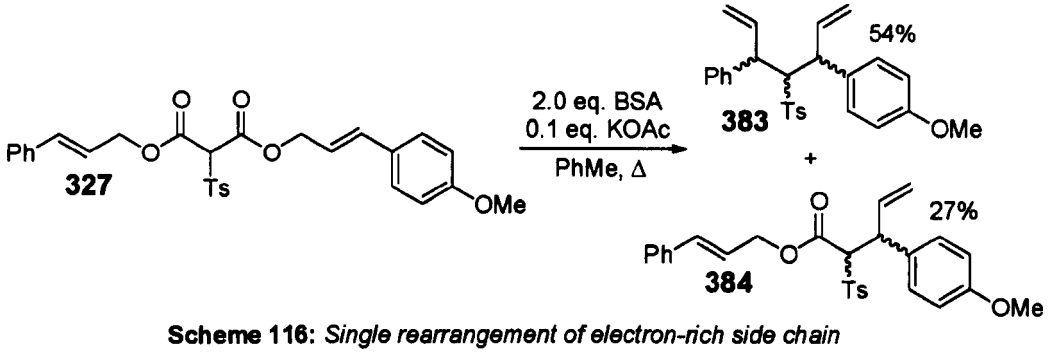



**Scheme 115:** *Single rearrangement of cinnamyl side chain <u>only</u>*

The two possible regioisomeric products **381** and **382** were distinguished most readily by their $^1$H-NMR spectra. The characteristic styryl olefin signal in

the substrate was entirely absent in the product and the presence of two diastereoisomers was unambiguous. (Note that at a later date, the same reaction was repeated in *o*-xylene at reflux, giving di-rearranged product **390** in addition to **381**).

Such a marked preference for one rearrangement over the other was notable and led us to investigate a range of unsymmetrical substrates. We hoped through appropriate choice of side chains to be able to recognise any reactivity trends inherent in the rearrangement. Clearly both steric and electronic factors might influence reactivity. We therefore opted to employ various side chains, some of which enabled us to decouple these two factors. For example, a 2-(toluene-4-sulfonyl)malonate **327** was prepared ($R^1$: *p*-MeO-$C_6H_4$, $R^2$: Ph) whose two side chains would possess distinctly different electronic properties, but which would be sterically essentially equivalent in the immediate region of the reactive array. When rearrangement was induced in toluene at reflux, the only singly rearranged product to result (**384**) was that in which the *p*-methoxycinnamyl side-chain had rearranged.




**Scheme 116:** *Single rearrangement of electron-rich side chain*

Structural elucidation of the singly rearranged product was difficult in the first instance. Strong evidence for the product regioisomer shown was obtained in the form of NOESY NMR spectroscopic data (connectivity was discernable from the aryl methoxy group across the aryl ring to the benzylic methine and from there to the α-sulfonyl methine). Such 2D data was essential for elucidation of many subsequent rearrangement products. Additional evidence for the formation of **384** is contained within the mass spectrum – a peak of high relative intensity is visible at *m/z* 134, corresponding to a non-rearranged cinnamyl fragment (by C–O bond scission). The singly rearranged product was recrystallised from EtOAc–hexane, one of the diastereoisomers (2*R**,3*S**) proving sufficiently crystalline to be subjected to X-ray crystallography (figure 2).

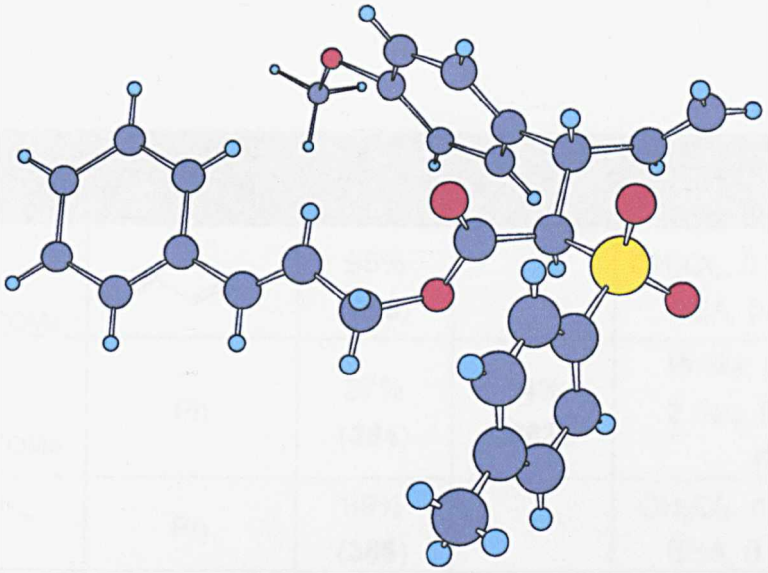
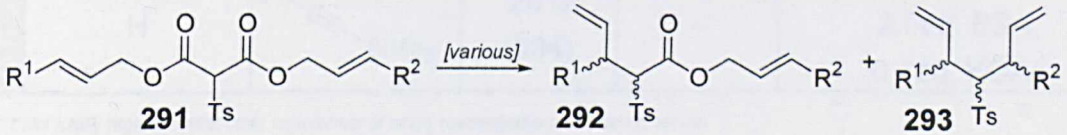


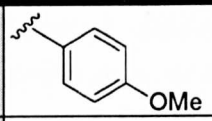
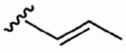
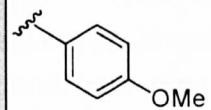
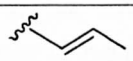
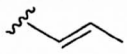
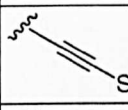
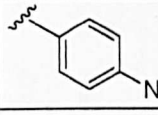
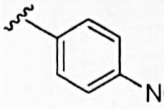
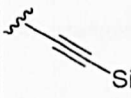
**Figure 2:** *X-Ray crystal structure of single rearrangement product* **384**

The motherliquor was also subjected to rigorous analysis to confirm the absence of the regioisomeric product. The total selectivity for the *p*-methoxycinnamyl side-chain hinted at a preference for the rearrangement of electron-rich allyl moieties. A precedent exists for rate enhancement in the Claisen rearrangement with electron-donating substituents in the γ-allylic position.[95] Clearly, though, more examples were needed if trends in this system were to be delineated with confidence. The isolation of a significant amount of di-rearranged material indicated the substrate to be of inherently higher reactivity, since thus far use of toluene at reflux had afforded single rearrangement only. Formation of both single and di-rearranged products reduced the degree of confidence with which conclusions could be drawn, since it could be argued that the first rearrangement was non-selective and that selectivity in the second rearrangement dictated product distribution. Only upon sole formation of singly rearranged product could that single rearrangement be said to be selective. For subsequent rearrangements we therefore varied the reaction conditions to effect single rearrangement only.

Several other unsymmetrical 2-(toluene-4-sulfonyl)malonates were subjected to single rearrangement (and di-rearrangement in some cases). The results of these further experiments are summarised in scheme 117 and table 3.




**Scheme 117:** *DCr reaction of unsymmetrical 2-(toluene-4-sulfonyl)malonates*

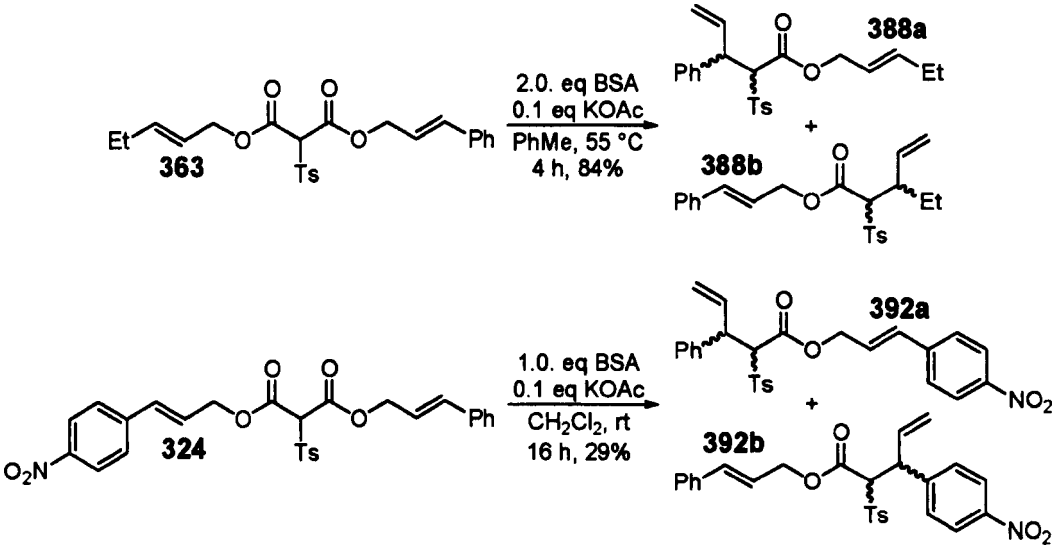
| Entry | $R^1$ | $R^2$ | % *Singly rearranged* | % *Di-rearranged* | Reaction conditions |
|---|---|---|---|---|---|
| 1 |  |  | 95% (**385**) | - | $CH_2Cl_2$, 0 °C, 2 h, 1.0eq. BSA, 0.1eq. KOAc |
| 2 |  | Ph | 27% (**384**) | 54% (**383**) | PhMe, reflux, 16 h, 2.0eq. BSA, 0.1eq. KOAc |
| 3 |  | Ph | 99% (**386**) | - | $CH_2Cl_2$, rt, 16 h, 1.0eq. BSA, 0.1eq. KOAc |
| 4 |  | Ph | 7% (**386**) | 19% (**387**) | PhMe, reflux, 16 h, 2.0eq. BSA, 0.1eq. KOAc |
| 5* | Ph | Et | 84% (**388**) | - | PhMe, 55 °C, 4 h, 2.0eq. BSA, 0.1eq. KOAc |
| 6* | Ph | Et | 16% (**388**) | 29% (**389**) | PhMe, reflux, 16 h, 2.0eq. BSA, 0.1eq. KOAc |
| 7 | Ph | H | 53% (**381**) | - | $CH_2Cl_2$, rt, 16 h, 1.0eq. BSA, 0.1eq. KOAc |
| 8 | Ph | H | 31% (**381**) | 12% (**390**) | PhMe, reflux, 16 h, 1.1eq. BSA, 0.1eq. KOAc |
| 9 | Ph |  | 82% (**391**) | - | $CH_2Cl_2$, rt, 16 h, 1.0eq. BSA, 0.1eq. KOAc |
| 10* | Ph |  | 29% (**392**) | - | $CH_2Cl_2$, rt, 16 h, 1.0eq. BSA, 0.1eq. KOAc |
| 11* | Ph |  | 6% (**392**) | 12% (**393**) | PhMe, reflux, 16 h, 2.0eq. BSA, 0.1eq. KOAc |
| 12 | H |  | 26% (**394**) | - | Neat, μw, 130 °C, 5 min, 2.0eq. BSA, 0.1eq. KOAc |

** Not totally regioselective: other regioisomer of singly rearranged product also observed*

**Table 3:** *Single rearrangement (and di-rearrangement) of unsymmetrical substrates*

A remarkable array of reactivity was observed. For example, in entry 1, the most reactive substrate underwent single rearrangement in essentially quantitative yield in 2 h and at 0 °C. In most other instances (those with a cinnamyl side-chain), single rearrangement could be induced at room temperature or slightly above. Only for the least reactive substrate (entry 12) were substantially more forcing conditions employed. 2-(Toluene-4-sulfonyl)malonate **368** ($R^1$: H, $R^2$: -C≡C-$SiMe_3$) appeared to be inert under all conditions tried when heated with an oil bath. Only under conditions of microwave irradiation neat in BSA was any single rearrangement observed (di-rearrangement was never observed). Whilst a degree of diastereoselectivity in the singly rearranged products was observed, this never exceeded 2:1.

Also quite remarkable was the observation that in all instances bar two, total regioselectivity in the singly rearranged product was observed, clearly indicating a significant difference between the activation energies of the two possible reactions. The only table entries for which total regioselectivity was not observed were 5,6,10 and 11. In these cases inseparable regio- and diastereoisomeric mixtures of single rearrangement products were isolated (scheme 118).

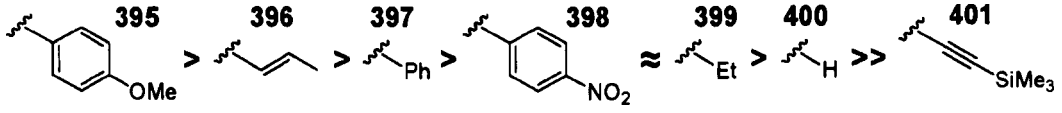



**Scheme 118:** *Only examples of single dCr displaying less than total regioselectivity*

The isolated mixtures consisted of (**388a:b**) and (**392a:b**), both in a regioisomeric ratio approximately 3:1. From this it may be concluded that a cinnamyl side-chain is more reactive than a pentenyl or *p*-nitrocinnamyl, but the difference in activation energy is less than in other instances.

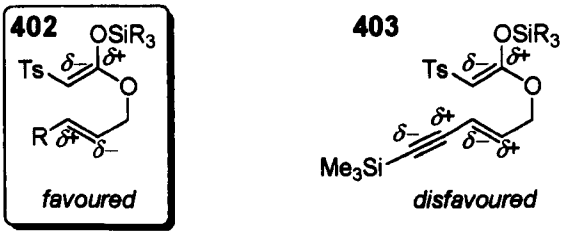
Nevertheless, the total regioselectivity observed in other instances implies that overall the reaction is remarkably susceptible to side-chain effects. The overall difference in activation energies for the most and least facile rearrangements is therefore sizeable.

From the results in table 3, it is possible to rank most of the side chains unambiguously in order of reactivity. This order is shown in scheme 119.



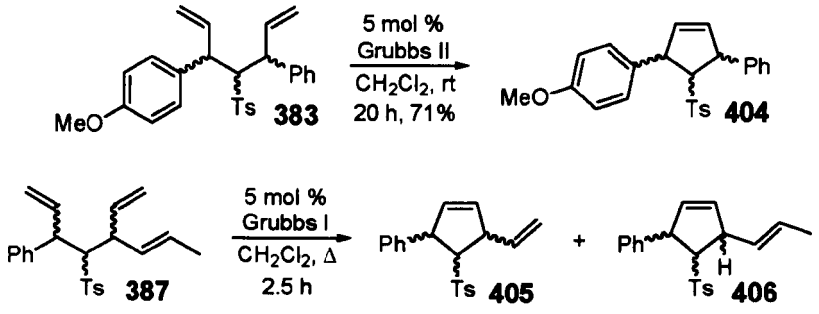

**Scheme 119:** *Order of reactivity of side-chains in single dCr of 2-(toluene-4-sulfonyl)malomates*

Note that a degree of ambiguity persists concerning the substituents "R: Et" **399** and "R: *p*-$NO_2$-$C_6H_4$-" **398**, since although they have both been shown to be slightly less reactive than "R: Ph" **397** (from the regioisomeric ratios), their reactivity with respect to each other has not been assessed. The early experiments with **327** ($R^1$: *p*-MeO-$C_6H_4$-, $R^2$: Ph) and **324** ($R^1$: Ph, $R^2$: *p*-$NO_2$-$C_6H_4$-) had appeared to indicate that the purely electronic trend was for electron rich side-chains to rearrange preferentially. This trend appears to be general for non-aromatic side-chains also, with an aryl (R: Ph) side chain rearranging in preference to an alkyl (R: Et) side chain and also the alkyl (R: Et) side-chain rearranging in preference to the unsubstituted (R: H) side chain. The rearrangement of the dienyl (R: CH=CH-$CH_3$) side-chain in preference to the cinnamyl (R: Ph) side-chain perhaps hints at a secondary preference for sterically less demanding side-chains. The low reactivity of the enynyl side-chain (it was inert to rearrangement) seems anomalous on first inspection. We ascribe this lack of reactivity not to the enynyl moiety itself, but to the trimethylsilyl group. This substituent, whilst bulky, is unlikely to exert a great steric influence as it is distant from the reactive array. Rather, we propose the –TMS group exerts an electronic influence, biasing the electronic distribution in the enyne in such a way as to be mismatched for rearrangement (**403**, scheme 120).




**Scheme 120**: *Possible electronic rationale for unreactivity of silylated enynyl side-chain in the dCr*

Various dual-dCr products of unsymmetrical 2-(toluene-4-sulfonyl)malonates were synthesised in addition to the single dCr products. This was a consequence of the need to vary conditions in each instance to find those which effected single rearrangement solely. Two of the unsymmetrical dual-dCr products were subjected to ring-closing olefin metathesis (scheme 121).



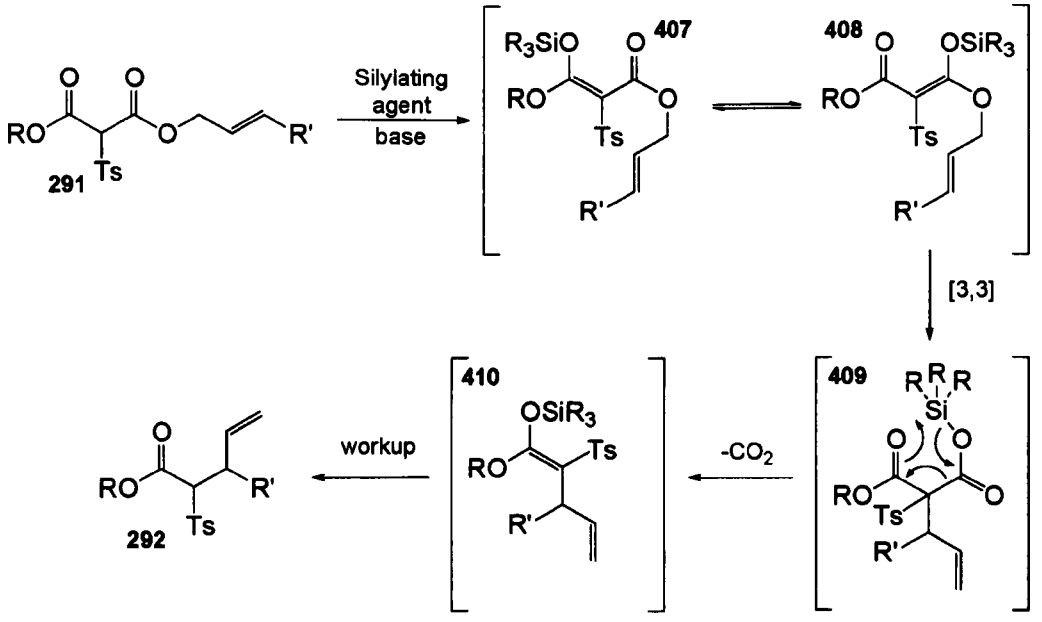

**Scheme 121:** *RCM of two unsymmetrical 2-(toluene-4-sulfonyl)malonate dual dCr products*

Ring-closing metathesis of **383** was routine. However, substrate **387** presented an interesting test of the chemoselectivity of the Grubbs catalyst. The less reactive Grubbs I system **202** was used and as expected, the species **405** from which the methyl group has been excised were the minority products. Accurate ratio quantitation was difficult due to the small scale of the reaction.

In all rearrangements in table 3 (and also of symmetrical 2-(toluene-4-sulfonyl)malonates, schemes 111 and 114), catalytic amounts of KOAc have been used, but stoichiometric amounts of BSA have been employed. Rearrangement of 2-(toluene-4-sulfonyl)malonates (be it single or di-rearrangement) appears distinct from the rearrangement of simple (toluene-4-sulfonyl)acetates in that it requires these stoichiometric amounts (or indeed excesses) of silylating agent. A catalytic amount of KOAc appears sufficient, however (indeed Mountford had established that in general larger amount of KOAc could in fact depress the yield).

Such observations might be explained as follows. Under reaction conditions which promote single rearrangement only, the single dCr product still contains an α-sulfonyl ester. It seems probable that the silyl ketene acetal of this ester is formed, effectively sequestering the silyl group, but that this silyl ketene acetal does not undergo the second rearrangement and so the silyl group is not released until workup, hence the requirement for stoichiometric amounts

of BSA. Note that for the first rearrangement of a 2-(toluene-4-sulfonyl)malonate, it is probable that a second reaction pathway is operating in addition (or in preference) to that outlined in scheme 86 (section 2.1.1.2). Loss of the first molar equivalent of $CO_2$ and formation of the second silyl ketene acetal may occur in a concerted silatropic rearrangement (scheme 122). This proposal is discussed further elsewhere.[88] This mechanism imposes no requirement for nucleophilic silyl group abstraction, hence perhaps the sufficiency of catalytic amounts of KOAc.



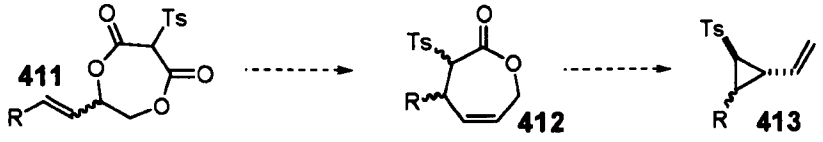

**Scheme 122:** *Alternative silatropic mechanism for single dCr of a 2-(toluene-4-sulfonyl)malonate*

The above explanation is valid for single rearrangements only. Under conditions where the second rearrangement occurs, a fully catalytic mechanism might reasonably be expected to operate, as the silyl group should be liberated at the time of the second decarboxylation. As stated earlier, we can only suppose that the reaction conditions required to effect the second rearrangement are harsh enough to degrade the BSA, hence the requirement for an excess.

## 2.1.4 – Cyclopropane-Forming Decarboxylative Claisen Rearrangement

### *2.1.4.1 – Original proposal*

Having synthesised and rearranged a variety of open-chain 2-(toluene-4-sulfonyl)malonates, we sought to expand the scope of the reaction to cyclic 2-(toluene-4-sulfonyl)malonates. It occurred to us[96] that the reaction could be employed in a novel cascade that would constitute a stereodefined synthesis of cyclopropanes (scheme 123).



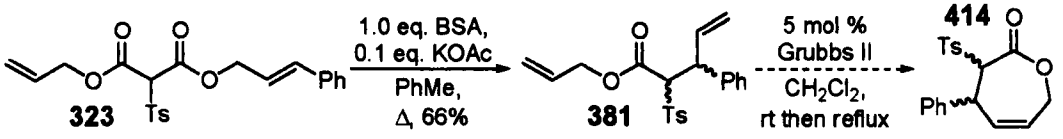

**Scheme 123:** *Proposed dual dCr of cyclic malonate, leading to cyclopropane*

In the first step the dCr reaction would result in the exocyclic olefin migrating into the ring. The second dCr reaction would yield the cyclopropane shown. As the substrate is cyclic, the silyl ketene acetal geometry would be constrained, leading to a defined relationship between two of the stereocentres in the product.

### *2.1.4.2 – Model system*

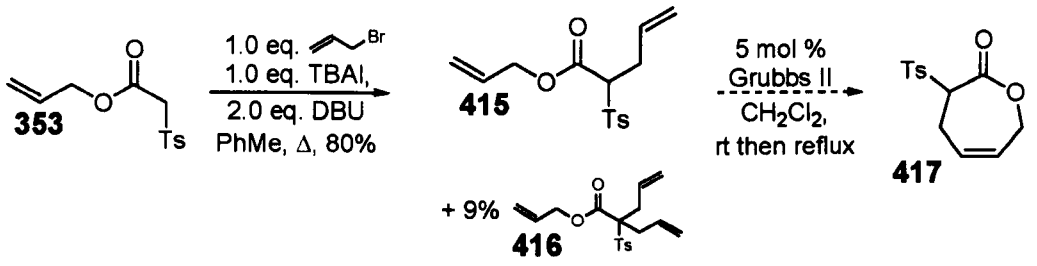
When this reaction sequence was first envisaged, the second of the two steps seemed perhaps the more speculative. Thus, rather than attempt the synthesis of **411**, it was decided to synthesise a seven-membered unsaturated cyclic lactone such as the intermediate **412** in the above scheme. This would serve as a model system for ascertaining the feasibility and moreover the facility of the cyclopropyl-forming step. Note that a literature precedent[97] exists for such a ring contraction/rearrangement, albeit differently substituted, without an α-sulfone and without decarboxylation.

The first attempt to synthesise a seven-ring lactone such as **414** (R=Ph) was via simple ring-closing metathesis of **381**, the single rearrangement product of **323** (scheme 124). To our initial surprise,[98] ring-closing metathesis of **381** was entirely unsuccessful. Starting material was gradually consumed, but none of the desired product was ever isolated.



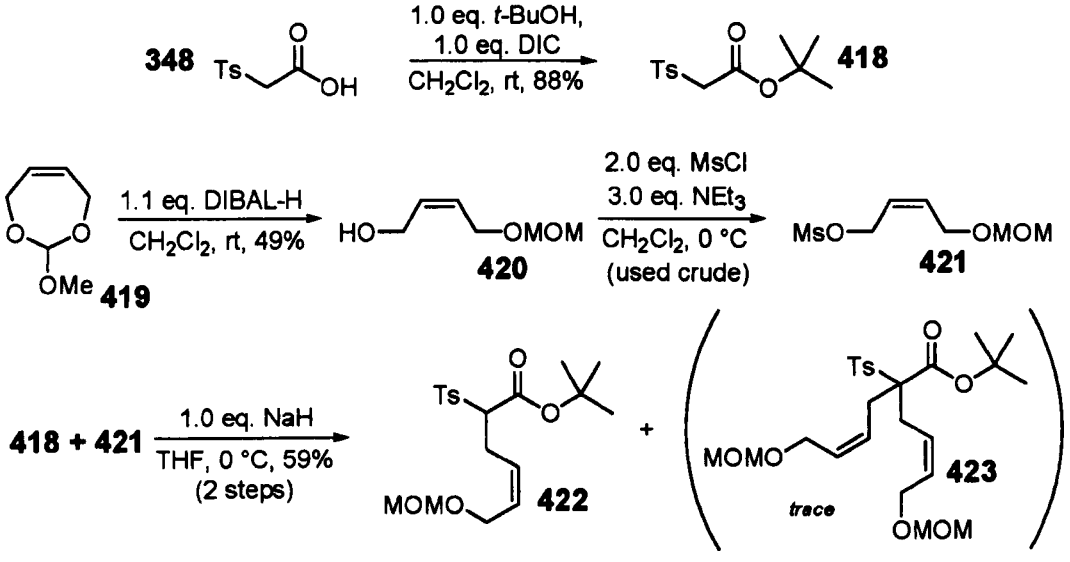

**Scheme 124:** *Ring-closing metathesis did not provide the unsaturated lactone*

Whilst it seemed unlikely the phenyl group was interfering with the metathesis, we attempted the unsubstituted closure to be sure. The corresponding RCM substrate with R=H (**415**) was easily synthesised in one step from previously-prepared allyl (toluene-4-sulfonyl)acetate **353** (also isolated diallylated compound, **416**). This too was not susceptible to ring-closing metathesis (scheme 125).



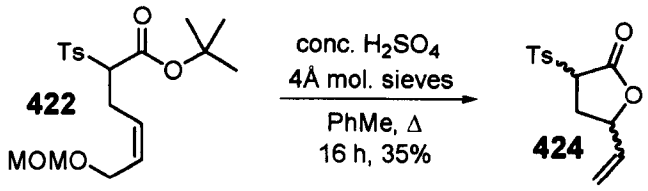

**Scheme 125:** *RCM of the unsubstituted analogue was similarly unsuccessful*

In view of this perplexing failure, it was decided to attempt synthesis of the lactone **417** via an alternative strategy, namely lactonisation as the last step. The doubly protected compound **422** was synthesised as shown in scheme 126. The starting material **419** was provided by a co-worker[99] and may be synthesised in one step from the corresponding diol and trimethyl orthoformate.



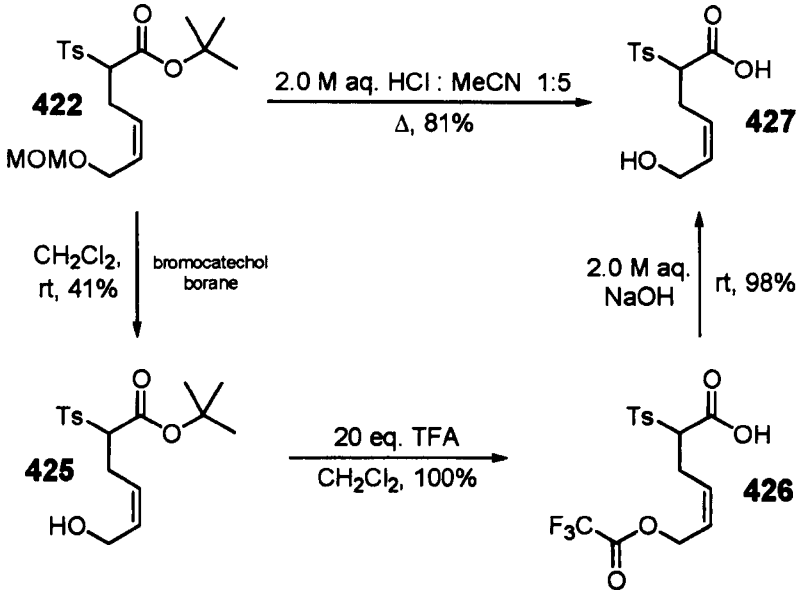

**Scheme 126:** *Synthesis of lactonisation precursor*

Double deprotection of the lactonisation precursor **422** was then attempted, under anhydrous acidic conditions in the first instance. The only isolated product **423** was that shown in scheme 127, presumably forming as a result of intramolecular interception during the cleavage of the –MOM group.



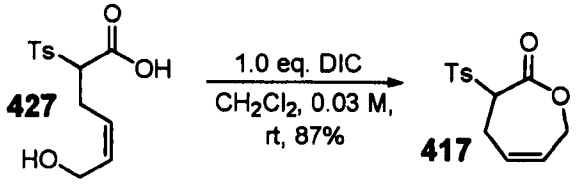

**Scheme 127:** *Formation of undesired γ-lactone product*

Such a result was initially taken to indicate that sequential deprotection steps would be required. The three-step sequential cleavage sequence is shown in scheme 128. Only at a later date was it determined that the cyclisation precursor **427** could indeed be formed in one step from the doubly protected (toluene-4-sulfonyl)acetate **422** under aqueous acidic conditions.



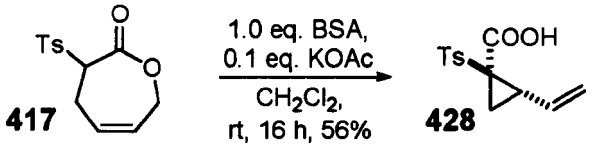

**Scheme 128:** *Synthesis of ω-hydroxyacid by sequential or one-step procedure*

With the cyclisation precursor **427** in hand, the cyclisation was executed under standard esterification conditions; use of very high dilution was not necessary.




**Scheme 129:** *Lactonisation was facile*

We then attempted to induce the dCr reaction under mild conditions. The reaction was extremely facile, giving quantitative conversion in 16 h by TLC at room temperature. Such mild conditions do not generally induce rearrangement of a (toluene-4-sulfonyl)acetate or the second rearrangement of a malonate. Spontaneous decarboxylation did *not* occur, however, the isolated product **428** being the acid (scheme 130). The stereochemistry shown has not been proven. It is only that which is predicted, assuming a [4n+2] thermal reaction.



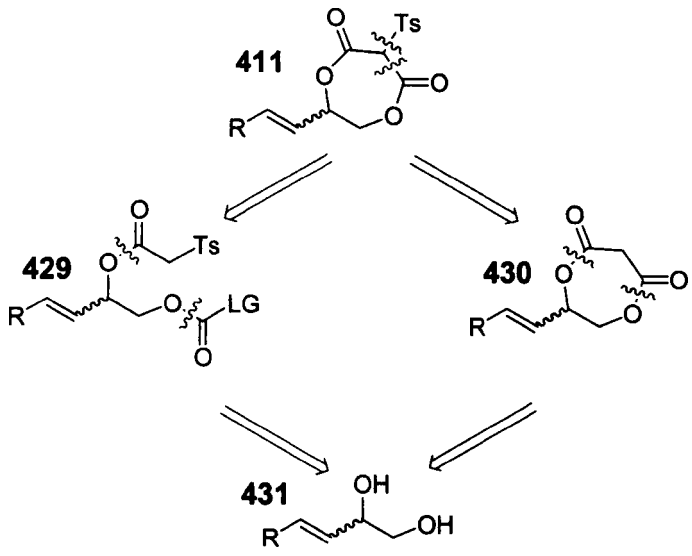

**Scheme 130:** *Successful cyclopropane formation*

Various explanations may be posited for the lack of spontaneous decarboxylation. For example, the orbital rehybridisation in a cyclopropane imparts enhanced *s*-character (and hence enhanced strength) to the C–C bond that is to be cleaved in the decarboxylation. Also, the anomalously mild conditions which effect cyclopropane formation may simply not be sufficiently forcing to effect the decarboxylation. At elevated temperatures, both processes might be observed in one pot.

### *2.1.4.3 – Studies towards the 7-membered cyclic malonate*

Rather than probe the properties of this cyclopropane further, we sought instead to synthesise the 7-membered cyclic malonate **411**. We considered our model study to have been essentially successful and believed it appropriate to study the cyclopropane formation further after assessing the viability or otherwise of the originally proposed cascade.

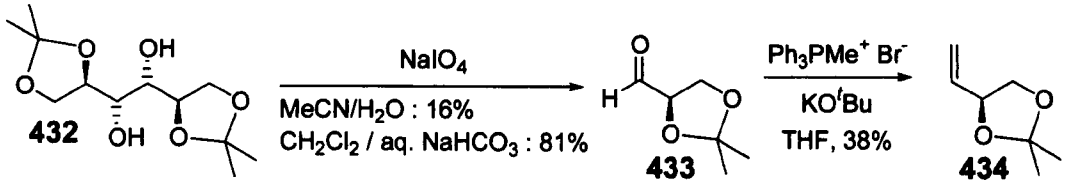
Retrosynthetic analysis of **411** suggested two fundamentally differing strategies. Formation of the malonate ring with the toluene-4-sulfonyl group already in place (from synthon **429**) might be viable. Alternatively, one could disconnect the C-S bond shown (leading to **430**) and attempt formation of the parent ring system before sulfonylation (scheme 131).




**Scheme 131:** *Possible routes to the cyclic 2-(toluene-4-sulfonyl)malonate*

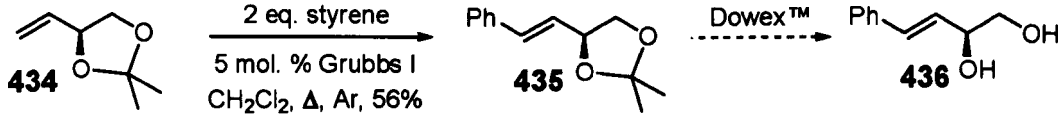
Regardless of which strategy is chosen, the intermediate synthons may be disconnected back to a common intermediate, 1-substituted 3,4-dihydroxybut-1-ene **431**. It was envisaged that the R- group could be introduced by cross-metathesis, either as the last step prior to dual rearrangement, or earlier in the synthetic scheme. 3,4-Dihydroxybut-1-ene itself is commercially available as the racemate. It was decided to also synthesise the enantiopure series, however, to facilitate studies on the stereoselectivity of the proposed rearrangement.

We proposed to access the desired enantiopure diol from a commercially available selectively protected sugar, as shown in scheme 132. Periodate cleavage of **432** to give aldehyde **433** was initially low yielding as **433** is volatile. Better results were obtained using a literature procedure[103] whereby a more volatile solvent system ($CH_2Cl_2$ / aq. $NaHCO_3$) was removed without significant product loss. Wittig methylenation of **433** to give **434** was also problematic as **434** was even more volatile and was never isolated in good yield.



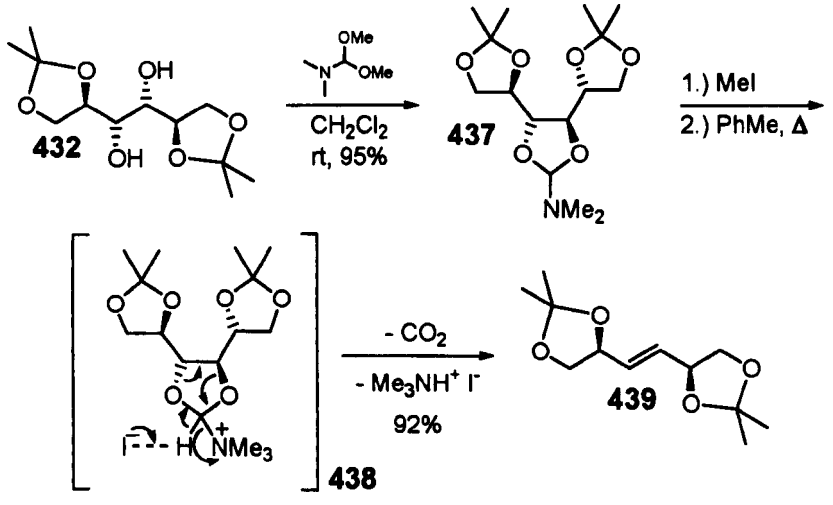

**Scheme 132:** *Protected diol formation was hampered by volatility*

Sufficient olefin **434** was isolated to permit an initial exploration of the feasibility of cross-metathesis at this stage. The cross metathesis partner chosen was styrene, which it was hoped would give enantiopure **435**. Such cross-metathesis components are classed as Type I and Type II (nomenclature due to Grubbs[100]) and as such Grubbs' 1st generation catalyst **202** was indicated for the reaction.[100] A literature precedent exists for such a cross-metathesis.[101] Olefin **435** was isolated in 56% yield (exclusively *E* isomer). Attempted Dowex™-catalysed deprotection of **435** failed, however, likely due to the presence of residual ethyl acetate from the column eluent in **435**, resulting in formation of a complex mixture of deprotection–transesterification products (scheme 133).



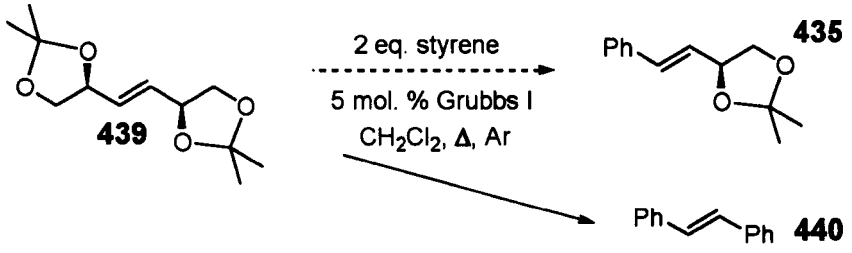

**Scheme 133:** *Cross-metathesis was successful; deprotection was not*

We were confident that deprotection of **435** would not fail upon subsequent attempts, were the substrate distilled to sufficient purity. The most vexing aspect of the synthetic scheme outlined above was loss of **434** due to its volatility. It was therefore decided to synthesise **435** and other substituted diols via cross-metathesis of the homodimer of **434**. It was thought that **439** would undergo cross metathesis to provide **435** just as easily but not be subject to the same volatility problems. Synthesis of **439** was via the *ortho*-amide species **437** which is easily synthesised from *N*,*N*'-dimethylformamide dimethyl acetal and subsequently fragments upon *N*-methylation (scheme 134). A literature precedent for the synthesis of **439** by this route exists.[102]



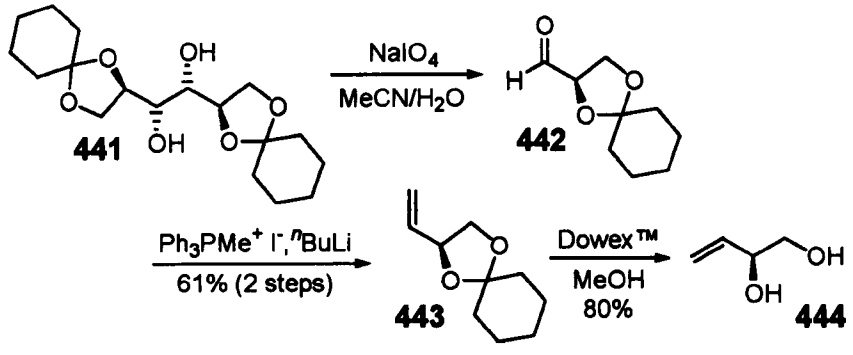

**Scheme 134:** *Formation of homodimer for cross-metathesis*

Olefin **439** was subjected to the cross-metathesis conditions employed for the conversion of **434** to **435**. Homodimer **439** initially appeared inert to cross metathesis, however, so the reaction time was increased. A new product was formed, but upon isolation it was shown to be *trans*-stilbene (scheme 135).




**Scheme 135:** *Unexpected* trans-*stilbene formation*

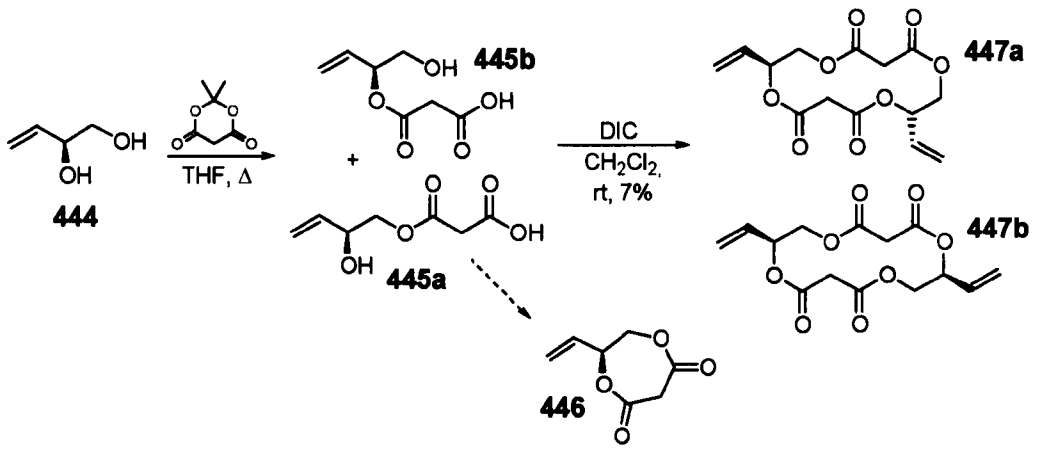
Such a result is not in keeping with the predictions of Grubbs.[100] As cross-metathesis could be performed later in the synthesis, it was decided not to pursue this further at that time. It was instead decided to optimise a route to the enantiopure diol **444** (i.e. **431**, R: H). To avoid volatility problems, a differently protected sugar starting material **441** was chosen. The bulkier protecting group was successful at avoiding problems of volatility and diol cleavage to **442** and Wittig methylenation to **443** were routinely high yielding. Additionally, deprotection of **443** to give enantiopure diol **444** (i.e. enantiopure **267**, R: H), while slow, was high yielding and uncomplicated. Other workers[103] have commented on the volatility of **434** and noted a preference for use of compounds such as **443**.




**Scheme 136:** *Route to enantiopure diol not beset with volatility problems*

Having synthesised enantiopure **444**, our attention turned to how best to incorporate this into the desired 7-membered cyclic malonate skeleton. We foresaw that reaction of **444** with Meldrum's acid would lead to a mixture of hydroxyacids **445** which should cyclise upon treatment with a coupling agent

at high dilution to give **446** (i.e. enantiopure **430** with R: H) as shown in scheme 137.

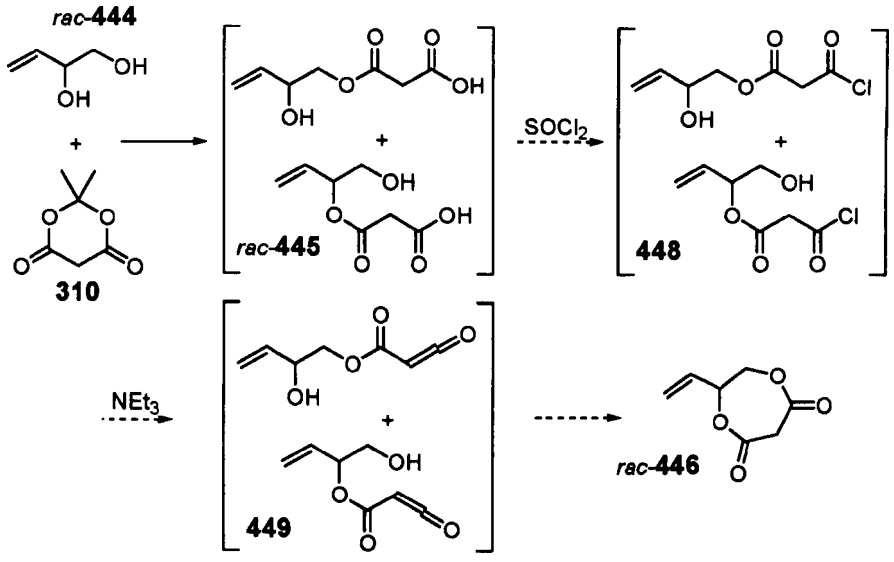



**Scheme 137:** *Attempted cyclic malonate formation resulted in dimer formation*

The mixture of intermediates **445** was taken on crude to the next step. The attempted cyclisation led to formation of many new species by TLC. Only the least polar of these was isolable in pure form. It transpired it was a mixture of the regioisomeric dimers **447** shown. Use of malonyl dichloride and triethylamine (or malonic acid and DIC) with diol **444** gave no desired product. Upon repetition of the procedure in scheme 137, the opening of Meldrum's acid was shown not to be a clean process – before all diol was consumed, a proportion of the hydroxyacid intermediates had decarboxylated to the corresponding diol monoacetates.

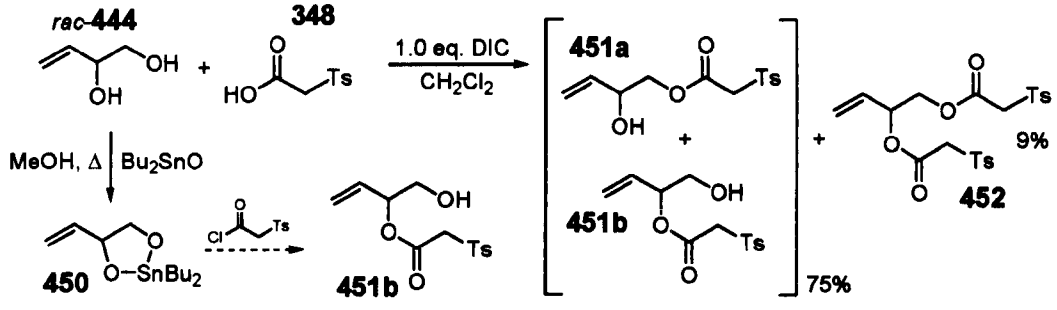
It seemed to us that of the two esterifications required to form the 7-membered cyclic malonate from the diol, the first (non-cyclising) one should be relatively facile. It appeared to be the second, cyclising esterification which presented problems. We thought use of a reactive electrophile such as a ketene in the second step might be able to achieve the desired cyclisation. It was therefore decided to synthesise the hydroxyacids **445** as previously and then to attempt acyl chloride formation (which may itself induce cyclisation) and elimination to the corresponding ketenes (scheme 138).

When ketene formation was attempted on this material, no desired product was detected; the only species isolated appeared to be the cyclic sulfite of the diol (from reaction with $SOCl_2$), indicating incomplete reaction in the formation of the hydroxyacids.




**Scheme 138:** *Proposal for hybrid acid / acyl chloride route*

We elected to explore an alternative strategy for incorporation of the diol fragment, i.e. the alternative retrosynthetic pathway illustrated in scheme 131 that proceeds via intermediate **429**. We tried to utilize the methodology developed in section 2.1.2.4 – single esterification of the diol with (toluene-4-sulfonyl)acetic acid, carboxylation of the remaining free alcohol and subsequent closure to the target **411** (R: H). Racemic diol was initially employed for this slightly speculative route. Single esterification of the diol with 1 equivalent of (toluene-4-sulfonyl)acetic acid and DIC in fact gave a mixture of primary and secondary mono-esters (along with a small amount of doubly esterified product and a small amount of unreacted diol, scheme 139).

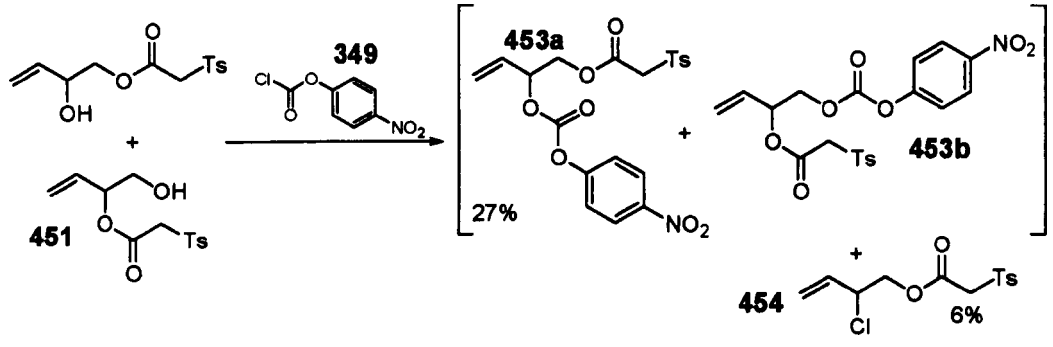



**Scheme 139:** *Esterification was not regiospecific*

Selectivity for the primary esterification product over the secondary was around 4:1 by NMR. The two regioisomeric mono-esters were totally inseparable. Interestingly, in all eluents the $R_f$ difference between the two products was sufficient to suggest that separation should be possible, yet total co-elution was always observed, perhaps implying an interaction on silica.

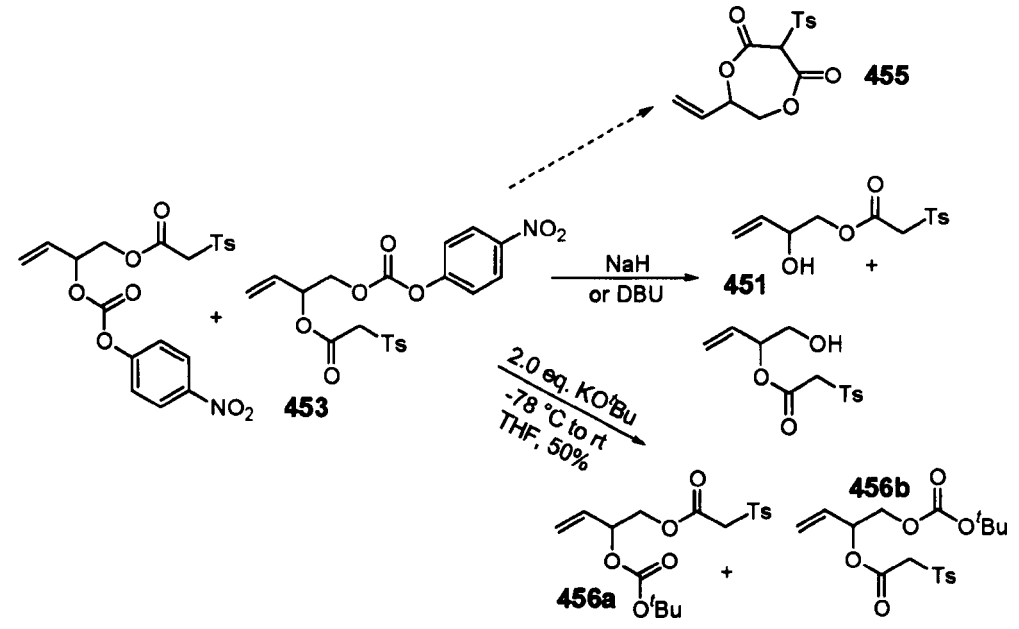
Attempts to render the reaction selective for either isomer were not successful – addition of the coupling agent to a mixture of the diol and acid dropwise over several hours via syringe pump resulted in the same selectivity. An attempt to improve selectivity by pre-forming the active ester (from (toluene-4-sulfonyl)acetic acid and *N,N'*-di*iso*propyl carbodiimide) and adding this slowly to the diol resulted only in isolation of active ester decomposition products and unreacted diol. Finally, formation of the stannylene acetal of the diol[104] and attempted reaction of this with (toluene-4-sulfonyl)acetyl chloride did not result in the isolation of any desired products.

The inseparability of regioisomers **451** need not necessarily hinder synthesis of the desired target **411**, as both regioisomers ultimately may be cyclised to the same product. The carbonyl fragment was introduced by use of *p*-nitrophenyl chloroformate (scheme 140), as previously. The resultant mixture of carbonates **453** was also inseparable, the two components having identical $R_f$ values in all eluents explored. A byproduct **454** was also isolated, the result of chloride displacement of the carbonate in the predominant isomer.



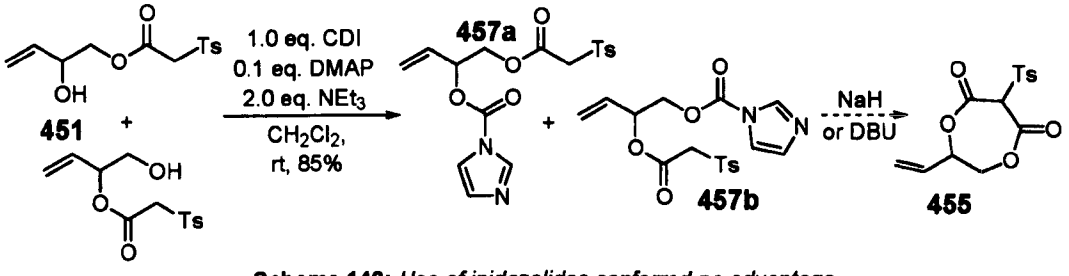

**Scheme 140:** *Formation of carbonates for intramolecular carboxylation (and byproduct)*

Cyclisation of **453** was attempted using a variety of bases and conditions (scheme 141). Use of potassium *tert*-butoxide led to isolation of the corresponding *tert*-butyl carbonates **456**, the result of nucleophilic addition of the base (as described in section 2.1.2.4). Use of DBU or NaH led to isolation of the mono-esters **451** (the formal result of carbonate hydrolysis) and an unidentified highly polar byproduct. Use of $NEt_3$ gave unreacted starting material.




**Scheme 141:** *Cyclisation by intramolecular carboxylation was not successful*

It was decided to utilize an alternative carbonyl surrogate. Reaction of **451** with *N,N'*-carbonyl diimidazole yielded the corresponding imidazolides **457** in good yield (scheme 142). These too were inseparable. Attempted cyclisation of **457** with NaH and DBU was unsuccessful, resulting only in formation of mono-esters **451**, as per the *p*-nitrophenyl carbonates

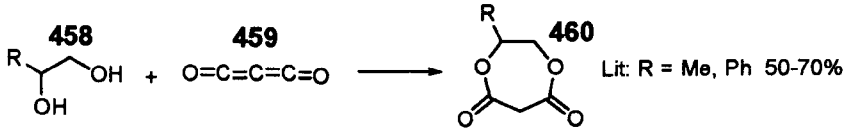



**Scheme 142:** *Use of inidazolides conferred no advantage*

We gave consideration to the possible causes of our repeated failure to form a cyclic malonate, sulfonylated or otherwise. One possibility is that in the attempted carboxylations above, the desired product was transiently formed, but was subsequently ring-opened by water, hydroxide or another nucleophilic species. The resulting open-chain species would then likely decarboxylate, affording the formal carbonate hydrolysis products that were in fact observed. To rationalize the implied reactivity of the 7-membered cyclic malonate towards incipient nucleophiles, it should be considered that the parent ring structure is likely highly strained and unstable. Both esters are constrained in the *s*-cis conformation and the two ester dipoles are necessarily aligned as to

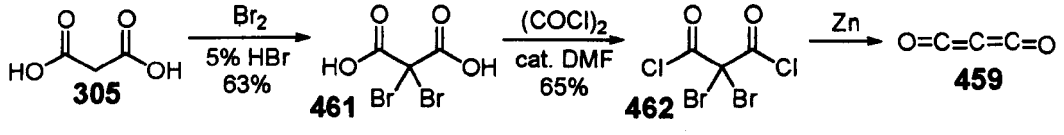
be additive. It is telling that reports of 7-membered cyclic malonates are sparse in the literature. An additional possibility is that such a ring closure was inherently disfavoured. The same arguments for instability of the cyclic system also suggest that for the acyclic precursor, the necessary conformation for cyclisation would be unlikely to be highly populated.

We found reports in the literature[105] of the synthesis of 7-membered cyclic malonates such as ours via use of "carbon suboxide" **459**. Originally prepared by Diels and Wolf,[106] this little-known heterocumulene species reportedly reacts selectively and in high yield with the diol precursor to afford the desired 7-membered rings in one step (scheme 143).




**Scheme 143:** *Literature precedent for use of carbon suboxide*

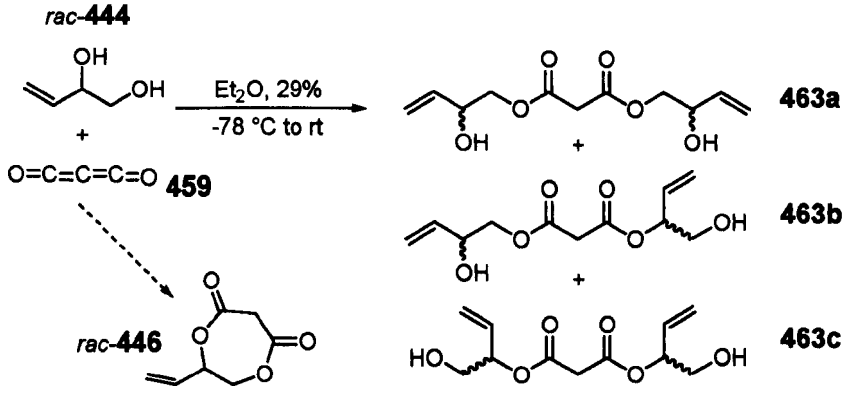
Tellingly, the authors note that synthesis of such rings via ring closure from malonic acid or derivatives is low yielding, giving impure oligomeric mixtures that are hard to purify. The use of carbon suboxide appeared potentially to be a succinct route to our target. We were initially discouraged by the practical difficulties that would have been entailed in generating $C_3O_2$ by the methods the authors reportedly used (passage of carbon monoxide through an ozonizer or pyrolysis of O-acetyltartaric anhydride[107] at 600–700°C). We then became aware of a report[108] from Staudinger who generated carbon suboxide **459** via zinc-mediated dehalogenation of 2,2-dibromomalonyl dichloride **462**. This procedure has been employed by other workers.[109] A recent report due to Padwa[110] provides a detailed experimental procedure. Malonic acid is treated with bromine in 5% aqueous HBr to afford 2,2-dibromomalonic acid **461**. This is reacted with oxalyl chloride to give **462**, a yellow solid, mp 39–42 °C. We found that this intermediate was passably stable upon prolonged cold storage as a solid, but that it may be most conveniently delivered as a liquid. Finally, precursor **462** is dehalogenated with zinc to give carbon suboxide (scheme 144) which is reacted *in situ* with a suitable bidentate nucleophile.




**Scheme 144:** *Generation of carbon suboxide from a perhalogenated precursor*

In practice this procedure was a little unwieldy. The bromination of malonic acid at the concentration stipulated gave a precipitate, the viscosity of which severely retarded stirring. Note also that upon removal of the ice bath, a significant exotherm was observed. The bis(acid chloride) **462** is purified by distillation under reduced pressure, which does afford pure product. The formation of carbon suboxide and its trapping was attempted in turn. Dropwise addition of an ethereal solution of **462** to activated zinc dust resulted in an exothermic reaction (after initiation through external heating, the dehalogenation reaction was sufficiently exothermic to maintain reflux throughout). The carbon suboxide formed ($bp_{760}$ 7 °C) was expected to co-distil with the ether vapour, into a cold finger at –78 °C fitted with a receiver flask. This contained an ethereal solution of nucleophile, also at –78 °C.

In the first instance, the receiver flask was simply charged with methanol. Upon application of the $C_3O_2$-generation procedure and subsequent warming of the receiver flask from –78 °C to rt over several hours, dimethyl malonate was isolated in 54% yield. Satisfied $C_3O_2$ was being generated as desired, we proceeded to use of an ethereal solution of diol *rac*-**444** in the receiver flask. Upon application of the same procedure, however, no desired product was detected. Instead, the unwanted product of double intermolecular addition **463** was isolated as a mixture of regio- and diastereoisomers (the majority product being that arising from double primary alcohol attack).




**Scheme 145:** *Attempted cyclic malonate synthesis gave only 2:1 adduct*

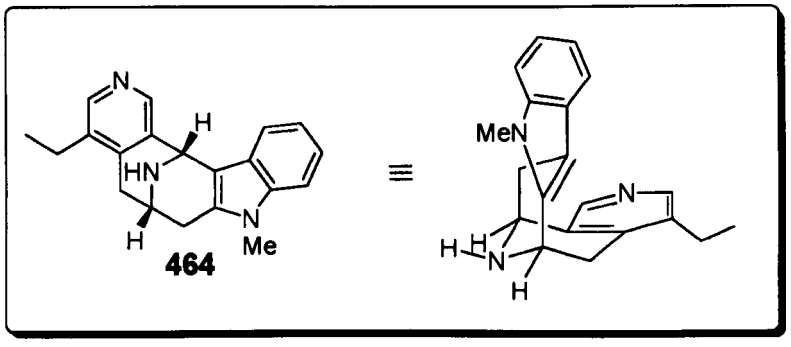
## 2.1.5 – Conclusions from Methodology Studies

The efforts described above constitute the methodology work to date on the dCr rearrangements of bis(allyl) 2-(toluene-4-sulfonyl)malonates. Many examples of this class of compound have been synthesised and their rearrangement characteristics elucidated. Progress has also been made towards the cyclic 7-membered malonate **411**. It is regrettable **411** was not prepared, but this author is of the opinion that further studies with carbon suboxide still represent a likely entry to the desired ring system. The formation of **463** could probably be suppressed by variation of the reaction conditions, for example employing a more dilute diol solution. Whilst the original proposal outlined in section 2.1.4.1 has yet to be fulfilled, the successful outcome of cyclopropane model studies provides significant impetus for it to be realized in future.

## 2.2 – Studies Towards the Total Synthesis of (–)-Suaveoline

### 2.2.1 – Background and Isolation

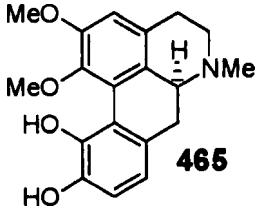
(–)-Suaveoline **464** is a pentacyclic macroline alkaloid isolated in 1972 from the trunk bark of *Rauvolfia suaveolens*.[111] It has since also been isolated from other species of the *Rauvolfia* family.[112] The structure is shown in scheme 146.




**Scheme 146:** *Structure of (-)-suaveoline*

Total syntheses of both (±)-suaveoline and (–)-suaveoline have been reported by three laboratories.[24,25,113] In addition, the synthesis detailed in section 1.5 constitutes a formal racemic synthesis.

Note that a different natural product **465**, an aporphine alkaloid isolated[114,115] in 1932, has also been named "suaveoline" (scheme 147); this ambiguity of nomenclature[116,117] does not appear to have been commented on in the literature. The efforts described herein were towards the indolyl structure **464** only.



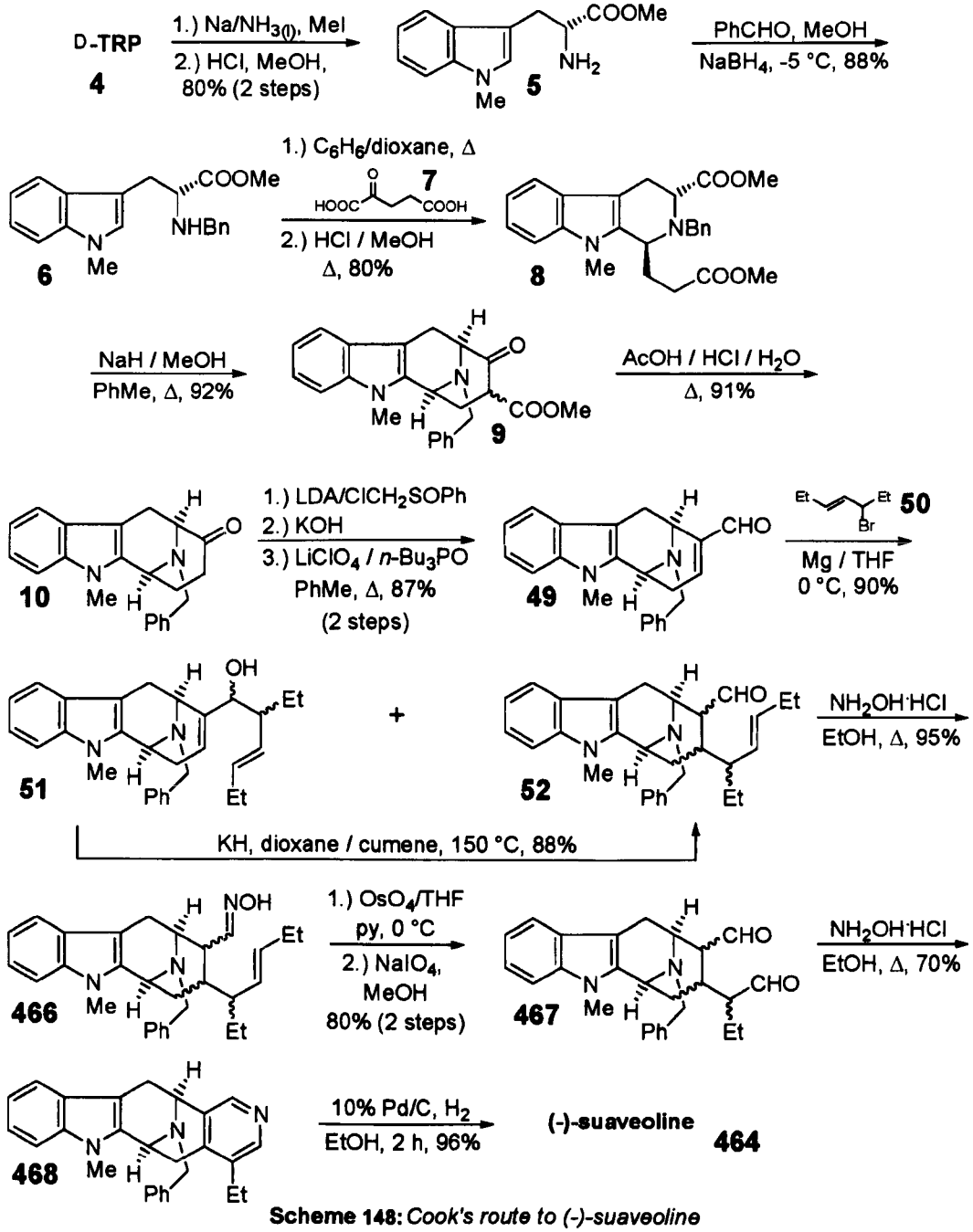

**Scheme 147:** *Alternative aporphine "suaveoline"*

The stereochemistry shown in scheme 147 was inferred from that of a related compound, di-*O*-methylmagnoflorine iodide.[118,119]

## 2.2.2: Other Workers' Syntheses

### *2.2.2.1: Cook's syntheses*

Cook and co-workers were the first to report the synthesis of (±)-suaveoline in 1989.[113a] Over the next 4 years the synthesis was refined[113b,113c] and an enantioselective synthesis[113d] was published in 1993 (scheme 148).



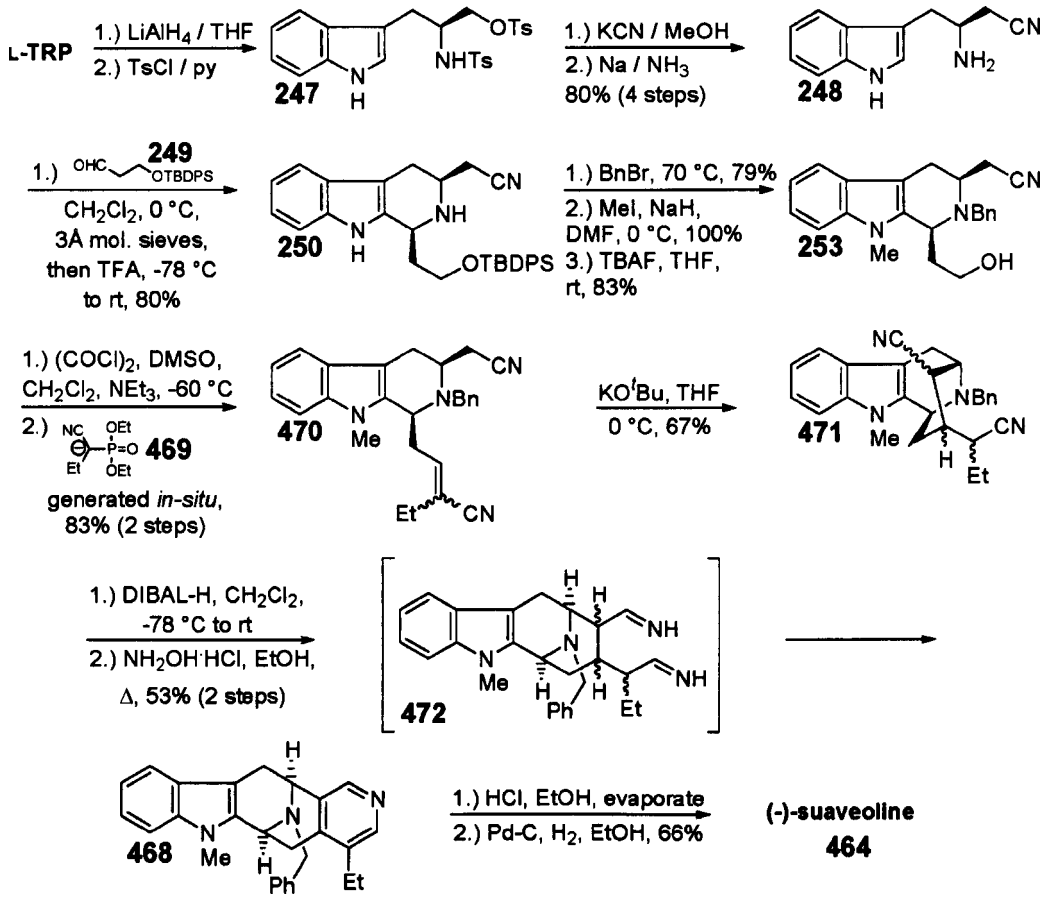

**Scheme 148:** *Cook's route to (-)-suaveoline*

The synthesis of tetracyclic ketone **10** was discussed in detail in section 1.2.1. The subsequent steps are similar to those employed in Cook's synthesis of (–)-norsuaveoline (section 1.2.5). They are discussed here only briefly. Ketone **10** was converted into α,β-unsaturated aldehyde **36** *via* rearrangement of an intermediate epoxide. This aldehyde was then homologated by means of a *pseudo*-symmetric Grignard reagent. Both 1,2- and 1,4-addition products resulted (in a 1:1 ratio). The undesired 1,2-addition product could be converted to the formal product of 1,4-addition by oxyanion–Cope rearrangement. To introduce the second aldehyde functionality required for pyridine formation, the pre-existing carbonyl was protected as an oxime. Careful (stoichiometric) osmylation of the olefin (in preference to the indole 2,3 bond) was followed by oxidative diol cleavage (as a discrete step) and regeneration of the original aldehyde. The dialdehyde was then cyclised to the desired pyridine with hydroxylamine. $N_{\beta}$-Deprotection then gave **464**.

This synthesis has several features of note, the first being that the starting material is unnatural D-tryptophan. The ensuing synthetic steps (14 in the longest linear sequence, proceeding in 18% overall yield) contain several features relevant to our own synthetic proposal. The use of a *pseudo*-symmetrical fragment for introduction of the ethyl group and the care that is needed to effect oxidative olefin/diol cleavage in the presence of an indole are themes which recur later in this section. It must be emphasised that Cook's work was not solely directed towards (–)-suaveoline. The efforts described above contain a great deal of methodology that Cook has systematically applied elsewhere to achieve syntheses of an array of related alkaloids.

### *2.2.2.2: Bailey's syntheses*

Bailey and co-workers first published on the subject of suaveoline[24a] in 1993, with an enantiospecific synthesis of ketone intermediate **10** in Cook's original racemic synthesis, thus constituting a formal enantiospecific synthesis. A year later they published[24b] a more extensive formal enantiospecific synthesis, converging on a later intermediate **36** in Cook's route. A further formal synthesis followed[24d] in 1997, although by this point the group had already reported[24c] their first enantiospecific total synthesis. Further efforts[24e] led to some refinement of this synthesis, the most recent route being published[24f,24g] in 2000. It is summarized in scheme 149.



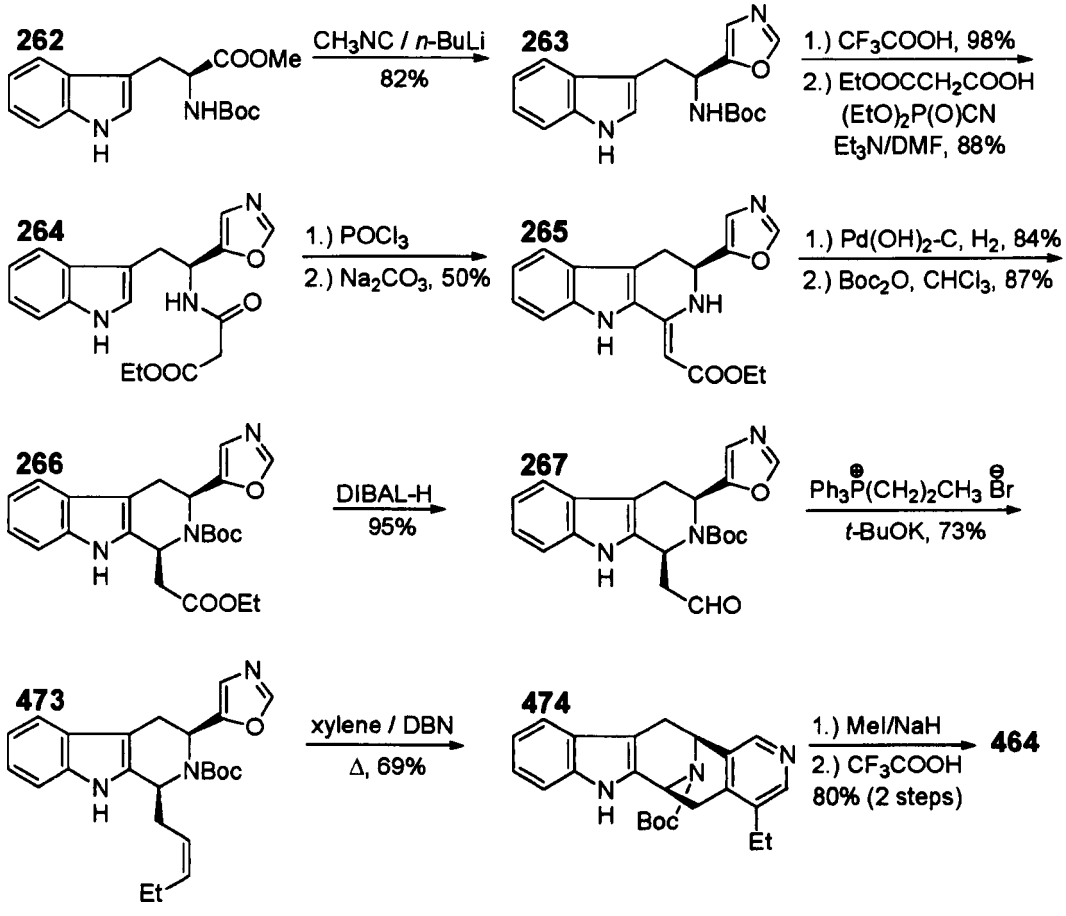

**Scheme 149:** *Bailey's route to (-)-suaveoline*

Starting from the proteinogenic amino acid, Bailey and co-workers accessed the aminonitrile **248** in 4 steps, by a protocol which requires no chromatography. The ensuing Pictet–Spengler cyclisation of the $N_\alpha$,$N_\beta$-unprotected substrate proceeded with total 1,3-*cis* selectivity. The choice of aldehyde coupling partner arose from extensive study – Bailey reports that at the time of this synthesis only two other examples were known that gave such diastereoselectivity, both with bulky side chains containing aromatic moieties; he speculates $\pi$-stacking may be involved in stereocontrol. $N_\alpha$- and $N_\beta$-alkylation and hydroxyl deprotection was followed by oxidation and Horner–Wadsworth–Emmons[120] reaction. The phosphonate anion was generated *in situ* by treatment of diethyl (cyanomethyl)phosphonate with NaH and EtBr, then a second equivalent of NaH. Such a strategy introduces the ethyl group at the carbon that will eventually become the pyridyl *meta* position *prior* to formation of the tetracycle. In so doing, the need to functionalise this position *in* the tetracycle (shown to be more hindered) was removed. Closure to the tetracycle **471** is by means of a vinylogous Thorpe cyclisation.[121] The

resultant 1,5-dinitrile may then be reductively transformed into a pyridine in a direct manner. $N_\beta$-debenzylation of the hydrochloride completes the synthesis (13 steps longest linear sequence, 8% overall yield). Interestingly, it was later shown that upon treatment of the dinitrile with DIBAL-H, subsequent treatment with $NH_2OH$ is not necessary - $N_\beta$-benzylsuaveoline is formed directly.

### *2.2.2.3: Ohba's synthesis*

The 2004 total synthesis of (–)-suaveoline reported by Ohba and co-workers[25] arose from their interest in oxazole–olefin Diels–Alder reactions as a route to annulated pyridines (scheme 150).

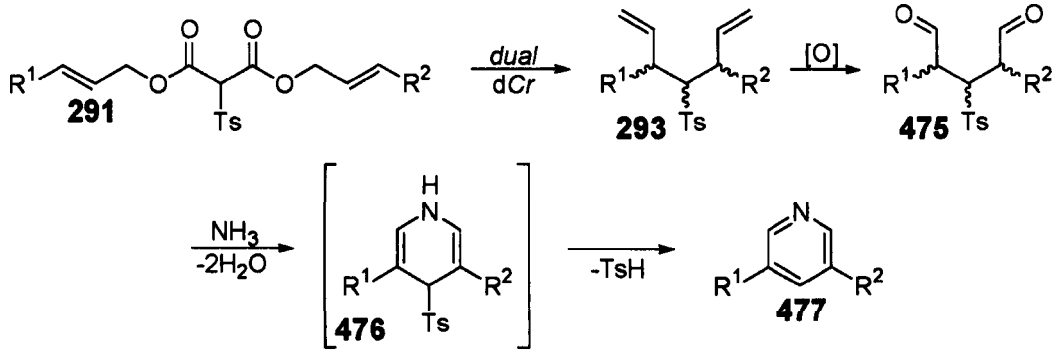



**Scheme 150:** *Ohba's route to (-)-suaveoline*

This synthesis is exceedingly similar to the synthesis of 1-demethyl-20-deethylsuaveoline detailed in section 1.9; the reader is directed to this section for a discussion of the noteworthy aspects of this work. This succinct synthesis proceeds in 11 steps and 10% overall yield from (*S*)-$N_\beta$-Boc-tryptophan methyl ester. It is noteworthy that $N_\alpha$-protection was unnecessary.

## 2.2.3: Relevant Methodology and Retrosynthesis

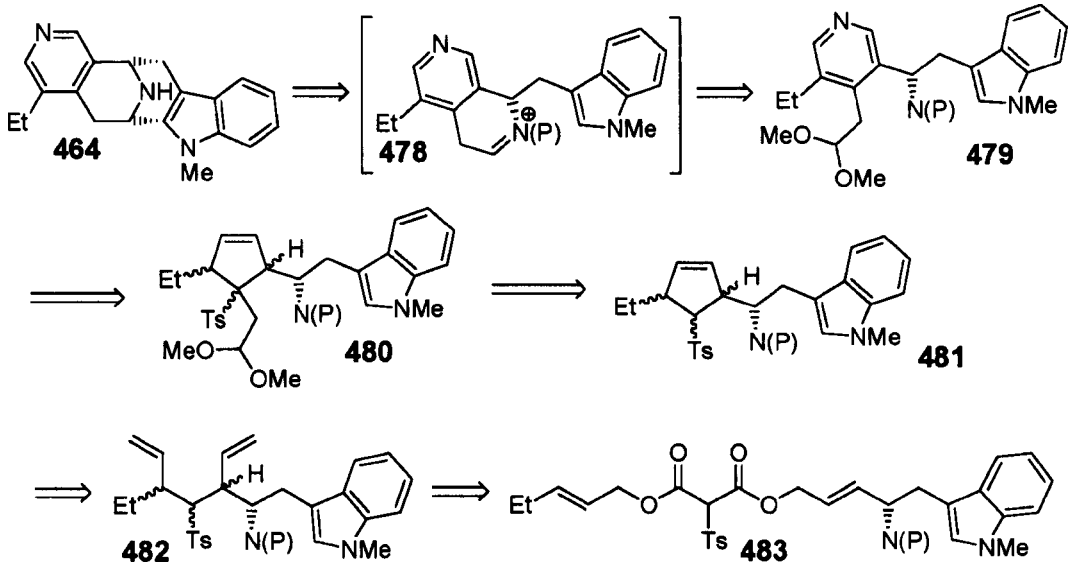
We propose a retrosynthetic analysis of (–)-suaveoline **464** which incorporates methodology for the synthesis of substituted pyridines developed by a co-worker within the Craig group[122] (scheme 151). The synthesis allows direct access to pyridines **477** by treatment of a 3-sulfonyl-1,5-dicarbonyl **475** with alcoholic ammonia, as the presence of the leaving group in the 3-position ensures the carbon backbone is already at the correct level of oxidation. Such a synthesis is pertinent to this author's work, as the 1,5-dicarbonyl substrates could be accessed by oxidative cleavage of the products of 2-(toluene-4-sulfonyl)malonate rearrangement.




**Scheme 151:** *Pyridine synthesis from 3-sulfonyl-1,5-dicarbonyls*

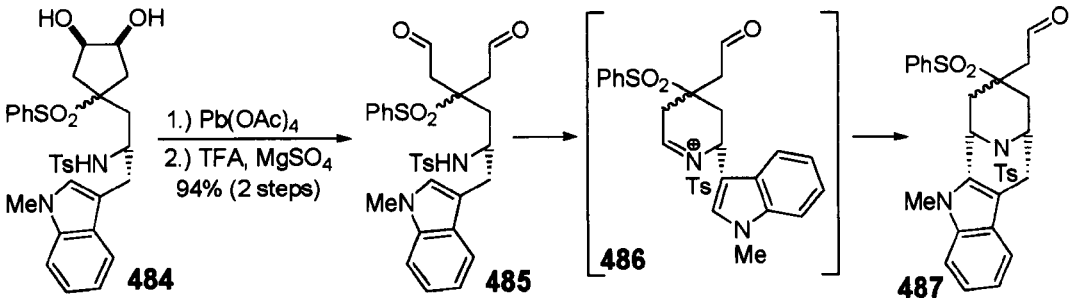
The synthesis has been shown to tolerate a wide variety of substitution patterns; the pyridine motif in (–)-suaveoline is in fact 3,4,5-substiuted. Substitution at the 4-position may be introduced by metallation and alkylation α- to the sulfone prior to oxidative cleavage of the olefin(s).

The proposed late-stage retrosynthetic strategy from (–)-suaveoline is shown in scheme 152. The initial disconnection is of the pentacyclic core to the indolyl pyridine **479** via a Pictet–Spengler cyclisation (a ubiquitous theme in the approach to many indole and isoquinoline alkaloids[123] that has been the subject of extensive investigation[124] from a stereochemical viewpoint). For the cyclisation to be the final major event is different from the approaches of Cook and Bailey. However, in this instance we were confident the reaction would furnish the desired *cis*-fused tetrahydro-βcarboline, as the work of a co-worker[125] towards the related alkaloid (–)-alstonerine showed that a structurally highly similar substrate **485** cyclised with total 1,3-*cis* selectivity (scheme 153).




**Scheme 152:** *Proposed late-stage retrosynthesis of (-)-suaveoline*

The indolyl pyridine **479** was in turn to be derived from the 3-(toluene-4-sulfonyl) cyclopentene **480**, by the pyridine-forming methodology described above. The two-carbon masked aldehyde fragment was to be introduced prior to pyridine formation by sulfone α-metallation and alkylation. The use of a 3-(toluene-4-sulfonyl)cyclopentene (formed by ring-closing metathesis) rather than the open-chain 4-(toluene-4-sulfonyl)-1,6-heptadiene was proposed to aid both the α-alkylation reaction (which was anticipated to be difficult) and oxidative cleavage of the olefin; it had been found previously that one-pot double olefin cleavage could afford lower yields of 1,5-dicarbonyl in some instances.[126]

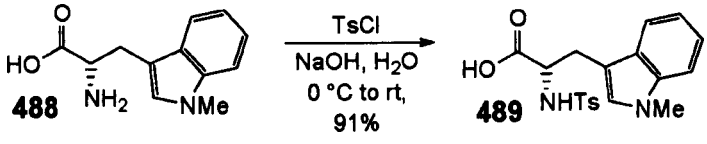



**Scheme 153:** *Precedent:* cis-*selective Pictet-Spengler reaction*

The 4-(toluene-4-sulfonyl)-1,6-heptadiene **482** was to be accessed by dual-dCr from the 2-(toluene-4-sulfonyl)malonate **483**. The envisaged lack of diastereoselectivity in the two dCr steps was not predicted to be detrimental to the synthesis, as all the uncontrolled stereocentres are destined to become $sp^2$-hybridised (upon their incorporation into the pyridine ring). (*E*)-Pent-2-en-1-yl alcohol being commercially available, the initial task was therefore to synthesise the indolyl allyl alcohol. Tryptophan was the obvious precursor for such a compound; in the event, L-$N_\alpha$-methyltryptophan **488** was commercially available and so was employed as starting material. Protection of the tryptophan amine nitrogen was in the first instance to be effected with a toluene-4-sulfonyl group, as the reaction in scheme 153 shows it to be compatible with the Pictet–Spengler cyclisation. There is also considerable experience in the Craig group pertaining to its removal.

## 2.2.4: Synthesis of Rearrangement Substrate

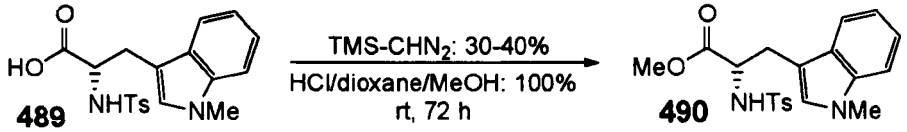
L-$N_\alpha$-Methyltryptophan **488** was *N*-sulfonylated in high yield according to previously established group methodology[127] (Scheme 154).




**Scheme 154:** *Amino acid* N-*sulfonylation*

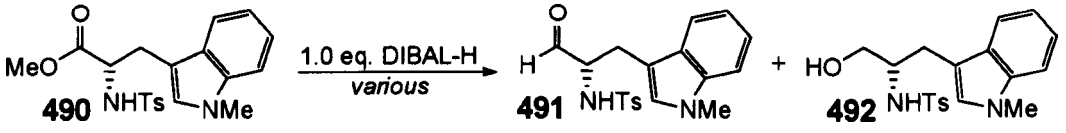
It was then required of us to synthesise the corresponding aldehyde Horner–Wadsworth–Emmons substrate. Such a transformation likely requires two steps and a variety of routes were explored. We first attempted synthesis of

the methyl ester. Use of TMS-diazomethane furnished the product in poor yield, along with a byproduct which appeared to be the 1-desmethyl analogue. Use of HCl / dioxane / methanol gave the desired product in quantitative yield (scheme 155).



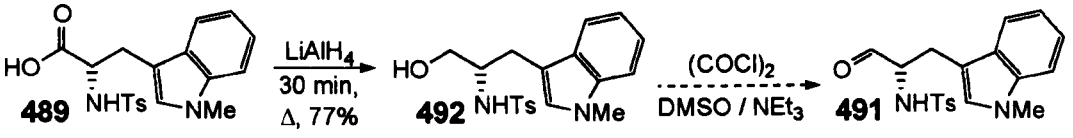

**Scheme 155:** *Methyl ester formation*

Attempted selective reduction of the ester to the aldehyde with DIBAL-H was capricious. Various reaction times, solvents, temperatures and quench procedures were tried; in each instance significant amounts of over-reduced alcohol product were isolated. Furthermore, separation of these two species was not viable as the aldehyde was unstable on silica (scheme 156).




**Scheme 156:** *Attempted selective ester reduction with DIBAL-H*

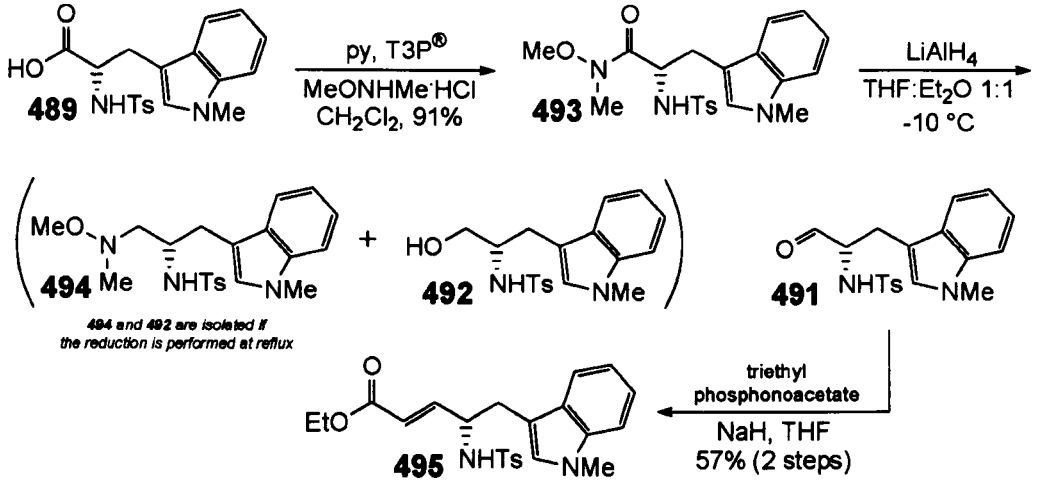
It was hoped that accessing the aldehyde *via* selective oxidation of the alcohol would be practically more straightforward. $LiAlH_4$-mediated reduction of the acid[127] cleanly gave the alcohol in 77% yield; attempted Swern oxidation of this species afforded a complex mixture (scheme 157).




**Scheme 157:** *Attempted aldehyde synthesis by Swern reaction*

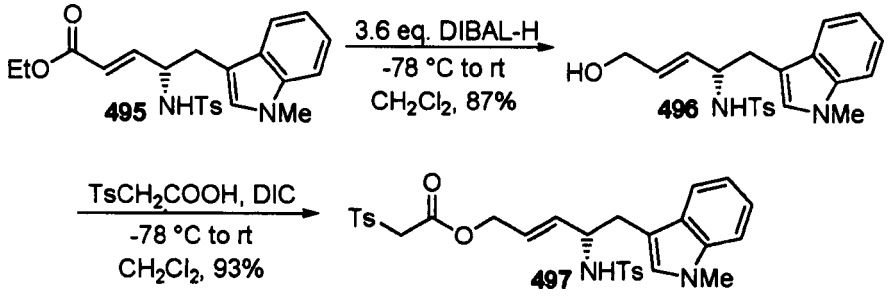
It appeared that use of a Weinreb amide[128] **493** might be necessary. This was prepared from the acid using the coupling agent T3P® (*n*-propylphosphonic acid anhydride). Reduction of the Weinreb amide with the Schwartz reagent[129] according to a recently reported protocol[130] gave the aldehyde cleanly and in good yield. Such a reagent is not economic for large-scale synthesis, however. Reduction of the Weinreb amide with $LiAlH_4$ was initially attempted in $Et_2O$:THF 1:1 at reflux. This afforded an amount of the over-reduced amine

**494** and alcohol **492** in addition to the desired aldehyde **491**. Reaction at –10 °C was a cleaner process, although trace amounts of the alcohol **492** were still observed when the reaction mixture was quenched directly with water as opposed to sequential addition of ethyl acetate then water. The aldehyde itself is unstable upon exposure to air, rapidly developing a yellow colour. It has proven necessary, therefore, to use the aldehyde in a Horner–Wadsworth–Emmons reaction immediately once it is prepared.



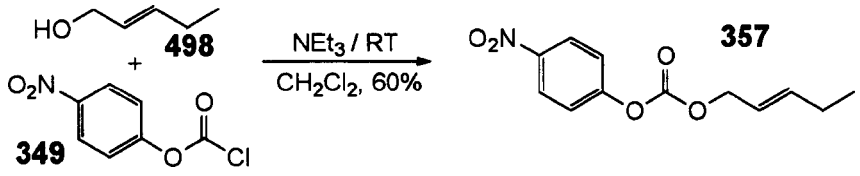

**Scheme 158:** *Synthesis of α,β-unsaturated ester*

The α,β-unsaturated ester **495** was isolated in 57% yield over two steps (scheme 158). This product was readily recrystallised from *iso*propanol. DIBAL-H reduction of the α,β-unsaturated ester was routine, as was esterification with (toluene-4-sulfonyl)acetic acid, proceeding in 87% and 93% yield respectively (scheme 159).



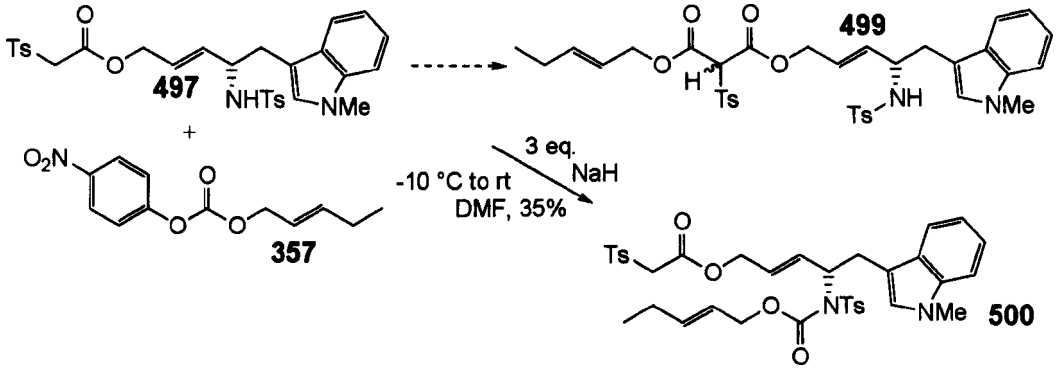

**Scheme 159:** *Synthesis of (toluene-4-sulfonyl)acetate*

The synthesis of the required carboxylation coupling partner **357** was facile, as detailed previously in section 2.1.2.4 (Scheme 160).



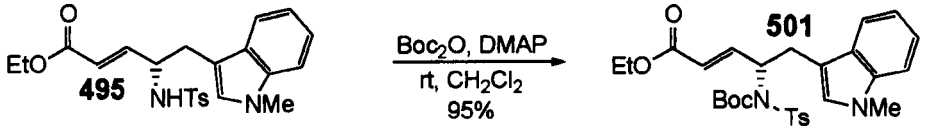

**Scheme 160:** *Synthesis of carboxylation partner*

We anticipated a problem with the carboxylation step, namely that the α-carbonyl protons of **497** were not the most acidic protons. Single deprotonation of the ester substrate **497** would lead to the *N*-anion and therefore *N*-carboxylation. We hoped to overcome this by using an extra equivalent of base to form the *N,O*-dianion. It was our hope that the more reactive anion would be the enolate and carboxylation would thus occur as desired. In the event, however, the undesired regioisomer was observed.



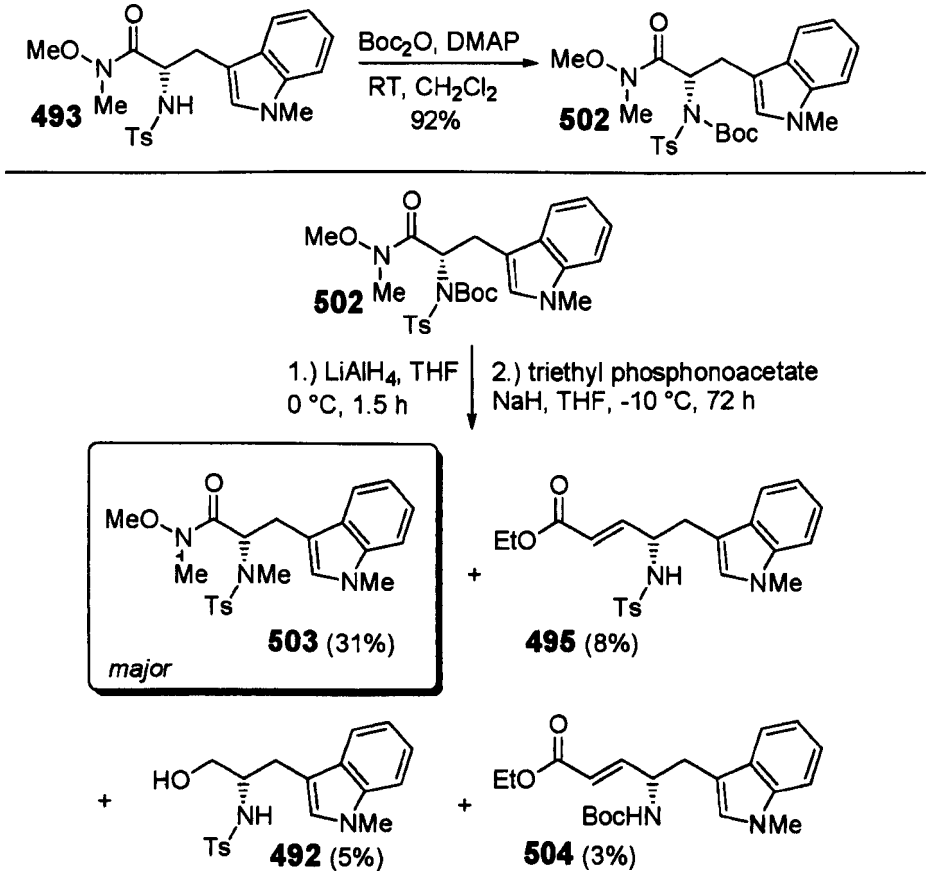

**Scheme 161:** *Formation of undesired carbamate species*

It is unclear whether the exclusive formation of this product implies the sulfonamide anion is the preferred site for carboxylation, or whether the dianion simply was not formed. Rather than expending additional efforts trying to generate the desired malonate product, it was decided to alter the protecting group strategy and doubly protect the amine. We anticipated such double protection would in all likelihood be necessary for later steps. While double protection necessitated an extra step, we reasoned that through appropriate choice of protecting group we could bypass the need for a distinct extra deprotection step. An acid-labile group would be cleaved under the conditions that initiate the Pictet–Spengler reaction, thus the two processes could hopefully be performed in one step. To this end we opted to protect the sulfonamide with a Boc group. We initially decided to introduce the Boc group at the α,β-unsaturated ester stage (Scheme 162).



