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A total synthesis of (±)-α-cyclopiazonic acid using a cationic cascade as a key step

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ABSTRACT

The indole alkaloid α-cyclopiazonic acid **1** has been synthesised by a route, which features at its core an acid-catalysed cationic cascade cyclisation terminated by a sulfonamide group.

1. Introduction

α-Cyclopiazonic acid **1** (α-CPA) was first identified as a metabolite of the fungal species *Penicillium cyclopium* in the late 1960s, along with a derived imine, and suggested as the main cause of its toxicity, especially significant in stored grain and derived products.[1] Subsequent biosynthetic studies resulted in the identification of β-cyclopiazonic acid **2** as a likely precursor in the fungus (Fig. 1).[2] Subsequently, the cyclopiazonic acids **1** and **2** have been found in a very large range of *Penicillium* species; for example, an examination[3] of some 1400 *Penicillium* extracts identified the presence in many of these.[4] Perhaps somewhat concerning is the fact that such fungal species grow especially well on cheese agar; it is therefore not surprising that α-cyclopiazonic acid **1** has been identified in the organisms responsible for producing two of the best known and arguably most delicious 'blue' cheeses, *Penicillium camemberti* and *Penicillium roqueforti*.[5] Fortunately, extracts from the latter source turn out to be amongst the least toxic of many examined.

The cyclopiazonic acids **1** and **2** belong to the prenylated alkaloid class of natural products.[6] The former has also gained considerable prominence in recent years as a standard in research into calcium-ATPase in the sarcoendoplasmic reticulum: its ability to inhibit this enzyme is the origin of its toxicity.[7] α-Cyclopiazonic acid **1** has found particular use as a standard in this area of research as this inhibition impacts upon calcium reuptake in muscle contraction and relaxation cycles. A literature search elicits around 500 hits during the past five years, either concerning its occurrence as a mould metabolite or applications as a standard in calcium-ATPase work.[8]

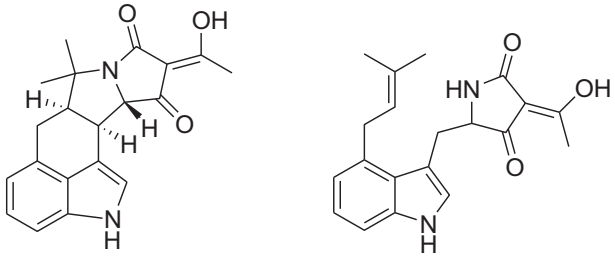

Fig. 1. α- and β-Cyclopiazonic acids **1** and **2**.

Only two total syntheses of α-cyclopiazonic acid **1** have so far been reported, from the Kozikowski group[9] and the Japanese duo of Muratake and Natsume;[10] both completed their total syntheses during the mid-1980s. These approaches share a common final strategy which, fortunately, significantly simplifies the initially arguably fearsome-looking pentacyclic structure **1** and consists of a classical method for formation of the substituted tetramic acid structural feature by a Dieckmann ring closure (Scheme 1). Thus, the less complex intermediate **3** is homologated at nitrogen by condensation with diketene **4** to give the keto-amide **5**, which is not

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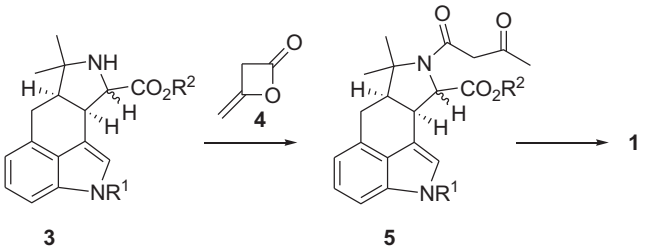
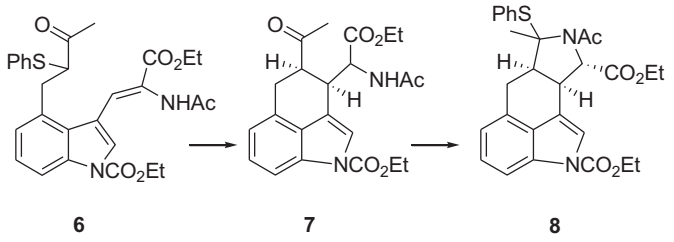
isolated as it undergoes a base-catalysed closure, which offers the additional benefit of delivering the correct stereochemistry at the tetramic acid stereogenic centre adjacent to nitrogen by epimerisation, should this prove necessary.



Scheme 1. The final synthetic steps to α-cyclopiazonic acid **1**.

Some recent biosynthesis studies suggest that this way of forming the tetramic acid residue may be, effectively, biomimetic.[11]

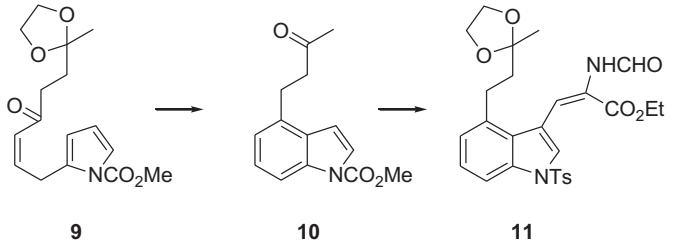
In the Kozikowski synthesis,[9] relatively well-established methodology was used to obtain the α-phenylthio-ketone **6** from indole-4-carboxaldehyde, which then underwent smooth intramolecular Michael ring closure and subsequent desulfurization to provide the necessary cis stereochemistry about the newly formed six-membered ring **7** (Scheme 2). In the absence of the phenylthio function, cyclisation led to the corresponding trans isomer, which could not then be further manipulated.



