Imperial College London

Total Synthesis of the Macroline-related Alkaloid (±)-Alstonerine

Richard Pett

June 2013

Thorpe Laboratory 860, Department of Chemistry, Imperial College London, London, SW7 2AZ, United Kingdom

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Imperial College London.

Abstract

This thesis examines the total synthesis of the macroline-related indole alkaloid alstonerine and related compounds. It is divided into three sections:

The first section provides a review of the total synthesis efforts reported by Cook, Martin, Kuethe, and Kwon, as well previous work within the Craig group.

The second section discusses the results of our investigations. The optimisation of the synthesis of key intermediate α,β-unsaturated lactam alcohol *via* directed-aziridine ring-opening is presented in detail. Our progress towards the synthesis of macroline-related alkaloids macroline, alstolactone, anhydromacrosalhine-methine and alstonerinal, as well as their N_4-tosyl derivatives, from the key intermediate is discussed. The findings from these studies are presented *en route* to the total synthesis of alstonerine.

The third section contains experimental procedures and characterisation data for compounds synthesised.

Table of contents

Copyright Declaration

Originality Declaration

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

Richard Pett

Acknowledgments

I would firstly like to thank Professor Donald Craig for giving me the opportunity to undertake my postgraduate research under his guidance. It has been a genuine pleasure to work for such an enthusiastic and knowledgeable supervisor, whose door was always open, and whose company was always fantastic when enjoying an occaisonal beer with us! I should also use this opportunity to thank Doctor Chris Braddock, who was an exceptional second mentor and provided useful feedback throughout my Ph.D. Thanks too, to Doctor Fred Goldberg, especially for his efforts in organising my CASE placement and providing guidance whilst at AZ, but also for taking Don and myself out for the occasional lunch!

I would like to thank my family for their continued love and support. I hope that they are aware that I would have been completely lost without the three of them over the duration of my studies, especially whilst in transit and when needing to release a little bit of chemistry-related anger over the phone! I consider myself very lucky to have such an amazing Mum, Dad and Dog (Bruno), I love you all very much. I suppose at this point I should mention my *wonderful* sister too, she has always been there for me and is also a really great friend.

Moving on to the DC group, I should say that I have enjoyed the company of every DC group member that I have ever met. Those that I have had the pleasure of sharing the Thorpe lab with will always be fondly remembered, particularly for their appalling tastes in music, excellent ability to orgainse fun and, in one instance, for a love of a particular glass instrument that came to a horrible death whilst in my care. It was a pleasure introducing you to the music that 'the kids' are listening to these days, and I will miss listening to *Westlife: The Greatest Hits* whilst working late! This CD has now been passed down to Honey Boo Boo Tobes, to whom I hope it will bring hope in moments of despair as it has done for me. From the moment I arrived in the DC group, Niels, Simon and the three-headed monster were brilliant company, I believe that I had visited the Holland Club with Niels and met Coco long before I had seen the NMR machines. Simon was deliciously inappropriate from day one, and continues to produce moments of filthy genius to this day. Jenny Lachs is certainly a lucky lady! Having already mentioned the three heads collectively, I feel that I should thank each one of them individually for being such great companions throughout our days in the DC group. In no particular order, here goes: I quickly learnt that apart from at concerts and, on rare occasions, Champions League matches,

that Claire is actually is great fun!! Although not my favourite Doyle, I was always glad to see her when forced into taking tea breaks. Moving on to Shu, as I am currently making a wage from being her whipping boy I will keep it positive. I feel that Shu has shown all of the attributes that a chemist should possess, the ability to consume large quanitites of meat, coffee-proof footwear, a taste for bitter lemon, a brown pooh-car that is usually in desperate need of a wash and possession of an incredible JoJo 'Hiiiyaaaa' impersonation. I sincerely thank you for being a great friend throughout our days in the Thorpe lab. This brings us on to the final head. I would like to thank her for adopting the 'suns out buns out' policy whenever possible; many a DC group sailor was lost at sea to that blue top! She was also responsible for such things as the DC group bondage calendar, the muurrdumps wiigstouunn, cheeseman and introducing me to drum n' bass Friday! As with the other two, I am genuinely grateful to you for looking after me during my Ph.D, it would not have been the same without you!

Now to the young'uns, namely Madamme JoJo, HBBT, Lee 'Sm***y D**K Walsh, Alex and Lewis. Joe, as well as being a fashion and chemistry icon to so many, you also managed to find time to introduce me to pie balms and other sayings/traditions that the southern softies within the group could not handle! My thanks to you for being a fabulous laugh, chemist and friend, ever since I informed you about how great the lab was innit during your open day. I am glad that I leave you in the company of the talented HBBT. Any man that is willing to rip a good pair of Chino's to squat a colleague is a winner in my book, even if that success eluded you on the flash tennis court!! Lee should be congratulated on his efforts in this field, although he always better at flash pennas than tennis. I will always remember his boring stories, lad nights out, odours appendage. Thank you to the remaing PP group members for adding to the fond memories of the lab for me, including Professor Phil Parsons, who was especially good fun after a viva lunch.

Finally I would like to thank those that have been unfortunate enough to cohabit with me during the past few years. Thank you to Jack and James for being great housemates and teaching me about purchase and how not to deal with pigeons! Thanks to Sheena and Dave for offering me shelter for the jip storms, and finally to Becca, my rock, my world….. Ha! In all seriousness I would probably still love you even if you stopped bringing home the bacon and putting a roof over my head, although I wouldn't risk it.

List of abbreviations

Ac	acetyl
app.	apparent
Ar	aryl
aq.	aqueous
BBN	9-borabicyclo[3.3.1]nonane
br.	broad
bp	boiling point
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzyl
Cbz	benzyloxycarbonyl
cat.	catalytic
CI	chemical ionisation
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
EDG	electron donating group
ee	enantiomeric excess
EI	electrical ionisation
equiv.	equivalents

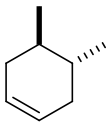
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
h	hour(s)
hex	hexyl
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyl disilazide
HOMO	highest occupied molecular orbital
^{i}	*iso*-
IR	infra-red
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
^{n}	*neo*-
Np	naphthalene
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Ns	2- or 4-nitrobenzenesulfonyl
o-	*ortho*-
p-	*para*-
Ph	phenyl
PTAB	phenyltrimethylammonium tribromide
Pr	propyl
PrOH	propanol
q	quartet
R_f	retention factor

rt	room temperature
s	singlet
^{s}	*sec*-
t	triplet
tt	triplet of triplets
^{t}	*tert*-
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMA	trimethylaluminium
Tol	tolyl
Ts	*para*-toluenesulfonyl
tt	triplet of triplets
υ_{max}	infrared absorption maximum
wt	weight

Stereochemical notation

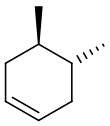
Throughout this report, the Maehr convention of indicating relative and absolute stereochemistry has been adopted.[1] Hence, solid and broken lines are used to denote racemates, whilst solid and broken wedges are used to denote absolute configuration. Furthermore, the narrowing of both solid and broken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

Illustration of the Maehr convention



Racemate

Relative stereochemistry



Single enantiomer

Absolute stereochemistry

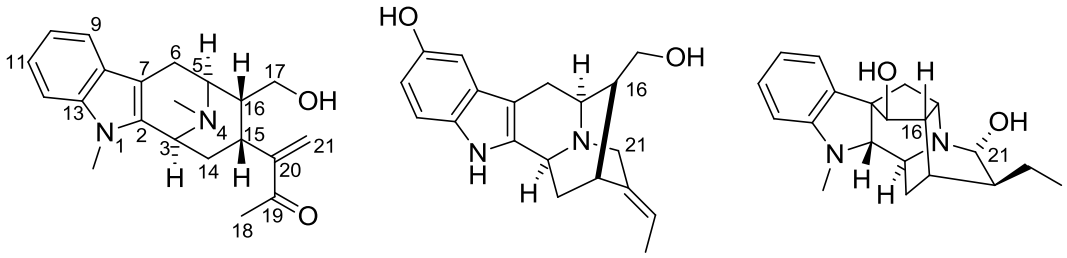
Chapter 1

Introduction

1.1 Introduction to macroline, sarpagine and ajmaline-related indole alkaloids

A huge variety of indole alkaloids are known,[2] and to date there is still a great deal of interest in their synthesis.[3] Although synthetic approaches towards alstonerine are the main focus of this report, frequent reference will be made to the synthesis and structures of other members of this class of alkaloid, which can be categorised into three families, those related to macroline **1**, sarpagine **2** or ajmaline **3** (Figure **1**).

Figure 1. Skeletal numbering of parent alkaloids according to LeMen and Taylor.



1 macroline **2** sarpagine **3** ajmaline

The biogenetic skeletal numbering proposed by LeMen and Taylor[4] is used throughout this report (Figure **1**). The most significant structural similarity shared by all three families in this class of alkaloids is the indole-annulated azabicyclo[3.3.1]nonane structure.

Macroline-related alkaloids are defined as those having the same skeletal connectivity as macroline **1**. They crucially do not possess an N_4–C21 linkage.

Sarpagine-related alkaloids are defined as those having the same skeletal connectivity as sarpagine **2**, specifically with an N_4–C21 linkage and the C16-(*R*) configuration shown.

Ajmaline-related alkaloids are defined as those having the same skeletal connectivity as ajmaline **3**, also with an N_4–C21 linkage and with C16-(*S*) configuration epimeric to that of sarpagine as shown.

Alkaloids that contain substituents at the C16 position are known, as are spirocyclic alkaloids that contain C7–C17 bonds and thus saturated C2–C7 indole bonds. These compounds may contain both N_1- and N_4-substitution, and possess indole ring oxygenation to give spirocyclic oxindole alkaloids, which can be considered an important class of natural products in their own

right.[5,6] Dimeric alkaloids that contain at least one macroline, sarpagine or ajamaline subunit are commonly referred to as bis(indole) alkaloids.

Whereas ajmaline and sarpagine have both been isolated from *Rauvolfia serpentina*,[7] macroline itself has never been isolated from natural sources. However it is believed that macroline is a likely biosynthetic precursor of various macroline- and sarpagine-related alkaloids.

The field of macroline, sarpagine and ajmaline-related alkaloids was reviewed extensively by Cook in 1994[8] and 1995[9], by Lounasmaa in 1999[10] and 2001[11], and by Lewis in 2006[12]. These provide synthetic endeavours relevant to the field in addition to an introduction to the species from which these alkaloids are isolated (mostly *Rauvolfia* and *Alstonia* species).

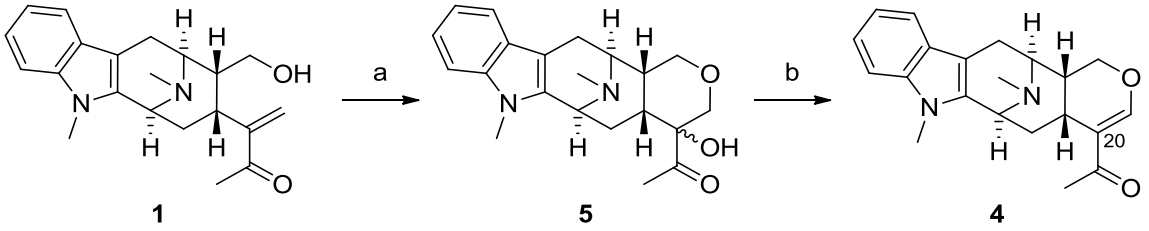
The focus of this report will be the macroline-related indole alkaloid alstonerine **4**, whose previous syntheses are herein discussed.

1.1.1 Alstonerine

Alstonerine **4** is a macroline-related indole alkaloid which has shown cytotoxic activity against human lung cancer cell lines,[13] and can be isolated from numerous species of Malayan *Alstonia*, including *Alstonia mycrophylla*, *Alstonia muelleriana* and *Alstonia angustifolia*. It was first isolated in 1959 from the bark of *Alstonia mycrophylla* by Elderfield and Gilman.[14]

The absolute configuration of (–)-alstonerine **4** was confirmed by the biomimetic synthesis of LeQuesne *et al.* in 1969.[15] Here, a sample of macroline was converted into alstonerine using an epoxidation, Michael reaction, and dehydration. As these reactions had ample biochemical precedent, the synthesis was regarded as biomimetic and, since the absolute configuration of macroline was known (from that of villalstonine), the absolute configuration of alstonerine **4** was inferred.

Scheme 1. Biomimetic synthesis of alstonerine **4** from macroline **5**.



1 **5** **4**

a) ^{t}BuOOH (excess) in MeOH, benzene, then Triton B; b) Freshly prepared P_2O_5, 24 h.

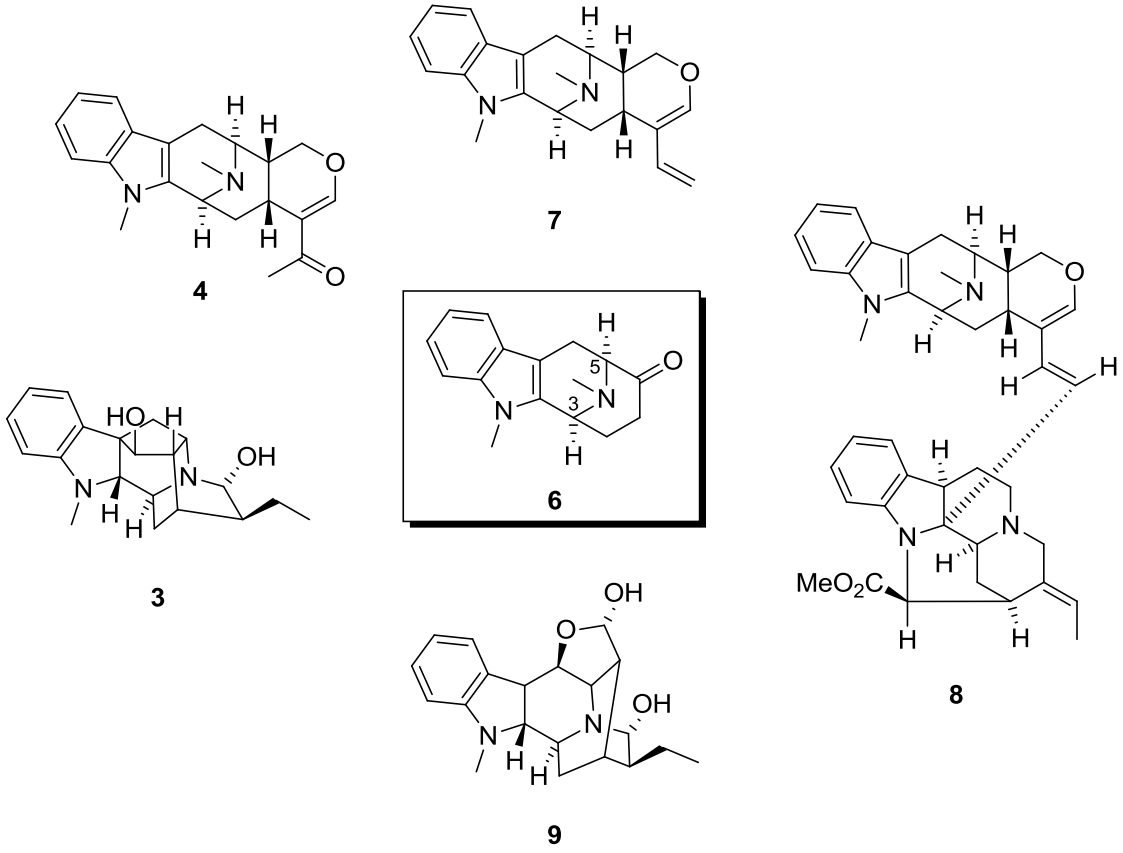
Alstonerine has since been the subject of significant total synthesis effort, most notably by Cook and co-workers,[3] with significant contributions also from the groups of Martin[3] and others.[3] These synthetic approaches, as well as those previously attempted within the Craig group, are discussed in this section.

The aim of this introduction is to highlight the methods used previously to construct both the azabicyclo[3.3.1]nonane core and the adjoining C20 acylated glycal E-ring, so that comparisons can be drawn to our synthesis, whose details are reported in chapter 2.

1.2 Cook's approach to (–)-alstonerine and related compounds

Central to Cook's work in this area of alkaloid synthesis was tetracyclic ketone intermediate **6** (Figure **2**), which was used to synthesise numerous macroline/sarpagine/ajmaline-related alkaloids, including (–)-alstonerine **4**,[16] (–)-anhydromacrosalhine-methine **7**,[17] (–)-macrocarpamine **8**,[18] (–)-ajamaline **3**,[19,20,21] and alkaloid G **9**.[21] Although the synthesis of tetracyclic ketone **6** has been reviewed previously,[3,9] we will discuss why its synthesis allowed Cook to access so many members of this natural product family.

Figure 2. Selection of alkaloids synthesised from Cook's common intermediate **6**.

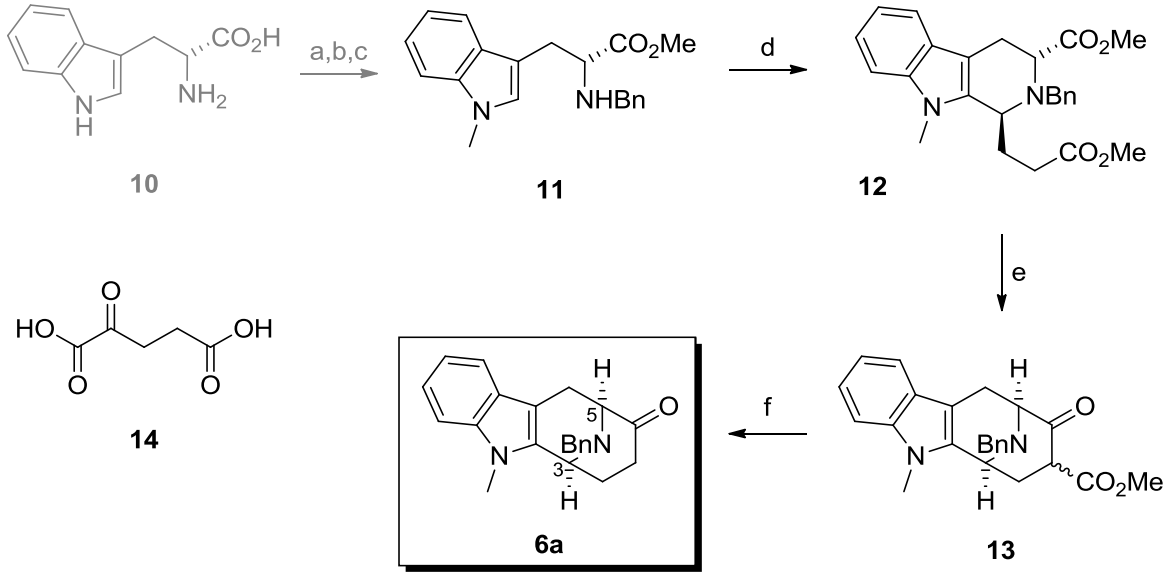


1.2.1 The tetracyclic ketone intermediate

For the synthesis of tetracyclic ketone **6** from D-tryptophan **10**, Cook and co-workers used sequential Pictet–Spengler[22] and Dieckmann cyclisations to build the C- and D-rings in the 4th and 5th steps respectively.[16] As the first three reactions of the synthesis were protection steps, the azabicyclo[3.3.1]nonane motif was established at the very beginning of the synthesis. The

synthesis of tetracyclic ketone **6a** is outlined below (Scheme **2**, below). It is worth noting that intermediate **6** includes the same (*S*)-configuration at the C5 position that is found in natural L-tryptophan. However it was synthesised using the unnatural amino acid D-tryptophan, which contains the (*R*)-configuration at this position. D-Tryptophan was used as a variety of bulky aldehydes had previously entered into stereoselective Pictet–Spengler cyclisations with N_4-benzyltryptophan methyl esters, to give only the corresponding *trans*-1,3-disubstituted-1,2,3,4-β-carbolines.[23] Having noted this preference, Cook purposely used the (*R*)-configured Pictet–Spengler substrate **11** to install the correct C3 stereochemistry in tetrahydro-β-carboline methyl esters **12**.

Scheme 2. Key intermediate in Cook's approaches to macroline-related indole alkaloids.

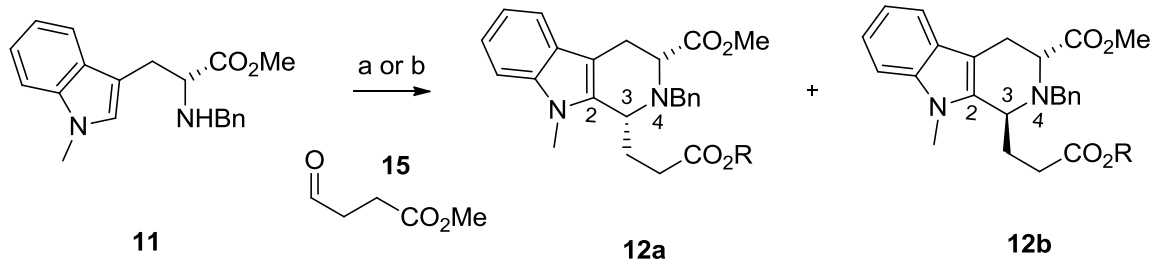


a) $Na/NH_{3(l)}$, MeI; b) HCl, MeOH, 80% over two steps; c) PhCHO, MeOH, then $NaBH_4$, –5°C, 88%; d) **14**, benzene/dioxane, Δ, then HCl, MeOH reflux, 80%; e) NaH, MeOH, toluene, reflux, 92%; f) aqueous HCl, AcOH, reflux, 91%.

The first stage of Cook's synthesis of the tetracyclic ketone intermediate was to form the C-ring and install the correct C3 stereochemistry. D-Tryptophan derivative **11** was heated with 2-ketoglutaric acid **14**, which gave a disappointing diastereomeric ratio of *cis*- and *trans*-tetrahydro-β-carboline monoacids (42:58 **12a**:**12b**, **R** = **H**, Scheme **3**, below).[24,25] An enhanced diastereomeric ratio in favour of *trans*-tetrahydro-β-carboline methyl esters **12** (28:72 **12a**:**12b**, **R** = **Me**, Scheme **3**) was achieved using methyl 3-formylpropionate **15**.[26] This

also removed a trivial esterification step from the synthesis; however the *trans*-selectivity remained insufficient for large scale synthesis.

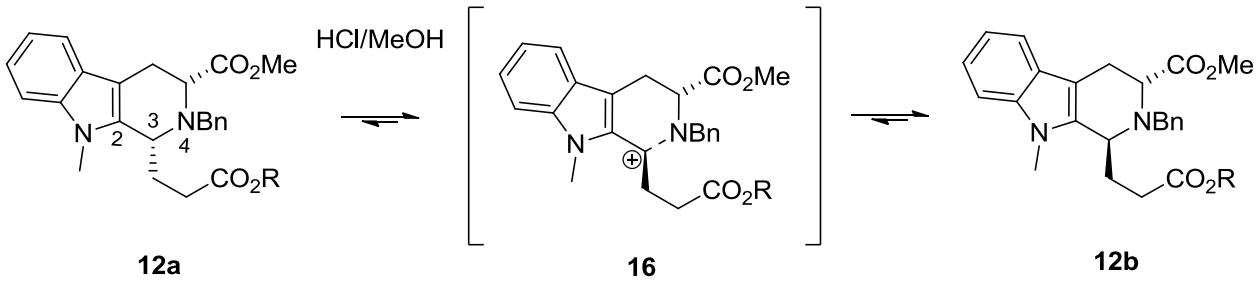
Scheme 3. Cook's strategy level C-ring forming Pictet–Spengler.



a) As before, 2-ketoglutaric acid **14**, benzene, 80%; b) methyl-3-formylpropionate **15**, benzene.

A large-scale enantiospecific route to the desired *trans*-diastereomer **12b** was eventually achieved using a post-Pictet–Spengler acid-mediated C3 isomerisation.[3] This allowed the *cis*-diastereomer of either monoacid **12a** (**R** = **H**, Scheme **3**), or diester (**R** = **Me**, Scheme **3**) to be epimerised into the more stable *trans*-isomer **12b**. This was achieved by heating **12a** in methanolic HCl, which caused fragmentation of the N4–C3 bond and gave stabilised 'allylic' C3 carbocation **16** that could undergo rotation and recyclisation. This allowed unfavourable (1,3)-diaxial interactions to be minimised, as shown below (Figure **3**).

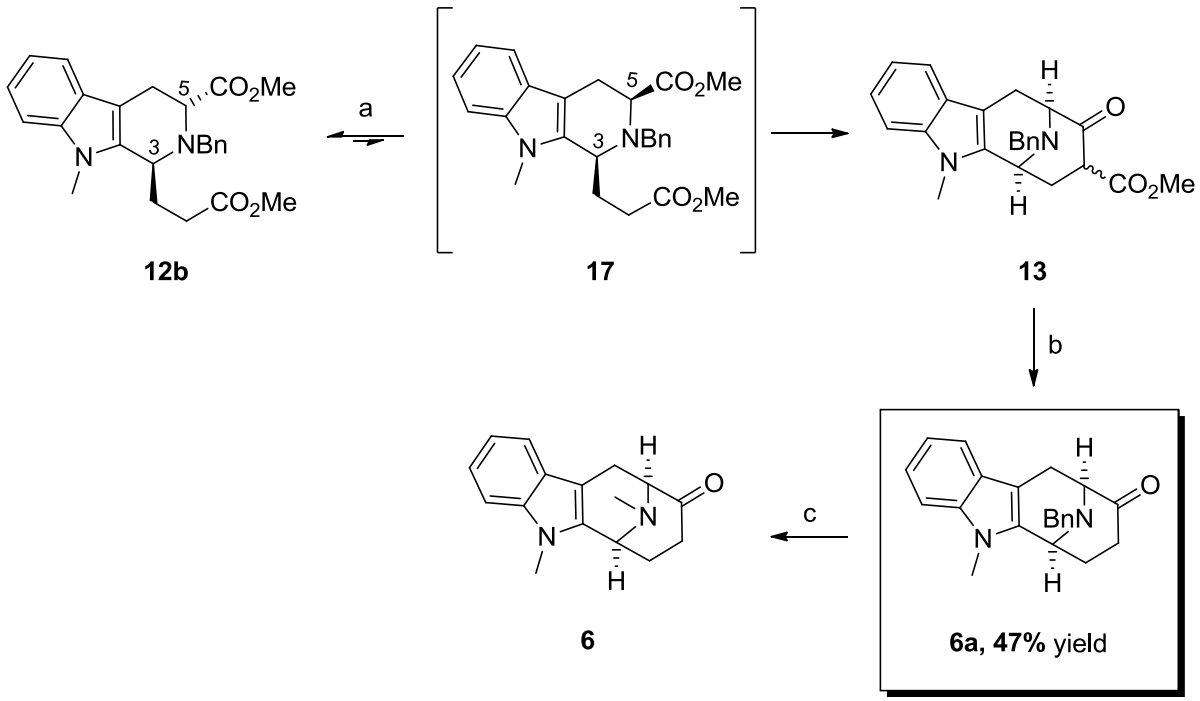
Figure 3. Acid-mediated epimerisation of C3,C5-*cis*-tetrahydro-β-carboline **12a**.



Having devised an efficient route to intermediate **12b** from D-tryptophan, it remained to invert the C5 stereochemistry in order to attain the *cis*-1,3-disubstituted carboline methyl ester **17** (Scheme **4**, below), that was required for the Dieckmann cyclisation to complete the azabicyclo[3.3.1]nonane motif. The C5 epimerisation and Dieckmann cyclisation steps were achieved in a one-pot process by treating *trans*-**12b** with sodium methoxide.[16] This effected reversible formation of the less favourable *cis*-diastereomer **17**, whose *cis*-configuration allowed an irreversible Dieckmann cyclisation to occur. This forced the equilibrium to the right and

favoured formation of the desired tetracyclic β-keto esters **13**. The synthesis was completed by acid-mediated decarboxylation, which yielded Cook's ubiquitous intermediate, tetracyclic ketone **6a** in 47% over seven steps.

Scheme 4. C5 epimerisation and Dieckmann cyclisation of **12b**.



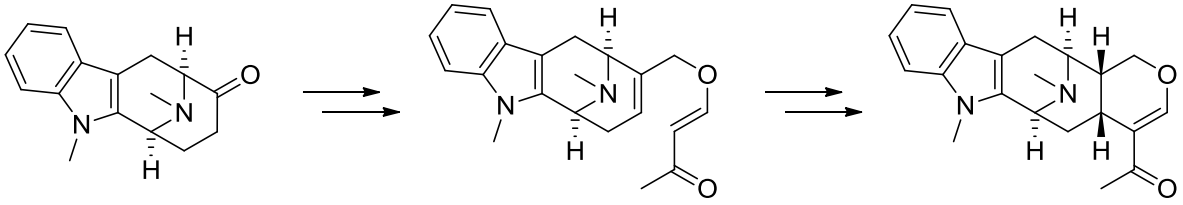
a) NaOMe, toluene, reflux, 92%; b) aqueous HCl, AcOH, reflux, 91%; c) MeOTf, then H_2/Pd/C, 80% over two steps.

1.2.2 Cook's first approach to (–)-alstonerine

In Cook's first approach, (–)-alstonerine was synthesised from tetracyclic ketone **6** using a 10-step sequence that utilised the C16 ketone functionality in **6** as a reactive handle to access the E-ring.[16] Excluding the required functional group interconversion (N_4-deprotection and methylation), the azabicyclic core motif remained untouched from its synthesis in steps 4 and 5.

The preinstalled azabicyclo[3.3.1]nonane structure of the tetracyclic ketone intermediate **6** was used to direct a stereospecific Claisen rearrangement and hydroboration, which generated the required C15 and C16 stereochemistry respectively.

Figure 4. Key intermediates in Cook's first synthesis of the alstonerine E-ring.



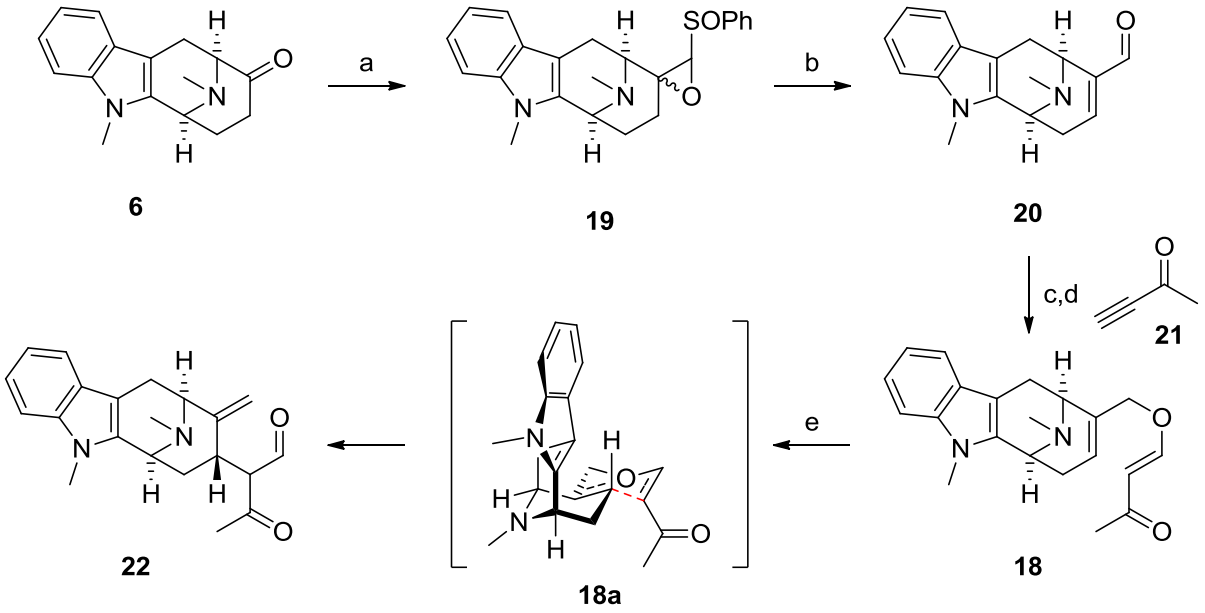
The synthesis of the Claisen rearrangement substrate is outlined below (Scheme **5**, Page **20**). N_4-Benzyl protected tetracyclic ketone **6a** was first converted into the N_4-methyl derivative **6** using methyl triflate and palladium-catalysed debenzylation conditions.[28] At this stage, the C16 ketone functional group was homologated to α,β-unsaturated aldehyde **20** and reduced to the corresponding allylic alcohol using LiAlH.

The homologation was achieved by reacting **6** with the anion of α-chloromethyl phenyl sulfoxide, generating a chlorohydrin intermediate that gave spirooxirane phenyl sulfoxide **19** upon base-induced cyclisation. It was the spiroepoxide **19** that was homologated using lithium perchlorate and tri-*n*-butylphosphine oxide. The synthesis of the Claisen substrate was completed by alkylation with butyn-3-one **21**, which gave enone **18** in 60% yield over four steps from tetracyclic ketone.

For the Claisen rearrangement, enone **18** was converted into the desired β-keto aldehyde **22** with the natural C15 stereochemistry, by heating **18** in benzene in a sealed tube at 145°C.[27] The stereoselectivity of the rearrangement was rationalised by presuming a chair-like transition state

18a, with attack occurring from the α-face of the azabicyclo[3.3.l]nonane system (Scheme **5**, below).

Scheme 5. Elaboration of tetracyclic ketone by Claisen rearrangement



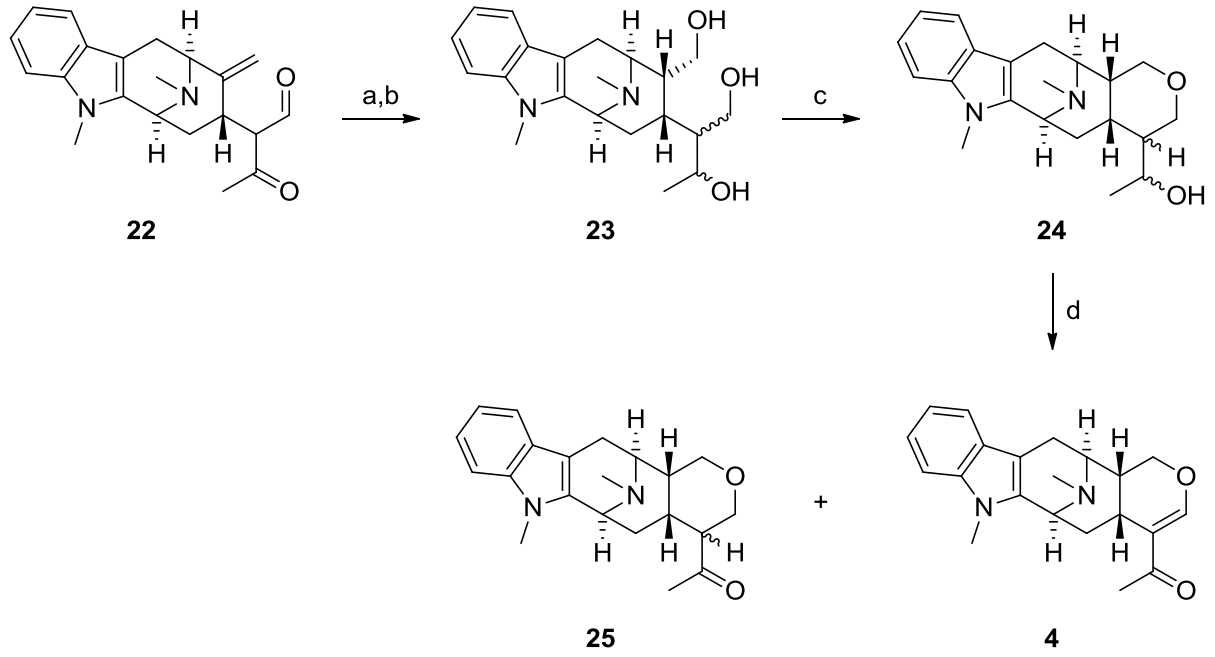
a) $PhS(O)CH_2Cl$, LDA, THF then KOH, 86%; b) $LiClO_4$, $Bu_3P(O)$, toluene, reflux, 84%; c) LiAlH, Et_2O, −20°C, 90%; d) Et_3N, **21**, dioxane, dark, 90%; e) benzene, 145°C, sealed tube, 65%.

Following the success of the Claisen rearrangement, a variety of approaches at completing the E-ring synthesis by chemoselective reduction proved difficult.[28] Numerous attempts at protecting the two carbonyl groups as acetal derivatives failed, as did attempted chemoselective reductions of the β-keto aldehyde to the corresponding β-hydroxy ketone using various borane reagents. Oxidation of the aldehyde functionality to the carboxyl equivalent also proved futile. Following numerous failed attempts at protecting or chemoselectively oxidising or reducing the β-dicarbonyl functionality, it was decided instead to attempt a hydroboration–oxidation of the exomethylene group to yield a triol intermediate (Scheme **6**, below).

Eventually, β-dicarbonyl **22** was reduced to triol **23** in two steps, by firstly reducing the β-dicarbonyl using sodium borohydride, followed by hydroboration–oxidation of the exocyclic methylene function with 9-BBN, H_2O_2/NaOH which was presumed to have occurred from the top face of the alkene.[28]

With triol **23** in hand, the E-ring skeleton was achieved by a one-pot tosylation and base-induced cyclisation process that gave tetrahydropyrans **24**. These were converted into an approximately 1:1 mixture of dihydroalstonerine **25** and alstonerine **4**, *via* a modified Swern oxidation. The poor selectivity of this reaction could be improved to a certain extent, by reducing the ketone functionality of dihydroalstonerine **25**, and resubmitting the resulting tetrahydropyrans **24** with the C19 alcohol to the modified Swern reaction. This allowed for an increase of up to 51% and gave alstonerine in an overall yield of 4.2% over 18 steps from D-tryptophan. Of these steps, ten had been required to synthesise the E-ring from N_4-benzyl tetracyclic ketone **6a**, in 6.2% yield.[16]

Scheme 6. Conclusion of Cook's first E-ring synthesis *via* selective hydroboration and oxidation level manipulation.



a) $NaBH_4$, EtOH, 80%; b) 9-BBN, THF, rt, 20 h then NaOH, H_2O_2, 40°C, 2 h, 85%; c) TsCl, pyridine then Et_3N, rt, 60%; d) $COCl_2$, DMSO, CH_2Cl_2, –78°C→–10°C, then Et_3N, 51% after recycling **SM**.

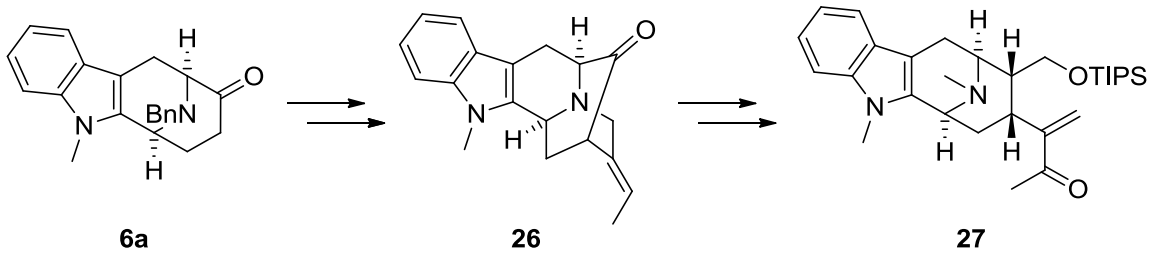
From Cook's first synthesis, it can be seen that whilst the azabicyclic[3.3.1]nonane core was readily accessed using successive Pictet–Spengler and Dieckmann cyclisations, the adjoining C20 acylated glycal E-ring was a challenging motif to synthesise, with multiple oxidation level adjustments required to complete its synthesis *via* Cook's Claisen approach.

1.2.3 Cook's second approach

In 2005, Cook published a second approach to alstonerine that again used tetracyclic ketone **6a** as an advanced intermediate.[29] However the construction of the E-ring was achieved by a completely novel approach that also provided a route to macroline, and allowed entry to sarpagine-related alkaloids.

Azabicyclic tetracyclic ketone **6a** was converted into alstonerine *via* naturally occurring sarpagine related alkaloid N_1-methylvellosimine **26**, which was then converted into the Tsuji–Wacker substrate **27** using a six-step sequence (Scheme **7**, below). This approach used a novel modification of Tsuji–Wacker oxidation conditions to convert the α-substituted α,β-unsaturated ketone **27** into alstonerine. The overall synthesis again required a total of 18 steps, and provided the natural product in an improved 10% overall yield from D-tryptophan.

Figure 5. Key intermediates in Cook's second approach.



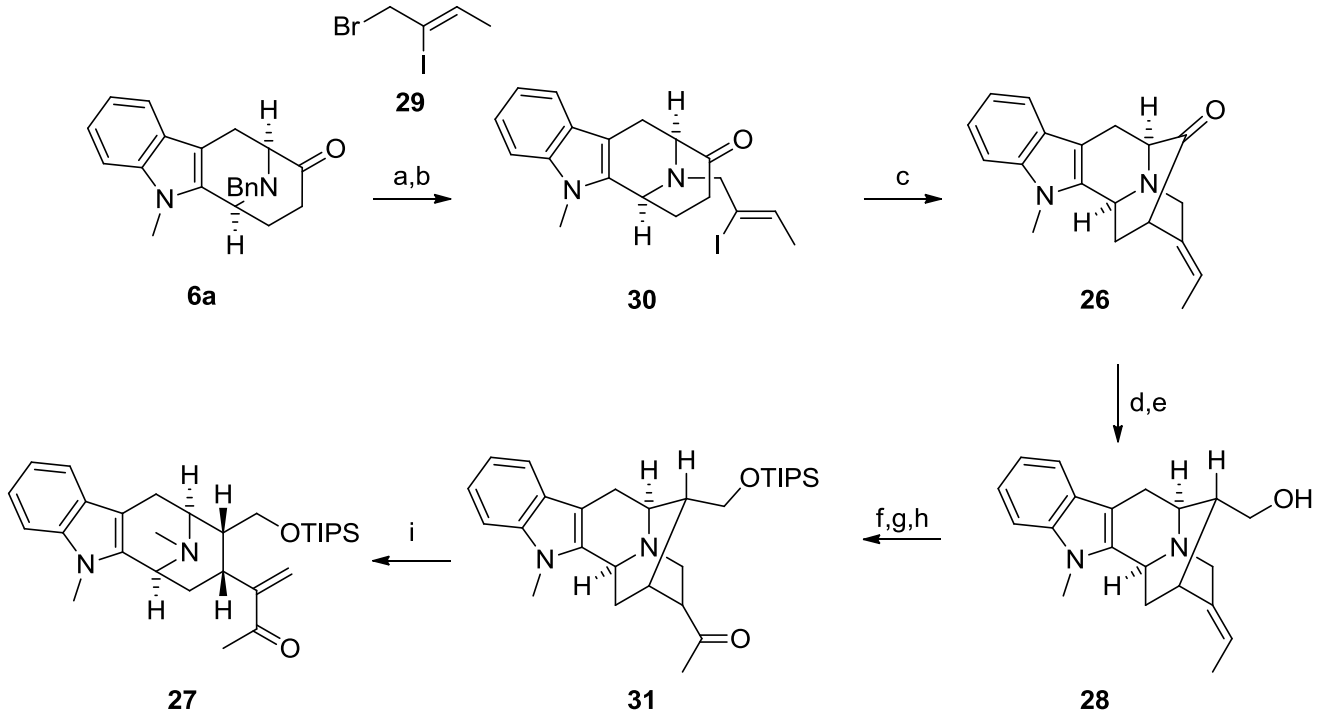
Cook's second approach again used a 10-step sequence to convert tetracyclic ketone **6a** into the penultimate intermediate, which in this case was the Tsuji–Wacker substrate **27**. Advantageous to this synthesis was the selectivity of the final oxidation step. Whereas the final step in Cook's first approach produced the natural product **4** and related dihydroalstonerine **25** in an approximately 1:1 ratio, the Tsuji–Wacker reaction gave alstonerine as the only product in 60% yield.[29,30]

The first stage of Cook's second E-ring synthesis was to convert tetracyclic ketone into affinisine **28** *via* N_1-methylvellosimine **26**, both of which have the same skeletal connectivity as sarpagine **2**, including the N_4–C21 linkage and (*R*)-configuration at the C16 position. This was achieved using the procedure outlined by Liu in 2002 (Scheme **7**, below).[31,32]

Tetracyclic ketone **6a** was converted into Heck substrate **30** using the previously successful catalytic hydrogenation debenzylation, followed by treatment with (*Z*)-1-bromo-2-iodo-2-butene **29**. This gave alkylated ketone **30** in 85% yield over two steps.[33] **30** was converted into N_1-methylvellosimine **26**, by palladium-catalysed α-vinylation using modified Buchwald–Hartwig arylation conditions as reported by Muratake and Natsume.[34] This enolate-driven cyclisation took place stereospecifically and afforded N_4–C21 fused **26** in 82% yield.[33] Having established the sarpagine skeleton, N_1-methylvellosimine **26** was converted into affinisine **28** using Wittig conditions followed by borohydride aldehyde reduction (Scheme **7**).[35]

Following *O*-silyl protection, the ethylidene moiety in affinisine **28** was converted into ketone **31** by hydroboration–oxidation and then Dess–Martin oxidation. **31** was converted into *O*-silyl protected macroline by N_4-methylation and elimination. This gave the Tsuji–Wacker substrate **27** in an overall yield of 21% from tetracyclic ketone **6a**.

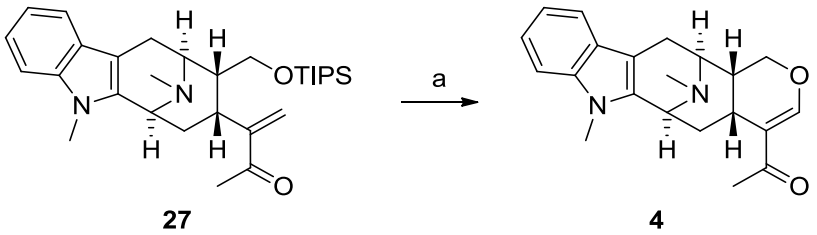
Scheme 7. Cook's second approach to alstonerine.



a) H_2/Pd/C, then HCl, EtOH; b) *Z*-1-bromo-2-iodo-2-butene **29**, K_2CO_3, reflux, 85% over two steps; c) $Pd(dba)_2$ (2 mol%), DPEphos (2.2 equiv.), ^tBuONa, THF, 70°C, 82%; d) $MeOCH_2Ph_3PCl$, KO^tBu, benzene, rt, 24 h; e) HCl, THF, 55°C, 5 h, 65% over two steps; $NaBH_4$, EtOH, 0°C; f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; g) BH_3/Me_2S (9.0 equiv.), THF, rt, 3 h, then $NaOH/H_2O_2$, rt, 2 h; HOAc, THF, reflux; h) Dess–Martin periodinane, CH_2Cl_2, 0°C, 63% over three steps; i) MeI, THF, then ^tBuOK, EtOH, THF, reflux, 90%.

The synthesis was completed using a novel modification of the Tsuji–Wacker oxidation to convert α-substituted α,β-unsaturated ketone **27** into (–)-alstonerine. Importantly, this one-pot cascade reaction gave alstonerine as the only product, in 60% yield (Scheme **8**).

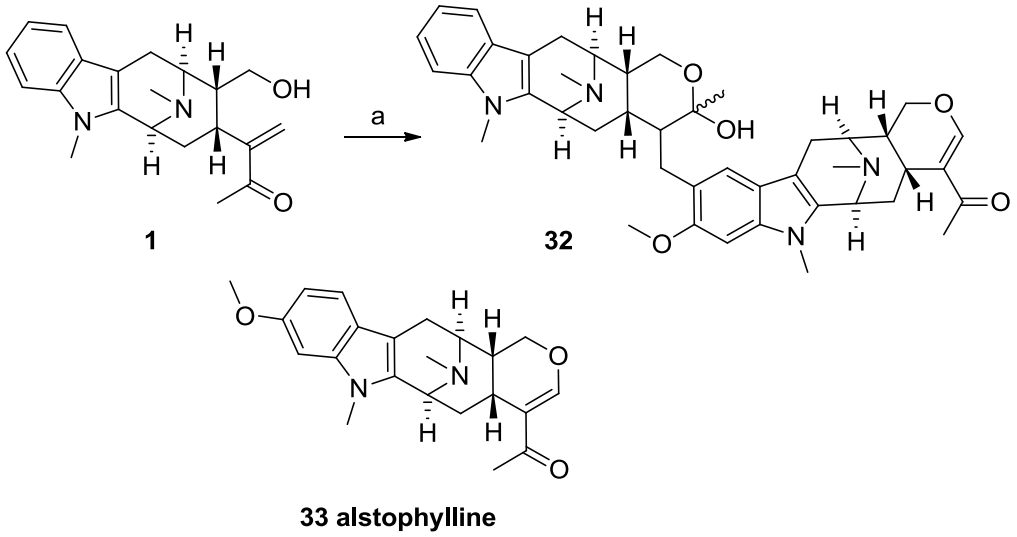
Scheme 8. Oxidation of *O*-protected macroline to (–)-alstonerine **4**.



a) Na_2PdCl_4, (40 mol%), ^tBuOOH (1.1 equiv.), HOAc:H_2O;^tBuOH (1:3:3), 80°C, 60%.

Cook's second approach to alstonerine led to an improved overall yield of 10% from D-tryptophan. Although the E-ring was synthesised in the same number of steps as the first approach, Cook's second approach provided access to the sarpagine related alkaloids as well as using a more versatile late stage intermediate **27**, which could be converted into both macroline and alstonerine. This in turn provided access into the bis(indole) alkaloids, as highlighted by the improved synthesis of macralstonine **32** (Scheme **9**).[36]

Scheme 9. Synthesis of bis(indole) alkaloid macralstonine **32**.

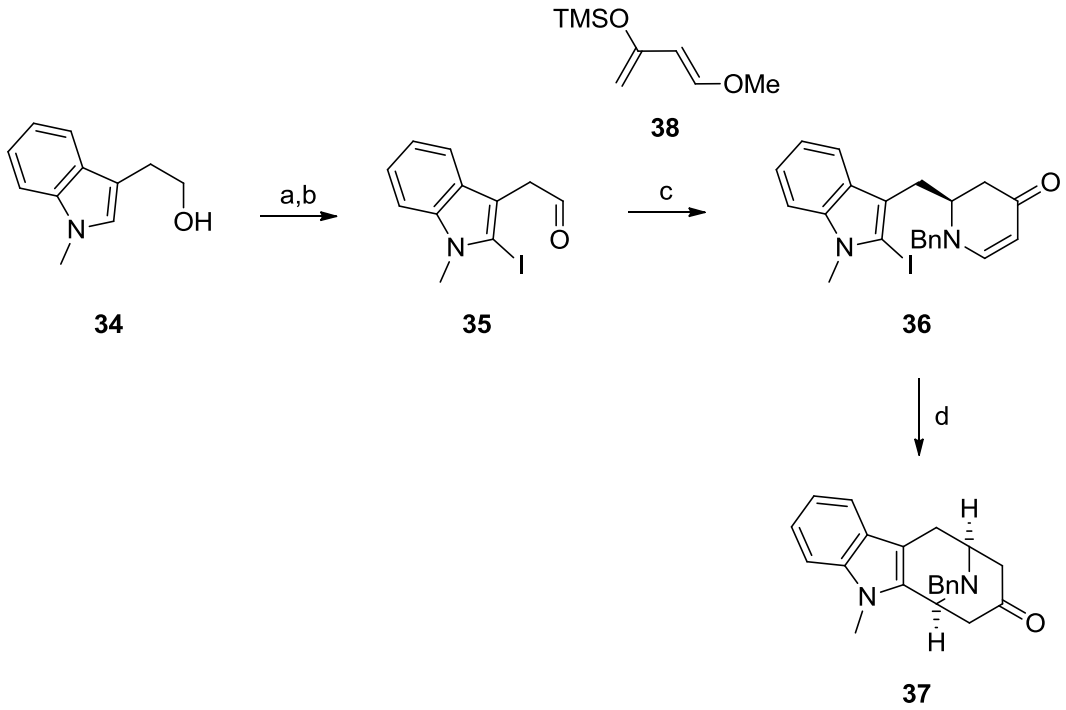


a) Alstophylline **33**, 0.2 N HCl.

1.3 Kuethe's aza-Diels–Alder approach

In 2002, Kuethe *et al*. reported an approach to the tetrahydro-β-carboline skeleton of the ajmaline/sarpagine alkaloids that used as key steps an aza-Diels–Alder and intramolecular Heck cyclisation to synthesise the D- and C-rings respectively.[37] This approach provided relatively rapid access to the azabicyclo[3.3.1]nonane motif, with tetracyclic intermediate **37** being synthesised in just 4 steps from 2-(1-methylindol-3-yl)- ethanol **34**, in an overall yield of 28% (Scheme **10**).

Scheme 10. Kuethe's aza-Diels–Alder/Heck based synthesis of the C- and D-rings.

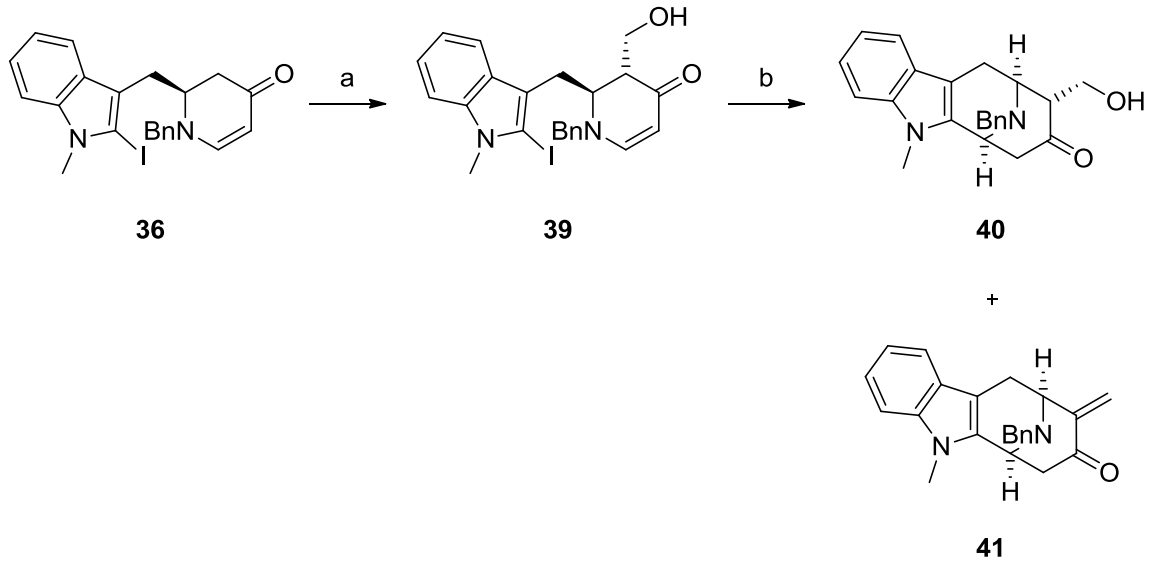


a) *n*-BuLi, MTBE, reflux, then I_2, 0°C; b) Dess–Martin, 47% over two steps; c) **38** (1.3 equiv.), $Zn(OTf)_2$ (1.1 equiv.), $BnNH_2$ (1.1 equiv.), CH_2Cl_2, rt, 3 h, 70%; d) $PdCl_2(CH_3CN)_2$ (1.0 equiv.), $^tBu_3P$ (2.0 equiv.), MeCN, reflux, 85%.

Having established a short, but moderate-yielding synthesis of **37**, an attempt to extend the methodology by introducing the E-ring was investigated. To this end the C16 hydroxymethyl-substituent was introduced by an aldol reaction with formaldehyde prior to the Heck cyclisation. Presumably this was attempted prior to formation of the C-ring, as the analogous reaction of tetracyclic substrate **40** suffers from a facile *retro*-aldol, as we have found in the Craig group (Scheme **21**, Page **39**). Kuethe was able to introduce the hydroxymethyl substituent in the C16

position by reacting the lithium enolate of **36** with paraformaldehyde, which gave β-hydroxy substituted pyridone in 67% yield and mentioned no observation of C2 lithium halogen exchange. β-Hydroxymethyl substituted pyridone **39** was converted into a ~ 1:1 mixture of tetracyclic **40** (33%) and exomethylene compound **41** (29%) using Heck conditions. (Scheme **11**)

Scheme 11. Kuethe's aza-Diels–Alder/Heck based synthesis of the C- and D-rings.



36 **39** **40** **41**

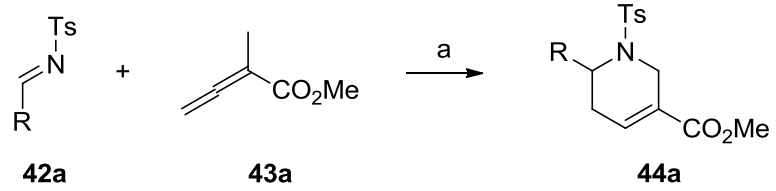
a) LiHMDS, $(CH_2O)_n$, –20°C, 67%; b) $Pd_2(dba)_3$, $^tBu_3P$, DMF, 100°C, 33% + **41** 29%.

Using this approach, Kuethe was able to synthesise β-hydroxymethyl substituted pyridone **40** from 2-(1-methylindol-3-yl)-ethanol **34** in 6.8% yield over 5 steps. Thus, this approach offers rapid access to the azabicyclo[3.3.1]nonane motif. However, previous work within the Craig group (as discussed later on Page **39**) had shown that converting β-hydroxymethyl pyridone **40** into (–)-alstonerine was difficult.

1.4 Kwon's phosphine-catalysed [4+2] annulation synthesis

Also published in 2005, Kwon reported a formal synthesis of (±)-alstonerine[38] that used a strategy based upon a series of phosphine-catalysed [4+2] annulation reactions between imines **42a** and allenes **43a** that had been reported by the group in 2003 (Scheme **12**).[39]

Scheme 12. Kwon's phosphine-catalysed [4+2] annulation approach to tetrahydropyridines **44a**.

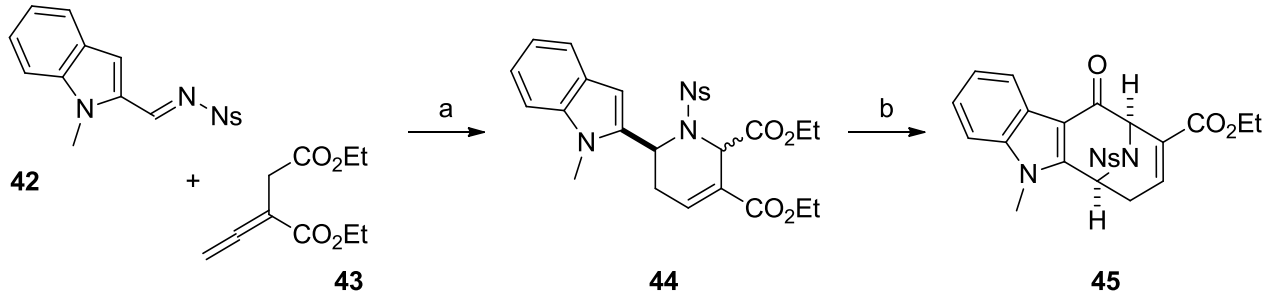


42a **43a** **44a**

a) Bu_3P (20 mol%), CH_2Cl_2, 86–98% depending on R group variant.

This methodology was used to synthesise the intermediate **45** that contained the carbon skeleton of the azabicyclo[3.3.1]nonane motif (Scheme **13**, below).[38]

Scheme 13. Kwon's phosphine-catalysed [4+2] annulation approach to tetrahydropyridine **44**.



43 **44** **45**

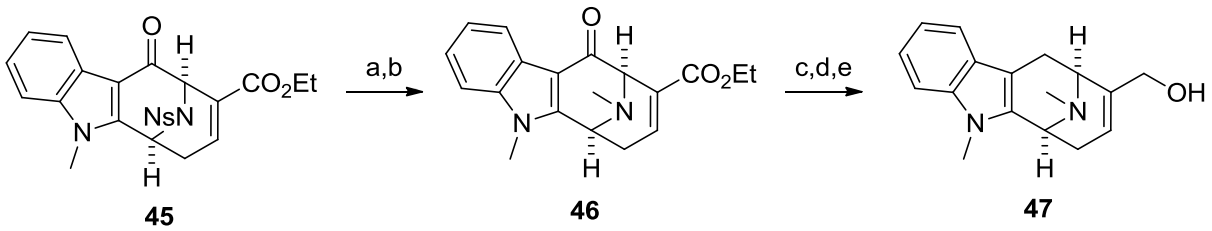
a) Bu_3P (30 mol%), CH_2Cl_2, rt, 73% d.r. 3:1 ; b) HCl, EtOAc, 90%.

Tetracyclic intermediate **45** was converted into Cook's allylic alcohol intermediate by reducing the carbonyl moieties and N_4-deprotection–methylation. The D-ring was synthesised using the [4+2] annulation methodology by reacting imine **42** with allene **43**. This gave diastereomeric esters **44** with correct C3 stereochemistry in good yield. The azabridged C-ring was formed *via* acid-catalysed intramolecular Friedel–Crafts acylation, which gave tetracyclic **45** in excellent yield.

Having established the azabicyclic core motif, tetrahydropyridine **45** was converted into Cook's intermediate **47** in a yield of 66% over 5 steps. (Scheme **14**, below) The N_4-nosyl

deprotection–methylation sequence was completed using Fukuymama denosylation conditions[40] followed by Eschweiler–Clarke methylation.[41] The chemoselective reductive deoxygenation of the C6 ketone group was eventually achieved using zinc-modified cyanoborohydride conditions. This gave a N_4–cyanoborane complex that was converted into the tertiary amine by refluxing in ethanol. The sequence was completed by reducing the α,β-unsaturated ester to allylic alcohol **47**, which had been converted (Cook's first approach) into a mixture of dihydroalstonerine and alstonerine in 6 steps. (Scheme **5**, Page **20**) This equated to a 9-step synthesis of the alstonerine E-ring from Kwon's N_4-methylated tetracyclic intermediate **46** (Scheme **14**).

Scheme 14. Completion of Kwon's formal synthesis.

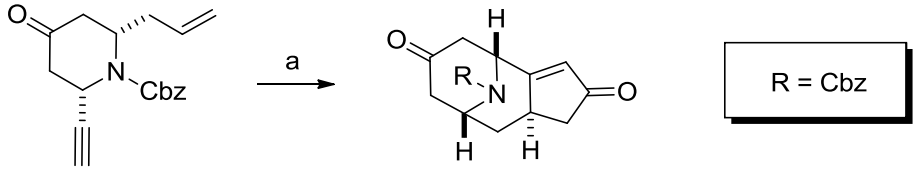


a) PhSH, K_2CO_3, DMF, 99%; b) 35% aqueous HCHO and 88% aqueous HCO_2H, reflux, 99%; c) $NaBH_3CN/ZnI_2$, CH_2Cl_2, reflux, 74%; d) EtOH, reflux, 98%; e) DIBAL, toluene, –73°C, 92%.

1.5 Martin's Pauson–Khand Synthesis

In 2007 the group of Prof. Martin at the University of Texas published a synthesis of alstonerine[42] that stemmed from their interest in alkaloid synthesis *via* transition metal-catalysed cascade reactions.[43] Whilst working on an enyne metathesis approach to a range of alkaloids containing azabicyclic core motifs, they became interested in the Pauson–Khand reactivity of their enyne metathesis substrates. The feasibility of such an approach was quickly proven using enyne **48a**, which gave the azabicyclo[3.3.1]nonane system **49a** as a single diastereomer. (Scheme **15**)

Scheme 15. Pauson–Khand azabicyclo[3.3.1]nonane synthesis **49a**.

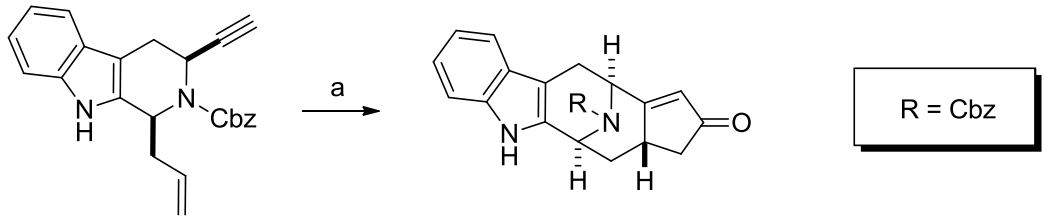


48a **49a**

a) $Co_2(CO)_8$, DMSO, THF, 65°C, 89%.

Having established the viability of his Pauson–Khand approach, Martin built his total synthesis of alstonerine around the construction of the indole annelated azabicyclo[3.3.1]nonane core motif from enyne **48** (Scheme **16**, below). Whereas Cook's approaches had required additional epimerisation reactions to synthesise the azabicyclo motif as a single enantiomer, Martin was able to achieve this in a single high yielding step as a single enantiomer *via* his strategy level Pauson–Khand reaction (Scheme **16**).

Scheme 16. Martins key step. The Pauson–Khand reaction of enyne **48**.



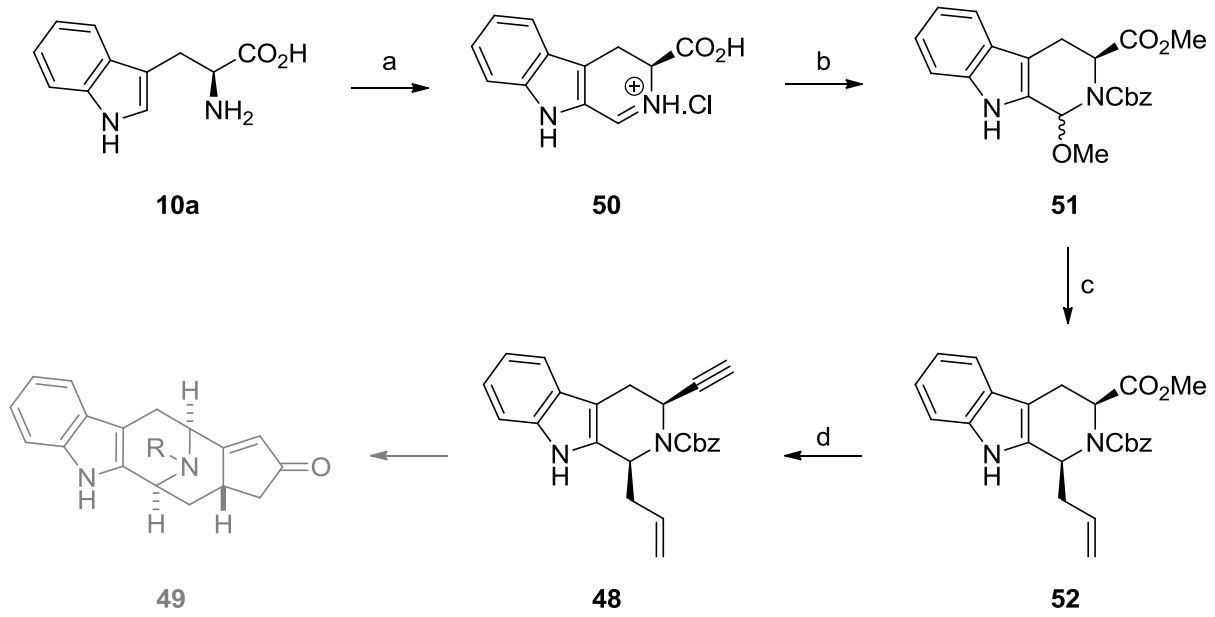
48 **49**

a) $Co_2(CO)_8$, DMSO, THF, 65°C, 94%.

This powerful reaction allowed Martin to synthesise alstonerine in just fifteen steps from L-tryptophan. This was a shorter route than either of those reported by Cook, but the overall yield of his synthesis was diminished by the disappointing yields of the two sequences adjoining the high yielding and selective Pauson–Khand step.

The first problem that Martin faced was the synthesis of the Pauson–Khand substrate, enyne **48** (Scheme **17**, below). This was synthesised from natural L-tryptophan using a four-step sequence, in which the C-ring was synthesised in the very first step of his total synthesis. Martin used a Bischler–Napieralski-like reaction, whereby L-tryptophan was first acylated with acetic anhydride and then heated with excess formic acid and concentrated HCl, to give carboline **50** in 63% (crude yield) as a single enantiomer. With the C-ring established, diastereomeric aminals **51** were produced in one pot by treating **50** with benzylchloroformate and methanol in the presence of triethylamine. BF_3-mediated allylation gave a 5.5:1 mixture in favour of *cis*-carboline **52**. At this stage, a novel one-pot partial DIBAL reduction/Ohira–Bestmann reaction was used covert methyl ester **52** into enyne **48**. This provided the Pauson–Khand substrate in 18% yield from L-tryptophan.

Scheme 17. Synthesis of Pauson–Khand substrate enyne **48**.



10a **50** **51** **52** **48** **49**

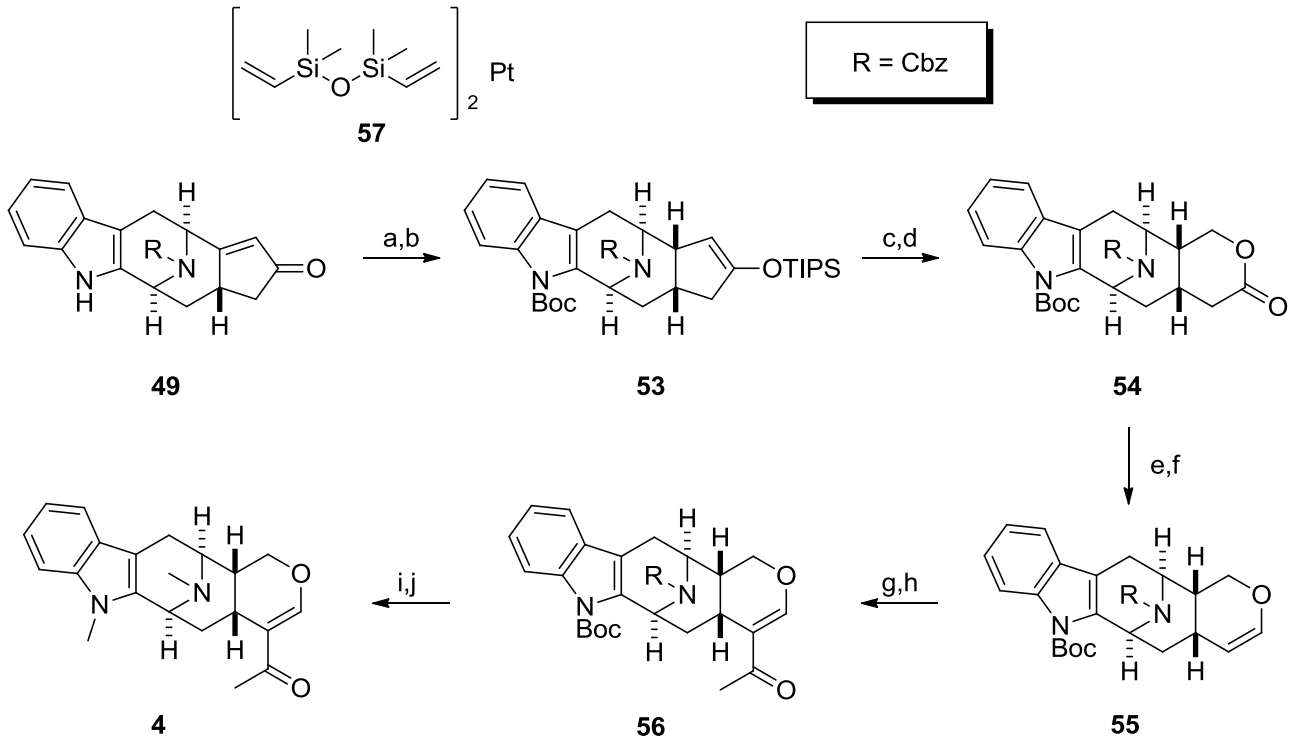
a) Ac_2O, HCO_2H, rt, then *conc*. HCl, 55°C, 63%; b) Cbz-Cl, Et_3N, CH_2Cl_2, −20°C, then MeOH, Et_3N, rt, 76%; c) allyl-TMS, $BF_3{\cdot}OEt_3$, CH_2Cl_2, 0°C, 72%; d) DIBAL, toluene, −78°C, then MeOH, NaOMe and O–B reagent, −78°C→rt, 55%.

Having established a short synthetic sequence to pentacyclic enone **49**, and with the correct azabicyclo[3.3.1]nonane motif in place, it remained to synthesise the fifth and final E-ring. However this again proved difficult, and presented Martin with his second obstacle in the total synthesis. When numerous attempts at the ring expansion and oxidation of the cyclopentenone **49** by Baeyer–Villiger conditions failed, an alternative oxidative cleavage route was envisaged.

If we again focus on the construction of the E-ring, as illustrated below (Scheme **18**), significant manipulation was required to elaborate the cyclopentenone moiety in **49** to the C20 acylated glycal structure **56** that was required for the natural product. Following N_1-protection, the enone moiety was converted into silyl enol ether **53** by a stereoselective hydrosilylation using a platinum divinyltetramethyl disiloxane complex **57** (Karstedt's catalyst) and five equivalents of bulky triisopropylsilane. Interestingly, less bulky silanes led to the formation of significant amounts of the parent cyclopentenone. The required oxidative cleavage of **53** had failed under ozonolysis conditions and instead silyl enol ether **53** was converted into *δ*-lactone **54** using Johnson–Lemieux conditions, followed by borohydride reduction of the intermediate aldehyde–ester and acid-induced lactonisation. The oxidation, reduction and lactonisation steps were carried out sequentially without purifying intermediates, giving rise to a moderate 55% yield. *δ*-Lactone **54** was first reduced using DIBAL to give an intermediate lactol, which gave dihydropyran **55** following *O*-mesylation and elimination. The final stage required for the E-ring synthesis was the C20 acylation. As Friedel–Craft type conditions led to competing indole acylation products, N_1- and N_4-protected dihydropyran **55** was converted into N_1- and N_4-protected alstonerine **56** using trichloroacetyl chloride followed by reduction of the trichloroacetyl moiety of the intermediate.

The synthesis was completed by carbamate deprotection using iodotrimethylsilane and a sequential N_4- and N_1-methylation. Thus, the total synthesis was completed in 15 steps from L-tryptophan in an overall yield of 4.4%. (Scheme **18**, below)

Scheme 18. Martin's oxidative cleavage approach to the alstonerine E-ring.



a) Boc_2O, DMAP, MeCN, 99%; b) **57**, $^{i}PrSiH$, toluene, 80°C, 93%; c) OsO_4 (10 mol%), $NaIO_4$, acetone:H_2O (3:1); d) $NaBH_4$, MeOH, then $TsOH{\cdot}H_2O$, CH_2Cl_2, 55% over two steps; e) DIBAL, toluene, –78°C; f) MsCl, Et_3N, CH_2Cl_2, 61% over two steps; g) $ClCOCCl_3$, pyridine, 65°C; h) Zn, AcOH, 75% over two steps; i) TMSI, MeCN, 78%; j) MeI, THF, then NaH, MeI, 72%.

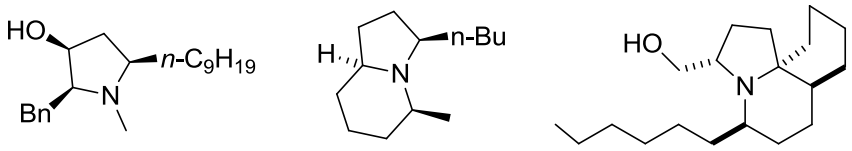
This synthesis represented the first use of the Pauson–Khand reaction to synthesise the azabicyclic motif of (–)-alstonerine. This step arguably provided a more selective route to the azabicyclo[3.3.1]nonane core than those previously reported by Cook, which required epimerisations to allow for the enantioselective synthesis of this motif. This approach, although shorter than those previously reported by Cook *et al*., had a significantly lower overall yield, due largely to the difficulty in synthesising the required enyne Pauson–Khand substrate **48**, and the number of steps required to convert the cyclopentenone into the alstonerine E-ring.

1.6 The Craig group's previous approaches to alstonerine

1.6.1 Background

The aziridine motif is highly valuable in the synthesis of nitrogen containing natural products.[44] Structurally analogous to epoxides and readily synthesised as single enantiomers,[44] they have found widespread use in asymmetric synthesis due to their ability to undergo both regio- and stereoselective nucleophilic ring-opening reactions.[45] Early work within the Craig group focused on using aziridines derived from α-amino acids in the assembly of pyrrolidines[46] and piperidines.[47] The antifungal agent (+)-preussin **58**,[48] (+)-monomorine **59** (a trail pheromone of the widespread pharoah's worker ant[49] *Monomorium pharaonis*) and cytotoxic marine alkaloid[50] lepadiformine **60**, are among those natural products synthesised within the Craig group using aziridine chemistry.[46,51,52]

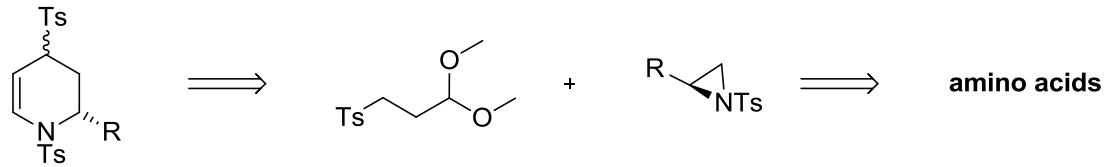
Figure 6. Synthesis of nitrogen containing natural products within the Craig group.



58 **59** **60**

During these early synthetic endeavours, aziridine-derived heterocycles, in particular the 1,4-bis(tolylsulfonyl)tetrahydropyridines **61a** synthesised from α-amino acids (Figure **7**, below), were found to be useful substrates for an extensive range of synthetic transformations. Their utility is enhanced by the simple nature of their preparation *via* aziridine ring-opening reactions between arylsulfonyl-substituted acetals **62** and α-amino acid-derived *N*-tosylaziridines **63a**, followed by cyclocondensation (Figure **7**).

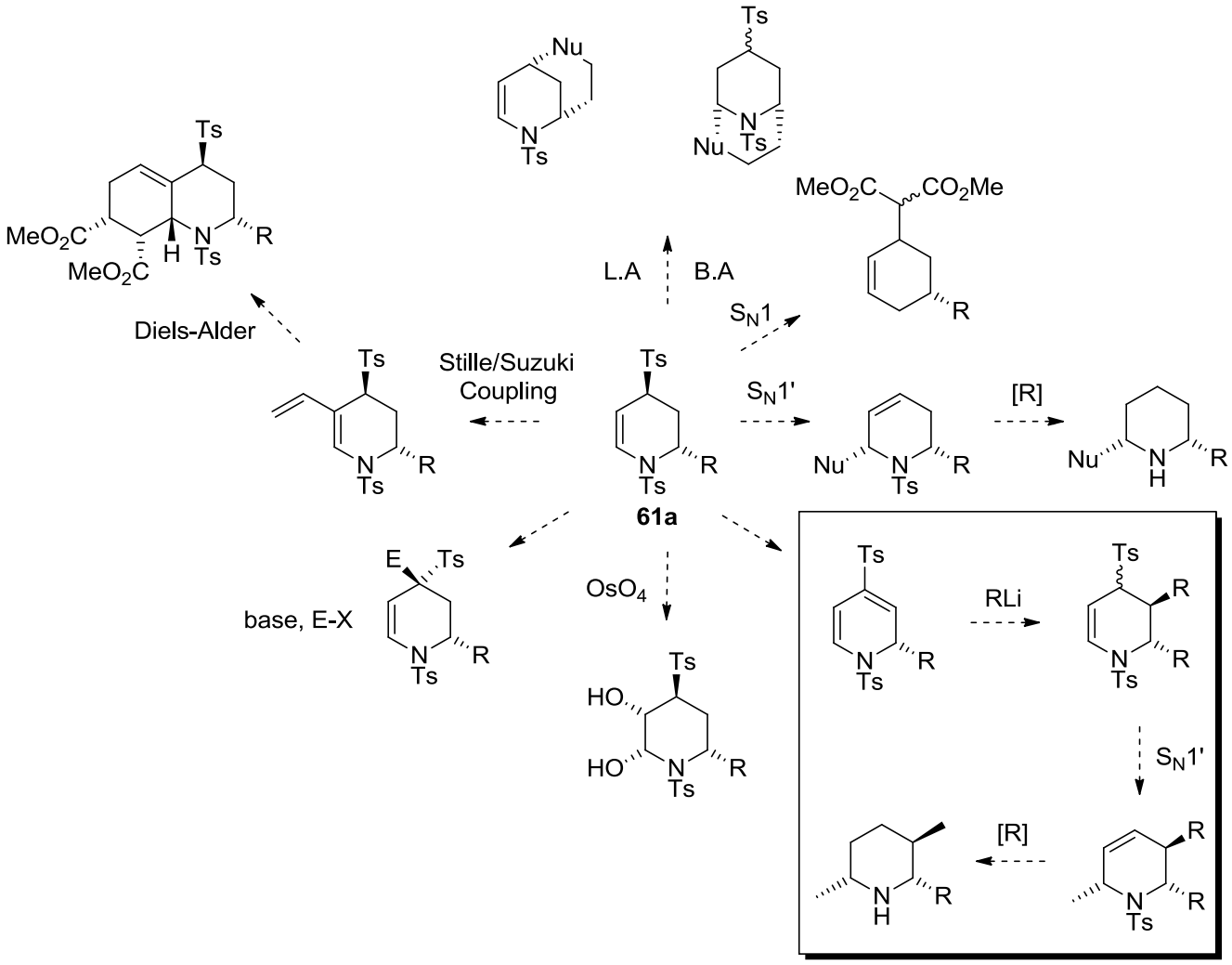
Figure 7. Synthesis of 1,4-bis(tolylsulfonyl)tetrahydropyridines **61a**.



61a **62** **63a**

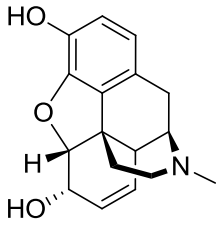
Tetrahydopyridines **61a** have been applied in highly stereoselective, S_N1 and S_N1' reactions,[53,47(a)] acid-catalysed reduction,[47(c)] homo- and hetero-Diels–Alder reactions,[54] *syn*-dihydroxylation[47(c)] and intramolecular cyclisation processes,[55,47(b),68] and as such, their usefulness as building blocks in organic synthesis has been proven, as outlined below (Figure **8**).

Figure 8. Synthetic applications of 1,4-bis(tolylsulfonyl)tetrahydropyridines **61a**.

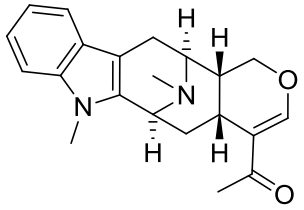


Having shown tetrahydropyridines **61a** to be useful in piperidine synthesis, the Craig group became interested in the synthesis of the piperidine containing alkaloid natural products, particularly benzylisoquinoline alkaloid morphine **64**, and the macroline-related alkaloids alstonerine **4** and suaveoline **65** (Figure **9**, below).

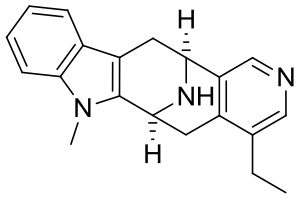
Figure 9. Possible applications of tetrahydropyridine chemistry in alkaloid synthesis.



64 (–)-morphine



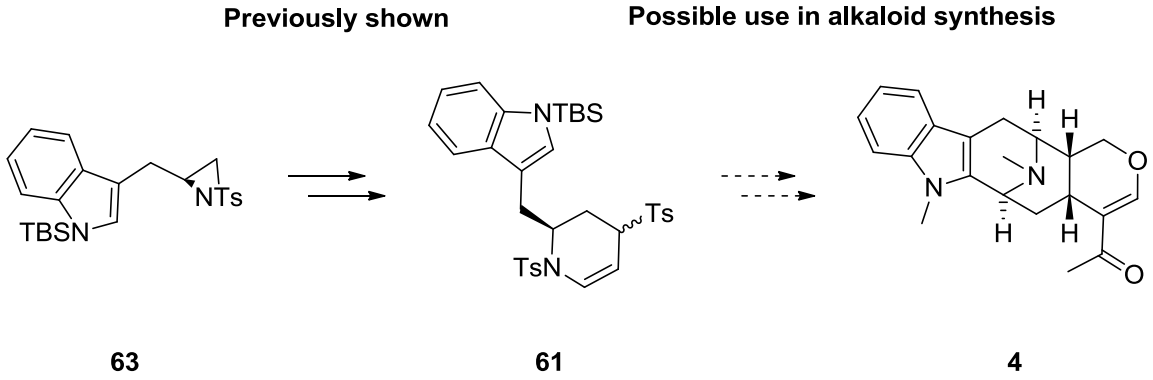
4 (–)-alstonerine



65 (–)-suaveoline

In particular, it was envisaged that the L-tryptophan derived bis(tolylsulfonyl)tetrahydropyridine **61** could be used as an advanced intermediate in the total synthesis of macroline-related alkaloids, alstonerine **4** and suaveoline **65** (Figure **10**, below). For progress on the synthesis of suaveoline **65**, see the theses of Lewis[56] and Tholen.[57]

Figure 10. Original strategy for bis(tolylsulfonyl)tetrahydropyridine **61** as intermediate in (–)-alstonerine **4** synthesis.

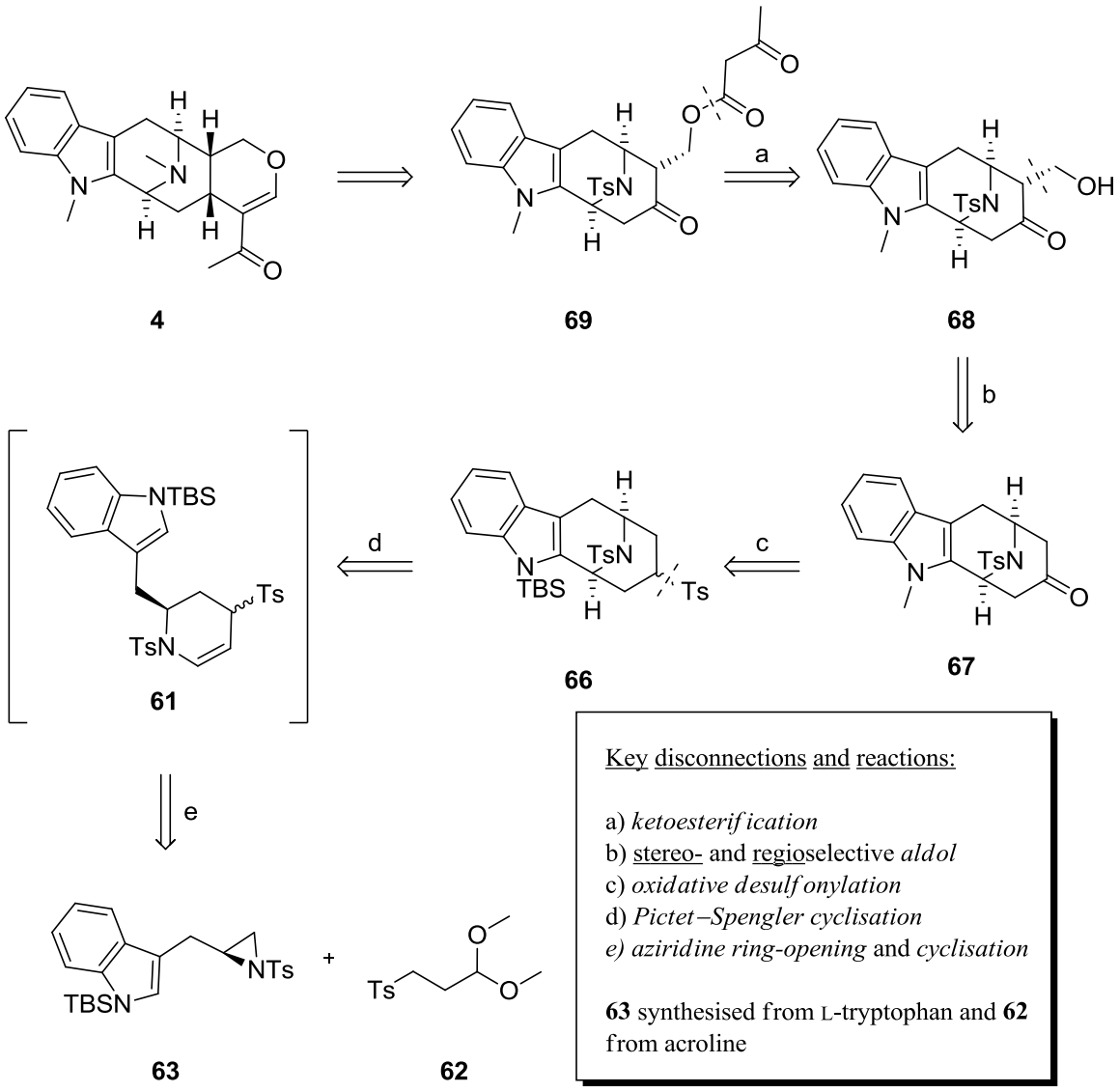


The following discussion describes previous synthesis approaches towards alstonerine as investigated in the Craig group.