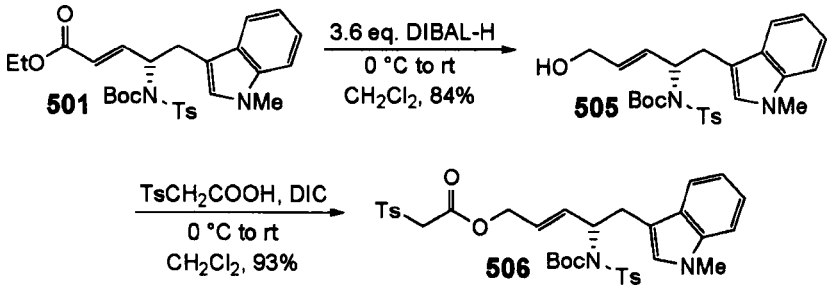

**Scheme 162:** *Introduction of the second protecting group*

As an aside, we also explored briefly the possibility of introducing the Boc group earlier in the synthesis, although we were mindful that it may prove to be reductively labile. We reasoned that if it were introduced prior to the aldehyde formation / Horner–Wadsworth–Emmons steps, the yield for these steps might be increased. (It was possible, for example, that the acidic proton on the singly protected tryptophan $N_{\beta}$ was quenching the phosphonate to some degree). Boc protection of the Weinreb amide proceeded in equivalent yield to that in scheme 162. However, the reduction / Horner–Wadsworth–Emmons protocol was found to be unsuccessful. A complex mixture of products resulted (scheme 163), from which were separable and characterisable several species corresponding to undesired over-reduced products (with the amide, carbamate and even the toluene-4-sulfonyl group reduced to an undesired degree). The major product **503** (isolated as an inseparable mixture with **495**) was tentatively assigned as that corresponding to reduction of the Boc group to a methyl group whilst the Weinreb amide moiety remained intact. The predominance of this species in the product mixture implied to us that reduction of the Boc group was the most facile process and as such this route was not pursued further.



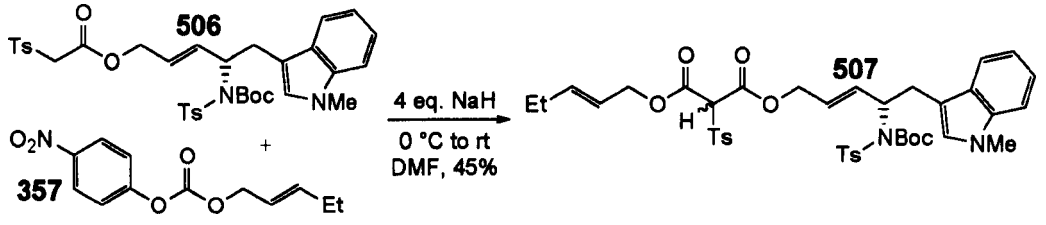

**Scheme 163**. *Earlier introduction of the Boc group is not viable.*

Reduction of the doubly *N*-protected α,β-unsaturated ester proceeded in comparable yield to the singly protected analogue. Esterification was also routine (Scheme 164).




**Scheme 164:** *Synthesis of doubly* N*-protected (toluene-4-sulfonyl)acetate*

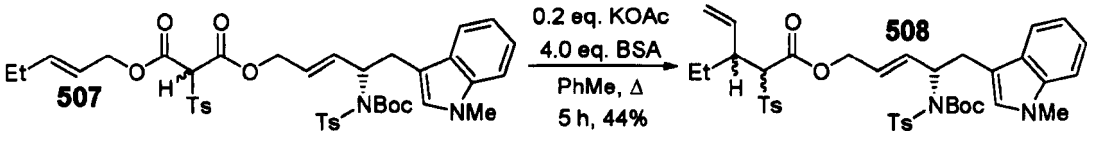
With the third valency on nitrogen now capped, we did not anticipate any scope for regiochemical ambiguity in the carboxylation step. As expected, the desired malonate was formed as the exclusive product in 45% (starting material was also recovered with near-quantitative mass balance).




**Scheme 165:** *Synthesis of rearrangement substrate*

## 2.2.5 Attempts at Decarboxylative Claisen Rearrangement

With the desired rearrangement substrate in hand, we duly attempted the decarboxylative Ireland–Claisen reaction. We wished to probe the regioselectivity of the reaction for this substrate by inducing single rearrangement only. At room temperature in $CH_2Cl_2$, no reaction was observed. However, in toluene at reflux complete conversion to the singly rearranged substrate was observed in 5 h (Scheme 166).



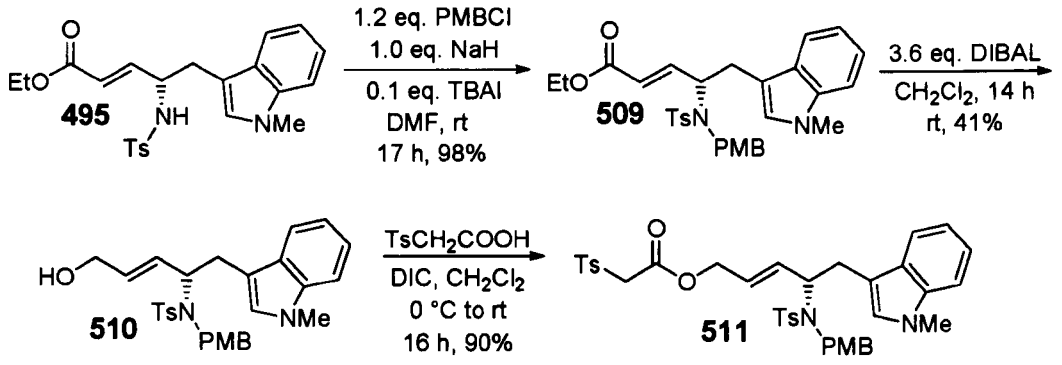

**Scheme 166:** *Observed regioselectivity in single rearrangement*

As shown, total regioselectivity was observed, with the less heavily-functionalised side chain rearranging preferentially. This is in accordance with the prediction derived from previous work, as the doubly protected amine is highly electron-withdrawing and bulky.

We duly attempted di-rearrangement of the substrate under more forcing conditions. Using microwave irradiation (5 min at 110 °C in $CH_2Cl_2$) gave singly rearranged product in a slightly improved 48% yield. Upon subjecting the substrate to 15 min at 140 °C in $CH_2Cl_2$, singly rearranged product was isolated in 55% yield. In neither case was any di-rearranged product observed; in the last example, however, a significant amount of a byproduct was formed. Whilst never conclusively identified, the NMR spectrum was noteworthy for containing all the peaks corresponding to the various functional groups in the substrate *with the exception of the Boc group*. Thermolytic cleavage of a Boc group is a precedented process.[131] In light of these results we were forced to conclude that use of –N(Ts)Boc was not a viable protecting group strategy, as thermolytic *N*-deprotection appeared to be occurring in preference to the desired second rearrangement.

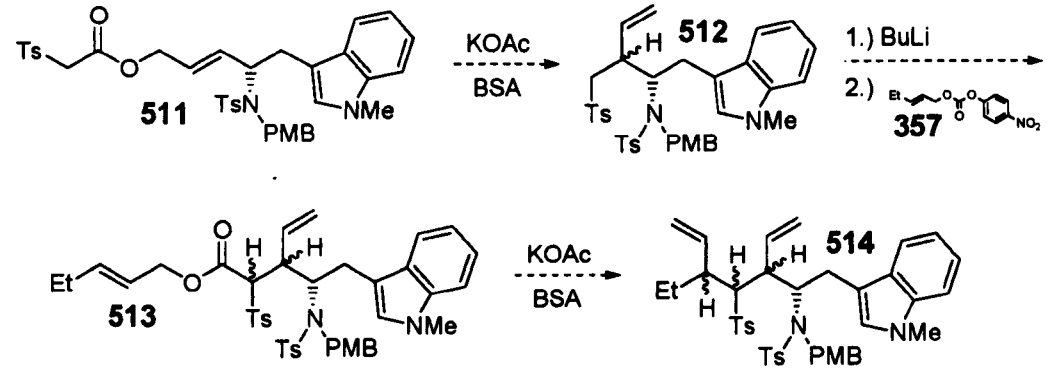
## 2.2.6: Alternative Protecting Group Strategies

As previous work had shown that the decarboxylative Ireland–Claisen rearrangement is highly susceptible to electronic effects, we reasoned that we would increase the likelihood of the desired di-rearrangement occurring with a more electron-donating protecting group on the third nitrogen valency (–N(Ts)Boc being an extremely electron-withdrawing and sterically demanding combination). We therefore sought to introduce a *para*-methoxybenzyl group as the second protecting group, as this would be less electron-withdrawing whilst maintaining the desired orthogonality of protecting groups. Introduction of this group at the α,β-unsaturated ester stage and subsequent elaboration (scheme 167) were routine (and maintained several steps common to the previous synthesis).




**Scheme** 167. p-*Methoxybenzyl strategy - substrate preparation*

Rather than use **511** to form the malonate, it occurred to us to attempt rearrangement of **511** itself. We reasoned that despite the less electron-withdrawing properties of the -PMB group, the other (pentenyl) side chain would likely still rearrange first in the malonate. Our desired indolyl side chain rearrangement would therefore once again be the second of two rearrangements of a 2-(toluene-4-sulfonyl)malonyl substrate. The work described in previous sections has shown the first rearrangement to be markedly more facile than this second one. Generally the corresponding (toluene-4-sulfonyl)acetate is intermediate in reactivity. It seemed, therefore, that the (toluene-4-sulfonyl)acetate could serve as a useful "model" system, in that if it proved inert to rearrangement, the corresponding malonate would almost certainly also be inert to di-rearrangement. Should it transpire that the (toluene-4-sulfonyl)acetate **511** rearranges but the malonate does not, the same desired 1,6-heptadienyl intermediate could still be accessed by sequential rearrangement/ester introduction/rearrangement (Scheme 168).



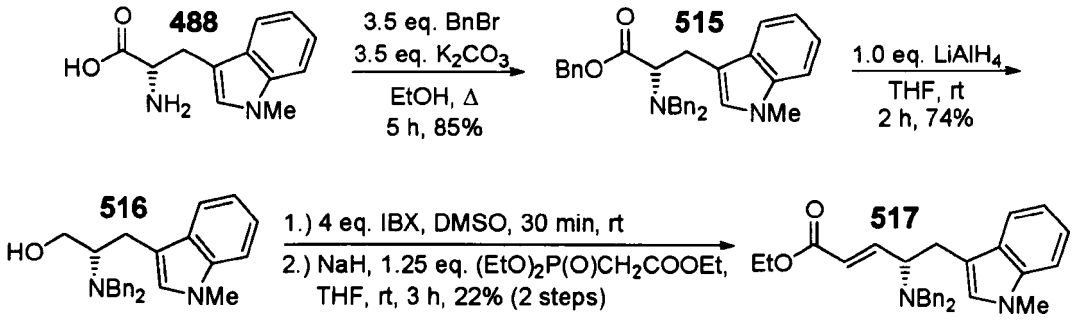

**Scheme 168:** *Alternative route to desired 1,6-heptadienyl intermediate*

We duly subjected the –N(Ts)PMB (toluene-4-sulfonyl)acetate **511** to rearrangement conditions (microwave irradiation, conditions as per –N(Ts)Boc case). In each instance, however, the desired rearrangement product was not detected and unreacted starting material was isolated in good yield.

In light of this negative result, we felt it was necessary to abandon not only the –N(Ts)PMB strategy, but protection of the amine as a sulfonamide altogether, as we could not conceive of a protecting group that would potentiate the electron-withdrawing properties of the (toluene-4-sulfonyl) group less than a PMB group. A completely new protecting group strategy was necessary and as introduction of the (toluene-4-sulfonyl) group was the first step in the synthesis, the synthesis would have to be redesigned from step one accordingly.

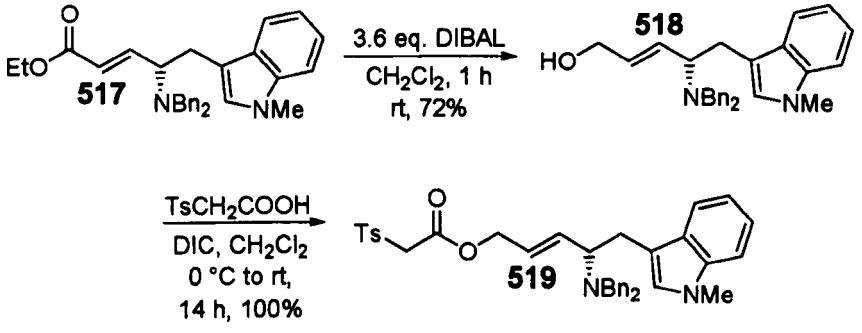
Various *N*-alkyl/aryl substituents were considered. *N*-allyl groups were ruled out due to potential side reactions in the ring-closing step. *N*-methyl groups were also disregarded due to the severity of the cleavage conditions that would likely need to be employed. Double protection of the amine as a triazone[132] was briefly considered, but ruled out as introduction of the protecting group requires use of formaldehyde, which would likely participate in an unwanted Pictet-Spengler reaction. Similarly, double protection as a phthalimide and an azide were also discounted (due to electron-withdrawing character and thermal lability respectively). We were also mindful that it would be desirable to maintain orthogonality of protecting groups if possible, in order to afford greater flexibility as regards the order of events in the late-stage strategy (for example Pictet-Spengler cyclisation and subsequent pyridine formation might be possible); no single, bifunctional protecting group would meet this criterion.

We eventually decided to employ a dibenzylamine,[133] as such a group would be easy to introduce, chemically inert to the various conditions we propose to subject it to and crucially, more electron-rich than a sulfonamide. It also fulfils the criterion of orthogonality, as conditions have been reported for selective monodebenzylation of a dibenzylamine if necessary (either under conditions of mild hydrogenolysis[134] or oxidation[135]). Having decided upon the group to employ, we set about accessing the α,β-unsaturated ester intermediate (scheme 169).




**Scheme 169:** *Early introduction of* N,N-*dibenzylamine group*

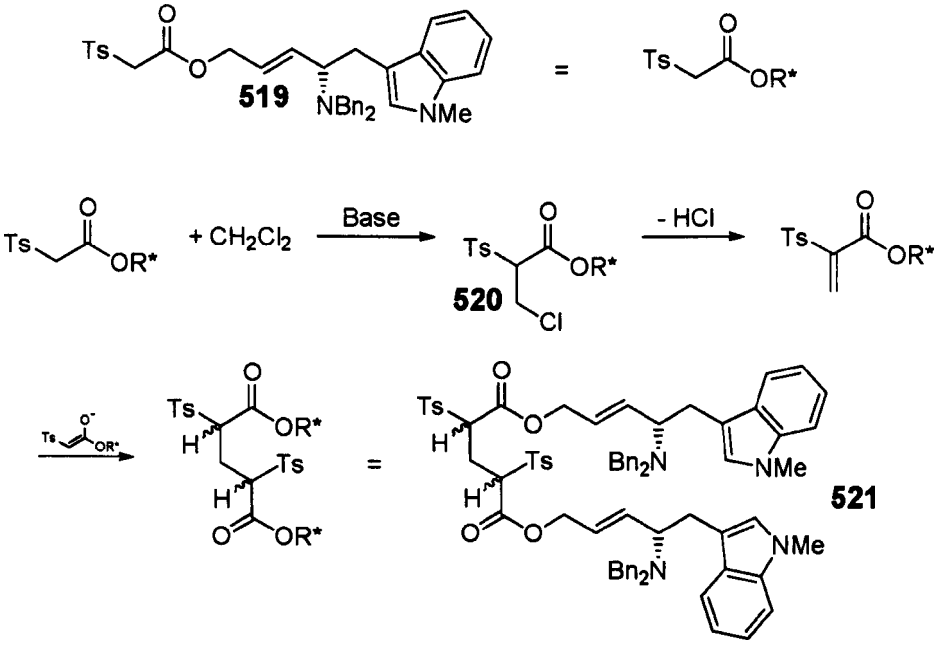
The tribenzylated intermediate formed in the first step could theoretically provide access to the desired aldehyde in one step via selective DIBAL-H reduction. However, previous experience has shown these reactions to be somewhat capricious. Since it was unknown at this point whether the dibenzylamine would undergo a successful dCr, no effort was yet expended in optimising reaction conditions and so a more protracted route was employed (scheme 169). With the α,β-unsaturated ester **517** in hand, we undertook its conversion to the corresponding (toluene-4-sulfonyl)acetate **519** (scheme 170). Once again, this was routine.




**Scheme 170:** *Elaboration to* N,N-*dibenzyl (toluene-4-sulfonyl)acetate*

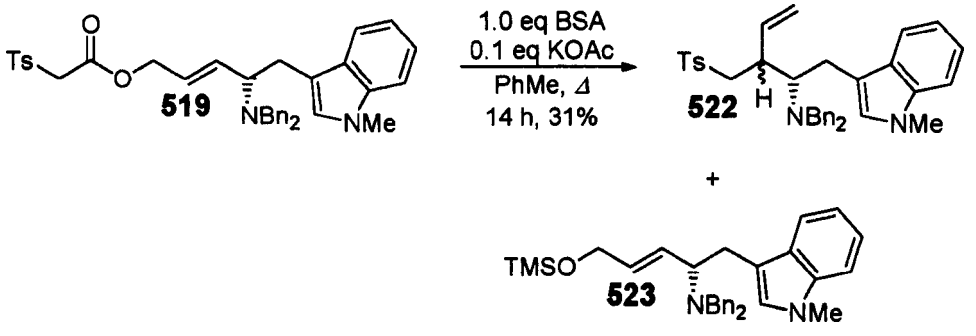
We then sought to rearrange this (toluene-4-sulfonyl)acetate **519**. Upon subjecting it to microwave irradiation (5 min at 110 °C in $CH_2Cl_2$), TLC analysis indicated the presence of a small amount of a new product, of slightly higher $R_f$ than the starting material (as is generally observed for the products of decarboxylative Claisen rearrangements). The reaction mixture was subjected to 15 min at 130 °C, after which time all starting material had been consumed. Upon isolation of the new product, it turned out disappointingly not to be the desired product, but in fact something spectroscopically very similar to the starting material. It was eventually deduced to be **521**, the methylene-

bridged dimer of the starting material (the parent ion mass peak providing convincing evidence), presumably formed by reaction with the solvent. Such a dimerisation, which may initially seem unlikely, may be assisted by *in situ* formation of a Michael acceptor (scheme 171).




**Scheme 171:** *Proposed mechanism for methylene dimer formation*

Whilst the lack of rearrangement product was dispiriting, we were aware of a precedent (from the work of a co-worker), wherein a similar substrate showed better rearrangement behaviour under classical thermal conditions than microwave conditions. We therefore exposed the mono-ester substrate to conditions of toluene at reflux and were gratified to isolate the desired product **522** in approximately 3:1 diastereoisomeric ratio. Also isolated was a small amount of silylated allyl alcohol **523**, presumably arising from ester hydrolysis.




**Scheme 172:** *Successful rearrangement of key substrate*

## 2.2.7: Optimisation of Route to Decarboxylative Claisen Rearrangement Substrate

Whilst the dCr yield of 31% is poor, we believed it would be improved upon and so this successful rearrangement provided the impetus for optimisation of the route to the substrate. The yield of 85% for the initial perbenzylation (corresponding to 94% for each benzylation) was considered sufficient. Also, repetition of the benzyl ester reduction and careful recrystallisation raised the yield of this step to 93%. By far the lowest yielding steps were the oxidation / Horner–Wadsworth–Emmons steps (22% over two steps). The best yield to date had been achieved by use of IBX as an oxidant. As stated above, within minutes of addition of the oxidant to the alcohol, the reaction mixture began to discolour. This continued at such a rate as to give a virtually opaque brown mixture after only a few minutes. It was assumed that aldehyde over-oxidation / decomposition was occurring and that alternative oxidants / conditions might suppress this. The IBX had been prepared as a precursor to Dess and Martin's periodinane.[136] This latter reagent was duly prepared and the oxidation / HWE sequence attempted once again. The enhanced solubility of Dess–Martin periodinane compared to IBX permitted the reaction to be performed in $CH_2Cl_2$ instead of DMSO (which had proved problematic to remove). Sadly, use of the Dess-Martin periodinane furnished the α,β-unsaturated ester in similarly poor yields; the rapid discolouration of the reaction mixture was observed once again.

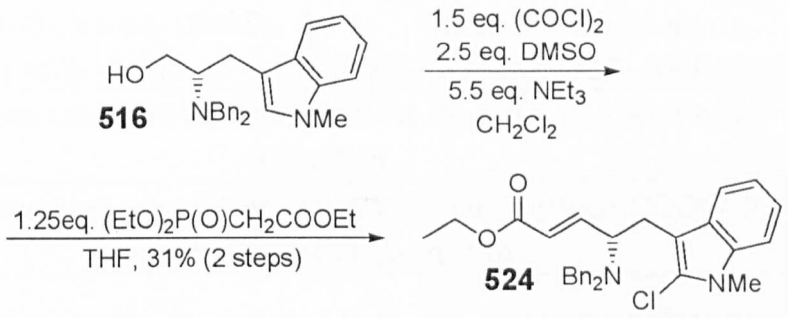
We were dismayed at this result, as the Dess–Martin periodinane is held to be one of the mildest selective oxidants available. Since even this was unable to effect the desired transformation cleanly, we were forced to adopt an alternative approach. Several procedures have been reported for the tandem oxidation of an alcohol to an aldehyde and subsequent (stabilised) Wittig reaction in one pot. One such procedure[137] due to Ley employs TPAP/NMO,[138] reportedly a very mild selective oxidant appropriate to such a reaction. We duly performed the oxidation in accordance with reported conditions, but regrettably the yield was not improved, at 21% over two steps, with the characteristic yellow colour developing rapidly once again.

Another tandem procedure, due to Taylor,[139] employs manganese dioxide to oxidise alcohols to aldehydes in the presence of the appropriate Wittig ylide reagent ($Ph_3P$=CHCOOEt in our case). The authors report that *unactivated*

alcohols are able to undergo this tandem process in high yield, in contradiction of accepted wisdom concerning the selectivity of manganese dioxide oxidations. We attempted the synthesis of our desired α,β-unsaturated ester under the reported conditions (10.0 equivalents $MnO_2$, 1.2 equivalents ylide, PhMe, reflux). No product was detected. It appears the initial oxidation of the alcohol was sluggish, the starting material taking 24 h to disappear by TLC. We speculate that the severity of the conditions are likely simply to have effected decomposition of the starting material (and any desired product), probably *via* indole oxidation.

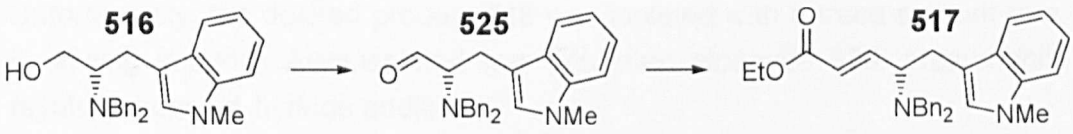
A third tandem procedure is due to Barrett,[140] wherein Dess–Martin periodinane is the *in situ* oxidant. Application of this protocol (1.2 equivalents periodinane, 2.0 equivalents ylide, 2.0 equivalents PhCOOH, $CH_2Cl_2$, rt) furnished the desired product in an improved 37% yield, although significant discolouration was still observed. Benzoic acid is employed in the reaction; this affords better yields and *E/Z* selectivity.[141,142] Upon omission of this additive, the yield of the reaction dropped to 13%. We have never observed any (*Z*)-isomer in any instance.

While Barrett's procedure afforded a higher yield, we felt this could be improved upon still further. We felt that if discolouration / decomposition was still occurring in this tandem procedure, this implied that either aldehyde decomposition was competing appreciably with reaction with the ylide, or alternatively the desired product itself was not stable with respect to the species present. We sought to expand our repertoire of oxidations, so turned our attention to the Parikh–Doering (py·$SO_3$-mediated) oxidation.[143] To date, there has been no report of the use of such an oxidation in a tandem system. We attempted a sequential one pot approach (whereby the oxidation was performed in a DMSO reaction mixture, to which was added the ylide once TLC indicated completion of the first step). Yields for such a procedure varied between 2 and 20%. A breakthrough came in the realisation that a discrete two-step procedure worked better, with the yield being highly dependent on the order of addition of the reagents. It was found that if the alcohol substrate and $NEt_3$ were pre-mixed in DMSO *prior* to addition of the py·$SO_3$, the product aldehyde was furnished in near quantitative yield within 30 min! This order of addition is stipulated by Parikh and von Doering. Note that when a standard Swern protocol is applied, the only isolable product of the two-step reaction is that in which the indole has undergone C2-chlorination, **524** (scheme 173).




**Scheme 173:** *Unexpected product from Swern oxidation*

With a procedure available that furnished the crude aldehyde **525** in high yield, we were able to compare the stabilised Wittig reaction with the Horner–Wadsworth–Emmons reaction for formation of the desired product **517**. Parikh–Doering oxidation then isolation of the crude aldehyde, quickly followed by Horner–Wadsworth–Emmons homologation in THF gave the desired α,β-unsaturated ester in much improved 63% yield. Use of a stabilised Wittig ylide proved even more efficacious, leading to a yield of 88%. High solubility of the ylide in $CH_2Cl_2$ allowed the Wittig reaction to be caried out at high concentration (1.0 M). The $Ph_3P{=}O$ byproduct was not problematic, as the product is appreciably non polar (due to the two benzyl groups) and thus is easily separated by chromatography. The two-step Parikh–Doering/Wittig sequence has been shown to be scaleable to multigram amounts, the yield further improving to 94%. The various oxidant combinations tried in this optimisation process are summarised in table 4.



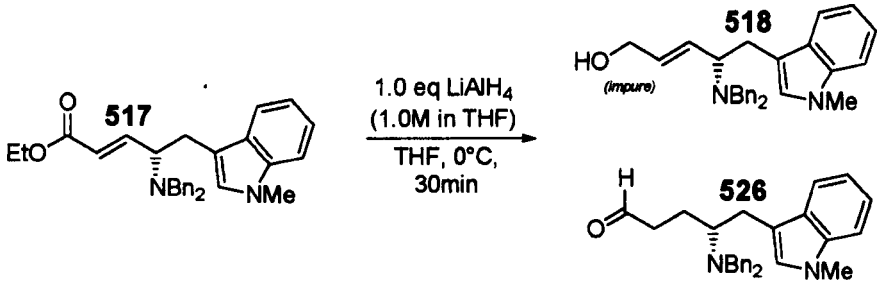

*(various conditions)*

| Step 1: Oxidation | Step 2: Homologation | Yield |
|---|---|---|
| 4 eq. IBX, DMSO, rt, 30min | 1 eq. NaH, 1.25 eq. $(EtO)_2P(O)CH_2COOEt$, THF, rt, 3h | 22% |
| 1.5 eq. Dess-Martin, $CH_2Cl_2$, rt, 30min | 1.2 eq. NaH, 1.25 eq. $(EtO)_2P(O)CH_2COOEt$, THF, rt, 14h | 31% |
| *[one-pot procedure]* 0.05 eq. TPAP, 1.05 eq. NMO, 4Å mol. sieves, $CH_2Cl_2$, rt, then add 1.5 eq. $Ph_3P{=}CHCOOEt$, $CH_2Cl_2$, rt | | 21% |

| | | |
|---|---|---|
| 1.5 eq. $(COCl)_2$, 2.5 eq. DMSO, 5.5 eq. $NEt_3$, $CH_2Cl_2$ | 1.2 eq. NaH, 1.25 eq. $(EtO)_2P(O)CH_2COOEt$, THF, rt, 3h | 31% *of* ***524*** |
| [*one-pot procedure*] 10 eq. $MnO_2$, 1.2 eq. $Ph_3P{=}CHCOOEt$, PhMe, reflux, 24h | | 0% |
| [*one-pot procedure*] 1.2 eq. Dess-Martin, 2.0 eq. $Ph_3P{=}CHCOOEt$, 2.0 eq. PhCOOH, $CH_2Cl_2$, rt, 14h | | 37% |
| [*one-pot procedure*] 1.2 eq. Dess-Martin, 2.0 eq. $Ph_3P{=}CHCOOEt$, $CH_2Cl_2$, rt then reflux, 14h | | 13% (+25% S.M.) |
| [*pseudo-one-pot procedure*] 1.) 3.0 eq. py·$SO_3$, DMSO, then add $NEt_3$ 2.) add 1.2 eq. $Ph_3P{=}CHCOOEt$ | | 20% (+71% S.M.) |
| 9.0 eq. $NEt_3$, DMSO, *then* add 3.0 eq. py·$SO_3$ | 1.2 eq. NaH, 1.25 eq. $(EtO)_2P(O)CH_2COOEt$, THF, rt, 14h | 63% |
| 9.0 eq. $NEt_3$, DMSO, *then* add 3.0 eq. py·$SO_3$ | 2.0 eq. $Ph_3P{=}CHCOOEt$ (1M w.r.t. aldehyde), $CH_2Cl_2$, rt, 14h | 88 to 94% |

**Table 4:** Oxidation/homologation conditions.

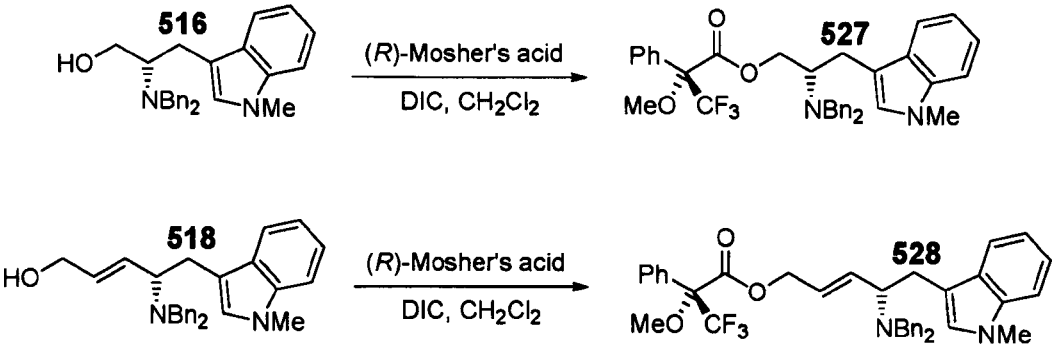
A yield of 72% had been achieved for the ester reduction, but it had been found to be variable, with yields in some instances as low as 60%. We wondered if the Lewis acidity of the DIBAL-H reductant was mediating product decomposition in some way. We therefore sought to explore an alternative reduction with $LiAlH_4$. We hoped that gradual introduction of $LiAlH_4$ to the cold reaction mixture would minimise the likelihood of over-reduction. Unfortunately, the desired product **518** was isolated with a trace amount of a co-eluting impurity. Also isolated was saturated aldehyde **526**, presumably resulting from 1,4-hydride addition.




**Scheme 174:** *$LiAlH_4$ reduction gave impure product and a byproduct*

Concurrent efforts had been made to improve on the yield of the DIBAL-H mediated reduction and thankfully, it was found that close monitoring of the reaction by TLC and *immediate* Rochelle's salt workup upon completion (typically <30 min) afforded the allyl alcohol **329** in a consistent 96% yield. We considered this sufficient optimisation of the route to the (toluene-4-sulfonyl)acetate dCr substrate, as the mean yield was 94.7% per step over 6 steps (72.1% overall).

## 2.2.8: Mosher's Esters



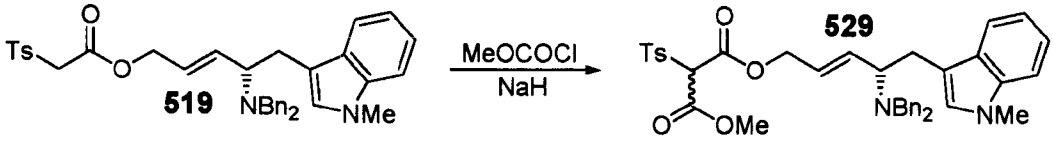

**Scheme 175:** *Mosher's esters of intermediates*

We wished to assess the extent of any erosion of *e.e.* during the synthesis by derivatising hydroxy intermediates as Mosher's esters (scheme 175). These were formed in near-quantitative yield by carbodiimide-mediated coupling. $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy of these esters indicated the presence of only one diastereoisomer in both instances. In the spectra of Mosher's esters derived from the corresponding intermediates synthesised from racemic 1-methyltryptophan, peak doubling was clearly visible.

## 2.2.9: Improvements to Decarboxylative Claisen Rearrangement

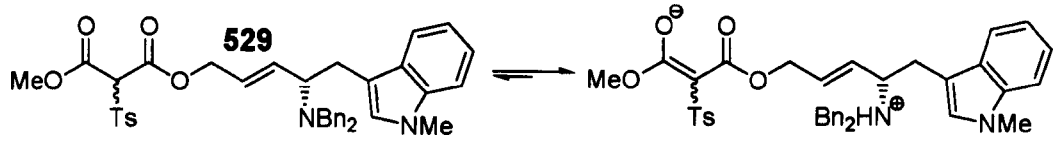
Mono-ester rearrangement had proceeded in only 31% yield. As has been stated previously, the first rearrangement of a 2-(toluene-4-sulfonyl)malonate has generally been observed to be more facile than that of the mono-ester. Synthesis of the corresponding pentenyl 2-(toluene-4-sulfonyl)malonate was not undertaken, however, as it was assumed preferential rearrangement of the pentenyl side chain would be observed, leaving reaction of the indole-containing side chain as the second (vastly less facile) rearrangement.

In order to exploit the enhanced reactivity of 2-(toluene-4-sulfonyl)malonates, therefore, we sought to adopt a derivatisation strategy – derivatising the mono-ester with a second "assisting" ester. Such a group should lend the substrate enhanced reactivity with respect to the dCr but be inert to rearrangement itself. A methyl ester fits these criteria and was easily introduced in 45% yield, in the first instance (scheme 176). No diastereoselectivity was observed.




**Scheme 176:** *Derivatisation of substrate*

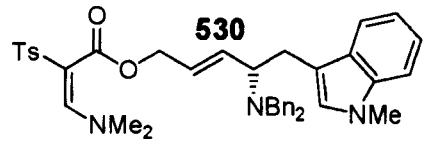
We had noticed the desired product behaved strangely on TLC, not giving a reproducible $R_f$ value. Upon consideration, it seems likely that the 2-(toluene-4-sulfonyl)malonate **529** exists as a zwitterion (scheme 177).




**Scheme 177:** *Likely zwitterionic form of 2-(toluene-4-sulfonyl)malonate dCr substrate*

This possible zwitterion complicates the isolation of the compound somewhat, but it has been found that a neutral aqueous workup (to remove DMF and NaCl), followed by chromatography of the crude product on extensively base-washed ($NEt_3$) silica allows isolation of the pure product. Unreacted starting material elutes quickly, whereas the product is significantly retarded on silica by a basic eluent. (The product sometimes required isolation from a toluene solution to remove residual $NEt_3$, possibly an azeotropic effect). It is noteworthy that while, in the course of our attempts to synthesise suaveoline, other 2-(toluene-4-sulfonyl)malonates were prepared, none has shown such unusual behaviour on silica. They had no propensity to form zwitterions because the relevant nitrogen had been sulfonylated, rendering it nonbasic.

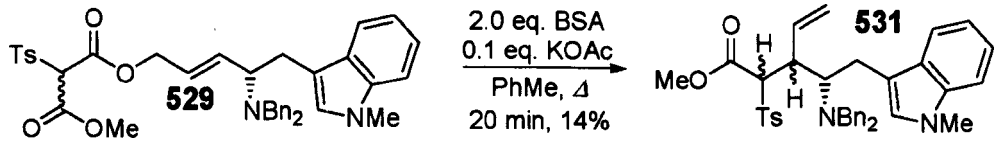
The carboxymethylation in scheme 176 was performed many times, and on one occasion a byproduct was isolated (**530**, scheme 178) which seemingly had formed via reaction with DMF (such a byproduct had never been observed in any other carboxylation of this type).




**Scheme 178:** *Byproduct arising from reaction with the solvent*

The enamine geometry in **530** is tentatively assigned as (*E*) on the basis of a cross-coupling in the NOESY spectrum between the *N*-dimethyl protons and those on the aryl ring *ortho*- to the sulfone. In light of the formation of this byproduct, the reaction was subsequently performed in THF and on a larger scale the yield increased slightly to 62% (with 33% unreacted starting material also isolated).

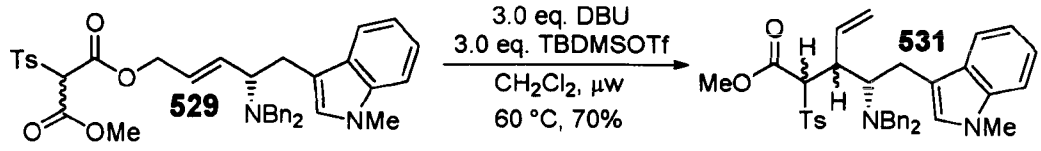
Initial results for rearrangement of the monoallyl malonate were disappointing. Under conditions of microwave irradiation in toluene (110 °C / 5 min, giving minimal product formation, then 130 °C / 15 min, seemingly giving no further product formation), the expected product was isolated in a poor 14% yield (with 28% unreacted starting material, scheme 179).




**Scheme 179:** *Rearrangement of derivatised substrate*

We were not unduly perturbed by this low yield, however, as a co-worker had concurrently developed a set of reaction conditions[88] which furnish dCr products in higher yields and with shorter reaction times. Use of stoichiometric amounts of DBU and TBDMSOTf effects rearrangement (*only* of 2-sulfonylmalonates) at rt in $CH_2Cl_2$. The use of a non-nucleophilic base and the inapplicability of these conditions to the rearrangement of simple (toluene-4-sulfonyl)acetates indicate that a different mechanism is operating, specifically the silatropic rearrangement discussed in section 2.1.3.2.

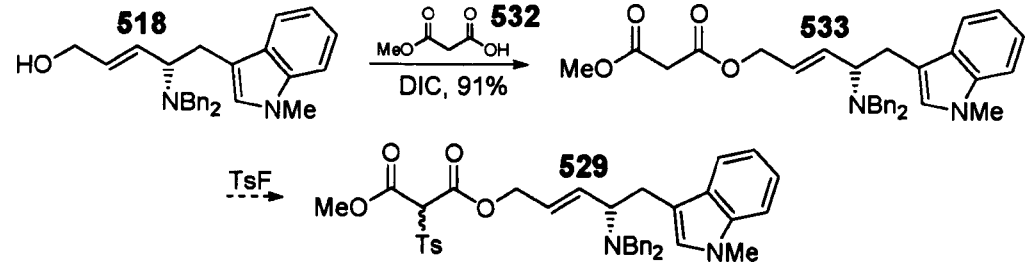
Applying the alternative dCr conditions to the "assisted" malonate substrate, we were gratified to obtain the desired product in higher yield. After optimisation, it was found that microwave irradiation gave the highest yield, of 70% (with 15% unreacted starting material, scheme 180).




**Scheme 180:** *Improved rearrangement of derivatised substrate*

With regard to diastereoselectivity, the $^1$H-NMR spectrum of the product seemingly indicates the presence of a major and a minor diastereoisomer in a ratio of approximately 2:1. Four diastereoisomers are possible; either two are not formed, or (in all likelihood) their signals are coincident.

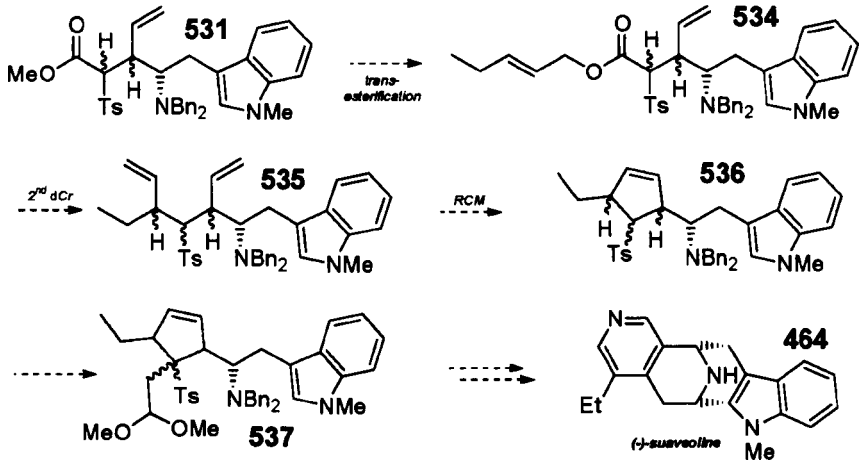
Such a yield for this key step was deemed far better, sufficient indeed for further elaboration of the product. An alternative synthesis of the malonate was briefly explored, but direct sulfonylation was unsuccessful in this instance (scheme 181).




**Scheme 181:** *Alternative route to rearrangement substrate was not successful*

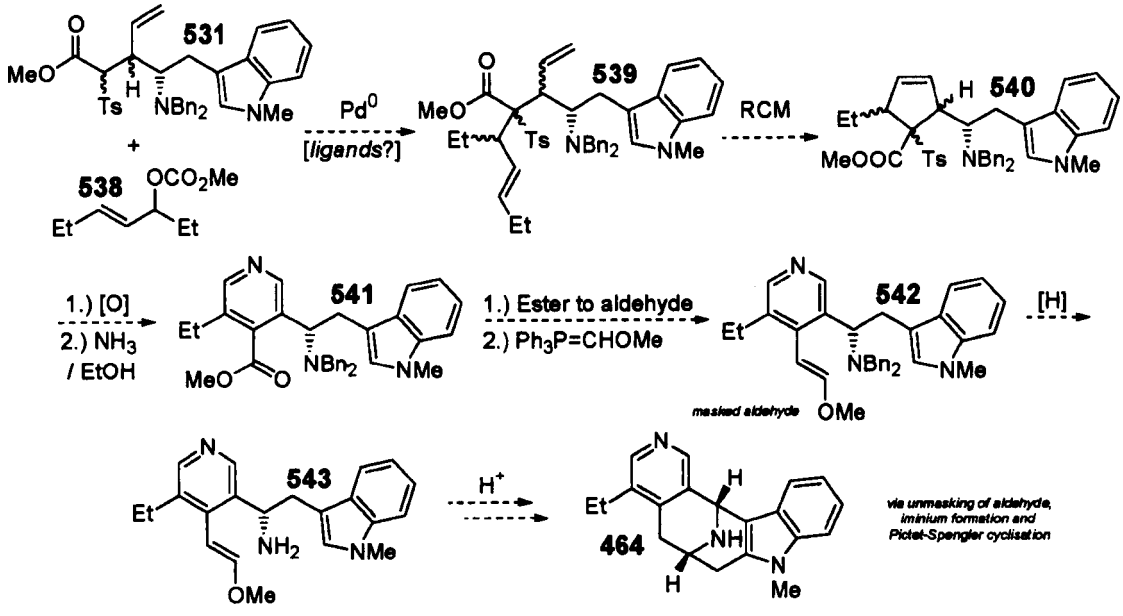
## 2.2.10: Attempted Transition-Metal Couplings

Our initial synthetic proposal was to access the pyridine precursor via two sequential dCr processes, either as a one-pot process or sequentially. It was understood, however, that the proposed introduction of the two-carbon masked aldehyde fragment would be challenging, as we would be seeking to form a quaternary centre in a highly sterically congested region (scheme 182).




**Scheme 182:** *Original proposal for accessing (-)-suaveoline*

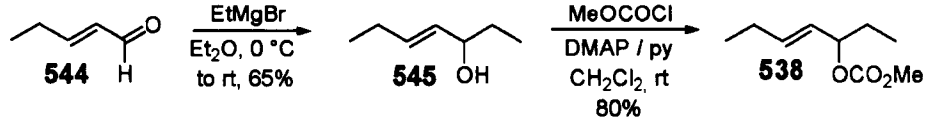
In light of this, we considered an alternative approach, employing $\pi$-allyl palladium chemistry to form this highly hindered bond. Such a strategy makes maximum use of the "assisting ester", as the methyl ester can provide a handle for derivatisation at this point, as well as facilitating the dCr itself. We wished to employ a *pseudo*-symmetrical $\pi$-allyl fragment, incorporating a "sacrificial" ethyl group, which would then be lost in the subsequent (ring-closing) step. The strategy is outlined in scheme 183. Far from needing to be removed, the methyl ester would then be the handle for 1-carbon homologation to the masked aldehyde. This has been illustrated in the scheme with a Wittig reaction, but other alternatives would be possible.




**Scheme 183:** *Proposed $Pd^0$-mediated route to (-)-suaveoline*

As can be seen, the $Pd^0$-mediated coupling is highly demanding – we are seeking to form a quaternary centre with α-branching on two of the substituents; such a coupling probably represents the limits of the scope of such methodology. If the coupling were to be successful, however, it would vastly simplify the final approach to (–)-suaveoline.

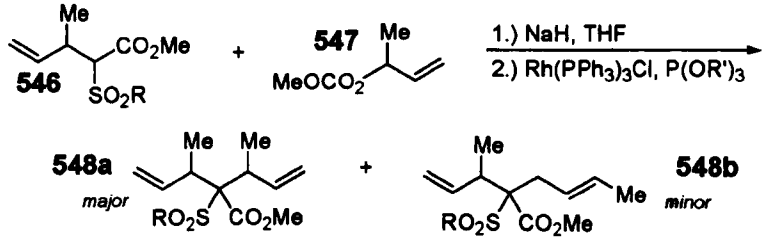
In order to attempt this $Pd^0$ coupling, it was first necessary to synthesise the pseudosymmetric carbonate coupling partner **538**. This was achieved in two steps from commercially available (*E*)-pent-2-enal (scheme 184).




**Scheme 184:** *Synthesis of coupling partner*

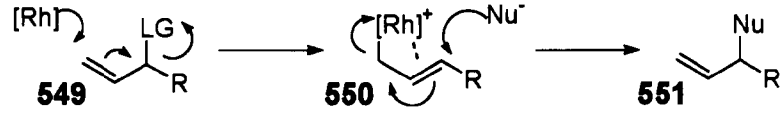
With both coupling partners in hand, we duly attempted the aforementioned reaction. Regrettably, we have had no success in this regard. Initial attempts involved the use of a slight excess of the carbonate in THF at rt, the catalyst being generated *in situ* from air-stable $Pd_2(dba)_3$ and $PPh_3$. Attempting the same reaction at reflux in THF also yielded no product. Perusal of the literature pertaining to Pd-mediated couplings led us to a review[144] which states that the $Pd_2(dba)_3$ / $PPh_3$ ligand system does in fact *not* generate $Pd(PPh_3)_4$ *in situ* and that in some instances, use of pre-prepared $Pd(PPh_3)_4$ affords greater reactivity. However, using such $Pd(PPh_3)_4$ in our system still yielded no product. Similarly, the use of a more electron-rich phosphine ligand, tris(trimethoxyphenyl)phosphine (TTMPP)[145] did not lead to any product formation.

The failure of the palladium-mediated reactions led us to search for more appropriate catalytic systems. Our attention turned to reports due to P.A. Evans,[146] where rhodium is employed in comparable couplings. The precedent is encouragingly close – coupling of an α-alkylated β-sulfonylester (exemplified in scheme 185).



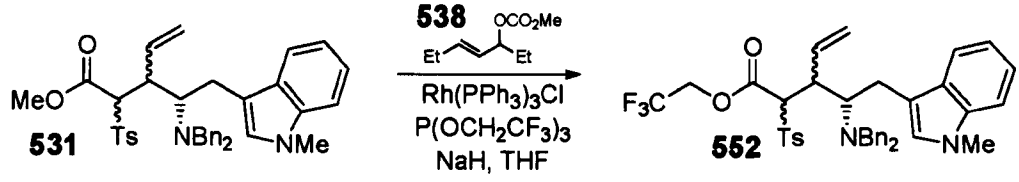

**Scheme 185:** *Rh-catalysed allylation precedent*

In light of the general predominance of the formal retention product **548a**, Evans contends that the reaction proceeds *via* an enyl ($\sigma+\pi$) organorhodium intermediate, rather than a $\pi$-allyl complex (scheme 186) and furthermore that $\sigma \rightarrow \pi \rightarrow \sigma$ isomerisation is slow with respect to displacement by the nucleophile. Not only is the precedent close, therefore, but the "sacrificial" ethyl group may not be required, reducing steric crowding on the carbonate.



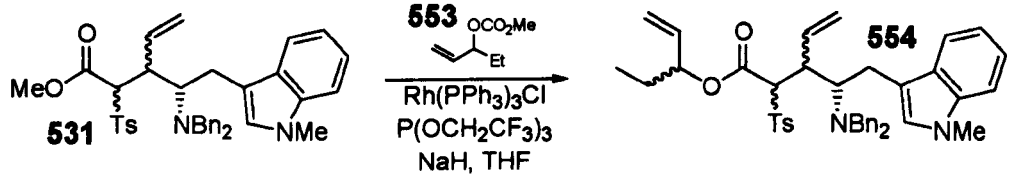

**Scheme 186:** *Likely mechanism for Rh-catalysed reaction*

The catalyst is generated *in situ* from Wilkinson's catalyst[147] and a trialkyl phosphite additive, the highly $\pi$-acidic tris(2,2,2-trifluoroethyl) phosphite affording the best regioselectivity. For a quick first attempt applying this system to our substrate we used the pseudosymmetrical carbonate already in hand, despite the fact one ethyl group was redundant. The desired product was not isolated, instead a small amount of ester **552**, seemingly arising from phosphite transesterification, was isolated (scheme 187).




**Scheme 187:** *Unexpected product #1 from attempted rhodium-mediated coupling*

Obviously, a more detailed exploration of the reaction's viability was needed and to this end the correct monoethyl carbonate **553** was synthesised. The coupling was attempted in turn, but once again no desired product was detected. In this instance a substance was isolated with spectroscopic characteristics very similar to those predicted for the desired product. It transpired, on closer investigation, to be a product presumably arising from carbonate hydrolysis and transesterification (scheme 188).

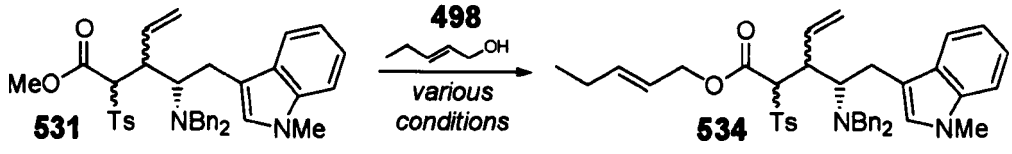



**Scheme 188:***Unexpected product #2 from attempted rhodium-mediated coupling*

In addition to the conditions reported by Evans (rt or below), more elevated temperatures were tried, as well as other solvents and microwave irraditation, all to no avail – only decarboxylation was observed. In view of the failure of both the palladium- and rhodium-mediated reactions to furnish synthetically relevant product(s), we were forced to conclude that the desired fragment union is so sterically demanding as to simply not be viable, in an intermolecular mode at least. (It is noteworthy that the literature does contain a few examples[148] of the formation of quaternary centres with an equivalent level of α-substitution and general steric crowding. All such examples are intramolecular, however.)

## 2.2.11: Second Rearrangements

Forced to return to our original synthetic proposal, we set about the synthesis of the substrate for the second dCr. We had misgivings about stepwise transesterification of the methyl ester, since any intermediate α-sulfonyl carboxylic acid would be likely susceptible to decarboxylation. Instead we opted to attempt a direct transesterification (scheme 189). Such a transformation was inadvertently induced in the studies on rhodium-catalysed coupling.

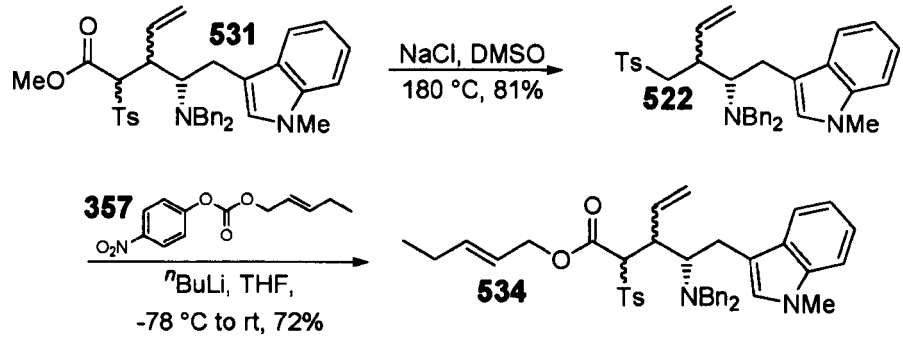



**Scheme 189:** *Direct transesterification of single dCr product*

This transesterification was far from trivial. We sought to sequester methanol in 4Å molecular sieves,[149] thus driving the equilibrium towards the desired product. In THF or PhMe with an amine base ($NEt_3$ or DBU) at rt or reflux, only starting material was isolated, however. An attempt to effect the transformation with Dowex™ in neat pentenol was similarly unsuccessful, as was use of $TiCl(O^iPr)_3$. Only upon use of 10 mol % $KO^tBu$ was any product observed (in 4% yield). Use of stoichiometric $KO^tBu$ did not improve this.

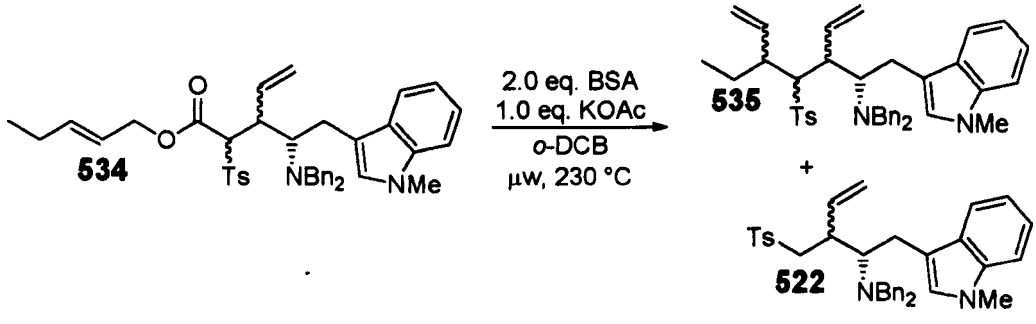
The diastereoisomeric ratio in the isolated material **534** was determined as being approximately 4:2:2:1 (by integration of the *o*-sulfonyl protons). To access the second dCr substrate in quantities sufficient for rearrangement, we instead adopted a more circuitous route, deliberately decarboxylating the

methyl ester in a discrete Krapcho[150] process, then metallating and carboxylating α- to the sulfone with the pentenyl *p*-nitrophenyl carbonate prepared earlier (scheme 190). Such a route was not considered ideal, but allowed exploration of the characteristics of the second key rearrangement.




**Scheme 190:** *Stepwise access to substrate for second dCr*

We anticipated that rearrangement of **534** would not be a facile process. We therefore proceeded directly to use of microwave irradiation, but were dismayed in the first instance to find that attempted reaction in toluene at 160–180 °C for 20 min gave only starting material. Upon increasing the severity of the conditions still further (*o*-dichlorobenzene, 200 °C, 10 min, microwave irradiation) no product was obtained once again. Only when comparable conditions were applied at a temperature of 230 °C were we able to isolate the desired dual rearrangement product **535** in 9% yield (scheme 191). Also isolated were 19% starting material, 4% decarboxylated product **522** and 13% by mass of an unidentified degradation product or products.




**Scheme 191:** *First successful dual dCr of indole-containing substrate*

We were heartened by the success of this second key rearrangement, albeit in poor yield. The isolation of of decarboxylated product is precedented in the observations of co-workers, who have observed the formation of such decarboxylated substrate in many challenging decarboxylative Claisen

rearrangements. We presume that at elevated temperatures and when the desired dCr is a slow process, competing ester hydrolysis (and subsequent decarboxylation) becomes a significant pathway.

In seeking to improve on the yield of this reaction, we were aware that increasing reaction temperature by any great amount would not be feasible and might well increase the proportion of ester hydrolysis/decarboxylation. It seems probable that for a slow reaction such as this one, other undesired processes may also occur, with catalyst death (decomposition of BSA) a likely problem, as alluded to previously. Since gradual addition of BSA (by syringe pump, *etc.*) would not be compatible with the microwave reactor used, we opted to employ BSA itself as the solvent for the reaction. One practical obstacle to this idea is the insolubility of the substrate in BSA. To overcome this, a small amount of $CH_2Cl_2$ was used as co-solvent. Typically a solution of substrate in $CH_2Cl_2$ would be transferred to the microwave vial, then concentrated in a stream of dry $N_2$ to a viscous gum. The vial would then be sealed, purged with $N_2$ and BSA introduced by syringe. The estimated proportion of $CH_2Cl_2$ remaining would typically be less than 5% by volume.

When these modified conditions were applied (at 225 °C for 15 min), the desired product was isolated in 11% yield (also 24% starting material and 10% decarboxylated product). This small increase in yield was disappointing, as we felt there were few experimental parameters remaining for us to vary that would effect further increases in the yield. A substrate possessing such a level of substitution clearly represents the limits of the scope of the dCr.

At this time, our attention was directed to a report in the literature from Ley and co-workers, of another demanding hindered Claisen rearrangement, in this instance an entry to the skeleton of azadirachtin.[151] The authors state that their rearrangement is capricious when performed under conditions of continuous microwave irradiation, with decomposition of material occurring on scale-up. A marked improvement was observed (both in terms of robustness and overall yield) when a pulsed irradiation protocol was adopted, with periods of irradiation interspersed with periods of cooling. To our knowledge, the origins of this effect remain unclear.

We considered that such a microwave pulse sequence might furnish our second dCr product in improved yield. After some experimentation, we

determined that with substrate in neat BSA and with 0.1 equivalents KOAc, a sequence of 10× 60 second pulses at 200 °C interspersed with 9× 60 second periods of cooling gave optimal results. The efficiency of the cooling was such that the reaction mixture would be cooled to ≈100 °C after 60 seconds and the irradiation pulses were timed as 60 seconds *once the target temperature had been reached*. This regime furnished the desired product in 15% yield, but more significantly also allowed isolation of 64% unreacted starting material, permitting recycling of material.

As regards characterisation, the presence of up to 8 (inseparable) diastereoisomers in the second rearrangement product complicates the NMR spectra somewhat. Only at 600 MHz are peaks sufficiently resolved as to give insight into possible diastereoselectivity (figure 3).

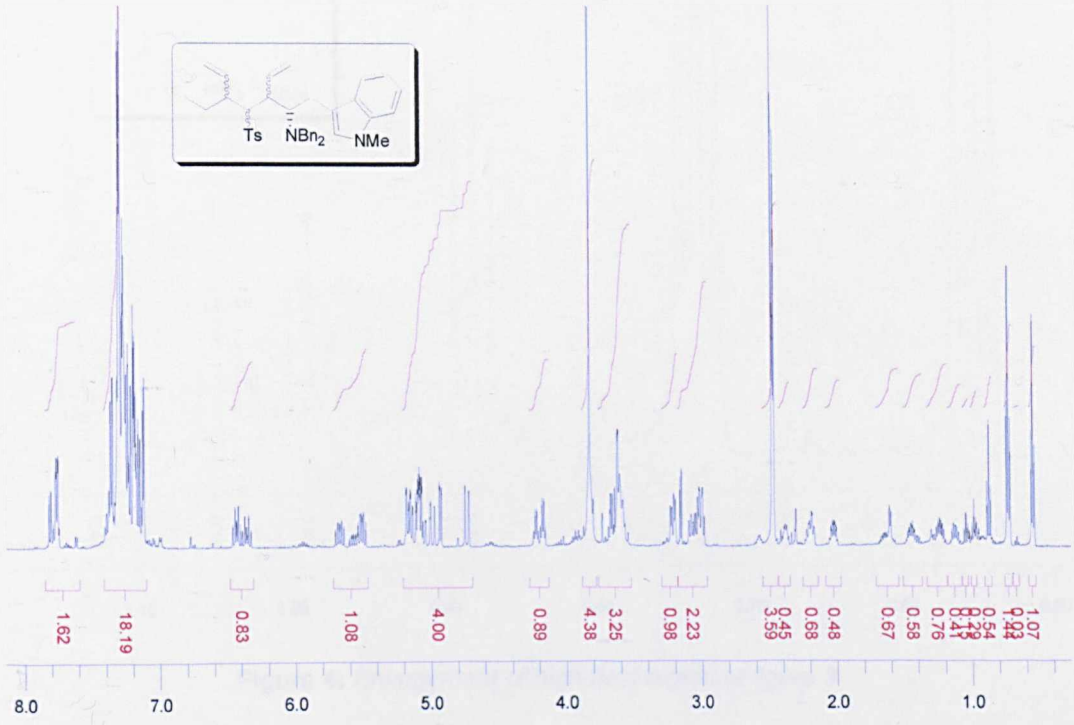



**Figure 3:** *600 MHz $^1$H-NMR spectrum of* **535**

Certain peaks act as useful diagnostic indicators due to their presence in regions of the spectrum deviod of other signals. For example, the high field triplets corresponding to the methyl group of the ethyl side-chain appear at first sight to indicate the presence of two major diastereoisomers and one more minor one. This is clearly at variance with the theoretical possibility of 8

discrete isomers. When the low yield of the rearrangement is considered, it seems possible that a diastereoisomeric resolution may be operating in this second dCr, with some isomers more amenable to rearrangement than others. If this were the case, then diastereoisomeric enrichment of the unreacted starting material would be expected. This was not observed upon inspection of the relevant spectra, however, and so must be ruled out. The spectrum in figure 3 could be explained in terms of coincidence of the signals of different diastereoisomers. Upon closer inspection, however, it may be seen that other, more minor triplets are present in the high field region (figure 4). One of very low integration is discernable at 0.67ppm, with two others at 0.99ppm and 1.05ppm (perhaps coincident with some -$CH_2$- resonances).

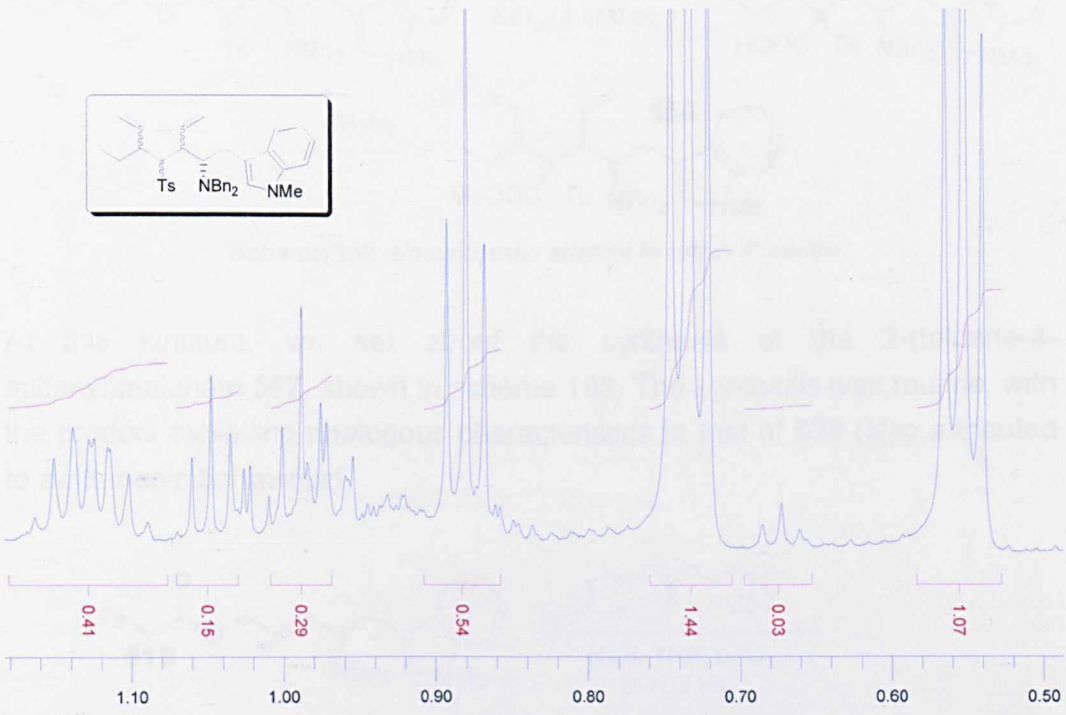
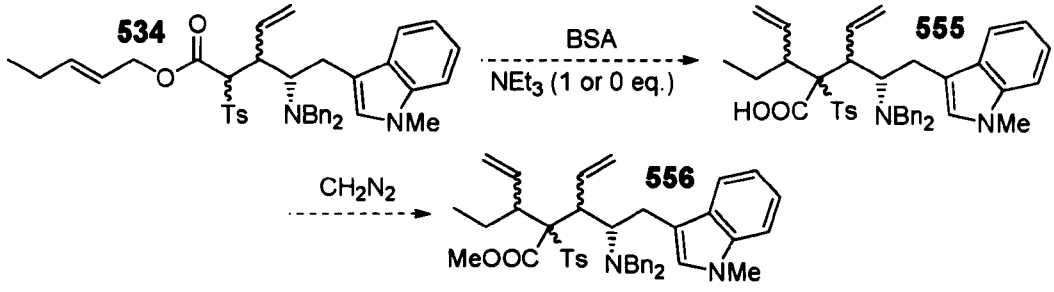



**Figure 4:** *Enlargement of high-field region of figure 3*

At least 6 diastereoisomers are therefore discernable. It may be seen from the integration that the ratio between the most and least abundant isomers is around 50:1.

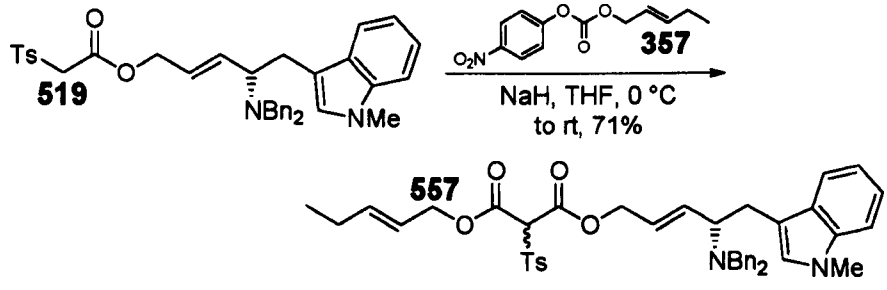
Having shown the second rearrangement to be viable, we briefly investigated whether it could be modified to assist quaternary centre formation. Co-workers had observed[79] that in certain instances, the dCr could be made to proceed in a non-decarboxylative mode, by use of BSA with a non-

nucleophilic base, or with no added base at all. We reasoned that during the course of the second dCr of our substrate, a quaternary centre was transiently formed at the α-sulfonyl carbon, which then decarboxylated. If this quaternary centre could be preserved and further elaborated, this would dispense with the requirement for its reintroduction at a later point. To this end, a non-decarboxylative rearrangement of **534** was attempted (scheme 192). No desired carboxylic acid product **555** was detected. Similarly, an attempt to trap any product formed by *in-situ* derivatisation with diazomethane was also unsuccessful.



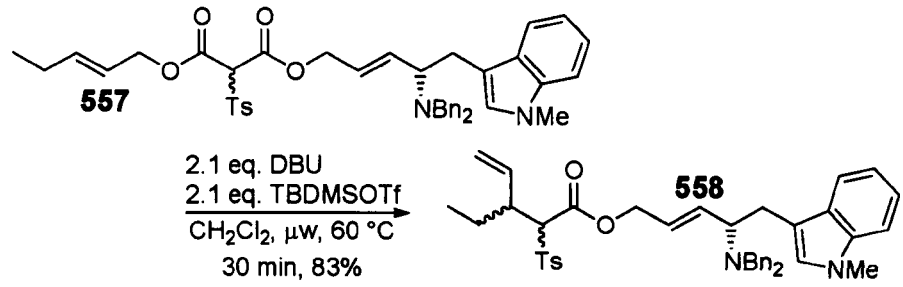

**Scheme 192**: *Unsuccessful attempt to retain 4° centre*

At this juncture, we set about the synthesis of the 2-(toluene-4-sulfonyl)malonate **557**, shown in scheme 193. The synthesis was routine, with the product exhibiting analogous characteristics to that of **529** (also attributed to zwitterionic behaviour).



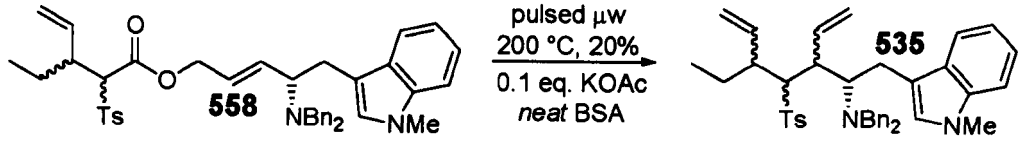

**Scheme 193:** *Synthesis of originally proposed 2-(toluene-4-sulfonyl)malonate*

It was our confident prediction that the first rearrangement of this 2-(toluene-4-sulfonyl)malonate would be that of the pentenyl side chain and that the other side-chain would be so unreactive in the more challenging second rearrangement as to be effectively inert. We subjected the substrate to the alternative conditions for single rearrangement and observed formation of singly rearranged product **558** with total regioselectivity, in line with predictions.



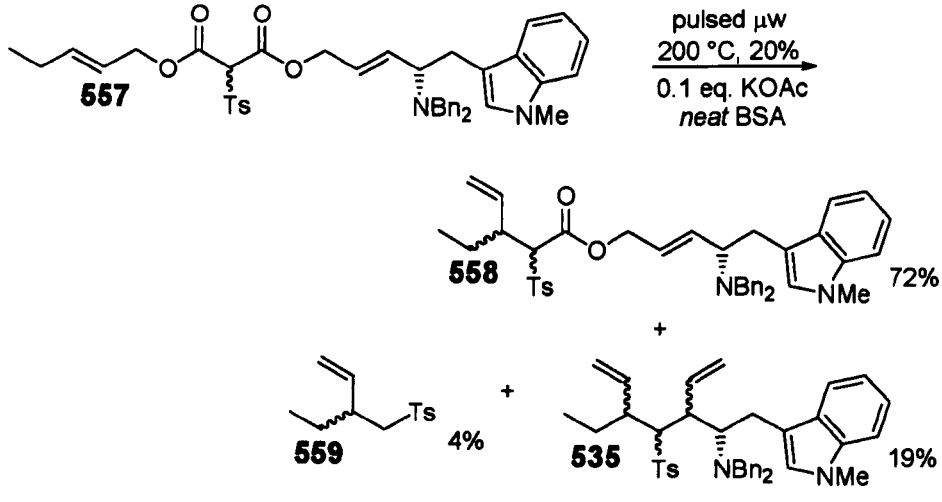

**Scheme 194:** *Single rearrangement of originally proposed 2-(toluene-4-sulfonyl)malonate*

We then subjected this singly rearranged product to the same conditions used to induce the second rearrangement of **534**, fully expecting to observe no reaction. In seeming contravention of trends observed so far, however, direarranged 4-(toluene-4-sulfonyl)-1,6-heptadiene **535** was isolated in 20% yield. Unreacted starting material (61%) was also isolated.




**Scheme 195:** *Highly unexpected second rearrangement*

We were further surprised to observe that direct dual rearrangement of the malonate **557** *is* in fact possible by use of the same microwave pulse sequence and conditions. In this instance, a small amount of ester hydrolysis / decarboxylation byproduct **559** was also isolated

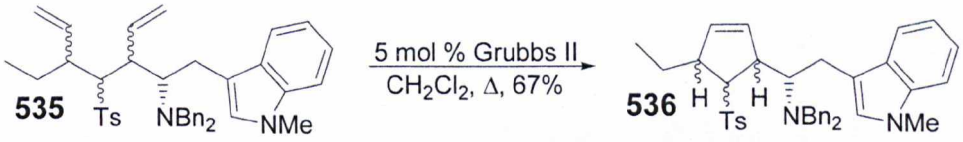



**Scheme 196:** *2-(Toluene-4-sulfonyl)malonate one-pot dual dCr is possible.*

Such a result is beneficial for the synthesis thus far, as this direct 2-(toluene-4-sulfonyl)malonate dual-dCr represents a saving of 3 steps compared to the assisting ester–sequential rearrangement approach. The yield is also slightly higher and the singly rearranged product may be recycled.

## 2.2.12: Cyclopentene Formation

The dual-dCr product was subjected to ring-closing metathesis conditions, using Grubbs' 2nd generation catalyst (scheme 197). The best yield obtained was 67%, with 16% unreacted starting material. The reaction seemingly could not be forced to completion and it was postulated once again that this may be due to differential reactivity of diastereoisomers. Once again, however, no spectroscopic evidence of diastereoisomeric enrichment of the unreacted starting material was observed to support this postulate.




**Scheme 197:** *Ring-closing metathesis to access cyclopentene*

Significantly, of all our (–)-suaveoline intermediates synthesised so far, this cyclopentene was the first for which separation of diastereoisomers was possible. The 67% isolated yield consists of 25% of a less polar, or "upper" mixture of diastereoisomers and 42% of a more polar, or "lower" mixture of diastereoisomers. Their 600 MHz $^1$H-NMR spectra merit examination and are shown in figures 5 and 6.

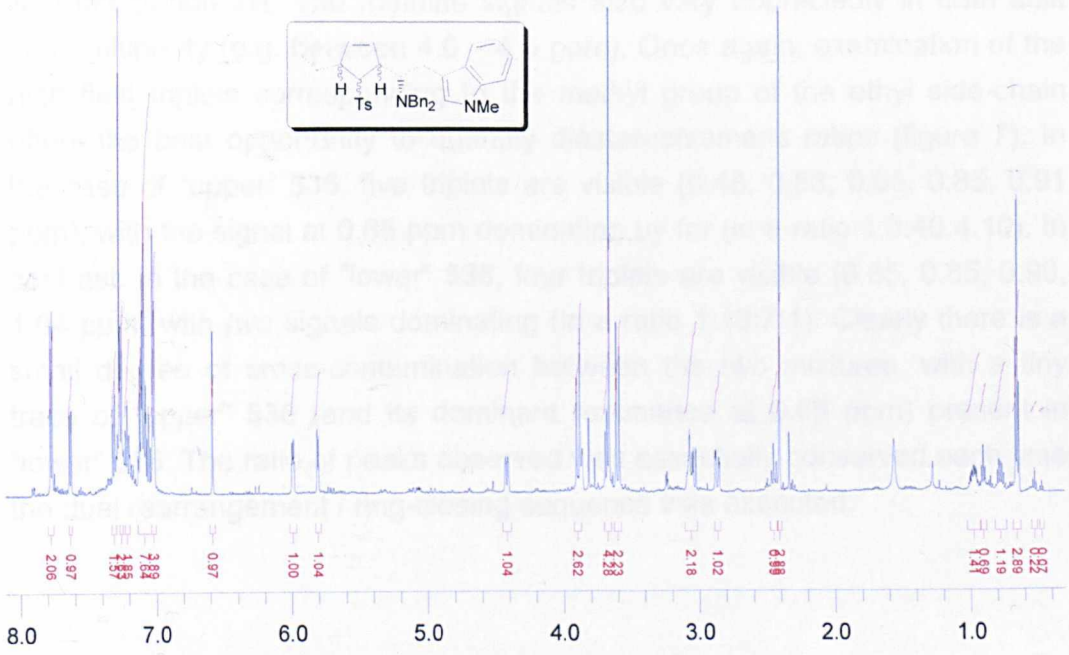



**Figure 5:** *$^1$H-NMR spectrum of* **536**, *"upper" diastereoisomeric mixture*

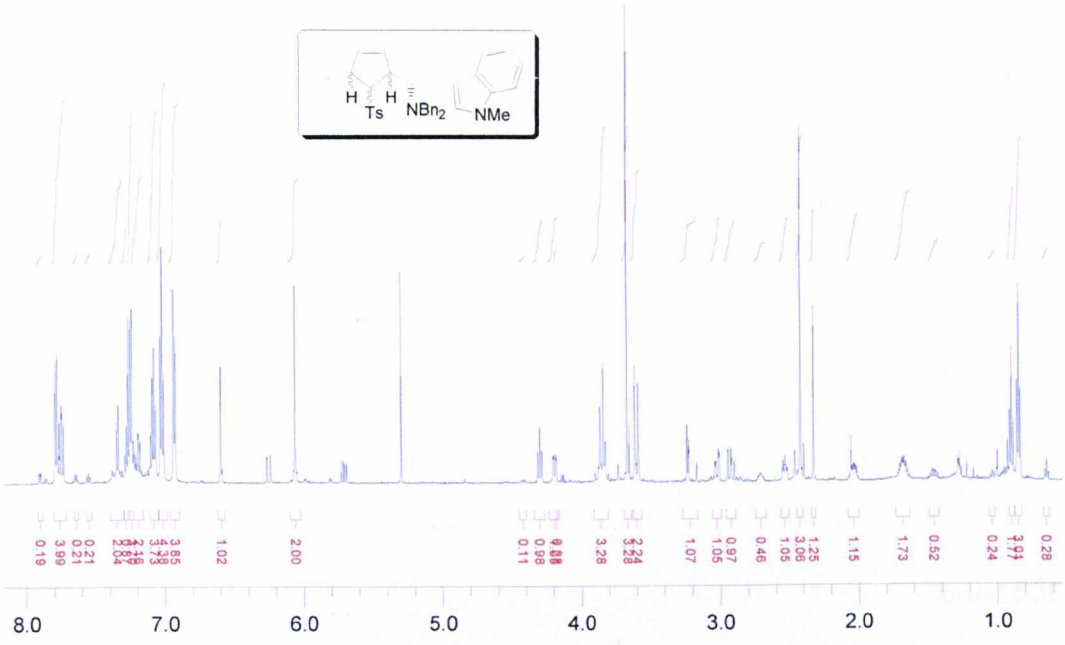



**Figure 6:** *$^1$H-NMR spectrum of* **536**, *"lower" diastereoisomeric mixture*

The most striking difference between the two spectra is in the olefinic region, with the "upper" **536** exhibiting two distinct resonances (with coupling), whereas the "lower" **536** has coincident resonances, giving rise to a singlet with integration 2H. The methine signals also vary appreciably in both shift and multiplicity (e.g. between 4.0 – 4.5 ppm). Once again, examination of the high field triplets corresponding to the methyl group of the ethyl side-chain offers the best opportunity to quantify diastereoisomeric ratios (figure 7). In the case of "upper" **536**, five triplets are visible (0.48, 0.53, 0.65, 0.85, 0.91 ppm), with the signal at 0.65 ppm dominating by far (in a ratio 1:3:40:4:10). In contrast, in the case of "lower" **536**, four triplets are visible (0.65, 0.85, 0.90, 1.04 ppm) with *two* signals dominating (in a ratio 1:13:7:1). Clearly there is a small degree of cross-contamination between the two mixtures, with a tiny trace of "upper" **536** (and its dominant resonance at 0.65 ppm) present in "lower" **536**. The ratio of peaks observed was essentially conserved each time the dual rearrangement / ring-closing sequence was executed.

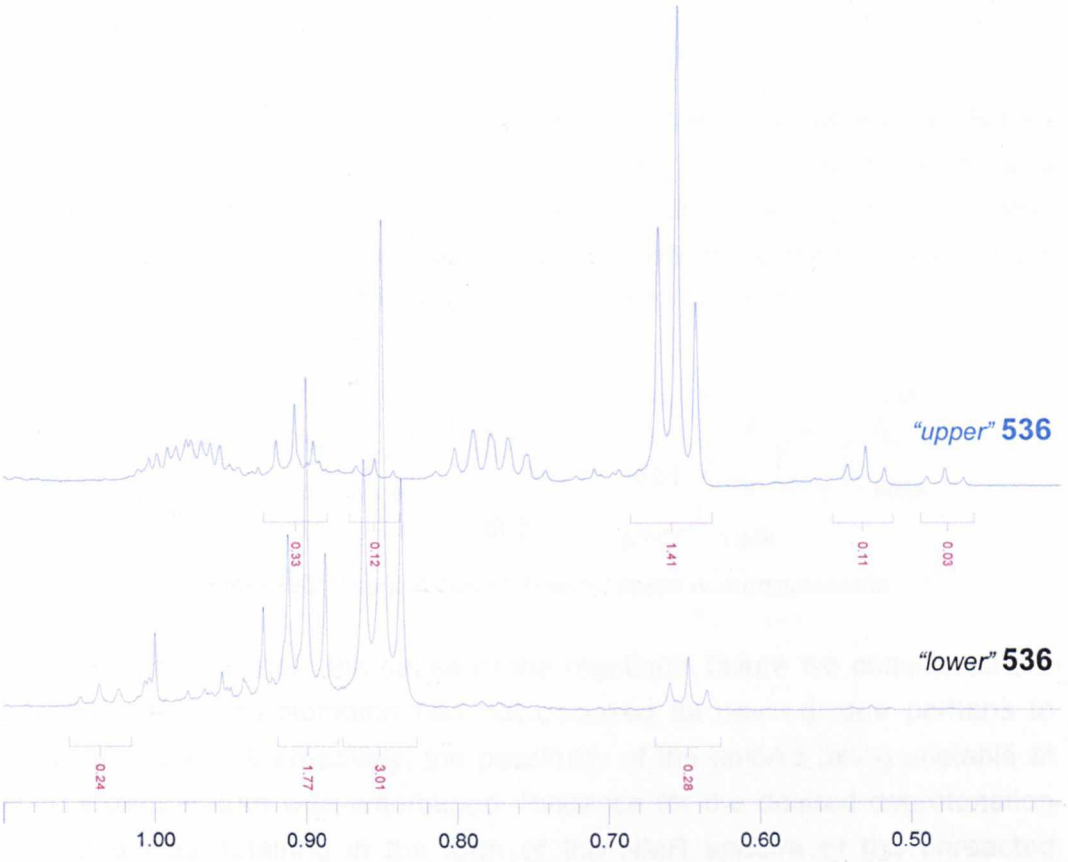



**Figure 7:** *Spectroscopic evidence for distribution of diastereoisomers*

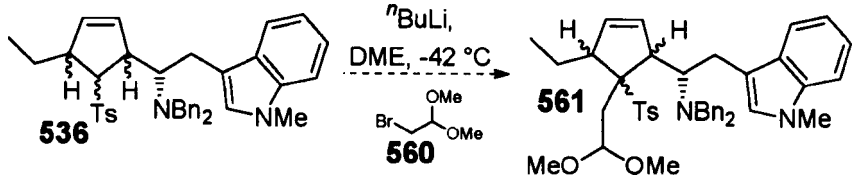
## 2.2.13: Attempts at Masked Aldehyde Introduction

### *2.2.13.1: Sulfonyl α-metallation*

Prior to pyridine formation, we proposed to introduce the 2-carbon masked aldehyde fragment. We hoped to effect metallation α- to the sulfone (the indole 2-position being the only other plausible site of deprotonation) and to alkylate with an appropriate electrophile. In seeking to form a quaternary centre with α-branching on two substituents we were undertaking a difficult transformation. We hoped, however, that the cyclic anion would prove more reactive than the open-chain 4-(toluene-4-sulfonyl)-1,6-heptadienyl equivalent and that, through astute choice of reaction conditions and electrophile, we would be able to effect the transformation.

In the first instance, we employed bromoacetaldehyde dimethyl acetal as the electrophile (scheme 198). We were aware that this is a poor electrophile, but it was attractive in that the fragment was at the correct oxidation level and the

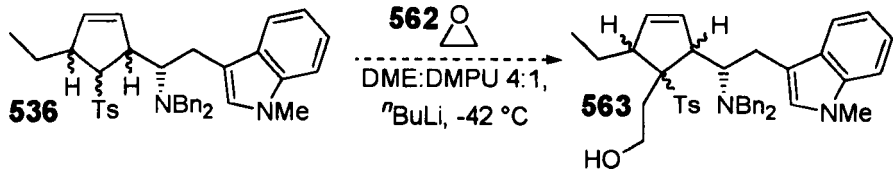
conditions required for aldehyde deprotection would also effect the Pictet–Spengler cyclisation. Unfortunately, however, upon deprotonation and subsequent electrophile addition, no reaction with either "upper" or "lower" diastereoisomeric mixtures **536** occurred, either cooled or at room temperature. Only unreacted starting material was isolated.




**Scheme 198:** *Incorporation of dimethyl acetal was unsuccessful*

In seeking to ascertain the cause of the reaction's failure we considered the possibility that deprotonation had not occurred as desired, due perhaps to steric hindrance. Alternatively, the possibility of the anion's being unstable at such a temperature was entertained. Evidence for the desired deprotonation occurring was obtained in the form of the NMR spectra of the unreacted starting material, which showed significant epimerisation had occurred (this is discussed in more detail below). To probe the stability of the anion, we effected deprotonation in DME at –42 °C and after 15 min quenched the anion with 1 equivalent of AcOH in DME, without introducing any electrophile. The unreacted starting material was isolated in good yield, displaying the same evidence of epimerisation. A comparable proton quench experiment in THF at –78 °C had the same outcome.

Convinced that the failure of the alkylation was therefore due to the poor reactivity of the electrophile, we sought to employ the equivalent iodide. This was not commercially available and our attempts to synthesise it by a Finkelstein reaction[152] were unsuccessful, the impure crude product decomposing with liberation of elemental iodine upon attempted distillation.[153] We considered alternative electrophiles, aware that we would not be able to install the fragment at the correct oxidation level. Oxidation could be carried out later in the synthesis; the overriding criterion for the 2-carbon electrophile was reactivity. To this end we opted to employ oxirane, in the hope that its sterically non-demanding nature and inherent ring strain would render it reactive in our system (scheme 199).




**Scheme 199:** *Incorporation of epoxide was also unsuccessful*

Conditions analogous to those for the prior electrophile were employed. Once again, no product was detected, even with the electrophile in vast excess. Epimerised starting material was isolated as before. Scope for increasing the reaction temperature was limited due to the volatility of epoxide. The hindered nature of the anion is illustrated by the failure to effect alkylation with this reactive 2-carbon electrophile.

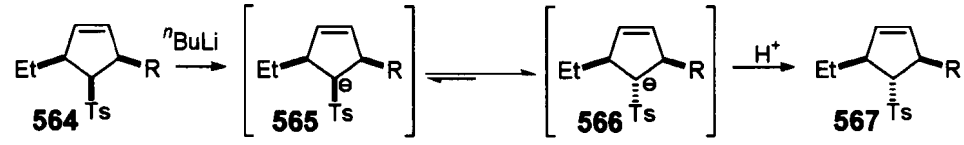
In order to assess the overall viability of alkylation at the desired position we sought to alkylate with various "test" electrophiles. In so doing we wished to show that an internal anion quench (e.g. with the proton from the indole C-2 position) was not occurring. Attempted alkylation with methyl iodide in DME:DMPU 4:1 was unsuccessful, both with sequential electrophile addition and with the electrophile present *in situ* prior to deprotonation. We then employed trimethylsilyl chloride (rigorously purified by centrifugation with $NEt_3$), mindful that as well as serving as a "test" electrophile, a silyl group might also act as a handle for derivatisation of the pyridyl 4-position. Regrettably no product was detected. Surprisingly, attempted deuterium incorporation was also unsuccessful. We were eventually forced to conclude that whilst anion formation is a viable process, quenching that anion with anything sterically more significant than a proton is not.

As mentioned above, upon attempting the metallation/alkylations, appreciable epimerisation (presumably α- to the sulfone) was observed. As "upper" and "lower" **536** were treated separately, we were able to discern certain trends

- When "upper" **536** was exposed to *n*-BuLi, around 70-85% of the material isolated was unchanged in composition; around 15-30% of the material epimerised to an isomer not previously observed with a triplet at 0.82 ppm, which had an $R_f$ value equivalent to that of "lower" **536**.
- When "lower" **536** was exposed to *n*-BuLi, material was isolated in which a far smaller amount remained unchanged. Most material (approximately 80%) had epimerised to an isomer with a triplet at 0.48 ppm. In one instance all material had epimerised. This new epimer was

noteworthy for no longer having the coincident olefinic signals of the starting material. (Note that whilst an epimer with a triplet at 0.48 ppm has been observed as a minor component of "upper" **536** (figure 7), all material isolated upon epimerisation of "lower" **536** retained the same "lower" $R_f$).

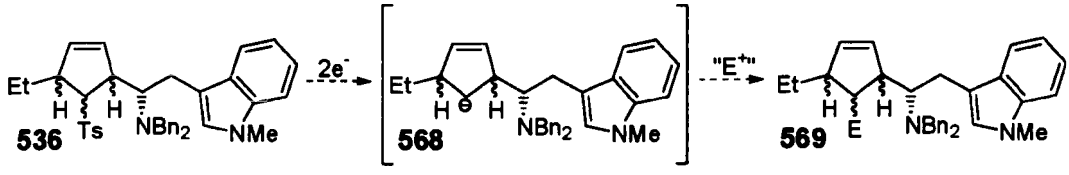
From the above observations we tentatively assign the major isomer in "lower" **536** (triplet at 0.85 ppm) at as being a cyclopentenyl 3,4,5-all *cis* isomer. The rationale for this is that the more extensive epimerisation of this isomer corresponds to extensive anion inversion as the molecule seeks to minimise steric repulsion by adopting a 3,4-*trans*, 4,5-*trans* configuration (scheme 200).




**Scheme 200:** *Possible rationale for epimerisation ratios observed*

*2.2.13.2: Reductive desulfonylation*

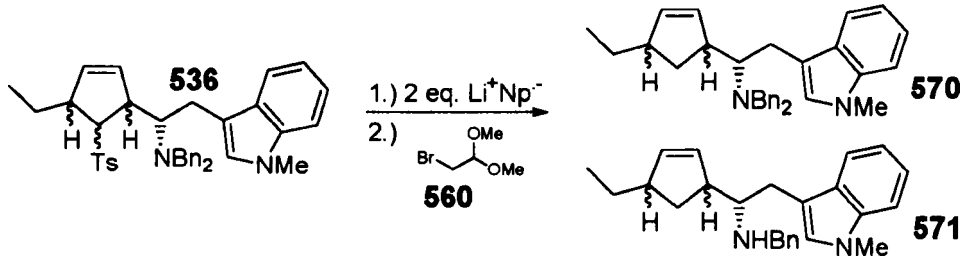
Our primary strategy for introduction of the masked aldehyde having been proven unsuccessful, we were forced to seek alternative approaches. We had ascribed the failure of our desired alkylation to steric hindrance of the tertiary carbanion. To overcome this, we proposed to induce reductive desulfonylation of the cyclopentene. The resultant secondary carbanion should be both less sterically hindered and less stabilised (hence hopefully more reactive) and as such be more amenable to trapping with electrophiles (scheme 201).




**Scheme 201:** *Proposed reductive desulfonylation / alkylation*

The loss of the sulfonyl group would render the substrate inappropriate for accessing the pyridine by the methodology described in section 2.2.3. However, oxidative cleavage and treatment with $NH_2OH$ should still enable us to access the pyridine via a classical Hantzsch-type intermediate,[154] the approach employed by Cook.

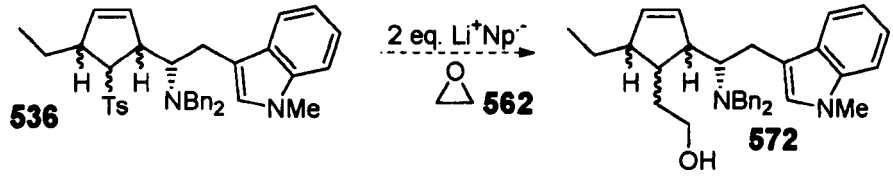
Initially we attempted to introduce our first-choice electrophile, bromoacetaldehyde dimethyl acetal. The reductant employed was lithium naphthalenide, the use of which is well precedented in the Craig group.[125] In THF at –78 °C, upon reductive desulfonylation of either "upper" or "lower" **536** and ensuing electrophile introduction only the desulfonylated product **570** was isolated in 63% yield, with 20% unreacted starting material (scheme 202). In one instance, a small amount of material **571** having undergone desulfonylation and *N*-monodebenzylation was also isolated.




**Scheme 202:** *Alkylation after reductive desulfonylation was not successful*

Fearing possible proton abstraction from the solvent,[155,156] we employed DME at –42 °C instead. The outcome was unchanged, desulfonylated cyclopentene being isolated in 79% yield, with 16% unreacted starting material. The reaction was also attempted with the electrophile *in situ*. No desired product was detected, with desulfonylated product isolated in a reduced 37% yield, with 51% unreacted starting material. This reduced yield may indicate a degree of competing reduction of the electrophile.

We moved in turn to use of oxirane as electrophile. In order to ensure the maximum possibility of success we employed oxirane not just as the *in situ* electrophile, but as solvent itself (at –78 °C the substrate displayed good solubility in liquid epoxide. The lithium naphthalenide was introduced in DME). Regrettably, this reaction also led solely to isolation of starting material (scheme 203).




**Scheme 203:** *Use of epoxide as solvent and* in-situ *electrophile afforded no advantage*

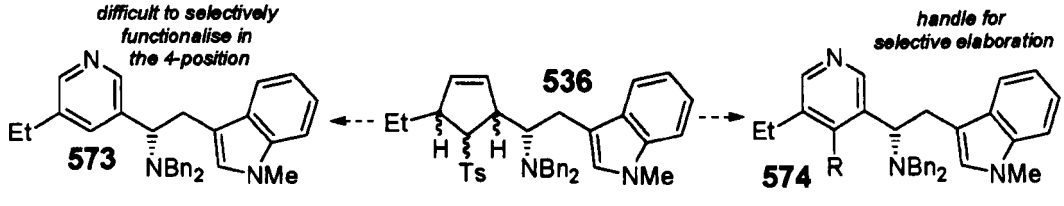
The total failure of attempted electrophile introduction was vexing. Clearly the reductive desulfonylation was occurring quickly. The failure to alkylate implied quenching of the secondary anion was occurring rapidly; we had taken rigorous steps to exclude moisture so the source of the quenching proton was

of interest. Proton abstraction from DME seemed unlikely. The possibility that an intramolecular quench may be operating from the indole C-2 position occurred to us, but no alkylation at this position (or anywhere else) was ever observed. One telling observation was that in the unreacted starting material recovered (scheme 202) significant epimerisation had occurred (comparable to that observed during the experiments on sulfone α-metallation). We reasoned therefore that an intermolecular quench may be a significant process, whereby the secondary anion formed is quenched by the α-sulfonyl proton of unreacted starting material. Inverse addition was not attempted, as it was feared *N*-debenzylation would result.

## 2.2.14: Pyridine *N*-oxide Methodology

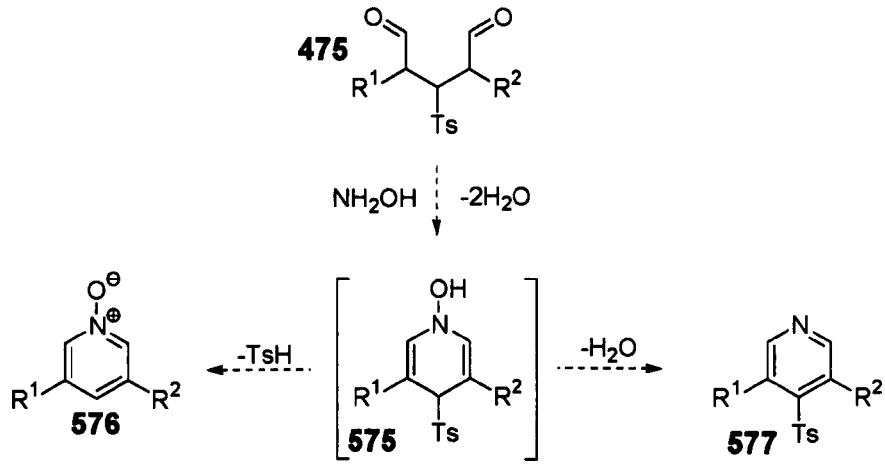
Faced with the failure of all attempts to append the 2-carbon masked aldehyde fragment onto the cyclopentene, we were forced to adopt fundamental changes to our synthetic strategy. We reasoned that if introduction of the desired fragment was not possible at this point, we were compelled to introduce the fragment later in the synthesis. If we could effect transformation of the cyclopentene (or a derivative thereof) to the pyridine, whilst somehow retaining the possibility of selectively functionalising the pyridyl 4-position, this would represent the smallest deviation from our original proposal. Crucially, it might also allow us to employ the intermediates that had been synthesised so far, rather than diverging from our established synthetic route.

If the cyclopentene **536** were subjected to oxidative cleavage and pyridine formation as detailed in section 2.2.3, the resultant 3,5-disubstituted pyridine would be difficult to *selectively* functionalise in the 4-position. If, however, functionality could be retained at the 4-position, that could provide a handle for regioselective elaboration (scheme 204).




**Scheme 204:** *A pyridine intermediate that can be selectively elaborated is desirable*

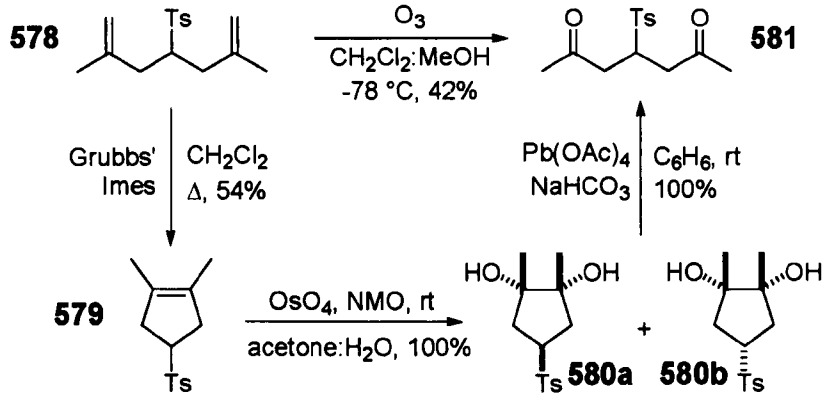
We were curious as to what would occur if a 3-sulfonyl-1,5-dialdehyde **475** were treated not with $NH_3$, but with $NH_2OH$ (scheme 205). One can envisage formation of a 4-(toluene-4-sulfonyl) pyridine **577**, with the intermediate losing a third equivalent of $H_2O$ as opposed to toluenesulfinic acid. Alternatively, loss of toluene-4-sulfinic acid might also occur, theoretically leading to a pyridine *N*-oxide **576**.