1.6.2 The Craig group's first approach to (–)-alstonerine

The approach to alstonerine anticipated that the azabicyclo[3.3.1]nonane containing tetracyclic ketone intermediate **67** would be synthesised *via* an acid-catalysed Pictet–Spengler cyclisation of the L-tryptophan-derived 1,4-bis(tolylsulfonyl)tetrahydropyridine **61**. The E-ring would be installed by a regio- and stereospecific aldol, β-ketoesterification and Knoevenagel reaction of **69**. Oxidation level adjustment and FGI would furnish (–)-alstonerine **4**.

Figure 11. Retrosynthetic analysis (–)-alstonerine **4**.

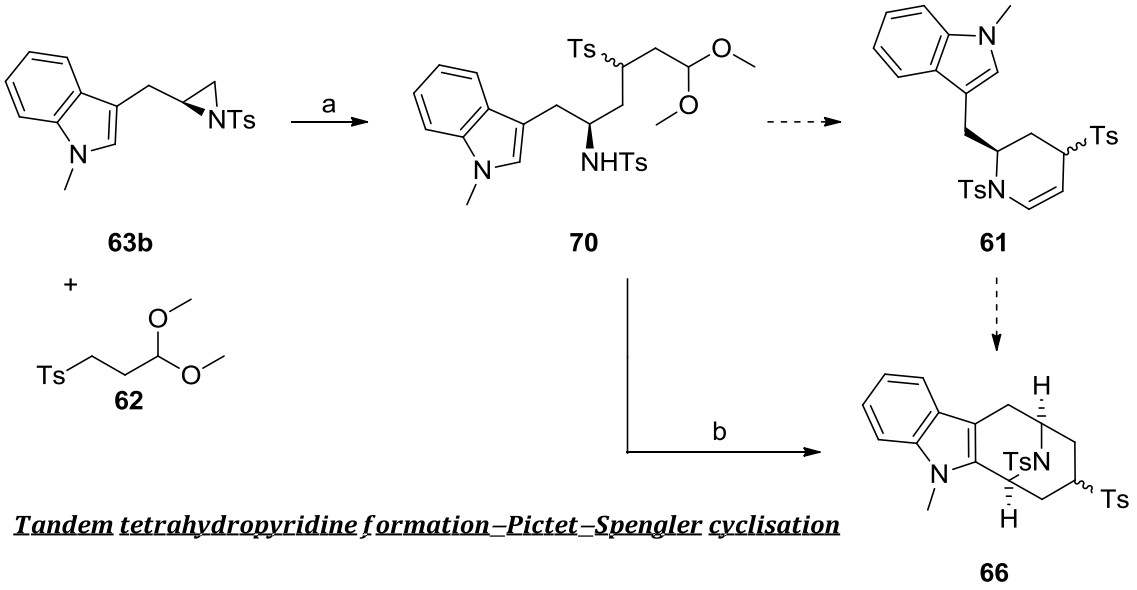


Forward Synthesis

In the first attempted total synthesis of (–)-alstonerine **4**, Ioannidis[58] successfully synthesised tetracyclic intermediate **66**, (Scheme **19**, below) without the need to isolate bis(tolylsulfonyl)tetrahydropyridine **61**. This was achieved *via* a modification of the previously discussed tetrahydropyridine chemistry, whereby the tetrahydropyridine formation and Pictet–Spengler cyclisation steps (b and c, Scheme **19**) were combined into a tandem process (d, Scheme **19**). Ring-opened intermediate **70** was obtained in >80% yield, by treating L-tryptophan-derived aziridine **63b** with the lithiated carbanion of sulfonyl acetal **62** (Scheme **19**).

Various conditions were investigated for the tandem tetrahydropyridine–Pictet–Spengler cyclisation, starting with those previously reported for the Pictet–Spengler cyclisation of tetrahydropyridine **61**[58] (c, Scheme **19**). However, TMSI,[59] catalytic sulfuric acid[47] and TFA gave only low yields of the desired tetracyclic intermediate **66**. Extensive N_1TBS deprotection was also observed under these conditions. The desired tetracycle **66** was eventually made in good yield, by treating **70** with stoichiometric (±)-CSA in CH_2C1_2 or *p*TSA in acetone.[58]

Scheme 19. Tandem tetrahydropyridine formation and Pictet–Spengler cyclisation of **70**.

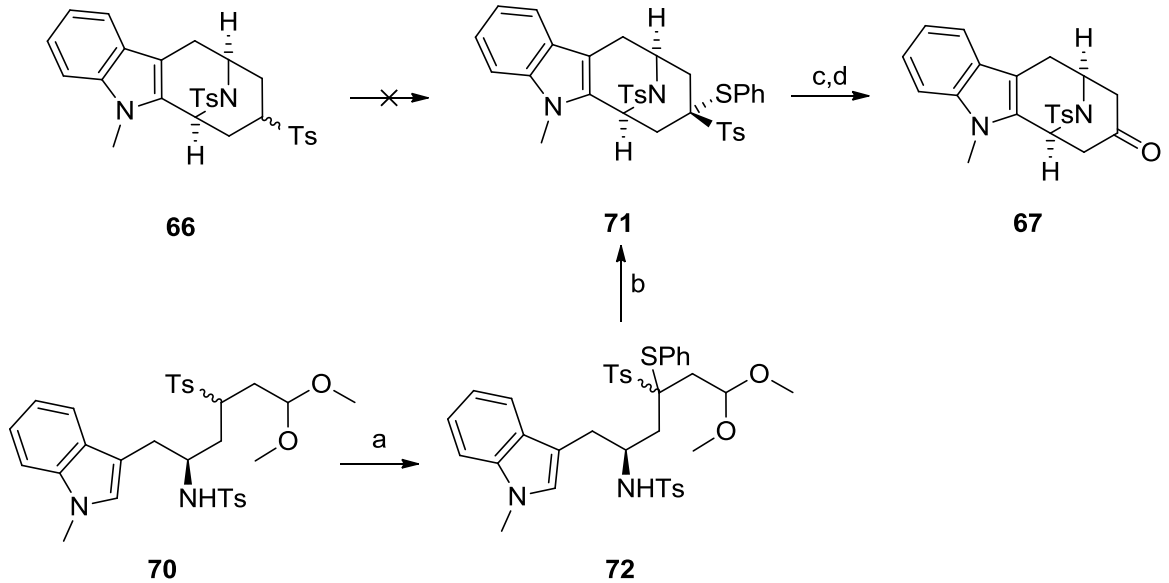


a) **62**+ *n*-BuLi (1.1 equiv.), THF–TMEDA, 0°C→rt, 1 h, >80%; b) (±)-CSA (1.0 equiv.), CH_2C1_2, rt, 1 h, >85% or *para*-TsOH (1.0 equiv.), acetone, rt, 30 min, >85%.

Having successfully optimised the tandem tetrahydropyridine–Pictet–Spengler cyclisation that installed the C- and D-rings of the azabicyclic core in a single step, and allowed rapid access to tetracyclic intermediate **66** from L-tryptophan, the final phase of the synthesis required installation of a C15 ketone moiety in place of the epimeric sulfone group to allow introduction of the E-ring. Numerous oxidative desulfonylation conditions were investigated.[58] The use of bis(trimethylsilyl)peroxide[60] and chlorodimethoxyborane[58] both failed. The possibility of Lewis acid-mediated thionium ion formation followed by hydrolysis was also explored. The α-sulfonyl anion derived from **66** was quenched with both PhSSPh or $PhSSO_2Ph$ (sources of PhS^+), however no dithioketal intermediate **71** was observed. Dithioketal **71** was eventually synthesised by installing the dithioketal functionality prior to the tandem tetrahydropyridine–Pictet–Spengler cyclisation.

Ring opened intermediate **70** was converted into dithioketal **72** in only 40% yield, by treating **70** with *n*-BuLi and $PhSSO_2Ph$. At this stage, dithioketal **72** was converted into the desired tetracyclic ketone **67** by tandem tetrahydropyridine–Pictet–Spengler cyclisation and aluminium-mediated diphenylthioketal formation, followed by treatment of **71** with mercury(II)chloride in the presence of proton scavenger $CaCO_3$.[58]

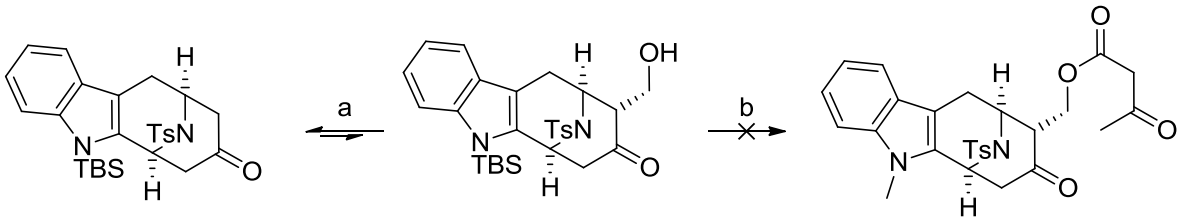
Scheme 20. Failed oxidative desulfonylation of tetracyclic intermediate **66**.



a) *n*-BuLi (2.2 equiv.), $PhSSO_2Ph$ (1.5 equiv.), THF–TMEDA, 0°C, 40%; b) (±)-CSA (1.0 equiv.), CH_2Cl_2, rt, 1 h, 80%; c) Me_2AlSPh (3.0 equiv.), CH_2Cl_2, rt, 4 h, 55%; d) $HgCl_2$ (2.2 equiv.), $CaCO_3$ (2.2 equiv.), acetone–H_2O, reflux, 12 h, 93%.

With conditions for the challenging oxidative desulfonylation established, attention turned to installing the alstonerine E-ring. Unfortunately, the aldol reaction of tetracyclic ketone **67** with formaldehyde (retrosynthesis, Page **36**) was plagued by a facile *retro*-aldol reaction that was ultimately responsible for the failure of this approach (Scheme **21**, below). Starting material recovery was always observed under standard aldol conditions. The facile nature of the *retro*-aldol was due to the axial orientation of the C16 hydroxymethyl-substituent in **68**, which allowed $\pi_{C=O} \rightarrow \sigma^*_{C-C}$ donation and made tetracyclic ketone **67** energetically favourable. Hydroxymethylation could be achieved using milder conditions outlined by Yamamoto *et al.*[61] whereby TMSOTf and Et_3N were used to form the TMS enol ether of **67**, which reacted with methylaluminium bis(2,6-diphenylphenoxide)-formaldehyde complex to give β-hydroxymethyl-ketone **68** in moderate yield. β-Ketoesterification of **68** using diketene and dioxinone failed, instead returning tetracyclic ketone **67** *via* the facile *retro*-aldol previously highlighted.[58] At this stage, due to the difficulty of the aldol and β-ketoesterification steps required, this approach towards the E-ring synthesis was abandoned.

Scheme 21. Unavoidable facile *retro*-aldol of **68**.



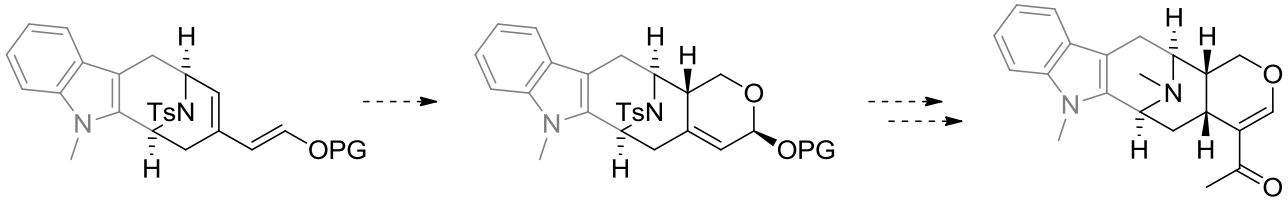
67 **68** **69**

a) Et_3N (4.0 equiv.), TMSOTf (2.0 equiv.), CH_2Cl_2, 0°C, 15 min, then MAPH-formaldehyde (1.5 equiv.), –78°C, 2 h, 54%.

1.6.3 Hetero-Diels–Alder approach

In the original approach, the required azabicyclo[3.3.1]nonane core had very successfully been installed *via* a tandem tetrahydropyridine–Pictet–Spengler cyclisation. The limitations of this approach had all arisen whilst attempting to synthesise the E-ring, namely the oxidative desulfonylation of **66**, subsequent aldol of tetracyclic ketone **67** and β-ketoesterification reactions, thus an alternative strategy was envisaged that retained the previous synthesis of the azabicyclic core *via* tandem tetrahydropyridine–Pictet–Spengler cyclisation, but included a revised hetero-Diels–Alder approach to the E-ring (Figure **12**, below).

Figure 12. Possible synthesis of the E-ring *via* hetero-Diels–Alder.

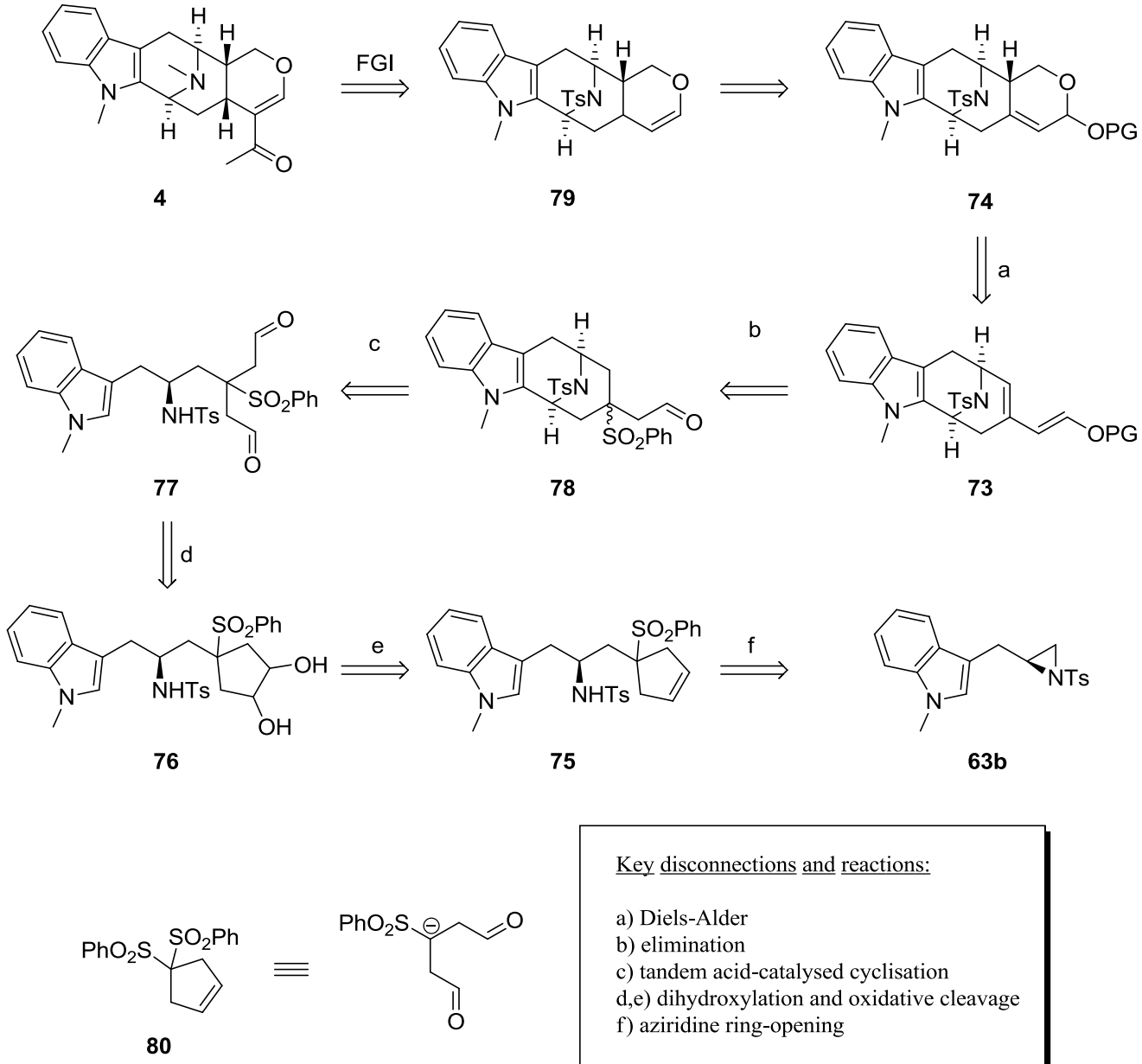


73 **74** **4**

For this approach to be successful the Diels–Alder reaction of **73** with formaldehyde would have to occur from the bottom face of the diene; this would install the correct C16 stereochemistry and provide pentacyclic substrate **74** from which to complete the synthesis.

The retrosynthesis established for the synthesis of the Diels–Alder diene substrate **73** is shown below (Figure **13**). The azabicyclic core of diene **73** would be synthesised as previously from di-aldehyde **77** *via* the acid-catalysed tandem tetrahydropyridine–Pictet–Spengler cyclisation that had been employed in the previous approach. The tandem cyclisation would be followed by base-mediated sulfone elimination and protection to give diene **73**. The synthesis of intermediate di-aldehyde **77** would require an alternative nucleophile for the aziridine ring-opening reaction. Work by Ioannidis[58] during the original approach found that sulfonyl nucleophiles were effective partners for aziridine **63b**, and as such cyclopentenyl sulfone **80** was chosen. The double bond in **80** would be used to introduce the di-aldehyde functionality when required.

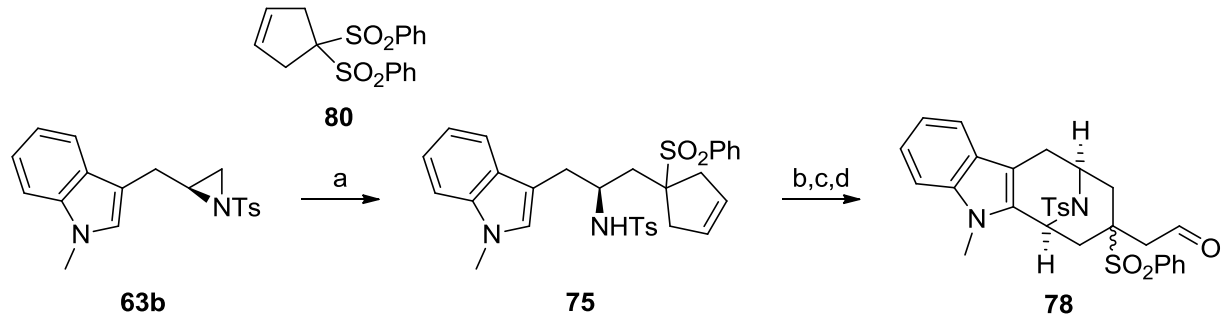
Figure 13. Retrosynthetic analysis (–)-alstonerine **4**.



Forward Synthesis

Both Rahn[62] and Ioannidis[58] showed that intermediate **75** could be obtained *via* nucleophilic ring-opening of L-tryptophan-derived aziridine **63b** by the sulfonyl anion derived from bis(phenylsulfonyl)cyclopentene **80**. Treatment of bis(phenylsulfonyl)cyclopentene **80** with freshly prepared lithium naphthalenide solution, followed by addition of aziridine **63b** gave intermediate **75** in 55–64% yield. Dihydroxylation of the cyclopentene containing ring-opening product **75** using $KMnO_4$ gave the corresponding diol in 61% yield (Scheme **22**). Oxidative cleavage of the resulting 1,2-diol and the acid-mediated tetrahydropyridine–Pictet–Spengler cyclisation under anhydrous conditions gave the azabicyclo[3.3.1]nonane containing tetracyclic aldehydes **78** in 94% yield over two steps (Scheme **22**).

Scheme 22. Synthesis of tetracyclic aldehyde **78**.



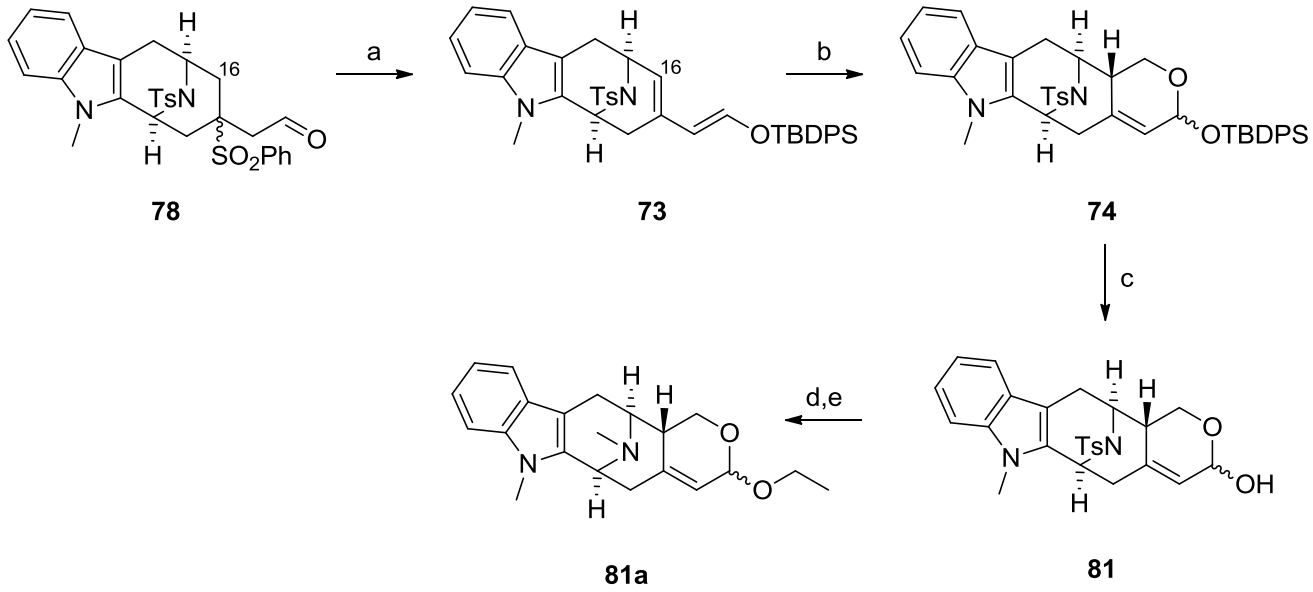
a) Li·Np (4.0 equiv.), THF, –20°C, 1,1-bis-(phenylsulfonyl)cyclopent-3-ene **80** (1.2 equiv.), THF, –78°C, then aziridine **63b** (1.0 equiv.), DMPU (3.0 equiv.), THF, –78°C→rt, o/n, 55–64%; b) $KMnO_4$ (1.5 equiv.), TBAB (1.6 equiv.), CH_2Cl_2, 0°C→rt, o/n, 61%; c) $Pb(OAc)_4$ (1.1 equiv.), $NaHCO_3$ (7.0 equiv.), 1,2-dichloroethane, 0°C, 30 min; d) TFA (1.1 equiv.), CH_2Cl_2, 30 min, 94% over two steps (c and d).

Tetracyclic aldehyde **78** was converted into *O*-silyl protected diene **73** in 95% yield using DBU, DMAP and TBDPSCl. Extensive investigations into the hetero-Diels–Alder reaction between diene **73** and formaldehyde were attempted. Diene **73** was exposed to a variety of formaldehyde sources in the presence of Lewis acid. A combination of monomeric formaldehyde, obtained using a modified Schlosser method,[63] in the presence of dimethylaluminium chloride gave pentacycle **74** in moderate yield.[62]

At this stage, whilst attempting to hydrogenate the allylic double bond in silyl ether **74** under standard conditions only complete desilylation was observed. When carried out immediately after the hetero-Diels–Alder reaction, this gave allylic alcohol **81** in an improved 66% yield over

two steps.[62] The C16 stereochemistry of alcohol **81** was established by X-ray crystallography and proved that the dienophile had preferentially attacked from the bottom face of diene **73**.

Scheme 23. Synthesis of pentacyclic intermediate **81a** with correct C16 stereochemistry.



78 **73** **74** **81** **81a**

a) TBDPSC1 (1.5 equiv.), DMAP (0.2 equiv.), DBU (5.0 equiv.), CH_2Cl_2, 0°C, 1.5h, 95%; b) monomeric-HCHO (1.5 equiv.), Me_2AlCl (3.0 equiv.), THF, 0°C→rt, 3 h; c) H_2/Pd/C (10 mol%), $NaHCO_3$ (1.6 equiv.), $CHCl_3$, o/n, 66% over two steps; d) Na·Np (0.5M in THF; 8.0 equiv.), THF, –78°C, 59%; e) aqueous HCHO (37% in H_2O; 50.0 equiv.), $NaBH_3CN$ (5.0 equiv.), AcOH (6.0 equiv.), 2.5 h, 98%.

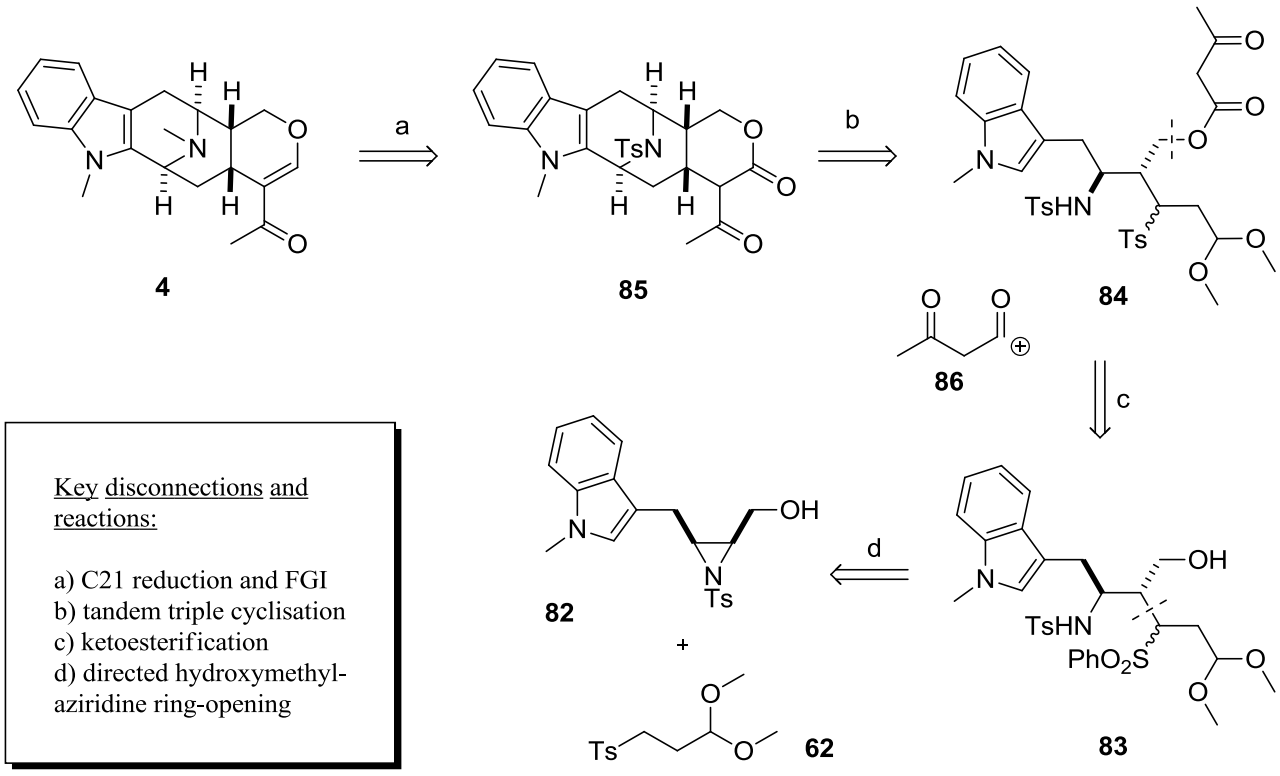
Although detosylation of **81** followed by N_4- methylation gave *O*- alkylated **81a** in 58% yield, elaboration of the E-ring in pentacycle **81** proved difficult.[62] The alcohol moiety in **81** proved unreactive towards standard oxidation conditions such as Dess-Martin periodinane, Swern, PDC, PCC, TPAP, DDQ, $AgCO_3$, SO_3-py and Jones. The double bond proved unreactive to hydrogenation and isomerisation using rhodium(I) catalyst, $RhCl(Ph_3P)_3$. Attempts at radical isomerisation of the double bond had inverted the stereochemistry of the C16 hydrogen, and as such another approach towards the final oxygen heterocyclic E-ring was investigated.

1.6.4 Conjugated iminium approach towards (±)-alstonerine

Following the failure to install the E-ring oxygen heterocycle of (–)-alstonerine *via* either of the previously outlined aldol or hetero-Diels–Alder approaches, it became clear that a change in strategy was required.

A modified approach was envisaged, whereby the hydroxymethyl-C16 substituent of the E-ring would be incorporated earlier in the sequence. This would be achieved *via* a directed nucleophilic ring-opening reaction of hydroxymethyl-aziridine **82**.[64,65] This strategy-level transformation would increase the level of convergence in the sequence, by implementing the entire carbon skeleton of alstonerine from three parent substrates. The three components **62**, **82** and **86** would be combined to give cyclisation substrate **84**, which contained all of the necessary carbon atoms required for the carbon skeleton of alstonerine (Figure **14**, below).

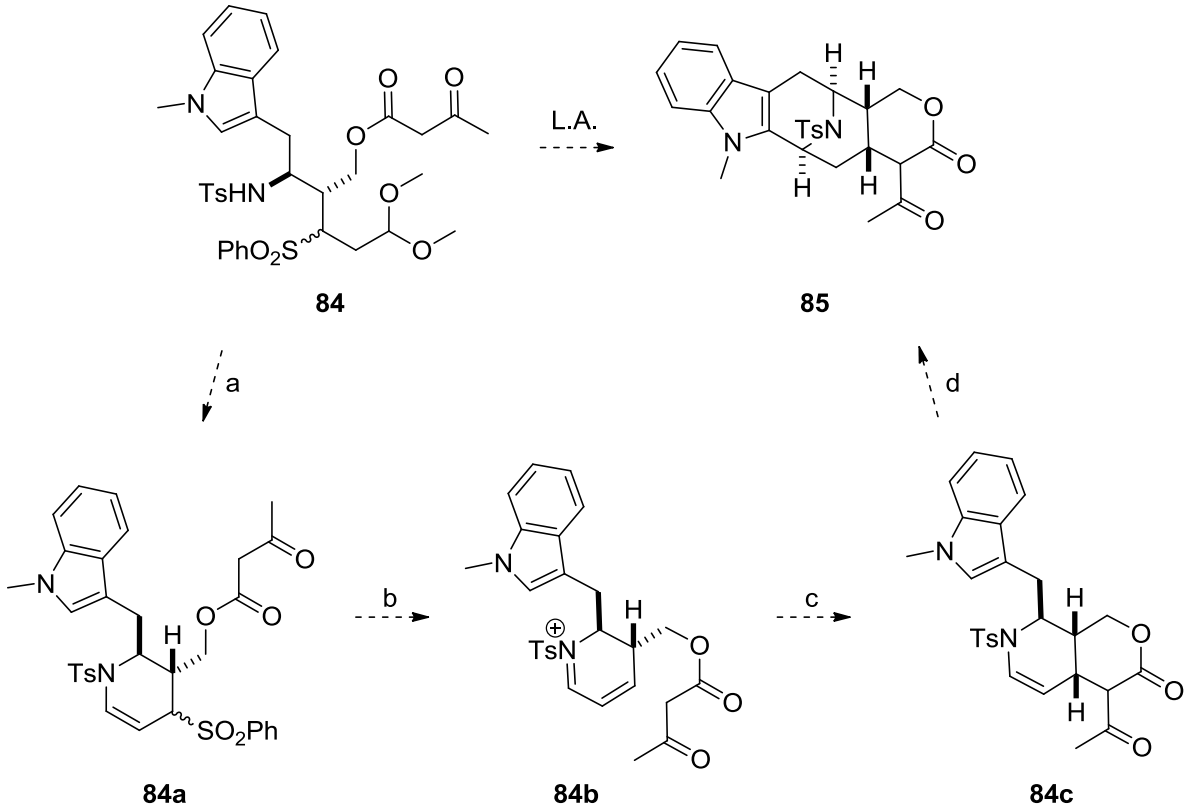
Figure 14. Retrosynthetic analysis (±)-alstonerine **4**.



The synthesis would be completed by combining the tandem tetrahydropyridine–Pictet–Spengler cyclisation with an intramolecular Michael-type addition. The ambitious triple cyclisation would be followed by FGI and oxidation level adjustment. The order of ring formation in the tandem

triple cyclisation would be pivotal to its success. Crucially, tetrahydropyridine **84a** must be formed first (Step a, Figure **15**). Michael-type addition must then follow (Step c, Figure **2**), which would allow the Pictet–Spengler cyclisation to take place (Step d, Figure **2**).

Figure 15. Lewis acid-catalysed tandem cyclisation of **84** in synthesis of (±)-alstonerine.



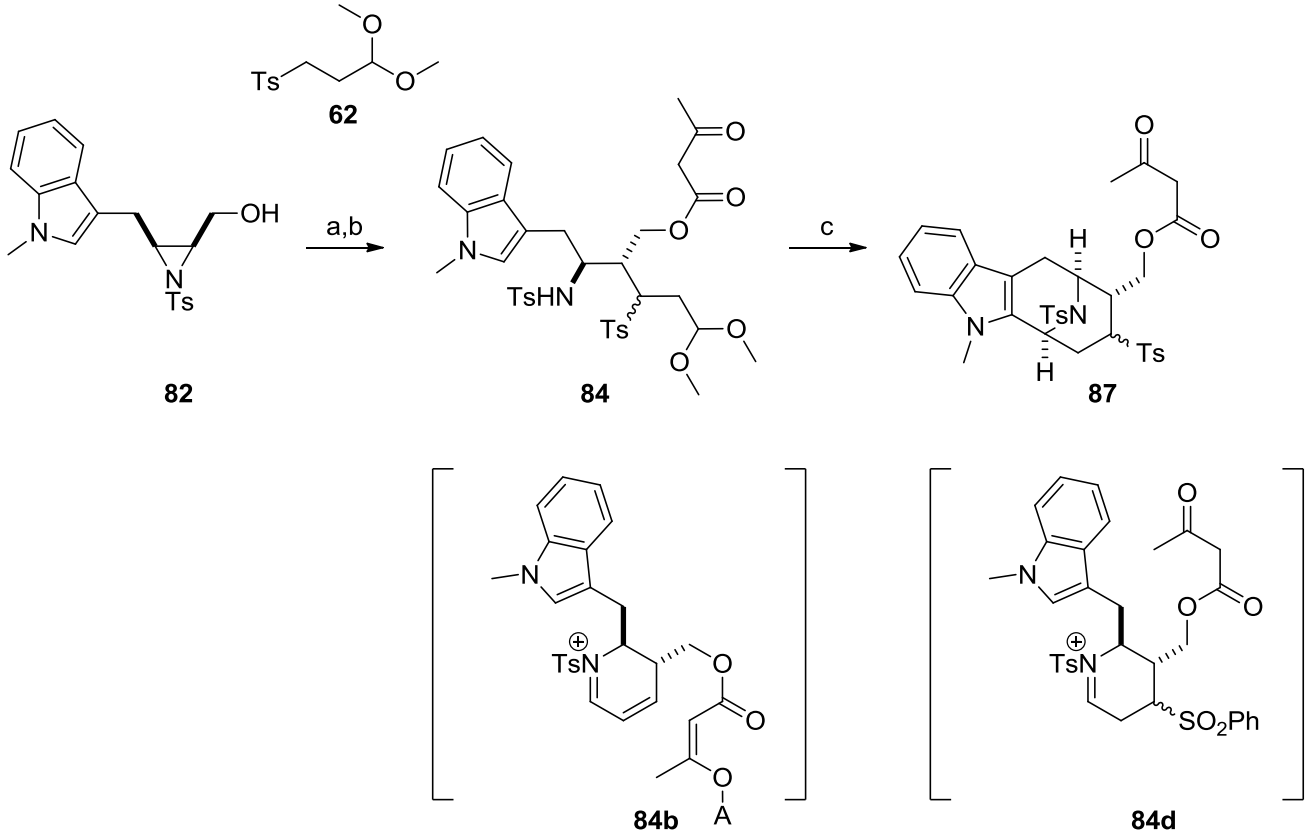
From the retrosynthesis (Page **44**), it can be seen that this approach required the synthesis of the new aziridine **82** that already possessed the hydroxymethyl-substituent required for the eventual C16 position. For the initial work, racemic hydroxymethyl-substituted **82** was synthesised in favour of the single enantiomer, as racemic **82** could be achieved from commercially available *Z*-2-butene-1,4-diol in a relatively short sequence. The synthesis of **82** is discussed later (Scheme **25**, Page **51**, Chapter **2**).

Forward Synthesis

When treated with *n*-BuLi, *O*-lithiated hydroxymethyl-substituted aziridine **82** was found to undergo completely regioselective and stereospecific ring-opening with the sulfone-stabilised carbanion of 1-phenylsulfonyl-3,3-dimethoxypropane **62**.[67] β-Ketoesterification of the resulting alcohol **83** using either NaOAc or DMAP as catalyst with diketene gave cyclisation precursor **84** in 54% yield. At this stage, numerous Lewis acidic cyclisation conditions were attempted.[66]

In all cases, tetrahydropyridine formation was immediately followed by intramolecular Pictet–Spengler cyclisation to give tetracyclic **87**, which prevented the synthesis of the alstonerine E-ring, as the premature Pictet–Spengler cyclisation removed the required 1,4-conjugation and meant that conjugated iminium intermediate **84b** could not be formed.

Scheme 24. Failed Lewis acid-catalysed tandem cyclisation of **84** in the synthesis of alstonerine.



a) **62** (1.5 equiv.) + *n*-BuLi, THF, –78°C→rt, o/n, 83%; b) Diketene (1.3 equiv.), DMAP (10 mol%), THF, rt, 2 h, 51%; c) TMSI (6.0 equiv.), MeCN, 0°C, 1 h, 86%.

It is important to note that during this approach, nucleophilic ring-opening reactions carried out on the MOM-protected derivative of aziridine **82** with the sulfone-stabilised anion of **62** showed

little regioselectivity, and as such the hydroxymethyl-substituent was identified as vital in directing the approach of the nucleophile.

Chapter 2

Results & Discussion

Introduction to the final approach

Having discussed previous endeavours towards the total synthesis of alstonerine in Chapter 1, the focus of this chapter will be to present the final approach, which culminated in an aziridine-based synthesis of (±)-alstonerine. The final approach relied heavily on the successful aspects of the Craig group's previous approaches,[67,68] notably the regioselective, stereospecific ring-opening of hydroxymethyl-substituted aziridine **82** and a reductive modification of the Pictet–Spengler cyclisation (*Retrosynthesis*, Figure **16**, below). The approach will be discussed in two sections.

Section 2.1 The synthesis of key intermediate α,β-unsaturated lactam alcohol 90

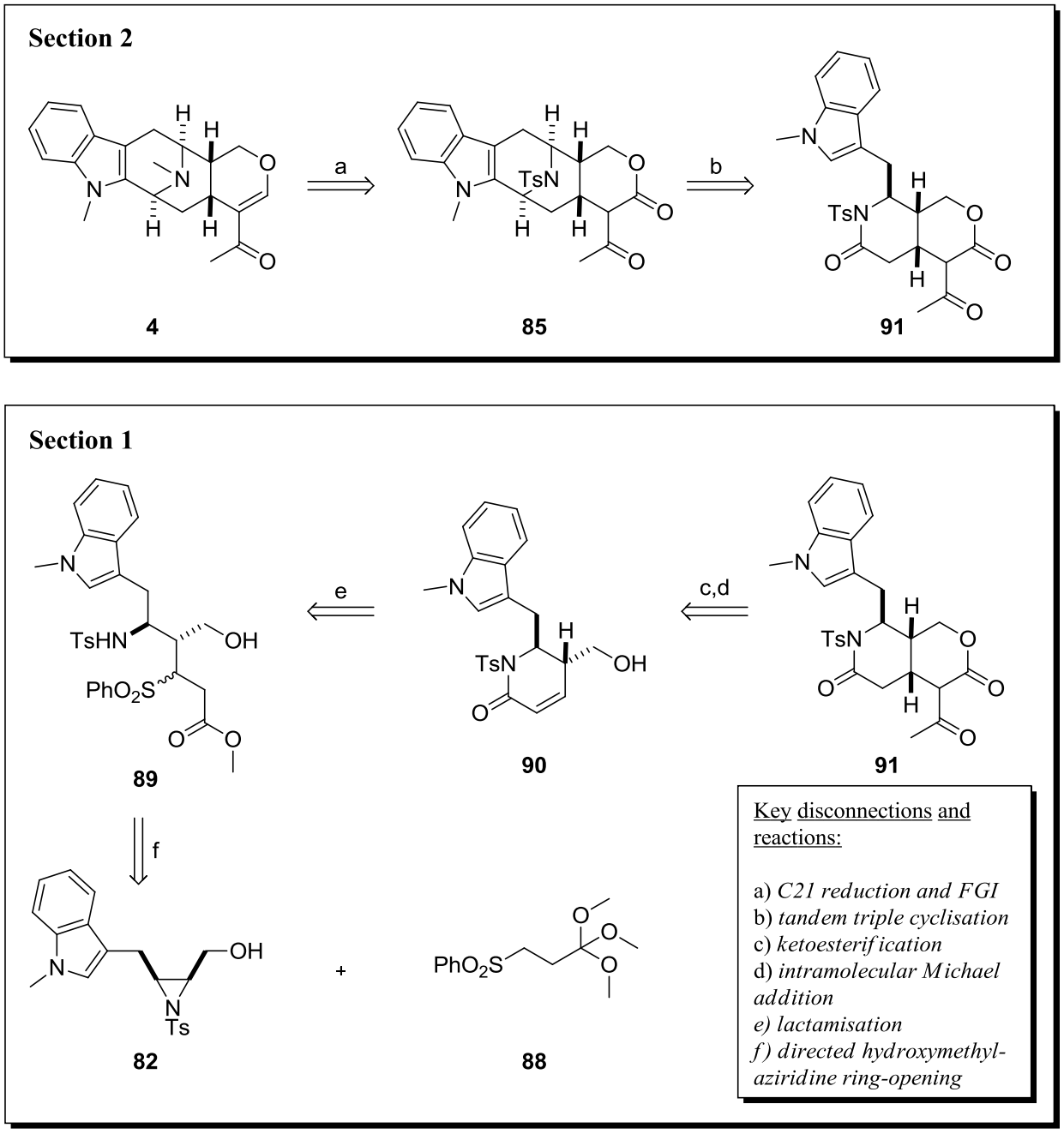
The premature Pictet–Spengler cyclisation of **84d** observed by Wildman (Scheme **24**, Page **46**),[66] would be addressed by altering the order in which the E- and C-rings were constructed. We would ensure that the Pictet–Spengler cyclisation could not occur before the E-ring is synthesised by synthesising an equivalent intermediate to the tetrahydropyridine **84c** used previously. The new intermediate **90** will contain an α,β-unsaturated lactam ring in-place of the tetrahydropyridine motif employed previously. This would act as a masked tetrahydropyridine and would remain unreactive to Pictet–Spengler cyclisation until partial reduction of the lactam carbonyl group. The E-ring would then be introduced, by stepwise β-ketoesterification of lactam alcohol **90** and diastereoselective intramolecular Michael addition of the resulting β-ketoester.

The masked tetrahydropyridine lactam–alcohol **90** would be synthesised by directed ring-opening of hydroxymethyl-substituted aziridine **82**, as discussed in the conjugated iminium approach, but the sulfone nucleophile would contain the orthoester moiety **88**, this would allow access into the lactam-oxidation level of **90**.

Section 2.2 Synthesis of Macroline-related alkaloids from lactam–alcohol 90

Following E-ring formation, the second stage of the synthesis would begin with partial reduction of the lactam carbonyl to unmask tetrahydropyridine **84c** and affect the Pictet–Spengler cyclisation. This would be followed by oxidation level adjustment of the E-ring and FGI to complete the synthesis of alstonerine. The synthesis of related indole alkaloids will also be discussed in this section.

Figure 16. Retrosynthesis for the final approach (±)-alstonerine **4**.



2.1 Synthesis of key intermediate α,β-unsaturated lactam–alcohol 90

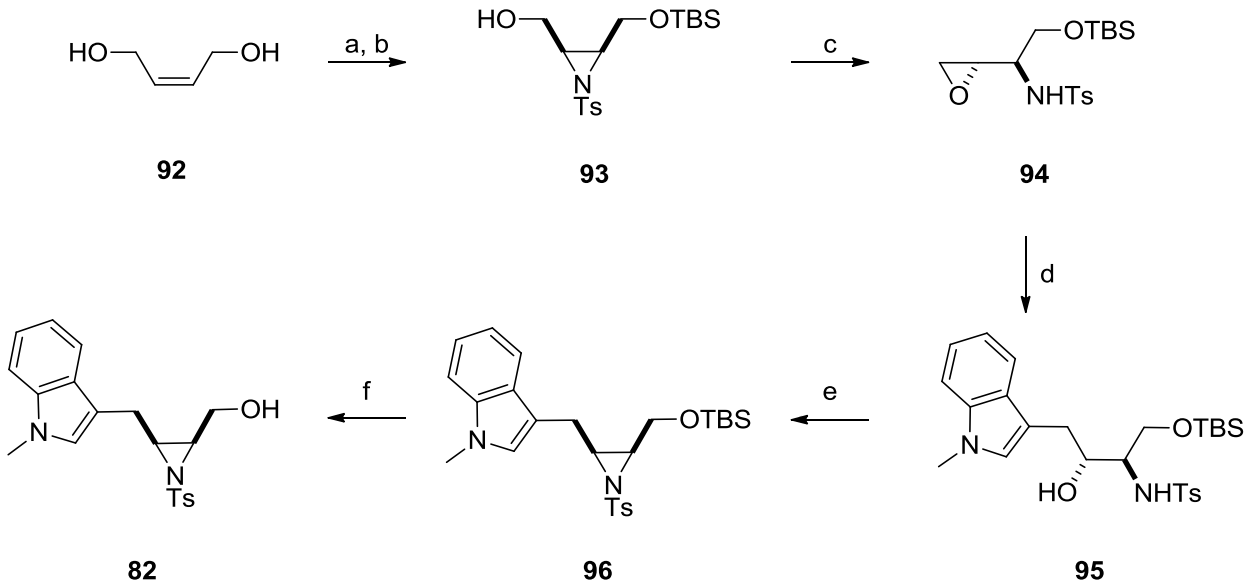
2.1.1. Synthesis of strategy-level directed aziridine ring-opening reaction substrates

In order to optimise the aziridine ring-opening reaction, we had first to carry out the synthesis of hydroxymethyl-substituted aziridine **82** and trimethyl 3-(phenylsulfonyl)orthopropionate **88** in a concise and efficient manner, such that large quantities of each would be readily accessible.

2.1.2. Synthesis of hydroxymethyl-substituted aziridine 82

Previous work within the group by Mathie[66] and Tholen[57] had established a robust route, by which hydroxymethyl-substituted aziridine **82** was prepared on multi-gram scale from *Z*-2-butene-1,4-diol **92**, in an overall yield of 50% over six steps. (Scheme **25**)

Scheme 25. Synthesis of hydroxymethyl-substituted aziridine **82**.



a) NaH (0.98 equiv.), THF, 0°C→rt, 24 h, then TBSCl (0.98 equiv.), rt, 24 h, 98%; b) Chloramine-T (1.2 equiv.), PTAB (0.1 equiv.), MeCN, rt, 48 h, 76%; c) NaH (4.0 equiv.), THF, 0°C→rt 4 h, then cooled to –78°C and saturated aqueous NH_4Cl (excess), 94%; d) 1-methylindole (2.0 equiv.), $BF_3{\cdot}OEt_2$ (1.1 equiv.), anhydrous $NaHCO_3$ (4.0 equiv.), CH_2Cl_2, –78°C, 6 h, 87%; e) DIAD (1.5 equiv.), Ph_3P (1.2 equiv.), THF, rt, 16 h, 86%; f) $TBAF{\cdot}3H_2O$ (1.1 equiv.), THF, 0°C→rt, 16 h, 95%.

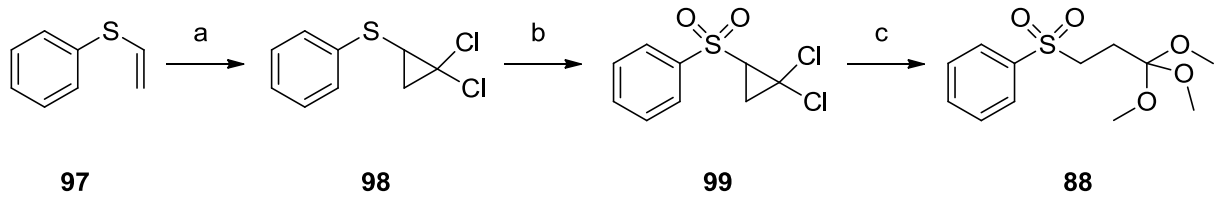
Monoprotection of *Z*-2-butene-1,4-diol **92** as the TBS silyl ether and subsequent hydroxyl-assisted aziridination[69] afforded *syn*-configured aziridine **93**. Sodium or potassium hydride-mediated aza-Payne rearrangement of **93** ensued stereospecifically with inversion of configuration at the C2 carbon *via* an S_N2 type mechanism, to give epoxide **94** in excellent yield.

Boron trifluoride etherate assisted ring-opening of epoxide **94** by N_1-methylindole occurred at the less hindered position to give *anti*-amino alcohol **95**. The *syn*-aziridine motif in **96** was reformed using Mitsunobu aziridination conditions.[70] *O*-Silyl deprotection using TBAF completed the synthesis of the hydroxymethyl-substituted aziridine **82**.

2.1.3. Synthesis of sulfone 88

Although Ghosez and co-workers had described the synthesis of trimethyl 3-(phenylsulfonyl)orthopropionate **88** from the methanolysis of the β-sulfonylnitrile derivative of acrylonitrile,[71] the work of Parham had been used previously within the group.[72,73,74] Dichlorocyclopropanation of phenyl vinyl sulfide **97** followed by *S*-oxidation to sulfone **99** and basic methanolysis gave orthoester **88** in ~ 50% yield on small scale (Scheme **26**).

Scheme 26. *Original synthesis of orthoester* **88**.



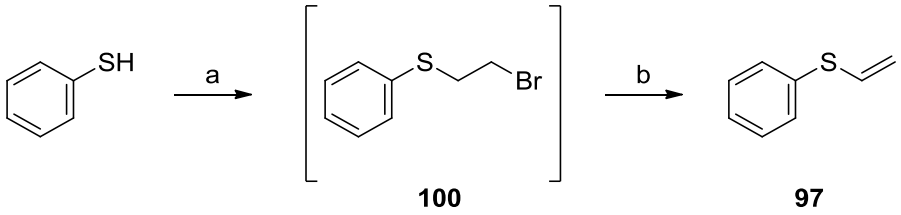
97 **98** **99** **88**

a) CCl_3CO_2Et (1.3 equiv.), NaOMe (1.5 equiv.), Petrol[80], –20°C→rt, 18 h, 61% following the method outlined by Tholen[57]; b) H_2O_2 (4.0 equiv.), HOAc, 100°C, 3 h, 90%; c) NaOMe (3.5 equiv.), MeOH, 65°C, 3 h, 98%.

Although yields were generally acceptable for the preparation of **88** on a small scale (~2.5 g), the expense of phenyl vinyl sulfide, duration of the sequence and poor cyclopropanation reaction led to an investigation into a more practical route for multi-gram synthesis.

Our first step was to find a scalable synthesis of phenyl vinyl sulfide. This was achieved by following the method of Carr and co-workers, whereby we were able to synthesise a 23 g batch of phenyl vinyl sulfide **97** in 68% yield from benzenethiol using a one-pot procedure.[75] Of the many reported syntheses of phenyl vinyl sulfide,[76,77,78,79] this method was chosen in order to avoid handling the powerful alkylating agent 1-phenylthio-2-bromoethane **100** and gaseous halogens (Scheme **27**, below).

Scheme 27. Scalable synthesis of phenyl vinyl sulfide **97**.



a) NaOEt (1.0 equiv.), $C_2H_4Br_2$ (1.5 equiv.), EtOH, –30°C→rt, 30 min, then NaOEt, 95°C, 24 h, 68%.

With a scalable route to phenyl vinyl sulfide in hand, optimisation of the dichlorocyclopropanation reaction would lead to a practical and scalable route to orthoester **88**.

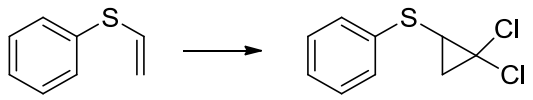
2.1.4 Recrystallisation of sulfone 99

The conditions outlined previously for the dichlorocyclopropanation of phenyl vinyl sulfide gave poor yields of purified 2,2-dichlorocyclopropyl phenyl sulfide **98**, due to product degradation during purification by distillation. To avoid this, the viability of *S*-oxidising the crude material obtained from dichlorocyclopropanation of phenyl vinyl sulfide was investigated. We knew that the resulting 2,2-dichlorocyclopropyl phenyl sulfone **99** was a crystalline solid. Therefore, we envisaged that upon *S*-oxidation, sulfone **99** could be separated from residual ethyl methyl carbonate, (produced from ethyl trichloroacetate during the cyclopropanation) by crystallisation. Investigations into a suitable solvent system found that a 2:1 petrol:ethanol solvent system allowed recovery of 2,2-dichlorocyclopropyl phenyl sulfone **99** from a mixture containing 50% ethyl methyl carbonate. Critically, *S*-oxidation of phenyl vinyl sulfide remaining from the dichlorocyclopropanation step resulted in phenyl vinyl sulfone, which could not be separated from the desired product *via* recrystallisation. Thus, in order purify 2,2-dichlorocyclopropyl phenyl sulfone **99** by recrystallisation on large scale, the dichlorocyclopropanation reaction required optimisation.

2.1.5 Optimisation of dichlorocyclopropanation synthesis of 98

Initial attempts using petrol distilled from calcium hydride and ethyl trichloroacetate as supplied from the manufacturer showed no conversion (Entry **1**, Table **1**). We suspected that this complete lack of reactivity was due to a competitive reaction between any olefinic impurities in the petrol and the reactive intermediate dichlorocarbene (Entry **2**, Table **1**). With this in mind, ethyl trichloroacetate was added at a rate of 6.0 mL min^{-1} to a solution of **97** and excess NaOMe in olefin free petrol[80] at –20°C. After warming to room temperature overnight and work-up, ^{1}H NMR analysis showed complete consumption of starting material (Entry **3**, Table **1**). Although these conditions were viable for small-scale synthesis, the difficulties involved in removing olefin impurities by washing litres of petrol with concentrated sulfuric acid and $KMnO_4$ led to the search for an alternative solvent for large scale synthesis. Concurrent dichlorocyclopropanation reactions were run in toluene, cyclohexane and CH_2Cl_2 at 0°C (Entries **4**, **5** and **6** respectively, Table **1**). Analysis by TLC after 1 h showed that the rate of reaction was hugely increased in CH_2Cl_2, reaching completion after 1 h (Entry **6**, Table **1**). The reaction temperature was decreased to −78°C, and the addition of ethyltrichloroacetate carried out dropwise *via* dropping funnel on large scale (Entry **7**, Table **1**). This eliminated the potentially dangerous temperature spike that was observed during small-scale reactions.

Table 1. Dichlorocyclopropanation of phenyl vinyl sulfide.



97 **98**

Entry	Conditions	Time	Temp.	Conversion%
1	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), Petrol[b]	24 h	−20°C	0
2	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), Petrol[c]	24 h	−20°C	50 − 60
3	CCl_3CO_2Et (1.3 equiv.),[d] NaOMe (1.5 equiv.), Petrol[c]	24 h	−20°C	90
4	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), PhMe	24 h	0°C	~ 60
5	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), C_6H_{12}	24 h	0°C	0
6	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), CH_2Cl_2	1 h	0°C	100
7	CCl_3CO_2Et (1.3 equiv.),[a] NaOMe (1.5 equiv.), CH_2Cl_2	4 h	−78 → 0°C	100

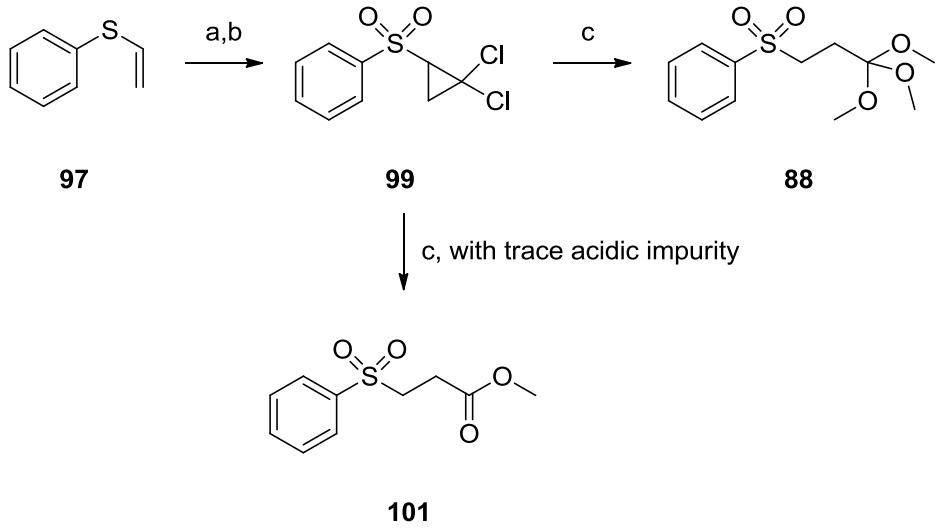
[a] ethyl trichloroacetate added in one portion dropwise; [b] petrol distilled over CaH_2; [c] olefin free petrol[80]; [d] ethyl trichloroacetate added at rate of 6.0 mL min^{-1}.

S-Oxidation of crude dichlorocyclopropane **98** obtained using CH_2Cl_2 (Entry **7**, Table **1**), was achieved using peracetic acid generated *in situ* from acetic acid and hydrogen peroxide. Recrystallisation from 2:1 petrol:ethanol yielded 2,2-dichlorocyclopropyl phenyl sulfone **98** in >90% over two steps.

2,2-Dichlorocyclopropyl phenyl sulfone **99** was converted into trimethyl 3-(phenylsulfonyl)orthopropionate **88** in 98% yield, by treating **99** with sodium methoxide in anhydrous methanol under reflux for 3 hours. Even trace acidic impurities remaining from the *S*-oxidation, led to complete hydrolysis and gave methyl-3-(phenylsulfonyl)propionate **101** in

quantitative yield. In order to avoid the formation of **101** during large scale production of sulfone **88**, dichlorocyclopropane **98** was purified by chromatography prior to methanolysis.

Scheme 28. Scalable synthesis of orthoester **88**.



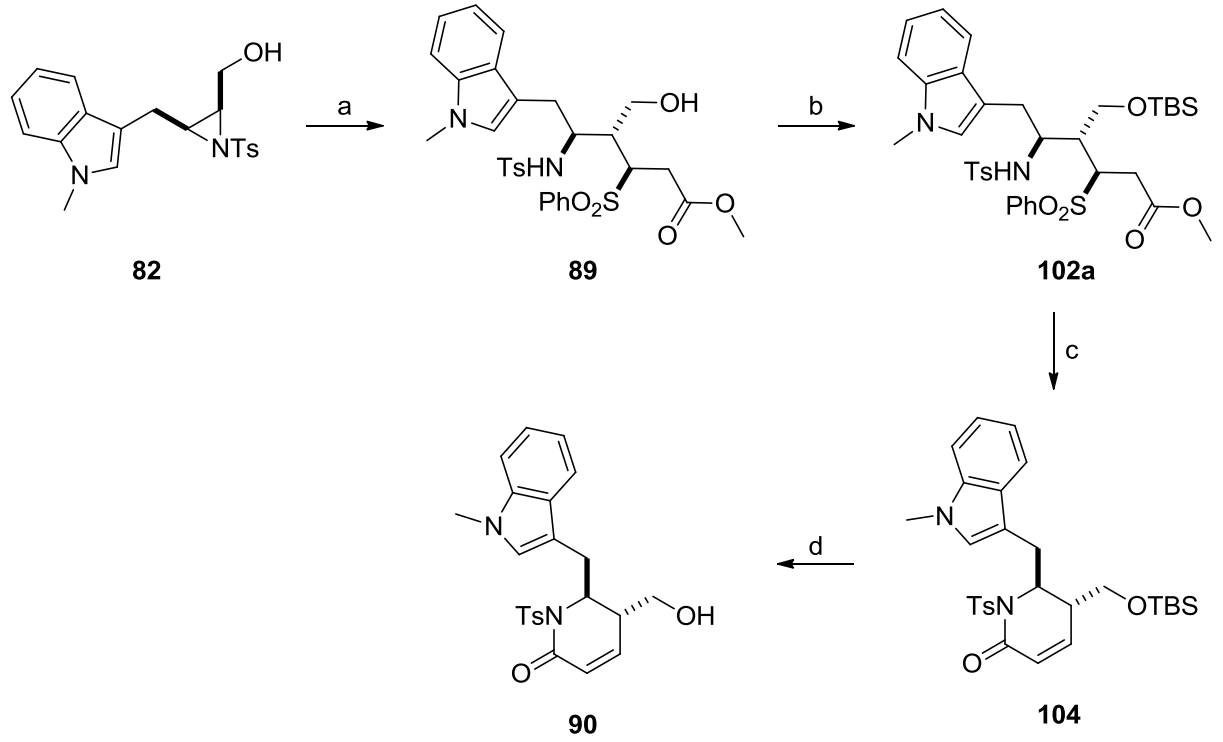
97 **99** **88** **101**

a) CCl_3CO_2Et (1.5 equiv.), NaOMe (2.0 equiv.), CH_2Cl_2, –78°C→rt, 6 h; b) H_2O_2 (4.0 equiv.), HOAc, 100°C, 4 h, 91% over two steps; c) NaOMe (3.5 equiv.), MeOH, 65°C, 3 h, 98%.

2.1.6 Initial work towards the synthesis of key intermediate lactam–alcohol 90

Initial investigations were based on the synthesis of methyl ester **102**, as outlined previously by Tholen.[81,57] Treatment of lithiated sulfone **88** with *O*-lithiated hydroxymethyl-substituted aziridine **82**, followed by mildly acidic work-up, reportedly gave methyl ester **89** as a single diastereoisomer. However, during initial investigations into moving from milligram test reactions to multigram synthesis, methyl ester **89** proved difficult to isolate.

Scheme 29. Original four step synthesis of α,β-unsaturated lactam–alcohol **90**.



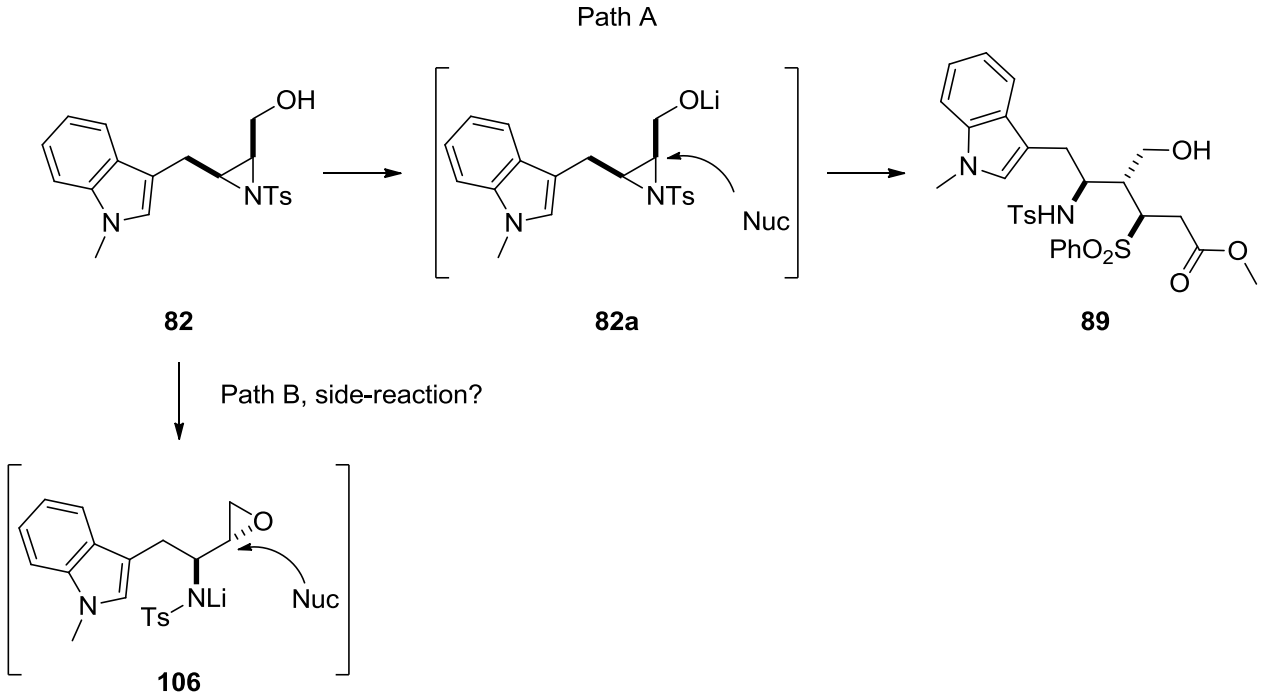
a) *n*-BuLi (4.1 equiv.), sulfone **88** (2.5 equiv.), THF, –40°C→rt overnight, then 10% citric acid, typically <30%; b) TBSCl (1.5 equiv.), imidazole (1.5 equiv.), DMAP (0.1 equiv.), DMF, rt, 3 h, 49%; c) 2M TMA (1.1 equiv.), toluene, rt, 30 min, then 80°C, 3 h, 49%; d) AcOH:H_2O:THF, rt, 30 h, 65%.

Although it was believed that the acidic orthoester hydrolysis conditions were responsible for the capricious nature and low yield of the aziridine ring-opening reaction, it was decided that the possibility of side reactions/starting material degradation should also be eliminated. To achieve this, basic stability/mechanistic studies were carried out on both sulfone **88** and hydroxymethyl-substituted aziridine **82**, and the reactivity of aziridine **82** towards nucleophilic ring-opening was confirmed by reaction with lithiated methyl phenyl sulfone.

2.1.7 Substrate stability and mechanistic investigation

We envisaged that degradation of starting materials could be contributing to the low yields observed for the ring-opening reaction. We also hoped to provide evidence to support our claim that ring-opening occurs *via* directed addition of the sulfone nucleophile to hydroxymethyl substituted aziridine **82a** (Path **A**, Figure **A**, below), rather than the possible alternative, whereby an aza-Payne rearrangement occurs, followed by addition to the resulting epoxide **106** (Path **B**, Figure **17**).

Figure 17. Plausible mechanisms for nucleophilic ring-opening of **82**.

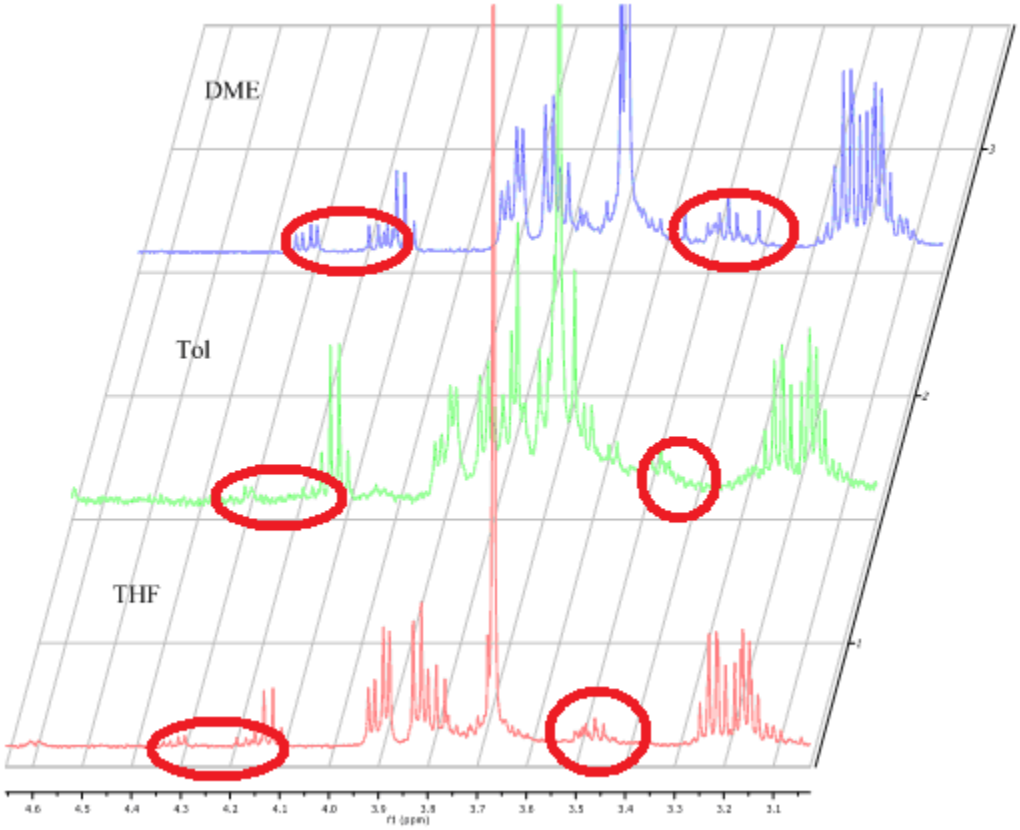


In order to probe its reactivity towards aza-Payne rearrangement, hydroxymethyl-aziridine **82** was treated with excess *n*-BuLi in various solvents, and the reaction followed by NMR over a prolonged time period. For reference, the suspected aza-Payne by-product **106** was first synthesised by treating hydroxymethyl-aziridine **82** with NaH in THF at 0°C (for experimental procedure, see Page **137**). This gave epoxide **106** in 77% yield.

To solutions of hydroxymethyl-aziridine **82** in THF, toluene and DME at −78°C was added *n*-BuLi. Small aliquots of reaction mixture were then taken at varying temperatures, subjected to identical aqueous work-up and analysed by ^{1}H NMR. (Figure **18**,

below) The spectra were then compared to that of epoxide **106**. ^{1}H NMR analysis (Figure **18**) provided evidence that hydroxymethyl substituted aziridine **82** does not undergo aza-Payne rearrangement in THF at temperatures below –30°C. The formation of the new doublet of doublets at 4.26 ppm in the DME and toluene reactions can be assigned to the product of aziridine ring-opening by water, due to trace amounts in the solvent or upon work-up.

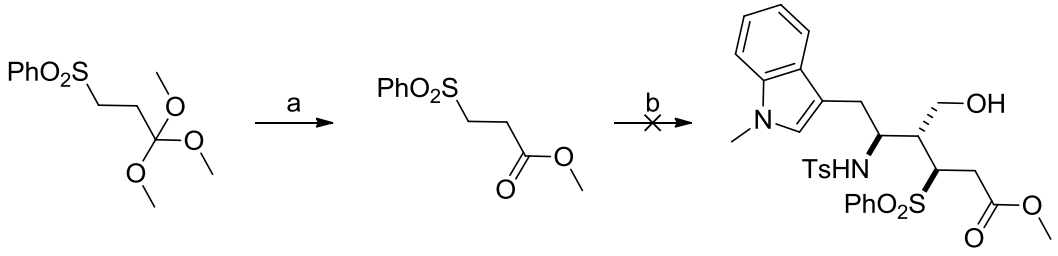
Figure 18. ^{1}H NMR analysis after 3 h at –30°C showing no aza-Payne rearrangement of **82**.



2.1.8 Sulfone stability

We also needed to assess the stability of lithiated sulfone **88** to hydrolysis under our reaction conditions. The suspected by-product was again synthesised for reference. Sulfonyl orthoester **88** was stirred in HCl:THF solution for 16 hours, yielding methyl ester **101** in 97% yield. No ring-opening products were observed when ester **101** was reacted with aziridine **82** under standard ring-opening conditions.

Scheme 30. Synthesis of suspected sulfone by-product **101** and attempted ring-opening of **82**.

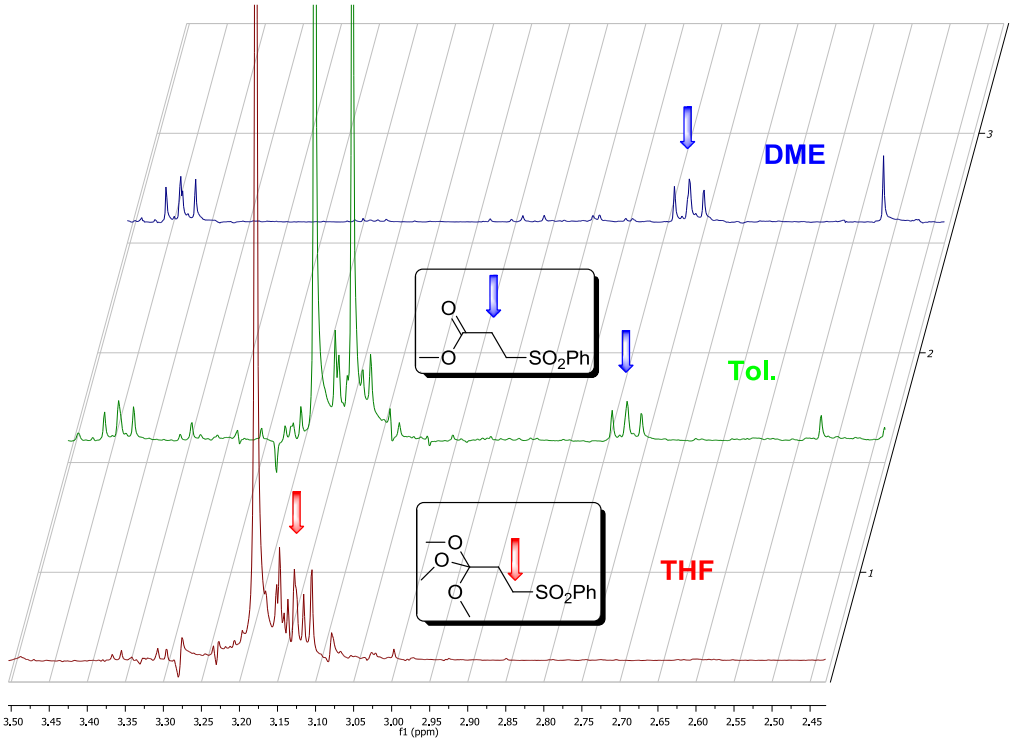


88 **101** **89**

a) aqueous 2M HCl (5.0 equiv.), THF, rt, 1 h, 97%; b) Standard aziridine ring-opening conditions.

To assess the extent of orthoester hydrolysis occurring during the ring-opening reaction, *n*-BuLi was added to solutions of sulfonyl orthoester **88** in THF, toluene and DME at –78°C. The reaction mixtures were allowed to warm slowly from –78°C to room temperature over a period of 24 hours, and small aliquots were again taken at varying temperatures, subjected to identical aqueous work-up and ^{1}H NMR (Figure **19**, below).

Figure 19. ^{1}H NMR analysis after 3 h at –35°C showing orthoester hydrolysis of **88**.

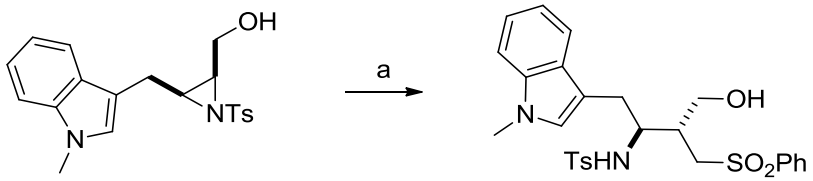


Analysis by ^{1}H NMR showed no trace of orthoester hydrolysis after 3 hours at –35°C in THF. Both reactions in toluene and DME showed considerable hydrolysis at this temperature. The reactions were allowed to warm slowly from –35°C to room temperature overnight. Following work-up and NMR, the spectra of the THF reaction showed negligible formation of methyl ester **101**. This provided evidence that orthoester hydrolysis was not responsible for the poor reaction yield.

2.1.9 Aziridine 81 reactivity towards sulfone nucleophiles

Having demonstrated that neither of our ring-opening reactants **82** or **88** was being consumed by side-reactions, and provided evidence to support the hydroxymethyl-directed aziridine ring-opening mechanistic hypothesis, it remained to confirm the reactivity of *O*-lithio hydroxymethyl-substituted aziridine **82** towards ring-opening. This was achieved by reacting *O*-lithio hydroxymethyl-substituted aziridine **82** with an analogue of the sulfone nucleophile. The lithio anion of phenyl methyl sulfone **105** was chosen as a model nucleophile. Importantly, **105** had previously been shown to undergo regio- and stereoselective ring-opening reactions with aziridines by the Craig group.[52] The combination of lithiated phenyl methyl sulfone **105** with the *O*-lithiated **82** and work-up with 10% aqueous citric acid effected stereospecific and completely regioselective aziridine ring-opening. Sulfonamidoalcohol **107** was isolated in 73% yield as a single diastereomer.

Scheme 31. Ring-opening reaction of hydroxymethyl-substituted aziridine **82** with model nucleophile **105**.



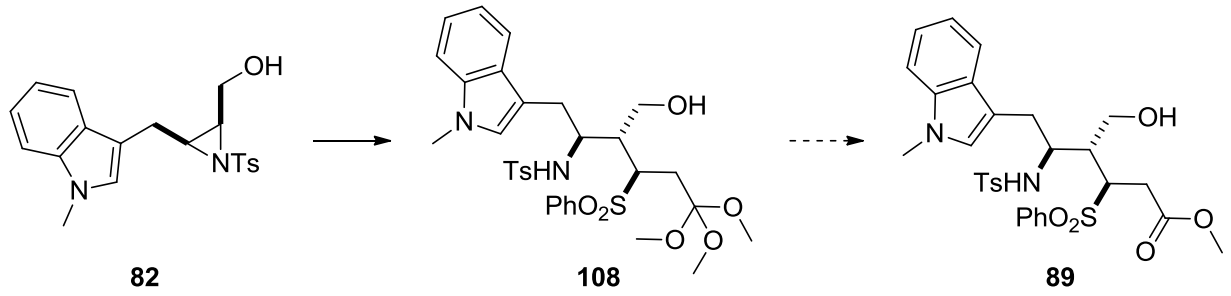
82 **107**

a) *n*-BuLi (2.5 equiv.), $MeSO_2Ph$ **105** (2.0 equiv.), THF, –40°C, 2 h, then 10% aqueous citric acid, 73%.

2.1.10 Orthoester hydrolysis in the synthesis of 89

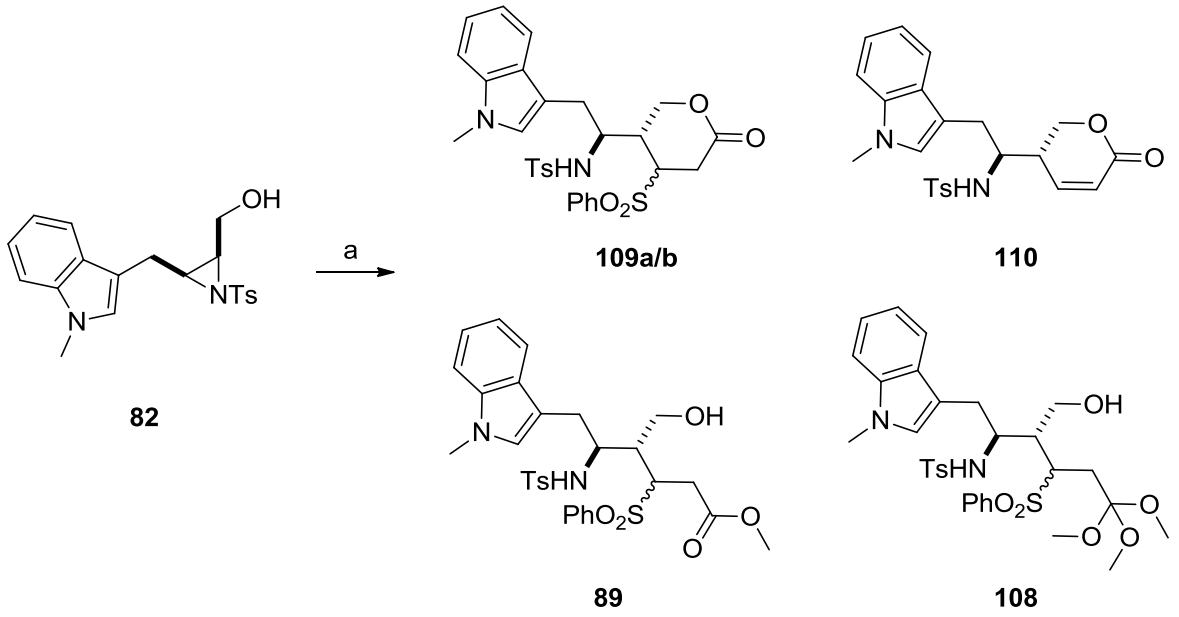
Having proven aziridine **82** was a suitably reactive electrophile and stable to degradation under the reaction conditions, and that sulfone **88** was not being consumed by side-reactions, our attention turned to evaluating the conditions required for the hydrolysis of the orthoester moiety in the ring-opened product **108**.

Figure 20. Problematic acid-induced hydrolysis of orthoester **108**.



Unfortunately, forming the desired methyl ester **89** proved less straightforward than expected. Initial attempts showed that use of excess saturated aqueous NH_4Cl to quench the ring-opening reaction (Entries **1** and **2**, Table **2**, below) provided an insufficiently acidic medium to effect hydrolysis of the orthoester moiety. Switching to aqueous 10% citric acid provided complex mixtures of products **89** and **108** (Entry **3**, Table **2**), without complete orthoester hydrolysis. Increasing the acidity by using saturated aqueous citric acid solution, gave mixtures of **109** and **89** (Entries **4**–**6**, Table **2**), but importantly no **108** meaning that complete hydrolysis had occurred. The next attempt used concentrated aqueous HCl solution and gave α,β-unsaturated *δ*-lactone **110** as the single product in good yield (Entry **8**, Table **2**). The use of 2M aqueous HCl solution also gave complete hydrolysis, giving lactones **109** as a mixture of sulfone epimers in good yield (Entry **7**, Table **2**). Attempts using acetic acid and TFA also failed to give **89** in reliable yield, and as such an alternative to the ring-opening of **82** was investigated.

Table 2. Hydroxymethyl-substituted aziridine **82** ring-opening optimisation.



Entry	a) **Conditions**	**Ratio**	**Yield%**
1	**88** (1.5 equiv.), *n*-BuLi (2.5 equiv.), –78°C → rt overnight, saturated NH_4Cl[a]	3 : 1 (**108**:**89**)	78
2	**88** (1.5 equiv.), *n*-BuLi (2.5 equiv.), –78°C → rt overnight, saturated NH_4Cl[b]	10 : 1 (**108**:**89**)	83
3	**88** (2.0 equiv.), *n*-BuLi (3.0 equiv.), –78°C → rt overnight, 10% citric acid[b]	3 : 1 (**108**:**89**)	73
4	**88** (2.0 equiv.), *n*-BuLi (3.0 equiv.), –78°C → rt overnight, saturated citric acid[b]	2:1 (**109**:**89**)	72
5	**88** (2.0 equiv.), *n*-BuLi (3.0 equiv.)[c], –78°C → rt overnight, saturated citric acid[b]	1:1 (**109**:**89**)	80
6	**88** (2.0 equiv.), *n*-BuLi (3.0 equiv.), –78°C → rt overnight, saturated citric acid[b]	3:1 (**89**:**109**)	63
7	**88** (1.5 equiv.), *n*-BuLi (2.8 equiv.), –78°C → rt overnight, 2M aqueous HCl[b]	**109**	80
8	**88** (1.5 equiv.), *n*-BuLi (3.0 equiv.), –78°C → rt overnight, *concentrated* aqueous HCl[b]	**110**	85[d]

[a] Base washed silica used for chromatography [b] silica used as supplied [c] concentrated n-BuLi used [d] yield estimated from crude ^1H NMR

In order to confirm that the ring-opening reaction was occurring with complete regioselectivity for the aziridine carbon atom proximal to the hydroxymethyl moiety, the structures of sulfones **109a** and **109b** were established by X-ray crystallography (Figures **21** and **22**, below). Pleasingly, the structures show that the ring-opening occurred with clean inversion of the aziridine carbon atom under attack, and illustrates the *anti*-relationship of the indolymethyl- and hydroxymethyl-substitutents (labelled C(12) and C(13) respectively, below).

Figure 21. The molecular structure of **109a**.

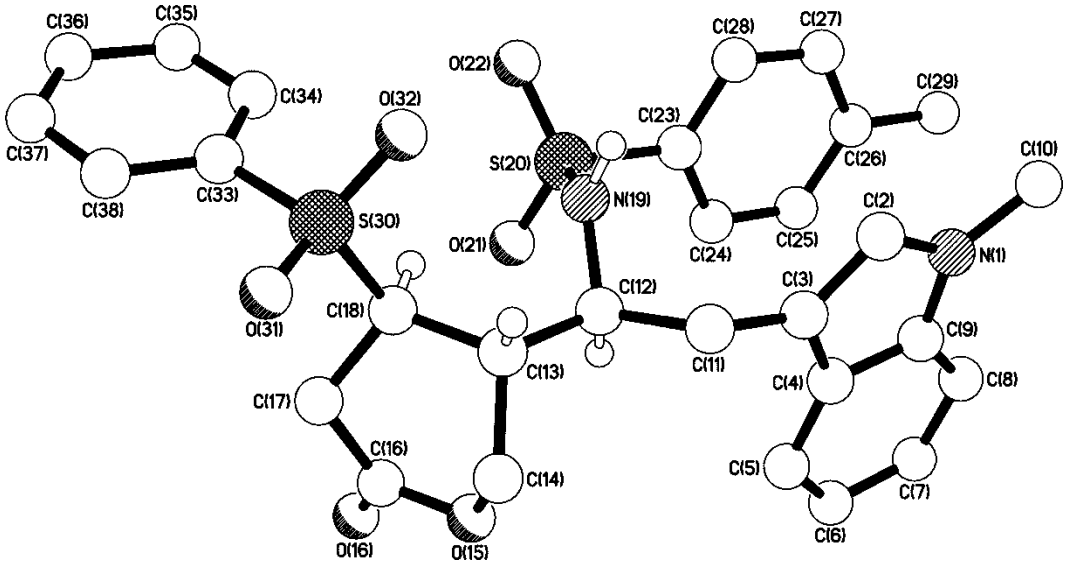
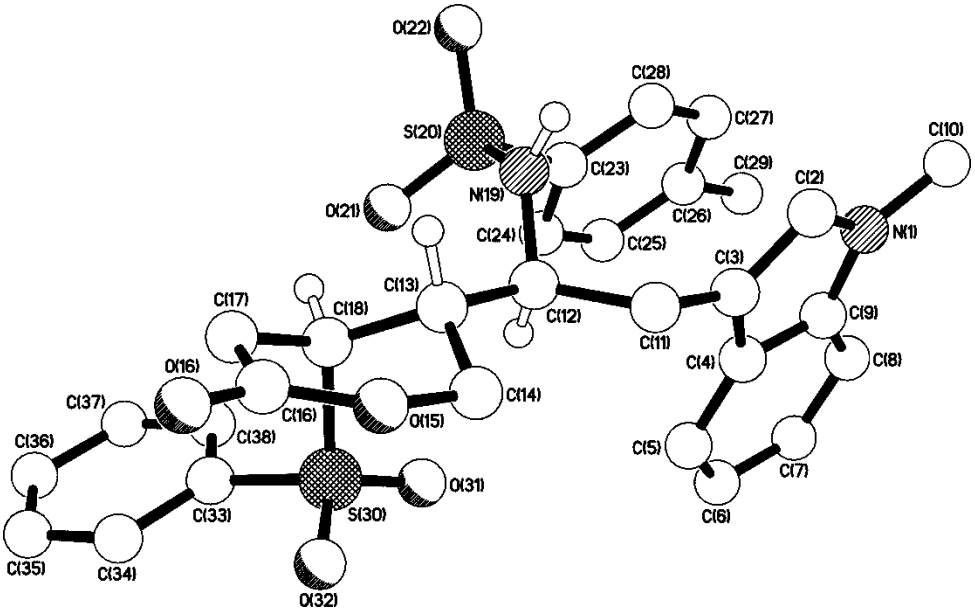


Figure 22. The molecular structure of **109b**.

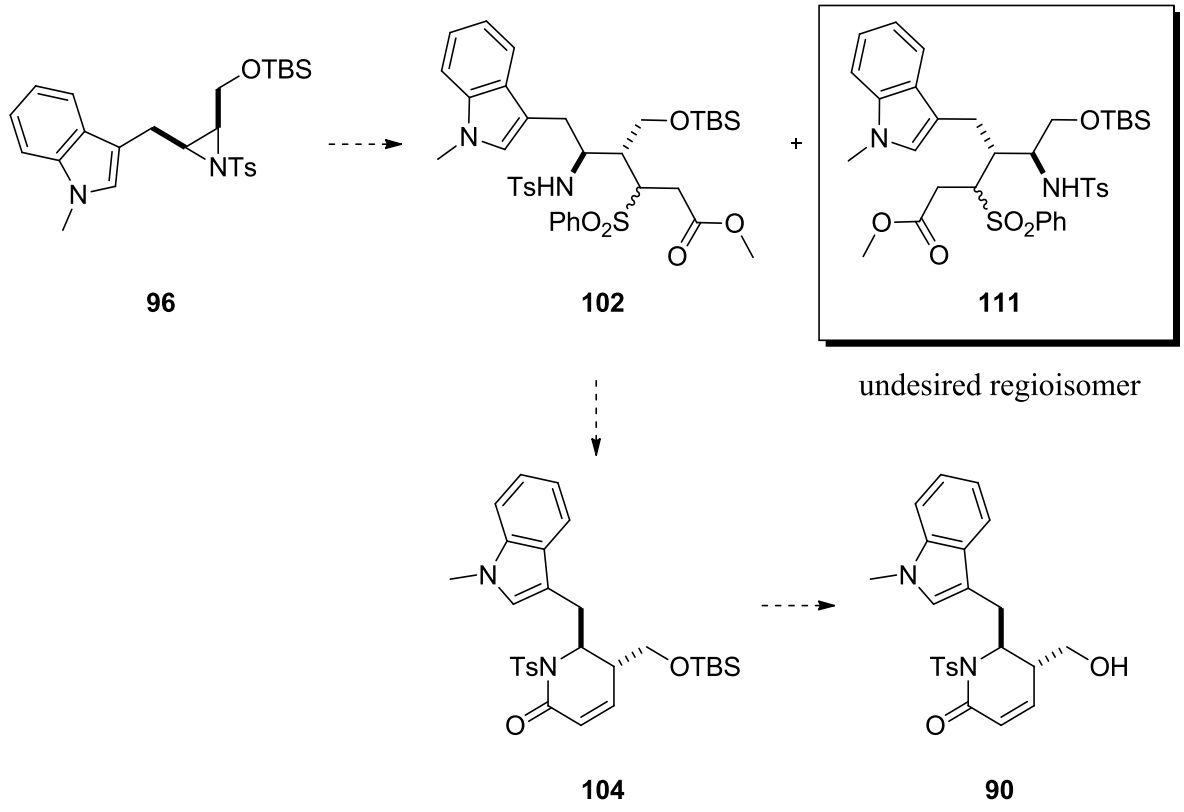


2.1.11 *O*-TBS protected aziridine 96 ring-opening strategy

With the unwanted lactonisation proving persistent, the possibility of using *O*-silyl protected hydroxymethyl-substituted aziridine **96** in the ring-opening reaction was briefly revisited. Previous work within the Craig group had found that when MOM-protected,[67] the regioselectivity of ring-opening reactions of hydroxymethyl-substituted aziridine **82** by the lithioanion of 1-phenylsulfonyl-3,3-dimethoxypropane **62** was severely eroded.

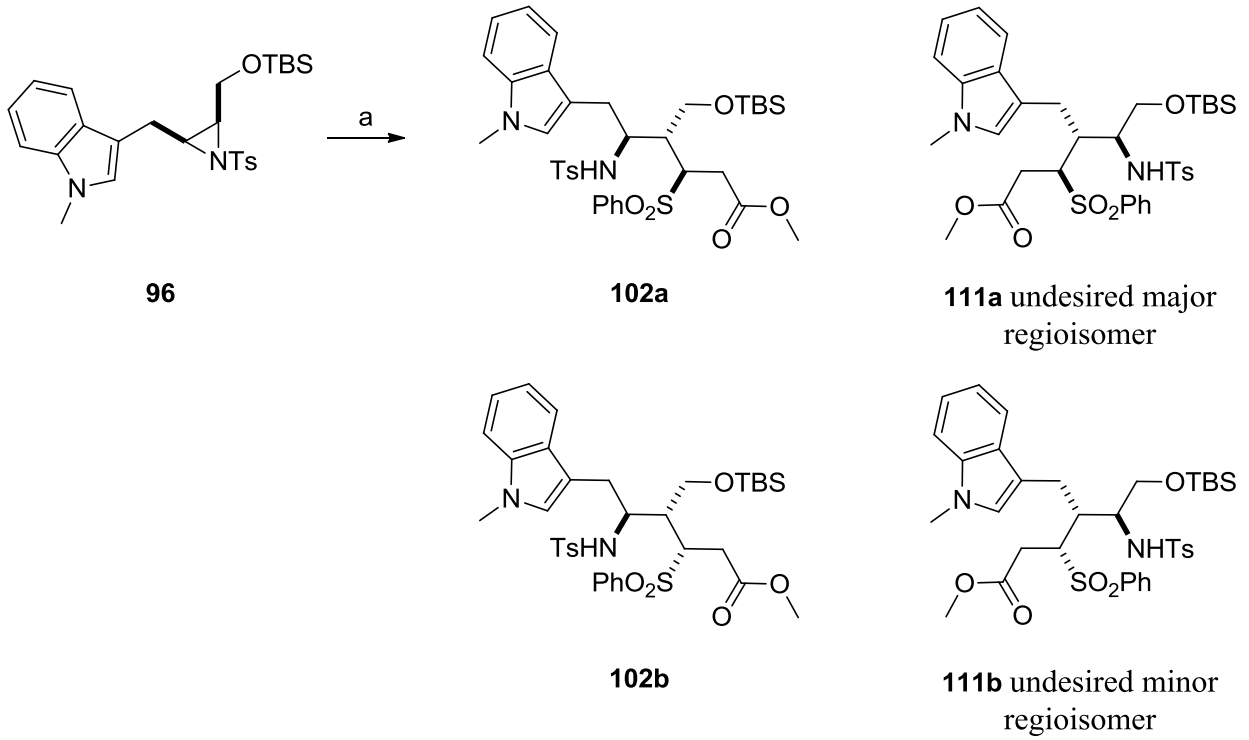
We rationalised that although *O*-silylation of hydroxymethyl-aziridine **82** was likely to decrease the regioselectivity of the ring-opening reaction, lactonisation of the resulting product **102** would be avoided. This would lead to a robust route to intermediate **90**, without altering the overall number of steps in the synthesis. Importantly, the regioisomers **111** must be separable. Lactam formation would give **104**, which would be deprotected to give α,β-unsaturated lactam–alcohol **90**.

Figure 23. Route to α,β-unsaturated lactam–alcohol **90** *via* *O*-TBS hydroxymethyl-substituted aziridine **96**.



O-TBS protected hydroxymethyl-substituted aziridine **96** was treated with a solution of lithiated trimethyl 3-(phenylsulfonyl)orthopropionate **88** at –78°C for 2 hours. Work-up with 2M aqueous HCl and chromatography gave a mixture of epimeric regioisomers (~15:10:6:5 **102a**:**111a**:**111b**:**102b**) in good yield. This equated to a synthesis of *O*-TBS ring-opened regioisomer **102** in approximately 41% yield as a 3:1 mixture of sulfone epimers (Scheme **32**, below).

Scheme 32. Ring-opening reaction of *O*-TBS hydroxymethyl-substituted aziridine **96**.



96 **102a** **111a** undesired major regioisomer

102b **111b** undesired minor regioisomer

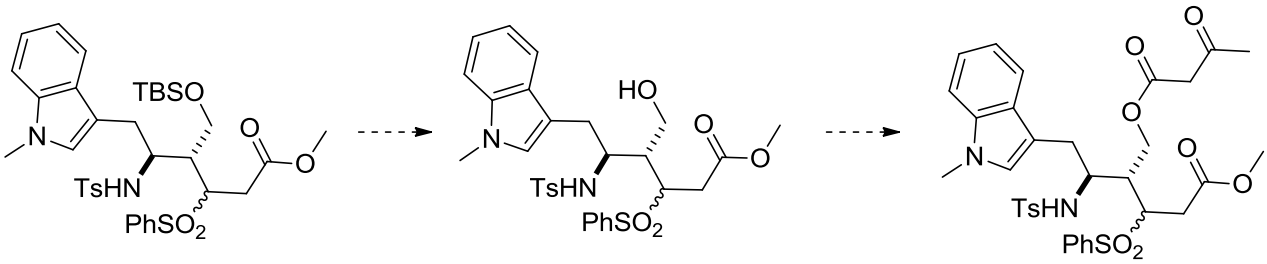
a) *n*-BuLi (2.0 equiv.), sulfone **88** (1.8 equiv.), THF, –78°C→rt o/n, then aqueous 2M HCl, 41%.

Although this route provided a reliable route to *O*-TBS-protected sulfonamidoalcohol **102**, the loss of regioselectivity in the ring-opening reaction was unacceptable for the final synthesis. The ring-opening of *O*-TBS **96**, did however provide us with significantly improved quantities of **102**. This allowed us to attempt the synthesis of the D- and E-rings, as well as providing material with which to investigate alternative routes to key intermediate lactam–alcohol **90** that did not require the need for *O*-silylation prior to lactamisation. In order to investigate these alternatives, we first required reliable desilylation conditions to convert *O*-TBS **102a** and **102b** into the target of the on-going aziridine ring-opening optimisation, sulfonamidoalcohol **89**.

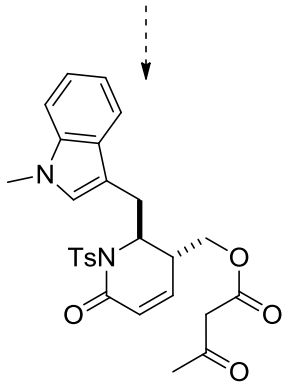
2.1.12 Deprotection of ring-opening product 102

With a route to larger quantities of *O*-TBS protected ester intermediate **102** established *via* ring-opening of *O*-TBS hydroxymethyl-substituted aziridine **96**, and with a view to removing the need for *O*-TBS protection prior to lactamisation from the eventual synthesis, we decided to investigate the selectivity of Lewis acid-catalysed cyclisation of intermediate **112** (Figure **24**, below). For these investigations, the cyclisation precursor **112** would be synthesised by deprotecting *O*-TBS ring-opening product **102** and subsequent β-ketoesterification of sulfonamidoalcohol **89**.

Figure 24. Route to β-ketoester lactam **113** *via* selective cyclisation of **112**.



AIMS;
Remove 2nd *O*-TBS protection
Chance to look at ketoesterification
Selectivity of intramolecular lactamisation

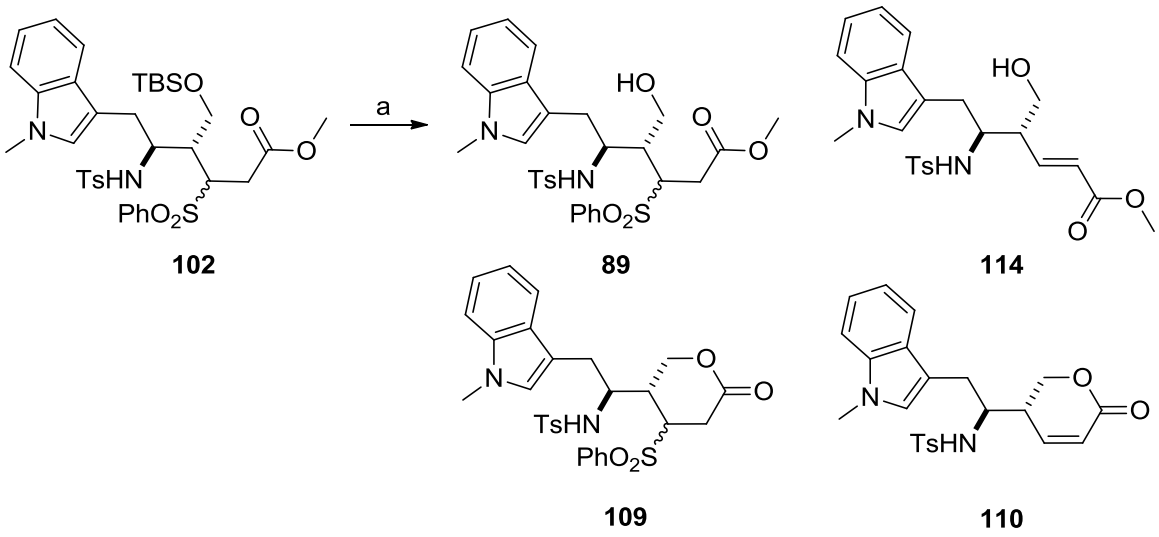


113

We initially attempted a one-pot simultaneous aziridine ring-opening of **96** and *O*-silyl deprotection by quenching with 10% HCl in MeOH. However, this proved unsuccessful and led to further investigations into conditions for the silyl deprotection of *O*-TBS **102**. Standard fluoride conditions were used for our initial attempts, but both TBAF[82] and HF-pyridine[83] gave *trans*-α,β-unsaturated ester **114** in 76 and 68% yields respectively. Therefore, alternative acidic

conditions[84] were attempted. This would avoid the unwanted elimination reaction that occurred rapidly in the presence of basic fluoride. When *O*-TBS **102** was stirred in a 1% HCl:EtOH solution, clean deprotection was observed, but acid-catalysed transesterification gave the ethyl ester derivative of **89** in quantitative yield. When repeated with a solution of 1% HCl:MeOH followed by neutralisation with solid $NaHCO_3$, filtration and concentration, deprotected methyl ester **89** was obtained in 63% yield. By decreasing the concentration to 0.01M and increasing the reaction time, complete conversion was observed by TLC analysis, although the low yield remained. Investigations into the method of quenching the reaction led to an increased yield of 98% when NH_3 in MeOH was used (Table **3**).

Table 3. Silyl ether **102** deprotection

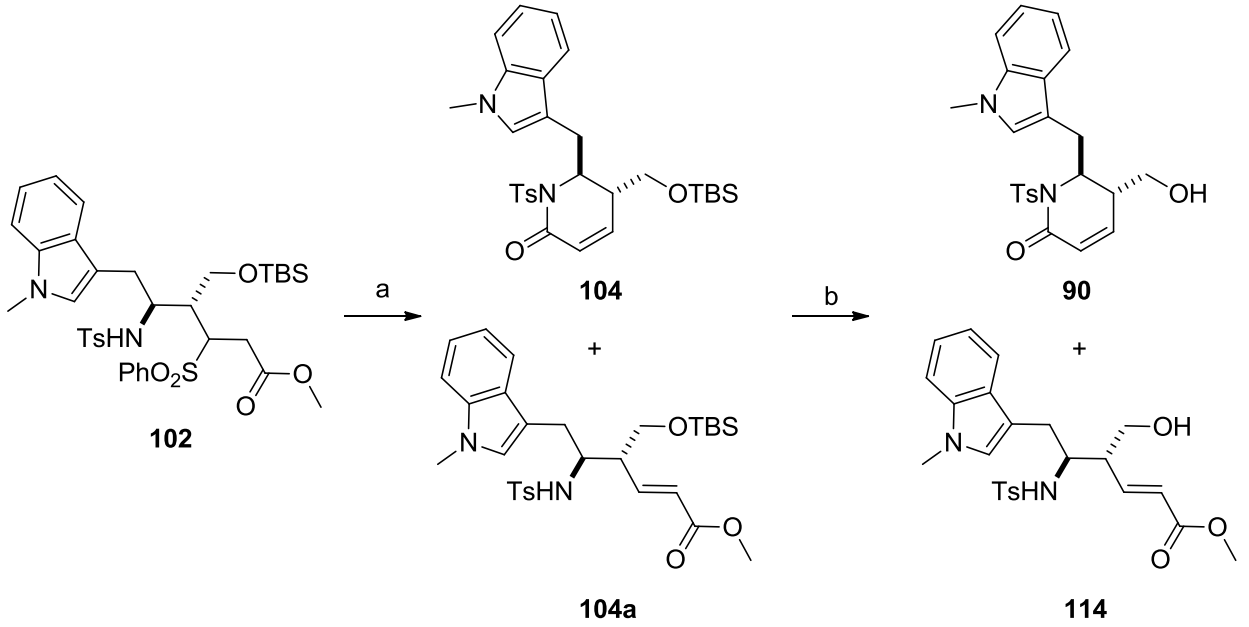


Entry	a) **Conditions**	**Ratio**	**Yield%**
1	TBAF·3H$_2$O (1.1 eq.), THF, 0°C, 15 min	**114**	76
2	HF·pyridine (1.1 eq.), THF, 0°C, 2 h	**114**	68
3	1% HCl in MeOH, 0.1M, rt, 6 h, aqueous $NaHCO_3$ (mg scale)	**89**	93
4	1% HCl in MeOH, 0.01M, rt, 16 h, aqueous $NaHCO_3$(>100 mg scale)	5:1 **89:114**	88
5	1% HCl in MeOH, 0.01M, rt, 16 h, then NH_3 in MeOH, –78°C, 15 min	**89**	98
6	1% HCl in MeOH, 0.01M, rt, 16 h, $MgSO_4$	**89**	67

2.1.13 Esterification of sulfonamidoalcohol 89 and subsequent TMA mediated cyclisation

The next stage of this approach was to synthesise the carbon skeletons of the D- and E-ring. As shown previously (Scheme **29**, Page **57**), ring-opened protected alcohol **102** was converted into α,β-unsaturated lactam–alcohol **90** (Scheme **33**, below). Although this route provided lactam–alcohol **90** which contained the core of the D-ring, the lactamisation suffered from a competing facile sulfone elimination reaction, as highlighted previously (Table **3**, Page **68**), which gave an inseparable mixture of *O*-TBS lactam **104** and eliminated *O*-TBS-*trans*-α,β-unsaturated ester **104a**. The unwanted *trans*-ester **104a** could be separated from the desired lactam–alcohol following *O*-TBS deprotection (Scheme **33**, below). Attempts to effect cyclisation of the *trans*-α,β-unsaturated ester **114** failed under prolonged thermal and microwave conditions, due to its rigid geometry (Scheme **33**, below).

Scheme 33. Original route to lactam–alcohol **90** and facile sulfone elimination of *O*-TBS **102**.

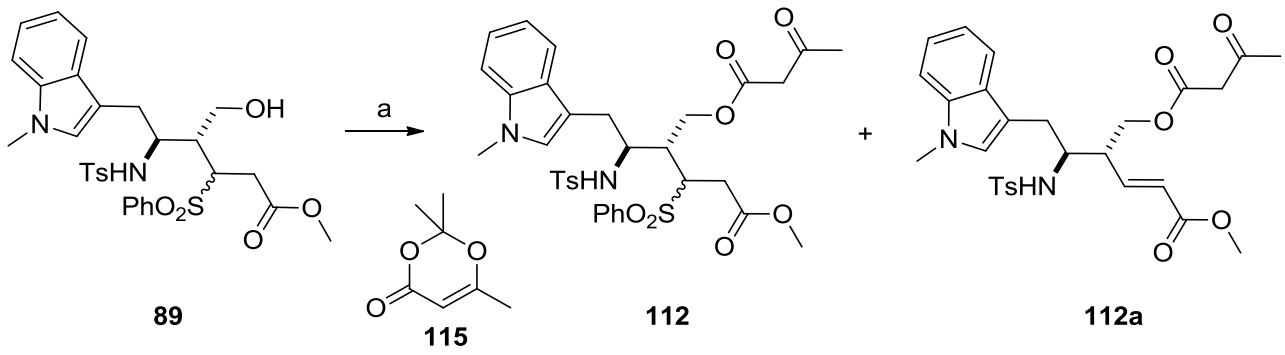


a) 2M TMA (1.1 equiv.), toluene, rt, 30 min, then 100°C, 3 h, 69%; b) AcOH:H_2O:THF, rt, 30 h, 65%.

With sulfonamidoalcohol **89** in hand as shown in the previous section (Table **3**, Page **68**), our attentions turned to removing the two protecting group steps by instead converting sulfonamidoalcohol **89** into the corresponding β-ketoester **112**. Both Wildman[66] and Tholen[57] had carried out similar transformations previously within the group, using either diketene or 4*H*-

2,2,6-trimethyl-1,3-dioxin-4-one. For the β-ketoesterification of **89** we chose the latter conditions, as we feared that the base-required in the diketene reaction would bring about the corresponding *trans*-α,β-unsaturated ester **112a** *via* the aforementioned facile sulfone elimination. Under thermal conditions (Entries **1**–**4**, Table **4**, below), only moderate yields of **112** were obtained as the prolonged reflux led to formation of *trans*-**112a**.[85] Decreasing the temperature to 90°C failed to improve the yield of **112**, however heating alcohol **89** with 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one **115** under microwave conditions significantly increased the yield of **112** (Entries **5**–**7**, Table **4**). Decreasing the duration of the microwave reaction provided **112** in 76% yield, with only trace amounts of **112a** (Entry **8**, Table **4**).

Table 4. β-ketoesterification of **89**.



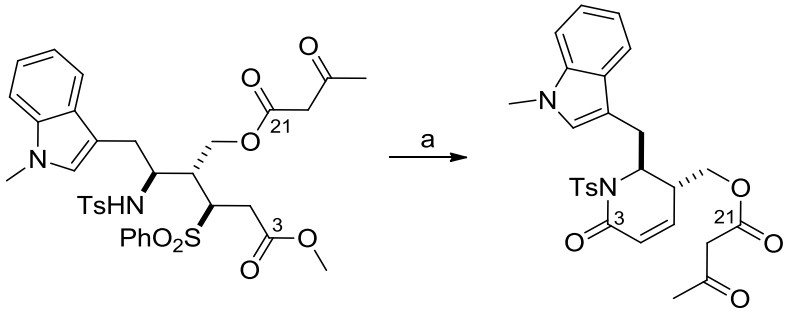
Entry	a) **Conditions**	Time	Temp.	Ratio 112:112a	Yield 112
1	**115** (1.1 equiv.), toluene	24 h	[a] 110°C	3:1	~ 30 – 50%
2	**115** (2.0 equiv.), toluene	24 h	[a] 110°C	3:1	~ 30 – 50%
3	**115** (2.0 equiv.), toluene	2 h	[a] 110°C	2:1	58%
4	**115** (1.5 equiv.), toluene	24 h	[a] 90°C	4:1	35%
5	**115** (1.5 equiv.), toluene	30 min	[b] 150°C	>90:1	75%
6	**115** (1.5 equiv.), toluene	30 min	[b] 130°C	trace **112a**	69%
7	**115** (1.5 equiv.), toluene	30 min	[b] 120°C	trace **112a**	68%
8	**115** (1.5 equiv.), toluene	30 min	[b] 150°C	trace **112a**	76%

[a] *Standard heating under reflux* [b] *Microwave heating in sealed tube*

Having established conditions for the synthesis of β-ketoester **112**, the cyclisation to α,β-unsaturated lactam β-ketoester **113** was attempted using the previously established

trimethylaluminium conditions. β-Ketoester **112** was converted into **113** *via* Lewis acid-catalysed lactamisation in 26% yield when using 2.0 equivalents of TMA. The reaction was selective in forming the desired N_4–C3 linked **113** over the possible N_4–C21 linked amide, however significant amounts of the corresponding *trans*-α,β-unsaturated ester were also formed, which was inseparable from the product. The yield of **113** was increased to 61% by decreasing the amount of TMA to 1.1 equivalents, but due to the persistence of the facile sulfone elimination, which persisted throughout the deprotection, β-ketoesterification and lactamisation steps of this approach, an alternative approach to the synthesis of the D-ring in lactam **113** was sought.

Scheme 34. Synthesis of the D-ring *via* lactamisation of β-ketoester **112**.



112 **113**

a) TMA (1.1 equiv.), toluene, 100°C, 1 h, saturated aqueous Rochelle salt, 26–61%.

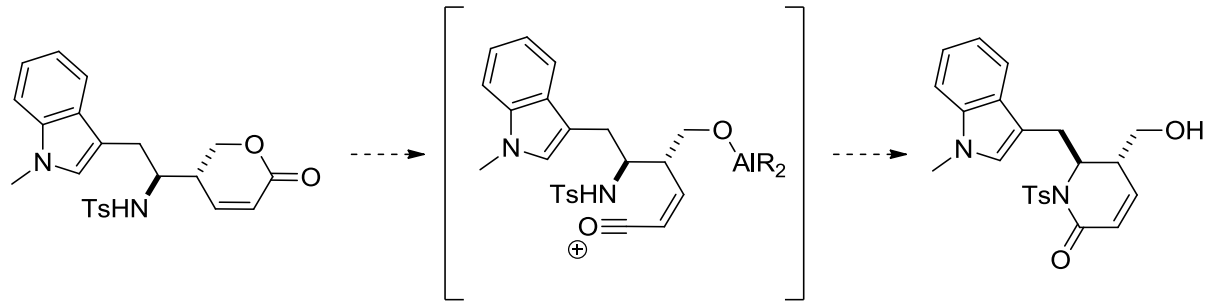
2.1.14 Final synthesis of α,β-unsaturated lactam–alcohol 90

At this stage, the synthesis of key intermediate α,β-unsaturated lactam–alcohol **90** *via* ring-opening hydroxymethyl-aziridine **82** had been hampered by lactone formation that gave almost exclusively lactones **109a** and **109b**, instead of the desired methyl ester **89**.

The most reliable route to lactam–alcohol **90** had been *via* the ring-opening reaction of *O*-TBS protected aziridine **96**. This reaction had shown complete consumption of aziridine starting material; however the regioselectivity had suffered to such an extent that its use was not viable in the final route to alstonerine. Sulfone elimination during both the attempted deprotection of *O*-TBS ring opened intermediate **102** and D-ring-forming lactamisaton of *O*-TBS **102** or β-ketoester **113** had led to significant amounts of the corresponding *trans*-α,β-unsaturated methyl esters, whose geometry prevented lactam formation. As such, attention was focused on using lactones **109a** and **109b** as intermediates in our synthesis. This decision had a huge impact on the final approach to alstonerine.

The possibility of Lewis acid mediated intramolecular *O*- → *N*-transacylation was investigated. We considered that subjecting lactone **110** to modified Friedel–Crafts type conditions may give rise to reactive acylium intermediate **116**; Subsequent cyclisation should favour the more thermodynamically stable lactam **90**.

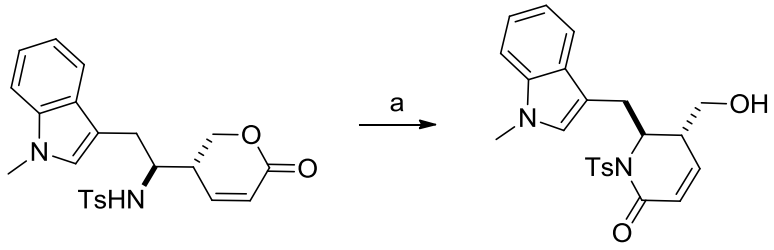
Figure 25. Lewis acid mediated intramolecular *O*- → *N*-transacylation.



α,β-Unsaturated lactone **110** was chosen as the substrate for initial experiments. We rationalised that treatment with oxaphilic trimethylaluminium would form acylium intermediate **116**. We hoped that the *cis*-geometry of the starting lactone **110** would be transferred to intermediate **116**

and that this may increase the rate of lactamisation. When 1.1 equivalents of Lewis acidic trimethyl aluminium in solution was added to α,β-unsaturated lactone **110** in toluene at room temperature, then heated at 100°C for 1 hour, complete *O*- to *N*-transacylation was observed and α,β-unsaturated lactam–alcohol **90** was isolated in excellent yield.

Scheme 35. Synthesis of **90** by intramolecular *O*- → *N*-transacylation.

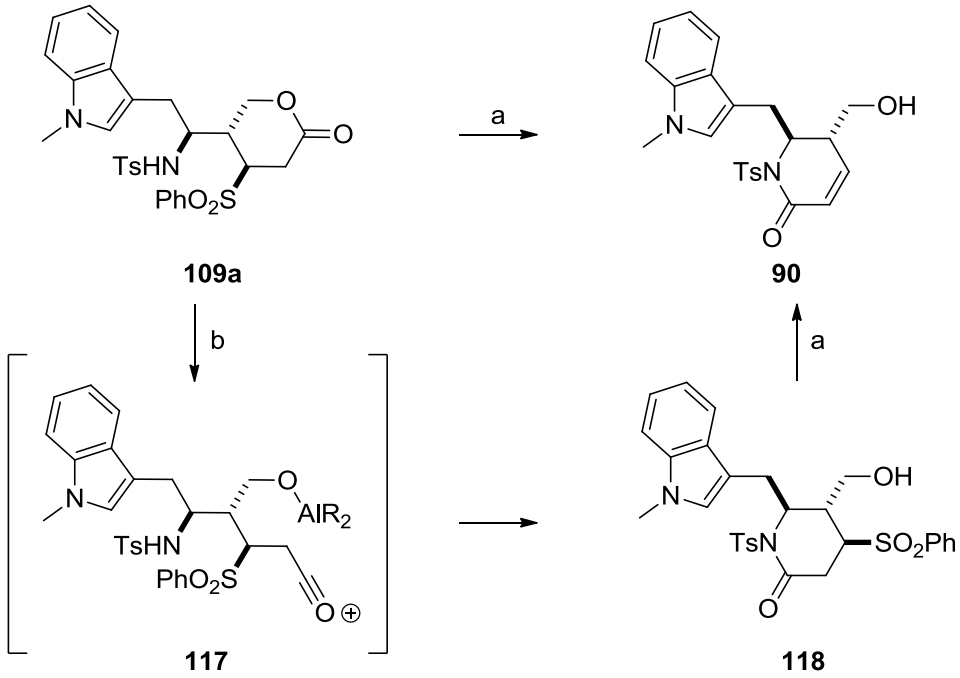


110 **90**

a) TMA (1.1 equiv.), toluene, rt, 1 h, then 100°C, 15 min, 91%.

We hoped to repeat this intramolecular transacylation lactamisation on sulfone-containing lactones **109a** and **109b**. This would provide the lactam oxidation level analogue of the previously discussed tetrahydropyridine intermediate **118**, and subsequent sulfone elimination would give α,β-unsaturated lactam–alcohol **90**. We also rationalised that were sulfone elimination to occur prior to *O*- to *N*-transacylation, then α,β-unsaturated lactone **110** would be formed, whose *cis*-geometry would allow cyclisation.

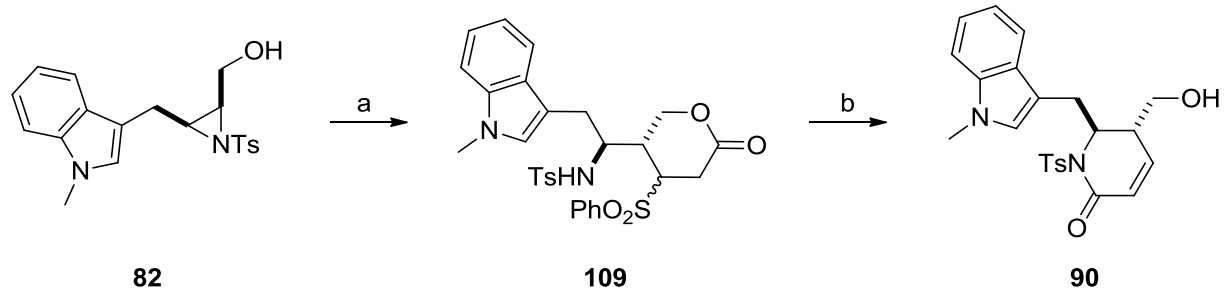
Scheme 36. Synthesis of α,β-unsaturated lactam **90** *via* intramolecular lactamisation–elimination.



a) TMA (1.5 equiv.), toluene, 120°C, 2 h, saturated aqueous Rochelle salt, 97%; b) TMA (1.1 equiv.), toluene, 0°C, 1 h, saturated aqueous, NH_4Cl, 73%.

That *O*- → *N*-acyl transfer preceded elimination was indicated by the isolation of *δ*-lactam **118** in good yield when lactone **109a** was exposed to trimethylaluminium at 0°C. The structure of **118** was confirmed by X-ray crystallography. Importantly, the *anti*-relationship between the indolylmethy- and hydroxymethyl substituents of **118** can clearly be seen (Figure **26**, below). Sulfonyllactam **118** was converted into α,β-unsaturated lactam **90** by resubmission to the trimethylaluminium reaction conditions. When applied to the large scale synthesis, we were able to reliably synthesis multigram batches of α,β-unsaturated lactam **90** in just two steps from hydroxymethyl-substituted aziridine **82** (Scheme **37**, below). In addition, by isolating lactones **109** from the ring-opening reaction of **82** and subsequently carrying out an *O*- to *N*-transacylation, we had removed the tedious and labour intensive protection and deprotection steps from our total synthesis.

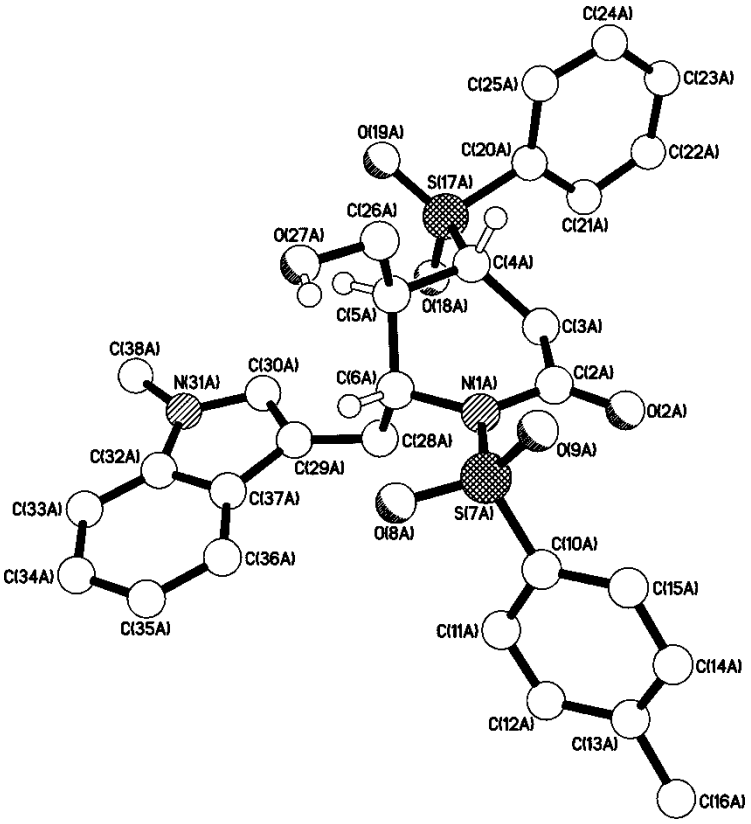
Scheme 37. Optimised route to α,β-unsaturated lactam **90**.



82 **109** **90**

a) Sulfone **88** (1.5 equiv.), *n*-BuLi (2.8 equiv.), THF, –78°C→rt o/n, then aqueous 2M HCl, 80%; b) TMA (1.5 equiv.), toluene, 120°C, 2 h, saturated aqueous Rochelle salt, 94%.

Figure 26. Molecular structure of *δ*-lactam intermediate **118**.

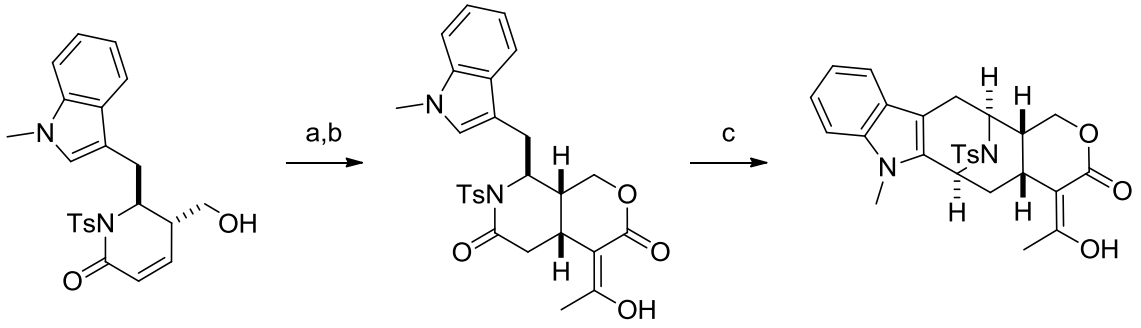


2.2 Synthesis of Macroline-related alkaloids from lactam–alcohol 90

2.2.1 Synthesis of lactam–lactone 91

We now aimed to use lactam–alcohol **90**, in the total synthesis of (±)-alstonerine. Previous attempts to construct the pentacyclic core of alstonerine **85** *via* an iminium ion-initiated cascade-style reaction had failed (Scheme **24**, Page **46**), as the facile Pictet–Spengler cyclisation had occurred prior to E-ring formation.[66] This had led to tetracycle **87**, from which point the E-ring could not be incorporated. Therefore an alternative approach, whereby the E-ring fragment was installed prior to the Pictet–Spengler cyclisation using stepwise β-ketoesterification and intermolecular Michael addition had been investigated by Tholen (Scheme **38**).[57] Our current approach retained the idea of building the E-ring prior to Pictet–Spengler cyclisation, due in part to the facile nature of the DBU-catalysed cyclisation, but more significantly, because we were aware of possible Michael-type indole addition (see below).

Scheme 38. Initial synthesis of pentacyclic lactone **85**.

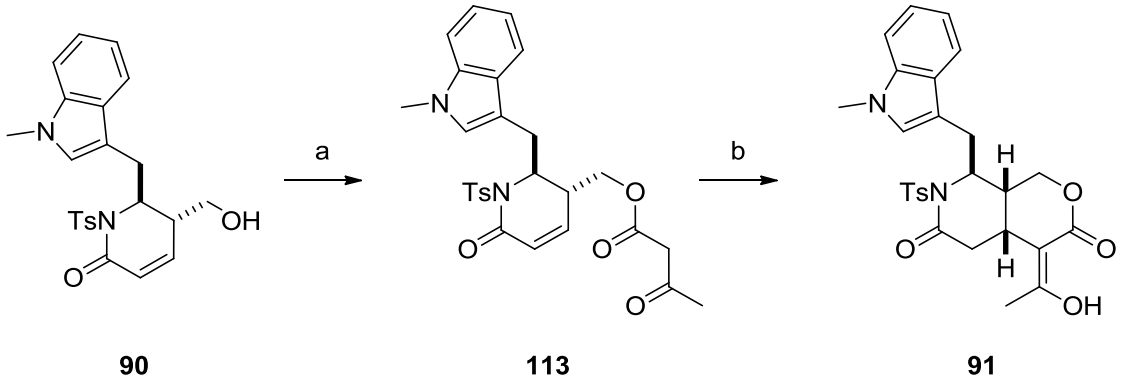


a) Diketene (1.3 equiv.), KOAc (0.1 equiv.), THF, 70°C, 1.25 h, 78%; b) DBU (0.2 equiv.), THF, rt, 3 h, 83%;
c) DIBAL (1.1 equiv.), THF, –78 °C, then TFA (0.1 equiv.), 78%.

Due to supply problems, an alternative reagent to diketene was investigated for the β-ketoesterification of lactam–alcohol **90**. During earlier studies towards the synthesis of the D-ring *via* β-ketoesterification of the aziridine ring-opening product (Table **4**, Page **70**), we found that β-ketoesterification occurred cleanly under microwave heating with 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one. Multi-gram quantities of β-ketoester **113** were reliably made using this process. On larger scales, we found that an increase from sub-stoichiometric

base to 2.0 equivalents of DBU was required to convert β-ketoester **113** into tetracyclic **91** in comparable yields to those reported for small-scale reactions.[57]

Scheme 39. Optimised, scalable synthesis of key intermediate lactam–lactone **91**.



a) 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one (1.5 equiv.), toluene, 150°C μW, 20 min, 97%; b) DBU (2.0 equiv.), THF, rt, 12 h, 93%.

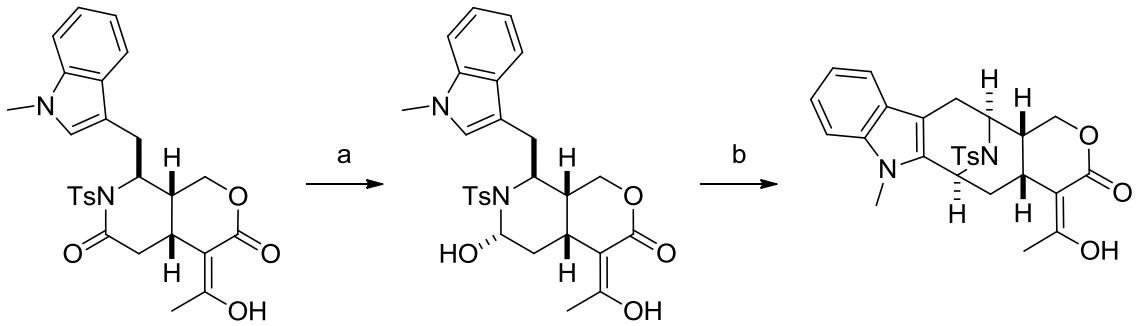
Having established a reliable and scalable synthesis of lactam–lactone **91**, our attentions turned to completing the assembly of the azabicyclo[3.3.1]nonane core motif *via* Pictet–Spengler cyclisation.

2.2.2 Synthesis of pentacyclic lactone 85 *via* C-ring forming Pictet–Spengler cyclisation

Previous investigations within the Craig group,[57,66–68] as well as significant precedent from Cook[3,8,9] and Bailey,[3] had shown that treatment of the hemiaminal derivative of lactam–lactone **91** with either Lewis or Brønsted acid facilitated the required stereospecific intramolecular Pictet–Spengler cyclisation. This formed the C2–C3 bond and provided the azabicyclic core motif as a single diastereomer.

Initially, we attempted to isolate hemiaminal **119** in order to investigate its reactivity towards Brønsted acids of varying pKa (Scheme **40**, below). The C3 carbonyl was partially reduced by treating lactam–lactone **91** with a stoichiometric quantity of DIBAL. Non-acidic work-up gave hemiaminal **119** in reasonable yield, which proved to be stable to saturated aqueous NH_4Cl and silica gel. For the iminium ion formation and subsequent cyclisation, sub-stoichiometric quantities of TFA were sufficiently acidic to effect the conversion of purified hemiaminal **119** into pentacyclic lactone **85** in 91% yield.

Scheme 40. Interrupted Pictet–Spengler cyclisation of **91**.

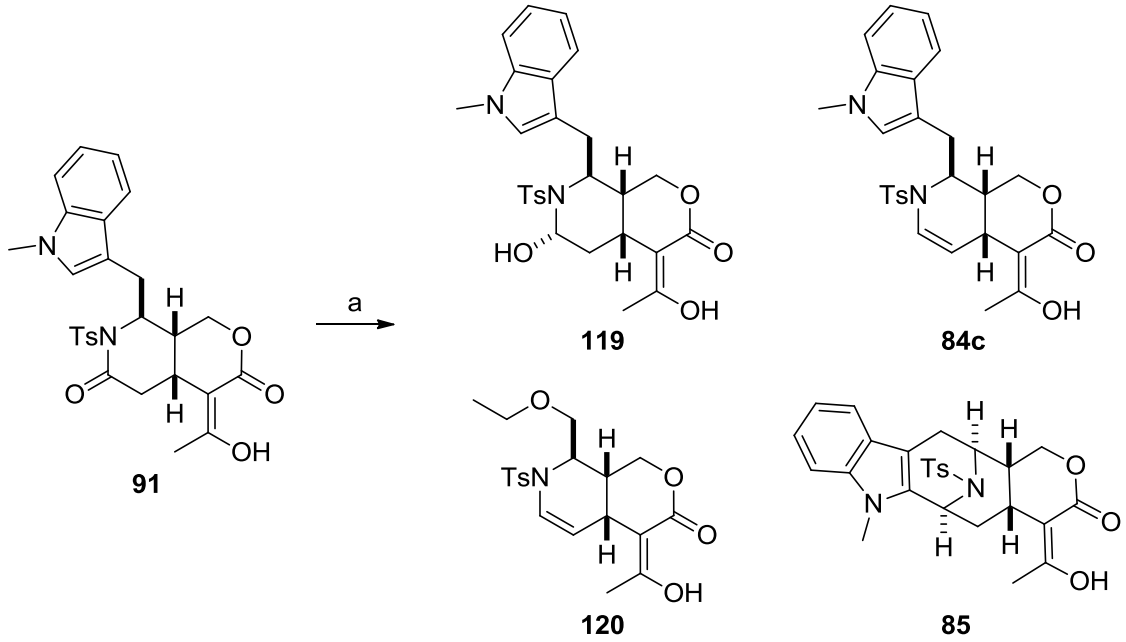


91 **119** **85**

a) DIBAL (1.5 equiv.), THF, –78°C, 1 h then wet EtOAc and saturated Rochelle salt, –78°C→rt, overnight, 51%;
b) TFA (0.1 equiv.), THF, –78°C, 2 h, 91%.

However, when attempting to combine the partial reduction and Pictet–Spengler cyclisation in a single step by quenching the DIBAL reaction with strong acid, the use of TFA gave negligible cyclised pentacycle **85**, instead yielding a complex mixture of reduced products (Scheme **41**, below). Whilst it was rationalised that hemiaminal **119** and tetrahydropyridine **84c** were a result of using insufficiently acidic conditions to quench the reaction, we were keen to establish the origin of unexpected tetrahydropyridine **120**.

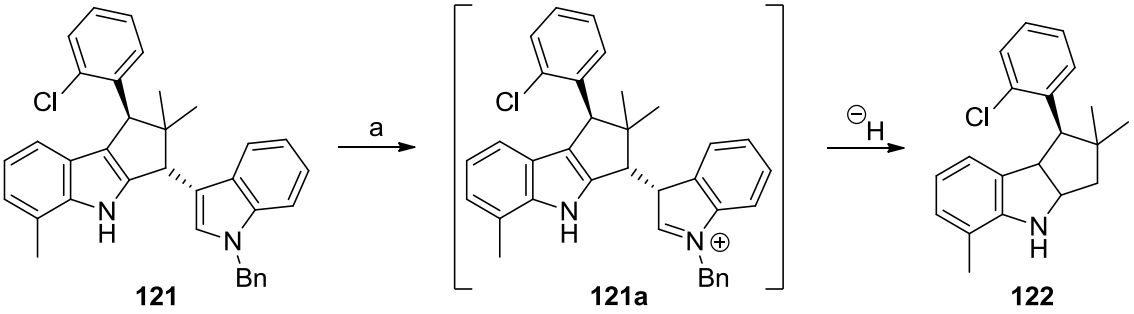
Scheme 41. Initial by-products from Pictet–Spengler cyclisation of **91**.



a) DIBAL (1.2 equiv), THF, –78°C, 2 h then wet EtOAc and TFA (1.0 equiv.), THF, –78 °C→rt, 30 min, (~3:2:2:1 **119**:**84c**:**85**:**120**), 80%.

The cleavage of an *N*-Bn-protected indole residue whilst attempting the triethylsilane-mediated indole reduction of **121** was reported by Guo (Scheme **42**).[86] Although the mechanism for the disconnection of the indole unit was stated as being unclear, we believed that a similar mode of action was leading to our by-product **120**. It was rationalised that under acidic conditions, iminium ion **121a** was produced by thermodynamic protonation of the indole substituent. This was subsequently intercepted in an S_N2' type 1,4-manner by hydride.

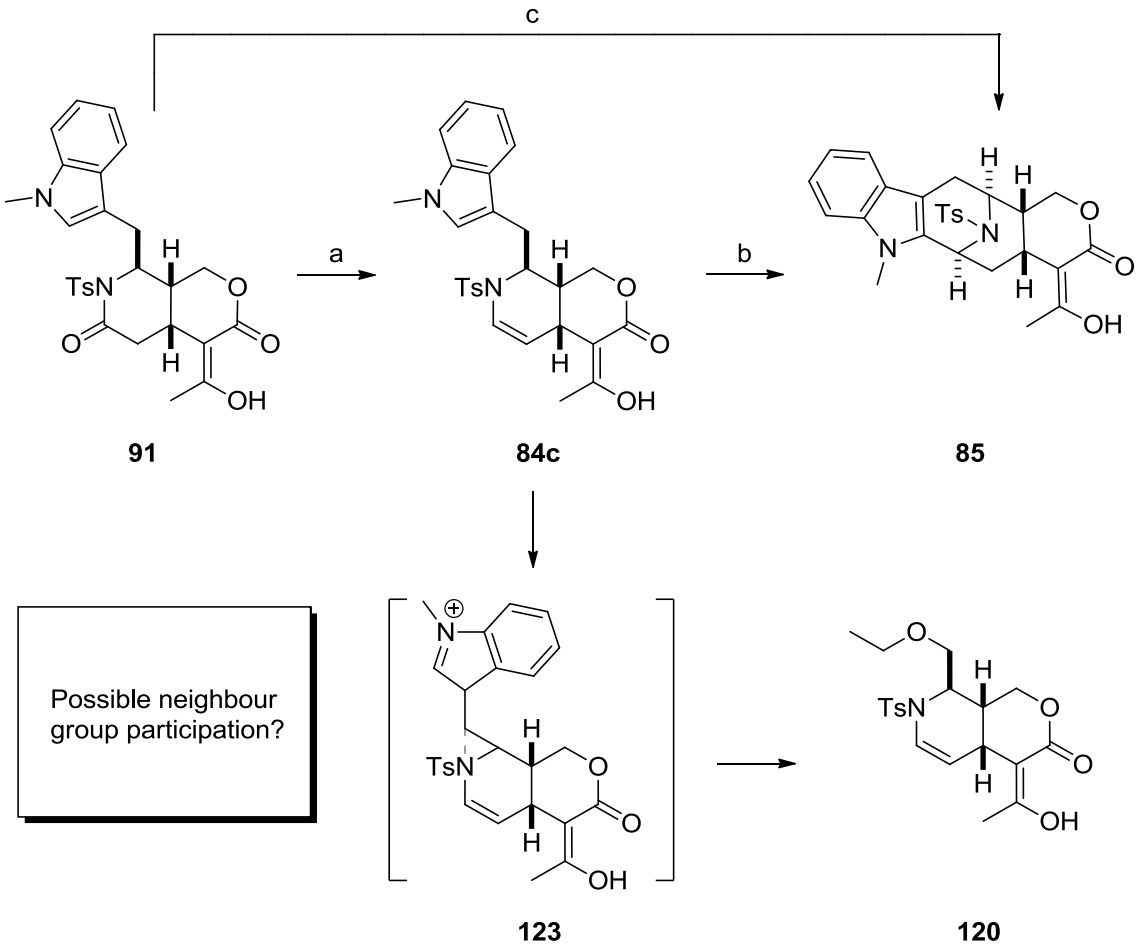
Scheme 42. Loss of indole moiety in **121**.



a) Et_3SiH (20.0 equiv.), TFA (excess), CH_2Cl_2, rt, 94%.

In our case, intermediate iminium **123** (Scheme **43**, below) was intercepted by ethanol in a similar fashion to that seen by Guo. The ethanol resulted from quenching the DIBAL reduction reaction with ethyl acetate. Thus we hoped to avoid the formation of **123** by switching from wet ethyl acetate to non-nucleophilic wet diethyl ether to quench the DIBAL reaction.

Scheme 43. Mechanism for loss of indole moiety *via* **123** and optimised synthesis of pentacyclic lactone **85**.



a) DIBAL (1.2 equiv.), THF, –78°C, 2 h then wet EtOAc and TFA (1.0 equiv.), THF, –78°C→rt, 30 min, 19% **84c**; b) Triflic acid (0.1 equiv.), THF, –78°C, 1 h, 100%; c) DIBAL (2.0 equiv.), THF, –78°C, 3 h then wet Et_2O and triflic acid (1.0 equiv.), THF, –78°C→rt, 30 min, 91%.

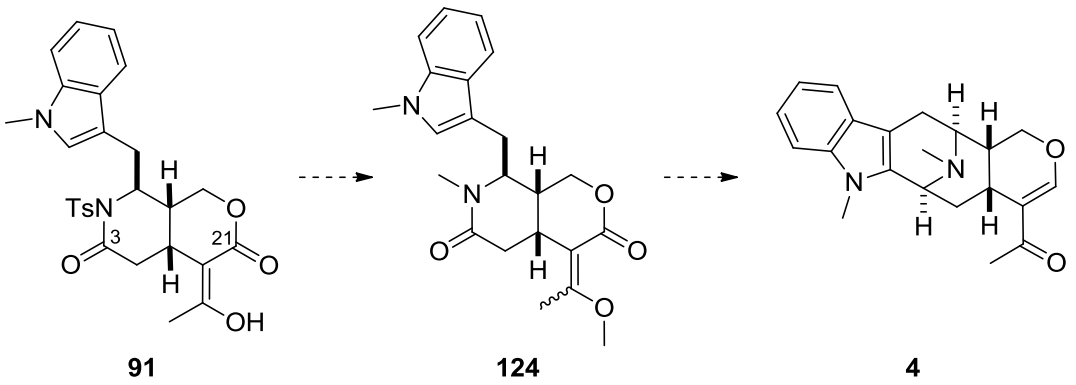
As tetrahydropyridine **84c** was similar to Wildman's intermediate (Scheme **24**, Page **46**), we rationalised that treatment with a strong acid would lead to rapid Pictet–Spengler cyclisation. In practice, treating tetrahydropyridine **84c** with sub-stoichiometric quantities of triflic acid gave

pentacyclic lactone **85** in quantitative yield. When the wet diethyl ether quench followed by triflic acid mediated Pictet–Spengler cyclisation conditions were applied to the DIBAL reduction of lactam–lactone **91**, pentacyclic lactone **85** was isolated in excellent yield as the sole product (c, Scheme **43**, above). Although alternative conditions were attempted for the quench of the DIBAL reduction, both 2.0 M and concentrated HCl, acetic acid and TFA all gave mixtures of aminal **119**, tetrahydropyridine **84c** and pentacycle **85**, with only triflic acid providing **85** cleanly and in 91%.

2.2.3 Attempts at N_4-and *O*-functionalisation of 91

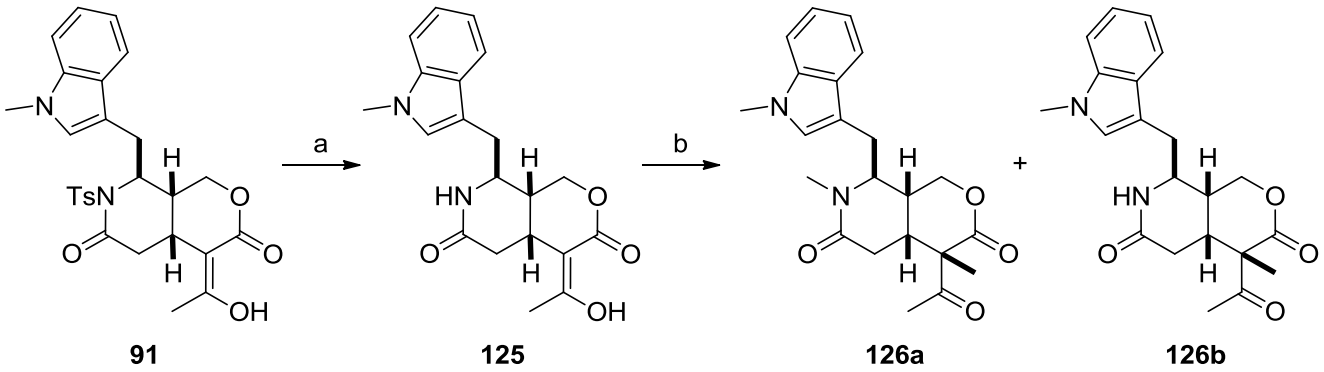
Having successfully synthesised pentacyclic lactone **85** our attention turned to adjusting the oxidation level of the E-ring. Our initial aim was to N_4-and *O*-functionalise lactam–lactone **91**, so a one-pot C3 and C21 carbonyl reduction combined with acid-mediated Pictet–Spengler cyclisation and lactol elimination could be accomplished. This would pave the way to complete the total synthesis (Figure **27**).

Figure 27. Proposed completion of alstonerine *via* Pictet–Spengler of N_4-and *O*-methylated **124**.



Our investigations began with the synthesis of both N_4-and *O*-methylated lactam–lactone **124**. The N_4-desulfonylation was completed as previously, by treating N_4-tosyl lactam–lactone **91** with 8.0 equivalents of sodium naphthalenide at –78°C.[87] This provided the free amine in good yield. For the *N*- and *O*-methylation, we hoped that treatment of 2.0 equivalents of base, followed by excess iodomethane would provide *bis*-methylated **124**. However in practice, treating **125** with either lithium or sodium bases gave no reaction (Entries **1** and **2**, Table **5**, below), due to the stability of the metalated enol intermediate. A switch to potassium bis(trimethylsilyl)amide (Entries **3**–**6**, Table **5**) provided a more reactive potassium enolate and led to the formation of *mono*-methylated **126b** and *bis*-methylated **126a**. Analysis by HMBC and NOESY NMR showed that *C*-methylation had been favoured under these conditions. That *C*-methylation was favoured over N_4-functionalisation was shown by isolation of *mono*-methylated **126b**, and despite increasing reaction duration and equivalents of both base and methylating agent, complete conversion to *bis*-methylated **126a** was never achieved.

Table 5. Attempted *N4*-and *O*-methylation of lactam–lactone **124**.



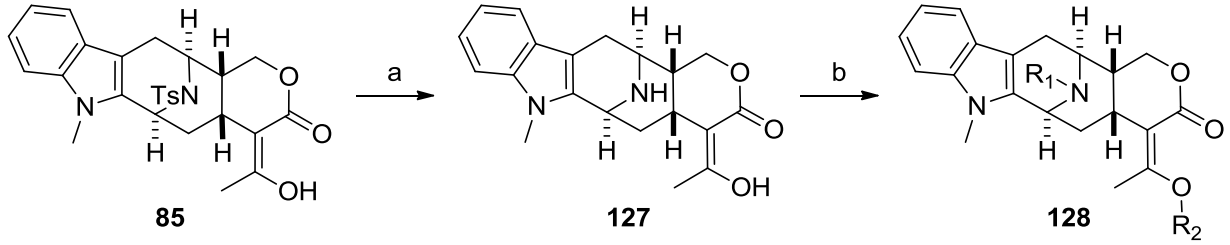
a) Na·Np (8.0 equiv.), THF, –78°C, 2 h, sat. aq. NH_4Cl, 99%; b) See Table **5**.

Entry	b) **Conditions**	**Time**	**Ratio 126a:126b**	**Yield%**
1	*n*-BuLi (2.0 equiv.), MeI (2.1 equiv.), –78°C→rt	16h	-	-
2	NaH (3.0 equiv.), MeI (2.8 equiv.), 0°C	16 h	-	-
3	KHMDS (2.5 equiv.), MeI (3.0 equiv.), 0°C	16 h	2:3	56
4	KHMDS (2.5 equiv.), MeI (3.0 equiv.), 0°C	74 h	1:3	68
5	KHMDS (2.5 equiv.), MeI (3.0 equiv.), –78°C	74 h	1:3	68
6	KHMDS (1.2 equiv.), MeI (1.1 equiv.), –78°C→rt	74 h	3:2	93

Having failed to synthesise *O*- and *N*-methylated Pictet–Spengler precursor **124** due to preferential *C*- rather than *O*-alkylation and low amine nucleophilicity, we decided to investigate the individual steps of the desired deprotection–reduction process. We rationalised that desulfonylation of pentacyclic lactone **85** would provide a secondary amine that should be highly reactive to N_4-methylation. For the reduction of the E-ring, we rationalised that *O*-silylation would occur preferentially to *C*-silylation, which would provide us with a substrate for final reduction of the E-ring. For the detosylation, sodium naphthalenide conditions were again used;[87] these gave the free N_4-H amine **127** in 92% yield. Analysis by ^{1}H NMR showed that approximately 60% of the resulting compound existed as the zwitterion in $CDCl_3$. However, when treated with the methylating conditions used in the synthesis of alstonerinal, amine **127** proved resistant to alkylation (Entry **3**, Table **6**, below). Starting amine was also recovered using

reductive amination and strongly basic conditions (Entries **1** and **2**, Table **6**) leading us to attempt the *O*-functionalisation prior to N_4-desulfonylation (Entries **4**–**11**, Table **6**).

Table 6. Detosylation and attempted *N4*-and *O*-methylation of pentacyclic lactone **85**.



a) Na·Np (8.0 equiv.), THF, –78°C, 2 h, sat. aq. NH_4Cl, 92%; b) See Table **6**.

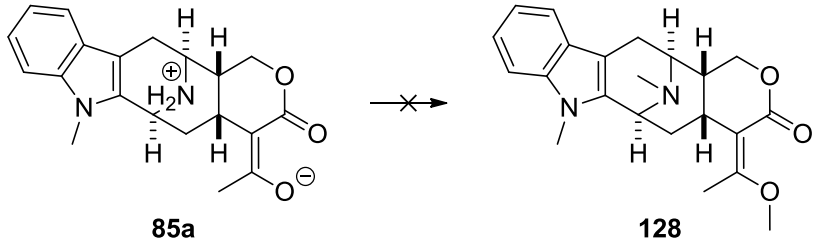
Entry	b) **Conditions**	**Time**	**Yield%**
Attempted N_4-methylation of **127**			
1	HCHO (50 equiv.), $NaBH_3CN$ (5.0 equiv.), AcOH (6.0 equiv.), MeCN, rt	16 h	-
2	Hünig's (3.0 equiv.), MeI (2.0 equiv.), DMF, –78°C→rt	16 h	**SM**
3	NaH (3.0 equiv.), MeI (1.0 equiv.), THF, –78°C→rt	16 h	**SM**
Attempted O-silylation of N_4-H **127**			
4	TBSOTf (1.5 equiv.), Et_3N (2.0 equiv.), $CDCl_3$, 0°C→rt	16 h	**SM**
5	TBSOTf (1.5 equiv.), DMAP (0.1 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0°C→rt	16 h	**SM**
Attempted O-silylation of N_4-Ts **85**			
6	TBSOTf (1.5 equiv.), Et_3N (2.0 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0°C→rt	74 h	**SM**
7	TBSCl (1.5 equiv.), imidazole (1.5 equiv.), DMF, rt	16 h	**SM**
8	KHMDS (1.1 equiv.), TBSOTf (1.5 equiv.), CH_2Cl_2, –78°C→rt	16 h	**SM**
9	KHMDS (1.1 equiv.), TBSOTf (1.5 equiv.), THF, –30°C→rt	16 h	**SM**
10	KHMDS (2.5 equiv.), TBSOTf (3.0 equiv.), THF, 60°C	32 h	trace
11	TBSOTf (1.8 equiv.), 2,6-lutidine (3.0 equiv.), CH_2Cl_2, rt	48 h	**SM**

From the table, is can be seen that *O*-functionalisation also proved difficult. Pentacyclic lactones **127** and **85** were unreactive to standard *O*-silylation conditions (Entries **4**–**11**, Table **6**, above),

even when forcing conditions such as extended heating with KHMDS and TBSOTf were applied, only trace amounts of O-TBS **128** (R_1=Ts) could be seen in the ^{1}H NMR of the crude material. At this stage, with pentacyclic lactone **85** showing unusual stability towards standard *O*-silylation conditions, and having already shown that *C*-rather than *O*-methylation was favoured, we decided to search for an alternative approach to the appropriately functionalised E-ring.

However, during these studies we had shown that both lactam–lactone **91** and pentacyclic lactone **85** could be deprotected using mild sodium naphthalenide conditions. We speculated also that the free amine derivative of **85** existed partially as the zwitterion **85a** in solution, rendering the secondary amine unreactive to N_4-methylation (see below).

Figure 28. Zwitterionic **85a**.



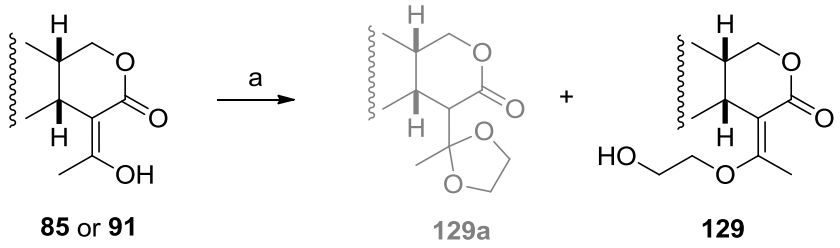
For the *O*-functionalisation, we had found that the enolate derived from deprotonation of **85** with either lithium or sodium bases was an unreactive nucleophile in alkylation reactions, due to the increase stability gained by interaction with the lactone carbonyl. This could be overcome by synthesising the potassium enolate, however this was susceptible to *C*-methylation. At this stage, we attempted the partial reduction of N_4- and C20-methylated compound **126a**, and although the products were not isolated, ^{1}H NMR and IR analysis of the crude material obtained strongly suggested that once the conjugated enol system had been broken by C19 methylation, the C21 carbonyl was readily reduced using similar DIBAL conditions to those used in our Pictet–Spengler cyclisation step.

2.2.4 Ketalisation of pentacyclic lactone 85

Following failed attempts to synthesise either *O*-methyl or *O*-silyl versions of pentacyclic lactone **85**, investigations into ketalisation of the C19 carbonyl moiety in pentacyclic lactone were carried out. Although all attempts at *O*-functionalisation using basic conditions had failed, whilst attempting to protect pentacyclic lactone **85** as the dimethylacetal equivalent, we had found **85** to be a suitable substrate for acid-catalysed Michael-type additions, as discussed later in our syntheses of alstonerinal and macroline (Scheme **49**, Page **98**).

As with our attempted dimethylketal formation, under standard ketalisation Dean Stark conditions using 3.0 equivalents of ethylene glycol, sub-stoichiometric quantities of PTSA and refluxing in toluene, an acid-catalysed Michael-addition–elimination occurred, giving rise to the corresponding enol ether instead of the desired ketal. Application of Noyori conditions[88] to enol **85** gave clean conversion into the corresponding enol ether **129** (Scheme **44**, below).

Scheme 44. Attempted C19 ketalisation of lactones **85** and **91**.

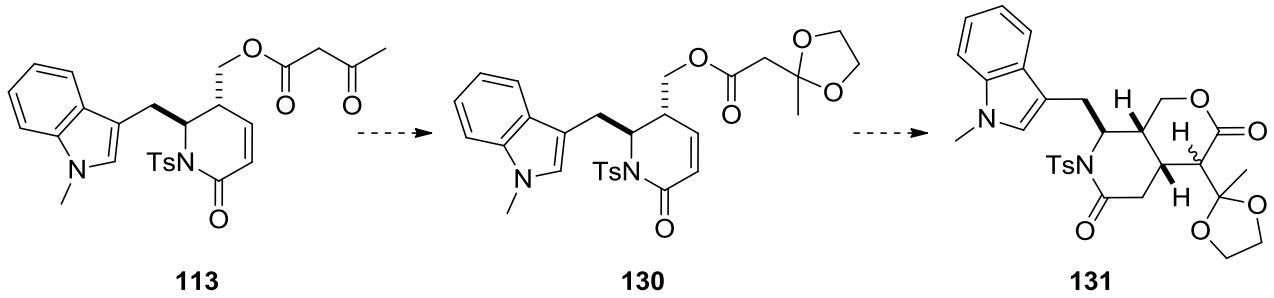


85 or **91** **129a** **129**

a) 1,2-bis(trimethylsiloxy)ethane (2.0 equiv.), TMSOTf (1 drop), CH_2Cl_2, –78°C, 93%.

After various C19 ketalisation conditions had instead converted either the pre-Pictet–Spengler lactam–lactone **91** or pentacyclic lactone **85** to the corresponding enol ether, we decided to attempt the C19 protection of β-ketoester **113** prior to the lactone E-ring formation. We rationalised that since **113** had been shown by ^{1}H NMR to exist predominantly as the β-keto tautomer, the lack of 1,4-conjugation may favour ketalisation rather than the Michael addition–elimination reaction that favoured formation of enol ethers **129**.

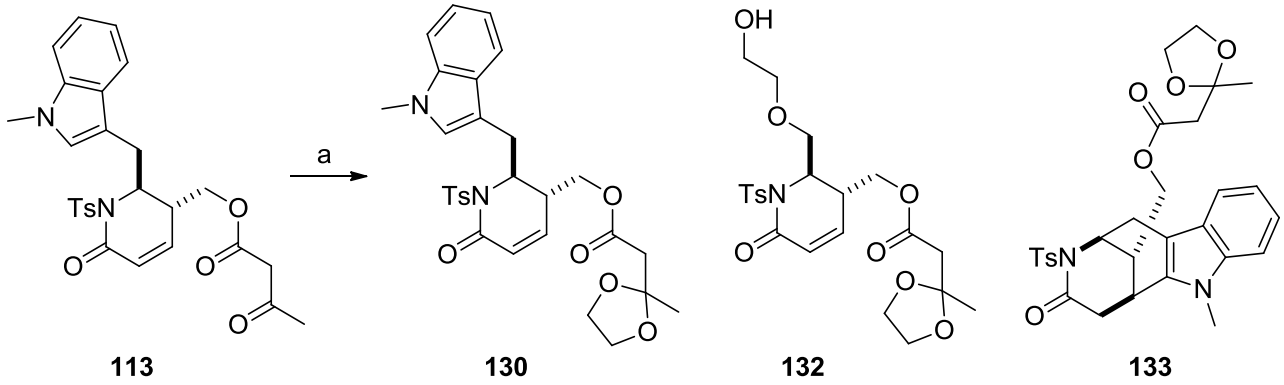
Figure 29. Proposed synthesis of the E-ring *via* Michael addition of **130**.



113 **130** **131**

During the initial optimisations, Noyori conditions gave almost quantitative conversion of β-ketoester **123** to dioxolane **130**. When these conditions were repeated on larger scale, a complex mixture of **130**, **132** and **133** was isolated in good yield (Scheme **45**, below). Although the desired dioxolane was the major product, significant quantities of **132**, which resulted from the loss of the indole residue *via* the acid-mediated S_N2' type mechanism was observed (Scheme **43**, Page **80**). Interestingly, a 1,4-intramolecular Michael-type cyclisation had also occurred between the C2 position of the indole and the C15 α,β-unsaturated lactam position.

Scheme 45. Attempted Noyori ketalisation of **113**.

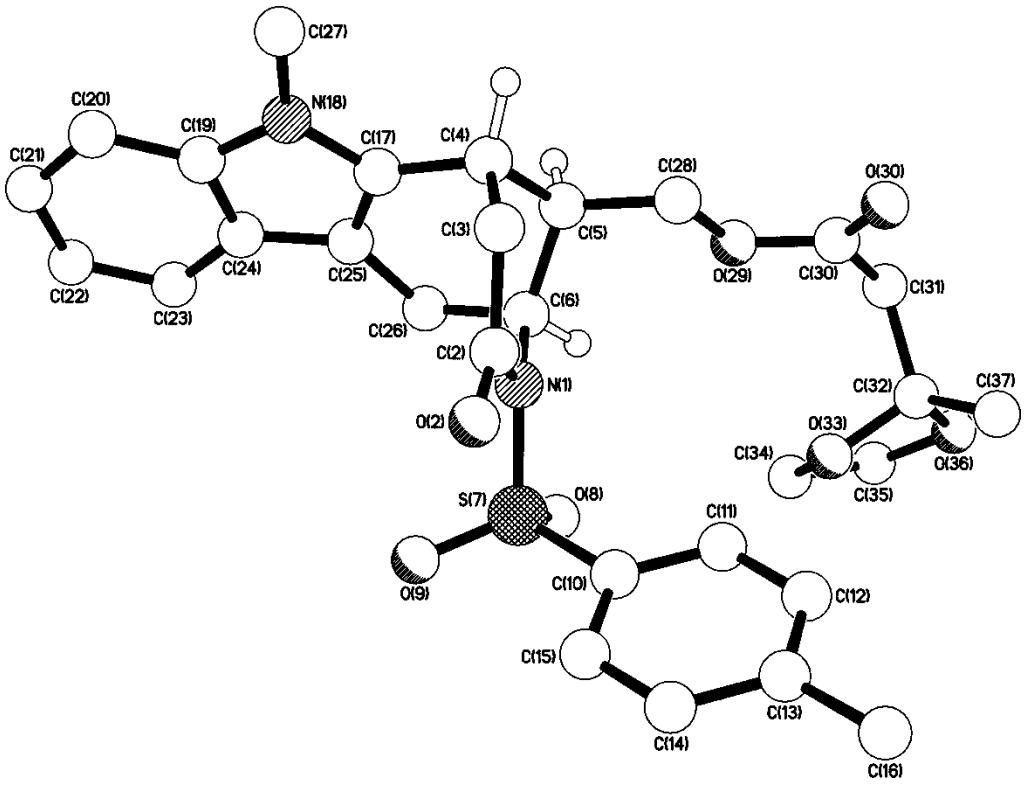


113 **130** **132** **133**

a) 1,2-bis(trimethylsiloxy)ethane (2.0 equiv.), TMSOTf (1 drop), CH_2Cl_2, –78°C→rt, 16 h, 83% **130**:**132**:**133**.

That cyclisation had occurred was proven by X-ray crystal structure of **133** (Figure **30**, below). Although it was not useful for the synthesis of macroline-related indole alkaloids, we were particularly pleased to note the acid-mediated cyclisation due to the formation of the 2-azabicyclo[3.3.1]nonane motif that is present in many pharmaceutically important compounds,[89,90] notably the pentacyclic curans of the *strychnos* alkaloids[91,92,] and is a motif that is still a popular target.[93]

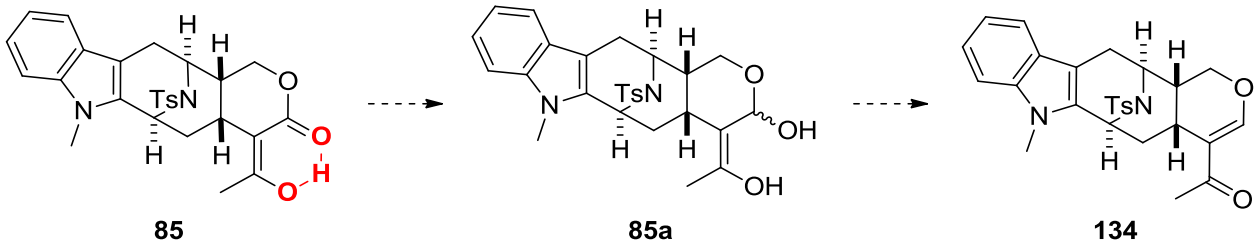
Figure 30. 1,4-Michael-type cyclisation following attempted Noyori ketalisation of **113**.



2.2.5 Reduction of pentacyclic lactone 85

With efforts towards *O*-functionalisation of pentacyclic lactone **85** thwarted, initial investigations into the synthesis of the (±)-alstonerine E-ring **4** *via* partial reduction of the C21 lactone carbonyl in **85** were revisited. As with the previous approaches, it was rationalised that were we able to suitably adjust the oxidation of the C21 carbonyl to the required lactol, subsequent dehydration would furnish the carbon skeleton of the natural product. However, initial investigations into the reduction of pentacyclic lactone **85** had shown it to be completely unreactive towards standard reagents and conditions, such as DIBAL,[94] Red-Al®,[97] lithium aluminium hydride,[95] L-selectride®[96] and superhydride.®[97] We envisaged that solvent choice and increased temperatures may attenuate the stabilising influence of the intramolecular hydrogen bond between the enol OH and the C21 carbonyl oxygen atom of pentacyclic lactone **85** and thus facilitate partial reduction.

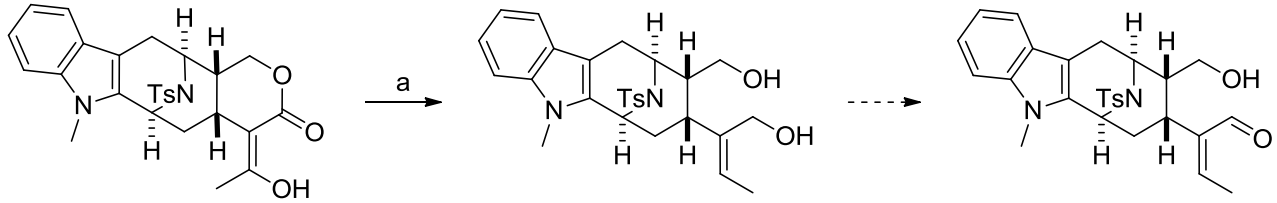
Figure 31. Proposed synthesis of of alstonerine **4** from pentacyclic lactone **85**.



During initial attempts, the reducing agent was added to a solution of pentacyclic lactone **85** in THF at –78°C. The reaction mixture was then allowed to warm to room temperature overnight. Although there are numerous procedures reported for the partial reduction of *δ*-lactones in total syntheses,[98,99,100] whilst using standard conditions we observed no consumption of starting material in all cases. At this point, with a view to combining this reduction with our previously optimised Pictet–Spengler cyclisation, we decided to focus our efforts on effecting this transformation using DIBAL under more forcing conditions. We envisaged that switching from the ethereal solvent THF to a non-coordinating solvent such as CH_2Cl_2 or toluene should increase the reactivity of DIBAL by decreasing the stability of the DIBAL complex. However, in practice, no reduction was observed in either of these solvents at room temperature.

At this point, with numerous attempts to reduce the pentacyclic lactone **85** having returned starting material at room temperature, the viability of heating was investigated. Although we feared a loss of selectivity, and thus over-reduction, the reduction was attempted by refluxing pentacyclic lactone **85** with 2.0 equivalents of DIBAL in THF. After work-up and chromatography, diol **135** was obtained in 46% yield. Despite numerous attempts at varying reducing agent, solvent, temperature and reagent concentration, either starting material or over-reduced diol **135** were always achieved.

Scheme 46. Over-reduction of pentacyclic lactone **85**.

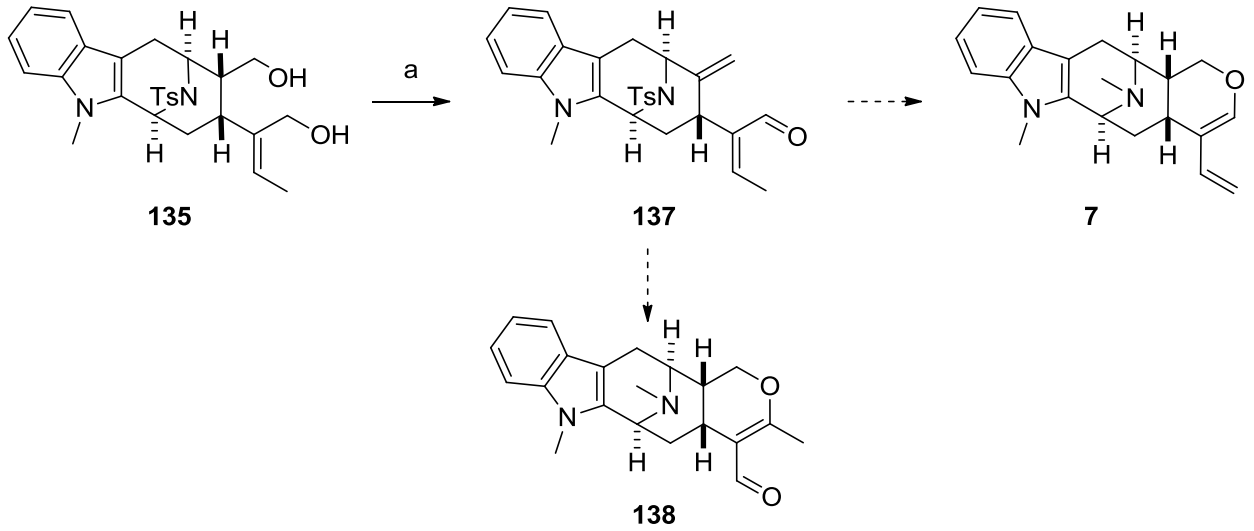


84 **135** **136**

a) DIBAL (2.0 equiv.), THF, 70°C, 1 h, 46%, *E*-geometric isomer.

With diol **135** persisting in the attempts at partial reduction, the idea of continuing our synthesis from diol **135** was briefly entertained. This would be achieved by re-establishing the E-ring *via* oxidation level adjustments. Selective allylic oxidation would give unsaturated aldehyde compound **136**, which may provide a route to either type A macrolines alstonerine and anhydromacrosalhine-methine **7**, or type B macroline alstonerinal (Scheme **47**, below).

Scheme 47. Proposed use of diol **135** in alkaloid synthesis.



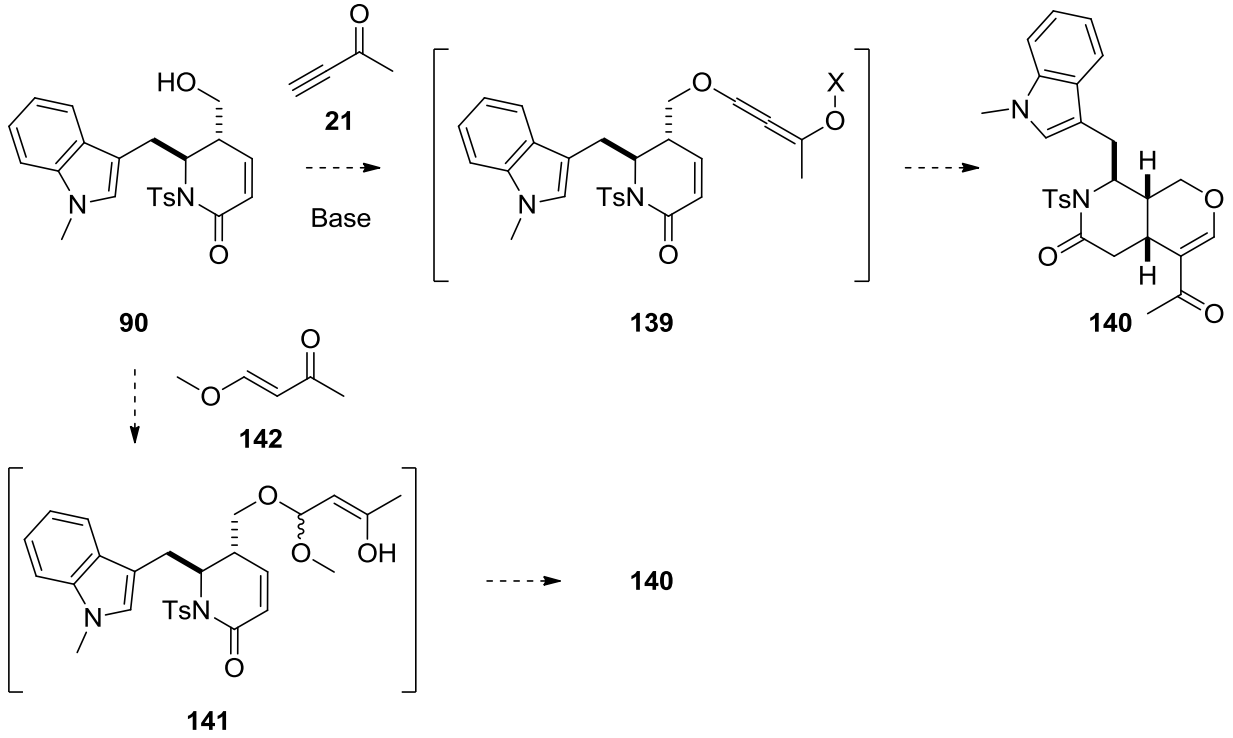
a) $COCl_2$ (1.4 equiv.), DMSO (2.8 equiv.), Et_3N (excess), –78°C→rt, 2 h. 97%.

135 was added to a solution of DMSO, Et_3N and $COCl_2$, which led to oxidation of the allylic alcohol moiety. In addition to allylic oxidation, elimination of the C17 alcohol occurred. This gave exocyclic methylene compound **137** as the major product in 97% yield. Although, it was feasible that **137** could have been converted into alstonerine,[3] the route would have involved numerous oxidation level adjustments, and, as such, this approach was abandoned.

2.2.6 Alternative routes to the alstonerine E-ring

After numerous unsuccessful attempts at *O*-functionalisation of pentacyclic lactone **85**, and having failed to find suitable conditions to adjust the oxidation of its E-ring to that required for alstonerine, an alternative approach to the synthesis was briefly investigated. The aim was to install the correct E-ring *via* either base-mediated Michael-type addition to 3-butyn-2-one **21** or acid-catalysed addition to *trans*-4-methoxy-3-buten-2-one **142** (Figure **32**, below).

Figure 32. Proposed synthesis of the E-ring *via* Michael-type addition to either **21** or **142**.



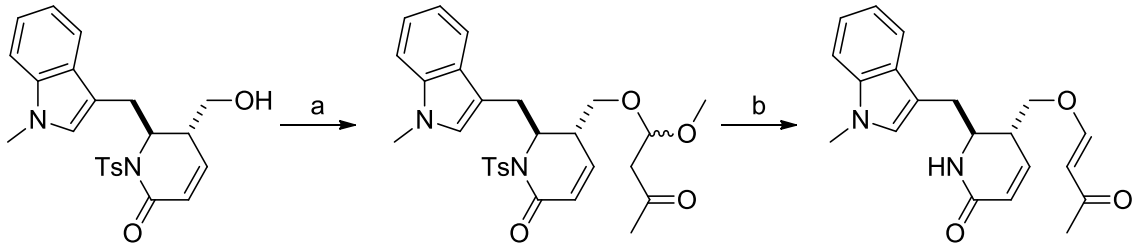
The former approach, although very similar to that applied in Cook's first synthesis (Scheme **5**, Page **20**) was quickly abandoned, as polymerisation side-reactions were difficult to avoid, both during the synthesis of 3-butyn-2-one **21** and during the Michael-addition with **90**.

During early investigations into the latter approach, Lactam–alcohol **90** was converted into β-keto acetal **141a** by reaction of **90** with *trans*-4-methoxy-3-buten-2-one **142** and sub-stoichiometric quantities of triflic acid at –78°C (Table **7**, below). This gave epimeric β-keto acetals **141a** in 97% yield, and provided evidence to suggest that the desired enol intermediate **141** (Figure **32**, above) had been formed during the course of the reaction, although

the second Michael-type addition cyclisation had not occurred under these conditions. It was envisaged that a second intramolecular Michael-type addition may be induced either basic conditions, or by heating in the presence of acid. We also hoped that heating the initial acid-catalysed intermolecular Michael-type reaction of **90** with *trans*-4-methoxy-3-buten-2-one **142** may bring about an irreversible cyclisation and complete the tandem double Michael-addition E-ring synthesis.

For the optimisation, we found that treating intermediate acetal **141** with sodium methoxide gave no reaction at either –78°C or room temperature (Table **7**, below). The *trans*-4-methoxy-3-buten-2-one **142** substrate had been synthesised by heating acetylacetaldehyde dimethyl acetal with sodium methoxide in methanol. Interestingly, when **141** was heated in methanol with excess sodium methoxide under microwave conditions, ^{1}H analysis of the crude material suggested that N_4-deprotected lactam **143** was the major product, however this was not isolated by chromatography. At this stage, we hoped that heating **143** under acidic conditions would facilitate the required 1,4-addition. However, C2–C15-cyclisations had also been shown to be possible under these conditions (Scheme **45**, Page **87**).

Table 7. Michael addition of **90** to *trans*-4-methoxy-3-buten-2-one **142**.



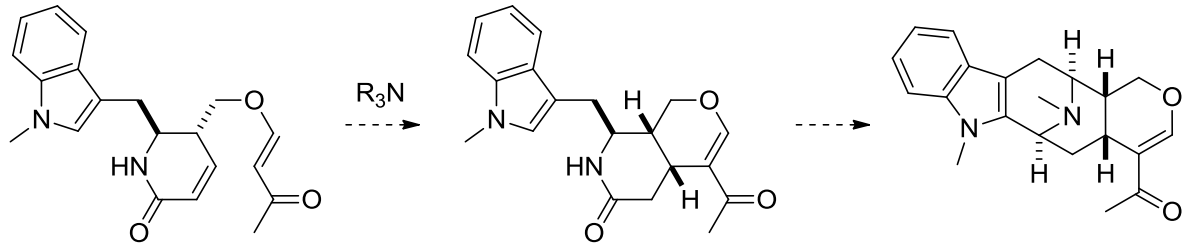
90 **141a** **143**

a) *trans*-4-methoxy-3-buten-2-one (10.0 equiv.), TfOH (1 drop), CH_2Cl_2, –78°C→rt, 2 h, 97%; b) see Table **7**.

Entry	a) **Conditions**	**Product**
1	KHMDS (0.5 equiv.), THF, –78°C→rt, 24 h	-
2	NaOMe (1.0 equiv.), MeOH, 140°C μW, 0.5 h	**143**
3	NaOMe (0.1 equiv.), MeOH, –78°C→rt, 24 h	-
4	TMSOTf (0.1 equiv.), CH_2Cl_2, –78°C→rt, 16 h	-

Although at this stage we had failed to complete the double Michael-type addition, we had isolated N_4-H vinylogous ester **143** in moderate yield, from which we envisaged the synthesis of the E-ring could be completed by a Baylis–Hillman-type cyclisation.

Figure 33. Baylis–Hillman approach to alstonerine E-ring in **144**.

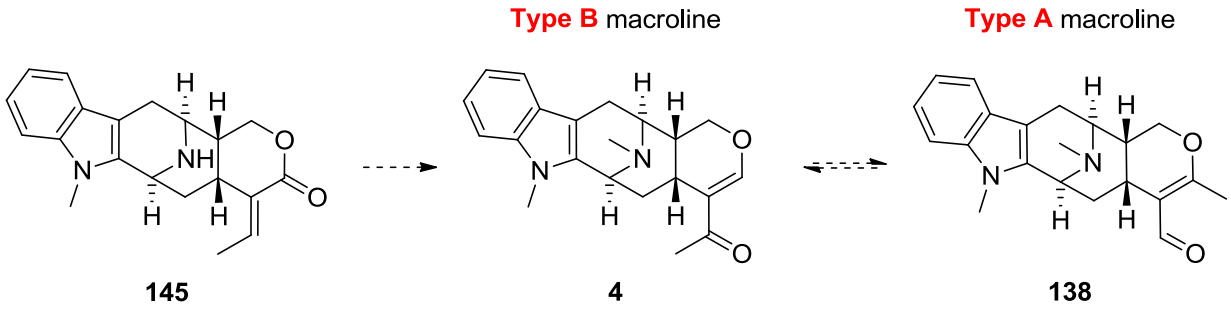


Although we were optimistic that treatment with nucleophilic amine base would bring about the E-ring cyclisation, before we could begin our optimisations, we found that the alstonerine carbon skeleton could be synthesised from lactam–lactone **91** in two steps, and therefore our Baylis–Hillman approach was abandoned in favour of the final approach to alstonerine.