**Scheme 205:** *Possible products from use of hydroxylamine*

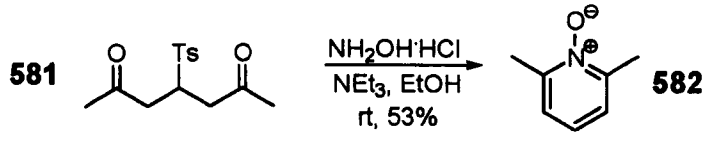
Were 4-(toluene-4-sulfonyl)pyridine **577** to result, this could possibly be elaborated by application of a reductive desulfonylation-alkylation protocol as above (perhaps proceeding *via* a Birch-like[157] intermediate). Alternatively, $S_NAr$ reactions of 4-sulfonylpyridines with cyanide are known.[158] If pyridine *N*-oxide **576** were formed, selective functionalisation at the 4-position might also be possible.[159]

We wished to determine which (if any) of these products would predominate and so set about briefly exploring a model system. Diene **578** was provided by a co-worker; its synthesis is detailed elsewhere.[122] Its transformation to diketone **581** was effected by two different methods. Direct ozonolysis furnished **581** in 42% (along with an unidentified crystalline byproduct). However, ozonolysis was unlikely to be appropriate to an indole-containing system. Alternatively, **578** was subjected to ring-closing metathesis, furnishing tetrasubstituted cyclic olefin **579** in 54% yield. Upjohn[160] dihydroxylation (in quantitative yield, with d.r. 7.4:1), followed by lead tetraacetate-induced cleavage (also in quantitative yield) gave diketone **581** too (scheme 206).



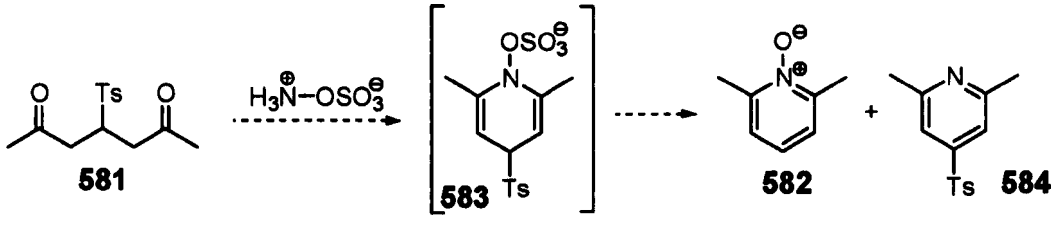

**Scheme 206:** *Routes to diketone model substrate*

Upon treatment of **581** with 1 equivalent of hydroxylamine hydrochloride and 1 equivalent of triethylamine in ethanol at room temperature, 2,6-lutidine-*N*-oxide **582** was isolated in 53% yield (scheme 207).




**Scheme 207:** *Formation of pyridine*-N-oxide

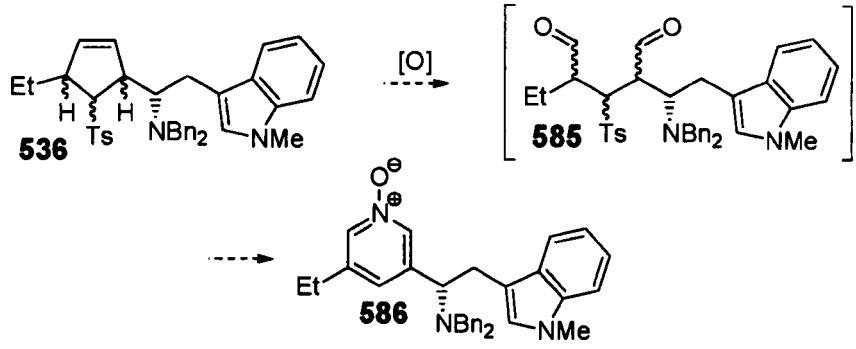
No 4-(toluene-4-sulfonyl)pyridine was observed. Such a novel pyridine-*N*-oxide synthesis may be of utility for the synthesis of (–)-suaveoline. We believed, however, that synthesis of a 4-(toluene-4-sulfonyl)pyridine might afford more options for further elaboration. In order to favour formation of the 4-(toluene-4-sulfonyl)pyridine in the above reaction, we sought to bias the intermediate in scheme 205 away from loss of *p*-tolylsulfinic acid. We aimed to introduce nitrogen by use of a reagent with a better *N*- leaving group; to achieve this we treated the diketone **581** with hydroxylamine-*O*-sulfonic acid ("HOSA", scheme 208).




**Scheme 208:** *Modification of the reaction with HOSA was unsuccessful*

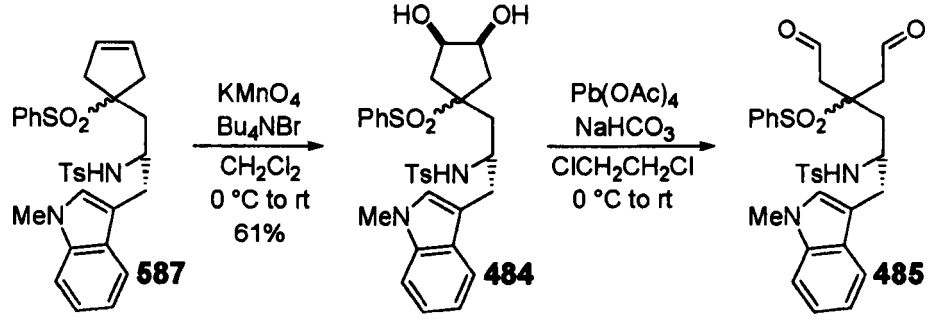
Neither expected product was formed. The material that was isolated was never conclusively identified. We therefore determined to progress the synthesis of (–)-suaveoline by pyridine-*N*-oxide formation.

## 2.2.15: Oxidative Cleavage and Indole Protection




**Scheme 209:** *Proposed oxidative cleavage and pyridine-N-oxide formation*

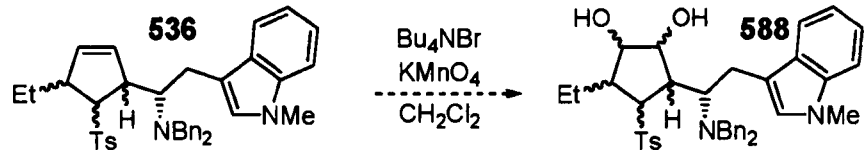
In order to effect pyridine-*N*-oxide formation, oxidative cleavage of the cyclic olefin was required (scheme 209). One major issue with the proposed transformation is the oxidative sensitivity of the indole. The indole 2,3-$\pi$ bond is electron-rich and reportedly undergoes facile oxidation, especially with ozone.[161] We believed success was more likely with an oxidative cleavage *via* the vicinal diol, either as an isolated intermediate (as in the model system, scheme 206), or in a one-pot Johnson-LeMieux[162] procedure. Cook has reported[113d] that careful monitoring of osmylation reactions in closely-related systems allows isolation of the desired diols without overoxidation to the oxindole (a well-known process[163]). Additionally, the work of co-workers towards (–)-alstonerine also provides a precedent once again[125] (scheme 210)




**Scheme 210:** *Precedent - successful olefin dihydroxylation in the presence of an indole*

After extensive optimisation it had been found that treatment of the cyclopentene **587** with tetrabutylammonium permanganate in dichloromethane at 0 °C to room temperature afforded the 1,2-diol **484** in

acceptable yield. We duly applied the reported conditions to our substrate **536** (scheme 211). At the reported concentration (0.02 M) no reaction occurred. Upon increasing the concentration and / or temperature, decomposition was observed. In one instance impure material was with an amide-like IR absorbance and $^{13}$C-NMR resonance, possibly an oxindole byproduct.

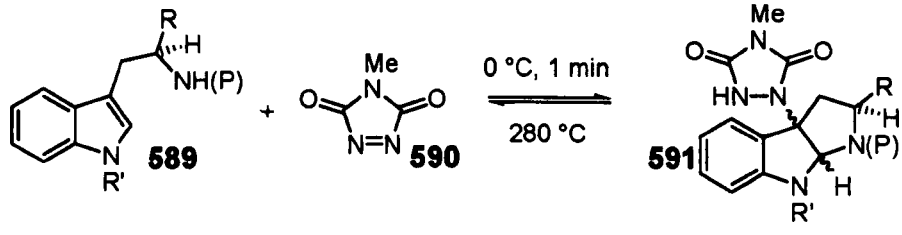



**Scheme 211:** *Attempted dihydroxylation with $Bu_4NMnO_4$ was unsuccessful*

We were aware that our cyclopentene was more sterically hindered than that in scheme 210, so instead attempted a double dihydroxylation of the open-chain 4-(toluene-4-sulfonyl)-1,6-heptadienyl precursor **535**, in which we took the olefins to be less hindered. Only complex mixtures ever resulted, in which were identifiable by accurate mass spectrometry only the diol(s), never the desired tetraol.

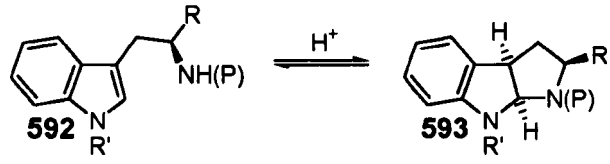
The use of $Bu_4NMnO_4$ having met with no success, we next attempted a Johnson-LeMieux cleavage direct to the dialdehyde, as reported by Cook.[113d] Cook's conditions (cat. $OsO_4$ / $NaIO_4$, 80% AcOH) afforded a complex mixture in which aldehydic signals were visible in the $^1$H-NMR spectrum. This mixture was treated with ethanolic $NH_2OH{\cdot}HCl$ and $NEt_3$, but none of the desired pyridine-*N*-oxide was detected. Use of milder, biphasic conditions (cat. $OsO_4$ / $NaIO_4$, DME / $H_2O$) also led to a complex aldehydic mixture. This mixture was subjected to the same pyridine-*N*-oxide-forming conditions, but none was observed.

We concluded from these failures that the oxidative instability of the indole precluded the desired selective oxidative cleavage. We inferred from this that protection of the indole was necessary. Corey has recently reported[164] use of MTAB as an indole 2,3-$\pi$ protecting group (scheme 212). The ene reaction for introduction of the urazole is reportedly highly facile, with deprotection via a *retro*-ene process being induced at high temperature.



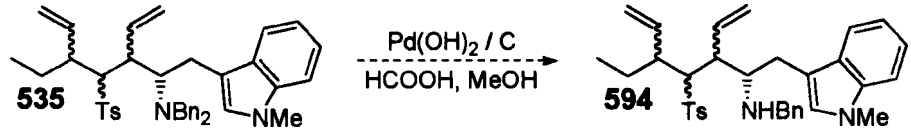

**Scheme 212:** *Indole 2,3-π protection by urazole ene reaction*

An alternative strategy for indole protection may be to use the protocol of Crich[165] (scheme 213). His approach (originally intended for the enantiospecific synthesis of α-substituted tryptophan derivatives) also involves formation of a hexahydropyrrolo[2,3-*b*]indole, in an acid-catalysed process. The tricycle may be elaborated as desired before acid-induced cycloreversion.



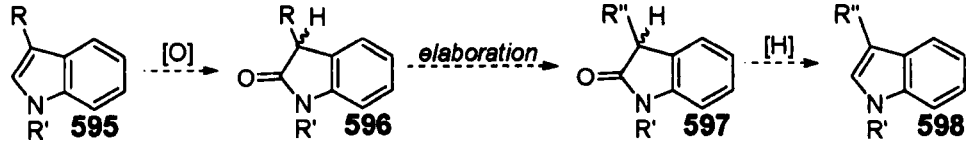

**Scheme 213:** *Crich's acid-mediated hexahydropyrrolo[2,3-b]indole formation*

One stipulation common to both these approaches is the requirement for a latent nucleophile elsewhere in the molecule (typically the tryptophan $N_\beta$) to intercept the indole ring (alternatively, the Corey procedure is also applicable for $N_\alpha$-unsubstituted indoles). As there is no spare $N_\beta$ valency in our intermediate(s), monodebenzylation was required before these indole protection strategies could be applied. To this end, we attempted selective monodebenzylation of **535** by a procedure[134] that employed Pearlman's catalyst[166] in transfer hydrogenation (scheme 214).



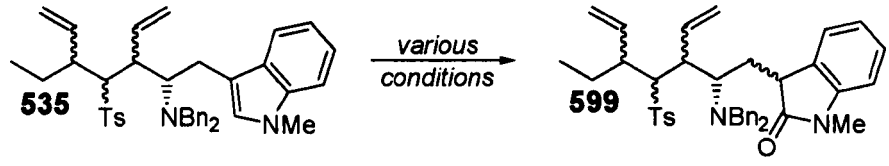

**Scheme 214:** *Attempted monodebenzylation with Pearlman's catalyst was not a clean process*

A complex mixture resulted. Rather than attempt refinement of these conditions, however, it was decided to pursue an entirely different protection strategy. It was reasoned that rather than protecting the indole against unwanted oxidation, we could seek to *deliberately* oxidise the indole to the oxindole. The resultant heterocycle (simply an *N*-acyl aniline) should then be far less reactive towards the olefin oxidative cleavage conditions. After formation of the pyridine-*N*-oxide (and possibly further elaboration), the indole could be regenerated reductively, a known process[167] (scheme 215).




**Scheme 215:** *Oxindole itself may be used as a protecting group*

We sought a procedure for oxindole formation and for a first attempt applied that due to Szabó.[168] The reaction is analogous to a Kornblum oxidation.[169] Treatment of open-chain intermediate **535** with concentrated $HCl_{(aq)}$ in DMSO afforded oxindole **599**, (scheme 216) but in low yield (30%) and with appreciable byproduct formation.

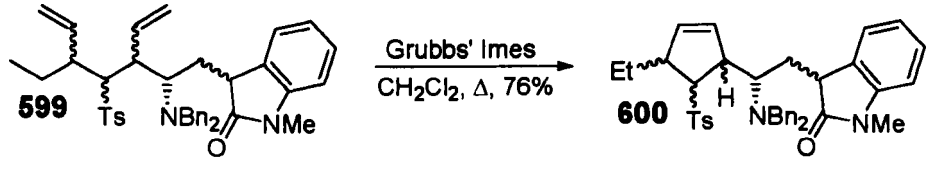



**Scheme 216:** *Formation of desired oxindole*

We next sought to effect the oxidation by use of *m*CPBA. Once again, the product oxindole was isolated impure and in low yield (35%). Both the above methods rely on harsh, acidic conditions. Far milder, neutral conditions have recently been reported by Zhang,[170] which employ DMDO to access oxindoles via the indole 2,3-epoxide. When these conditions were applied (1 equivalent DMDO, $CH_2Cl_2$, –78 °C to room temperature, 30 min), the desired oxindole **599** was isolated cleanly and in 72% yield.

## 2.2.16: Final Approaches to an Advanced (–)-Suaveoline Intermediate

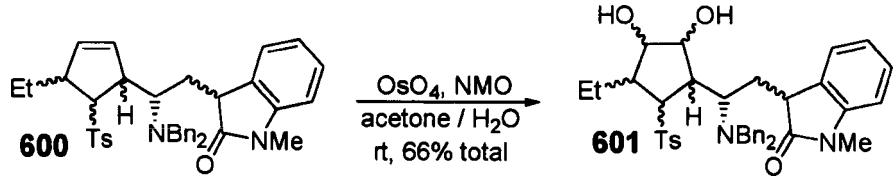
Ring-closing metathesis to furnish the cyclopentene-oxindole was routine, the product being isolated as three discrete mixtures of diastereoisomers. Interestingly, upon reversal of the sequence of events, attempted oxidation of the cyclopentene-indole **536** to the oxindole **600** was not successful. Perhaps the more electron-rich disubstituted olefin competes to a greater degree for oxidation.




**Scheme 217:** *Ring-closing metathesis provided cyclopentene-oxindole in good yield*

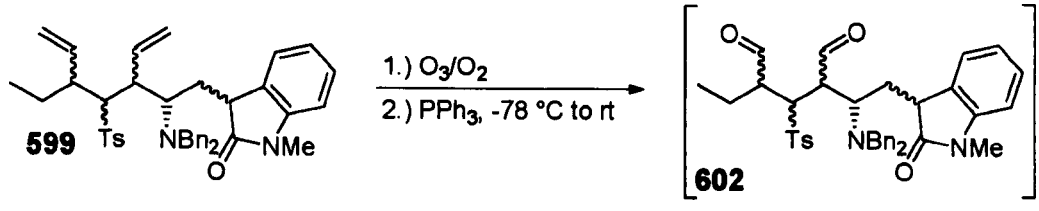
It was decided to attempt oxidative cleavage to the dialdehyde both *via* the 1,2-diol and also by direct ozonolysis. As per the model system (scheme 206),

cyclopentene-oxindole **600** underwent Upjohn dihydroxylation to furnish the cyclopentene-1,2-diol **601**. This was formed as five discrete isolable diastereoisomeric mixtures, of which only one was formed in sufficient yield for full characterisation (all were recombined for further reaction). The presence of such a number of diastereoisomeric mixtures is not surprising when it is considered that up to 32 of 64 possible diastereoisomers may be present (assuming *syn*-dihydroxylation).




**Scheme 218:** *Dihydroxylation led to many diastereoisomers*

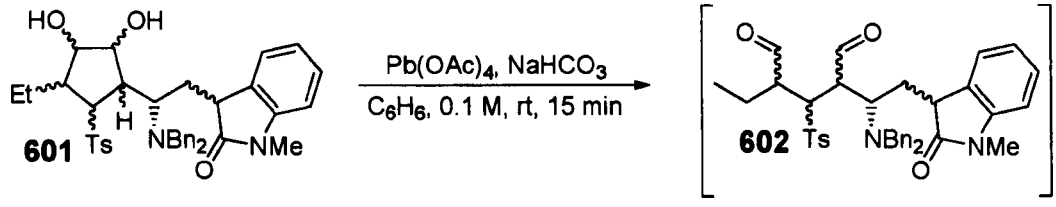
We first attempted oxidative cleavage to the 1,5-dialdehyde by direct ozonolysis of open-chain oxindole **599** (Scheme 219). One equivalent of trifluoroacetic acid was added to **599** at –78 °C in $CH_2Cl_2$ (to transiently protect the tertiary amine) before passage of a stream of $O_3/O_2$. Starting material was consumed within 10 min, whereupon triphenylphosphine was added. After 1 h at –78 °C, the reaction mixture was allowed to warm to room temperature, whereupon it turned lurid orange. This was taken as indicating that decomposition was occurring, thus the reaction mixture was quickly quenched with $NaHCO_{3(s)}$, filtered and concentrated. A TLC of the crude "dialdehyde" **602** indicated the presence of many discrete species, four of which each had a different colour discernable by simple visual inspection.




**Scheme 219:** *Ozonolysis afforded a complex mixture, seemingly highly unstable*

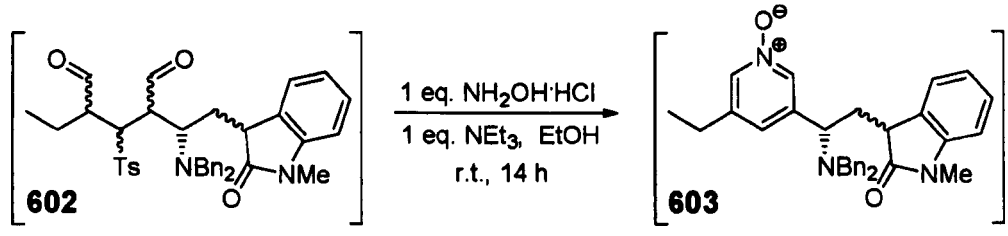
We were concerned that over-ozonolysis may have effected unwanted additional oxidative transformations. Alternatively, the acidic conditions may have led to decomposition. However, the $^1$H-NMR spectrum of the highly impure crude "dialdehyde" did contain aldehydic resonances, so the material was treated with $NH_2OH{\cdot}HCl$ and $NEt_3$ in EtOH as previously. No desired product **603** was detected.

We were hopeful of achieving a cleaner dialdehyde formation by use of lead tetraacetate (which in the model system had formed the dicarbonyl in quantitative yield). We duly treated cyclopentene-1,2-diol **601** in benzene with $Pb(OAc)_4$ and $NaHCO_3$ (scheme 220).




**Scheme 220:** *Attempted alternative 1,5-dialdehyde formation*

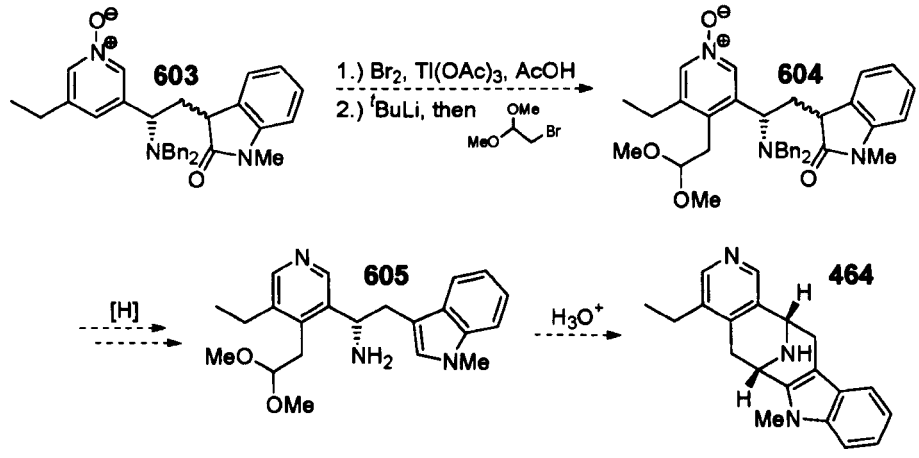
To our dismay, after 15 minutes, the reaction mixture began to discolour, exactly as it had done in the ozonolysis experiment. The reaction mixture was quickly filtered and concentrated; a TLC indicated the impurity profile to be the same as in the previous case. This crude "dialdehyde" **602** was also treated with $NH_2OH{\cdot}HCl$ and $NEt_3$ in EtOH at room temperature overnight (scheme 221). The reaction mixture was shown to contain in excess of 10 species detectable by TLC. Extensive purification of the crude material by repeated chromatography led to the isolation of trace amounts (<1 mg) of material which by nominal +ve FAB mass spectrometry was shown to contain a species giving rise to a peak at *m/z* 492, possibly the protonated parent ion of desired product **603**. Further characterisation was not possible.




**Scheme 221:** *Attempted formation of desired* N*-oxide led to trace amounts of material tentatively assigned as the deisred product*

## 2.2.17: Concluding Remarks and Future Prospects

The failure to synthesise the pyridine-*N*-oxide in appreciable yield is regrettable. Were this species accessible, we envisage the final approach to (–)-suaveoline would necessitate only functionalisation at the pyridine-*N*-oxide *para*-position (e.g. by selective bromination[159] and lithium-halogen exchange), reduction of the *N*-oxide, oxindole and tertiary amine, then unmasking of the latent aldehyde and Pictet–Spengler cyclisation (scheme 222).




**Scheme 222:** *Possible route from advanced intermediate to (-)-suaveoline*

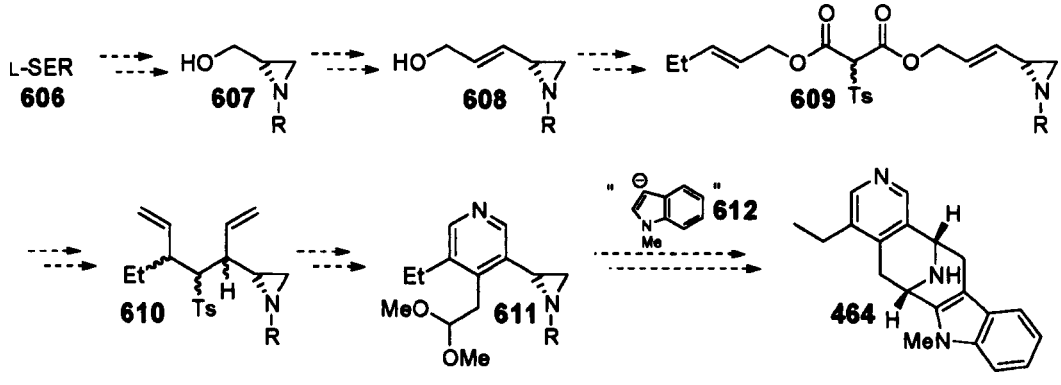
The fact that two different protocols for 1,5-dialdehyde generation gave material with the same impurity profile strongly suggests inherent aldehyde instability. In order to overcome this, formation of the dialdehyde with the hydroxylamine present *in situ* could be attempted (subject to compatibility of this reagent with the dialdehyde-forming conditions).

As regards the work completed to date towards (–)-suaveoline, the cyclopentene-oxindole **600** was accessed in ten steps from L-$N_\alpha$-methyl-tryptophan. The yield for the dual-dCr is low, as noted above, but singly rearranged product may be recycled. In four cycles for the dCr step, 49% conversion may be achieved (this is the greatest number of cycles that appeared to be possible, as material degraded upon repeated exposure to the reaction conditions). If material is similarly recycled in the formation of the rearrangement substrate, then **600** may be accessed in 16% yield over the 10 steps, a mean yield of 83% per step.

Whilst the synthesis of (–)-suaveoline itself has not been achieved, valuable insight has been gained into the dCr, with specific reference to the limits of the

substitution that is tolerated by the reaction. The forcing conditions needed to effect dual-dCr in this study can reasonably be seen to mean that little extra functionality would be tolerated. The dual-dCr described is the first example of dual rearrangement of an indole-containing substrate and the use of pulsed microwave irradiation is also unprecedented for this reaction. The utility of two dCr-inducing reagent systems with complimentary characteristics has been demonstrated. The formation of a pyridine-*N*-oxide from a 3-sulfonyl-1,5-dicarbonyl is, to our knowledge, unprecedented. It is anticipated this transformation will be the subject of further study in the Craig group.

When the various observations laid out in this section are taken into consideration, it is interesting to speculate what overarching strategic changes to the retrosynthetic approach might be adopted, were the synthesis of (–)-suaveoline to be attempted "from scratch" once again. The electron-rich nature (and hence oxidative instability) of the indole ring has been highlighted in this work by the difficulties encountered both in allyl alcohol formation and also in olefinic oxidative cleavage. More success might be had from a strategy in which introduction of the indole moiety were a late-stage event. For example, if serine were used as the starting material, the amino acid nitrogen could be masked as an aziridine, in accordance with group methodology.[127] This could perhaps be used for allyl alcohol formation, incorporation into a 2-(toluene-4-sulfonyl)malonate, dual-dCr (perhaps more facile with a less sterically-demanding side-chain), olefinic oxidative cleavage and pyridine (or *N*-oxide) formation (scheme 223). Only once other key events had occurred would the aziridine be opened[171] with an indole 3-nucleophile, installing the indole ring and simultaneously deprotecting the amine.




**Scheme 223:** *Speculative aziridine-based route to (-)-suaveoline*

It is this author's fond hope that synthetic studies on (–)-suaveoline will continue.

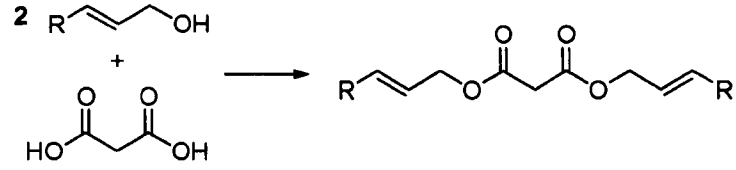
# 3. Experimental

## 3.1 General Laboratory Procedures

All reactions were performed under nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 5000 FTIR spectrometer. Proton magnetic resonance ($^1$H NMR) spectra, carbon magnetic resonance ($^{13}$C NMR) spectra and fluorine magnetic resonance ($^{19}$F NMR) spectra were recorded on a Brüker DRX-300, a Brüker DRX-400, a Brüker Avance 400, a Brüker AM500 or a Brüker Avance 600 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent ($^1$H NMR: 7.27 ppm for $CDCl_3$; $^{13}$C NMR: 77.0 ppm for $CDCl_3$). Mass spectra (CI, FAB, ESI) were recorded using VG-7070B, VG707E, VG Autospec Q, Brüker Apex II FTICR or Jeol SX-102 instruments. Elemental analyses were performed at the microanalytical laboratory of Dr. Stephen Boyer, London Metropolitan University or by Exeter Analytical Ltd, Brunel science park, Uxbridge. Optical rotations were measured by Warwick Analytical Services Ltd, Lyons road, Coventry. Analytical thin layer chromatography (TLC) was performed on precoated aluminium-backed Merck Kieselgel 60 $F_{254}$ plates. Visualisation was effected with ultraviolet light or potassium permanganate. Flash chromatography was performed using BDH (40–63 $\mu$m) silica gel. Standard solvents were distilled under nitrogen prior use; $Et_2O$, DME and THF from sodium-benzophenone ketyl, $CH_2Cl_2$ and DMPU from CaH, toluene from sodium. Petrol refers to the fraction $bp_{760}$ 40–60 °C. DMF, DMSO and benzene were supplied by Fluka, >99.5% pure, over molecular sieves (<0.005% $H_2O$). Ethanol (99.7-100%, AnalaR grade), *iso*propanol (GPR grade) and acetonitrile (HiPerSolv grade) were supplied by BDH. All liquid reagents except acids and alkalis were distilled prior to use unless otherwise stated. Potassium acetate was oven-dried at 120 °C for several days prior to use. Sodium hydride was a 60% w/w dispersion in mineral oil. Microwave reactions were performed in a Biotage Initiator.

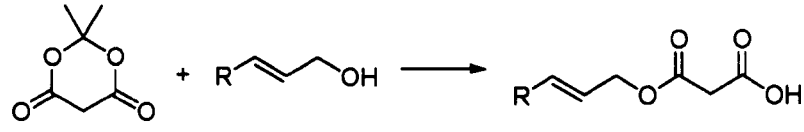
## 3.2 General Synthetic Procedures

### General Procedure *(i)*: Synthesis of symmetrical malonates



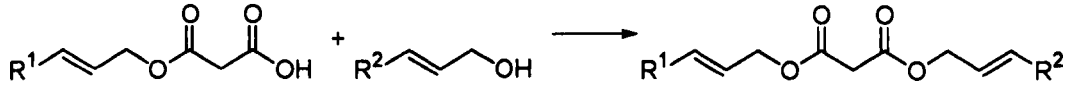
To *substituted allyl alcohol* (40 mmol scale, 2.0 equiv) was added a slurry of *malonic acid* (1.0 equiv) in $CH_2Cl_2$ (0.1 M). The reaction mixture was cooled to 0 °C and *N,N'*-di*iso*propyl carbodiimide (2.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at rt for 14 h, then filtered. Concentration under reduced pressure and chromatography and/or recrystallisation yielded the desired *substituted diallyl malonate*.

### General Procedure *(ii)*: Synthesis of malonyl monoesters



To a solution of *Meldrum's acid* (10 to 20 mmol scale, 1.0 equiv) in THF or neat was added *substituted allyl alcohol* (1.0 equiv). The reaction mixture was heated to reflux for 14 h, then concentrated under reduced pressure to give *malonyl monoester*, which was used directly without purification.

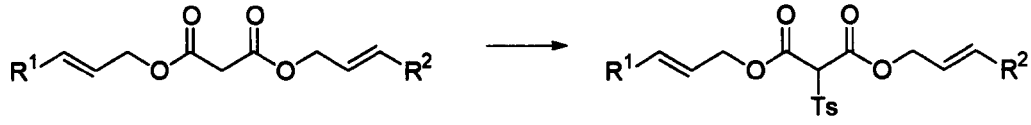
### General Procedure *(iii)*: Synthesis of unsymmetrical malonates from malonyl monoesters



To *substituted allyl alcohol* (10 to 20 mmol scale, 1.0 equiv) was added *malonyl monoester* (1.0 equiv) in $CH_2Cl_2$ (0.1 M). The reaction mixture was

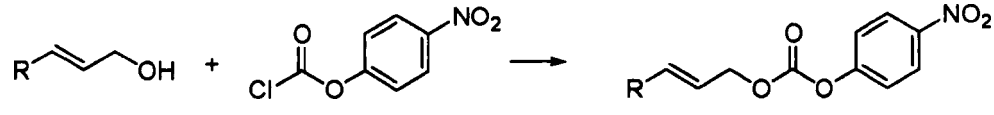
cooled to 0 °C and *N,N'*-di*iso*propyl carbodiimide or *N,N'*-dicyclohexyl carbodiimide (1.0 equiv) was added dropwise or as a solid. The reaction mixture was stirred at 0 °C for 30 min and at rt for 14 h, then filtered. Concentration under reduced pressure and chromatography yielded the desired *unsymmetrical substituted diallyl malonate.*

**General Procedure *(iv)*: Synthesis of 2-(toluene-4-sulfonyl)malonates from malonates**



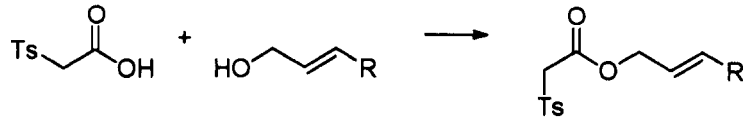

To a suspension of *malonate* (7.8 to 20 mmol scale, 1.0 equiv) and potassium *tert*-butoxide (2.0 equiv, as a solid or in solution) in THF at 0 °C was added toluene-4-sulfonyl fluoride (1.3 equiv) as a solid or in THF. The reaction mixture was stirred at 0 °C for 30 min and at rt for 16 h. Acetic acid (1.5 equiv) was added. The reaction mixture was partitioned between EtOAc and $H_2O$. The aqueous layer was washed with EtOAc, then combined organic layers were washed with saturated aq. NaCl (×2), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by chromatography (twice in some cases) to give *2-(toluene-4-sulfonyl)malonate*; also isolated was unreacted *malonate*.

**General Procedure *(v)*: Synthesis of *p*-nitrophenyl carbonates**



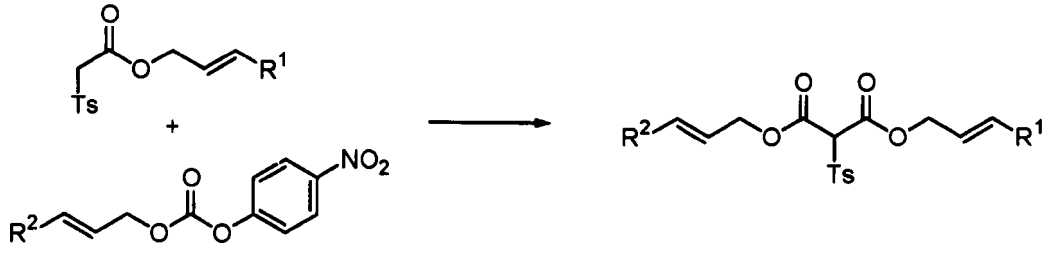

To a solution of *desired allyl alcohol* (5.0 to 27 mmol scale, 1.0 equiv) in $CH_2Cl_2$ (0.2 M) was added *p*-nitrophenyl chloroformate (1.1 equiv). The reaction mixture was stirred at –10 °C for 5 min, then triethylamine (2.0 equiv) was added. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was partitioned between EtOAc and saturated aq. $NH_4Cl$. The organic phase was washed with saturated aq. $NH_4Cl$ (×3), dried ($Na_2SO_4$) and concentrated under reduced pressure. Chromatography and/or recrystallisation yielded the desired *4-nitrophenyl carbonate*.

**General Procedure *(vi)*: Synthesis of (toluene-4-sulfonyl)acetates**



To *desired allyl alcohol* (0.16 to 28 mmol scale, 1.0 equiv) was added (toluene-4-sulfonyl)acetic acid (1.0 equiv) in $CH_2Cl_2$ (0.25 M). The reaction mixture was cooled to 0 °C and *N,N'*-di*iso*propyl carbodiimide (1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 1 h then at rt for 14 h. The reaction mixture was filtered and concentrated under reduced pressure. Chromatography gave the desired *(toluene-4-sulfonyl)acetate.*

**General Procedure *(vii)*: Synthesis of 2-(toluene-4-sulfonyl)malonates from (toluene-4-sulfonyl)acetates and *p*-nitrophenyl carbonates**

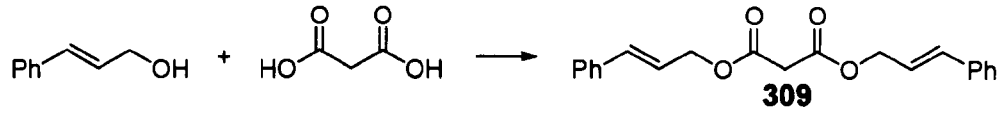


To sodium hydride (0.51 to 20 mmol scale, 2.0 equiv) was added a solution of *(toluene-4-sulfonyl)acetate* (1.0 equiv) in DMF or THF (final concentration 0.2 M) at 0 °C. The reaction mixture was stirred for 30 min, then a solution of p-*nitrophenyl carbonate* (1.0 or 2.0 equiv) in DMF or THF was added dropwise by cannula. The reaction mixture was stirred at 0 °C for 30 min and at rt for 14 h, then diluted with EtOAc washed with saturated aq. $NH_4Cl$ solution (×3) and dried ($Na_2SO_4$). The organic phase was concentrated under reduced pressure and purified (in some instances several times) by column chromatography to give the desired *2-(toluene-4-sulfonyl)malonate.*

## 3.3 Individual synthetic procedures and compound data

- **3.3.1 Symmetrical malonates**

### Dicinnamyl malonate (309)




**309**

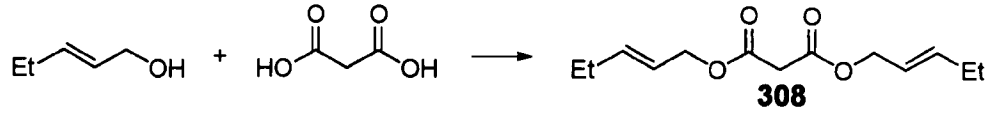
*General procedure (i)* was applied, using cinnamyl alcohol (5.37 g, 40.0 mmol), malonic acid (2.08 g, 20.0 mmol), $CH_2Cl_2$ (50 mL) and *N,N'*-di*iso*propyl carbodiimide (6.26 mL, 40.0 mmol). Chromatography (10→20% EtOAc–petrol) yielded *dicinnamyl malonate* **309** (3.84 g, 57%) as a pale yellow solid; a small portion was recrystallised from EtOAc–hexane to give a white crystalline solid; mp 58 °C; $R_f$ 0.35 (20% EtOAc–petrol); $\nu_{max}$ (film) 3059, 3027, 3006, 1748, 1731, 1494, 1447, 1328, 1264, 1178, 1146, 967, 745, 692 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.40-7.26 (10H, m, ArH), 6.69 (2H, d, *J* 16.0 Hz, Ph-CH=), 6.30 (2H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.84 (4H, d, *J* 6.5 Hz, -$CH_2$O-), 3.50 (2H, s, -$CH_2$-COO-); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (C=O), 136.0, 134.8, 128.7, 128.2, 126.7, 122.4, 66.2 (-$OCH_2$-), 41.6 (-$CH_2$-COO-); *m/z* (CI) 354 $[M+NH_4]^+$, 233, 194 $[M+H-C_{10}H_9O_2]^+$, 151, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 354.1706. $C_{21}H_{20}O_4$ requires $[M+NH_4]^+$, 354.1705) (Found: C, 75.11; H, 6.18. $C_{21}H_{20}O_4$ requires C, 74.98; H, 5.99%).[172]

### Diallyl malonate (307)


**307**

*General procedure (i)* was applied, using allyl alcohol (2.32 g, 40 mmol) malonic acid (2.08 g, 20 mmol), $CH_2Cl_2$ (50 mL) and *N,N'*-di*iso*propyl carbodiimide (6.26 mL, 40 mmol). Chromatography (10% EtOAc–petrol) gave *diallyl malonate* **307** (3.59 g, 97%) as a colourless liquid; $\delta_H$ (300 MHz, $CDCl_3$) 5.98-5.84 (2H, m, $H_2C$=C*H*-), 5.34 (2H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.26 (2H, m, *cis* -CH=C*H*), 4.65 (4H, d, *J* 5.0 Hz, $H_2C$=CH-C$H_2$-), 3.44 (2H, s, -$CH_2$-COO-); Data in agreement with those reported previously.[173,174]

**Bis((*E*)-pent-2-enyl) malonate (308)**

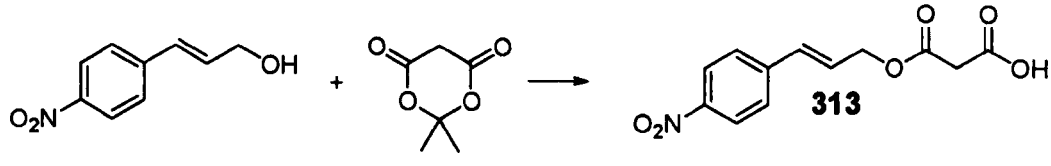



**308**

*General procedure (i)* was applied, using *trans*-2-penten-1-ol (3.45 g, 40 mmol) malonic acid (2.08 g, 20 mmol), $CH_2Cl_2$ (50 mL) and *N,N'*-di*iso*propyl carbodiimide (6.26 mL, 40 mmol). Chromatography (5% EtOAc–petrol) gave *bis((*E*)-pent-2-enyl) malonate* **308** (4.35 g, 91%) as a pale yellow oil; $R_f$ 0.49 (20% EtOAc–petrol); $\nu_{max}$ (film) 1753, 1738, 1672, 1460, 1412, 1379, 1329, 1269, 1147, 972 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 5.86 (2H, dt, *J* 15.5, 6.0 Hz, =C*H*-$CH_2$-$CH_3$), 5.57 (2H, dt, *J* 15.5, 6.5 Hz, -$OCH_2$-C*H*=), 4.60 (4H, d, *J* 6.5 Hz, -$OCH_2$-), 3.41 (2H, s, -$CH_2$-COO-), 2.14-2.06 (4H, m, -C*H*$_2$-$CH_3$), 1.02 (6H, t, *J* 7.5 Hz, -$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 166.4 (C=O), 138.7 (-$OCH_2$-*C*H=), 122.2 (=*C*H-$CH_2$-$CH_3$), 66.3 (-$OCH_2$-CH=), 41.7 (-*C*H$_2$-COO-), 25.3 (=CH-*C*H$_2$-$CH_3$), 13.1 (-$CH_3$); *m/z* (CI) 498 $[2M+NH_4]^+$, 326, 258 $[M+NH_4]^+$, 241 $[M+H]^+$, 173 $[M+NH_4-C_5H_9O]^+$, 86, 85, 69, 68 (Found: $[M+NH_4]^+$, 258.1712. $C_{13}H_{20}O_4$ requires $[M+NH_4]^+$, 258.1705) (Found: C, 64.81; H, 8.35. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%).[172]

- **3.3.2 Malonyl monoesters**

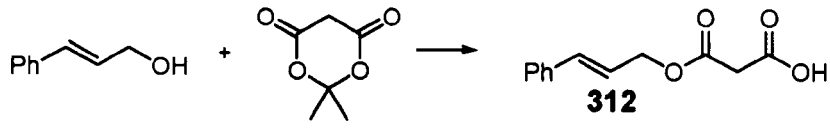
**(*E*)-3-(3-(4-Nitrophenyl)allyloxy)-3-oxopropanoic acid (313)**




**313**

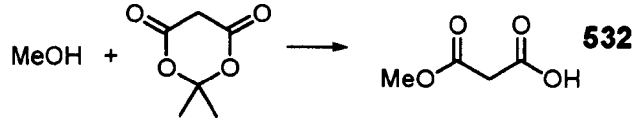
*General procedure (ii)* was applied, using Meldrum's acid (1.44 g, 10 mmol) in THF (50 mL) and *p*-nitrocinnamyl alcohol (1.79 g, 10 mmol) to give crude *(*E*)-3-(3-(4-nitrophenyl)allyloxy)-3-oxopropanoic acid* **313** as an orange semi-crystalline oil; $R_f$ 0.15 (EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 10.34 (1H, br s, -COOH), 8.19 (2H, d, *J* 7.5 Hz, *o*-$NO_2Ar$), 7.53 (2H, d, *J* 7.5 Hz, *m*-$NO_2Ar$), 6.76 (1H, d, *J* 16.0 Hz, Ar-CH=), 6.48 (1H, dt, *J* 16.0, 6.0 Hz, Ar-CH=C*H*-), 4.89 (2H, d, *J* 6.0 Hz, -$CH_2O$-), 3.53 (2H, s, -OCO-$CH_2$-COO-).

**3-(Cinnamyloxy)-3-oxopropanoic acid (312)**




*General procedure (ii)* was applied, using cinnamyl alcohol (2.68 g, 20 mmol) and Meldrum's acid (2.88 g, 20 mmol) to give crude *3-(cinnamyloxy)-3-oxopropanoic acid* **312** as a yellow oil; $\delta_H$ (300 MHz, $CDCl_3$) 7.47-7.28 (5H, m, Ar-H), 6.71 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.30 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.85 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 3.51 (2H, s, -$CH_2$-COOH).

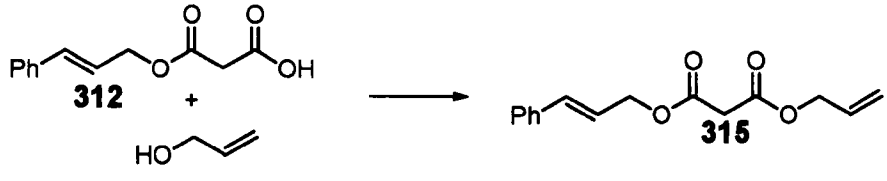
**3-Methoxy-3-oxopropanoic acid (532)**




*General procedure (ii)* was applied, using methanol (641 mg, 20 mmol) and Meldrum's acid (2.88 g, 20 mmol) to give crude *3-methoxy-3-oxopropanoic acid* **532** as a colourless oil; $\delta_H$ (300 MHz, $CDCl_3$) 9.98 (1H, br s, -COOH), 3.81 (3H, s, -$OCH_3$), 3.48 (2H, s, -$CH_2COO$-); data in agreement with those previously reported.[175]

- **3.3.3 Unsymmetrical malonates from malonyl monoesters**

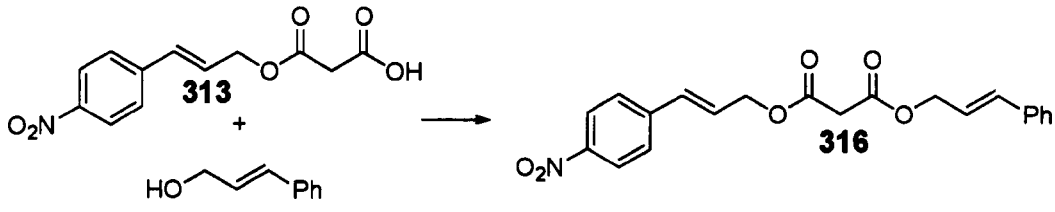
**Allyl cinnamyl malonate (315)**




*General procedure (iii)* was applied, using monoester **312** (assumed to be 20 mmol), $CH_2Cl_2$ (100 mL), allyl alcohol (1.36 mL, 20 mmol) and *N,N'*-dicyclohexyl carbodiimide (4.13 g, 20 mmol). Chromatography (20% EtOAc–petrol) gave *allyl cinnamyl malonate* **315** (3.38 g, 65% over 2 steps) as a yellow liquid; $R_f$ 0.21 (20% EtOAc–petrol); $\nu_{max}$ (film) 3083, 3059, 3027, 1753, 1738, 1650, 1578, 1494, 1449, 1412, 1379, 1366, 1329, 1271, 1181, 1149,

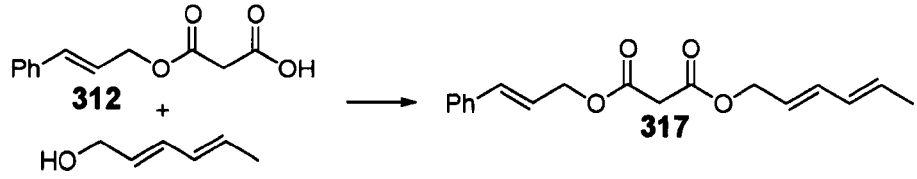
992, 970, 938, 833, 747, 694 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.42-7.28 (5H, m, Ar-H), 6.69 (1H, d, *J* 16.0 Hz, Ar-CH=), 6.30 (1H, dt, *J* 16.0, 6.5 Hz, Ar-CH=C*H*-), 5.99-5.87 (1H, m, -C*H*=$CH_2$), 5.36 (1H, dd, *J* 17.0, 1.5 Hz, *trans* -CH=C*H*H), 5.26 (1H, dd, *J* 10.5, 1.5 Hz, *cis* -CH=CH*H*), 4.83 (2H, d, *J* 6.5 Hz, Ar-CH=CH-C$H_2$-), 4.68 (2H, d, *J* 5.5Hz, -OC$H_2$-CH=$CH_2$), 3.48 (2H, s, -$CH_2$-COO-); $\delta_C$ (75 MHz, $CDCl_3$) [166.3, 166.2] (2× C=O), 136.0, 134.9, 131.5, 128.7, 128.2, 126.7, 122.4, 118.9, 66.1 (2× -$OCH_2$-), 41.5 (-$CH_2$-COO-); *m/z* (CI) 278 $[M+NH_4]^+$, 233, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 278.1395. $C_{15}H_{16}O_4$ requires $[M+NH_4]^+$, 278.1392) (Found: C, 69.36; H, 6.31. $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20%).

**Cinnamyl (*E*)-3-(4-nitrophenyl)allyl malonate (316)**



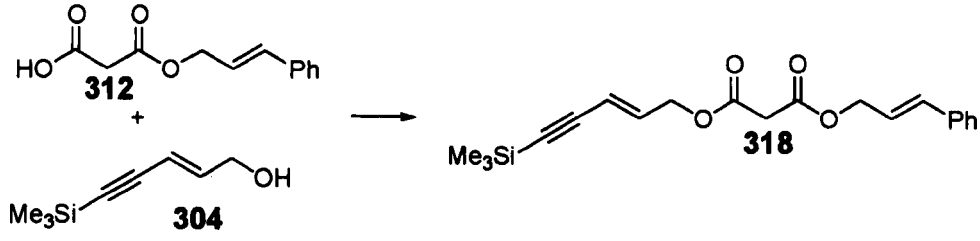

*General procedure (iii)* was applied, using monoester **313** (assumed to be 10.0 mmol), $CH_2Cl_2$ (25 mL), cinnamyl alcohol (1.34 g, 10.0 mmol) and *N,N'*-di*iso*propyl carbodiimide (1.57 mL, 10 mmol). Chromatography (20% EtOAc–petrol) gave *cinnamyl (E)-3-(4-nitrophenyl)allyl malonate* **316** as a yellow oil (2.57 g, 67%); $R_f$ 0.56 (50% EtOAc–petrol); $\nu_{max}$ (film) 3026, 1752, 1734, 1597, 1517, 1494, 1449, 1380, 1343, 1269, 1182, 1148, 1109, 969, 861, 821, 744, 693, 668 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 8.12 (2H, dt, *J* 9.0, 2.0 Hz, *o*-$NO_2$Ar), 7.46 (2H, dt, *J* 9.0, 2.0 Hz, *m*-$NO_2$Ar), 7.36-7.24 (5H, m, other Ar-H), 6.71 (1H, d, *J* 16.0 Hz, $NO_2$-Ar-CH=), 6.66 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.42 (1H, dt, *J* 16.0, 6.0 Hz, $NO_2$-Ar-CH=C*H*-), 6.27 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.86 (2H, dd, *J* 6.0, 1.5 Hz, $NO_2$-Ar-CH=CH-C$H_2$-), 4.82 (2H, dd, *J* 6.5, 1.5 Hz, Ph-CH=CH-C$H_2$-), 3.50 (2H, s, -$CH_2$-COO-); $\delta_C$ (75 MHz, $CDCl_3$) [166.2, 166.1] (2× C=O), 147.3, 142.4, 135.9, 134.9, 131.7, 128.7, 128.3, 127.4, 127.2, 126.7, 124.0, 122.3, [66.2, 65.2] (2× -$CH_2$O-), 41.5 (-$CH_2$-COO-); *m/z* (CI) 399 $[M+NH_4]^+$, 239, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 399.1555. $C_{21}H_{19}NO_6$ requires $[M+NH_4]^+$, 399.1556) (Found: C, 66.29; H, 4.92; N, 3.55. $C_{21}H_{19}NO_6$ requires C, 66.14; H, 5.02; N, 3.67%).

**Cinnamyl (2*E*,4*E*)-hexa-2,4-dienyl malonate (317)**




*General procedure (iii)* was applied, using monoester **312** (assumed to be 20 mmol), $CH_2Cl_2$ (50 mL), sorbyl alcohol (1.96 g, 20 mmol) and *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol). *NOTE:* Concentration under reduced pressure took place *without heating.* Chromatography (5% EtOAc–petrol) gave *cinnamyl (2E,4E)-hexa-2,4-dienyl malonate* **317** (2.41 g, 40%) as a colourless oil; $R_f$ 0.31 (20% EtOAc–petrol); $\nu_{max}$ (film) 3026, 1733, 1661, 1494, 1449, 1411, 1379, 1332, 1267, 1147, 1061, 987, 745, 693 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.42-7.26 (5H, m, Ar-H), 6.69 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.34-6.24 (2H, m, Ph-CH=C*H*-, $CH_3$-CH=CH-C*H*=), 6.08-5.99 (1H, m, $CH_3$-CH=C*H*-), 5.82-5.58 (2H, m, $CH_3$-CH=CH-CH=C*H*-, $CH_3$-C*H*=), [4.82, 4.67] (2× 2H, d, *J* 6.5 Hz, -$CH_2$O-), 3.46 (2H, s, -$CH_2$-COO-), 1.77 (3H, d, *J* 6.5 Hz, =$CH_2$-C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (×2, C=O), 136.1 (4°), 135.5 (3°), 134.7 (3°), 131.7 (3°), 130.3 (3°), 128.7 (3°), 128.2 (3°), 126.7 (3°), 122.9 (3°), 122.5 (3°), 66.1 (2× -$OCH_2$-), 41.6 (-*C*$H_2$-COO-), 18.2 (=CH-*C*$H_3$); *m/z* (CI) 618 $[2M+NH_4]^+$, 434, 318 $[M+NH_4]^+$, 197, 151, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 98 $[C_6H_{10}O]^+$, 76 (Found: $[M+NH_4]^+$, 318.1714. $C_{18}H_{20}O_4$ requires $[M+NH_4]^+$, 318.1705).

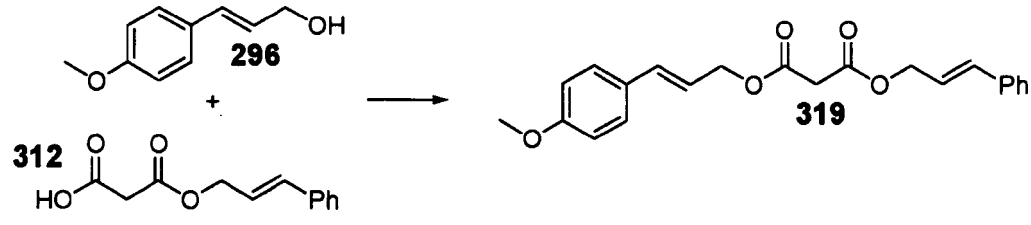
**Cinnamyl (*E*)-5-(trimethylsilyl)pent-2-en-4-ynyl malonate (318)**




*General procedure (iii)* was applied, using monoester **312** (assumed to be 20 mmol), alcohol **304** (3.09 g, 20 mmol), $CH_2Cl_2$ (100 mL) and *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol). Chromatography (5→15% EtOAc–petrol) gave *cinnamyl (E)-5-(trimethylsilyl)pent-2-en-4-ynyl malonate* **318** (3.91 g, 55%) as a colourless oil; $R_f$ 0.43 (20% EtOAc–petrol); $\nu_{max}$ (film) 3028, 2179, 2135, 1755, 1738, 1495, 1448, 1410, 1379, 1331, 1252, 1147, 1086, 1066,

985, 968, 847, 760, 746, 694 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.41-7.25 (5H, m, Ar-H), 6.68 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.28 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 6.21 (1H, dt, *J* 16.0, 6.0 Hz, -C*H*=CH-C≡C-), 5.79 (1H, dt, *J* 16.0, 1.5 Hz, =CH-C≡C-), 4.81 (2H, dd, *J* 6.5, 1.5 Hz, Ph-CH=CH-C$H_2$O-), 4.68 (2H, dd, *J* 6.0, 1.5 Hz, -OC$H_2$-CH=CH-C≡), 3.47 (2H, s, -$CH_2$-COO-), 0.21 (9H, s, -Si($CH_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 166.1 (Ph-CH=CH-$CH_2$-O*C*(O)-), 165.9 (≡C-CH=CH-$CH_2$-O*C*(O)-), 136.5 (-C≡C-CH=*C*H-), 136.0 (*i*-Ph), 134.9 (Ph-CH=), 128.6 (3°), 128.2 (3°), 126.7 (3°), 122.3 (Ph-CH=*C*H-), 113.9 (≡C-*C*H=), 102.2 (-C≡*C*-CH=), 96.6 (-*C*≡C-CH=), 66.2 (Ph-CH=CH-*C*$H_2$O-), 64.8 (≡C-CH=CH-*C*$H_2$O-), 41.4 (-*C*$H_2$-COO-), –0.2 (-Si($CH_3$)$_3$); *m/z* (CI) 374 $[M+NH_4]^+$, 357 $[M+H]^+$, 311, 253, 214, 181, 151, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 90, 52 (Found: $[M+H]^+$, 357.1513. $C_{20}H_{24}O_4Si$ requires $[M+H]^+$, 357.1522) (Found: C, 67.24; H, 7.04. $C_{20}H_{24}O_4Si$ requires C, 67.38; H, 6.79%).

**Cinnamyl (*E*)-3-(4-methoxyphenyl)allyl malonate (319)**




*General procedure (iii)* was applied, using monoester **312** (assumed to be 20.0 mmol), $CH_2Cl_2$ (100 mL), alcohol **296** (3.27 g, 20.0 mmol) and *N,N'*-di*iso*propyl carbodiimide (3.12 mL, 20.0 mmol). Chromatography (5→12% EtOAc–petrol) gave *cinnamyl (E)-3-(4-methoxyphenyl)allyl malonate* **319** (4.55 g, 62%) as a colourless oil; $R_f$ 0.20 (20% EtOAc–petrol); $\nu_{max}$ (film) 3028, 3005, 1749, 1732, 1657, 1606, 1577, 1512, 1448, 1412, 1381, 1329, 1306, 1252, 1176, 1147, 1063, 1032, 968, 845, 804, 746, 694 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.41-7.26 (7H, m, Ph-H, *m*-MeOAr), 6.86 (2H, d, *J* 8.5 Hz, *o*-MeOAr), [6.69, 6.64] (2× 1H, d, *J* 16.0 Hz, Ph-CH=, MeO-Ar-C*H*=), [6.30, 6.17] (2× 1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-, MeO-Ar-CH=C*H*-), [4.83, 4.81] (2× 2H, d, *J* 6.5 Hz, -$OCH_2$-), 3.82 (3H, s, Ar-$OCH_3$), 3.50 (2H, s, -OCO-$CH_2$-COO-); $\delta_C$ (75 MHz, $CDCl_3$) 166.4 (2× C=O), 159.7 (4° MeOAr), 136.1 (4° Ph), 134.8 (3°), 134.7 (3°), 128.8 (4° MeOAr), 128.7 (3°), 128.2 (3°), 128.0 (3°), 126.7 (3°), 122.4 (3°), 120.1 (3°), 114.1 (3°), [66.5, 66.1] (-$CH_2$O-), 55.3 (Ar-$OCH_3$), 41.7 (-OCO-$CH_2$-COO-); *m/z* (CI) 384 $[M+NH_4]^+$, 367 $[M+H]^+$, 249, 224, 194, 163 $[C_{10}H_{11}O_2]^+$, 147 $[C_{10}H_{11}O]^+$, 134 $[C_9H_{10}O]^+$, 121, 117 $[C_9H_9]^+$

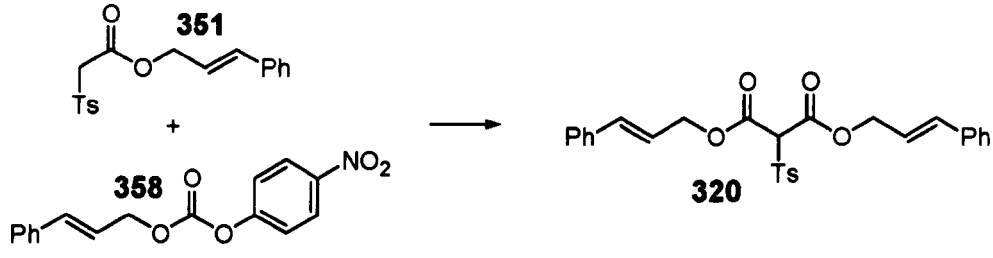
(Found: $[M+NH_4]^+$, 384.1810. $C_{22}H_{22}O_5$ requires $[M+NH_4]^+$, 384.1811) (Found: C, 72.21; H, 5.95. $C_{22}H_{22}O_5$ requires C, 72.12; H, 6.05%).

- **3.3.4 2-(Toluene-4-sulfonyl)malonates from malonates**

**Dicinnamyl 2-(toluene-4-sulfonyl)malonate (320)**


*Procedure A*

*General procedure (iv)* was applied, using malonate **309** (3.79 g, 11.3 mmol), THF (55 mL), toluene-4-sulfonyl fluoride (2.55 g, 14.7 mmol) and solid potassium *tert*-butoxide (2.54 g, 22.6 mmol). Chromatography (10→30% EtOAc–petrol) gave *dicinnamyl 2-(toluene-4-sulfonyl)malonate* **320** (455 mg, 8%) as a pale yellow solid; unreacted **309** was also isolated (3.15 g, 83%)




*Procedure B*

*General procedure (vii)* was applied, using sodium hydride (158 mg, 5.90 mmol), ester **351** (974 mg, 2.95 mmol), DMF (30 mL total) and carbonate **358** (1.76 g, 5.90 mmol). Purification twice by chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L eluent, then 10% PhMe–$CH_2Cl_2$) gave *dicinnamyl 2-(toluene-4-sulfonyl)malonate ester* **320** (382 mg, 26%) as a creamy solid.

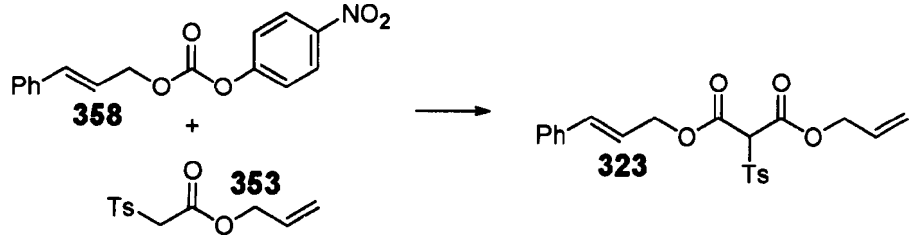
**320:** mp 77.5–79.5 °C; $R_f$ 0.18 (20% EtOAc–petrol); $\nu_{max}$ (film) 3058, 3026, 1741, 1595, 1494, 1448, 1378, 1335, 1291, 1264, 1212, 1193, 1180, 1149, 1082, 968, 745, 693 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.44-7.21 (12H, m, other Ar-H), 6.66 (2H, d, *J* 16.0 Hz, Ph-CH=), 6.20 (2H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 5.07 (1H, s, -CH(Ts)-), 4.85 (4H, d, *J* 6.5 Hz, -$OCH_2$-), 2.35 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.1 (C=O), 146.1, 135.8, 135.7, 134.0, 130.3, 129.5, 128.7, 128.4, 126.8, 121.3, 74.6 (-CH(Ts)-

COO-), 67.5 (-$OCH_2$-), 21.7 (Ts-$CH_3$); *m/z* (FAB) 490 $[M]^+$, 290, 233, 133, 117, 91, 77 (Found: $[M]^+$, 490.1439. $C_{28}H_{26}O_6S$ requires $[M]^+$, 490.1450) (Found: C, 68.36; H, 5.47. $C_{28}H_{26}O_6S$ requires C, 68.55; H, 5.34%).

**(±)-1-Allyl 3-cinnamyl 2-(toluene-4-sulfonyl)malonate (323)**


*Procedure A*

*General procedure (iv)* was applied, using malonate **315** (3.34 g, 12.8 mmol), THF (25 mL), toluene-4-sulfonyl fluoride (2.90 g, 16.7 mmol) and potassium *tert*-butoxide (2.88 g, 25.6 mmol, as a slurry in THF, 30 mL). Chromatography (15→30% EtOAc–petrol) gave *(±)-1-allyl 3-cinnamyl 2-(toluene-4-sulfonyl)malonate* **323** (1.16 g, 22%) as a pale yellow oil.




*Procedure B*

*General procedure (vii)* was applied, using sodium hydride (480 mg, 20 mmol), ester **353** (2.54 g, 10 mmol), DMF (160 mL total) and carbonate **358** (5.98 g, 20.0 mmol). Purification twice by column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L eluent, then 3% EtOAc–PhMe) gave *(±)-1-allyl 3-cinnamyl 2-(toluene-4-sulfonyl)malonate* **323** (1.89 g, 46%) as a colourless oil.

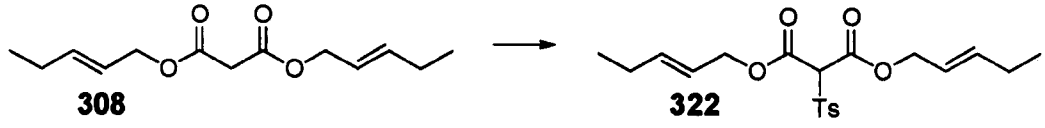
**323:** $R_f$ 0.34 (50% EtOAc–petrol); $\nu_{max}$ (film) 3058, 3027, 1743, 1667, 1596, 1494, 1449, 1336, 1305, 1292, 1276, 1193, 1180, 1151, 1084, 988, 970, 939, 846, 815, 747, 705, 694, 673 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.40-7.28 (7H, m, other Ar-H), 6.66 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.19 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 5.91-5.80 (1H, m, -C*H*=$CH_2$), 5.35 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.26 (1H, d, *J* 10.5 Hz, *cis* -CH=C$H_2$), 5.05 (1H, s, -CH(Ts)-), 4.84 (2H, d, *J* 6.5 Hz, Ph-CH=CH-C$H_2$-), 4.69 (2H, d, *J* 5.0 Hz, -C$H_2$-CH=$CH_2$), 2.40 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [160.8, 160.7]

(2× C=O), 146.1, 135.8, 134.1, 130.5, 130.3, 129.6, 128.7, 128.5, 126.8, 121.3, 119.7, 74.6 (-$SO_2$-CH<), 67.5 (×2, -$OCH_2$), 21.8 (Ts-$CH_3$); *m/z* (CI) 432 $[M+NH_4]^+$, 388, 356, 272, 202, 174, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 432.1481. $C_{22}H_{22}O_6S$ requires $[M+NH_4]^+$, 432.1481) (Found: C, 63.78; H, 5.40. $C_{22}H_{22}O_6S$ requires C, 63.75; H, 5.35%).

**Diallyl 2-(toluene-4-sulfonyl)malonate (321)**


*General procedure (iv)* was applied, using malonate **307** (3.59 g, 19.5 mmol), THF (100 mL), toluene-4-sulfonyl fluoride (4.41 g, 25.3 mmol) and solid potassium *tert*-butoxide (4.37 g, 39.0 mmol). Chromatography (5→10% EtOAc–petrol) to give *diallyl 2-(toluene-4-sulfonyl)malonate* **321** (582 mg, 9%) as a yellow liquid; $R_f$ 0.24 (20% EtOAc–petrol); $\nu_{max}$ (film) 3089, 3026, 1743, 1649, 1597, 1493, 1450, 1361, 1336, 1297, 1279, 1194, 1182, 1151, 1084, 991, 939, 843, 816, 706, 673 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.93-5.79 (2H, m, -$OCH_2$-C*H*=$CH_2$), 5.35 (2H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$) 5.28 (2H, d, *J* 10.5 Hz, *cis* -$CH_2$-CH=C$H_2$), 5.03 (1H, s, -CH(Ts)-COO-), 4.68 (4H, d, *J* 5.5 Hz, -$OCH_2$-), 2.47 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.1 (C=O), 146.1, 134.2, 130.5, 130.2, 129.6, 119.7 (=$CH_2$), 74.6 (-$SO_2$-CH<), 67.4 (-$OCH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 356 $[M+NH_4]^+$, 272, 250, 202, 108, 58 (Found: $[M+NH_4]^+$, 356.1171. $C_{16}H_{18}O_6S$ requires $[M+NH_4]^+$, 356.1168) (Found: C, 56.61; H, 5.20. $C_{16}H_{18}O_6S$ requires C, 56.79; H, 5.36%).

**Di(*E*)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate (322)**

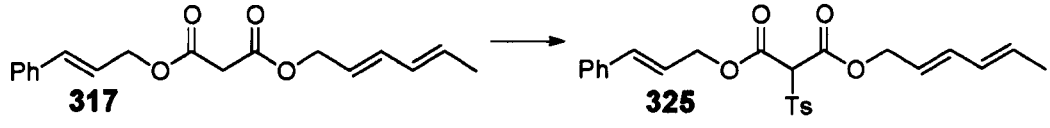



*General procedure (iv)* was applied, using malonate **308** (4.20 g, 17.5 mmol), toluene-4-sulfonyl fluoride (3.96 g, 22.7 mmol), THF (100 mL) and solid potassium *tert*-butoxide (3.96 g, 35.0 mmol, 2.0 equiv). Chromatography (10→12% EtOAc–petrol) to give *di*(E)*-pent-2-enyl 2-(toluene-4-*

*sulfonyl)malonate* **322** (867 mg, 13%) as a yellow oil; Also isolated was unreacted **308** (2.73 g, 65%).

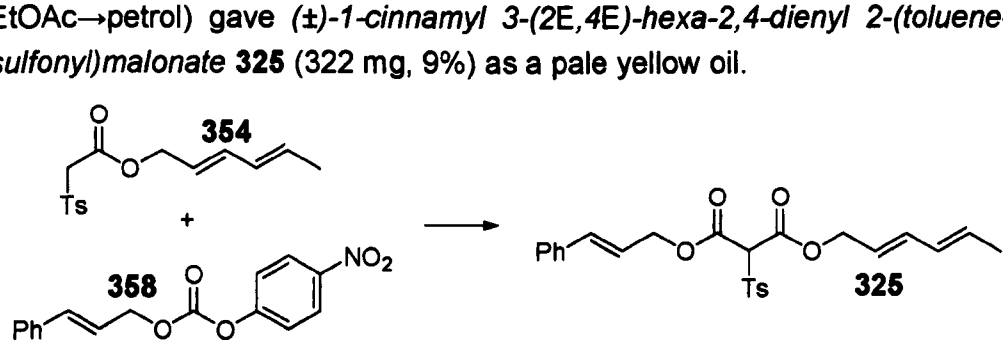
**322:** $R_f$ 0.29 (20% EtOAc–petrol); $\nu_{max}$ (film) 3030, 1743, 1672, 1597, 1493, 1458, 1377, 1338, 1292, 1271, 1194, 1180, 1153, 1084, 1018, 972, 926, 845, 816, 706, 673 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.34 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.83 (2H, dt, *J* 15.5, 6.0 Hz, =C*H*-$CH_2$-$CH_3$), 5.48 (2H, dt, *J* 15.5, 6.5 Hz, -$OCH_2$-C*H*=), 4.98 (1H, s, -CH(Ts)-), 4.60 (4H, d, *J* 6.5 Hz, -$OCH_2$-), 2.45 (3H, s, Ts-$CH_3$), 2.11-2.04 (4H, m, -$CH_2$-$CH_3$), 1.00 (6H, t, *J* 7.5 Hz, -$CH_2$-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.8 (C=O), 145.9 (4°), 138.4 (-$OCH_2$-CH=), 134.2 (4°), 130.3 (3°), 129.4 (3°), 121.3 (=CH-$CH_2$-$CH_3$), 74.6 (-CH(Ts)-COO-), 67.7 (-$OCH_2$-), 25.3 (-$CH_2$-$CH_3$), 21.8 (Ts-$CH_3$), 13.0 (-$CH_2$-$CH_3$); *m/z* (CI) 412 $[M+NH_4]^+$, 400, 346, 300, 276, 258, 218, 190, 174, 108, 86, 58 (Found: $[M+NH_4]^+$, 412.1785. $C_{20}H_{26}O_6S$ requires $[M+NH_4]^+$, 412.1794) (Found: C, 60.73; H, 6.50. $C_{20}H_{26}O_6S$ requires C, 60.89; H, 6.64%).

**(±)-1-Cinnamyl 3-(2*E*,4*E*)-hexa-2,4-dienyl 2-(toluene-4-sulfonyl)malonate (325)**




*Procedure A*

*General procedure (iv)* was applied, using malonate **317** (2.34 g, 7.84 mmol), THF (15 mL), potassium *tert*-butoxide (1.0 M in THF; 15.7 mL, 15.7 mmol) and toluene-4-sulfonyl fluoride (1.78 g, 10.2 mmol, in THF, 5 mL, introduced dropwise by syringe pump over 20 min). Chromatography (5-12% EtOAc→petrol) gave *(±)-1-cinnamyl 3-(2E,4E)-hexa-2,4-dienyl 2-(toluene-4-sulfonyl)malonate* **325** (322 mg, 9%) as a pale yellow oil.



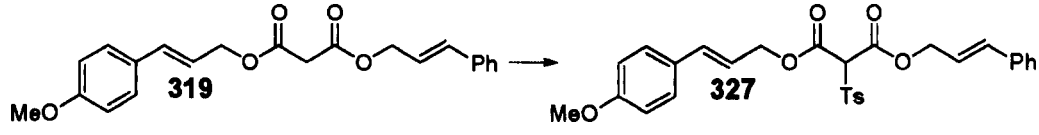

*Procedure B*

*General procedure (vii)* was applied, using sodium hydride (480 mg, 20 mmol), ester **354** (2.94 g, 10 mmol), DMF (100 mL total) and carbonate **358**

(5.98 g, 20 mmol). Purification twice by column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L eluent, then 4% EtOAc–PhMe) gave *(±)-2-(p-toluenesulfonyl)malonic acid cinnamyl sorbyl ester* **325** (1.36 g, 30%) as a yellow oil.

**325:** $R_f$ 0.18 (20% EtOAc–petrol); $\nu_{max}$ (film) 3026, 1741, 1660, 1597, 1495, 1448, 1379, 1336, 1271, 1180, 1151, 1082, 991, 970, 914, 814, 746, 706, 692, 673 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.39-7.28 (7H, m, other Ar-H), 6.66 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.29-6.14 (2H, m, Ph-CH=C*H*-, $CH_3$-CH=CH-C*H*=), 6.05-5.96 (1H, m, $CH_3$-CH=C*H*-), 5.83-5.73 (1H, m, $CH_3$-CH=CH-CH=C*H*-), 5.58-5.49 (1H, m, $CH_3$-C*H*=), 5.03 (1H, s, -CH(Ts)-COO-), [4.84, 4.68] (2× 2H, d, *J* 6.5 Hz, -$CH_2O$-), 2.40 (3H, s, Ts-$CH_3$), 1.77 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH=); $\delta_C$ (75 MHz, $CDCl_3$) 160.8 (×2, C=O), 146.0 (4° -$SO_2Ar$), 136.4, 135.8 (4° -$SO_2Ar$), 135.6, 134.1 (4° Ph), 132.3, 130.3, 130.2, 129.5, 128.7, 128.4, 126.8, 121.8, 121.2, 74.6 (-CH(Ts)-COO-), [67.5, 67.4] (2× -$OCH_2$-), 21.8 (Ts-$CH_3$), 18.2 (=CH-*C*$H_3$); *m/z* (CI) 472 $[M+NH_4]^+$, 436, 348, 312, 297, 231, 188, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 98 $[C_6H_{10}O]^+$, 81 $[C_6H_9]^+$ (Found: 472.1777. $[M+NH_4]^+$, $C_{25}H_{26}O_6S$ requires $[M+NH_4]^+$, 472.1794).

**1-Cinnamyl 3-(*E*)-3-(4-methoxyphenyl)allyl 2-(toluene-4-sulfonyl)malonate (327)**



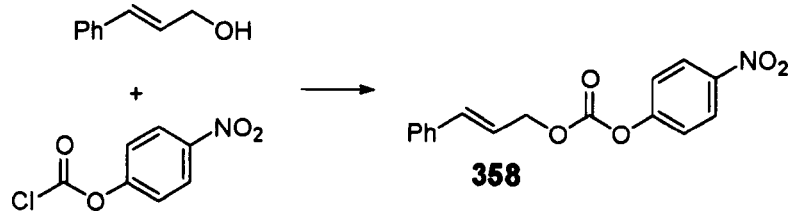

*General procedure (iv)* was applied, using malonate **319** (5.36 g, 14.6 mmol), potassium *tert*-butoxide (3.29 g, 29.3 mmol, 2.0 equiv), THF (90 mL) and toluene-4-sulfonyl fluoride (3.21 g, 19.0 mmol, in THF, 10 mL). Chromatography (twice, 7.5→25% EtOAc–petrol) gave *1-cinnamyl 3-(E)-3-(4-methoxyphenyl)allyl 2-(toluene-4-sulfonyl)malonate* **327** (338 mg, 4%) as a pale yellow oil; Also isolated was unreacted **319** (1.87 g, 35%).

**327:** $R_f$ 0.62 (50% EtOAc–petrol); $\nu_{max}$ (film) 3028, 3005, 1741, 1655, 1606, 1577, 1512, 1495, 1448, 1421, 1377, 1334, 1306, 1252, 1176, 1149, 1082, 1032, 970, 914, 843, 814, 746, 706, 694, 671 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.85 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.36-7.21 (9H, m, other Ar-H), 6.84 (2H, dt, *J*

9.0, 2.5 Hz, *o*-MeOAr), [6.64, 6.59] (2× 1H, d, *J* 16.0 Hz, Ph-CH=, MeOAr-C*H*=), [6.17, 6.04] (2× 1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-, MeOAr-CH=C*H*-), 5.04 (1H, s, -OCO-CH(Ts)-COO-), [4.82, 4.80] (2× 2H, ddd, *J* 6.5, 3.0, 1.5 Hz, 2× -$OCH_2$-), 3.81 (3H, s, Ar-$OCH_3$), 2.35 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.8 (2× C=O), 159.9 (4° MeOAr), 146.0 (4°), 135.8 (4°), 135.6 (3°), 135.6 (3°), 134.1 (4°), 130.3 (3°), 129.5 (3°), 128.7 (3°), 128.6 (4° MeOAr), 128.4 (3°), 128.1 (3°), 126.8 (3°), 121.3 (3°), 118.9 (3°), 114.1 (3°), 74.6 (-OCO-*C*H(Ts)-COO-), [67.9, 67.5] (2× -$OCH_2$-), 55.3 (Ar-$OCH_3$), 21.7 (Ts-$CH_3$); *m/z* (FAB) 521 $[M+H]^+$, 520 $[M]^+$, 430, 338, 147 $[C_{10}H_{11}O]^+$, 117 $[C_9H_9]^+$, 109, 97 (Found: $[M]^+$, 520.1570. $C_{29}H_{28}O_7S$ requires $[M]^+$, 520.1556) (Found: C, 66.85; H, 5.60. $C_{29}H_{28}O_7S$ requires C, 66.91; H, 5.42%).

- **3.3.5 *p*-Nitrophenyl carbonates**

**Cinnamyl 4-nitrophenyl carbonate (358)**

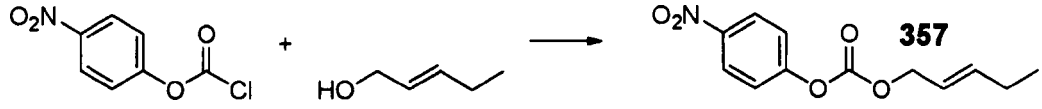



**358**

*General procedure (v)* was applied, using cinnamyl alcohol (671 mg, 5.0 mmol), $CH_2Cl_2$ (25 mL), *p*-nitrophenyl chloroformate (1.11 g, 5.5 mmol) and triethylamine (1.39 mL, 20.0 mmol). Chromatography (5→7.5% EtOAc–petrol) yielded *cinnamyl 4-nitrophenyl carbonate* **358** (983 mg, 66%) as a yellow solid. Alternatively, the crude product was recrystallised from 20% TBME–petrol to give *cinnamyl 4-nitrophenyl carbonate* **358** (86%) as a white crystalline solid; mp 78 °C (lit.[176] 77 °C); $R_f$ 0.28 (20% EtOAc–petrol); $\nu_{max}$ (film) 3116, 3084, 3060, 3028, 1763, 1616, 1593, 1523, 1493, 1448, 1348, 1255, 1211, 1109, 968, 858, 746, 692 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.31 (2H, d, *J* 9.0 Hz, *o*-$NO_2Ar$), 7.47-7.28 (7H, m, other Ar-H), 6.80 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.38 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.96 (2H, d, *J* 6.5 Hz, -$CH_2O$-); $\delta_C$ (75 MHz, $CDCl_3$) 155.6 (4° $NO_2Ar$), 152.4 (-$OCO_2$-), 145.4 (4° $NO_2Ar$), 136.3, 135.7 (4° Ph), 128.8, 128.6, 126.8, 125.4, 121.9, 121.2, 69.9 (-$CH_2O$-); *m/z* (CI) 317 $[M+NH_4]^+$, 273, 252, 226, 157, 151, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 317.1147. $C_{16}H_{13}NO_5$ requires $[M+NH_4]^+$,

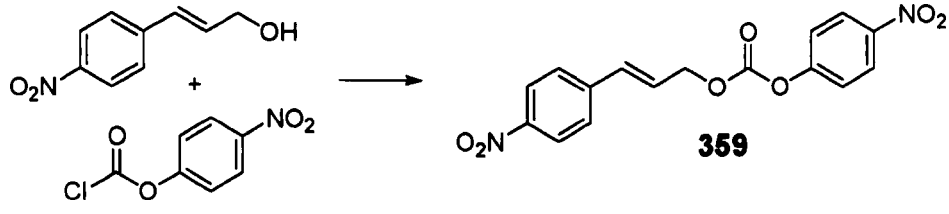
317.1137) (Found: C, 64.34; H, 4.27; N, 4.58. $C_{16}H_{13}NO_5$ requires C, 64.21; H, 4.38; N, 4.68%). Datum in agreement with that previously reported.[176]

**(*E*)-4-Nitrophenyl pent-2-enyl carbonate (357)**




*General procedure (v)* was applied, using *trans*-2-penten-1-ol (2.34 g, 27.2 mmol), *p*-nitrophenol (5.48 g, 27.2 mmol), $CH_2Cl_2$ (200 mL) and triethylamine (3.79 mL, 27.2 mmol). Chromatography (7.5% EtOAc–petrol) to give *(E)-4-nitrophenyl pent-2-enyl carbonate* **357** (4.07 g, 60%) as a pale yellow solid; mp 26 °C; $R_f$ 0.40 (10% EtOAc–petrol); $\nu_{max}$ (film) 3119, 3086, 1766, 1616, 1594, 1526, 1493, 1348, 1256, 1215, 1165, 1108, 972, 862 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.26 (2H, d, *J* 9.0 Hz, *o*-$NO_2Ar$), 7.38 (2H, d, *J* 9.0 Hz, *m*-$NO_2Ar$), 5.95 (1H, m, =C*H*-$CH_2$-$CH_3$), 5.64 (1H, dt, *J* 15.5, 6.5 Hz, -$OCH_2$-C*H*=), 4.71 (2H, d, *J* 6.5 Hz, -$CH_2O$-), 2.16-2.07 (2H, m, -C$H_2CH_3$), 1.03 (3H, t, *J* 7.5 Hz, -$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 155.6 (4°), 152.3 (4°), 145.3 (4°), 140.4 (3°), 125.2 (3°), 121.8 (3°), 121.3 (3°), 70.1 (2°), 25.3 (2°), 12.5 (1°); *m/z* (CI) 269 $[M+NH_4]^+$, 239, 225, 157 (Found: 269.1145. $C_{12}H_{13}NO_5$ requires $[M+NH_4]^+$ 269.1137) (Found: C, 57.38; H, 5.22; N, 5.53. $C_{12}H_{13}NO_5$ requires C, 57.37; H, 5.22; N, 5.58%).

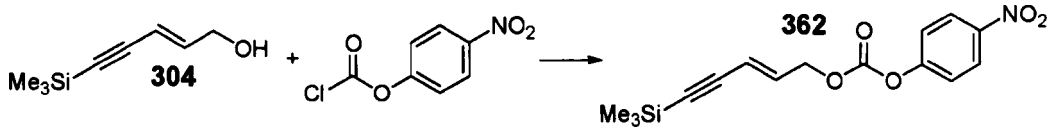
**(*E*)-4-Nitrophenyl 3-(4-nitrophenyl)allyl carbonate (359)**




*General procedure (v)* was applied, using *p*-nitrophenyl chloroformate (1.11 g, 5.5 mmol), *p*-nitrocinnamyl alcohol (896 mg, 5.0 mmol), $CH_2Cl_2$ (25 mL) and triethylamine (1.39 mL, 10.0 mmol). Purification 3 times by column chromatography (50% EtOAc–petrol, then 25% EtOAc–petrol, then 25% EtOAc–petrol + 3 drops AcOH per 1 L eluent) gave impure *(E)-4-nitrophenyl 3-(4-nitrophenyl)allyl carbonate* **359** (706 mg, 41%, ≈30% pure) as a yellow solid, seemingly unstable; $R_f$ 0.15 (EtOAc–petrol); *m/z* (CI) 362 $[M+NH_4]^+$, 174, 157, 148, 139, 132, 116 (Parent ion too weak for accurate mass

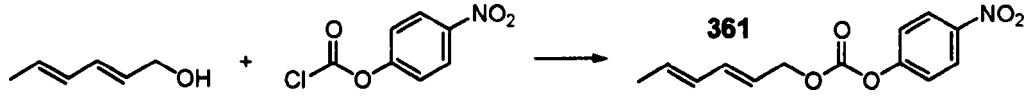
measurement) (Found: C, 55.65; H, 3.47; N, 8.21. $C_{16}H_{12}N_2O_7$ requires C, 55.82; H, 3.51; N, 8.14%).

**(*E*)-4-Nitrophenyl 5-(trimethylsilyl)pent-2-en-4-ynyl carbonate (362)**




*General procedure (v)* was applied, using **304** (1.54 g, 10 mmol), *p*-nitrophenyl chloroformate (2.22 g, 11 mmol), $CH_2Cl_2$ (50 mL) and triethylamine (2.79 mL, 20 mmol). Chromatography (15% EtOAc–petrol) to give *(E)-4-nitrophenyl 5-(trimethylsilyl)pent-2-en-4-ynyl carbonate* **362** (2.40 g, 75%) as a colourless oil; $R_f$ 0.52 (20% EtOAc–petrol); $\nu_{max}$ (film) 3118, 3087, 2177, 2137, 1768, 1616, 1595, 1527, 1493, 1448, 1350, 1252, 1215, 1165, 1111, 1084, 1041, 1012, 953, 920, 847, 775, 760 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.29 (2H, d, *J* 9.0 Hz, *o*-$NO_2Ar$), 7.39 (2H, d, *J* 9.0 Hz, *m*-$NO_2Ar$), 6.28 (1H, dt, *J* 16.0, 6.5 Hz, -$OCH_2$-C*H*=), 5.90 (1H, d, *J* 16.0 Hz, -$OCH_2$-CH=C*H*-), 4.80 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 0.21 (9H, s, -$Si(CH_3)_3$); $\delta_C$ (75 MHz, $CDCl_3$) 155.4, 152.2, 145.5, 135.3, 125.4, 121.8, 115.4, 101.8 (-*C*≡C-$Si(CH_3)_3$), 97.6 (-C≡*C*-$Si(CH_3)_3$), 68.4 (-$OCH_2$-), –0.2 (-$Si(CH_3)_3$); *m/z* (CI) 337 $[M+NH_4]^+$, 307, 229, 171, 154, 137, 90, 76, 52 (Found: $[M+NH_4]^+$, 337.1219. $C_{15}H_{17}NO_5Si$ requires $[M+NH_4]^+$, 337.1220) (Found: C, 56.69; H, 5.27; N, 4.36. $C_{15}H_{17}NO_5Si$ requires C, 56.41; H, 5.36; N, 4.39%).

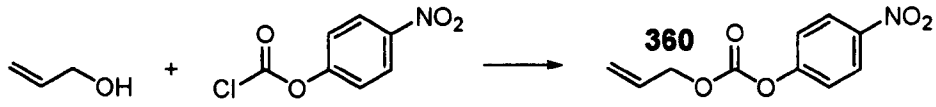
**(2*E*,4*E*)-Hexa-2,4-dienyl 4-nitrophenyl carbonate (361)**




*General procedure (v)* was applied, using *p*-nitrophenyl chloroformate (4.44 g, 22 mmol), sorbyl alcohol (1.96 g, 20 mmol), $CH_2Cl_2$ (100 mL) and triethylamine (5.58 mL, 40 mmol). Chromatography (15% EtOAc–petrol) afforded *(2E,4E)-hexa-2,4-dienyl 4-nitrophenyl carbonate* **361** (3.99 g, 76%) as a white solid; mp 92 °C; $\delta_H$ (300 MHz, $CDCl_3$) 8.31 (2H, d, *J* 9.0 Hz, *o*-$NO_2Ar$), 7.40 (2H, d, *J* 9.0 Hz, *m*-$NO_2Ar$), 6.38 (1H, dd, *J* 15.0, 10.5 Hz, -$OCH_2$-CH=C*H*-), 6.15-6.07 (1H, m, -$OCH_2$-CH=CH-C*H*=), 5.92-5.66 (2H, m,

-$OCH_2$-C*H*=CH-CH=C*H*-$CH_3$), 4.79 (2H, d, *J* 7.0 Hz, -$OCH_2$-), 1.81 (3H, d, *J* 6.5 Hz, =CH-C*H*$_3$); data in agreement with those previously reported.[177]

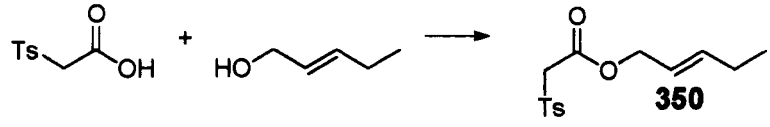
**Allyl 4-nitrophenyl carbonate (360)**




*General procedure (v)* was applied, using *p*-nitrophenyl chloroformate (4.44 g, 22 mmol), $CH_2Cl_2$ (100 mL), allyl alcohol (1.36 mL, 20 mmol) and triethylamine (11.1 mL, 80 mmol). Chromatography (15% EtOAc–petrol) afforded *allyl 4-nitrophenyl carbonate* **360** (4.04 g, 91%) as an off-white solid; mp 49 °C; $\delta_H$ (300 MHz, $CDCl_3$) 8.30 (2H, d, *J* 9.0 Hz, *o*-$NO_2$Ar), 7.41 (2H, d, *J* 9.0 Hz, *m*-$NO_2$Ar), 6.09-5.96 (1H, m, -C*H*=$CH_2$), 5.48 (1H, dd, *J* 17.0, 1.0 Hz, *trans* -CH=C$H_2$), 5.39 (1H, dd, *J* 10.5, 1.0 Hz, *cis* -CH=C$H_2$), 4.80 (2H, d, *J* 6.0 Hz, -$OCH_2$-), data in agreement with those previously reported.[178]

- **3.3.6 (Toluene-4-sulfonyl)acetates**

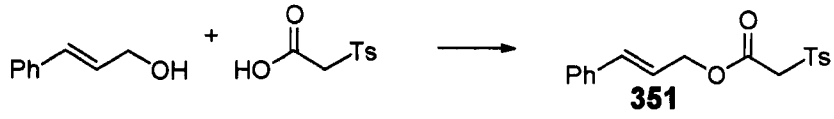
**(*E*)-Pent-2-enyl (toluene-4-sulfonyl)acetate (350)**




*General procedure (vi)* was applied, using *trans*-2-penten-1-ol (431 mg, 5.0 mmol), (toluene-4-sulfonyl)acetic acid (1.07 g, 5.0 mmol), $CH_2Cl_2$ (20 mL) and *N,N'*-di*iso*propyl carbodiimide (0.79 mL, 5.0 mmol). *Alteration to procedure:* The reaction mixture was stirred at 0 °C for 1 h then at rt for 40 h. DMAP (61 mg, 0.5 mmol, 0.1 equiv) was added and the reaction mixture stirred at rt for 72 h and 4 h at reflux. *Note: product subsequently shown to have same $R_f$ as starting material.* Chromatography (10% EtOAc–petrol) gave *(E)-pent-2-enyl (toluene-4-sulfonyl)acetate* **350** (1.29 g, 91%) as a colourless oil; $R_f$ 0.21; $\nu_{max}$ (film) 1741, 1672, 1597, 1497, 1456, 1400, 1381, 1329, 1306, 1277, 1215, 1153, 1117, 1086, 1043, 1018, 970, 914, 897, 814, 785, 727, 646 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.0 Hz, *o*-$SO_2$Ar), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2$Ar), 5.81-5.74 (1H, m, =C*H*-$CH_2$-$CH_3$), 5.48-5.38 (1H, m, -$OCH_2$-C*H*=), 4.51 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 4.11 (2H, s, -$SO_2CH_2$-), 2.45 (3H, s, Ts-$CH_3$),

2.09-2.01 (2H, m, -C*H*$_2$CH$_3$), 0.99 (3H, t, *J* 7.5 Hz, -CH$_2$C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.3 (C=O), 145.4 (4°), 139.3 (3°), 135.8 (4°), 129.8 (3°), 128.6 (3°), 121.6 (3°), 67.0 (2°), 61.1 (2°), 25.2 (-*C*H$_2$-CH$_3$), 21.7 (Ts-CH$_3$), 13.0 (=CH-CH$_2$-*C*H$_3$); *m/z* (CI) 300 $[M+NH_4]^+$, 232, 188 (Found: $[M+NH_4]^+$, 300.1260. $C_{14}H_{18}O_4S$ requires $[M+NH_4]^+$ 300.1270) (Found: C, 59.35; H, 6.29. $C_{14}H_{18}O_4S$ requires C, 59.55; H, 6.43%).

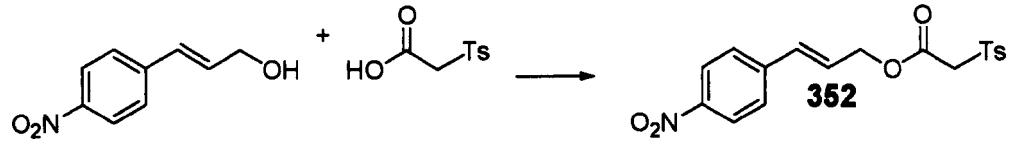
**Cinnamyl (toluene-4-sulfonyl)acetate (351)**




**351**

*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (4.29 g, 20.0 mmol), cinnamyl alcohol (2.68 g, 20 mmol), $CH_2Cl_2$ (60 mL) and *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol). Chromatography (1% $Et_2O$–$CH_2Cl_2$) to give *cinnamyl (toluene-4-sulfonyl)acetate* **351** (4.72 g, 71%) as a waxy white solid; mp 42–44 °C; $R_f$ 0.51 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 3057, 3028, 3005, 1741, 1658, 1597, 1577, 1495, 1448, 1400, 1379, 1327, 1304, 1275, 1213, 1151, 1117, 1086, 968, 912, 814, 781, 737, 694 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$); 7.82 (2H, d, *J* 8.0 Hz, *o*-SO$_2$Ar), 7.35-7.26 (7H, m, other ArH), 6.59 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.12 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.72 (2H, d, *J* 6.5 Hz, -OCH$_2$-), 4.17 (2H, s, -SO$_2$CH$_2$-), 2.35 (3H, s, Ts-CH$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.4 (C=O), 145.4 (4°), 135.9 (4°), 135.6 (4°), 135.3 (3°), 129.9 (3°), 128.7 (3°), 128.6, (3°) 128.4 (3°), 126.7 (3°), 121.7 (3°), 66.7 (-OCH$_2$-), 61.1 (-SO$_2$CH$_2$-), 21.7 (Ts-CH$_3$); *m/z* (CI) 678 $[2M+NH_4]^+$, 464, 348 $[M+NH_4]^+$, 233, 188, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 64 (Found: $[M+NH_4]^+$, 348.1273 $C_{18}H_{18}O_4S$ requires $[M+NH_4]^+$, 348.1270)

**(*E*)-3-(4-Nitrophenyl)allyl (toluene-4-sulfonyl)acetate (352)**

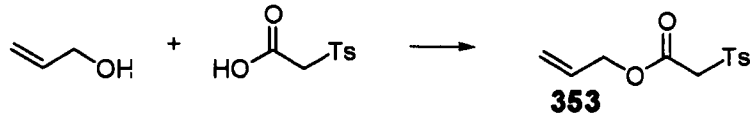



**352**

*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (536 mg, 2.5 mmol), *p*-nitrocinnamyl alcohol (448 mg, 2.5 mmol) and *N,N'*-

di*iso*propyl carbodiimide (0.39 mL, 2.5 mmol). Chromatography (40% EtOAc–petrol) to give *(E)-3-(4-nitrophenyl)allyl (toluene-4-sulfonyl)acetate* **352** (884 mg, 94%) as a pale yellow solid; mp 90–91 °C; $R_f$ 0.44 (50% EtOAc–petrol); $\nu_{max}$ (film) 3107, 3076, 3006, 1743, 1660, 1597, 1516, 1495, 1450, 1400, 1377, 1344, 1327, 1304, 1275, 1184, 1151, 1111, 1086, 972, 912, 862, 816, 741, 690 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.19 (2H, d, *J* 8.5 Hz, *o*-$NO_2Ar$), 7.82 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.51 (2H, d, *J* 8.5 Hz, *m*-$NO_2Ar$), 7.34 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.71 (1H, d, *J* 16.0 Hz, Ar-CH=), 6.35 (1H, dt, *J* 16.0, 5.5 Hz, Ar-CH=C*H*-), 4.81 (2H, d, *J* 5.5 Hz, -$OCH_2$-), 4.19 (2H, s, -$SO_2CH_2$-), 2.41 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.2 (C=O), 147.3 (4°), 145.6 (4°), 142.3 (4°), 135.7 (4°), 132.0 (3°), 129.9 (3°), 128.6 (3°), 127.3 (3°), 126.7 (3°), 124.1 (3°), 65.8 (-$OCH_2$-), 61.0 (Ts-$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 393 $[M+NH_4]^+$, 321, 222, 205, 188, 134, 52 (Found: $[M+NH_4]^+$, 393.1122 $C_{18}H_{17}NO_6S$ requires $[M+NH_4]^+$, 393.1120) (Found: C, 57.76; H, 4.56; N, 3.85. $C_{18}H_{17}NO_6S$ requires C, 57.59; H, 4.56; N, 3.73%).