2.2.7 Total synthesis of type A macroline-related indole alkaloid alstonerinal 138

During our continued attempts to synthesise the E-ring of type B macroline indole alkaloid alstonerine **4**, we became interested in the corresponding type A macroline alstonerinal **138**. Compound **138** can also be found in the stem-bark extract of both *Alstonias angustifolia*[101] and *macrophylla*[102] and is an isomer of both our target compound alstonerine **4**, and the lactone containing alkaloid alstolactone **145**, whose synthesis is discussed later. Alstonerinal **138** differs only from alstonerine in the E-ring, which contains a C17–*O*–C19 linkage rather than the C17–*O*–C21 linkage of alstonerine **4**. Whereas it is hard to imagine the transformation of alstolactone **145** to alstonerine **4** occurring in a single step, we thought it feasible that under certain conditions, the interconversion of type A and B macrolines may be achieved.

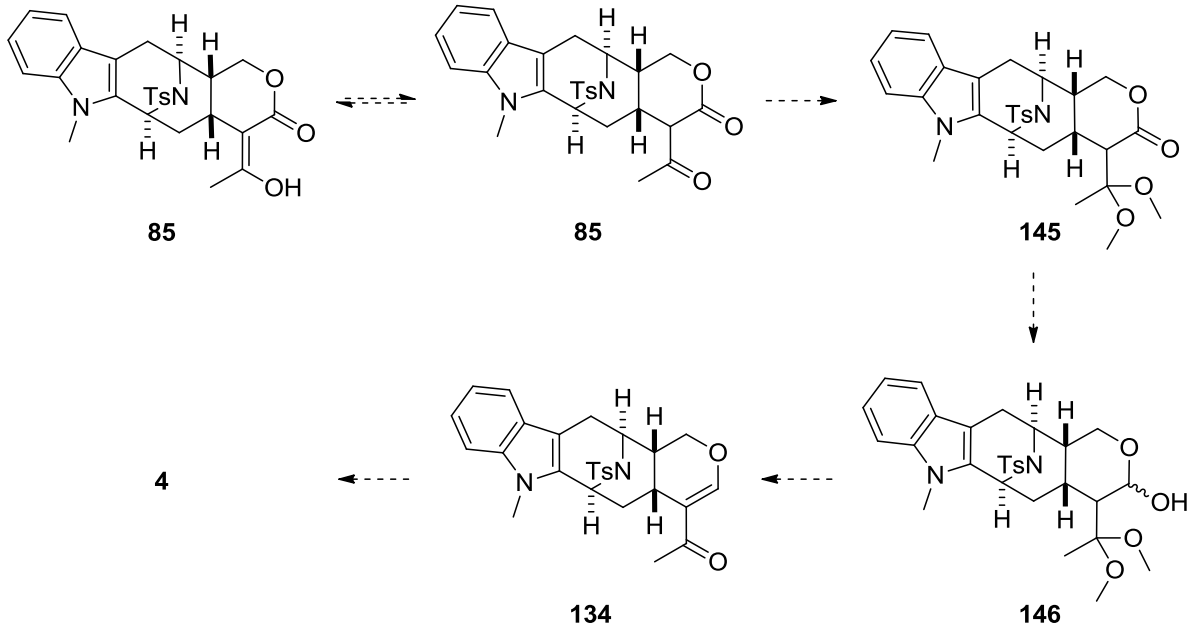
Figure 34. Structural relationship of type B macroline alstonerine **4** its type A isomer **138**.



We first observed the type A macroline structure whilst attempting to tautomerise pentacyclic enol **85**, and protect the C19 carbonyl of the consequent β-ketoester as the corresponding dimethyl ketal **145** (Figure **35**, below). Upon successful protection, treatment of **143** with DIBAL would effect the desired partial 1,2-reduction of the C21 lactone carbonyl, rendering the tosyl protected natural product **134**. Desulfonylation and methylation would complete the synthesis of (±)-alstonerine **4** (Figure **35**, below).

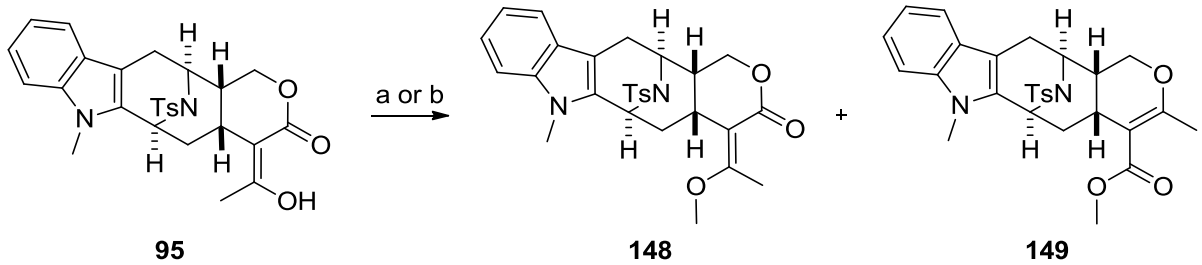
For the synthesis of dimethyl ketal **145** we predicted that treating pentacyclic lactone **85** with sub-stoichiometric quantities of Brønsted acid in excess methanol would lead to the β-keto tautomer, the addition of dehydrating agent trimethyl orthoformate would then drive the equilibrium towards the formation of dimethyl ketal **145**.

Figure 35. Proposed synthesis of (±)-alstonerine.



Initial attempts at ketalisation using 3Å molecular sieves as the dehydrating agent showed no conversion at room temperature. Switching from sieves to trimethyl orthoformate as the dehydrating agent led to the formation of two isomeric compounds (isomer ratio 2:1) in 91% yield. Based on interpretation of the ^{1}H and ^{13}C spectra, these were initially considered to be geometric isomers of type B macroline methyl ester **147**. However, analysis of the IR spectra and comparison to known compounds[101,102] suggested that the major isomer was the result of a rearrangement in the E-ring,[103] corresponding to type A macroline methyl ester **148**. The minor isomer was assigned as type B macroline *E*-methyl ester **147** (Scheme **48**, below). These assignments were confirmed by HMBC NMR.

Scheme 48. Acid-catalysed rearrangement of pentacyclic lactone **85** to type A analogue **148**.

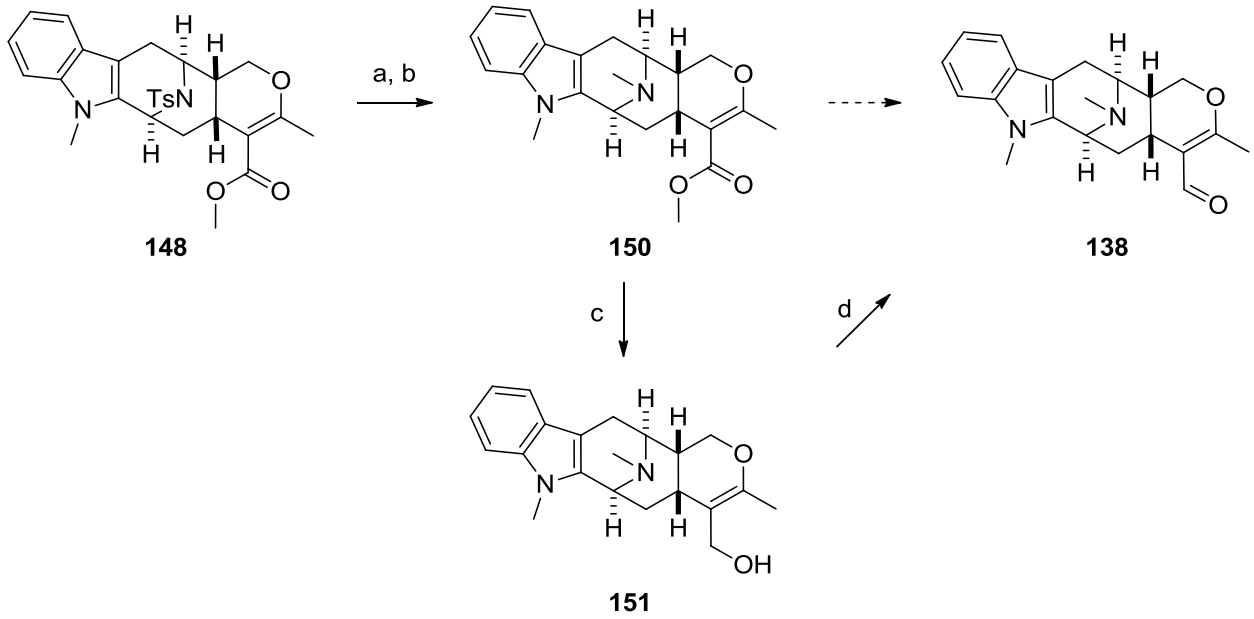


a) CSA (0.1 equiv.), $HC(OMe)_3$ (1.5 equiv.), $MeOH/CH_2Cl_2$, rt, 16 h, 91% (2:1 ratio of **148**:**147**); b) CSA (0.1 equiv.), $HC(OMe)_3$ (2.0 equiv.), $MeOH/CH_2Cl_2$, reflux, 72 h, 67% **148**.

We expected that decreasing the reaction temperature would influence this ratio in favour of the desired type B compound **147**. Unfortunately the (2:1 **148**/**147**) ratio persisted when the reaction was carried out at room temperature over extended time periods of over three days. In turn extended reflux at 70°C for 72 hours favoured the rearrangement product **148** in 67% yield (3:1 **148**/**147**). We envisaged the ratio may yet be inverted by decreasing the temperature to –78°C and using catalytic super acidic reagent, such as triflic acid, to increase the reactivity, however at this point we chose to investigate the potential reductions of **148** and **147** to give the carbon skeletons of alstonerinal and alstonerine respectively.

For the conversion of **148** into alstonerinal, sodium naphthalenide was again chosen as our first attempt at the N_4-detosylation (Scheme **49**, below). Treatment of type A macroline methyl ester **148** with a ~2M solution of sodium naphthalenide in THF at –78°C gave the free N_4-H amine **149** in 92% yield. Previous attempts at N_4-methylation using reductive amination with formaldehyde had failed, thus similar conditions to those outlined in Martin's alstonerine synthesis were chosen (Scheme **18**, Page **32**).[3] The addition of excess Hünig's base and iodomethane at –78°C in THF and warming to room temperature overnight gave alstonerinal precursor **150** in 87% yield. At this stage we faced the often problematic task of the partially reducing the C21 methyl ester functionality of **150**. Initial attempts carried out using both Red-Al and DIBAL failed to give the natural product **138**, but gave the over reduced allylic alcohol **151** in good yield, and L-selectride showed no reaction. Literature precedent for the reduction of vinylogous carbonates such as **150** often favours a two-step process, presumably due to the relative ease of the complete reduction and allylic oxidation.[104,105] We were also encouraged as alcohol **151** was a known compound, and was reported as the result of $NaBH_4$ reduction of alstonerinal **138**. Allylic alcohol **151** had also been oxidised to alstonerinal using MnO_2 by Kam *et. al*. in the isolation paper.[102] However, initial attempts at the oxidation using MnO_2 proved difficult, therefore Dess-Martin oxidation conditions[106] were used, giving rise to alstonerinal, albeit in minute quantities (Scheme **49**, below).

Scheme 49. Completion of the (±)-alstonerinal synthesis.



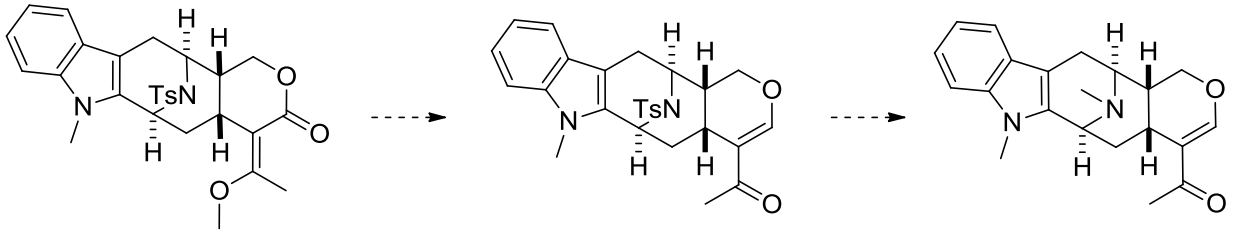
148 **150** **138** **151**

a) Na·Np (8.0 equiv.), THF, –78°C, 2h 30 min, 92%; b) Iodomethane (1.4 equiv.), Hünig's (3.0 equiv.), THF, –78°C → rt, 16 h, 81%; c) DIBAL (1.0 equiv.), toluene, –92°C, 1 h, 99%; d) Dess-Martin Periodinane (1.5 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, 0°C, 2 h, 13% + **SM** recovery.

2.2.8 Synthesis of N_4-*tosyl*-macroline 152

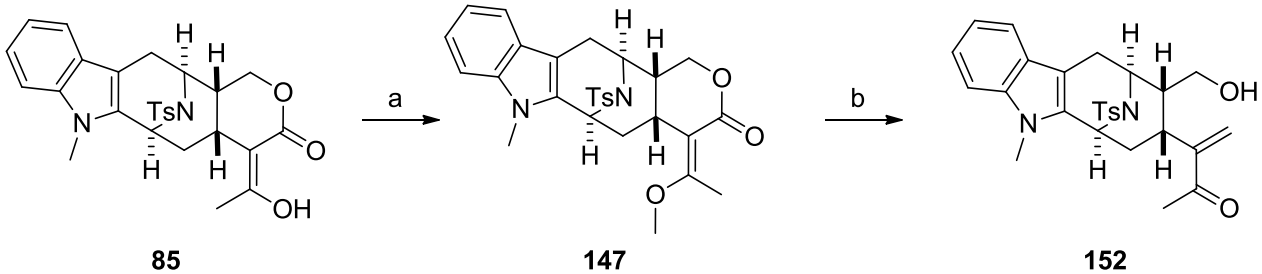
With type B macroline *E*-methyl ester **147** in hand, albeit in disappointing yield, we attempted the final steps of our original approach to alstonerine **4**.

Figure 36. Proposed alstonerine synthesis from type B methyl ester **147**.



We again hoped that partial 1,2-reduction of the C21 lactone carbonyl followed by acid-catalysed hydrolysis would give tosyl protected alstonerine **134**. We rationalised that the N_4-desulfonylation and methylation required to complete the synthesis would be achievable either pre- or post-reduction. For the reduction we again turned to previously successful conditions. After treatment with DIBAL in CH_2Cl_2 at −78°C for 1 hour, TLC assay showed the formation of a new product. Following work-up with Rochelle salt and chromatography, NMR analysis showed the appearance of two new low field singlets at ~ δ 6.00 and 5.60 corresponding to the methylene protons of N_4-*Ts*-macroline **152**. Comparison of the IR with that of the known compound confirmed the presence of the ring-opened unsaturated ketone in the E-ring.[3]

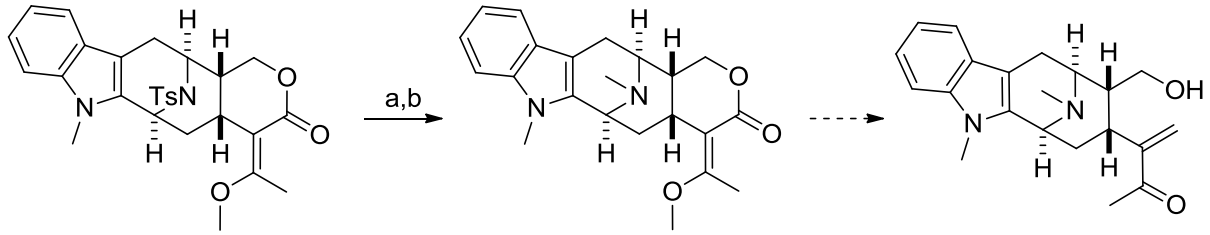
Scheme 50. DIBAL reduction of methyl ester **147** to give $N_{(4)}$-*Ts*-macroline **152**.



a) CSA (0.1 equiv.), $HC(OMe)_3$ (1.5 equiv.), $MeOH/CH_2Cl_2$, rt, 16 h, 91% (2:1 ratio of **148**:**147**); b) DIBAL (1.1 equiv.), CH_2Cl_2, –78°C, 1 h, 32% + **SM** recovery.

The N_4-methyl macroline precursor **153** was prepared using sodium naphthalenide desulfonylation conditions, followed by treatment with iodomethane and Hünig's base. This gave macroline precursor **153** in excellent yield over two steps.

Scheme 51. Synthesis of macroline precursor **153**.



147 **153** **1** (±)-macroline

a) Na·Np (5.0 equiv.), THF, –78°C, 2 h, 86%; b) Iodomethane (1.4 equiv.), Hünig's (3.0 equiv.), THF, –78°C → rt, 16 h, 81%.

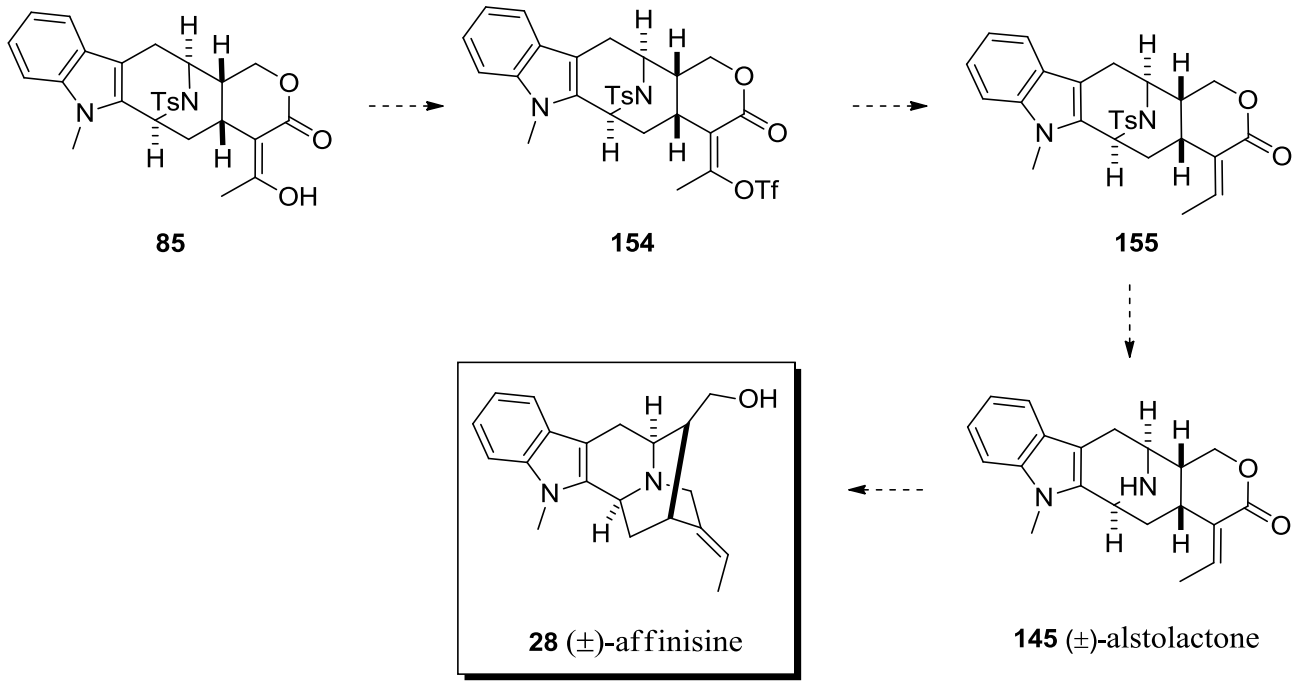
With macroline precursor **153** in hand, repeating the reduction conditions that had been carried out on the N_4-tosyl equivalent would provide macroline **1**. However, at this late stage of the project, all efforts were focused on the synthesis of alstonerine.

2.2.9 Towards the synthesis of (±)-alstolactone

Alstolactone **145** is a macroline-related indole obtained from the leaf extract of *Alstonia angustifolia var. Latifolia.*,[101] and is the only example from the macroline indole family to contain a lactone functionality in the E-ring. As such it's synthesis was investigated as a possible precursor to alstonerine **4**.

With pentacyclic lactone **85** in hand, activation of the C-19 carbonyl as the corresponding enol triflate **154** and subsequent hydrogenolysis would give N_4-tosyl-alstolactone **155**, and desulfonylation would deliver the desired N_4-*H* natural product **145** (Figure **36**).

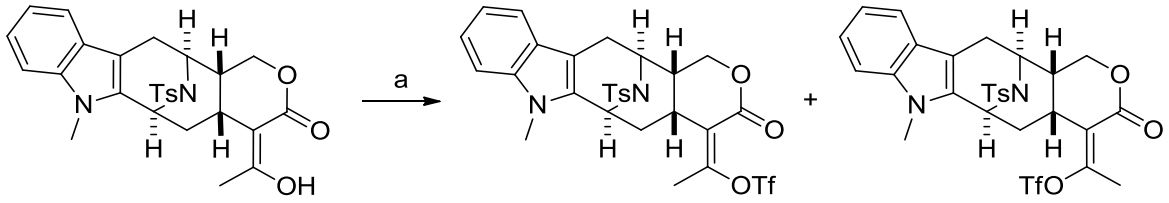
Figure 36. Proposed synthesis of alstolactone **155** and possible entry to sarpagine-related **28**.



Although early work focused on their use as precursors to vinyl cations and alkylidene carbenes, vinyl triflates have since been found to be excellent cross-coupling partners. This has led to extensive reviews on their synthesis from carbonyl groups and subsequent applications.[107] The synthesis of enol triflate **154** was initially carried out by treating pentacyclic lactone **85** directly with trifluoromethanesulfonic anhydride in the presence of non-nucleophilic base.[108] When Et_3N was used as the base in CH_2Cl_2 at room temperature a mixture of geometric isomers was obtained (3:2 **154/155**) in 32% yield (Entry 1, Table **8**). Switching base from Et_3N to Hünig's

base had little effect on the (Z-:E-) ratio. An improved ratio of (2:1 **154/155**) in 63% yield was obtained by decreasing the equivalents of triflic acid, reaction concentration and temperature (Entry **3**, Table **8**).

Table 8. Synthesis of β-ketoester enol triflates **154/155**.



95 **154** **155**

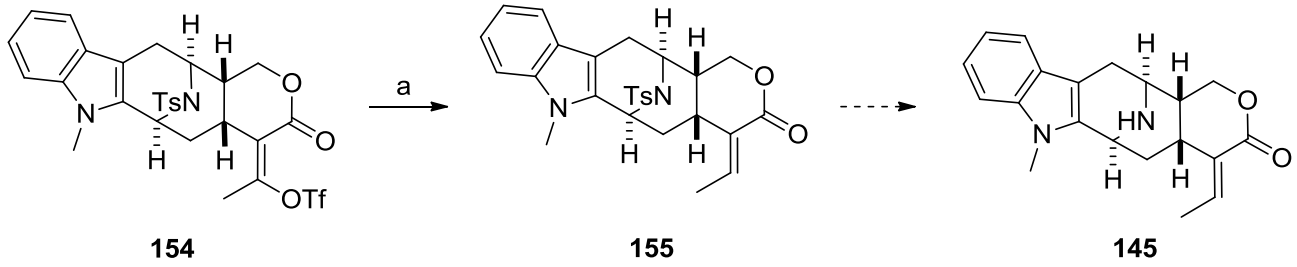
Entry	a) Conditions	Ratio 154:155	Yield 154
1	Et_3N (3.0 equiv.), Tf_2O (1.5 equiv.), CH_2Cl_2, rt, 1 h.	~3:2	32
2	Hünig's (3.0 equiv.), Tf_2O (1.5 equiv.), −50°C, 30 min.	~3:2	55
3	Et_3N (2.0 equiv.), Tf_2O (1.5 equiv.), −78°C, 30 min.	~2:1	63

*A more detailed optimisation of this reaction can be found on pages **108** to **110**.*

There are two approaches that dominate literature procedures for the palladium-catalysed reduction of vinyl triflates. The transformation can be achieved using either tributyltin hydride,[109] or triethylsilane[109] as the hydrogen donor, with catalytic Pd^0 in the presence of lithium chloride. Conditions using Et_3N and formic acid together with catalytic $Pd(OAc)_2$ and Ph_3P are also prevalent.[110] We chose the latter for the hydrogenolysis of enol triflate **154** into the N_4-tosyl protected natural product **155**.

Microwave modified conditions similar to those of Trudell were used.[111] Enol triflate **154** was heated in the microwave for 20 minutes at 80°C with sub-stoichiometric $Pd(OAc)_2$, and Ph_3P in excess Et_3N, formic acid and DMF. Filtration over celite, followed by washing with aqueous 5% LiCl solution and chromatography gave N_4-tosyl-alstolactone **155** in 44% yield. This was improved to 73% when chromatography was carried out immediately upon reaction completion (Scheme.

Scheme 52. Hydrogenolysis of enol triflate **155** and desulfonylation to alstolactone **145**.



154 **155** **145**

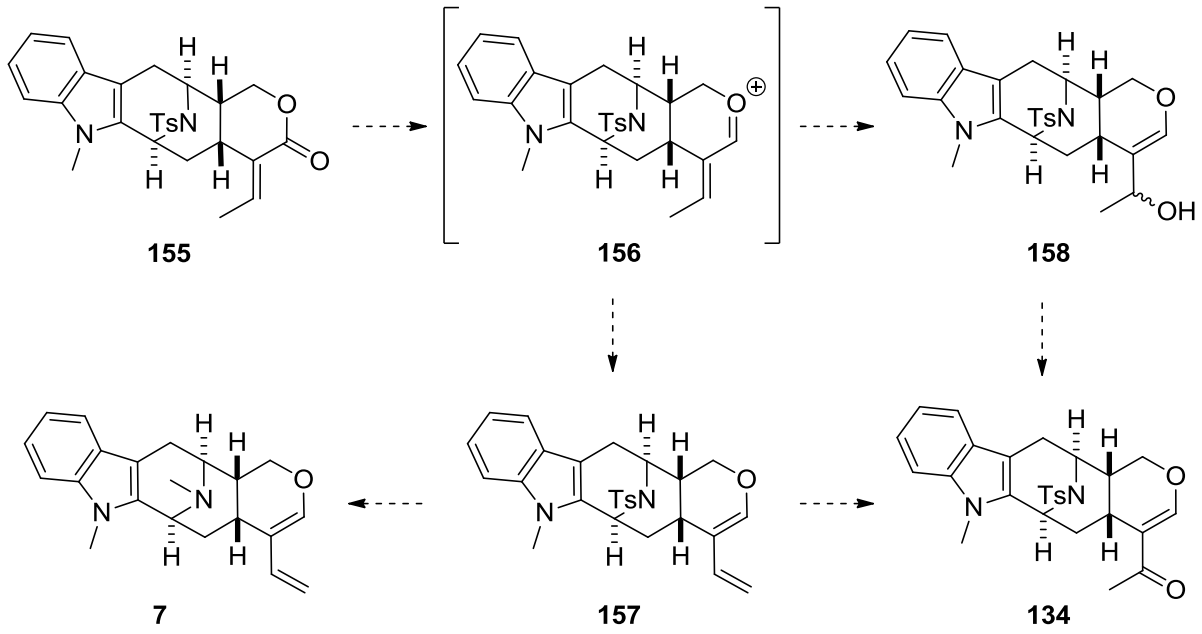
a) $Pd(OAc)_2$ (0.1 equiv.), Ph_3P (0.3 equiv.), HCO_2H (2.0 equiv.), Et_3N (3.0 equiv.), DMF, 80°C, 20 min, 73%;
b) Desulfonylation conditions.

At this stage, all that remained to complete the synthesis was to remove the N_4-tosyl protecting group. Strongly acidic conditions reported for this transformation, such as HBr and phenol in refluxing acetic acid,[112] or $HClO_4$[113] were avoided in order to alleviate rearrangement of the E-ring. The previously successful sodium naphthalenide conditions gave no conversion into the natural product, and led to degradation of **155**. The competitive reduction of the α,β-unsaturated lactone E-ring was suspected as causing the poor reactivity. Several other recently documented methods of sulfonamide cleavage also failed to complete the synthesis alstolactone. These were: SmI_2/amine and water in THF,[114] magnesium in anhydrous methanol under ultrasonic conditions[115] and TBAF in THF, under both prolonged reflux and microwave heating.[116] In all cases starting material was recovered in quantitative yield.

2.2.10 Synthesis of *N_4-tosyl*-(±)-anhydromacrosalhine-methine 7

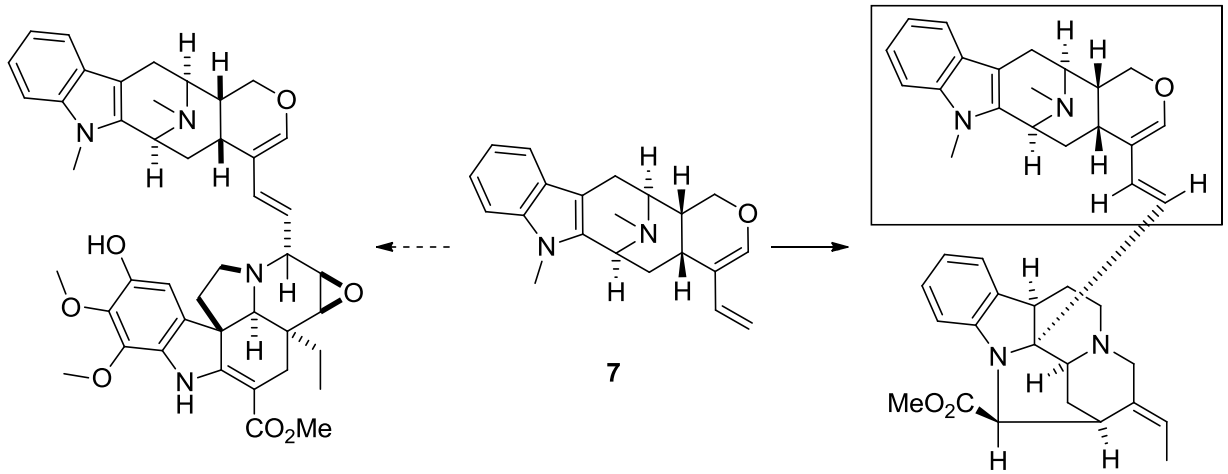
As multiple attempts at the deprotection of N_4-*tosyl*-alstolactone had failed, focus was returned to synthesising of the alstonerine E-ring. With **155** in hand, we hoped to probe the reactivity of the cyclic conjugated oxonium ion intermediate **156** that would result from a 1,2-reduction of its lactone carbonyl and subsequent acid-catalysed dehydration. We expected that under aqueous conditions, intermediate **156** may react with hydroxide to give epimeric allylic alcohol **158** and that a Swern oxidation (Cook[3] Scheme **6**, Page **21**) and desulfonylation/methylation would give alstonerine. Alternatively, anhydrous acidic conditions may effect a 1,4-elimination to give conjugated diene **157**. At which point, desulfonylation/methylation would give (±)-anhydromacrosalhine-methine **7** and Wacker-Tsuji oxidation of **157** may provide access to alstonerine E-ring.

Figure 37. Proposed use of N_4-tosyl alstolactone **155** as an intermediate for alkaloid synthesis.



The synthesis of anhydromacrosalhine-methine **7** would also offer a potential synthetic route to antiamoebic bis(indole) alkaloids, and is a known intermediate[17] in Cook's total synthesis of macrocarpamine[117] **8** (the most potent of the *Alstonia angustifolia* bis(indole)s used against amoebic dysentery by the people of Malaya[118]).

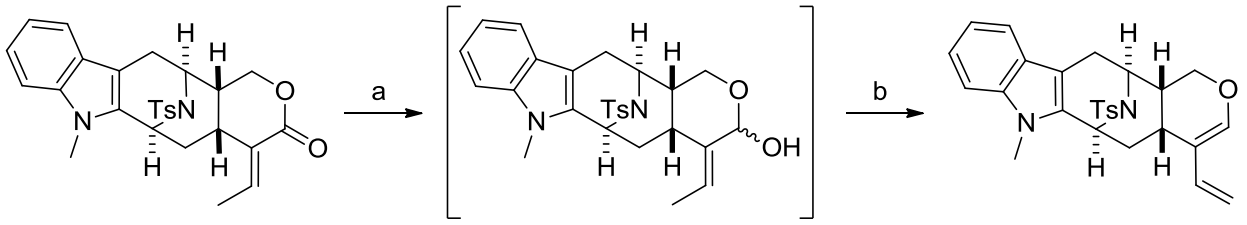
Figure 38. Cook's partial synthesis of macrocarpamine **8** from **7**.



159 pandicine **8** macrocarpamine

In practice, when N_4-tosyl alstolactone **155** was treated with DIBAL in CH_2Cl_2 at −78°C for 3 hours, TLC assay of the crude material showed that multiple new products had been formed. Four products were separated using preparative TLC, however ^{1}H NMR analysis illustrated that all four products had undergone further reaction during purification, to give a single new product. The ^{1}H NMR analysis showed that the unusually low field quartet of doublets at δ 7.11 and the methyl doublet at δ 1.45 of **155** had been replaced with a new doublet of doublets at δ 6.00 and doublets at δ 4.57 and δ 4.38. These corresponded to the olefinic protons of N_4-*tosyl*-(±)-anhydromacrosalhine-methine **157**.

Scheme 53. DIBAL reduction of N_4-*tosyl*-alstolactone **155**.

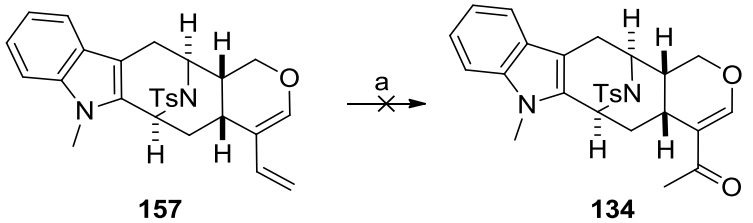


155 **160** **157**

a) DIBAL (1.1 equiv.), CH_2Cl_2, −78°C, 3 h, 94%; b) Silica, CH_2Cl_2, 15 min, 100%.

Having found reducing N_4-tosyl alstolactone **155** with DIBAL gave only the conjugated diene **157** and no epimeric allylic alcohols **158** that we had hoped to isolate, the Swern approach to alstonerine was abandoned. For the oxidation of diene **157**, Wacker–Tsuji oxidation conditions[119] were attempted. However, extended reflux led only to loss of the terminal alkene, with no formation of the C19 ketone of alstonerine.

Scheme 54. Attempted Wacker–Tsuji oxidation of **157**.



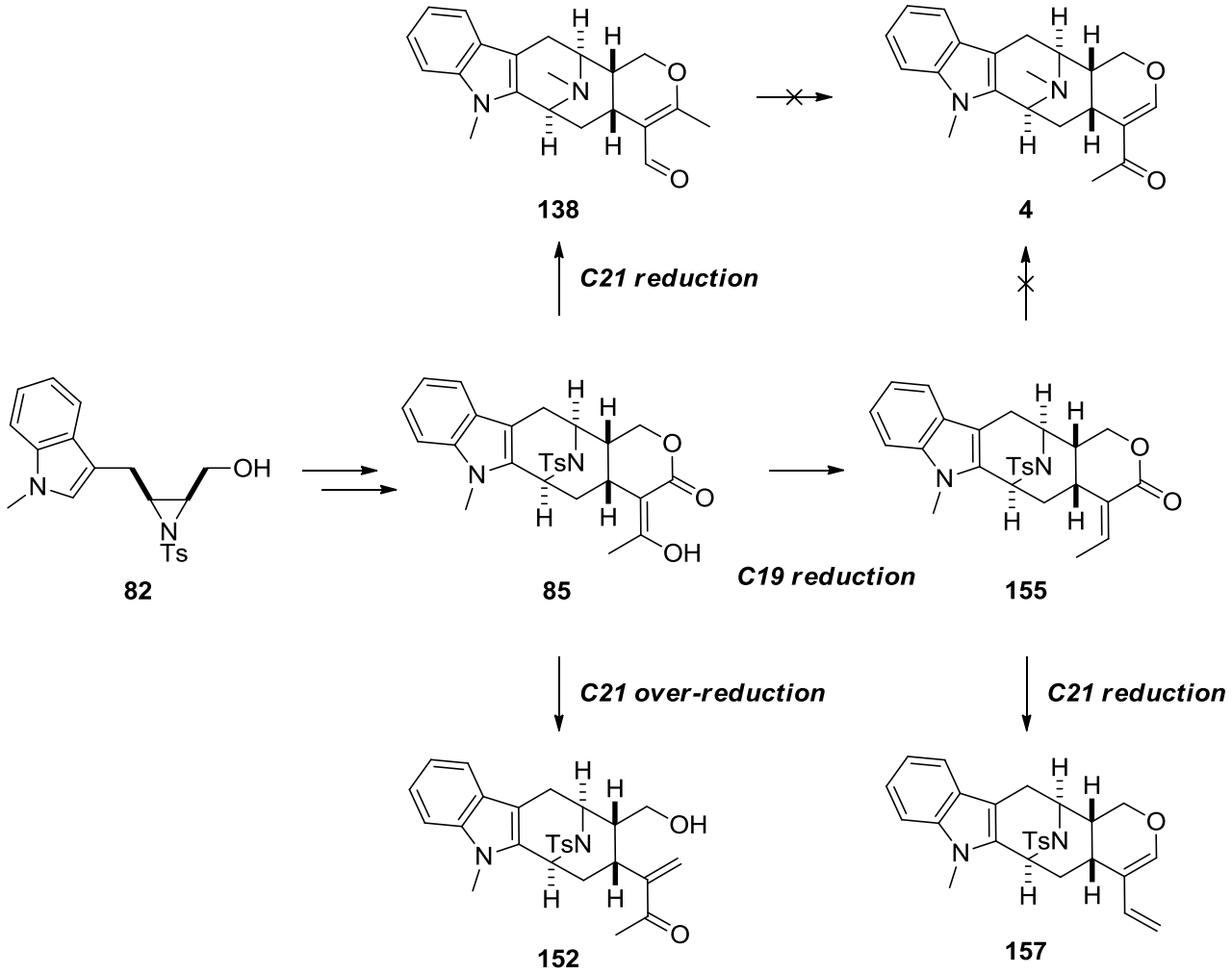
157 **134**

a) $PdCl_2$ (0.1 equiv.), $CuCl_2$ (2.1 equiv.), DMF: H_2O (5:1), 95°C, 16 h.

2.2.11 Total synthesis of (±)-alstonerine

At this stage the utility of the hydroxymethyl-substituted aziridine based approach to macroline-related indole alkaloids had been proven by the total synthesis of alstonerinal **138**. Pentacyclic lactone **85** had also been be converted into the N_4-tosyl protected derivatives of alstolactone **155**, anhydromacrosalhine-methine **157** and macroline **152** (the compound after which the family of alkaloids is named), however it remained to complete our alstonerine **4** synthesis.

Figure 39. The Craig group's approach to macroline-related indole alkaloids.



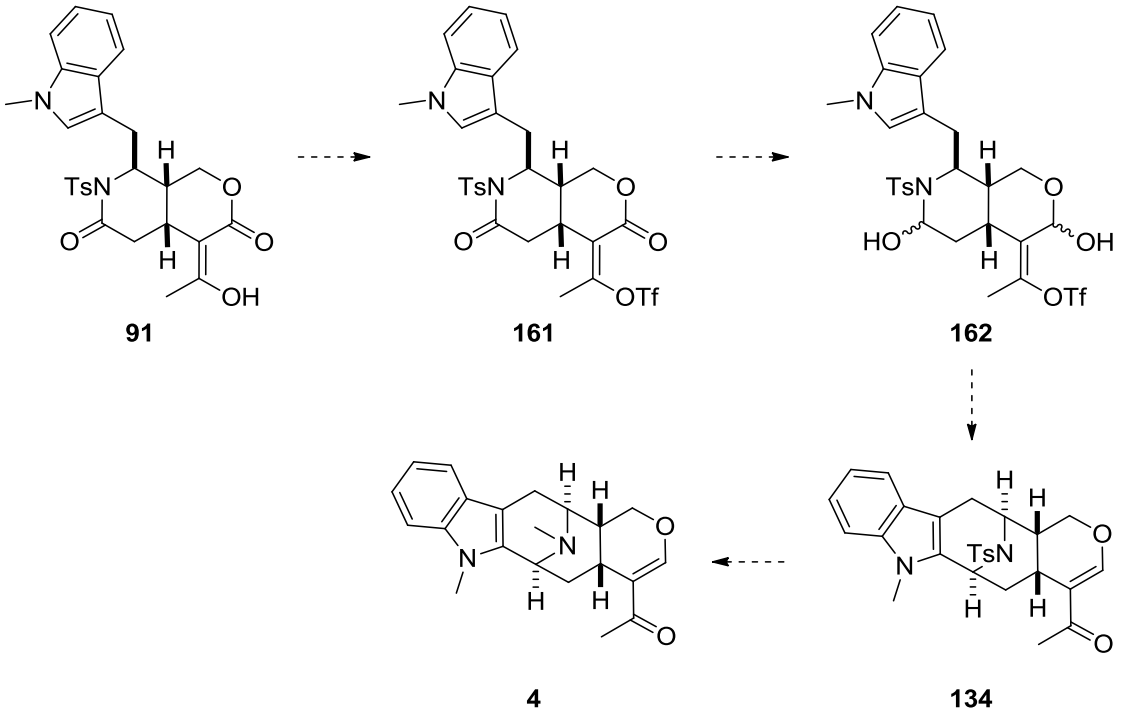
Pentacyclic **85** was found to be readily available by partial reduction of the C3 carbonyl in lactam–lactone **91** using DIBAL, followed by triflic acid mediated Pictet–Spengler cyclisation.

The C19 carbonyl of **85** had been reduced using palladium-catalysed hydrogenolysis of the enol triflate **154**, and the C21 lactone carbonyl had also been reduced by first converting **85** into the corresponding methyl enol ether. This negated the stabilising effect of the intramolecular hydrogen bond, and lead to the synthesis of the ring-opened macroline E-ring.

Therefore, despite numerous attempts, the partial reduction of the C21 lactone carbonyl group and subsequent C20−C21 double bond-forming acid-catalysed dehydration was yet to be accomplished.

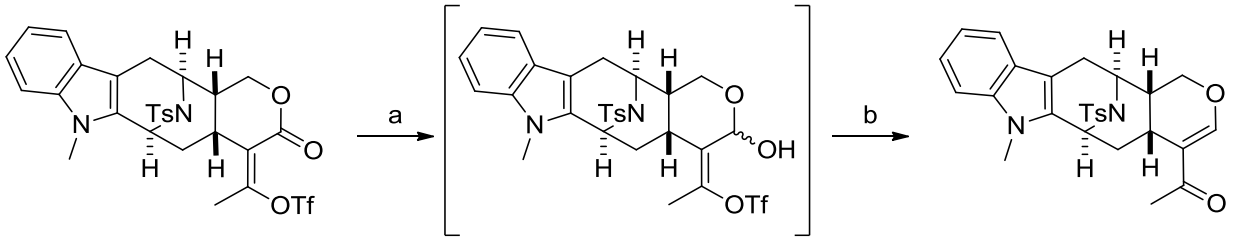
For the final approach to the E-ring, we reasoned that functionalisation of the C19 enol with an electron-withdrawing group may render the C21 lactone carbonyl more electron-deficient, and therefore more reactive towards partial reduction. In addition, optimisation studies of the Pictet–Spengler cyclisation (Scheme **43**, Page **80**) had shown that stoichiometric quantities of triflic acid were required to convert partially reduced lactam–lactone **91** into pentacyclic lactone **85**. With this in-mind, it was hoped that on partial reduction of enol triflate **161** (Figure **40**, below) and hydrolysis of partially reduced triflate intermediate **162**, an equivalent of triflic acid would be released, which would in turn mediate the Pictet–Spengler cyclisation, as shown below.

Figure 40. Proposed synthesis of alstonerine **4**.



Pentacyclic triflate **154** was chosen to initially probe what would constitute the final stages of the envisaged reduction–Pictet–Spengler reaction. **154** was converted into lactol intermediate **163** using DIBAL. At this stage we were delighted to observe that only a proton NMR of an intermediate, assumed to be **163**, could be obtained before a colour change from colourless to dark brown was observed in the NMR sample. ^{1}H NMR analysis of the sample following the colour change showed that spontaneous triflate hydrolysis had occurred, facilitating the C20–C21 double bond-forming acid-catalysed dehydration. *N*$_4$-*Tosyl*alstonerine was isolated in quantitative yield following chromatography.

Scheme 55. DIBAL reduction of enol triflate **154**.



154 **163** **134**

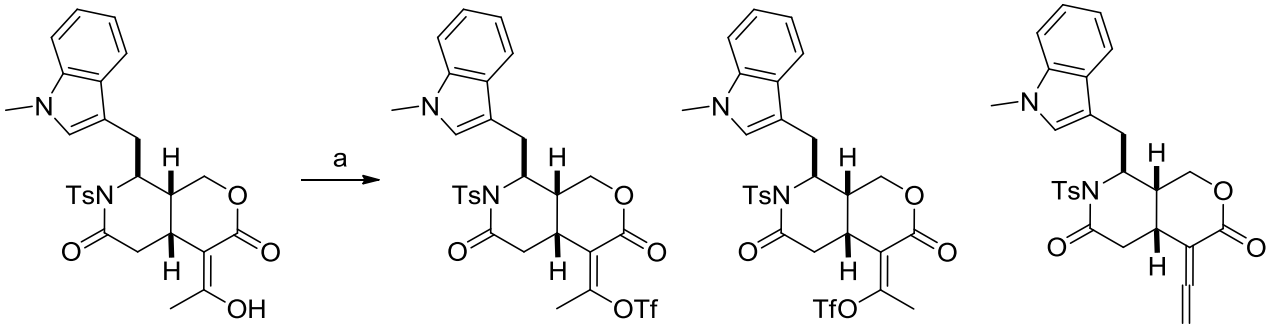
a) DIBAL (1.5 equiv.), CH_2Cl_2, −78°C, 3 h; b) $CDCl_3$, 1 h, 100%.

Encouraged by finally having established the alstonerine E-ring, we attempted to combine this reduction with the Pictet–Spengler cyclisation, in a one-pot reduction–Pictet–Spengler cyclisation of enol triflate **161** that would provide the polycyclic core of alstonerine. During the reaction the enol triflate would serve the multiple purposes of protecting the C19 ketone from reduction whilst simultaneously activating the C21 carbonyl, and as a latent reagent for the Pictet–Spengler cyclisation and acid-catalysed dehydration.

For the synthesis of enol triflate **161**, our first attempt returned to those conditions used in our synthesis of *N*$_4$-*tosyl*-alstolactone **155**. Lactam–lactone **91** was treated with triflic anhydride in the presence of non-nucleophilic amines Hünig's base and triethylamine in CH_2Cl_2 at low temperatures (Entries **1** and **2**, Table **10**, below). The ^{1}H NMR spectra of the crude material obtained from both reactions showed that two products had been formed, yet both gave low yields of **161** following chromatography. In an attempt to improve on this yield, the reaction was run in various solvents. Triflic anhydride reacted with THF to give *bis*-triflylbutane, with complete starting material return (Entry **15**, Table **10**). The combination of CH_2Cl_2 as a solvent

and organic bases gave poor *Z*- selectivity (Entries **1**–**4**, Table **10**). Interestingly the *E*-isomer was never isolated. Instead its existence in the crude material was assumed *via* a process of elimination. During early attempts at enol triflate formation (Entries **1**–**4**, Table **10**), complete conversion of starting material was observed by TLC assay, and confirmed by ^{1}H NMR analysis of the crude material obtained which showed that a mixture of two products had been formed. However following chromatography, only mixtures of the desired *Z*-isomer **161** and starting enol **91** were isolated. It was assumed that mixtures of geometric isomers were formed during the reaction, but the *E*-isomer was unstable towards hydrolysis on silica. This assumption was further supported by attempts to isolate both the sodium and potassium enolates of **91**. When enol **91** was subjected to exact repeats of the triflylation conditions (Entries **8** and **9**, Table **10**) without triflylating agent, ^{1}H NMR analysis of the crude material obtained from identical work-ups to those used in the synthesis of **161**, showed only clean starting material **91**. The next attempt was to switch to KHMDS, in order to form a potassium enolate that was previously shown to be reactive to *C*-alkylation (Table **5**, Page **83**). This led to increased reactivity, and favoured the desired *Z*-isomer, yet the yield was still poor. We hoped that switching to co-ordinating ethereal THF may increase the reactivity of the enolate intermediate; therefore we required an alternative triflylating agent to triflic anhydride, as this had been shown to react with THF. Lactam–lactone **91** was converted cleanly into *Z*-enol triflate **161** using 1.1 equivalents of KHMDS and *N*-phenyl-bis(trifluoromethanesulfonamide).[120] Importantly, no *E*-isomer was observed in the ^{1}H NMR of the crude material. Notably, when DMF was used as the solvent, allene **165** was achieved as the major product after 15 minutes at –78°C (Entry **13**, Table **10**). When treated with DIBAL, allene **165** was converted into inseparable mixtures of N_4-*tosyl*-alsoterinal and the N_4-tosyl derivative of alstonerinal precursor allylic alcohol **151** in good yield. When aqueous conditions were applied to lactam–lactone **91** (Entry **17**, Table **10**),[121] only starting material was obtained, possibly due to the formation of only the *E*-isomer.

Table 10. Synthesis of enol triflate **161**.



91 **161** **164** **165**

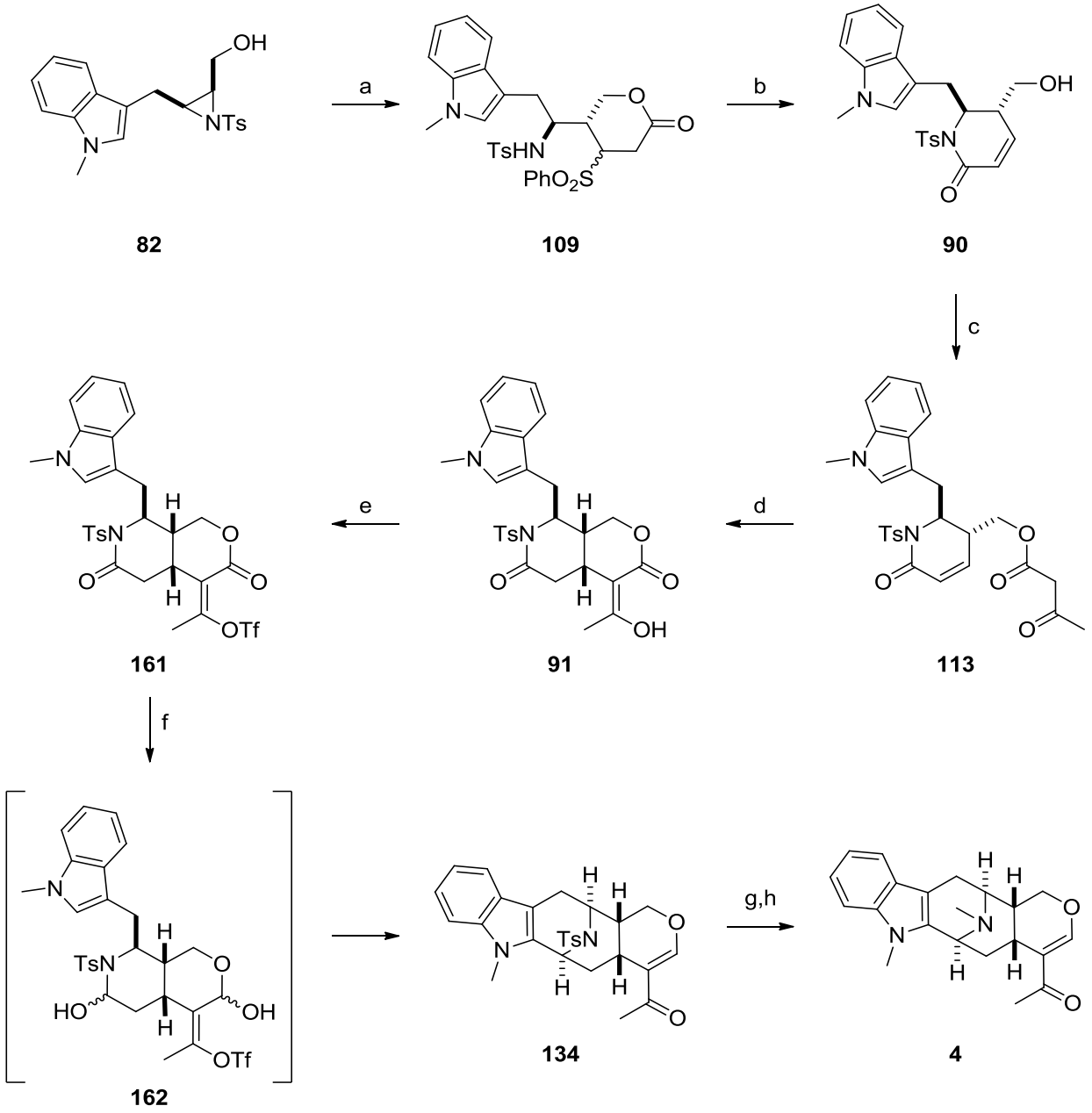
Entry	a) **Conditions**	**Temp**	**~ Ratio[a] 161:164: 165**	**Yield[b] 165**
1	Hünig's (3.0 eq.), Tf_2O (1.2 eq.), CH_2Cl_2, 0.5 h	−78°C	1:5:1	6%
2	Et_3N (1.5 eq.), Tf_2O (1.2 eq.), CH_2Cl_2, 0.5 h	−78°C	1:2:0	22%
3	Hünig's (3.0 eq.), Tf_2NPh (1.2 eq.), CH_2Cl_2, 0.25 h	rt	1:5:0	11%
4	Hünig's (3.0 eq.), Tf_2NPh (1.2 eq.), CH_2Cl_2, 0.5 h	−78°C	0:1:0	**SM**
5	Hünig's (3.0 eq.), Tf_2NPh (1.2 eq.), CH_2Cl_2, 3.0 h	−78°C	0:1:0	**SM**
6	KHMDS (1.5 eq.), Tf_2NPh (1.1 eq.), CH_2Cl_2, 3.0 h	−78°C→rt	1:1:0	14%
7	DBU (1.5 eq.), Tf_2NPh (1.1 eq.), CH_2Cl_2, 3.0 h	−78°C→rt	1:9:0	-
8	KHMDS (1.5 eq.), Tf_2NPh (1.1 eq.), CH_2Cl_2, 16 h	−78°C→rt	1:3:0	23%
9	NaH (1.0 eq.), Tf_2O (1.1 eq.), CH_2Cl_2, 16 h	0°C→rt	1:5:0	**SM**
10	**KHMDS (1.2 eq.), Tf_2NPh (1.1 eq.), THF, o/n**	**−78°C→rt**	**5:1:0**	**74%**
11	NaH (1.0 eq.), Tf_2O (1.1 eq.), THF, 16 h	0°C	-	-
12	**KHMDS (1.1 eq.), Tf_2NPh (1.1 eq.), THF, 16 h**	**−78°C→rt**	**5:1:0**	**69%**
13	**Hünig's (3.0 eq.), Tf_2NPh (1.1 eq.), DMF, 0.5 h**	**−78°C**	**1:0:11**	**88%**
14	DBU (3.0 eq.), Tf_2NPh (1.2 eq.), THF, 16 h	rt	1:9:0	**SM**
15	DBU (3.0 eq.), Tf_2O (1.2 eq.), THF, 0.25 h	−78°C	0:0:0	**SM**
16	NaH (5.0 eq.), Commins (2.0 eq.), THF, 1 h	0°C	-	-
17	LiOH (5.0 eq.), Tf_2O (2.5 eq.), toluene, H_20 1 h	0°C	0:1:0	**SM**
18	KHMDS (1.1 eq.), Tf_2NPh (1.1 eq.), toluene, 16 h	−78°C→rt	1:5:0	**SM**

[a]Ratio of **161:164:165** visible in ^{1}H NMR of crude material, during chromatography **164** underwent hydrolysis to give only **SM 91**; [b]Isolated yield following chromatography

Having established a reliable method for converting lactam–lactone **91** into *Z*-enol triflate **161**, the stage was set for our postulated one-pot reduction–dehydration–Pictet–Spengler cyclisation. Previously, we had shown that the enol-triflate E-ring of **154** was converted into the appropriately functionalised E-ring for alstonerine in tosyl protected **134** (Scheme **55**, Page **108**). We had also shown that an equivalent of triflic acid was required to complete the Pictet–Spengler cyclisation of **91** to pentacyclic lactone **85** (c, Scheme **43**, Page **80**). We were delighted to observe that treatment *Z*-enol triflate **161** with 2.25 equivalents DIBAL, followed by wet Et_2O–Rochelle salt work-up gave an unstable intermediate, presumed to be the crude hemiaminal–lactol **162**. Upon stirring in wet CH_2Cl_2 or K_2CO_3 treated $CDCl_3$, **162** underwent triflic acid elimination and instantaneous Pictet–Spengler cyclisation, to give cleanly N_4-tosylalstonerine **134** in excellent yield and as the sole product, as observed by ^{1}H NMR.

Overjoyed with the success of our one-pot reduction–dehydration–Pictet–Spengler cyclisation,[122] all that remained to complete the synthesis was desulfonylation and alkylation. Having achieved this transformation during our total synthesis of alstonerinal, we first turned to sodium naphthalenide conditions. Treatment of N_4-tosylalstonerine with 8.0 equivalents sodium naphthalenide solution in THF at –78°C gave N_4-demethylalstonerine in 57% yield. A loss of the dark green colour during this reaction indicated that over reduction of the enone moiety in the E-ring may be occurring due to the excess reducing agent. When the concentration of sodium naphthalenide was reduced to 5.0 equivalents, **134** was converted into N_4-demethylalstonerine **166** in 83% yield. Various alternative desulfonylation conditions were attempted, however all failed to improve on this yield. The synthesis was completed using the methylation conditions outlined previously (Scheme **49**, Page **98**). Iodomethane was added to N_4-demethylalstonerine **166** and excess Hünig's base in THF at –78°C, giving alstonerine **4** in 91% yield (Scheme **56**, below). This led to the synthesis of alstonerine in just 8 steps from hydroxymethyl substituted aziridine **82** and in an overall yield of 37%. Aziridine **82** and sulfone **88** were previously shown to be readily accessible (Schemes **25** and **28** respectively).

Scheme 56. Final FGI and completed total synthesis of alstonerine **4**.

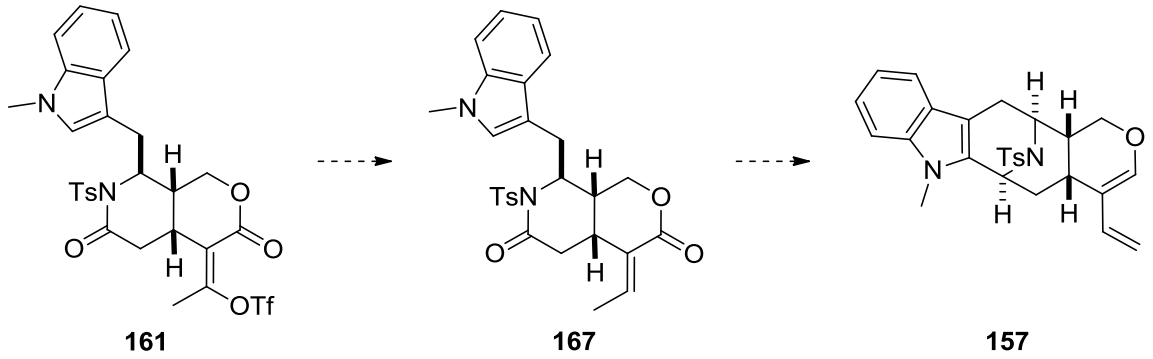


a) Sulfone **88** (1.5 equiv.), *n*-BuLi (2.8 equiv.), THF, –78°C→rt o/n, then aqueous 2M HCl, 80%; b) TMA (1.5 equiv.), toluene, 120°C, 2 h, saturated aqueous Rochelle salt, 94%; c) 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one (1.5 equiv.), toluene, 150°C µW, 20 min, 97%; d) DBU (2.0 equiv.), THF, rt, 12 h, 93%; e) KHMDS (1.2 equiv.), Tf_2NPh (1.1 equiv.), THF, –78°C→rt, o/n, 74%; g) DIBAL (2.5 equiv.), CH_2Cl_2, −78°C, 2.25 h, then wet CH_2Cl_2, 1 h, 98%; g) Na·Np (5.0 equiv.), THF, –78°C, 2 h, 83%; h) Iodomethane (2.0 equiv.), Hünig's (3.0 equiv.), THF, –78°C→rt, 16 h, 91%.

2.2.12 Improved route to N_4-tosylanhydromacrosalhine-methine 157

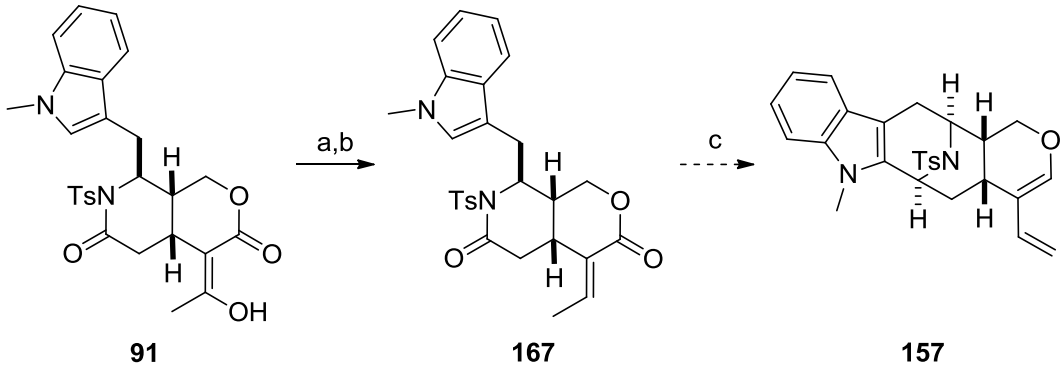
As with our total synthesis of alstonerine, we envisaged the synthesis of (±)-anhydromacrosalhine-methine **7** *via* a reduction–Pictet–Spengler cyclisation of intermediate **167**. The E-ring of intermediate **167** would be synthesized by hydrogenolysis of enol triflate **161**.

Scheme 57. Proposed synthesis of *N*4-Tosylanhydromacrosalhine-methine **157**.



Enol triflate **161** was converted into Pictet–Spengler cyclisation precursor **167** in an improved yield of 85%. We now envisaged that DIBAL reduction followed by acid-catalysed dehydration would give us N_4-tosylanhydromacrosalhine-methine **157**. However, in practice, when **167** was reacted with DIBAL and subjected to acidic work-up with triflic acid, a complex mixture of pentacyclic products was isolated. The conjugated diene E-ring of **157** is known to be acid-sensitive, thus in order to complete our improved synthesis of anhydromacrosalhine-methine, optimisation of the acidic Pictet–Spengler and 1,4-elimination conditions is required.

Scheme 58. Failed tandem reduction–Pictet–Spengler cyclisation of **167**.



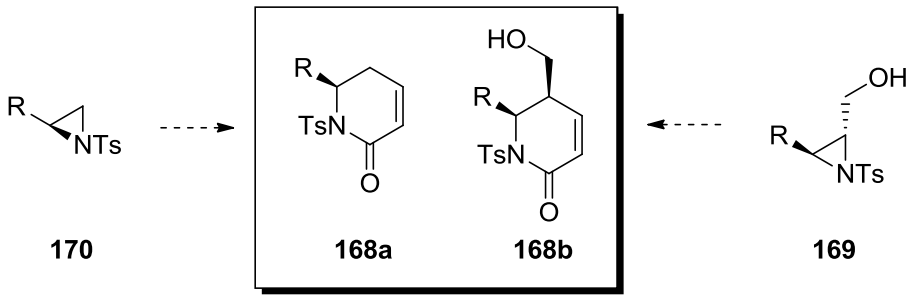
a) KHMDS (1.2 equiv.), Tf_2NPh (1.1 equiv.), THF, –78°C→rt o/n, 74%; b) $Pd(OAc)_2$ (0.1 equiv.), Ph_3P (0.3 equiv.), HCO_2H (4.0 equiv.), Et_3N (3.0 equiv.), DMF, 80°C, 20 min, 85%; c) DIBAL (2.0 equiv.), CH_2Cl_2, −78°C, 3 h, then TfOH (2.5 equiv.), rt, 15 min, degradation.

2.2.13 Extension of methodology

Having successfully applied our aziridine ring-opening based synthesis of α,β-unsaturated-*δ*-lactam **90** to the total synthesis of alstonerine **4**, our attention turned to extending the scope of this sequence, by synthesising optically pure lactams **168a**. We hoped to show that, α,β-unsaturated-*δ*-lactams **168**, in addition to themselves being useful building blocks in organic synthesis, can be partially reduced which allows them to participate in tetrahydropyridine-like chemistry, as outlined previously (Figure **8**, Page **34**).

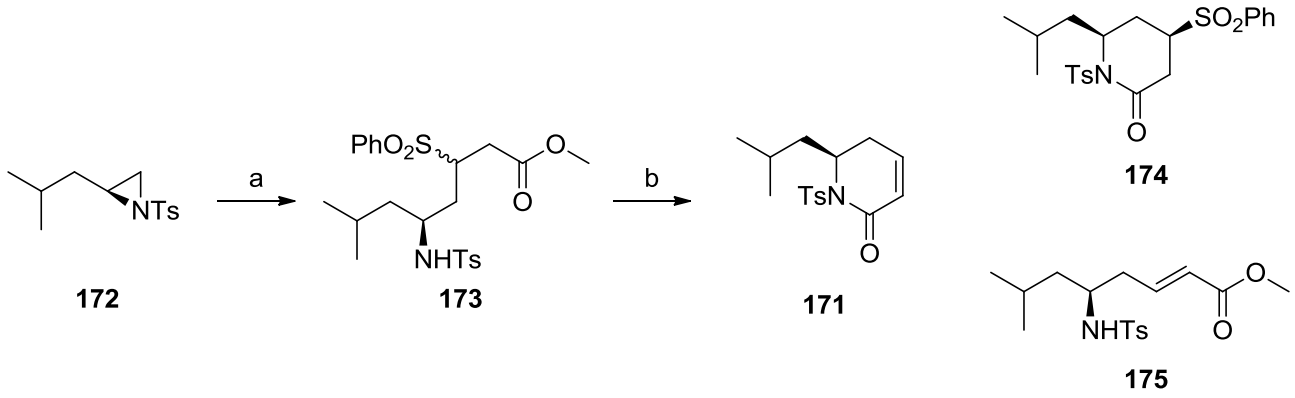
We also hoped that the ring opening of optically pure hydroxymethyl-substituted aziridines **169** would allow access to *bis*-substituted lactams **168b**. In addition, by altering the configuration of aziridines **169**, an enantiospecific route to each of the four possible enantiomers of lactam **168** would be possible.

Figure 41. Synthesis of optically pure amino acid-derived lactams **168**.



We began by investigating the synthesis of optically pure D-leucine-derived α,β-unsaturated *δ*-lactam **171**. L-leucine was first converted into aziridine **172** in 56% yield using a sequence previously reported by the Craig group.[123] Aziridine **172** was then reacted with the lithiated anion of nucleophile trimethyl 3-(phenylsulfonyl)orthopropionate **88**. Acidic work-up gave epimeric sulfones **173** in excellent yield. Compound **173** was then treated with trimethylaluminium under the microwave conditions, as outlined in our alstonerine total synthesis. This gave a mixture of the desired α,β-unsaturated lactam **171**, the intermediate piperidine **174** and *trans*-α,β-unsaturated non-cyclised methyl ester **175**, which as previously, could not be converted into the desired heterocycle **171**.

Scheme 59. Synthesis of optically pure α,β-unsaturated lactam **171**.

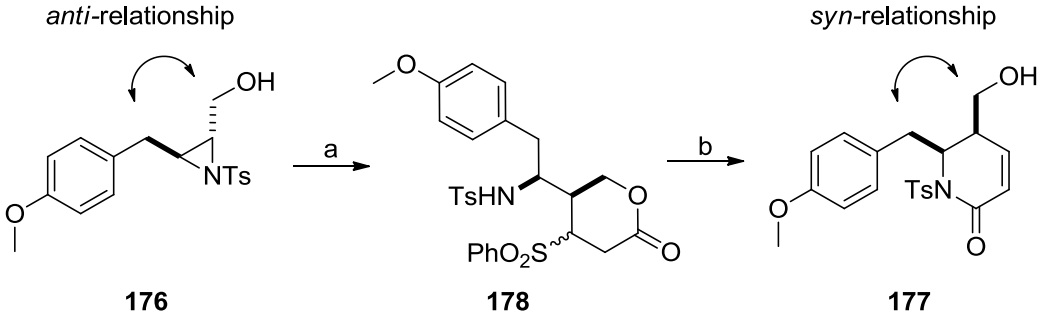


a) trimethyl 3-(phenylsulfonyl)orthopropionate **88** 2.0 (equiv.), *n*-BuLi (4.0 equiv.), THF, –78°C→rt, 16 h, 82% (7:3 sulfone epimers); b) TMA (1.1 equiv.), toluene, 150°C, 30 min, saturated aqueous Rochelle salt, 93% conversion as a mixture of **171**, **174** and **175**.

Importantly, intermediate **174** was converted into the desired compound **171** by resubmission to the original reaction conditions. At this stage, having shown that optically pure mono-substituted lactam **171** was available from the L-leucine, the synthesis of *bis*-substituted lactams **168b** was briefly investigated. Racemic *anti*-substituted aziridine **176** was chosen as our first substrate, as we hoped to provide evidence to support our assumption that *anti*-substituted aziridine **176** would provide *syn*-substituted α,β-unsaturated lactam **177**.

In practice, *anti*-substituted **176** was converted into the corresponding lactones **178** as a 2:1 mixture of sulfone epimers. Lactones **178** were then converted into α,β-unsaturated lactam **177** in good yield using the previously established trimethylaluminium microwave conditions. Importantly the corresponding α,β-unsaturated ester **179** was avoided by isolating lactones **178** in place of the open-chain methyl ester. We hope that exposing **177** to acidic conditions will bring about a similar cyclisation similar to that seen with our indole containing substrate (Scheme **45**, Page **87**). This will provide a selective route to the benzomorphan containing alkaloids, which include numerous important pharmaceutical compounds.[124]

Scheme 60. Synthesis of *syn*-substituted racemic α,β-unsaturated lactam **177**.

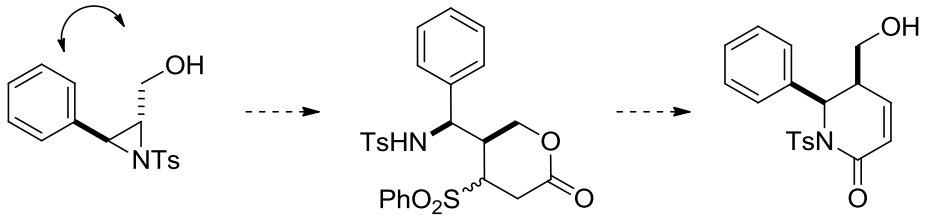


176 **178** **177**

a) trimethyl 3-(phenylsulfonyl)orthopropionate **88** 2.0 (equiv.), *n*-BuLi (4.0 equiv.), THF, –78°C→rt, 16 h, 87% (2:1 sulfone epimers); b) TMA (1.5 equiv.), toluene, 150°C, 10 min, saturated aqueous Rochelle salt, 56% and **SM** recovery.

We also aimed to investigate selectivity the nucleophilic ring-opening reaction of aziridine **180** which contains both our directing hydroxymethyl-substituent and a phenyl-substituent that also has a directing effect (Scheme **61**, below).

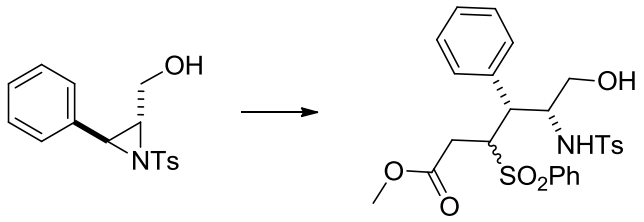
Figure 42. Selectivity of aziridine **180** with both phenyl- and hydroxymethyl-directing groups.



180 **181** **182**

Aziridine **180** was synthesised from cinnamyl alcohol using Sharpless conditions[69] and subjected to our standard aziridine ring-opening condition. Unfortunately, this gave a very complicated mixture of products, from which only those products of phenyl-directed aziridine ring-opening **183** were isolated in suitable yield for complete characterisation (Scheme **61**, below).

Scheme 61. Ring-opening of aziridine **180**.



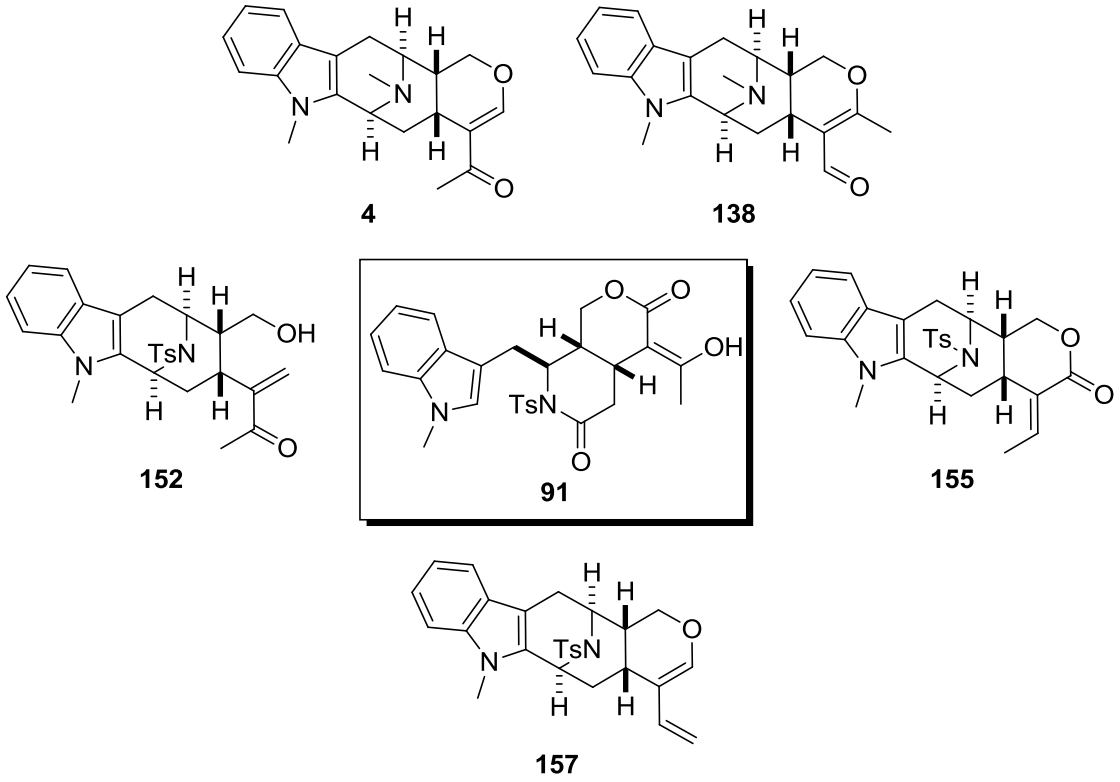
180 **183**

a) trimethyl 3-(phenylsulfonyl)orthopropionate 2.0 (equiv.), *n*-BuLi (4.0 equiv.), THF, –78°C→rt, 16 h, 67% of complex mixture of Phenyl-directed aziridine ring-opening.

2.2.14 Conclusion

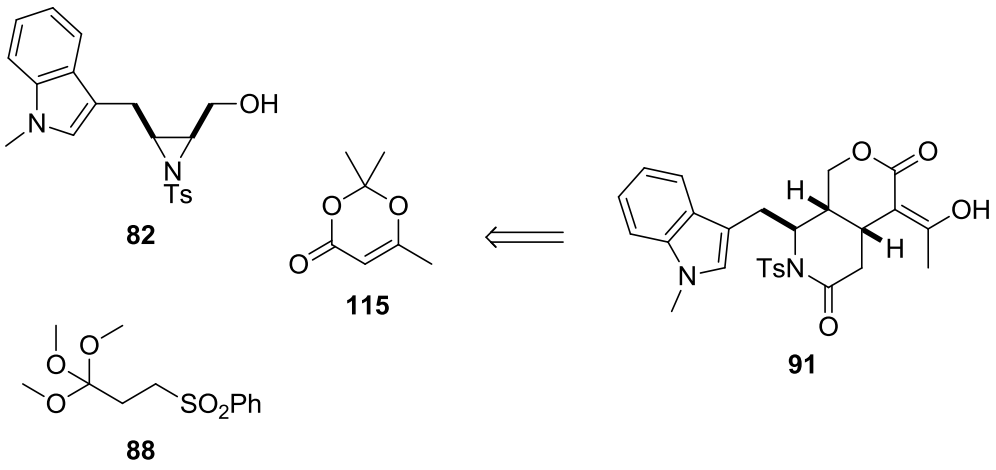
We report the concise aziridine-based total syntheses of macroline-related indole alkaloids (±)-alstonerine[122] **4** and (±)-alstonerinal **138**, which were achieved in eight and ten steps respectively from hydroxymethyl-substituted aziridine **81**. We also showed our approach to be amenable to the synthesis of related compounds macroline **1**, alstolactone **145** and anhydromacrosalhine-methine **7** by synthesising their N_4-tosyl derivatives **152**, **155** and **157**, the latter of which provides access to the *bis*-indole alkaloids, particularly macrocarpamine **8**.

Figure 43. Alkaloids synthesised from lactam–lactone intermediate **91**.



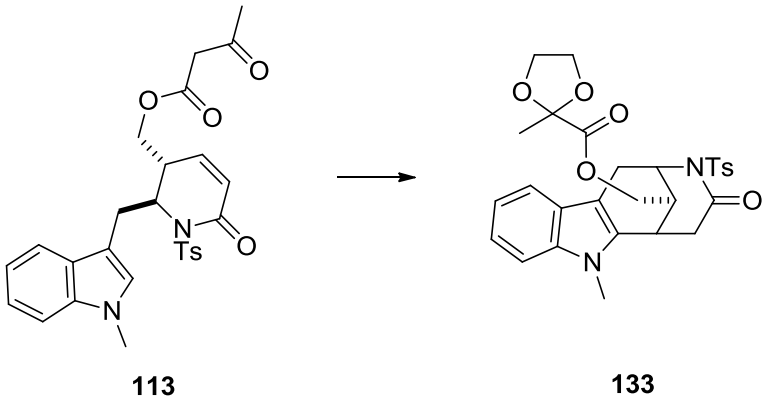
Late-stage intermediate lactam–lactone **91** was rapidly assembled from three simple components in four high-yielding steps, those being hydroxymethyl-substituted aziridine **82**, and trimethyl 3-(phenylsulfonyl)orthopropionate **88** and 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one **115**.

Figure 44. Late stage intermediate **91** synthesised from three simple components.



We have also shown this approach to macroline-related alkaloids to be amenable to the synthesis of the indolomorphan motif, by an intramolecular acid-mediated Michael-type addition that was used to synthesise **133** (Figure **45**, below).

Figure 45. Synthesis of the indolomorphan motif, by an intramolecular acid-mediated Michael-type addition.



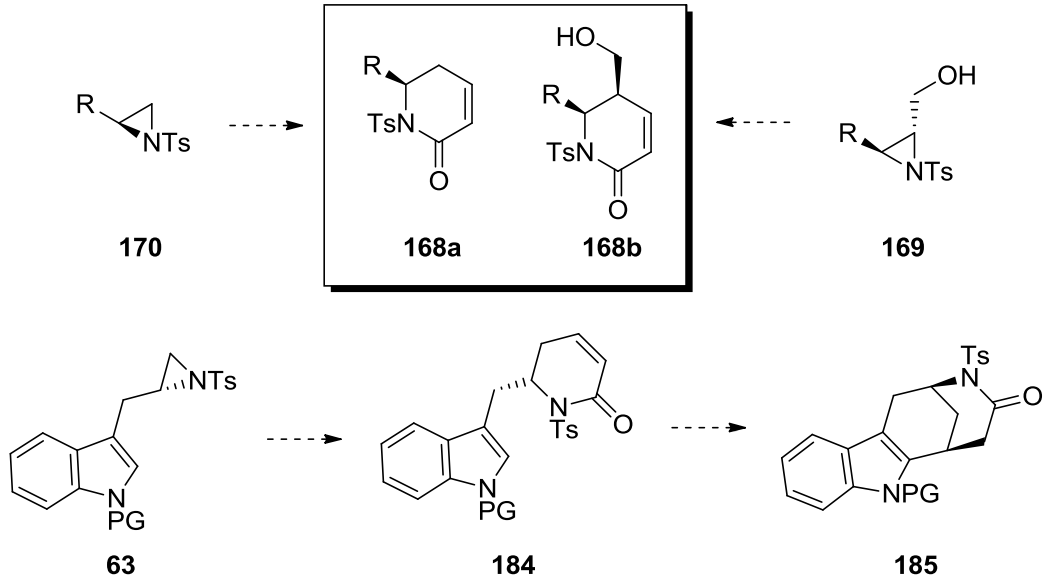
In addition, α,β-unsaturated lactam **177** was also synthesized, from which we hope that acid-catalysed cyclisation would provide access to benzomorphan related alkaloids.

We also proved that optically pure α,β-unsaturated lactams can be synthesised using this method, by the synthesis of L-leucine-derived **171**. Our initial probes into the directing effect of the hydroxymethyl substituent showed that when a phenyl-substituted aziridine **180** was subjected to our ring-opening conditions, the directing effect of the $\pi_{(C-C)} \rightarrow \sigma^*_{(C-N)}$ donation from the phenyl ring led to only phenyl-directed ring-opening products being isolated **183**.

2.2.15 Future Work

Having carried out initial studies into the synthesis of optically pure amino acid-derived lactams, there remains scope to synthesise a series of amino acid-derived lactams, so that particularly their 1,4-acid induced Michael-type cyclisations as well as Pictet–Spengler reactivity could be assessed. This would provide a complementary lactam oxidation level alternative to the Craig group's previous tetrahydropyridine work. Of particular interest would be the synthesis of tryptophan-derived **63** which would provide access to the indolomorphan motif following our methodology.

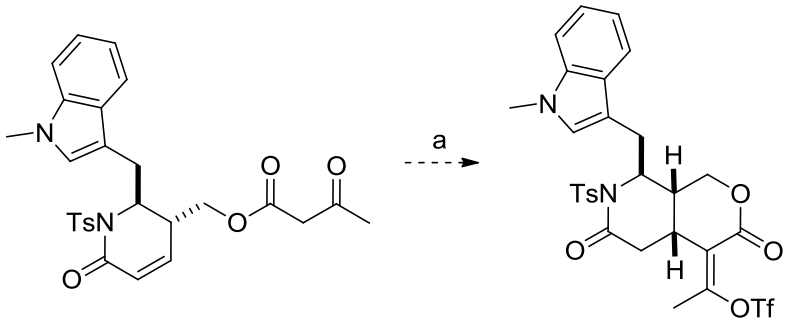
Figure 46. Synthesis of optically pure lactams.



For the synthesis of macroline-related alkaloids, specifically the Michael-type addition of β-ketoester **112**, future preparations may seek to combine this addition with the formation of enol triflate **161**, by simply using KHMDS as the base for the Michael addition and then adding *N*-phenyl-bis(trifluoromethanesulfonamide) to the potassium enolate product. This should remove a step from the synthesis by producing enol triflate **161** in place of enol **91**.

.

Figure 47. Revised one-pot synthesis of enol triflate **161**.

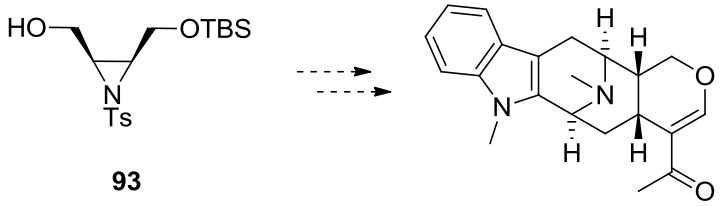


113 **161**

Suggested conditions: *a) KHMDS (1.5 equiv.), THF, −78°C→rt, 12 h, then Tf_2NPh (2.0 equiv.), THF −78°C→rt, 16 h.*

Having established a concise route to racemic alstonerine, the synthesis of optically pure aziridine **93** (Figure **48**, below) should provide rapid access to large quantities of macroline-related alkaloids.[65] This in turn could be applied to the synthesis of bis(indole)alkaloids and sarpagine-related alkaloids as shown below. As an intermediate in our racemic synthesis, optically pure aziridine **93** would provide naturally occurring (–)-alstonerine in 12 steps (or 11 using the aforementioned revision of the synthesis of enol triflate **161**), which offers a significantly shorter route to those previously reported.

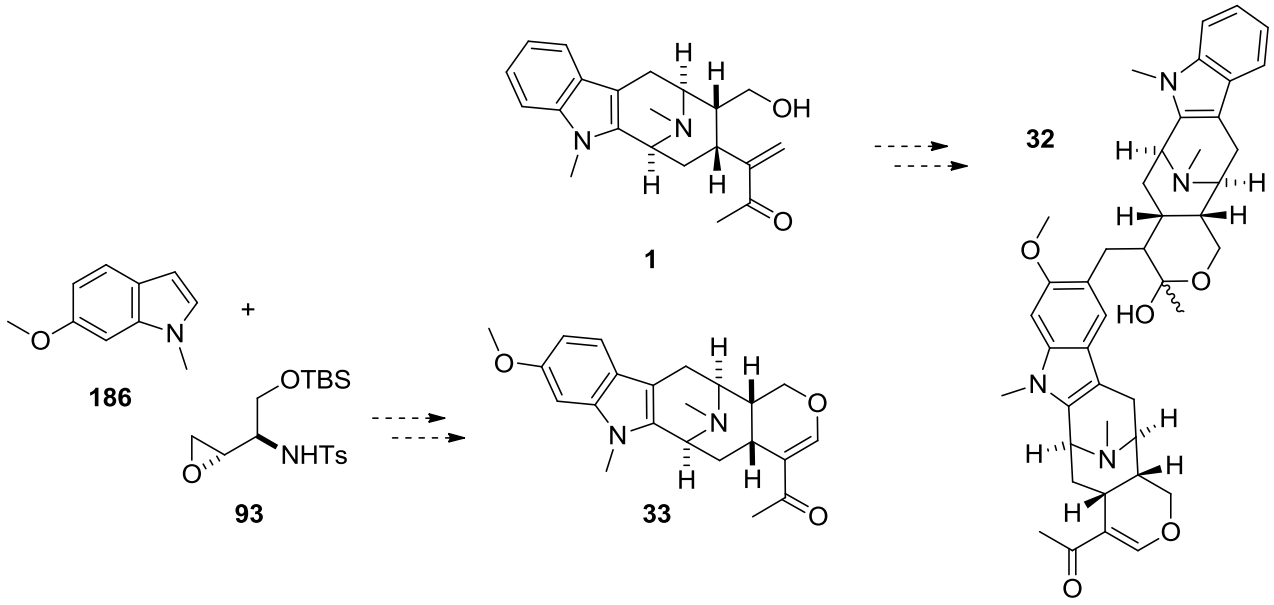
Figure 48. Known optically pure **93**.



93

Due to the convergent nature of our synthesis, alkaloids containing indole oxidation could be rapidly accessed, by using the equivalent methoxy substituted indole (Figure **49**, below). For example the synthesis of alstophylline **33** and in turn bis(indole) macralstonine **32** should be readily achieved by introducing N_1-methyl-6-methoxyindole **186** into our previous synthetic route in the place of N_1-methylindole.

Figure 49. Synthesis of bis(indole) alkaloid macralstonine **32**.



Chapter 3

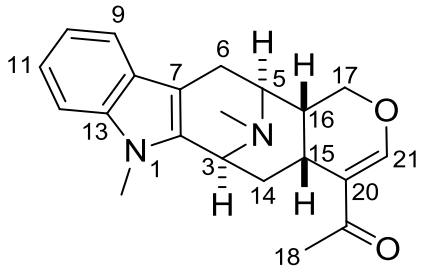
Experimental

3.1. General experimental procedures

Standard laboratory techniques were employed when handling air-sensitive reagents. All reactions were performed under a nitrogen atmosphere unless otherwise stated. Melting points were determined using a Stuart Scientific SMP1 or Büchi B-545 melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin–Elmer Spectrum RX FT-IR or Spectrum One FT-IR spectrometers. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultra-Shield AV-400 or AV-500 spectrometers. Chemical shifts (δ_H and δ_C) are expressed in parts per million (ppm), referenced to the appropriate residual solvent peak. Mass spectra (CI, EI and FAB) were recorded using a Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier spectrometer. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Thin-layer chromatography was performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck Kieselgel 60 F254), which were developed using standard visualising agents: ultraviolet fluorescence (254 nm) and/or potassium permanganate and/or vanillin. Chromatography refers to flash column chromatography performed using BDH flash chromatography silica gel (40-63 μm) unless otherwise stated. Standard solvents were distilled under nitrogen prior to use: THF was distilled from sodiumbenzophenone ketyl, CH_2Cl_2, Et_3N and Hünig's base from CaH_2 and MeOH from Mg/MeOH. Hexane refers to the fraction of petroleum boiling between 67–70°C. All other solvents and reagents were used as received from the supplier unless otherwise noted.