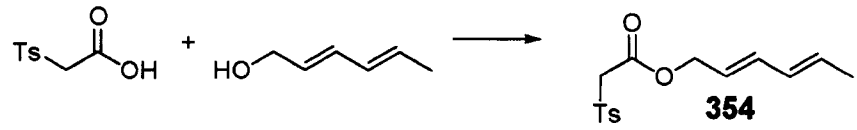
**Allyl (toluene-4-sulfonyl)acetate (353)**




**353**

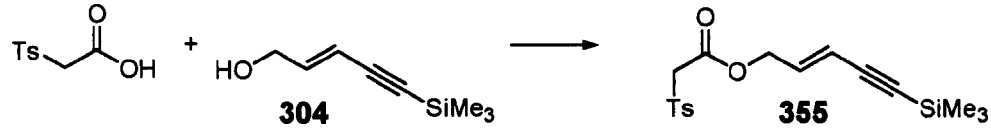
*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (4.29 g, 20 mmol), $CH_2Cl_2$ (100 mL), allyl alcohol (1.36 mL, 20 mmol) and *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol). Chromatography (35% EtOAc–petrol) to give *allyl (toluene-4-sulfonyl)acetate* **353** (4.67 g, 92%) as a white solid; mp 41 °C; $R_f$ 0.49 (50% EtOAc–petrol); $\nu_{max}$ (film) 3087, 3066, 3005, 1739, 1649, 1597, 1495, 1450, 1400, 1361, 1327, 1292, 1215, 1186, 1151, 1119, 1086, 1018, 989, 935, 814, 729, 646 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.35 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.83-5.73 (1H, m, -C*H*=$CH_2$), 5.20-5.30 (2H, m, -CH=C$H_2$), 4.56 (2H, d, *J* 5.5 Hz, -$OCH_2$-), 4.12 (2H, s, -$SO_2CH_2$-), 2.44 (Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.2 (C=O), 145.5 (4°), 135.8 (4°), 130.9 (3°), 129.9 (3°), 128.6 (3°), 119.4 (3°), 66.7 (-$OCH_2$-), 61.0 (-$SO_2$-$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 272 $[M+NH_4]^+$, 255 $[M+H]^+$, 174, 155, 139, 108, 93, 91, 58 (Found: $[M+NH_4]^+$, 272.0969. $C_{12}H_{14}O_4S$ requires $[M+NH_4]^+$, 272.0957) (Found: C, 56.63; H, 5.81. $C_{12}H_{14}O_4S$ requires C, 56.68; H, 5.55%).

**(2*E*,4*E*)-Hexa-2,4-dienyl (toluene-4-sulfonyl)acetate (354)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (4.29 g, 20 mmol), sorbyl alcohol (1.96 g, 20 mmol), $CH_2Cl_2$ (80 mL) and *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol, 1.0 equiv). Chromatography (30% EtOAc–petrol) gave *(2E,4E)-hexa-2,4-dienyl (toluene-4-sulfonyl)acetate* **354** (5.12 g, 87%) as a yellow oil; $R_f$ 0.18 (20% EtOAc–petrol); $\nu_{max}$ (film) 3005, 1741, 1703, 1660, 1597, 1494, 1446, 1440, 1381, 1329, 1304, 1277, 1151, 1117, 1086, 991, 966, 926, 814, 727 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.31 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.15 (1H, dd, *J* 15.0, 10.5 Hz, -$OCH_2$-CH=C*H*-CH=), 5.97 (1H, dd, *J* 15.0, 10.5 Hz, -$OCH_2$-CH=CH-C*H*=), [5.75-5.67, 5.48-5.38] (2H, m, -C*H*=CH-CH=C*H*-), 4.52 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 2.40 (3H, s, Ts-$CH_3$), 1.73 (3H, d, *J* 6.5 Hz, =CH-C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.3 (C=O), 145.4 (4°), 135.9 (3°), 135.7 (4°), 131.9 (3°), 130.2 (3°), 129.8 (3°), 128.6 (3°), 122.2 (3°), 66.6 (-$OCH_2$-), 61.0 (-$SO_2CH_2$-), 21.7 (Ts-$CH_3$), 18.2 (=CH-$CH_3$); *m/z* (CI) 606 $[2M+NH_4]^+$, 312 $[M+NH_4]^+$, 188, 115, 98, 81, 64 (Found: $[M+NH_4]^+$, 312.1265. $C_{15}H_{18}O_4S$ requires $[M+NH_4]^+$, 312.1263).

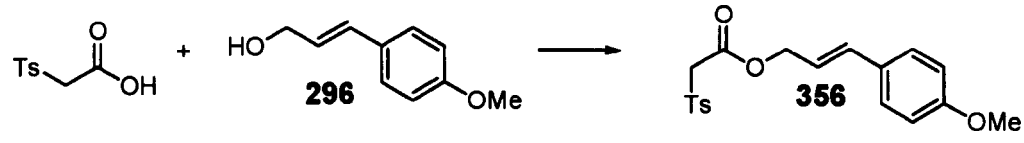
**(*E*)-5-(Trimethylsilyl)pent-2-en-4-ynyl (toluene-4-sulfonyl)acetate (355)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (3.21 g, 15 mmol), **304** (2.31 g, 15 mmol), $CH_2Cl_2$ (37.5 mL) and *N,N'*-di*iso*propyl carbodiimide (2.35 mL, 15 mmol, 1.0 equiv). Chromatography (30% EtOAc–petrol) to give *(E)-5-(trimethylsilyl)pent-2-en-4-ynyl (toluene-4-sulfonyl)acetate* **355** (3.40 g, 65%) as a pale yellow solid. A small portion was recrystallised from EtOAc/hexanes to give a white crystalline solid; mp 78 °C; $R_f$ 0.57 (50% EtOAc–petrol); $\nu_{max}$ (film) 3003, 2179, 2135, 1745, 1597, 1448,

1402, 1381, 1329, 1304, 1269, 1252, 1186, 1151, 1117, 1086, 955, 845, 760, 727, 700 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.28 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.91 (1H, dt, *J* 16.0, 6.0 Hz, -$OCH_2$-C*H*=), 5.53 (1H, d, *J* 16.0 -$OCH_2$-CH=C*H*-), 4.47 (2H, d, *J* 6.0 Hz, -$OCH_2$-), 4.07 (2H, s, -$SO_2$-$CH_2$-), 2.36 (3H, s, Ts-$CH_3$), 0.12 (9H, s, -$Si(CH_3)_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.0 (C=O), 145.4 (4°), 136.0 (3°), 135.6 (4°), 129.9 (3°), 128.5 (3°), 114.0 (3°), 102.3 (4°), 96.6 (4°), 65.1 (-$OCH_2$-), 60.8 (-$SO_2CH_2$-), 21.7 (Ts-$CH_3$), –0.2 (-$Si(CH_3)_3$); *m/z* (CI) 368 $[M+NH_4]^+$, 339, 214, 188, 154, 90 (Found: $[M+NH_4]^+$, 368.1344. $C_{17}H_{22}O_4SSi$ requires $[M+NH_4]^+$, 368.1352)

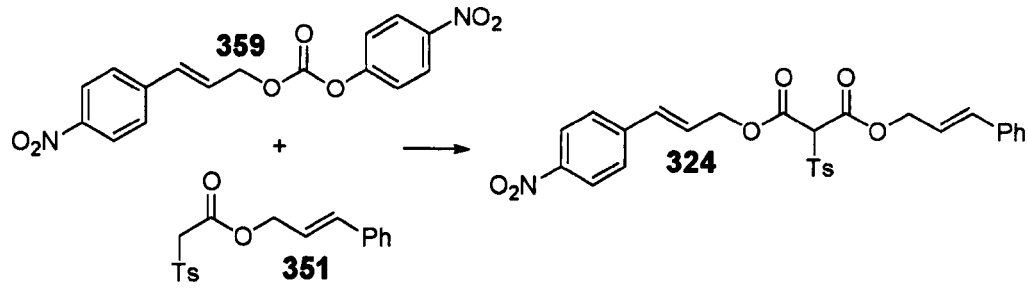
**(*E*)-3-(4-Methoxyphenyl)allyl (toluene-4-sulfonyl)acetate (356)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (5.99 g, 28.0 mmol), **296** (4.59 g, 28.0 mmol), $CH_2Cl_2$ (150 mL) and *N,N'*-di*iso*propyl carbodiimide (4.38 mL, 28.0 mmol). Chromatography (35% EtOAc–petrol) to give *(E)-3-(4-methoxyphenyl)allyl (toluene-4-sulfonyl)acetate* **356** (7.66 g, 76%) as a white crystalline solid; mp 81 °C; $R_f$ 0.59 (50% EtOAc–petrol); $\nu_{max}$ (film) 3033, 3005, 1739, 1654, 1606, 1577, 1512, 1456, 1444, 1421, 1400, 1379, 1327, 1304, 1275, 1250, 1177, 1149, 1117, 1084, 1032, 966, 891, 843, 814, 727, 646 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.33-7.28 (4H, m, *m*-$SO_2Ar$, *m*-MeOAr), 6.89 (2H, d, *J* 8.5 Hz, *o*-MeOAr), 6.57 (1H, d, *J* 16.0 Hz, Ar-CH=), 6.02 (1H, dt, *J* 16.0, 6.5 Hz, Ar-CH=C*H*-), 4.73 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 4.14 (2H, s, -$SO_2CH_2$-), 3.84 (3H, s, -$OCH_3$), 2.41 (Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.4 (4°), 159.9 (4°), 145.4 (4°), 135.7 (4°), 135.3 (3°), 130.6 (4°), 129.8 (3°), 128.7 (3°), 128.0 (3°), 119.3 (3°), 114.1 (3°), 67.0 (-$OCH_2$-), 61.2 (-$SO_2CH_2$-), 55.3 (-$OCH_3$), 21.7 (Ts-$CH_3$); *m/z* (CI) 378 $[M+NH_4]^+$, 352, 314, 236, 224, 188, 147, 121 (Found: $[M+NH_4]^+$, 378.1379. $C_{19}H_{20}O_5S$ requires $[M+NH_4]^+$, 378.1375) (Found: C, 63.37; H, 5.70. $C_{19}H_{20}O_5S$ requires C, 63.32; H, 5.59%).

- **3.3.7 2-(Toluene-4-sulfonyl)malonates from (toluene-4-sulfonyl)acetates**

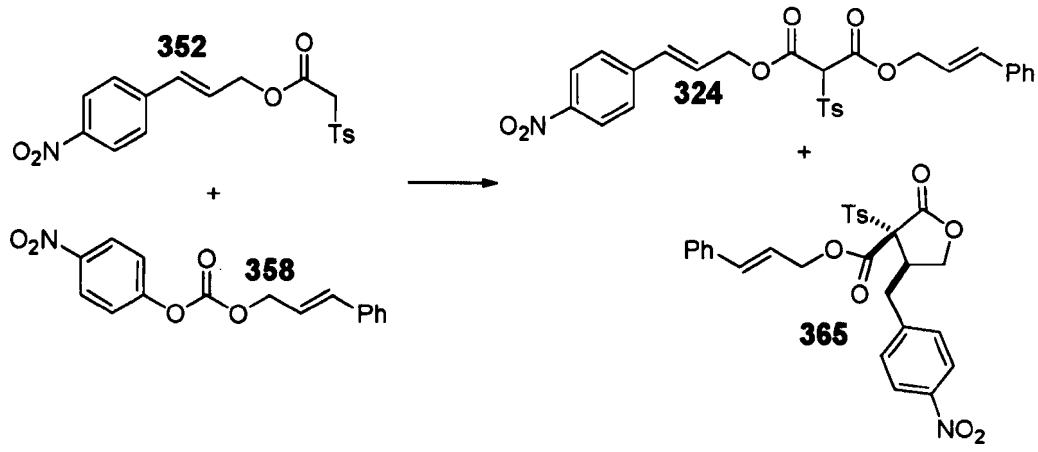
**(±)-1-Cinnamyl 3-(*E*)-3-(4-nitrophenyl)allyl 2-(toluene-4-sulfonyl)malonate (324) and (3*S**,4*R**)-Cinnamyl 4-(4-nitrobenzyl)-2-oxo-3-(toluene-4-sulfonyl)tetrahydrofuran-3-carboxylate (365)**




*Procedure A*

To potassium *t*-butoxide (561 mg, 5.0 mmol, 2.0 equiv) was added a solution of **351** (826 mg, 2.5 mmol, 1.0 equiv) in THF (7.5 mL). This was stirred at –78 °C for 10 min before being added dropwise by cannula to a solution of **359** (947 mg, 2.75 mmol, 1.1 equiv) in THF (5 mL). The reaction mixture was stirred at –78 °C for 20 min, then was allowed to warm to rt over 14 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aq. $NH_4Cl$ (3× 100 mL). The aqueous phases were washed with EtOAc (50 mL). The combined organic phases were dried ($Na_2SO_4$), concentrated under reduced pressure and purified twice by column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops AcOH per 1 L eluent, then 15% EtOAc–PhMe) to give *(±)-1-cinnamyl 3-(E)-3-(4-nitrophenyl)allyl 2-(toluene-4-sulfonyl)malonate* **324** (135 mg, 10%) as a yellow oil.

*Procedure B*



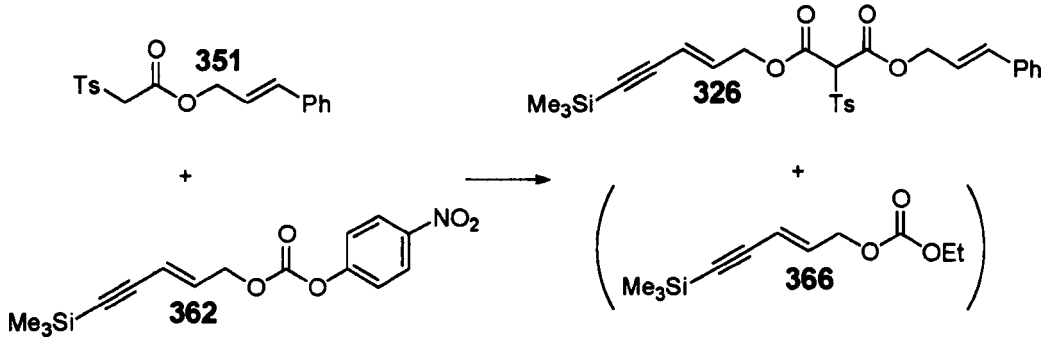

*General procedure (vii)* was applied, using sodium hydride (50 mg, 2.09 mmol) DMF (20 mL total), **352** (783 mg, 2.09 mmol) and carbonate **358** (625 mg, 2.09 mmol). Column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L of eluent) gave *(3S*,4R*)-cinnamyl 4-(4-nitrobenzyl)-2-oxo-3-(toluene-4-sulfonyl)tetrahydrofuran-3-carboxylate* **365** (383 mg, 34%) as a pale yellow solid and *(±)-1-cinnamyl 3-(E)-3-(4-nitrophenyl)allyl 2-(toluene-4-sulfonyl)malonate* **324** (261 mg, 23%) as a yellow oil.

**324:** $R_f$ 0.63 (5% $Et_2O$–petrol); $\nu_{max}$ (film) 3113, 3059, 3028, 1743, 1657, 1597, 1516, 1495, 1448, 1377, 1342, 1149, 1082, 1016, 970, 912, 862, 816, 737, 706, 692, 671 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.12 (2H, dd, *J* 9.0, 2.0 Hz, *o*-$NO_2Ar$), 7.86 (2H, dd, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.44 (2H, dd, *J* 9.0, 2.0 Hz, *m*-$NO_2Ar$), 7.34-7.26 (7H, m, other Ar-H), 6.71 (1H, d, *J* 16.0 Hz, $O_2N$-$C_6H_4$-C*H*=), 6.62 (1H, dd, *J* 16.0, 1.0 Hz, Ph-CH=), 6.36 (1H, dt, *J* 16.0, 6.0 Hz, $O_2N$-$C_6H_4$-CH=C*H*-), 6.15 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 5.10 (1H, s, -CH(Ts)-), 4.90 (2H, d, *J* 6.0 Hz, $O_2N$-$C_6H_4$-CH=CH-C$H_2$O-), 4.82 (2H, ddd, *J* 6.5, 2.5, 1.5 Hz, Ph-CH=CH-C$H_2$O-), 2.38 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.7 (2× C=O), 147.4 (4° $NO_2$-Ar), 146.2 (4° $SO_2Ar$), 142.2 (4° $NO_2Ar$), 135.9 (Ph-CH=), 135.7 (4° Ph), 134.1 (4° $SO_2Ar$), 132.3 ($O_2N$-$C_6H_4$-CH=), [130.2, 129.6] (3° $SO_2Ar$), [128.7, 128.6] (3° Ph), 127.3 (3° $NO_2Ar$), 126.7 (3° Ph), 126.2 ($O_2N$-$C_6H_4$-CH=CH-), 124.0 (3° $NO_2Ar$), 121.1 (Ph-CH=CH-), 74.5 (-CH(Ts)-), 67.6 (Ph-CH=CH-$CH_2O$-), 66.5 ($O_2N$-$C_6H_4$-

CH=CH-$CH_2O$-), 21.8 (Ts-$CH_3$); *m/z* (FAB) 536 $[M+H]^+$, 486, 391, 133, 117, 91, 77, 69, 57 (Found: C, 63.09; H, 4.95; N, 2.65. $C_{28}H_{25}NO_8S$ requires C, 62.79; H, 4.71; N, 2.62%).

**365**: mp 192 °C; $R_f$ 0.74 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 3107, 3078, 3059, 3028, 1793, 1751, 1597, 1522, 1495, 1448, 1379, 1348, 1329, 1308, 1244, 1213, 1178, 1151, 1111, 1084, 1059, 1038, 1018, 970, 910, 879, 854, 816, 735, 694, 665 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 8.14 (2H, d, *J* 8.5 Hz, *o*-$NO_2Ar$), 8.02 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.36-7.25 (9H, m, *m*-$NO_2Ar$, *m*-$SO_2Ar$, 5× Ph-H), 6.65 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.15 (1H, dt, *J* 16.0, 7.0 Hz, Ph-CH=C*H*-), [4.88, 4.75] (2H, ddd, *J* 12.5, 6.5, 1.0 Hz, -CH=CH-C$H_2$-), [4.31 (1H, t, *J* 8.5 Hz), 4.03 (1H, t, *J* 9.0 Hz)] (lactone -$OCH_2$-), 3.95-3.88 (1H, m, Ts-C-CH<), [3.56 (1H, dd, *J* 13.5, 3.5 Hz), 2.59 (1H, t, *J* 13.5 Hz)] (*p*-$O_2N$-$C_6H_4$-C$H_2$-), 2.36 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [166.9, 162.1] (2× C=O), 147.3 (4°), 146.7 (4°), 144.2 (4°), 137.1 (3°), 135.4 (4°), 132.3 (4°), 132.1 (3°), 129.6 (3°), 129.3 (3°), 128.8 (3°), 126.8 (3°), 124.3 (3°), 120.5 (3°), 78.1 (-OCO-*C*(Ts)-COO-), 70.0 (lactone -$OCH_2$-), 67.8 (Ph-CH=CH-$CH_2O$-), 42.7 (Ts-C-*C*H<), 35.4 (*p*-$O_2N$-$C_6H_4$-$CH_2$-), 21.8 (Ts-$CH_3$); *m/z* (FAB) 536 $[M+H]^+$, 248, 117 (Found: $[M+H]^+$, 536.1364. $C_{28}H_{25}NO_8S$ requires $[M+H]^+$, 536.1379) (Found: C, 62.59; H, 4.62; N, 2.59. $C_{28}H_{25}NO_8S$ requires C, 62.79; H, 4.70; N, 2.62%).

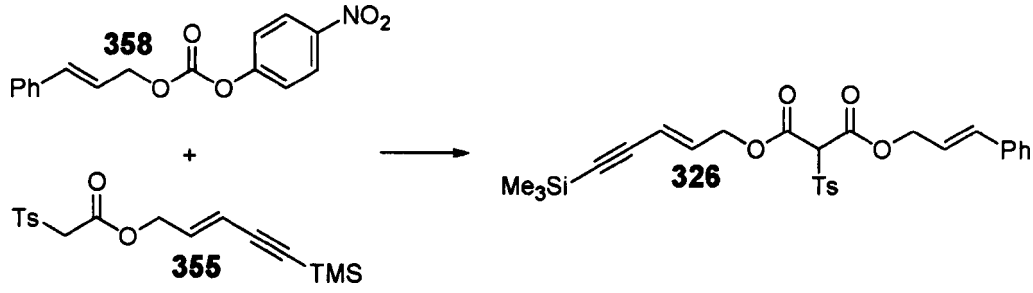
**(±)-1-Cinnamyl 3-(*E*)-5-(trimethylsilyl)pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)malonate (326) and (*E*)-Ethyl 5-(trimethylsilyl)pent-2-en-4-ynyl carbonate (366)**




*Procedure A*

To potassium *t*-butoxide (1.63 g, 13.3 mmol, 2.0 equiv) was added a solution of **351** (2.20 g, 6.65 mmol, 1.0 equiv) in THF (25 mL) at –78 °C. This was stirred for 10 min before being added dropwise by cannula to a solution of **362** (2.34 g, 7.32 mmol, 1.1 equiv) in THF (10 mL) at –78 °C. The reaction mixture

was stirred at –78 °C for 30 min and at rt for 16 h, then diluted with $Et_2O$ (200 mL) and washed with saturated aq. $NH_4Cl$ (3× 200ml). The organic phase was dried over ($Na_2SO_4$), concentrated under reduced pressure and purified three times by column chromatography (1% $Et_2O$–DCM + 3 drops AcOH per 1 L eluent, then 100% $CH_2Cl_2$, then 5% EtOAc–PhMe) to give *(±)-1-cinnamyl 3-(E)-5-(trimethylsilyl)pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)malonate* **326** (51 mg, 2%) as a colourless oil. Also isolated was *(E)-ethyl 5-(trimethylsilyl)pent-2-en-4-ynyl carbonate* **366** (trace, <1%).




*Procedure B*

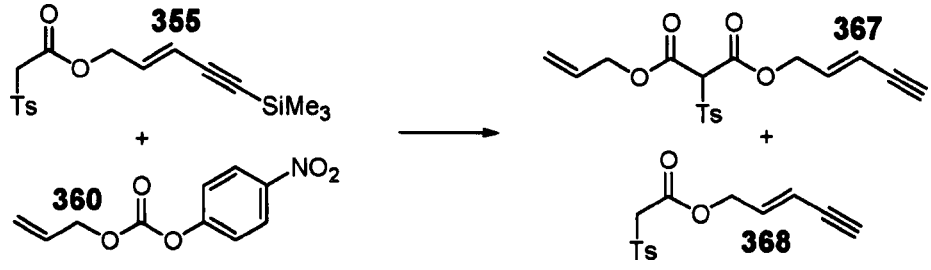
*General procedure (vii)* was applied, using sodium hydride (80 mg, 2.00 mmol), DMF (23 mL total), **355** (351 mg, 1.00 mmol) and carbonate **358** (299 mg, 1.00 mmol). Chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L eluent) to give *(±)-1-cinnamyl 3-(E)-5-(trimethylsilyl)pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)malonate* **326** (143 mg, 28%) as a yellow oil.

**326:** $R_f$ 0.70 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 3059, 3028, 2179, 2135, 1745, 1655, 1635, 1597, 1495, 1448, 1404, 1377, 1336, 1306, 1292, 1252, 1194, 1180, 1151, 1084, 1018, 968, 910, 847, 816, 760, 706, 694, 669 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.84 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.40-7.26 (7H, m, *m*-$SO_2Ar$, Ph-H), 6.65 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.18 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 6.10 (1H, dt, *J* 16.0, 6.0 Hz, -C*H*=CH-C≡), 5.73 (1H, dt, *J* 16.0, 1.5 Hz, -CH=C*H*-C≡), 5.04 (1H, s, -CH(Ts)-), [4.85, 4.81] (2× 1H, ddd, *J* 12.5, 6.5, 1.5 Hz, -C*H*$_2$-CH=CH-Ph), [4.71, 4.67] (2× 1H, ddd, *J* 14.0, 6.0, 1.5 Hz, -C*H*$_2$-CH=CH-C≡), 2.41 (3H, s, Ts-$CH_3$), 0.22 (9H, s, -Si($CH_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) [160.7, 160.5] (2× C=O), 146.2 (4° $SO_2Ar$), 135.8 (Ph-CH=), 135.8 (*i*-Ph), 135.3 (-CH=CH-C≡), 134.0 (4° $SO_2Ar$), 130.2 (*o*-$SO_2Ar$), 129.6 (*m*-$SO_2Ar$), 128.7 (3°), 128.5 (3°), 126.8 (3°), 121.2 (Ph-CH=*C*H-), 114.8 (-CH=*C*H-C≡), 102.0 (-*C*≡C-Si($CH_3$)$_3$), 97.2 (-C≡*C*-Si($CH_3$)$_3$), 74.5 (-CH(Ts)-), 67.5 (-*C*H$_2$-CH=CH-Ph), 65.9 (-*C*H$_2$-CH=CH-C≡), 21.8 (Ts-$CH_3$), –0.2

(-Si($CH_3$)$_3$); *m/z* (–ve CI) 509 [M-H]$^-$, 375, 213, 169, 155, 138 (Found: C, 63.71; H, 6.16. $C_{27}H_{30}O_6SSi$ requires C, 63.50; H, 5.92%).

**366:** $R_f$ 0.83 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 2177, 2135, 1749, 1633, 1446, 1396, 1381, 1365, 1257, 1084, 1007, 953, 847, 791, 760, 700, 656 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 6.23 (1H, dt, *J* 16.0, 6.0 Hz, -$OCH_2$-C*H*=CH-), 5.81 (1H, d, *J* 16.0 Hz, -$OCH_2$-CH=C*H*-), 4.65 (2H, d, *J* 6.0 -O*C*$H_2$-CH=), 4.21 (2H, q, *J* 7.0 Hz, -O*C*$H_2$-$CH_3$), 1.32 (3H, t, *J* 7.0 Hz, -$OCH_2$-*C*$H_3$), 0.20 (9H, s, -Si($CH_3$)$_3$); $\delta_C$ (75.4 MHz, $CDCl_3$) 154.8 (C=O), 136.8 (-$OCH_2$-*C*H=), 113.9 (-$OCH_2$-CH=*C*H-), 102.2 (-*C*≡C-Si($CH_3$)$_3$), 96.6 (-C≡*C*-Si($CH_3$)$_3$), 66.9 (-O*C*$H_2$-CH=), 64.2 (-$OCH_2$-$CH_3$), 14.3 (-$OCH_2$-*C*$H_3$), –0.2 (-Si($CH_3$)$_3$); *m/z* (CI) 244 [M+$NH_4$]$^+$, 227 [M+H]$^+$, 171, 154, 90, 52 (Found: [M+$NH_4$]$^+$, 244.1367 $C_{11}H_{18}O_3Si$ requires [M+$NH_4$]$^+$, 244.1369)

**(±)-(*E*)-1-Allyl 3-pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)malonate (367) and (*E*)-Pent-2-en-4-ynyl (toluene-4-sulfonyl)acetate (368)**



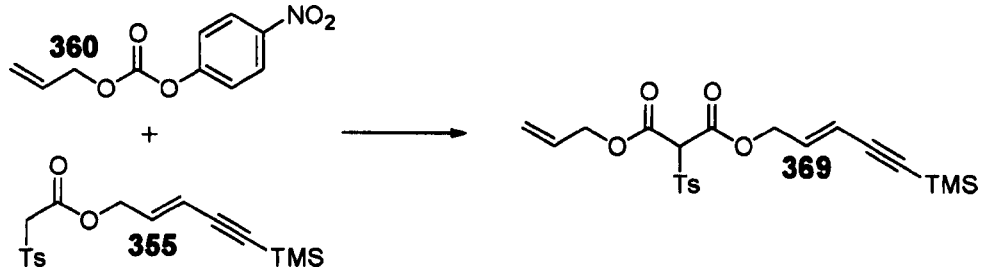

*General procedure (vii)* was applied, using sodium hydride (80 mg, 2.0 mmol), DMF (23 mL total), **355** (351 mg, 1.00 mmol) and carbonate **360** (223 mg, 1.00 mmol). Purification twice by column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops of AcOH per 1 L eluent, then 4% EtOAc–PhMe) gave *(±)-(E)-1-allyl 3-pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)malonate* **367** (106 mg, 29%) as a yellow oil. Also isolated was *(E)-pent-2-en-4-ynyl (toluene-4-sulfonyl)acetate* **368** (87 mg, 31%) as a pale yellow solid. *[In-situ loss of –TMS group]*

**367:** $R_f$ 0.34 (10% EtOAc-PhMe); $\nu_{max}$ (film) 3280, 3087, 3068, 3051, 3030, 2108, 1925, 1745, 1649, 1597, 1493, 1448, 1402, 1379, 1361, 1336, 1292, 1213, 1182, 1151, 1082, 991, 958, 845, 816, 706, 671 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.0 Hz, *o*-$SO_2$Ar), 7.37 (2H, d, *J* 8.0 Hz, *m*-$SO_2$Ar), 6.09 (1H, dt, *J* 16.0, 6.0 Hz, HC≡C-CH=C*H*-), 5.86-5.78 (1H, m, $H_2C$=C*H*-), 5.66 (1H, d, *J* 16.0 Hz, HC≡C-C*H*=), 5.31 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.24

(1H, d, *J* 10.5 Hz, *cis* -CH=C*H*$_2$), 5.00 (1H, s, -CH(Ts)-), [4.66, 4.63] (4H, dt, *J* 6.0, 1.5 Hz, 2× -OC$H_2$-), 2.98 (1H, s, ≡CH), 2.42 (3H, s, Ts-C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.5 (2× C=O), 146.3 (4°), 136.3 (3°), 134.1 (4°), 130.2 (3°), 129.7 (3°), 119.9 (=$CH_2$), 113.5 (3°), [80.7, 79.5] (H-*C*≡*C*-), 74.4 (-CH(Ts)-), [67.5, 65.8] (2× -O$CH_2$-), 21.8 (Ts-$CH_3$); *m/z* (CI) 380 $[M+NH_4]^+$, 272, 226, 188, 174, 139, 118 (Found: $[M+NH_4]^+$, 380.1170. $C_{18}H_{18}O_6S$ requires $[M+NH_4]^+$, 380.1168) (Found: C, 59.38; H, 4.87. $C_{18}H_{18}O_6S$ requires C, 59.66; H, 5.01%).

**368:** mp 70 °C; $R_f$ 0.27 (10% EtOAc-PhMe); $\nu_{max}$ (film) 3280, 3050, 3005, 2106, 1925, 1743, 1597, 1495, 1448, 1400, 1381, 1327, 1304, 1281, 1217, 1186, 1151, 1119, 1086, 1036, 1018, 960, 908, 814, 783, 727, 648 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0 Hz, *o*-$SO_2$Ar), 7.38 (2H, d, *J* 8.0 Hz, *m*-$SO_2$Ar), 6.09 (1H, dt, *J* 16.0, 6.0 Hz, HC≡C-CH=C*H*-), 5.62 (1H, d, *J* 16.0 Hz, HC≡C-C*H*=), 4.60 (2H, d, *J* 6.0 Hz, -O$CH_2$-), 4.13 (2H, s, -$SO_2CH_2$-), 2.97 (1H, s, ≡CH), 2.46 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.0 (C=O), 145.7 (4°), 136.7 (3°), 135.6 (4°), 130.0 (3°), 128.6 (3°), 113.3 (3°), [80.7, 79.4] (H-*C*≡*C*-), 65.1 (-O$CH_2$-), 61.0 (-$SO_2CH_2$-), 21.8 (Ts-$CH_3$); *m/z* (CI) 296 $[M+NH_4]^+$, 272, 188, 174, 142, 82 (Found: $[M+NH_4]^+$, 296.0958. $C_{14}H_{14}O_4S$ requires $[M+NH_4]^+$, 296.0957) (Found: C, 60.63; H, 5.06. $C_{14}H_{14}O_4S$ requires C, 60.42; H, 5.07%).

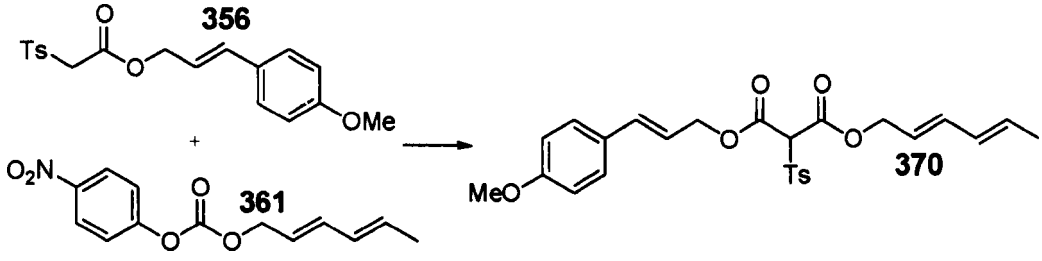
**(±)-(*E*)-1-Allyl 3-(5-(trimethylsilyl)pent-2-en-4-ynyl) 2-(toluene-4-sulfonyl)malonate (369)**




*General procedure (vii)* was applied, using sodium hydride (80 mg, 2.0 mmol), **355** (azeotropically dried from PhMe, 351 mg, 1.0 mmol), DMF (5 mL total) and carbonate **360** (azeotropically dried from PhMe, 223 mg, 1.0 mmol) in a flame-dried flask. Concentration under reduced pressure *without heating* and chromatography (4% EtOAc-PhMe + 3 drops of $NEt_3$ per 1 L eluent) gave *(±)-(E)-1-allyl 3-(5-(trimethylsilyl)pent-2-en-4-ynyl) 2-(toluene-4-sulfonyl)malonate* **369** (73 mg, 17%) as a colourless oil; $R_f$ 0.32 (5% EtOAc-PhMe); $\nu_{max}$ (film)

2137, 1742, 1597, 1449, 1337, 1250, 1151, 1082, 950, 843, 814, 760, 706 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.35 (2H, d, *J* 8.5 Hz, *m*-$SO_2Ar$), 6.07 (1H, dt, *J* 16.0, 6.0 Hz, ≡C-CH=C*H*-), 5.89-5.80 (1H, m, $H_2C$=C*H*-), 5.70 (1H, d, *J* 16.0 Hz, ≡C-C*H*=CH-), 5.34 (1H, d with fine struct., *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.27 (1H, d with fine struct., *J* 10.5 Hz, *cis* -CH=C$H_2$), 4.98 (1H, s, -OCO-CH(Ts)-COO-), 4.66 (4H, d, *J* 6.5 Hz, 2× -$CH_2O$-), 2.45 (3H, s, Ts-$CH_3$), 0.18 (9H, s, -Si$(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 160.5 (C=O), 146.1 (4°), 135.2 (3°), 134.1 (4°), 130.4 (3°), 130.2 (3°), 129.6 (3°), 119.0 (=$CH_2$), 114.8 (3°), 101.9 ($Me_3Si$-C≡C-), 97.1 ($Me_3Si$-C≡), 74.5 (-OCO-CH(Ts)-COO-), [67.5, 66.0] (2× -$CH_2O$-), 21.8 (Ts-$CH_3$), –0.2 (-Si$(CH_3)_3$); *m/z* (–ve ESI) 433 $[M-H]^-$, 361 (Found: 433.1128. $C_{21}H_{26}O_6SSi$ requires $[M-H]^-$ 433.1147) (Found: C, 58.31; H, 6.17. $C_{21}H_{26}O_6SSi$ requires C, 58.04; H, 6.03%).

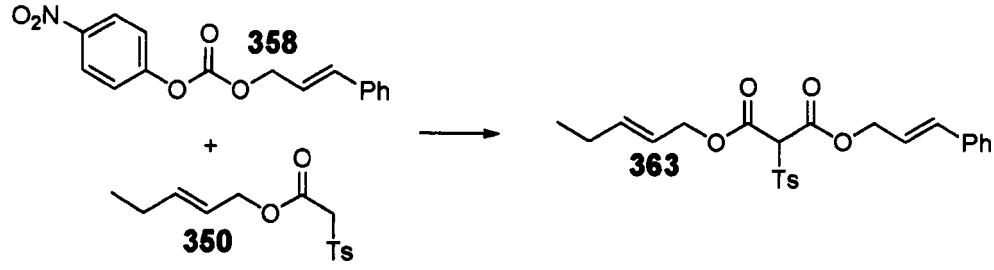
**1-(2*E*,4*E*)-Hexa-2,4-dienyl 3-(*E*)-3-(4-methoxyphenyl)allyl 2-(toluene-4-sulfonyl)malonate (370)**




*General procedure (vii)* was applied, using sodium hydride (254 mg, 6.34 mmol), **356** (1.14 g, 3.17 mmol), DMF (15 mL total) and carbonate **361** (834 mg, 3.17 mmol). Concentration under reduced pressure *without heating* and chromatography (7% EtOAc-PhMe + 3 drops of $NEt_3$ per 1 L eluent) gave an inseparable mixture of the desired product and **356** starting material. This mixture was dissolved in DMF (15 mL), to which was added at 0 °C DBU (1.59 mL, 15.9 mmol, 5.0 equiv) and sodium iodoacetate (3.30 g, 15.9 mmol, 5.0 equiv). The reaction mixture was allowed to warm to rt with stirring over 2 h, then diluted with $CH_2Cl_2$ (40 mL). The resultant white suspension was washed with $H_2O$ (40 mL). The aqueous layer was extracted with a small portion of $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure *without heating* and purified by chromatography (20% EtOAc in hexane + 3 drops of $NEt_3$ per 1 L eluent) to give *1-(2E,4E)-hexa-2,4-dienyl 3-(E)-3-(4-methoxyphenyl)allyl 2-(toluene-4-*

*sulfonyl)malonate* **370** (249 mg, 16%) as a colourless oil; $R_f$ 0.18 (20% EtOAc-hexane); $\nu_{max}$ (film) 1738, 1606, 1612, 1444, 1378, 1333, 1247, 1175, 1148, 1082, 1031, 991, 968, 841, 814, 706 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.31-7.25 (4H, m, *m*-MeOAr, *m*-$SO_2Ar$), 6.86 (2H, d, *J* 9.0 Hz, *o*-MeOAr), 6.58 (1H, d, *J* 16.0 Hz, MeO-$C_6H_4$-C*H*=), 6.21 (1H, dd, *J* 15.0, 10.5 Hz, -$OCH_2$-CH=C*H*-CH=), 6.03 (1H, dt, *J* 16.0, 6.5 Hz, MeO-$C_6H_4$-CH=C*H*-), 6.01-5.94 (1H, m, -$OCH_2$-CH=CH-C*H*=), 5.78-5.70 (1H, m, -$OCH_2$-C*H*=CH-CH=), 5.50 (1H, dt, *J* 14.5, 7.0 Hz, =C*H*-$CH_3$), 4.98 (1H, s, -OCO-CH(Ts)-COO-), [4.77 (2H, d, *J* 5.5 Hz), 4.65 (2H, d, *J* 7.0 Hz)] (2× -$CH_2O$-), 3.81 (3H, s, -$OCH_3$), 2.38 (3H, s, Ts-$CH_3$), 1.75 (3H, d, *J* 6.5 Hz, =CH-C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 160.8 (C=O), 159.8 (4°), 145.9 (4°), 136.3 (3°), 135.5 (3°), 134.2 (4°), 132.2 (3°), 130.2 (×2, 3°), 129.4 (3°), 128.6 (4°), 128.0 (3°), 121.8 (3°), 119.0 (3°), 114.1 (3°), 74.7 (-OCO-CH(Ts)-COO-), [67.7, 67.4] (2× -$CH_2O$-), 55.3 (-$OCH_3$), 21.7 (Ts-$CH_3$), 18.1 (=CH-C*H*$_3$); *m/z* (–ve ESI) 483 $[M-H]^-$, 457 (Found: 483.1467. $C_{26}H_{28}O_7S$ requires $[M-H]^-$ 483.1483) (Found: C, 64.37; H, 6.04. $C_{26}H_{28}O_7S$ requires C, 64.45; H, 5.82%).

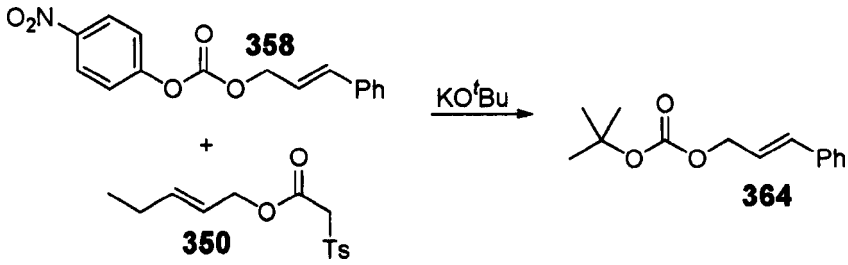
**(±)-1-Cinnamyl 3-(*E*)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate (363)**




*General procedure (vii)* was applied using sodium hydride (80 mg, 2.0 mmol), **350** (282 mg, 1.0 mmol), DMF (10 mL total) and carbonate **358** (598 mg, 2.0 mmol). Column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops AcOH per 1 L of eluent) afforded *(±)-1-cinnamyl 3-(E)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate* **363** (250 mg, 56%) as a yellow oil; $R_f$ 0.62 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 3028, 1741, 1597, 1495, 1450, 1377, 1336, 1290, 1261, 1180, 1149, 1082, 968, 928, 845, 814, 744, 706, 694, 669 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.29-7.19 (7H, m, other ArH), 6.57 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.19 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 5.84 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-CH=C*H*-$CH_2$-), 5.50 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=CH-$CH_2$-), 5.04 (1H, s, -CH(Ts)-), 4.84 (2H, d, *J* 6.5 Hz, Ph-CH=CH-C*H*$_2$-), 4.63 (2H, d, *J* 6.5 Hz, -C*H*$_2$-CH=CH-$CH_2$-$CH_3$), 2.40 (3H, s, Ts-

$CH_3$), 2.10-2.01 (2H, m, -C*H*$_2$CH$_3$), 0.99 (3H, t, *J* 7.0 Hz, -CH$_2$C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) [160.9, 160.8] (2× C=O), 146.0 (4° $SO_2Ar$), 139.7 (-OCH$_2$-CH=*C*H-CH$_2$-), 135.8 (*i*-Ph), 135.6 (Ph-CH=), 134.1 (4° $SO_2Ar$), [130.3, 129.5] (3° $SO_2Ar$), [128.7, 128.4, 126.8] (3° Ph), [121.3, 121.2] (Ph-CH=*C*H-, -OCH$_2$-*C*H=CH-CH$_2$), 74.6 (-CH(Ts)-), 67.8 (-O*C*H$_2$-CH=CH-CH$_2$-), 67.5 (Ph-CH=CH-*C*H$_2$-), 25.3 (-*C*H$_2$CH$_3$), 21.8 (Ts-CH$_3$), 13.0 (-CH$_2$*C*H$_3$); *m/z* (CI) 460 $[M+NH_4]^+$, 338, 300, 188, 174, 146, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$ (Found: $[M+NH_4]^+$, 460.1784 $C_{24}H_{26}O_6S$ requires $[M+NH_4]^+$, 460.1794) (Found: C, 65.31; H, 6.11. $C_{24}H_{26}O_6S$ requires C, 65.14; H, 5.92%).

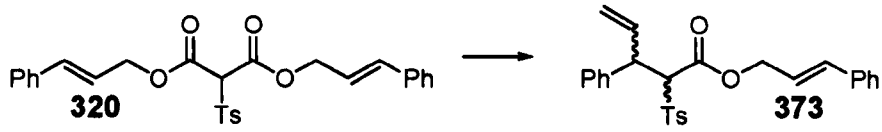
**_tert_-Butyl cinnamyl carbonate (364)**




To a solution of **350** (282 mg, 1.0 mmol, 1.0 equiv) and **358** (329 mg, 1.1 mmol, 1.1 equiv) in THF (8 mL) at –78 °C was added potassium *tert*-butoxide (1.0 M; in THF, 2.0 mL, 2.0 mmol, 2.0 equiv). Reaction mixture was stirred at –78 °C for 10 min then at rt for 16 h. Reaction mixture was diluted with $Et_2O$ (100 mL), then washed with saturated aq. $NH_4Cl$ (3× 100 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Column chromatography (1% $Et_2O$–$CH_2Cl_2$ + 3 drops AcOH per 1 L of eluent) afforded tert-*butyl cinnamyl carbonate* **364** (184 mg, 71% with respect to **358**) as a yellow oil; $R_f$ 0.76 (5% $Et_2O$–$CH_2Cl_2$); $\delta_H$ (300 MHz, $CDCl_3$) 7.43-7.26 (5H, m, Ar-H), 6.70 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.33 (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-), 4.75 (2H, d, *J* 6.5 Hz, -OCH$_2$-), 1.54 (9H, s, -OC(CH$_3$)$_3$); data in agreement with those previously reported.[179]

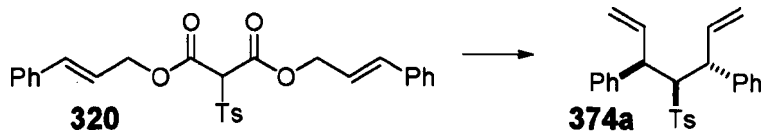
## 3.3.8 Decarboxylative Claisen Rearrangements

**(2*R**,3*R**)-Cinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate and (2*R**,3*S**)-Cinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate (373)**



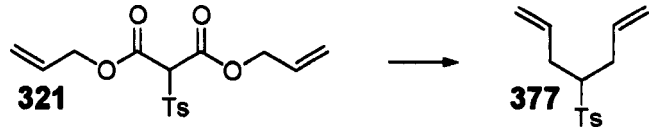

To a solution of **320** (375 mg, 0.76 mmol, 1.0 equiv) in PhMe (7 mL) was added potassium acetate (8 mg, 0.08 mmol, 0.1 equiv) after which *N,O*-bis(trimethylsilyl)acetamide (0.37 mL, 1.53 mmol, 2.0 equiv) was introduced. The reaction mixture was stirred at 90 °C for 16 h, after which concentration under reduced pressure and chromatography (10% EtOAc–petrol) afforded *cinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **373** (216 mg, 63%) as a pale yellow oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.35 (20% EtOAc–petrol); $\nu_{max}$ (film) 3061, 3029, 1738, 1597, 1493, 1451, 1324, 1304, 1279, 1205, 1183, 1144, 1083, 967, 913, 814, 744, 700 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.43-7.09 (12H, m, other Ar-H), [6.66 (min. diast.), 6.36 (maj. diast.)] (1H, d, *J* 16.0 Hz, Ph-C*H*=CH-), 6.23-6.14 (1H, m, min. diast. Ph-CH=C*H*-, maj. diast. $H_2C$=C*H*-), 5.92 (1H for min. diast., ddd, *J* 17.0, 10.0, 8.5 Hz, min. diast. $H_2C$=C*H*-), 5.64 (1H for maj. diast., dt, *J* 16.0, 6.5 Hz, maj. diast. Ph-CH=C*H*-), [5.18 (maj. diast.), 5.05 (min. diast.)] (1H, d, *J* 10.0 Hz, *cis* -CH=C$H_2$), [5.16 (maj. diast.), 5.13 (min. diast.)] (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 4.76 (2H for min. diast., d, *J* 6.5 Hz, min. diast. -$OCH_2$-), [4.52 (min. diast., d, *J* 10.5 Hz), 4.50 (maj. diast., d, J 11.5 Hz)] (1H, Ts-CH<), [4.32 (ddd, *J* 12.5, 6.5, 1.0 Hz), 4.25 (ddd, *J* 12.5, 7.0, 1.0 Hz)] (2H for maj. diast., maj. diast. -$OCH_2$), [4.20-4.25 (m, min. diast.), 4.09 (dd, *J* 11.5, 8.5 Hz, maj. diast.)] (1H, Ph-CH<), [2.38 (maj. diast.), 2.32 (min. diast.)] (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [165.0, 164.9] (C=O, 2× diast.), 145.5, 144.7, 139.1, 138.0, 136.8, 136.6, 136.0, 135.9 (×2), 135.2, 134.9, 129.7, 129.5, 129.4, 128.8 (×2), 128.7, 128.6, 128.4, 128.3 (×2), 128.0, 127.5, 127.4, 126.7, 122.0, 121.6, 118.0, 117.9, [75.4, 74.9] (-$SO_2CH$<, 2× diast.), [66.8, 66.3] (-$OCH_2$-, 2× diast.), 49.3 (×2) (-C(Ph)H-), [21.7, 21.6] (Ts-$CH_3$, 2× diast.); *m/z* (CI) 464 $[M+NH_4]^+$, 391, 310, 304, 151, 134 $[C_9H_{10}O]^+$, 131, 117 $[C_9H_9]^+$, 106, 90, 77 (Found: $[M+NH_4]^+$, 464.1891. $C_{27}H_{26}O_4S$ requires $[M+NH_4]^+$, 461.1896) (Found: C, 72.69; H, 5.91. $C_{27}H_{26}O_4S$ requires C, 72.62; H, 5.87%).

**(3*R**,5*R**)-3,5-Diphenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (374a)**




To a solution of **320** (376 mg, 0.77 mmol, 1.0 equiv) in *o*-xylene (10 mL, dried over 4Å mol. sieves) was added potassium acetate (30 mg, 0.31 mmol, 0.4 equiv). The reaction mixture was heated to reflux, after which time *N,O*-bis(trimethylsilyl) acetamide (1.49 mL, 6.14 mmol, 8.0 equiv) was added dropwise *by syringe* pump to the top of the condenser over 3.5 h; the reaction mixture was heated to reflux for a further 6 h, concentrated under reduced pressure and purified by column chromatography (5% EtOAc–petrol) to give *3,5-diphenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **374** (186 mg, 60%) as an inseparable mixture of diastereoisomers. This was recrystallised from $Et_2O$ to give *(3R*,5R*)-3,5-diphenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **374a** (118 mg, 38%); mp 69–72 °C; $R_f$ 0.32 (20% EtOAc–petrol); $\nu_{max}$ (film) 3061, 3031, 1637, 1598, 1494, 1452, 1419, 1316, 1289, 1186, 1143, 1084, 1014, 917, 813, 749, 734, 699, 668 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.28-6.96 (14H, m, Ar-H), 6.60 (1H, dt, *J* 17.0, 10.0 Hz, $H_2C$=C*H*-), 6.21 (1H, dt, *J* 17.0, 10.0 Hz, $H_2C$=C*H*-), 5.35-5.12 (4H, m, both *H*$_2$C=CH-), 4.27-4.08 (3H, m, 2× Ph-C(H)<, -$SO_2$-C(H)<), 2.36 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 143.4, 142.4, 140.9, 138.6, 137.3, 136.3, 129.2, 128.6, 128.3, 127.9, 127.7, 127.5, 126.6, 126.4, [118.9, 118.2] (-CH=*C*H$_2$), 74.0 (-$SO_2$-C(H)<), [49.9, 48.7] (Ar-*C*(H)-), 21.5 (Ts-$CH_3$); *m/z* (CI) 420 $[M+NH_4]^+$, 403 $[M+H]^+$, 304 $[M+NH_4-C_9H_9]^+$, 189, 174, 131 (Found: $[M+H]^+$, 403.1729. $C_{26}H_{26}O_2S$ requires $[M+H]^+$, 403.1732) (Found: C, 77.58; H, 6.58. $C_{26}H_{26}O_2S$ requires C, 77.58; H, 6.51%).

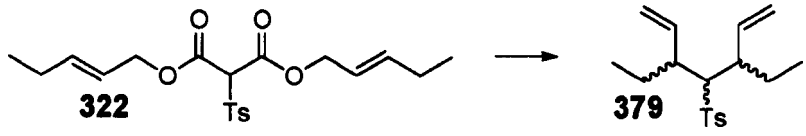
**(±)-4-(Toluene-4-sulfonyl)hepta-1,6-diene (377)**




To a solution of **321** (529 mg, 1.56 mmol, 1.0 equiv) in *o*-xylene (25 mL, dried over 4Å mol. sieves) was added potassium acetate (61 mg, 0.62 mmol, 0.4 equiv) and *N,O*-bis(trimethylsilyl)acetamide (3.04 mL, 12.5 mmol, 8.0 equiv). The reaction mixture was heated to reflux for 18 h. Concentration under

reduced pressure and chromatography (5→7.5% EtOAc–petrol) afforded *(±)-4-(toluene-4-sulfonyl)hepta-1,6-diene* **377** (147 mg, 37%) as a pale yellow liquid; $R_f$ 0.42 (20% EtOAc–petrol); $\nu_{max}$ (film) 3078, 1641, 1597, 1495, 1439, 1416, 1402, 1381, 1302, 1288, 1215, 1184, 1146, 1086, 1039, 1016, 995, 920, 843, 816, 739, 705, 661 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.82-5.68 (2H, m, $H_2C$=C*H*-), 5.07 (2H, d, *J* 9.5 Hz, *cis* -CH=C$H_2$), 5.06 (2H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 3.09-3.02 (1H, m, -$SO_2$CH<), 2.67-2.56 (2H, m, $H_2C$=CH-C*H*H-), 2.46 (3H, s, Ts-$CH_3$), 2.46-2.34 (2H, m, $H_2C$=CH-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 144.8 (4°), 134.8 (4°), 133.4 (3°), 129.8 (3°), 128.8 (3°), 118.4 ($H_2C$=CH-), 63.8 (-$SO_2$CH<), 31.8 ($H_2C$=CH-$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 518 $[2M+NH_4]^+$, 406, 389, 314, 268 $[M+NH_4]^+$, 251 $[M+H]^+$, 185, 139, 95 (Found: $[M+H]^+$, 251.1103. $C_{14}H_{18}O_2S$ requires $[M+H]^+$, 251.1106) (Found: C, 66.94; H, 7.05. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25%).

**(3*R**,5*R**)-3,5-Diethyl-4-(toluene-4-sulfonyl)hepta-1,6-diene, (3*R**,4*R**,5*S**)-3,5-Diethyl-4-(toluene-4-sulfonyl)hepta-1,6-diene and (3*R**,4*S**,5*S**)-3,5-Diethyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (379)**

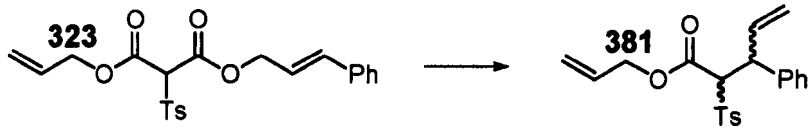



To a solution of **322** (843 mg, 2.14 mmol, 1.0 equiv) in *o*-xylene (35 mL, dried over 4Å mol. sieves) was added potassium acetate (84 mg, 0.86 mmol, 0.4 equiv) and *N,O*-bis(trimethylsilyl)acetamide (4.10 mL, 17.1 mmol, 8.0 equiv). The reaction mixture was heated to reflux for 14 h. Concentration under reduced pressure and chromatography (5% EtOAc–petrol) afforded *3,5-diethyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **379** (512 mg, 78%) as a yellow oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.40 (20% EtOAc–petrol); $\nu_{max}$ (film) 3076, 1637, 1597, 1494, 1456, 1419, 1379, 1315, 1302, 1286, 1227, 1143, 1084, 1016, 999, 966, 916, 816, 800, 771, 742, 717, 679, 656 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.32 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.02-5.80 (2H, m, 2× $H_2C$=C*H*-), 5.10-4.86 (4H, m, 2× $H_2$C=CH-), 3.18-3.14 (1H, m, -$SO_2$CH<) 2.42 (3H, s, Ts-$CH_3$), 2.50-2.32 (2H, m, 2× $H_2C$=CH-C*H*-) [1.89-1.80 (1H, m), 1.69-1.47 (3H, m)] (2× $H_3C$-$CH_2$-), 0.85-0.66 (6H, m, 2× $H_3$C-$CH_2$-); $\delta_C$ (75 MHz, $CDCl_3$) 144.2, 139.4, 139.2, 138.9, 138.7, 137.6, 129.7, 128.4, 117.2, 117.0, 116.4, [72.1, 71.7, 71.5]

(-$SO_2CH$<, 3× diast.), [45.4, 45.3, 44.8] ($H_2C$=CH-*C*H-, 3× diast.), [25.0, 24.9, 24.3] ($H_3C$-$CH_2$-, 3× diast.), [21.6, 21.0] (Ts-$CH_3$, 3× diast.), [12.5, 12.2, 12.1] ($H_3C$-$CH_2$-, 3× diast.); *m/z* (CI) 324 $[M+NH_4]^+$, 307 $[M+H]^+$, 151, 139, 121, 109, 95 (Found: $[M+H]^+$, 307.1734. $C_{18}H_{26}O_2S$ requires $[M+H]^+$, 307.1732).

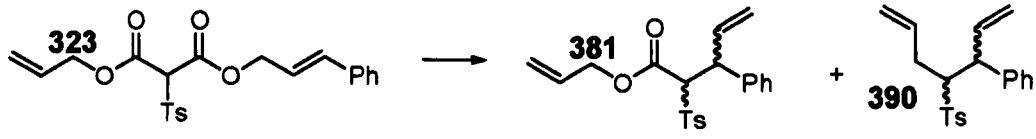
**(2*R**,3*R**)-Allyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate and (2*R**,3*S**)-Allyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate (381)**

**(3*R**,4*R**)-3-Phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene and (3*R**,4*S**)-3-Phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (390)**




*Procedure A*

To a solution of **323** (1.14 g, 2.76 mmol, 1.0 equiv) in PhMe (25 mL) was added potassium acetate (27 mg, 0.28 mmol, 0.1 equiv) and *N,O*-bis(trimethylsilyl)acetamide (1.34 mL, 5.52 mmol, 2.0 equiv). The reaction mixture was heated to reflux for 14 h, after which concentration under reduced pressure and chromatography (2→12.5% EtOAc–petrol) gave *allyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **381** (670 mg, 66%) as a pale yellow oil and as an inseparable mixture of diastereoisomers.



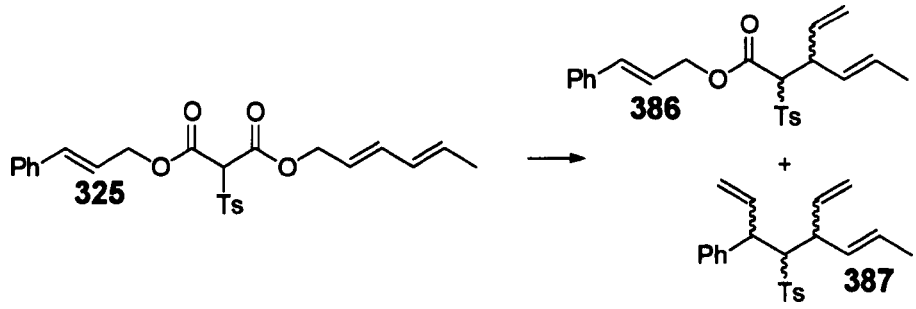

*Procedure B*

To **323** (207 mg, 0.5 mmol, 1.0 equiv) was added *o*-xylene (5 mL). Potassium acetate (≈5 mg, 0.05 mmol, 0.1 equiv) was added in one portion, then *N,O*-bis(trimethylsilyl)acetamide (134 μL, 0.55 mmol, 1.1 equiv) was introduced. The reaction mixture was stirred at reflux for 16 h, concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give *3-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **390** (19 mg, 12%) as a yellow oil and as an inseparable mixture of diastereoisomers. Also isolated was *allyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **381** (58 mg, 31%), as a yellow oil and as an inseparable mixture of diastereoisomers.

**381:** $R_f$ 0.26 (20% EtOAc–petrol); $\nu_{max}$ (film) 3084, 3062, 3030, 1741, 1639, 1597, 1493, 1454, 1327, 1290, 1279, 1205, 1146, 1084, 989, 928, 858, 816, 760, 744, 702, 665 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [7.83 (maj. diast.), 7.77 (min. diast.)] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.41-7.11 (7H, m, other Ar-H), 6.24-6.13 (1H, m, $H_2C$=C*H*-$CH_2$-, 2× diast.), 5.97-5.81 (1H, m, $H_2C$=C*H*-C(Ph)H-, 2× diast.), 5.42-4.95 (4H, m, both -CH=C$H_2$, 2× diast.), [4.65-4.49, 4.24-4.01] (4H, m, -$OCH_2$-, -$SO_2$CH<, $H_2C$=CH-C(Ph)*H*-, 2× diast.), [2.48 (maj. diast.), 2.39 (min. diast.)] (3H, s, Ts-$CH_3$, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) [165.3, 165.2] (C=O, 2× diast.), 145.9 (4°), 145.0 (4°), 139.6 (4°), 138.2 (4°), 137.1 (3°), 137.0 (3°), 136.4 (4°), 135.3 (4°), 132.1 (3°), 131.5 (3°), 131.4 (3°), 131.1 (3°), 130.2 (3°), 129.9 (3°), 129.8 (×2) (3°), 129.2 (3°), 129.1 (3°), 129.0 (3°), 128.8 (3°), 128.4 (3°), 127.9 (3°), 127.7 (3°), 127.1 (3°), 119.8 (2°), 119.6 (2°), 119.5 (2°), 119.3 (2°), 118.4 (2°), 118.2 (2°), [75.8, 75.3] (-$SO_2$CH<, 2× diast.), [67.2, 66.7] (-$OCH_2$-, 2× diast.), [49.8, 49.7] ($H_2C$=CH-*C*(Ph)H-, 2× diast.), [22.1, 22.0] (Ts-$CH_3$, 2× diast.); *m/z* (CI) 388 $[M+NH_4]^+$, 312, 214, 174, 61, 44 (Found: $[M+NH_4]^+$, 388.1576. $C_{21}H_{22}O_4S$ requires $[M+NH_4]^+$, 388.1583) (Found: C, 67.97; H, 5.86. $C_{21}H_{22}O_4S$ requires C, 68.08; H, 5.99%).

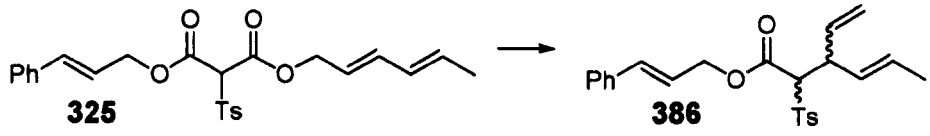
**390:** $R_f$ 0.40 (20% EtOAc–petrol); $\nu_{max}$ (film) 3078, 3062, 3028, 3003, 1637, 1597, 1495, 1452, 1435, 1417, 1313, 1300, 1288, 1144, 1084, 991, 918, 814, 700, 667 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.70, 7.60] (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$, 2× diast.), 7.30-7.06 (7H, m, *m*-$SO_2Ar$, 5× Ph-H), [6.14, 6.09] (1H, ddd, *J* 17.0, 10.0, 9.0 Hz, $H_2C$=C*H*-C(Ph)H-, 2× diast.), 5.68-5.55 (1H, m, $H_2C$=C*H*-$CH_2$-), 5.23-5.07 (2H, m, $H_2$C=CH-C(Ph)H-), 4.98-4.74 (2H, m, $H_2$C=CH-$CH_2$-), [4.10 (dd, *J* 9.0, 5.0 Hz), 3.98 (t, *J* 8.5 Hz)] (1H, Ph-C(H)<, 2× diast.), [3.56 (dt, *J* 7.5, 5.5 Hz), 3.48 (q, *J* 5.5 Hz)] (1H, -$SO_2$CH<, 2× diast.), [2.65-2.79, 2.34-2.38] (2H, m, $H_2C$=CH-C$H_2$-, 2× diast.), [2.41, 2.43] (3H, s, Ts-$CH_3$, 2× diast.); $\delta_C$ (100 MHz, $CDCl_3$) 144.4 (4°), 144.2 (4°), 141.0 (4°), 140.3 (4°), 138.0 (3°), 136.5 (4°), 136.2 (4°), 135.6 (3°), 134.4 (3°), 133.5 (3°), 129.5 (×2, 3°), 128.8 (3°), 128.6 (3°), 128.5 (×2, 3°), 128.3 (3°), 128.0 (3°), 127.0 (3°), 126.8 (3°), 118.7 (2°), 118.1 (2°), 117.6 (2°), 116.9 (2°), [68.8, 68.4] (Ts-CH<), [49.2, 48.2] (Ph-CH<), [31.8, 30.0] ($H_2C$=CH-*C*$H_2$-), 21.6 (Ts-$CH_3$); *m/z* (CI) 344 $[M+NH_4]^+$, 327 $[M+H]^+$, 170, 131, 108, 91 (Found: $[M+H]^+$, 327.1408. $C_{20}H_{22}O_2S$ requires $[M+H]^+$, 327.1419).

**(*E*)-5-Etheny-3-phenyl-4-(toluene-4-sulfonyl)octa-1,6-diene (387), diastereoisomers as shown and Cinnamyl (*E*)-3-ethenyl-2-(toluene-4-sulfonyl)hex-4-enoate (386), diastereoisomers as shown.**




*Procedure A*

To a solution of **325** (288 mg, 0.634 mmol, 1.0 equiv) in PhMe (5 mL) was added potassium acetate (approx 6 mg, 0.06 mmol, 0.1 equiv). *N,O*-Bis(trimethylsilyl)acetamide (0.31 mL, 1.27 mmol, 2.0 equiv) was added, then the reaction mixture was heated to reflux for 14 h, concentrated under reduced pressure and purified by chromatography (5→7% EtOAc–petrol) to give *(E)-5-etheny-3-phenyl-4-(toluene-4-sulfonyl)octa-1,6-diene* **387** (44 mg, 19%) as a pale yellow oil and as an inseparable mixture of diastereoisomers. Also isolated was *cinnamyl (E)-3-ethenyl-2-(toluene-4-sulfonyl)hex-4-enoate* **386** (18 mg, 7%) as a pale yellow oil and as an inseparable mixture of diastereoisomers.




*Procedure B*

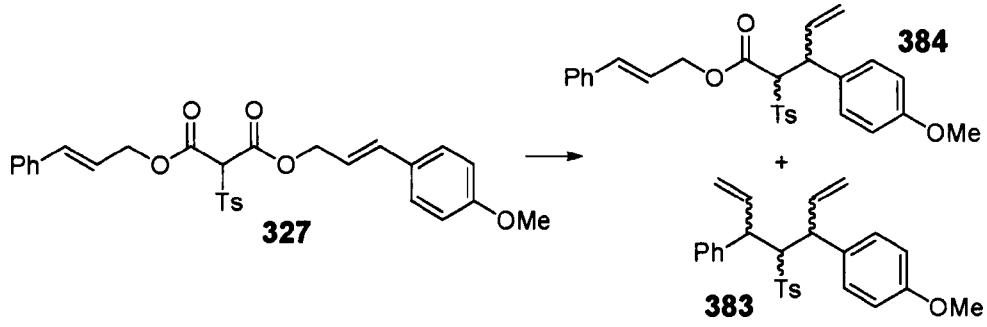
To **325** (567 mg, 1.25 mmol, 1.0 equiv) was added potassium acetate (12 mg, 0.13 mmol, 0.1 equiv) in one portion. $CH_2Cl_2$ (12.5 mL) was introduced, then *N,O*-bis(trimethylsilyl)acetamide (0.30 mL, 1.25 mmol, 1.0 equiv) was added. The reaction mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give *cinnamyl (E)-3-ethenyl-2-(toluene-4-sulfonyl)hex-4-enoate* **386** (407 mg, 99%) as a pale yellow oil and as an inseparable mixture of diastereoisomers.

**387:** $R_f$ 0.43 (20% EtOAc–petrol); $\nu_{max}$ (film) 3079, 3064, 3030, 1672, 1635, 1599, 1495, 1452, 1414, 1378, 1317, 1300, 1288, 1182, 1142, 1084, 993, 970, 916, 843, 814, 735, 702, 658 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.69 (2H, d, *J* 7.0 Hz, *o*-$SO_2Ar$), 7.29-6.94 (7H, m, other Ar-H), 6.36-5.48 (4H, m, -C*H*=C*H*-,

2× -C*H*=$CH_2$), 5.33-4.78 (4H, m, 2× -CH=C$H_2$), [4.06-3.95, 3.79-3.71, 3.21-3.18] (3H, m, Ph-C(H)<, –$SO_2$-C(H)<, $H_2C$=CH-C(*H*)<), [2.43, 2.33, 2.32] (3H, s, Ts-$CH_3$), [1.74, 1.70, 1.59, 1.57] (3H, dd, *J* 6.5, 1.5 Hz, -CH=CH-C$H_3$, 4× diast.); $\delta_C$ 144.2 (×2), 143.1, 143.0, 141.8, 141.7, 140.6, 140.5, 140.0, 138.9, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 137.4, 136.5, 131.5, 130.6, 129.4, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 128.0, 127.6, 127.4 (×2), 127.2, 126.9, 126.6, 117.2, 117.1, 116.9, 115.8, 115.5, [73.7, 73.6, 73.4] (-$SO_2$-CH<), [50.1, 50.0, 49.9] (Ph-CH<), [46.7 (×2), 46.6] ($H_2C$=CH-*C*H<), [21.6, 21.5] (Ts-$CH_3$), [18.2, 18.0] (-CH=CH-*C*$H_3$); *m/z* (CI) 384 $[M+NH_4]^+$, 367 $[M+H]^+$, 348, 279, 210, 174, 131, 117, 95 (Found: $[M+H]^+$, 367.1721. $C_{23}H_{26}O_2S$ requires $[M+H]^+$, 367.1732).

**386:** $R_f$ 0.31 (20% EtOAc–petrol); $\nu_{max}$ (film) 3028, 3060, 3028, 1739, 1637, 1597, 1495, 1448, 1379, 1325, 1306, 1213, 1146, 1084, 966, 924, 847, 816, 744, 708, 694, 660 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.76, 7.75] (2H, dd, *J* 8.5, 2.0 Hz, *o*-$SO_2$Ar, 2× diast.), 7.36-7.25 (7H, m, other Ar-H), [6.57, 6.58] (1H, dt, *J* 16.0, 1.5 Hz, Ph-CH=, 2× diast.), [6.05, 6.08] (1H, dt, *J* 16.0, 6.5 Hz, Ph-CH=C*H*-, 2× diast.), [5.90, 5.73] (1H, ddd, *J* 17.5, 10.0, 7.5 Hz, $H_2C$=C*H*-, 2× diast.), [5.58 (dqd, *J* 14.5, 6.5, 1.0 Hz), 5.53 (dqd, *J* 15.0, 6.5, 1.0 Hz)] (1H, $H_3C$-C*H*=, 2× diast.), [5.38 (ddq, *J* 14.0, 7.5, 1.5 Hz), 5.33 (ddq, *J* 15.5, 8.5, 1.5 Hz)] (1H, $H_3C$-CH=C*H*-, 2× diast.), [5.16, 5.09] (1H, dt, *J* 17.0, 1.0 Hz, *trans* -CH=C$H_2$, 2× diast.), [5.16, 5.04] (1H, dt, *J* 10.5, 1.0 Hz, *cis* -CH=C$H_2$, 2× diast.), [4.64 (ddd *J* 6.5, 1.0, 1.0 Hz), 4.61 (ddd, *J* 6.5, 2.5, 1.5 Hz)] (2H, -$CH_2$O-, 2× diast.), 4.07 (1H, d, *J* 9.5 Hz, -OCO-CH(Ts)-), 3.62-3.51 (1H, m, $H_3C$-CH=CH-C*H*(CH=$CH_2$)-, 2× diast.), [2.35, 2.36] (3H, s, Ts-$CH_3$, 2× diast.), [1.67, 1.56] (3H, dd, *J* 6.5, 1.5 Hz, =CH-C$H_3$, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 165.2 (C=O), 145.3, 145.2, 136.2, 136.0, 135.7, 135.6, 135.2, 135.1, 129.6, 129.5, 129.4, 129.3, 129.2, 128.7, 128.3 (×2), 128.0, 127.4, 126.7, 121.9, 117.5, 117.4, [74.4, 74.3] (-OCO-*C*H(Ts)-, 2× diast.), [66.5, 66.4] (-$CH_2$O-, 2× diast.), 46.3 ($H_3C$-CH=CH-*C*H(CH=$CH_2$)-, 2× diast.), 21.7 (Ts-$CH_3$), [18.1, 18.0] (=CH-*C*$H_3$, 2× diast.); *m/z* (CI) 428 $[M+NH_4]^+$, 268, 255, 197, 174, 156, 139, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 95 (Found: $[M+NH_4]^+$, 428.1897. $C_{24}H_{26}O_4S$ requires $[M+NH_4]^+$, 428.1896).

**3-(4-Methoxyphenyl)-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (383), diastereoisomers as shown and (2*R**,3*S**)-Cinnamyl 3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate (384)**

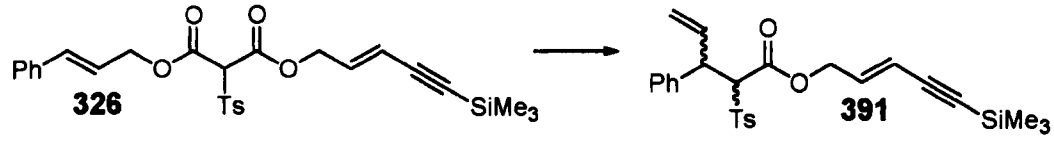



To a solution of **327** (288 mg, 0.553 mmol, 1.0 equiv) in PhMe (5 mL) was added potassium acetate (approx 5 mg, 0.06 mmol, 0.1 equiv) and *N,O*-bis(trimethylsilyl)acetamide (0.27 mL, 1.11 mmol, 2.0 equiv). The reaction mixture was heated to reflux for 14 h, concentrated under reduced pressure and purified by chromatography (5→12% EtOAc–petrol) to give *3-(4-methoxyphenyl)-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **383** (130 mg, 54%) as a pale yellow oil and as an inseparable mixture of diastereoisomers. Also isolated was *cinnamyl 3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **384** (70 mg, 27%) as a pale yellow oil and as an inseparable mixture of diastereoisomers.

**383** was recrystallised from hexane/EtOAc to give a white solid, a mixture of diastereoisomers (57 mg, 24%); $R_f$ 0.23 (20% EtOAc–petrol); $\nu_{max}$ (film) 3076, 3062, 3028, 1635, 1608, 1599, 1512, 1495, 1454, 1315, 1302, 1290, 1250, 1180, 1144, 1084, 1034, 997, 920, 831, 814, 742, 725, 702, 667, 650 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.26-6.95 (11H, m, Ar-H), [6.87, 6.79] (2H, d, *J* 8.5 Hz, *o*-MeOAr, diast.), 6.66-6.51 (2H, m, *o*-MeO-Ar, -C*H*=$CH_2$), 6.25-6.13 (1H, m, -C*H*=$CH_2$), 5.35-5.12 (4H, m, -CH=C$H_2$), 4.29-4.21 (1H, m, Ts-C*H*<), 4.11-4.02 (2H, m, 2× $H_2C$=CH-C*H*<), [3.80, 3.76] (3H, s, Ar-$OCH_3$), 2.36 (3H, s, Ts-$CH_3$); $\delta_C$ 158.3, 158.0, 143.4, 143.2, 142.6, 141.0, 138.8, 138.6, 137.8, 137.2, 136.8, 136.2, 134.4, 132.7, 129.2, 129.1, 128.9, 128.6, 128.3 (×2), 127.9, 127.8, 127.6, 126.5, 126.4, 118.9, 118.4, 118.2, 117.7, 113.8, 74.2 (Ts-C(H)<), 55.3 (Ar-$OCH_3$), [49.8, 49.2, 48.8, 48.0] (Ph-CH<, MeO-$C_6H_4$-CH<), 21.5 (Ts-$CH_3$); *m/z* (CI) 450 $[M+NH_4]^+$, 304, 279, 174, 163, 161, 154, 147, 137, 131, 101, 91, 74, 52 (Found: $[M+NH_4]^+$, 450.2086. $C_{27}H_{28}O_3S$ requires $[M+NH_4]^+$, 450.2103).

**384** was recrystallised from hexane/EtOAc to give a white crystalline solid as a single diastereoisomer, *(2R*,3S*)-cinnamyl 3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate* (34 mg, 13%), determined by X-ray crystallography; mp 116–118 °C; $R_f$ 0.16 (20% EtOAc–petrol); $\nu_{max}$ (film) 3080, 3059, 3028, 1738, 1637, 1608, 1597, 1512, 1495, 1448, 1377, 1323, 1306, 1279, 1259, 1178, 1142, 1084, 1032, 966, 918, 862, 816, 779, 729, 708, 692, 668, 650 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.34-7.23 (7H, m, other Ar-H), 7.06 (2H, dt, *J* 9.5, 2.5 Hz, *m*-MeOAr), 6.73 (2H, dt, *J* 9.5, 2.5 Hz, *o*-MeOAr), 6.33 (1H, d, *J* 16.0 Hz, Ph-CH=), 6.17 (1H, ddd, *J* 18.0, 9.0, 7.5 Hz, -C*H*=$CH_2$), 5.66 (1H, dt, *J* 16.0, 7.0 Hz, Ph-CH=C*H*-), 5.16 (1H, d, *J* 9.5 Hz, *cis* -CH=C$H_2$), 5.13 (1H, d, *J* 17.5 Hz, *trans* -CH=C$H_2$), 4.46 (1H, d, *J* 11.5 Hz, -OCO-C(H)Ts-), [4.37, 4.28] (2× 1H, ddd, *J* 12.5, 7.0, 1.0 Hz, -$CH_2O$-), 4.05 (1H, dd, *J* 11.5, 8.5 Hz, MeO-$C_6H_4$-C*H*<), 3.62 (3H, s, Ar-$OCH_3$), 2.38 (3H, s, Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.0 (C=O), 158.8 (4° MeOAr), 145.4 (4° -$SO_2Ar$), 137.1 (-*C*H=$CH_2$), 135.9 (4° Ph), 135.0 (4° -$SO_2Ar$), 134.8 (Ph-CH=), 131.1 (4° MeOAr), 129.7 (3° -$SO_2Ar$), 129.5 (3° -$SO_2Ar$), 129.1 (3° MeOAr), [128.6, 128.2, 126.6] (3° Ph), 121.7 (Ph-CH=*C*H-), 117.7 (=$CH_2$), 114.2 (3° MeOAr), 75.6 (-OCO-*C*(Ts)H-), 66.3 (-$CH_2O$-), 55.1 (Ar-$OCH_3$), 48.4 (MeO-$C_6H_4$-*C*H<), 21.7 (Ts-$CH_3$); *m/z* (CI) 494 $[M+NH_4]^+$, 450, 340, 334, 279, 224, 174, 161, 147, 134 $[C_9H_{10}O]^+$, 117 $[C_9H_9]^+$, 101 (Found: $[M+NH_4]^+$, 494.1983. $C_{28}H_{28}O_5S$ requires $[M+NH_4]^+$, 494.2001).

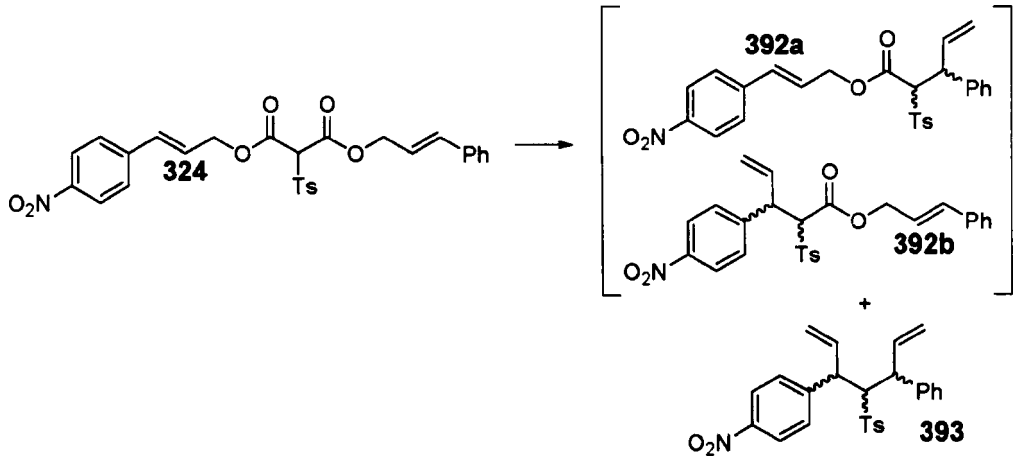
**(2*R**,3*R**)-(*E*)-5-(Trimethylsilyl)pent-2-en-4-ynyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate and (2*R**,3*S**)-(*E*)-5-(Trimethylsilyl)pent-2-en-4-ynyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate (391)**




To a solution of **326** (143 mg, 0.279 mmol, 1.0 equiv) in $CH_2Cl_2$ (3 mL) was added potassium acetate (3 mg, 0.028 mmol, 0.1 equiv). *N,O*-bis(trimethylsilyl)acetamide (70 µL, 0.279 mmol, 1.0 equiv) was added by syringe. The reaction mixture was stirred at rt for 16 h before concentration under reduced pressure and purification by column chromatography (20% EtOAc–petrol) to give *(E)-5-(trimethylsilyl)pent-2-en-4-ynyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **391** (102 mg, 82%) as a yellow oil and as

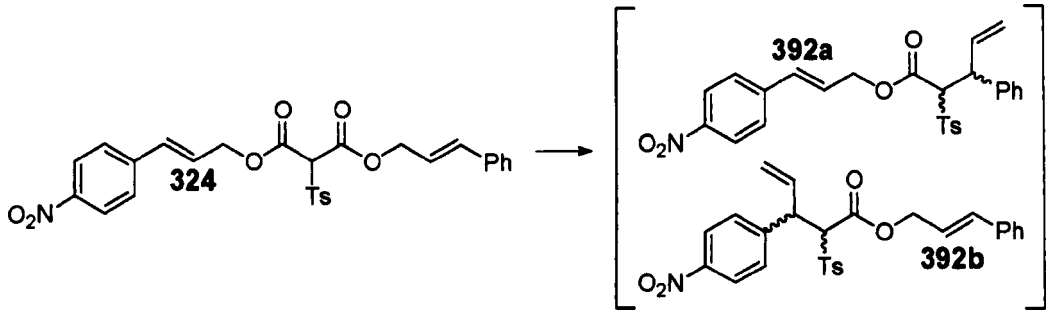
an inseparable mixture of diastereoisomers; $R_f$ 0.32 (20% EtOAc–petrol); $\nu_{max}$ (film) 3064, 3032, 2179, 2135, 1743, 1637, 1597, 1493, 1454, 1406, 1377, 1329, 1306, 1277, 1252, 1205, 1184, 1146, 1084, 987, 951, 926, 847, 760, 739, 702, 654 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.79 (d, *J* 8.0 Hz, *o*-$SO_2Ar$ for 1 diast.), 7.38-7.08 (m, other Ar-H)] (9H), [6.18 (ddd, *J* 18.0, 9.0, 7.5 Hz, 1st diast.), 5.89 (ddd, *J* 18.0, 9.0, 8.0 Hz, 2nd diast.)] (1H, $H_2C$=C*H*-), [6.07 (1st diast.), 5.54 (2nd diast.)] (1H, dt, *J* 16.0, 6.0 Hz, -$OCH_2$-C*H*=), [5.73 (1st diast.), 5.29 (2nd diast.)] (1H, d, 16.0 Hz, -$OCH_2$-CH=C*H*-), 5.19-5.05 (2H, m, -CH=C$H_2$), 4.60 (2H for 1st diast., d, *J* 6.0 Hz, -$OCH_2$-), [4.47 (d, *J* 8.0 Hz), 4.49 (d, *J* 7.0 Hz)] (1H, -$SO_2$-CH<, 2× diast.), 4.22-4.05 (m, 1H + 2H for 2nd diast., Ph-CH< for 2× diast., -$OCH_2$- for 2nd diast.), [2.46, 2.37] (3H, s, Ts-$CH_3$), 0.20 (9H, s, -$Si(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 164.7 (×2, C=O), [145.6, 144.8] (*p*-$SO_2Ar$), [139.0, 137.8] (*i*-Ph), [136.6 (1st diast.), 136.4 (2nd diast.)] ($H_2C$=*C*H-), [136.0 (1st diast.), 135.6 (2nd diast.)] (-$OCH_2$-*C*H=), [135.8, 134.8] (*i*-$SO_2Ar$), 129.7 (3°), 129.6 (3°), 129.4 (3°), 128.9 (3°), 128.7 (3°), 128.6 (3°), 128.3 (3°), 127.9 (3°), 127.7 (3°), 127.4 (3°), [118.1, 117.9] (-CH=*C*$H_2$), [114.3 (1st diast.), 113.8 (2nd diast.)] (-$OCH_2$-CH=*C*H-), 102.2 (-$OCH_2$-CH=CH-*C*≡), [96.7, 96.6] (-$OCH_2$-CH=CH-C≡*C*-), [75.3, 74.8] (-$SO_2$CH<), [65.4 (1st diast.), 64.9 (2nd diast)] (-$OCH_2$-), [49.3, 49.3] (Ph-CH<), [21.8, 21.7] (Ts-$CH_3$), –0.2 (-$Si(CH_3)_3$); *m/z* (CI) 484 $[M+NH_4]^+$, 467 $[M+H]^+$, 311, 182, 157, 141, 117, 91 (Found: $[M+NH_4]^+$, 484.1966. $C_{26}H_{30}O_4SSi$ requires $[M+NH_4]^+$, 484.1978).

**p-Nitrocinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate (392a) and Cinnamyl 3-(4-nitrophenyl)-2-(toluene-4-sulfonyl)pent-4-enoate (392b), inseparable mixture, diastereoisomers as shown.**
**3-(4-Nitrophenyl)-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (393), diastereoisomers as shown**




*Procedure A*

To **324** (197 mg, 0.368 mmol, 1.0 equiv) and potassium acetate (4 mg, 0.04 mmol, 0.1 equiv) was added PhMe (3 mL) and *N,O*-bis(trimethylsilyl)acetamide (179 μL, 0.736 mmol, 2.0 equiv). The reaction mixture was heated to reflux for 10 h, concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give *p-nitrocinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **392a** and *cinnamyl 3-(4-nitrophenyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **392b** (12 mg, 6%) as a yellow gum and as an inseparable mixture of regio- and diastereoisomers. Also isolated was *3-(4-nitrophenyl)-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **393** (19 mg, 12%) as a yellow gum and as a mixture of 4 diastereoisomers. This was recrystallised from TBME to give 6 mg (4%), 2 diastereoisomers by NMR.




*Procedure B*

To **324** (255 mg, 0.476 mmol, 1.0 equiv) and potassium acetate (5 mg, 0.048 mmol, 0.1 equiv) was added $CH_2Cl_2$ (5 mL) and *N,O*-

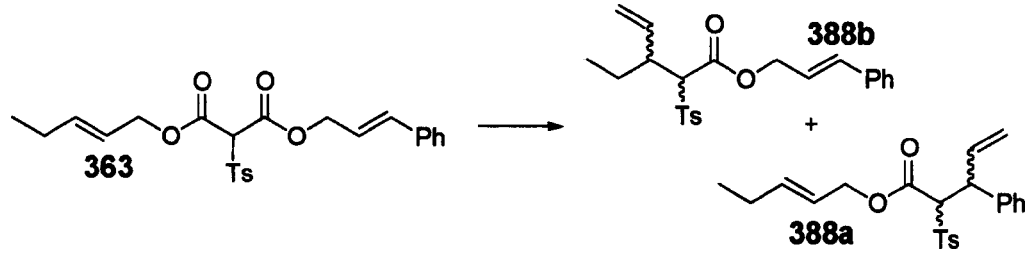
bis(trimethylsilyl)acetamide (116 μL, 0.476 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by column chromatography (30% EtOAc–petrol) to give *p-nitrocinnamyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **392a** and *cinnamyl 3-(4-nitrophenyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **392b** (67 mg, 29%) as a yellow gum and as an inseparable mixture of regio- and diastereoisomers. Ester **392a** was the major regioisomer in a ratio **392a**:**b** 3:1.

**392:** $R_f$ 0.44 (30% EtOAc–petrol); $\nu_{max}$ (film) 3064, 3030, 3007, 1741, 1597, 1518, 1493, 1454, 1377, 1344, 1327, 1304, 1290, 1205, 1184, 1146, 1111, 1084, 1016, 972, 914, 860, 814, 733, 702, 665, 650 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [8.22, 8.20] (2H, d, *J* 8.5 Hz, *o*-$NO_2Ar$), [7.84 (d, *J* 8.0 Hz), 7.54 (d, *J* 8.5 Hz), 7.44-7.08 (m)] (11H, *o*-$SO_2Ar$, *m*-$NO_2Ar$, *m*-$SO_2Ar$, Ph-H), 6.79 (1H **392a** min. diast., d, *J* 16.0 Hz, $NO_2Ar$-C*H*=), 6.44 (1H **392b** maj. diast., d, *J* 16.0 Hz, Ph-C*H*=), 6.42 (1H **392a** maj. diast. and **392b** min. diast., d, *J* 16.0 Hz, $NO_2Ar$-C*H*= and Ph-C*H*=), [6.20-6.08, 5.94-5.91] (1H, m, -C*H*=$CH_2$), [5.99-5.97, 5.91-5.79, 5.44-5.36] (1H, m, $NO_2Ar$-CH=C*H*- and Ph-CH=C*H*-), [5.18 (d, *J* 9.5 Hz), 5.06 (d, *J* 10.0 Hz)] (1H, *cis* -CH=C$H_2$), 5.15 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), [4.93-4.74 (m), 4.45 (dd, *J* 13.5, 6.0 Hz), 4.35 (dd, *J* 13.5, 6.0 Hz)] (2H, -$OCH_2$-), [4.59 (d, *J* 4.0 Hz), 4.57 (d, *J* 3.5 Hz), 4.54 (d, *J* 4.0 Hz)] (1H, Ts-CH<), [4.25-4.12 (m), 4.06 (dd, *J* 11.0, 4.0 Hz)] (1H, Ts-CH-C*H*<), [2.46, 2.44, 2.37, 2.36] (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 164.9, 147.3, 145.6, 144.7, 142.5, 142.4, 142.3, 142.1, 139.3, 139.2, 137.6, 136.6 (×2), 136.0, 134.9, 132.2, 132.0, 131.8, 131.5, 129.8, 129.6, 129.4, 128.9 (×2), 128.7, 128.6, 128.4, 128.0, 127.5, 127.4, 127.3, 127.2, 127.0, 126.7, 124.3, 124.1, 123.9, 123.8, 123.7, 118.2, 117.8, 77.3, 75.3, 75.0, 65.9, 65.4, 62.5, 62.0, 49.5, 49.4, 29.7, 22.7, 21.8, 21.6; *m/z* (CI) 509 $[M+NH_4]^+$, 437, 419, 293, 236, 219 (Found: $[M+NH_4]^+$, 509.1748. $C_{27}H_{25}NO_6S$ requires $[M+NH_4]^+$, 509.1746).

**393:** $R_f$ 0.29 (20% EtOAc–petrol); $\nu_{max}$ (film) 3078, 3030, 1597, 1518, 1498, 1450, 1346, 1313, 1286, 1142, 1120, 1084, 922, 852, 814, 748, 698, 669 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [8.14 (d, *J* 8.5 Hz), 7.88 (d, *J* 8.5 Hz), 7.42 (d, *J* 8.5 Hz)] (15H, $NO_2Ar$, $SO_2Ar$, Ph-H), [6.72 (dt, *J* 16.5, 9.5 Hz), 6.40 (dt, *J* 16.0, 10.0 Hz), 6.15 (dt, *J* 17.0, 10.0 Hz)] (2H, 2× -C*H*=$CH_2$), 5.52-5.21 (4H, m, 2 ×-CH=C$H_2$), 4.39-4.04 (3H, m, -$SO_2$CH<, Ph-CH<, *p*-$O_2N$-$C_6H_4$-C*H*<), [2.37, 2.35] (3H, s, Ts-$CH_3$, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 148.4, 146.4, 144.2, 141.4, 138.3, 136.8, 136.0, 129.3, 129.1, 128.7, 128.5, 128.3, 127.9, 127.7,

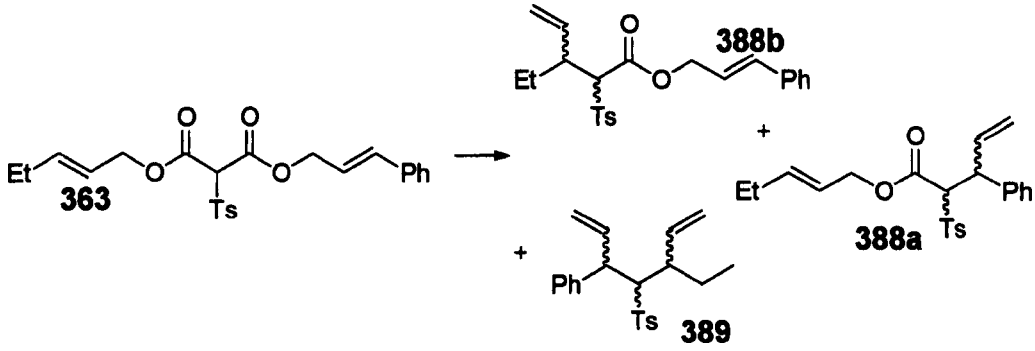
127.4, 126.8, 123.4, 123.3, 119.8, 119.0, 73.6, 50.1, 49.6, 49.0, 48.5, 21.5; *m/z* (CI) 465 $[M+NH_4]^+$, 448 $[M+H]^+$, 435, 304, 291, 174 (Found: $[M+NH_4]^+$, 465.1837. $C_{26}H_{25}NO_4S$ requires $[M+NH_4]^+$, 465.1846).

**(2*R**,3*R**)-Cinnamyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate, (2*R**,3*S**)-Cinnamyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate (240) and (2*R**,3*R**)-(*E*)-Pent-2-enyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate, (2*R**,3*S**)-(*E*)-Pent-2-enyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate (388) (inseparable mixture).**
**3-Ethyl-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene (389), diastereoisomers as shown**




*Procedure A*

To **363** (250 mg, 0.565 mmol, 1.0 equiv) and potassium acetate (5 mg, 0.06 mmol, 0.1 equiv) was added PhMe (5 mL) and *N,O*-bis(trimethylsilyl)acetamide (0.275ml, 1.13 mmol, 2.0 equiv). The reaction mixture was heated to 60 °C for 12 h, concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give an inseparable mixture of *cinnamyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate* **388b** and *(E)-pent-2-enyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **388a** (190 mg, 84%) as a yellow oil and as an inseparable mixture of diastereoisomers;




*Procedure B*

To **383** (156 mg, 0.353 mmol, 1.0 equiv) and potassium acetate (4 mg, 0.04 mmol, 0.1 equiv) was added PhMe (3 mL). *N,O*-bis(trimethylsilyl)acetamide

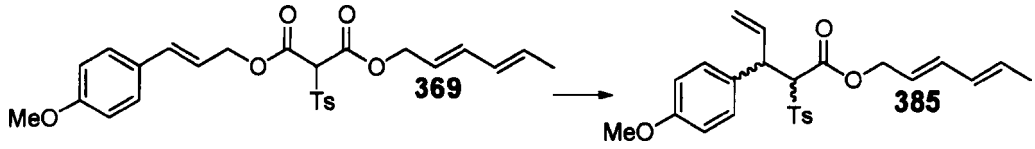
(171 μL, 0.706 mmol, 2.0 equiv) was added and the reaction mixture was heated to reflux for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give *3-ethyl-5-phenyl-4-(toluene-4-sulfonyl)hepta-1,6-diene* **389** (36 mg, 29%) as a yellow oil and as an inseparable mixture of diastereoisomers; Also isolated was an inseparable mixture of *cinnamyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate* **388b** and *(E)-pent-2-enyl 3-phenyl-2-(toluene-4-sulfonyl)pent-4-enoate* **388a** (22 mg, 16%).

**388:** $R_f$ 0.34 (20% EtOAc–petrol); $\nu_{max}$ (film) 3082, 3062, 3030, 1739, 1671, 1639, 1597, 1493, 1454, 1415, 1401, 1379, 1327, 1306, 1279, 1205, 1182, 1146, 1084, 1018, 970, 926, 814, 760, 746, 702, 663 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.84-7.78 (2H, m, *o*-$SO_2Ar$), 7.42-7.11 (7H, m, other Ar-H), [6.60, 6.54] (1H for **388b**, d, *J* 16.5 Hz, Ph-CH=, 2× diast. of **388b**), 6.25-4.92 (5H, m, olefinic **388b**, **388a**), [4.68, 4.54, 4.50] (2H, d, *J* 6.5 Hz, -$OCH_2$- for **388b**, **388a**), 4.24-4.00 (2H, m, -$SO_2CH$<, Ph-CH< for **388a**), 3.72-3.49 (1H, m, $SO_2CH$< for **388b**), 2.89-2.75 (1H, $H_3C$-$CH_2$-C*H*< for **388b**), [2.46, 2.38, 2.35, 2.33] (3H, s, Ts-$CH_3$ for 2× diast. each of **388b, 388a**), [2.09, 1.93] (2H, t, *J* 7.0 Hz, $H_3C$-C$H_2$-, 2× diast. of **388a**), 1.59-1.11 (2H, m, $H_3C$-C$H_2$, 2× diast. of **388b**), 1.05-0.80 (3H, m, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [165.7, 165.3, 165.0, 164.9] (C=O for 2× diast. of **388b**, **388a**), [145.4, 145.3, 145.2, 144.6] (4° -$SO_2Ar$ for 2× diast. of **388b**, **388a**), 139.3, 139.1, 138.5, 138.0, 136.9, 136.6, 136.5, 136.0, 136.0, 135.5, 135.3, 135.1, 129.8, 129.6, 129.5, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.4, 127.3, 126.7, 121.9, 121.5, 118.9, 118.5, 117.9, 117.8, [75, 75.0, 74.9, 74.3] (-$SO_2CH$< for 2× diast. of **388b**, **388a**), [67.0, 66.5, 66.3] (-$CH_2O$-), [49.3, 49.3] (Ph-CH< for 2× diast. of **388a**), [44.8, 44.6] ($H_3C$-$CH_2$-CH< for 2× diast. of **388b**), [25.3, 25.2] ($H_3C$-$CH_2$-), [21.7, 21.6] (Ts-$CH_3$), [13.1, 13.0] ($H_3C$-$CH_2$- for 2× diast. of **388a**), [11.2, 11.0] ($H_3C$-$CH_2$- for 2× diast. of **388b**); *m/z* (CI) 416 $[M+NH_4]^+$, 372 $[M+NH_4-CO_2]^+$, 348, 316, 304, 262, 256, 237 (Found: $[M+NH_4]^+$, 416.1896. $C_{23}H_{26}O_4S$ requires $[M+NH_4]^+$, 416.1896).

**389:** $R_f$ 0.27 (20% EtOAc–petrol); $\nu_{max}$ (film) 3076, 3028, 1637, 1599, 1493, 1454, 1417, 1379, 1344, 1315, 1300, 1286, 1227, 1142, 1084, 999, 918, 814, 717, 702, 656 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.77-7.72 (2H, m, *o*-$SO_2Ar$), 7.34-6.91 (7H, m, other Ar-H), 6.36-5.55 (2H, m, -C*H*=$CH_2$), 5.27-4.77 (4H, m, =$CH_2$), 4.09-3.93 (1H, m, -$SO_2CH$<), 3.77-3.70 (1H, m, Ph-CH<), 2.91-2.84 (1H, m, $H_3C$-$CH_2$-C*H*<), [2.46, 2.46, 2.35, 2.33] (3H, s, Ts-$CH_3$, 4× diast.),

[1.99-1.81, 1.69-1.54, 1.52-1.46] (2H, m, $H_3C$-C$H_2$-, 4× diast.), [0.91, 0.75, 0.62] (3H, t, *J* 7.5 Hz, -$CH_2$-C$H_3$, 4× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 144.1 (×2), 143.0, 142.9, 141.9, 140.9, 140.6, 139.6, 139.1, 139.0, 138.8 (×2), 138.7, 138.6, 138.4, 138.0, 129.4, 129.2, 129.1, 128.9 (×2), 128.8, 128.3 (×2), 128.2, 128.0, 127.9, 127.4, 127.3, 126.9, 126.5, 118.0, 117.5, 116.9, 116.8, 116.7, [73.5, 73.1, 72.3] (-$SO_2$CH<), [50.5, 50.3, 50.0, 49.7] (Ph-CH<, 4× diast.), [46.5, 46.2, 46.2, 45.7] ($H_3C$-$CH_2$-CH<, 4× diast.), [26.0, 24.6, 23.2, 22.6] ($H_3C$-$CH_2$-, 4× diast.), [21.6, 21.5] (Ts-$CH_3$), [12.9, 12.7, 12.5] (-$CH_2CH_3$) *m/z* (CI) 372 $[M+NH_4]^+$, 355 $[M+H]^+$, 284, 276, 237, 198 (Found: $[M+H]^+$, 355.1726. $C_{22}H_{26}O_2S$ requires $[M+H]^+$, 355.1732).

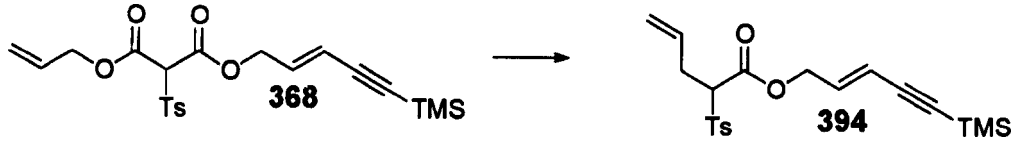
**(2*E*,4*E*)-Hexa-2,4-dienyl (2*R**,3*R**)-3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate and (2*E*,4*E*)-Hexa-2,4-dienyl (2*R**,3*S**)-3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate (385)**




To **369** (64 mg, 0.132 mmol, 1.0 equiv) was added potassium acetate (1 mg, 0.013 mmol, 0.1 equiv). The reaction vessel was purged with $N_2$, then $CH_2Cl_2$ (1.3 mL) was introduced by syringe. The reaction mixture was cooled to 0 °C and *N,O*-bis(trimethylsilyl)acetamide (33 µL, 0.132 mmol, 1.0 equiv) was added by syringe. The reaction mixture was stirred at 0 °C for 2 h, concentrated under reduced pressure and purified by column chromatography (12.5% EtOAc–hexane + 3 drops of $NEt_3$ Per 1 L eluent) to give *(2E,4E)-hexa-2,4-dienyl 3-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **385** (55 mg, 95%) as a colourless oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.40 (20% EtOAc–hexane); $\nu_{max}$ (film) 1736, 1608, 1597, 1511, 1443, 1375, 1323, 1304, 1247, 1178, 1141, 1082, 1032, 990, 923, 814 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *o*-$SO_2$Ar, maj. diast.), 7.40 (2H, d, *J* 8.5 Hz, *o*-$SO_2$Ar, min. diast.), 7.31 (2H, d, *J* 8.0 Hz, *m*-$SO_2$Ar, maj. diast.), 7.12 (2H, d, *J* 8.5 Hz, *m*-$SO_2$Ar, min. diast.), 7.03 (2H, dt, *J* 8.5, 2.0 Hz, *m*-MeOAr, maj. diast.), 6.99 (2H, dt, *J* 9.0, 2.0 Hz, *m*-MeOAr, min. diast.), 6.76 (2H, dt, *J* 8.5, 2.0 Hz, *o*-MeOAr, maj. diast.), 6.69 (2H, dt, *J* 9.0, 2.0 Hz, *o*-MeOAr, min. diast.), 6.25-5.29 (5H, m, olefinic methine H), 5.14 (1H, d, *J* 10.5 Hz, *cis* CH=C$H_2$, 2× diast.), 5.10 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$, 2× diast.), 5.04-4.96 (1H, m, -OC*H*H-, maj, diast.), 4.61-4.56 (1H, m, -OCH*H*-,

maj, diast.), 4.42 (1H, d, *J* 10.5 Hz, -OC(O)-C(Ts)*H*-, min. diast.), 4.40 (1H, d, *J* 11.5 Hz, -OC(O)-C(Ts)*H*-, maj. diast.), 4.19-3.99 (3H min. diast + 1H maj. diast., -$OCH_2$- min. diast, MeO-$C_6H_4CH$< 2× diast.), [3.75 (min. diast.), 3.73 (maj. diast.)] (3H, s, -$OCH_3$), [2.44 (maj. diast.), 2.37 (min. diast.)] (3H, s, Ts-$CH_3$), 1.76 (3H, t, *J* 7.0 Hz, =CH-$CH_3$, 2× diast.); $\delta_C$ (100 MHz, $CDCl_3$) [165.0, 164.9] (C=O, 2× diast.), [158.8, 158.7] (4° MeOAr, 2× diast.), [145.3, 144.4] (4° $SO_2Ar$, 2× diast.), 137.0 (3°), 136.7 (3°), 136.0 (3°), 135.9 (4°), 135.4 (3°), 134.9 (4°), 131.8 (3°), 131.4 (3°), 131.1 (4°), 130.2 (3°), 129.7 (4°), 129.7 (3°), 129.4 (3°), 129.3 (3°), 129.2 (3°), 129.0 (3°), 128.7 (3°), 127.9 (3°), 122.4 (3°), 122.2 (3°), [117.6, 117.4] (=$CH_2$, 2× diast.), 114.1 (3°), 114.0 (3°), 113.9 (3°), [75.5, 75.0] (-OC(O)-*C*(Ts)H-, 2× diast.), [66.7, 66.2] (-$OCH_2$-, 2× diast.), 55.1 (×2, -$OCH_3$, 2× diast.), [48.4, 48.3] (MeO-$C_6H_4$-*C*(H)<, 2× diast.), [21.7, 21.6] (Ts-$CH_3$, 2× diast.), 18.1 (=CH-$CH_3$); *m/z* (–ve ESI, +ve ESI) 439 $[M-H]^-$, 351, 281, 226 (Found: 903.3212. $C_{25}H_{28}O_5S$ requires $[2M+Na]^+$ 903.3206).

**(±)-(*E*)-5-(Trimethylsilyl)pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)pent-4-enoate (394)**




To **368** (43 mg, 0.099 mmol, 1.0 equiv) in a microwave vial was added potassium acetate (1 mg, 0.001 mmol, 0.1 equiv). The vial was purged with $N_2$, then $CH_2Cl_2$ (2.5 mL) was introduced by syringe. *N,O*-bis(trimethylsilyl)acetamide (49 µL, 0.198 mmol, 2.0 equiv) was added by syringe and the reaction mixture was heated under microwave conditions to 130 °C for 5 min. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (10% EtOAc-hexane) to give *(±)-(E)-5-(trimethylsilyl)pent-2-en-4-ynyl 2-(toluene-4-sulfonyl)pent-4-enoate* **394** (10 mg, 26%) as a colourless oil; $R_f$ 0.24 (10% EtOAc-hexane); $\nu_{max}$ (film) 2136, 1743, 1643, 1597, 1440, 1376, 1328, 1305, 1250, 1169, 1147, 1084, 951, 924, 843, 814, 760 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.97 (1H, dt, *J* 16.0, 6.0 Hz, ≡C-CH=C*H*-), 5.71-5.60 (1H, m, $H_2C$=C*H*-), 5.62 (1H, d, *J* 16.0 Hz, ≡C-C*H*=CH-), 5.11 (1H, dd, *J* 17.0, 1.5 Hz, *trans* -CH=C$H_2$), 5.09 (1H, dd, *J* 10.0, 1.0 Hz, *cis* -CH=C$H_2$), 4.56 (1H, ddd, *J* 13.0, 5.0, 1.5 Hz, -C*H*HO-), 4.51 (1H, ddd, *J* 13.0, 5.0, 2.0 Hz, -CH*H*O-), 3.98 (1H, dd, *J* 11.5, 4.0 Hz, -OC(O)-CH(Ts)-), 2.85-2.78 (1H, m, $H_2C$=CH-C*H*H-), 2.69 (1H, ddd, *J* 14.0, 11.5, 7.5

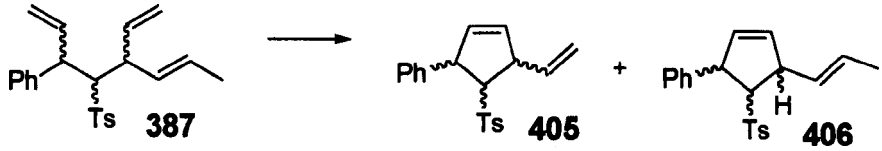
Hz, $H_2C$=CH-CH*H*-), 2.46 (3H, s, Ts-$CH_3$), 0.19 (9H, s, -Si($CH_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.0 (C=O), 145.6 (4°), 135.8 (3°), 134.0 (4°), 131.7 (3°), 129.8 (3°), 129.4 (3°), 119.2 (=$CH_2$), 114.4 (3°), 102.0 ($Me_3$Si-C≡*C*-), 96.9 ($Me_3$Si-*C*≡), 70.1 (-OCO-*C*H(Ts)-), 65.2 (-$CH_2$O-), 30.8 ($H_2C$=CH-C*H*$_2$-), 21.7 (Ts-$CH_3$), –0.2 (-Si($CH_3$)$_3$); *m/z* (CI) 413 $[M+Na]^+$, 391 $[M+H]^+$, 235, 137 (Found: 413.1211. $C_{20}H_{26}O_4SSi$ requires $[M+Na]^+$ 413.1213).

- **3.3.9 Ring-closing metathesis**

**(3*R**,5*R**)-3,5-Diphenyl-4-cyclopentenyl 4-methylphenyl sulfone (375)**


To a solution of dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (2.6 mg, 0.003 mmol, 5 mol %) in $CH_2Cl_2$ (2 mL) was added **374a** (25 mg, 0.062 mmol, 1.0 equiv) in $CH_2Cl_2$ (7 mL) under Ar. The reaction mixture was stirred at rt for 1 h then at reflux for 16 h. Concentration under reduced pressure and chromatography (1→8% EtOAc–petrol) gave *(3R*,5R*)-3,5-diphenyl-4-cyclopentenyl 4-methylphenyl sulfone* **375** (7 mg, 30%) as a colourless gum; $R_f$ 0.25 (20% EtOAc–petrol); $\nu_{max}$ (film) 3060, 3029, 1597, 1492, 1453, 1403, 1379, 1349, 1316, 1301, 1288, 1263, 1182, 1143, 1086, 1030, 962, 911, 871, 850, 813, 733, 704, 654 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.26-7.10 (10H, m, Ar-H), 7.04 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 6.96 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.93-5.79 (2H, m, -CH=CH-), 4.64 (1H, dd, *J* 7.0, 1.5 Hz, Ph-C(H)<), 4.54 (1H, dd, *J* 9.0, 1.5 Hz, Ph-C(H)<), 4.21 (1H, dd, *J* 9.0, 7.0 Hz, -$SO_2$C(H)<), 2.30 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 143.5 (4°), 141.4 (4°), 136.8 (4°), 136.3 (4°), 134.2 (3°), 133.4 (3°), 130.4 (3°), 129.2 (3°), 128.5 (3°), 127.9 (3°), 127.8 (3°), 127.5 (3°), 126.9 (3°), 74.0 (-$SO_2$CH<), [53.1, 52.5] (Ph-C(H)<), 21.5 (Ts-$CH_3$); *m/z* (CI) 392 $[M+NH_4]^+$, 296 , 279, 265, 219, 218, 188, 74, 52 (Found: $[M+NH_4]^+$, 392.1691. $C_{24}H_{22}O_2S$ requires $[M+NH_4]^+$, 392.1684)

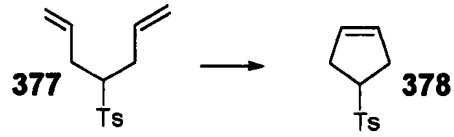
**3-Ethenyl-5-phenyl-4-cyclopentenyl 4-methylphenyl sulfone (405), diastereoisomers as shown and (*E*)-3-Phenyl-5-(prop-1-enyl)-4-cyclopentenyl 4-methylsulfone (406), diastereoisomers as shown**




To benzylidene bis(tricyclohexylphosphine)dichlororuthenium (5 mg, 0.006 mmol, 0.05 equiv) under Ar was added **387** (36 mg, 0.098 mmol, 1.0 equiv) as a solution in $CH_2Cl_2$ (1.3 mL). The reaction mixture was stirred at rt for 16 h and at reflux for 2½ h, concentrated under reduced pressure and purified by

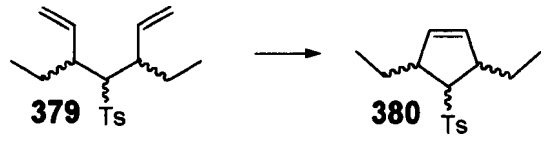
chromatography (EtOAc 7.5-12.5%–petrol) to give an inseparable mixture of *3-ethenyl-5-phenyl-4-cyclopentenyl 4-methylphenyl sulfone* **405** and *(E)-3-phenyl-5-(prop-1-enyl)-4-cyclopentenyl 4-methylsulfone* **406**, (12 mg) as a colourless oil and as an inseparable mixture of diastereoisomers, with **406** as the major product; $R_f$ 0.19 (20% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.65-7.47 (2H, m, *o*-$SO_2Ar$), 7.36-7.14 (7H, m, other Ar-H), [5.83-5.62, 5.43-5.36, 5.25-5.04] (4H, m, olefinic), [4.45-4.38 (m), 4.24 (t, *J* 8.5 Hz)] (1H, -$SO_2CH$<), [4.04-3.81 (m), 3.27 (t, *J* 8.0 Hz)] (2H, >C(*H*)-CH=CH-C(*H*)<), [2.48, 2.44, 2.39, 2.37] (3H, s, Ts-$CH_3$), [1.70 (d, *J* 5.0 Hz), 1.49 (d, *J* 6.0 Hz)] (3H, =CH-C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 141.9, 141.6, 136.2, 135.7, 135.4, 134.8, 134.3, 134.1, 130.9, 130.7, 129.4, 128.8, 128.6, 128.2, 128.0, 127.5, 127.2, 127.0 (×2), 126.5, 126.3, 125.8, 125.7, 125.5, 125.4, 125.2, 124.8, 124.6, 123.8, 116.5, 114.2, 111.9, 111.8, 70.6, 70.4, 66.3, 53.1, 51.1, 50.9, 49.9, 49.6, 48.8, 48.2, 47.5, 28.8, 27.6, 19.5, 19.4, 15.8, 15.7, 15.6; *m/z* (CI) 356 $[M+NH_4]^+$ (**406**), 342 $[M+NH_4]^+$ (**405**), 339, 199, 183 (Found: **405**, $[M+NH_4]^+$, 342.1522. $C_{20}H_{20}O_2S$ requires $[M+NH_4]^+$, 342.1528).

**4-Cyclopentenyl 4-methylphenyl sulfone (378)**



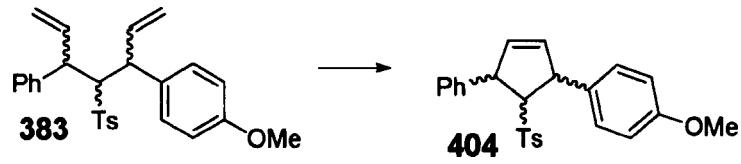

To dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (25 mg, 0.029 mmol, 5 mol %) was added **377** (147 mg, 0.585 mmol, 1.0 equiv) in $CH_2Cl_2$ (2.2 mL). The reaction mixture was stirred at rt for 19 h, concentrated under reduced pressure and purified by chromatography (5→10% EtOAc–petrol) gave *4-cyclopentenyl 4-methylphenyl sulfone* **378** (76 mg, 58%) as a yellow solid; $R_f$ 0.18 (20% EtOAc–petrol); $\nu_{max}$ (film) 3060, 1622, 1597, 1495, 1441, 1402, 1340, 1302, 1263, 1146, 1088, 1049, 1018, 987, 918, 818, 704, 665 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.27 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.53 (2H, br s, -C*H*=C*H*-), 3.76 (1H, tt, *J* 9.5, 6.0 Hz, -$SO_2CH$<), 2.80 (2H, dd, *J* 15.5, 6.0 Hz, =CH-C*H*H-), 2.53 (2H, dd, *J* 15.5, 9.5 Hz, =CH-CH*H*-), 2.36 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.5 (4°), 135.5 (4°), 129.8 (3°), 128.5 (3°), 128.2 (3°), 61.9 (-$SO_2CH$<), 33.8 (-$CH_2$-CH=), 21.5 (Ts-$CH_3$); *m/z* (CI) 462 $[2M+NH_4]^+$, 240 $[M+NH_4]^+$, 223 $[M+H]^+$, 174, 156, 139 (Found: $[M+NH_4]^+$, 240.1055. $C_{12}H_{14}O_2S$ requires $[M+NH_4]^+$, 240.1058).

**(3*R**,5*R**)-3,5-Diethyl-4-cyclopentenyl 4-methylphenyl sulfone, (3*R**,4*R**,5*S**)-3,5-Diethyl-4-cyclopentenyl 4-methylphenyl sulfone and (3*R**,4*S**,5*S**)-3,5-Diethyl-4-cyclopentenyl 4-methylphenyl sulfone(380)**




To dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (35 mg, 0.041 mmol, 2.5 mol % equiv) was added **379** (498 mg, 1.62 mmol, 1.0 equiv) in $CH_2Cl_2$ (7 mL). The reaction mixture was stirred at rt for 13 h then at reflux for 4 h. Concentration under reduced pressure and chromatography (5% EtOAc–petrol) gave *3,5-diethyl-4-cyclopentenyl 4-methylphenyl sulfone* **380** (203 mg, 45%) as a brown gum and as an inseparable mixture of diastereoisomers; $R_f$ 0.29 (20% EtOAc–petrol); $\nu_{max}$ (film) 3057, 1597, 1495, 1460, 1381, 1315, 1302, 1288, 1146, 1088, 1018, 889, 816, 739, 708, 663 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.83-7.79 (2H, m, *o*-$SO_2Ar$, 3× diast.), 7.36 (2H, d, *J* 7.5 Hz, *m*-$SO_2Ar$, 3× diast.), 5.96 (2H, s, 1× diast. -C*H*=C*H*-), [5.85, (1H, d, *J* 5.5 Hz, -C*H*=CH-), 5.66 (1H, d, *J* 5.5 Hz, -CH=C*H*-)] (1× diast.), 5.62 (2H, s, 1× diast. -C*H*=C*H*-), [3.82, 3.52] (1H, t, *J* 7.5 Hz, -$SO_2$-CH<, 3× diast.), [3.15-2.94, 2.69-2.61] (2H, m, 2× -$SO_2$CH-(C*H*<)$_2$, 3× diast.), 2.46 (3H, s, Ts-$CH_3$, 3× diast.), [2.30-2.19, 1.75-1.07] (4H, m, 2× $H_3$C-C*H*$_2$-, 3× diast.), [0.99-0.86 (m), 0.81 (t, *J* 7.5 Hz), 0.67 (t, *J* 7.5 Hz)] (6H, 2× *H*$_3$C-$CH_2$-, 3× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 144.5 (4°), 144.3 (4°), 144.2 (4°), 138.2 (4°), 137.6 (4°),135.5 (4°), 133.2 (3°), 132.3 (3°), 131.9 (3°), 131.8 (3°), 129.9 (3°), 129.8 (3°), 129.7 (3°), 128.9 (3°), 128.3 (3°), 127.7 (3°), [72.2, 69.7, 68.3] (-$SO_2$CH<, 3× diast.), [49.6, 48.8, 48.3, 47.4] ($H_2$C=CH-C*H*-, 3× diast.), [29.1, 26.4, 23.7] ($H_3$C-$CH_2$-, 3× diast.), 21.7 (Ts-$CH_3$, 3× diast.), [12.9, 12.3, 11.4, 10.9] ($H_3$C-$CH_2$-, 3× diast.); *m/z* (CI) 296 $[M+NH_4]^+$, 279 $[M+H]^+$, 139, 122, 107, 93, 91, 81, 79 (Found: $[M+NH_4]^+$, 296.1681. $C_{16}H_{22}O_2S$ requires $[M+NH_4]^+$, 296.1684).

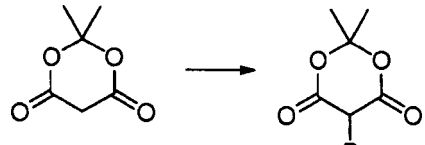
**3-(4-Methoxyphenyl)-5-phenyl-4-cyclopentenyl 4-methylphenyl sulfone (404), diastereoisomers as shown**




To dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (4 mg, 0.0045 mmol, 0.05 equiv) was added **383** (39 mg, 0.090 mmol, 1.0 equiv). $CH_2Cl_2$ (0.8 mL) was introduced by syringe, and the reaction mixture was stirred at rt for 20 h. Concentration under reduced pressure and chromatography (7.5→10% EtOAc–petrol) gave *3-(4-methoxyphenyl)-5-phenyl-4-cyclopentenyl 4-methylphenyl sulfone* **404** (26 mg, 71%) as a brown gum and as an inseparable mixture of diastereoisomers; $R_f$ 0.15 (20% EtOAc–petrol); $\nu_{max}$ (film) 3060, 3030, 1610, 1599, 1512, 1493, 1454, 1317, 1302, 1288, 1250, 1178, 1144, 1086, 1034, 958, 912, 874, 829, 814, 769, 731, 698, 675 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.28-6.97 (11H, m, Ar-H), [6.80, 6.73] (2H, d, *J* 8.5 Hz, *o*-MeOAr), 5.95 (2H, br s, -CH=CH-), 4.64-4.52 (2H, m, Ph-CH<, MeO-$C_6H_4$-C*H*<), 4.18 (1H, app dd, *J* 8.0, 7.0 Hz, Ts-CH<), [3.83, 3.78] (3H, s, Ar-$OCH_3$), [2.32, 2.34] (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [158.6, 159.0] (4° MeOAr), [143.5, 141.4] (4° -$SO_2$Ar), 136.9, 136.4, 134.5, 133.9, 133.6, 133.4, 133.2, 131.3, 130.4, 129.1, 128.5, 128.5, 128.2, 127.9, 127.9, 127.8, 127.5, 127.5, 126.8, 113.9, 113.2, [74.1, 73.9] (-$SO_2$C(H)<), [55.3, 55.2] (Ar-$OCH_3$), [53.0, 52.4, 52.3, 51.7] (Ph-CH<, MeO-$C_6H_4$-*C*H<), 21.5 (Ts-$CH_3$); *m/z* (CI) 422 $[M+NH_4]^+$, 391, 316, 249, 174, 159, 77, 52 (Found: $[M+NH_4]^+$, 422.1790. $C_{25}H_{24}O_3S$ requires $[M+NH_4]^+$, 422.1790).

- **3.3.10 Compounds relevant to (Toluene-4-sulfonyl)–Meldrum's acid**

**5-Bromo-2,2-dimethyl-1,3-dioxane-4,6-dione (bromo-Meldrum's acid) (337)**



**337**

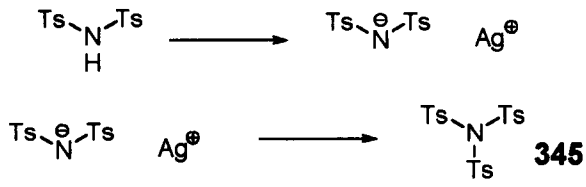
To a solution of Meldrum's acid, (14.4 g, 100 mmol, 1.0 equiv) dissolved in aq. NaOH (1.0 M; 100 mL, 100 mmol, 1.0 equiv) was added bromine (5.12 mL, 100 mmol, 1.0 equiv) dropwise at 0 °C over several minutes. The resultant precipitate was filtered off and dissolved in $CH_2Cl_2$ (100 mL). The organic phase was washed with two portions of $H_2O$ (50 mL) and dried ($Na_2SO_4$). Concentration under reduced pressure and recrystallisation from PhMe (40 mL) gave *5-bromo-2,2-dimethyl-1,3-dioxane-4,6-dione (bromo-Meldrum's acid)* **337** (8.40 g, 38%) as a grey crystalline solid; mp 80–82 °C (lit.[180] 85–86 °C); $\delta_H$ (300 MHz, $CDCl_3$) 5.20 (1H, s, -CHBr-), [1.92, 1.85] (2× 3H, s, -$C(CH_3)_2$-); data in agreement with those previously reported.[181]

***N*,4-Dimethyl-*N*-(trifluoromethanesulfonyl)benzenesulfonamide (342)**

**342**

This was synthesised according to literature procedure.[182] To sodium hydride (washed with hexane, 565 mg, 39.2 mmol, 1.3 equiv) in $CH_2Cl_2$ (10 mL) at –78 °C was added a solution of *N*-methyl-*p*-toluenesulfonamide in $CH_2Cl_2$ (20 mL). Once effervescence had ceased, trifluoromethanesulfonic anhydride (6.37 mL, 37.7 mmol 1.25 equiv) was introduced. The reaction mixture was stirred at –78 °C for 1 h and at rt for 2 h. To the reaction mixture was added iced water, then concentrated aq. HCl until pH=1. The aqueous layer was extracted with $CH_2Cl_2$ (3× 100 mL). Combined organic fractions were dried ($Na_2SO_4$), concentrated under reduced pressure and recrystallised from *i*-PrOH to give *N,4-dimethyl-N-(trifluoromethanesulfonyl)benzenesulfonamide* **342** (5.17 g, 54%) as a colourless solid; mp 80–81 °C (lit.[182] 81–82 °C); $\delta_H$ (300 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.42 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 3.42 (3H, s, N-$CH_3$), 2.50 (3H, s, Ts-$CH_3$); data agree with those previously reported.[182]

**Tris(toluene-4-sulfonyl)amine (345)**

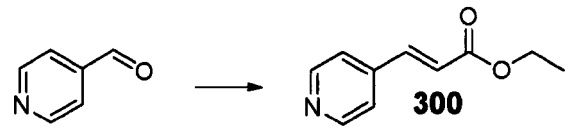



This was synthesised according to a literature procedure.[94] 4-Methyl-*N*-(toluene-4-sulfonyl)benzenesulfonamide (24.00 g, 73.8 mmol, 1.0 equiv) was suspended in $H_2O$ (1.5 L, distilled), to which was added aq. $AgNO_3$ (0.55 M; 148 mL, 81.1 mmol, 1.1 equiv) at rt. The reaction mixture was stirred at rt for 1h, before careful removal of approximately 50% of the solvent under reduced pressure. The reaction mixture was cooled to +4 °C and the precipitate filtered off and dried under high vacuum over $P_2O_5$ to give *silver (I) bis(toluene-4-sulfonyl)amide* (31.87 g, 99%) as a white solid; mp 292–296 °C (lit.[94] 304–306 °C); $\delta_H$ (300 MHz, DMSO-$d_6$) 7.98 (4H, d, *J* 8.0 Hz, *o*-$SO_2$-Ar), 7.19 (4H, d, *J* 8.0 Hz, *m*-$SO_2$-Ar), 2.33 (6H, s, Ts-$CH_3$); data in agreement with those previously reported.[94]

To *silver (I) bis(toluene-4-sulfonyl)amide* (32.00 g, 74.0 mmol, 1.0 equiv) was added toluene-4-sulfonyl chloride (28.23 g, 148.1 mmol, 2.0 equiv). The two solids were mixed, and heated to 170 °C with stirring for 4 h. The sides of the flask needed heating with a heat gun periodically to melt toluene-4-sulfonyl chloride which has solidified there. The reaction mixture was allowed to cool and the resultant solid was broken up with a glass rod and washed thoroughly with chlorobenzene (150 mL). This was filtered to remove AgCl. The filtrate was cooled to –10 °C overnight. The resultant crystals of toluene-4-sulfonyl chloride were filtered off and discarded. The filtrate was concentrated under reduced pressure and the resultant oil was recrystallised from benzene to give *tris(toluene-4-sulfonyl)amine* **345** (17.58 g, 66%) as a white solid; mp 227–229 °C (lit.[94] 230 °C); $\delta_H$ (300 MHz, benzene-$d_6$) 8.12 (6H, d, *J* 8.0 Hz, *o*-$SO_2$-Ar), 6.74 (6H, d, *J* 8.0 Hz, *m*-$SO_2$-Ar), 1.86 (9H, s, Ts-$CH_3$); data in agreement with those previously reported.[94] .

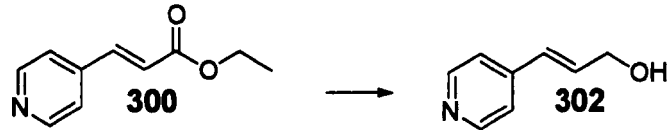
- **3.3.11 Compounds relevant to allyl alcohol preparation**

**(*E*)-Ethyl 3-(4-pyridinyl)propenoate (300)**




To a suspension of sodium hydride (720 mg, 30 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added triethyl phosphonoacetate (7.06 g, 31.5 mmol, 1.05 equiv, solution in THF, 60 mL) dropwise by cannula. The reaction mixture was stirred for 15 min at 0 °C, then pyridine-4-carboxaldehyde (3.21 g, 30 mmol, 1.0 equiv) was introduced dropwise *with vigorous stirring*. The reaction mixture was allowed to warm to rt and stirred for 22 h before dilution with EtOAc (100 mL). The organic phase was washed with saturated aq. $NH_4Cl$ (3× 100 mL), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by chromatography (50% EtOAc–petrol) to give *(E)-ethyl 3-(4-pyridinyl)propenoate* **300** (4.73 g, 89%) as a cream-coloured crystalline solid; mp 61–62 °C; $R_f$ 0.32 (EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 8.62 (2H, d, *J* 5.0 Hz, *o*-pyH), 7.56 (1H, d, *J* 16.0 Hz, py-CH=), 7.33 (2H, d, *J* 5.0 Hz, *m*-pyH), 6.56 (1H, d, *J* 16.0 Hz, py-CH=C*H*-), 4.25 (2H, q, *J* 7.0 Hz, -OC*H*$_2$-$CH_3$), 1.31 (3H, t, *J* 7.0 Hz, -$OCH_2$-C*H*$_3$); data in agreement with those previously reported.[84]

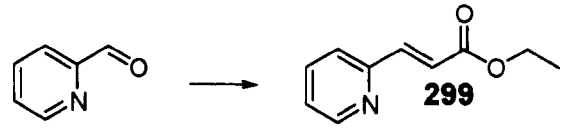
**(*E*)-3-(4-Pyridinyl)prop-2-en-1-ol (302)**




To a solution of **300** (4.71 g, 27.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) at –78 °C was added dropwise over 15 min di*iso*butylaluminium hydride (1.0 M in $CH_2Cl_2$; 95.7 mL, 95.7 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 30min then allowed to warm to rt over 3 h. Dropwise addition of EtOAc (10 mL) to the reaction mixture was followed by the reaction mixture being *slowly* poured into a saturated solution of aqueous sodium potassium tartrate (100 mL) and $H_2O$ (100 mL) *with vigorous stirring*. The reaction mixture was stirred at rt for 16 h then washed with saturated aq. NaCl (3× 100 mL), dried ($Na_2SO_4$), concentrated under reduced pressure *without heating* and purified by chromatography (EtOAc) to give impure *(E)-3-(4-*

*pyridinyl)prop-2-en-1-ol* **302** (1.77 g, 49%) as a creamy-coloured solid; $R_f$ 0.23 (10% MeOH–$CH_2Cl_2$); $\delta_H$ (300 MHz, $CDCl_3$) 8.49 (2H, d, *J* 5.5 Hz, *o*-pyH), 7.24 (2H, d, *J* 5.5 Hz, *m*-pyH), 6.60 (2H, s, Ar-C*H*=CH-, Ar-CH=C*H*-), 4.39 (2H, s, -$CH_2O$-); *m/z* (CI) 136 $[M+H]^+$, 118, 106, 93 (Found: $[M+H]^+$, 136.0759. $C_8H_9NO$ requires $[M+H]^+$, 136.0762). $^1$H-NMR data in agreement with those previously reported.[87]

**(*E*)-Ethyl 3-(2-pyridinyl)propenoate (299)**



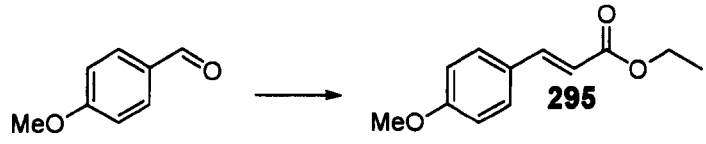

To a suspension of sodium hydride (washed with hexane, 1.44 g, 60 mmol, 1.0 equiv) in THF (120 mL) at 0 °C was added triethyl phosphonoacetate (14.1 g, 63 mmol, 1.05 equiv, solution in THF, 120 mL) dropwise by cannula. The reaction mixture was stirred for 1 h at 0 °C, then pyridine-2-carboxaldehyde (6.43 g, 60 mmol, 1.0 equiv) was introduced dropwise *by syringe with vigorous stirring*. The reaction mixture was allowed to warm to rt and stirred for 14 h before dilution with EtOAc (200 mL). The organic phase was washed with saturated aq. $NH_4Cl$ (3× 100ml), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by chromatography (30% EtOAc–petrol) to give *(E)-ethyl 3-(2-pyridinyl)propenoate* **299** (9.99 g, 94%) as a cream-coloured solid; mp 24–25 °C (lit.[183] 26–27 °C); $R_f$ 0.55 (EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 8.61 (1H, br s, py C6-H), 7.70-7.62 (2H, m, py C4-H, Ar-CH=), 7.39 (1H, d, *J* 8.0 Hz, py C3-H), 7.22 (1H, td, *J* 6.0, 1.0 Hz, C5-H), 6.89 (1H, d, *J* 16.0 Hz, Ar-CH=C*H*-), 4.24 (2H, q, *J* 7.0 Hz, -OC*H*$_2$CH$_3$), 1.30 (3H, t, *J* 7.0 Hz, -OCH$_2$C*H*$_3$); data in agreement with those previously reported.[85]

**(*E*)-3-(2-Pyridinyl)prop-2-en-1-ol (301)**


To a solution of **299** (5.32 g, 30 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) at –78 °C was added dropwise over 15 min di*iso*butylaluminium hydride (1.0 M in $CH_2Cl_2$; 108 mL, 108 mmol, 3.6 equiv). The reaction mixture was stirred at –

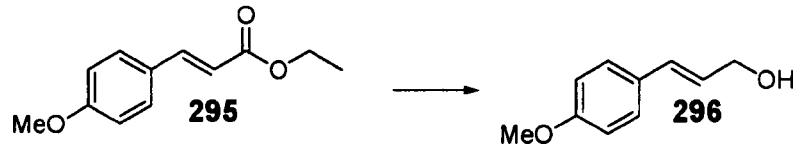
78 °C for 15 min then allowed to warm to rt over 3 h. Dropwise addition of EtOAc (10 mL) to the reaction mixture by syringe was followed by the reaction mixture being *slowly* poured into a saturated solution of aqueous sodium potassium tartrate (200 mL) and $H_2O$ (200 mL) *with vigorous stirring*. The reaction mixture was stirred at rt for 16 h, then the aqueous phase was washed with $CH_2Cl_2$ (2× 10 mL) and the combined organic phases were washed with saturated aq. NaCl (3× 100 mL), dried ($Na_2SO_4$), concentrated under reduced pressure *without heating* and purified by chromatography (30→70% EtOAc–petrol) to give highly impure *(E)-3-(2-pyridinyl)prop-2-en-1-ol* **301** (603 mg, 15%) as a cream-coloured solid; $R_f$ 0.15 (EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 8.51 (1H, br s, py C6-H), 7.67-7.58 (1H, m, py C4-H), 7.28 (1H, d, *J* 8.0 Hz, py C3-H), 7.11 (1H, dd, *J* 6.5, 5.0 Hz, C5-H), 6.89-6.69 (2H, m, Ar-C*H*=C*H*-), 4.38 (2H, d, *J* 3.5 Hz, -$OCH_2$-); data in agreement with those previously reported.[86]

**(*E*)-Ethyl 3-(4-methoxyphenyl)propenoate (295)**



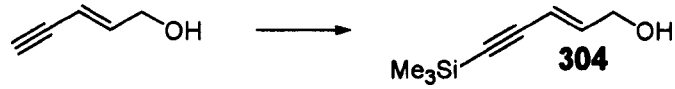

To a suspension of sodium hydride (720 mg, 30 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added triethyl phosphonoacetate (7.06 g, 31.5 mmol, 1.05 equiv, solution in THF, 30 mL) dropwise by cannula. The reaction mixture was stirred for 30 min at 0 °C, then *p*-anisaldehyde (3.64 mL, 30 mmol, 1.0 equiv, solution in THF, 30 mL) was introduced dropwise by cannula *with vigorous stirring*. The reaction mixture was allowed to warm to rt and stirred for 41 h before dilution with EtOAc (100 mL). The organic phase was washed with saturated aq. $NH_4Cl$ (2× 75 mL), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by chromatography (5% EtOAc–petrol) to give *(E)-ethyl 3-(4-methoxyphenyl)propenoate* **295** (4.78 g, 77%) as a colourless solid; mp 47–48 °C (lit.[184] 48 °C); $R_f$ 0.35 (20% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.65 (1H, d, *J* 16.0 Hz, Ar-CH=), 7.48 (2H, d, *J* 8.5 Hz, *m*-MeOAr), 6.91 (2H, d, *J* 8.5 Hz, *o*-MeOAr), 6.32 (1H, d, *J* 16.0 Hz, Ar-CH=C*H*-), 4.26 (2H, q, *J* 7.0 Hz, -$OCH_2CH_3$), 3.84 (3H, s, Ar-$OCH_3$), 1.34 (3H, t, *J* 7.0 Hz, -$OCH_2CH_3$); data in agreement with those previously reported.[82]

**(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol (296)**




To a solution of **296** (4.78 g, 23.2 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) at –78 °C was added dropwise over 5 min di*iso*butylaluminium hydride (1.0 M in $CH_2Cl_2$; 83.5 mL, 83.5 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 30 min then allowed to warm to rt over 45 min. Dropwise addition of EtOAc (10 mL) to the reaction mixture was followed by the reaction mixture being *slowly* poured into a solution of saturated aq. sodium potassium tartrate (100 mL) and $H_2O$ (100 mL) *with vigorous stirring*. The reaction mixture was stirred at rt for 14 h. The organic phase was washed with saturated aq. NaCl (2× 100ml), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by chromatography (20→50% EtOAc–petrol) to give *(E)-3-(4-methoxyphenyl)prop-2-en-1-ol* **296** (3.27 g, 86%) as a white crystalline solid; mp 76–78 °C (lit.[83] 72–74 °C); $R_f$ 0.09 (20% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.0 Hz, *m*-MeOAr), 6.88 (2H, d, *J* 8.0 Hz, *o*-MeOAr), 6.57 (1H, d, *J* 16.0 Hz, Ar-CH=), 6.25 (1H, dt, *J* 16.0, 6.0 Hz, Ar-CH=C*H*-), 4.31 (2H, d, *J* 6.0 Hz, -$CH_2O$-), 3.83 (3H, s, Ar-$OCH_3$), 1.63 (1H, br s, -OH); data in agreement with those previously reported.[83]

**(*E*)-5-(Trimethylsilyl)pent-2-en-4-yn-1-ol (304)**

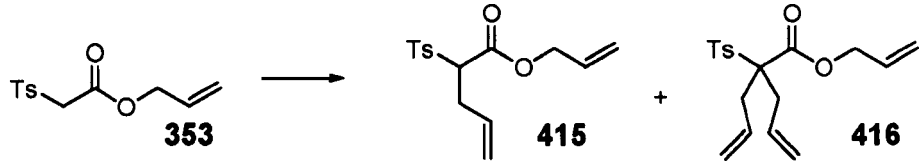



This was prepared in accordance with literature procedures.[185] To a solution of pent-2-en-4-yn-1-ol (mixture of *E/Z* isomers, 4.11 g, 50 mmol, 1.0 equiv) in THF (85 mL) at –78 °C was added *n*-BuLi (2.48 M in THF; 40.3 mL, 100 mmol, 2.0 equiv). A green precipitate formed; to this was added chlorotrimethylsilane (10.86 g, 100 mmol, 2.0 equiv). The reaction mixture was stirred at –78 °C for 30 min then allowed to warm to rt over 30 min. The reaction mixture was poured over aq. HCl (2.0 M; 200 mL), and extracted with $Et_2O$ (100 mL). The organic phase was washed with aq. HCl (2.0 M; 200 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. Chromatography (15% EtOAc–petrol) yielded *(E)-5-(trimethylsilyl)pent-2-en-4-yn-1-ol* **304** (983

mg, 66%) as a colourless liquid; $bp_{30}$ 119 °C (lit.[186] $bp_{21}$ 113 °C); $\delta_H$ (300 MHz, $CDCl_3$) 6.31 (1H, dt, *J* 16.0, 5.0 Hz, HO-$CH_2$-C*H*=), 5.78 (1H, d, *J* 16.0 Hz, HO-$CH_2$CH=C*H*-), 4.20 (2H, d, *J* 5.0 Hz, HO-$CH_2$-), 1.80 (1H, br s, -OH), 0.20 (9H, s, -Si($CH_3$)$_3$); data in agreement with those previously reported.[185]

- **3.3.12 Compounds relevant to cyclopropane formation**

**(±)-Allyl 2-(toluene-4-sulfonyl)pent-4-enoate (415) and Allyl 2-allyl-2-(toluene-4-sulfonyl)pent-4-enoate (416)**



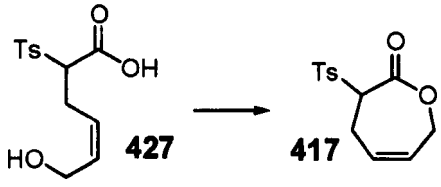

To **353** (2.03 g, 7.98 mmol, 1.0 equiv) and tetra-*N*-butylammonium iodide (2.95 g, 7.98 mmol, 1.0 equiv) in PhMe (10 mL) at rt was added DBU (2.38 mL, 16.0 mmol, 2.0 equiv). The reaction mixture was stirred for 1 h, then allyl bromide (687 µL, 7.98 mmol, 1.0 equiv) was added dropwise, resulting in an exotherm. The reaction mixture was stirred for 1 h then diluted with EtOAc (50 mL), washed with aq. HCl (2.0 M; 3× 50 mL) and $H_2O$ (50 mL), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by column chromatography (15% EtOAc–petrol) to give *allyl 2-allyl-2-(toluene-4-sulfonyl)pent-4-enoate* **416** (240 mg, 9%) as a colourless oil; also isolated was *(±)-allyl 2-(toluene-4-sulfonyl)pent-4-enoate* **415** (1.88 g, 80%), as a colourless oil.

**416:** $R_f$ 0.38 (20% EtOAc–petrol) $\nu_{max}$ (film) 3080, 3024, 1734, 1639, 1597, 1439, 1379, 1360, 1323, 1304, 1290, 1273, 1213, 1146, 1082, 1034, 995, 974, 924, 885, 818, 800, 785, 708, 663 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.32 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.87-5.73 (3H, m, 3× -C*H*=$CH_2$), 5.31-5.13 (6H, m, 3× -CH=C*H*$_2$), 4.51 (2H, d, *J* 5.5 Hz, -$OCH_2$-), 2.91 (2H, dd, *J* 14.5, 6.5 Hz, Ts-C(-C*H*H-CH=$CH_2$)$_2$-), 2.81 (2H, dd, *J* 14.5, 7.5 Hz, Ts-C(-CH*H*-CH=$CH_2$)$_2$-), 2.43 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 167.1 (C=O), 145.4 (4°), 133.2 (4°), 131.4 (3°), 130.9 (3°), 130.4 (3°), 129.4 (3°), [120.1, 119.3] (=$CH_2$), 75.2 (Ts-*C*($C_3H_5$)$_2$-), 66.7 (-$OCH_2$-), 34.8 (Ts-C($CH_2$-CH=$CH_2$)$_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 352 $[M+NH_4]^+$, 335 $[M+H]^+$ (Found: $[M+H]^+$, 335.1327. $C_{18}H_{22}O_4S$ requires $[M+H]^+$, 335.1317).

**415:** $R_f$ 0.32 (20% EtOAc–petrol) $\nu_{max}$ (film) 3084, 3012, 1741, 1643, 1597, 1493, 1441, 1417, 1404, 1365, 1327, 1306, 1292, 1271, 1238, 1201, 1173, 1149, 1084, 1039, 1018, 989, 930, 850, 816, 719, 665 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.82-5.61 (2H, m, 2× -C*H*=$CH_2$), 5.30-5.08 (4H, m, 2× -CH=C*H*$_2$), 4.55 (2H, dd, *J* 2.5, 1.5 Hz, -$OCH_2$-), 4.02 (1H, dd, *J* 11.0, 4.0 Hz, Ts-C*H*($C_3H_5$)-), 2.82-2.68

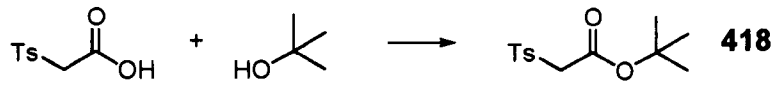
(2H, m, Ts-CH(-C*H*$_2$-CH=CH$_2$)-), 2.46 (3H, s, Ts-CH$_3$); $\delta_C$ (75 MHz, CDCl$_3$) 165.2 (C=O), 145.5 (4°), 134.0 (4°), 131.7 (3°), 131.0 (3°), 129.8 (3°), 129.4 (3°), [119.2, 119.1] (=CH$_2$), 70.2 (Ts-C*H*(C$_3$H$_5$)-), 66.6 (-OCH$_2$-), 31.0 (Ts-CH(-C*H*$_2$-CH=CH$_2$)-), 21.7 (Ts-CH$_3$); *m/z* (CI) 312 $[M+NH_4]^+$, 295 $[M+H]^+$ (Found: $[M+H]^+$, 295.1015. $C_{15}H_{18}O_4S$ requires $[M+H]^+$, 295.1004) (Found: C, 61.00; H, 6.01. $C_{15}H_{18}O_4S$ requires C, 61.20; H, 6.16%).

**(±)-(*Z*)-3-(Toluene-4-sulfonyl)-3,4-dihydrooxepin-2(*7H*)-one (417)**




To a solution of **427** (222 mg, 0.781 mmol, 1.0 equiv) in $CH_2Cl_2$ (25 mL) at 0 °C was added dropwise *N,N'*-di*iso*propyl carbodiimide (134 µL, 0.859 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 10 min, at rt for 16 h, filtered, concentrated under reduced pressure, and purified by column chromatography (30% EtOAc–petrol) to give *(±)-(Z)-3-(toluene-4-sulfonyl)-3,4-dihydrooxepin-2(7*H*)-one* **417** (180 mg, 87%) as a white solid; mp 132–134 °C; $R_f$ 0.43 (50% EtOAc–petrol); $\nu_{max}$ (film) 3041, 1745, 1597, 1471, 1435, 1400, 1387, 1352, 1321, 1257, 1225, 1176, 1146, 1084, 1049, 1016, 943, 912, 879, 816, 800, 766, 729, 706, 660 cm$^{-1}$; $\delta_H$ (500 MHz, CDCl$_3$) 7.98 (2H, d, *J* 8.0 Hz, *o*-SO$_2$Ar), 7.38 (2H, d, *J* 8.0 Hz, *m*-SO$_2$Ar), [5.92-5.88, 5.86-5.82] (2H, m, -C*H*=C*H*-), [4.91 (app d quint, *J* 15.5, 3.0 Hz), 4.46 (ddd, *J* 15.0, 7.0, 1.0 Hz)], (2H, -OCH$_2$-), 4.70 (1H, dd, *J* 13.0, 4.0 Hz, Ts-CH<), [3.16-3.10, 2.69-2.61], (2H, m, Ts-CH-C*H*$_2$-CH=), 2.45 (3H, s, Ts-CH$_3$); $\delta_C$ (67.5 MHz, CDCl$_3$) 166.7 (C=O), 145.7 (4°), 133.6, (4°), 130.6 (3°), 129.7 (3°), 129.5 (3°), 124.3, (3°), 64.3 (Ts-CH<), 64.0 (-OCH$_2$-), 27.1 (Ts-CH-CH$_2$-CH=), 21.8 (Ts-CH$_3$); *m/z* (CI) 284 $[M+NH_4]^+$, 189, 174, 130, 77 (Found: $[M+NH_4]^+$, 284.0957. $C_{13}H_{14}O_4S$ requires $[M+NH_4]^+$, 284.0957) (Found: C, 58.51; H, 5.47. $C_{13}H_{14}O_4S$ requires C, 58.63; H, 5.30%).

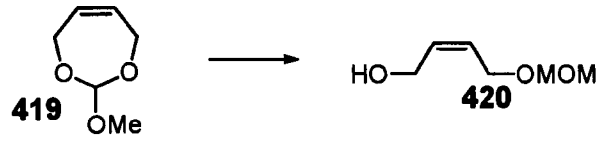
**_tert_-Butyl (toluene-4-sulfonyl)acetate (418)**



**418**

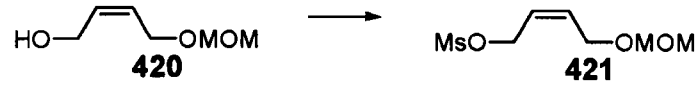
To *tert*-butanol (1.48 g, 20 mmol, 1.0 equiv) and (toluene-4-sulfonyl)acetic acid (4.28 g, 20 mmol, 1.0 equiv) in $CH_2Cl_2$ (50 mL) at 0 °C was added dropwise *N,N'*-di*iso*propyl carbodiimide (3.13 mL, 20 mmol, 1.0 equiv). The reaction mixture was stirred at 0 °C for 10 min, at rt for 1 h, then was filtered, concentrated under reduced pressure and purified by column chromatography (35% EtOAc–petrol) to give tert-*butyl (toluene-4-sulfonyl)acetate* **418** (4.78 g, 88%) as a colourless oil; $\delta_H$ (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 4.01 (2H, s, -$SO_2CH_2$-), 2.45 (Ts-$CH_3$), 1.39 (9H, s, -$C(CH_3)_3$); data in agreement with those previously reported.[187]

**(*Z*)-4-(Methoxymethoxy)but-2-en-1-ol (420)**



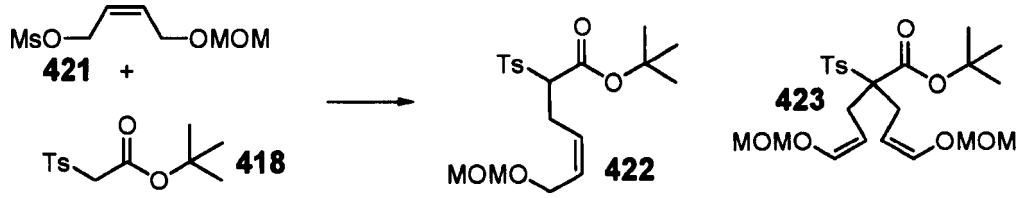

To (*Z*)-2-methoxy-4,7-dihydro-1,3-dioxepine[99] **419** (6.88 g, 52.9 mmol, 1.0 equiv) in $CH_2Cl_2$ (75 mL) at 0 °C was added dropwise di*iso*butylaluminium hydride (1.0 M in $CH_2Cl_2$; 58.2 mL, 58.2 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 1 h then at rt for 16 h. A small amount of EtOAc was introduced. The reaction mixture was poured into a saturated aq. solution of sodium potassium tartrate (125 mL) and $H_2O$ (125 mL). This was stirred vigorously for 30 min. The aqueous layer was washed with a small portion of $CH_2Cl_2$. The combined organic phases were washed with saturated aq. NaCl (2× 150ml), dried ($Na_2SO_4$), concentrated under reduced pressure and purified by column chromatography (70% EtOAc–petrol) to give *(Z)-4-(methoxymethoxy)but-2-en-1-ol* **420** (3.14 g, 49%) as a colourless oil; $R_f$ 0.58 (50% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 5.89-5.64 (2H, m, -C*H*=C*H*-), 4.64 (2H, s, -$OCH_2O$-), [4.20, 4.18], (each 2H, d, *J* 6.5 Hz, -$OCH_2$-CH=), 3.38 (3H, s, -$OCH_3$), 2.36 (1H, br s, -OH); data in agreement with those previously reported.[188]

**(*Z*)-4-(Methoxymethoxy)but-2-enyl methanesulfonate (421)**




To **420** (2.34 g, 17.7 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) at 0 °C was added triethylamine (7.39 mL, 53.0 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 15 min, then methanesulfonyl chloride (2.74 mL, 35.4 mmol, 2.0 equiv) was introduced dropwise. The reaction mixture was stirred at 0 °C for 30 min washed with aq. HCl (2.0 M; 100 mL) and saturated aq. $NaHCO_3$ (2× 100 mL). The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure to give crude *(Z)-4-(methoxymethoxy)but-2-enyl methanesulfonate* **421** as a yellow oil, used immediately without purification; $R_f$ 0.31 (50% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 5.91-5.70 (2H, m, -C*H*=C*H*-), 4.82 (2H, d, *J* 6.5 Hz, =CH-C$H_2$-$OSO_2$-), 4.60 (2H, s, -$OCH_2O$-), 4.16 (2H, d, 6.0 Hz, =CH-C$H_2$-$OCH_2$-), 3.34 (3H, s, -$OSO_2$-$CH_3$), 3.00 (3H, s, -$OCH_3$).

**(±)-(*Z*)-*tert*-Butyl 6-(methoxymethoxy)-2-(toluene-4-sulfonyl)hex-4-enoate (422) and (*Z*)-*tert*-Butyl 5-(methoxymethoxy)-2-((*Z*)-3-(methoxymethoxy)allyl)-2-(toluene-4-sulfonyl)pent-4-enoate (423)**



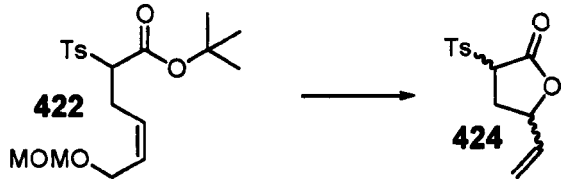

To sodium hydride (washed with hexane, 424 mg, 17.7 mmol, 1.0 equiv) suspended in THF (30 mL) at 0 °C was added dropwise by cannula a solution of **418** (azeotropically dried with PhMe, 4.78 g, 17.7 mmol, 1.0 equiv) in THF (30 mL). The reaction mixture was stirred at 0 °C for 30 min, then a solution of crude **421** (assumed to be 17.7 mmol, 1.0 equiv) in THF (20 mL) was added dropwise by cannula. The reaction mixture was stirred at 0 °C for 30 min then at rt for 16 h. The solvent was removed under reduced pressure and the crude product was suspended in EtOAc (150 mL), washed with saturated aq. $NH_4Cl$ (100 mL), $H_2O$ (100 mL) and saturated aq. $NH_4Cl$ (100 mL). The organic phase was dried ($Na_2SO_4$), concentrated under reduced pressure and purified by column chromatography (35% EtOAc–petrol) to give *(±)-(Z)-tert-butyl 6-(methoxymethoxy)-2-(toluene-4-sulfonyl)hex-4-enoate* **422** (4.04 g, 59%) as a colourless oil; also isolated was *(Z)-tert-butyl 5-(methoxymethoxy)-*

(trace) as a colourless oil.

**422:** $R_f$ 0.58 (50% EtOAc–petrol); $\nu_{max}$ (film) 1732, 1699, 1597, 1456, 1396, 1369, 1327, 1306, 1292, 1246, 1213, 1147, 1105, 1086, 1047, 993, 947, 920, 883, 837, 816, 760, 714, 667 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.33 (2H, d, *J* 8.5 Hz, *m*-$SO_2Ar$), [5.68-5.63, 5.44-5.39] (2H, m, -C*H*=C*H*-), 4.58 (2H, s, -$OCH_2O$-), [4.10, 4.01] (2× 1H, dd, *J* 12.5, 6.5 Hz, =CH-C$H_2$O-), 3.84 (1H, dd, *J* 10.5, 4.5 Hz, Ts-CH<), 3.32 (3H, s, -$OCH_3$), 2.75-2.70 (2H, m, Ts-CH-C$H_2$-CH=), 2.43 (3H, s, Ts-$CH_3$), 1.31 (9H, s, -$C(CH_3)_3$); $\delta_C$ (75 MHz, $CDCl_3$) 164.4 (C=O), 145.3 (4°), 134.4 (4°), 130.2 (3°), 129.6 (3°), 129.4 (3°), 126.2 (3°), 95.8 (-$OCH_2O$-), 83.3 (-*C*$(CH_3)_3$), 70.6 (Ts-*C*H-COO-), 62.8 (-$OCH_2$-CH=), 55.3 (-$OCH_3$), 27.6 (-C(*C*$H_3)_3$), 25.3 (Ts-CH-*C*$H_2$-CH=), 21.7 (Ts-$CH_3$); *m/z* (CI) 402 $[M+NH_4]^+$, 358 $[M+NH_4-CH_2OCH_3]^+$, 346, 323, 314, 302, 288, 284, 232, 197, 192, 174, 139 (Found: $[M+NH_4]^+$, 402.1948. $C_{19}H_{28}O_6S$ requires $[M+NH_4]^+$, 402.1950) (Found: C, 59.21; H, 7.37. $C_{19}H_{28}O_6S$ requires C, 59.35; H, 7.34%).

**423:** $R_f$ 0.50 (50% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.35 (2H, d, *J* 8.5 Hz, *m*-$SO_2Ar$), [5.73-5.59] (4H, m, -C*H*=C*H*-), 4.63 (4H, s, -$OCH_2O$-), 4.10 (4H, s, =CH-C$H_2$O-), 3.38 (6H, s, -$OCH_3$), 2.82 (4H, s, Ts-C-C$H_2$-CH=), 2.47 (3H, s, Ts-$CH_3$), 1.44 (9H, s, -$C(CH_3)_3$); further characterisation not performed due to small amount of material isolated.

**(3*R**,5*R**)-5-Ethenyl-3-(toluene-4-sulfonyl)dihydrofuran-2(3*H*)-one and (3*R**,5*S**)-5-Ethenyl-3-(toluene-4-sulfonyl)dihydrofuran-2(3*H*)-one (424)**

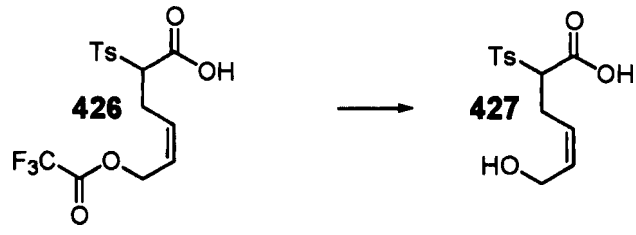



To a solution of **422** (192 mg, 0.5 mmol, 1.0 equiv) in PhMe (50 mL) were added 4Å molecular sieves and concentrated $H_2SO_4$ (3 drops). The reaction was stirred at rt for 2 h, resulting in formation of some red precipitate. This was broken up with a glass rod and the reaction mixture was heated to reflux for 16 h. The reaction mixture was filtered through a plug of celite, then washed with saturated aq. $NaHCO_3$ (100 mL) and $H_2O$ (100 mL). The organic

phase was dried ($Na_2SO_4$) concentrated under reduced pressure and purified by column chromatography (35→40% EtOAc–petrol) to give *5-ethenyl-3-(toluene-4-sulfonyl)dihydrofuran-2(*3H*)-one* **424** (47 mg, 35%) as a colourless oil and as an inseparable mixture of diastereoisomers. Also isolated was unreacted **422** (55 mg, 29%).

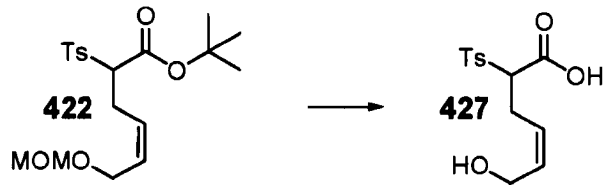
**424:** $R_f$ 0.56 (50% EtOAc–petrol); $\nu_{max}$ (film) 3089, 3066, 3053, 3030, 1780, 1736, 1597, 1495, 1448, 1431, 1404, 1381, 1369, 1323, 1306, 1292, 1259, 1174, 1147, 1086, 1047, 991, 951, 928, 845, 816, 777, 706, 694, 669 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.85, 7.82], (2H, dd, *J* 8.5, 1.5 Hz, *o*-$SO_2Ar$, 2× diast.), [7.40, 7.39] (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$, 2× diast.), 5.93-5.79 (1H, m, -C*H*=$CH_2$), [5.42 (1st diast.), 5.39 (2nd diast.)], (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.32 (1H, d, *J* 10.5 Hz, *cis* -CH=C$H_2$, 2× diast.), [5.19 (1st diast.), 4.86 (2nd diast.)], (1H, q, *J* 7.0 Hz, -OCH<), [4.25 (t, *J* 9.5 Hz, 2nd diast.), 4.07 (dd, *J* 10.0, 3.5 Hz, 1st diast.)], (1H, Ts-CH<), [3.16 (ddd, *J* 14.5, 7.0, 3.5 Hz), 2.43 (ddd, *J* 14.5, 10.0, 8.5 Hz)], (2H for 1st diast., Ts-CH-C$H_2$-, 1st diast.), [2.87 (ddd, *J* 14.0, 10.0, 7.0 Hz), 2.64 (ddd, *J* 14.0, 9.5, 8.0 Hz)], (2H for 2nd diast., Ts-CH-C$H_2$-, 2nd diast.), [2.47, 2.46] (3H, s, Ts-$CH_3$, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) [167.7, 167.4], (C=O, 2× diast.), 146.2 (4°), 145.9 (4°), 134.4 (3°), 133.8 (4°), 133.7, (4°), 130.0 (3°), 129.9 (3°), 129.7 (3°), 129.4, (3°), [119.8, 119.4] (=$CH_2$, 2× diast.), [80.0, 78.5], (Ts-*C*H<, 2× diast.), [64.8, 64.0], (-*O*CH<, 2× diast.), [30.3, 29.5], (-$CH_2$-, 2× diast.), 21.8 (Ts-$CH_3$); *m/z* (CI) 284 $[M+NH_4]^+$, 246, 174, 130 (Found: $[M+NH_4]^+$, 284.0954. $C_{13}H_{14}O_4S$ requires $[M+NH_4]^+$, 284.0957).

**(±)-(*Z*)-6-Hydroxy-2-(toluene-4-sulfonyl)hex-4-enoic acid (427)**




*Procedure A*

To **426** (173 mg, 0.46 mmol, 1.0 equiv) was added aq. NaOH (2.0 M; 50 mL). The reaction mixture was stirred at rt for 2 h, then acidified to pH 1 with concentrated aq. HCl. The reaction mixture was extracted with $CH_2Cl_2$ (5× 30 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure to give *(±)-(Z)-6-hydroxy-2-(toluene-4-sulfonyl)hex-4-enoic acid* **427** (127 mg, 98%) as a pale orange oil.

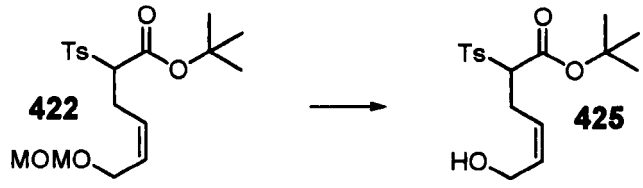



*Procedure B*

To a solution of **422** (882 mg, 2.29 mmol, 1.0 equiv) in MeCN (25 mL) was added aq. HCl (2.0 M; 5 mL). The reaction mixture was heated to reflux for 2 h, then partitioned between $CH_2Cl_2$ (75 mL) and $H_2O$ (75 mL). The aqueous phase was washed with $CH_2Cl_2$ (8× 25ml). Combined organic washings were dried ($Na_2SO_4$), concentrated under reduced pressure and recrystallised from $CHCl_3$/petrol to give *(±)-(Z)-6-hydroxy-2-(toluene-4-sulfonyl)hex-4-enoic acid* **427** (577 mg, 81%) as a white crystalline solid.

**427:** mp 116 °C; $\nu_{max}$ (film) 3480, 3029, 1732, 1597, 1444, 1401, 1383, 1319, 1303, 1292, 1246, 1146, 1084, 1016, 815, 711, 663 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.75 (2H, d, *J* 7.0 Hz, *o*-$SO_2Ar$), 7.47 (2H, d, *J* 7.0 Hz, *m*-$SO_2Ar$), [5.60-5.53, 5.30-5.22] (2H, m, -C*H*=C*H*-), 4.20 (1H, dd, *J* 7.5, 3.5 Hz, Ts-CH<), 3.99-3.83 (2H, m, HO-C$H_2$-), 2.56-2.50 (2H, m, Ts-CH-C$H_2$-CH=), 2.42 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, DMSO-$d_6$) 166.8 (C=O), 145.5, 134.8, 134.6, 130.2, 129.4, 123.9, 69.6, 57.2, 25.4, 21.6; *m/z* (CI) 284 $[M+NH_4-H_2O]^+$, 258, 240, 223, 174, 156, 139, 130 (Found: $[M+NH_4-H_2O]^+$, 284.0968. $C_{13}H_{16}O_5S$ requires $[M+NH_4-H_2O]^+$, 284.0957) (Found: C, 54.76; H, 5.49. $C_{13}H_{16}O_5S$ requires C, 54.92; H, 5.67%).

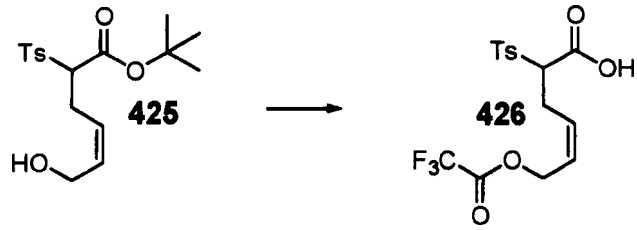
**(±)-(Z)-*tert*-Butyl 6-hydroxy-2-(toluene-4-sulfonyl)hex-4-enoate (425)**




To bromocatecholborane (99 mg, 0.5 mmol, 1.0 equiv) was added a solution of **422** (192 mg, 0.5 mmol, 1.0 equiv) in $CH_2Cl_2$ (2.5 mL) at rt. The reaction mixture was stirred at rt for 6 h, then quenched with $H_2O$ (2 mL). The reaction mixture was diluted with $CH_2Cl_2$ (50 mL), washed with $H_2O$ (50 mL), aq. NaOH (3.0 M; 50 mL) and saturated aq. NaCl (50 mL). The organic phase was dried over ($Na_2SO_4$), concentrated under reduced pressure and purified

by column chromatography (40% EtOAc–petrol) to give *(±)-(Z)-tert-butyl 6-hydroxy-2-(toluene-4-sulfonyl)hex-4-enoate* **425** (70 mg, 41%) as a colourless oil; $R_f$ 0.42 (50% EtOAc–petrol); $\nu_{max}$ (film) 3535, 3444, 1732, 1597, 1493, 1475, 1456, 1394, 1369, 1325, 1306, 1248, 1215, 1200, 1144, 1084, 1036, 1020, 985, 924, 883, 837, 816, 760, 714, 667 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 7.5 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 7.5 Hz, *m*-$SO_2Ar$), [5.79-5.71, 5.40-5.32] (2H, m, -C*H*=C*H*-), 4.21-4.06 (2H, m, -C$H_2$-OH), 3.89 (1H, dd, *J* 7.5, 3.5 Hz, Ts-CH<), 2.88-2.68 (2H, m, Ts-CH-C$H_2$-CH=), 2.46 (3H, s, Ts-$CH_3$), 2.09 (1H, br s, -OH), 1.31 (9H, s, -C($CH_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 164.7 (C=O), 145.5 (4°), 134.3 (4°), 133.0 (3°), 129.7 (3°), 129.3 (3°), 125.1 (3°), 83.7 (-*C*($CH_3$)$_3$), 70.5 (Ts-CH-), 58.1 (HO-*C*$H_2$-CH=), 27.7 (-C(*C*$H_3$)$_3$), 25.0 (Ts-CH-*C*$H_2$-CH=), 21.7 (Ts-$CH_3$); *m/z* (CI) 358 $[M+NH_4]^+$, 302, 284 $[M+H-C_4H_9]^+$ 202, 185, 174, 148, 146, 139, 130 (Found: $[M+NH_4]^+$, 358.1686. $C_{17}H_{24}O_5S$ requires $[M+NH_4]^+$, 358.1688) (Found: C, 59.79; H, 6.93. $C_{17}H_{24}O_5S$ requires C, 59.98; H, 7.11%).

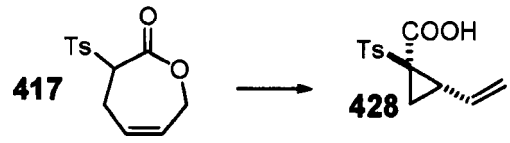
**(±)-(Z)-2-(Toluene-4-sulfonyl)-6-(2,2,2-trifluoroacetoxy)hex-4-enoic acid (426)**




To **425** (259 mg, 0.761 mmol, 1.0 equiv) was added $CH_2Cl_2$ (10 mL) and trifluoroacetic acid (1.74 g, 15.2 mmol, 20 equiv). The reaction mixture was stirred at rt for 72 h, then concentrated under reduced pressure to give *(±)-(Z)-2-(toluene-4-sulfonyl)-6-(2,2,2-trifluoroacetoxy)hex-4-enoic acid* **426** (289 mg, 100%) as a brown oil; $\nu_{max}$ (film) 3032, 1784 [$\nu_{C=O}$ $F_3C$-COO-], 1726 [$\nu_{C=O}$ COOH], 1597, 1442, 1385, 1325, 1306, 1221, 1149, 1086, 1043, 1024, 984, 818, 775, 714, 663 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 10.23 (1H, br s, -COOH), 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.34 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.65 (2H, br s, -C*H*=C*H*-), 4.89-4.76 (2H, m, -C$H_2$O-), 3.94 (1H, dd, *J* 10.0, 4.5 Hz, Ts-CH<), 2.86-2.72 (2H, m, Ts-CH-C$H_2$-CH=), 2.43 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 166.8 (-COOH), 157.2 (q, $^2J_{C-F}$ 42.5 Hz, $F_3C$-*C*OO-), 145.6 (4°), 134.1 (4°), 130.4 (3°), 129.8 (3°), 129.2 (3°), 125.1 (3°), 114.4 (q, $^1J_{C-F}$ 285.5 Hz, -$CF_3$), 69.6 (Ts-*C*H-COO-), 63.3 (-O$CH_2$-), 25.4 (Ts-CH-*C*$H_2$-CH=), 21.7 (Ts-$CH_3$);

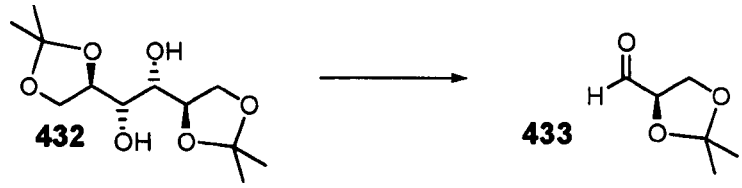
*m/z* (CI) 398 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 398.0876. $C_{15}H_{15}F_3O_6S$ requires $[M+NH_4]^+$, 398.0885)

**(±)-(1*R**,2*S**)-2-Ethenyl-1-(Toluene-4-sulfonyl)cyclopropanecarboxylic acid (428)**



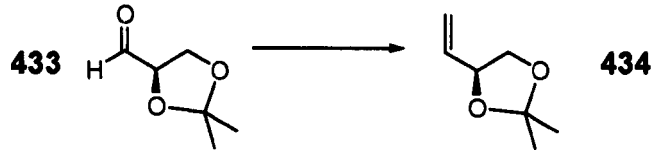

To a solution of **417** (51 mg, 0.190 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) was added potassium acetate (2 mg, 0.019 mmol, 0.1 equiv) in one portion. *N,O*-bis(trimethylsilyl)acetamide (48 µL, 0.190 mmol, 1.0 equiv) was added by syringe. The reaction mixture was stirred at rt for 16 h, diluted with $CH_2Cl_2$ (50 mL) and washed with aq. HCl (2.0 M; 10 mL) and $H_2O$ (5× 20 mL). Combined aqueous phases were concentrated under reduced pressure, then azeotropically dried with PhMe to give *(±)-(1*R**,2*S**)-2-ethenyl-1-(toluene-4-sulfonyl)cyclopropanecarboxylic acid* **428** (29 mg, 56%) as a white solid; mp 118–120 °C; $\nu_{max}$ (film) 3430, 3361, 3208, 1664, 1612, 1495, 1392, 1284, 1209, 1138, 1086, 1053, 999, 920, 874, 816, 665 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$d_6$) 7.80 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.32 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.87-5.78 (1H, m, -C*H*=$CH_2$), 5.31 (1H, d, *J* 17.5 Hz, *trans* -CH=C$H_2$), 4.98 (1H, d, *J* 10.5 Hz, *cis* -CH=C$H_2$), 2.41-2.29 (1H, m, $H_2C$=CH-C*H*<), 2.37 (3H, s, Ts-$CH_3$), [1.67 (1H, dd, *J* 10.0, 3.5 Hz), 1.62-1.57 (1H, m)], (-$CH_2$-); $\delta_C$ (75 MHz, DMSO-$d_6$) 163.8 (C=O), 142.6 (4°), 139.9 (4°), 136.7 (-*C*H=$CH_2$), 129.2 (3°), 128.9 (3°), 116.4 (=$CH_2$), 52.5 (Ts-C<), 29.0 ($H_2C$=CH-*C*H-), 21.8 (Ts-$CH_3$), 18.7 (-$CH_2$-); *m/z* (CI) 284 $[M+NH_4]^+$, 270, 242, 240, 174, 77, 60 (Found: $[M+NH_4]^+$, 284.0964. $C_{13}H_{14}O_4S$ requires $[M+NH_4]^+$, 284.0957).

**(*4R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (433)**



This was prepared exactly according to a literature procedure.[189] To 1,2;5,6-di-*O*-*iso*propylidene-D-mannitol **432** (6.70 g, 25.5 mmol, 1.0 equiv) in $CH_2Cl_2$ (60 mL) was added a saturated aq. solution of $NaHCO_3$ (2.7 mL). Sodium periodate (10.9 g, 51.0 mmol, 2.0 equiv) was added as a solid, resulting in an exotherm. The reaction mixture was stirred for 1.5 h at rt, then the precipitate was filtered off and the filtrate was concentrated under reduced pressure. Distillation under reduced pressure gave *(4R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde* **433** (5.36g, 81%) as a colourless liquid; $bp_{30}$ 59 °C (lit.[190] $bp_{35}$ 64–66 °C); $R_f$ 0.35 (50% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 9.71 (1H, s, -CHO), 4.40-4.36 (1H, m, >C*H*-CHO), 4.08-4.19 (2H, m, $OCH_2$-), 1.48 (3H, s, >C($CH_3$)($CH_3$)), 1.41 (3H, s, >C($CH_3$)($CH_3$)); data in agreement with those previously reported.[189]

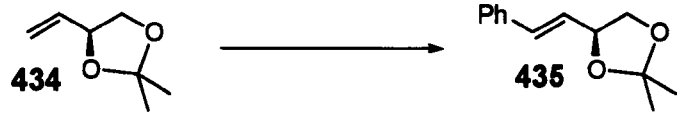
**(*4S*)-2,2-Dimethyl-4-ethenyl-1,3-dioxolane (434)**



This was prepared according to a literature procedure,[191] except a shorter reaction time was employed. To a suspension of methyltriphenylphosphonium bromide (13.8 g, 38.6 mmol, 1.10 equiv) in THF (50 mL) at 0 °C was added solid potassium *tert*-butoxide (4.13 g, 36.8 mmol, 1.05 equiv) as one portion, resulting in the formation of a yellow suspension. This was stirred at 0 °C for 30 min before dropwise addition by cannula of a solution of **433** (4.57 g, 35.1 mmol, 1.00 equiv) in $Et_2O$ (25 mL). The reaction mixture was stirred at 0 °C for 1 h and at rt for 30 min, then partitioned between $H_2O$ (50 mL) and $Et_2O$ (50 mL). The organic phase was washed with saturated aq. NaCl (2× 100 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure with minimal heating. Distillation under reduced pressure yielded the product contaminated with some *tert*-butanol, so the product was suspended in $Et_2O$

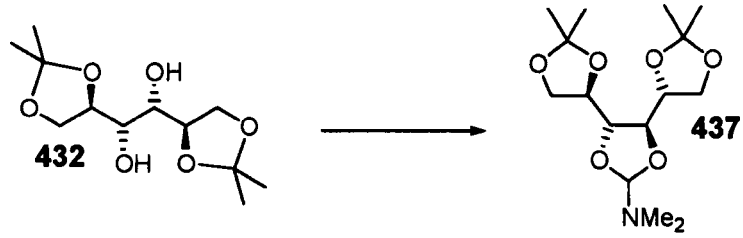
(50 mL) and washed with aq. NaOH (2.0 M; 3× 25ml). The organic phase was dried over $Na_2SO_4$, and concentrated under reduced pressure *with minimal heating* to give *(4S)-2,2-dimethyl-4-ethenyl-1,3-dioxolane* **434** (1.69 g, 38%) as a colourless liquid; $bp_{760}$ 123-125 °C (lit.[192] $bp_{760}$ 125 °C); $R_f$ 0.67 (50% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 5.88-5.76 (1H, m, -C*H*=$CH_2$), 5.34 (1H, d, *J* 17.0 Hz, *trans* -CH=C*H*$_2$), 5.21 (1H, d, *J* 10.0 Hz, *cis* -CH=C*H*$_2$), 4.53-4.46 (1H, m, $H_2C$=CH-C*H*<), 4.12-4.07 (1H, m, -OC*H*H-), 3.62-3.57 (1H, m, -OCH*H*-), 1.42 (3H, s, >C(C*H*$_3$)($CH_3$)), 1.39 (3H, s, >C($CH_3$)(C*H*$_3$)); data in agreement with those previously reported.[191]

**(*4S,E*)-2,2-Dimethyl-4-(2-phenylethenyl)-1,3-dioxolane (435)**




This was prepared by a method partially based on a literature procedure.[101] To benzylidene bis(tricyclohexylphosphine)dichlororuthenium (552 mg, 0.661 mmol, 0.05 equiv) under Ar was added a solution of **434** (1.69 g, 13.2 mmol, 1.00 equiv) in $CH_2Cl_2$ (50 mL). Styrene (3.04 mL, 26.4 mmol, 2.00 equiv) was added by syringe and the reaction mixture was heated to reflux for 16 h. The reaction mixture was concentrated under reduced pressure and purified by chromatography (10% EtOAc–petrol) to give *(4S,E)-2,2-dimethyl-4-(2-phenylethenyl)-1,3-dioxolane* **435** (0.507 g, 17%) as a brown oil; $R_f$ 0.27 (10% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.39-7.23 (5H, m, Ar-H), 6.65 (1H, d, 16.0 Hz, Ph-CH=), 6.14 (1H, dd, *J* 16.0, 7.5 Hz, Ph-CH=C*H*-), 4.72-4.63 (1H, m, Ph-CH=CH-C*H*<), 4.17-4.09 (1H, m, -OC*H*H-), 3.73-3.64 (1H, m, -OCH*H*-), 1.47 (3H, s, >C(C*H*$_3$)($CH_3$)), 1.42 (3H, s, >C($CH_3$)(C*H*$_3$)); data in agreement with those previously reported.[193]

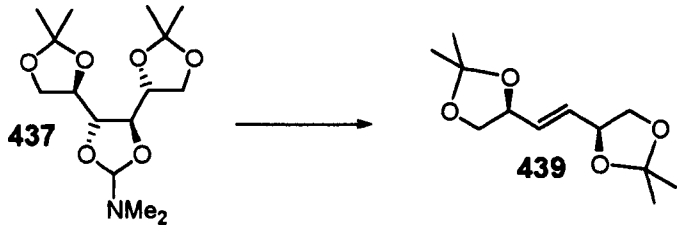
**1,2;5,6-Di-*O*-*iso*propylidene-3,4-(*N*,*N*-dimethylamino)methylidene-D-mannitol (437)**



**432** **437**

This was prepared by a method based on a literature procedure,[102a,b] for which little experimental detail was given. To 1,2;5,6-di-*O*-*iso*propylidene-D-mannitol **432** (2.62 g, 10.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) was added *N*,*N*,dimethylformamide dimethyl acetal (13.3 mL, 100 mmol, 10 equiv). The reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and dried to give *1,2;5,6-di-O-isopropylidene-3,4-(*N,N*-dimethylamino)methylidene-D-mannitol* **437** (3.00 g, 95%) as a white crystalline solid; mp 44–45 °C; $R_f$ 0.39 (50% EtOAc–petrol); $[\alpha]_D^{25}$ +5.9 (c=0.97, $CHCl_3$); $\nu_{max}$ (film) 1479, 1458, 1381, 1371, 1311, 1257, 1214, 1157, 1111, 1072, 968, 845 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 5.54 (1H, s, $(H_3C)_2NCH$), 4.25-3.92 (8H, m, $-OCH_2$, -OCH<), 2.35 (6H, s, $-N(CH_3)_2$), [1.44 (6H), 1.35 (6H)] (s, 2× $>C(CH_3)(CH_3)$); $\delta_C$ (75 MHz, $CDCl_3$) 113.4 ($(H_3C)_2NCH$<), [109.8, 109.7] (2× $-OC(CH_3)_2O-$), [78.4, 76.8, 76.4, 76.0] (4× -OCH<), [66.7, 66.1] (2× $-OCH_2-$), 36.8 ($-N(CH_3)_2$), [26.6, 26.5, 25.4, 25.0] (4× C-$CH_3$); *m/z* (CI) 318 $[M+H]^+$, 273, 216, 187, 101, 91, 74 (Found: $[M+H]^+$, 318.1908. $C_{15}H_{27}NO_6$ requires $[M+H]^+$, 318.1917) (Found: C, 56.63; H, 8.81; N, 4.47. $C_{15}H_{27}NO_6$ requires C, 56.77; H, 8.57; N, 4.41%).

**(*E*)-1,2-Bis((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethene (439)**

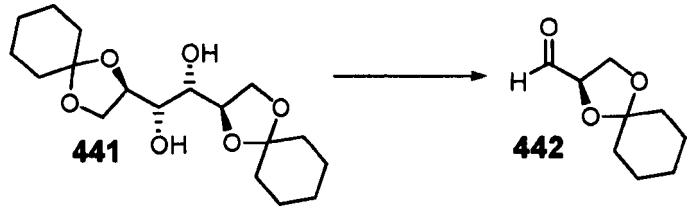


**437** **439**

This was prepared by a method based on a literature procedure,[102a,b] for which little experimental detail was given. To **437** (3.34 g, 10.5 mmol, 1.0 equiv) in PhMe (50 mL) was added methyl iodide (6.54 mL, 105 mmol, 10 equiv) by syringe. The reaction mixture was stirred at rt for 30 min, resulting in formation of a precipitate. The reaction mixture was heated to 60 °C for 30

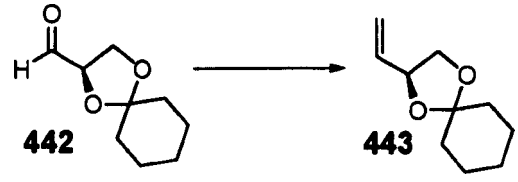
min, heated to reflux for 15 min, then allowed to cool. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. Chromatography (40% EtOAc–petrol) gave *(E)-1,2-bis((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethene* **439** (2.20 g, 92%) as a pale orange solid; mp 65 °C (lit.[102a,b] 82 °C); $[\alpha]_D^{25}$ +51.0 (c=1.1, $CHCl_3$); $\delta_H$ (300 MHz, $CDCl_3$) 5.79 (2H, dd, *J* 4.0, 2.0 Hz, -C*H*=C*H*-), 4.51 (2H, m, 2× -OCH<), 4.07 (2H, dd, *J* 8.0, 6.0 Hz, 2× -OC*H*H-), 3.57 (2H, t, *J* 8.0 Hz, 2× -OCH*H*-), [1.41, 1.37] (2× 6H, q, *J* 0.5 Hz, -OC($CH_3$)($CH_3$)O-); data in agreement with those previously reported.[102a,b]

**(2*R*)-1,4-Dioxaspiro[4.5]decane-2-carbaldehyde (442)**



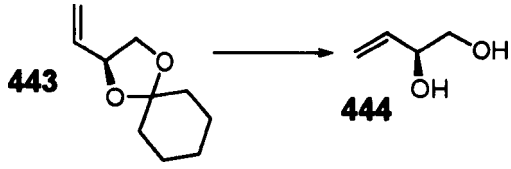

This was prepared according to a literature procedure,[194] except a lower reaction temperature was used and $CH_2Cl_2$ was substituted for $CHCl_3$. To a suspension of 1,2;5,6-di-*O*-cyclohexylidene-D-mannitol **441** (13.7 g, 40.0 mmol, 1.0 equiv) in MeCN:$H_2O$ 60:40 (120 mL) at –10 °C was added sodium periodate (17.1 g, 80.0 mmol, 2.0 equiv) in small portions over 1 min. The reaction mixture was stirred at –10 °C for 20 min, then at rt for 1 h. The reaction mixture was diluted with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (3× 100 mL). The organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure to give crude *(2R)-1,4-dioxaspiro[4.5]decane-2-carbaldehyde* **442** as a colourless liquid used immediately without purification; $\delta_H$ (300 MHz, $CDCl_3$) 9.71 (1H, s, -CHO), 4.40-4.35 (1H, m, >C*H*-CHO), 4.18-4.07 (2H, m, -$OCH_2$-), 1.65-1.62 (8H, m, cyclohexyl-H), 1.42 (2H, br s, cyclohexyl-H); data in agreement with those previously reported.[194]

**(2*S*)-1,4-dioxa-2-ethenylspiro[4.5]decane (443)**



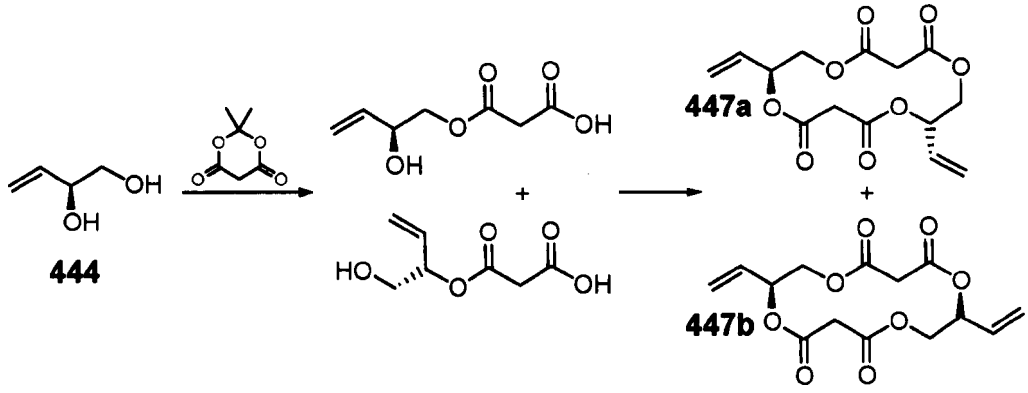
This was prepared exactly according to a literature procedure.[103] To a suspension of methyltriphenylphosphonium bromide (38.8 g, 96.0 mmol, 1.2 equiv) in THF (296 mL) at 0 °C was added *n*-BuLi (1.75 M in hexanes; 54.9 mL, 96.0 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 15 min, at rt for 45 min, then was cooled to –78 °C. A solution of **442** (assumed to be 80 mmol, 1.0 equiv) in THF (100 mL) was added dropwise by cannula. The reaction mixture was stirred at –78 °C for 1 h, then at rt for 16 h. A small amount of acetone was added by syringe, then saturated aq. $NH_4Cl$ (200 mL) was added. The reaction mixture was extracted with EtOAc (3× 100 mL). The organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by column chromatography (petrol) to give *(2S)-1,4-dioxa-2-ethenylspiro[4.5]decane* **443** (10.3 g, 61%) as a colourless oil; $[\alpha]_D^{25}$ +4.8 (c=2.0, EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 5.88-5.76 (1H, m, -C*H*=$CH_2$), 5.34 (1H, dd, *J* 17.0, 1.0 Hz, *trans* -CH=C*H*$_2$), 5.20 (1H, d, *J* 10.0 Hz, *cis* -CH=C*H*$_2$), 4.49-4.44 (1H, m, $H_2C$=CH-C*H*<), [4.11-4.07, 3.60-3.54] (2H, m, -$OCH_2$-), 1.60 (8H, br s, cyclohexyl-H), 1.38 (2H, br s, cyclohexyl-H); data in agreement with those previously reported.[103]

**(*S*)-But-3-ene-1,2-diol (444)**



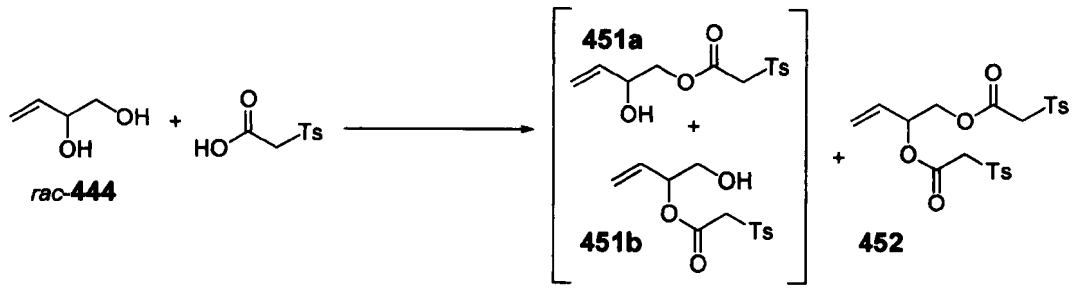

This was prepared according to a literature procedure,[103] except a longer reaction time and a different grade of Dowex™ were employed. To **443** (2.22 g, 13.2 mmol, 1.0 equiv) in MeOH (30 mL) was added Dowex™ 50WX4-200 (7.0 g). The reaction mixture was gently stirred at rt for 72 h. The Dowex™ was filtered off and the filtrate was concentrated under reduced pressure and purified by column chromatography (70% EtOAc–petrol) to give *(S)-but-3-ene-1,2-diol* **444** (931 mg, 80%) as a colourless oil; $R_f$ 0.21 (70% EtOAc–petrol); $[\alpha]_D^{25}$ –27.6 (c=0.80, EtOAc); $\delta_H$ (300 MHz, $CDCl_3$) 5.85-5.73 (1H, m, -C*H*=$CH_2$), 5.31 (1H, d, *J* 16.0 Hz, *trans* -CH=C*H*$_2$), 5.17 (1H, d, *J* 10.0 Hz, *cis* -CH=C*H*$_2$), 4.20 (1H, br s, $H_2C$=CH-C*H*<), [3.60, 3.44] (2× 1H, br s, -$OCH_2$-); values in agreement with previously reported data.[103]

**(2*S*,10*S*)-2,10-Diethenyl-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone and (2*S*,19*S*)-2,9-Diethenyl-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone (447)**




To a solution of (*S*)-but-3-ene-1,2-diol **444** (632 mg, 7.17 mmol, 1.0 equiv) in THF (15 mL) was added Meldrum's acid (1.03 g, 7.17 mmol, 1.0 equiv). The reaction mixture was heated to reflux for 22 h, then concentrated under reduced pressure. The crude intermediate was redissolved in $CH_2Cl_2$ (30 mL), and *N,N'*-di*iso*propyl carbodiimide (1.12 mL, 7.17 mmol, 1.0 equiv) was added. The reaction mixture was stirred at rt for 14 h, concentrated under reduced pressure and purified by chromatography (35% EtOAc–petrol) to give *(2S,10S)-2,10-diethenyl-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone* **447b** and *(2S,9S)-2,9-diethenyl-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone* **447a** (149 mg, 7%) as a colourless oil and as an inseparable mixture; $R_f$ 0.44 (40% EtOAc–petrol); $[\alpha]_D^{25}$ +48.0 (c=1.00, $CHCl_3$); $\nu_{max}$ (film) 3647, 3554, 3473, 3091, 1739, 1730, 1649, 1452, 1415, 1385, 1309, 1242, 1157, 1022, 964, 948, 849, 806, 732, 688 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 5.76-5.66 (2H, m, 2× -C*H*=$CH_2$), [5.55-5.5, 5.46-5.42] (2H, m, 2× -OCH<), 5.35 (2H, d, *J* 17.5 Hz, 2× *trans* -CH=C$H_2$), 5.28 (2H, d, *J* 10.5 Hz, 2× *cis* -CH=C$H_2$), 4.23-4.11 (4H, m, 2× -$OCH_2$-), [3.38, 3.37] (4H, s, 2× -$CH_2$-COO-); $\delta_C$ (100 MHz, $CDCl_3$) [165.5, 164.8, 164.7] (C=O), [131.0, 130.8] (-*C*H=$CH_2$), [120.0, 119.9] (-CH=*C*$H_2$), [73.2, 72.8] (-OCH<), [65.7, 65.3] (-$OCH_2$-), [42.3, 41.9, 41.7] (-*C*$H_2$-COO-); *m/z* (CI) 330 $[M+NH_4]^+$, 313 $[M+H]^+$, 139 (Found: 330.1182. $C_{14}H_{16}O_8$ requires $[M+NH_4]^+$ 330.1189).

**(±)-2-Hydroxybut-3-enyl (toluene-4-sulfonyl)acetate and (±)-1-Hydroxybut-3-en-2-yl (toluene-4-sulfonyl)acetate (451) and (±)-But-3-ene-1,2-diyl bis((toluene-4-sulfonyl)acetate) (452)**



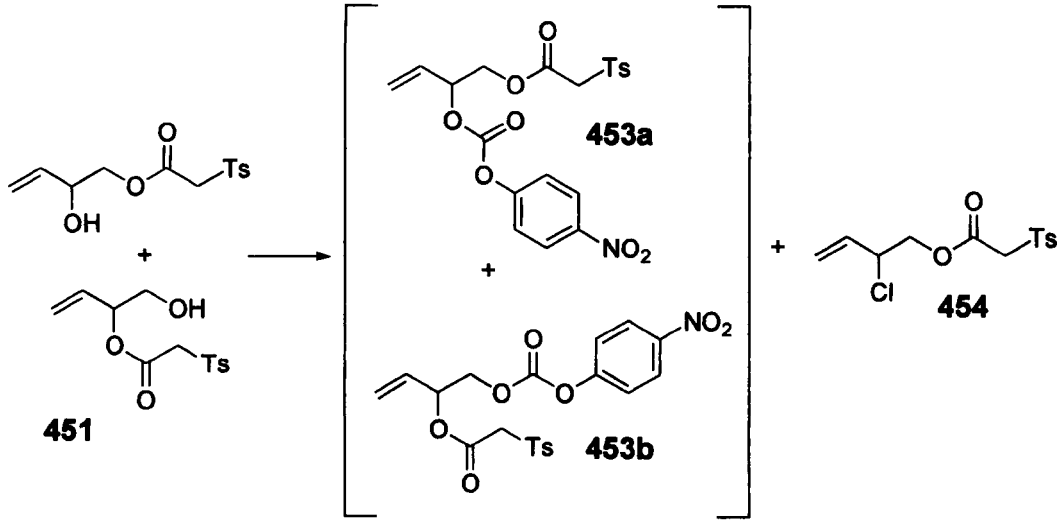

To (±)-3,4-dihydroxybut-1-ene *rac*-**444** (581 mg, 6.59 mmol, 1.0 equiv) and (toluene-4-sulfonyl)acetic acid (1.41 g, 6.59 mmol, 1.0 equiv) in $CH_2Cl_2$ (65 mL) at 0 °C was added dropwise by syringe *N,N'*-di*iso*propyl carbodiimide (1.03 mL, 6.59 mmol, 1.0 equiv). The solution was stirred at 0 °C for 15 min then at rt for 64 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure and purified by chromatography (50% EtOAc–petrol) to give *(±)-2-hydroxybut-3-enyl (toluene-4-sulfonyl)acetate* and *(±)-1-hydroxybut-3-en-2-yl (toluene-4-sulfonyl)acetate* **451** (1.40 g, 75%) as a pale yellow oil. Also isolated was *(±)-but-3-ene-1,2-diyl bis((toluene-4-sulfonyl)acetate)* **452** (285 mg, 9%) as a colourless foam.