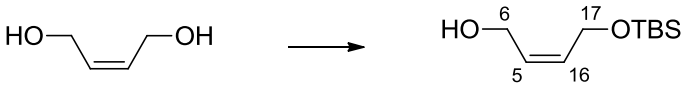
For the purposes of reporting NMR data, all compounds herein reported are numbered such that the skeletal numbering corresponds to the final position of each carbon atom in the final natural product, (±)-alstonerine **4** (Figure **50**).

Figure 50. Compound numbering



3.1.1 *Procedures from the synthesis of hydroxymethyl-substituted aziridine* ***82***

(*Z*)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (187)



92 **187**

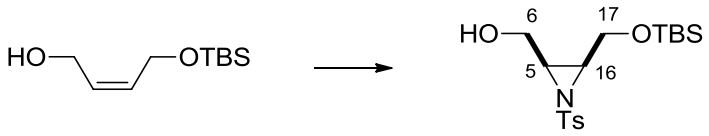
To a suspension of 60 wt% NaH (22.2 g, 556.2 mmol, 0.98 equiv.) in THF (500 mL) at 0°C, was added a solution of *cis*-but-2-ene-1,4-diol **92** (46.6 mL, 567.5 mmol, 1.0 equiv.) in THF (300 mL) slowly *via* dropping funnel. The resulting cloudy white suspension was allowed to stir slowly from 0°C to rt overnight. The solution was then cooled to 0°C and a solution of TBSCl (84.0 g, 556.2 mmol, 0.98 equiv.) in THF (300 mL) was added dropwise *via* dropping funnel and the reaction mixture stirred at rt for 24 h.

The resulting creamy suspension was diluted with Et_2O (500 mL) and poured onto ice cold saturated aqueous NH_4Cl (500 mL). The aqueous phase was extracted with Et_2O (2×500 mL), the combined organics dried over $MgSO_4$, filtered and concentrated under reduced pressure. Distillation under reduced pressure yielded *(Z)-4-(tert-butyldimethylsilyloxy)but-2-en-1-ol* ***187*** (110 g, 98%) as a colourless oil (b.p. 92–95°C at 2.4 mbar); R_f 0.51 (30% EtOAc–hexane); FTIR (film) υ_{max}: 3400, 2928, 2961, 2857, 1474, 1465, 1253, 1082, 1029, 833, 774 cm^{-1}; *m/z* (CI) 220 $[M+NH_4]^+$, 203 $[M+H]^+$ (Found $[M+H]^+$, 203.1465. $C_{10}H_{22}O_2Si$ requires $[M+H]^+$, 203.1467);

δ_H (400 MHz, $CDCl_3$) 5.75—5.58 (2H, m, **5** and **16**), 4.25 (2H, d, *J* 5.0 Hz, **6**), 4.19 (2H, d, *J* 5.5 Hz, **17**), 2.10 (1H, br. s, *O***H**), 0.90 (9H, s, **Me**$_3$CSi), 0.08 (6H, s, **Me**$_2$Si);

δ_C (100 MHz, $CDCl_3$) 131.1 (**C5**), 120.9 (**C16**), 59.6 (**C6**), 58.8 (**C17**), 25.7 (**Me**$_3$CSi), 18.3 (Me$_3$***C***Si), –5.3 (**Me**$_2$Si). Data is in accordance with that previously reported.[57]

((2*R,3*S**)-3-((*tert*-Butyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methanol (93)**



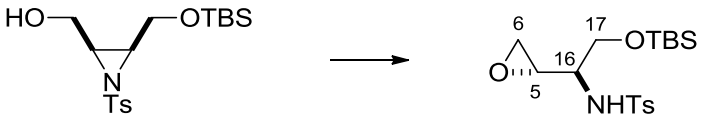
187 **93**

To a solution of olefin **187** (54.8 g, 270.9 mmol, 1.0 equiv.) and chloramine-T (91.6 g, 325.1 mmol, 1.2 equiv.) in MeCN (1300 mL) at rt was added PTAB (10.2 g, 27.0 mmol, 0.1 equiv.), and the resulting cloudy yellow suspension stirred at rt for 48 h. The reaction mixture was concentrated under reduced pressure and the solid impurities triturated with Et_2O (2×250 mL). The residue was filtered, (washing with Et_2O) and concentrated under reduced pressure. Chromatography (30% EtOAc–hexane) yielded *((2R*,3S*)-3-((tert-butyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methanol* ***93*** (72.4 g, 76%) as a colourless oil; R_f 0.61 (50% EtOAc–heptane); FTIR (film) υ_{max}: 3500, 2933, 2861, 1601, 1466, 1324, 1264, 1159, 1089, 948, 834, 669 cm^{-1}; *m/z* (CI) 372 $[M+H]^+$ (Found $[M+H]^+$, 372.1431. $C_{17}H_{29}NO_4SSi$ requires $[M+H]^+$, 372.1587);

δ_H (400 MHz, $CDCl_3$) 7.82 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.33 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 3.91 (1H, dd, *J* 11.5, 5.5 Hz, **5**), 3.79—3.55 (3H, m, **16**, **6a** and **6b**), 3.09 (2H, dt, *J* 30.0, 14.5 Hz, **17a** and **17b**), 2.45 (3H, s, *Ts***Me**), 0.87 (9H, s, **Me**$_3$CSi), 0.05 (3H, s, **Me**$_2$Si), 0.04 (3H, s, **Me**$_2$Si);

δ_C (100 MHz, $CDCl_3$) 135.3 (*para*-**Ts**) 134.5 (*ipso*-**Ts**), 129.8 (*ortho*-**Ts**), 128.0 (*meta*-**Ts**), 60.38 (**C6**), 59.2 (**C17**), 44.0 (**C5**), 42.9 (**C16**), 25.7 (**Me**$_3$CSi), 21.4 (*Ts***Me**), 18.2 (Me$_3$***C***Si), –5.5 (**Me**$_2$Si). Data is in accordance with that previously reported.[57]

_N_-((_R_*)-2-(_tert_-Butyldimethylsilyloxy)-1-((_S_*)-oxiran-2-yl)ethyl)-4-methylbenzenesulfonamide (94)



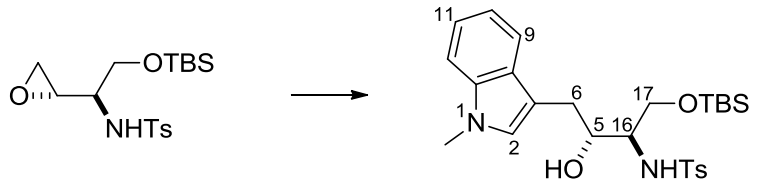
93 **94**

To a suspension of 60 wt% NaH in mineral oil (35.7 g, 643.8 mmol, 4.0 equiv.) in THF (300 mL) at 0°C was added dropwise, a solution of aziridine **93** (59.8 g, 160.9 mmol, 1.0 equiv.) over 30 min. The reaction mixture was stirred at 0°C for 4 h then cooled to –78°C and saturated aqueous NH_4Cl solution (250 mL) added dropwise. On warming to rt, the aqueous layer was extracted with Et_2O (2×300 mL), the combined organics dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (30% EtOAc–heptane) yielded *N-((R*)-2-(tert-butyldimethylsilyloxy)-1-((S*)-oxiran-2-yl)ethyl)-4-methylbenzenesulfonamide **94*** (56.2 g, 94%) as a colourless oil; R_f 0.51 (30% EtOAc–hexane); FTIR (film) υ_{max}: 2928, 2857, 1600, 1474, 1336, 1253, 1163, 1092, 899, 836, 814 $cm^{-1;}$ *m/z* (CI) 372 $[M+H]^+$ (Found $[M+H]^+$, 372.1667. $C_{17}H_{29}NO_4SSi$ requires $[M+H]^+$, 372.1587);

δ_H (400 MHz, $CDCl_3$) 7.78 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.33 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 4.72 (1H, d, *J* 8.0 Hz, N_4**H**Ts), 3.60—3.46 (3H, m, **16**, **17a** and **17b**), 3.17—3.14 (1H, m, **5**), 2.66 (1H, dd, *J* 4.5, 4.0 Hz, **6a**), 2.57 (1H, dd, *J* 4.5, 3.0 Hz, **6b**), 2.45 (3H, s, *Ts***Me**), 0.87 (9H, s, $\mathbf{Me}_3$CSi), 0.02 (6H, s, $\mathbf{Me}_2$Si);

δ_C (100 MHz, $CDCl_3$) 144.8 (*para*-**Ts**) 134.5 (*ipso*-**Ts**), 129.8 (*meta*-**Ts**), 128.0 (*ortho*-**Ts**), 60.3 (**C17**), 59.5 (**C16**), 51.2 (**C5**), 43.4 (**C6**), 25.7 ($\mathbf{Me}_3$CSi), 21.7 (*Ts***Me**), 18.2 (Me_3***C***Si), –5.5 ($\mathbf{Me}_2$Si). Data is in accordance with that previously reported.[57]

***N*-((2*R**,3*R**)-1-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4-(1-methylindol-3-yl)butan-2-yl)-4-methylbenzenesulfonamide (95)**



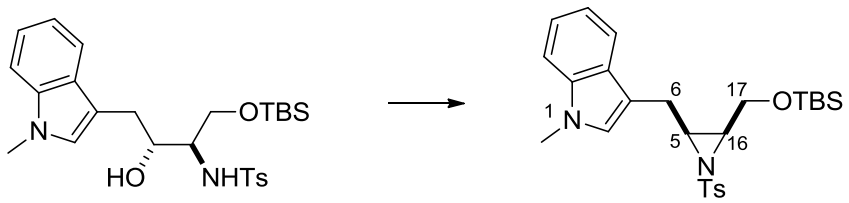
94 **95**

To a suspension of epoxide **94** (7.00 g, 18.84 mmol, 1.0 equiv.), 1-methylindole (4.70 mL, 37.68 mmol, 2.0 equiv.) and anhydrous $NaHCO_3$ (6.33 g, 75.36 mmol, 4.0 equiv.) in CH_2Cl_2 (50 mL) at –78°C was added $BF_3{\cdot}OEt_2$ (2.56 mL, 20.78 mmol, 1.1 equiv.) dropwise and the reaction mixture was stirred at –78°C for 6 h. Water (20 mL) was added slowly and the resulting suspension allowed to warm from –78°C to rt. The aqueous layer was extracted with Et_2O (3×50 mL), the combined organics dried over Na_2SO_4 and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *N-((2R*,3R*)-1-(tert-butyldimethylsilyloxy)-3-hydroxy-4-(1-methylindol-3-yl)butan-2-yl)-4-methylbenzenesulfonamide* ***95*** (8.61 g, 94%) as a colourless amorphous solid; R_f 0.24 (33% EtOAc–hexane); FTIR (film) υ_{max}: 3507, 3288, 2954, 2929, 2857, 1616, 1474, 1330, 1160, 1092, 1073, 838, 734 cm^{-1}; *m/z* (CI) 520 $[M+NH_4]^+$, 503 $[M+H]^+$ (Found $[M+H]^+$, 503.2322. $C_{26}H_{38}N_2O_4SSi$ requires $[M+H]^+$, 503.2415);

δ_H (400 MHz, $CDCl_3$) 7.78 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.48 (1H, d, *J* 8.0 Hz, **12**), 7.33—7.24 (3H, m, **9** and *meta*-**Ts**), 7.22 (1H, t, *J* 7.5 Hz, **11**), 7.09 (1H, t, *J* 7.5 Hz, **10**), 6.66 (1H, s, **2**), 5.32 (1H, d, *J* 9.0 Hz, N_4**H**Ts), 4.24 (1H, t, *J* 6.5 Hz, **5**), 3.73 (3H, s, N_1**Me**), 3.68 (1H, dd, *J* 10.0, 5.0 Hz, **17a**), 3.63 (1H, dd, *J* 10.0, 3.0 Hz, **17b**), 3.41—3.34 (1H, m, **16**), 2.76 (2H, qd, *J* 11.0, 7.0 Hz, **6a** and **6b**), 2.45 (3H, s, *Ts***Me**) 0.88 (9H, s, **Me**$_3$CSi), –0.01 (6H, s, **Me**$_2$Si);

δ_C (100 MHz, $CDCl_3$) 143.4 (*para*-**Ts**), 138.7 (*ipso*-**Ts**), 137.1 (**C13**), 129.9 (*ortho*-**Ts**), 128.0 (*meta*-**Ts**), 127.7 (**C2**), 127.3 (**C8**), 121.8 (**C11**), 119.0 (**C10**), 119.0 (**C12**), 110.0 (**C9**), 109.3 (**C7**), 72.1 (**C5**), 65.7 (**C17**), 55.4 (**C16**), 32.6 (N_1**Me**), 29.5 (**C6**), 25.8 (**Me**$_3$CSi), 21.5 (*Ts***Me**), 18.1 (Me$_3$***C***Si), –5.7 (**Me**$_2$Si). Data is in accordance with that previously reported.[57]

3-(((2*S,3*S**)-3-((*tert*-Butyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methyl)-1-methylindole (96)**



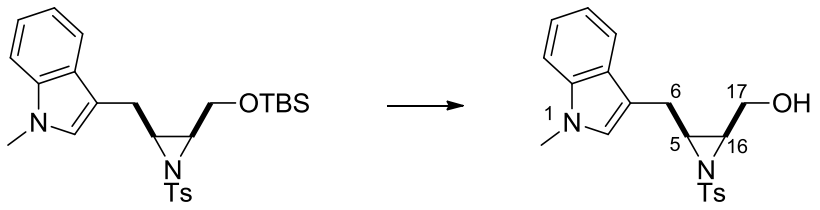
95 **96**

To a solution of hydroxysulfonamide **95** (7.10 g, 14.12 mmol, 1.0 equiv.) and Ph_3P (4.45 g, 16.95 mmol, 1.2 equiv.) in THF (150 mL) at rt was added DIAD (4.20 mL, 21.19 mmol, 1.5 equiv.) dropwise and the reaction mixture stirred at rt for 16 h. Concentration under reduced pressure and chromatography (30% EtOAc–hexane) yielded *3-(((2S*,3S*)-3-((tert-butyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methyl)-1-methylindole* ***96*** (5.91 g, 86%) as a pale yellow oil; R_f 0.44 (20% EtOAc–hexane); FTIR (film) υ_{max}: 2953, 2929, 2884, 1725, 1598, 1474, 1330, 1160, 1122 838, 734 cm^{-1}; *m/z* (CI) 485 $[M+H]^+$ (Found $[M+H]^+$, 485.2309. $C_{26}H_{36}N_2O_3SSi$ requires $[M+H]^+$, 485.2294);

δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.48 (1H, d, *J* 8.0 Hz, **12**), 7.27—7.20 (2H, m, **9** and **11**), 7.12 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.13—7.06 (1H, m, **10**), 6.85 (1H, s, **2**), 3.90 (1H, dd, *J* 11.0, 5.5 Hz, **17a**), 3.78 (1H, dd, *J* 11.0, 6.5 Hz, **17b**), 3.68 (3H, s, N_1**Me**), 3.18 (1H, app. q, *J* 6.5 Hz, **16**), 3.11 (1H, app. q, *J* 6.5 Hz **5**), 2.99 (1H, dd *J* 15.5, 5.5 Hz, **6a**), 2.89 (1H, dd *J* 15.5, 7.5 Hz, **6b**), 2.40 (3H, s, *Ts***Me**), 0.88 (9H, s, **Me**$_3$CSi), 0.04 (6H, s, **Me**$_2$Si);

δ_C (100 MHz, $CDCl_3$) 143.9 (*para*-**Ts**), 136.8 (*ipso*-**Ts**), 134.9 (**C13**), 129.2 (*ortho*-**Ts**), 127.9 (*meta*-**Ts**), 127.5 (**C2**), 126.9 (**C8**), 121.6 (**C11**), 118.9 (**C10**), 118.6 (**C12**), 110.1 (**C9**), 109.1 (**C7**), 60.3 (**C17**), 44.8 (**C5**), 44.6 (**C16**), 32.6 (N_1**Me**), 25.9 (**Me**$_3$CSi), 22.9 (**C6**), 21.6 (*Ts***Me**), (Me$_3$***C***Si), –5.53 (**Me**$_2$Si). Data is in accordance with that previously reported.[57]

((2*S,3*S**)-3-((1-Methylindol-3-yl)methyl)-1-tosylaziridin-2-yl)methanol (82)**



96 **82**

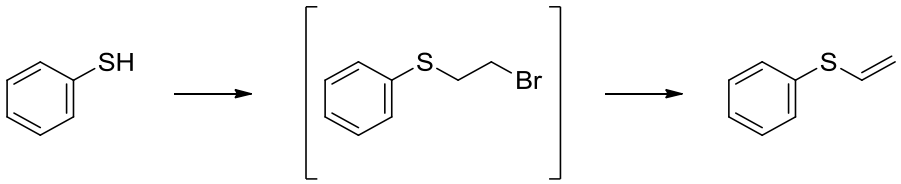
To a solution of *O*-TBS protected aziridine **96** (5.90 g, 12.17 mmol, 1.0 equiv.) in THF (50 mL) at 0°C was added TBAF·$3H_2O$ (4.22 g, 13.39 mmol, 1.1 equiv.) and the reaction mixture allowed to warm slowly from 0°C to rt overnight. Saturated aqueous NH_4Cl (2 mL) was added, the aqueous layer extracted with CH_2Cl_2 (3×50 mL), the combined organics dried over Na_2SO_4 and filtered. Concentration under reduced pressure and chromatography (50% EtOAc–hexane) yielded *((2S*,3S*)-3-((1-methylindol-3-yl)methyl)-1-tosylaziridin-2-yl)methanol* ***82*** (4.28 g, 95%) as a pale yellow oil; R_f 0.31 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3508, 3364, 2933, 1810, 1783, 1598, 1325, 1184, 1091, 739 cm^{-1}; *m/z* (CI) 371 $[M+H]^+$ (Found $[M+H]^+$, 371.1351. $C_{20}H_{22}N_2O_3S$ requires $[M+H]^+$, 371.1351);

δ_H (400 MHz, $CDCl_3$) 7.64 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.48 (1H, d, *J* 8.0 Hz, **12**), 7.27—7.20 (2H, m, **9** and **11**), 7.12 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 7.12—7.06 (1H, m, **10**), 6.78 (1H, s, **2**), 3.90 (1H, ddd, *J* 11.0, 7.5, 5.5 Hz, **17a**), 3.78 (1H, dd, *J* 11.0, 6.5 Hz, **17b**), 3.68 (3H, s, N_1**Me**), 3.18 (1H, app. q, *J* 6.5 Hz, **5**), 3.11 (1H, app. q, *J* 6.5 Hz, **16**), 2.99 (1H, dd, *J* 15.5, 5.5 Hz, **6a**), 2.89 (1H, dd, *J* 15.5, 7.5 Hz **6b**), 2.40 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$) 144.2 (*para*-**Ts**), 136.8 (*ipso*-**Ts**), 134.4 (**C13**), 129.9 (*ortho*-**Ts**), 128.1 (*meta*-**Ts**), 127.8 (**C2**), 127.3 (**C8**), 121.7 (**C11**), 119.0 (**C10**), 118.5 (**C12**), 109.9 (**C9**), 109.2 (**C7**), 62.4 (**C17**), 45.5 (**C5**), 43.8 (**C16**), 32.7 (N_1**Me**), 22.9 (**C6**), 21.6 (*Ts***Me**). Data is in accordance with that previously reported.[67]

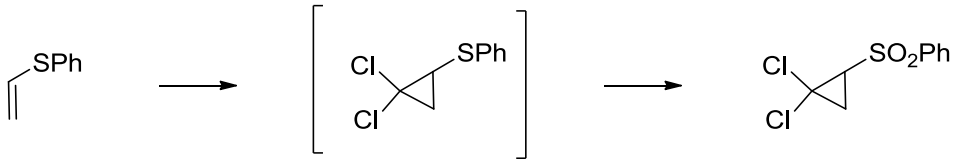
3.1.2 *Procedures from the synthesis of sulfone* ***88***

Phenyl vinyl sulfide (97)



To ethanol (400 mL) in a 1 L three-necked round-bottomed flask fitted with a condenser was added sodium metal (23 g, 1000 mmol, 1.0 equiv.) in small pieces. Once the sodium had dissolved, benzenethiol (102 mL, 1000 mmol, 1.0 equiv.) was added *via* dropping funnel. The resulting solution was then transferred *via* cannula into a 2 L three-necked round-bottomed flask containing a stirred solution of 1,2-dibromoethane (124 mL, 1450 mmol, 1.45 equiv.) in ethanol (28 mL) dropwise over 45 min. The reaction temperature was maintained at 25–30°C throughout the addition. The resulting slurry was then allowed to stir at rt for 30 min, before ethanolic sodium ethoxide prepared from dissolving sodium (40 g, 1740 mmol, 1.74 equiv.) in ethanol (800 mL) was added and the reaction mixture stirred under reflux for 8 h. The reaction mixture was then cooled, before toluene (750 mL) and water (750 mL) were added. The aquesous layer was extracted with toluene (3×500 mL) and the organics phases were combined, washed with water (2×50 mL) and brine (100 mL). Concentrated under reduced pressure and distillation gave phenyl vinyl sulphide **97** (92.6 g, 68%) as a colourless oil; (b.p. 93°C at 33.3 mbar); Data is in accordance with that previously reported.[75]

(2,2-Dichlorocyclopropylsulfonyl)benzene (99)



97 **98** **99**

To a slurry of freshly prepared sodium methoxide (15.9 g, 293.7 mmol, 2.0 equiv.) and phenyl vinyl sulfide **97** (20.0 g, 146.8 mmol, 1.0 equiv.) in CH_2Cl_2 (500 mL) at –78°C was added dropwise via dropping funnel ethyl trichloroacetate (30.5 mL, 220.2 mmol, 1.5 equiv.) and the solution allowed to warm slowly from –78°C to rt over 6 h. H_2O (300 mL) was then added, and the aqueous layer extracted with CH_2Cl_2 (3×300 mL), dried over $MgSO_4$ and filtered. Concentration under reduced pressure yielded crude intermediate *(2,2-dichlorocyclopropyl)phenylsulfide **98*** as a dark brown oil.

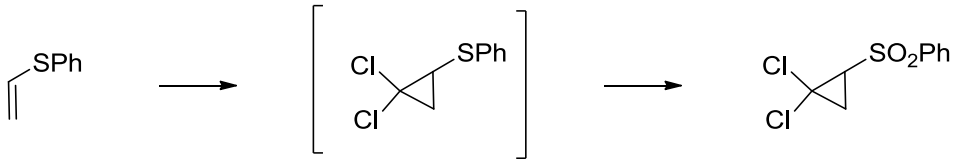
To a solution of crude intermediate *(2,2-dichlorocyclopropyl)phenylsulfide **98*** (47.8 g, 219.3 mmol, 1.0 equiv.) and AcOH (354 mL, 5886 mmol, ~25 equiv.) was added aqueous 30% H_2O_2 solution (103 mL, 907 mmol, ~4.0 equiv.) dropwise. The solution was then stirred under reflux at 100°C for 4 h, after which the reaction mixture was partitioned over Et_2O (3×500 mL), neutralised with K_2CO_3, washed with brine (500 mL) and filtered over a pad of silica.

Concentration under reduced pressure and flash column chromatography (30% EtOAc–hexane) yielded *(2,2-dichlorocyclopropylsulfonyl)benzene **99*** (33.4 g, 91%, over two steps) as a crystalline solid; R_f 0.45 (50% EtOAc–hexane); m.p. = 88°C (lit.[72,73,74] m.p. 87–88°C); υ_{max} (film) 3112, 3033, 1446, 1322, 1214, 1158, 1087, 723 cm^{-1}; *m/z* (CI) 268 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 267.9970. $C_9H_8Cl_2O_2S$ requires $[M+H]^+$, 267.9966);

δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.73 (1H, t, *J* 8.0 Hz, *para*-**Ph**SO_2), 7.62 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 3.20 (1H, dd, *J* 10.5, 2.5 Hz, **14a**), 2.45 (1H, t, *J* 8.0 Hz, **15**), 2.17 (1H, dd, *J* 10.5, 2.5 Hz, **14b**);

δ_C (100 MHz, $CDCl_3$) 139.6 (*para*-**Ph**SO_2), 134.3 (*ipso*-**Ph**SO_2), 129.5 (*ortho*-**Ph**SO_2), 128.1 (*meta*-**Ph**SO_2), 55.4 (**C3**), 47.9 (**C15**), 26.3 (**C14**). Data is in accordance with that previously reported.[72,73,74]

(2,2-Dichlorocyclopropylsulfonyl)benzene (99) – *Small Scale Prep.*



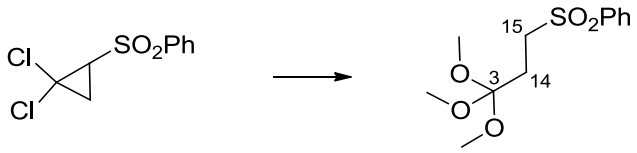
97 **98** **99**

Sodium metal (63.30 mg, 27.53 mmol, 1.5 equiv.) was dissolved in dry methanol (10 mL). Concentration under reduced pressure yielded sodium methoxide (1.49 g, 27.53 mmol, 1.5 equiv.), to which was added olefin-free petrol[80] (14 mL) and phenyl vinyl sulphide **97** (2.4 mL, 18.35 mmol, 1.0 equiv.) and the reaction mixture cooled to – 20°C. Ethyl trichloroacetate (3.3 mL, 23.86 mmol, 1.3 equiv.) was added at a rate of 6 mL / min *via* syringe pump addition, and the reaction mixture stirred at – 20°C for 6 h, before being allowed to warm to rt slowly overnight. H_2O (30 mL) was then added, and the aqueous layer extracted with CH_2Cl_2 (3×30 mL), dried over $MgSO_4$ and filtered. Concentration under reduced pressure and distillation yielded crude intermediate *compound **98*** (5.16 g) as a dark brown oil.

To a solution of crude intermediate **98** (10.05g, 45.86 mmol, 1.0 equiv.) and AcOH (70 mL, 1177 mmol, 25 equiv.) was added 30% H_2O_2 solution (20.5 mL, 181.5 mmol, 4.0 equiv.) dropwise. The solution was then stirred under reflux at 100°C for 3 h, after which the reaction mixture was partitioned over Et_2O (3×100 mL), neutralised with K_2CO_3 over, washed with brine (100 mL) and filtered. Concentration under reduced pressure and flash column chromatography (30% EtOAc–hexane) yielded *(2,2-dichlorocyclopropylsulfonyl)benzene **99*** (7.74 g, 84%, over two steps) as a crystalline solid;

***N.B.** For the original synthesis of **98** (as outlined in **Scheme 26**), see the thesis of Tholen.*[57]

Trimethyl 3-(phenylsulfonyl)orthopropionate (88)



99 **88**

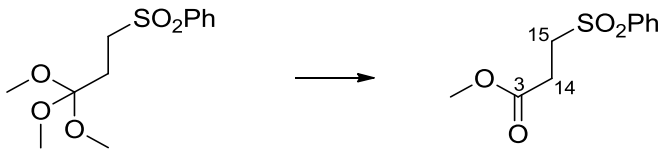
To dry MeOH (200 mL) at 0°C was added sodium (3.68 g, 153.3 mmol, 3.5 equiv.) portionwise. Following formation of *in situ* sodium methoxide, dichloro-sulfone **99** (11.0 g, 43.80 mmol, 1.0 equiv.) in MeOH (100 mL) was added and the reaction mixture stirred under reflux at 65°C for 3 h, cooled to rt and concentrated under reduced pressure. The concentrate was then partitioned over H_2O (200 mL) and Et_2O (200 mL), and the aqueous layer extracted with Et_2O (3×300 mL). The organic phases were combined, dried over $NaSO_4$, and filtered. Concentration under reduced pressure and chromatography yielded *trimethyl 3-(phenylsulfonyl)orthopropionate* ***88*** (11.8, 98%) as a colourless oil; R_f 0.50 (66% EtOAc–hexane); υ_{max} (film) 2947, 2840, 1446, 1284, 1240, 1143, 1076, 100 cm^{-1}; *m/z* (CI) 292 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 292.1219. $C_{12}H_{18}O_5S$ requires $[M+NH_4]^+$, 292.1219);

δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, *J* 8.5 Hz, *ortho*-**Ph**SO_2), 7.67 (1H, t, *J* 7.5 Hz, *para*-**Ph**SO_2), 7.58 (2H, t, *J* 7.5 Hz, *meta*-**Ph**SO_2), 3.17 (9H, s, 3×*O***Me**), 3.13 (2H, dt, *J* 16.5, 4.0 Hz, **15**), 2.17 (2H, dt, *J* 16.5, 4.0 Hz, **14**);

δ_C (100 MHz, $CDCl_3$) 138.9 (*para*-**Ph**SO_2), 134.1 (*ipso*-**Ph**SO_2), 129.4 (*ortho*-**Ph**SO_2), 128.1 (*meta*-**Ph**SO_2), 114.28 (**C3**), 51.4 (*O***Me**), 49.6 (**C15**), 23.9 (**C14**). Data is in accordance with that previously reported.[72,73,74]

3.1.3 *Procedures from sulfone stability and aziridine reactivity* (Sections **2.1.7-2.1.9**)

Methyl 3-(phenylsulfonyl)propanoate (101)



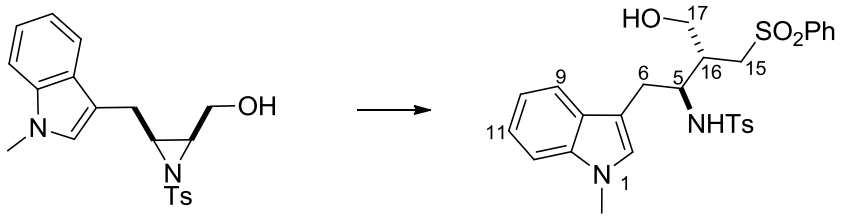
88 **101**

To a solution of orthoester **88** (30 mg, 0.109 mmol, 1.0 equiv.) in THF (2 mL) was added aqueous HCl (2 M; 0.5 mL, 1.00 mmol, 10 equiv.) and the solution stirred at rt overnight. Saturated aqueous NH_4Cl (5 mL) was added, and the aqueous layer extracted with EtOAc (3×20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and filtered. Concentration under reduced pressure yielded *methyl 3-(phenylsulfonyl)propanoate* ***101*** (24.1 mg, 97%) as a colourless amorphous solid; R_f 0.51 (30% EtOAc–hexane); υ_{max} (film) 2955, 1736, 1586, 1586, 1447, 1439, 1148, cm^{-1}; *m/z* (CI) 246 $[M+NH_4]^+$, 229 $[M+H]^+$.

δ_H (400 MHz, $CDCl_3$) 7.92 (2H, app. d, *J* 7.5 Hz, *ortho*-**Ph**SO_2), 7.69 (1H, t, *J* 7.5 Hz, *para*-**Ph**SO_2), 7.58 (2H, t, *J* 7.5 Hz, *meta*-**Ph**SO_2), 3.64 (3H, s, *O***Me**), 3.44 (2H, t, *J* 7.5 Hz, **15**), 2.79 (2H, t, *J* 7.5 Hz, **14**);

δ_C (100 MHz, $CDCl_3$) 170.5 (**C3**), 138.4 (*ipso*-**Ph**SO_2), 134.1 (*para*-**Ph**SO_2), 129.5 (*ortho*-**Ph**SO_2), 128.2 (*meta*-**Ph**SO_2), 52.3 (**C15**), 51.5 (*O***Me**), 27.6 (**C14**). Data is in accordance with that previously reported.[57]

_N_-((2_S_*,3_R_*)-4-Hydroxy-1-(1-methylindol-3-yl)-3-(phenylsulfonylmethyl)butan-2-yl)-4-methylbenzenesulfonamide (107)



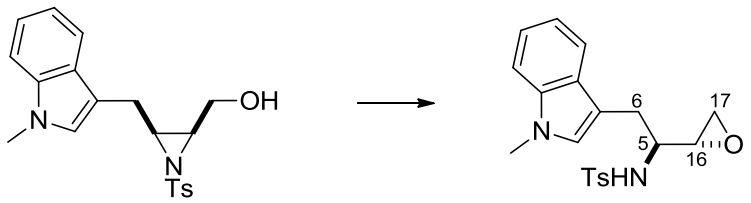
82 **107**

To a solution of methyl phenyl sulfone **105** (165.3 mg, 1.058 mmol, 2.5 equiv.) in THF (0.5 mL) at –40°C was added *n*-BuLi (2.48 M in hexanes; 0.44 mL, 1.058 mmol, 2.5 equiv.) and the solution stirred at –40°C for 30 min. A solution of hydroxymethyl-aziridine **82** (0.85 M in THF; 0.5 mL, 0.423 mmol, 1.0 equiv.) was added and the reaction mixture stirred at –40°C for 2 h. 10% Aqueous citric acid (1 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The combined organics layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (20% EtOAc–hexane) yielded *N-((2S*,3R*)-4-hydroxy-1-(1-methylindol-3-yl)-3-(phenylsulfonylmethyl)butan-2-yl)-4-methylbenzenesulfonamide* ***107*** (162.0 mg, 73%) as a colourless oil; R_f 0.35 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3505, 3299, 3054, 2928, 1598, 1447, 1304, 1152 cm^{-1}; *m/z* (CI) 527 $[M+H]^+$ (Found $[M+H]^+$, 527.1667. $C_{27}H_{30}N_2O_5S_2$ requires $[M+H]^+$, 527.1597);

δ_H (400 MHz, $CDCl_3$) 7.92 (2H, app. d, *J* 7.5 Hz, *ortho*-**Ph**SO_2), 7.60 (1H, t, *J* 7.5 Hz, *para*-**Ph**SO_2), 7.50 (2H, t, *J* 7.5 Hz, *meta*-**Ph**SO_2), 7.45 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.19—7.06 (3H, m, **12**, **11** and **9**), 7.00—6.91 (3H, m, *meta*-**Ts** and **10**), 6.69 (1H, s, **2**), 5.52 (1H, d, *J* 7.5 Hz, N_4**H**Ts), 3.84 (2H, m, **17a** and **17b**), 3.73 (1H, m, **5**), 3.56 (3H, s, N_1**Me**), 3.40 (1H, dd, *J* 15.0, 4.5 Hz, **15a**), 3.27 (1H, dd, *J* 15.0, 7.0 Hz, **15b**), 2.97 (1H, br. s, *O***H**), 2.83 (1H, dd, *J* 15.0, 6.5 Hz, **6a**), 2.70 (1H, dd, *J* 15.0, 8.0 Hz, **6b**), 2.53 (1H, br. m, **16**), 2.31 (3H, s, *Ts***Me**);

δ_C (400 MHz, $CDCl_3$) 143.1 (*para*-**Ts**), 139.2 (*para*-**Ph**SO_2), 136.9 (**C13**), 136.6 (*ipso*-**Ts**), 133.9 (*ipso*-**Ph**SO_2), 129.4 (*ortho*-**Ph**SO_2), 129.2 (*meta*-**Ts**), 128.0 (*meta*-**Ph**SO_2), 127.4 (**C8**), 126.7 (*ortho*-**Ts**), 126.6 (**C2**), 121.5 (**C11**), 119.0 (**C10**), 118.4 (**C12**), 109.2 (**C9**), 108.7 (**C7**), 62.5 (**C17**), 54.4 (**C15**), 53.7 (**C5**), 39.3 (**C16**), 32.5 (N_1**Me**), 28.3 (**C6**), 21.6 (*Ts***Me**).

4-Methyl-*N*-((*S)-2-(1-methylindol-3-yl)-1-((*R**)-oxiran-2-yl)ethyl)benzenesulfonamide (106)**



82 **106**

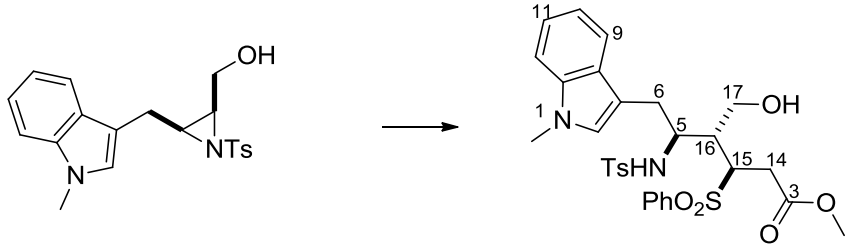
To a suspension of 60 wt% NaH in mineral oil (86.30 mg, 2.158 mmol, 3.0 equiv.) in THF (1 mL) at 0°C was added *via* cannula, a solution of hydroxymethyl-aziridine **82** (260 mg, 0.719 mmol, 1.0 equiv.). The reaction mixture was allowed to warm slowly from 0°C to rt over 5 h, cooled to 0°C and saturated aqueous NH_4Cl (5 mL) added dropwise. On warming to rt, the aqueous layer was extracted with EtOAc (3×12 mL) and the combined organics were dried over $MgSO_4$. Concentration of the filtrate under reduced pressure and flash column chromatography (20% EtOAc–hexane) yielded *4-methyl-N-((S*)-2-(1-methylindol-3-yl)-1-((R*)-oxiran-2-yl)ethyl)benzenesulfonamide* ***106*** (66.5 mg, 77%) as a colourless gum; R_f 0.51 (20% EtOAc–hexane); FTIR (film) υ_{max}: 2928, 2857, 1600, 1474, 1336, 1253, 1163, 1092, 899, 836, 814 $cm^{-1;}$ *m/z* (CI) 371 $[M+H]^+$ (Found $[M+H]^+$, 371.1351. $C_{20}H_{22}N_2O_3S$ requires $[M+H]^+$, 371.1351);

δ_H (400 MHz, $CDCl_3$) 7.56 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.33 (1H, app. d, *J* 8.0 Hz, **9**), 7.24—7.18 (2H, m, **12** and **11**), 7.11 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 7.06 (1H, dt, *J* 8.0, 2.0 Hz, **10**), 6.81 (1H, s, **2**), 4.70 (1H, d, *J* 8.0 Hz, N_4**H**Ts), 3.78 (1H, dt, *J* 8.0, 2.0 Hz, **5**), 3.68 (3H, s, N_1**Me**), 3.09 (1H, dt, *J* 4.0, 2.0 Hz, **16**), 3.03—2.89 (2H, m, **6a** and **6b**), 2.74 (1H, dd, *J* 4.5, 4.0 Hz, **17a**), 2.68 (1H, t, *J* 4.5 Hz, **17b**), 2.37 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$) 143.1 (*para*-**Ts**), 137.4 (*ipso*-**Ts**), 137.0 (**C13**), 129.4 (*ortho*-**Ts**), 127.8 (**C2**), 127.6 (**C8**), 126.8 (*meta*-**Ts**) 121.7 (**C11**), 119.1 (**C10**), 118.6 (**C12**), 109.3 (**C9**), 108.9 (**C7**), 53.0 (**C17**), 52.9 (**C16**), 44.8 (**C5**), 32.7 (N_1**Me**), 29.5 (**C6**), 21.6 (*Ts***Me**).

3.1.4 *Procedures from initial work towards the synthesis of key intermediate lactam–alcohol* ***90*** (Sections **2.1.6-2.1.13**)

(3*R,4*R**,5*S**)-Methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (89)**



82 **89**

To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (141.8 mg, 0.518 mmol, 2.5 equiv.) in THF (2 mL) at –40°C was added *n*-BuLi (2.48 M in hexanes; 0.27 mL, 0.673 mmol, 3.3 equiv.) and the solution stirred for 1 h at –40°C.

Meanwhile, *n*-BuLi (2.48 M in hexanes; 0.1 mL, 0.227 mmol, 1.1 equiv.) was added to a solution of hydroxymethyl-aziridine **82** (76.5 mg, 0.207 mmol, 1.0 equiv.) in THF (1 mL) at –40°C and the solution stirred for 1 h at –40°C.

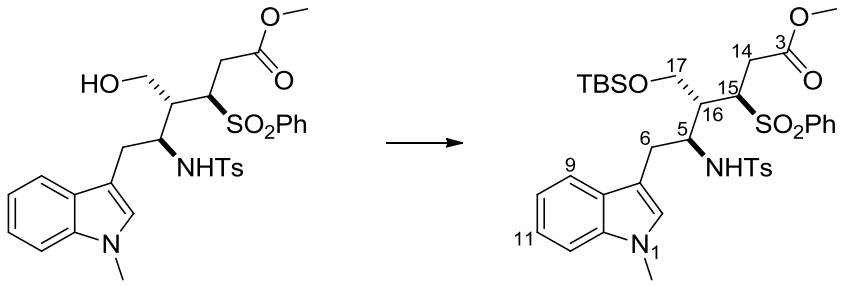
The dark red solution of deprotonated **88** was added dropwise *via* cannula to the dark green solution of *O*-lithio hydroxymethyl-aziridine **82**, maintaining both solutions at –40°C throughout the addition. The reaction mixture was allowed to warm slowly from –40°C to rt overnight. Aqueous 10% citric acid (1 mL) was added and the solution stirred for 3 h at rt. The aqueous layer was then extracted with EtOAc (3×30 mL) and CH_2Cl_2 (3×30 mL), the organic layers combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and flash column chromatography (20% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate* ***89*** (33.4 mg, 27%) as an amorphous solid; R_f 0.16 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3528, 3305, 3060, 2952, 1738, 1156 cm^{-1}; *m/z* (CI) 599 $[M+H]^+$ (Found $[M+H]^+$, 599.1862. $C_{30}H_{34}N_2O_7S_2$ requires $[M+H]^+$, 599.1870);

δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.70—7.63 (1H, m, **11**), 7.60—7.53 (3H, m, *meta*-**Ph**SO_2 and *para*-**Ph**SO_2), 7.24—7.15 (2H, m, *ortho*-**Ts** and **12**), 7.07 (2H, d, *J* 8.0

Hz, *meta*-**Ts**), 7.04—6.94 (2H, m, **10** and **9**), 6.80 (1H, s, **2**), 5.84 (1H, d, *J* 9.0 Hz, N_4**H**Ts), 4.32 (1H, dt, *J* 3.0, 6.0 Hz, **15**), 4.14—3.88 (3H, **5** and **17**), 3.64 (3H, s, N_1**Me**), 3.40 (3H, s, *O***Me**), 3.07 (2H, dd, *J* 14.5, 7.0 Hz, **6**), 2.93—2.81 (2H, m, **14**), 2.54—2.46 (1H, m, **16**), 2.37 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$); 170.7 (**C3**), 142.9 (*para*-**Ts**), 137.8 (*ipso*-**Ph**SO_2), 137.6 (*ipso*-**Ts**), 134.2 (**C13**), 129.8 (*ortho*-**Ts**), 129.3 (*ortho*-**Ph**SO_2), 129.2 (*meta*-**Ts**), 129.0 (*meta*-**Ph**SO_2), 128.8 (*ortho*-**Ph**SO_2), 127.7 (**C2**), 126.8 (*ortho*-**Ts**), 121.7 (**C11**), 119.1 (**C10**), 118.5 (**C12**), 109.0 (**C9**), 107.5 (**C7**), 60.1 (**C17**), 59.2 (*O***Me**), 53.2 (**C15**), 52.2 (**C5**), 46.8 (**C16**), 34.1 (**C14**), 32.5 (N_1**Me**), 29.0 (**C6**), 21.6 (*Ts***Me**). Data is in accordance with that previously reported.[57]

(3*R,4*R**,5*S**)-Methyl 4-((*tert*-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (102a) – *Small Scale Original Prep.***

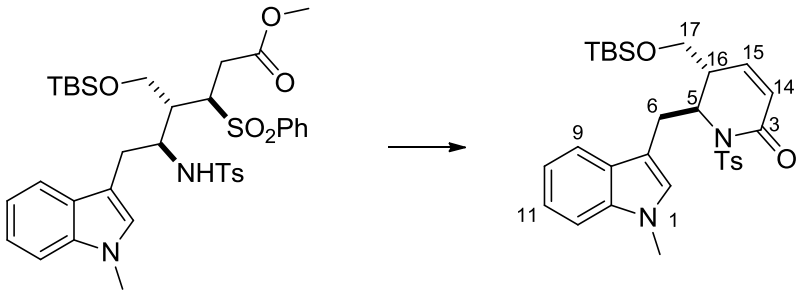


89 **102a**

To a stirred solution of amino alcohol **89** (96.5 mg, 0.161 mmol, 1.0 equiv.), imidazole (16.0 mg, 0.242 mmol, 1.5 equiv.) and TBSCl (36.5 mg, 0.242 mmol, 1.5 equiv.) in DMF (0.2 mL) was added DMAP (2.0 mg, 0.016 mmol, 10 mol%) and the reaction mixture stirred at rt for 3 h. H_2O (1 mL) was added and the reaction mixture was poured onto aqueous 10% citric acid. The aqueous layer was extracted with EtOAc (3×10 mL) and the organic phases combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 4-((tert-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate* ***102a*** (56.1 mg, 49%) as a pale yellow oil; R_f 0.90 (66% EtOAc–hexane); FTIR (film) υ_{max}: 2928, 2859, 1742, 1156 cm^{-1}; *m/z* (CI) 713

$[M+H]^+$ (Found $[M+H]^+$, 713.2740. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+H]^+$, 713.2672). For data, please refer to *O*-TBS ring-opening reaction (Page **143**).

(5*R,6*S**)-5-((*tert*-Butyldimethylsilyloxy)methyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one (104) – *Small Scale Original Prep.***



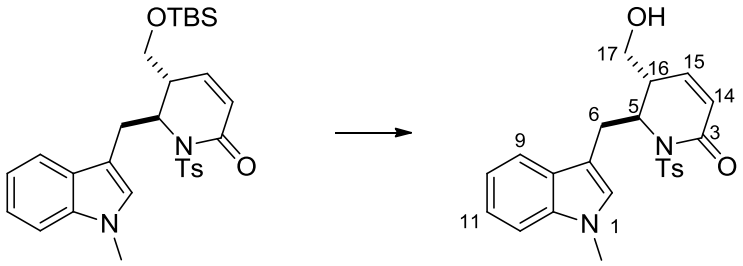
102a **104**

To a stirred solution of *O*-TBS protected amino alcohol **102a** (32.9 mg, 0.046 mmol, 1.0 equiv.) in toluene (1 mL) was added trimethylaluminium (2.0 M in hexane; 26 μL, 0.051 mmol, 1.1 equiv.) and the solution stirred at rt for 30 min. After 30 min at rt, the reaction mixture was heated to 80°C for 3 h and cooled to rt. Saturated aqueous NH_4Cl (1 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(5R*,6S*)-5-((tert-butyldimethylsilyloxy)methyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one **104*** (56.1 mg, 49%) as a pale yellow oil; R_f 0.65 (33% EtOAc–hexane); FTIR (film) υ_{max}: 3050, 2953, 2856, 1687 cm^{-1}; *m/z* (CI) 538 $[M+H]^+$ (Found $[M+H]^+$, 538.2383. $C_{29}H_{38}N_2O_4SSi$ requires $[M+H]^+$, 539.2322).

δ_H (400 MHz, $CDCl_3$) 8.01 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**) 7.69 (1H, d, *J* 8.0 Hz, **9**), 7.33—7.18 (3H, m, **12** and *meta*-**Ts**), 7.24 (1H, t, *J* 8.0 Hz, **11**), 7.14 (1H, t, *J* 8.0 Hz, **10**), 6.92 (1H, s, **2**), 6.50 (1H, ddd, *J* 10.0, 6.0, 1.5 Hz, **15**), 5.90 (1H, d, *J* 10.0 Hz, **14**), 5.21 (1H, dd, *J* 11.5, 4.0 Hz, **5**), 3.75 (3H, s, N_1**Me**), 3.45 (1H, dd, *J* 10.0, 5.5 Hz, **17a**), 3.33 (1H, dt, *J* 10.0, 4.0 Hz, **17b**) 3.26 (1H, t, *J* 14.0 Hz, **6a**), 3.14 (1H, dd, *J* 14.0, 12.0 Hz, **6b**), 2.65 (1H, dt, *J* 10.0, 5.5 Hz, **16**), 2.42 (3H, s, *Ts***Me**), 0.77 (9H, s, **Me**$_3$CSi), –0.05 (3H, s, **Me**Si),–0.19 (3H, s, **Me**Si);

δ_C (100 MHz, $CDCl_3$) 161.6 (**C3**), 145.0 (*para*-**Ts**), 142.4 (**C15**), 137.2 (**C13**), 136.6 (*ipso*-**Ts**), 129.7 (*meta*-**Ts**), 129.4 (*ortho*-**Ts**), 127.9 (**C2**), 127.5 (**C8**), 125.7 (**C14**), 122.0 (**C11**), 119.5 (**C10**), 119.1 (**C12**), 109.5 (**C7**), 109.3 (**C9**), 62.9 (**C17**), 56.9 (**C5**), 39.8 (**C16**), 32.9 (N_1**Me**), 30.1 (**C6**), 25.9 (**Me**$_3$CSi), 21.7 (*Ts***Me**), 18.0 (Me$_3$***C***Si), –5.6 (Me$_2$***C***Si)$_2$. Data is in accordance with that previously reported.[57]

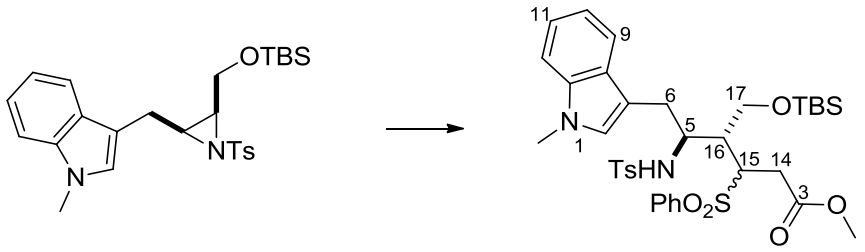
(5*R,6*S**)-5-(Hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one (90) – *Small Scale Original Prep.***



104 **90**

To a stirred solution of *O*-TBS protected lactam **104** (32.9 mg, 0.046 mmol, 1.0 equiv.) in THF (1 mL) at rt was added AcOH:H_2O (1 mL:1 mL) and the reaction mixture stirred at rt for 30 h. Water (1 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (66% EtOAc–hexane) yielded *(5R*,6S*)-5-(hydroxymethyl)-6-(1-methylindol-3-yl)methyl)-1-(4-methylphenylsulfonamido)-5,6-dihydropyridine-2(1H)-one **90*** (20.3 mg, 65%) as an amorphous solid; R_f 0.25 (66% EtOAc–hexane); For data, please refer to the final approach to alstonerine (Page **153**).

Procedure for ring-opening of *O*TBS-hydroxymethyl-substituted aziridine (96)

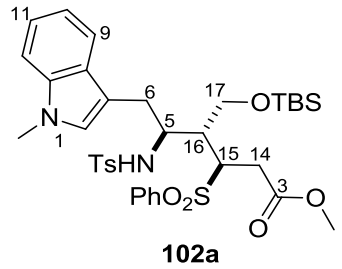


96 **102**

To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (1.90 g, 6.93 mmol, 1.8 equiv.) in THF (2 mL) at –78°C was added *n*-BuLi (2.44 M in hexanes; 3.3 mL, 8.05 mmol, 2.0 equiv.) and the solution stirred for 1 h at –78°C.

The dark red solution of deprotonated **88** was then added dropwise *via* cannula to a solution of *O*-TBS hydroxymethyl-aziridine **96** (3.9 M in THF; 1.0 mL, 3.90 mmol, 1.0 equiv.), maintaining both solutions at –78°C throughout the addition. The reaction mixture was allowed to warm slowly from –78°C to rt overnight. Aqueous HCl (2 M; 20 mL, 40.0 mmol, ~10 equiv.) was added and the solution stirred for 1 h. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (10→25% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 4-((tert-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (**102a**)* and *(3S*,4R*,5S*)-methyl 4-((tert-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (**102b**)* as amorphous solids (1.17g, 41%) and the unwanted regioisomers *(3R*,4S*,5R*)-methyl 6-(tert-butyldimethylsilyloxy)-4-((1-methylindol-3-yl)methyl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate* (***111a***) and *(3S*,4S*,5R*)-methyl 6-(tert-butyldimethylsilyloxy)-4-((1-methylindol-3-yl)methyl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (**111b**)* as amorphous solids (~15:10:6:5 **102a**:**111a**:**111b**:**102b** ratio obtained by ^{1}H NMR analysis of the crude material);

(3*R,4*R**,5*S**)-Methyl 4-((*tert*-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (102a)**



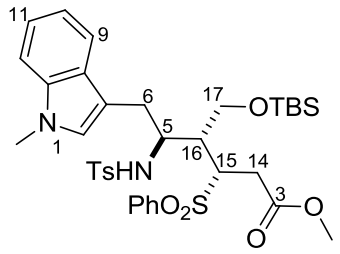
102a

R_f 0.41 (20% EtOAc–hexane). FTIR (film) υ_{max}: 2928, 2859, 1742, 1156 cm^{-1}; *m/z* (CI) 713 $[M+H]^+$ (Found $[M+H]^+$, 713.2747. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+H]^+$, 713.2750).

δ_H (500 MHz, $CDCl_3$) 7.67—7.60 (4H, m, *ortho*-**Ts** and *ortho*-**Ph**SO_2), 7.57 (1H, t, *J* 8.0 Hz, *para*-**Ph**SO_2), 7.41 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 7.29—7.21 (2H, m, **12** and **9**), 7.21 (1H, t, *J* 8.0 Hz, **11**) 7.16 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.01 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.83 (1H, s, **2**), 5.91 (1H, d, *J* 9.0 Hz, N_4**H**), 4.23 (1H, dt, *J* 8.5, 4.0 Hz, **15**), 3.79—3.71 (1H, m, **5**), 3.71—3.65 (4H, s, *O***Me** then **17a**), 3.53 (1H, dd, *J* 10.5 5.5 Hz, **17b**), 3.45 (3H, s, N_1**Me**), 3.10 (1H, dd, *J* 14.5, 6.5 Hz, **6a**), 2.98 (1H, dd, *J* 18.0, 3.0 Hz, **14a**), 2.87 (1H, dd, *J* 14.5, 6.5 Hz, **6b**), 2.76 (1H, dd, *J* 18.0, 9.0 Hz, **14b**), 2.60 (1H, m, **16**), 2.39 (3H, s, *Ts***Me**), 0.75 (9H, s, **Me**$_3$CSi), –0.09 (3H, s, **Me**Si), –0.13 (3H, s, **Me**Si);

δ_C (125 MHz, $CDCl_3$) 171.1 (**C3**), 142.9 (*para*-**Ts**), 138.2 (*ipso*-**Ph**SO_2), 138.0 (*ipso*-**Ts**), 136.9 (**C13**), 133.7 (*para*-**Ph**SO_2), 129.4 (*meta*-**Ts**), 129.1 (*meta*-**Ph**SO_2), 128.8 (*ortho*-**Ph**SO_2), 128.2 (**C2**), 128.1 (**C8**), 126.8 (*ortho*-**Ts**), 121.5 (**C11**), 119.1 (**C10**), 118.6 (**C12**), 109.2 (**C9**), 108.8 (**C7**), 62.8 (**C17**), 61.0 (**C15**), 52.4 (**C5**), 51.9 (*O***Me**), 42.9 (**C16**), 32.6 (N_1**Me**), 30.9 (**C14**), 29.5 (**C6**), 25.6 (**Me**$_3$CSi), 21.5 (*Ts***Me**), 17.9 (Me$_3$***C***Si), –5.8 (**Me**Si), –5.9 (**Me**Si).

(3*S,4*R**,5*S**)-Methyl 4-((*tert*-butyldimethylsilyloxy)methyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (102b)**



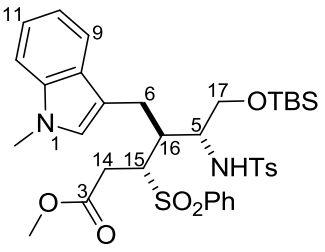
102b

R_f 0.14 (20% EtOAc–hexane); υ_{max} (film) 2928, 2858, 1734, 1471, 1447, 1152 cm^{-1}; *m/z* (ES) 735 $[M+Na]^+$ (Found $[M+Na]^+$, 735.2568. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+Na]^+$, 735.2570);

δ_H (400 MHz, $CDCl_3$) 7.86 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.54 (1H, t, *J* 7.5 Hz, *para*-**Ph**SO_2), 7.45 (2H, t, *J* 7.5 Hz, *meta*-**Ph**SO_2), 7.39 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.15 (2H, d, *J* 3.5 Hz, **12** and **9**), 7.04—6.91 (4H, m, **10**, **11** and *meta*-**Ts**), 6.66 (1H, s, **2**), 4.66 (1H, d, *J* 8.0 Hz, N_4**H**), 4.05 (1H, dt, *J* 8.0, 2.5 Hz, **15**), 4.00 (1H, dd, *J* 7.0, 3.0 Hz, **5**), 3.94 (1H, dd, *J* 10.0, 3.0 Hz, **17a**), 3.85 (1H, dd, *J* 10.0, 4.0 Hz, **17b**), 3.62 (3H, s, N_1**Me**), 3.57 (3H, s, *O***Me**), 3.15 (1H, dd, *J* 18.0, 3.0 Hz, **14a**), 2.86 (1H, dd, *J* 18.0, 8.5 Hz, **14b**), 2.86 (1H, dd, *J* 14.5, 6.5 Hz, **6a**), 2.65—2.56 (2H, m, **6b** and **16**), 2.31 (3H, s, *Ts***Me**), 0.82 (9H, s, **Me**$_3$CSi), 0.06 (3H, s, **Me**Si), 0.00 (3H, s, **Me**Si);

δ_C (100 MHz, $CDCl_3$) 171.9 (**C3**), 143.0 (*para*-**Ts**), 137.3 (*ipso*-**Ph**SO_2), 136.9 (**C13**), 136.3 (*ipso*-**Ts**), 133.9 (*para*-**Ph**SO_2), 129.1 (*meta*- and *ortho*-**Ph**SO_2), 127.5 (**C8**), 127.4 (**C2**), 127.0 (*ortho*- and *meta*-**Ts**), 121.6 (**C11**), 119.0 (**C10**), 118.5 (**C12**), 109.1 (**C9**), 108.8 (**C7**), 59.8 (**C17**), 59.3 (**C15**), 53.0 (**C5**), 52.4 (*O***Me**), 41.5 (**C16**), 32.5 (N_1**Me**), 30.2 (**C14**), 28.9 (**C6**), 25.8 (**Me**$_3$CSi), 23.9, 21.6 (Ts**Me**), 18.0 (Me$_3$***C***Si), –5.5 (**Me**Si), –5.6 (**Me**Si).

(3*R,4*S**,5*R**)-Methyl 6-(*tert*-butyldimethylsilyloxy)-4-((1-methylindol-3-yl)methyl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (111a)**



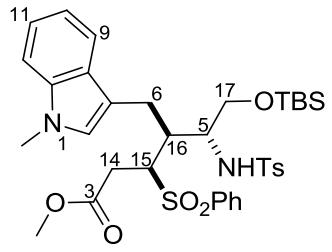
111a

R_f 0.36 (20% EtOAc–hexane); υ_{max} (film) 2928, 2859, 1742, 1156 cm^{-1}; *m/z* (ES) 713 $[M+H]^+$ (Found $[M+H]^+$, 713.2750. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+H]^+$, 713.2755);

δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 8.0 Hz, **12**), 7.93 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.68 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.62 (1H, t, *J* 8.0 Hz, *para*-**Ph**SO_2), 7.51 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 7.30—7.20 (4H, m, **9**, **11** and *meta*-**Ts**), 7.18—7.12 (2H, m, **10** and **2**), 5.16 (1H, d,
J 9.5 Hz, N_4**H**), 4.31 (1H, dd, *J* 8.0, 2.5 Hz, **15**), 3.78 (3H, s, N_1**Me**), 3.61—3.56 (1H, m, **5**), 3.48 (3H, s, *O***Me**), 3.29—3.21 (2H, m, **14a** and **6a**), 3.13 (1H, dd, *J* 10.5, 2.5 Hz, **17a**), 3.01—2.86 (4H, m, **17b**, **14b, 16** and **6b**), 2.39 (3H, s, *Ts***Me**), 0.71 (9H, s, **Me**$_3$CSi), 0.24 (3H, s, **Me**Si), –0.26 (3H, s, **Me**Si);

δ_C (100 MHz, $CDCl_3$) 172.0 (**C3**), 143.6 (*para*-**Ts**), 137.8 (*ipso*-**Ts**), 137.8 (*para*-**Ph**SO_2), 137.2 (**C13**), 133.7 (*ipso*-**Ph**SO_2), 129.8 (*meta*-**Ts**), 129.1 (*ortho*-**Ph**SO_2), 129.1 (*meta*-**Ph**SO_2), 128.6 (**C2**), 127.8 (**C8**), 127.0 (*ortho*-**Ts**), 121.5 (**C11**), 119.9 (**C12**), 119.1 (**C10**), 111.7 (**C7**), 108.9 (**C9**), 65.0 (**C17**), 60.0 (**C15**), 54.0 (**C5**), 52.2 (*O***Me**), 39.5 (**C16**), 32.6 (N_1**Me**), 30.3 (**C14**), 25.7 (**Me**$_3$CSi), 24.2 (**C6**), 21.5 (*Ts***Me**), 18.2 (Me$_3$***C***Si), –5.5 (**Me**Si), –5.6 (**Me**Si).

(3*S,4*S**,5*R**)-Methyl 6-(*tert*-butyldimethylsilyloxy)-4-((1-methylindol-3-yl)methyl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (111b)**



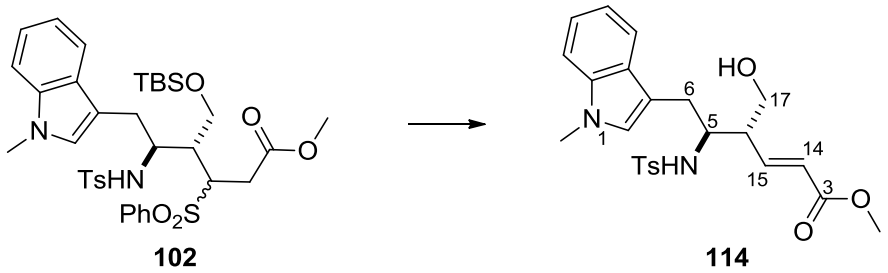
111b

R_f 0.23 (20% EtOAc–hexane); υ_{max} (film) 2955, 2931, 2860, 1734, 1471, 1444, 1157 cm^{-1}; *m/z* (ES) 713 $[M+H]^+$ (Found $[M+H]^+$, 713.2750. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+H]^+$, 713.2755);

δ_H (400 MHz, $CDCl_3$) 7.85 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.40 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.36—7.26 (3H, m, *meta*-**Ts** and *para*-**Ph**SO_2), 7.14—7.08 (3H, m, **9**, **11** and **12**), 6.98—6.88 (3H, m, *meta*-**Ph**SO_2 and **10**), 6.72 (1H, s, **2**), 6.31 (1H, d, *J* 9.0 Hz, N_4**H**), 4.25 (1H, dd, *J* 8.0, 3.5 Hz, **15**), 3.87 (1H, dd, *J* 10.5, 1.5 Hz, **17a**), 3.76—3.70 (1H, m, **17b**), 3.63 (2×3H, s, N_1**Me** and *O***Me**), 3.56—3.48 (1H, m, **5**), 3.00—2.88 (2H, m, **14a** and **6a**), 2.81 (1H, dt, *J* 10.0, 3.5 Hz, **16**), 2.50—2.36 (5H, m, **14b**, **6b** and 3H, s, *Ts***Me**), 0.91 (9H, s, **Me**$_3$CSi), 0.03 (3H, s, **Me**Si), –0.03 (3H, s, **Me**Si);

δ_C (100 MHz, $CDCl_3$) 172.1 (**C3**), 143.4 (*para*-**Ts**), 139.1 (*ipso*-**Ts**), 137.8 (*para*-**Ph**SO_2), 137.0 (**C13**), 132.9 (*ipso*-**Ph**SO_2), 129.9 (*meta*-**Ts**), 126.6 (**C2**), 128.0 (*ortho*-**Ph**SO_2), 127.9 (**C8**), 127.0 (*meta*-**Ph**SO_2), 126.9 (*ortho*-**Ts**), 121.5 (**C11**), 118.8 (**C12**), 118.7 (**C10**), 110.3 (**C7**), 109.2 (**C9**), 63.1 (**C17**), 61.3 (**C15**), 55.8 (**C5**), 52.3 (*O***Me**), 38.6 (**C16**), 32.5 (N_1**Me**), 29.3 (**C14**), 26.4 (**C6**), 26.0 (**Me**$_3$CSi), 21.5 (*Ts***Me**), 18.3 (Me$_3$***C***Si), –5.50 (**Me**$_2$Si).

(4*R,5*S**,*E*)-Methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)hex-2-enoate (114)**



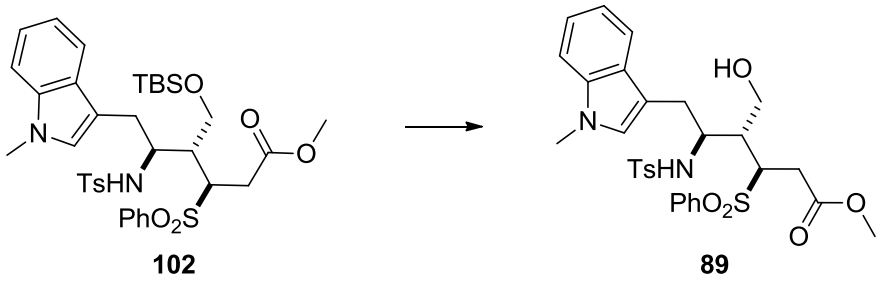
102 **114**

To a solution of *O*TBS-amino alcohol **102** (58.3 mg, 0.081 mmol, 1.0 equiv.) in THF (3 mL) at 0°C was added TBAF·$3H_2O$ (28.4 mg, 0.090 mmol, 1.1 equiv.) and the reaction mixture allowed to stir for 15 min. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The organic layers were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and flash column chromatography (50% EtOAc–hexane) yielded *(4R*,5S*,E)-methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)hex-2-enoate* ***114*** (36.9 mg, 76%) as a pale yellow gum; R_f 0.32 (50% EtOAc–hexane); υ_{max} (film) 3508, 3364, 2933, 1810, 1783, 1598, 1325, 1184, 1091, 739 cm^{-1}; *m/z* (CI) 457 $[M+H]^+$ (Found $[M+H]^+$, 457.1790. $C_{24}H_{28}N_2O_5S$ requires $[M+H]^+$, 457.1751);

δ_H (400 MHz, $CDCl_3$) 7.45 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.20—7.10 (3H, m, **9, 12** and **11**), 7.04—6.97 (3H, m, *meta*-**Ts** and **10**), 6.91 (1H, dd, *J* 16.0, 9.0 Hz, **15**), 6.63 (1H, s, **2**), 5.99 (1H, d, *J* 16.0 Hz, **14**), 5.02 (1H, d, *J* 9.0 Hz, N_4**H**Ts), 4.00—3.89 (2H, m, **17a** and **17b**), 3.77 (3H, s, N_1**Me**), 3.59 (3H, s, *O***Me**), 3.03 (1H, dd, *J* 8.0, 6.0 Hz, **5**), 2.80—2.69 (2H, m, **6a** and **16**), 2.61 (1H, dd, *J* 14.5 Hz, **6b**), 2.34 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$) 166.6 (**C3**), 144.1 (**C15**), 143.0 (*para*-**Ts**), 136.9 (ipso-**Ts** and **C13**), 129.8 (*ortho*-**Ts**), 129.1 (*meta*-**Ts**), 127.4 (**C8**), 127.3 (**C2**), 126.6 (**C9**), 125.3 (**C14**), 121.6 (**C11**), 119.0 (**C10**), 118.4 (**C12**), 109.2 (**C7**), 61.9 (**C17**), 53.3 (**C5**), 51.8 (*O***Me**), 48.1 (**C16**), 32.5 (N_1**Me**), 29.7 (**C6**), 21.6 (*Ts***Me**).

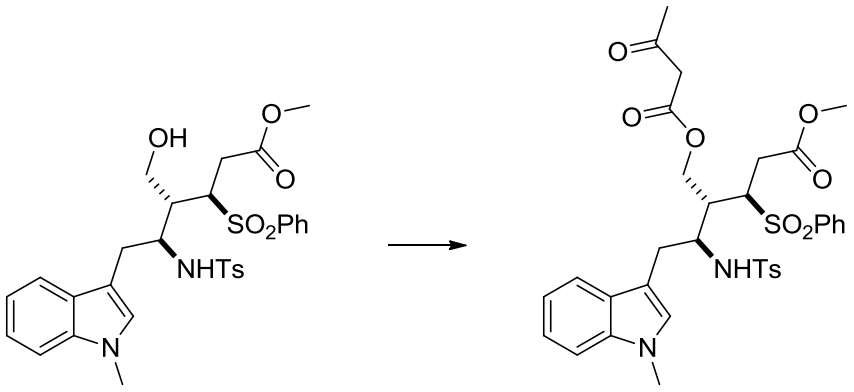
(3*R,4*R**,5*S**)-Methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate (89)**



102 **89**

To a solution of *O*TBS-amino alcohol **102** (23.0 mg, 0.032 mmol, 1.0 equiv.) in MeOH (3 mL) at rt was added concentrated HCl (1 drop) and the solution stirred for 16 h. The reaction mixture was then cooled to –78°C and NH_3 (~0.1 M in MeOH; 0.50 mL, 0.05 mmol, ~1.5 equiv.) and the solution stirred for 15 minutes. Concentration under reduced pressure and flash column chromatography (33% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 4-(hydroxymethyl)-6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate* **89** (18.7 mg, 98%) as a pale yellow oil; R_f 0.32 (50% EtOAc–hexane). Data is in accordance with that previously reported (Page **138**).

(3*R,4*R**,5*S**)-Methyl 6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-4-((3-oxobutanoyloxy)methyl)-3-(phenylsulfonyl)hexanoate (112)**



89 **112**

To a solution of amino alcohol **89** (250 mg, 0.418 mmol, 1.0 equiv.) in toluene (1 mL) at rt was added 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.11 mL, 0.884 mmol, 2.0 equiv.) and the reaction mixture heated under reflux at 110°C for 2 h. Saturated aqueous NH_4Cl (1 mL) was added and

the aqueous layer extracted with EtOAc (3×20 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (20% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-4-((3-oxobutanoyloxy)methyl)-3-(phenylsulfonyl)hexanoate* ***112*** (151.7 mg, 58%) as an amorphous solid; R_f 0.55 (66% EtOAc–hexane); R_f 0.24 (50% EtOAc–hexane); υ_{max} (film) 2925, 1734, 1275, 1156 cm^{-1}; *m/z* (CI) 683 $[M+H]^+$ (Found $[M+H]^+$, 683.2041. $C_{34}H_{38}N_2O_9S_2$ requires $[M+H]^+$, 683.2019);

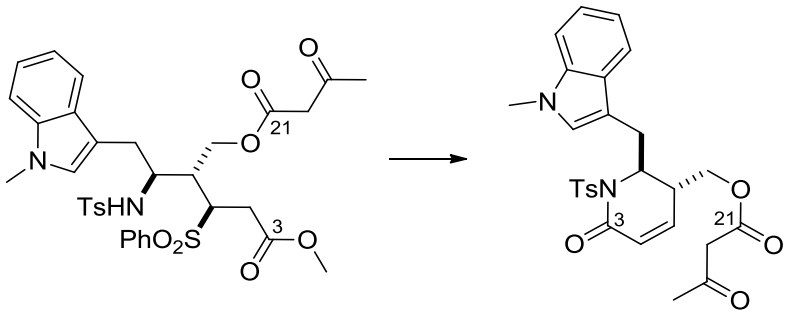
δ_H (400 MHz, $CDCl_3$) 7.86 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.71—7.59 (5H, m, Ar**H**), 7.25—7.10 (3H, m, Ar**H**), 7.06—6.95 (3H, m, Ar**H**), 6.90 (1H, s, **2**), 5.70 (1H, d, *J* 9.0 Hz, N_4**H**), 4.40 (1H, dd, *J* 11.5, 6.5 Hz, **15**), 4.22 (1H, dt, *J* 6.0, 3.0 Hz, **17a**), 4.05—3.83 (3H, m, **5** and **17b**), 3.68 (3H, s, N_1**Me**), 3.38 (3H, s, *O***Me**), 3.21—3.11 (2H, m, **14a** and **14b**), 2.93—2.81 (2H, m, **6a** and **6b**), 2.54—2.46 (1H, m, **16**), 2.38 (3H, s, *Ts***Me**), 2.14 (3H, s, **18**), 2.04 (2H, s, **20**);

δ_C (100 MHz, $CDCl_3$); 205.3 (**19**), 170.7 (**21**), 166.6 (**C3**), 142.9 (*para*-**Ts**), 137.8 (*ipso*-**Ph**SO_2), 137.6 (*ipso*-**Ts**), 136.9 (**C13**), 134.2 (*para*-**Ph**SO_2), 129.6 (**C8**), 129.3 (*meta*-**Ts**), 129.2 (*meta*-**Ph**SO_2), 129.0 (*ortho*-**Ph**SO_2), 128.8 (*ortho*-**Ts**), 127.7 (**C2**), 121.7 (**C11**), 119.1 (**C10**), 118.5 (**C12**), 109.0 (**C9**), 107.5 (**C7**), 60.1 (**C17**), 59.2 (*O***Me**), 53.2 (**C15**), 52.2 (**C5**), 46.8 (**C16**) 37.2 (**C14**), 35.9 (**C18**), 34.1 (**C20**), 32.5 (N_1**Me**), 29.0 (**C6**), 21.6 (*Ts***Me**).

Microwave Prep. For **(112)**

To a solution of amino alcohol **89** (15.0 mg, 0.025 mmol, 1.0 equiv.) in toluene (1 mL) in a microwave vial was added 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.005 mL, 0.038 mmol, 1.5 equiv.) and the reaction mixture heated in the microwave at 150°C for 30 min. Saturated aqueous NH_4Cl (1 mL) was added and the aqueous layer extracted with EtOAc (3×5 mL) and CH_2Cl_2 (3×5 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (20% EtOAc–hexane) yielded *(3R*,4R*,5S*)-methyl 6-(1-methylindol-3-yl)-5-(4-methylphenylsulfonamido)-4-((3-oxobutanoyloxy)methyl)-3-(phenylsulfonyl)hexanoate* ***112*** (14.1 mg, 76%) as an amorphous solid.

((2*S,3*R**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate (113)**

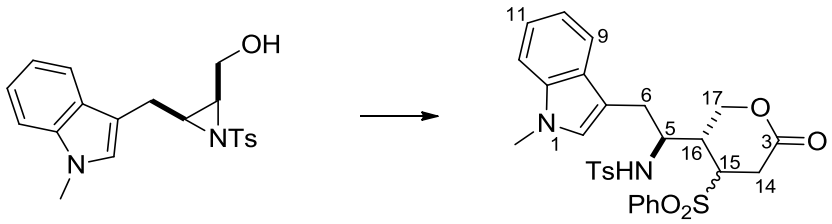


112 **113**

To **112 (**31.0 mg, 0.045 mmol, 1.0 equiv.) in toluene (1 mL) was added trimethylaluminium (2.0 M in hexanes; 0.025 mL, 0.05 mmol, 1.1 equiv.) and the reaction heated under reflux at 100°C for 1 hour. The reaction mixture was then cooled to rt and saturated aqueous NH_4Cl (5 mL) was added. The aqueous layer was extracted with EtOAc (3×20 mL) and CH_2Cl_2 (3×20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(5R*,6S*)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***90*** as an amorphous solid (14.1 mg, 61%); Data is in accordance with that reported later (Page **154**).

3.1.5 *Procedures from final synthesis of key intermediate lactam–alcohol* ***90*** (Sections **2.1.14**)

4-Methyl-*N*-((*S)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (109a)** and **4-methyl-*N*-((*S**)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (109b)**



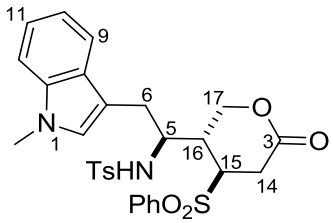
82 **109**

To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (7.43g, 27.08 mmol, 1.5 equiv.) in THF (30 mL) at –78 °C was added *n*-BuLi (2.48 M in hexanes; 12.0 mL, 29.80 mmol, 1.7 equiv.) and the solution stirred for 1 h at –78°C.

Meanwhile, *n*-BuLi (2.48 M in hexanes; 8.0 mL, 19.9 mmol, 1.1 equiv.) was added to a solution of hydroxymethyl aziridine **82** (6.69 g, 18.05 mmol, 1.0 equiv.) in THF (10.0 mL) at –78°C and the solution stirred for 1 h at –78°C.

The dark red solution of deprotonated **88** was added dropwise *via* cannula to the dark green solution of *O*-lithio hydroxymethyl aziridine **82**, maintaining both solutions at –78°C throughout the addition. The reaction mixture was allowed to warm slowly from –78°C to rt overnight. Aqueous HCl (2 M; 50 mL, 100.0 mmol, 100 equiv.) was added and the solution stirred for 3 h. The aqueous layer was extracted with EtOAc (3×200 mL) and CH_2Cl_2 (3×100 mL), and the combined organic layers washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50% EtOAc–hexane) yielded *lactones **109*** (8.18 g, 80%) as a 2:1 mixture of sulfone epimers.

4-Methyl-*N*-((*S)-2-(1-methylindol-3-yl)-1-((3*R**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (109a)**



109a

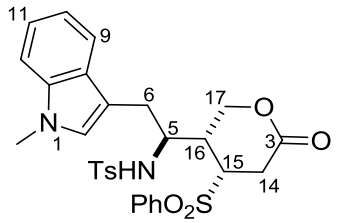
R_f 0.25 (50% EtOAc–hexane); 225.9–226.6°C; FTIR (film) υ_{max}: 3297, 2921, 1739, 1599 cm^{-1}; *m/z* (CI) 567 $[M+H]^+$ (Found $[M+H]^+$, 567.1614. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1624); (Found C, 61.38; H, 5.40; N, 5.05%. $C_{29}H_{30}N_2O_6S_2$ requires C, 61.46; H, 5.34; N, 4.94%);

δ_H (400 MHz, $CDCl_3$) 8.00 (2H, dd, *J* 8.0, 1.0 Hz, *meta*-**Ph**SO_2), 7.84 (2H, dd, *J* 8.0, 1.0 Hz, *ortho*-**Ph**SO_2), 7.66 (1H, tt, *J* 7.5, 1.0 Hz, *para*-**Ph**SO_2), 7.45 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.24—7.22 (2H, m, **9** and **11**), 7.11—7.01 (4H, m, *meta*-**Ts**, **12** and **10**), 6.72 (1H, s, **2**), 4.70 (1H, d, *J* 7.5 Hz, N_4**H**), 4.49 (1H, dd, *J* 12.5, 4.0 Hz, **17a**), 4.31 (1H, dd, *J* 12.5, 4.0 Hz,

17b), 3.81—3.76 (1H, m, **15**), 3.69 (3H, s, N_1**Me**), 3.66—3.60 (1H, m, **5**), 2.97 (1H, dd, *J* 15.0, 5.0 Hz, **6a**), 2.82—2.74 (2H, m, **6b** and **14a**), 2.61 (1H, dd, *J* 16.0, 7.0 Hz, **14b**), 2.36 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$) 168.7 (**C3**), 143.5 (*para*-**Ts**), 137.0 (**C13**), 136.2 (*ipso*-**Ph**SO_2), 135.6 (*ipso*-**Ts**), 134.5 (*para*-**Ph**SO_2), 129.6 (*ortho*-**Ph**SO_2), 129.5 (*meta*-**Ts**), 129.1 (*meta*-**Ph**SO_2), 127.8 (**C8**), 127.4 (**C2**), 126.7 (*ortho*-**Ts**), 122.1 (**C11**), 119.6 (**C10**), 118.2 (**C12**), 109.5 (**C9**), 107.2 (**C7**), 66.5 (**C17**), 56.8 (**C15**), 53.7 (**C5**), 36.6 (**C16**), 32.7 (N_1**Me**), 29.0 (**C14**), 28.1 (**C6**), 21.6 (*Ts***Me**).

4-Methyl-*N*-((*S)-2-(1-methylindol-3-yl)-1-((3*R**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (109b)**



109b

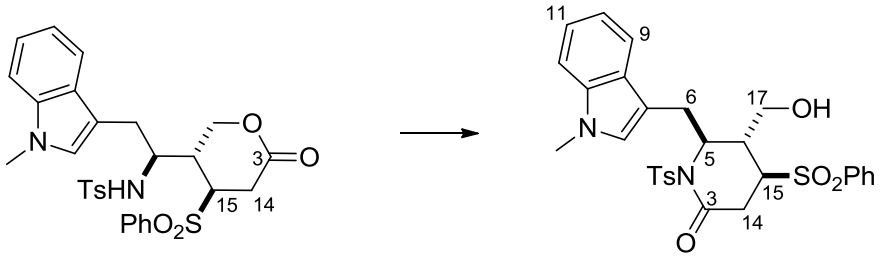
R_f 0.15 (50% EtOAc–hexane); 214.5–215.0°C FTIR (film) υ_{max}: 3297, 2921, 1739, 1599 cm^{-1}; *m/z* (CI) 567 $[M+H]^+$ (Found $[M+H]^+$, 567.1614. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1624). (Found C, 61.38; H, 5.40; N, 5.05%. $C_{29}H_{30}N_2O_6S_2$ requires C, 61.46; H, 5.34; N, 4.94%);

δ_H (400 MHz, $CDCl_3$) 8.03—7.98 (2H, m, *ortho*-**Ph**SO_2), 7.71 (1H, tt, *J* 7.5, 1.0 Hz, *para*-**Ph**SO_2), 7.61 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 7.42—7.35 (3H, m, *ortho*-**Ts** and **12**), 7.17 (2H, d, *J* 4.0 Hz, **9** and **11**), 7.01—6.95 (1H, m, **10**), 6.92 (2H, *J* 8.0 Hz, *meta*-**Ts**), 6.71 (1H, s, **2**), 5.35 (1H, d, *J* 6.5 Hz, N_4**H**), 5.03 (1H, dd, *J* 12.0, 8.0 Hz, **17a**), 4.43—4.21 (2H, m, **17b** and **5**), 4.03—3.96 (1H, m, **15**), 3.63 (3H, s, N_1**Me**), 3.18—3.02 (2H, m, **6a** and **16**), 2.92—2.74 (2H, m, **6b** and **14a**), 2.51 (1H, dd, *J* 18.0, 7.0 Hz, **14b**), 2.29 (3H, s, *Ts***Me**);

δ_C (100 MHz, $CDCl_3$) 166.9 (**C3**), 143.2 (*para*-**Ts**), 137.7 (*para*-**Ph**SO_2), 137.0 (**C13**), 135.8 (*ipso*-**Ts**), 134.7 (*ipso*-**Ph**SO_2), 129.8 (*ortho*-**Ph**SO_2), 129.2 (*meta*-**Ts**), 128.8 (*meta*-**Ph**SO_2), 127.4 (**C8**), 127.2 (**C2**), 126.7 (*ortho*-**Ts**), 121.9 (**C11**), 119.4 (**C10**), 118.6 (**C12**),

109.3 (**C9**), 108.3 (**C7**), 68.8 (**C17**), 57.3 (**C15**), 52.7 (**C5**), 38.9 (**C16**), 32.6 (N_1**Me**), 31.6 (**C14**), 28.1(**C6**), 21.6 (*Ts***Me**).

(4*S,5*R**,6*S**)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-4-(phenylsulfonyl)-1-tosylpiperidin-2-one (118)**



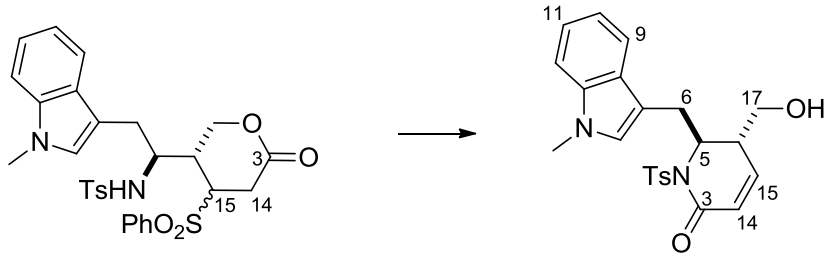
To a stirred solution of *4-Methyl-N-((S*)-2-(1-methylindol-3-yl)-1-((3R*,4R*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2H-pyran-3-yl)ethyl)benzenesulfonamide* ***109a*** (1.5 g, 2.65 mmol, 1.0 equiv.) in toluene (9 mL) at 0°C was added trimethyl aluminium (2.0 M in hexanes; 1.6 mL, 3.18 mmol, 1.2 equiv.) and the reaction mixture stirred at 0°C for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer extracted with EtOAc (3×50 mL) and CH_2Cl_2 (3×50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(4S*,5R*,6S*)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-4-(phenylsulfonyl)-1-tosylpiperidin-2-one* ***118*** as a crystalline white solid (0.99 g, 30%) and *(5R*,6S*)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***90*** as an amorphous solid (1.49 g, 69%); 266.0–269.0°C; R_f 0.75 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3529, 2925, 1704, 1162 cm^{-1}; *m/z* (ES) 567 $[M+H]^+$ (Found $[M+H]^+$, 567.1711. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1739). Found C, 61.53; H, 5.27; N, 4.92%. $C_{23}H_{24}N_2O_4S$ requires C, 61.46; H, 5.34; N, 4.94%;

δ_H (400 MHz, $CDCl_3$) 8.02—7.89 (3H, m, *ortho*-**Ph**SO_4 and *para*-**Ph**SO_4), 7.89—7.79 (2H, m, *ortho*-**Ts**), 7.69 (1H, tt, *J* 8.0, 1.0 Hz, **10**), 7.57 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_4), 7.34 (1H, d, *J* 8.0 Hz, **11**), 7.31—7.15 (4H, m, *meta*-**Ts**, **9** and **12**), 5.10 (1H, t, *J* 8.0 Hz, **5**), 3.80 (3H, s, N_1**Me**), 3.48—3.36 (2H, m, **17a** and **15**), 3.35—3.17 (3H, m, **6a, 6b** and **17b**), 3.10 (1H, dd, *J* 15.5, 13.0

Hz, **14a**), 2.98 (1H, td, *J* 7.0, 4.5 Hz, **16**), 2.41 (3H, s, *Ts***Me**), 2.36 (1H, dd, *J* 15.5, 7.0 Hz, **14b**), 1.76 (1H, dd, *J* 7.0, 5.0 Hz, *O***H**);

δ_C (100 MHz, $CDCl_3$) 166.8 (**C3**), 145.3 (*para*-**Ts**) , 137.3 (*para*-**Ph**SO_2), 136.8 (**C13**), 135.4 (*ipso*-**Ts**), 134.6 (*ipso*-**Ph**SO_2), 129.7 (*ortho*-**Ph**SO_2), 129.3 (**C2** and *meta*-**Ts**), 129.2 (*ortho*-**Ts**), 128.6 (*meta*-**Ph**SO_2), 127.5 (**C8**) 121.9 (**C11**), 119.5 (**C10**), 119.3 (**C12**), 109.4 (**C9**), 108.7 (**C7**), 64.9 (**C17**), 58.1 (**C15**), 57.5 (**C5**), 35.5 (**C16**), 33.2 (**C14**), 32.8 (N_1**Me**), 32.1 (**C6**), 21.7 (*Ts***Me**).

(5*R,6*S**)-5-(Hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (90)**



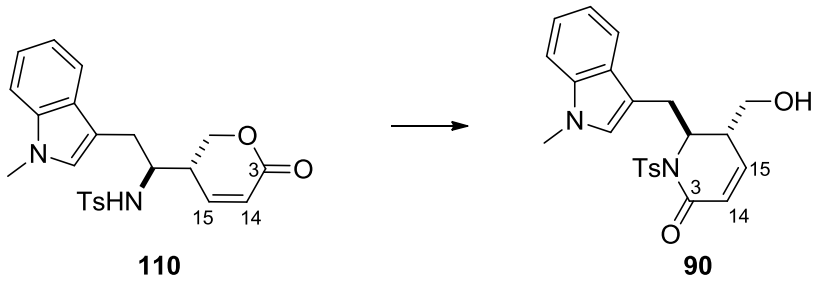
109 **90**

To a solution of lactones **109** (7.76 g, 13.71 mmol, 1.0 equiv.) in toluene (50 mL) was added trimethylaluminium (2.0 M in hexanes; 10.5 mL, 21.0 mmol, 1.5 equiv.) and the reaction mixture heated under reflux at 120°C for 2 h. The reaction mixture was cooled to rt before saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension was stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (1 mL) was added and the aqueous layer extracted with EtOAc (3×100 mL) and CH_2Cl_2 (3×100 mL). The organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(5R*,6S*)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***90*** as a colourless, amorphous solid (5.66 g, 94%); R_f 0.25 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3530, 3056, 2917, 1687 cm^{-1}; *m/z* (CI) 425 $[M+H]^+$ (Found $[M+H]^+$, 425.1530. $C_{23}H_{24}N_2O_4S$ requires $[M+H]^+$, 425.1535). Found C, 64.94; H, 5.63; N, 6.57%. $C_{23}H_{24}N_2O_4S$ requires C, 65.07; H, 5.70; N, 6.60%;

δ_H (400 MHz, $CDCl_3$) 7.99 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.68 (1 H, d, *J* 8.0 Hz, **12**), 7.33—7.21 (4H, m, *ortho*-**Ts**, **9** and **11**), 7.15 (1H, t, *J* 8.0 Hz, **10**), 6.90 (1H, s, **2**), 6.57 (1H, ddd, *J* 10, 8.0, 1.5 Hz, **15**), 5.94 (1H, d, *J* 10.0 Hz, **14**), 5.16 (1H, dd, *J* 11.0, 4.0 Hz, **5**), 3.75 (3H, s, N_1**Me**), 3.57 (1H, dd, *J* 11.0, 6.0 Hz, **17a**), 3.38 (1H, t, *J* 9.0 Hz, **17b**), 3.31 (1H, dd, *J* 14.0, 4.0 Hz, **6a**), 3.14 (1H, dd, *J* 14.0, 11.0 Hz, **6b**), 2.69 (1H, dt, *J* 7.5, 6.0 Hz, **16**), 2.42 (3H, s, *Ts***Me**), 1.59 (1H, br. s, *O***H**);

δ_C (100 MHz, $CDCl_3$) 161.6 (**C3**), 144.7 (*para*-**Ts**), 142.4 (**C15**), 137.0 (**C13**), 136.4 (*ipso*-**Ts**), 129.3 (*meta*-**Ts**), 129.1 (*ortho*-**Ts**), 127.94 (**C2**), 127.85 (**C8**), 125.9 (**C14**), 121.9 (**C11**), 119.4 (**C10**), 118.9 (**C12**), 109.5 (**C7**), 109.4 (**C9**), 62.9 (**C17**), 57.0 (**C5**), 39.9 (**C16**), 32.7 (N_1**Me**), 29.9 (**C6**), 21.7 (*Ts***Me**).

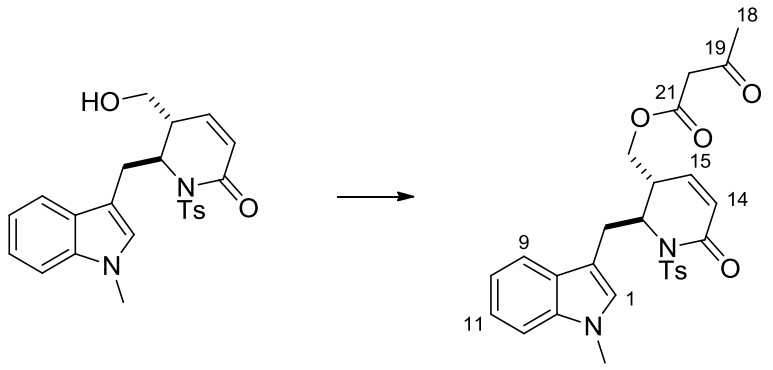
Experimental procedure for *O*- → *N*-transacylation of sulfone (110)



To a solution of crude lactone **110** (366.2 mg, 0.863 mmol, 1.0 equiv.) in toluene (2 mL) was added trimethylaluminium (2.0 M in hexanes; 0.5 mL, 0.95 mmol, 1.1 equiv.) and the reaction mixture stirred at rt for 1 h. The reaction mixture was then heated to 100°C for 15 min in the microwave, cooled to rt and saturated aqueous NH_4Cl (5 mL) was added. The aqueous layer was extracted with EtOAc (3×20 mL) and CH_2Cl_2 (3×20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(5R*,6S*)-5-(hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***90*** as an amorphous solid (334 mg, 91%); Data is in accordance with that previously reported (Page **154**).

3.1.6 *Procedures from synthesis of pentacyclic lactone **85*** (Sections **2.2.1** and **2.2.2**)

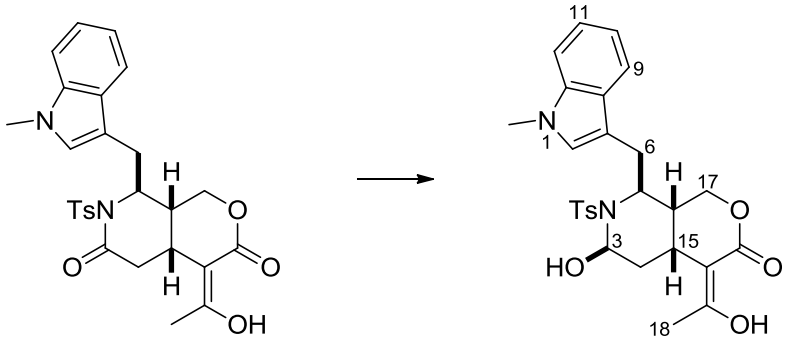
((2*S,3*R**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate (113) – *Small Scale Original Prep.***



90 **113**

To a stirred solution of lactam alcohol **90** (10.9 mg, 0.026 mmol, 1.0 equiv.) and KOAc (0.25 mg, 0.003 mmol, 0.1 equiv.) in THF (0.15 mL) at rt was added diketene (0.66M in THF; 0.05 mL, 0.033 mmol, 1.3 equiv.) and the reaction mixture heated under reflux at 70°C for 1.25 h. After cooling to rt, water (0.5 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure chromatography (40% EtOAc–hexane) yielded *((2S*,3R*)-2-((1-methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate **113*** (17.1 mg, 100%) as an amorphous solid; For data, please refer to optimised route (Page **162**).

(4a*R,6*R**,8*S**,8a*R**,*Z*)-6-Hydroxy-4-(1-hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosylhexahydro-1*H*-pyrano[3,4-*c*]pyridin-3(4*H*)-one (119)**



91 **119**

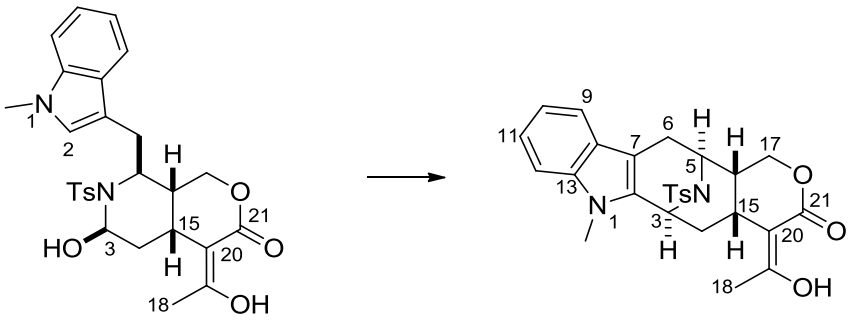
To a solution of enol **91** (54.7 mg, 0.108 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.22 mL, 0.215 mmol, 2.0 equiv.) and the solution stirred at –78°C for 3 h. MeOH (1 mL) was added and the reaction mixture was allowed to warm slowly from –78°C to rt. Saturated aqueous Rochelle salt (5 mL) and EtOAc (15 mL) were added and the resulting suspension stirred vigorously at rt overnight. The aqueous phase was extracted with EtOAc (3×50 mL) and the organic phases were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and preparative thin layer chromatography (50% EtOAc–hexane) yielded *(4aR*,6R*,8S*,8aR*,Z)-6-hydroxy-4-(1-hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosylhexahydro-1H-pyrano[3,4-c]pyridin-3(4H)-one* ***119*** (28.0 mg, 51%) as a white amorphous solid; R_f 0.61 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3481, 2925, 1631, 1614, 1477, 1439 cm^{-1}; *m/z* (ES) 509 $[M–H]^-$ (Found $[M–H]^-$, 509.1754. $C_{27}H_{30}N_2O_6S$ requires $[M–H]^-$, 509.1746);

δ_H (400 MHz, $CDCl_3$) 13.85 (1H, s, 19-O***H***), 7.69 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.37—7.23 (3H, m, **9**, **11** and **12**), 7.17 (1H, t, *J* 8.0 Hz, **10**), 6.89 (1H, s, **2**), 5.53 (1H, br. s, **3**), 3.96 (1H, dd, *J* 12.0, 3.0, Hz, **5**), 3.77 (3H, s, N_1**Me**), 3.69—3.55 (3H, m, **17a**, **17b** and **6a**) 3.51—3.38 (2H, m, **6b** and **15**), 3.17 (1H, s, **3**-*O***H**), 2.46 (3H, s, *Ts***Me**), 2.37—2.28 (1H, m, **16**) 2.20 (3H, s, **18**), 1.91 (1H, dd, *J* 14.0, 4.5 Hz, **14a**), 1.49 (1H, td, *J* 14.0, 3.5 Hz, **14b**);

δ_C (100 MHz, $CDCl_3$) 176.8 (**C19**), 171.8 (**C21**), 144.2 (*para*-**Ts**), 137.3 (**C13**), 137.2 (*ipso*-**Ts**), 130.1 (*meta*-**Ts**), 129.2 (**C8**), 127.5 (**C2**), 126.6 (*ortho*-**Ts**), 122.0 (**C11**), 119.4 (**C10**), 119.2

(**C12**), 111.2 (**C9**), 109.4 (**C7**), 96.6 (**C20**), 67.1 (**C17**), 54.3 (**C5**), 32.7 (N_1**Me**), 32.5 (**C6**), 31.3 (**C16**), 22.1 (**C15**), 21.6 (*Ts***Me**), 18.2 (**C18**).

Pentacyclic lactone (85)



119 **85**

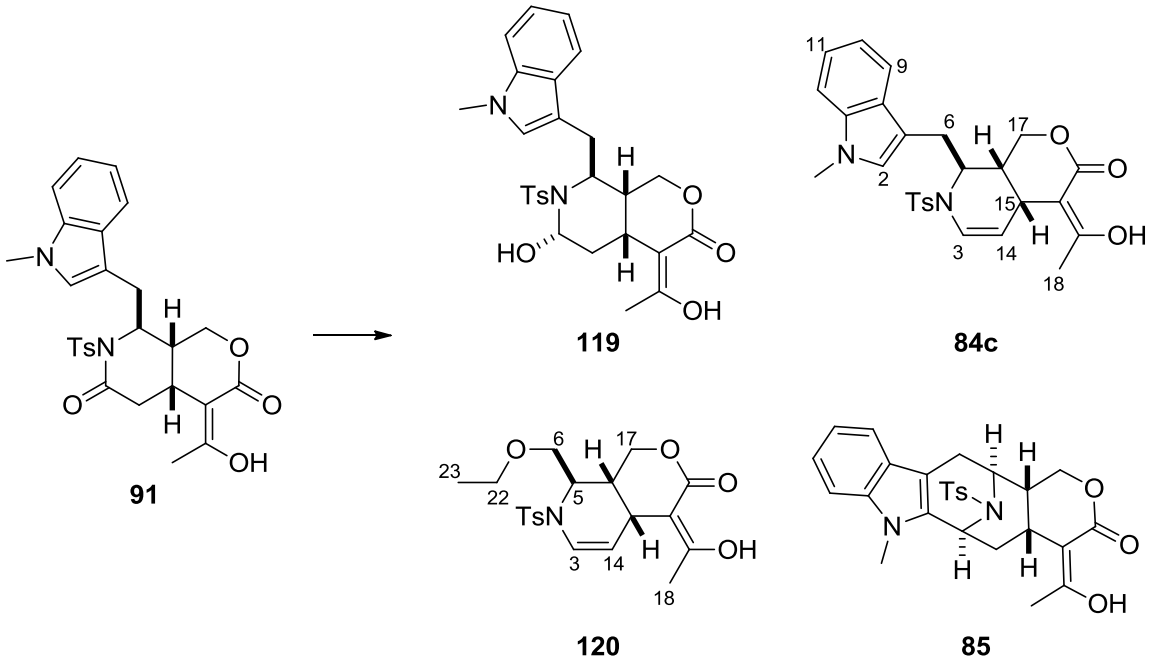
To a solution of aminol **119** (20 mg, 0.049 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added TFA (1 drop) and the solution stirred at –78°C for 2 h. Saturated aqueous $NaHCO_3$ (2 mL) was added, and the aqueous phase extracted with EtOAc (3×5 mL) and CH_2Cl_2 (2×5 mL). The organic phases were washed with brine, combined, dried over $MgSO_4$, and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *pentacyclic lactone* ***85*** (21.9 mg, 91%) as an amorphous solid; R_f 0.60 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3049, 2924, 2854, 1634, 1610, 1468 cm^{-1}; *m/z* (CI) 493 $[M+H]^+$ (Found $[M+H]^+$, 493.1779. $C_{27}H_{28}N_2O_5S$ requires $[M+H]^+$, 493.1797);

δ_H (400 MHz, $CDCl_3$) 14.04 (1H, s, **19-*O*H**), 7.36 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28—7.15 (3H, m, **9**, **11** and **12**), 7.04 (1H, t, *J* 7.0 Hz, **10**), 6.81 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.30 (1H, br. s, **3**), 4.70 (1H, t, *J* 12.0 Hz, **17a**), 4.41 (1H, ddd, *J* 12.0, 4.5, 1.0 Hz, **17b**), 4.32 (1H, br. d, *J* 7.5, **5**), 3.68 (3H, s, N_1**Me**), 2.94 (1H, dd, *J* 16.5, 8.0 Hz, **6a**), 2.75 (1H, dt, *J* 12.5 2.5 Hz, **15**), 2.50 (1H, d, *J* 16.5 Hz, **6b**), 2.26—2.15 (2H, m, **14a** and **16**), 2.03 (3H, s, *Ts***Me**), 1.74 (1H, ddd, *J* 14.0, 4.5, 3.0 Hz, **14b**), 1.65 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 176.8 (**C19**), 172.0 (**C21**), 143.7 (*para*-**Ts**), 136.9 (**C13**), 135.9 (*ipso*-**Ts**), 131.4 (**C2**), 128.9 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.0 (**C8**) 121.9 (**C11**), 119.4 (**C10**), 118.0 (**C12**), 109.0 (**C9**), 107.2 (**C7**), 95.7 (**C20**), 67.5 (**C17**), 49.3 (**C3**), 48.1 (**C5**), 39.7

(**C16**), 32.7 (**C14**), 29.3 (*N*$_1$**Me**), 26.1 (**C15**), 25.3 (**C6**), 21.1 (*Ts***Me**), 18.1 (**C18**). Data is in accordance with that previously reported.[57]

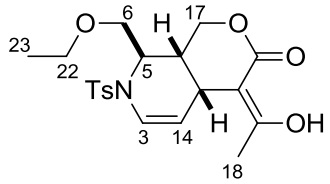
(4a*R,8*R**,8a*R**,*Z*)-8-(Ethoxymethyl)-4-(1-hydroxyethylidene)-7-tosyl-4,4a,8,8a-tetrahydro-1*H*-pyrano[3,4-*c*]pyridin-3(7*H*)-one (120)** and **(4a*R**,8*S**,8a*R**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyl-4,4a,8,8a-tetrahydro-1*H*-pyrano[3,4-*c*]pyridin-3(7*H*)-one (84c)**



To a solution of lactam–lactone **91** (50.0 mg, 0.098 mmol, 1.0 equiv.) in THF (5 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.12 mL, 0.12 mmol, 1.2 equiv.) and the solution stirred at –78°C for 2 h. The reaction mixture was quenched with wet EtOAc (1 mL) before trifluoroacetic acid (0.08 mL, 0.10 mmol, 1.0 equiv.) was added and the reaction mixture was allowed to warm slowly from –78 °C to rt over 30 min. EtOAc (30 mL) and saturated aqueous Rochelle salt (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the aqueous phase extracted with EtOAc (3×50 mL) and CH_2Cl_2 (2×50 mL). The organic phases were washed with brine, combined, dried over $MgSO_4$, and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) gave *(4aR*,6R*,8S*,8aR*,Z)-6-Hydroxy-4-(1-hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosylhexahydro-1H-pyrano[3,4-c]pyridin-3(4H)-one **119*** (16.3 mg,

33%), *(4aR*,8S*,8aR*,Z)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyl-4,4a,8,8a-tetrahydro-1H-pyrano[3,4-c]pyridin-3(7H)-one* ***84c*** (8.86 mg, 19%), *pentacyclic lactone* ***85*** (8.40 mg, 17%) and *(4aR*,8R*,8aR*,Z)-8-(Ethoxymethyl)-4-(1-hydroxyethylidene)-7-tosyl-4,4a,8,8a-tetrahydro-1H-pyrano[3,4-c]pyridin-3(7H)-one* ***120*** (4.48 mg, 11%).

(4a*R,8*R**,8a*R**,*Z*)-8-(Ethoxymethyl)-4-(1-hydroxyethylidene)-7-tosyl-4,4a,8,8a-tetrahydro-1*H*-pyrano[3,4-*c*]pyridin-3(7*H*)-one (120)**



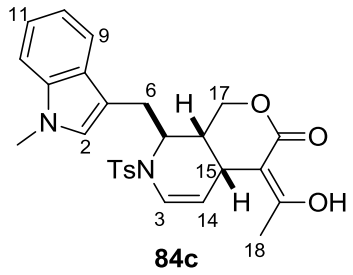
120

R_f 0.50 (50% EtOAc–hexane). FTIR (film) υ_{max}: 3055, 1693, 1598, 1448, cm^{-1}; *m/z* (CI) 408 $[M+H]^+$ (Found $[M+H]^+$, 408.1465. $C_{20}H_{25}NO_6S$ requires $[M+H]^+$, 408.1797);

δ_H (400 MHz, $CDCl_3$) 14.01 (1H, s, **19**-O***H***), 7.67 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.34 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 6.81 (1H, dd, *J* 8.5, 1.5 Hz, **3**), 4.62 (1H, dt, *J* 8.5, 1.5 Hz, **14**), 3.86 (1H, ddd, *J* 10.0, 5.0, 1.5 Hz, **5**), 3.68 (1H, dd, *J* 10.0, 5.0 Hz, **22a**), 3.71—3.44 (3H, m, **6a**, **6b** and **22b**), 3.30—3.21 (2H, m, **15** and **17a**), 3.12 (1H, t, *J* 12.0 Hz, **17b**), 2.56—2.48 (1H, m, **16**), 2.45 (3H, s, *Ts***Me**), 2.10 (3H, s, **18**), 1.19 (3H, t, *J* 7.0 Hz, **23**);

δ_C (100 MHz, $CDCl_3$) 178.2 (**C19**), 172.2 (**C21**), 144.8 (*para*-**Ts**), 135.6 (*ipso*-**Ts**), 130.2 (*meta*-**Ts**), 126.8 (*ortho*-**Ts**), 122.5 (**C3**), 106.5 (**C14**), 95.2 (**C20**), 69.4 (**C22**), 66.9 (**C6**), 66.4 (**C17**), 52.3 (**C5**), 28.6 (**C16**), 26.6 (**C15**), 21.7 (*Ts***Me**), 18.7 (**C18**), 15.1 (**C23**).

(4a*R,8*S**,8a*R**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyl-4,4a,8,8a-tetrahydro-1*H*-pyrano[3,4-*c*]pyridin-3(7*H*)-one (84c)**



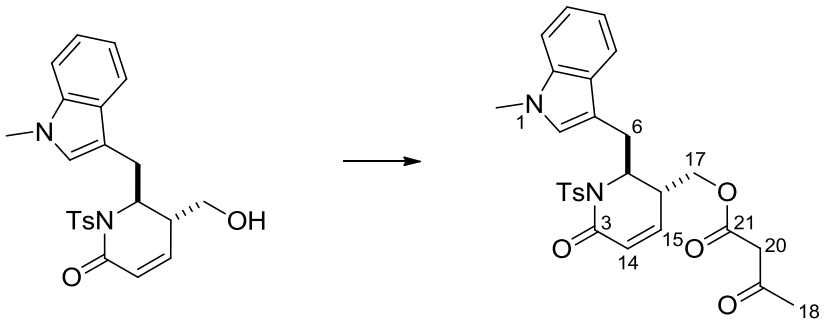
84c

R_f 0.40 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3055, 2931, 1691, 1598, 1447, cm^{-1}; *m/z* (ES) 493 $[M+H]^+$ (Found $[M+H]^+$, 493.1799. $C_{27}H_{28}N_2O_5S$ requires $[M+H]^+$, 493.1797);

δ_H (400 MHz, $CDCl_3$) 14.02 (1H, s, **19**-*O***H**), 7.84 (1H, d, *J* 8.0 Hz, **9**), 7.72 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.37—7.20 (5H, m, **10, 11**, **12** and *meta*-**Ts**), 6.88 (1H, s, **2**), 6.77 (1H, dd, *J* 8.5, 1.5 Hz, **14**), 4.69 (1H, dt, *J* 8.5, 1.5 Hz, **3**), 4.01 (1H, br. d, *J* 10.5 Hz, **5**), 3.77 (3H, s, N_1**Me**), 3.45—3.37 (2H, m, **6a** and **15**), 3.17—2.97 (3H, m, **6b**, **17a** and **17b**), 2.42 (3H, s, *Ts***Me**), 2.16 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 178.1 (**C19**), 172.3 (**C21**), 144.6 (*para*-**Ts**), 137.2 (**C13**), 136.1 (*ipso*-**Ts**), 130.2 (*meta*-**Ts**), 127.6 (**C2**), 126.7 (*ortho*-**Ts**), 122.5 (**C3**), 122.1 (**C11**), 119.5 (**C10**), 119.0 (**C9**), 109.6 (**C12**), 109.1 (**C7**), 105.9 (**C14**), 95.4 (**C20**), 66.7 (**C17**), 53.9 (**C5**), 32.8 (N_1**Me**), 29.8 (**C6**), 29.4 (**C16**), 26.4 (**C15**), 21.7 (*Ts***Me**), 18.8 (**C18**).

((2*S,3*R**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate (113)**



90 **113**

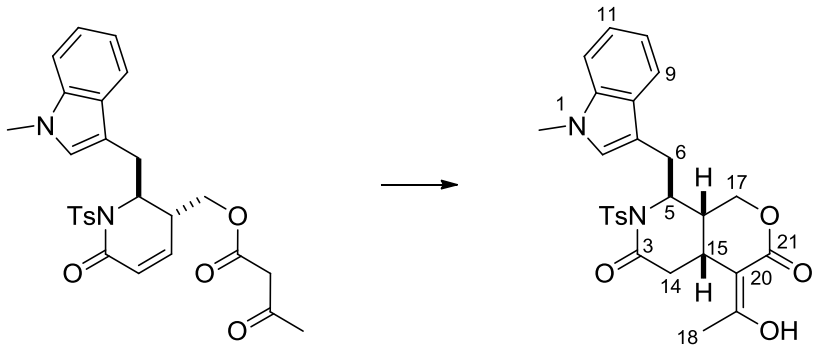
A solution of alcohol **90** (3.53 g, 8.33 mmol, 1.0 equiv.) and 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one **115** (1.66 mL, 12.49 mmol, 1.5 equiv.) in toluene (15 mL) was heated to 150°C in the microwave for 20 min in a sealed tube. On cooling to rt, saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer extracted with EtOAc (3×50 mL) and CH_2Cl_2 (3×50 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (20→50% EtOAc–hexane) yielded *((2S*,3R*)-2-((1-methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate* ***113*** (4.11 g, 97%) as a colourless, amorphous solid; R_f 0.63 (66% EtOAc–hexane); FTIR (film) υ_{max}: 2923, 1747, 1717, 1690, 1596, 1351 cm^{-1}; (New C=O, no OH); *m/z* (CI) 509 $[M+H]^+$ (Found $[M+H]^+$, 509.1735. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$, 509.1746). Found C, 63.80; H, 5.63; N, 5.37%. $C_{27}H_{28}N_2O_6S$ requires C, 63.76; H, 5.55; N, 5.51%;

δ_H (400 MHz, $CDCl_3$) 8.03 (2 H, app. d, *J* 8.5 Hz, *meta*-**Ts***)*, 7.79 (1 H, app. d, *J* 8.0 Hz, **12**), 7.38—7.23 (4H, m, *ortho*-**Ts**, **9**, and **11**), 7.17 (1H, t, *J* 7.5 Hz, **10**), 6.88 (1H, s, **2**), 6.49 (1H, ddd, *J* 10.0, 6.0, 1.5 Hz, **15**), 5.98 (1H, d, *J* 10.0 Hz, **14**), 5.14 (1H, dd, *J* 11.5, 4.0 Hz, **5**), 4.08 (1H, dd, *J* 11.5, 4.5 Hz, **17a**), 3.84 (1H, dd, *J* 11.5, 8.5 Hz, **17b**), 3.76 (3H, s, N_1**Me**), 3.36 (1H, dd, *J* 14.0, 4.0 Hz, **6a**), 3.23—3.03 (3H, m, **20a**, **20b** and **6b**), 2.89—2.82 (1H, m, **16**), 2.43 (3H, s, *Ts***Me**), 2.10 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 200.3 (**C19**), 166.6 (**C21**), 161.2 (**C3**), 145.0 (*para*-**Ts**), 140.0 (**C15**), 137.2 (**C13**), 136.2 (*ipso*-**Ts**), 129.4 (*meta*-**Ts**), 129.2 (*ortho*-**Ts**), 127.9 (**C2**), 127.5 (**C8**), 126.7

(**C14**), 122.0 (**C11**), 119.5 (**C10**), 119.1 (**C12**), 109.5 (**C9**), 109.3 (**C7**), 63.6 (**C17**), 56.9 (**C5**), 49.2 (**C20**), 36.6 (**C16**), 32.9 (*N*$_1$**Me**), 30.3 (**C6**), 30.1 (**C18**), 21.7 (*Ts***Me**).

(4a*R,8*S**,8a*R**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (91)**



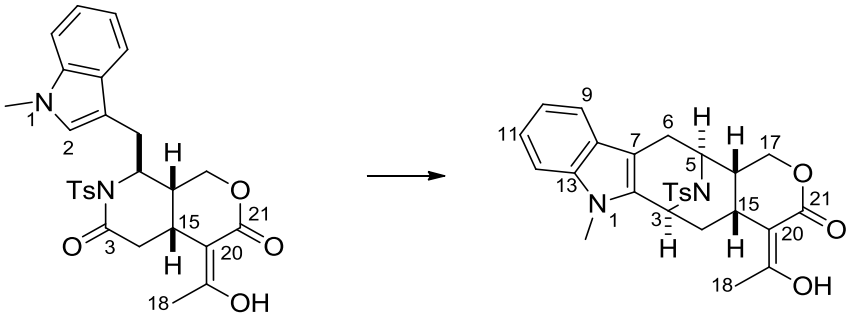
113 **91**

To a solution of malonate ester **113** (3.48 g, 6.85 mmol, 1.0 equiv.) in THF (23 mL) at rt was added DBU (2.0 mL, 13.7 mmol, 2.0 equiv.). The reaction mixture was allowed to stir at rt for 12 h, saturated aqueous NH_4Cl (2 mL) was added and the aqueous layer extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(4aR*,8S*,8aR*,Z)-4-(1-hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione* ***91*** (3.34 g, 93%) as an amorphous solid; R_f 0.24 (33% EtOAc–hexane); FTIR (film) υ_{max}: 3058, 2923, 2855, 2252, 1690, 1636, 1612, 1597 cm^{-1}; *m/z* (CI) 509 $[M+H]^+$ (Found $[M+H]^+$, 509.1741. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$, 509.1746);

δ_H (400 MHz, $CDCl_3$) 13.72 (1H, s, **19**-O***H***), 7.94 (2H, d, *J* 8.5 Hz, *meta*-**Ts**), 7.72 (1H, d, *J* 8.0 Hz, **9**), 7.38—7.30 (3H, m, *ortho*-**Ts** and **12**), 7.27 (1H, t, *J* 8.0 Hz, **11**), 7.17 (1H, t, *J* 8.0 Hz, **10**), 6.94 (1H, s, **2**), 4.78 (1H, ddd, *J* 8.0, 3.0, 2.0 Hz, **5**), 4.21 (1H, ddd, *J* 11.5, 4.5 1.5 Hz, **17a**), 4.03 (1H, t, *J* 12.0 Hz, **17b**), 3.78 (3H, s, N_1**Me**), 3.54 (1H, dd, *J* 15.0, 4.0 Hz, **6a**), 3.21 (1H, dd, 15.0, 10.0 Hz, **6b**), 3.16—3.07 (1H, m, **15**), 2.61—2.46 (2H, m, **14a** and **16**), 2.45 (3H, s, *Ts***Me**), 2.17 (1H, dd, *J* 19.0, 10.5 Hz, **14b**), 1.74 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 177.3 (**C19**), 171.0 (**C21**), 167.4 (**C3**), 145.4 (*para*-**Ts**), 137.0 (**C13**), 135.7 (*ipso*-**Ts**), 129.5 (*meta*-**Ts**), 129.1 (*ortho*-**Ts**), 128.2 (**C2**), 127.7 (**C8**), 122.3 (**C11**), 119.8 (**C10**), 118.6 (**C12**), 109.7 (**C9**), 108.3 (**C7**), 96.2 (**C20**), 66.9 (**C17**), 57.3 (**C5**), 36.6 (**C14**), 32.9 (N_1**Me**), 31.5 (**C6**), 26.0 (**C15**), 21.7 (*Ts***Me**), 18.0 (**C18**).

Pentacyclic lactone (85)

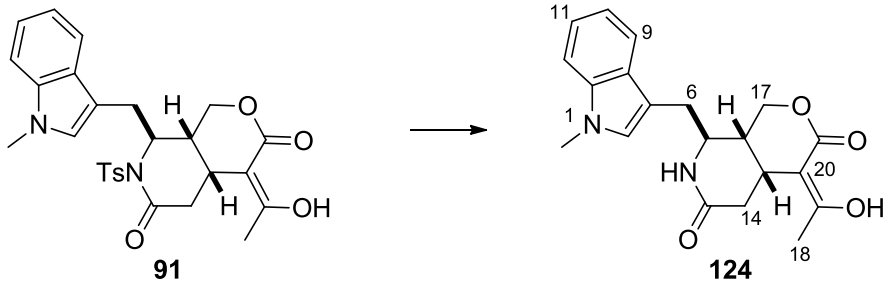


91 **85**

To a solution of lactam–lactone **91** (0.87 g, 1.71 mmol, 1.0 equiv.) in THF (5.7 mL) at –78°C was added DIBAL (1.0 M in toluene; 3.4 mL, 3.40 mmol, 2.0 equiv.) and the solution stirred at –78°C for 3 h. The reaction was quenched with wet Et_2O (2 mL) and allowed to warm to rt, then trifluoromethanesulfonic acid (0.16 mL, 1.71 mmol, 1.0 equiv.) was added and the solution allowed to stir for 30 minutes. Saturated aqueous Rochelle salt (10 mL) and EtOAc (30 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the aqueous phase extracted with EtOAc (3×50 mL) and CH_2Cl_2 (2×50 mL). The organic phases were washed with brine, combined, dried over $MgSO_4$, and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *pentacyclic lactone* ***85*** (0.77 g, 91%) as an amorphous solid. Data is in accordance with that previously reported (Page **158**).[57]

3.1.7 *Procedures from attempted synthesis of functionalised pentacyclic lactone* (Sections **2.2.3**-**2.2.6**)

(4a*R,8*S**,8a*R**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (124)**

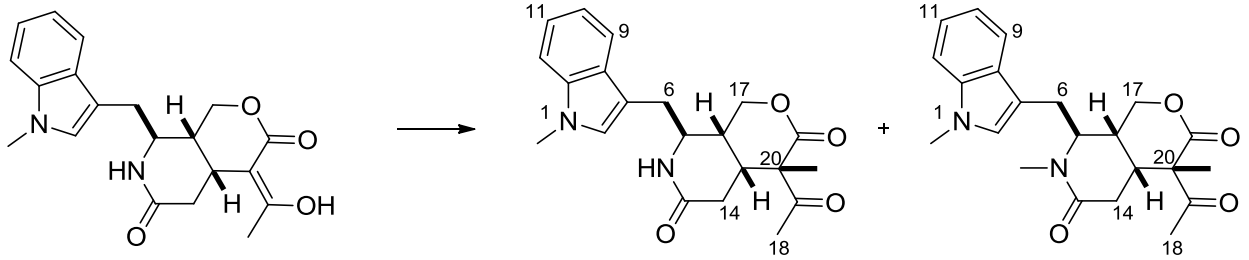


To a solution of naphthalene (0.91 g, 7.01 mmol, 8.0 equiv.) in THF (24 mL) at rt was added sodium (163 mg, 7.01 mmol, 8.0 equiv.) and the reaction mixture stirred at rt for 2 h. The resulting dark green\blue solution was cooled to –78°C and added to a solution of lactam–lactone **91** (450 mg, 0.890 mmol, 1.0 equiv.) in THF (5 mL) at –78°C. The reaction mixture was stirred at –78°C for 2 h. Saturated aqueous NH_4Cl (12 mL) was added and the solution allowed to warm slowly from –78°C to rt. The aqueous layer was then extracted with EtOAc (3×50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (100% EtOAc) yielded *(4aR*,8S*,8aR*,Z)-4-(1-hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)tetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione **124*** (312 mg, 99%) as a pale yellow oil; R_f 0.10 (100% EtOAc); FTIR (film) υ_{max}: 3212, 2917, 2247, 1635, 1475, 1423, 1240, 1328 cm^{-1}; m/z (ES) 355 $[M+H]^+$ (Found $[M+H]^+$, 355.1642. $C_{20}H_{22}N_2O_4$ requires $[M+H]^+$, 355.1658);

δ_H (400 MHz, $CDCl_3$) 13.84 (1H, s, **21**), 7.51 (1H, d, *J* 8.0 Hz, **9**), 7.33 (1H, d, *J* 8.0 Hz, **12**), 7.26 (1H, t, *J* 8.0 Hz, **11**), 7.13 (1H, t, *J* 8.0 Hz, **10**), 6.93 (1H, s, **2**), 6.35 (1H, s, N_4**H**), 4.38 (1H, t, *J* 12.0 Hz, **17a**), 4.22 (1H, ddd, *J* 12.0, 5.0, 1.5 Hz, **17b**), 3.78 (3H, s, N_1**Me**), 3.56—3.48 (1H, m, **5**), 3.12—3.00 (3H, m, **6a**, **6b** and **15**), 2.54 (1H, dd, *J* 18.0, 6.0 Hz, **14a**), 2.47—2.40 (1H, m, **16**), 2.24 (1H, dd, *J* 18.0, 12.0 Hz, **14b**), 1.99 (3H, s, **18**);

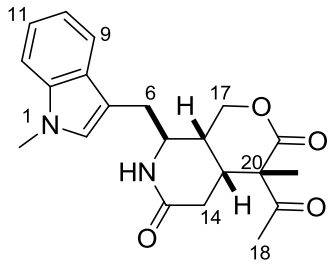
δ_C (100 MHz, $CDCl_3$) 176.9 (**C19**), 171.4 (**C21**), 169.5 (**C3**), 137.2 (**C13**), 127.9 (**C2**), 127.3 (**C8**), 122.3 (**C11**), 119.5 (**C10**), 118.3 (**C12**), 109.7 (**C9**), 108.6 (**C7**), 96.4 (**C20**), 67.1 (**C17**), 52.4 (**C5**), 34.1 (**C6**), 33.5 (**C16**), 32.8 (N_1**Me**), 26.8 (**C15**), 18.2 (**C18**).

(4*S,4a*R**,8*S**,8a*R**)-4-Acetyl-4-methyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (126a)** and **(4*S**,4a*R**,8*S**,8a*R**)-4-acetyl-4,7-dimethyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (126b)**



To a solution of deprotected N_4H lactam **124** (31.0 mg, 0.061 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added KHMDS (0.5 M in toluene; 0.15 mL, 0.073 mmol, 1.2 equiv.) and the solution stirred at –78°C for 1 h. Iodomethane (0.5 mL, 0.067 mmol, 1.1 equiv.) was added and the solution allowed to warm slowly from –78°C to rt overnight. The reaction was quenched with wet Et_2O (2 mL), 10% aqueous citric acid (5 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL) and EtOAc (3×30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (25→50% EtOAc–hexane) yielded *(4S*,4aR*,8S*,8aR*)-4-acetyl-4-methyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione* ***126a*** and *(4S*,4aR*,8S*,8aR*)-4-acetyl-4,7-dimethyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione* ***126b*** (28.8 mg, 93%) as amorphous solids;

(4*S,4a*R**,8*S**,8a*R**)-4-Acetyl-4-methyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (126a)**



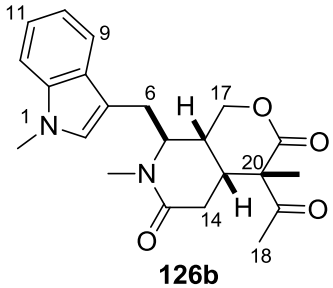
126a

R_f 0.65 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3284, 2918, 2249, 1736, 1706, 1659, 1474 cm^{-1}; *m/z* (ES) 369 $[M+H]^+$ (Found $[M+H]^+$, 369.1800. $C_{21}H_{24}N_2O_4$ requires $[M+H]^+$, 369.1814);

δ_H (400 MHz, $CDCl_3$) 7.51 (1H, d, *J* 8.0 Hz, **9**), 7.34 (1H, d, *J* 8.0 Hz, **12**), 7.27 (1H, t, *J* 8.0 Hz, **11**), 7.15 (1H, t, *J* 8.0 Hz, **10**), 6.93 (1H, s, **2**), 6.10 (1H, s, N_4**H**), 4.41 (1H, dd, *J* 12.0, 6.5 Hz, **17a**), 4.30 (1H, t, *J* 12.0 Hz, **17b**), 3.77 (3H, s, N_1**Me**), 3.76—3.70 (1H, m, **5**), 3.03 (1H, dd, *J* 14.5, 5.5 Hz, **6a**), 2.87 (1H, dd, *J* 14.5, 9.0 Hz, **6b**), 2.66 (1H, dd, *J* 15.5, 11.5 Hz, **14a**), 2.60—2.34 (3H, m, **16**, **15** and **14b**), 2.31 (3H, s, **22**), 1.54 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 205.9 (**C19**), 171.1 (**C21**), 170.3 (**C3**), 137.3 (**C13**), 127.7 (**C2**), 127.3 (**C8**), 122.4 (**C11**), 119.6 (**C10**), 118.3 (**C12**), 109.7 (**C9**), 108.0 (**C7**), 67.7 (**C17**), 58.0 (**C20**), 51.8 (**C5**), 36.0 (**C15**), 33.9 (**C16**), 32.8 (N_1**Me**), 31.0 (**C6**), 30.9 (**C14**), 28.9 (**C22**), 23.1 (**C18**).

(4*S,4a*R**,8*S**,8a*R**)-4-Acetyl-4,7-dimethyl-8-((1-methylindol-3-yl)methyl)tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (126b)**



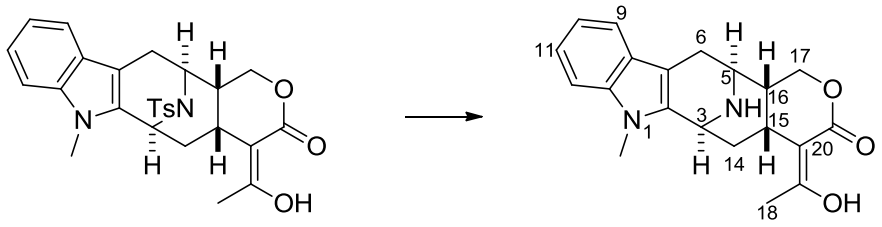
126b

R_f 0.65 (50% EtOAc–hexane). FTIR (film) υ_{max}: 2922, 1732, 1707, 1659, 1468 cm^{-1}; *m/z* (ES) 383 $[M+H]^+$ (Found $[M+H]^+$, 383.1958. $C_{22}H_{26}N_2O_4$ requires $[M+H]^+$, 383.1971).

δ_H (400 MHz, $CDCl_3$) 7.53 (1H, d, *J* 8.0 Hz, **9**), 7.36 (1H, d, *J* 8.0 Hz, **12**), 7.29 (1H, t, *J* 8.0 Hz, **11**), 7.16 (1H, t, *J* 8.0 Hz, **10**), 6.88 (1H, s, **2**), 4.35 (1H, t, *J* 12.0 Hz, **17a**), 4.16 (1H, dd, *J* 12.0, 6.5 Hz, **17b**), 3.79 (3H, s, N_1**Me**), 3.43 (1H, dd, *J* 10.5, 4.0 Hz, **5**), 3.37 (1H, dd, *J* 14.5, 4.0 Hz, **6a**), 3.14 (3H, s, N_4**Me**), 2.86 (1H, dd, *J* 14.5, 10.5 Hz, **6b**), 2.61—2.54 (2H, m, **15** and **16**), 2.50 (1H, dd, *J* 17.5, 6.0 Hz, **14a**), 2.33 (3H, s, **22**), 2.29 (1H, dd, *J* 17.5, 12.0 Hz, **14b**), 1.41 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 206.2 (**C19**), 171.2 (**C21**), 166.5 (**C3**), 137.2 (**C13**), 127.2 (**C2**), 122.4 (**C11**), 119.5 (**C10**), 118.2 (**C12**), 109.8 (**C9**), 109.0 (**C7**), 68.1 (**C17**), 60.0 (**C5**), 57.6 (**C20**), 34.6 (**C16**), 34.6 (N_4**Me**), 32.8 (N_1**Me**), 31.3 (**C14**), 30.3 (**C22**), 28.8 (**C15**), 28.3 (**C14**), 24.5 (**C18**).

N_4-Demethyl pentacyclic lactone (85a)



85 **85a**

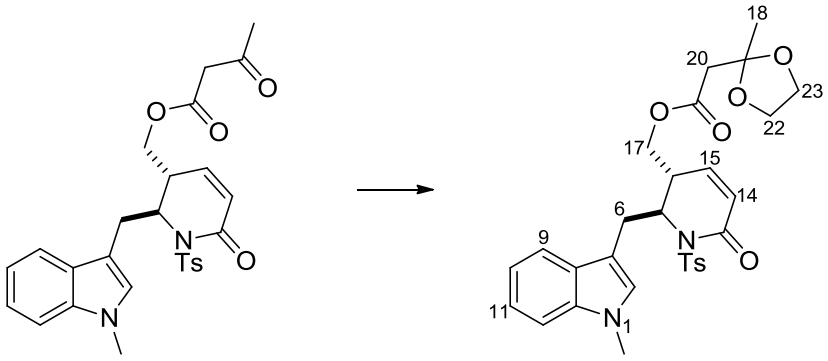
To a solution of naphthalene (157 mg, 1.23 mmol, 8.0 equiv.) in THF (2 mL) at rt was added sodium (28.2 mg, 1.23 mmol, 8.0 equiv.) and the reaction mixture stirred at rt for 2 h. The resulting dark green\blue solution was cooled to –78°C and added to a solution of pentacyclic lactone **85** (75.4 mg, 0.153 mmol, 1.0 equiv.) in THF (1 mL) at –78°C. The reaction mixture was stirred at –78°C for 2 h. Saturated aqueous NH_4Cl (12 mL) was added and the solution allowed to warm slowly from –78°C to rt. The aqueous layer was then extracted with EtOAc (3×50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50→100% EtOAc–hexane) yielded *N_4-demethyl pentacyclic lactam* ***85a*** (47.6 mg, 92%) as a pale yellow gum; R_f 0.10 (100%

EtOAc); FTIR (film) υ_{max}: 2928, 2247, 1729, 1635, 1469, 1420 cm^{-1}; m/z (CI) 356 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 356.1969. $C_{20}H_{22}N_2O_3$ requires $[M+NH_4]^+$, 356.1974).

δ_H (400 MHz, $CDCl_3$) 7.47 (1H, dd, *J* 12.5, 8.0 Hz, Ar**H**), 7.31 (1H, dd, *J* 8.0, 5.5 Hz, Ar**H**), 7.28—7.20 (1H, m, Ar**H**), 7.13 (1H, q, *J* 8.0 Hz, Ar**H**), 6.12 (0.6H, t, *J* 3.0 Hz, $\mathbf{3_a}$), 5.18 (0.4H, t, *J* 3.0 Hz, $\mathbf{3_b}$), 5.06 (0.4H, d, *J* 7.5 Hz, $\mathbf{5_b}$), 4.55—4.26 (2H, m, **17a** and **17b**), 4.18 (0.6H, d, *J* 7.0 Hz, $\mathbf{5_a}$), 3.71 (1.2H, s, $N_1\mathbf{Me_b}$), 3.70 (1.8H, s, $N_1\mathbf{Me_a}$), 3.40 (1H, ddd, *J* 17.0, 10.0, 7.5 Hz, **6a**), 2.86 (0.6H, d, *J* 16.0 Hz, $\mathbf{6b_a}$), 2.73 (0.4H, d, *J* 16.0 Hz, $\mathbf{6b_b}$), 2.57 (1H, ddd, *J* 18.0, 11.5, 6.5 Hz, $\mathbf{14a_a}$), 2.37—2.21 (3H, m, $\mathbf{14a_a}$ and **14b**), 2.20 (1.2H, s, *Ts*$\mathbf{Me_b}$), 2.11 (1.8H, s, *Ts*$\mathbf{Me_a}$), 2.08—1.91 (1.2H, m, $\mathbf{18_a}$), 1.74—1.62 (1.8H, m, $\mathbf{18_b}$);

δ_C (100 MHz, $CDCl_3$) 169.6 (**C19**), 169.4 (**C19**), 168.9 (**C21**), 168.4 (**C21**), 137.2 (**C13**), 137.1 (**C13**), 133.2 **(C2)**, 131.8 (**C2**), 125.8 (**C8**), 125.8 (**C8**), 122.2 (**C11**), 121.9 (**C11**), 119.8 (**C10**), 119.6 (**C10**), 118.4 (**C12**), 117.9 (**C12**), 109.3 (**C9**), 109.2 (**C9**), 108.8 (**C7**), 106.8 (**C7**), 68.4 (**C17**), 68.0 (**C17**), 50.1 (**C5**), 49.0 (**C3**), 43.8 (**C5**), 43.0 (**C3**), 38.2 (**C16**), 37.7 (**C16**), 34.3 (**C15**), 34.2 (**C15**), 31.7 (**C14**), 30.5 (**C14**), 29.4 (N_1**Me**), 29.4 (N_1**Me**), 27.5 (**C6**), 26.0 (**C6**), 24.5, 21.6 (**C18**), 21.1 (**C18**).

((2*S,3*R**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate (130)**



113 **130**

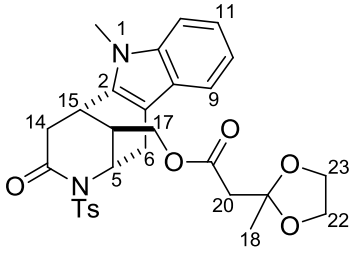
To a stirred solution of β-ketoester **113** (48.0 mg, 0.094 mmol, 1.0 equiv.) and 1,2-bis(trimethylsiloxy)ethane (0.05 mL, 0.190 mmol, 2.0 equiv.) in CH_2Cl_2 (5 mL) at –78°C was added trimethylsilyl trifluoromethanesulfonate (1 drop) and the reaction mixture was stirred

at –78°C for 3 h. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50% EtOAc–hexane) yielded *((2S*,3R*)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate* ***130*** (48.3 mg, 93%) as an amorphous solid; R_f 0.25 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3059, 2987, 1738. 1689. 1598, 1473 cm^{-1}; *m/z* (ES) 575 $[M+Na]^+$ (Found $[M+Na]^+$, 575.1804. $C_{29}H_{32}N_2O_7S$ requires $[M+Na]^+$, 575.1828);

δ_H (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.77 (1H, d, *J* 8.0 Hz, **12**), 7.73—7.20 (4H, m, *ortho*-**Ts**, **11** and **9**) 7.16 (1H, td, *J* 7.5, 1.0 Hz, **10**), 6.89 (1H, s, **2**), 6.49 (1H, ddd, *J* 10.0, 6.0, 1.5 Hz, **15**), 5.95 (1H, dd, *J* 10.0, 0.5 Hz, **14**), 5.16 (1H, dd, *J* 11.0, 4.0 Hz, **5**), 4.04—3.71 (10H, m, N_1**Me**, **17a**, **17b**, **22a**, **22b**, **23a** and **23b**), 3.37 (1H, dd, *J* 14.0, 4.0 Hz, **6a**), 3.12 (1H, dd, *J* 14.0, 11.0 Hz, **6b**), 2.84 (1H, dt, *J* 14.0, 5.0 Hz, **16**), 2.45—2.30 (5H, m, *Ts***Me**, **20a** and **20b**), 1.36 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 169.0 (**C21**), 161.2 (**C3**), 144.9 (*para*-**Ts**), 140.3 (**C15**), 137.2 (**C13**), 136.3 (*ipso*-**Ts**), 129.3 (*ortho*-**Ts**), 129.2 (*para*-**Ts**), 127.8 (**C2**), 127.6 (**C8**), 126.6 (**C14**), 122.0 (**C11**), 119.4 (**C10**), 119.2 (**C12**), 109.4 (**C7**), 64.8 (**C22**), 64.7 (**C23**), 63.0 (**C17**), 57.0 (**C5**), 43.5 (**C20**), 36.4 (**C16**), 32.8 (N_1**Me**), 30.4 (**C6**), 24.3 (**C18**), 21.7 (*Ts***Me**).

Tetracyclic indolomorphan lactam (133)



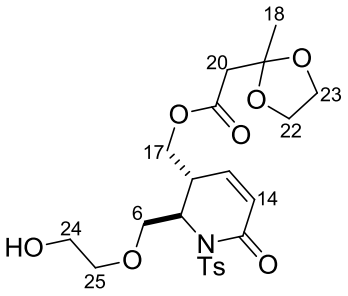
133

R_f 0.15 (50% EtOAc–hexane); 279.0–283.6°C; FTIR (film) υ_{max}: 2989, 1736, 1695, 1613, 1597, 1470 cm^{-1}; *m/z* (CI) 575 $[M+Na]^+$ (Found $[M+Na]^+$, 575.1840. $C_{29}H_{32}N_2O_7S$ requires $[M+Na]^+$, 575.1828).

δ_H (400 MHz, $CDCl_3$) 7.85 (2H, app. d, *J* 8.5 Hz, *ortho*-**Ts**), 7.48 (1H, d, *J* 8.0 Hz, **12**), 7.30—7.20 (4H, m, *meta*-**Ts**, **11** and **9**), 7.12 (1H, td, *J* 8.0, 1.0 Hz, **10**), 5.17 (1H, br. s, **5**), 4.27 (2H, d, *J* 7.5 Hz, **17a** and **17b**), 4.03 (4H, br. s, **22**, **23**), 3.63 (3H, s, N_1**Me**), 3.44 (1H, dd, *J* 17.0, 1.5 Hz, **6a**), 3.36 (1H, t, *J* 4.0 Hz, **15**), 3.19 (1H, dd, *J* 17.0, 4.0 Hz, **6b**), 2.79—2.65 (3H, m, **20a**, **20b** and **16**), 2.70 (1H, dd, *J* 18.5, 5.5 Hz, **14a**), 2.48 (1H, d, *J* 18.5 Hz, **14b**), 2.37 (3H, s, *Ts***Me**), 1.56 (3H, s, **18**);

δ_C (100 MHz, $CDCl_3$) 169.3 (**C21**), 168.1 (**C3**), 144.8 (*para*-**Ts**), 137.6 (**C13**), 136.3 (*ipso*-**Ts**), 136.2 (**C2**), 129.3, (*ortho*-**Ts**) 128.9 (*meta*-**Ts**), 126.6 (**C8**), 121.99 (**C11**), 119.6 (**C10**), 118.5 (**C12**), 109.1 (**C9**), 107.6 (**C19**), 104.0 (**C7**), 64.9 (**22** and **23**), 63.23 (**C17**), 53.6 (**C5**), 44.2 (**C20**), 37.6 (**C16**), 35.8 (**C14**), 30.5 (**C6**) 29.0 (N_1**Me**), 26.6 (**C15**), 24.7 (**C18**), 21.66 (*Ts***Me**).

((2*R,3*R**)-2-(2-Hydroxyethoxy)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate (132)**



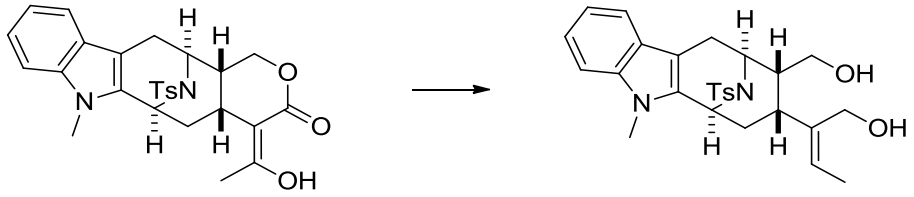
132

R_f 0.35 (50% EtOAc–hexane). FTIR (film/cm^{-1}) υ_{max}: 2983, 2885, 1739, 1691, 1597, 1349, 1168 cm^{-1}; *m/z* (ES) 506 $[M+Na]^+$ (Found $[M+Na]^+$, 506.1265. $C_{22}H_{29}NO_9S$ requires $[M+Na]^+$, 506.1461).

δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.31 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 6.54 (1H, ddd, *J* 10.0, 6.0, 1.5 Hz, **15**), 5.91 (1H, dd, *J* 10.0, 0.5 Hz, **14**), 4.94 (1H, ddt, *J* 9.0, 5.0, 1.0 Hz, **5**), 4.14 (1H, dd, *J* 11.5, 4.5 Hz, **17a**), 4.02—3.98 (4H, br. m, **22** and **23**), 3.92 (1H, dd, *J* 11.5, 8.5 Hz, **17b**), 3.62 (1H, dd, *J* 10.0, 5.0 Hz, **6a**), 3.59—3.44 (3H, m, **6b** and **24**), 3.15––3.07 (1H, m, **16**), 2.67 (2H, s, **20**), 1.60 (1H, s, *O***H**), 1.53 (3H, s, **18**), 1.18 (3H, t, *J* 7.0 Hz, **25**);

δ_C (100 MHz, $CDCl_3$) 169.2 (**C21**), 161.1 (**C3**), 145.0 (*para*-**Ts**), 140.5 (**C15**), 136.0 (*ipso*-**Ts**), 129.3 (*ortho*-**Ts**), 129.2 (*para*-**Ts**), 126.4 (**C14**), 107.4 (**C19**), 70.2 (**C6**), 66.8 (**C24**), 64.8 (**C22** and **C23**), 63.1 (**C17**), 55.3 (**C5**), 43.9 (**C20**), 35.4 (**C16**), 24.5 (**C18**), 21.7 (*Ts***Me**), 15.1 (**C25**).

Allylic diol (135)



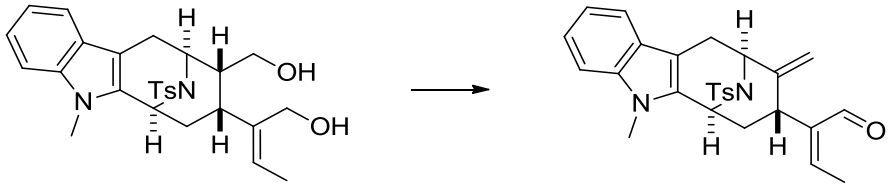
85 **135**

To a solution of pentacyclic lactone **85** (34.0 mg**,** 0.069 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.14 mL, 0.138 mmol, 2.0 equiv.) and the solution stirred under reflux at 70°C for 1 h. Saturated aqueous Rochelle salt (5 mL) and EtOAc (15 mL) were added and the resulting suspension stirred vigorously at rt overnight. The aqueous phase was extracted with EtOAc (3×50 mL) and CH_2Cl_2 (3×20 mL) and the organic phases were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and preparative thin layer chromatography (50% EtOAc–hexane) yielded *allylic diol **135*** (15.2 mg, 46%) as an amorphous solid; R_f 0.10 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3401, 2921, 1469, 1338, 1160 cm^{-1}; *m/z* (ES) 481 $[M+H]^+$ (Found $[M+H]^+$, 481.2092. $C_{27}H_{32}N_2O_4S$ requires $[M+H]^+$, 481.2161).

δ_H 7.32 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28—7.22 (1H, m, **9**), 7.19—7.13 (2H, m, **12** and **11**), 7.01 (1H, t, *J* 7.5 Hz, **10**), 6.77 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.56 (1H, q, *J* 7.0 Hz, **19**), 5.40 (br. t, *J* 3.5 Hz, **3**), 4.59 (1H, d, *J* 8.5 Hz, **5**), 4.09—3.92 (3H, m, **21a**, **21b** and **17a**), 3.70 (1H, dd, *J* 11.0, 5.0, **17b**), 3.67 (3H, s, N_1**Me**), 3.16—3.08 (1H, m, **14a**), 2.84 (1H, dd, *J* 16.5, 8.0 Hz, **6a**), 2.56 (1H, td, *J* 13.5, 4.5 Hz, **14b**), 2.47—2.40 (2H, m, **6b** and *O***H**), 2.02 (3H, s, *Ts***Me**) 1.73—1.63 (2H, m, **15** and *O***H**), 1.48 (3H, d, *J* 7.0 Hz, **18**);

δ_C (100 MHz, $CDCl_3$) δ 143.3 (*para*-**Ts**), 138.9 (**C13**), 136.7 (**C20**), 136.0 (*ipso*-**Ts**), 132.3 (**C2**), 128.8 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.0 (**C8**) 125.8 (**C19**), 121.5 (**C11**), 119.1 (**C10**), 117.9 (**C12**), 108.8 (**C9**), 107.8 (**C7**), 66.7 (**C21**), 60.6 (**C17**), 49.4 (**C5**), 48.2 (**C3**), 47.9 (**C15**), 29.5 (**C14**), 29.0 (N_1**Me**), 24.8 (**C6**), 21.1 (*Ts***Me**), 13.4 (**C18**).

Exomethylene compound (137)



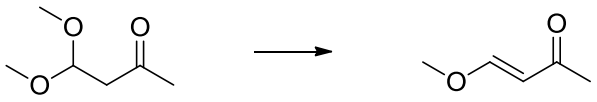
135 **137**

To a solution of oxalyl chloride (1.0 M in CH_2Cl_2; 0.06 ml, 0.059 mmol, 1.4 equiv.) at –78°C was added DMSO (0.01 mL, 0.12 mmol, 2.8 equiv.) and the solutions stirred at –78°C for 15 min. Allylic diol **135** was added (~0.85M in CH_2Cl_2; 0.5 mL, 0.042 mmol, 1.0 equiv.) and the solution allowed to warm from –78°C to –10°C over 2 h. Et_3N (0.1 mL, excess) was added at –10°C and the solution allowed to warm from –10°C to rt over 15 min. Water (2 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50% EtOAc–hexane) yielded *exomethylene aldehyde **137*** (18.8 mg, 97%) as colourless amorphous solid; R_f 0.40 (50% EtOAc–hexane); FTIR (film) υ_{max}: 2921, 1706, 1469, 1338, 1160 cm^{-1}; *m/z* (ES) 481 $[M+H]^+$ (Found $[M+H]^+$, 461.1904. $C_{27}H_{28}N_2O_3S$ requires $[M+H]^+$, 461.1899).

δ_H (500 MHz, $CDCl_3$) 9.89 (1H, br. t, **21**), 7.37 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28—7.23 (2H, m, **9** and **12**), 7.19—7.14 (1H, m, **11**), 7.02 (1H, t, *J* 7.5 Hz, **10**), 6.78 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.72 (1H, q, *J* 7.0 Hz, **19**), 5.38 (br. t, *J* 3.5 Hz, **3**), 4.92 (1H, br. d, *J* 8.5 Hz, **5**), 4.34 (1H, d, *J* 11.0 Hz, **17a**), 4.08 (1H, d, *J* 11.0 Hz, **17b**), 3.68 (3H, s, N_1**Me**), 3.23—3.17 (1H, m, **14a**), 3.08 (1H, dd, *J* 16.5, 8.0 Hz, **6a**), 2.60—2.55 (1H, m, **14b**), 2.50 (1H, d, *J* 16.5 Hz, **6b**), 2.05—2.01 (1H, m, **15**), 1.98 (3H, s, *Ts***Me**), 1.48 (3H, d, *J* 7.0 Hz, **18**);

δ_C (100 MHz, $CDCl_3$) 201.8 (**C21**), 143.7 (*para*-**Ts**), 136.7 (**C13**), 136.3 (*ipso*-**Ts**), 135.4 (**C20**), 132.0 (**C19**), 130.6 (**C2**), 128.7 (*meta*-**Ts**), 126.6 (*ortho*-**Ts**), 125.8 (**C8**), 121.8 (**C11**), 119.3 (**C3**), 117.8 (**C12**), 108.9 (**C9**), 106.9 (**C7**), 57.7 (**C16**), 49.1 (**C5**), 48.7 (**C17**), 48.1 (**C3**), 29.9 (**C15**), 29.2 (**C14**), 29.0 (N_1**Me**), 24.6 (**C6**), 21.1 (*Ts***Me**), 13.7 (**C18**).

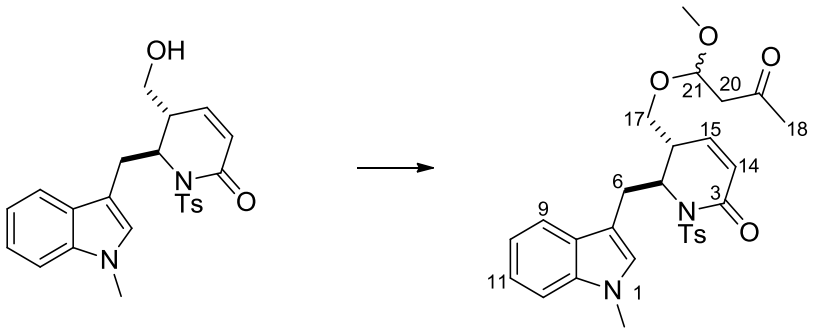
***trans*-4-Methoxy-3-buten-2-one (142)**



188 **142**

To a solution of β-ketodimethylacetal **188** (10.0 mL, 76.2 mmol, 1.0 equiv.) in MeOH (5 mL) at rt was added sodium methoxide (80.0 mg, 1.54 mmol, 0.02 equiv.) and the solution heated to 120°C in the microwave for 1 h. Concentration under reduced pressure and distillation under reduced pressure yielded a 72:28 ratio of *starting material **188*** to *trans-4-methoxy-3-buten-2-one* **142** as colourless oil (9.6 mL) as a colourless oil. Data is in accordance with that previously reported by Brannock *et al*.[125]

(5*R,6*S**)-5-((1-Methoxy-3-oxobutoxy)methyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one (141)**



90 **141**

A solution of lactam alcohol **90** (80.0 mg, 0.185 mmol, 1.0 equiv.) and *trans*-4-methoxy-3-buten-2-one (0.74 mL, 1.85 mmol, 10 equiv.) in CH_2Cl_2 (1 mL) at –78°C was added 1 drop of triflic acid and the solution stirred at –78°C for 2 h. Saturated $NaHCO_3$ (2 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL) and CH_2Cl_2 (3×10 mL). The organics were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and flash column chromatography (40→60% EtOAc–hexane) yielded the *(5R*,6S*)-5-((1-Methoxy-3-oxobutoxy)methyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***141*** as a 1:1 mixture of epimers (94.1 mg, 97%) as a colourless amorphous solid; R_f 0.31 (66%

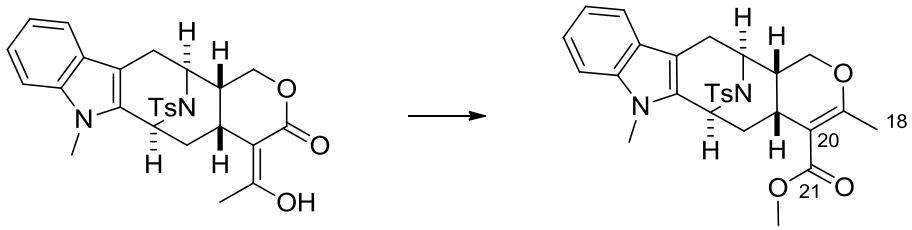
EtOAc–hexane); FTIR (film) υ_{max}: 2921, 1712, 1689, 1472, 1350, 1168 cm^{-1}; *m/z* (ES) 547 $[M+Na]^+$ (Found $[M+Na]^+$, 547.1873. $C_{28}H_{32}N_2O_6S$ requires $[M+Na]^+$, 547.1879);

δ_H (400 MHz, $CDCl_3$) 8.06—7.99 (2H, m, Ar**H**), 7.77—7.68 (2H, m, Ar**H**), 7.35—7.21 (4H, m, Ar**H**), 7.18—7.12 (1H, m, Ar**H**), 6.88 (1H, d, *J* 8.0 Hz, Ar**H**), 6.54—6.47 (1H, m, **15**), 5.93—5.88 (1H, 2×d, *J* 10.0 Hz, **14**), 5.15 (1H, 2×dd, *J* 11.0, 4.0 Hz, **5**), 4.73 (0.5H, t, *J* 5.5 Hz, **21$_a$**), 4.65 (0.5H, t, *J* 5.5 Hz, **21$_b$**), 3.76 and 3.75 (3H, s, N_1**Me**), 3.51 (0.5H, dd, *J* 10.0, 5.5 Hz, **17a$_a$**), 3.42—3.28 (2.5H, m, **17a$_b$, 17b$_a$** and **6a**), 3.28—3.21 (2H, **17b$_b$** and *O***Me$_a$**), 3.16—3.05 (2.5H, **6b** and *O***Me$_b$**), 2.76 (1H, dt, *J* 10.0, 6.0 Hz, **16**), 2.58 (1H, d, *J* 6.0 Hz, **20a**), 2.54 (0.5H, d, *J* 5.5 Hz, **20b$_a$**), 2.46 (0.5H, d, *J* 5.5 Hz, **20b$_b$**), 2.43—2.41 (3H, *Ts***Me**), 2.09 (1.5H, s, **18$_a$**), 1.93 (1.5H, s, **18$_b$**);

δ_H (400 MHz, $CDCl_3$) 205.4 (**C19**), 205.3 (**C19**), 161.6 (**C3**), 161.5 (**C3**), 144.8 (*para*-**Ts**), 141.9 (**C15**), 137.1 (**ArC**), 136.5 (*ipso*-**Ts**), 129.3 (*meta*-**Ts**), 129.2 (*meta*-**Ts**), 127.8 (**ArC**), 125.9 (**C14**), 121.9 (**ArC**), 119.4 (**ArC**), 119.4 (**ArC**), 119.2 (**ArC**), 119.0 (**ArC**), 109.6 (**ArC**), 109.3 (**ArC**), 101.1 (**C21**), 100.7 (**C21**), 66.7 (**C17**), 66.0 (**C17**), 57.2 (**C5**), 56.7 (**C5**), 53.8 (*O***Me**), 53.7 (*O***Me**), 47.2 (**C20**), 47.0 (**C20**), 37.7 (**C16**), 37.5 (**C16**), 32.7 (N_1**Me**), 31.1 (**C18**), 31.0 (**C18**), 30.1 (**C6**), 30.0 (**C6**), 21.7 (*Ts***Me**).

3.1.8 *Procedures from total synthesis of type A macroline-related alkaloid alstonerinal **138*** (Section **2.2.8**)

Type a methyl ester (148)



85 **148**

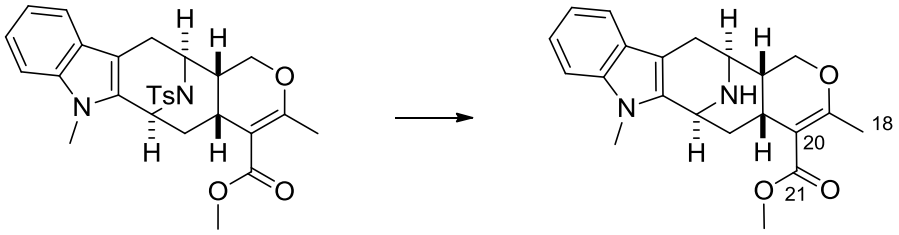
To a solution of the enol **85** (281 mg, 0.571 mmol, 1.0 equiv.) in MeOH:CH_2Cl_2 (1:1) (2 mL) at rt was added CSA (13 mg, 0.057 mmol, 0.1 equiv.) and trimethylorthoformate (1.20 mL, 1.14 mmol, 2.0 equiv.) and the reaction heated under reflux for 72 h. The reaction mixture was then cooled to rt after which saturated $NaHCO_3$ was added dropwise. The aqueous layers were then

extracted with CH_2Cl_2 (3×30 mL), and the combined organics washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and purification *via* preparative thin layer chromatography (50% EtOAc–Hexane) yielded *N_4-(±)-tosylalstonerinal precursor* ***148*** (194 mg, 67%) as an amorphous solid; R_f 0.50 (50% EtOAc–hexane); FTIR (film) υ_{max}: 2935, 1702, 1612, 1469, 1343 cm^{-1}; *m/z* (ES) 507 $[M+H]^+$ (Found $[M+H]^+$, 507.1970. $C_{28}H_{30}N_2O_5S$ requires $[M+H]^+$, 507.1954);

δ_H (400 MHz, $CDCl_3$) 7.41—7.33 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.29—7.22 (1H, m, **12**), 7.22—7.09 (2H, td, *J* 8.0, 1.5 Hz, **9** and **11**), 7.05—6.95 (1H, td, *J* 7.0, 1.0 Hz, **10**), 6.83—6.76 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.26 (1H, br. t, *J* 3.0 Hz, **3**), 4.35—4.13 (3H, m, **5**, **17a** and **17b**), 3.67 (3H, s, *O***Me**), 3.51 (3H, s, N_1**Me**), 2.90 (1H, dd, *J* 16.0, 7.0 Hz, **6a**), 2.72 (1H, br. dt, *J* 12.0, 3.0 Hz, **15**), 2.47 (1H, d, *J* 16.0 Hz, **6b**), 2.19 (3H, s, *Ts***Me**) 2.08—2.16 (1H, m, **16**), 2.01 (3H, s, **18**), 1.92—2.01 (2H, m, **14**);

δ_C (100 MHz, $CDCl_3$) 168.2 (**C19**), 165.5 (**C21**), 143.4 (*para*-**Ts**), 136.9 (**C13**), 136.2 (*ipso*-**Ts**), 132.1 (**C2**), 128.2 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.2 (**C8**), 121.4 (**C11**), 119.0 (**C10**), 117.8 (**C12**), 108.9 (**C9**), 107.0 (**C7**), 104.1 (**C20**), 65.8 (**C17**), 50.9 (*O***Me**), 49.6 (**C5**), 48.6 (**C3**), 38.5 (**C16**), 32.9 (**C14**), 29.2 (N_1**Me**), 25.7 (**C6**), 25.4 (**C15**), 21.1 (*Ts***Me**), 20.6 (**C18**).

N_4H-(±)-Alstonerinal precursor (191)



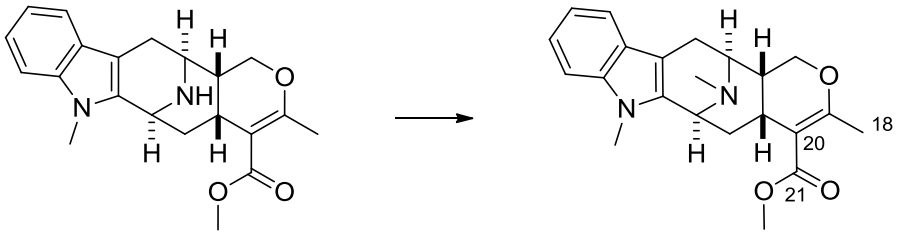
To a solution of naphthalene (51 mg, 0.40 mmol, 8.0 equiv.) in THF (1 mL) at rt was added sodium (9.0 mg, 0.40 mmol, 8.0 equiv.) and the reaction mixture stirred at rt for 1 h. The dark green\blue solution was then cooled to –78°C and (~0.1 M in THF; 1.00 mL, 0.400 mmol, 8.0 equiv.) was added to a solution of N_4-*Ts* protected type A macroline methyl ester **148** (24 mg, 0.05 mmol, 1.0 equiv.) in THF (1 mL). The reaction mixture was stirred at –78°C for 30 min. Saturated aqueous $NaHCO_3$ (2 mL) was added and the solution allowed to

warm slowly from –78°C to rt over 2 hours. The aqueous layer was then extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (100% EtOAc) yielded *N_4H-(±)-alstonerinal precursor* ***191*** (12.9 mg, 92%) as a pale yellow oil; R_f 0.45 (25% MeOH–EtOAc); FTIR (film) υ_{max}: 3329, 2923, 1733, 1704, 1613, 1469, 1239 cm^{-1}; *m/z* (ES) 353 $[M+H]^+$ (Found $[M+H]^+$, 353.1856. $C_{21}H_{24}N_2O_3$ requires $[M+H]^+$, 353.1865);

δ_H (400 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz, **12**), 7.31 (1H, d, *J* 8.0 Hz, **9**), 7.21 (1H, t, *J* 8.0 Hz, **11**), 7.11 (1H, t, *J* 8.0 Hz, **10**), 4.40 (1H, t, *J* 11.5 Hz, **17a**), 4.25 (1H, t, *J* 3.5 Hz, **3**), 4.15 (1H, ddd, *J* 10.5, 4.0, 1.5 Hz, **17b**), 3.64 (3H, s, N_1**Me**), 3.52—3.44 (4H, s, *O***Me** and **5**), 3.26 (1H, dd, *J* 16.5, 7.0 Hz, **6a**), 2.74—2.60 (2H, m, **6b** and **15**), 2.19 (3H, d, *J* 0.5 Hz, **18**), 2.08—2.01 (1H, m, **14a**), 1.96—1.84 (2H, m, **16** and **14b**);

δ_C (100 MHz, $CDCl_3$) 168.5 (**C21**), 165.2 (**C19**), 136.9 (**C13**), 126.8 (**C2**) 121.1 (**C11**), 118.9 (**C10**), 117.9 (**C12**), 108.9 (**C9**), 107.1 (**C7**), 105.1 (**C20**), 67.0 (**C17**), 50.8 (*O***Me**), 48.5 (**C5**), 46.7 (**C3**), 38.0 (**C16**), 32.1 (**C14**), 29.0 (N_1**Me**), 28.8 (**C6**), 26.1 (**C15**), 20.5 (**C18**).

N_4-Methyl-(±)-alstonerinal precursor (150)



191 **150**

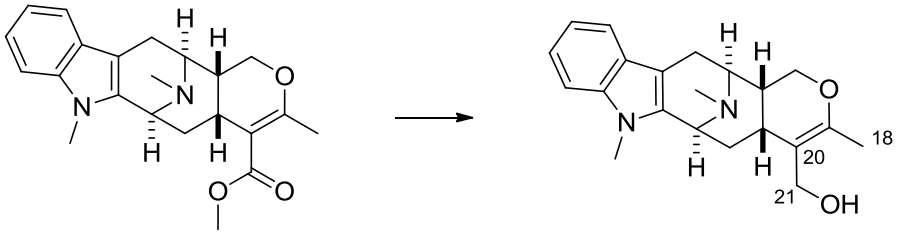
To a stirred solution of secondary *N_4H* amine **191** (12.0 mg, 0.034 mmol, 1.0 equiv.) in THF (0.5 mL) at –78°C was added Hünig's Base (0.02 mL, 0.102 mmol, 3.0 equiv.) and iodomethane (0.002 mL, 0.05 mmol, 1.4 equiv.) and the solution allowed to warm slowly from –78°C to rt overnight. Water (2 mL) was added to the resulting cloudy solution and the aqueous layer extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification *via* preparative thin layer chromatography yielded *N_4-Methyl-(±)-alstonerinal precursor* ***150*** as a pale yellow oil (9.9 mg, 81%); R_f 0.67

(20% MeOH–EtOAc); FTIR (film) υ_{max}: 2928, 1703, 1613, 1469, 1434, 1076 cm^{-1}; *m/z* (CI) 367 $[M+H]^+$ (Found $[M+H]^+$, 367.2032. $C_{22}H_{26}N_2O_3$ requires $[M+H]^+$, 367.2022);

δ_H (400 MHz, $CDCl_3$) 7.51 (1H, br. d, *J* 8.0 Hz, **12**), 7.33 (1H, br. d, *J* 8.0 Hz, **9**), 7.21 (1H, td, *J* 8.0, 1.0 Hz, **11**), 7.12 (1H, td, *J* 8.0, 1.0 Hz, **10**), 4.85 (1H, t, *J* 12.0 Hz, **17a**), 4.22 (1H, ddd, *J* 12.0, 4.0, 2.0 Hz, **17b**), 3.90 (1H, br. s, **3**), 3.65 (3H, s, N_1**Me**), 3.50 (3H, s, *O***Me**), 3.32 (1H, dd, *J* 16.0, 7.0 Hz, **6a**), 3.07 (1H, br. d, *J* 7.0 Hz, **5**), 2.88 (1H, m, **15**), 2.49 (1H, d, *J* 16.0 Hz, **6b**), 2.43 (3H, d, ^4J 1.0 Hz, **18**), 2.32 (3H, br. s N_4**Me**), 2.05 (1H, m, **16**), 1.99 (2H, m, **14a** and **14b**);

δ_C (100 MHz, $CDCl_3$) 170.1 (**C19**), 167.2 (**C21**), 137.1 (**C13**), 133.2 (**C2**), 127.6 (**C20**), 126.7 (**C8**), 120.8 (**C11**), 118.8 (**C10**), 118.0 (**C12**), 108.7 (**C9**), 106.3 (**C7**), 68.8 (**C17**), 62.1 (*O***Me**), 54.8 (**C22**), 54.7 (**C5**), 53.7 (**C3**), 41.6 (N_4**Me**), 39.8 (**C16**), 29.9 (**C14**), 29.0 (N_1**Me**), 25.8 (**C15**), 22.5 (**C6**), 15.2 (**C18**).

Over-reduced-(±)-alstonerinal precursor (151)



150 **151**

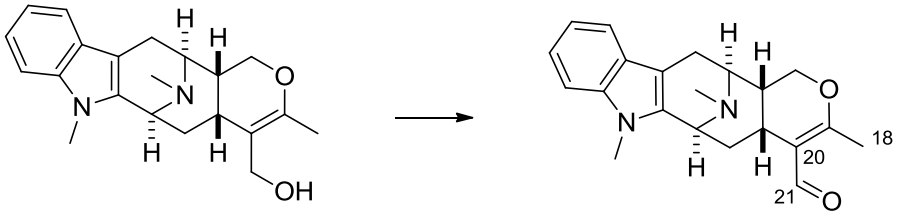
To a solution of N_4-methyl-(±)-alstonerinal precursor **150** (9.3 mg, 0.025 mmol, 1.0 equiv.) in toluene (0.5 mL) at –92°C was added DIBAL (1.0 M in toluene; 0.05 mL, 0.05 mmol, 2.0 equiv.). and the solution stirred at –92°C for 1 h. Wet Et_2O (2 mL) was added and the reaction mixture was allowed to warm slowly from –92°C to rt. Saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. The aqueous phase extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×20 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$ and filtered. Concentrated under reduced pressure and purification *via* preparative thin layer chromatography (3% MeOH–EtOAc) yielded *over-reduced-(±)-alstonerinal precursor **151*** (8.4 mg, 99%) as an amorphous solid; R_f

0.39 (5% MeOH–EtOAc); FTIR (film) υ_{max}: 3350, 2913, 1670, 1469, 1380 cm^{-1}; *m/z* (ES) 339 $[M+H]^+$ (Found $[M+H]^+$, 339.2079. $C_{21}H_{26}N_2O_2$ requires $[M+H]^+$, 339.2073);

δ_H (500 MHz, $CDCl_3$) 7.49 (1H, br. d, *J* 8.0 Hz, **9**), 7.31 (1H, br. d, *J* 8.0 Hz, **12**), 7.20 (1H, td, *J* 8.0, 1.0 Hz, **11**), 7.11 (1H, td, *J* 8.0, 1.0 Hz, **10**), 4.24 (1H, t, *J* 12.0 Hz, **17a**), 3.99 (1H, ddd, *J* 12.0, 4.0, 2.0 Hz, **17b**), 3.96—3.82 (3H, m, **3** and **21a**), 3.85 (1H, d, *J* 12.0 Hz, **21b**), 3.64 (3H, s, N_1**Me**), 3.30 (1H, dd, *J* 16.0, 7.0 Hz, **6a**), 3.09 (1H, br. d, *J* 7.0 Hz, **5**), 2.49 (1H, d, *J* 16.0 Hz, **6b**), 2.33 (3H, s, N_4**Me**), 2.08 (1H, dt, *J* 12.0, 6.0 Hz, **15**), 1.96—1.86 (3H, m, **14a**, **14b** and **16**), 1.83 (3H, d ^4J 1.0 Hz, **18**);

δ_C (125 MHz, $CDCl_3$) 150.5 (**C19**), 137.5 (**C13**), 133.4 (**C2**), 127.2 (**C8**), 120.9 (**C11**), 118.9 (**C10**), 118.0 (**C9**), 109.9 (**C20**), 108.9 (**C12**), 106.2 (**C7**), 66.6 (**C21**), 62.0 (**C17**), 55.1 (**C5**), 53.7 (**C3**), 41.8 (N_4**Me**), 40.6 (**C16**), 33.5 (**C14**), 29.1 (N_1**Me**), 27.0 (**C15**), 22.9 (**C6**), 16.3 (**C18**). Data is in accordance with that previously reported by T. Kam *et al*.[101]

(±)-Alstonerinal (138)



151 **138**

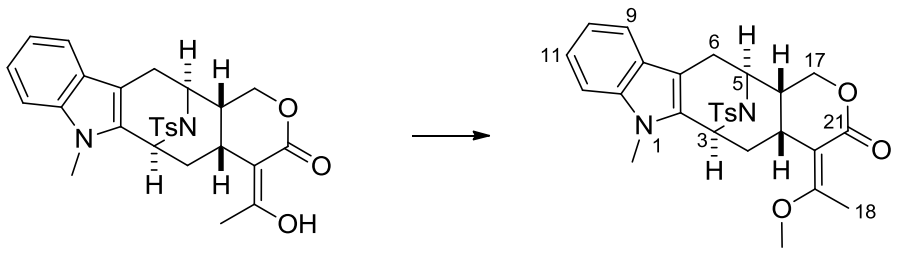
To a solution of alcohol **151**, (9.0 mg, 0.026 mmol, 1.0 equiv.) and pyridine (0.007 mL, 0.079 mmol, 3.0 equiv.) at 0°C was added Dess–Martin periodinane (16.8 mg, 0.040 mmol, 1.5 equiv.) and the solution stirred at 0°C for 2 h. Water (1 mL) was added and the aqueous phase extracted with EtOAc (3×10 mL) and CH_2Cl_2 (2×10 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$ and filtered. Concentrated under reduced pressure and purification *via* preparative thin layer chromatography (5% MeOH–EtOAc) yielded *(±)-alstonerinal **138*** (1.2 mg, 13%) as a colourless oil; R_f 0.2 (5% MeOH–EtOAc);

δ_H (500 MHz, $CDCl_3$) 9.65 (1H, s, **21**), 7.44 (1H, br. d, *J* 8.0 Hz, **9**), 7.31 (1H, br. d, *J* 8.0 Hz, **12**), 7.20 (1H, td, *J* 8.0, 1.0 Hz, **11**), 7.11 (1H, td, *J* 8.0, 1.0 Hz, **10**), 4.46 (1H, t, *J* 12.0 Hz, **17a**), 4.18 (1H, ddd, *J* 12.0, 4.0, 2.0 Hz, **17b**), 3.86 (1H, br. d, **3**), 3.63 (3H, s, N_1**Me**), 3.31 (1H, dd,

J 16.0, 7.0 Hz, **6a**), 3.09 (1H, br. d, *J* 7.0 Hz, **5**), 2.61 (1H, dt, *J* 12.0, 6.0 Hz, **15**), 2.49 (1H, d, *J* 16.0 Hz, **6b**), 2.33 (3H, s, N_4**Me**,), 2.15 (3H, s, **18**), 2.12 (1H, ddd, *J* 12.0, 5.0, 3.0 Hz, **14a**), 1.89—1.83 (1H, m, **16**), 1.79 (1H, td, *J* 12.0, 3.0 Hz, **14b**). Data is in accordance with that previously reported by T. Kam *et al*.[101]

3.1.9 *Procedures from synthesis of N_4-tosyl macroline **152*** (Section **2.2.8**)

***Z*-N_4-(±)-Tosylmacroline precursor (147)**



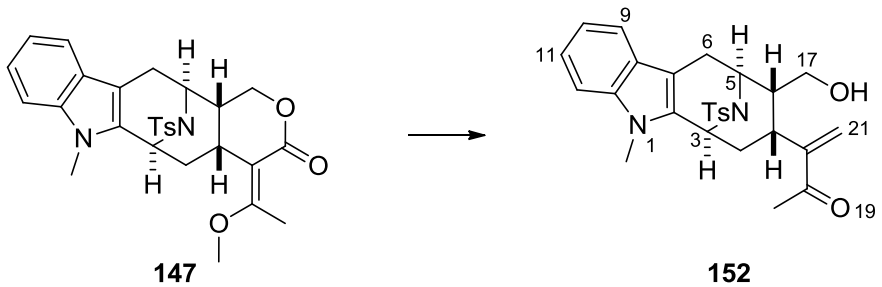
85 **147**

To a solution of the enol **85** (51 mg, 0.104 mmol, 1.0 equiv.) in MeOH:CH_2Cl_2 (1:1) (0.5 mL) at rt was added CSA (3 mg, 0.010 mmol, 0.1 equiv.) and trimethylorthoformate (0.16 mL, 0.155 mmol, 1.5 equiv.) and the reaction stirred for 16 h. Saturated $NaHCO_3$ was added dropwise and the aqueous layers were then extracted with CH_2Cl_2 (3×30 mL), and the combined organics washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and purification *via* preparative thin layer chromatography (50% EtOAc–Hexane) yielded *Z-N_4-(±)-tosylmacroline precursor **147*** as an amorphous solid (16.3 mg, 31%) and *N_4-(±)-tosylalstonerinal precursor **148*** (31.6 mg, 60%) as an amorphous solid; R_f 0.15 (50% EtOAc–Hexane); FTIR (film) υ_{max}: 2932, 1687, 1584, 1468 cm^{-1}; *m/z* (ES) 507 $[M+H]^+$ (Found $[M+H]^+$, 507.1941. $C_{28}H_{30}N_2O_5S$ requires $[M+H]^+$, 507.1954);

δ_H (400 MHz, $CDCl_3$) 7.36 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.24—7.29 (1H, m, **12**), 7.14—7.20 (2H, m, **9** and **11**), 7.02 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.80 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.27 (1H, br. t, *J* 3.0 Hz, **3**), 4.66 (1H, t, *J* 12.0 Hz, **17a**), 4.24—4.33 (2H, m, **17b** and **5**), 3.67 (3H, s, N_1**Me**), 3.51 (3H, s, *O***Me**), 3.02—3.10 (1H, m, **15**), 2.90 (1H, dd, *J* 16.5, 7.5 Hz, **6a**), 2.44—2.49 (1H, m, **6b**), 2.44 (3H, s, *Ts***Me**), 1.97—2.15 (6H, m, **18**, **14a**, **14b** and **16**);

δ_C (100 MHz, $CDCl_3$) 170.8 (**C19**), 166.4 (**C21**), 143.4 (*para*-**Ts**), 136.8 (**C13**), 136.0 (*ipso*-**Ts**), 132.1 (**C2**), 128.8 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.2 (**C8**), 121.5 (**C11**), 119.1 (**C10**), 117.9 (**C12**), 108.8 (**C9**), 107.2 (**C7**), 104.6 (**C20**), 67.1 (**C17**), 55.1 (*O***Me**), 49.6 (**C5**), 48.5 (**C3**), 39.2 (**C16**), 29.9 (**C14**), 29.1 (*N*$_1$**Me**), 25.9 (**C6**), 25.3 (**C15**), 21.1 (*Ts***Me**), 15.3 (**C18**).