**451a, 451b:** $R_f$ 0.46 (70% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.40 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.88-5.76 (1H, m, -C*H*=$CH_2$), 5.45-5.26 (2H, m, -CH=C$H_2$), [4.40 (br s), 4.28-4.04 (m), 3.75-3.71 (m)] (5H, Ts-$CH_2$-, -$OCH_2$-, $H_2C$=CH-C*H*<), 2.48 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.4 (C=O), 145.8, 135.6, 135.2, 130.0, 128.5, 119.7, 117.6, 78.2 ($H_2C$=CH-CH<, **451b**), [70.3, 69.4] (-$OCH_2$-, **451a**, $H_2C$=CH-CH-, **451a**), 64.1 (-C$H_2$-OH, *21b*), [61.6 (**451b**), 61.2 (**451a**)] (Ts-$CH_2$-), 21.8 (Ts-$CH_3$); *m/z* (CI) 302 $[M+NH_4]^+$, 267, 232, 188, 174, 148 (Found: $[M+NH_4]^+$, 302.1066. $C_{13}H_{16}O_5S$ requires $[M+NH_4]^+$, 302.1062).

**452:** $R_f$ 0.61 (70% EtOAc–petrol); $\nu_{max}$ (film) 1745, 1662, 1597, 1450, 1400, 1326, 1306, 1290, 1155, 1084, 914, 814, 733 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.80 (4H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.37 (4H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.70-5.62 (1H, m, -C*H*=$CH_2$), 5.47 (1H, br s, O-CH<), 5.40 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.32 (1H, d, *J* 10.5 Hz, *cis* -CH=C$H_2$), 4.24-4.12 (6H, m, 2× Ts-$CH_2$-, -$OCH_2$-), 2.46 (6H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [162.2, 161.7] (2× C=O), 145.6, 135.8, 130.3, 130.0, 129.9, 128.5 (×2), 120.6, 73.4, 65.5, [61.0, 60.8] (Ts-

$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 498 $[M+NH_4]^+$, 344, 302, 267, 188, 174, 139 (Found: $[M+NH_4]^+$, 498.1250. $C_{22}H_{24}O_8S_2$ requires $[M+NH_4]^+$, 498.1256). (Found: C, 54.76; H, 4.95. $C_{22}H_{24}O_8S_2$ requires C, 54.99; H, 5.03%).

**(±)-2-((4-Nitrophenoxy)carbonyloxy)but-3-enyl (toluene-4-sulfonyl)acetate and (±)-1-((4-Nitrophenoxy)carbonyloxy)but-3-en-2-yl (toluene-4-sulfonyl)acetate (453) and 2-chlorobut-3-enyl (toluene-4-sulfonyl)acetate (454)**



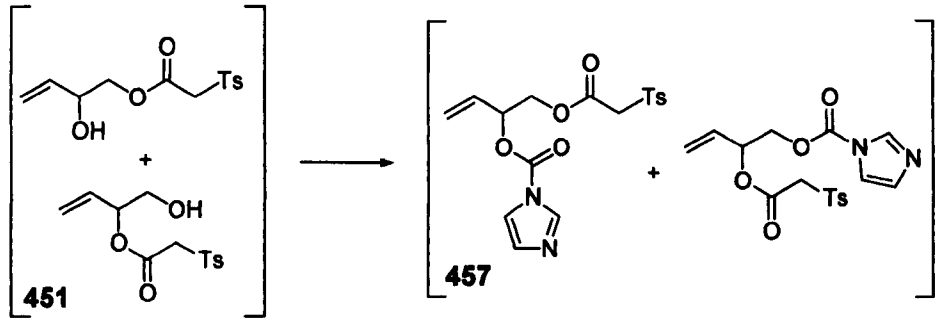

To a solution of **451** (553 mg, 1.94 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at –10 °C was added by syringe triethylamine (270 µL, 1.94 mmol, 1.0 equiv). The reaction mixture was stirred at –10 °C for 30 min, then was added by cannula to a solution of *p*-nitrophenyl chloroformate (392 mg, 1.94 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL). The reaction mixture was stirred at –10 °C for 20 min, then at rt for 10 h. The reaction mixture was quenched with saturated aq. $NH_4Cl$ (100 mL) and extracted into EtOAc (200 mL). This organic layer was washed with further saturated aq. $NH_4Cl$ (2× 100 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (35→70% EtOAc–petrol) to give *(±)-2-((4-nitrophenoxy)carbonyloxy)but-3-enyl (toluene-4-sulfonyl)acetate* and *(±)-1-((4-nitrophenoxy)carbonyloxy)but-3-en-2-yl (toluene-4-sulfonyl)acetate* **453** (233 mg, 27%) as a yellow gum and *2-chlorobut-3-enyl (toluene-4-sulfonyl)acetate* **454** (35 mg, 6%) as a yellow gum.

**453:** $R_f$ 0.27 (35% EtOAc–petrol); $\nu_{max}$ (film) 3116, 3085, 1768, 1747, 1595, 1525, 1493, 1348, 1329, 1217, 1157, 1084, 860, 731 $cm^{-1}$; $\delta_H$ (300 MHz,

$CDCl_3$) 8.27 (2H, d, *J* 9.0 Hz, *o*-$NO_2Ar$), 7.84 (2H, d, *J* 7.5 Hz, *o*-$SO_2Ar$), 7.44-7.35 (4H, m, *m*-$SO_2Ar$, *m*-$NO_2Ar$), 5.85-5.72 (1H, m, -C*H*=$CH_2$), 5.63-5.37 (3H, m, -CH=C$H_2$, $H_2C$=CH-C*H*<), 4.44-4.25 (2H, m, -$OCH_2$-), [4.18, 4.17] (2H, s, Ts-$CH_2$-), 2.44 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.3 (4°), 161.7 (4°), 155.5 (4°), 155.4 (4°), 152.3 (4°), 151.8 (4°), 145.6 (4°), 135.7 (4°), 130.2 (3°), 130.1 (3°), 130.0 (3°), 128.6 (3°), 125.3 (3°) 122.0 (3°), 121.2 (2°), 120.8 (2°), 77.2 (3°), 73.6 (3°), 68.7 (2°), 65.7 (2°), 61.1 (2°), 61.0 (2°), 21.7 (1°); *m/z* (CI) 467 $[M+NH_4]^+$, 437, 401, 384, 302, 267, 188, 174, 157, 132 (Found: $[M+NH_4]^+$, 467.1121. $C_{20}H_{19}NO_9S$ requires $[M+NH_4]^+$, 467.1124).

**454:** $R_f$ 0.41 (35% EtOAc–petrol); $\nu_{max}$ (film) 1747, 1597, 1450, 1402, 1329, 1278, 1153, 1086, 991, 939, 814, 731 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.83 (2H, dd, *J* 8.0 2.0 Hz, *o*-$SO_2Ar$), 7.37 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.79 (1H, ddd, *J* 17.0, 10.0, 8.0 Hz, -C*H*=$CH_2$), 5.37 (1H, dt, *J* 17.0, 1.0 Hz, *trans* -CH=C$H_2$), 5.26 (1H, d, *J* 10.0 Hz, *cis* -CH=C$H_2$), 4.45 (1H, qt, *J* 7.0, 1.0 Hz, $H_2C$=CH-C*H*<), 4.28 (1H, dd, *J* 11.5, 6.0 Hz, -OC*H*H-), 4.26 (1H, dd, *J* 11.5 7.0 Hz, -OCH*H*-), 4.14 (2H, s, Ts-$CH_2$-), 2.46 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.1 (C=O), 145.6 (4°), 135.7 (4°), 133.7 (-*C*H=$CH_2$), 130.0 (3°), 128.6 (3°), 119.8 (-CH=$CH_2$), 68.2 (-$OCH_2$-), 60.8 (Ts-$CH_2$-), 57.9 (Cl-CH<), 21.7 (Ts-$CH_3$); *m/z* (CI) [322, 320] $[M+NH_4]^+$, 286, 226, 188 (Found: $[M+NH_4]^+$, 320.0728. $C_{13}H_{15}ClO_4S$ requires $[M+NH_4]^+$, 320.0723).

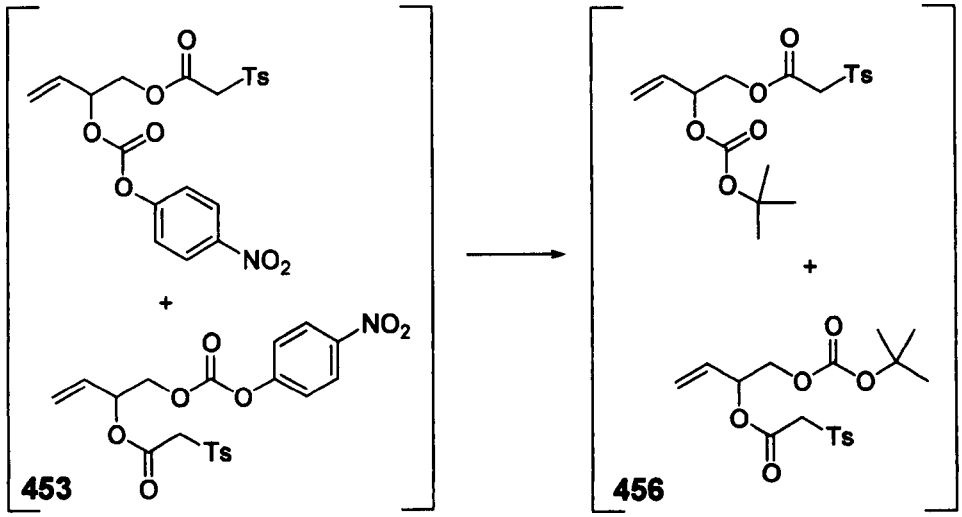
**(±)-1-(2-(toluene-4-sulfonyl)acetoxy)but-3-en-2-yl imidazole-1-carboxylate and (±)-2-(2-(toluene-4-sulfonyl)acetoxy)but-3-enyl imidazole-1-carboxylate (457)**




To a solution of **451** (247 mg, 0.868 mmol, 1.0 equiv) and carbonyl diimidazole (422 mg, 2.60 mmol, 3.0 equiv) in $CH_2Cl_2$ (43 mL) in $CH_2Cl_2$ (43 mL) was added 4-(*N*,*N*-dimethylamino)pyridine (11 mg, 0.087 mmol, 0.1

equiv) and triethylamine (242 μL, 1.74 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 16 h, then washed with saturated aq. $NH_4Cl$ (3× 50 mL). The organic layer was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (70% EtOAc–petrol) to give *(±)-1-(2-(toluene-4-sulfonyl)acetoxy)but-3-en-2-yl imidazole-1-carboxylate* and *(±)-2-(2-(toluene-4-sulfonyl)acetoxy)but-3-enyl imidazole-1-carboxylate* **457** (280 mg, 85%) as a pale yellow oil; $R_f$ 0.33 (70% EtOAc–petrol); $\nu_{max}$ (film) 3132, 1761, 1597, 1475, 1394, 1325, 1290, 1242, 1155, 1086, 1001, 816, 768 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.14 (1H, s, Im-H), 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.43 (1H, s, Im-H), 7.34 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.08 (1H, s, Im-H) 5.93-5.72 (1H, m, -C*H*=$CH_2$), 5.65-5.30 (3H, m, -CH=C$H_2$, $H_2C$=CH-C*H*<), 4.56-4.30 (2H, m, -$OCH_2$-), [4.16, 4.13] (2H, s, Ts-$CH_2$-), 2.44 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.2 (4°), 161.6 (4°), 147.8 (4°), 145.7 (4°), 137.2 (3°), 135.8 (4°), 130.8 (3°), 130.0 (3°), 128.4 (3°), 121.5 (2°), 121.0 (2°), 117.2 (3°), 76.1 (3°), 73.5 (3°), 67.5 (2°), 65.6 (2°), 61.0 (2°), 60.8 (2°), 21.7 (1°); *m/z* (CI) 379 $[M+H]^+$, 302, 225, 86, 69 (Found: $[M+H]^+$, 379.0959. $C_{17}H_{18}N_2O_6S$ requires $[M+H]^+$, 379.0964).

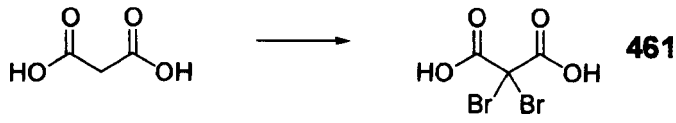
**2-(*tert*-Butoxycarbonyloxy)but-3-enyl (toluene-4-sulfonyl)acetate and 1-(*tert*-Butoxycarbonyloxy)but-3-en-2-yl (toluene-4-sulfonyl)acetate (456)**




To a solution of **453** (79 mg, 0.176 mmol, 1.0 equiv, azeotropically dried from PhMe) in THF (5 mL) at –78 °C was added by syringe potassium *tert*-butoxide (1.0M in THF; 0.352 mL, 0.352 mmol, 2.0 equiv). The reaction mixture was stirred at –78 °C for 15 min, then at rt for 1 h. The reaction mixture was

quenched with saturated aq. $NH_4Cl$ (100 mL) and extracted into EtOAc (200 mL). This organic layer was further washed with saturated aq. $NH_4Cl$ (2× 100 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (3→5% $Et_2O$-$CH_2Cl_2$ + 3 drops AcOH per 1 L eluent) to give *2-(*tert*-butoxycarbonyloxy)but-3-enyl (toluene-4-sulfonyl)acetate and 1-(*tert*-butoxycarbonyloxy)but-3-en-2-yl (toluene-4-sulfonyl)acetate* **456** (34 mg, 50%) as a yellow gum; $R_f$ 0.58 (5% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 1743, 1597, 1396, 1371, 1328, 1290, 1254, 1157, 1086, 937, 813, 727 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.38 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.79-5.67 (1H, m, -C*H*=$CH_2$), [5.49-5.45, 5.23-5.17] (1H, m, >C*H*-CH=$CH_2$), 5.43-5.29 (2H, m, -CH=C$H_2$) 4.31-4.03 (4H, m, -$OCH_2$-, Ts-$CH_2$-), 2.47 (3H, s, Ts-$CH_3$), 1.49 (9H, s, -$C(CH_3)_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.3 (4°), 161.6 (4°), 153.1 (4°), 145.5 (4°), 135.7 (4°), 131.5 (3°), 130.8 (3°), 129.9 (3°), 128.7 (3°), 120.2 (2°), 119.7 (2°), 82.8 (-*C*$(CH_3)_3$), [74.2, 74.3] ($H_2C$=CH-*C*H<), [66.6, 66.3] (-$OCH_2$-), [61.1, 60.8] (Ts-$CH_2$-), 27.7 (-$C(CH_3)_3$), 21.7 (Ts-$CH_3$); *m/z* (CI) 402 $[M+NH_4]^+$, 346, 302, 188, 52 (Found: $[M+NH_4]^+$, 402.1577. $C_{18}H_{24}O_7S$ requires $[M+NH_4]^+$, 402.1586).

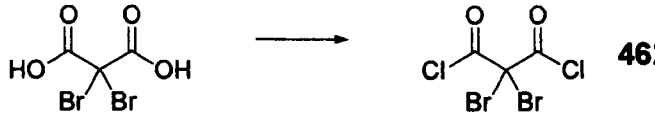
**Dibromomalonic acid (461)**



**461**

This was prepared in exactly accordance with a literature procedure.[110] To malonic acid (20.0 g, 192 mmol, 1.0 equiv) in aq. HBr (5%, 20 mL) at 0 °C in air was added dropwise bromine (19.7 mL, 384 mmol, 2.0 equiv) over 30 min with vigorous stirring. A thick brown suspension resulted. This was allowed to warm to rt, *resulting in a significant exotherm*, then stirred for 14 h. The precipitate was filtered and washed with copious amounts of pentane, then dried over NaOH under vacuum for 4 d to give crude *dibromomalonic acid* **461** (31.3 g, 63%) as a heterogeneous orange solid, used immediately without purification; mp 137–141 °C (lit.[195] mp 147 °C); $\delta_C$ (75 MHz, $CDCl_3$) 166.8, 45.4; *m/z [no parent ion detected]* (Found: C, 13.95; H, 0.83. $C_3H_2Br_2O_4$ requires C, 13.76; H, 0.77%).

**Dibromomalonyl dichloride (462)**

**461** 

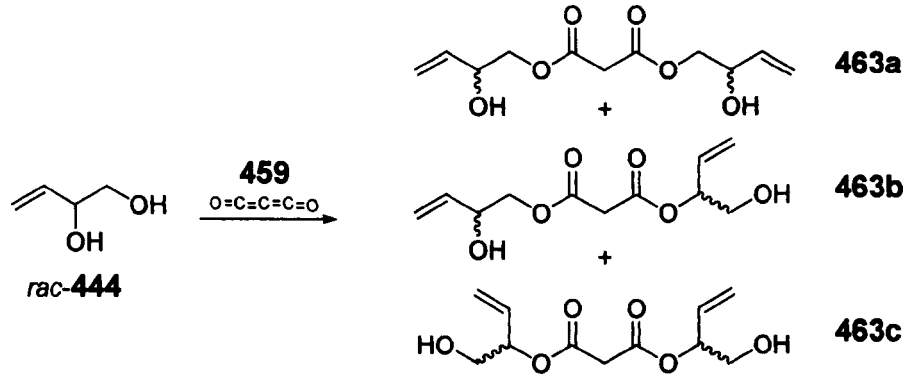
**462**

This was prepared exactly in accordance with a literature procedure.[110] To dibromomalonic acid **461** (21.3 g, 81.3 mmol, 1.0 equiv) was added $CH_2Cl_2$ (35 mL) and DMF (1 drop). Oxalyl chloride (21.3 mL, 244 mmol, 3.0 equiv) was added dropwise over 1.5 h, resulting in effervescence and reflux. The reaction mixture was stirred at rt for 14 h. The reaction mixture was concentrated under reduced pressure, then purified by distillation under reduced pressure (product solidified in condenser) to give *dibromomalonyl dichloride* **462** (15.8 g, 65%) as a yellow solid; $bp_{1.5}$ 57 °C (lit.[108] $bp_{15}$ 75–77 °C); mp 39–41 °C (lit.[110] 39–42 °C); $\nu_{max}$ (film) 1793, 1063, 1022, 999, 783, 715, 688 $cm^{-1}$; $\delta_C$ (75 MHz, $CDCl_3$) 161.2, 62.1; *m/z [no parent ion detected]*; data in agreement with those previously reported.

**General Procedure (*viii*): Generation of carbon suboxide (459)**


A two-necked flask was fitted with a dropping funnel and connected to a cold finger at –78 °C by means of a still head. To the bottom of the cold finger was attached a receiver flask. The flask was charged with zinc dust (12.0 equiv, Sigma-Aldrich, >10μm, 98%, unactivated) and the system was purged with $N_2$. The receiver flask was charged with a solution of the desired nucleophile in $Et_2O$ (1.0 equiv, 5 mmol scale, 0.04 M). The dropping funnel was charged with dibromomalonyl dichloride **462** (4.0 equiv) in $Et_2O$ (0.04 M). The solution of **462** was added dropwise to the zinc dust. External heating with a heat gun was required to initiate the reaction, after which reflux was maintained by the inherent exothermicity. The carbon suboxide produced co-distilled with the $Et_2O$ and condensed on the cold finger before dripping into the receiver flask.

**1,3-*Bis*(2-hydroxybut-3-enyl)malonate, 1-(2-Hydroxybut-2-enyl)-3-(1-hydroxymethylprop-2-enyl)malonate and 1,3-*Bis*(1-hydroxymethylprop-2-enyl)malonate (292), diastereoisomers as shown**

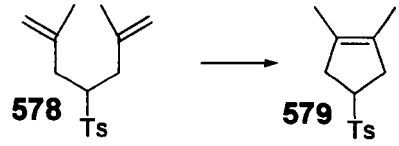



General procedure (*viii*) was applied, using zinc dust (3.92 g, 60 mmol, 12.0 equiv), dibromomalonyl dichloride (5.97 g, 20 mmol, 4.0 equiv) and (±)-3,4-dihydroxybut-1-ene (440 mg, 5.0 mmol, 1.0 equiv). After generation of carbon suboxide, the reaction mixture in the receiver flask was stirred at –78 °C for 1 h and at rt for 14 h. Concentration under reduced pressure and chromatography (5% MeOH–$CH_2Cl_2$) gave *1,3-bis(2-hydroxybut-3-enyl)malonate, 1-(2-hydroxybut-2-enyl)-3-(1-hydroxymethylprop-2-*

*enyl)malonate and 1,3*-bis*(1-hydroxymethylprop-2-enyl)malonate* **292** (223 mg, 29%) as a colourless oil and as an inseparable mixture of regio- and diastereoisomers with *1,3*-bis*(2-hydroxybut-3-enyl)malonate* **292a** the major constituent; Rf 0.30 (10% MeOH–$CH_2Cl_2$); $\nu_{max}$ (film) 3440, 1734, 1650, 1411, 1381, 134, 1275, 1190, 1149, 1086, 1016, 933, 874 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 5.90-5.73 (2H, m, **292a** -C*H*=$CH_2$), 5.45-5.16 (m, minor olefinic signals) 5.39 (2H, d, *J* 17.5 Hz, **292a** *trans* -CH=C*H*$_2$), 5.24 (2H, d, *J* 10.5 Hz, **292a** *cis* -CH=C*H*$_2$), 4.40 (2H, br s, **292a** $H_2C$=CH-C*H*<), 4.25 (2H, dd, *J* 11.5, 3.0 Hz, **292a** -OC*H*H-), 4.08 (2H, dd, *J*, 11.5, 8.0 Hz, **292a** -OCH*H*-), 3.74-3.63 (m, minor -$OCH_2$-), 3.47 (2H, s, **292a** -$CH_2COO$-), 3.16 (4H, br s, -OH); $\delta_C$ (75 MHz, $CDCl_3$) 166.6, 166.4, 166.3, 166.0, 135.6, 132.2, 130.9, 120.0, 119.0, 117.4, 73.2, 70.5, 69.6, 68.8, 67.0, 65.5, 64.0, 41.8, 41.5, 41.4, 41.2; *m/z* (CI) 262 $[M+NH_4]^+$, 227, 192, 170, 157, 139 (Found: $[M+NH_4]^+$, 262.1291. $C_{11}H_{16}O_6$ requires $[M+NH_4]^+$, 262.1291).

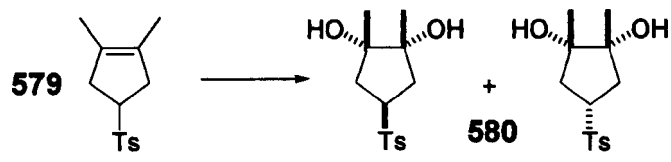
- **3.3.13 Compounds relevant to Pyridine *N*-oxide formation**

**1,2-Dimethyl-4-cyclopentenyl 4-methylphenyl sulfone (579)**




Diene **578**[196] (140 mg, 0.50 mmol, 1.0 equiv) and dichloro (tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) (benzylidene)ruthenium (42 mg, 0.050 mmol, 0.1 equiv) were placed in a microwave vial, which was sealed and purged with $N_2$. $CH_2Cl_2$ (10 mL) was introduced by syringe and the reaction mixture was heated to 80 °C under conditions of microwave irradiation. Concentration under reduced pressure and chromatography (5→10% EtOAc–petrol) gave *1,2-dimethyl-4-cyclopentenyl 4-methylphenyl sulfone* **579** (68 mg, 54%) as a colourless oil; $R_f$ 0.44 (20% EtOAc–petrol); $\nu_{max}$ (film) 3085, 3061, 3047, 3029, 1597, 1494, 1445, 1402, 1383, 1301, 1261, 1219, 1182, 1145, 1088, 1041, 1019, 932, 922, 812, 717, 697, 657 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.33 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 3.81-3.70 (1H, m, Ts-CH<), 2.81 (2H, dd, *J* 13.0, 3.5 Hz, Ts-CH-C*H*H-), 2.46 (2H, dd, *J* 13.0, 9.5 Hz, Ts-CH-CH*H*-), 2.43 (3H, s, Ts-$CH_3$), 1.52 (6H, s, =C-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.4 (4° Ar), 135.6 (4° Ar), 129.8 (3° Ar), 128.9 (olefinic), 128.5 (3° Ar), 60.8 (Ts-CH<), 38.8 (Ts-CH-$CH_2$-), 21.6 (Ts-$CH_3$), 13.4 (=C-$CH_3$); *m/z* (CI) 518 $[2M+NH_4]^+$, 268 $[M+NH_4]^+$, 94 (Found: $[M+NH_4]^+$, 268.1381. $C_{14}H_{18}O_2S$ requires $[M+NH_4]^+$, 268.1371) (Found: C, 67.02; H, 7.15. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25%).

**(1*S**,2*R**,4*R**)-1,2-Dimethyl-4-(toluene-4-sulfonyl)cyclopentane-1,2-diol and (1*S**,2*R**,4*S**)-1,2-Dimethyl-4-(toluene-4-sulfonyl)cyclopentane-1,2-diol (580)**



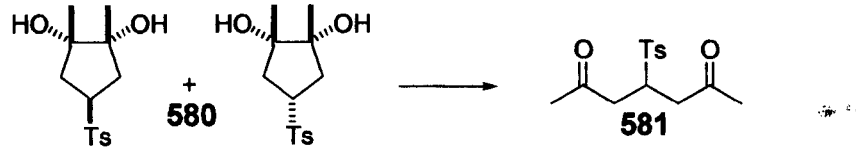
Olefin **579** (68 mg, 0.272 mmol, 1.0 equiv) and *N*-methylmorpholine *N*-oxide (65 mg, 0.558 mmol, 2.05 equiv) were dissolved in acetone (2.5 mL). One drop of $H_2O$ was added, resulting in some precipitation. $OsO_4$ (4% wt. in $H_2O$, 43 µL, 0.0068 mmol, 0.025 equiv) was added by syringe, resulting in the reaction mixture becoming slightly darker and the precipitate disappearing. The reaction mixture was stirred for 14 h at rt. Saturated aq. $Na_2SO_3$ (1.0 mL) was added and the reaction mixture stirred for 1 h, then partitioned between EtOAc (25 mL) and $H_2O$ (25 mL). The aqueous layer was washed with EtOAc (10 mL). Combined organic phases were washed with aq. $Na_2SO_3$ (10 mL), $H_2O$ (10 mL) and brine (10 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (60% EtOAc–petrol) to give *(1S*,2R*,4R*)-1,2-dimethyl-4-(toluene-4-sulfonyl)cyclopentane-1,2-diol and (1S*,2R*,4S*)-1,2-dimethyl-4-(toluene-4-sulfonyl)cyclopentane-1,2-diol* **580** (78 mg, 100%) as a colourless oil and as a 7.4:1 ratio of diastereoisomers; $R_f$ 0.17 (50% EtOAc–petrol); $\nu_{max}$ (film) 3473, 3063, 3047, 3032, 1597, 1494, 1449, 1382, 1362, 1300, 1286, 1214, 1184, 1144, 1086, 1042, 1019, 985, 945, 912, 861, 817, 755, 734, 707, 691, 659 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.34 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), [3.82-3.77 (maj. diast.), 3.57-3.46 (min. diast.)] (1H, m, Ts-CH<), 2.79 (2H, br s, -OH), 2.43 (3H, s, Ts-$CH_3$), 2.19-2.00 (4H, m, 2× -$CH_2$-), [1.23 (maj. diast.), 1.14 (min. diast.)] (6H, s, HO-C-C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.8 (4° Ar), 135.5 (4° Ar), [130.1, 128.5] (3° Ar, min. diast.), [129.9, 128.3] (3° Ar, maj. diast.), [80.2 (maj. diast.), 79.8 (min. diast.)] (COH), [59.3 (maj. diast.), 58.3 (min. diast.)] (Ts-CH<), [38.4 (maj. diast.), 38.2 (min. diast.)] (-$CH_2$-), 22.9 (HO-C-$CH_3$), 21.6 (Ts-$CH_3$), 21.3 (min. diast. of HO-C-$CH_3$ or Ts-$CH_3$); *m/z* (CI) 302 $[M+NH_4]^+$, 285 $[M+H]^+$, 266 (Found: $[M+NH_4]^+$, 302.1431. $C_{14}H_{20}O_4S$ requires $[M+NH_4]^+$, 302.1426).

**4-(Toluene-4-sulfonyl)heptane-2,6-dione (581)**


*Procedure A*

Through diene **578**[196] (122 mg, 0.438 mmol, 1.0 equiv) in $CH_2Cl_2$:MeOH 4:1 (10 mL) at –78 °C was passed a stream of $O_3$ in $O_2$ until the reaction mixture turned blue. Gas flow was discontinued and solid-supported $PPh_3$ (3 mmol/g,

292 mg, 0.8766 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 1h at –78 °C, then allowed to warm to rt. $Na_2SO_4$ was added. The reaction mixture was filtered and the filtrate concentrated under reduced pressure and purified by chromatography (35% EtOAc–petrol) to give *4-(toluene-4-sulfonyl)heptane-2,6-dione* **581** (52 mg, 42%) as a colourless oil.




*Procedure B*

To **580** (39 mg, 0.137 mmol, 1.0 equiv) and $NaHCO_3$ (81 mg, 0.962 mmol, 7.0 equiv) was added benzene (1.4 mL). The reaction mixture was stirred, giving a white suspension. Lead tetraacetate (67 mg, 0.151 mmol, 1.1 equiv) was added quickly in one portion. The reaction mixture was stirred at rt for 30 min, resulting in a qualitative change in the precipitate. The reaction mixture was filtered (washed through with additional benzene) and concentrated under reduced pressure. The resulting solid was redissolved in $CH_2Cl_2$ (25 mL) and washed with $H_2O$ (25 mL). The aqueous phase was extracted with $CH_2Cl_2$ (5 mL). Combined organic fractions were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (50% EtOAc–petrol) to give *4-(toluene-4-sulfonyl)heptane-2,6-dione* **581** (39 mg, 100%) as a colourless oil.

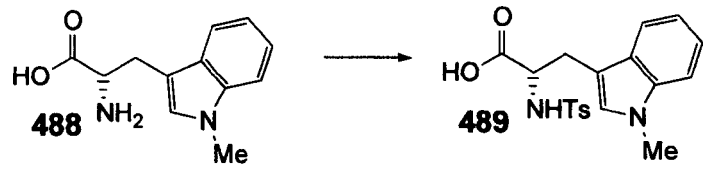
**581:** $R_f$ 0.32 (50% EtOAc–petrol); $\nu_{max}$ (film) 1721, 1667, 1597, 1494, 1418, 1363, 1301, 1289, 1254, 1227, 1203, 1145, 1086, 1019, 895, 818, 728, 664 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 4.26-4.19 (1H, m, Ts-CH<), 3.05 (2H, dd, *J* 18.0, 5.0 Hz, Ts-CH-C*H*H-), 2.65 (2H, dd, *J* 18.0, 7.5 Hz, Ts-CH-CH*H*-), 2.45 (3H, s, Ts-$CH_3$), 2.13 (6H, s, $H_3C$-C(O)-); $\delta_C$ (75 MHz, $CDCl_3$) 203.9 (C=O), 145.3 (4° Ar), 134.1 (4° Ar), 130.0 (3° Ar), 128.9 (3° Ar), 55.8 (Ts-CH<), 41.5 (-C(O)-$CH_2$-), 30.0 (-C(O)-$CH_3$), 21.7 (Ts-$CH_3$), 11.0 (-$CH_2CH_3$); *m/z* (FAB) 283 $[M+H]^+$, 157 (Found: $[M+H]^+$, 283.1014. $C_{14}H_{18}O_4S$ requires $[M+H]^+$, 283.1004).

**2,6-Lutidine *N*-oxide (582)**


To **581** (52 mg, 0.184 mmol, 1.0 equiv) and hydroxylamine hydrochloride (13 mg, 0.184 mmol, 1.0 equiv) was added EtOH (0.9 mL) and $NEt_3$ (26 μL, 0.184 mmol, 1.0 equiv) by syringe. The reaction mixture was stirred at rt for 14 h, then concentrated under reduced pressure. Chromatography (50:45:5 EtOAc:petrol:$NEt_3$ → 75:25 EtOAc:$NEt_3$) gave *2,6-lutidine* N-*oxide* **582** (12 mg, 53%) as a colourless oil.; $\delta_H$ (300 MHz, $CDCl_3$) 7.30-6.95 (3H, m, Ar-H), 2.47 (6H, s, $-CH_3$); *m/z* (CI) 141 $[M+NH_4]^+$, 124 $[M+H]^+$, 108, 102, 86 (Found: 141.1031. $C_7H_9NO$ requires $[M+NH_4]^+$ 141.1028); data in agreement with those previously reported[197] and with those of an authentic sample.

- **3.3.14 Compounds relevant to studies on (-)-suaveoline**

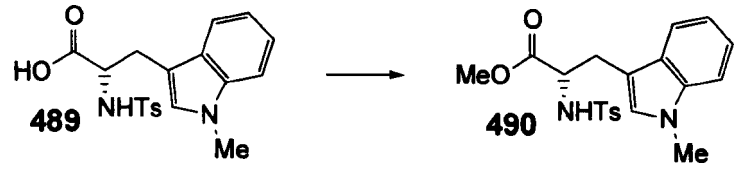
**(*S*)-3-(1-Methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanoic acid (489)**




This was synthesised by a method based on a literature procedure[127] for the sulfonylation of tryptophan. To L-$N_\alpha$-methyltryptophan **488** (8.47 g, 38.8 mmol, 1.0 equiv) was added aq. NaOH (2.0 M; 38.8 mL, 77.6 mmol, 2.0 equiv) to give a viscous pale yellow solution. This was cooled to 0 °C, then toluene-4-sulfonyl chloride (7.40 g, 38.8 mmol, 1.0 equiv) was added as one portion. The reaction mixture was stirred at 0 °C for 30 min, then at rt for 16 h. The reaction mixture was diluted with a little aq. NaOH (1.0 M) until all material was dissolved. The aqueous reaction mixture was washed with $Et_2O$ (3× 200 mL). The combined organic phases were extracted with a small portion of aq. NaOH (1.0 M). The combined aqueous phases were cooled to –10 °C, then acidified to pH 1 with concentrated HCl, resulting in the precipitation of a large amount of material. The reaction mixture was extracted with $CH_2Cl_2$ (1 L), resulting in a very slow phase separation. The aqueous phase was extracted with a further portion of $CH_2Cl_2$ (100 mL). Combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure to give crude *(S)-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanoic acid* **489** (13.1 g, 91%) as a brown foam, used without further purification; a portion was recrystallised from $Et_2O$/$^iPr_2O$ to give a white crystalline solid; mp 141°C; $[\alpha]_D^{25}$ +9.2 (c=1.36, $CHCl_3$); $[\alpha]_D^{25}$ –27.2 (c=1.20, MeOH); $\nu_{max}$ (film) 3270, 1724, 1598, 1474, 1375, 1326, 1248, 1155, 1090, 1044, 945, 847, 813, 740 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.49 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.40 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.22 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.18 (1H, td, *J* 7.5, 1.0 Hz, indolyl H-5), 7.06 (2H, br d, *J* 8.5 Hz, *m*-$SO_2Ar$), 7.01 (1H, ddd, *J* 8.0, 6.5, 1.0 Hz, indolyl H-6), 6.82 (1H, s, indolyl H-2), 5.21 (1H, d, *J* 8.0 Hz, N-H), 4.19 (1H, ddd, *J* 8.0, 6.5, 5.0 Hz, -NH-C(*H*)<), 3.66 (3H, s, N-$CH_3$), 3.24 (1H, dd, *J* 15.0, 5.0 Hz, indolyl-C*H*H-), 3.15 (1H, dd, *J* 15.0, 6.5 Hz, indolyl-CH*H*-), 2.32 (Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.4 (-COOH), 143.5 (4°), 136.9 (4°), 136.3 (4°), 129.4 (3°), 128.2 (3°), 127.8 (4°), 126.9 (3°), 121.8 (3°), 119.3 (3°), 118.6 (3°), 109.3 (3°), 107.1 (4°), 55.9 (HOOC-CH-), 32.6 (N-$CH_3$), 28.8 (indolyl-

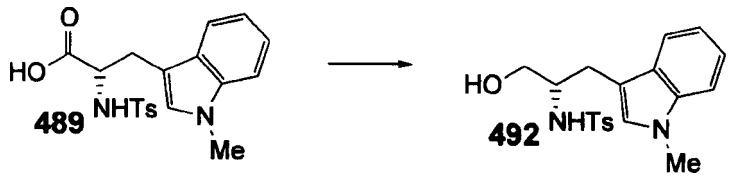
$CH_2$-), 21.5 (Ts-$CH_3$); *m/z* (–ve ESI, +ve ESI) 371 $[M-H]^-$, 278, 239 (Found: 373.1212. $C_{19}H_{20}N_2O_4S$ requires $[M+H]^+$ 373.1217) (Found: C, 61.24; H, 5.40; N, 7.50. $C_{19}H_{20}N_2O_4S$ requires C, 61.27; H, 5.41; N, 7.52%).

**(*S*)-Methyl 3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanoate (490)**



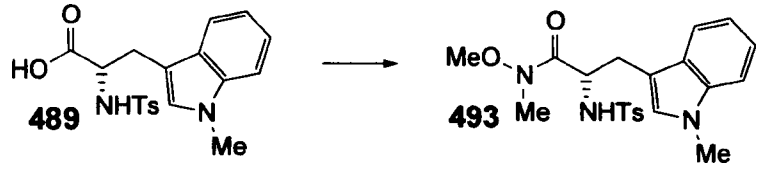

Crude **489** (2.80 g, 7.52 mmol, 1.0 equiv) was dissolved in MeOH (200 mL), to which was added 4M HCl in dioxane (20 mL). The reaction mixture was stirred at rt for 72 h, diluted with $Et_2O$ (500 mL) and washed with aq. NaOH (0.05 M; 100 mL), $H_2O$ (2× 100 mL), and saturated aq. NaCl (100 mL). The organic layer was dried over $Na_2SO_4$, then concentrated under reduced pressure to give crude *(S)-methyl 3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanoate* **490** (2.88 g, 100%) as a brown foam, pure by $^1$H-NMR; a portion was recrystallised from $^i$PrOH to give a pale pink crystalline solid; mp 94°C; $R_f$ 0.52 (40% EtOAc-hexane); $[\alpha]_D^{25}$ –1.9 (c=1.05, $CHCl_3$); $[\alpha]_D^{25}$ –20.0 (c=1.41, MeOH); $\nu_{max}$ (film) 3283, 3049, 1740, 1598, 1474, 1431, 1327, 1205, 1160, 1091, 909, 813, 736 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.43 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.28-7.24 (2H, m, indolyl H-4,5), 7.19 (2H, d, *J* 8.5 Hz, *m*-$SO_2Ar$), 7.08 (1H, td, *J* 7.5, 1.0 Hz, indolyl H-6), 6.89 (1H, s, indolyl H-2), 5.15 (1H, d, *J* 9.0 Hz, N-H), 4.26 (1H, dt, *J* 10.5, 4.5 Hz, -OC(O)-C*H*<), 3.73 (3H, s, N-$CH_3$), 3.47 (3H, s, O-$CH_3$), 3.24 (2H, d, 5.5 Hz, indolyl-$CH_2$-), 2.40 (3H, s, Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.6 (C=O), 143.3 (4°), 136.8 (4°), 136.7 (4°), 129.4 (3°), 128.0 (3°), 127.6 (4°), 127.0 (3°), 121.7 (3°), 119.1 (3°), 118.5 (3°), 109.2 (3°), 107.3 (4°), 56.1 (MeOOC-CH<), 52.3 (-$OCH_3$), 32.6 (N-$CH_3$), 29.1 (indolyl-$CH_2$-), 21.4 (Ts-$CH_3$); *m/z* (CI) 387 $[M+H]^+$, 216, 156, 142 (Found: 387.1370. $C_{20}H_{22}N_2O_4S$ requires $[M+H]^+$ 387.1373) (Found: C, 61.97; H, 5.73; N, 7.16. $C_{20}H_{22}N_2O_4S$ requires C, 62.16; H, 5.74; N, 7.25%).

**(*S*)-3-(1-Methylindol-3-yl)-2-(4-methylphenylsulfonamido)propan-1-ol (492)**



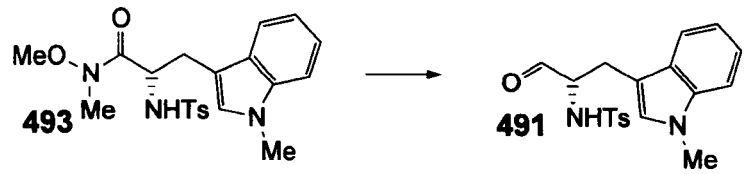

To a suspension of $LiAlH_4$ (171 mg, 4.52 mmol, 3.0 equiv) in $Et_2O$ (10 mL) at rt was added dropwise over 20 min a solution of **489** in $Et_2O$:THF 1:1 (10 mL). The reaction mixture was heated to reflux for 30 min, then cooled to –10 °C. NaOH (1.0 M; 4.5 mL) was added dropwise, then stirred at –10 °C for 10 min. The reaction mixture was filtered through a plug of celite, then washed through with EtOAc (100 mL). The organic layer was washed with aq. HCl (0.1 M). The aqueous layer was diluted with saturated aq. NaCl (200 mL) and extracted with EtOAc (3× 10 mL). Combined organic layers were washed with saturated aq. NaCl (50 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to give crude *(S)-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propan-1-ol* **492** (415 mg, 77%) as a colourless oil; $R_f$ 0.18 (40% EtOAc-hexane); $[\alpha]_D^{25}$ +36.8 (c=1.06, $CHCl_3$); $[\alpha]_D^{25}$ –61.9 (c=1.63, MeOH); $\nu_{max}$ (film) 3291, 1597, 1472, 1422, 1376, 1324, 1151, 1089, 1036, 969, 811, 738 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.48 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.25-7.16 (3H, m, indolyl H-4,5,7), 7.03 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.00-6.98 (1H, m, indolyl H-6), 6.74 (1H, s, indolyl H-2), 4.92 (1H, d, *J* 6.0 Hz, N-H), 3.67 (1H, dd, *J* 11.5, 4.0 Hz, -C*H*H-OH), 3.67 (3H, s, N-$CH_3$), 3.59 (1H, dd, *J* 11.5, 5.0 Hz, -CH*H*-OH), 3.51-3.44 (1H, m, -NH-C*H*<), 2.92 (1H, dd, *J* 15.0, 6.5 Hz, indolyl-C*H*H-), 2.81 (1H, dd, *J* 15.0, 7.5 Hz, indolyl-CH*H*-), 2.33 (Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 143.1 (4°), 137.0 (4°), 136.5 (4°), 129.3 (3°), 127.6 (3°), 127.5 (4°), 126.8 (3°), 121.7 (3°), 119.1 (3°), 118.5 (3°), 109.2 (3°), 109.0 (4°), 64.6 (-$CH_2OH$), 55.6 (HO$CH_2$CH<), 32.5 (N-$CH_3$), 27.3 (indolyl-$CH_2$-), 21.5 (Ts-$CH_3$); *m/z* (CI) 359 $[M+H]^+$, 188 (Found: 359.1414. $C_{19}H_{22}N_2O_3S$ requires $[M+H]^+$ 359.1424).

**(*S*)-*N*-Methoxy-*N*-methyl-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanamide (493)**



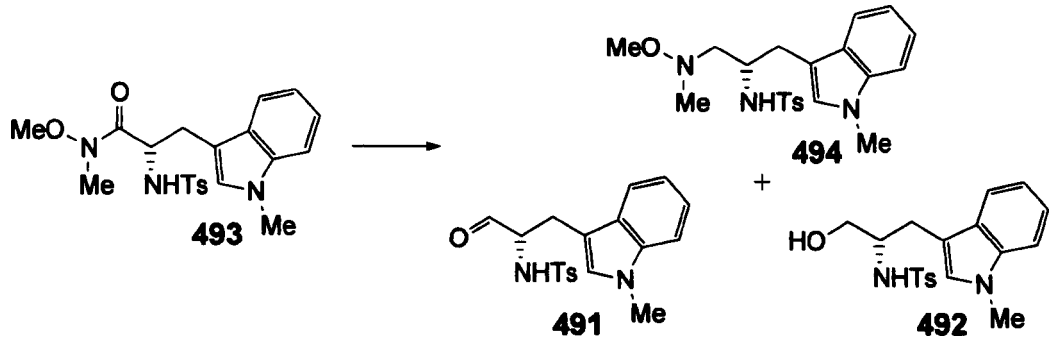

To a suspension of **489** (1.012 g, 2.72 mmol, 1.0 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (318 mg, 3.26 mmol, 1.2 equiv) in $CH_2Cl_2$ (25 mL) at rt was added pyridine (658 μL, 8.16 mmol, 3.0 equiv). The solution was stirred for 5 min at rt, then *n*-propylphosphonic acid anhydride (T3P®, 50% solution in EtOAc, 1.76 mL, 3.04 mmol, 1.1 equiv) was added. The reaction mixture was stirred at rt for 16 h, diluted with $CH_2Cl_2$ (75 mL) and washed with aq. $Na_2CO_3$ (0.05 M; 2× 100 mL), resulting in slow phase separation. The organic phase was washed further with $H_2O$ (100 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (50% EtOAc in hexane) to give *(S)-N-methoxy-N-methyl-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanamide* **493** (1.00 g, 89%) as a pink/white foam; $R_f$ 0.32 (50% EtOAc-hexane); $[\alpha]_D^{25}$ +25.3 (c=0.97, $CHCl_3$); $[\alpha]_D^{25}$ –14.6 (c=1.10, MeOH); $\nu_{max}$ (film) 3220, 1645, 1584, 1473, 1423, 1378, 1326, 1153, 1093, 986, 953, 809, 741 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.42 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.21-7.14 (2H, m, indolyl H-4,5), 7.05-7.01 (3H, m, *m*-$SO_2Ar$, indolyl H-6), 6.85 (1H, s, indolyl H-2), 5.81 (1H, d, *J* 9.0 Hz, N-H), 4.60-4.57 (1H, m, -NH-C*H*<), 3.63 (3H, s, indolyl N-$CH_3$), 3.50 (3H, s, -$OCH_3$), 3.14 (1H, dd, *J* 14.5, 5.0 Hz, Ar-C*H*H-), 3.00 (3H, s, C(O)N-$CH_3$), 3.02-2.96 (1H, m, Ar-CH*H*-), 2.31 (Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.5 (C=O), 142.7 (4°), 136.8 (4°), 136.6 (4°), 128.8 (3°), 127.9 (3°), 127.6 (4°), 126.8 (3°), 121.2 (3°), 118.7 (3°), 118.2 (3°), 109.0 (3°), 108.2 (4°), 61.2 (-$OCH_3$), 53.3 (NC(O)-*C*H<), 32.3 (indolyl N-$CH_3$), 31.9 (-C(O)N-$CH_3$), 28.9 (indolyl-$CH_2$-), 21.3 (Ts-$CH_3$); *m/z* (CI) 416 $[M+H]^+$, 386, 245 (Found: 416.1635. $C_{21}H_{25}N_3O_4S$ requires $[M+H]^+$ 416.1639) (Found: C, 60.89; H, 5.85; N, 9.92. $C_{21}H_{25}N_3O_4S$ requires C, 60.70; H, 6.06; N, 10.11%).

**(*S*)-3-(1-Methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanal (491)**




To a suspension of $LiAlH_4$ (41 mg, 1.06 mmol, 1.3 equiv) in $Et_2O$:THF 1:1 (15 mL) at –10 °C was added dropwise a solution of **493** in $Et_2O$:THF (15 mL). The reaction mixture was stirred at –10 °C for 90 min, then aq. NaOH (1.0 M; 1.0 mL) was added. The mixture was stirred at –10 °C for 15 min, filtered through a plug of celite and washed through with EtOAc (200 mL). The organic filtrate was washed with saturated aq. NaCl (2× 50 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to give crude *(S)-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propanal* **491**, used immediately without purification. $\delta_H$ (400 MHz, $CDCl_3$) 9.54 (1H, s, -CHO), 7.51 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.32 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.23-7.12 (2H, m, indolyl H-4,5), 7.07 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.01 (1H, t, *J* 8.0 Hz, indolyl H-6), 6.79 (1H, s, indolyl H-2), 5.30 (1H, d, *J* 9.0 Hz, N-H), 3.99 (1H, q, *J* 6.0 Hz, -NH-C(*H*)<), 3.66 (3H, s, indolyl N-$CH_3$), 3.13 (2H, d, *J* 6.5 Hz, indolyl-$CH_2$-), 2.31 (Ts-$CH_3$).

**(*S*)-*N*-Methoxy-*N*-methyl-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propylamine (494)**

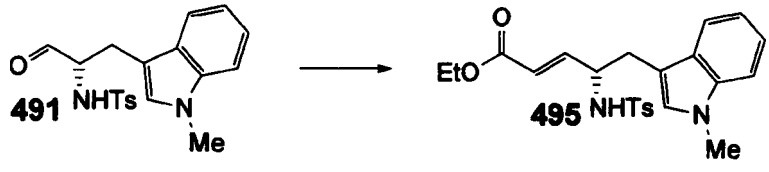



To $LiAlH_4$ (1.0M in THF, 15 mL, 15 mmol, 5.0 equiv) at –10 °C was added dropwise a solution of **493** (1.26 g, 3.02 mmol, 1.0 equiv) in $Et_2O$:THF 1:1 (20 mL). The reaction mixture was allowed to warm to rt, then heated to reflux for 1 h. After cooling to rt, the reaction mixture was quenched by addition of acetone (2 mL), $H_2O$ (3 mL), aq. NaOH (2.0 M; 3 mL) and $H_2O$ (9 mL). The

resultant gel was filtered through a plug of arbocel and washed through with EtOAc (200 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (20→50% EtOAc-hexane) to give *(S)*-N-*methoxy*-N-*methyl-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propylamine* **494** (179 mg, 15%) as a pale orange oil; Also isolated was **491** (162 mg, 15%) and **492** (47 mg, 4%).

**494**: $R_f$ 0.62 (50% EtOAc-hexane); $[\alpha]_D^{25}$ +44.4 (c=1.74, $CHCl_3$); $[\alpha]_D^{25}$ –30.3 (c=0.92, MeOH); $\nu_{max}$ (film) 3285, 1598, 1471, 1375, 1325, 1248, 1155, 1092, 1044, 975, 813, 740 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.42 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.21-7.14 (2H, m, indolyl H-4,5), 7.05-7.01 (3H, m, *m*-$SO_2Ar$, indolyl H-6), 6.85 (1H, s, indolyl H-2), 5.81 (1H, d, *J* 9.0 Hz, N-H), 4.60-4.57 (1H, m, -NH-C*H*<), 3.63 (3H, s, indolyl N-$CH_3$), 3.50 (3H, s, -$OCH_3$), 3.14 (1H, dd, *J* 14.5, 5.0 Hz, indolyl-C*H*H-), 3.00 (3H, s, C(O)N-$CH_3$), 3.02-2.96 (1H, m, indolyl-CH*H*-), 2.31 (Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.5 (C=O), 142.7 (4°), 136.8 (4°), 136.6 (4°), 128.8 (3°), 127.9 (3°), 127.6 (4°), 126.8 (3°), 121.2 (3°), 118.7 (3°), 118.2 (3°), 109.0 (3°), 108.2 (4°), 61.2 (-$OCH_3$), 53.3 (NC(O)-CH<), 32.3 (indolyl N-$CH_3$), 31.9 (-C(O)N-$CH_3$), 28.9 (indolyl-$CH_2$-), 21.3 (Ts-$CH_3$); *m/z* (CI) 416 $[M+H]^+$, 386, 245 (Found: 416.1635. $C_{21}H_{27}N_3O_3S$ requires $[M+H]^+$ 416.1639).

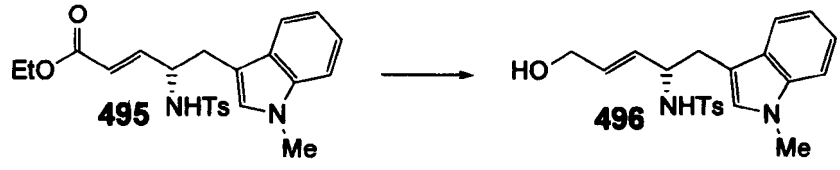
**(*S,E*)-Ethyl 5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido) pent-2-enoate (495)**




To NaH (40% w/w, 40 mg, 0.98 mmol, 1.2 equiv) at –10 °C was added by cannula a solution of triethyl phosphonoacetate (229 mg, 1.02 mmol, 1.25 equiv) in THF (8 mL). The reaction mixture was stirred at –10 °C for 30 min, then a solution of **491** (assumed to be 0.819 mmol, 1.0 equiv) in THF (8 mL) was added by cannula. The reaction mixture was stirred at –10 °C for 30 min, then at rt for 16 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aq. $NH_4Cl$ (50 mL). The aqueous phase was extracted with EtOAc (10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography

(35→50% EtOAc-hexane) to give *(S,E)-ethyl 5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido)pent-2-enoate* **495** (203 mg, 58% over 2 steps) as a deep yellow foam; a portion was recrystallised from *i*-PrOH to give pale brown needles; mp 154–155°C; $R_f$ 0.36 (35% EtOAc-hexane); $[\alpha]_D^{25}$ –71.6 (c=1.74, $CHCl_3$); $[\alpha]_D^{25}$ –42.7 (c=1.41, MeOH); $\nu_{max}$ (film) 3297, 1707, 1644, 1599, 1481, 1450, 1421, 1309, 1260, 1247, 1152, 1111, 1094, 1042, 1030, 999, 975, 929, 808, 738 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.49 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.26-7.18 (3H, m, indolyl H-4,5,7), 7.05 (2H, br d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.00 (1H, ddd, *J* 8.0, 7.0, 1.5 Hz, indolyl H-6), 6.83 (1H, dd, *J* 15.5, 6.0 Hz, -C(O)-CH=C*H*-), 6.78 (1H, s, indolyl H-2), 5.90 (1H, dd, *J* 15.5, 1.0 Hz, -C(O)-C*H*=CH-), 4.74-4.67 (1H, m, N-H), 4.15 (2H, q, *J* 7.0 Hz, -$OCH_2$-), 4.19-4.09 (1H, m, -NH-C(*H*)<), 3.69 (3H, s, N-$CH_3$), 3.00 (1H, dd, *J* 15.0, 6.0 Hz, indolyl-C*H*H-), 2.86 (1H, dd, *J* 14.5, 7.0 Hz, indolyl-CH*H*-), 2.34 (3H, s, Ts-$CH_3$), 1.26 (3H, t, *J* 7.0 Hz, -$OCH_2$-C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 165.9 (C=O), 147.1 (3°), 143.1 (4°), 137.0 (4°), 136.7 (4°), 129.3 (3°), 127.9 (3°), 127.4 (4°), 126.8 (3°), 122.1 (3°), 121.8 (3°), 119.2 (3°), 118.6 (3°), 109.3 (3°), 107.6 (4°), 60.4 (-$OCH_2$-), 54.6 (=CH-*C*(NHTs)H-), 32.6 (N-$CH_3$), 30.9 (indolyl-$CH_2$-), 21.4 (Ts-$CH_3$), 14.2 (-$OCH_2$-$CH_3$); *m/z* (CI) 444 $[M+NH_4]^+$, 427 $[M+H]^+$, 256 (Found: 427.1676. $C_{23}H_{26}N_2O_4S$ requires $[M+H]^+$ 427.1686) (Found: C, 64.77; H, 6.14; N, 6.58. $C_{23}H_{26}N_2O_4S$ requires C, 64.77; H, 6.14; N, 6.57%).

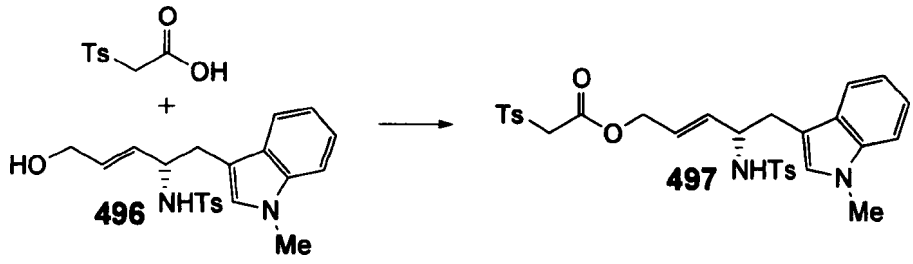
**(*S,E*)-5-(1-Methylindol-3-yl)-4-(4-methylphenylsulfonamido)prop-2-en-1-ol (496)**




To a solution of **495** (201 mg, 0.470 mmol, 1.0 equiv) in $CH_2Cl_2$ at –78 °C was added DIBAL-H (1.0M in $CH_2Cl_2$; 1.69 mL, 1.69 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 10 min, then at rt for 90 min. The reaction mixture was quenched with EtOAc (2 mL), diluted with $CH_2Cl_2$ (100 mL) and poured into saturated aq. sodium potassium tartrate (50 mL) and $H_2O$ (50 mL). The mixture was stirred vigorously for 1 h. The aqueous phase was washed with $CH_2Cl_2$ (20 mL), then the combined organic phases were washed with saturated aq. NaCl (2× 50 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (70% EtOAc-

hexane) to give *(S,E)-5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido)prop-2-en-1-ol* **496** (157 mg, 87%) as a colourless oil; $R_f$ 0.43 (70% EtOAc-hexane); $[\alpha]_D^{25}$ –46.1 (c=1.23, $CHCl_3$); $[\alpha]_D^{25}$ –34.2 (c=1.72, MeOH); $\nu_{max}$ (film) 3510, 3344, 1616, 1597, 1556, 1474, 1399, 1375, 1326, 1291, 1184, 1150, 1085, 1012, 960, 853, 809, 743 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.47 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.29 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.22 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.18 (1H, td, *J* 7.0, 1.0 Hz, indolyl H-5), 7.04 (2H, br d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.00 (1H, ddd, *J* 8.0, 6.5, 1.5 Hz, indolyl H-6), 6.78 (1H, s, indolyl H-2), 5.69 (1H, dt, *J* 15.5, 5.0 Hz, HO-$CH_2$-C*H*=), 5.62 (1H, dd, *J* 15.5, 6.0 Hz, HO-$CH_2$-CH=C*H*-), 4.94 (1H, d, *J* 6.0 Hz N-H), 4.04-3.98 (1H, m, -NH-C*H*<), 3.97 (2H, d, *J* 5.0 Hz, HO-C$H_2$-), 3.66 (3H, s, N-$CH_3$), 2.93 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-C*H*H-), 2.84 (1H, dd, *J* 14.5, 7.0 Hz, indolyl -CH*H*-), 2.33 (Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 142.9 (4°), 137.1 (4°), 137.0 (4°), 131.4 (3°), 130.8 (3°), 129.1 (3°), 127.8 (3°), 127.7 (4°), 126.9 (3°), 121.6 (3°), 118.9 (3°), 118.7 (3°), 109.2 (3°), 108.7 (4°), 62.6 (-$OCH_2$-), 55.3 (=CH-CH(NHTs)-), 32.5 (N-$CH_3$), 31.6 (indolyl-$CH_2$-), 21.4 (Ts-$CH_3$); *m/z* (CI) 385 $[M+H]^+$, 367, 214 (Found: 385.1576. $C_{21}H_{24}N_2O_3S$ requires $[M+H]^+$ 385.1581).

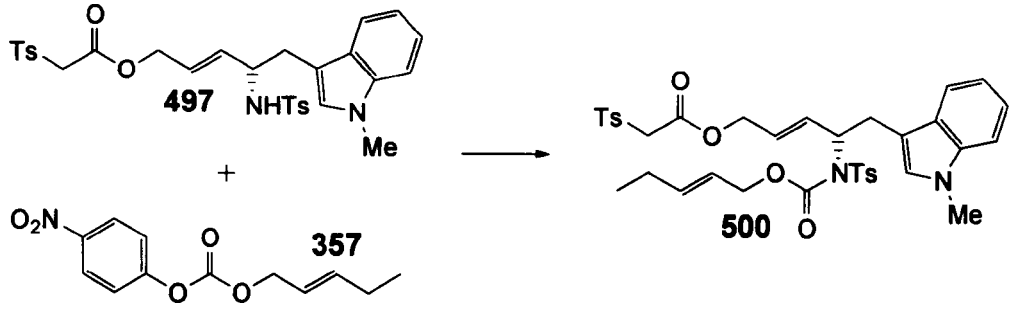
**(*S,E*)-5-(1-Methylindol-3-yl)-4-(4-methylphenylsulfonamido)pent-2-enyl (toluene-4-sulfonyl)acetate (497)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (156 mg, 0.73 mmol), alcohol **496** (280 mg, 0.73 mmol), $CH_2Cl_2$ (10 mL) and *N,N'-di*isopropyl carbodiimide (114 µL, 0.73 mmol). Chromatography (40% EtOAc–petrol) gave *(S,E)-5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido) pent-2-enyl (toluene-4-sulfonyl)acetate* **497** (392 mg, 93%) as a colourless oil; $R_f$ 0.39 (50% EtOAc–petrol); $[\alpha]_D^{25}$ –17.0 (c=0.97, $CHCl_3$); $[\alpha]_D^{25}$ –12.6 (c=0.97, MeOH); $\nu_{max}$ (film) 3288, 3052, 1742, 1597, 1473, 1378, 1326, 1157, 1086, 970, 912, 814, 737, 666 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.47 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.33 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$),

7.25-7.21 (2H, m, indolyl H-4,7), 7.19 (1H, t, *J* 7.5 Hz, indolyl H-5), 7.07 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.00 (1H, t, *J* 7.5 Hz, indolyl H-6), 6.80 (1H, s, indolyl H-2), 5.70 (1H, dd, *J* 15.5, 6.0 Hz, -$OCH_2$-CH=C*H*-), 5.58 (1H, dt, *J* 15.5, 5.5 Hz, -$OCH_2$-C*H*=), 4.79 (1H, d, *J* 6.5 Hz, N-H), 4.46 (2H, d, *J* 5.5 Hz, -$OCH_2$-), 4.08 (2H, s, Ts-C*H*$_2$-COO-), 4.03-3.97 (1H, m, -NH-C*H*<), 3.69 (3H, s, N-$CH_3$), 2.92 (1H, dd, *J* 14.5, 6.0 Hz, indolyl-C*H*H-), 2.81 (1H, dd, *J* 14.5 7.0 Hz, indolyl-CH*H*-), [2.43, 2.35] (2× 3H, s, Ts-$CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 162.2 (4°), 145.6 (4°), 143.2 (4°), 137.1 (4°), 135.8 (4°), 135.5 (3°), 129.9 (3°), 129.4 (3°), 128.6 (3°), 128.0 (3°), 127.7 (4°), 127.0 (3°), 124.3 (3°), 121.8 (3°), 119.2 (3°), 118.7 (3°), 109.4 (3°), 108.1 (4°), 65.6 (2°), 61.0 (2°), 55.0 (3°), 32.7 (1°), 31.4 (2°), 21.7 (1°), 21.5 (1°); *m/z [no parent ion peak observed]*

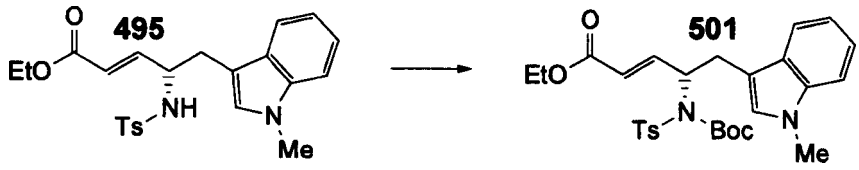
**(*S*,*E*)-5-(1-Methylindol-3-yl)-4-(4-methyl-N-(((*E*)-pent-2-enyloxy)carbonyl)phenylsulfonamido)pent-2-enyl (toluene-4-sulfonyl)acetate (500)**




*General procedure (vii)* was applied, using sodium hydride (62 mg, 1.54 mmol, 3.0 equiv), **497** (298 mg, 0.513 mmol), DMF (5.5 mL total) and carbonate **357** (142 mg, 0.564 mmol, 1.1 equiv). Chromatography (35% EtOAc–petrol) gave *(S,E)-5-(1-methylindol-3-yl)-4-(4-methyl-N-(((E)-pent-2-enyloxy)carbonyl)phenylsulfonamido)pent-2-enyl (toluene-4-sulfonyl)acetate* **500** (125 mg, 35%) as a colourless oil; $R_f$ 0.35 (35% EtOAc–petrol); $[\alpha]_D^{25}$ –8.3 (c=1.15, $CHCl_3$); $[\alpha]_D^{25}$ –5.1 (c=1.03, MeOH); $\nu_{max}$ (film) 3054, 3029, 1735, 1597, 1552, 1449, 1351, 1329, 1266, 1165, 1086, 971, 814, 741, 670 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.65 (1H, d, *J* 7.5 Hz, indolyl H-7), 7.35-7.23 (6H, m, *o*-$SO_2Ar$, *m*-$SO_2Ar$, indolyl H-4,5), 7.15 (1H, t, *J* 7.0 Hz, indolyl H-6), 7.03 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.77 (1H, s, indolyl H-2), 6.23 (1H, dd, *J* 15.5, 7.0 Hz, N(Ts)-CH-C*H*=), [5.82-5.68 (2H), 5.47-5.34 (2H)] (m, -NH-C*H*<, other olefinics), 4.58 (4H, br d, *J* 5.5 Hz, 2× -$OCH_2$-), 4.11 (2H, s, Ts-$CH_2$-COO-), 3.65 (3H, s, N-$CH_3$), 3.48 (1H, dd, *J* 14.0, 8.5 Hz,

indolyl-C*H*H-), 3.31 (1H, dd, *J* 14.5, 7.0 Hz, indolyl-CH*H*-), [2.45, 2.38] (2× 3H, s, Ts-$CH_3$), 2.09-2.03 (2H, m, -C$H_2$-$CH_3$), 1.01 (3H, t, *J* 7.5 Hz, -$CH_2$-C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.2 (4°), 151.8 (4°), 145.6 (4°), 143.8 (4°), 139.2 (3°), 137.0 (4°), 136.7 (4°), 135.7 (4°), 134.3 (3°), 129.9 (3°), 128.8 (3°), 128.6 (3°), 128.3 (3°), 127.9 (4°), 127.8 (3°), 126.0 (3°), 121.7 (3°), 119.2 (3°), 118.8 (3°), 110.1 (4°), 109.2 (3°), 67.7 (2°), 65.9 (2°), 61.1 (2°), 60.4 (3°), 32.6 (1°), 29.1 (2°), 25.2 (2°), 21.7 (1°), 21.6 (1°), 13.1 (1°); *m/z* (FAB) 692 $[M]^+$, 410, 144 (Found: 692.2212. $C_{36}H_{40}N_2O_8S_2$ requires $[M]^+$ 692.2226) (Found: C, 62.17; H, 5.89; N, 3.96. $C_{36}H_{40}N_2O_8S_2$ requires C, 62.41; H, 5.82; N, 4.04%).

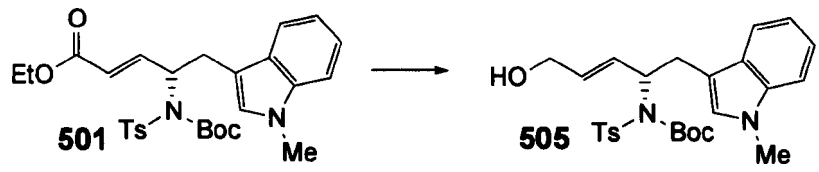
**(*S*,*E*)-Ethyl 4-(*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enoate (501)**




To a solution of **495** (853 mg, 2.00 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at rt was added a solution of $Boc_2O$ (546 mg, 2.50 mmol, 1.25 equiv) in $CH_2Cl_2$ (5 mL). After 5 min, a solution of 4-(*N*,*N*-dimethylamino)pyridine (48 mg, 0.40 mmol, 0.2 equiv) in $CH_2Cl_2$ was added. The reaction mixture was stirred at rt for 3 h. Glycine (75 mg, 1.0 mmol, 0.5 equiv) was added in one portion in an attempt to remove unreacted $Boc_2O$; the glycine was insoluble, however. The reaction mixture was stirred for 30 min at rt, then washed with aq. $NaHCO_3$ (1.0 M; 20 mL). The organic layer was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (20% EtOAc-hexane) to give *(S,E)-ethyl 4-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enoate* **501** (1.00 g, 95%) as a colourless oil; $R_f$ 0.23 (20% EtOAc–petrol); $[\alpha]_D^{25}$ –4.7 (c=1.28, $CHCl_3$); $[\alpha]_D^{25}$ –9.6 (c=1.23, MeOH); $\nu_{max}$ (film) 3053, 1723, 1656, 1597, 1475, 1355, 1310, 1278, 1152, 1088, 1047, 977, 813, 740, 670 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.67 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.34-7.23 (5H, m, *o*-$SO_2Ar$, indolyl H-4,5, -C(O)-CH=C*H*-), 7.16 (1H, t, *J* 6.5 Hz, indolyl H-6), 7.01 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.81 (1H, s, indolyl H-2), 6.01 (1H, dd, *J* 16.0, 1.5 Hz, -C(O)-CH=), 5.50-5.46 (1H, m, BocN(Ts)-C*H*<), 4.22 (2H, q, *J* 7.0 Hz, -$OCH_2$-), 3.68 (3H, s, N-$CH_3$), 3.57 (1H, dd, *J* 14.5, 9.0 Hz, indolyl-C*H*H-), 3.39 (1H, dd, *J* 14.5, 7.0 Hz, indolyl-CH*H*-), 2.38 (3H, s, Ts-$CH_3$), 1.41 (9H, s, -Boc), 1.31 (3H, t, *J* 7.0Hz, -$OCH_2$-

$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 166.2 (4°), 150.3 (4°), 146.4 (3°), 143.6 (4°), 137.0 (4°), 128.8 (3°), 127.9 (3°), 127.8 (3°), 122.7 (3°), 121.9 (3°), 119.3 (3°), 118.9 (3°), 109.8 (4°), 109.2 (3°), 84.6 (4°), 60.5 (2°), 59.4 (3°), 32.6 (1°), 28.7 (2°), 28.0 (1°), 21.6 (1°), 14.3 (1°); *m/z* (FAB) 526 $[M]^+$, 430, 338 (Found: 526.2166. $C_{28}H_{34}N_2O_6S$ requires $[M]^+$ 526.2138) (Found: C, 63.64; H, 6.50; N, 5.30. $C_{28}H_{34}N_2O_6S$ requires C, 63.86; H, 6.51; N, 5.32%).

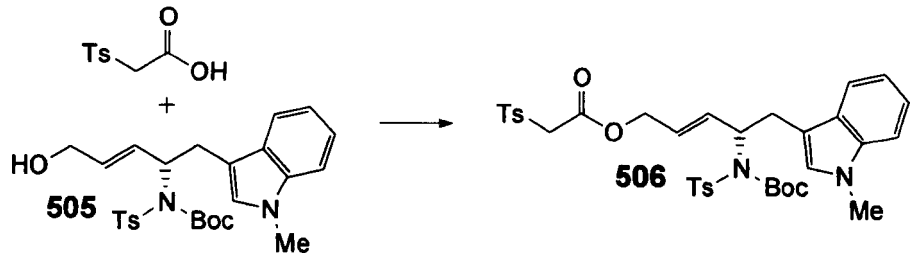
**(*S,E*)-*tert*-Butyl 5-hydroxy-1-(1-methylindol-3-yl)pent-3-en-2-yl(toluene-4-sulfonyl)carbamate (505)**




To a solution of **501** (817 mg, 1.55 mmol, 1.0 equiv) in $CH_2Cl_2$ (9.5 mL) at –78 °C was added DIBAL-H (1.0 M in $CH_2Cl_2$; 5.58 mL, 5.58 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 5 min, then at rt for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and poured onto saturated aq. sodium potassium tartrate (50 mL) and $H_2O$ (50 mL). The reaction mixture was stirred vigorously for 30 min. The aqueous phase was washed with EtOAc (20 mL). The combined organic phases were washed with sat[d] aq. NaCl (50 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (45% EtOAc-hexane) to give *(S,E)*-tert-*butyl 5-hydroxy-1-(1-methylindol-3-yl)pent-3-en-2-yl(toluene-4-sulfonyl)carbamate* **505** (628 mg, 84%) as a colourless oil; $R_f$ 0.38 (50% EtOAc–petrol); $[\alpha]_D^{25}$ –10.7 (c=1.67, $CHCl_3$); $[\alpha]_D^{25}$ –11.3 (c=1.08, MeOH); $\nu_{max}$ (film) 3540, 3053, 1725, 1597, 1474, 1351, 1152, 1088, 1013, 971, 912, 738, 670 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.68 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.33-7.22 (4H, m, *o*-$SO_2Ar$, indolyl H-4,5), 7.14 (1H, t, *J* 7.0 Hz, indolyl H-6), 7.00 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.81 (1H, s, indolyl H-2), 6.20 (1H, dd, *J* 15.5, 6.5 Hz, HO-$CH_2$-CH=C*H*-), 5.90 (1H, dt, *J* 15.5, 4.5 Hz, HO-$CH_2$-C*H*=), 5.38-5.34 (1H, m, BocN(Ts)-C*H*<), 4.15 (2H, br d, *J* 4.5 Hz, HO-C$H_2$-), 3.66 (3H, s, N-$CH_3$), 3.56 (1H, dd, *J* 15.0, 9.0 Hz, indolyl-C*H*H-), 3.33 (1H, dd, *J* 15.0, 7.0 Hz, indolyl-CH*H*-), 2.36 (3H, s, Ts-$CH_3$), 1.39 (9H, s, -Boc); $\delta_C$ (75 MHz, $CDCl_3$) 150.6 (4°), 143.4 (4°), 137.5 (4°), 137.0 (4°), 132.3 (3°), 130.5 (3°), 128.7 (3°), 128.1 (4°), 127.8 (3°), 121.7 (3°), 119.1 (3°), 110.7 (4°), 109.2 (3°), 84.2 (4°), 63.0 (2°), 60.8 (3°), 32.6 (1°), 29.2 (2°), 28.0 (1°), 21.5 (1°); *m/z* (CI) 502 $[M+NH_4]^+$,

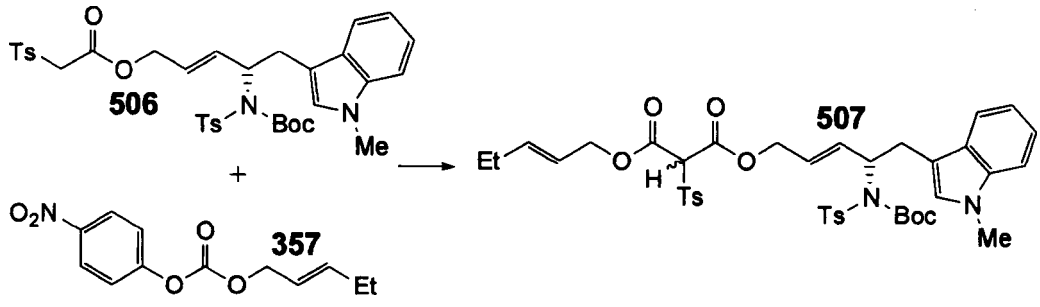
485 $[M+H]^+$, 429, 385, 289, 214, 146, 144 (Found: 485.2090. $C_{26}H_{32}N_2O_5S$ requires $[M+H]^+$ 485.2110).

**(*S*,*E*)-4-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate (506)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (176 mg, 0.819 mmol), **505** (397 mg, 0.819 mmol), $CH_2Cl_2$ (10 mL) and *N,N'*-di*iso*propyl carbodiimide (128 μL, 0.819 mmol). Chromatography (40→45% EtOAc–petrol) to give *(S,E)-4-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate* **506** (520 mg, 93%) as a colourless solid; mp 56–58 °C; $R_f$ 0.24 (35% EtOAc–petrol); $[\alpha]_D^{25}$ –1.39 (c=0.18, $CHCl_3$); $[\alpha]_D^{25}$ –5.56 (c=0.63, MeOH); $\nu_{max}$ (film) 3051, 1728, 1597, 1474, 1352, 1329, 1278, 1151, 1086, 970, 912, 813, 736, 670 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.78 (2H, dt, *J* 8.5, 2.0 Hz, *o*-$SO_2Ar$), 7.64 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.32 (2H, d, 8.0 Hz, *o*-$SO_2Ar$), 7.29 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.25 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 7.24 (1H, t, *J* 7.5 Hz, indolyl H-5), 7.13 (1H, t, *J* 7.5 Hz, indolyl H-6), 7.01 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.79 (1H, s, indolyl H-2), 6.23 (1H, dd, *J* 15.5, 6.5 Hz, -$OCH_2$-CH=C*H*-), 5.69 (1H, dtd, *J* 15.5, 6.0, 1.0 Hz, -$OCH_2$-C*H*=), 5.33-5.29 (1H, m, BocN(Ts)-C*H*<), 4.57 (2H, d, *J* 6.0 Hz, -$OCH_2$-), 4.09 (2H, s, Ts-$CH_2$-COO-), 3.66 (3H, s, N-$CH_3$), 3.49 (1H, dd, *J* 14.5, 8.5 Hz, indolyl-C*H*H-), 3.30 (1H, dd, *J* 14.5, 7.0 Hz, indolyl-CH*H*-), 2.42 (3H, s, Ts-$CH_3$), 2.38 (3H, s, Ts-$CH_3$), 1.36 (9H, s, -Boc); $\delta_C$ (75 MHz, $CDCl_3$) 162.2 (4°), 150.5 (4°), 145.5 (4°), 143.5 (4°), 137.4 (4°), 137.0 (4°), 135.7 (4°), 134.8 (3°), 129.9 (3°), 128.8 (3°), 128.6 (3°), 127.9 (4°), 127.8 (×2, 3°), 125.6 (3°), 121.7 (3°), 119.2 (3°), 119.0 (3°), 110.3 (4°), 109.2 (3°), 84.3 (4°), 66.0 (2°), 61.1 (2°), 60.2 (3°), 32.6 (1°), 29.1 (2°), 28.0 (1°), 21.7 (1°), 21.5 (1°); *m/z* (FAB) 680 $[M]^+$, 410, 196, 144 (Found: 680.2254. $C_{35}H_{40}N_2O_8S_2$ requires $[M]^+$ 680.2226) (Found: C, 61.62; H, 5.94; N, 4.12. $C_{35}H_{40}N_2O_8S_2$ requires C, 61.74; H, 5.92; N, 4.11%).

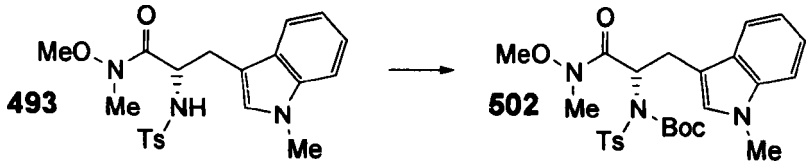
**1-(*S*,*E*)-4-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl 3-(*E*)-pent-2-enyl (2*R*)-2-(toluene-4-sulfonyl)malonate and 1-(*S*,*E*)-4-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl 3-(*E*)-pent-2-enyl (2*S*)-2-(toluene-4-sulfonyl)malonate (507)**




*General procedure (vii)* was applied, using sodium hydride (88 mg, 2.19 mmol, 4.0 equiv), **506** (372 mg, 0.543 mmol), DMF (5 mL total) and carbonate **357** (275 mg, 1.09 mmol). Chromatography (1% $Et_2O$-$CH_2Cl_2$ + 3 drops AcOH per 1 L eluent) gave product, co-eluted with significant amounts of *p*-nitrophenol. Thus the impure product was dissolved in $CH_2Cl_2$ and this was washed with aq. NaOH (1.0 M; 50 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified again by chromatography (30% EtOAc–petrol) to give *1-(*S,E*)-4-(*N-*(*tert-*butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl 3-(*E*)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate* **507** (192 mg, 45%) as a pale yellow oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.31 (1% $Et_2O$–$CH_2Cl_2$); $\nu_{max}$ (film) 3052, 1731, 1596, 1473, 1455, 1339, 1278, 1152, 1085, 971, 842, 814, 740, 670 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.82, 7.81] (2H, d, *J* 8.0 Hz, *C*-Ts *o*-$SO_2Ar$, 2× diast.), 7.65 (1H, d, *J* 7.5 Hz, indolyl H-7), 7.31-7.22 (6H, m, indolyl H-4,5, *C*-Ts *m*-$SO_2Ar$, *N*-Ts *o*-$SO_2Ar$), 7.13 (1H, t, *J* 7.5 Hz, indolyl H-6), 7.03 (2H, d, *J* 7.5 Hz, *N*-Ts *m*-$SO_2Ar$), 6.81 (1H, s, indolyl H-2), 6.27 (1H, dd, *J* 15.5, 6.5 Hz, BocN(Ts)-CH-C*H*=), 5.83 (1H, dt, *J* 15.5, 6.0 Hz, =C*H*-$CH_2$-$CH_3$), 5.73 (1H, dt, *J* 15.5, 6.0 Hz, BocN(Ts)-CH-CH=C*H*-), 5.49 (1H, dt, *J* 15.5, 5.5 Hz, -C*H*=CH-$CH_2$-$CH_3$), 4.97 (1H, s, -CH(Ts)-COO-), 4.65 (2H, d, *J* 5.5 Hz, BocN(Ts)-CH-CH=CH-C$H_2$O-), 4.60 (2H, d, *J* 6.0 Hz, -OC$H_2$-CH=CH-$CH_2$-$CH_3$), 3.66 (×2, 3H, s, indolyl N-$CH_3$, 2× diast.), 3.50 (1H, dd, *J* 14.0, 8.5 Hz, indolyl-C*H*H-), 3.30 (1H, dd, *J* 14.5, 7.0 Hz, indolyl-C*H*H-), [3.32 (dd, *J* 14.5, 7.5 Hz), 3.31 (dd, *J* 14.0, 7.5 Hz)] (1H, indolyl-CH*H*-, 2× diast.), 2.42 (×2, 3H, s, Ts-$CH_3$ 2× diast.), 2.36 (3H, s, Ts-$CH_3$), 2.10-2.03 (2H, m, -C$H_2$$CH_3$), 1.36 (9H, s, -Boc), 0.99 (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (100

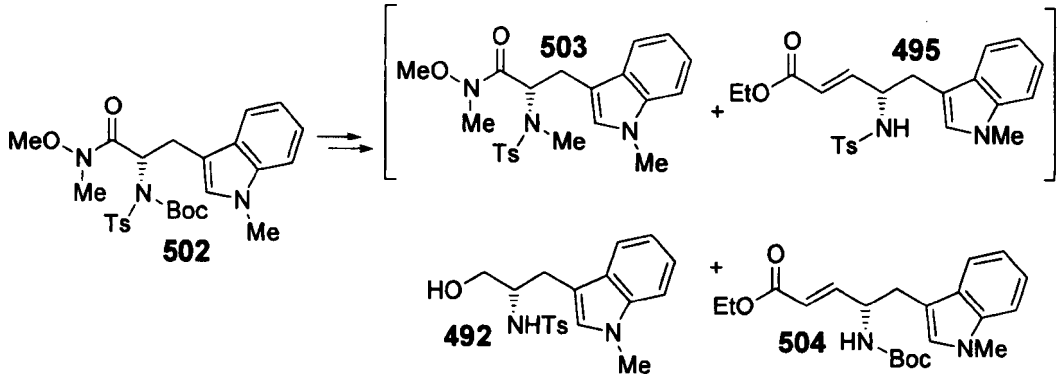
MHz, $CDCl_3$) 160.7 (4°), 150.4 (4°), 146.0 (4°), 143.5 (4°), 139.6 (3°), 137.3 (4°), 136.9 (4°), 134.9 (×2, 3°), 134.1 (4°), 130.2 (×2, 3°), 129.5 (×2, 3°), 128.8 (3°), 127.8 (3°), 127.7 (3°), 125.3 (3°), 121.7 (3°), 121.3 (3°), 119.1 (3°), 118.9 (3°), 110.3 (4°), 109.1 (3°), 84.3 (4°), 74.6 (3°), 67.8 (2°), 66.7 (2°), 60.1 (3°), 32.5 (1°), 29.7 (2°), 29.1 (2°), 28.0 (1°), 25.2 (2°), 21.7 (1°), 21.5 (1°), 13.0 (1°); *m/z* (FAB) 792 $[M]^+$, 522, 144, 73 *[Peak intensity too low for accurate mass measurement]*

**(*S*)-*tert*-Butyl 1-(methoxy(methyl)amino)-3-(1-methylindol-3-yl)-1-oxopropan-2-yl(toluene-4-sulfonyl)carbamate (502)**




To a solution of **493** (831 mg, 2.00 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at rt was added a solution of $Boc_2O$ (546 mg, 2.50 mmol, 1.25 equiv) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred for 5 min, then a solution of 4-(*N*,*N*-dimethylamino)pyridine (48 mg, 0.40 mmol, 0.2 equiv) in $CH_2Cl_2$ was added. The reaction mixture was stirred at rt for 16 h, then washed with aq. $NaHCO_3$ (1.0 M; 20 mL). The organic layer was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (20% EtOAc-hexane) to give *(S)-tert-butyl 1-(methoxy(methyl)amino)-3-(1-methylindol-3-yl)-1-oxopropan-2-yl(toluene-4-sulfonyl)carbamate* **502** (947 mg, 92%) as a colourless oil; $R_f$ 0.30 (20% EtOAc–petrol); $\nu_{max}$ (film) 3054, 1731, 1677, 1597, 1474, 1354, 1282, 1254, 1153, 1088, 911, 813, 736, 670 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.75 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.46 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.34-7.23 (2H, m, indolyl H-4,5), 7.18 (1H, t, *J* 7.0 Hz, indolyl H-6), 7.09 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 6.89 (1H, s, indolyl H-2), 5.65-5.61 (1H, m, -C(O)-C*H*<), 3.77 (3H, s, indolyl N-$CH_3$), 3.77-3.72 (1H, m, indolyl-C*H*H-), 3.68 (3H, s, N(OC*H*$_3$)-$CH_3$), 3.59 (1H, dd, *J* 14.5, 8.5 Hz, indolyl-CH*H*-), 3.28 (3H, s, N(OC$H_3$)-C$H_3$), 2.39 (3H, s, Ts-$CH_3$), 1.35 (9H, s, -Boc); $\delta_C$ (75 MHz, $CDCl_3$) 169.5 (4°), 150.7 (4°), 143.7 (4°), 137.3 (4°), 136.9 (4°), 128.8 (3°), 128.7 (3°), 128.3 (3°), 128.0 (4°), 121.6 (3°), 119.1 (3°), 118.8 (3°), 110.1 (4°), 109.2 (3°), 84.3 (4°), 61.5 (1°), 58.6 (3°), 32.7 (1°), 32.6 (1°), 27.9 (1°), 25.9 (2°), 21.6 (1°); *m/z* (CI) 516 $[M+H]^+$, 416 $[M+H\text{-}Boc]^+$, 362, 262, 174 (Found: 516.2159. $C_{26}H_{33}N_3O_6S$ requires $[M+H]^+$ 516.2168).

**(*S*,*E*)-Ethyl 4-(*tert*-butoxycarbonylamino)-5-(1-methylindol-3-yl)pent-2-enoate (504), (*S*)-*N*-Methoxy-*N*-methyl-3-(1-methylindol-3-yl)-2-(*N*,4-dimethylphenylsulfonamido)propanamide (503, *tentative assignment*) and (*S*,*E*)-Ethyl 5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido)pent-2-enoate (495)**



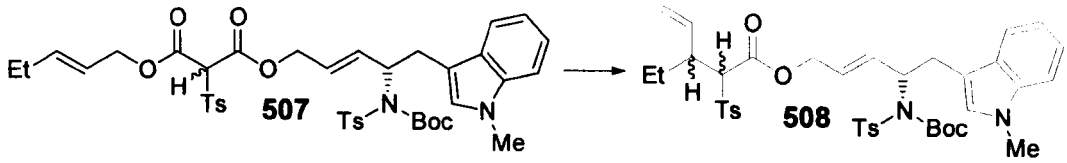

To **502** (783 mg, 1.52 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added $LiAlH_4$ (1.0M in THF; 3.77 mL, 3.77 mmol, 2.5 equiv). The reaction mixture was stirred at 0 °C for 90 min, then quenched by careful addition of $H_2O$ (3.8 mL), NaOH (2.0 M; 3.8 mL) and $H_2O$ (11.4 mL). The resultant gel (which began to discolour within minutes) was filtered through harbolite and washed with copious amounts of ether. The filtrate was dried over $Na_2SO_4$, concentrated under reduced pressure and used immediately without further purification.

To NaH (60% w/w in mineral oil, 73mg, 1.82 mmol, 1.2 equiv) at –10 °C was added a solution of triethyl phosphonoacetate (426 mg, 1.90 mmol, 1.25 equiv) in THF (10 mL). The reaction mixture was stirred for 30 min, then the crude aldehyde was added by cannula as a solution in THF (10 mL). The reaction mixture was stirred at –10 °C for 30 min, then at rt for 72 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aq. $NH_4Cl$ (2× 50ml). The aqueous phases were washed with EtOAc (20 mL). Combined organic phases were dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (35-EtOAc–petrol) to give *(S,E)-ethyl 4-(tert-butoxycarbonylamino)-5-(1-methylindol-3-yl)pent-2-enoate* **504** (16 mg, 3%) as a colourless oil; Also isolated were *(S)-3-(1-methylindol-3-yl)-2-(4-methylphenylsulfonamido)propan-1-ol* **492** (25 mg, 5%) and an inseparable mixture tentatively assigned as *(S)*-N-*methoxy*-N-*methyl-3-(1-methylindol-3-yl)-2-(N,4-dimethylphenylsulfonamido)propanamide* **503** (31%) and *(S,E)-ethyl 5-(1-methylindol-3-yl)-4-(4-methylphenylsulfonamido)pent-2-enoate* **495** (8%); 253 mg total, **317**:**310** ≈4:1 by NMR.

**504:** $R_f$ 0.55 (35% EtOAc–petrol); $[\alpha]_D^{25}$ +6.84 (c=1.06, MeOH); $[\alpha]_D^{25}$ –3.24 (c=1.08, $CHCl_3$); $\nu_{max}$ (film) 3054, 3027, 1708, 1657, 1614, 1475, 1390, 1367, 1327, 1305, 1285, 1262, 1164, 1094, 1042, 979, 911, 865, 800, 739 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.59 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.37-7.23 (2H, m, indolyl H-4,5), 7.14 (1H, t, *J* 7.0 Hz, indolyl H-6), 7.00 (1H, dd, *J* 15.5, 4.5 Hz, -OC(O)-CH=C*H*-), 6.91 (1H, s, indolyl H-2), 5.91 (1H, d, *J* 15.5 Hz, -C(O)-C*H*=CH-), 4.66 (2H, br s, BocNH-C*H*<, N-H), 4.19 (2H, q, *J* 7.0 Hz, $H_3C$-C$H_2$-), 3.77 (3H, s, N-$CH_3$), 3.08-3.01 (2H, m, indolyl-$CH_2$-), 1.43 (9H, s, -$C(CH_3)_3$), 1.29 (3H, t, *J* 7.0 Hz, $H_3C$-$CH_2$-); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (ester C=O), 155.2 (Boc C=O), 148.6 (3°), 137.0 (3°), 128.1 (4°), 127.6 (3°), 121.8 (3°), 120.9 (3°), 119.2 (3°), 119.0 (3°), 109.3 (3°), 108.9 (4°), 79.8 (-*C*$(CH_3)_3$), 60.4 (-$OCH_2$-), 51.8 (N-CH<), 32.7 (N-$CH_3$), 30.5 (Ar-$CH_2$-), 28.3 (-C(*C*$H_3)_3$), 14.3 ($H_3C$-$CH_2$-); *m/z* (CI) 390 $[M+NH_4]^+$, 373 $[M+H]^+$, 334, 317, 273 $[M+H-Boc]^+$, 144, 120 (Found: 373.2132. $C_{21}H_{28}N_2O_4$ requires $[M+H]^+$ 373.2127).

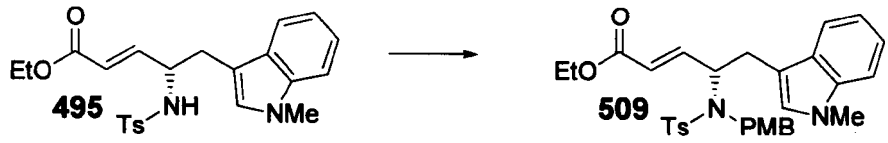
**503** and **495:** $R_f$ 0.36 (35% EtOAc–petrol); $\nu_{max}$ (film) 3288, 3054, 3029, 1714, 1657, 1615, 1598, 1551, 1472, 1442, 1377, 1328, 1290, 1260, 1160, 1093, 1046, 1018, 975, 912, 814, 738, 667 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.74 (2H for **503**, d, *J* 8.0 Hz, *o*-$SO_2$Ar for **503**), 7.56 (1H for **503**, d, *J* 8.0 Hz, indolyl H-7 for **503**), 7.49 (2H for **495**, d, *J* 8.0 Hz, *o*-$SO_2$Ar for **495**), 7.30-7.04 (5H for **503** and 6H for **495**, m, indolyl H-7 for **495**, *m*-$SO_2$Ar, indolyl H-4,5,6 for **503** and **495**), 6.87 (1H for **503**, s, indolyl H-2 for **503**), 6.83 (1H for **495**, dd, *J* 15.5, 6.0 Hz, -C(O)-CH=C*H*- for **495**), 6.80 (1H for **495**, s, indolyl H-2 for **495**), 5.90 (1H for **495**, d, *J* 15.5 Hz, -C(O)-C*H*=CH- for **495**), 5.31 (1H for **503**, d, *J* 5.0 Hz, -C(O)-C*H*< for **503**), 5.13 (1H for **495**, d, *J* 6.5 Hz, N-H for **495**, 4.22-4.15 (3H for **495**, m, N-CH<, -$OCH_2$- for **495**), 3.72 (3H for **503**, s, indolyl N-$CH_3$ for **503**), 3.68 (3H for **495**, s, indolyl N-$CH_3$ for **495**), 3.43 (3H for **503**, s, O-$CH_3$ for **503**), [3.13, 3.11] (3H for **503**, s, -N($OCH_3$)C$H_3$ for **503**), 3.02 (1H for **495**, dd, *J* 14.5, 6.0 Hz, indolyl-C*H*H- for **495**), 2.86 (1H for **495**, dd, *J* 14.5, 7.0 Hz, indolyl-CH*H*- for **495**), 2.65 (1H for **503**, dd, *J* 13.5, 6.5 Hz, indolyl-C*H*H- for **503**), 2.55 (1H for **503**, dd, *J* 13.5, 5.5 Hz, indolyl-CH*H*- for **503**), 2.47 (3H for **503**, s, N(Ts)-$CH_3$ for **503**), 2.40 (3H for **503**, s, Ts-$CH_3$ for **503**), 2.36 (3H for **495**, s, Ts-$CH_3$ for **495**), 1.28 (3H for **495**, t, *J* 7.0 Hz, -$OCH_2$-C$H_3$ for **495**); $\delta_C$ (75 MHz, $CDCl_3$) 166.1, 147.4, 143.2, 137.4, 137.1, 136.9, 136.8, 129.5, 129.3, 129.1, 128.5, 128.2, 128.1, 127.7, 127.5, 127.1, 126.9, 126.4, 122.2, 121.8, 121.5, 119.4, 119.2, 119.0 (×2), 118.6, 109.5, 109.4, 109.2, 107.8, 62.7, 60.5, 59.3, 54.6, 52.5, 32.7, 31.0, 28.6, 21.6, 14.3; *m/z [no parent ion found].*

**(4*S*,*E*)-4-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate (508), diastereoisomers as shown**




To **507** (48 mg, 0.0606 mmol, 1.0 equiv) was added potassium acetate (1 mg, 0.01 mmol, 0.2 equiv). The reaction vessel was purged with $N_2$, then PhMe (1.0 mL) was introduced. *N,O*-bis(trimethylsilyl)acetamide (60 μL, 0.241 mmol, 4.0 equiv) was added. The reaction mixture was heated to reflux for 5 h, concentrated under reduced pressure and purified by chromatography (20% EtOAc–petrol) to give *(4S,E)-4-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate* **508** (20 mg, 44%) as a colourless oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.21 (20% EtOAc–petrol); $\nu_{max}$ (film) 3055, 3030, 1730, 1597, 1473, 1455, 1352, 1338, 1279, 1258, 1151, 1085, 1017, 970, 915, 840, 814, 769, 738, 707, 670 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.75-7.63 (4H, m, 2× *o*-$SO_2Ar$), 7.31-7.21 (5H, m, *m*-$SO_2Ar$, indolyl H-4,5,7), 7.14 (1H, t, *J* 7.5 Hz, indolyl H-6), 7.00 (2H, d, *J* 6.5 Hz, *m*-$SO_2Ar$), [6.80, 6.79] (1H, s, indolyl H-2), [6.25-6.21 (m), 6.19 (dd, *J* 15.5, 6.0 Hz)] (-$OCH_2$-CH=C*H*-), 5.73-5.63 (1H, m, -$OCH_2$-C*H*=), 5.63-5.48 (1H, m, -C*H*=$CH_2$), 5.31-5.28 (1H, m, N-CH<), [5.21 (d, *J* 10.0 Hz), 5.13-5.00 (m)] (2H, -CH=C$H_2$), [4.57-4.42 (m), 4.40 (dd, *J* 13.0, 6.0 Hz), 4.28 (dd, *J* 13.0, 6.0 Hz)] (2H, -$OCH_2$-), 3.99-3.97 (1H, m, Ts-CH<), 3.66 (3H, s, N-$CH_3$), 3.53-3.47 (1H, m, indolyl-C*H*H-), 3.31-3.21 (1H, m, indolyl-CH*H*-), 2.82-2.68 (1H, m, $H_3C$-$CH_2$-C*H*<), [2.41, 2.36] (2× 3H, s, Ts-$CH_3$), [2.08-2.01 (m), 1.51-1.42 (m), 1.30-1.21 (m)] (2H, m, $H_3C$-C$H_2$-), [0.89 (t, *J* 7.0 Hz), 0.81 (t, *J* 7.5 Hz)] (3H, -$CH_2$-C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 165.6 (4°), 165.3 (4°), 150.5 (4°), 145.6 (4°), 143.5 (4°), 137.4 (4°), 137.0 (4°), 136.5 (3°), 135.9 (3°), 135.4 (3°), 135.3 (3°), 134.7 (3°), 134.4 (3°), 129.6 (×2, 3°), 129.4 (3°), 129.3 (×2, 3°), 128.8 (3°), 127.9 (4°), 127.8 (×2, 3°), 125.9 (3°), 125.8 (×2, 3°), 125.7 (3°), 121.8 (3°), 119.2 (3°), 119.0 (=$CH_2$), 118.9 (3°), 118.5 (=$CH_2$), 110.3 (4°), 109.2 (3°), 84.3 (-C$(CH_3)_3$), [75.1, 74.6] (Ts-CH<), [65.8, 65.6] (-$OCH_2$-), 60.2 (N-CH<), [44.7, 44.5] ($H_3C$-$CH_2$-CH<), 32.6 (N-$CH_3$), 29.1 (indolyl-$CH_2$-), 28.4 (-C($CH_3)_3$), 25.1 ($H_3C$-$CH_2$-), [21.7, 21.6] (Ts-$CH_3$), [11.2, 11.0] ($H_3C$-$CH_2$-); *m/z* (FAB) 748 $[M]^+$, 338, 144 (Found: 748.2885. $C_{40}H_{48}N_2O_8S_2$ requires $[M]^+$ 748.2852).