***N*$_4$-Tosyl-(±)-macroline (152)**



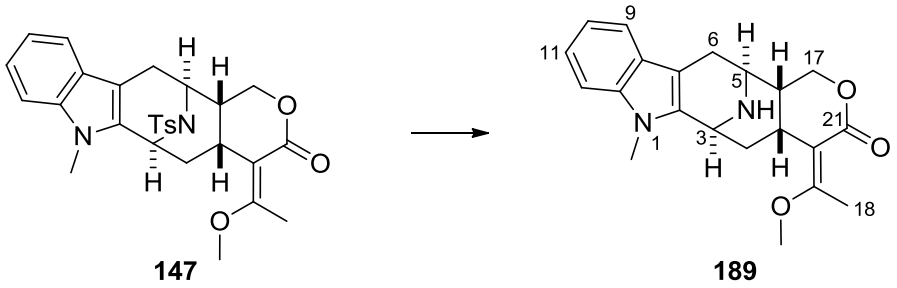
147 **152**

To a solution of type B macroline methyl enol **147** (39.0 mg, 0.076 mmol, 1.0 equiv.) in CH_2Cl_2 (0.75 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.084 mL, 0.084 mmol, 1.1 equiv.). and the solution stirred at –78°C for 1 h. Wet Et_2O (2 mL) was added and the reaction mixture was allowed to warm slowly from –78°C to rt. Saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. The aqueous phase extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×20 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$ and filtered. Concentrated under reduced pressure and purification *via* preparative thin layer chromatography (50% EtOAc–hexane) yielded *N*$_4$*-tosyl-(±)-macroline* ***152*** (11.7 mg, 32% + 55% **147** recovery) as an amorphous solid; R_f 0.10 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3480, 2928, 1674, 1469, 1339, 116 cm^{-1}; *m/z* (ES) 479 $[M+H]^+$ (Found $[M+H]^+$, 479.1985. $C_{27}H_{30}N_2O_4S$ requires $[M+H]^+$, 479.2005);

δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.22 (1H, d, *J* 8.0 Hz, **12**), 7.18 (1H, d, *J* 8.0 Hz, **9**), 7.15 (1H, td, *J* 8.0, 1.0 Hz, **11**), 7.01 (1H, dt, *J* 8.0, 1.0 Hz, **10**), 6.77 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.09 (1H, d, *J* 1.0 Hz, **21a**), 5.66 (1H, d, *J* 1.5 Hz, **21b**), 5.44 (1H, t, *J* 3.5 Hz, **3**), 4.60 (1H, br. d, *J* 8.0 Hz, **5**), 3.90 (1H, td, *J* 11.0, 5.5 Hz, **17a**), 3.65 (3H, s, *N*$_1$**Me**), 3.39 (1H, ddd, *J* 11.0, 7.0, 4.5 Hz, **17b**), 3.20 (1H, dt, *J* 13.5, 4.0 Hz, **15**), 2.78 (1H, dd, *J* 16.5, 8.0 Hz, **6a**), 2.58 (1H, d, *J* 16.5 Hz, **6b**), 2.37 (1H, td, *J* 13.0, 4.0 Hz, **14a**), 2.26 (3H, s, **18**), 2.19—2.14 (2H, m, **16** and *O***H**), 2.03 (3H, s, *Ts***Me**) 1.45 (1H, dt, *J* 13.0, 3.0 Hz, **14b**);

δ_C (125 MHz, $CDCl_3$) 198.6 (**C19**), 149.2 (**C21**), 143.3 (*para*-**Ts**), 136.7 (**C13**), 136.0 (*ipso*-**Ts**), 132.0 (**C2**), 128.8 (*meta*-**Ts**), 126.3 (*ortho*-**Ts**), 126.1 (**C8**), 124.6 (**C20**), 121.4 (**C11**), 119.1 (**C10**), 118.3 (**C12**), 108.7 (**C9**), 108.1 (**C7**), 59.6 (**C17**), 48.5 (**C5**), 48.0 (**C21**), 44.5 (**C16**), 30.2 (**C14**), 29.3 (**C15**), 29.2 (N_1**Me**), 26.3 (**C18**), 24.3 (**C6**), 21.1 (*Ts***Me**).

***Z*-N_4H-(±)-Macroline precursor (189)**



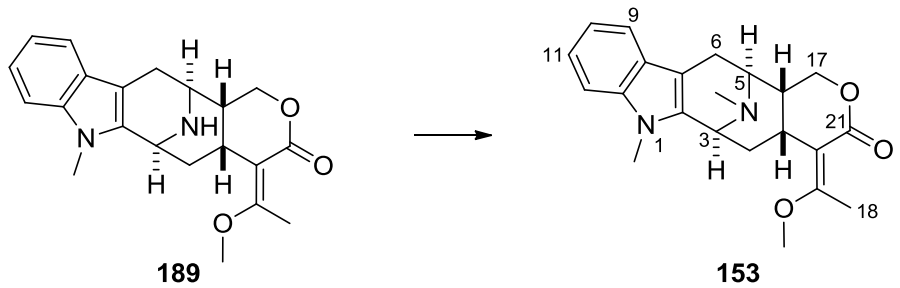
To a solution of naphthalene (40 mg, 0.319 mmol, 8.0 equiv.) in THF (3 mL) at rt was added sodium (8.0 mg, 0.319 mmol, 8.0 equiv.) and the reaction mixture stirred at rt for 1 h.

The dark green\blue solution was then cooled to –78 °C and (~0.1 M in THF; 2.0 mL, 0.200 mmol, 5.0 equiv.) was added to a solution of N_4-Ts protected type B macroline methyl enol **147** (20.3 mg, 0.040 mmol, 1.0 equiv.) in THF (1 mL). The reaction mixture was stirred at –78°C for 2 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the solution allowed to warm slowly from –78°C to rt. The aqueous layer was then extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (100% EtOAc) yielded *Z-N_4H-(±)-macroline precursor **189*** (12.1 mg, 86%) as a pale yellow oil; R_f 0.11 (100% EtOAc); FTIR (film) υ_{max}: 2935, 1702, 1612, 1469, 1343 cm^{-1}; *m/z* (CI) 353 $[M+H]^+$ (Found $[M+H]^+$, 353.1856. $C_{22}H_{25}N_2O_3$ requires $[M+H]^+$, 353.1685);

δ_H (400 MHz, $CDCl_3$) 7.41—7.33 (2H, app. d, *ortho*-**Ts**), 7.29—7.22 (1H, m, **12**), 7.22—7.09 (2H, td, *J* 7.0, 1.5 Hz, **9** and **11**), 7.05—6.95 (1H, td, *J* 7.0, 1.0 Hz, **10**), 6.83—6.76 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.26 (1H, br. t, *J* 3.0 Hz, **3**), 4.35—4.13 (3H, m, **5**, **17a** and **17b**), 3.67 (3H, s, *O***Me**), 3.51 (3H, s, N_1**Me**), 2.90 (1H, dd, *J* 16.0, 7.0 Hz, **6a**), 2.72 (1H, br. dt, *J* 12.0, 3.0 Hz, **15**), 2.47 (1H, d, *J* 16.0 Hz, **6b**), 2.19 (3H, s, *Ts***Me**) 2.08—2.16 (1H, m, **16**), 2.01 (3H, s, **18**), 1.92—2.01 (2H, m, **14a** and **14b**);

δ_C (100 MHz, $CDCl_3$) 168.2 (**C19**), 165.5 (**C21**), 143.4 (*ortho*-**Ts**), 136.9 (**C13**), 136.2 (*ipso*-**Ts**), 132.1 (**C2**), 128.2 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.2 (**C8**), 121.4 (**C11**), 119.0 (**C10**), 117.8 (**C12**), 108.9 (**C9**), 107.0 (**C7**), 104.1 (**C20**), 65.8 (**C17**), 50.9 (*O***Me**), 49.6 (**C5**), 48.6 (**C3**), 38.5 (**C16**), 32.9 (**C14**), 29.2 (*N*$_1$**Me**), 25.7 (**C6**), 25.4 (**C15**), 21.1 (*Ts***Me**), 20.6 (**C18**).

N_4-Methyl-(±)-macroline precursor (153)



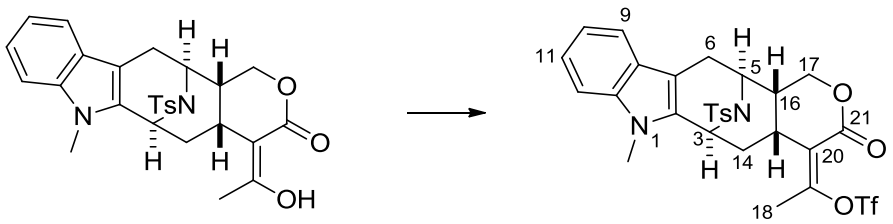
To a stirred solution of type B macroline methyl enol N_4H amine **189** (12.0 mg, 0.034 mmol, 1.0 equiv.) in THF (0.5 mL) at –78°C was added Hünig's Base (0.02 mL, 0.102 mmol, 3.0 equiv.) and iodomethane (0.002mL, 0.05 mmol, 1.4 equiv.) and the solution allowed to warm slowly from –78°C to rt overnight. Water (2 mL) was added to the resulting cloudy solution and the aqueous layer extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification *via* preparative thin layer chromatography yielded *N_4-methyl-(±)-macroline precursor* ***153***compound as a pale yellow oil (9.9 mg, 81%); R_f 0.67 (20% MeOH–EtOAc); FTIR (film) υ_{max}: 2921, 1701, 1613, 1469, 1379 cm^{-1}; *m/z* (ES) 367 $[M+H]^+$ (Found $[M+H]^+$, 367.2036. $C_{22}H_{26}N_2O_3$ requires $[M+H]^+$, 367.2022);

δ_H (400 MHz, $CDCl_3$) 7.51 (1H, br. d, *J* 8.0 Hz, **12**), 7.33 (1H, br. d, *J* 8.0 Hz, **9**), 7.21 (1H, td, *J* 8.0, 1.0 Hz, **11**), 7.12 (1H, td, *J* 8.0, 1.0 Hz, **10**), 4.37 (1H, t, *J* 12.0 Hz, **17a**), 4.11 (1H, ddd, *J* 12.0, 4.0, 2.0 Hz, **17b**), 3.90 (1H, br. t, **3**), 3.65 (3H, s, *N*$_1$**Me**), 3.50 (3H, s, *O***Me**), 3.32 (1H, dd, *J* 16.0, 7.0 Hz, **6a**), 3.12 (1H, br. d, *J* 7.0 Hz, **5**), 2.47—2.59 (2H, m, **15** and **6b**), 2.33 (3H, d, ^4J 1.0 Hz, **18**), 2.19 (3H, br. s, *N*$_4$**Me**), 2.05 (1H, m, **16**), 1.86—1.97 (2H, m, **14a** and **14b**);

δ_C (100 MHz, $CDCl_3$) 168.6 (**C19**), 165.2 (**C21**), 133.3 (**C2**), 126.7 (**C8**), 120.8 (**C10**), 118.8 (**C11**), 118.0 (**C9**), 108.9 (**C12**), 106.1 (**C7**), 67.4 (**C17**), 54.8 (**C3**), 53.9 (**C5**), 41.7 (**C16**), 38.5 (**C14**), 29.0 (N_1**Me**), 25.4 (**C15**), 24.9 (N_4**Me**), 22.8 (**C6**), 22.7 (**C18**).

3.1.10 *Procedures from progress towards total synthesis of alstolactone* (Section **2.2.9**) *and improved route to N_4-tosyl-anhydromacrosalhine-methine* **157** (Section **2.2.12)**

***Z*-Pentacyclic triflate (154)**



85 **154**

To a solution of enol **85** (155 mg, 0.315 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) at –78°C was added Hünig's base (0.11 mL, 0.630 mmol, 2.0 equiv.) and triflic anhydride (0.08 mL, 0.473 mmol, 1.5 equiv.) and the reaction mixture stirred at –78°C for 30 min.

H_2O (1 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organics were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and flash column chromatography (20% EtOAc–hexane) yielded the *Z-pentacyclic triflate **154*** (124 mg, 63%) as a white amorphous solid; R_f 0.23 (33% EtOAc–hexane); FTIR (film) υ_{max}: 3528, 3305, 3060, 2952, 1738, 1156 cm^{-1}; *m/z* (CI) 625 $[M+H]^+$ (Found $[M+H]^+$, 625.1300. $C_{28}H_{27}F_3N_2O_7S_2$ requires $[M+H]^+$, 625.1290).

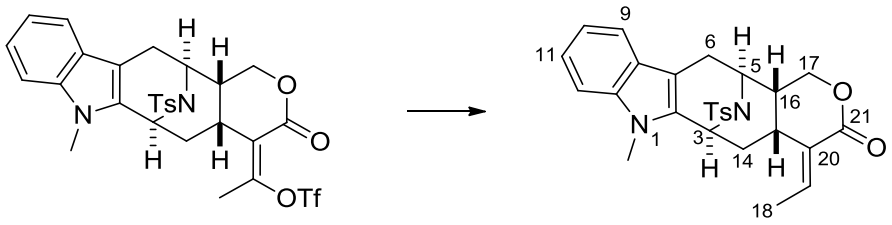
δ_H (400 MHz, $CDCl_3$) 7.36 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28—7.15 (3H, m, **9**, **11** and **12**), 7.04 (1H, td, *J* 7.0, 1.0 Hz, **10**), 6.82 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.37 (1H, br. s, **3**), 4.78 (1H, t, *J* 12.0 Hz, **17a**), 4.47 (1H, ddd, *J* 12.0, 5, 1.0 Hz, **17b**), 4.29 (1H, br. d, *J* 7.0, **5**), 3.68 (3H, s, N_1**Me**), 2.89—3.00 (2H, m, **6a** and **15**), 2.51 (1H, d, *J* 16.0 Hz, **6b**), 2.30—2.40 (2H, m, **14a** and **16**), 2.03 (3H, s, *Ts***Me**), 1.75 (3H, s, **18**), 1.69 (1H, ddd, *J* 14.0, 4.5, 3.0 Hz, **14b**);

δ_C (100 MHz, $CDCl_3$) 160.2 (**C21**), 153.7 (**C19**), 143.9 (*para*-**Ts**), 137.0 (**C13**), 135.5 (**C20**), 130.8 (**C8**), 129.0 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 125.8 (**C8**), 122.2 (**C11**), 120.1 (*ipso*-**Ts**), 119.6

(**C10**), 118.0 (**C9**), 109.1 (**C12**), 107.4 (**C7**), 67.7 (**C17**), 49.0 (**C5**), 47.6 (**C3**), 38.8 (**C16**), 30.3 (**C14**) 29.5 (**C15**), 29.3 (*N*$_1$**Me)**, 25.0 (**C6**), 21.2 (*Ts***Me**), 18.2 (**C18**);

δ_F (100 MHz, $CDCl_3$) –74.49 (C***F***$_3$).

N_4-Tosyl-alstolactone (155)



154 **155**

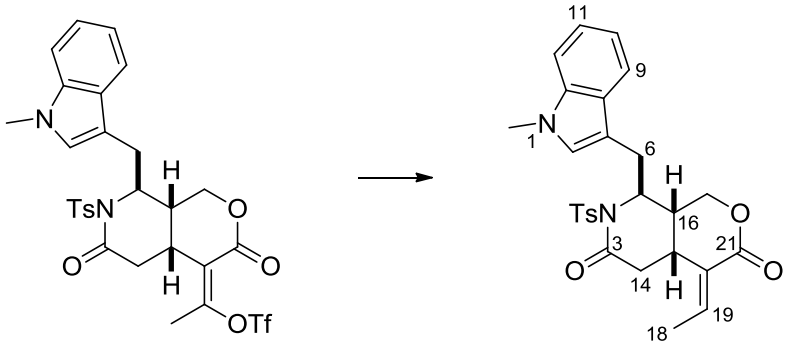
To a solution of palladium(II)acetate (4.0 mg, 0.018 mmol, 0.1 equiv.), Ph_3P (14.0 mg, 0.054 mmol, 0.3 equiv.), Et_3N (0.08 mL, 0.537 mmol, 3.0 equiv.) and formic acid (0.015 mL, 0.358 mmol, 2.0 equiv.) in a microwave vial was added enol triflate **154** (112 mg, 0.0.179 mmol, 1.0 equiv.) and the solution heated at 80°C for 20 min in the microwave.

Concentration under reduced pressure and chromatography (20% EtOAc–hexane) yielded *N_4-tosyl-alstolactone **155*** (52.8 mg, 73%) as a white amorphous solid; R_f 0.16 (66% EtOAc–hexane); FTIR (film) υ_{max}: 3051. 2920, 1710, 1630, 1597, 1469, 1159 cm^{-1}; *m/z* (ES) 477 $[M+H]^+$ (Found $[M+H]^+$, 477.1849. $C_{27}H_{28}N_2O_4S$ requires $[M+H]^+$, 476.1848);

δ_H (400 MHz, $CDCl_3$) 7.36 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.33—7.10 (4H, m, **9**, **11**, **12** and **19**) 7.04 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.82 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 5.33 (1H br. s, **3**), 4.77 (1H, t, *J* 12.0 Hz, **17a**), 4.39 (1H, ddd, *J* 12.0, 5.0, 2.0 Hz, **17b**), 4.30 (1H, br. d, *J* 7.0 Hz, **5**), 3.69 (3H, s, *N*$_1$**Me**), 2.89—3.00 (2H, m, **6a** and **15**), 2.50 (1H, d, *J* 16.0 Hz, **6b**), 2.30—2.18 (2H, m, **14a** and **16**), 2.03 (3H, s, *Ts***Me**), 1.74 (1H, ddd, *J* 14.0, 5.0, 3.0 Hz, **14b**), 1.46 (3H, d, *J* 7.0 Hz, **18**);

δ_C (100 MHz, $CDCl_3$) 164.9 (**C21**), 143.7 (**C19**), 143.3 (*para*-**Ts**), 136.9 (**C13**) , 135.9 (*ipso*-**Ts**), 131.3 (**C2**), 128.9 (*meta*-**Ts**), 127.6 (**C20**), 126.4 (*ortho*-**Ts**), 126.0 (**C8**) 121.9 (**C11**), 119.4 (**C10**), 118.0 (**C12**), 109.0 (**C9**), 107.5 (**C7**), 67.1 (**C17**), 49.2 (**C5**), 48.0 (**C3**), 39.0 (**C16**), 30.5 (**C14**), 29.3 (*N*$_1$**Me**), 26.6 (**C15**), 25.3 (**C6**), 21.1 (*Ts***Me**), 13.9 (**C18**).

(4a*R,8*S**,8a*R**,*E*)-4-Ethylidene-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (167)**



161 **167**

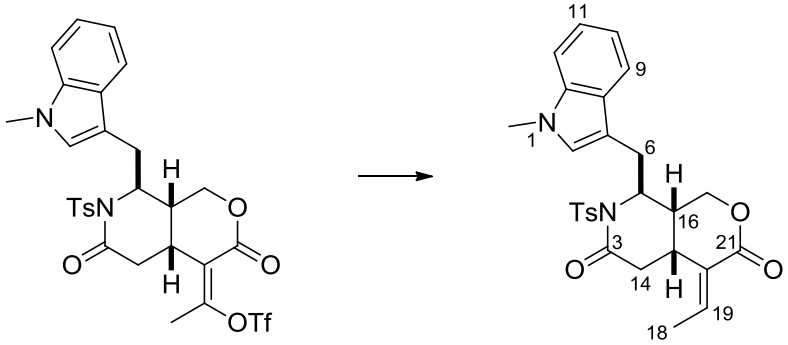
To a solution of enol triflate **161** (109 mg, 0.17 mmol, 1.0 equiv.), palladium(II)acetate (4.0 mg, 0.017 mmol, 0.1 equiv.), Ph_3P (14.0 mg, 0.051 mmol, 0.3 equiv.), and formic acid (0.04 mL, 0.068 mmol, 4.0 equiv.) in DMF (1 mL) in a microwave vial was added Et_3N (0.4 mL, 0.85 mmol, 5.0 equiv.) and the solution heated at 80°C for 30 min in the microwave.

Immediate chromatography (20% EtOAc–hexane), concentration under reduced pressure and DMF removal by washing a solution of the title compound in EtOAc (25 mL) sequentially with water (25 mL), 5% aqueous LiCl solution (25 mL), water (25 mL) and brine (25 mL) yielded *(4aR*,8S*,8aR*,E)-4-ethylidene-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione* ***167*** (71.2 mg, 85%) as a white amorphous solid; R_f 0.19 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3057, 2924, 2855, 1716, 1695, 1638, 1612, 1596, 1477 cm^{-1}; m/z (CI) 493 [M+H]+ (Found [M+H]+, 493.1790. $C_{27}H_{28}N_2O_5S$ requires [M+H]+, 493.1797).

δ_H (400 MHz, $CDCl_3$) 7.94 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.73 (1H, d, *J* 8.0 Hz, **9**), 7.37—7.23 (4H, m, *meta*-**Ts** and **12**, then **11**), 7.16 (1H, t, *J* 8.0 Hz, **10**), 7.08 (1H, q, *J* 8.0 Hz, **19**), 6.96 (1H, s, **2**), 4.81—4.74 (1H, m, **5**), 4.21—4.04 (2H, m, **17a** and **17b**), 3.78 (3H, s, N_1**Me**), 3.56 (1H, dd, *J* 14.5, 3.5 Hz, **6a**), 3.46—3.37 (1H, m, **15**), 3.20 (1H, dd, *J* 14.5, 10.0 Hz, **6b**), 2.64—2.50 (2H, m, **16** and **14a**), 2.44 (3H, s, *Ts***Me**), 2.19 (1H, dd, *J* 18.5, 10.5 Hz, **14b**), 1.63 (3H, d, *J* 7.0 Hz, **18**);

δ_C (100 MHz, $CDCl_3$) 167.3 **(C3)**, 164.2 **(C21)**, 145.4 (*para*-**Ts**), 143.9 (**C19**), 137.1 (**C13**), 135.7 (*ipso*-**Ts**), 129.5 (*ortho*-**Ts**), 129.2 (*meta*-**Ts**), 128.1 (**C2**), 127.7 **(C11)**, 127.3 **(C8)**, 122.3 (**C20**), 119.8 **(C10)**, 118.6 **(C12)**, 109.7 **(C9)**, 108.4 (**C7**), 66.7 (**C17**), 57.7 (**C5**), 34.6 (**C14**), 32.9 (N_1**Me**), 32.4 (**C16**), 31.7 (**C6**), 26.5 (**C15**), 21.7 (*Ts***Me**), 13.8 (**C18**).

(4a*R,8*S**,8a*R**,*E*)-4-Ethylidene-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (167)**



161 **167**

To a solution of enol triflate **161** (109 mg, 0.170 mmol, 1.0 equiv.), palladium(II)acetate (4.0 mg, 0.017 mmol, 0.1 equiv.), Ph_3P (14.0 mg, 0.051 mmol, 0.3 equiv.), and formic acid (0.04 mL, 0.068 mmol, 4.0 equiv.) in DMF (1 mL) in a microwave vial was added Et_3N (0.4 mL, 0.850 mmol, 5.0 equiv.) and the solution heated at 80°C for 30 min in the microwave.

Immediate chromatography (20% EtOAc–hexane), concentration under reduced pressure and DMF removal by washing a solution of the title compound in EtOAc (25 mL) sequentially with water (25 mL), 5% aqueous LiCl solution (25 mL), water (25 mL) and brine (25 mL) yielded *(4aR*,8S*,8aR*,E)-4-ethylidene-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione **167*** (71.2 mg, 85%) as a white amorphous solid; R_f 0.19 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3057, 2924, 2855, 1716, 1695, 1638, 1612, 1596, 1477 cm^{-1}; m/z (CI) 493 [M+H]+ (Found [M+H]+, 493.1790. $C_{27}H_{28}N_2O_5S$ requires [M+H]+, 493.1797).

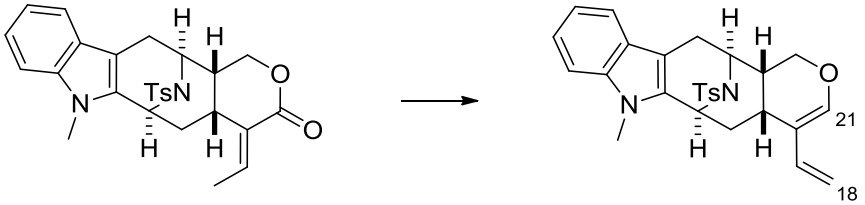
δ_H (400 MHz, $CDCl_3$) 7.94 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.73 (1H, d, *J* 8.0 Hz, **9**), 7.37—7.23 (4H, m, *meta*-**Ts** and **12**, then **11**), 7.16 (1H, t, *J* 8.0 Hz, **10**), 7.08 (1H, q, *J* 8.0 Hz, **19**), 6.96 (1H, s, **2**), 4.81—4.74 (1H, m, **5**), 4.21—4.04 (2H, m, **17a** and **17b**), 3.78 (3H, s,

N_1**Me**), 3.56 (1H, dd, *J* 14.5, 3.5 Hz, **6a**), 3.46—3.37 (1H, m, **15**), 3.20 (1H, dd, *J* 14.5, 10.0 Hz, **6b**), 2.64—2.50 (2H, m, **16** and **14a**), 2.44 (3H, s, *Ts***Me**), 2.19 (1H, dd, *J* 18.5, 10.5 Hz, **14b**), 1.63 (3H, d, *J* 7.0 Hz, **18**);

δ_C (100 MHz, $CDCl_3$) 167.3 **(C3)**, 164.2 **(C21)**, 145.4 (*para*-**Ts**), 143.9 (**C19**), 137.1 (**C13**), 135.7 (*ipso*-**Ts**), 129.5 (*ortho*-**Ts**), 129.2 (*meta*-**Ts**), 128.1 (**C2**), 127.7 **(C11)**, 127.3 **(C8)**, 122.3 (**C20**), 119.8 **(C10)**, 118.6 **(C12)**, 109.7 **(C9)**, 108.4 (**C7**), 66.7 (**C17**), 57.7 (**C5**), 34.6 (**C14**), 32.9 (N_1**Me**), 32.4 (**C16**), 31.7 (**C6**), 26.5 (**C15**), 21.7 (*Ts***Me**), 13.8 (**C18**).

3.1.11 *Procedures from synthesis of N_4-tosyl anhydromacrosalhine-methine **157*** (Section **2.2.10**)

N_4-Tosyl-anhydromacrosalhine-methine (157)



To a solution of N_4-tosylalstolactone **154** (28.6 mg, 0.060 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.07 mL, 0.660 mmol, 1.1 equiv.) and the solution stirred at –78°C for 3h. Wet Et_2O (5 mL) was added and the reaction mixture was allowed to warm slowly from –78°C to rt. Saturated aqueous Rochelle salt (5 mL) and EtOAc (15 mL) were added and the resulting suspension stirred vigorously at rt overnight. Saturated $NaHCO_3$ (10 mL) was added and the aqueous phase extracted with EtOAc (3×50 mL). The organic phases were combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and preparative thin layer chromatography (50% EtOAc–hexane) yielded *N_4-tosyl-anhydromacrosalhine-methine **157*** (26.0 mg, 94%) as a white amorphous solid; R_f 0.35 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3420, 2890, 1630, 1470 cm^{-1}; *m/z* (CI) 461 $[M+H]^+$ (Found $[M+H]^+$, 461.1895. $C_{27}H_{29}N_2O_3S$ requires $[M+H]^+$, 561.1899).

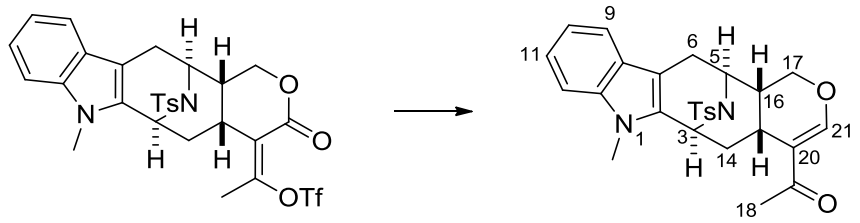
δ_H (400 MHz, $CDCl_3$) 7.40 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28—7.25 (1H, m, **9**), 7.20—7.15 (2H, m, **11** and **12**), 7.03 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.84 (2H, app. d, *J* 8.0 Hz,

meta-**Ts**), 6.47 (1H, s, **21**), 6.0.0 (1H, dd, *J* 17.5, 11.0 Hz, **19**), 5.29 (1H, br. t, *J* 3.5 Hz, **3**), 4.57 (1H, dd, *J* 11.5, 0.5 Hz, **18a**), 7.39 (1H, d, *J* 17.5 Hz, **18b**), 4.33 (1H, d, *J* 7.5 Hz, **5**), 4.26 (1H, t, *J* 11.5 Hz, **17a**), 4.11 (1H, ddd, *J* 11.5, 4.0, 1.5 Hz, **17b**), 3.67 (3H, s, N_1**Me**), 2.93 (1H, dd, *J* 16.5, 7.5 Hz, **6a**), 2.57 (1H, t, *J* 4.5 Hz, **15**), 2.52 (1H, d, *J* 16.5 Hz, **6b**), 2.17 (1H, ddd, *J* 14.0, 5.0, 3.0 Hz, **14a**), 2.10—2.00 (5H, m, **14b**, **16**, *Ts***Me**);

δ_C (400 MHz, $CDCl_3$) 145.6 (**C21**), 143.4 (*para*-**Ts**), 136.9 (**C13**), 136.3 (*ipso*-**Ts**), 133.7 (**C19**), 132.0 (**C2**), 128.9 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 126.2 (**C8**), 121.6 (**C11**), 119.2 (**C10**), 117.9 (**C12**), 115.9 **(C20)**, 108.9 (**C9**), 107.4(**C7**), 106.7 (**C18**), 65.3 (**C17**), 49.7 (**C5**), 48.5 (**C3**), 38.5 (**C16**), 32.1 (**C14**), 29.2 (N_1**Me**), 25.8 (**C6**), 23.5 (**C15**), 21.1 (*Ts***Me**).

3.1.12 *Procedures from total synthesis of alstonerine **4*** (Section **2.2.11**)

N_4-Tosylalstonerine (134)

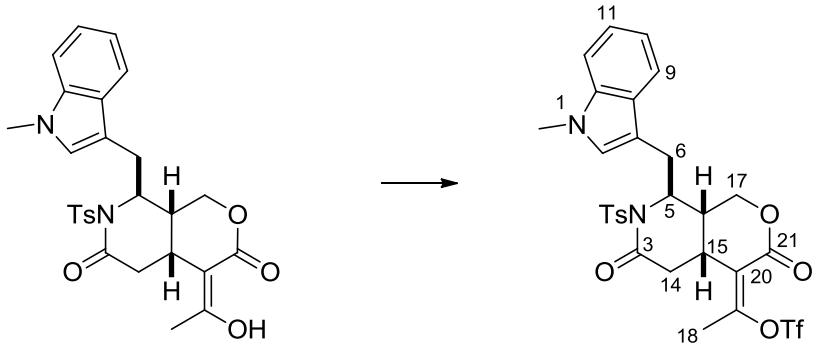


154 **134**

To a solution of pentacyclic triflate **154** (26.0 mg, 0.042 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.065 mL, 0.065 mmol, 1.5 equiv.) and the solution stirred at –78°C for 3 h. Wet Et_2O (5 mL) was added and the reaction mixture was allowed to warm slowly from –78°C to rt. Saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the aqueous phase extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×20 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the intermediate lactol as an amorphous, colourless solid.

Purification by chromatography (50% EtOAc–hexane) yielded *N_4-tosylalstonerine **134*** (19.8 mg, 100%) as an amorphous solid. For data see final approach (Page **191**).

(*Z*)-1-((4a*R,8*S**,8a*R**)-8-((1-Methylindol-3-yl)methyl)-3,6-dioxo-7-tosyl-1*H*-pyrano[3,4-*c*]pyridin-4(3*H*,4a*H*,5*H*,6*H*,7*H*,8*H*,8a*H*)ylidene)ethyl trifluoromethanesulfonate (161)**



91 **161**

To a solution of enol **91** (31.0 mg, 0.061 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added KHMDS (0.5 M in toluene; 0.15 mL, 0.073 mmol, 1.2 equiv.) and the solution stirred at –78°C for 1 h. A solution of $PhNTf_2$ (0.13 M in THF; 0.5 mL, 0.067 mmol, 1.1 equiv.) was added and the solution allowed to warm slowly from –78°C to rt overnight. The reaction was quenched with wet Et_2O (2 mL), 10% aqueous citric acid (5 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL) and EtOAc (3×30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (25→50% EtOAc–hexane) yielded the title compound (28.8 mg, 74%) as an amorphous solid; R_f 0.65 (50% EtOAc–hexane); FTIR (film) υ_{max}: 2925, 1726, 1695, 1643, 1596, 1476, 1415, 1354 cm^{-1}; *m/z* (CI) 663 $[M+Na]^+$ (Found $[M+Na]^+$, 663.1062. $C_{28}H_{27}N_2O_8S_2F_3$ requires $[M+Na]^+$, 663.1059);

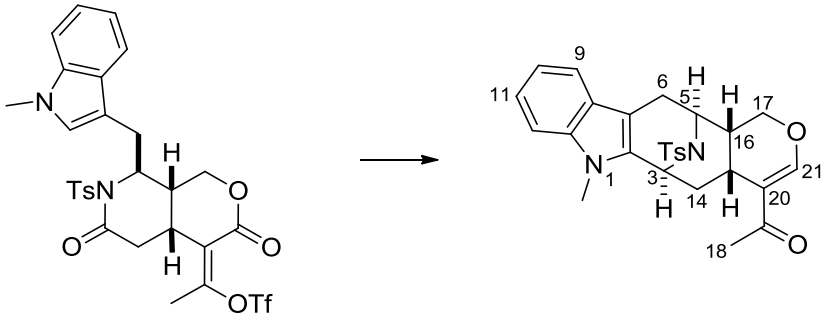
δ_H (400 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.5 Hz, *ortho*-**Ts**), 7.83 (1H, d, *J* 8.0 Hz, **12**), 7.37—7.32 (3H, m, *meta*-**Ts**, **9**), 7.29 (1H, t, *J* 8.0 Hz, **11**), 7.19 (1H, t, *J* 8.0 Hz, **10**), 6.99 (1H, s, **2**), 4.87 (1H, ddd, *J* 8.0, 3.0, 2.0 Hz, **5**), 4.20 (1H, ddd, *J* 11.5, 4.5 1.5 Hz, **17a**), 4.15—4.06 (1H, m, **17b**), 3.87—3.79 (1H, m, **15**), 3.78 (3H, s, N_1**Me**), 3.65 (1H, dd, *J* 15.0, 4.0 Hz, **6a**), 3.00 (1H, dd, *J* 15.0, 10.0 Hz, **6b**), 2.90 (1H, dd, *J* 19.0, 8.0 Hz, **14a**), 2.55 (1H, m, **16**), 2.52 (3H, s, **18**), 2.45 (3H, s, *Ts***Me**), 2.34 (1H, dd, *J* 19.0, 9.5 Hz, **14b**);

δ_C (100 MHz, $CDCl_3$) 166.5 (**C3**), 161.8 (**C21**), 159.8 (**C19**), 145.5 (*ipso*-**Ts**), 137.3 (**C13**), 135.5 (*para*-**Ts**), 129.5 (*meta*-**Ts**), 129.3 (*ortho*-**Ts**), 128.0 (**C2**), 127.2 (**C8**), 122.3 (**C11**), 121.5

(**C20**), 119.7 (**C10**), 119.0 (**C12**), 109.6 (**C9**), 108.2 (**C7**), 67.8 (**C17**), 57.1 (**C5**), 34.2 (**C14**), 32.8 (N_1**Me**), 31.9 (**C6**), 31.2 (**C16**) 28.2 (**C15**), 21.8 (*Ts***Me**), 19.7 (**C18**);

δ_F NMR (100 MH*z*, $CDCl_3$) –73.8 (C***F***$_3$).

N_4-Tosylalstonerine (134)



161 **134**

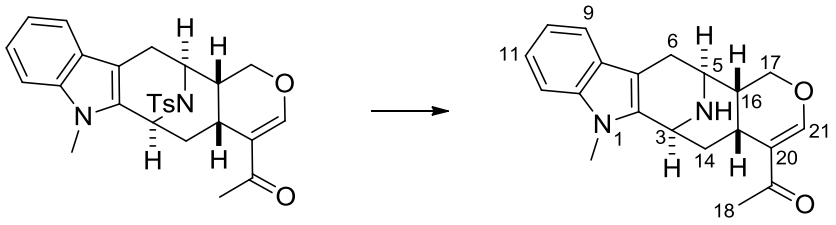
To a solution of the enol triflate derivative of **161** prepared as described above (200 mg, 0.312 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at –78°C was added DIBAL (1.0 M in toluene; 0.78 mL, 0.781 mmol, 2.5 equiv.) and the solution stirred at –78°C for 2.25 h. Wet Et_2O (5 mL) was added and the reaction mixture was allowed to warm slowly from –78°C to rt. Saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the aqueous phase extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×20 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the intermediate lactol as an amorphous, colourless solid.

The intermediate lactol was then taken up in wet CH_2Cl_2 (10 mL) and stirred at rt for 1 h. The dark brown solution was then filtered over basic alumina to give crude N_4-tosylalstonerine **134** as an amorphous, colourless solid. Purification by chromatography (50% EtOAc–hexane) yielded *N_4-tosylalstonerine **134*** (146 mg, 98%) as an amorphous solid; R_f 0.56 (50% EtOAc–hexane); FTIR (film) υ_{max}: 2988, 2301, 1619, 1449, 2338, 2276, 1261 cm^{-1}; *m/z* (CI) 477 $[M+H]^+$ (Found $[M+H]^+$, 477.1838. $C_{27}H_{28}N_2O_4S$ requires $[M+H]^+$, 477.1848);

δ_H (400 MHz, $CDCl_3$) 7.55 (1H, s, **21**), 7.35 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.25 (1H, d, *J* 8.0 Hz, **9**), 7.18–7.10 (2H, m, **12** and **11**), 6.99 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.79 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 5.24 (1H, br. t, *J* 3.0 Hz, **3**), 4.35—4.25 (3H, m, **17a**, **17b** and **5**), 3.67 (3H, s, N_1**Me**), 2.88 (1H, dd, *J* 16.5, 8.0 Hz, **6a**), 2.84—2.76 (1H, m, **15**), 2.47 (1H, d, *J* 16.5, **6b**), 2.17 (1H, ddd, *J* 12.0, 5.0, 3.0 Hz, **14a**), 2.10 (3H, s, **18**), 2.00 (3H, s, *Ts***Me**), 1.98—1.85 (2H, m, **14b** and **16**);

δ_C (100 MHz, $CDCl_3$) 195.2 (**C19**), 157.5 (**C21**), 143.4 (*para*-**Ts**), 136.9 (**C13**), 136.1 (*ipso*-**Ts**), 131.9 (**C2**), 128.8 (*meta*-**Ts**), 126.3 (*ortho*-**Ts**), 126.1 (**C8**), 121.5 (**C11**), 120.2 (**C20**), 119.0 (**C10**), 117.7 (**C12**), 108.9 (**C9**), 106.8 (**C7**), 66.2 (**C17**), 49.4 (**C5**), 48.5 (**C3**), 38.0 (**C15**), 32.3 (**C14**), 29.2 (N_1**Me**), 25.6 (**C6**), 25.0 (**C18**), 22.8 (**C16**), 21.1 (*Ts***Me**).

N_4-Demethylalstonerine (190)



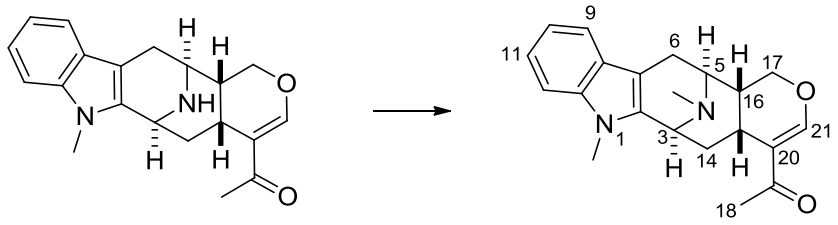
134 **190**

To a solution of naphthalene (200 mg, 1.60 mmol) in THF (16 mL) at rt was added sodium (40.0 mg, 1.60 mmol) and the reaction mixture stirred at rt for 1 h. The resulting dark green\blue solution was cooled to –78°C and (~0.1 M in THF; 0.33 mL, 0.031 mmol, 5.0 equiv.) was added to a solution of **134** (31.3 mg, 0.066 mmol, 1.0 equiv.) in THF (3 mL) at –78°C. The reaction mixture was stirred at –78°C for 2 h. Saturated aqueous $NaHCO_3$ (3 mL) was added and the solution allowed to warm slowly from –78°C to rt. The aqueous layer was then extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and purification *via* chromatography (2→10% MeOH–CH_2Cl_2) yielded N_4-demethylalstonerine ***190*** (17.6 mg, 83%) as a pale yellow oil; R_f 0.3 (3% MeOH–CH_2Cl_2); FTIR (film) υ_{max}: 2923, 1704, 1651, 1617, 1470 cm^{-1}; *m/z* (CI) 323 $[M+H]^+$ (Found $[M+H]^+$, 3323.1774. $C_{20}H_{22}N_2O_2$ requires $[M+H]^+$, 323.1760);

δ_H (400 MHz, $CDCl_3$) 7.54 (1H, s, **21**), 7.47 (1H, d, *J* 8.0 Hz, **9**), 7.31 (1H, d, *J* 8.0 Hz, **12**), 7.21 (1H, t, *J* 7.5 Hz, **11**), 7.09 (1H, t, *J* 7.5 Hz, **10**), 4.45 (1H, t, *J* 11.5 Hz, **17a**), 4.36—4.24 (2H, m, **17b** and **5**), 3.64 (3H, s, N_1**Me**), 3.50 (1H, d, *J* 7.0 Hz, **6a**), 3.27 (1H, dd, *J* 16.5, 7.0 Hz, **6b**), 3.11 (1H, br. s, N_4**H**), 2.77—2.66 (1H, m, **15**), 2.16—2.04 (4H, s, **18** and **14a**), 1.92 (1H, dt, *J* 12.0, 4.5 Hz, **16**), 1.81 (1H, td, *J* 12.0, 4.5 Hz, **14b**);

δ_C (100 MHz, $CDCl_3$) 195.4 (**C19**), 157.5 (**C21**), 136.9 (**C13**), 136.7 (**C2**), 126.8 (**C8**), 121.3 (**C20**), 121.1 (**C11**), 118.7 (**C10**), 117.8 (**C9**), 109.0 (**C12**), 107.1 (**C7**), 67.5 (**C17**), 48.3 (**C3**), 46.5 (**C5**), 37.4 (**C16**), 31.6 (**C14**), 29.0 (N_1**Me**), 28.9 (**C6**), 25.0 (**C18**), 23.6 (**C15**). Data is in accordance with that previously reported by T. Kam *et al*.[101]

(±)-Alstonerine (4)



190 **4**

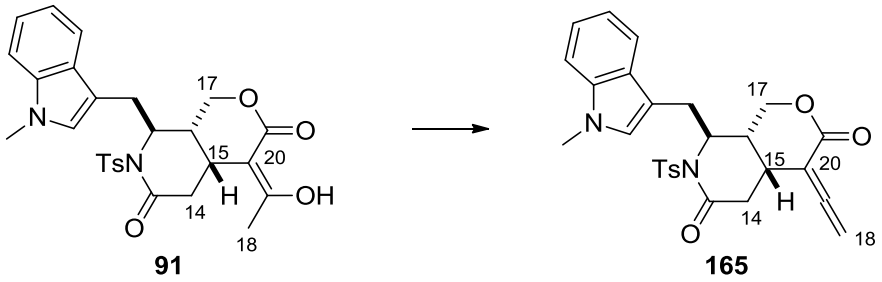
To a solution of N_4-demethylalstonerine **190** (13.0 mg, 0.040 mmol, 1.0 equiv.) in THF (1 mL) at –78°C was added Hünig's Base (0.02 mL, 0.120 mmol, 3.0 equiv.) and iodomethane (0.005mL, 0.080 mmol, 2.0 equiv.) and the solution allowed to warm slowly to rt overnight. To the resulting cloudy solution was added saturated aqueous $NaHCO_3$ (3 mL) and the aqueous phase extracted with CH_2Cl_2 (4×20 mL) and EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50→75% EtOAc–hexane) yielded *(±)-alstonerine* **4** as a pale yellow oil (12.2 mg, 91%). R_f 0.3 (100% EtOAc); FTIR (film) υ_{max}: 1652, 1618 cm^{-1}; *m/z* (CI) 337 $[M+H]^+$ (Found $[M+H]^+$, 337.1908. $C_{21}H_{24}N_2O_2$ requires $[M+H]^+$, 337.1916);

δ_H (400 MHz, $CDCl_3$) 7.53 (1H, s, **21**), 7.48 (1H, d, *J* 8.0 Hz, **9**), 7.32 (1H, d, *J* 8.0 Hz, **12**), 7.20 (1H, t, *J* 7.5 Hz, **11**), 7.09 (1H, t, *J* 7.5 Hz, **10**), 4.41 (1H, t, *J* 11.0 Hz, **17a**), 4.17 (1H, ddd, *J* 11.0, 4.0, 1.5 Hz, **17b**), 3.89 (1H, br. t, *J* 3.5 Hz, **3**), 3.65 (3H, s, N_1**Me**),

3.33 (1H, dd, *J* 16.5, 7.0 Hz, **6a**), 3.10 (1H, d, *J* 7.0 Hz, **5**), 2.66—2.58 (1H, m, **15**), 2.51 (1H, d, *J* 16.5 Hz, **6b**), 2.33 (3H, br. s, N_4**Me**), 2.15 (1H, dd, *J* 5.0, 3.0 Hz, **14a**), 2.13—2.01 (4H, m, **14b** then **18**), 1.91 (1H, dt, *J* 12.0, 4.5 Hz, **16**), 1.81 (1H, td, *J* 12.0, 4.5 Hz, **14**);

δ_C (100 MHz, $CDCl_3$) 195.5 (**C19**), 157.5 (**C21**), 137.1 (**C13**) 133.1 (**C2**), 126.6 (**C8**), 121.1 (**C10**), 120.8 (**C20**), 118.7 (**C11**), 117.9 (**C9**), 109.0 (**C12**), 105.9 (**C7**), 67.8 (**C17**), 54.7 (**C3**), 53.8 (**C5**), 41. 8 (**C16**), 38.5 (**C14**), 32.4 (**C15**), 29.1 (N_1**Me**), 25.1 (N_4**Me**), 22.9 (**C18**), 22.8 (**C6**). Data is in accordance with that previously reported.[3,101]

(4a*R,8*S**,8a*R**)-8-((1-Methylindol-3-yl)methyl)-7-tosyl-4-vinylidenetetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (165)**



To a solution of lactam–lactone **91** (34.0 mg, 0.067 mmol, 1.0 equiv.) and $PhNTf_2$ (26.0 mg, 0.074 mmol, 1.1 equiv.) in DMF (1 mL) at rt was added Hünig's base (0.35 mL, 0.200 mmol, 3.0 equiv.) and the reaction mixture stirred for 30 min at rt. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The organic layers were washed with brine and water, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (25→50% EtOAc–hexane) yielded *(4aR*,8S*,8aR*)-8-((1-methylindol-3-yl)methyl)-7-tosyl-4-vinylidenetetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione* ***165*** (19.2 mg, 88%) as an amorphous solid; R_f 0.33 (50% EtOAc–hexane); FTIR (film) υ_{max}: 1700, 1345, 1164 cm^{-1}; *m/z* (ES) 491 $[M+H]^+$, 513 $[M+Na]^+$, (Found $[M+Na]^+$, 513.1465. $C_{27}H_{26}N_2O_5S$ requires $[M+Na]^+$, 513.1460).

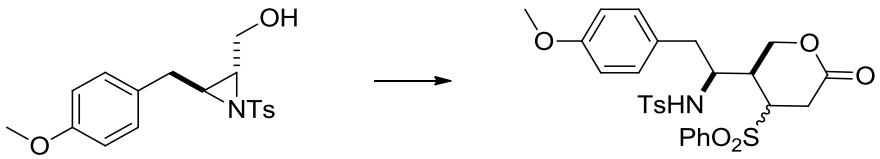
δ_H (400 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.69 (1H, d, *J* 8.0 Hz, Ar**H**), 7.38—7.30 (3H, m, Ar**H** and *meta*-**Ts**), 7.28 (1H, t, *J* 7.5 Hz, Ar**H**), 7.18 (1H, t, *J* 7.5 Hz, Ar**H**), 7.07 (1H, s, **2**), 5.12 (1H, dd, *J* 15.5, 4.5 Hz, **18a**), 4.95 (1H, dt, *J* 8.0, 4.0 Hz, **5**), 4.63 (1H, dd, *J* 15.5, 4.5

Hz, **18b**), 4.24 (1H, dd, *J* 12.0, 3.5 Hz, **17a**), 4.11 (1H, dd, *J* 12.0, 6.0 Hz, **17b**), 3.80 (3H, s, N_1**Me**), 3.48 (1H, dd, *J* 14.5, 3.5 Hz, **6a**), 3.23 (1H, dd, *J* 14.5, 8.5 Hz, **6b**), 3.10 (1H, h, *J* 5.0 Hz, **15**), 2.51 (1H, tq, *J* 9.5, 5.5, 4.5 Hz, **16**), 2.43 (3H, s, *Ts***Me**), 2.38 (1H, dd, *J* 17.5, 5.0 Hz, **14a**), 2.16 (1H, dd, *J* 17.5, 5.5 Hz, **14b**).

δ_C (100 MHz, $CDCl_3$) 214.2 (**C19**), 168.0 (**C3**), 163.3 (**C21**), 145.0 (*para*-**Ts**), 136.9 (**C13**), 135.4 (*ipso*-**Ts**), 129.4 (*meta*-Ts), 127.9 (*ortho*-**Ts**), 122.2 (**C11**), 119.8 (**C10**), 118.5 (**C12**), 109.7 (**C9**), 107.6 (**C7**), 96.5 (**C20**), 82.2 (**C18**), 69.3 (**C17**), 56.9 (**C5**), 36.7 (**C14**), 33.8 (**C16**), 32.9 (N_1**Me**), 32.6 (**C6**), 30.6 (**C15**), 21.7 (*Ts***Me**).

3.1.13 *Procedures from extension of methodology* (Section **2.2.13**)

***N*-((*S**)-2-(4-Methoxyphenyl)-1-((3*S**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2H-pyran-3-yl)ethyl)-4-methylbenzenesulfonamide (178a)** and ***N*-((*S**)-2-(4-Methoxyphenyl)-1-((3*S**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2H-pyran-3-yl)ethyl)-4-methylbenzenesulfonamide (178b)**



178 **178**

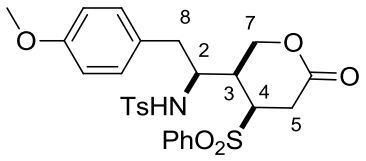
To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (305 mg, 1.11 mmol, 2.0 equiv.) in THF (1 mL) at –78°C was added *n*-BuLi (2.48 M in hexanes; 0.67 mL, 1.67 mmol, 2.5 equiv.) and the solution stirred for 1 h at –78°C.

Meanwhile, *n*-BuLi (2.48 M in hexanes; 0.34 mL, 0.840 mmol, 1.5 equiv.) was added to a solution of hydroxymethyl-aziridine **178** (193 mg, 0.556 mmol, 1.0 equiv.) in THF (1 mL) at –78°C and the solution stirred at –78°C for 1 h.

The dark red solution of deprotonated **88** was added dropwise *via* cannula to the solution of *O*-lithio hydroxymethyl-aziridine **178**, maintaining both solutions at –78°C throughout the addition. The reaction mixture was allowed to warm slowly from –78°C to rt overnight.

Aqueous HCl (2 M; 6.0 mL, 12.0 mmol, ~20 equiv.) was added and the solution stirred for 2 h at rt. The aqueous layer was extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *lactones* ***178*** (120.7 mg, 82%) as a 2:1 mixture of sulfone epimers.

_N_-((_S_*)-2-(4-Methoxyphenyl)-1-((3_S_*,4_R_*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2_H_-pyran-3-yl)ethyl)-4-methylbenzenesulfonamide (178a)



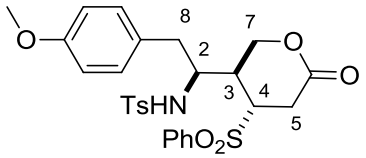
178a

R_f 0.50 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3266, 2942, 1751, 1611, 1514, 1446 cm^{-1}; *m/z* (CI) 544 $[M+H]^+$ (Found $[M+H]^+$, 544.1447. $C_{27}H_{29}NO_7S_2$ requires $[M+H]^+$, 544.1464).

δ_H (400 MHz, $CDCl_3$) 7.80 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.71—7.64 (3H, m, *ortho*-Ts and *para*-**Ph**SO_2), 7.54 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 7.23 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.69 (4H, ap. q, *J* 9.0 Hz, *ortho*- and *meta*-**PMB**), 5.82 (1H, d, *J* 9.5 Hz, **2**), 4.42 (1H, dd, *J* 12.0, 6.0 Hz, **7a**), 4.32 (1H, dd, *J* 12.0, 4.5 Hz, **7b**), 4.25 (1H, q, *J* 13.0 Hz, **4**), 3.75 (3H, s, O**Me**), 3.69—3.61 (1H, m, **2**), 2.81 (2H, dd, *J* 7.0, 1.5 Hz, **5a** and **5b**), 2.58—2.47 (2H, m, **8a** then **3**), 2.39 (3H, s, *Ts***Me**), 2.30 (1H, dd, *J* 14.0, 6.0 Hz, **8b**);

δ_C (400 MHz, $CDCl_3$) 169.9 (**C6**), 158.6 (*para*-**PMB**), 143.9 (*para*-**Ts**), 136.6 (*ipso*-**Ts**), 136.2 (*ipso*-**Ph**SO_2),134.3 (*para*-**Ph**SO_2), 129.9 (*meta*-**Ts**), 129.7 (*meta*-**PMB**), 129.6 (*meta*-**Ph**SO_2), 129.1 (*ortho*-**Ph**SO_2), 127.7 (*ipso*-**PMB**), 127.2 (*ortho*-**Ts**), 114.3 (*ortho*-**PMB**), 64.9 (**C7**), 57.3 (**C2**), 56.9 (**C4**), 55.2 (O**Me**), 37.6 (**C8**), 34.7 (**C3**), 28.8 (**C5**), 21.6 (*Ts***Me**).

***N*-((*S**)-2-(4-Methoxyphenyl)-1-((3*S**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)-4-methylbenzenesulfonamide (178b)**



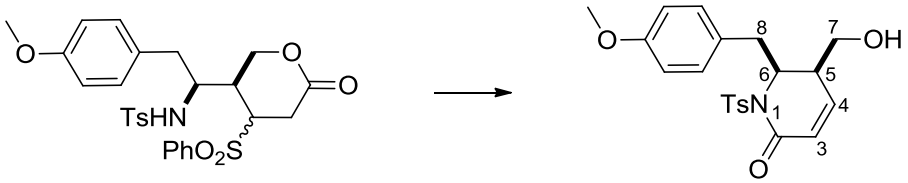
178b

R_f 0.35 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3270, 2925, 1735, 1615, 1514, 1448 cm^{-1}; *m/z* (CI) 544 $[M+H]^+$ (Found $[M+H]^+$, 544.1457. $C_{27}H_{29}NO_7S_2$ requires $[M+H]^+$, 544.1464);

δ_H (400 MHz, $CDCl_3$) 7.87 (2H, app. d *J* 8.0 Hz, *ortho*-**Ph**SO_2), 7.20 (1H, td, *J* 8.0, 1.0 Hz, *para*-**Ph**SO_2), 7.64—7.55 (4H, m, *ortho*-**Ts** and *meta*-**Ph**SO_2), 7.20 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.91 (2H, d, *J* 8.0 Hz, *meta*-**PMB**), 6.68 (2H, d, *J* 8.0 Hz, *ortho*-**PMB**), 4.85 (1H, d, *J* 9.5 Hz, **2**), 4.75 (1H, dd, *J* 12.0, 6.0 Hz, **7a**), 4.58—4.44 (1H, m, **7b**), 3.75 (4H, s, O**Me** and **4**), 3.69—3.64 (1H, m, **2**), 3.00 (1H, dd, *J* 7.0, 1.5 Hz, **5a**), 2.89—2.74 (2H, m, **8a** then **5b**), 2.60—2.50 (2H, m, **3** and **8b**), 2.43 (3H, s, *Ts***Me**);

δ_C (400 MHz, $CDCl_3$) 166.6 (**C6**), 158.8 (*para*-**PMB**), 143.5 (*para*-**Ts**), 137.7 (*ipso*-**Ts**), 137.1 (*ipso*-**Ph**SO_2),134.7 (*para*-**Ph**SO_2), 130.5 (*meta*-**Ts**), 130.0 (*meta*-**PMB**), 129.8 (*meta*-**Ph**SO_2), 129.7 (*ortho*-**Ph**SO_2), 128.6 (*ipso*-**PMB**), 127.2 (*ortho*-**Ts**), 114.3 (*ortho*-**PMB**), 69.1 (**C7**), 58.0 (**C2**), 55.2 (**C4**), 53.1 (O**Me**), 39.9 (**C8**), 38.1 (**C3**), 31.5 (**C5**), 21.6 (*Ts***Me**).

(5*S,6*S**)-5-(Hydroxymethyl)-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (177)**



178 **177**

To a solution of lactones **178** (10.0 mg, 0.018 mmol, 1.0 equiv.) in toluene (1 mL) was added trimethylaluminium (2 M in hexanes; 0.025 mL, 0.050 mmol, 2.8 equiv.) in a

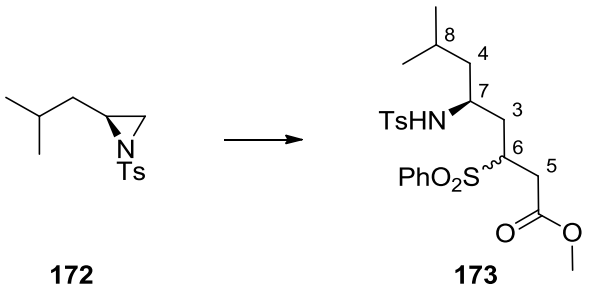
sealed tube and the reaction mixture stirred at rt for 1 h, then heated to 50°C for 5 min in the microwave.

On cooling to rt, saturated aqueous Rochelle salt (5 mL) and EtOAc (10 mL) were added and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added and the aqueous layer extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×30 mL). The combined organics were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(5S*,6S*)-5-(hydroxymethyl)-6-(4-methoxybenzyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***177*** (6.91 mg, 96%) as a colourless amorphous solid; R_f 0.35 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3530, 3056, 2917, 1687 3420, 2890, 1630, 1470 cm^{-1}; *m/z* (CI) 424 $[M+Na]^+$ (Found $[M+Na]^+$, 424.1198. $C_{21}H_{23}NO_5S$ requires $[M+Na]^+$, 424.1195);

δ_H (500 MHz, $CDCl_3$) 7.80 (2H, app. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.23 (2H, app. d, *J* 8.0 Hz, *meta*-**Ts**), 7.18 (2H, app. d, *J* 8.0 Hz, *meta*-**PMB**), 6.82 (2H, app. d, *J* 8.0 Hz, *ortho*-**PMB**), 6.49 (1H, dt, *J* 10.0, 2.0 Hz, **4**), 5.91 (1H, dd, *J* 10.0, 3.0 Hz, **3**), 5.29—5.25 (1H, m, **6**), 3.80 (3H, s, *O***Me**), 3.67—3.62 (2H, m, **7a** and **7b**), 3.27—3.21 (1H, m, **5**), 3.00 (1H, dd, *J* 14.0, 8.0 Hz, **8a**), 2.91 (1H, dd, *J* 14.0, 8.0 Hz, **8b**), 2.40 (3H, s, *Ts***Me**);

δ_C (125 MHz, $CDCl_3$) 162.5 (**C2**), 158.9 (*para*-**PMB**), 144.5 (*para*-**Ts**), 143.2 (**C4**), 136.5 (*ipso*-**Ts**), 130.4 (*meta*-**PMB**), 129.2 (*meta*-**Ts**), 128.9 (*ortho*-**Ts**), 124.9 (*ipso*-**PMB**), 114.4 (*meta*-**PMB**), 61.5 (**C7**), 58.5 (**C6**), 55.2 (*O***Me**), 43.6 (**C5**), 35.3 (**C8**), 21.6 (*Ts***Me**).

(*S*)-Methyl 7-methyl-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)octanoate (173)



172 **173**

To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (305 mg, 1.11 mmol, 2.0 equiv.) in THF (1 mL) at –78°C was added *n*-BuLi (2.48 M in hexanes; 0.67 mL, 1.67 mmol, 2.5 equiv.)

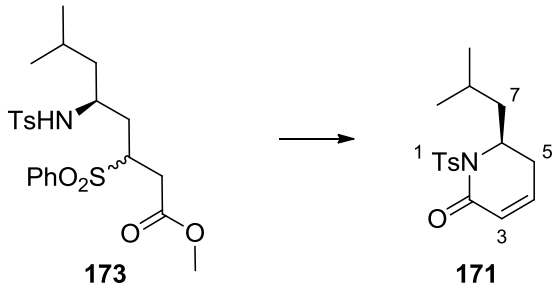
and the solution stirred for 1 h at –78°C. A solution of (*S*)-2-isobutyl-1-tosylaziridine **172** was added and the solution allowed to warm slowly from –78°C to rt overnight.

Aqueous HCl (2 M; 6.0 mL, 12.0 mmol, ~20 equiv.) was added and the solution stirred for 2 h at rt. The aqueous layer was extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(S)-methyl 7-methyl-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)octanoate **173*** (121 mg, 82%) as a colourless oil and a 7:3 mixture of sulfone epimers; R_f 0.50 (50% EtOAc–hexane); $[\alpha]_D$ – 6.6 (*c* 0.73, CH_2Cl_2); FTIR (film) υ_{max}: 3279, 2955, 1738, 1598, 1447, 1305, 1156 cm^{-1}; *m/z* (ES) 482 $[M+H]^+$ (Found $[M+H]^+$, 482.1664. $C_{23}H_{31}NO_6S_2$ requires $[M+H]^+$, 482.1671).

δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.31 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.63 (3H, br. t, *J* 8.0 Hz, Ar**H**), 5.86 (2H, dd, *J* 10.0, 3.0 Hz, Ar**H**), 4.88 (1H, dt, *J* 10.5, 5.0 Hz, **6**), 2.73 (1H, ddt, *J* 18.5, 6.0, 2.5 Hz, **5**), 2.50—2.38 (4H, m, *Ts***Me**), 1.72 (1H, ddd, *J* 14.0, 10.0, 4.5 Hz, **5a**), 1.65—1.44 (3H, m, **5b**, **4a** and **4b**), 1.00 (3H, d, *J* 6.5 Hz, *i*Pr), 0.94 (3H, d, *J* 6.5 Hz, *i*Pr);

δ_C (100 MHz, $CDCl_3$) 172.2 (**CO**), 141.7 (*par*a-**Ts**), 129.2 (*meta*-**Ts**), 129.0 (*ortho*-**Ts**), 124.9 (*ipso*-**Ts**), 53.6 (**C6**), 42.0 (**C7**), 28.4 (**C5**), 25.4 (**C8**), 23.4 (*i*Pr**Me**), 21.7 (Ts**Me**), 21.4 (*i*Pr**Me**).

(*S*)-6-Isobutyl-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (171)



173 **171**

To a stirred solution (*S*)-methyl 7-methyl-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)octanoate **173** (305 mg, 1.11 mmol, 2.0 equiv.) in toluene (1 mL) at –78°C was added trimethylaluminium (2.0 M in toluene; 0.67 mL, 1.67 mmol, 2.5 equiv.) and

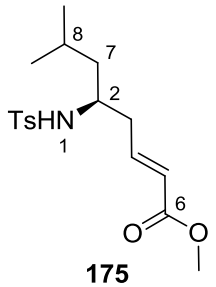
the solution allowed to warm slowly from –78°C to rt overnight. The reaction mixture was then heated under reflux at 120°C for 1 h and cooled to rt.

Saturated aqueous Rochelle salt (2 mL) and EtOAc (5 mL) were added and the solution stirred vigorously for 2 h at rt. The aqueous layer was extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded *(S)-6-isobutyl-1-tosyl-5,6-dihydropyridin-2(1H)-one* ***171*** (121 mg, 82%) as a colourless oil; R_f 0.50 (50% EtOAc–hexane); $[\alpha]_D$ – 17.0 (*c* 0.47, CH_2Cl_2); FTIR (film) υ_{max}: 2956, 1736, 1686, 1597, 1384, 1345, 1167 cm^{-1}; *m/z* (ES) 308 $[M+H]^+$ (Found $[M+H]^+$, 3081344. $C_{16}H_{21}NO_3S$ requires $[M+H]^+$, 308.1320).

δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.31 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.63 (1H, br. t, *J* 8.0 Hz, **4**), 5.86 (1H, dd, *J* 10.0, 3.0 Hz, **3**), 4.88 (1H, dt, *J* 10.5, 5.0 Hz, **6**), 2.73 (1H, ddt, *J* 18.5, 6.0, 2.5 Hz, **5**), 2.50—2.38 (4H, m, *Ts***Me** and **7**), 1.72 (1H, ddd, *J* 14.0, 10.0, 4.5 Hz, **8**), 1.65—1.44 (3H, m, *i*Pr), 1.00 (3H, d, *J* 6.5 Hz, *i*Pr), 0.94 (3H, d, *J* 6.5 Hz, *i*Pr);

δ_C (100 MHz, $CDCl_3$) 141.7 (*par*a-**Ts**), 129.2 (*meta*-**Ts**), 129.0 (*ortho*-**Ts**), 124.9 (*ipso*-**Ts**), 53.6 (**C6**), 42.0 (**C7**), 28.4 (**C5**), 25.4 (**C8**), 23.4 (*i*Pr**Me**), 21.7 (Ts**Me**), 21.4 (*i*Pr**Me**).

(*S*,*E*)-Methyl 7-methyl-5-(4-methylphenylsulfonamido)oct-2-enoate (175)



175

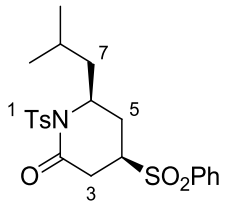
R_f 0.50 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3280, 1723, 1708, 1658, 1599, 1327, 1159 cm^{-1}; *m/z* (ES) 340 $[M+H]^+$ (Found $[M+H]^+$, 340.1584. $C_{16}H_{21}NO_3S$ requires $[M+H]^+$, 340.1583).

δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.33 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 6.78 (1H, dt, *J* 15.5, 7.5 Hz, **4**), 5.76 (1H, dt, *J* 15.5, 1.5 Hz, **5**), 4.30 (1H, d, *J* 8.5 Hz, *N***H**Ts), 3.75 (3H, s, *O***Me**), 3.46 (1H, tq, *J* 8.5, 5.5 Hz,), 2.46 (3H, s, *Ts***Me**), 2.34 (2H, dddd, *J* 15.0, 12.5,

9.0, 7.0 Hz, **3**), 1.73—1.44 (2H, m, **7a** and **7b**), 1.38—1.09 (2H, m, **7**), 0.83 (3H, d, *J* 6.5 Hz, **Me**), 0.70 (3H, d, *J* 6.5 Hz, **Me**).

δ_C (100 MHz, $CDCl_3$) 143.6 (*par*a-**Ts**), 137.8 (beta C=C), 129.8 (*meta*-**Ts**), 127.1 (*ortho*-**Ts**), 124.5 (*ipso*-**Ts**), 51.6 (*O***Me**), 51.0 (**C2**), 44.0 (**C7**), 38.2 (**C3**), 24.4 (**C8**), 22.8 (*i*Pr**Me**), 21.7 (*i*Pr**Me**), 21.6 (*Ts***Me**).

(4*R,6*S**)-6-Isobutyl-4-(phenylsulfonyl)-1-tosylpiperidin-2-one (174)**



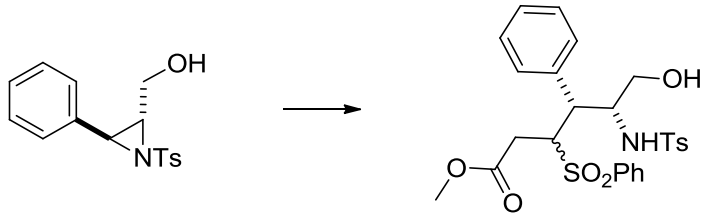
174

R_f 0.50 (50% EtOAc–hexane); FTIR (film) υ_{max}: 2957, 1739, 1693, 1596, 1447, 1348, 1166 cm^{-1}; *m/z* (ES) 450 $[M+H]^+$ (Found $[M+H]^+$, 450.1419. $C_{22}H_{27}NO_5S_2$ requires $[M+H]^+$, 450.1409).

δ_H (400 MHz, $CDCl_3$) 7.95—7.80 (4H, m, Ar**H**), 7.79—7.65 (1H, m, Ar**H**), 7.59 (2H, td, *J* 7.5, 4.0 Hz, Ar**H**), 7.30 (2H, d, *J* 8.0 Hz, Ar**H**), 4.78 (1H, ddq, *J* 10.0, 5.0, 3.0 Hz, **4**), 3.56—3.29 (1H, m, **6**), 2.84—2.70 (1H, m, **3a**), 2.68—2.52 (2H, m, **3b**), 2.51—2.36 (5H, m, **5a**, **7b** and *Ts***Me**), 1.95 (1H, td, *J* 13.5, 4.5 Hz, **5b**), 1.76 (1H, dtd, *J* 12.5, 9.0, 8.5, 4.5 Hz, **7a**), 1.71—1.50 (2H, m,), 1.44 (1H, ddd, *J* 14.5, 10.5, 4.5 Hz, **8**). 1.04—0.91 (6H, m *i*Pr);

δ_C (100 MHz, $CDCl_3$) 166.0, 145.2, 135.9, 134.6, 129.7, 129.5, 129.4, 129.3, 129.1, 129.0, 128.7, 56.0, 54.3, 53.6, 53.4, 46.2, 43.5, 33.6, 32.8, 25.3, 25.1, 23.6, 21.7, 20.9.

(3*R,4*R**,5*S**)-Methyl 6-(*tert*-butyldimethylsilyloxy)-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate (183a)** and **(3*S**,4*R**,5*S**)-Methyl 6-hydroxy-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate (183b)**



180 **183**

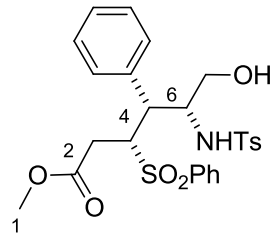
To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **88** (150 mg, 0.456 mmol, 2.0 equiv.) in THF (5 mL) at –78°C was added *n*-BuLi (2.48 M in hexanes; 0.28 mL, 0.684 mmol, 1.5 equiv.) and the solution stirred for 1 h at –78°C.

Meanwhile, *n*-BuLi (2.48 M in hexanes; 0.14 mL, 0.342 mmol, 1.5 equiv.) was added to a solution of hydroxymethyl-aziridine **180** (70.0 mg, 0.228 mmol, 1.0 equiv.) in THF (1 mL) at –78°C and the solution stirred at –78°C for 1 h.

The dark red solution of deprotonated **88** was added dropwise *via* cannula to the solution of *O*-lithio hydroxymethyl-aziridine **180**, maintaining both solutions at –78°C throughout the addition. The reaction mixture was allowed to warm slowly from –78°C to rt overnight.

Aqueous HCl (2 M; 4.0 mL, 8.0 mmol, ~10 equiv.) was added and the solution stirred for 2h at rt. The aqueous layer was extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded a complex mixture that included *(3R*,4R*,5S*)-methyl 6-(tert-butyldimethylsilyloxy)-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate* ***183a*** *and (3S*,4R*,5S*)-methyl 6-hydroxy-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate* ***183b***.

(3*R,4*R**,5*S**)-Methyl 6-(*tert*-butyldimethylsilyloxy)-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate (183a)**



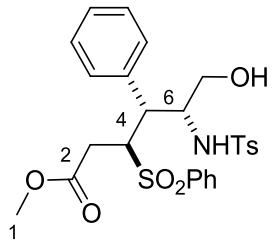
183a

R_f 0.25 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3482, 3249, 2930, 1731, 1444, 1160 cm^{-1}; *m/z* (ES) 532 $[M+H]^+$ (Found $[M+H]^+$, 532.1442. $C_{26}H_{29}NO_7S_2$ requires $[M+H]^+$, 532.1464).

δ_H (400 MHz, $CDCl_3$) 8.00—7.94 (2H, m, *ortho*-**Ph**SO_2), 7.82—7.77 (2H, m, *ortho*-**Ts**), 7.69—7.63 (1H, m, *para*-**Ph**SO_2), 7.60—7.54 (2H, m, *meta*-**Ph**SO_2), 7.31 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.28—7.24 (2H, m, *ortho*-**Ph**), 7.18—7.12 (2H, m, *meta*-**Ph**), 4.83 (1H, d, *J* 9.0 Hz, N_4**H**), 4.59—4.36 (2H, m, **4** and **6**), 3.81 (1H, dd, *J* 8.0, 4.5 Hz, **5**), 3.52—3.42 (1H, m, **7a**), 3.31 (3H, s, *O***Me**), 3.28—3.17 (1H, dd, *J* 11.5, 5.5 Hz, **7b**), 2.52—2.41 (4H, m, **3a** and *Ts***Me**), 2.30—2.18 (1H, dd, *J* 18.0, 5.5 Hz, **3b**);

δ_C (100 MHz, $CDCl_3$) 170.4 (**C2**), 143.7 (*para*-**Ts**), 137.7 (*ipso*-**Ph**SO_2), 137.1 (*ipso*-**Ts**), 135.3 (*ipso*-**Ph**), 134.1 (*para*-**Ph**SO_2), 130.3 (**Ph**), 129.8 (*ortho*-**Ph**), 129.3 (*meta*-***Ts***), 129.2 (*meta*-**Ph**SO_2), 128.9 (*ortho*-**Ph**SO_2), 128.2 (**Ph**), 127.5 (*ortho*-**Ts**), 63.1 (**C7**), 59.9 (**C4**), 56.2 (**C6**), 52.0 (*O***Me**), 44.7 (**C5**), 33.3 (**C3**), 21.6 (*Ts***Me**).

(3*S,4*R**,5*S**)-Methyl 6-hydroxy-5-(4-methylphenylsulfonamido)-4-phenyl-3-(phenylsulfonyl)hexanoate (183b)**



183b

R_f 0.18 (50% EtOAc–hexane); FTIR (film) υ_{max}: 3484, 3249, 2930, 1734, 1447, 1156 cm^{-1}; *m/z* (ES) 532 $[M+H]^+$ (Found $[M+H]^+$, 532.1434. $C_{26}H_{29}NO_7S_2$ requires $[M+H]^+$, 532.1464).

δ_H (400 MHz, $CDCl_3$) 7.67—7.62 (2H, m, *ortho*-**Ts**), 7.56—7.49 (3H, m, *ortho*- and *para*-**Ph**SO_2), 7.41—7.34 (2H, m, *meta*-**Ph**SO_2), 7.32—7.25 (2H, s, *meta*-**Ts**), 7.23—7.15 (1H, m, *para*-**Ph**), 7.11—7.02 (4H, m, *ortho*- and *meta*-**Ph**), 4.44—4.33 (1H, m, **4**), 4.21—4.10 (1H, m, **5**), 3.75 (3H, s, *O***Me**), 3.69—3.60 (1H, m, **6**), 3.60—3.50 (1H, m, **7a**), 3.41—3.30 (1H, q, *J* 6.0 Hz, **7b**), 3.13 (1H, dd, *J* 17.5, 5.0 Hz, **3a**), 2.99 (1H, dd, *J* 17.5, 7.5 Hz, **3b**), 2.45 (3H, s, *Ts***Me**);

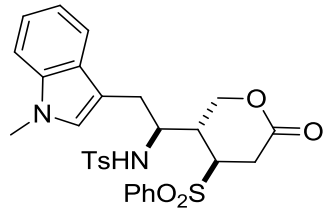
δ_C (100 MHz, $CDCl_3$) 171.1 (**C2**), 143.9 (*para*-**Ts**), 139.8 (*para*-**Ph**SO_2), 137.1 (*ipso*-**Ts**), 134.9 (*ipso*-**Ph**), 133.2 (*ipso*-**Ph**SO_2), 129.9 (*meta*-***Ts***), 129.8 (*ortho*-**Ph**), 129.0 (*meta*-**Ph**), 128.7 (*meta*-**Ph**SO_2), 128.1 (*para*-**Ph**), 127.9 (*ortho*-**Ph**SO_2), 127.1 (*ortho*-**Ts**), 62.9 (**C4**), 62.8 (**C7**), 55.3 (**C5**), 52.4 (*O***Me**), 45.7 (**C6**), 31.1 (**C3**), 21.6 (*Ts***Me**).

Chapter 4

Appendix

4.1 X-Ray Crystallography data

4.1.1 4-Methyl-*N*-((*S*)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R*,4*R*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (109a)



109a

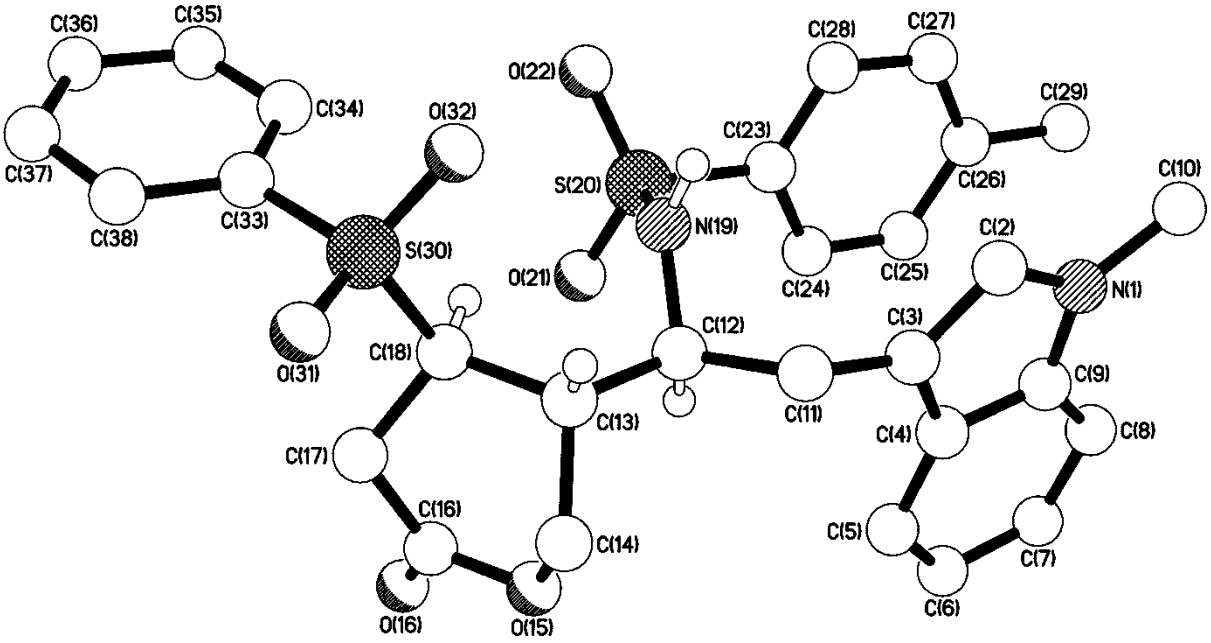


Table 1. Crystal data and structure refinement for **109a**.

Identification code	DC1202
Formula	C29 H30 N2 O6 S2
Formula weight	566.67
Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å

Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 7.95229(13) Å α = 90°
	b = 16.6978(3) Å β = 90.4896(17)°
	c = 20.2810(4) Å γ = 90°
Volume, Z	2692.93(8) $Å^3$, 4
Density (calculated)	1.398 Mg/m^3
Absorption coefficient	0.245 mm^{-1}
F(000)	1192
Crystal colour / morphology	Colourless blocky needles
Crystal size	0.44 x 0.17 x 0.14 mm^3
θ range for data collection	3.00 to 29.56°
Index ranges	-10<=h<=10, -22<=k<=21, -26<=l<=22
Reflns collected / unique	22471 / 6598 [R(int) = 0.0253]
Reflns observed [F>4σ(F)]	5366
Absorption correction	Analytical
Max. and min. transmission	0.970 and 0.929
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6598 / 1 / 359
Goodness-of-fit on F^2	1.051
Final R indices [F>4σ(F)]	R1 = 0.0394, wR2 = 0.0933
R indices (all data)	R1 = 0.0530, wR2 = 0.0998
Extinction coefficient	0.0015(4)
Largest diff. peak, hole	0.332, -0.379 $eÅ^{-3}$

Mean and maximum shift/error 0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC1202.

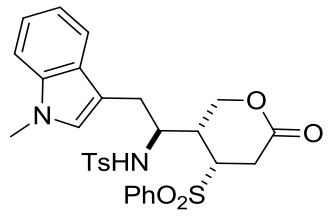
N(1)-C(9)	1.375(2)
N(1)-C(2)	1.377(2)
N(1)-C(10)	1.457(2)
C(2)-C(3)	1.363(2)
C(3)-C(4)	1.436(2)
C(3)-C(11)	1.500(2)
C(4)-C(5)	1.398(2)
C(4)-C(9)	1.420(2)
C(5)-C(6)	1.388(2)
C(6)-C(7)	1.400(3)
C(7)-C(8)	1.380(3)
C(8)-C(9)	1.396(2)
C(11)-C(12)	1.535(2)
C(12)-N(19)	1.4627(18)
C(12)-C(13)	1.5596(18)
C(13)-C(14)	1.522(2)
C(13)-C(18)	1.547(2)
C(14)-O(15)	1.454(2)
O(15)-C(16)	1.346(2)
C(16)-O(16)	1.200(2)
C(16)-C(17)	1.504(2)
C(17)-C(18)	1.535(2)
C(18)-S(30)	1.7949(15)
N(19)-S(20)	1.6142(13)
S(20)-O(22)	1.4274(13)
S(20)-O(21)	1.4379(13)
S(20)-C(23)	1.7643(15)
C(23)-C(24)	1.382(2)

C(23)-C(28)	1.392(2)
C(24)-C(25)	1.388(2)
C(25)-C(26)	1.381(2)
C(26)-C(27)	1.386(2)
C(26)-C(29)	1.513(2)
C(27)-C(28)	1.384(2)
S(30)-O(32)	1.4394(12)
S(30)-O(31)	1.4401(11)
S(30)-C(33)	1.7651(16)
C(33)-C(38)	1.387(2)
C(33)-C(34)	1.393(2)
C(34)-C(35)	1.383(2)
C(35)-C(36)	1.387(3)
C(36)-C(37)	1.377(3)
C(37)-C(38)	1.387(2)
C(9)-N(1)-C(2)	108.41(13)
C(9)-N(1)-C(10)	126.23(14)
C(2)-N(1)-C(10)	125.31(15)
C(3)-C(2)-N(1)	110.71(14)
C(2)-C(3)-C(4)	106.35(13)
C(2)-C(3)-C(11)	126.16(15)
C(4)-C(3)-C(11)	127.45(14)
C(5)-C(4)-C(9)	118.35(15)
C(5)-C(4)-C(3)	134.75(14)
C(9)-C(4)-C(3)	106.89(13)
C(6)-C(5)-C(4)	119.38(15)
C(5)-C(6)-C(7)	120.96(16)
C(8)-C(7)-C(6)	121.35(16)
C(7)-C(8)-C(9)	117.52(15)
N(1)-C(9)-C(8)	129.91(14)

N(1)-C(9)-C(4)	107.64(13)
C(8)-C(9)-C(4)	122.43(15)
C(3)-C(11)-C(12)	114.92(12)
N(19)-C(12)-C(11)	110.35(12)
N(19)-C(12)-C(13)	110.19(11)
C(11)-C(12)-C(13)	110.04(11)
C(14)-C(13)-C(18)	108.13(12)
C(14)-C(13)-C(12)	111.89(12)
C(18)-C(13)-C(12)	112.02(11)
O(15)-C(14)-C(13)	111.06(12)
C(16)-O(15)-C(14)	116.23(12)
O(16)-C(16)-O(15)	119.47(15)
O(16)-C(16)-C(17)	124.92(16)
O(15)-C(16)-C(17)	115.61(14)
C(16)-C(17)-C(18)	111.69(12)
C(17)-C(18)-C(13)	113.65(12)
C(17)-C(18)-S(30)	110.81(10)
C(13)-C(18)-S(30)	109.08(10)
C(12)-N(19)-S(20)	124.07(11)
O(22)-S(20)-O(21)	119.57(8)
O(22)-S(20)-N(19)	106.86(7)
O(21)-S(20)-N(19)	106.25(7)
O(22)-S(20)-C(23)	107.53(7)
O(21)-S(20)-C(23)	107.72(8)
N(19)-S(20)-C(23)	108.52(7)
C(24)-C(23)-C(28)	120.86(14)
C(24)-C(23)-S(20)	120.03(12)
C(28)-C(23)-S(20)	119.11(12)
C(23)-C(24)-C(25)	119.03(15)
C(26)-C(25)-C(24)	121.36(16)

C(25)-C(26)-C(27)	118.47(15)
C(25)-C(26)-C(29)	120.88(17)
C(27)-C(26)-C(29)	120.65(17)
C(28)-C(27)-C(26)	121.62(16)
C(27)-C(28)-C(23)	118.64(15)
O(32)-S(30)-O(31)	118.50(8)
O(32)-S(30)-C(33)	107.88(7)
O(31)-S(30)-C(33)	109.01(7)
O(32)-S(30)-C(18)	106.90(7)
O(31)-S(30)-C(18)	109.14(7)
C(33)-S(30)-C(18)	104.51(7)
C(38)-C(33)-C(34)	121.60(15)
C(38)-C(33)-S(30)	119.25(12)
C(34)-C(33)-S(30)	119.07(12)
C(35)-C(34)-C(33)	118.72(16)
C(34)-C(35)-C(36)	120.13(16)
C(37)-C(36)-C(35)	120.49(17)
C(36)-C(37)-C(38)	120.50(17)
C(33)-C(38)-C(37)	118.51(15)

4.1.2 4-methyl-*N*-((*S*)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R*,4*S*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (**109b**)



109b

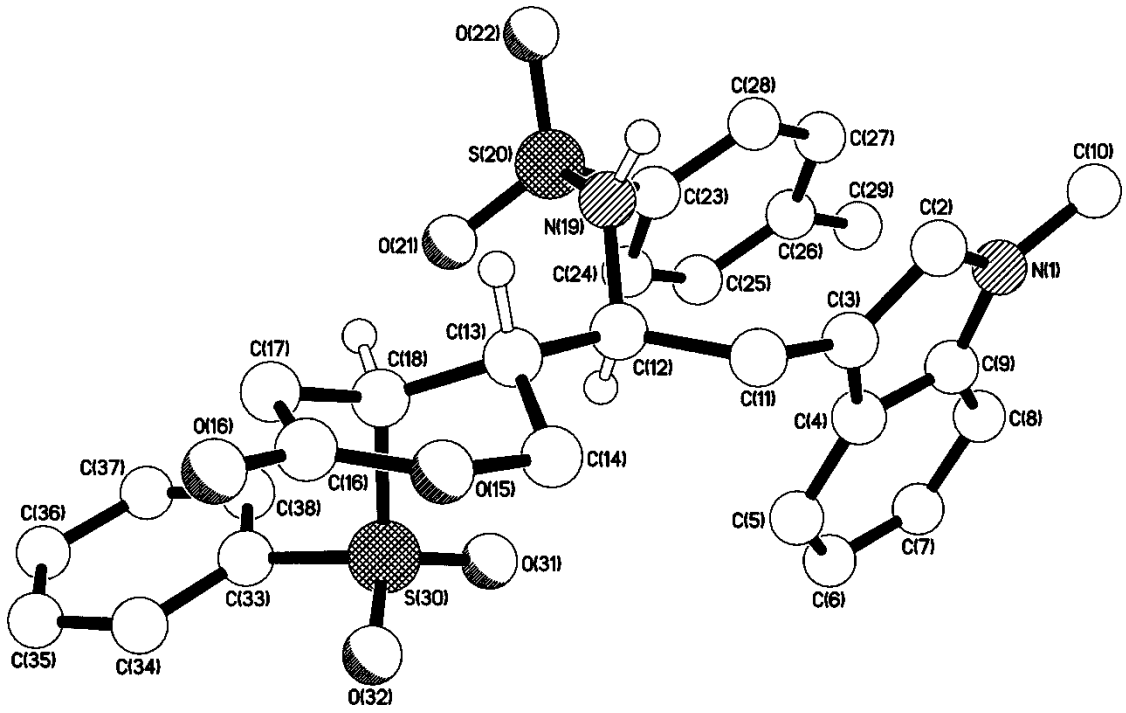


Table 1. Crystal data and structure refinement for **109b**.

Identification code	DC1201
Formula	C29 H30 N2 O6 S2
Formula weight	566.67
Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å

Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.7991(3) Å α = 71.755(4)°
	b = 12.5139(6) Å β = 73.837(3)°
	c = 12.5365(4) Å γ = 70.745(4)°
Volume, Z	1351.79(10) $Å^3$, 2
Density (calculated)	1.392 Mg/m^3
Absorption coefficient	0.244 mm^{-1}
F(000)	596
Crystal colour / morphology	Colourless needles
Crystal size	0.47 x 0.16 x 0.09 mm^3
θ range for data collection	3.10 to 32.73°
Index ranges	-14<=h<=13, -17<=k<=17, -18<=l<=18
Reflns collected / unique	14838 / 8847 [R(int) = 0.0170]
Reflns observed [F>4σ(F)]	7123
Absorption correction	Analytical
Max. and min. transmission	0.981 and 0.931
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8847 / 1 / 358
Goodness-of-fit on F^2	1.055
Final R indices [F>4σ(F)]	R1 = 0.0420, wR2 = 0.1110
R indices (all data)	R1 = 0.0560, wR2 = 0.1195
Largest diff. peak, hole	0.497, -0.415 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC1201.