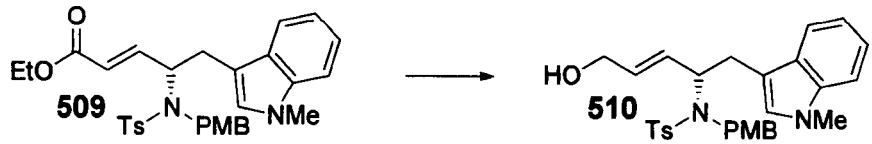
**(*S*,*E*)-Ethyl 4-(*N*-(4-methoxybenzyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enoate (509)**




To NaH (31.6 mg, 0.79 mmol, 1.0 equiv) at 0 °C was added by cannula a solution of **495** (337 mg, 0.79 mmol, 1.0 equiv) in DMF (8 mL). The reaction mixture was stirred at 0 °C for 10 min, then *p*-methoxybenzyl chloride (108 µL, 0.79 mmol, 1.0 equiv) was added by syringe. After 2 h at 0 °C, TLC indicated minimal conversion, thus tetrabutylammonium iodide (4 mg, 0.08 mmol, 0.1 equiv) in DMF (1 mL) was added by syringe. The reaction mixture was stirred at rt for 1 h, after which time TLC indicated consumption of all PMB-Cl, but not all **495**. A further 0.2 equiv of *p*-methoxybenzyl chloride (22 µL, 0.16 mmol) was introduced by syringe. The reaction mixture was stirred for 14 h, after which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (50 mL), washed with $H_2O$ (2× 50 mL) and saturated aq. NaCl (50 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (30% EtOAc–petrol) to give *(S,E)-ethyl 4-(N-(4-methoxybenzyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enoate* **509** (422 mg, 98%) as a colourless oil; $R_f$ 0.38 (35% EtOAc–petrol); $[\alpha]_D^{25}$ +3.96 (c=1.33, MeOH); $[\alpha]_D^{25}$ +12.2 (c=1.05, $CHCl_3$); $\nu_{max}$ (film) 3052, 3028, 1717, 1656, 1612, 1586, 1513, 1468, 1445, 1367, 1331, 1305, 1272, 1248, 1212, 1176, 1157, 1130, 1115, 1092, 1035, 980, 909, 878, 814, 740, 671 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.31-7.20 (7H, m, *m*-$SO_2Ar$, *m*-MeOAr, indolyl H-4,5,7), 7.06 (1H, t, *J* 6.5 Hz, indolyl H-6), 6.84 (2H, d, *J* 8.5 Hz, *o*-MeOAr), 6.75 (1H, dd, *J* 16.0, 7.0 Hz, -OC(O)-CH=C*H*-), 6.68 (1H, s, indolyl H-2), 5.53 (1H, d, *J* 16.0 Hz, -OC(O)-C*H*=CH-), 4.75-4.68 (1H, m, N-C*H*<), 4.48 (1H, d, *J* 15.5 Hz, MeO-$C_6H_4$-C*H*H-), 4.34 (1H, d, *J* 15.5 Hz, MeO-$C_6H_4$-CH*H*-), 4.12 (2H, q, *J* 7.0 Hz, $H_3C$-C$H_2$-), 3.81 (3H, s, -$OCH_3$), 3.67 (3H, s, N-$CH_3$), 3.13 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-C*H*H-), 2.96 (1H, dd, *J* 14.5, 9.0 Hz, indolyl-CH*H*-), 2.42 (3H, s, Ts-$CH_3$), 1.28 (3H, t, *J* 7.0 Hz, *H*$_3$C-$CH_2$-); $\delta_C$ (75 MHz, $CDCl_3$) 165.7 (C=O), 159.3 (4°), 145.0 (3°), 143.2 (4°), 137.8 (4°), 137.0 (4°), 130.0 (3°), 129.6 (3°), 129.2 (4°), 127.6 (3°), 127.5 (4°), 127.2 (3°), 123.8 (3°), 121.6 (3°), 118.9 (3°), 118.7 (3°), 114.0 (3°), 109.6 (4°), 109.2 (3°), 60.4 (-$OCH_2$-), 58.9 (N-CH<), 55.3 (-$OCH_3$), 48.8 (MeO-$C_6H_4$-$CH_2$-), 32.6 (N-$CH_3$), 29.7 (indolyl-$CH_2$-), 21.6 (Ts-$CH_3$), 14.2

($H_3C$-$CH_2$-); *m/z* (CI) 547 $[M+H]^+$, 393 288 258 189 174 139 121 (Found: 547.2256. $C_{31}H_{34}N_2O_5S$ requires $[M+H]^+$ 547.2267).

**(*S*,*E*)-5-(1-Methylindol-3-yl)-4-(*N*-(4-methoxybenzyl)-4-methylphenylsulfonamido)prop-2-en-1-ol (510)**

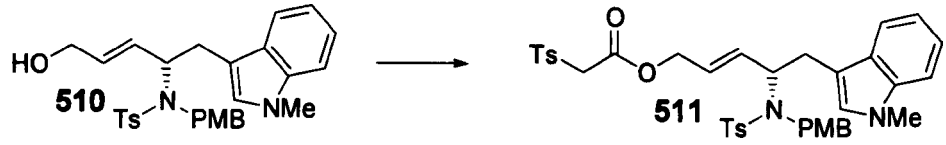



To a solution of **509** (388 mg, 0.711 mmol, 1.0 equiv) in $CH_2Cl_2$ (4.5 mL) at –78 °C was added DIBAL-H (1.0 M in $CH_2Cl_2$; 2.56 mL, 2.56 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 10 min, then at rt for 14 h, whereupon TLC indicated incomplete reaction. Regardless, the reaction mixture was quenched with EtOAc (100 mL) and poured onto saturated aq. sodium potassium tartrate (50 mL) and $H_2O$ (50 mL). The reaction mixture was stirred vigorously for 1 h. The aqueous phase was washed with a small portion of EtOAc. The combined organic phases were washed with $H_2O$ (2× 50 mL) and saturated aq. NaCl (50 mL), and dried over $Na_2SO_4$. Concentration under reduced pressure and chromatography (45→50% EtOAc–petrol) gave *(S,E)-5-(1-methylindol-3-yl)-4-(N-(4-methoxybenzyl)-4-methylphenylsulfonamido)prop-2-en-1-ol* **510** (146 mg, 41%) as a colourless oil; Also isolated was unreacted starting material **509** (129 mg, 33%).

**510:** $R_f$ 0.28 (50% EtOAc–petrol); $[\alpha]_D^{25}$ +2.74 (c=1.10, MeOH); $[\alpha]_D^{25}$ +3.21 (c=1.09, $CHCl_3$); $\nu_{max}$ (film) 3523, 3052, 3028, 1611, 1586, 1513, 1467, 1443, 1424, 1376, 1328, 1304, 1247, 1176, 1154, 1130, 1090, 1033, 1014, 974, 900, 880, 814, 741, 672, 655 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.35-7.17 (7H, m, *m*-$SO_2Ar$, *m*-MeOAr, indolyl H-4,5,7), 7.04 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.84 (2H, d, *J* 8.5 Hz, *o*-MeOAr), 6.66 (1H, s, indolyl H-2), 5.58 (1H, dd, *J* 15.5, 7.0 Hz, $HOCH_2$-CH=C*H*-), 5.39 (1H, dt, *J* 15.5, 5.0 Hz, $HOCH_2$-C*H*=CH-), 4.61-4.54 (1H, m, N-C*H*<), 4.46 (1H, d, *J* 15.5 Hz, MeO-$C_6H_4$-C*H*H-), 4.37 (1H, d, *J* 15.5 Hz, MeO-$C_6H_4$-CH*H*-), 3.85 (2H, m, HO-C$H_2$-), 3.82 (3H, s, -$OCH_3$), 3.67 (3H, s, N-$CH_3$), 3.04 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-C*H*H-), 2.90 (1H, dd, *J* 14.5, 9.0 Hz, indolyl -CH*H*-), 2.41 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 159.1 (4°), 143.0 (4°), 138.2 (4°), 136.8 (4°), 132.8 (3°), 129.9 (3°), 129.4 (3°), 127.7 (4°), 127.4 (3°), 127.3 (3°), 121.5 (3°),

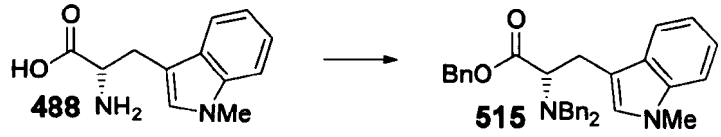
118.8 (3°), 118.7 (3°), 113.8 (3°), 110.5 (4°), 109.1 (3°), 62.9 ($HOCH_2$-), 60.0 (N-CH<), 55.3 (-$OCH_3$), 48.4 (MeO-$C_6H_4$-$CH_2$-), 32.6 (N-$CH_3$), 30.0 (indolyl-$CH_2$-), 21.5 (Ts-$CH_3$); *m/z* (CI) 505 $[M+H]^+$, 436, 214, 188, 146, 136, 121, 119 (Found: 505.2138. $C_{29}H_{32}N_2O_4S$ requires $[M+H]^+$ 505.2161).

**(*S,E*)-4-(*N*-(4-Methoxybenzyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate (511)**



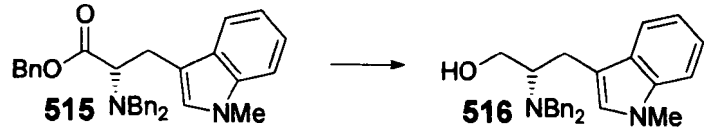

*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (55 mg, 0.258 mmol), **510** (130 mg, 0.258 mmol), $CH_2Cl_2$ (5 mL) and *N,N'*-di*iso*propyl carbodiimide (40 μL, 0.258 mmol). Chromatography (40% EtOAc–petrol) to give *(S,E)-4-(N-(4-methoxybenzyl)-4-methylphenylsulfonamido)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate* **511** (162 mg, 90%) as a colourless oil; $R_f$ 0.52 (50% EtOAc–petrol); $[\alpha]_D^{25}$ +1.34 (c=0.94, MeOH); $[\alpha]_D^{25}$ +2.57 (c=1.07, $CHCl_3$); $\nu_{max}$ (film) 3051, 3028, 1743, 1706, 1663, 1612, 1598, 1513, 1466, 1377, 1328, 1304, 1247, 1155, 1087, 1035, 973, 911, 814, 736, 672 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.65 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.29-7.16 (9H, m, 2× *m*-$SO_2Ar$, *m*-MeOAr, indolyl H-4,5,7), 7.05 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.84 (2H, d, *J* 8.5 Hz, *o*-MeOAr), 6.67 (1H, s, indolyl H-2), 5.64 (1H, dd, *J* 16.0, 7.0 Hz, -C(O)O-$CH_2$-CH=C*H*-), 5.26 (1H, dt, *J* 16.0, 6.5 Hz, -C(O)O-$CH_2$-C*H*=CH-), 4.60-4.53 (1H, m, N-C*H*<), 4.45 (1H, d, *J* 15.0 Hz, MeO-$C_6H_4$-C*H*H-), 4.35 (1H, d, *J* 15.0 Hz, MeO-$C_6H_4$-CH*H*-), 4.34 (2H, d, *J* 6.5 Hz, -$OCH_2$-), 4.03 (2H, s, Ts-$CH_2$-), 3.82 (3H, s, -$OCH_3$), 3.66 (3H, s, N-$CH_3$), 3.04 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-C*H*H-), 2.89 (1H, dd, *J* 14.5, 9.5 Hz, indolyl -CH*H*-), [2.43, 2.41] (2× 3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.1 (4°), 159.2 (4°), 145.5 (4°), 143.1 (4°), 138.1 (4°), 136.9 (4°), 135.7 (4°), 133.5 (3°), 130.0 (3°), 129.9 (3°), 129.6 (4°), 129.5 (3°), 128.5 (3°), 127.6 (3°), 127.2 (3°), 126.3 (3°), 121.5 (3°), 118.8 (3°), 118.7 (3°), 113.8 (3°), 110.0 (4°), 109.2 (3°), 65.7 (2°), 60.9 (2°), 59.6 (3°), 55.3 (1°), 48.4 (2°), 32.6 (1°), 29.9 (2°), 21.7 (1°), 21.6 (1°); *m/z* (FAB) 700 $[M]^+$, 556, 410, 144, 121 (Found: 700.2301. $C_{38}H_{40}N_2O_7S_2$ requires $[M]^+$ 700.2277).

**(*S*)-Benzyl 2-(dibenzylamino)-3-(1-methylindol-3-yl)propanoate (515)**



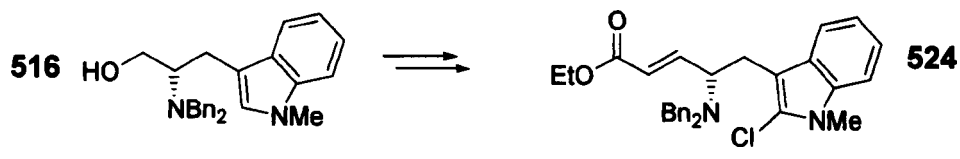

This was prepared by a method based on a literature procedure[198] for the perbenzylation of *O*-methyltyrosine. To L-1-methytryptophan **488** (10.0 g, 45.8 mmol, 1.0 equiv) in absolute ethanol (270 mL) was added potassium carbonate (22.2 g, 160 mmol, 3.5 equiv) and benzyl bromide (19.1 mL, 160 mmol, 3.5 equiv). The reaction mixture was heated to reflux for 5 h, then concentrated under reduced pressure. The residue was suspended in $CH_2Cl_2$ (500 mL) and washed with $H_2O$ (250 mL). The aqueous phase was extracted with a small portion of $CH_2Cl_2$. Combined organic phases were washed with saturated aq. NaCl (250 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (10% EtOAc–petrol) to give *(S)-benzyl 2-(dibenzylamino)-3-(1-methylindol-3-yl)propanoate* **515** (19.1 g, 85%) as a colourless oil; $R_f$ 0.30 (10% EtOAc–petrol); $[\alpha]_D^{25}$ –38.2 (c=1.72, MeOH); $[\alpha]_D^{25}$ –69.7 (c=1.27, $CHCl_3$); $\nu_{max}$ (film) 3084, 3060, 3029, 1728, 1602, 1494, 1474, 1453, 1375, 1328, 1252, 1210, 1163, 1129, 1073, 1028, 910, 738, 698 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.44-7.27 (17H, m, 15× Ph-H, indolyl H-5,7), 7.24 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.04 (1H, td, *J* 7.5, 1.0 Hz, indolyl H-6), 6.71 (1H, s, indolyl H-2), 5.30 (1H, d, *J* 12.5 Hz, Ph-C*H*HO-), 5.15 (1H, d, *J* 12.5 Hz, Ph-CH*H*O-), 4.07 (2H, d, *J* 14.0 Hz, Ph-C*H*H-N-), 3.92 (1H, dd, *J* 9.5, 5.5 Hz, N-CH<), 3.68 (3H, s, N-$CH_3$), 3.64 (2H, d, *J* 14.0 Hz, Ph-C*H*H-N-), 3.47 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-C*H*H-), 3.17 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 172.4 (C=O), 139.7 (4°), 136.9 (4°), 136.2 (4°), 128.9 (3°), 128.6 (3°), 128.3 (3°), 128.0 (4°), 127.7 (3°), 127.1 (3°), 121.4 (3°), 119.0 (3°), 118.8 (3°), 110.4 (4°), 109.1 (3°), 66.0 (Ph-$CH_2$O-), 61.7 (N-CH<), 54.7 (Ph-$CH_2$N<), 32.6 (N-$CH_3$), 26.1 (indolyl-$CH_2$-); *m/z* (CI) 489 $[M+H]^+$, 427, 344, 294, 196, 146 (Found: 489.2555. $C_{33}H_{32}N_2O_2$ requires $[M+H]^+$ 489.2542) (Found: C, 80.98; H, 6.76; N, 5.73. $C_{33}H_{32}N_2O_2$ requires C, 81.11; H, 6.60; N, 5.73%).

**(*S*)-2-(Dibenzylamino)-3-(1-methylindol-3-yl)propan-1-ol (516)**




To **515** (19.1 g, 39.0 mmol, 1.0 equiv) in THF (225 mL) at 0 °C was added $LiAlH_4$ (1.0M in THF; 39.0 mL, 39.0 mmol, 1.0 equiv) by syringe. The reaction mixture was stirred at 0 °C for 30 min and at rt for 2 h, then was quenched by careful addition of $H_2O$ (39.0 mL) and NaOH (2.0 M; 39.0 mL). The resultant precipitate was filtered and washed with copious amounts of ether. The filtrate was dried over $Na_2SO_4$, concentrated under reduced pressure and recrystallised from EtOH to give *(S)-2-(dibenzylamino)-3-(1-methylindol-3-yl)propan-1-ol* **516** (14.0 g, 93%) as a white solid; mp 133°C; $R_f$ 0.41 (35% EtOAc–petrol); $[\alpha]_D^{25}$ +6.78 (c=1.00, MeOH); $[\alpha]_D^{25}$ +28.7 (c=1.11, $CHCl_3$); $\nu_{max}$ (film) 3393, 3084, 3059, 3027, 1602, 1493, 1473, 1453, 1374, 1328, 1249, 1206, 1156, 1129, 1075, 1026, 912, 788, 740, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.50 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.46-7.22 (12H, m, 10× Ph-H, indolyl H-4,5), 7.11 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.80 (1H, s, indolyl H-2), 4.07 (2H, d, *J* 13.5 Hz, Ph-C*H*H-N-), 3.76 (3H, s, N-$CH_3$), 3.62 (2H, d, *J* 13.5 Hz, Ph-CH*H*-N-), 3.57-3.44 (2H, m, N-CH<, HO-C*H*H-), 3.31-3.23 (2H, m, HO-CH*H*-, indolyl-C*H*H-), 3.09 (1H, br s, -OH), 2.67 (1H, dd, *J* 15.0, 11.0 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 139.4 (4°), 137.0 (4°), 129.1 (3°), 128.6 (3°), 127.8 (4°), 127.3 (3°), 126.8 (3°), 121.7 (3°), 118.9 (3°), 111.4 (4°), 109.3 (3°), 61.0 (-$CH_2$OH), 59.7 (N-CH<), 53.3 (Ph-$CH_2$-N<), 32.7 (N-$CH_3$), 20.7 (indolyl-$CH_2$-); *m/z* (CI) 385 $[M+H]^+$, 293, 240, 146 (Found: 385.2280. $C_{26}H_{28}N_2O$ requires $[M+H]^+$ 385.2280) (Found: C, 81.37; H, 7.22; N, 7.19. $C_{26}H_{28}N_2O$ requires C, 81.21; H, 7.34; N, 7.29%).

**(*S,E*)-Ethyl 5-(2-chloro-1-methylindol-3-yl)-4-(dibenzylamino)pent-2-enoate (524)**

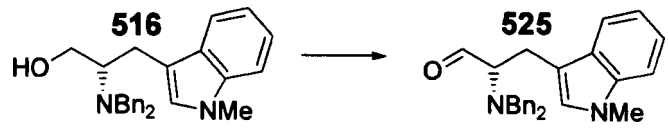



To oxalyl chloride (105 µL, 1.2 mmol, 1.2 equiv) in $CH_2Cl_2$ (2 mL) at –78 °C was added dimethyl sulfoxide (177 µL, 2.5 mmol, 2.5 equiv) dropwise by

syringe over 15 min. The reaction mixture was stirred at –78 °C for 15 min, then a solution of **516** (385 mg, 1.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (4 mL) was added dropwise by cannula. The reaction mixture was stirred at –78 °C for 2 h, then triethylamine (767 µL, 5.5 mmol, 5.5 equiv) was added dropwise by syringe. The reaction mixture was stirred at –78 °C for 5 min and allowed to warm to rt before dilution with $CH_2Cl_2$ (50 mL) and washing with $H_2O$ (50 mL) and saturated aq. NaCl (50 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and used immediately without further purification.

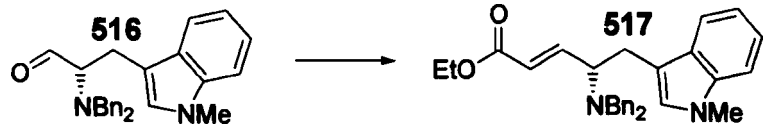
To NaH (60% w/w in mineral oil, 48 mg, 1.2 mmol, 1.2 equiv) at 0 °C was added by cannula a solution of triethyl phosphonoacetate (280 mg, 1.25 mmol, 1.25 equiv) in THF (2 mL). The reaction mixture was stirred for 10 min at 0 °C, then the crude aldehyde was added by cannula as a solution in THF (8 mL). The reaction mixture was stirred at 0 °C for 15 min, then at rt for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and quickly washed with aq. HCl (2.0 M; 50 mL), $H_2O$ (50 mL) and saturated NaCl (50 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (10% EtOAc–petrol) to give *(S,E)-ethyl 5-(2-chloro-1-methylindol-3-yl)-4-(dibenzylamino)pent-2-enoate* **524** (151 mg, 31%) as a colourless oil; $R_f$ 0.29 (10% EtOAc–petrol); $[\alpha]_D^{25}$ –44.4 (c=1.16, MeOH); $[\alpha]_D^{25}$ –24.9 (c=1.38, $CHCl_3$); $\nu_{max}$ (film) 3084, 3060, 3027, 1718, 1649, 1552, 1494, 1467, 1454, 1428, 1368, 1328, 1268, 1247, 1207, 1163, 1121, 1073, 1029, 986, 909 ($\nu_{C\text{-}Cl}$), 739, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.39-7.18 (12H, 10× Ph-H, indolyl H-5,7), 7.12 (1H, d, *J* 7.0 Hz, indolyl H-4), 7.04 (1H, dd, *J* 15.5, 7.5 Hz, -OC(O)-CH=C*H*-), 7.00 (1H, t, *J* 6.5 Hz, indolyl H-6), 5.85 (1H, d, *J* 15.5 Hz, -OC(O)-C*H*=CH-), 4.22 (2H, q, *J* 7.0 Hz, $H_3C$-C$H_2$-), 3.97 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.77-3.74 (1H, m, N-CH<), 3.71 (3H, s, N-$CH_3$), 3.62 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.26 (1H, dd, *J* 14.0, 5.5 Hz, indolyl-C*H*H-), 3.08 (1H, dd, *J* 14.0, 9.5 Hz, indolyl-CH*H*-), 1.32 (3H, t, *J* 7.0 Hz, *H*$_3$C-$CH_2$-); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (C=O), 146.9 (3°), 139.7 (4°), 135.7 (4°), 128.5 (3°), 128.3 (3°), 127.0 (3°), 126.6 (4°), 124.4 (4°), 123.6 (3°), 121.7 (3°), 119.6 (3°), 118.4 (3°), 109.0 (3°), 107.7 (4°), 60.4 (-$OCH_2$-), 59.0 (N-CH<), 53.9 (Ph-$CH_2$-), 29.9 (N-$CH_3$), 26.5 (indolyl-$CH_2$-), 14.3 ($H_3C$-$CH_2$-); *m/z* (CI) 489/487 $[M+H]^+$, 308, 258, 198, 196 (Found: 487.2158. $C_{30}H_{31}ClN_2O_2$ requires $[M+H]^+$ 487.2152) (Found: C, 73.89; H, 6.35; N, 5.72. $C_{30}H_{31}ClN_2O_2$ requires C, 73.98; H, 6.42; N, 5.75%).

**(*S*)-2-(Dibenzylamino)-3-(1-methylindol-3-yl)propanal (525)**




To **516** (4.21 g, 11.0 mmol, 1.0 equiv) in DMSO (dry, 10 mL) at rt was added $NEt_3$ (13.7 mL, 98.5 mmol, 9.0 equiv) by syringe. Separately, a solution of py·$SO_3$ (5.23 g, 32.9 mmol, 3.0 equiv) in DMSO (dry, 40 mL) was prepared. This was added dropwise by cannula to the reaction mixture. After 50 min the reaction mixture was diluted with EtOAc (250 mL). The reaction mixture was washed with alternating $H_2O$ (100 mL) and saturated aq. NaCl (100 mL) portions, 6 in total. The organic layer was dried over $Na_2SO_4$, then concentrated under reduced pressure to give crude *(S)-2-(dibenzylamino)-3-(1-methylindol-3-yl)propanal* **525**, used immediately in the next step (assumed 100% yield); $R_f$ 0.56 (20% EtOAc–petrol); $\nu_{max}$ (film) 3083, 3058, 3027, 1726, 1614, 1553, 1492, 1453, 1425, 1374, 1328, 1250, 1206, 1155, 1129, 1073, 1028, 1013, 978, 909, 862, 786, 738, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 9.88 (1H, s, -CHO), 7.56-7.28 (13H, m, 10× benzyl Ar-H, indolyl H-4,5,7), 7.21 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.94 (1H, s, indolyl H-2), 4.02 (2H, d, *J* 13.5 Hz, Ph-C*H*H-), 3.92 (2H, d, *J* 13.5 Hz, Ph-CH*H*-), 3.85-3.78 (1H, m, N-CH<), 3.78 (3H, s, $N-CH_3$), 3.44 (1H, dd, *J* 14.5, 9.0 Hz, indolyl-C*H*H-), 3.27 (1H, dd, *J* 14.5, 4.5 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 202.9 (C=O), 139.4, 137.0, 129.0, 128.6, 128.1, 127.8, 127.4, 121.7, 118.9, 118.9, 110.9, 109.4, 67.1 (N-CH<), 55.0 ($N-CH_2$-Ph), 32.7 ($N-CH_3$), 19.9 (Ind-$CH_2$-); *m/z* (CI) 383 $[M+H]^+$, 198, 188 (Found: 383.2125. $C_{26}H_{26}N_2O$ requires $[M+H]^+$ 383.2123)

**(*S,E*)-Ethyl 4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enoate (517)**




To crude **516** (4.19 g, 11.0 mmol, 1.0 equiv) at rt was added by cannula a solution of ethyl (triphenylphosphoranylidene)acetate (7.63 g, 21.9 mmol, 2.0 equiv) in $CH_2Cl_2$ (11 mL). The reaction mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by chromatography (10% EtOAc–petrol) to give *(S,E)-ethyl 4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enoate* **517** (4.68 g, 94% over 2 steps) as a colourless oil; $R_f$ 0.21

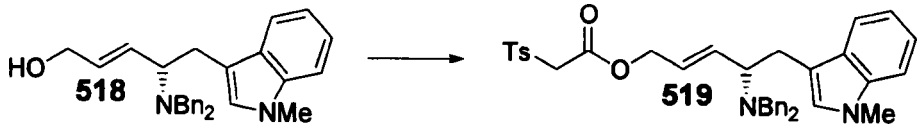
(10% EtOAc–petrol); $[\alpha]_D^{25}$ –1.34 (c=1.31, MeOH); $[\alpha]_D^{25}$ +2.58 (c=1.17, $CHCl_3$); $\nu_{max}$ (film) 3083, 3058, 3027, 1716, 1649, 1493, 1473, 1453, 1369, 1328, 1299, 1268, 1249, 1212, 1193, 1164, 1129, 1071, 1029, 984, 739, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.44-7.19 (13H, 10× Ph-H, indolyl H-4,5,7), 7.09 (1H, dd, *J* 16.0, 7.5 Hz, -OC(O)-CH=C*H*-), 7.00 (1H, t, *J* 6.5 Hz, indolyl H-6), 6.74 (1H, s, indolyl H-2), 5.90 (1H, dd, *J* 16.0, 1.0 Hz, -OC(O)-C*H*=CH-), 4.23 (2H, q, *J* 7.0 Hz, $H_3C$-C$H_2$-), 3.93 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.79-3.73 (1H, m, N-CH<), 3.73 (3H, s, N-$CH_3$), 3.63 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.31 (1H, dd, *J* 14.5, 5.0 Hz, indolyl-C*H*H-), 3.02 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-CH*H*-), 1.33 (3H, t, *J* 7.0 Hz, *H*$_3$C-$CH_2$-); $\delta_C$ (75 MHz, $CDCl_3$) 166.5 (C=O), 147.5 (3°), 139.8 (4°), 137.0 (4°), 128.6 (3°), 128.3 (3°), 127.9 (4°), 127.2 (3°), 127.0 (3°), 123.5 (3°), 121.5 (3°), 118.9 (3°), 118.7 (3°), 111.0 (4°), 109.1 (3°), 60.4 (-$OCH_2$-), 59.1 (N-CH<), 53.9 (Ph-$CH_2$-), 32.6 (N-$CH_3$), 27.0 (indolyl-$CH_2$-), 14.3 ($H_3C$-$CH_2$-); *m/z* (CI) 453 $[M+H]^+$, 308, 258, 198, 196, 146 (Found: 453.2550. $C_{30}H_{32}N_2O_2$ requires $[M+H]^+$ 453.2542) (Found: C, 79.65; H, 6.98; N, 6.15. $C_{30}H_{32}N_2O_2$ requires C, 79.61; H, 7.13; N, 6.19%).

**(*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-en-1-ol (518)**


To a solution of **517** (775 mg, 1.71 mmol, 1.0 equiv) in $CH_2Cl_2$ (11 mL) at –78 °C was added DIBAL-H (1.0M in $CH_2Cl_2$; 6.16 mL, 6.16 mmol, 3.6 equiv). The reaction mixture was stirred at –78 °C for 10 min, then at rt for 30 min. The reaction mixture was re-cooled to –78 °C, quenched with EtOAc (100 mL) and poured onto saturated aq. sodium potassium tartrate (100 mL) and $H_2O$ (100 mL). The reaction mixture was stirred vigorously for 1 h. The aqueous phase was washed with a small portion of EtOAc. The combined organic phases were washed with $H_2O$ (2× 50 mL) and saturated aq. NaCl (50 mL), dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (35% EtOAc–petrol) to give *(S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-en-1-ol* **518** (673 mg, 96%) as a colourless oil; $R_f$ 0.27 (35% EtOAc–petrol); $[\alpha]_D^{25}$ –4.77 (c=1.10, MeOH); $[\alpha]_D^{25}$ +9.15 (c=1.53, $CHCl_3$); $\nu_{max}$ (film) 3340, 3082, 3057, 3026, 1601, 1493, 1472, 1453, 1424, 1374, 1327, 1247, 1127, 1072, 1028, 975, 910, 739, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.41-7.21 (13H, 10× Ph-H, indolyl H-4,5,7), 7.04 (1H, t, *J* 6.5 Hz,

indolyl H-6), 6.74 (1H, s, indolyl H-2), 5.83 (1H, dd, *J* 15.5, 7.5 Hz, $HOCH_2$-CH=C*H*-), 5.68 (1H, dt, *J* 15.5, 5.0 Hz, $HOCH_2$-C*H*=CH-), 4.15 (2H, d, *J* 5.0 Hz, HO-C$H_2$-), 3.93 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.73 (3H, s, N-$CH_3$), 3.70-3.62 (1H, m, N-CH<), 3.62 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.26 (1H, dd, *J* 14.5, 5.0 Hz, indolyl-C*H*H-), 3.01 (1H, dd, *J* 14.5, 9.0 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 140.4 (4°), 136.9 (4°), 132.5 (3°), 130.3 (3°), 128.7 (3°), 128.2 (3°), 127.2 (3°), 126.8 (3°), 121.4 (3°), 119.2 (3°), 118.5 (3°), 112.1 (4°), 109.1 (3°), 63.5 (HO-$CH_2$-), 60.0 (N-CH<), 53.9 (Ph-$CH_2$-), 32.6 (N-$CH_3$), 28.0 (indolyl-$CH_2$-); *m/z* (CI) 411 $[M+H]^+$, 266, 214, 198, 196, 146 (Found: 411.2438. $C_{28}H_{30}N_2O$ requires $[M+H]^+$ 411.2436).

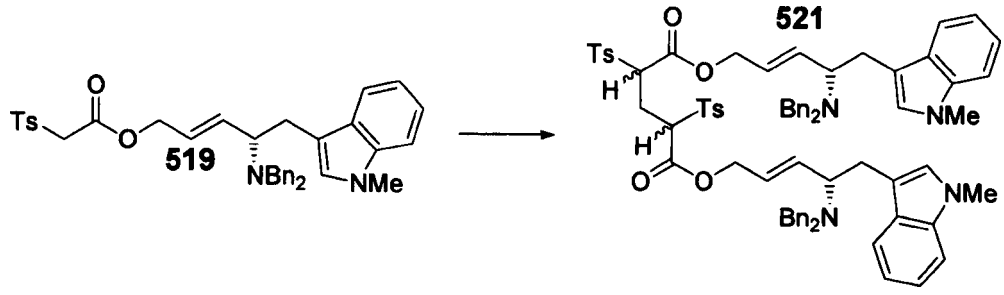
**(*S,E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate (519)**




*General procedure (vi)* was applied, using (toluene-4-sulfonyl)acetic acid (35 mg, 0.163 mmol), **518** (67 mg, 0.163 mmol), $CH_2Cl_2$ (5 mL) and *N,N'*-di*iso*propyl carbodiimide (25 µL, 0.163 mmol). Chromatography (30% EtOAc–petrol) to give *(S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl (toluene-4-sulfonyl)acetate* **519** (102 mg, 100%) as a colourless oil; $R_f$ 0.43 (35% EtOAc–petrol); $[\alpha]_D^{25}$ –10.0 (c=1.28, $CHCl_3$); $[\alpha]_D^{25}$ –11.7 (c=1.41, MeOH); $\nu_{max}$ (film) 3082, 3058, 3027, 1741, 1703, 1597, 1493, 1453, 1375, 1328, 1304, 1277, 1207, 1152, 1117, 1085, 1028, 972, 813, 740, 700 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.44-7.16 (15H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,7), 7.02 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.76 (1H, s, indolyl H-2), 5.91 (1H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-), 5.51 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=CH-), 4.62 (2H, d, *J* 6.0 Hz, -$OCH_2$-), 4.10 (2H, s, Ts-$CH_2$-), 3.91 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.72 (3H, s, N-$CH_3$), 3.67-3.58 (1H, m, N-CH<), 3.56 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.26 (1H, dd, *J* 14.5, 4.5 Hz, indolyl-C*H*H-), 2.99 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-CH*H*-), 2.36 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.3 (C=O), 145.4 (4°), 140.2 (4°), 137.0 (4°), 135.7 (4°), 135.1 (3°), 129.8 (3°), 128.7 (3°), 128.6 (3°), 128.3 (3°), 128.0 (4°), 127.3 (3°), 126.9 (3°), 125.9 (3°), 121.3 (3°), 119.0 (3°), 118.5 (3°), 111.6 (4°), 109.2 (3°), 66.5 (-$OCH_2$-), 61.1 (Ts-$CH_2$-), 59.7 (N-CH<), 53.8 (N-$CH_2$-), 32.6

(N-$CH_3$), 27.8 (indolyl-$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI) 607 $[M+H]^+$, 393, 259, 198, 196, 189, 188, 146, 144 (Found: 607.2613. $C_{37}H_{38}N_2O_4S$ requires $[M+H]^+$ 607.2631) (Found: C, 73.11; H, 6.38; N, 4.52. $C_{37}H_{38}N_2O_4S$ requires C, 73.23; H, 6.31; N, 4.62%).

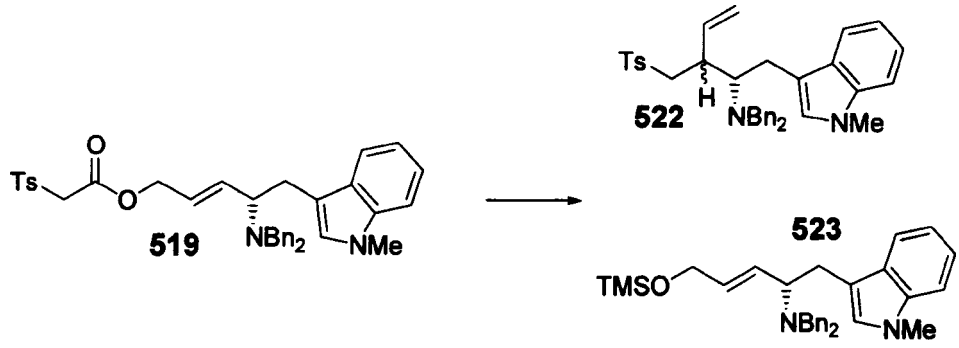
**Bis((4*S*,*E*)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 2,4-bis(toluene-4-sulfonyl)pentanedioate (521), diastereoisomers as shown.**




To **519** (90 mg, 0.148 mmol, 1.0 equiv) in a microwave vial was added potassium acetate (1.5 mg, 0.015 mmol, 0.1 equiv). The reaction vessel was capped and purged with $N_2$, then $CH_2Cl_2$ (1.5 mL) was introduced by syringe. *N,O*-bis(trimethylsilyl)acetamide (37 µL, 0.148 mmol, 1.0 equiv) was added by syringe. The reaction mixture was heated to 110 °C for 5 min under conditions of microwave irradiation. TLC indicated only minimal conversion, so the reaction mixture was heated to 140 °C for 15 min under conditions of microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified by chromatography (20% EtOAc–petrol) to give *bis((4S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 2,4-bis(toluene-4-sulfonyl)pentanedioate* **521** (40 mg, 44%) as a colourless oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.52 (35% EtOAc–petrol); $\nu_{max}$ (film) 3084, 3059, 3027, 1740, 1671, 1597, 1493, 1453, 1375, 1327, 1305, 1249, 1148, 1084, 1028, 975, 910, 814, 737, 700, 670 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.57-7.51 (4H, m, 2× *o*-$SO_2Ar$), 7.39-6.97 (32H, 20× Ph-H, 2× *m*-$SO_2Ar$, 2× indolyl H-4,5,6,7), 6.75 (2H, s, indolyl H-2), 5.89 (2H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-), 5.46-5.32 (2H, m, -$OCH_2$-C*H*=CH-), 4.61-4.50 (4H, m, -$OCH_2$-), [4.37, 4.26] (2× 1H, t, *J* 7.0 Hz, Ts-C*H*-$CH_2$-C*H*-Ts), 3.89 (4H, d, *J* 14.0 Hz, 4× Ph-C*H*H-), 3.67 (6H, s, 2× N-$CH_3$), 3.62-3.51 (6H, m, 2× N-CH<, 4× Ph-CH*H*-), 3.27-3.23 (2H, m, 2× indolyl-C*H*H-), 3.01-2.94 (2H, m, 2× indolyl-CH*H*-), 2.81-2.62 (2H, m, Ts-CH-C$H_2$-CH-Ts), 2.25 (6H, br s, 2× Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [164.8, 164.6] (C=O), 145.8 (4°), 140.2 (4°), 137.0

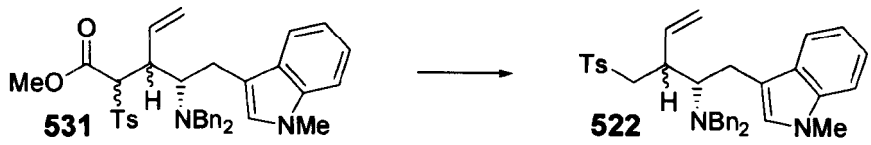
(4°), 135.1 (3°), 135.0 (3°), 133.7 (4°), 133.6 (4°), 133.5 (4°), 133.4 (4°), 133.1 (4°), 129.8 (3°), 129.4 (4°), 129.3 (3°), 129.2 (3°), 129.1 (3°), 128.9 (4°), 128.7 (3°), 128.3 (3°), 128.0 (4°), 127.3 (3°), 126.8 (3°), 125.8 (3°), 125.7 (3°), 125.6 (3°), 121.3 (3°), 119.0 (3°), 118.5 (3°), 111.5 (4°), 109.1 (3°), [67.3, 67.1] (Ts-CH<), 66.8 (-$OCH_2$-), 59.6 (N-CH<), 53.8 (Ph-$CH_2$-), 32.6 (N-$CH_3$), 28.1 (indolyl-$CH_2$-), [28.0, 27.9] (Ts-CH-$CH_2$-), 21.6 (Ts-$CH_3$); *m/z* (FAB) 1225 $[M+H]^+$, 1080, 688, 196, 144 (Found: 1225.5162. $C_{75}H_{76}N_4O_8S_2$ requires $[M+H]^+$ 1225.5183).

**(2*S*,3*R*)-*N*,*N*-Dibenzyl-1-(1-methylindol-3-yl)-3-((toluene-4-sulfonyl)methyl)pent-4-en-2-amine and (2*S*,3*S*)-*N*,*N*-Dibenzyl-1-(1-methylindol-3-yl)-3-((toluene-4-sulfonyl)methyl)pent-4-en-2-amine (522) and (*S*,*E*)-*N*,*N*-Dibenzyl-1-(1-methylindol-3-yl)-5-(trimethylsilyloxy)pent-3-en-2-amine (523)**




*Procedure A*

To **519** (121 mg, 0.20 mmol, 1.0 equiv) was added potassium acetate (2.0 mg, 0.02 mmol, 0.1 equiv). The reaction vessel was purged with $N_2$, then *N,O*-bis(trimethylsilyl)acetamide (37 µL, 0.241 mmol, 1.0 equiv) was introduced by syringe. PhMe (2 mL) was added by syringe. The reaction mixture was heated to reflux for 14 h, concentrated under reduced pressure and purified by chromatography (17% EtOAc–pentane) to give N,N-*dibenzyl-1-(1-methylindol-3-yl)-3-((toluene-4-sulfonyl)methyl)pent-4-en-2-amine* **522** (35 mg, 31%) as a colourless oil and as an inseparable mixture of diastereoisomers; on one occasion also isolated was *(*S,E*)*-N,N-*dibenzyl-1-(1-methylindol-3-yl)-5-(trimethylsilyloxy)pent-3-en-2-amine* **523** (9 mg, 9%), as a yellow oil.




*Procedure B*

To **531** (779 mg, 1.26 mmol, 1.0 equiv) in a microwave vial was added DMSO (5 mL, *not* dried) and NaCl (184 mg, 3.14 mmol, 2.5 equiv). The reaction mixture was heated under conditions of microwave irradiation to 170 °C for 5 min and to 180 °C for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and washed with alternating $H_2O$ (50 mL) and sat[d] brine (50 mL) portions, 6 in total. The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure. Chromatography (17.5% EtOAc–petrol) gave *N,N-dibenzyl-1-(1-methylindol-3-yl)-3-((toluene-4-sulfonyl)methyl) pent-4-en-2-amine* **522** (574 mg, 81%). Also isolated was unreacted **531** (46 mg, 6%).

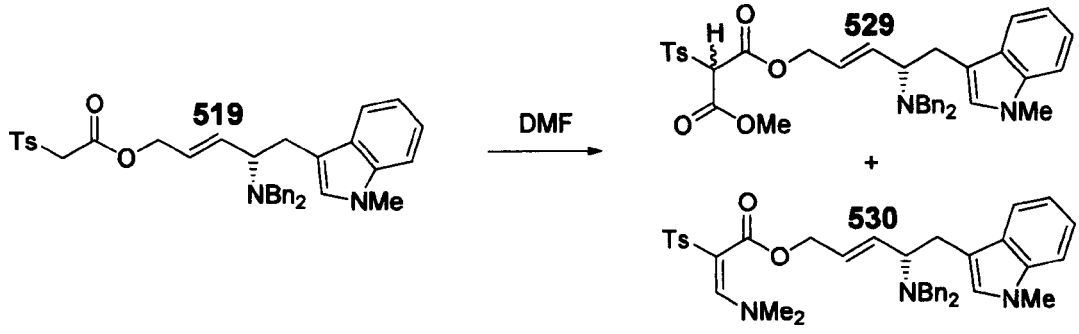
**522:** $R_f$ 0.42 (20% EtOAc–petrol); $\nu_{max}$ (film) 3082, 3058, 3027, 1598, 1493, 1453, 1375, 1325, 1300, 1249, 1145, 1087, 1073, 912, 815, 738, 700 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.69 (maj. diast.), 7.44 (min. diast.)] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.33-6.95 (16H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7, 2× diast.), [6.80 (min. diast.), 6.75 (maj. diast.)] (1H, s, indolyl H-2), [5.86-5.78 (1H maj, diast., m), 5.48-5.40 (1H min. diast., m)] ($H_2C$=C*H*-), 5.14 (1H min, d, *J* 10.0 Hz, *cis* $H_2C$=CH-, min. diast.), 5.13 (1H maj. diast., d, *J* 17.0 Hz, *trans* $H_2C$=CH-, maj. diast.), 5.06 (1H min. diast., d, *J* 17.0 Hz, *trans* $H_2C$=CH-, min. diast.), 4.96 (1H maj. diast., d, *J* 11.0 Hz, *cis* $H_2C$=CH-, min. diast.), 3.98-3.94 (1H maj. diast., m, Ts-C*H*H-, maj. diast.), [3.90 (min. diast.), 3.74 (maj. diast.)] (2H, d, *J* 14.0 Hz, Ph-C*H*H-, 2× diast.), 3.77 (3H, s, N-$CH_3$, 2× diast.), [3.52 (min. diast.), 3.44 (maj. diast)] (2H, d, *J* 14.0 Hz, Ph-CH*H*-, 2× diast.), 3.22 (1H min. diast., dd, *J* 15.0, 7.5 Hz, Ts-C*H*H-, min. diast.), 3.13-2.86 (4H, indolyl-$CH_2$-, N-CH<, $H_2C$=CH-C*H*<, 2× diast.), [2.79 (min. diast., dd, *J* 15.0, 3.5 Hz), 2.66 (maj. diast., dd, *J* 14.0, 10.0 Hz)] (1H, Ts-CH*H*-), [2.44 (maj. diast.), 2.36 (min. diast.)] (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.2 (4°), 143.8 (4°), 140.2 (4°), 139.9 (4°), 139.5 (3°), 137.7 (4°), 137.5 (3°), 137.1 (4°), 137.0 (4°), 136.7 (4°), 136.1 (4°), 129.6 (3°), 129.4 (3°), 129.2 (3°), 129.1 (3°), 128.6 (×2, 3°), 128.4 (3°), 128.2 (3°), 128.0 (3°), 127.8 (4°), 127.7 (3°), 127.3 (3°), 127.2 (3°), 127.0 (3°), 126.8 (3°), 121.7 (3°), 121.3 (3°), 119.3 (3°), 119.0 (3°), 118.8 (3°), [118.7, 118.5] (=$CH_2$), 113.3 (4°), 111.9 (4°), 109.3 (3°), 109.0 (3°), [61.9 (min. diast.), 60.2 (maj. diast.)] (N-CH<), [59.1 (min. diast.), 58.9 (maj. diast.)] (Ts-$CH_2$-), [56.0 (min. diast.), 53.7 (maj. diast.)] (Ph-$CH_2$-), [42.8 (maj. diast.), 41.1 (min. diast.)] ($H_2C$=CH-CH<), [32.8 (maj. diast.), 32.5 (min.

diast.)] (N-$CH_3$), [23.3 (maj. diast.), 21.4 (min. diast.)] (indolyl-$CH_2$-), [21.7 (maj. diast.), 21.1 (min. diast.)] (Ts-$CH_3$); *m/z* (CI) 563 $[M+H]^+$, 354, 198, 196, 174, 146 (Found: 563.2736. $C_{36}H_{38}N_2O_2S$ requires $[M+H]^+$ 563.2732).

**523:** $R_f$ 0.65 (20% EtOAc–petrol); $[\alpha]_D^{25}$ –24.7 (c=0.79, MeOH); $[\alpha]_D^{25}$ –34.5 (c=0.86, $CHCl_3$); $\nu_{max}$ (film) 3057, 3027, 1493, 1472, 1453, 1375, 1327, 1250, 1115, 1069, 1027, 1014, 974, 870, 841 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.46-7.05 (13H, 10× benzyl Ar-H, indolyl H-4,5,7), 6.98 (1H, t, *J* 7.5 Hz, indolyl H-6), 6.69 (1H, s, indolyl H-2), 5.77 (1H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-), 5.60 (1H, dt, *J* 15.5, 5.0 Hz, -$OCH_2$-C*H*=), 4.17 (2H, d, *J* 5.0 Hz, -$OCH_2$-), 3.87 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.71 (3H, s, N-$CH_3$), 3.58-3.53 (1H, m, N-CH<), 3.53 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.20 (1H, dd, *J* 14.5, 5.5 Hz, indolyl-C*H*H-), 2.95 (1H, dd, *J* 14.5, 8.5 Hz, indolyl-CH*H*-), 0.13 (9H, s, -$Si(CH_3)_3$); $\delta_C$ (75 MHz, $CDCl_3$) 140.4 (4°), 136.9 (4°), 132.7 (3°), 128.9 (3°), 128.7 (3°), 128.1 (3°), 127.2 (3°), 126.6 (3°), 121.2 (3°), 119.1 (3°), 118.4 (3°), 112.1 (4°), 108.9 (3°), 63.3 (-$OCH_2$-), 59.5 (N-CH), 53.7 (N-$CH_2$-Ph), 32.5 (N-$CH_3$), 28.1 (Ind-$CH_2$-), –0.2 (-$Si(CH_3)_3$); *m/z* (CI) 483 $[M+H]^+$, 338, 286, 198, 196, 167, 146 (Found: 483.2837. $C_{31}H_{38}N_2OSi$ requires $[M+H]^+$ 483.2831).

**1-(4*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-methyl (2*S*)-2-(toluene-4-sulfonyl)malonate and 1-(4*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-methyl (2*R*)-2-(toluene-4-sulfonyl)malonate (529)**

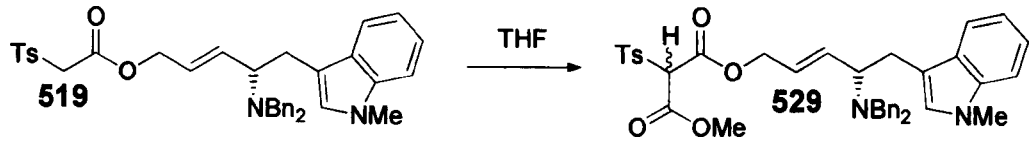
**(*E*)-((*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3-(dimethylamino)-2-(toluene-4-sulfonyl)propenoate (530)**




*Procedure A*

To NaH (149 mg, 3.74 mmol, 1.83 equiv) at 0 °C was added by cannula a solution of **519** (1.24 g, 2.05 mmol, 1.0 equiv) in DMF (5 mL). The reaction mixture was stirred for 30 min, then methyl chloroformate (159 µL, 2.06 mmol, 1.01 equiv) was introduced by syringe. The reaction mixture was stirred at 0

°C for 15 min, then at rt for 14 h. The reaction mixture was diluted with EtOAc (75 mL) and washed with dilute aq. $NaHCO_3$ (50 mL), $H_2O$ (50 mL) and saturated aq. NaCl (50 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (4:2:94 EtOAc:$NEt_3$:PhMe) to give *1-(4S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-methyl 2-(toluene-4-sulfonyl)malonate* **529** (554 mg, 45%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated was unreacted **519** (355 mg, 29%). On one occasion also isolated was byproduct *(E)-((S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3-(dimethylamino)-2-(toluene-4-sulfonyl)propenoate* **530** (108 mg, 8%), as a pink foam.




*Procedure B*

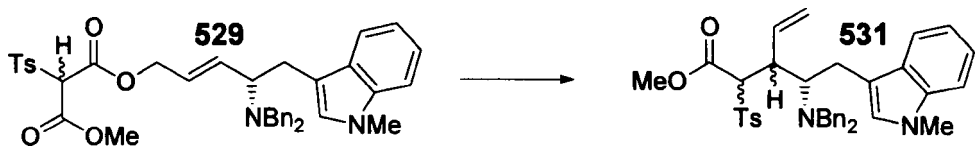
To NaH (299 mg, 7.48 mmol, 2.0 equiv) at –10 °C was added by cannula a solution of ester **519** (2.27 g, 2.05 mmol, 1.0 equiv) in THF (10 mL), resulting in effervescence. The reaction mixture was stirred for 30 min, then methyl chloroformate (578 µL, 7.48 mmol, 2.0 equiv) in was introduced by syringe. The reaction mixture was stirred at –10 °C for 15 min, then at rt for 14 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with dilute aq. $NaHCO_3$ (50 mL), $H_2O$ (50 mL) and saturated aq. NaCl (50 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (4:2:94 EtOAc:$NEt_3$:PhMe, → EtOAc) to give *1-(4S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-methyl 2-(toluene-4-sulfonyl)malonate* **529** (1.54 g, 62%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated was unreacted **519** (757 mg, 33%).

**529:** $R_f$ 0.43 (35% EtOAc–petrol); $\nu_{max}$ (film) 3084, 3058, 3027, 1745, 1669, 1596, 1494, 1453, 1375, 1336, 1291, 1194, 1151, 1132, 1083, 1027, 975, 911, 847, 814, 740, 701 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [7.82, 7.79] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$, 2× diast.), 7.45-7.03 (16H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7, 2× diast.), 6.79 (1H, s, indolyl H-2, 2× diast.), 5.98 (1H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-, 2× diast.), 5.58 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=CH-, 2× diast.), [5.06, 5.05] (1H, s, Ts-CH<, 2× diast.), 4.78-4.64 (2H, m,

-$OCH_2$-, 2× diast.), 3.94 (2H, d, *J* 14.0 Hz, Ph-C*H*H-, 2× diast.), 3.80 (3H, s, N-$CH_3$, 2× diast.), [3.74, 3.73] (3H, s, -$OCH_3$, 2× diast.), 3.69-3.62 (1H, m, N-CH<, 2× diast.), 3.59 (2H, d, *J* 14.0 Hz, Ph-CH*H*-, 2× diast.), 3.30 (1H, dd, *J* 14.5, 4.5 Hz, indolyl-C*H*H-, 2× diast.), 3.06-2.98 (1H, m, indolyl-CH*H*-, 2× diast.), [2.43, 2.39] (3H, s, Ts-$CH_3$, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 161.6 (×2, C=O), 160.8 (C=O), 146.1 (4°), 140.2 (4°), 137.0 (4°), 135.5 (3°), 134.2 (4°), 134.0 (4°), 130.1 (3°), 129.6 (3°), 129.1 (3°), 128.7 (3°), 128.3 (3°), 128.0 (3°), 127.4 (3°), 126.9 (3°), 125.5 (3°), 125.4 (3°), 121.4 (3°), 119.0 (3°), 118.6 (3°), 111.5 (4°), 109.2 (3°), 74.6 (Ts-CH<), 67.3 (-$OCH_2$-), 59.6 (N-CH<), 53.8 (Ph-$CH_2$-), 32.6 (N-$CH_3$), 27.9 (indolyl-$CH_2$-), [21.8, 21.6] (Ts-$CH_3$); *m/z* (FAB) 665 $[M+H]^+$, 520, 242, 144 (Found: 665.2655. $C_{39}H_{40}N_2O_6S$ requires $[M+H]^+$ 665.2685).

**530:** $R_f$ 0.28 (50% EtOAc–petrol); $[\alpha]_D^{25}$ –24.0 (c=0.91, MeOH); $[\alpha]_D^{25}$ –22.6 (c=1.00, $CHCl_3$); $\nu_{max}$ (film) 3083, 3058, 3027, 1688, 1613, 1493, 1483, 1453, 1433, 1388, 1361, 1327, 1295, 1285, 1243, 1196, 1141, 1117, 1091, 1029, 1016, 960, 910, 845, 813, 735, 701, 660 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.96 (1H, s, =C*H*N$(CH_3)_2$), 7.64 (2H, d, *J* 8.0 Hz, *o*-$SO_2$Ar), 7.41 (4H, d, *J* 7.5 Hz, *o*-Ph), 7.34 (4H, t, *J* 7.5 Hz, *m*-Ph), 7.32 (1H, d, *J* 7.5 Hz, indolyl H-4), 7.28 (2H, t, *J* 7.5 Hz, *p*-Ph), 7.26 (1H, d, *J* 8.5 Hz, indolyl H-7), 7.21 (1H, t, *J* 7.0 Hz, indolyl H-5), 7.03 (1H, td, *J* 7.5 1.0 Hz, indolyl H-6), 6.94 (2H, d, *J* 8.0 Hz, *m*-$SO_2$Ar), 6.80 (1H, s, indolyl H-2), 5.88 (1H, dd, *J* 15.5, 8.0 Hz, -$OCH_2$-CH=C*H*-), 5.46 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=), 4.55 (1H, dd, *J* 13.0, 6.0 Hz, -OC*H*H-), 4.50 (1H, dd, *J* 13.0, 6.5 Hz, -OCH*H*-), 3.91 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), 3.71 (3H, s, N-$CH_3$), 3.61-3.57 (1H, m, N-CH<), 3.57 (2H, d, *J* 14.0 Hz, N-CH*H*-Ph), 3.26 (1H, dd, *J* 14.5, 5.0 Hz, indolyl-C*H*H-), 3.24 (3H, br s, $H_3$C-N$(CH_3)$-), 2.99 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-CH*H*-), 2.90 (3H, br s, $H_3$C-N$(CH_3)$-), 2.25 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 162.1 (C=O), 155.7 (=*C*HN$(CH_3)_2$), 142.5 (*p*-$SO_2$Ar), 140.3 (*i*-Ph), 136.9 (indolyl C-7a), 133.7 (-$OCH_2$-CH=*C*H-), 128.9 (*m*-$SO_2$Ar), 128.6 (*o*-Ph), 128.2 (*m*-Ph), 128.0 (indolyl C-3a), 127.4 (×2, *o*-$SO_2$Ar, *i*-$SO_2$Ar, indolyl C-2), 127.0 (-$OCH_2$-*C*H=), 126.7 (*p*-Ph), 121.2 (indolyl C-5), 118.9 (indolyl C-4), 118.4 (indolyl C-6), 111.6 (indolyl C-3), 109.1 (indolyl C-7), 100.1 (>*C*=CHN$(CH_3)_2$), 64.8 (-$OCH_2$-), 59.5 (N-CH<), 53.8 (N-$CH_2$Ph), [47.9, 42.2] (-N$(CH_3)_2$), 32.5 (indolyl N-$CH_3$), 27.9 (indolyl-$CH_2$-), 21.3 (Ts-$CH_3$); *m/z* (FAB) 662 $[M+H]^+$, 517, 393, 252 (Found: $[M+H]^+$, 662.3076. $C_{40}H_{43}N_3O_4S$ requires $[M+H]^+$, 662.3053) (Found: C, 72.63; H, 6.42; N, 6.22. $C_{40}H_{43}N_3O_4S$ requires C, 72.59; H, 6.55; N, 6.35%).

**Methyl 3-((1*S*)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate (531), diastereoisomers as shown**




*Procedure A*

To **529** (75 mg, 0.113 mmol, 1.0 equiv) in a microwave vial was added potassium acetate (1 mg, 0.011 mmol, 0.1 equiv). The reaction vessel was capped and purged with $N_2$. PhMe (1.1 mL) was introduced by syringe, followed by *N,O*-bis(trimethylsilyl)acetamide (57 µL, 0.226 mmol, 2.0 equiv). The reaction mixture was heated to 110 °C for 5 min under conditions of microwave irradiation. TLC indicated only minimal conversion, so the reaction mixture was heated to 130 °C for 15 min under conditions of microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified by chromatography (20→40% EtOAc–petrol) to give *methyl 3-((1S)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **531** (10 mg, 14%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated was unreacted **529** (21 mg, 28%)

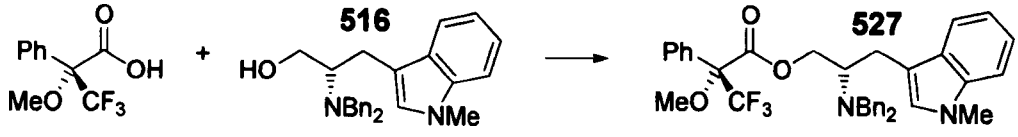
*Procedure B*

To a flame-dried microwave vial was added by cannula **529** (1.69 g, 2.55 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.1 mL). To the stirred reaction mixture was added DBU (1.14 mL, 7.64 mmol, 3.0 equiv) dropwise by syringe over 1 min. *tert*-Butyldimethylsilyl triflate (1.75 mL, 7.64 mmol, 3.0 equiv) was added dropwise over 5 min by syringe, resulting in an exotherm. The reaction mixture was heated under conditions of microwave irradiation to 60 °C for 1 h, then concentrated under reduced pressure. Chromatography (20% EtOAc–petrol) gave *methyl 3-((1S)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **531** (1.11 g, 70%) as a colourless foam and as an inseparable mixture of diastereoisomers; also isolated was unreacted **529** (258 mg, 15%).

**531:** $R_f$ 0.46 (35% EtOAc–petrol); $\nu_{max}$ (film) 3061, 3027, 1742, 1598, 1493, 1470, 1452, 1434, 1375, 1324, 1291, 1249, 1209, 1146, 1083, 1013, 913, 813, 738, 701 $cm^{-1}$; $\delta_H$ (300 MHz, major diastereoisomer only) 7.68 (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), 7.58-6.94 (16H, m, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7),

6.80 (1H, s, indolyl H-2), 5.98 (1H, dt, *J* 17.0, 10.0 Hz, $H_2C$=C*H*-), 5.35 (1H, dd, *J* 17.0, 1.5 Hz, *trans* $H_2C$=CH-), 5.10 (1H, dd, *J* 10.0, 1.5 Hz, *cis* $H_2C$=CH-), 4.97 (1H, d, *J* 2.0 Hz, Ts-CH<), 3.84 (2H, d, *J* 13.5 Hz, Ph-C*H*H-), 3.78 (3H, s, N-$CH_3$), 3.53 (1H, td, *J* 10.0, 2.0 Hz, $H_2C$=CH-C*H*<), 3.49-3.44 (1H, m, N-CH<), 3.45 (2H, d, *J* 13.5 Hz, Ph-CH*H*-), 3.27 (3H, s, -$OCH_3$), 3.17 (1H, dd, *J* 15.5, 6.5 Hz, indolyl-C*H*H-), 3.00 (1H, dd, *J* 15.5, 5.0 Hz, indolyl-CH*H*-), 2.46 (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 165.1 (C=O), 144.5 (4°), 139.5 (4°), 137.4 (4°), 137.1 (4°), 134.4 (3°), 129.3 (3°), 129.0 (3°), 128.6 (3°), 128.4 (3°), 128.1 (3°), 128.0 (4°), 127.9 (4°), 127.3 (3°), 127.1 (3°), 126.9 (3°), 121.7 (3°), 120.1 (=$CH_2$), 119.3 (3°), 118.5 (3°), 113.5 (4°), 109.2 (3°), 70.1 (Ts-CH<), 58.3 (N-CH<), 53.8 (Ph-$CH_2$-), 51.9 (-$OCH_3$), 45.7 ($H_2C$=CH-CH<) 32.8 (N-$CH_3$), 23.2 (indolyl-$CH_2$-), 21.7 (Ts-$CH_3$); *m/z* (CI, FAB) 621 $[M+H]^+$, 467, 355, 353, 338, 263, 198, 189, 146 (Found: 621.2783. $C_{38}H_{40}N_2O_4S$ requires $[M+H]^+$ 621.2787).

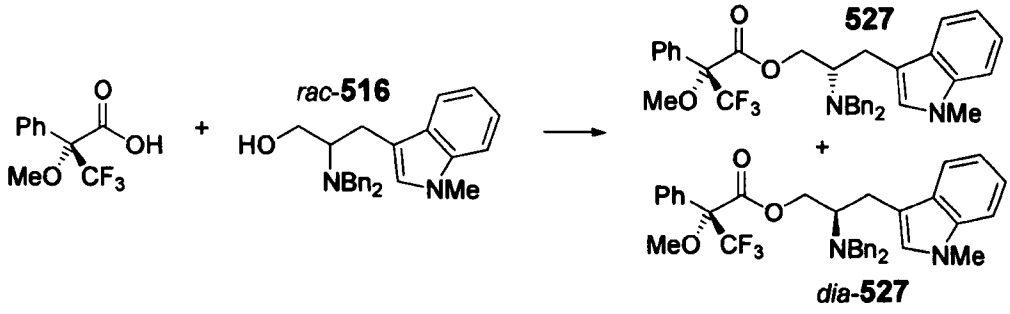
**(*R*)-((*S*)-2-(Dibenzylamino)-3-(1-methylindol-3-yl)propyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (527)**




To alcohol **516** (192 mg, 0.500 mmol, 1.0 equiv) and (*R*)-Mosher's acid (351 mg, 1.500 mmol, 3.0 equiv) in $CH_2Cl_2$ (5 mL) at rt was added *N,N'*-di*iso*propyl carbodiimide (234 µL, 1.500 mmol, 1.0 equiv) by syringe. The reaction mixture was stirred at rt for 30 min, then 4-(*N,N*-dimethylamino)pyridine (6 mg, 50.0 µmol, 0.10 equiv) was added. The reaction mixture was stirred at rt for 72 h, concentrated under reduced pressure and purified by chromatography (8% EtOAc–petrol) to give *(R)-((S)-2-(dibenzylamino)-3-(1-methylindol-3-yl)propyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* **527** (285 mg, 95%) as a colourless oil; $R_f$ 0.51 (20% EtOAc–petrol); $[\alpha]_D^{25}$ +0.92 (c=1.09, $CHCl_3$); $\nu_{max}$ (film) 3060, 3027, 1746, 1494, 1453, 1375, 1328, 1270, 1254, 1169, 1124, 1080, 1027, 1000, 740, 720, 699 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 7.0 Hz, Mosher *o*-Ph), 7.50-7.43 (3H, m, Mosher *m*-Ph, *p*-Ph), 7.34-7.22 (12H, m, 10× benzyl Ar-H, indolyl H-4,5), 7.20 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.02 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.67 (1H, s, indolyl H-2), 4.51 (1H, dd, *J* 11.5, 7.0 Hz, -OC*H*H-), 4.35 (1H, dd, *J* 11.5, 3.5 Hz, -OCH*H*-), 3.80 (2H, d, *J* 14.0 Hz, Ph-

C*H*H-), 3.72 (3H, s, N-$CH_3$), 3.65 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.53 (3H, s, -$OCH_3$), 3.47 (1H, br s, N-CH<), 3.20-3.18 (1H, m, indolyl-C*H*H-), 2.91 (1H, dd, *J* 14.0, 10.5 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 166.9 (C=O), 139.9, 137.1, 132.4, 129.7, 128.7, 128.6, 128.3, 127.7, 127.3, 127.3, 127.0, 125.5, 121.6, 118.9, 111.2, 109.2, 84.6 (q, $^2J_{CF}$ 27.2 Hz, *C*-$CF_3$), 66.4 (-$OCH_2$-), 56.3, 55.7, 54.2 (N-$CH_2$-Ph), 32.6 (N-$CH_3$), 23.8 (Ind-$CH_2$-); $\delta_F$ (376.5 MHz, $CDCl_3$) –70.06; *m/z* (CI) 601 $[M+H]^+$, 456, 367, 252, 198 (Found: 601.2668. $C_{36}H_{35}F_3N_2O_3$ requires $[M+H]^+$ 601.2678) (Found: C, 71.86; H, 5.75; N, 4.60. $C_{36}H_{35}F_3N_2O_3$ requires C, 71.98; H, 5.87; N, 4.66%).

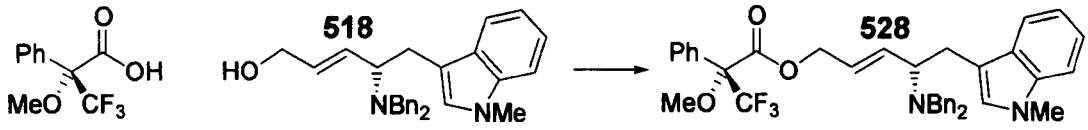
**(*R*)-((*S*)-2-(Dibenzylamino)-3-(1-methylindol-3-yl)propyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (527) and (*R*)-((*R*)-2-(Dibenzylamino)-3-(1-methylindol-3-yl)propyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*dia*-527)**




*This was synthesised as per the single enantiomer, but utilising amino alcohol prepared from racemic 1-methyl tryptophan.* Esters **527** and *dia*-**527** (117 mg, 89%) were isolated as a colourless oil and as an inseparable mixture of diastereoisomers; $\delta_H$ (400 MHz, $CDCl_3$) [7.62, 7.59] (2H, d, *J* 7.0 Hz, Mosher *o*-Ph-H, 2× diast.), 7.49-7.38 (3H, m, Mosher *m*-Ph-H, *p*-Ph-H), 7.33-7.23 (12H, m, 10× benzyl Ar-H, indolyl H-4,5), [7.19, 7.18] (1H, d, *J* 8.0 Hz, indolyl H-7, 2× diast.), 7.00 (1H, t, *J* 7.0 Hz, indolyl H-6), [6.68, 6.66] (1H, s, indolyl H-2, 2× diast.), [4.52-4.47 (m), 4.35 (dd, *J* 11.5, 3.5 Hz)] (2H, -$OCH_2$-, 2× diast.), [3.84, 3.78] (2H, d, *J* 13.5 Hz, Ph-C*H*H-, 2× diast.), 3.72 (3H, s, N-$CH_3$), [3.71, 3.67] (2H, d, *J* 13.5 Hz, Ph-CH*H*-, 2×, diast.), [3.57, 3.51] (3H, s, -OMe, 2× diast.), 3.47 (1H, br s, -N-CH<), [3.18, 3.17] (1H, dd, *J* 14.5, 4.5 Hz, indolyl-C*H*H-, 2× diast.), [2.95, 2.89] (1H, dd, *J* 14.5, 10.5 Hz, indolyl-CH*H*-, 2× diast.); $\delta_C$ (75 MHz, $CDCl_3$) 166.9 (C=O), 139.9 (×2), 137.1, 132.4 (×2), 129.7, 128.7 (×2), 128.6, 128.3, 128.0, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 127.0, 125.4, 121.6, 118.9 (×2), 111.2 (×2), 109.2, 84.6 (q, $^2J_{CF}$

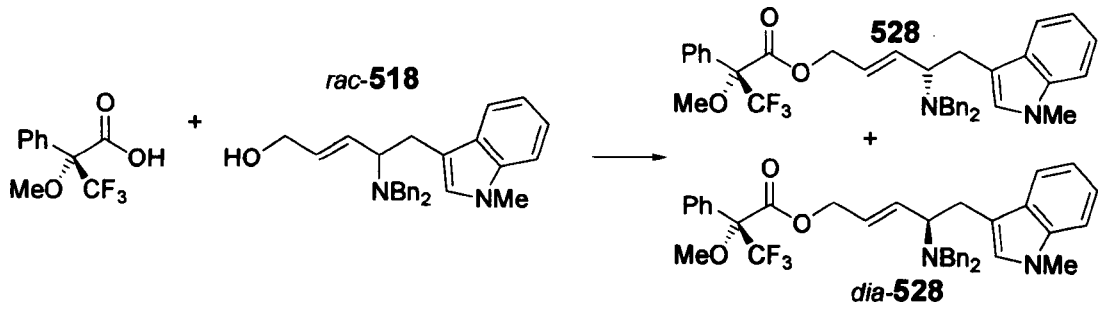
27.2 Hz, *C*-$CF_3$), [66.4, 66.0] (-$OCH_2$, 2× diast.), [56.3, 55.7, 55.6] (N-CH<, -$OCH_3$, 2× diast.), 54.2 (N-$CH_2$-Ph), [31.9, 31.8] (N-$CH_3$, 2× diast.), [24.1, 23.8] (Ind-$CH_2$-, 2× diast.); $\delta_F$ (376.5 MHz, $CDCl_3$) [–70.87, –71.02] (2× diast.); other data as for single isomer **527**.

**(*R*)-((*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (528)**



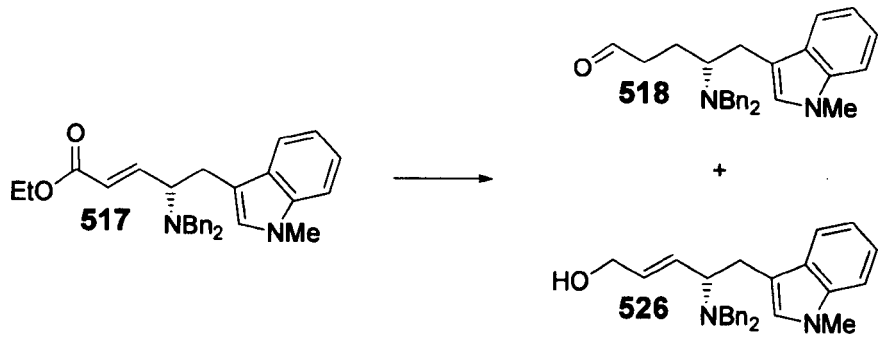

To allyl alcohol **518** (221 mg, 0.538 mmol, 1.0 equiv) and (*R*)-Mosher's acid (378 mg, 1.61 mmol, 3.0 equiv) in $CH_2Cl_2$ (6 mL) at rt was added *N,N'*-di*iso*propyl carbodiimide (252 µL, 1.61 mmol, 3.0 equiv) by syringe. The reaction mixture was stirred at rt for 14 h, then 4-(*N,N*-dimethylamino)pyridine (7 mg, 54 µmol, 0.10 equiv) was added by cannula as a solution in $CH_2Cl_2$ (0.5 mL) The reaction mixture was stirred at rt for 72 h, concentrated under reduced pressure and purified by chromatography (6→30% EtOAc–petrol) to give *(R)-((S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* **528** (327 mg, 97%) as a colourless oil; $R_f$ 0.50 (20% EtOAc–petrol); $[\alpha]_D^{25}$ +3.61 (c=0.83, MeOH); $[\alpha]_D^{25}$ +8.57 (c=1.26, $CHCl_3$); $\nu_{max}$ (film) 3060, 3027, 1748, 1602, 1493, 1453, 1425, 1375, 1327, 1269, 1247, 1170, 1122, 1080, 1016, 979, 910, 792, 740, 699 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.59 (2H, d, *J* 7.0 Hz, Mosher *o*-Ph), 7.44-7.22 (16H, m, Mosher *m*-Ph, *p*-Ph-H, 10× benzyl Ar-H, indolyl H-4,5,7), 7.04 (1H, t, *J* 7.5 Hz, indolyl H-6), 6.72 (1H, s, indolyl H-2), 5.97 (1H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-), 5.68 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=), 4.90-4.80 (2H, m, -$OCH_2$-), 3.92 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), 3.70 (3H, s, N-$CH_3$), 3.63-3.61 (1H, m, N-CH<), 3.57 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.54 (3H, s, -$OCH_3$), 3.29-3.26 (1H, m, indolyl-C*H*H-), 2.99 (1H, dd, *J* 14.0, 9.5 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (C=O), 140.1, 137.0, 135.6, 132.4, 129.7, 128.6, 128.5, 128.3, 128.0, 127.4, 127.2, 126.9, 125.8, 121.4, 119.0, 118.6, 117.7, 111.5, 109.1, 84.6 (q, $^2J_{CF}$ 27.7 Hz, *C*-$CF_3$), 66.5 (-$OCH_2$-), 59.6 (N-CH), 55.5 (O-$CH_3$), 53.8 (N-$CH_2$-Ph), 32.5 (N-$CH_3$), 27.7 (Ind-$CH_2$-); $\delta_F$ (376.5 MHz, $CDCl_3$) –70.46; *m/z* (CI) 627 $[M+H]^+$, 482, 395, 361, 252, 250, 198, 196, 146 (Found: 627.2845. $C_{38}H_{37}F_3N_2O_3$ requires $[M+H]^+$ 627.2834) (Found: C, 72.72; H, 5.90; N, 4.45. $C_{38}H_{37}F_3N_2O_3$ requires C, 72.83; H, 5.95; N, 4.47%).

**(*R*)-((*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (528) and (*R*)-((*R*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*dia*-528)**




*This was synthesised as per the single enantiomer, but utilising amino allyl alcohol prepared from racemic 1-methyl tryptophan.* Esters **528** and *dia*-**528** (235 mg, 91%) were isolated as a colourless oil; $\delta_H$ (400 MHz, $CDCl_3$) [7.59, 7.54] (2H, d, *J* 7.0 Hz, Mosher *o*-Ph-H, 2× diast.), 7.39-7.18 (16H, m, Mosher *m*-Ph-H and *p*-Ph-H, 10× benzyl Ar-H, indolyl H-4,5,7), 7.06 (1H, t, *J* 7.5 Hz, indolyl H-6), [6.69, 6.68] (1H, s, indolyl H-2), 5.99-5.94 (1H, m, -$OCH_2$-CH=C*H*-), 5.69-5.62 (1H, m, -$OCH_2$-C*H*=), 4.87-4.79 (2H, m, -$OCH_2$-), 3.92 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), [3.65, 3.64] (3H, s, N-$CH_3$, 2× diast.), 3.64-3.61 (1H, m, -NH), 3.57 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), [3.52, 3.51] (3H, s, -OMe, 2× diast.), 3.26 (1H, dd, *J* 14.0, 4.5 Hz, indolyl-C*H*H-), 2.99 (1H, dd, *J* 14.0, 9.0 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 166.3 (C=O), 140.2, 137.1, 135.9, 135.7, 132.4, 129.8, 129.5, 129.3, 128.7, 128.6, 128.4, 128.1, 127.4, 127.3, 127.0, 126.5, 125.8, 121.6, 121.5, 119.1, 118.7, 117.8, 111.6, 109.2, 84.7 (q, $^2J_{CF}$ 27.7 Hz, *C*-$CF_3$), 66.6 (-$OCH_2$-), 59.7 (N-CH<), 55.5 (-$OCH_3$), 53.9 (N-$CH_2$-Ph), 32.5 (N-$CH_3$), 27.8; $\delta_F$ (376.5 MHz, $CDCl_3$) [–71.38, –71.45] (2× diast.); other data as for single isomer **528**.

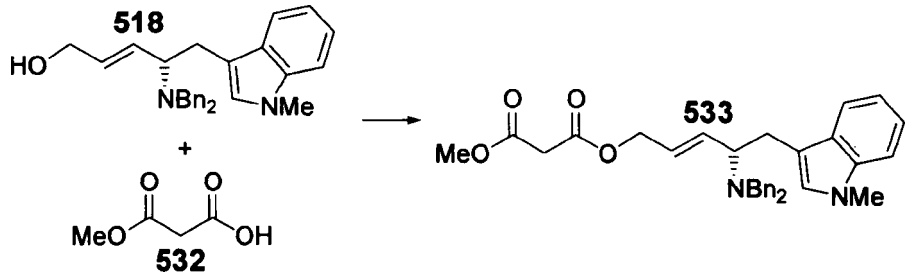
**(*R*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pentanal (526)**




To **517** (425 mg, 0.939 mmol, 1.0 equiv) in THF (9 mL) at 0 °C was added $LiAlH_4$ (1.0M in THF; 0.94 mL, 0.94 mmol, 1.0 equiv) by syringe. The reaction mixture was stirred at 0 °C for 30 min, then quenched by careful dropwise addition by syringe of $H_2O$ (0.94 mL), followed by NaOH (2.0 M in $H_2O$; 0.94 mL). The precipitate was filtered off and the filtrate diluted with $Et_2O$ (50 mL). The organic layer was washed with $H_2O$ (50 mL) and brine (50 mL), then dried over $Na_2SO_4$. The organic phase was concentrated under reduced pressure and purified by chromatography (20→30% EtOAc–petrol) to give *(R)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pentanal* **526** (19 mg, 5%) as a colourless oil; Also isolated was slightly impure *(R)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pentan-1-ol* **518**.

**518:** $R_f$ 0.78 (35% EtOAc–petrol); $[\alpha]_D^{25}$ +40.5 (c=0.50, MeOH); $[\alpha]_D^{25}$ +28.2 (c=0.20, $CHCl_3$); $\nu_{max}$ (film) 3082, 3058, 3027, 1720, 1601, 1493, 1453, 1374, 1327, 1247, 1128, 1075, 1026, 1013, 972, 910, 789, 740, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 9.62 (1H, s, -CHO), 7.48-7.19 (13H, m, 10× benzyl Ar-H, indolyl H-4,5,7), 7.07 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.81 (1H, s, indolyl H-2), 3.96 (2H, d, *J* 13.5 Hz, Ph-C*H*H-), 3.75 (3H, s, N-$CH_3$), 3.64 (2H, d, *J* 13.5 Hz, Ph-CH*H*-), 3.35 (1H, dd, *J* 14.0, 2.5 Hz, indolyl-C*H*H-), 2.99-2.92 (1H, m, NCH<), 2.75-2.61 (2H, m, indolyl-CH*H*- & -C*H*H-CHO), 2.30-2.20 (1H, m, -CH*H*-CHO), 1.86-1.70 (2H, m, -C$H_2$-$CH_2$-CHO); $\delta_C$ (75 MHz, $CDCl_3$) 203.3 (C=O), 140.1 (4°), 137.0 (4°), 128.9 (3°), 128.3 (3°), 127.9 (4°), 127.1 (3°), 127.0 (3°), 121.5 (3°), 118.9 (3°), 118.6 (3°), 112.4 (4°), 109.2 (3°), 57.9 (N-CH), 53.4 (N-$CH_2$-Ph), 42.1 (-$CH_2$CHO), 32.7 (N-$CH_3$), [23.7, 23.4] (indolyl-$CH_2$- & -$CH_2CH_2$CHO); *m/z* (CI) 411 $[M+H]^+$, 355, 338, 146 (Found: 411.2418. $C_{28}H_{30}N_2O$ requires $[M+H]^+$ 411.2436)

**(*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl methyl malonate (533)**




*General procedure (iii)* was applied, using 3-methoxy-3-oxopropanoic acid **532** (203 mg, 1.72 mmol), alcohol **518** (673 mg, 1.64 mmol), $CH_2Cl_2$ (15 mL) and *N,N'*-di*iso*propyl carbodiimide (269 μL, 1.72 mmol). Chromatography (20% EtOAc–petrol) gave *(S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl methyl malonate* **533** (797 mg, 91%) as a yellow oil; $R_f$ 0.27 (20% EtOAc–petrol); $[\alpha]_D^{25}$ –26.9 (c=1.05, MeOH); $[\alpha]_D^{25}$ –23.2 (c=1.19, $CHCl_3$); $\nu_{max}$ (film) 3083, 3058, 3026, 1752, 1736, 1670, 1602, 1493, 1472, 1453, 1410, 1375, 1328, 1268, 1248, 1205, 1148, 1071, 1027, 1013, 976, 910, 740, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.44-7.25 (13H, 10× benzyl Ar-H, indolyl H-4,5,7), 7.08 (1H, t, *J* 7.0 Hz, indolyl H-6), 6.77 (1H, s, indolyl H-2), 5.97 (1H, dd, *J* 15.5, 7.5 Hz, -$OCH_2$-CH=C*H*-), 5.69 (1H, dt, *J* 15.5, 6.0 Hz, -$OCH_2$-C*H*=), 4.73 (2H, d, *J* 5.5 Hz, -$OCH_2$-), 3.96 (2H, d, *J* 14.0 Hz, Ph-C*H*H-), [3.81, 3.77] (2× 3H, s, N-$CH_3$, -$OCH_3$), 3.70-3.61 (1H, m, N-CH<), 3.63 (2H, d, *J* 14.0 Hz, Ph-CH*H*-), 3.48 (2H, s, -$CH_2$COO-), 3.31 (1H, dd, *J* 14.5, 5.0 Hz, indolyl-C*H*H-), 3.03 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-CH*H*-); $\delta_C$ (75 MHz, $CDCl_3$) 166.2 (C=O), 140.2 (4°), 136.9 (4°), 134.4 (3°), 128.6 (3°), 128.2 (3°), 128.1 (4°), 127.2 (3°), 126.8 (3°), 126.5 (3°), 121.3 (3°), 119.1 (3°), 118.5 (3°), 111.7 (4°), 109.0 (3°), 65.8 (-$OCH_2$-), 59.6 (N-CH), 53.8 (N-$CH_2$-Ph), 52.6 (-$OCH_3$), 41.4 (-$CH_2$COO-), 32.6 (N-$CH_3$), 27.7 (Ind-$CH_2$-); *m/z* (CI) 511 $[M+H]^+$, 250, 227, 198, 196 (Found: 511.2596. $C_{32}H_{34}N_2O_4$ requires $[M+H]^+$ 511.2597) (Found: C, 75.18; H, 6.73; N, 5.38. $C_{32}H_{34}N_2O_4$ requires C, 75.27; H, 6.71; N, 5.49%).

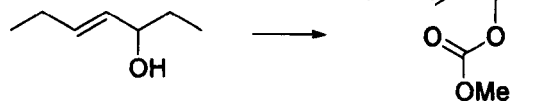
**(±)-(*E*)-Hept-4-en-3-ol (545)**


**545**

To ethylmagnesium chloride (1.8 M in $Et_2O$; 26.7 mL, 48.0 mmol, 1.01 equiv) at 0 °C was added dropwise by cannula over 30 min a solution of *trans*-pent-2-enal (4.00 g, 47.6 mmol, 1.00 equiv) in $Et_2O$ (5 mL). The reaction mixture was allowed to warm to rt and stirred for 2 h. Upon re-cooling to 0 °C, HCl (1.0 M in $H_2O$; 100 mL) was added *with care*. The reaction mixture was extracted with $Et_2O$ (4× 100 mL). Combined $Et_2O$ extracts were washed with $H_2O$ (100 mL) and brine (100 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. Distillation under reduced pressure (water aspirator) gave *(±)-(E)-hept-4-en-3-ol* **545** (3.50 g, 65%) as a colourless liquid; $bp_{760}$ 156 °C (lit.[113d] $bp_{760}$ 153–155 °C); $\delta_H$ (300 MHz, $CDCl_3$) 5.67 (1H, dt, *J* 15.5, 6.0 Hz, $H_3C$-$CH_2$-C*H*=), 5.42 (1H, dd, *J* 15.5 7.0 Hz, HO-CH-C*H*=), 3.95 (1H, app q, *J* 6.5 Hz, HO-C*H*<), 2.08-1.96 (2H, m, -$CH_2$-), 1.61-1.44 (3H, m, -$CH_2$-, -OH), [0.98, 0.88] (2× 3H, t, *J* 7.5 Hz, -$CH_3$); data in agreement with those for a sample prepared by a different method.[199]

**(±)-(*E*)-Hept-4-en-3-yl methyl carbonate (538)**

**545**

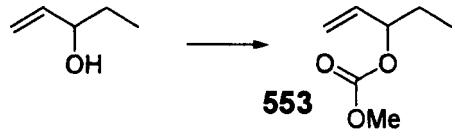



**538**

To **545** (2.88 g, 25.2 mmol, 1.0 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (156 mg, 1.28 mmol, 0.05 equiv) at 0 °C was added $CH_2Cl_2$ (20 mL). Methyl chloroformate (1.95 mL, 25.2 mmol, 1.0 equiv) was added by syringe, then pyridine (2.04 mL, 25.2 mmol, 1.0 equiv) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 10 min, then at rt for 80 min. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL) and washed with aq. HCl (2.0 M; 100 mL), $H_2O$ (100 mL) and brine (100 mL). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. Distillation under reduced pressure (water aspirator) gave *(±)-(E)-hept-4-en-3-yl methyl carbonate* **538** (3.47 g, 80%) as a colourless liquid; $\delta_H$ (300 MHz, $CDCl_3$) 5.82 (1H, dt, *J* 15.5, 6.5 Hz, $H_3C$-$CH_2$-C*H*=), 5.39 (1H, dd, *J* 15.5, 7.5 Hz, -OCH-C*H*=), 4.95 (1H, app q, *J* 7.0 Hz, -OCH<), 3.77 (3H, s, -$OCH_3$), [2.12-2.02,

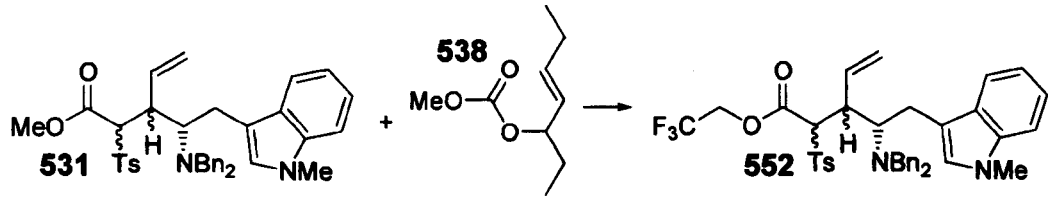
1.76-1.57] (2× 2H, m, -$CH_2$-), [1.00, 0.91] (each 3H, t, *J* 7.5 Hz, -$CH_3$); data in agreement with those previously reported[200] (no preparative details given).

**(±)-Pent-1-en-3-yl methyl carbonate (553)**




To (±)-pent-1-en-3-ol (2.58 g, 3.08 mL, 30.0 mmol, 1.0 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (183 mg, 1.5 mmol, 0.05 equiv) at 0 °C in $CH_2Cl_2$ (30 mL) was added methyl chloroformate (2.32 mL, 30.0 mmol, 1.0 equiv), then pyridine (2.43 mL, 30.0 mmol, 1.0 equiv), dropwise. The reaction mixture was stirred at 0 °C for 10 min, then at rt for 14 h. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL) and washed with aq. HCl (2.0 M; 100 mL), $H_2O$ (100 mL) and brine (100 mL). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. Chromatography ($CH_2Cl_2$), then distillation under atmospheric pressure gave *(±)-pent-1-en-3-yl methyl carbonate* **553** as a colourless liquid; $bp_{760}$ 155 °C; $\delta_H$ (300 MHz, $CDCl_3$) 5.78 (1H, ddd, *J* 17.0, 10.5, 6.5 Hz -C*H*=$CH_2$), 5.29 (1H, d, *J* 17.0 Hz, *trans* -CH=C$H_2$), 5.21 (1H, d, *J* 10.5 Hz, *cis* -CH=C$H_2$), 4.98 (1H, q, *J* 6.5 Hz, -C*H*-CH=$CH_2$), 3.77 (-$OCH_3$), 1.75-1.60 (2H, m, -C$H_2$$CH_3$), 0.93 (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); data in agreement with those previously reported,[201,202] (no preparative details given).

**2,2,2-Trifluoroethyl 3-((1*S*)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate (552), diastereoisomers as shown**

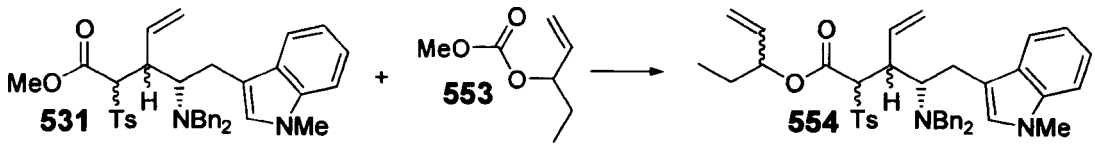



This reaction was attempted according to a literature procedure.[146a] To Wilkinson's catalyst (54 mg, 0.0582 mmol, 0.05 equiv) under Ar was added THF (1.5 mL). The catalyst mixture was heated to 30 °C, then tris(2,2,2-trifluoroethyl) phosphite (61 μL, 0.233 mmol, 0.20 equiv) was added. The

catalyst mixture was stirred at 30 °C for 30 min. Separately, a solution of **531** (722 mg, 1.16 mmol, 1.0 equiv) in THF (3.5 mL) was added to NaH (60% in mineral oil, 46.5 mg, 1.16 mmol, 1.0 equiv). The reaction mixture was stirred at rt until effervescence ceased. The reaction mixture was added by cannula to the catalyst mixture. The combined reaction mixture was stirred at 30 °C for 10 min, then cooled to –10 °C. Carbonate **538** (211 μL, 1.16 mmol, 1.0 equiv) was added by syringe and the reaction mixture was stirred at –10 °C for 4 h, after which TLC indicated the presence of starting materials only. A reflux condenser was fitted and the reaction mixture was heated to reflux for 15 h. The reaction mixture was concentrated under reduced pressure and purified by chromatography (17.5% EtOAc–petrol) to give *2,2,2-trifluoroethyl 3-((1S)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **552** (69 mg, 9%) as a colourless oil and as an inseparable mixture of diastereoisomers; Also isolated was unreacted **531** (580 mg, 80%).

**552:** $R_f$ 0.29 (20% EtOAc–petrol); $\nu_{max}$ (film) 3059, 3028, 1759, 1614, 1598, 1494, 1484, 1472, 1453, 1416, 1375, 1326, 1305, 1285, 1250, 1167, 1149, 1084, 1029, 1016, 998, 975, 911, 839, 813, 738, 702, 661 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) [7.92 (dd, *J* 8.0, 1.0 Hz), 7.71 (d, *J* 8.5 Hz)] (2H, *o*-$SO_2Ar$), [7.64 (1H, d, *J* 8.0 Hz), 7.58-7.46 (2H, m), 7.36 (1H, d, *J* 8.0 Hz), 7.32-7.11 (12H, m)] (10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), [6.89, 6.88] (1H, s, indolyl H-2), [6.21, 6.02, 5.75] (1H, d, *J* 17.0, 10.0 Hz, -C*H*=$CH_2$), [5.51 (dd, *J* 17.0, 1.0 Hz), 5.45 (dd, *J* 17.0, 1.5 Hz)] (1H, *trans* -CH=C*H*$_2$), [5.38, 5.19] (1H, dd, *J* 10.0, 1.5 Hz, *cis* -CH=C*H*$_2$), [5.10 (d, *J* 2.5 Hz), 4.24 (d, *J* 8.0 Hz)] (1H, Ts-CH<), 4.01 (1H, dq, $^2J_{HH}$ 12.5 Hz, $^3J_{HF}$ 8.5 Hz, -OC*H*H-), 3.90 (1H, dq, $^2J_{HH}$ 12.5 Hz, $^3J_{HF}$ 8.5 Hz, -OCH*H*-), 3.88 (2H, d, *J* 13.0 Hz, N-C*H*H-Ph), [3.81, 3.80 (×2)] (3H, s, N-$CH_3$), [3.66 (1H, td, *J* 10.0, 2.0 Hz), 3.55-3.51 (3H, m)] (N-CH*H*-Ph, N-CH<, C*H*-CH=$CH_2$), [3.27 (dd, *J* 10.5, 3.5 Hz), 3.24 (dd, *J* 15.5, 7.0 Hz)] (1H, indolyl-C*H*H-), 3.08 (1H, dd, *J* 15.5, 5.0 Hz, indolyl-CH*H*-), [2.49, 2.45] (3H, s, Ts-$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 163.4 (C=O), 144.7 (4°), 139.8 (4°), 139.4 (4°), 137.2 (4°), 137.1 (4°), 133.8 (3°), 129.5 (3°), 129.4 (3°), 129.1 (3°), 128.8 (3°), 128.7 (3°), 128.2 (3°), 127.8 (3°), 127.3 (3°), 127.0 (3°), 126.8 (3°), 124.3 (4°), 121.7 (3°), 121.6 (2°), 120.6 (4°), 119.3 (3°), 119.0 (3°), 118.8 (3°), 113.3 (4°), 109.3 (3°), 71.5 (3°), 69.6 (3°), 60.8 (2°, q, $^2J_{CF}$ 35.9 Hz), 58.6 (3°), 54.0 (2°), 53.7 (2°), 47.0 (3°), 45.8 (3°), 32.8 (1°), 23.8 (2°), 23.4 (2°), 21.7 (1°), 21.5 (1°), 21.1 (1°); *m/z* (FAB) 689 $[M+H]^+$, 544, 353 (Found: $[M+H]^+$, 689.2632. $C_{39}H_{39}F_3N_2O_4S$ requires $[M+H]^+$, 689.2661).

**Pent-1-en-3-yl 3-((1*S*)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate (554), diastereoisomers as shown.**

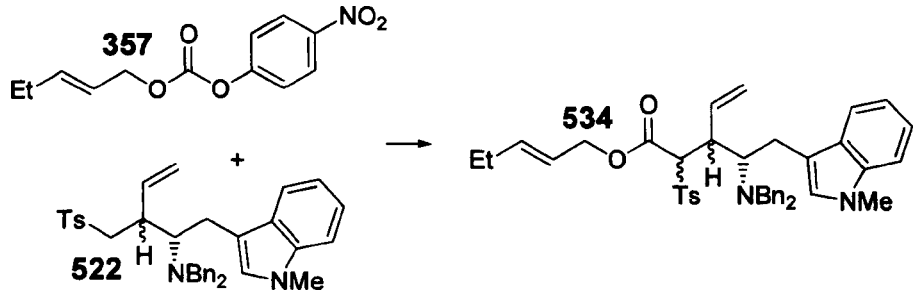



This reaction was attempted according to a literature procedure.[146a] To Wilkinson's catalyst (43 mg, 0.0468 mmol, 0.05 equiv) under Ar was added THF (1.5 mL). The catalyst mixture was heated to 30 °C, then tris(2,2,2-trifluoroethyl) phosphite (50 μL, 0.187 mmol, 0.20 equiv) was added. The catalyst mixture was stirred at 30 °C for 30 min. Separately, a solution of **531** (580 mg, 0.935 mmol, 1.0 equiv) in THF (3.5 mL) was added to NaH (60% in mineral oil, 37 mg, 0.935 mmol, 1.0 equiv). The reaction mixture was stirred at rt until effervescence ceased. The reaction mixture was added to the catalyst mixture. The combined reaction mixture was stirred at 30 °C for 10 min, then cooled to –10 °C. Carbonate **553** (135 mg, 0.935 mmol, 1.0 equiv) was added by syringe and the reaction mixture was stirred at –10 °C for 2 h, at rt for 2 h and at reflux for 7 h. Concentration under reduced pressure and chromatography (17.5% EtOAc–petrol) to give *pent-1-en-3-yl 3-((1S)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **554** (49 mg, 8%) as a colourless oil and as an inseparable mixture of diastereoisomers; Also isolated was unreacted starting material (496 mg, 86%).

**554:** $R_f$ 0.40 (20% EtOAc–petrol); $\nu_{max}$ (film) 3082, 3060, 3028, 1737, 1614, 1598, 1494, 1484, 1471, 1454, 1424, 1376, 1323, 1304, 1291, 1250, 1210, 1170, 1146, 1084, 1028, 1011, 995, 967, 913, 813, 737, 701, 659 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) [7.70, 7.67 (×2), 7.61, 7.58] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.34-7.09 (16H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), [6.85, 6.83, 6.82, 6.76, 6.74] (1H, s, indolyl H-2), [6.25-6.20, 6.11-5.91, 5.67-5.61] (2H, m, 2× -C*H*=$CH_2$), 5.57-5.01 (4H, m, 2× -CH=C*H*$_2$), [4.98, 4.94, 4.91] (1H, d, *J* 2.5 Hz, Ts-CH<), [4.85, 4.79] (1H, q, *J* 6.5 Hz, $H_2C$=CH-C*H*(Et)O-), 3.89 (2H, br d, *J* 12.0 Hz, N-C*H*H-Ph), [3.78, 3.77 (×2), 3.76] (3H, s, N-$CH_3$), 3.64-3.47 (4H, m, N-CH*H*-Ph, N-CH<, Ts-CH-C*H*-CH=$CH_2$), 3.20 (1H, dd, *J* 15.5, 6.5 Hz, indolyl-C*H*H-), 3.05-2.97 (1H, m, indolyl-CH*H*-), [2.47, 2.45, 2.44] (3H, s, Ts-$CH_3$), 1.36-1.26 (2H, m, -C*H*$_2$$CH_3$), [1.02, 0.98, 0.70, 0.68, 0.62] (3H, t, *J* 7.5 Hz, -$CH_2$C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) [164.4, 164.4, 163.9] (C=O), 144.4 (4°),

144.3 (4°), 140.0 (4°), 139.6 (4°), 139.5 (4°), 138.3 (3°), 137.6 (4°), 137.3 (4°), 137.1 (4°), 137.0 (4°), 135.2 (3°), 135.1 (3°), 134.6 (3°), 129.3 (3°), 129.1 (3°), 129.0 (3°), 128.7 (3°), 128.4 (3°), 128.1 (3°), 127.9 (4°), 127.4 (4°), 127.3 (3°), 127.1 (4°), 126.9 (3°), 126.7 (4°), 121.9 (3°), 121.6 (×2, 3°), 120.9 (2°), 119.4 (3°), 118.6 (3°), 117.7 (2°), 117.5 (2°), 113.5 (4°), 113.4 (2× 4°), 109.1 (3°), 78.4 (3°), 78.1 (3°), 78.0 (3°), 70.2 (3°), 70.1 (3°), 69.9 (3°), 66.2 (2°), 59.6 (3°), 58.6 (3°), 54.3 (2°), 54.0 (2°), 53.8 (2°), 45.7 (3°), 32.7 (1°), 26.8 (2°), 26.6 (2°), 25.3 (2°), 23.4 (2°), 23.3 (2°), 23.2 (2°), 21.7 (1°), 13.2 (1°), 9.2 (1°); *m/z* (FAB) 675 $[M+H]^+$, 530, 353 (Found: $[M+H]^+$, 675.3238. $C_{42}H_{46}N_2O_4S$ requires $[M+H]^+$, 675.3257).

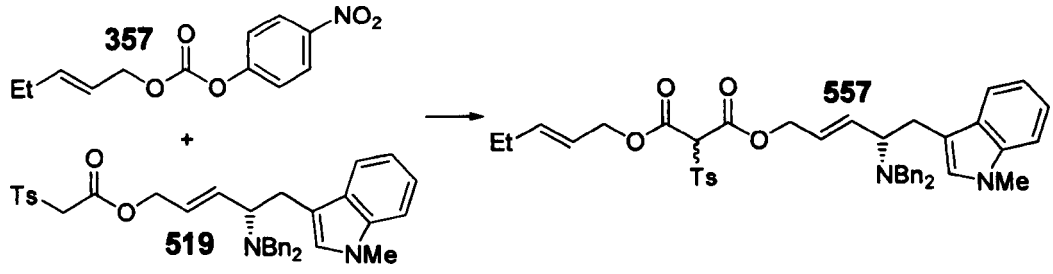
**(*E*)-Pent-2-enyl 3-((1*S*)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate (534), diastereoisomers as shown.**




To **522** (545 mg, 0.970 mmol, 1.0 equiv) in THF (2 mL) at –78 °C was added *n*-BuLi (2.30M in hexanes; 0.42 mL, 0.97 mmol, 1.0 equiv) dropwise by syringe. The reaction mixture was allowed to warm to rt, then was re-cooled to –78 °C. Carbonate **357** (487 mg, 1.94 mmol, 2.0 equiv) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm to rt, then was re-cooled to –78 °C. A further portion of *n*-BuLi (2.30M in hexanes; 0.42 mL, 0.97 mmol, 1.0 equiv) was added dropwise by syringe. The reaction mixture was allowed to warm to rt and was stirred for 15 min. The reaction mixture was extracted with EtOAc (100 mL). The yellow organic phase was washed repeatedly with dilute aq. $NaHCO_3$ until it became colourless. The organic phase was further washed with $H_2O$ (50 mL) and brine (50 mL), then dried over $Na_2SO_4$. Concentration under reduced pressure and chromatography (17.5% EtOAc–petrol) gave *(E)-pent-2-enyl 3-((1S)-1-(dibenzylamino)-2-(1-methylindol-3-yl)ethyl)-2-(toluene-4-sulfonyl)pent-4-enoate* **534** (468 mg, 72%) as a colourless oil; $R_f$ 0.31 (20% EtOAc–petrol); $\nu_{max}$ (film) 3082, 3060, 3028, 1738, 1672, 1638, 1614, 1598, 1555, 1493, 1484, 1471, 1454, 1424, 1376,

1324, 1304, 1290, 1272, 1250, 1211, 1145, 1084, 1028, 1016, 1001, 969, 911, 813, 736, 701, 658 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [7.73, 7.63, 7.57, 7.52] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$, 4× diast.), 7.44-6.96 (16H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), 6.84 (1H, s, indolyl H-2), 6.25-6.07 (2H, m, -C*H*=C*H*-$CH_2CH_3$), 5.69-5.59 (1H, m, -C*H*=$CH_2$), 5.56-5.16 (2H, m, -CH=C$H_2$), 5.00 (1H, br s, Ts-CH<), [4.34 (d, *J* 8.0 Hz), 4.16 (d, *J* 6.0 Hz)] (2H, -$OCH_2$-), 4.09-3.39 (2H, m, N-CH<, -C*H*-CH=$CH_2$), 3.90 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), [3.81, 3.80] (3H, s, N-$CH_3$), 3.51 (2H, d, *J* 14.0 Hz, N-CH*H*-Ph), 3.28-3.18 (1H, m, indolyl-C*H*H-), 3.05 (1H, dd, *J* 15.0, 5.5 Hz, indolyl-CH*H*-), [2.49, 2.47, 2.36] (3H, s, Ts-$CH_3$), 2.11-2.00 (2H, m, -C$H_2CH_3$), 1.07-0.93 (3H, m, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [165.9, 164.4] (C=O), 144.7 (4°), 144.5 (4°), 144.3 (4°), 140.0 (3°), 139.6 (3°), 138.8 (4°), 138.4 (4°), 138.3 (4°), 137.7 (4°), 137.1 (×2, 4°), 136.4 (4°), 134.7 (3°), 134.4 (3°), 133.0 (3°), 129.5 (3°), 129.4 (3°), 129.3 (3°), 129.1 (3°), 129.0 (4°), 128.7 (3°), 128.4 (3°), 128.1 (3°), 128.0 (3°), 127.8 (3°), 127.5 (4°), 127.3 (3°), 127.1 (3°), 126.9 (3°), 126.6 (3°), 121.9 (3°), 121.8 (3°), 121.7 (3°), 121.5 (2°), 120.9 (2°), 119.4 (3°), 119.2 (3°), 118.7 (3°), 113.5 (4°), 112.3 (4°), 109.2 (3°), 109.1 (3°), [72.3, 69.9] (Ts-CH<), [66.6, 66.3, 66.2] (-$OCH_2$-), [59.9, 58.6] (N-CH<), [54.0, 53.8] (N-$CH_2$-Ph), [46.4, 46.1, 45.7] ($H_2C$=CH-*C*H<), [32.8, 32.7] (N-$CH_3$), [25.3, 23.9, 23.4] (indolyl-$CH_2$-, $H_3C$-$CH_2$-), 21.7 (Ts-$CH_3$), 13.2 (-$CH_2CH_3$); *m/z* (FAB) 675 $[M+H]^+$, 530, 353 (Found: $[M+H]^+$, 675.3225. $C_{42}H_{46}N_2O_4S$ requires $[M+H]^+$, 675.3257).

**1-(4*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-(*E*)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate (557), diastereoisomers as shown**

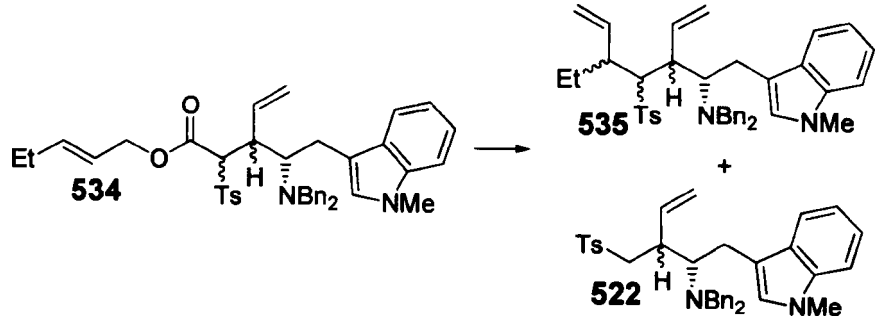



*General procedure (vii)* was applied, using ester **519** (10.3 g, 17.0 mmol), carbonate **357** (8.56 g, 34.1 mmol), NaH (1.36g, 34.1 mmol) and THF (85 mL). Chromatography (4:94:2 EtOAc:PhMe:$NEt_3$) gave *1-(4S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-(E)-pent-2-enyl 2-(toluene-4-sulfonyl)malonate* **557** (8.70 g, 71%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated were unreacted

carbonate **357** (3.95 g, 46% with respect to starting mass) and unreacted monoester **519** (1.00 g, 10% with respect to starting mass).

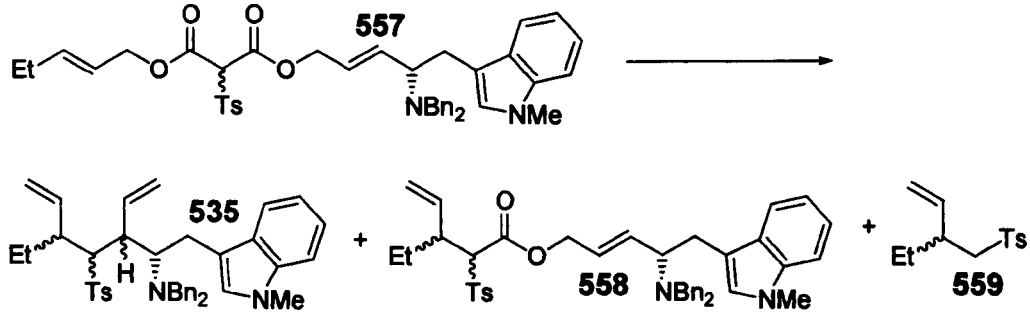
**557:** $R_f$ 0.36 (20% EtOAc–petrol); $\nu_{max}$ (film) 3083, 3058, 3027, 1744, 1670, 1614, 1597, 1493, 1471, 1453, 1375, 1336, 1291, 1268, 1193, 1181, 1152, 1131, 1083, 1027, 1013, 973, 911, 844, 815, 740, 701, 672 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.82 (2H, d, *J* 7.5 Hz, *o*-$SO_2Ar$), [7.43 (4H, d, *J* 7.5 Hz), 7.36 (4H, t, *J* 7.5 Hz), 7.31-7.27 (3H, m), 7.23 (1H, t, *J* 7.5 Hz)] (10× Ph-H, indolyl H-4,5,7), 7.18 (2H, d, *J* 7.5 Hz, *m*-$SO_2Ar$), 7.05 (1H, t, *J* 7.5 Hz, indolyl H-6) 6.79 (1H, s, indolyl H-2), 5.98 (1H, dd, *J* 15.5, 8.0 Hz, indolyl-$CH_2$-CH($NBn_2$)-C*H*=), 5.86 (1H, dt, *J* 15.5, 6.0 Hz, indolyl-$CH_2$-CH($NBn_2$)-CH=C*H*-), 5.60-5.50 (2H, m, -C*H*=C*H*-$CH_2CH_3$), 5.06 (1H, s, -CH(Ts)-COO-), 4.73 (2H, br s, -O*C*$H_2$-CH=CH-CH($NBn_2$)-), 4.65 (2H,d, *J* 5.5 Hz, -O*C*$H_2$-CH=CH-$CH_2CH_3$), 3.94 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), 3.72 (3H, s, N-$CH_3$), 3.65-3.61 (1H, m, N-CH<), 3.60 (2H, d, *J* 14.0 Hz, N-CH*H*-Ph), 3.30 (1H, dd, *J* 14.5, 4.5 Hz, indolyl-C*H*H-), 3.03 (1H, dd, *J* 14.5, 9.5 Hz, indolyl-CH*H*-), 2.38 (3H, s, Ts-$CH_3$), 2.10 (2H, quint, *J* 7.0 Hz, -C$H_2CH_3$), 1.04 (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) [161.0, 160.9] (C=O), 146.0 (4°), 140.3 (3°), 139.6 (4°), 137.1 (4°), 135.3 (4°), 134.3 (4°), 130.2 (3°), 129.5 (3°), 128.8 (3°), 128.4 (3°), 128.1 (3°), 127.5 (3°), 126.9 (3°), 125.7 (3°), 121.4 (3°), 119.1 (3°), 118.6 (3°), 111.6 (4°), 109.2 (3°), 74.8 (Ts-CH<), [67.8, 67.2] (2× -$OCH_2$-), 59.7 (N-CH<), 53.9 (N-$CH_2$-), 32.6 (N-$CH_3$), [28.0, 25.4] (indolyl-$CH_2$-, $H_3C$-$CH_2$-), 21.8 (Ts-$CH_3$), 13.2 (-$CH_2CH_3$); *m/z* (FAB) 719 $[M+H]^+$, 574, 522, 393 (Found: $[M+H]^+$, 719.3126. $C_{43}H_{46}N_2O_6S$ requires $[M+H]^+$, 719.3155).

**(2*S*)-*N*,*N*-Dibenzyl-3-ethenyl-5-ethyl-1-(1-methylindol-3-yl)-4-(toluene-4-sulfonyl)hept-6-en-2-amine (535), diastereoisomers as shown, (±)-2-Ethylbut-3-en-1-yl 4-methylphenyl sulfone (559) and (4*S*,*E*)-4-(Dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate (558), diastereoisomers as shown**




*Procedure A*

Ester **534** (182 mg, 0.270 mmol, 1.0 equiv) was transferred to a microwave vial in $CH_2Cl_2$ and concentrated to near-dryness under a stream of $N_2$. Potassium acetate, (oven-dried, 3 mg, 0.031 mmol, 0.11 equiv) was added. The vial was purged with $N_2$. *N*,*O*-bis(trimethylsilyl)acetamide (1.00 mL, 3.96 mmol, 14.7 equiv) was introduced by syringe. The reaction mixture was heated to 225 °C for 15 min under conditions of microwave irradiation, concentrated under reduced pressure and purified by chromatography (15→25% EtOAc–petrol) to give *(2S)-N,N-dibenzyl-3-ethenyl-5-ethyl-1-(1-methylindol-3-yl)-4-(toluene-4-sulfonyl)hept-6-en-2-amine* **535** (18 mg, 11%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated were unreacted starting material (44 mg, 24%) and decarboxylated ester hydrolysis product *N,N-dibenzyl-1-(1-methylindol-3-yl)-3-((toluene-4-sulfonyl)methyl)pent-4-en-2-amine* **522** (15 mg, 10%) as a colourless oil.




*Procedure B*

Malonate **557** (488 mg, 0.679 mmol, 1.0 equiv) was transferred to a microwave vial in $CH_2Cl_2$ and concentrated to near-dryness under a stream of

$N_2$. Potassium acetate, (oven-dried, 7 mg, 0.068 mmol, 0.10 equiv) was added and the vial was quickly sealed and purged with $N_2$. *N,O*-bis(trimethylsilyl)acetamide (3.00 mL, 11.9 mmol, 17.5 equiv) was introduced by syringe. The reaction mixture was subjected to a pulse sequence of microwave irradiation: A 60 s pulse at 200 °C (60 s beginning only once the target temperature was reached) was followed by 60 s of cooling. This was repeated such that in total 10× 60 s pulses at 200 °C were interspersed with 9× 60 s cooling pulses. The efficiency of the cooling was such that the reaction mixture was cooled to ≈100 °C before the next heating pulse began. After cooling to rt, the reaction mixture was concentrated under reduced pressure and purified by chromatography (15→25% EtOAc–petrol) to give *(2S)*-N,N-*dibenzyl-3-ethenyl-5-ethyl-1-(1-methylindol-3-yl)-4-(toluene-4-sulfonyl)hept-6-en-2-amine* **535** (82 mg, 19%) as a colourless oil and as an inseparable mixture of diastereoisomers; also isolated were singly rearranged product *(4S,E)-4-(dibenzylamino)-5-(1-methylindol-3-yl)pent-2-enyl 3-ethyl-2-(toluene-4-sulfonyl)pent-4-enoate* **558** (331 mg, 72%), as a colourless oil, and decarboxylated ester hydrolysis product *(±)-2-ethylbut-3-en-1-yl 4-methylphenyl sulfone* **559** (7 mg, 4%), as a colourless oil. Singly rearranged product **558** may be recycled, by subjecting it to identical conditions as described in this procedure for **557**

**535:** $R_f$ 0.46 (20% EtOAc–petrol); $\nu_{max}$ (film) 3060, 3027, 1597, 1493, 1454, 1375, 1143, 1085, 969, 916, 815, 740, 700 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) [7.81 (d, *J* 8.5 Hz), 7.76 (×2) (d, *J* 8.0 Hz)] (2H, *o*-$SO_2Ar$), 7.41-7.12 (17H, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-2,4,5,6,7), [6.43 (dt, *J* 17.0, 10.5 Hz), 6.36 (dt, *J* 17.0, 10.5 Hz), 5.67 (ddd, *J* 17.0, 10.0, 9.0 Hz), 5.57 (ddd, *J* 17.0, 10.0, 8.5 Hz), 5.51 (ddd, *J* 17.0, 10.0, 9.0 Hz)] (2H, 2× -C*H*=$CH_2$), [5.17 (dd, *J* 17.0, 1.5 Hz), 5.15 (dd, *J* 17.0, 2.0 Hz), 5.02 (d, *J* 17.0 Hz), 4.99 (d, *J* 17.0), 4.74 (d, *J* 17.0 Hz)] (2H, *trans* -CH=C$H_2$), [5.10 (dd, *J* 10.0, 2.0 Hz), 5.09 (dd, *J* 10.0, 2.0 Hz), 5.08 (dd, *J* 10.0, 2.0 Hz), 5.05 (d, *J* 11.0 Hz), 4.93 (dd, *J* 10.0, 1.5 Hz)] (2H, *cis* -CH=C$H_2$), [4.22, 4.17] (1H, app q, *J* 7.0 Hz, Ts-CH<), 3.95-3.79 (1H, m, N-CH<), 3.83 (3H, s, N-$CH_3$), [3.66 (d, *J* 13.0 Hz), 3.64 (d, *J* 13.5 Hz), 3.60 (d, *J* 13.5 Hz), 3.56 (d, *J* 14.0 Hz)] (4H, N-C$H_2$-Ph), 3.22 (1H, dd, *J* 15.5, 6.0 Hz, indolyl-C*H*H-), 3.16-2.98 (2H, m, indolyl-CH*H*-, $Bn_2$N-CH-C*H*-CH=), [2.48 (×2), 2.47] (3H, s, Ts-$CH_3$), [2.42-2.30, 2.24-2.17] (1H, m, $H_2$C=CH-C*H*(Et)-), [2.03 (dqd, *J* 13.5, 7.5, 2.0 Hz), 1.65 (dqd, *J* 15.0, 7.5, 5.0 Hz), 1.45 (dqd, *J* 14.5, 7.5, 4.5 Hz), 1.24 (dq, *J* 11.5, 7.0 Hz), 1.13 (dq, *J* 9.5, 7.5 Hz)] (2H, -C$H_2$$CH_3$), [1.05, 0.99, 0.88, 0.73, 0.67, 0.55] (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz,

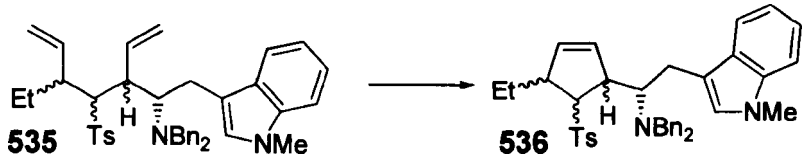
$CDCl_3$) 144.2, 143.7, 143.5, 140.0, 139.9, 139.0, 138.9, 138.6, 137.6, 137.1, 136.7, 136.4, 136.2, 136.0, 135.8, 129.8, 129.7, 129.4, 129.2, 129.1, 128.9, 128.7, 128.5, 128.2 (×2), 128.0, 127.7, 127.3, 127.1, 126.9, 121.4, 119.6, 119.4, 119.2, 118.7, 118.5, 117.8, 117.2, 117.0, 113.9, 109.2, 109.0, 72.9, 68.3, 67.8, 60.9, 60.7, 60.4, 53.8, 49.3, 48.1, 47.2, 46.2, 43.4, 40.2, 32.8, 32.2, 32.0, 30.1, 29.7, 29.4, 27.3, 25.9, 24.8, 23.7, 23.6, 22.3, 21.7, 19.6, 18.2, 13.4, 12.7, 11.5, 11.0; *m/z* (FAB) 631 $[M+H]^+$, 486, 353, 330, 144 (Found: $[M+H]^+$, 631.3378. $C_{41}H_{46}N_2O_2S$ requires $[M+H]^+$, 631.3358).

**558:** $R_f$ 0.43 (20% EtOAc–petrol); $\nu_{max}$ (film) 3081, 3058, 3027, 1739, 1640, 1614, 1597, 1493, 1484, 1472, 1453, 1424, 1402, 1376, 1326, 1305, 1290, 1267, 1215, 1207, 1141, 1084, 1028, 1014, 975, 923, 838, 815, 739, 700, 659 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) [7.70, 7.69, 7.66, 7.63] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$, 4× diast.), 7.35-6.96 (16H, m, 10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), [6.74, 6.73, 6.71] (1H, s, indolyl H-2), 5.91-5.78 (1H, m, -$OCH_2$-CH=C*H*-), 5.66-5.47 (1H, m, -C*H*=$CH_2$), 5.53-5.34 (1H, m, -$OCH_2$-C*H*=CH-), [5.21 (d, *J* 9.5 Hz), 5.02 (d, *J* 9.0 Hz)] (1H, *cis* -CH=C$H_2$), [5.10 (d, *J* 17.0 Hz), 5.04 (d, *J* 16.5 Hz), 5.00 (d, *J* 17.0 Hz)] (1H, *trans* -CH=$CH_2$), [4.60-4.54, 4.50-4.30] (2H, m, -$OCH_2$-), [4.02 (d, *J* 9.0 Hz), 3.99 (d, *J* 8.5 Hz), 3.97 (d, *J* 8.5 Hz)] (1H, Ts-CH<), 3.87 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), [3.70 (×2), 3.69 (×2)] (3H, s, N-$CH_3$), 3.55-3.49 (3H, m, N-CH*H*-Ph, N-CH<), [3.23, 3.22] (1H, dd, *J* 14.5, 4.5 Hz, indolyl-C*H*H-), 2.98-2.90 (1H, m, indolyl-CH*H*-), 2.81-2.66 (1H, m, $H_2C$=CH-C*H*<), [2.33, 2.32, 2.29, 2.28] (3H, s, Ts-$CH_3$), [2.06-1.99, 1.54-1.44, 1.29-1.21] (2H, m, -C$H_2CH_3$), [0.89, 0.81] (3H, t, *J* 7.5 Hz, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [165.6, 165.2] (C=O), 145.1 (*p*-$SO_2Ar$), 140.1 (*i*-Ph), 136.9 (indolyl C-7a), 136.5 (-CH=$CH_2$), [135.9 (×2), 135.3] (*i*-$SO_2Ar$), [135.1, 134.7, 134.6] (-$OCH_2$-CH=CH-), [129.6 (×2), 129.5, 129.3, 129.2] (*o*-$SO_2Ar$, *m*-$SO_2Ar$), 128.6 (*o*-Ph), 128.2 (*m*-Ph), 128.0 (×2, indolyl C-3a), 127.2 (indolyl C-2), 126.8 (*p*-Ph), [126.1, 125.9, 125.8] (-$OCH_2$-CH=), 121.3 (indolyl C-5), 118.9 (indolyl C-4), 118.8 (=$CH_2$), 118.5 (indolyl C-6), 111.6 (indolyl C-3), 109.0 (indolyl C-7), [75.1, 74.4] (Ts-CH<), [59.6, 59.5] (N-CH<), 53.7 (N-$CH_2$-), [44.7, 44.5] (-CH-CH=$CH_2$), 32.6 (N-$CH_3$), [27.9, 27.8, 27.5] (indolyl-$CH_2$-), 25.2 (-$CH_2CH_3$), 21.6 (Ts-$CH_3$), [11.2, 10.9 (×2)] (-$CH_2CH_3$); *m/z* (FAB) 675 $[M+H]^+$, 530, 478 (Found: $[M+H]^+$, 675.3242. $C_{42}H_{46}N_2O_4S$ requires $[M+H]^+$, 674.3257).

**559:** $R_f$ 0.34 (20% EtOAc–petrol); $\nu_{max}$ (film) 3063, 3028, 1640, 1598, 1494, 1454, 1422, 1403, 1378, 1316, 1301, 1289, 1251, 1183, 1145, 1087, 1019,

995, 970, 948, 917, 817, 741, 702, 661, 631 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.36 (2H, d, *J* 8.0 Hz, *m*-$SO_2Ar$), 5.61-5.49 (1H, m, -C*H*=$CH_2$), 5.03 (1H, d, *J* 10.0 Hz, *cis* -CH=C*H*$_2$), 5.00 (1H, d, *J* 17.0 Hz, *trans* -CH=C*H*$_2$), 3.14 (1H, d, *J* 6.5 Hz, Ts-$CH_2$-), 2.56-2.34 (1H, m, $H_2C$=CH-C*H*<), 2.46 (3H, s, Ts-$CH_3$), [1.70-1.57, 1.47-1.28] (2H, m, -C*H*$_2$$CH_3$), 0.86 (3H, t, *J* 7.5 Hz, -$CH_2$C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.6 (4° Ar), 138.9 (-*C*H=$CH_2$), 137.1 (4° Ar), 129.8 (3° Ar), 128.1 (3° Ar), 116.4 (=$CH_2$), 60.7 (Ts-$CH_2$-), 40.2 ($H_2C$=CH-*C*H<), 27.4 (-*C*$H_2$$CH_3$), 21.7 (Ts-$CH_3$), 11.0 (-$CH_2$*C*$H_3$); *m/z* (CI) 256 $[M+NH_4]^+$, 239 $[M+H]^+$, 139 (Found: $[M+H]^+$, 239.1106. $C_{13}H_{18}O_2S$ requires $[M+H]^+$, 239.1106).

**(1*S*)-*N,N*-Dibenzyl-1-(4-ethyl-5-(toluene-4-sulfonyl)cyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine (536), diastereoisomers as shown**



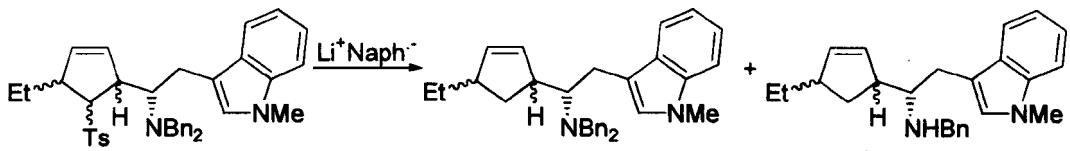

To dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (6.7 mg, 0.0079 mmol, 0.1 equiv) was added by cannula a solution of **535** (50 mg, 0.0793 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.7 mL). The reaction mixture was heated to reflux for 14 h. Concentration under reduced pressure and chromatography (10→20% EtOAc–petrol) gave *(1S)-N,N-dibenzyl-1-(4-ethyl-5-(toluene-4-sulfonyl)cyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine* **536** as two discrete isolable mixtures of diastereoisomers: "upper" **536** (12 mg, 25%) and "lower" **536** (20 mg, 42%). Also isolated was unreacted starting material (8 mg, 16%).

**"upper" 536:** Colourless oil; $R_f$ 0.43 (20% EtOAc–petrol); $\nu_{max}$ (film) 3059, 3026, 1597, 1493, 1454, 1423, 1401, 1375, 1314, 1301, 1287, 1250, 1208, 1182, 1143, 1085, 1027, 1015, 970, 912, 837, 814, 738, 700, 669 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), [7.64 (1H, d, *J* 8.0 Hz), 7.32 (1H, d, *J* 8.0 Hz), 7.26 (2H, d, *J* 8.0 Hz), 7.21 (2H, t, *J* 8.0 Hz), 7.13-7.08 (5H, m), 7.06 (1H, t, *J* 7.0 Hz), 7.02 (4H, br d, *J* 7.0 Hz)] (10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), 6.59 (1H, s, indolyl H-2), 5.99 (1H, dt, *J* 6.0, 2.0 Hz, -C*H*=CH-), 5.81 (1H, dt, *J* 6.0, 1.5 Hz, -CH=C*H*-), 4.42 (1H, d with fine struct., *J* 10.0 Hz, Ts-CH<), 3.89 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), 3.69-3.66 (1H, m, N-

CH<), 3.66 (3H, s, Ts-$CH_3$), 3.60 (2H, d, *J* 14.0 Hz, N-CH*H*-Ph), 3.09-3.06 (1H, m, =CH-C*H*-C($NBn_2$)H-), 3.05 (1H, dd, *J* 15.5, 11.5 Hz, indolyl-C*H*H-), 2.87 (1H, dd, *J* 15.5, 3.0 Hz, indolyl-CH*H*-), 2.47-2.43 (1H, m, =CH-C*H*(Et)-), [2.41, 2.34] (3H, s, Ts-$CH_3$), [1.01-0.94, 0.81-0.74] (2H, m, -$CH_2CH_3$), [0.85, 0.65, 0.53, 0.48] (3H, t, *J* 7.5 Hz, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.4, 140.3, 139.7, 137.8, 133.6, 131.1, 129.8, 129.4, 129.2, 129.0, 128.9, 128.7, 128.5, 128.2, 128.0, 127.8, 127.6, 127.4, 127.3, 127.1, 126.9, 126.8, 126.4, 126.1, 120.7, 119.4, 118.1, 112.9, 109.2, 109.0, 108.6, [70.1, 68.7] (Ts-CH<), [59.3, 58.9] (N-CH<), [54.1, 53.4] (N-$CH_2$-), [48.5, 48.3] (>CH-CH=CH-CH<), [32.7, 32.5] (N-$CH_3$), [26.0, 24.6] (indolyl-$CH_2$-, $H_3C$-$CH_2$-), 21.6 (Ts-$CH_3$), 10.9 (-$CH_2CH_3$); *m/z* (FAB) 603 $[M+H]^+$ (Found: $[M+H]^+$, 603.3065. $C_{39}H_{42}N_2O_2S$ requires $[M+H]^+$, 603.3045).

**"lower" 536:** Colourless oil; $R_f$ 0.37 (20% EtOAc–petrol); $\nu_{max}$ (film) 3058, 3027, 1615, 1597, 1493, 1469, 1454, 1424, 1399, 1376, 1316, 1302, 1289, 1262, 1206, 1183, 1144, 1086, 1028, 1016, 982, 968, 910, 859, 813, 734, 700, 664 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) [7.78, 7.75, 7.73] (2H, d, *J* 8.5 Hz, *o*-$SO_2Ar$), [7.34 (2H, d, *J* 8.0 Hz), 7.24 (2H, d, *J* 8.0 Hz), 7.22-7.17 (1H, m), 7.10-7.06 (3H, m), 7.01 (4H, t, *J* 7.5 Hz), 6.93 (4H, d, *J* 7.5 Hz)] (10× Ph-H, *m*-$SO_2Ar$, indolyl H-4,5,6,7), [6.59, 6.58] (1H, s, indolyl H-2), 6.06 (2H, s, -C*H*=C*H*-), [4.31 (1H, t, *J* 9.0 Hz), 4.19 (1H, dd, *J* 11.5, 2.0 Hz)] (Ts-CH<, N-CH-C*H*-CH=), 3.90-3.83 (1H, m, N-CH<), 3.85 (2H, d, *J* 14.0 Hz, N-C*H*H-Ph), [3.67, 3.65] (3H, s, Ts-$CH_3$), 3.60 (2H, d, *J* 14.0 Hz, N-CH*H*-Ph), 3.02 (1H, dd, *J* 15.5, 3.0 Hz, indolyl-C*H*H-), 2.92 (1H, dd, *J* 15.5, 12.0 Hz, indolyl-CH*H*-), [2.73-2.69, 2.55-2.51] (1H, m, =CH-C*H*(Et)-), [2.46, 2.42, 2.40, 2.33] (3H, s, Ts-$CH_3$), [2.03 (dqd, *J* 15.0 7.5 3.5 Hz), 1.72-1.64 (m), 1.46 (dq, *J* 13.5, 7.5 Hz)] (2H, -$CH_2CH_3$), [1.04, 0.90, 0.85, 0.65] (3H, t, *J* 7.5 Hz, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 144.1, 140.3, 138.2, 136.6, 133.9, 131.5, 129.8, 129.5, 129.2, 129.0, 128.9, 128.3, 128.0, 127.9, 127.6, 127.5, 127.1, 126.8, 126.4, 126.3, 120.8, 119.6, 118.3, 112.8, 108.7, 67.3 (Ts-CH<), 58.9 (N-CH<), 54.0 (N-$CH_2$-), [49.9, 47.7, 47.6, 47.3] (>CH-CH=CH-CH<), [32.8, 32.5] (N-$CH_3$), [29.7, 25.0, 24.8] (indolyl-$CH_2$-, $H_3C$-$CH_2$-), 21.6 (Ts-$CH_3$), 12.5 (-$CH_2CH_3$); *m/z* (FAB) 603 $[M+H]^+$ (Found: $[M+H]^+$, 603.3040. $C_{39}H_{42}N_2O_2S$ requires $[M+H]^+$, 603.3045).

**(1*S*)-*N*,*N*-Dibenzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine (570), diastereoisomers as shown, and (1*S*)-*N*-Benzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine (571), diastereoisomers as shown. *[Both from "lower" 536]***




**536** **570** **571**

Lithium naphthalenide was prepared by addition of THF (25 mL) to Li shot (0.5% Na content, 174 mg, 25.0 mmol) and naphthalene (3.21 g, 25.0 mmol) and sonication at rt for 8 h to give a dark green/black solution, assumed to be 1.0 M.

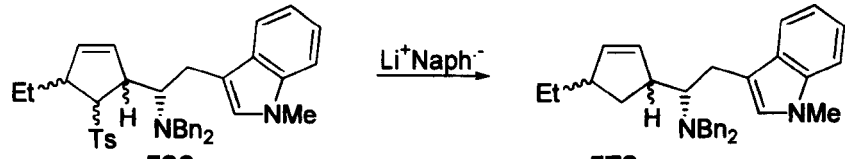
**"lower" 536** (36 mg, 0.0597 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and cooled to –78 °C. Lithium naphthalenide (1.0 M in THF; 119 µL, 0.119 mmol, 2.0 equiv) was added dropwise by syringe. The reaction mixture changed from colourless to yellow to red. After 15 s, bromoacetaldehyde dimethyl acetal (70 µL, 0.597 mmol, 10.0 equiv) was added by syringe, resulting in the reaction mixture turning yellow. The reaction mixture was allowed to warm to rt with stirring over 14 h, then was diluted with EtOAc (50 mL). This was washed with $H_2O$ (50 mL). The aqueous phase was extracted with EtOAc (10 mL). Combined organic phases were washed with $H_2O$ (3× 25 mL) and brine (25 mL), then dried over $Na_2SO_4$. Concentration under reduced pressure and chromatography (0→10→30% EtOAc–petrol) gave *(1S)*-N,N-*dibenzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethyl amine* **570** (17 mg, 63%) as a colourless oil (electrophile incorporation unsuccessful). Also isolated was *(1S)*-N-*benzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine* **571** (trace) as a colourless oil.

**570 (from "lower"):** $R_f$ 0.65 (20% EtOAc–petrol); $\nu_{max}$ (film) 3058, 3027, 1493, 1470, 1454, 1374, 1325, 1248, 1127, 1071, 1027, 1013, 967, 910, 790, 738, 699 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.31 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.24-7.18 (11H, m, 10× Ph-H, indolyl H-5), 7.07 (1H, t, *J* 7.5 Hz, indolyl H-6), 6.64 (1H, s, indolyl H-2), 5.62 (1H, dt, *J* 5.5, 2.0 Hz, -C*H*=CH-), 5.57 (1H, dt, *J* 5.5, 2.0 Hz, -CH=C*H*-), 3.78 (2H, d, *J* 13.5 Hz, N-C*H*H-Ph), [3.76, 3.75 (×2)] (3H, s, $N-CH_3$), 3.64 (2H, d, *J* 13.5 Hz, N-CH*H*-Ph), 3.16 (1H, dd, *J* 15.0, 6.5 Hz, indolyl-C*H*H-), 3.13-3.08 (1H, m, N-CH-C*H*-CH=), 2.93 (1H, app q, *J* 7.0 Hz, N-CH<), 2.87 (1H, dd, *J* 15.0, 5.5 Hz, indolyl-

CH*H*-), 2.51-2.46 (1H, m, =CH-C*H*(Et)-), 2.33 (1H, dt, *J* 13.0, 8.0 Hz, >CH-C*H*H-CH<), 1.37-1.26 (2H, m, -C*H*$_2$CH$_3$), 1.20 (1H, dt, *J* 13.0, 7.5 Hz, >CH-CH*H*-CH<), [0.97, 0.87, 0.79, 0.69, 0.54] (3H, t, *J* 7.5 Hz, -CH$_2$C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 140.5 (*i*-Ph), 136.9 (indolyl C-7a), 135.9 (olefinic), 132.8 (olefinic), 129.0 (*o*-Ph), 128.2 (indolyl C-3a), 128.0 (*m*-Ph), 127.1 (indolyl C-2), 126.6 (*p*-Ph), 121.3 (indolyl C-5), 119.2 (indolyl C-4), 118.5 (indolyl C-6), 114.0 (indolyl C-3), 109.0 (indolyl C-7), 62.6 (N-CH<), 53.9 (N-CH$_2$-), 48.6 (N-CH-CH-CH=), 46.6 (=CH-CH(Et)-), 35.8 (>CH-CH$_2$-CH<), 32.6 (N-CH$_3$), 29.1 (indolyl-CH$_2$-), 23.7 (-CH$_2$CH$_3$), 12.3 (-CH$_2$CH$_3$); *m/z* (CI) 449 $[M+H]^+$, 304, 248 (Found: $[M+H]^+$, 449.2947. $C_{32}H_{36}N_2$ requires $[M+H]^+$, 449.2957).

**571:** *(Characterisation incomplete due to small amount of material isolated)*; $R_f$ 0.09 (20% EtOAc–petrol); $\delta_H$ (300 MHz, $CDCl_3$) 7.82-6.91 (14H, 10× Ph-H, indolyl H-4,5,6,7), 6.86 (1H, s, indolyl H-2), 5.75 (1H, br s, -C*H*=CH-), 5.60 (1H, d, *J* 5.5 Hz, -CH=C*H*-), 3.85-3.54 (4H, m, N-C*H*$_2$ Ph), 3.76 (3H, s, N-CH$_3$), [2.95-2.87 (2H), 2.80-2.05 (3H)] (m, indolyl-C*H*$_2$-, N-CH<, >*H*C-CH=CH-C*H*<), 1.47-1.28 (4H, m, -C*H*$_2$CH$_3$, >HC-C*H*$_2$-CH<), 0.98-0.75 (3H, m, -CH$_2$C*H*$_3$); *m/z* (CI) 359 $[M+H]^+$ (Found: $[M+H]^+$, 359.2448. $C_{25}H_{30}N_2$ requires $[M+H]^+$, 359.2487).

**(1*S*)-*N*,*N*-Dibenzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine (570), diastereoisomers as shown,** ***[From "upper" 536]***




**536** **570**

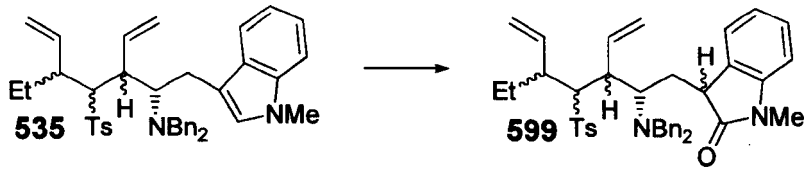
Lithium naphthalenide was prepared by addition of DME (25 mL) to Li shot (0.5% Na content, 174 mg, 25.0 mmol) and naphthalene (3.21 g, 25.0 mmol) and sonication at rt for 8 h to give a dark green/black solution, assumed to be 1.0 M.

**"upper" 536** (51 mg, 0.0846 mmol, 1.0 equiv) was dissolved in DME (0.5 mL) and cooled to –78 °C. Lithium naphthalenide (1.0 M in DME; 169 µL, 0.169 mmol, 2.0 equiv) was added dropwise by syringe. The reaction mixture changed from colourless to yellow to red. After 15 s, bromoacetaldehyde dimethyl acetal (80 µL, 0.676 mmol, 8.0 equiv) was added by syringe, resulting in the reaction mixture turning yellow. DMPU (150 µL) was added by

syringe. The reaction mixture was allowed to warm to rt with stirring over 14 h, then was diluted with EtOAc (50 mL). This was washed with $H_2O$ (50 mL). The aqueous phase was extracted with EtOAc (10 mL). Combined organic phases were washed with $H_2O$ (3× 25 mL) and brine (25 mL), then dried over $Na_2SO_4$. Concentration under reduced pressure and chromatography (0→10→30% EtOAc–petrol) gave *(1S)*-N,N-*dibenzyl-1-(4-ethylcyclopent-2-enyl)-2-(1-methylindol-3-yl)ethylamine* **570** (17 mg, 63%) as a colourless oil and as an inseparable mixture of diastereoisomers (electrophile incorporation unsuccessful). *Addition of electrophile prior to addition of lithium naphthalenide also did not result in electrophile incorporation. Use of epoxide as both solvent and electrophile also did not result in electrophile incorporation.*

**570 ("from upper"):** $R_f$ 0.65 (20% EtOAc–petrol); $\nu_{max}$ (film) 3080, 3057, 3025, 1492, 1484, 1471, 1453, 1422, 1374, 1326, 1248, 1207, 1155, 1129, 1071, 1027, 1013, 996, 912, 788, 737, 699 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.48 (1H, d, *J* 8.0 Hz, indolyl H-4), 7.31 (1H, d, *J* 8.0 Hz, indolyl H-7), 7.24-7.15 (11H, m, 10× Ph-H, indolyl H-5), 7.07 (1H, t, *J* 7.0 Hz, indolyl H-6), [6.66, 6.65] (1H, s, indolyl H-2), 5.67-5.65 (1H, m, -C*H*=CH-), 5.63-5.52 (1H, m, -CH=C*H*-), 3.78 (2H, d, *J* 13.5 Hz, N-C*H*H-Ph), 3.75 (×2) (3H, s, N-$CH_3$), 3.66-3.61 (2H, m, N-CH*H*-Ph), [3.16-3.06 (2H, m), 3.03-2.90 (1H, m), 2.83 (1H, dd, *J* 15.0, 5.5 Hz), 2.45-2.41 (1H, m)] (N-CH<, indolyl-C$H_2$-, >*H*C-CH=CH-C*H*<), [2.07-2.01, 1.73-1.69, 1.40-1.26] (4H, m, -C$H_2$$CH_3$, >HC-C$H_2$-CH<), [0.90, 0.84, 0.79] (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 140.6, 136.9, 136.1, 132.8, 129.0, 128.9, 128.2 (×2), 127.9, 127.3, 127.0, 126.6, 121.3, 119.3, 118.5, 114.0, 109.0, 62.2, 54.2, 54.0, 47.8, 47.7, 45.9, 35.4, 32.6, 28.7, 23.6, 12.2; *m/z* (CI) 449 $[M+H]^+$, 355, 338, 305 (Found: $[M+H]^+$, 449.2941. $C_{32}H_{36}N_2$ requires $[M+H]^+$, 449.2957).

**3-((2*S*)-2-(Dibenzylamino)-3-ethenyl-5-ethyl-4-(toluene-4-sulfonyl)hept-6-enyl)-1-methylindolin-2-one (599), diastereoisomers as shown.**

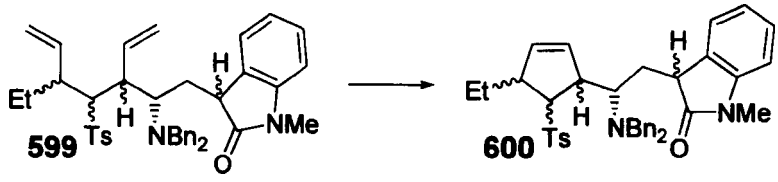



DMDO was prepared according to the method of Adam.[203] Titration against methyl phenyl sulfide showed the DMDO concentration to be 0.054 M.

To **535** (114 mg, 0.181 mmol, 1.0 equiv) in $CH_2Cl_2$ (3 mL) at –78 °C was added dropwise by syringe DMDO (0.054 M in acetone, 3.35 mL, 0.181 mmol, 1.0 equiv). The reaction mixture was stirred at –78 °C for 30 min, then at rt for 30 min. Concentration under reduced pressure and chromatography (15% EtOAc–petrol) gave *3-((2S)-2-(dibenzylamino)-3-ethenyl-5-ethyl-4-(toluene-4-sulfonyl)hept-6-enyl)-1-methylindolin-2-one* **599** (84 mg, 72%) as a colourless oil; $R_f$ 0.23 (20% EtOAc–petrol); $\nu_{max}$ (film) 3061, 3029, 1710, 1613, 1494, 1469, 1454, 1401, 1377, 1348, 1299, 1143, 1086, 1021, 917, 816, 733, 701 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.58 (×2) (2H, d, *J* 7.5 Hz, *o*-$SO_2Ar$, min. diast.), [7.45-7.43, 7.33-7.19] (16H, m, *o*-$SO_2Ar$ maj. diast., *m*-$SO_2Ar$, 10× Ph-H, oxindolyl H-4,6), [7.12-7.09 (m), 6.87 (t, *J* 7.5 Hz)] (1H, oxindolyl H-5), [6.79, 6.76] (1H, d, *J* 7.5 Hz, oxindolyl H-7), [6.69, 6.59, 6.48, 6.37] (1H, dt, *J* 17.0, 10.5 Hz, -CH($NBn_2$)-CH-C*H*=$CH_2$), [5.79 (ddd, *J* 17.0, 10.0, 9.0 Hz), 5.68 (ddd, *J* 17.0, 10.0, 9.0 Hz), 5.60 (ddd, *J* 17.0, 10.0, 9.0 Hz), 5.46 (ddd, *J* 20.0, 10.0, 1.5 Hz)] (1H, CH(Et)-C*H*=$CH_2$), [5.38 (dd, *J* 10.0, 2.0 Hz), 5.37 (dd, *J* 10.0, 2.0 Hz), 5.14 (dd, *J* 10.0, 1.5 Hz), 5.12 (dd, *J* 9.0, 1.5 Hz), 5.06 (dd, *J* 10.0, 1.5 Hz), 5.02 (dd, *J* 9.5, 1.0 Hz)] (2H, *cis* -CH=C$H_2$), [5.32 (dd, *J* 17.0, 1.5 Hz), 5.30 (dd, *J* 17.0, 2.0 Hz), 4.98 (d, *J* 16.5 Hz), 4.79 (d, *J* 17.0 Hz), 4.78 (d, *J* 17.5 Hz)] (2H, *trans* -CH=C$H_2$), [4.15-4.12, 4.09-4.06, 4.02-3.99] (1H, m, Ts-CH<), [3.95 (d, *J* 13.5 Hz), 3.93 (d, *J* 13.5 Hz), 3.77 (d, *J* 14.0 Hz)] (2H, N-C*H*H-Ph), 3.85-3.78 (1H, m, N-CH<), [3.72 (d, *J* 13.5 Hz), 3.70 (d, *J* 13.5 Hz), 3.55 (d, *J* 14.0 Hz)] (2H, N-CH*H*-Ph), 3.46-3.41 (1H, m, oxindolyl H-3), [3.31 (ddd, *J* 10.5, 5.5, 2.0 Hz), 3.28-3.24 (m)] (1H, $H_2C$=CH-C*H*-CH($NBn_2$)-), 3.24 (×2) (3H, s, Ts-$CH_3$), [2.49, 2.46 (×2), 2.44] (3H, s, Ts-$CH_3$), [2.43-2.35, 2.24-2.20, 2.10-2.04] (3H, m, $H_2C$=CH-C*H*(Et)-, $Bn_2N$-CH-C$H_2$-), [1.50 (qd, *J* 7.5, 5.0 Hz), 1.35 (dq, *J* 11.5, 7.5 Hz), 1.32-1.15 (m)] (2H, -C$H_2CH_3$), [0.90, 0.76, 0.57] (3H, t, *J* 7.5 Hz, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) [178.9, 178.3, 178.2] (C=O), 144.1 (4°), 143.9 (4°), 143.6 (4°), 142.8 (4°), 139.9 (×2, 4°), 139.6 (4°), 139.1 (3°), 138.7 (4°), 138.4 (3°), 138.1 (4°), 137.4 (4°), 137.3 (4°), 136.7 (3°),

136.1 (3°), 135.9 (3°), 135.5 (3°), 130.2 (4°), 129.5 (3°), 129.1 (3°), 128.5 (3°), 128.3 (×2, 3°), 127.9 (3°), 127.7 (3°), 127.4 (3°), 126.9 (3°), 125.6 (3°), 125.5 (3°), 124.0 (3°), 123.1 (3°), 122.3 (3°), 121.8 (3°), 121.7 (3°), 121.2 (2°), 121.0 (2°), 120.4 (2°), 117.4 (2°), 117.1 (2°), 107.7 (3°), 107.5 (3°), 70.4 (3°), 69.5 (3°), 68.3 (3°), 67.6 (3°), 60.3 (3°), 59.6 (3°), 59.0 (3°), 53.7 (2°), 53.6 (2°), 48.5 (3°), 47.9 (3°), 47.2 (3°), 47.1 (3°), 47.0 (3°), 46.8 (3°), 46.2 (3°), 46.0 (3°), 45.6 (3°), 43.2 (3°), 42.4 (3°), 42.1 (3°), 30.9 (2°), 30.6 (2°), 30.4 (2°), 29.6 (2°), 26.1 (1°), 24.5 (2°), 22.6 (2°), 22.3 (2°), 21.6 (1°), 21.0 (1°), 14.1 (1°), 12.7 (1°), 11.5 (1°), 11.4 (1°); *m/z* (FAB) 647 $[M+H]^+$, 369 (Found: $[M+H]^+$, 647.3304. $C_{41}H_{46}N_2O_3S$ requires $[M+H]^+$, 647.3307).

**3-((2*S*)-2-(Dibenzylamino)-2-(4-ethyl-5-(toluene-4-sulfonyl)cyclopent-2-enyl)ethyl)-1-methylindolin-2-one (370), diastereoisomers as shown.**




To dichloro(tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)(benzylidene)ruthenium (16 mg, 0.0193 mmol, 0.1 equiv) was added a solution of **599** (125 mg, 0.193 mmol, 1.0 equiv) in $CH_2Cl_2$ (38 mL). The reaction mixture was heated to reflux for 14 h, then concentrated under reduced pressure and purified by chromatography (20% EtOAc–petrol) to give *3-((2S)-2-(Dibenzylamino)-2-(4-ethyl-5-(toluene-4-sulfonyl)cyclopent-2-enyl)ethyl)-1-methylindolin-2-one* **600** (76% total), isolable as three discrete mixtures of diastereoisomers, **"upper" 600** (69 mg, 57%), **"middle" 600** (11 mg, 9%) and **"lower" 600** (12 mg, 10%).

**"upper" 600:** Colourless oil; $R_f$ 0.67 (50% EtOAc–petrol); $\nu_{max}$ (film) 3060, 3029, 1703, 1613, 1597, 1493, 1469, 1455, 1420, 1376, 1351, 1316, 1312, 1287, 1264, 1144, 1088, 1023, 979, 911, 816, 749, 732, 701, 663 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [7.80, 7.75] (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.42-7.12 (14H, m, *m*-$SO_2Ar$, 10× Ph-H, oxindolyl H-4,6), 6.90-6.67 (2H, m, oxindolyl H-5,7), [6.19 (dd, *J* 14.0, 7.5 Hz), 6.02-5.92 (m)] (2H, -C*H*=C*H*-), [5.73 (d, *J* 6.0 Hz), 4.43 (dd, *J* 13.0, 3.0 Hz)] (1H, Ts-CH<), 4.24-4.08 (3H, m, N-C*H*H-Ph, N-CH<), 3.78-3.64 (3H, m, N-CH*H*-Ph, oxindolyl H-3), 3.57-3.44 (1H, m, =CH-C*H*-CH($NBn_2$)-), [3.24, 3.23] (3H, s, N-$CH_3$), [2.86-2.70, 2.55-2.12] (3H, =CH-

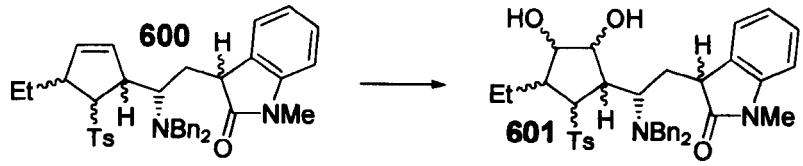
C*H*(Et)-, $Bn_2N$-CH-C$H_2$-), [1.75-1.66, 1.31-1.18] (2H, m, -C$H_2$$CH_3$), [0.91, 0.74, 0.67] (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 179.7 (C=O), 144.5 (4°), 144.3 (4°), 143.3 (4°), 139.9 (4°), 139.6 (4°), 138.1 (4°), 134.3 (3°), 134.1 (3°), 131.1 (3°), 130.5 (3°), 130.0 (3°), 129.8 (3°), 129.5 (3°), 129.4 (3°), 129.2 (3°), 128.8 (3°), 128.5 (3°), 128.3 (3°), 128.1 (3°), 127.7 (3°), 127.4 (3°), 127.0 (3°), 126.9 (3°), 126.7 (3°), 126.5 (3°), 126.2 (3°), 125.6 (3°), 123.2 (3°), 122.4 (3°), 122.1 (3°), 121.9 (3°), 121.3 (3°), 106.9 (3°), 70.5 (2°), 69.6 (3°), 67.1 (3°), 54.8 (3°), 54.6 (3°), 53.5 (2°), 53.3 (2°), 48.6 (3°), 48.0 (3°), 47.3 (3°), 47.1 (3°), 46.9 (3°), 45.7 (3°), 42.1 (3°), 31.8 (2°), 31.6 (2°), 29.7 (2°), 26.2 (1°), 26.1 (1°), 25.8 (2°), 24.7 (2°), 21.6 (1°), 21.1 (1°), 14.2 (1°), 12.2 (1°), 10.6 (1°); *m/z* (FAB) 619 $[M+H]^+$, 527, 385, 369 (Found: $[M+H]^+$, 619.2999. $C_{39}H_{42}N_2O_3S$ requires $[M+H]^+$, 619.2994).

**"middle" 600:** Colourless oil; $R_f$ 0.63 (50% EtOAc–petrol); $\nu_{max}$ (film) 3060, 3029, 1721, 1615, 1597, 1495, 1470, 1455, 1419, 1376, 1349, 1317, 1305, 1253, 1205, 1144, 1123, 1109, 1088, 1021, 1000, 911, 816, 733, 698, 664 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [8.07 (d, *J* 8.0 Hz), 7.88 (d, *J* 8.0 Hz), 7.79 (d, *J* 7.5 Hz), 7.74 (d, *J* 8.5 Hz)] (2H, *o*-$SO_2$Ar), 7.33-7.00 (15H, m, *m*-$SO_2$Ar, 10× Ph-H, oxindolyl H-4,5,6), [6.83 (d, *J* 7.5 Hz), 6.73 (d, *J* 8.5 Hz)] (1H, oxindolyl H-7), [6.04, 5.87] (2× 1H, d, *J* 5.5 Hz, -C*H*=C*H*-), 4.85 (1H, d, *J* 9.5 Hz, Ts-CH<), 4.32 (1H, t, *J* 9.0 Hz, oxindolyl H-3), 4.19-4.04 (1H, m, N-CH<), 3.67-3.60 (1H, m, =CH-C*H*-CH($NBn_2$)-), 3.36-3.22 (4H, m, N-C$H_2$-Ph), 3.30 (3H, s, N-$CH_3$), 2.96-2.91 (1H, m, =CH-C*H*(Et)-), [2.48-2.35, 1.76-1.66] (2H, m, $Bn_2N$-CH-C$H_2$-), 2.22 (3H, s, Ts-$CH_3$), 1.30-1.05 [2H, m, -C$H_2$$CH_3$], [0.86, 0.54] (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 171.8, 144.6, 143.2, 140.3, 139.9, 137.8, 135.2, 134.3, 131.8, 130.0, 129.8, 129.6, 129.3, 129.1, 128.7, 128.4, 128.3, 128.1, 127.8, 126.9, 126.7, 124.6, 123.5, 123.2, 122.4, 108.0, 66.0, 56.6, 48.4, 48.0, 46.1, 35.2, 35.0, 32.2, 29.7, 26.4, 26.2, 25.2, 23.4, 22.7, 21.6, 21.4, 12.6; *m/z* (FAB) 619 $[M+H]^+$, 458, 385, 369 (Found: $[M+H]^+$, 619.2993. $C_{39}H_{42}N_2O_3S$ requires $[M+H]^+$, 619.2994).

**"lower" 600:** Colourless oil; $R_f$ 0.59 (50% EtOAc–petrol); $\nu_{max}$ (film) 3061, 3030, 3002, 1722, 1615, 1597, 1495, 1470, 1456, 1421, 1376, 1347, 1316, 1303, 1289, 1252, 1204, 1144, 1121, 1108, 1087, 1020, 1001, 911, 815, 762, 699, 658 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) [8.07 (d, *J* 8.0 Hz), 7.88 (d, *J* 8.0 Hz)] (2H, *o*-$SO_2$Ar), 7.41-7.01 (15H, m, *m*-$SO_2$Ar, 10× Ph-H, oxindolyl H-4,5,6), 6.80 (1H, d, *J* 7.5 Hz, oxindolyl H-7), [5.79, 5.70] (2× 1H, d, *J* 6.0 Hz, -C*H*=C*H*-), 5.38-5.32 (1H, d, *J* 9.5 Hz, Ts-CH<), 4.18-4.04 (1H, m, oxindolyl

H-3), 3.62 (2H, d, *J* 12.5 Hz, N-C*H*H-Ph), 3.36-3.21 (3H, m, N-CH*H*-Ph, N-CH<), 3.25 (3H, s, N-$CH_3$), 2.89-2.76 (1H, m, =CH-C*H*-CH($NBn_2$)-), 2.50-2.39 (1H, m, , =CH-C*H*(Et)-), 2.35 (3H, s, Ts-$CH_3$), [1.87-1.82, 1.23-1.05, 0.97-0.85] (4H, m, N-CH-C$H_2$-, -C$H_2$$CH_3$), 0.53 (3H, t, *J* 7.5 Hz, -$CH_2$C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 178.5, 144.5, 143.3, 137.8, 137.6, 136.8, 134.4, 132.1, 129.9, 129.8, 129.6, 129.3, 129.1, 129.0, 128.7, 128.4, 128.3, 128.1, 127.7, 127.4, 127.0, 123.3, 122.2, 107.9, 68.6, 66.1, 56.8, 48.5, 48.0, 47.8, 46.2, 35.3, 35.1, 31.9, 29.7, 29.3, 26.3, 26.1, 25.2, 22.7, 21.5, 14.2, 12.6, 10.9; *m/z* (FAB) 619 $[M+H]^+$, 458, 385, 369.

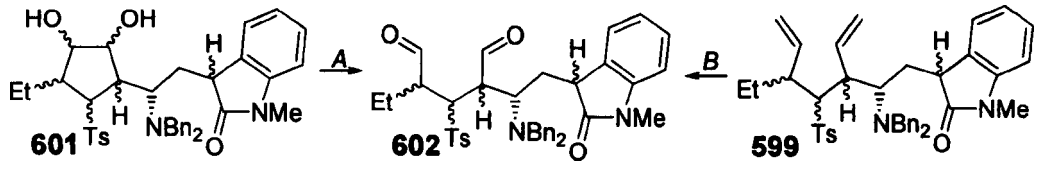
**3-((2*S*)-2-(Dibenzylamino)-2-(3-ethyl-4,5-dihydroxy-2-(toluene-4-sulfonyl)cyclopentyl)ethyl)-1-methylindolin-2-one (601), diastereoisomers as shown.**




Oxindole **600** (69 mg, 0.111 mmol, 1.0 equiv) and *N*-methylmorpholine *N*-oxide (27 mg, 0.228 mmol, 2.05 equiv) were dissolved in acetone (1.5 mL). One drop of $H_2O$ was added, resulting in some precipitation. $OsO_4$ (4% wt. in $H_2O$, 17.5 µL, 0.00278 mmol, 0.025 equiv) was added by syringe, resulting in the reaction mixture becoming slightly darker and the precipitate disappearing. The reaction mixture was stirred for 14 h at rt. Saturated aq. $Na_2SO_3$ (0.5 mL) was added and the reaction mixture was stirred for 1 h, then partitioned between EtOAc (25 mL) and $H_2O$ (25 mL). The aqueous layer was washed with EtOAc (10 mL). Combined organic phases were washed with aq. $Na_2SO_3$ (10 mL), $H_2O$ (10 mL) and brine (10 mL). The organic phase was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by chromatography (50% EtOAc–petrol) to give *3-((2S)-2-(dibenzylamino)-2-(3-ethyl-4,5-dihydroxy-2-(toluene-4-sulfonyl)cyclopentyl)ethyl)-1-methylindolin-2-one* **601** as a colourless oil; only the major diastereoisomeric mixture (13 mg, 17%) was isolated in sufficient quantity for full characterisation. Major and minor product spots were combined after characterisation; total yield 48 mg, 66%.

**601:** $R_f$ 0.35 (70% EtOAc–petrol); $\nu_{max}$ (film) 3452, 3060, 3028, 3002, 1712, 1613, 1597, 1494, 1470, 1454, 1419, 1378, 1352, 1300, 1289, 1208, 1140, 1084, 1028, 1003, 911, 814, 733, 699 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.0 Hz, *o*-$SO_2Ar$), 7.33-7.04 (14H, m, *m*-$SO_2Ar$, 10× Ph-H, oxindolyl H-4,5,6), 6.83 (1H, d, *J* 7.5 Hz, oxindolyl H-7), [5.69-5.63, 5.58-5.51, 5.32-5.27, 4.61-4.57, 4.25-4.04] (3H, m, Ts-CH, 2× -C(OH)*H*), [3.91-3.76, 3.67-3.54] (4H, m, N-C$H_2$-Ph), [3.31-3.24] (1H, m, oxindolyl H-3), 3.19 (3H, s, N-$CH_3$), 3.09-3.07 (1H, m, N-CH<), 2.47-2.41 (3H, m, Ts-CH-C*H*-CH($NBn_2$), C(=O)CH-C$H_2$-), 2.38 (3H, s, Ts-$CH_3$), 1.77-1.70 (1H, m, $H_3C$-$CH_2$-C*H*<), 1.30-1.06 (2H, m, -C$H_2CH_3$), [0.98, 0.87] (3H, t, *J* 7.5 Hz, -$CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 179.1, 177.9, 144.2, 143.7, 142.3, 138.8, 137.9, 135.2, 132.0, 129.6, 129.4, 129.1, 128.7, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 127.3, 126.5, 126.4, 126.3, 123.4, 123.1, 122.5, 108.2, 75.6, 72.0, 67.8, 65.2, 59.9, 57.4, 54.8, 52.5, 52.3, 44.4, 43.1, 37.4, 32.9, 31.9, 29.6, 29.3, 26.1, 23.4, 22.6, 21.8, 21.8, 21.5, 21.2, 14.1, 13.5, 12.3; *m/z* (FAB) 635 $[M+H-H_2O]^+$, 492, 385, 367 (Found: $[M+H-H_2O]^+$, 635.2923. $C_{39}H_{44}N_2O_5S$ requires $[M+H-H_2O]^+$, 635.2944).

**2-((1*S*)-1-(Dibenzylamino)-2-(1-methyl-2-oxoindolin-3-yl)ethyl)-4-ethyl-3-(toluene-4-sulfonyl)pentanedial (602), diastereoisomers as shown.**



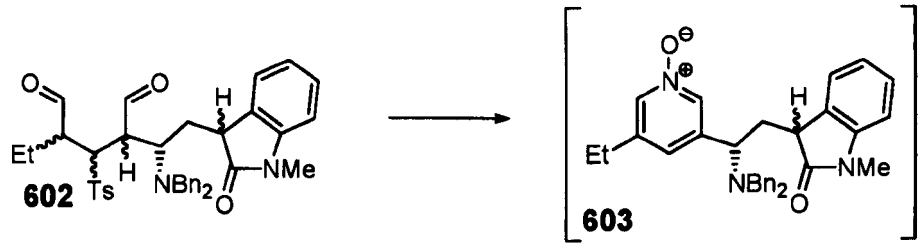

*Procedure A*

To **601** (48 mg, 0.0734 mmol, 1.0 equiv) and $NaHCO_3$ (43 mg, 0.514 mmol, 7.0 equiv) was added benzene (0.7 mL). The reaction mixture was stirred, resulting in a white suspension. Lead tetraacetate (36 mg, 0.0807 mmol, 1.1 equiv) was added in one portion. The reaction mixture was stirred at rt for 5 min, resulting in a qualitative change in the precipitate and the discolouration of the reaction mixture to a deep orange. The reaction mixture was quickly filtered (washed through with additional benzene) and concentrated under reduced pressure. A TLC of the filtrate indicated the presence of many components, including 4 discrete highly coloured spots (two yellow, one orange, one purple). The crude product (assumed to be highly unstable) was used immediately without any characterisation.

*Procedure B*

To diene **599** (84 mg, 0.130 mmol, 1.0 equiv) in $CH_2Cl_2$ (5 mL) at –78 °C was added trifluoroacetic acid (9.7 µL, 0.130 mmol, 1.0 equiv). A stream of $O_3$ in $O_2$ was passed through the reaction mixture for 10 min. TLC indicated absence of starting material. Gas flow was discontinued and $PPh_3$ (102 mg, 0.390 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 1 h at –78 °C (no discernable change by TLC), then allowed to warm to rt. Upon warming to rt, the reaction mixture turned deep orange. The reaction mixture was quickly neutralized with excess $NaHCO_3$, filtered and concentrated under reduced pressure. A TLC of the filtrate indicated the same impurity profile as for procedure A. The crude product (assumed to be highly unstable) was used immediately without any characterisation.

**3-((1*S*)-1-(Dibenzylamino)-2-(1-methyl-2-oxoindolin-3-yl)ethyl)-5-ethylpyridine-1-oxide, (603), diastereoisomers as shown.** ***[Tentative assignment]***

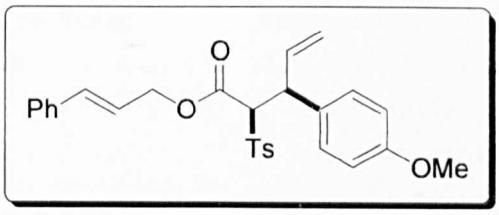


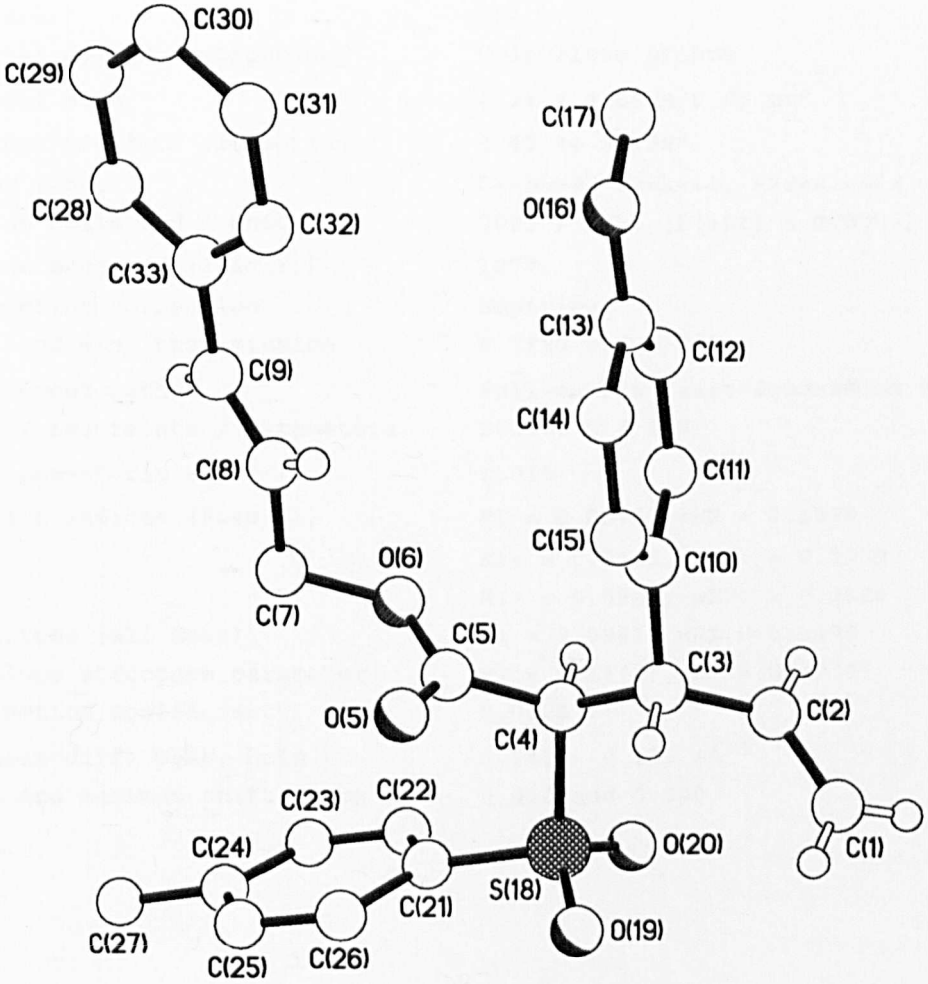

To crude aldehyde **602** (assumed to be 0.0734 mmol, 1.0 equiv) and hydroxylamine hydrochloride (5 mg, 0.073 mmol, 1.0 equiv) was added EtOH (1.0 mL) and $NEt_3$ (10.2 µL, 0.0734 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 14 h, then concentrated under reduced pressure. Chromatography of the highly impure reaction mixture (5% MeOH–$CH_2Cl_2$) gave a trace amount of material (sufficient only for mass spectrometry), tentatively assigned as *3-((1S)-1-(dibenzylamino)-2-(1-methyl-2-oxoindolin-3-yl)ethyl)-5-ethylpyridine-1-oxide* **603**; $R_f$ 0.09 (5% MeOH–$CH_2Cl_2$); *m/z* (FAB) 492 $[M+H]^+$, 410, 367.

# *4. Appendices*

## 4.1 X-Ray Structures

### *4.1.1 – Single rearrangement product* **384**



Crystal data and structure refinement for **235**

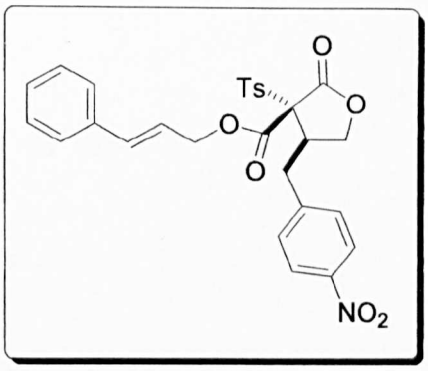
| | |
|---|---|
| Identification code | DC0308 |
| Empirical formula | C28 H28 O5 S |
| Formula weight | 476.56 |
| Temperature | 293(2) K |
| Diffractometer, wavelength | Bruker P4, 1.54178 Å |
| Crystal system, space group | Monoclinic, Pn |
| Unit cell dimensions | a = 8.1024(11) Å α = 90° |
| | b = 6.0389(19) Å β = 91.852(13)° |
| | c = 25.8931(15) Å γ = 90° |
| Volume, Z | 1266.3(4) $Å^3$, 2 |
| Density (calculated) | 1.250 $Mg/m^3$ |
| Absorption coefficient | 1.426 $mm^{-1}$ |
| F(000) | 504 |
| Crystal colour / morphology | Colourless prisms |
| Crystal size | 0.23 x 0.09 x 0.07 $mm^3$ |
| θ range for data collection | 3.42 to 59.98° |
| Index ranges | 0<=h<=9, 0<=k<=6, -29<=l<=29 |
| Reflns collected / unique | 2035 / 2035 [R(int) = 0.0000] |
| Reflns observed [F>4σ(F)] | 1277 |
| Absorption correction | Empirical |
| Max. and min. transmission | 0.7180 and 0.2658 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2035 / 2 / 297 |
| Goodness-of-fit on $F^2$ | 1.015 |
| Final R indices [F>4σ(F)] | R1 = 0.0545, wR2 = 0.1279 |
| | R1+ = 0.0545, wR2+ = 0.1279 |
| | R1- = 0.0569, wR2- = 0.1324 |
| R indices (all data) | R1 = 0.0941, wR2 = 0.1490 |
| Absolute structure parameter | x+ = 0.13(9), x- = 0.87(9) |
| Extinction coefficient | 0.0026(7) |
| Largest diff. peak, hole | 0.148, -0.155 $eÅ^{-3}$ |
| Mean and maximum shift/error | 0.000 and 0.000 |

Bond lengths [Å] and angles [°] for **235**

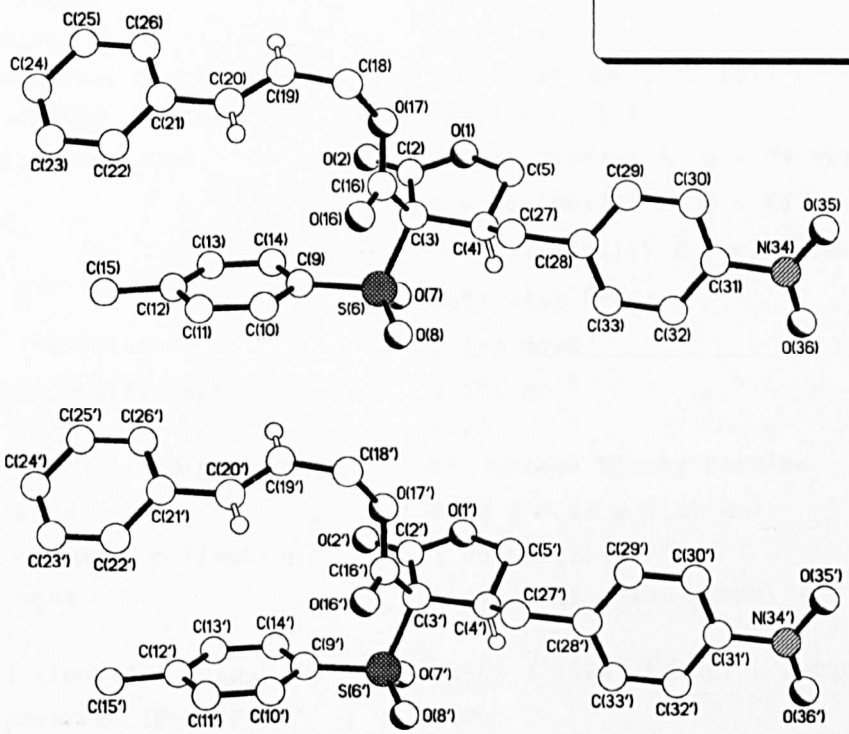
| | |
|---|---|
| C(1)-C(2) | 1.309(14) |
| C(2)-C(3) | 1.486(12) |
| C(3)-C(10) | 1.538(12) |
| C(3)-C(4) | 1.568(11) |
| C(4)-C(5) | 1.489(11) |
| C(4)-S(18) | 1.815(8) |
| C(5)-O(5) | 1.207(10) |
| C(5)-O(6) | 1.324(10) |
| O(6)-C(7) | 1.464(10) |
| C(7)-C(8) | 1.509(13) |
| C(8)-C(9) | 1.279(12) |
| C(9)-C(33) | 1.456(10) |
| C(10)-C(11) | 1.360(12) |
| C(10)-C(15) | 1.371(11) |
| C(11)-C(12) | 1.417(13) |
| C(12)-C(13) | 1.361(11) |
| C(13)-O(16) | 1.354(11) |
| C(13)-C(14) | 1.390(13) |
| C(14)-C(15) | 1.384(13) |
| O(16)-C(17) | 1.423(13) |
| S(18)-O(19) | 1.445(6) |
| S(18)-O(20) | 1.461(5) |
| S(18)-C(21) | 1.736(9) |
| C(21)-C(22) | 1.391(12) |
| C(21)-C(26) | 1.408(11) |
| C(22)-C(23) | 1.367(13) |
| C(23)-C(24) | 1.378(13) |
| C(24)-C(25) | 1.391(13) |
| C(24)-C(27) | 1.508(14) |
| C(25)-C(26) | 1.362(13) |
| C(28)-C(29) | 1.3900 |
| C(28)-C(33) | 1.3900 |
| C(29)-C(30) | 1.3900 |
| C(30)-C(31) | 1.3900 |
| C(31)-C(32) | 1.3900 |
| C(32)-C(33) | 1.3900 |

| | |
|---|---|
| C(1)-C(2)-C(3) | 124.5(11) |
| C(2)-C(3)-C(10) | 113.4(7) |
| C(2)-C(3)-C(4) | 112.5(7) |
| C(10)-C(3)-C(4) | 108.2(7) |
| C(5)-C(4)-C(3) | 111.2(6) |
| C(5)-C(4)-S(18) | 110.0(6) |
| C(3)-C(4)-S(18) | 111.5(6) |
| O(5)-C(5)-O(6) | 124.7(8) |
| O(5)-C(5)-C(4) | 125.2(8) |
| O(6)-C(5)-C(4) | 110.1(7) |
| C(5)-O(6)-C(7) | 115.5(7) |
| O(6)-C(7)-C(8) | 111.3(8) |
| C(9)-C(8)-C(7) | 125.5(9) |
| C(8)-C(9)-C(33) | 130.9(9) |
| C(11)-C(10)-C(15) | 118.8(8) |
| C(11)-C(10)-C(3) | 121.1(8) |
| C(15)-C(10)-C(3) | 120.1(9) |
| C(10)-C(11)-C(12) | 121.7(8) |
| C(13)-C(12)-C(11) | 118.8(9) |
| O(16)-C(13)-C(12) | 126.4(9) |
| O(16)-C(13)-C(14) | 114.1(8) |
| C(12)-C(13)-C(14) | 119.5(9) |
| C(15)-C(14)-C(13) | 120.7(8) |
| C(10)-C(15)-C(14) | 120.4(9) |
| C(13)-O(16)-C(17) | 116.9(8) |
| O(19)-S(18)-O(20) | 119.5(4) |
| O(19)-S(18)-C(21) | 109.0(4) |
| O(20)-S(18)-C(21) | 107.3(4) |
| O(19)-S(18)-C(4) | 109.1(5) |
| O(20)-S(18)-C(4) | 105.9(4) |
| C(21)-S(18)-C(4) | 105.1(4) |
| C(22)-C(21)-C(26) | 119.4(9) |
| C(22)-C(21)-S(18) | 120.8(6) |
| C(26)-C(21)-S(18) | 119.7(7) |
| C(23)-C(22)-C(21) | 119.9(8) |
| C(22)-C(23)-C(24) | 121.8(9) |
| C(23)-C(24)-C(25) | 117.6(9) |
| C(23)-C(24)-C(27) | 121.3(10) |
| C(25)-C(24)-C(27) | 121.1(9) |
| C(26)-C(25)-C(24) | 122.6(9) |
| C(25)-C(26)-C(21) | 118.6(9) |
| C(29)-C(28)-C(33) | 120.0 |
| C(30)-C(29)-C(28) | 120.0 |
| C(29)-C(30)-C(31) | 120.0 |
| C(32)-C(31)-C(30) | 120.0 |
| C(33)-C(32)-C(31) | 120.0 |
| C(32)-C(33)-C(28) | 120.0 |
| C(32)-C(33)-C(9) | 120.7(6) |
| C(28)-C(33)-C(9) | 119.3(6) |

### 4.1.2 – *Unexpected lactone product* **365**




The unit cell was found to be composed of two independent (highly similar) conformers (shown below)




Two representations of the disorder in the two independent conformers are shown below

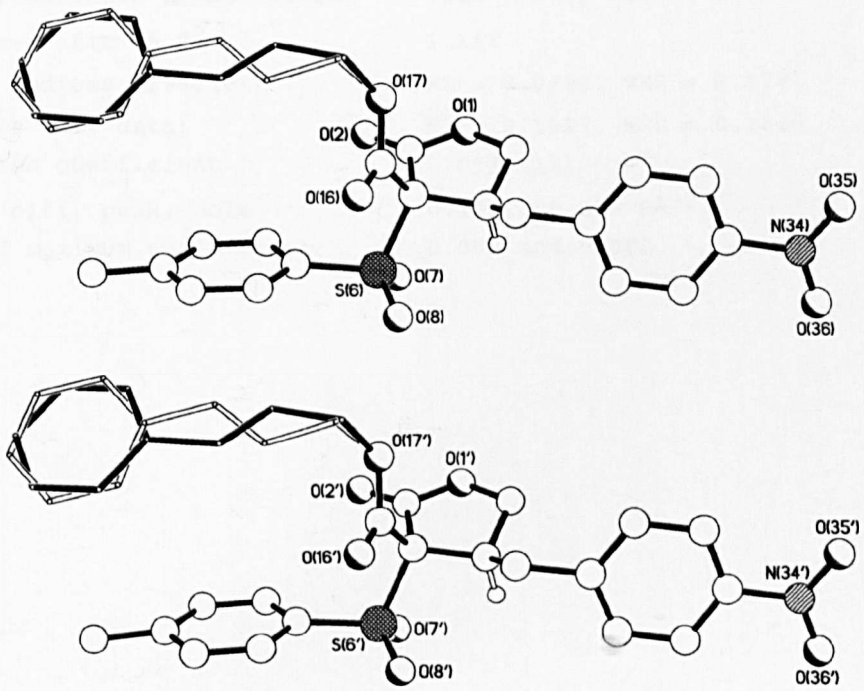


Table 1. Crystal data and structure refinement for **218**

| | |
|---|---|
| Identification code | DC0312B |
| Empirical formula | C28 H25 N O8 S |
| Formula weight | 535.55 |
| Temperature | 293(2) K |
| Diffractometer, wavelength | Bruker X8-Apex, 0.71073 Å |
| Crystal system, space group | Triclinic, P-1 |
| Unit cell dimensions | a = 10.7096(6) Å α = 89.661(2)° |
| | b = 12.1681(7) Å β = 89.691(2)° |
| | c = 21.1853(11) Å γ = 74.251(2)° |
| Volume, Z | 2657.1(3) $Å^3$, 4 |
| Density (calculated) | 1.339 $Mg/m^3$ |
| Absorption coefficient | 0.173 $mm^{-1}$ |
| F(000) | 1120 |
| Crystal colour / morphology | Colourless blocky needles |
| Crystal size | 0.42 x 0.19 x 0.17 $mm^3$ |
| θ range for data collection | 1.98 to 23.53° |
| Index ranges | -12<=h<=12, -13<=k<=13, -23<=l<=23 |
| Reflns collected / unique | 34513 / 7588 [R(int) = 0.0305] |
| Reflns observed [F>4σ(F)] | 5903 |
| Absorption correction | Empirical |
| Max. and min. transmission | 0.9712 and 0.9309 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 7588 / 68 / 714 |
| Goodness-of-fit on $F^2$ | 1.143 |
| Final R indices [F>4σ(F)] | R1 = 0.0822, wR2 = 0.1781 |
| R indices (all data) | R1 = 0.1027, wR2 = 0.1846 |
| Extinction coefficient | 0.0193(12) |
| Largest diff. peak, hole | 0.292, -0.236 $eÅ^{-3}$ |
| Mean and maximum shift/error | 0.000 and 0.000 |

Table 2. Bond lengths [Å] and angles [°] for **218**

| | | | |
|---|---|---|---|
| O(1)-C(2) | 1.326(6) | C(12')-C(13') | 1.366(8) |
| O(1)-C(5) | 1.448(6) | C(12')-C(15') | 1.506(8) |
| C(2)-O(2) | 1.180(6) | C(13')-C(14') | 1.375(7) |
| C(2)-C(3) | 1.531(7) | C(16')-O(16') | 1.183(6) |
| C(3)-C(16) | 1.518(6) | C(16')-O(17') | 1.316(6) |
| C(3)-C(4) | 1.547(6) | O(17')-C(18') | 1.480(8) |
| C(3)-S(6) | 1.826(4) | O(17')-C(18B) | 1.487(15) |
| C(4)-C(5) | 1.510(6) | C(18')-C(19') | 1.472(12) |
| C(4)-C(27) | 1.534(6) | C(19')-C(20') | 1.324(13) |
| S(6)-O(7) | 1.423(4) | C(20')-C(21') | 1.488(10) |
| S(6)-O(8) | 1.434(4) | C(21')-C(22') | 1.3900 |
| S(6)-C(9) | 1.742(5) | C(21')-C(26') | 1.3900 |
| C(9)-C(10) | 1.370(6) | C(22')-C(23') | 1.3900 |
| C(9)-C(14) | 1.376(7) | C(23')-C(24') | 1.3900 |
| C(10)-C(11) | 1.371(7) | C(24')-C(25') | 1.3900 |
| C(11)-C(12) | 1.370(8) | C(25')-C(26') | 1.3900 |
| C(12)-C(13) | 1.361(7) | C(18B)-C(19B) | 1.464(18) |
| C(12)-C(15) | 1.508(8) | C(19B)-C(20B) | 1.348(17) |
| C(13)-C(14) | 1.384(7) | C(20B)-C(21B) | 1.474(15) |
| C(16)-O(16) | 1.183(6) | C(21B)-C(22B) | 1.3900 |
| C(16)-O(17) | 1.315(6) | C(21B)-C(26B) | 1.3900 |
| O(17)-C(18) | 1.480(7) | C(22B)-C(23B) | 1.3900 |
| O(17)-C(18A) | 1.484(15) | C(23B)-C(24B) | 1.3900 |
| C(18)-C(19) | 1.465(12) | C(24B)-C(25B) | 1.3900 |
| C(19)-C(20) | 1.316(14) | C(25B)-C(26B) | 1.3900 |
| C(20)-C(21) | 1.481(11) | C(27')-C(28') | 1.504(6) |
| C(21)-C(22) | 1.3900 | C(28')-C(33') | 1.370(7) |
| C(21)-C(26) | 1.3900 | C(28')-C(29') | 1.375(6) |
| C(22)-C(23) | 1.3900 | C(29')-C(30') | 1.381(7) |
| C(23)-C(24) | 1.3900 | C(30')-C(31') | 1.356(7) |
| C(24)-C(25) | 1.3900 | C(31')-C(32') | 1.375(7) |
| C(25)-C(26) | 1.3900 | C(31')-N(34') | 1.458(6) |
| C(18A)-C(19A) | 1.464(18) | C(32')-C(33') | 1.378(7) |
| C(19A)-C(20A) | 1.332(18) | N(34')-O(35') | 1.209(6) |
| C(20A)-C(21A) | 1.465(15) | N(34')-O(36') | 1.210(6) |
| C(21A)-C(22A) | 1.3900 | | |
| C(21A)-C(26A) | 1.3900 | C(2)-O(1)-C(5) | 111.8(4) |
| C(22A)-C(23A) | 1.3900 | O(2)-C(2)-O(1) | 122.9(5) |
| C(23A)-C(24A) | 1.3900 | O(2)-C(2)-C(3) | 127.0(5) |
| C(24A)-C(25A) | 1.3900 | O(1)-C(2)-C(3) | 110.1(4) |
| C(25A)-C(26A) | 1.3900 | C(16)-C(3)-C(2) | 111.4(4) |
| C(27)-C(28) | 1.492(6) | C(16)-C(3)-C(4) | 113.5(4) |
| C(28)-C(29) | 1.374(7) | C(2)-C(3)-C(4) | 103.3(4) |
| C(28)-C(33) | 1.388(7) | C(16)-C(3)-S(6) | 111.8(3) |
| C(29)-C(30) | 1.366(7) | C(2)-C(3)-S(6) | 109.0(3) |
| C(30)-C(31) | 1.369(7) | C(4)-C(3)-S(6) | 107.4(3) |
| C(31)-C(32) | 1.373(7) | C(5)-C(4)-C(27) | 113.5(4) |
| C(31)-N(34) | 1.480(7) | C(5)-C(4)-C(3) | 103.1(4) |
| C(32)-C(33) | 1.382(7) | C(27)-C(4)-C(3) | 116.1(4) |
| N(34)-O(35) | 1.194(7) | O(1)-C(5)-C(4) | 106.3(4) |
| N(34)-O(36) | 1.204(7) | O(7)-S(6)-O(8) | 119.0(3) |
| O(1')-C(2') | 1.326(6) | O(7)-S(6)-C(9) | 108.7(2) |
| O(1')-C(5') | 1.444(6) | O(8)-S(6)-C(9) | 108.8(2) |
| C(2')-O(2') | 1.195(6) | O(7)-S(6)-C(3) | 104.5(2) |
| C(2')-C(3') | 1.536(7) | O(8)-S(6)-C(3) | 105.5(2) |
| C(3')-C(16') | 1.514(6) | C(9)-S(6)-C(3) | 110.0(2) |
| C(3')-C(4') | 1.536(6) | C(10)-C(9)-C(14) | 119.5(5) |
| C(3')-S(6') | 1.838(4) | C(10)-C(9)-S(6) | 120.1(4) |
| C(4')-C(5') | 1.505(6) | C(14)-C(9)-S(6) | 120.1(4) |
| C(4')-C(27') | 1.524(6) | C(9)-C(10)-C(11) | 119.5(5) |
| S(6')-O(7') | 1.424(4) | C(12)-C(11)-C(10) | 121.9(5) |
| S(6')-O(8') | 1.426(4) | C(13)-C(12)-C(11) | 118.0(5) |
| S(6')-C(9') | 1.738(5) | C(13)-C(12)-C(15) | 120.7(6) |
| C(9')-C(14') | 1.369(7) | C(11)-C(12)-C(15) | 121.2(6) |
| C(9')-C(10') | 1.382(7) | C(12)-C(13)-C(14) | 121.4(5) |
| C(10')-C(11') | 1.367(8) | C(9)-C(14)-C(13) | 119.6(5) |
| C(11')-C(12') | 1.369(8) | O(16)-C(16)-O(17) | 126.3(5) |

| | | | |
|---|---|---|---|
| O(16)-C(16)-C(3) | 124.0(5) | O(7')-S(6')-O(8') | 118.7(3) |
| O(17)-C(16)-C(3) | 109.7(4) | O(7')-S(6')-C(9') | 109.0(2) |
| C(16)-O(17)-C(18) | 115.7(6) | O(8')-S(6')-C(9') | 108.9(2) |
| C(16)-O(17)-C(18A) | 115.0(13) | O(7')-S(6')-C(3') | 104.6(2) |
| C(18)-O(17)-C(18A) | 5.6(12) | O(8')-S(6')-C(3') | 105.4(2) |
| C(19)-C(18)-O(17) | 109.8(7) | C(9')-S(6')-C(3') | 110.1(2) |
| C(20)-C(19)-C(18) | 121.6(13) | C(14')-C(9')-C(10') | 119.6(5) |
| C(19)-C(20)-C(21) | 127.7(10) | C(14')-C(9')-S(6') | 120.2(4) |
| C(22)-C(21)-C(26) | 120.0 | C(10')-C(9')-S(6') | 119.8(4) |
| C(22)-C(21)-C(20) | 119.8(8) | C(11')-C(10')-C(9') | 119.2(5) |
| C(26)-C(21)-C(20) | 120.2(8) | C(10')-C(11')-C(12') | 122.2(5) |
| C(23)-C(22)-C(21) | 120.0 | C(13')-C(12')-C(11') | 117.8(5) |
| C(24)-C(23)-C(22) | 120.0 | C(13')-C(12')-C(15') | 121.3(6) |
| C(25)-C(24)-C(23) | 120.0 | C(11')-C(12')-C(15') | 120.8(6) |
| C(24)-C(25)-C(26) | 120.0 | C(12')-C(13')-C(14') | 121.6(5) |
| C(25)-C(26)-C(21) | 120.0 | C(9')-C(14')-C(13') | 119.7(5) |
| C(19A)-C(18A)-O(17) | 112.4(14) | O(16')-C(16')-O(17') | 126.0(5) |
| C(20A)-C(19A)-C(18A) | 121(2) | O(16')-C(16')-C(3') | 124.2(5) |
| C(19A)-C(20A)-C(21A) | 127.3(17) | O(17')-C(16')-C(3') | 109.8(4) |
| | | C(16')-O(17')-C(18') | 115.9(7) |
| C(22A)-C(21A)-C(26A) | 120.0 | C(16')-O(17')-C(18B) | 114.8(14) |
| C(22A)-C(21A)-C(20A) | 120.8(15) | C(18')-O(17')-C(18B) | 4.9(12) |
| C(26A)-C(21A)-C(20A) | 119.2(15) | C(19')-C(18')-O(17') | 109.2(8) |
| | | C(20')-C(19')-C(18') | 120.2(13) |
| | | C(19')-C(20')-C(21') | 127.2(10) |
| C(21A)-C(22A)-C(23A) | 120.0 | C(22')-C(21')-C(26') | 120.0 |
| C(24A)-C(23A)-C(22A) | 120.0 | C(22')-C(21')-C(20') | 119.4(8) |
| C(23A)-C(24A)-C(25A) | 120.0 | C(26')-C(21')-C(20') | 120.6(8) |
| C(24A)-C(25A)-C(26A) | 120.0 | C(21')-C(22')-C(23') | 120.0 |
| C(25A)-C(26A)-C(21A) | 120.0 | C(24')-C(23')-C(22') | 120.0 |
| C(28)-C(27)-C(4) | 111.0(4) | C(23')-C(24')-C(25') | 120.0 |
| C(29)-C(28)-C(33) | 117.7(5) | C(24')-C(25')-C(26') | 120.0 |
| C(29)-C(28)-C(27) | 122.0(5) | C(25')-C(26')-C(21') | 120.0 |
| C(33)-C(28)-C(27) | 120.3(5) | C(19B)-C(18B)-O(17') | 112.6(14) |
| C(30)-C(29)-C(28) | 122.4(5) | C(20B)-C(19B)-C(18B) | 123(2) |
| C(29)-C(30)-C(31) | 118.6(5) | C(19B)-C(20B)-C(21B) | 127.1(17) |
| C(30)-C(31)-C(32) | 121.4(5) | C(22B)-C(21B)-C(26B) | 120.0 |
| C(30)-C(31)-N(34) | 119.9(5) | C(22B)-C(21B)-C(20B) | 119.0(13) |
| C(32)-C(31)-N(34) | 118.7(5) | C(26B)-C(21B)-C(20B) | 120.9(13) |
| C(31)-C(32)-C(33) | 118.8(5) | C(23B)-C(22B)-C(21B) | 120.0 |
| C(32)-C(33)-C(28) | 121.0(5) | C(24B)-C(23B)-C(22B) | 120.0 |
| O(35)-N(34)-O(36) | 124.3(6) | C(25B)-C(24B)-C(23B) | 120.0 |
| O(35)-N(34)-C(31) | 118.0(6) | C(24B)-C(25B)-C(26B) | 120.0 |
| O(36)-N(34)-C(31) | 117.6(6) | C(25B)-C(26B)-C(21B) | 120.0 |
| C(2')-O(1')-C(5') | 111.4(4) | C(28')-C(27')-C(4') | 111.2(4) |
| O(2')-C(2')-O(1') | 123.3(5) | C(33')-C(28')-C(29') | 118.6(4) |
| O(2')-C(2')-C(3') | 127.0(5) | C(33')-C(28')-C(27') | 120.4(4) |
| O(1')-C(2')-C(3') | 109.8(4) | C(29')-C(28')-C(27') | 121.0(4) |
| C(16')-C(3')-C(4') | 114.4(4) | C(28')-C(29')-C(30') | 121.3(5) |
| C(16')-C(3')-C(2') | 110.9(4) | C(31')-C(30')-C(29') | 118.8(4) |
| C(4')-C(3')-C(2') | 103.6(4) | C(30')-C(31')-C(32') | 121.4(5) |
| C(16')-C(3')-S(6') | 111.3(3) | C(30')-C(31')-N(34') | 120.0(5) |
| C(4')-C(3')-S(6') | 107.7(3) | C(32')-C(31')-N(34') | 118.7(5) |
| C(2')-C(3')-S(6') | 108.6(3) | C(31')-C(32')-C(33') | 119.0(5) |
| C(5')-C(4')-C(27') | 114.3(4) | C(28')-C(33')-C(32') | 120.9(5) |
| C(5')-C(4')-C(3') | 103.0(4) | O(35')-N(34')-O(36') | 122.4(5) |
| C(27')-C(4')-C(3') | 116.1(4) | O(35')-N(34')-C(31') | 118.7(5) |
| O(1')-C(5')-C(4') | 106.7(4) | O(36')-N(34')-C(31') | 118.7(5) |

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