N(1)-C(9)	1.370(2)
N(1)-C(2)	1.3753(18)
N(1)-C(10)	1.4533(19)
C(2)-C(3)	1.3681(19)
C(3)-C(4)	1.4375(19)
C(3)-C(11)	1.4969(17)
C(4)-C(5)	1.399(2)
C(4)-C(9)	1.4233(19)
C(5)-C(6)	1.390(2)
C(6)-C(7)	1.405(3)
C(7)-C(8)	1.361(3)
C(8)-C(9)	1.402(2)
C(11)-C(12)	1.5395(17)
C(12)-N(19)	1.4654(16)
C(12)-C(13)	1.5607(16)
C(13)-C(14)	1.5253(17)
C(13)-C(18)	1.5438(16)
C(14)-O(15)	1.4582(15)
O(15)-C(16)	1.3445(16)
C(16)-O(16)	1.2123(15)
C(16)-C(17)	1.5079(18)
C(17)-C(18)	1.5286(16)
C(18)-S(30)	1.8069(13)
N(19)-S(20)	1.6074(11)
S(20)-O(21)	1.4368(10)
S(20)-O(22)	1.4403(10)
S(20)-C(23)	1.7662(12)
C(23)-C(24)	1.3844(19)

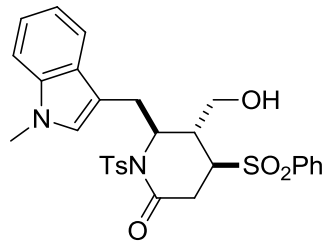
C(23)-C(28)	1.3921(18)
C(24)-C(25)	1.3911(19)
C(25)-C(26)	1.387(2)
C(26)-C(27)	1.390(2)
C(26)-C(29)	1.5068(19)
C(27)-C(28)	1.3853(18)
S(30)-O(31)	1.4398(10)
S(30)-O(32)	1.4403(10)
S(30)-C(33)	1.7657(13)
C(33)-C(34)	1.384(2)
C(33)-C(38)	1.387(2)
C(34)-C(35)	1.399(2)
C(35)-C(36)	1.376(3)
C(36)-C(37)	1.376(3)
C(37)-C(38)	1.387(2)

C(9)-N(1)-C(2)	108.75(11)
C(9)-N(1)-C(10)	125.86(14)
C(2)-N(1)-C(10)	125.37(14)
C(3)-C(2)-N(1)	110.30(13)
C(2)-C(3)-C(4)	106.64(12)
C(2)-C(3)-C(11)	126.93(13)
C(4)-C(3)-C(11)	126.43(12)
C(5)-C(4)-C(9)	119.32(13)
C(5)-C(4)-C(3)	134.30(13)
C(9)-C(4)-C(3)	106.37(12)
C(6)-C(5)-C(4)	118.49(15)
C(5)-C(6)-C(7)	120.98(16)
C(8)-C(7)-C(6)	121.93(15)
C(7)-C(8)-C(9)	117.79(15)

N(1)-C(9)-C(8)	130.59(14)
N(1)-C(9)-C(4)	107.93(12)
C(8)-C(9)-C(4)	121.49(15)
C(3)-C(11)-C(12)	112.96(10)
N(19)-C(12)-C(11)	109.87(10)
N(19)-C(12)-C(13)	108.53(9)
C(11)-C(12)-C(13)	113.05(9)
C(14)-C(13)-C(18)	109.13(10)
C(14)-C(13)-C(12)	115.45(10)
C(18)-C(13)-C(12)	114.27(9)
O(15)-C(14)-C(13)	111.94(10)
C(16)-O(15)-C(14)	123.17(10)
O(16)-C(16)-O(15)	117.51(12)
O(16)-C(16)-C(17)	121.59(12)
O(15)-C(16)-C(17)	120.69(11)
C(16)-C(17)-C(18)	115.44(10)
C(17)-C(18)-C(13)	107.96(9)
C(17)-C(18)-S(30)	109.13(9)
C(13)-C(18)-S(30)	113.13(8)
C(12)-N(19)-S(20)	124.57(9)
O(21)-S(20)-O(22)	119.42(6)
O(21)-S(20)-N(19)	108.67(6)
O(22)-S(20)-N(19)	105.31(6)
O(21)-S(20)-C(23)	106.09(6)
O(22)-S(20)-C(23)	107.22(6)
N(19)-S(20)-C(23)	109.96(6)
C(24)-C(23)-C(28)	120.36(12)
C(24)-C(23)-S(20)	119.71(10)
C(28)-C(23)-S(20)	119.60(10)
C(23)-C(24)-C(25)	119.22(13)

C(26)-C(25)-C(24)	121.44(13)
C(25)-C(26)-C(27)	118.28(13)
C(25)-C(26)-C(29)	120.54(14)
C(27)-C(26)-C(29)	121.18(14)
C(28)-C(27)-C(26)	121.30(13)
C(27)-C(28)-C(23)	119.38(12)
O(31)-S(30)-O(32)	118.90(7)
O(31)-S(30)-C(33)	109.37(6)
O(32)-S(30)-C(33)	108.32(7)
O(31)-S(30)-C(18)	108.42(6)
O(32)-S(30)-C(18)	107.82(6)
C(33)-S(30)-C(18)	102.81(6)
C(34)-C(33)-C(38)	121.76(13)
C(34)-C(33)-S(30)	119.81(11)
C(38)-C(33)-S(30)	118.42(11)
C(33)-C(34)-C(35)	118.34(16)
C(36)-C(35)-C(34)	120.28(17)
C(35)-C(36)-C(37)	120.51(15)
C(36)-C(37)-C(38)	120.46(17)
C(33)-C(38)-C(37)	118.62(16)

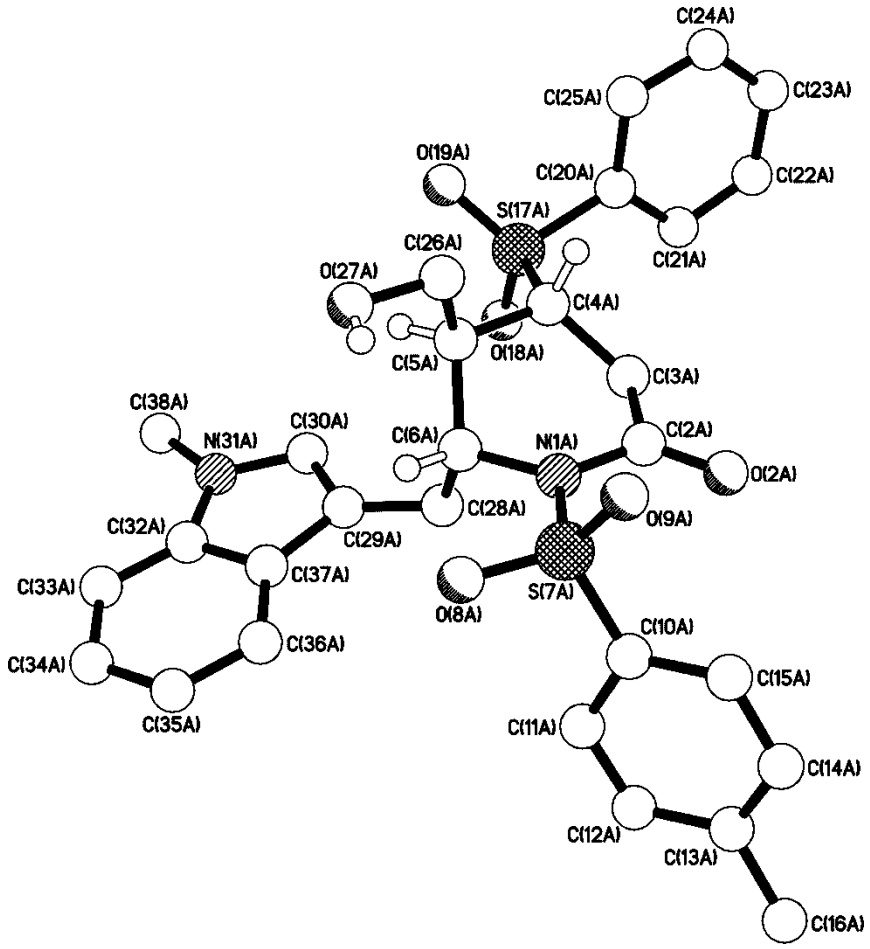
4.1.3 4-Methyl-*N*-((*S*)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R*,4*R*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (**118**)



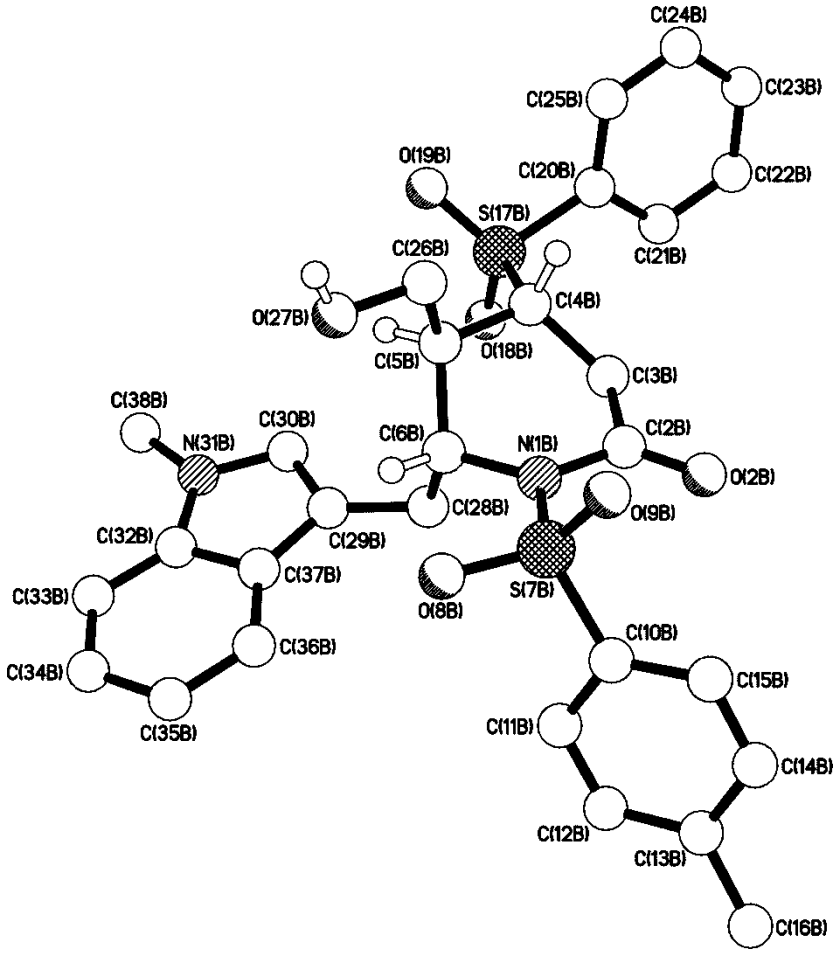
118

The unit cell was found to be composed of six independent (highly similar) conformers (shown below)

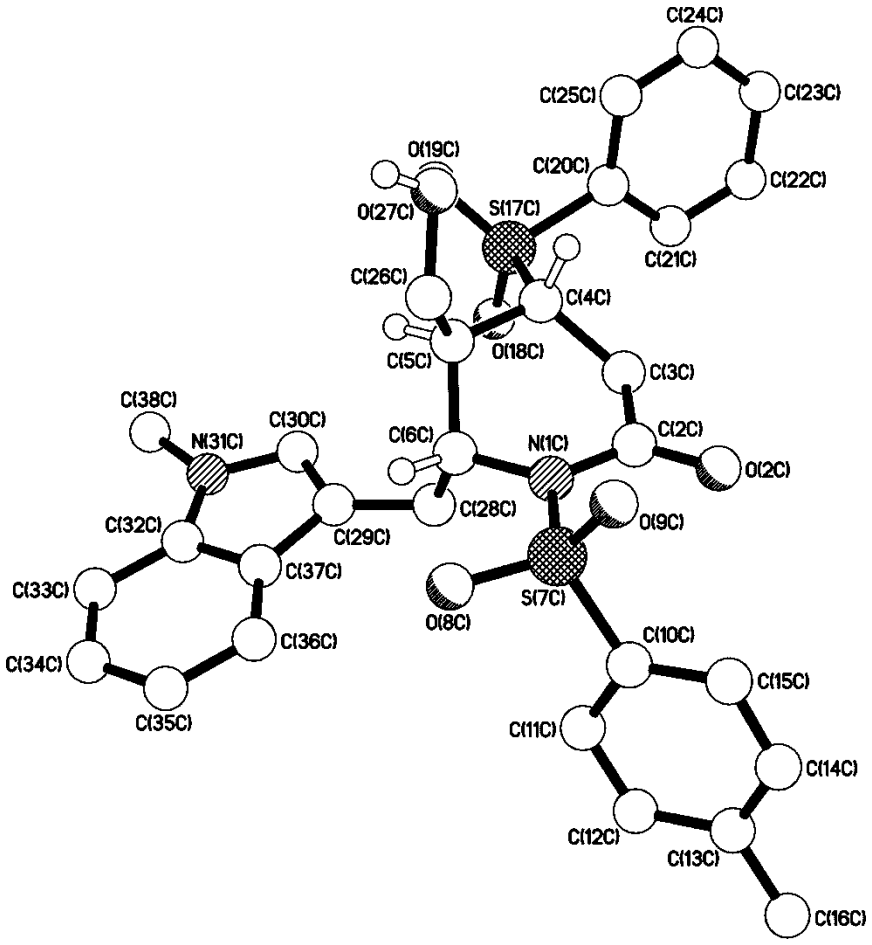
Conformer 1:



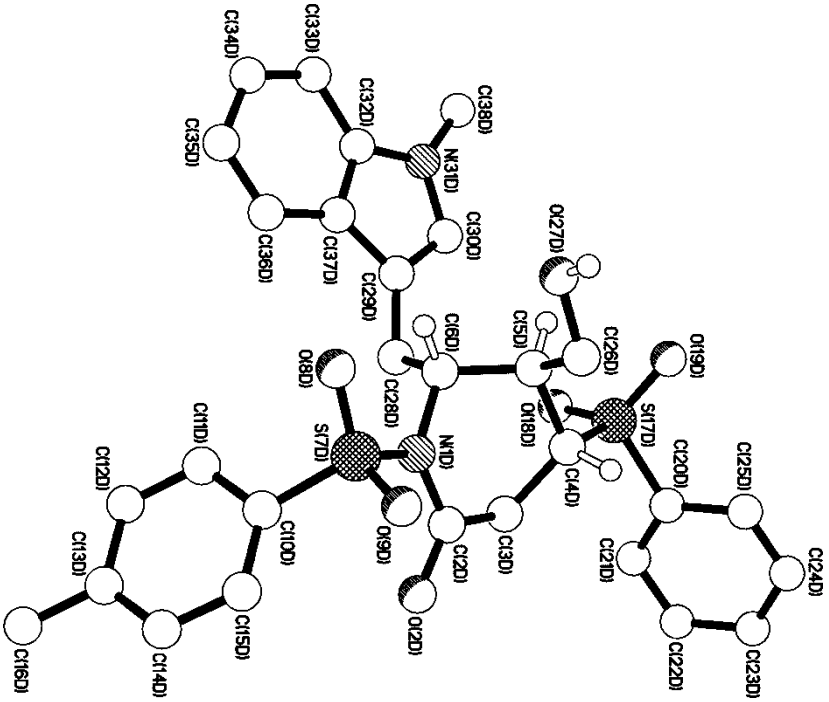
Conformer 2:


C(24B)
C(25B)
C(23B)
O(19B)
C(20B)
C(22B)
S(17B)
C(21B)
C(26B)
C(4B)
O(27B)
C(5B)
O(18B)
C(3B)
C(38B)
C(30B)
C(6B)
C(2B)
N(31B)
N(1B)
O(2B)
C(28B)
O(9B)
C(32B)
C(29B)
C(37B)
S(7B)
C(33B)
O(8B)
C(10B)
C(36B)
C(34B)
C(15B)
C(11B)
C(35B)
C(14B)
C(12B)
C(13B)
C(16B)

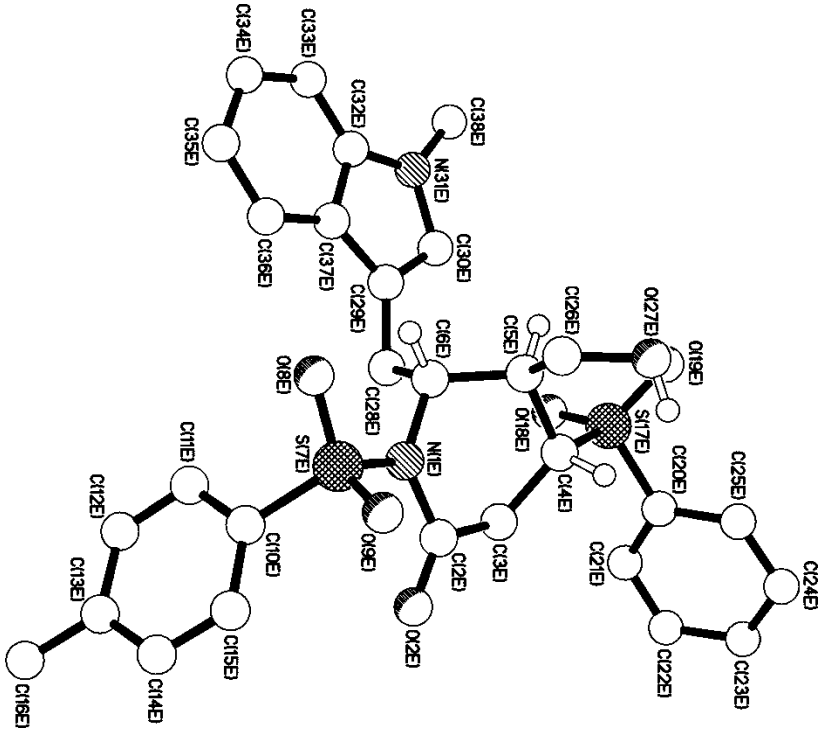
Conformer 3:


C(24C)
C(25C)
C(23C)
O(19C)
C(20C)
C(22C)
O(27C)
S(17C)
C(21C)
C(26C)
C(4C)
C(5C)
O(18C)
C(3C)
C(38C)
C(30C)
C(6C)
N(1C)
C(2C)
N(31C)
O(2C)
C(32C)
C(28C)
O(9C)
C(29C)
C(37C)
C(33C)
S(7C)
O(8C)
C(10C)
C(36C)
C(34C)
C(15C)
C(11C)
C(35C)
C(14C)
C(12C)
C(13C)
C(16C)

Conformer 4:



Conformer 5:



Conformer 6:

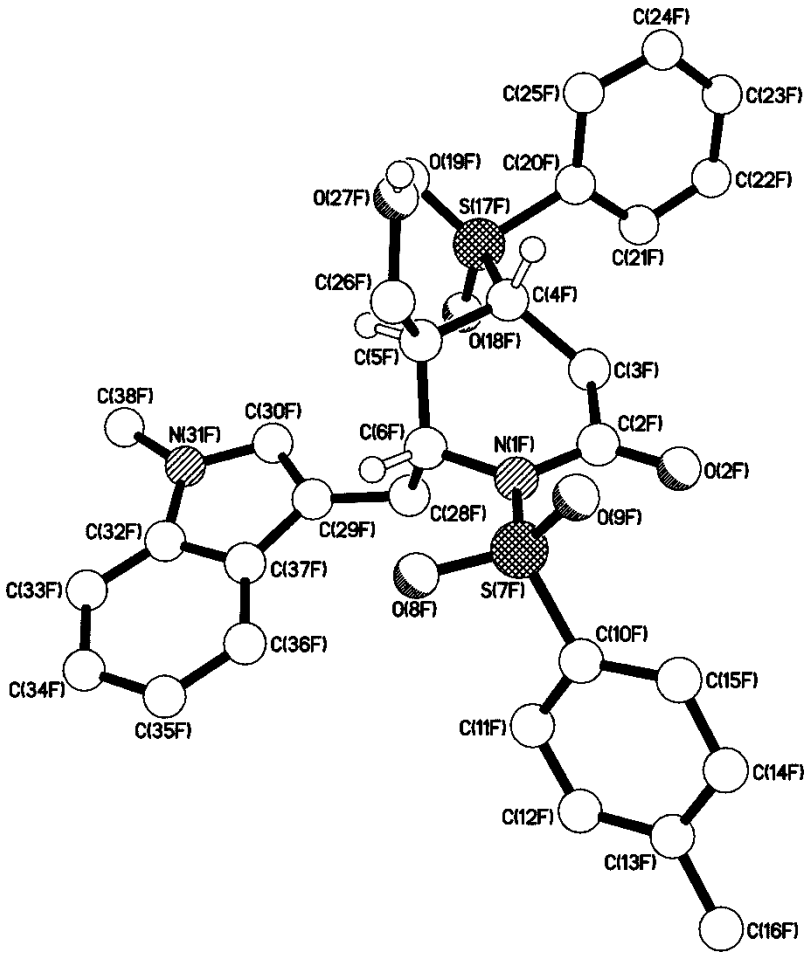


Table 1. Crystal data and structure refinement for **118**.

Identification code	DC1103
Formula	C29 H30 N2 O6 S2, 0.54(H2 O)
Formula weight	576.43
Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 15.3984(12) Å α = 74.763(6)°

	b = 20.8685(14) Å β = 77.711(6)°
	c = 28.0277(19) Å γ = 77.023(6)°
Volume, Z	8353.8(11) $Å^3$, 12
Density (calculated)	1.375 Mg/m^3
Absorption coefficient	0.240 mm^{-1}
F(000)	3641
Crystal colour / morphology	Colourless blocks
Crystal size	0.21 x 0.10 x 0.06 mm^3
θ range for data collection	2.97 to 28.49°
Index ranges	-20<=h<=19, -27<=k<=27, -36<=l<=31
Reflns collected / unique	62992 / 34197 [R(int) = 0.0782]
Reflns observed [F>4σ(F)]	7583
Absorption correction	Analytical
Max. and min. transmission	0.988 and 0.967
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	34197 / 156 / 2185
Goodness-of-fit on F^2	0.842
Final R indices [F>4σ(F)]	R1 = 0.0965, wR2 = 0.1666
R indices (all data)	R1 = 0.3302, wR2 = 0.2429
Largest diff. peak, hole	0.548, -0.364 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC1103.

N(1A)-C(2A)	1.364(8)
N(1A)-C(6A)	1.505(8)
N(1A)-S(7A)	1.694(6)
C(2A)-O(2A)	1.216(8)
C(2A)-C(3A)	1.514(9)
C(3A)-C(4A)	1.528(8)
C(4A)-C(5A)	1.558(9)
C(4A)-S(17A)	1.777(7)
C(5A)-C(26A)	1.515(8)
C(5A)-C(6A)	1.535(8)
C(6A)-C(28A)	1.540(8)
S(7A)-O(8A)	1.419(5)
S(7A)-O(9A)	1.430(5)
S(7A)-C(10A)	1.710(8)
C(10A)-C(15A)	1.382(10)
C(10A)-C(11A)	1.387(9)
C(11A)-C(12A)	1.387(10)
C(12A)-C(13A)	1.379(11)
C(13A)-C(14A)	1.379(10)
C(13A)-C(16A)	1.525(10)
C(14A)-C(15A)	1.409(9)
S(17A)-O(19A)	1.440(5)
S(17A)-O(18A)	1.442(5)
S(17A)-C(20A)	1.742(8)
C(20A)-C(21A)	1.384(10)
C(20A)-C(25A)	1.419(9)
C(21A)-C(22A)	1.398(11)
C(22A)-C(23A)	1.336(11)
C(23A)-C(24A)	1.371(11)
C(24A)-C(25A)	1.418(10)

C(26A)-O(27A)	1.394(7)
C(28A)-C(29A)	1.466(9)
C(29A)-C(30A)	1.373(9)
C(29A)-C(37A)	1.443(9)
C(30A)-N(31A)	1.384(8)
N(31A)-C(32A)	1.368(9)
N(31A)-C(38A)	1.460(9)
C(32A)-C(33A)	1.387(9)
C(32A)-C(37A)	1.417(9)
C(33A)-C(34A)	1.428(11)
C(34A)-C(35A)	1.404(11)
C(35A)-C(36A)	1.374(10)
C(36A)-C(37A)	1.409(8)
N(1B)-C(2B)	1.398(8)
N(1B)-C(6B)	1.481(8)
N(1B)-S(7B)	1.676(6)
C(2B)-O(2B)	1.211(7)
C(2B)-C(3B)	1.527(8)
C(3B)-C(4B)	1.540(8)
C(4B)-C(5B)	1.533(8)
C(4B)-S(17B)	1.793(6)
C(5B)-C(6B)	1.545(8)
C(5B)-C(26B)	1.553(9)
C(6B)-C(28B)	1.546(8)
S(7B)-O(9B)	1.426(5)
S(7B)-O(8B)	1.446(5)
S(7B)-C(10B)	1.776(6)
C(10B)-C(15B)	1.366(9)
C(10B)-C(11B)	1.405(9)
C(11B)-C(12B)	1.353(10)

C(12B)-C(13B)	1.385(11)
C(13B)-C(14B)	1.417(10)
C(13B)-C(16B)	1.510(9)
C(14B)-C(15B)	1.340(9)
S(17B)-O(19B)	1.436(5)
S(17B)-O(18B)	1.443(5)
S(17B)-C(20B)	1.756(7)
C(20B)-C(25B)	1.364(9)
C(20B)-C(21B)	1.389(10)
C(21B)-C(22B)	1.408(11)
C(22B)-C(23B)	1.368(10)
C(23B)-C(24B)	1.363(10)
C(24B)-C(25B)	1.363(10)
C(26B)-O(27B)	1.390(9)
C(28B)-C(29B)	1.516(9)
C(29B)-C(30B)	1.380(9)
C(29B)-C(37B)	1.392(9)
C(30B)-N(31B)	1.385(9)
N(31B)-C(32B)	1.383(9)
N(31B)-C(38B)	1.471(9)
C(32B)-C(33B)	1.395(10)
C(32B)-C(37B)	1.420(9)
C(33B)-C(34B)	1.367(10)
C(34B)-C(35B)	1.414(10)
C(35B)-C(36B)	1.393(10)
C(36B)-C(37B)	1.381(9)
N(1C)-C(2C)	1.347(9)
N(1C)-C(6C)	1.463(8)
N(1C)-S(7C)	1.682(6)
C(2C)-O(2C)	1.226(8)

C(2C)-C(3C)	1.501(10)
C(3C)-C(4C)	1.546(9)
C(4C)-C(5C)	1.500(9)
C(4C)-S(17C)	1.820(8)
C(5C)-C(26C)	1.537(8)
C(5C)-C(6C)	1.542(9)
C(5C)-C(26I)	1.549(9)
C(6C)-C(28C)	1.522(8)
S(7C)-O(9C)	1.420(5)
S(7C)-O(8C)	1.450(5)
S(7C)-C(10C)	1.792(7)
C(10C)-C(15C)	1.370(10)
C(10C)-C(11C)	1.391(9)
C(11C)-C(12C)	1.396(10)
C(12C)-C(13C)	1.380(11)
C(13C)-C(14C)	1.348(10)
C(13C)-C(16C)	1.481(10)
C(14C)-C(15C)	1.378(10)
S(17C)-O(19C)	1.436(5)
S(17C)-O(18C)	1.437(5)
S(17C)-C(20C)	1.774(9)
C(20C)-C(25C)	1.372(9)
C(20C)-C(21C)	1.373(10)
C(21C)-C(22C)	1.380(11)
C(22C)-C(23C)	1.388(11)
C(23C)-C(24C)	1.376(12)
C(24C)-C(25C)	1.374(12)
C(26C)-O(27C)	1.401(9)
C(26I)-O(27I)	1.422(10)
C(28C)-C(29C)	1.490(9)

C(29C)-C(30C)	1.378(9)
C(29C)-C(37C)	1.436(10)
C(30C)-N(31C)	1.369(8)
N(31C)-C(32C)	1.394(9)
N(31C)-C(38C)	1.460(8)
C(32C)-C(37C)	1.388(10)
C(32C)-C(33C)	1.416(10)
C(33C)-C(34C)	1.358(11)
C(34C)-C(35C)	1.395(11)
C(35C)-C(36C)	1.378(10)
C(36C)-C(37C)	1.385(10)
N(1D)-C(2D)	1.382(9)
N(1D)-C(6D)	1.510(8)
N(1D)-S(7D)	1.707(6)
C(2D)-O(2D)	1.270(9)
C(2D)-C(3D)	1.482(10)
C(3D)-C(4D)	1.548(9)
C(4D)-C(5D)	1.548(10)
C(4D)-S(17D)	1.792(8)
C(5D)-C(26D)	1.525(8)
C(5D)-C(26J)	1.533(9)
C(5D)-C(6D)	1.534(9)
C(6D)-C(28D)	1.527(8)
S(7D)-O(8D)	1.410(5)
S(7D)-O(9D)	1.421(5)
S(7D)-C(10D)	1.741(8)
C(10D)-C(15D)	1.376(10)
C(10D)-C(11D)	1.385(9)
C(11D)-C(12D)	1.403(10)
C(12D)-C(13D)	1.402(11)

C(13D)-C(14D)	1.371(10)
C(13D)-C(16D)	1.497(10)
C(14D)-C(15D)	1.398(10)
S(17D)-O(19D)	1.435(5)
S(17D)-O(18D)	1.444(5)
S(17D)-C(20D)	1.785(8)
C(20D)-C(21D)	1.371(9)
C(20D)-C(25D)	1.404(9)
C(21D)-C(22D)	1.399(11)
C(22D)-C(23D)	1.372(10)
C(23D)-C(24D)	1.380(10)
C(24D)-C(25D)	1.357(10)
C(26D)-O(27D)	1.412(9)
C(26J)-O(27J)	1.407(9)
C(28D)-C(29D)	1.481(9)
C(29D)-C(30D)	1.375(9)
C(29D)-C(37D)	1.460(10)
C(30D)-N(31D)	1.367(9)
N(31D)-C(32D)	1.381(9)
N(31D)-C(38D)	1.453(9)
C(32D)-C(37D)	1.405(9)
C(32D)-C(33D)	1.427(10)
C(33D)-C(34D)	1.339(11)
C(34D)-C(35D)	1.398(11)
C(35D)-C(36D)	1.361(11)
C(36D)-C(37D)	1.416(11)
N(1E)-C(2E)	1.413(9)
N(1E)-C(6E)	1.482(8)
N(1E)-S(7E)	1.707(6)
C(2E)-O(2E)	1.204(8)

C(2E)-C(3E)	1.495(9)
C(3E)-C(4E)	1.522(9)
C(4E)-C(5E)	1.548(9)
C(4E)-S(17E)	1.819(7)
C(5E)-C(6E)	1.515(8)
C(5E)-C(26E)	1.546(8)
C(6E)-C(28E)	1.562(8)
S(7E)-O(9E)	1.419(5)
S(7E)-O(8E)	1.433(5)
S(7E)-C(10E)	1.752(7)
C(10E)-C(11E)	1.378(9)
C(10E)-C(15E)	1.381(9)
C(11E)-C(12E)	1.384(9)
C(12E)-C(13E)	1.383(11)
C(13E)-C(14E)	1.411(10)
C(13E)-C(16E)	1.495(10)
C(14E)-C(15E)	1.365(9)
S(17E)-O(18E)	1.421(5)
S(17E)-O(19E)	1.440(5)
S(17E)-C(20E)	1.717(8)
C(20E)-C(21E)	1.369(9)
C(20E)-C(25E)	1.387(10)
C(21E)-C(22E)	1.387(10)
C(22E)-C(23E)	1.377(11)
C(23E)-C(24E)	1.384(11)
C(24E)-C(25E)	1.382(11)
C(26E)-O(27E)	1.370(7)
C(28E)-C(29E)	1.475(9)
C(29E)-C(30E)	1.397(10)
C(29E)-C(37E)	1.422(9)

C(30E)-N(31E)	1.404(9)
N(31E)-C(32E)	1.350(9)
N(31E)-C(38E)	1.473(9)
C(32E)-C(33E)	1.362(10)
C(32E)-C(37E)	1.449(9)
C(33E)-C(34E)	1.355(10)
C(34E)-C(35E)	1.398(10)
C(35E)-C(36E)	1.380(10)
C(36E)-C(37E)	1.392(9)
N(1F)-C(2F)	1.324(9)
N(1F)-C(6F)	1.474(8)
N(1F)-S(7F)	1.689(6)
C(2F)-O(2F)	1.212(8)
C(2F)-C(3F)	1.547(10)
C(3F)-C(4F)	1.562(9)
C(4F)-C(5F)	1.504(9)
C(4F)-S(17F)	1.809(7)
C(5F)-C(6F)	1.515(9)
C(5F)-C(26F)	1.542(7)
C(5F)-C(26L)	1.568(9)
C(6F)-C(28F)	1.539(8)
S(7F)-O(8F)	1.426(5)
S(7F)-O(9F)	1.438(5)
S(7F)-C(10F)	1.766(7)
C(10F)-C(11F)	1.378(9)
C(10F)-C(15F)	1.390(10)
C(11F)-C(12F)	1.378(10)
C(12F)-C(13F)	1.363(11)
C(13F)-C(14F)	1.398(10)
C(13F)-C(16F)	1.495(10)

C(14F)-C(15F)	1.398(9)
S(17F)-O(18F)	1.434(5)
S(17F)-O(19F)	1.445(6)
S(17F)-C(20F)	1.749(8)
C(20F)-C(21F)	1.383(10)
C(20F)-C(25F)	1.387(10)
C(21F)-C(22F)	1.403(12)
C(22F)-C(23F)	1.322(12)
C(23F)-C(24F)	1.366(11)
C(24F)-C(25F)	1.393(11)
C(26F)-O(27F)	1.409(8)
C(26L)-O(27L)	1.431(10)
C(28F)-C(29F)	1.475(9)
C(29F)-C(30F)	1.355(10)
C(29F)-C(37F)	1.402(10)
C(30F)-N(31F)	1.373(9)
N(31F)-C(32F)	1.376(9)
N(31F)-C(38F)	1.474(9)
C(32F)-C(33F)	1.360(10)
C(32F)-C(37F)	1.395(9)
C(33F)-C(34F)	1.410(11)
C(34F)-C(35F)	1.416(11)
C(35F)-C(36F)	1.364(10)
C(36F)-C(37F)	1.420(10)

C(2A)-N(1A)-C(6A)	122.3(6)
C(2A)-N(1A)-S(7A)	118.7(5)
C(6A)-N(1A)-S(7A)	119.0(5)
O(2A)-C(2A)-N(1A)	123.8(7)
O(2A)-C(2A)-C(3A)	121.5(6)

N(1A)-C(2A)-C(3A) 114.5(6)

C(2A)-C(3A)-C(4A) 113.2(6)

C(3A)-C(4A)-C(5A) 116.6(5)

C(3A)-C(4A)-S(17A) 112.8(5)

C(5A)-C(4A)-S(17A) 111.0(5)

C(26A)-C(5A)-C(6A) 113.2(6)

C(26A)-C(5A)-C(4A) 108.0(5)

C(6A)-C(5A)-C(4A) 111.0(6)

N(1A)-C(6A)-C(5A) 108.8(5)

N(1A)-C(6A)-C(28A) 111.5(5)

C(5A)-C(6A)-C(28A) 112.7(6)

O(8A)-S(7A)-O(9A) 119.6(3)

O(8A)-S(7A)-N(1A) 105.2(3)

O(9A)-S(7A)-N(1A) 107.7(3)

O(8A)-S(7A)-C(10A) 108.2(3)

O(9A)-S(7A)-C(10A) 110.0(3)

N(1A)-S(7A)-C(10A) 105.0(3)

C(15A)-C(10A)-C(11A) 117.5(7)

C(15A)-C(10A)-S(7A) 120.7(6)

C(11A)-C(10A)-S(7A) 121.5(6)

C(12A)-C(11A)-C(10A) 120.5(8)

C(13A)-C(12A)-C(11A) 121.7(7)

C(14A)-C(13A)-C(12A) 118.6(7)

C(14A)-C(13A)-C(16A) 120.5(8)

C(12A)-C(13A)-C(16A) 120.8(7)

C(13A)-C(14A)-C(15A) 119.5(8)

C(10A)-C(15A)-C(14A) 121.9(7)

O(19A)-S(17A)-O(18A) 117.6(3)

O(19A)-S(17A)-C(20A) 108.2(3)

O(18A)-S(17A)-C(20A) 109.8(3)

O(19A)-S(17A)-C(4A) 107.7(3)

O(18A)-S(17A)-C(4A) 107.8(3)

C(20A)-S(17A)-C(4A) 105.0(3)

C(21A)-C(20A)-C(25A) 121.9(8)

C(21A)-C(20A)-S(17A) 120.6(6)

C(25A)-C(20A)-S(17A) 117.4(6)

C(20A)-C(21A)-C(22A) 117.2(8)

C(23A)-C(22A)-C(21A) 123.8(9)

C(22A)-C(23A)-C(24A) 118.8(9)

C(23A)-C(24A)-C(25A) 122.3(8)

C(24A)-C(25A)-C(20A) 115.9(7)

O(27A)-C(26A)-C(5A) 108.7(5)

C(29A)-C(28A)-C(6A) 113.0(5)

C(30A)-C(29A)-C(37A) 105.3(6)

C(30A)-C(29A)-C(28A) 125.3(7)

C(37A)-C(29A)-C(28A) 129.4(6)

C(29A)-C(30A)-N(31A) 109.8(6)

C(32A)-N(31A)-C(30A) 110.3(6)

C(32A)-N(31A)-C(38A) 124.8(7)

C(30A)-N(31A)-C(38A) 124.9(7)

N(31A)-C(32A)-C(33A) 132.0(7)

N(31A)-C(32A)-C(37A) 106.0(7)

C(33A)-C(32A)-C(37A) 122.0(7)

C(32A)-C(33A)-C(34A) 117.7(7)

C(35A)-C(34A)-C(33A) 119.7(8)

C(36A)-C(35A)-C(34A) 122.3(8)

C(35A)-C(36A)-C(37A) 118.8(7)

C(36A)-C(37A)-C(32A) 119.5(6)

C(36A)-C(37A)-C(29A) 131.8(7)

C(32A)-C(37A)-C(29A) 108.7(6)

C(2B)-N(1B)-C(6B) 121.6(6)

C(2B)-N(1B)-S(7B) 119.3(5)

C(6B)-N(1B)-S(7B) 119.1(5)

O(2B)-C(2B)-N(1B) 122.2(6)

O(2B)-C(2B)-C(3B) 123.1(7)

N(1B)-C(2B)-C(3B) 114.7(6)

C(2B)-C(3B)-C(4B) 112.5(6)

C(5B)-C(4B)-C(3B) 115.9(5)

C(5B)-C(4B)-S(17B) 109.8(4)

C(3B)-C(4B)-S(17B) 109.5(5)

C(4B)-C(5B)-C(6B) 113.5(5)

C(4B)-C(5B)-C(26B) 106.6(6)

C(6B)-C(5B)-C(26B) 111.3(6)

N(1B)-C(6B)-C(5B) 109.1(5)

N(1B)-C(6B)-C(28B) 110.0(5)

C(5B)-C(6B)-C(28B) 112.0(6)

O(9B)-S(7B)-O(8B) 120.4(3)

O(9B)-S(7B)-N(1B) 107.1(3)

O(8B)-S(7B)-N(1B) 104.9(3)

O(9B)-S(7B)-C(10B) 107.9(3)

O(8B)-S(7B)-C(10B) 108.1(3)

N(1B)-S(7B)-C(10B) 107.9(3)

C(15B)-C(10B)-C(11B) 121.2(6)

C(15B)-C(10B)-S(7B) 122.0(5)

C(11B)-C(10B)-S(7B) 116.8(6)

C(12B)-C(11B)-C(10B) 117.7(7)

C(11B)-C(12B)-C(13B) 122.3(7)

C(12B)-C(13B)-C(14B) 118.0(7)

C(12B)-C(13B)-C(16B) 121.8(7)

C(14B)-C(13B)-C(16B) 120.3(7)

C(15B)-C(14B)-C(13B) 120.3(7)

C(14B)-C(15B)-C(10B) 120.4(6)

O(19B)-S(17B)-O(18B) 118.4(3)

O(19B)-S(17B)-C(20B) 106.7(3)

O(18B)-S(17B)-C(20B) 109.9(3)

O(19B)-S(17B)-C(4B) 107.2(3)

O(18B)-S(17B)-C(4B) 110.0(3)

C(20B)-S(17B)-C(4B) 103.6(3)

C(25B)-C(20B)-C(21B) 118.1(7)

C(25B)-C(20B)-S(17B) 121.6(6)

C(21B)-C(20B)-S(17B) 120.2(5)

C(20B)-C(21B)-C(22B) 119.4(7)

C(23B)-C(22B)-C(21B) 119.2(8)

C(24B)-C(23B)-C(22B) 121.9(9)

C(23B)-C(24B)-C(25B) 117.8(7)

C(24B)-C(25B)-C(20B) 123.6(8)

O(27B)-C(26B)-C(5B) 106.8(6)

C(29B)-C(28B)-C(6B) 112.8(5)

C(30B)-C(29B)-C(37B) 106.1(6)

C(30B)-C(29B)-C(28B) 127.8(7)

C(37B)-C(29B)-C(28B) 126.1(6)

C(29B)-C(30B)-N(31B) 109.6(7)

C(32B)-N(31B)-C(30B) 109.1(6)

C(32B)-N(31B)-C(38B) 126.8(7)

C(30B)-N(31B)-C(38B) 124.1(7)

N(31B)-C(32B)-C(33B) 130.1(7)

N(31B)-C(32B)-C(37B) 105.4(6)

C(33B)-C(32B)-C(37B) 124.4(7)

C(34B)-C(33B)-C(32B) 117.7(7)

C(33B)-C(34B)-C(35B) 120.2(8)

C(36B)-C(35B)-C(34B) 120.4(8)

C(37B)-C(36B)-C(35B) 121.7(7)

C(36B)-C(37B)-C(29B) 134.7(7)

C(36B)-C(37B)-C(32B) 115.5(7)

C(29B)-C(37B)-C(32B) 109.8(6)

C(2C)-N(1C)-C(6C) 120.5(6)

C(2C)-N(1C)-S(7C) 120.1(5)

C(6C)-N(1C)-S(7C) 119.4(5)

O(2C)-C(2C)-N(1C) 123.0(8)

O(2C)-C(2C)-C(3C) 118.6(8)

N(1C)-C(2C)-C(3C) 118.3(7)

C(2C)-C(3C)-C(4C) 111.4(7)

C(5C)-C(4C)-C(3C) 115.6(6)

C(5C)-C(4C)-S(17C) 110.9(5)

C(3C)-C(4C)-S(17C) 110.3(5)

C(4C)-C(5C)-C(26C) 114.8(7)

C(4C)-C(5C)-C(6C) 114.3(6)

C(26C)-C(5C)-C(6C) 103.8(7)

C(4C)-C(5C)-C(26I) 105.1(6)

C(26C)-C(5C)-C(26I) 9.8(8)

C(6C)-C(5C)-C(26I) 109.4(9)

N(1C)-C(6C)-C(28C) 114.5(5)

N(1C)-C(6C)-C(5C) 107.6(5)

C(28C)-C(6C)-C(5C) 111.9(6)

O(9C)-S(7C)-O(8C) 118.6(3)

O(9C)-S(7C)-N(1C) 108.1(3)

O(8C)-S(7C)-N(1C) 104.6(3)

O(9C)-S(7C)-C(10C) 109.0(4)

O(8C)-S(7C)-C(10C) 109.7(3)

N(1C)-S(7C)-C(10C) 106.0(3)

C(15C)-C(10C)-C(11C) 122.4(7)

C(15C)-C(10C)-S(7C) 119.5(6)

C(11C)-C(10C)-S(7C) 118.1(6)

C(10C)-C(11C)-C(12C) 117.9(8)

C(13C)-C(12C)-C(11C) 120.2(7)

C(14C)-C(13C)-C(12C) 119.3(8)

C(14C)-C(13C)-C(16C) 121.7(9)

C(12C)-C(13C)-C(16C) 119.0(8)

C(13C)-C(14C)-C(15C) 123.3(8)

C(10C)-C(15C)-C(14C) 117.0(7)

O(19C)-S(17C)-O(18C) 118.4(4)

O(19C)-S(17C)-C(20C) 108.9(4)

O(18C)-S(17C)-C(20C) 108.5(4)

O(19C)-S(17C)-C(4C) 106.5(4)

O(18C)-S(17C)-C(4C) 108.9(3)

C(20C)-S(17C)-C(4C) 104.8(4)

C(25C)-C(20C)-C(21C) 121.9(8)

C(25C)-C(20C)-S(17C) 117.6(7)

C(21C)-C(20C)-S(17C) 120.4(6)

C(20C)-C(21C)-C(22C) 120.0(8)

C(21C)-C(22C)-C(23C) 117.5(9)

C(24C)-C(23C)-C(22C) 122.3(9)

C(25C)-C(24C)-C(23C) 119.1(9)

C(20C)-C(25C)-C(24C) 118.9(9)

O(27C)-C(26C)-C(5C) 115.7(9)

O(27I)-C(26I)-C(5C) 106.1(9)

C(29C)-C(28C)-C(6C) 115.4(5)

C(30C)-C(29C)-C(37C) 108.0(7)

C(30C)-C(29C)-C(28C) 127.0(7)

C(37C)-C(29C)-C(28C) 125.0(7)

N(31C)-C(30C)-C(29C) 109.7(7)

C(30C)-N(31C)-C(32C) 106.8(6)

C(30C)-N(31C)-C(38C) 125.5(7)

C(32C)-N(31C)-C(38C) 127.5(7)

C(37C)-C(32C)-N(31C) 110.5(7)

C(37C)-C(32C)-C(33C) 121.1(8)

N(31C)-C(32C)-C(33C) 128.3(8)

C(34C)-C(33C)-C(32C) 116.3(8)

C(33C)-C(34C)-C(35C) 123.0(8)

C(36C)-C(35C)-C(34C) 120.6(8)

C(35C)-C(36C)-C(37C) 117.8(8)

C(36C)-C(37C)-C(32C) 121.1(8)

C(36C)-C(37C)-C(29C) 134.0(8)

C(32C)-C(37C)-C(29C) 104.8(7)

C(2D)-N(1D)-C(6D) 119.6(6)

C(2D)-N(1D)-S(7D) 121.5(6)

C(6D)-N(1D)-S(7D) 118.7(5)

O(2D)-C(2D)-N(1D) 117.7(8)

O(2D)-C(2D)-C(3D) 124.7(7)

N(1D)-C(2D)-C(3D) 117.5(7)

C(2D)-C(3D)-C(4D) 110.9(7)

C(3D)-C(4D)-C(5D) 115.5(6)

C(3D)-C(4D)-S(17D) 110.3(5)

C(5D)-C(4D)-S(17D) 108.2(5)

C(26D)-C(5D)-C(26J) 10.2(8)

C(26D)-C(5D)-C(6D) 111.4(8)

C(26J)-C(5D)-C(6D) 101.4(7)

C(26D)-C(5D)-C(4D) 105.1(6)

C(26J)-C(5D)-C(4D) 112.1(9)

C(6D)-C(5D)-C(4D) 113.0(6)

N(1D)-C(6D)-C(28D) 111.5(5)

N(1D)-C(6D)-C(5D) 108.9(6)

C(28D)-C(6D)-C(5D) 112.7(6)

O(8D)-S(7D)-O(9D) 117.6(3)

O(8D)-S(7D)-N(1D) 106.0(3)

O(9D)-S(7D)-N(1D) 108.2(3)

O(8D)-S(7D)-C(10D) 109.3(3)

O(9D)-S(7D)-C(10D) 109.2(4)

N(1D)-S(7D)-C(10D) 105.9(3)

C(15D)-C(10D)-C(11D) 119.3(7)

C(15D)-C(10D)-S(7D) 120.6(6)

C(11D)-C(10D)-S(7D) 119.1(6)

C(10D)-C(11D)-C(12D) 120.8(7)

C(13D)-C(12D)-C(11D) 119.3(7)

C(14D)-C(13D)-C(12D) 118.8(8)

C(14D)-C(13D)-C(16D) 121.9(8)

C(12D)-C(13D)-C(16D) 119.3(8)

C(13D)-C(14D)-C(15D) 121.7(8)

C(10D)-C(15D)-C(14D) 119.8(8)

O(19D)-S(17D)-O(18D) 118.2(4)

O(19D)-S(17D)-C(20D) 108.9(4)

O(18D)-S(17D)-C(20D) 109.9(4)

O(19D)-S(17D)-C(4D) 106.6(4)

O(18D)-S(17D)-C(4D) 108.7(3)

C(20D)-S(17D)-C(4D) 103.6(3)

C(21D)-C(20D)-C(25D) 123.5(8)

C(21D)-C(20D)-S(17D) 120.4(6)

C(25D)-C(20D)-S(17D) 116.1(7)

C(20D)-C(21D)-C(22D) 117.0(7)

C(23D)-C(22D)-C(21D) 120.6(8)

C(22D)-C(23D)-C(24D) 120.1(8)

C(25D)-C(24D)-C(23D) 121.7(8)

C(24D)-C(25D)-C(20D) 116.9(8)

O(27D)-C(26D)-C(5D) 107.7(8)

O(27J)-C(26J)-C(5D) 119.7(11)

C(29D)-C(28D)-C(6D) 112.8(6)

C(30D)-C(29D)-C(37D) 105.6(7)

C(30D)-C(29D)-C(28D) 131.1(7)

C(37D)-C(29D)-C(28D) 123.3(7)

N(31D)-C(30D)-C(29D) 111.0(7)

C(30D)-N(31D)-C(32D) 108.3(7)

C(30D)-N(31D)-C(38D) 125.1(7)

C(32D)-N(31D)-C(38D) 126.5(7)

N(31D)-C(32D)-C(37D) 108.6(7)

N(31D)-C(32D)-C(33D) 128.6(7)

C(37D)-C(32D)-C(33D) 122.7(8)

C(34D)-C(33D)-C(32D) 115.4(8)

C(33D)-C(34D)-C(35D) 124.7(8)

C(36D)-C(35D)-C(34D) 119.4(8)

C(35D)-C(36D)-C(37D) 120.4(9)

C(32D)-C(37D)-C(36D) 117.4(8)

C(32D)-C(37D)-C(29D) 106.4(7)

C(36D)-C(37D)-C(29D) 136.2(8)

C(2E)-N(1E)-C(6E) 122.8(6)

C(2E)-N(1E)-S(7E) 116.2(5)

C(6E)-N(1E)-S(7E) 120.5(5)

O(2E)-C(2E)-N(1E) 122.8(7)

O(2E)-C(2E)-C(3E) 125.9(7)

N(1E)-C(2E)-C(3E) 110.9(7)

C(2E)-C(3E)-C(4E) 114.1(6)

C(3E)-C(4E)-C(5E) 115.9(6)

C(3E)-C(4E)-S(17E) 111.1(5)

C(5E)-C(4E)-S(17E) 110.2(5)

C(6E)-C(5E)-C(26E) 108.3(6)

C(6E)-C(5E)-C(4E) 110.6(5)

C(26E)-C(5E)-C(4E) 112.8(6)

N(1E)-C(6E)-C(5E) 109.5(5)

N(1E)-C(6E)-C(28E) 109.8(5)

C(5E)-C(6E)-C(28E) 114.9(6)

O(9E)-S(7E)-O(8E) 117.2(3)

O(9E)-S(7E)-N(1E) 108.9(3)

O(8E)-S(7E)-N(1E) 103.6(3)

O(9E)-S(7E)-C(10E) 110.1(3)

O(8E)-S(7E)-C(10E) 109.2(3)

N(1E)-S(7E)-C(10E) 107.3(3)

C(11E)-C(10E)-C(15E) 121.0(7)

C(11E)-C(10E)-S(7E) 119.0(6)

C(15E)-C(10E)-S(7E) 120.0(5)

C(10E)-C(11E)-C(12E) 117.7(7)

C(13E)-C(12E)-C(11E) 123.3(8)

C(12E)-C(13E)-C(14E) 116.8(7)

C(12E)-C(13E)-C(16E) 121.1(8)

C(14E)-C(13E)-C(16E) 122.1(9)

C(15E)-C(14E)-C(13E) 120.7(7)

C(14E)-C(15E)-C(10E) 120.4(7)

O(18E)-S(17E)-O(19E) 119.4(4)

O(18E)-S(17E)-C(20E) 108.8(4)

O(19E)-S(17E)-C(20E) 107.9(4)

O(18E)-S(17E)-C(4E) 108.3(3)

O(19E)-S(17E)-C(4E) 106.9(3)

C(20E)-S(17E)-C(4E) 104.7(3)

C(21E)-C(20E)-C(25E) 118.3(8)

C(21E)-C(20E)-S(17E) 121.1(6)

C(25E)-C(20E)-S(17E) 120.6(6)

C(20E)-C(21E)-C(22E) 119.8(8)

C(23E)-C(22E)-C(21E) 121.2(8)

C(22E)-C(23E)-C(24E) 120.0(9)

C(25E)-C(24E)-C(23E) 117.7(9)

C(24E)-C(25E)-C(20E) 122.9(9)

O(27E)-C(26E)-C(5E) 113.6(7)

C(29E)-C(28E)-C(6E) 110.5(5)

C(30E)-C(29E)-C(37E) 106.6(6)

C(30E)-C(29E)-C(28E) 126.5(7)

C(37E)-C(29E)-C(28E) 126.9(7)

C(29E)-C(30E)-N(31E) 107.4(7)

C(32E)-N(31E)-C(30E) 112.3(6)

C(32E)-N(31E)-C(38E) 126.7(7)

C(30E)-N(31E)-C(38E) 121.0(7)

N(31E)-C(32E)-C(33E) 132.8(7)

N(31E)-C(32E)-C(37E) 105.0(7)

C(33E)-C(32E)-C(37E) 122.2(7)

C(34E)-C(33E)-C(32E) 118.5(7)

C(33E)-C(34E)-C(35E) 121.7(9)

C(36E)-C(35E)-C(34E) 120.7(8)

C(35E)-C(36E)-C(37E) 119.6(7)

C(36E)-C(37E)-C(29E) 134.0(7)

C(36E)-C(37E)-C(32E) 117.2(7)

C(29E)-C(37E)-C(32E) 108.8(7)

C(2F)-N(1F)-C(6F)   120.1(7)

C(2F)-N(1F)-S(7F)   117.9(5)

```
C(6F)-N(1F)-S(7F)     121.5(6)
O(2F)-C(2F)-N(1F)     125.9(8)
O(2F)-C(2F)-C(3F)     117.7(8)
N(1F)-C(2F)-C(3F)     116.5(6)
C(2F)-C(3F)-C(4F)     110.7(6)
C(5F)-C(4F)-C(3F)     115.8(6)
C(5F)-C(4F)-S(17F)    111.2(5)
C(3F)-C(4F)-S(17F)    109.8(5)
C(4F)-C(5F)-C(6F)     111.9(6)
C(4F)-C(5F)-C(26F)    116.2(6)
C(6F)-C(5F)-C(26F)    107.2(6)
C(4F)-C(5F)-C(26L)    106.9(8)
C(6F)-C(5F)-C(26L)    107.5(10)
C(26F)-C(5F)-C(26L)    11.0(9)
N(1F)-C(6F)-C(5F)     109.9(6)
N(1F)-C(6F)-C(28F)    112.9(6)
C(5F)-C(6F)-C(28F)    114.8(6)
O(8F)-S(7F)-O(9F)     119.9(3)
O(8F)-S(7F)-N(1F)     103.8(3)
O(9F)-S(7F)-N(1F)     108.8(3)
O(8F)-S(7F)-C(10F)    106.4(3)
O(9F)-S(7F)-C(10F)    109.3(3)
N(1F)-S(7F)-C(10F)    108.0(3)
C(11F)-C(10F)-C(15F) 121.7(7)
C(11F)-C(10F)-S(7F)   118.7(6)
C(15F)-C(10F)-S(7F)   119.6(6)
C(12F)-C(11F)-C(10F) 116.6(8)
C(13F)-C(12F)-C(11F) 124.5(8)
C(12F)-C(13F)-C(14F) 118.3(7)
C(12F)-C(13F)-C(16F) 122.3(8)
```

C(14F)-C(13F)-C(16F) 119.4(8)

C(13F)-C(14F)-C(15F) 119.3(8)

C(10F)-C(15F)-C(14F) 119.6(7)

O(18F)-S(17F)-O(19F) 119.5(4)

O(18F)-S(17F)-C(20F) 109.7(4)

O(19F)-S(17F)-C(20F) 107.5(4)

O(18F)-S(17F)-C(4F) 108.1(4)

O(19F)-S(17F)-C(4F) 105.9(4)

C(20F)-S(17F)-C(4F) 105.2(4)

C(21F)-C(20F)-C(25F) 120.3(9)

C(21F)-C(20F)-S(17F) 120.5(7)

C(25F)-C(20F)-S(17F) 119.2(7)

C(20F)-C(21F)-C(22F) 121.1(9)

C(23F)-C(22F)-C(21F) 117.3(10)

C(22F)-C(23F)-C(24F) 123.1(11)

C(23F)-C(24F)-C(25F) 121.0(9)

C(20F)-C(25F)-C(24F) 116.9(8)

O(27F)-C(26F)-C(5F) 113.0(7)

O(27L)-C(26L)-C(5F) 102.6(12)

C(29F)-C(28F)-C(6F) 113.4(6)

C(30F)-C(29F)-C(37F) 105.8(7)

C(30F)-C(29F)-C(28F) 126.4(8)

C(37F)-C(29F)-C(28F) 127.8(7)

C(29F)-C(30F)-N(31F) 110.4(8)

C(30F)-N(31F)-C(32F) 108.4(7)

C(30F)-N(31F)-C(38F) 127.5(7)

C(32F)-N(31F)-C(38F) 124.0(7)

C(33F)-C(32F)-N(31F) 130.6(8)

C(33F)-C(32F)-C(37F) 123.1(8)

N(31F)-C(32F)-C(37F) 106.3(7)

C(32F)-C(33F)-C(34F) 118.1(8)

C(33F)-C(34F)-C(35F) 120.2(8)

C(36F)-C(35F)-C(34F) 120.4(8)

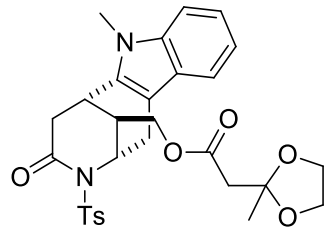
C(35F)-C(36F)-C(37F) 119.9(7)

C(32F)-C(37F)-C(29F) 109.1(7)

C(32F)-C(37F)-C(36F) 118.3(7)

C(29F)-C(37F)-C(36F) 132.5(7)

4.1.4. 4-Methyl-*N*-((*S*)-2-(1-methyl-1*H*-indol-3-yl)-1-((3*R*,4*R*)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (**133**)



133

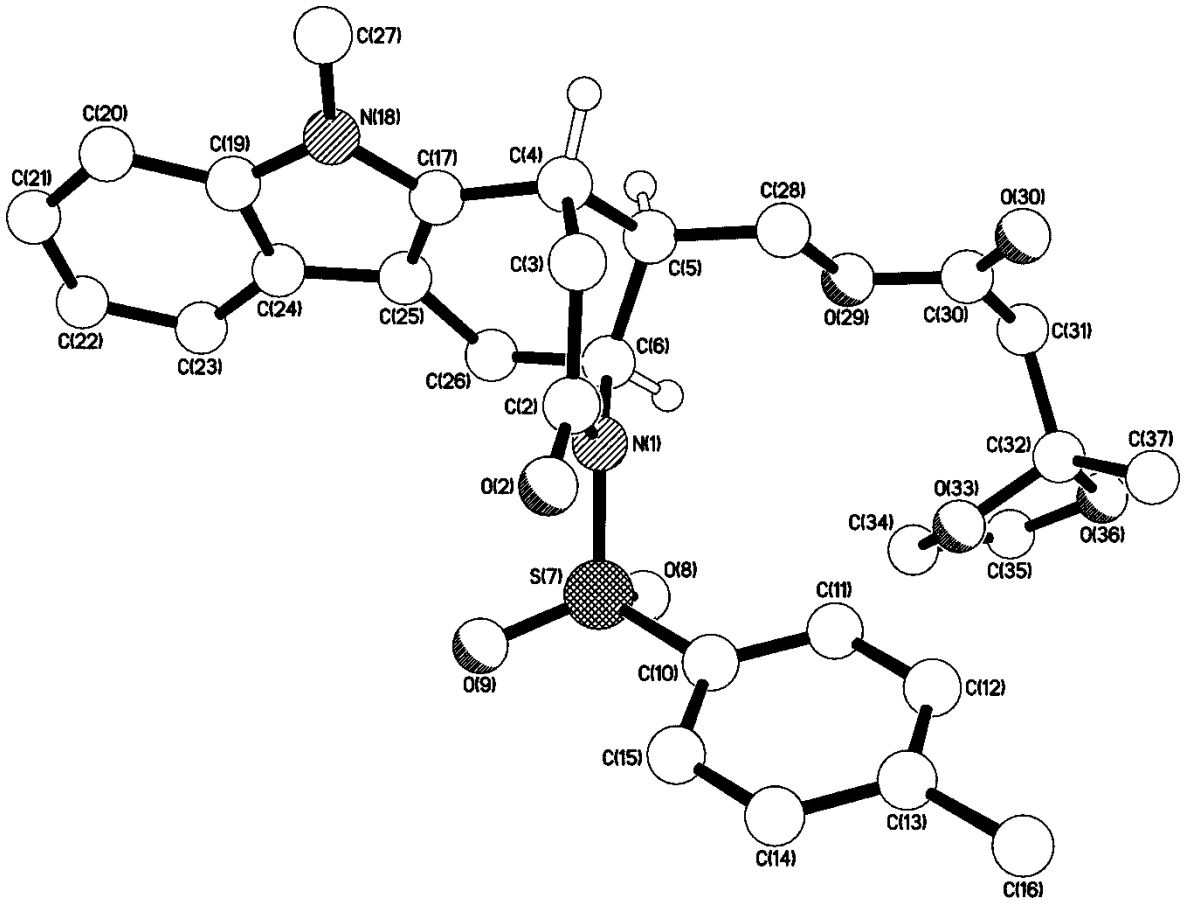


Table 1. Crystal data and structure refinement for **133**.

Identification code	DC1203
Formula	C29 H32 N2 O7 S
Formula weight	552.63

Temperature	173 K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.1649(5) Å α = 82.205(4)°
	b = 10.4773(4) Å β = 74.919(4)°
	c = 13.9025(6) Å γ = 67.702(4)°
Volume, Z	1321.60(11) $Å^3$, 2
Density (calculated)	1.389 Mg/m^3
Absorption coefficient	0.174 mm^{-1}
F(000)	584
Crystal colour / morphology	Colourless tabular needles
Crystal size	0.47 x 0.17 x 0.03 mm^3
θ range for data collection	3.18 to 32.65°
Index ranges	-13<=h<=15, -15<=k<=15, -20<=l<=19
Reflns collected / unique	14479 / 8609 [R(int) = 0.0188]
Reflns observed [F>4σ(F)]	6815
Absorption correction	Analytical
Max. and min. transmission	0.994 and 0.958
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8609 / 0 / 354
Goodness-of-fit on F^2	1.044
Final R indices [F>4σ(F)]	R1 = 0.0443, wR2 = 0.1154
R indices (all data)	R1 = 0.0610, wR2 = 0.1233

Largest diff. peak, hole 0.429, -0.298 eÅ^{-3}

Mean and maximum shift/error 0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for DC1203.

N(1)-C(2)	1.3963(15)
N(1)-C(6)	1.4940(15)
N(1)-S(7)	1.6962(10)
C(2)-O(2)	1.2209(15)
C(2)-C(3)	1.5144(17)
C(3)-C(4)	1.5317(17)
C(4)-C(17)	1.5006(16)
C(4)-C(5)	1.5419(17)
C(5)-C(28)	1.5231(16)
C(5)-C(6)	1.5314(16)
C(6)-C(26)	1.5366(17)
S(7)-O(9)	1.4296(10)
S(7)-O(8)	1.4366(10)
S(7)-C(10)	1.7553(13)
C(10)-C(15)	1.3842(18)
C(10)-C(11)	1.3916(18)
C(11)-C(12)	1.3871(19)
C(12)-C(13)	1.394(2)
C(13)-C(14)	1.393(2)
C(13)-C(16)	1.507(2)
C(14)-C(15)	1.3901(18)
C(17)-C(25)	1.3699(17)
C(17)-N(18)	1.3890(15)
N(18)-C(19)	1.3843(16)
N(18)-C(27)	1.4471(18)
C(19)-C(20)	1.4004(17)

C(19)-C(24)	1.410(2)
C(20)-C(21)	1.385(2)
C(21)-C(22)	1.402(3)
C(22)-C(23)	1.383(2)
C(23)-C(24)	1.4023(19)
C(24)-C(25)	1.4345(17)
C(25)-C(26)	1.4962(17)
C(28)-O(29)	1.4521(15)
O(29)-C(30)	1.3445(15)
C(30)-O(30)	1.2041(18)
C(30)-C(31)	1.5060(19)
C(31)-C(32)	1.549(2)
C(32)-O(36)	1.4160(17)
C(32)-O(33)	1.4214(17)
C(32)-C(37)	1.517(2)
O(33)-C(34)	1.428(2)
C(34)-C(35)	1.526(2)
C(35)-O(36)	1.4233(18)

C(2)-N(1)-C(6)	125.12(10)
C(2)-N(1)-S(7)	117.45(8)
C(6)-N(1)-S(7)	116.58(8)
O(2)-C(2)-N(1)	120.52(11)
O(2)-C(2)-C(3)	121.48(11)
N(1)-C(2)-C(3)	117.89(10)
C(2)-C(3)-C(4)	114.13(10)
C(17)-C(4)-C(3)	108.79(10)
C(17)-C(4)-C(5)	107.62(10)
C(3)-C(4)-C(5)	109.34(9)
C(28)-C(5)-C(6)	113.62(10)

C(28)-C(5)-C(4)	111.31(10)
C(6)-C(5)-C(4)	108.76(9)
N(1)-C(6)-C(5)	109.68(9)
N(1)-C(6)-C(26)	110.88(10)
C(5)-C(6)-C(26)	110.45(9)
O(9)-S(7)-O(8)	118.60(7)
O(9)-S(7)-N(1)	110.04(6)
O(8)-S(7)-N(1)	104.12(6)
O(9)-S(7)-C(10)	110.24(6)
O(8)-S(7)-C(10)	108.56(6)
N(1)-S(7)-C(10)	104.21(5)
C(15)-C(10)-C(11)	121.45(12)
C(15)-C(10)-S(7)	120.08(10)
C(11)-C(10)-S(7)	118.39(10)
C(12)-C(11)-C(10)	118.63(13)
C(11)-C(12)-C(13)	121.21(13)
C(14)-C(13)-C(12)	118.71(12)
C(14)-C(13)-C(16)	120.59(14)
C(12)-C(13)-C(16)	120.71(13)
C(15)-C(14)-C(13)	121.00(13)
C(10)-C(15)-C(14)	118.90(12)
C(25)-C(17)-N(18)	110.08(10)
C(25)-C(17)-C(4)	125.12(11)
N(18)-C(17)-C(4)	124.36(11)
C(19)-N(18)-C(17)	107.87(11)
C(19)-N(18)-C(27)	124.96(11)
C(17)-N(18)-C(27)	127.16(11)
N(18)-C(19)-C(20)	129.59(14)
N(18)-C(19)-C(24)	108.30(11)
C(20)-C(19)-C(24)	122.10(13)

C(21)-C(20)-C(19)	117.14(15)
C(20)-C(21)-C(22)	121.56(13)
C(23)-C(22)-C(21)	121.15(14)
C(22)-C(23)-C(24)	118.70(15)
C(23)-C(24)-C(19)	119.35(12)
C(23)-C(24)-C(25)	133.78(13)
C(19)-C(24)-C(25)	106.84(11)
C(17)-C(25)-C(24)	106.91(11)
C(17)-C(25)-C(26)	122.61(11)
C(24)-C(25)-C(26)	130.39(11)
C(25)-C(26)-C(6)	110.11(10)
O(29)-C(28)-C(5)	107.35(10)
C(30)-O(29)-C(28)	114.41(10)
O(30)-C(30)-O(29)	123.13(13)
O(30)-C(30)-C(31)	124.30(12)
O(29)-C(30)-C(31)	112.55(12)
C(30)-C(31)-C(32)	111.25(11)
O(36)-C(32)-O(33)	105.06(11)
O(36)-C(32)-C(37)	108.86(12)
O(33)-C(32)-C(37)	108.94(13)
O(36)-C(32)-C(31)	109.31(11)
O(33)-C(32)-C(31)	110.20(11)
C(37)-C(32)-C(31)	114.06(12)
C(32)-O(33)-C(34)	106.67(12)
O(33)-C(34)-C(35)	104.58(13)
O(36)-C(35)-C(34)	104.86(13)
C(32)-O(36)-C(35)	107.52(11)

Symmetry transformations used to generate equivalent atoms:

4.2 References

[1] Maehr, H., *J. Chem. Ed.* **1985**, *62*, 114.

[2] Keawpradub, N.; Kirby, G. C.; Steele, J. C.; Houghton, P. J., *Planta Med.* **1999**, *65*, 690.

[3] (a) Bi, Y.; Zhang, L.-H.; Hamaker, L. K.; Cook, J. M., *J. Am. Chem. Soc.* **1994**, *116*, 9027; (b) Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M., *Org. Lett.* **2005**, *7*, 3501; (c) Liao, X.; Zhou, H.; Yu, J.; Cook, J. M., *J. Org. Chem.* **2006**, *71*, 8884; (d) Miller, K. A.; Shanahan, C. S.; Martin, S. F., *Tetrahedron* **2008**, *64*, 6884 and references therein; (e) Bailey, P. D.; Morgan, K. M., *J. Chem. Soc. Perkin Trans. 1* **2000**, 3578; (f) Kuthe, J.; Wong, A.; Davies, I. W.; Reider, P. J., *Tetrahedron Lett.* **2002**, *43*, 3871.

[4] LeMen, J.; Taylor, W. I., *Experientia* **1965**, *21*, 508.

[5] Trost, B. M.; Brennan, M. K., *Synthesis* **2009**, *18*, 3003.

[6] (a) Kam, T.; Choo, Y. *Bisindole Alkaloids, In The Alkaloids*, Vol. *63*; Cordell, G. A., Ed.; Academic Press: New York, **2006**, 181; (b) Saxton, J. E. *Synthesis of the Aspidosperma Alkaloids, In The Alkaloids*, Vol. *50*; Cordell, G. A., Ed.; Academic Press: New York, **1998**, 343.

[7] Stoll, A.; Hofmann, A., *Helv. Chim. Acta* **1953**, *36*, 1143.

[8] (a) Bi, Y.; Hamaker, L. K.; Cook, J. M., *The Synthesis of Macroline Related Indole Alkaloids in Studies in Natural Product Chemistry* **1993**, *13*, 383; (b) Bi, Y.; Hamaker Y.; Cook, J. M., *The Synthesis of Macroline-Related Indole Alkaloids; Studies in Natural Products Chemistry*, Pergamon, London, **1994**, vol. 9.

[9] Hamaker, L. K.; Cook, J. M., *The Synthesis of Macroline Related Sarpagine Alkaloids*. *Alkaloids: Chemical and Biological Perspectives*, Elsevier Science, New York, **1995**, Vol. 9.

[10] Lounasmaa, M.; Hanhinen, P.; Westersund, M., *The Sarpagine Group of Indole Alkaloids*, Academic, San Diego, CA, **1999**, Vol. 52.

[11] Lounasmaa, M.; Hanhinen, P., *The Ajmaline Group of Indole Alkaloids,* Alkaloids, **2001**, *55*, 1.

[12] Lewis, S. E., *Tetrahedron* **2006**, *62*, 8655.

[13] Keawpradub, N.; Eno-Amooquaye, E.; Burke, P. J.; Houghton, P. J., *Planta Med.* **1999**, *65*, 311.

[14] Gilman, R. E., *Diss. Abs*., **1959**, *20*, 1578.

[15] Cook, J. M.; Le Quesne, P. W.; Elderfield, R. C., *J. Chem. Soc. D.* **1969**, *22*, 1306.

[16] Zhang, L.-H.; Cook, J. M., *J. Am. Chem. Soc.* **1990**, *112*, 4088.

[17] Gan, T.; Cook, J. M., *Tetrahedron Lett.* **1996**, *37*, 5033; (b) Gan, T.; Cook, J. M., *J. Org. Chem.* **1998**, *63*, 1478.

[18] Gan, T.; Cook, J. M., *Tetrahedron Lett.* **1996**, *37*, 5037.

[19] Li, J.; Cook, J. M., *J. Org. Chem.* **1998**, *63,* 4166.

[20] Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M., *J. Am. Chem. Soc.* **1999**, *121,* 6998.

[21] Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M., *Org. Lett.* **2001**, *3*, 345.

[22] For a review on the Pictet–Spengler condensation, see Cook, J. M.; Cox, E. D. *Chem. Rev.* **1995**, *95*, 1797.

[23] (a) Jawdosiuk, M.; Cook, J. M., *J. Org. Chem.* **1984**, *49,* 2699; (b) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M., *J. Org. Chem.* **1981**, *46*, 164; (c) Czerwinski, K. M.; Deng, L.; Cook, J. M., *Tetrahedron Lett*. **1992**, *33*, 4721.

[24] (a) Trudell, M. L., Soerens, D.; Webber, R. W.; Hutchins, L.; Grubisha, D.; Bennett, D.; Cook, J. M., *Tetrahedron* **1992**, *48*, 1805; (b) Zhang, L-H.; Bi, Y-Z.; Yu, F-X.; Menzia, G.; Cook, J. M., *Heterocycles* **1992** , *34*, 517.

[25] Bailey, P. D.; Mclay, N. R., *J. Chem. Soc. Perkin Trans. 1* **1993**, 441.

[26] (a) Zhang, L.-H.; Cook, J. M., *Heterocycles*, **1988**, *27*, ***6***, 1353; (b) Zhang, L.-H.; Cook, J. M., *Heterocycles*, **1988**, *27*, ***12***, 2795.

[27] Zhang, L.-H.; Trudell, M. L.; Hollinshead, S. P.; Cook, J. M., *J. Am. Chem. Soc.* **1989**, *111*, 8263.

[28] Bi, Y.; Zhang, L.-H.; Hamaker, L. K.; Cook, J. M., *J. Am. Chem. Soc.* **1994**, *116*, 9027.

[29] Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M., *Org. Lett.* **2005**, *7*, 3501.

[30] Liao, X.; Zhou, H.; Yu, J.; Cook, J. M., *J. Org. Chem.* **2006**, *71*, 8884.

[31] Liu, X.; Zhang, C.; Liao, X.; Cook, J. M., *Tetrahedron Lett.* **2002**, *43*, 7373.

[32] Wang, T.; Cook, J. M., *Org. Lett.* **2000**, *2*, 2057.

[33] Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M., *J. Org. Chem.* **2003**, *68*, 7565.

[34] Muratake, H.; Natsume, M., *Tetrahedron Lett.* **1997**, *38*, 7581.

[35] Cao, H.; Yu, J.; Wearing, X.; Zhang, C.; Liu, X.; Deschamps, J.; Cook, J. M. *Tetrahedron Lett.* **2003,** *44*, 8013.

[36] Liu, X.; Deschamp, J. R.; Cook, J. M., *Org. Lett.* **2002**, *4*, 3339.

[37] Kuethe, J. T.; Wong, A.; Davies, I. W.; Reider, P. J., *Tetrahedron Lett.* **2002**, *43*, 3871.

[38] Tran, Y. S.; Kwon, O., *Org. Lett.* **2005**, *7*, 4289.

[39] Zhu, X.-F.; Lan, J.; Kwon, O., *J. Am. Chem. Soc.* **2003**, *125*, 4716.

[40] Fukuyama, T.; Cheung, M.; Kan, T., *Synlett* **1999**, 1301.

[41] (a) Eschweiler, W., *Ber.* **1905**, *38*, 880; (b) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z., *J. Am. Chem. Soc.* **1933**, *55*, 4571; (c) Newman, M. S.; Lloyd, H. A., *J. Am. Chem. Soc.* **1952**, *74*, 2672.

[42] Miller, K. A.; Martin, S. F., *Org. Lett.* **2007**, *9*, 1113.

[43] Miller, K. A.; Shanahan, C. S.; Martin, S. F. *Tetrahedron* **2008**, *64*, 6884.

[44] For reviews/reports on the synthesis and applications of aziridines, see (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599; (b) Mccoull, W.; Davis, F. A. *Synthesis* **2000**, 1347; (c) Sweeney, J. B., *Chem Soc Rev* **2002**, *31*, 247.

[45] (a) Vandekerckhove, S.; H'Hooghe, M., *Bioorg. & Med. Chem.* **2013**, 21, 3643; (b) Bera, M.; Roy, S., *Tetrahedron Lett.* **2007**, *48*, 7144; (c) Chawla, R.; Singh, A. K.; Yadlav, L. D. S., *RSC Advances* **2013**, *3*, 11385.

[46] (a) Craig, D.; Jones, P. S.; Rowlands, G. J., *Synlett* **1997**, *12*, 1423; (b) Berry, B.; Rowlands, G.; Craig, D.; Jones, P. S., *Chem. Commun.* **1997**, 2141; (c) Caldwell, J. J.; Craig, D.; East, S. P., *Synlett* **2001**, *10*, 1602.

[47] (a) Craig, D.; Mccague, R.; Potter, G. A.; Williams, M. R. V., *Synlett* **1998**, *1*, 55; (b) Craig, D.; Mccague, R.; Potter, G. A.; Williams, M. R. V., *Synlett* **1998**, *1*, 58; c) Adelbrecht, J.-C.; Craig, D.; Dymock, B. W.; Thorimbert, S., *Synlett* **2000**, *4*, 467.

[48] Pak, C. S.; Lee, G. H., *J. Org. Chem.* **1991**, *56*, 1128.

[49] Toyooka, N.; Zhou, D.; Nemoto, H., *J. Org. Chem.* **2008**, *73*, 4575.

[50] Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercuateren, J.; Wber, J. F.; Boukef, K., *Tetrahedron Lett.* **1994**, *35*, 2691.

[51] Berry, M. B.; Rowlands, G. J.; Craig, D.; Jones, P. S., *Chem. Commun.* **1997**, *22*, 2141.

[52] Caldwell, J. J.; Craig, D., *Angew. Chem., Int. Ed. Engl.* **2007**, *119*, 2685.

[53] Adelbrecht, J.-C.; Craig, D.; Thorimbert, S., *Tetrahedron Lett.* **2001**, *42*, 8369.

[54] Adelbrecht, J.-C.; Craig, D.; Flemming, A. J.; Martin, F. M., *Synlett* **2005**, *17*, 2643.

[55] Carballares, S.; Craig, D.; Hyland, C. J. T.; Lu, P.; Mathie, T.; White, A. J. P., *Chem. Commun.* **2009**, *4*, 451.

[56] Lewis, S. E. *Ph.D Thesis*, Imperial College London, **2005**.

[57] Tholen, N. T. H., *Ph.D Thesis*, Imperial College London, **2010**.

[58] Ioannidis, S., *Ph.D Thesis*, University of London, **1999**.

[59] For the use of TMSI for cleaving ethers, see Jung, M. E.; Andrus, W. A.; Ornstein, P. L., *Tetrahedron Lett.* **1977**, *18*, 4175.

[60] Hwu, J. R., *J. Org. Chem.* **1983**, *48*, 4432.

[61] Maruoka, K.; Concepcion, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, H., *J. Am. Chem. Soc.* **1993**, *115*, 3943.

[62] Rahn, V. S., *Ph.D Thesis*, Imperial College London, **2002**.

[63] (a) Schlosser, M.; Coffinet, D., *Synthesis* **1971**, 7, 380; (b) Schlosser, M.; Titus, J.; Guggisberg, Y., *Synlett* **1990**, *11*, 704.

[64] (a) Tanner, D.; Somfai, P. *Tetrahedron Lett.* 1987, 28, 1211; (b) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613 (c) Tanner, D.; Somfai, P., *Tetrahedron* **1988**, *44*, 619.

[65] Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y., *Heterocycles* **1996**, *42*, 701.

[66] Mathie, T., *Towards the Total Synthesis of Alstonerine*, Craig Group internal document, **2008**.

[67] Carballares, S.; Craig, D.; Hyland, C. J. T.; Lu, P.; Mathie, T.; White, A. J. P., *Chem. Commun.* **2009**, *4*, 451.

[68] Cox, P.; Craig, D.; Ioannidis, S. ; Rahn, V. S., *Tetrahedron Lett.* **2005**, *46*, 4687.

[69] (a) Jeong, J. U.; Tao, B.; Sagasser, I; Henniges, H.; Sharpless, K. B., *J. Am. Chem. Soc.* **1998**, *120*, 6844; (b) Ichiki, M.; Tanimoto, H.; Miwa, S.; Saito, R.; Sato, T.; Chida, N., *Chemistry – A European Journal* **2013**, *19*, 264.

[70] Smith, A. B.; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247.

[71] De Lombaert, S. ; Nemery, I. ; Roekens, B.; Carretero, J. C. ; Kimmel, T.; Ghosez, L., *Tetrahedron Lett.* **1986**, *27*, 5099.

[72] Parham, W. E.; Schweizer, E. E., *J. Org. Chem.* **1959**, *24*, 1733.

[73] Parham, W. E.; Christensen, L.; Groen, S. H.; Dodson, R. M., *J. Org. Chem.* **1964**, *29*, 2211.

[74] Parham, W. E.; McKnow, W. D.; Nelson, V.; Kajigaeshi, S.; Ishikawa, N., *J. Org. Chem.* **1973**, *38*, 1361.

[75] Carr, R. V. C.; Williams, R. V.; Paquette, L. A., *J. Org. Chem.* **1983**, *48*, 4976.

[76] Kirner, W. R.; Richter, G. H., *J. Am. Chem. Soc.* **1929**, *51*, 3409.

[77] Van Der Schaaf, P. A.; Kolly, R.; Kirner, H.-J.; Rime, F., Mühlebach, A.; Hafner, A., *J. Organometallic Chem.* **2000**, *606*, 65.

[78] Russel, G. A.; Hershberger, J., *J. Am. Chem. Soc.* **1980**, *102*, 7603.

[79] Cuadrado, P.; González–Nogal, A. M., *Tetrahedron Lett.* **2000**, *41*, 1111.

[80] Armarego, W. L. F.; Chai, C., *Purification of Laboratory Chemicals*, Elsevier Science, New York, **2013**, Vol. 7, 126.

[81] Craig, D.; Lu, P.; Mathie, T.; Tholen, N. T. H., *Tetrahedron*, **2010**, *66*, 6376.

[82] Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T., *J. Am. Chem. Soc.* **2004**, *126*, 8744.

[83] Nicolaou, K.C.; Webber, S. E., *Synthesis* **1986**, *6*, 453.

[84] Mohan, P.; Koushik, K.; Fuertes, M. J. *Tetrahedron Lett.* **2012**, *53*, 2730.

[85] Clemens, R. J., *J. Am. Chem. Soc.* **1989**, *11*, 1989.

[86] Tsunoda, T.; Suzuki, M.; Noyori, R., *Tetrahedron Lett.* **1980**, *21*, 1357.

[87] Padwa, A.; Nara, S.; Wang, Q., *J. Org. Chem.* **2005**, *70*, 8538.

[88] Tsunoda, T.; Suzuki, M.; Noyori, R., *Tetrahedron Lett.* **1980**, *21*, 1357.

[89] Peters, S.; Eckhardt, M.; Hamilton, B. S.; Himmelsbach, F.; Kley, J.; Lehmann-Lintz, T., *Alicyclic carboxylic acid derivatives of benzomorphans and related scaffolds, medicaments containing such compounds and their use.* **2009**, US Patent 0269791.

[90] Aurrecoechea, J. M.; Gorgojo, J. M.; Saornil, C., *J. Org. Chem.* **2005**, *70*, 9640.

[91] Bonjoch, J.; Solé, D.; García–Rubio, S.; Bosch, J., *J. Am. Chem. Soc.* **1997**, *119*, 7230.

[92] Bosch, J.; Bonjoch, J.; Diez, A.; Linares, A.; Moral, M.; Rubiralta, M., *Tetrahedron* **1985**, *41*, 1753.

[93] Diaba, F.; Bonjoch, J., *Org. Biomol. Chem.* **2009**, *7*, 2517.

[94] Park, A.-Y.; Kim, W. H.; Kang, J.-A.; Lee, H. J.; Lee, C.-K.; Moon, H. R., *Bioorg. & Med. Chem.* **2011**, *19*, 3945.

[95] Abdelkafi, H.; Evanno, L.; Deville, A.; Dubost, L.; Chiaroni, A.; Nay, B., *Eur. J. Org. Chem.* **2011**, *15*, 2789.

[96] Knight, S. D.; Overman, L. E.; Pairaudeau, G., *J. Am. Chem. Soc.* **1993**. *115*, 9293.

[97] (a) Fan, X.; Sans, V.; Yaseneva, P.; Plaza, D. D.; Williams, J.; Lapkin, A., *Org. Process R&D* **2012**, *16*, 1039; (b) Takano, S.; Satoh, S.; Ogasawara, K., *J. Chem. Soc., Chem Commun.* **1988**, *1*, 59.

[98] Shing, T. K. M.; Jiang, Q., *J. Org. Chem.* **2000**, *65*, 7059.

[99] Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P., *J. Org. Chem.* **2011**, *76*, 1269.

[100] Shimawaki, K.; Fujisawa, Y.; Sato, F.; Fujitani, N; Kurogochi, M.; Hoshi, H.; Hinou, H.; Nishamura, S.-I., *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 3074.

[101] Kam, T. S.; Choo, Y. M., *Phytochemistry* **2004**, *65*, 603.

[102] (a) Kam, T. S.; Iek, I.-H.; Choo, Y. M., *Phytochemistry* **1999**, *51*, 839; (b) Kam, T. S.; Choo, Y. M., *J. Nat. Products* **2004**, 67, 547.

[103] Taskinen, E., *J. Phys. Org. Chem.* **2007**, *20*, 539.

[104] Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J., *J. Am. Chem. Soc.* **1995**, *117*, 5720.

[105] Koci, J.; Grandclaude, V.; Massonneau, M.; Richard, J.-A.; Romieu, A.; Renard, P.-Y., *Chem. Commun.* **2011**, *47*, 6713.

[106] Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P., *Org. Lett.* **2009**, *11*, 1591.

[107] For a review on the chemistry and synthetic applications of lactam-derived vinyl triflates and phosphates, see Occhiato, E. G., *Mini-Rev. Org. Chem.* **2004**, *1*, 149.

[108] Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I., *J. Am. Chem. Soc.* **1989**, *11*, 278.

[109] Scott, W. J.; Stille, J. K., *J. Am. Chem. Soc.* **1986**, *108*, 3033.

[110] Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I., *J. Am. Chem. Soc.* **1989**, *11*, 278.

[111] Chen, Z.; Izenwasser, S.; Katz, J. L.; Zhu, N.; Klein, C. L.; Trudell, M. L., *J. Med. Chem.* **1996**, *39*, 4744.

[112] Walker, T. L.; Malasi, W.; Bhide, S.; Parker, T.; Zhang, D.; Freedman, A.; Modarelli, J. M.; Engle, J.T.; Ziegler, C. J., Custer, P.; Youngs, W. J.; Taschner, M. J., *Tetrahedron Lett.* **2012**, *53*, 6548.

[113] Kneiss, T.; Laube, M.; Bergmann, R.; Sehn, F.; Graf.; Steinbach, J.; Wuest, F.; Pietzsch, J., *Bioorg. & Med. Chem.* **2012**, *20*, 3410.

[114] Ankner, T.; Hilmersson, G. R., *Org. Lett.* **2009**, *11*, 503.

[115] (a) Nyasse, B.; Grehn, L.; Ragnarsson, U., *Chem. Commun.* **1997**, *11*, 1017; (b) Sridhar, M.; Kumar, B. A.; Narender, R., *Tetrahedron Lett.* **1998**, *39*, 2847.

[116] Youn, S. W.; Bihn, J. H.; Kim, B. S., *Org. Lett.* **2011**, *13*, 3738.

[117] Mayerl, F.; Hesse, M., *Helv. Chim. Acta* **1978**, *61*, 337.

[118] Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C., *Phytotheraphy Research* **1992**, *6*, 121.

[119] Aggarwal, V. K.; Astle, C. J.; Rogers–Evans, M., *Org. Lett.* **2004**, *6*, 1469.

[120] Davies, H. M. L.; Matasi, J.; Hodges, M.; Huby, N.; Thornley, C.; Kong, N.; Houser, J. *J. Org. Chem.* **1997**, *62*, 1095.

[121] (a) Babinski, D.; Soltani, O.; Frantz, D. E., *Org. Lett.* **2008**, *10*, 2901; (b) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H., *Org. Lett.* **2002**, *4*, 4717.

[122] Craig, D.; Goldberg, F. W.; Pett, R. W.; Tholen, N. T. H.; White, A. P., *Chem. Commun.* **2013**, 81, 9275.

[123] Berry, M. B.; Craig, D., *Synlett* **1992**, *1*, 41.

[124] Nemoto, T.; Yamamoto, N.; Wada, N.; Harada, Y.; Tomatsu, M.; Ishighara, M.; Hirayama, S.; Iwai, T.; Fujii, H.; Nagase, H., *Bioorg. & Med. Chem. Lett.* **2013**, *23*, 268.

[125] Royals, E. E.; Brannock, K. C., *J. Am. Chem. Soc.* **1954**, *76*, 3041.