Scheme 2. Key cyclisation steps in the Kozikowski synthesis of **1**.

A second ring closure leading to the pyrrolidine **8** was achieved by treatment of intermediate **7** with thiophenol and magnesium triflate. Replacement of the sulfur group by methyl was then carried out using, specifically, dimethylzinc; *N*-deprotection then led into the final sequence shown in Scheme 1.

The Muratake–Natsume synthesis[10] first exploits this group's approach to indoles, which features construction of the benzene ring onto an existing pyrrole (Scheme 3). Cyclisation of the precursor **9** is achieved by exposure to tin(IV) chloride; subsequent homologation of the resulting indole **10** then gave the 3-substituted indole **11**.

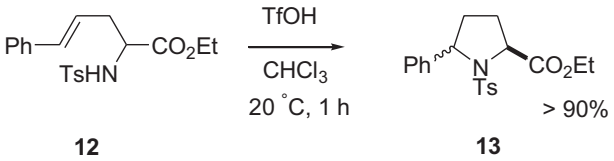


Scheme 3. Key stages of the Natsume synthesis of **1**.

As in the Kozikowski synthesis, direct Michael ring closure of the ketone derived from indole **11** by dioxolane hydrolysis led to the undesired trans-ring fusion but, in this case, epimerisation was used to obtain the cis-stereochemistry by prior cyclic imine formation.

2. Results and discussion

Our ideas for a new cyclopiazonic acid synthesis were stimulated by our discovery that homoallylic sulfonamides such as the cinnamyl derivative **12** underwent smooth and rapid cyclisation to give the corresponding pyrrolidines **13**, as a mixture of isomers, when exposed to strong acid (Scheme 4).[12] All accumulated evidence suggests a benzylic carbenium ion trapping mechanism.



Scheme 4. Trapping a benzylic carbenium ion with a sulfonamide group.

In addition to this, we have also found that cascade cyclisations, which have some resemblance to those found in terpene biosynthesis, are possible in this type of chemistry. Thus, brief exposure of the geranyl glycine derivative **14** to strong acid gives an excellent yield of the bicyclic products **15**.[12]

That β-cyclopiazonic acid **2** is a likely biosynthetic precursor to the target **1**[2] led us to speculate that this could form the basis of a new synthesis featuring interception of a benzylic carbenium ion rather than the biologically more likely interaction between the indolylic methylene and the 'lower' alkene carbon (Fig. 2). This idea of achieving a biomimetic synthesis from the precursor **2** has been highlighted before by the Aggarwal group.[13]

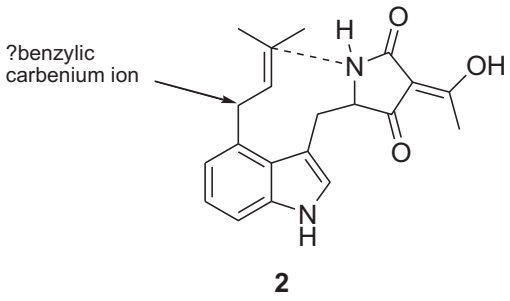
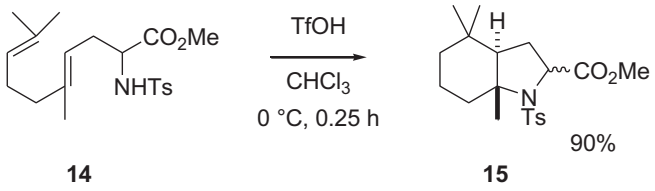


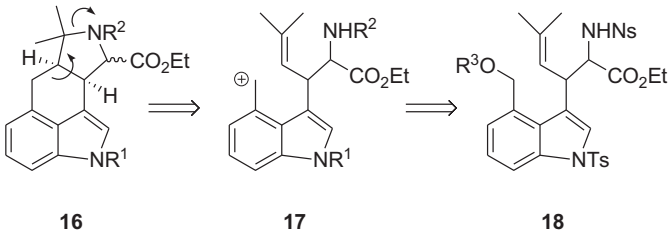
Fig. 2. A (bio)synthetic speculation.

Our plans, however, followed a different idea: we speculated that a suitable precursor **16** for the final sequence of tetramic acid assembly (Scheme 1) could be obtained by a cascade cyclisation in which the benzylic carbenium ion **17** was trapped. Hence, the synthesis led us back to the 3,4-disubstituted indole **18** (Scheme 6). While this looked to be an obtainable target, we were concerned about the sense of stereocontrol which would result from the key acid-catalysed cyclisation which would have to lead to the cis-isomer **16** as, by this stage, there would be no easy way to epimerise either of the stereogenic centres at the new ring junction. Happily, both our own molecular models and the preferred conformations similarly deduced for the natural product itself **1** in the original report of its isolation[1a] suggested that formation of the desired cis-isomer would be a favoured outcome of such a cascade cyclisation. Of course, such models are just that and it was clearly still a somewhat risky plan. As will become plain subsequently, these predictions were fine but we missed a crucial feature shown by the models, that of the steric crowding present in the various intermediates.

We felt it prudent to carry out a simpler mimic of the projected key step to determine that a pyrrolidine could indeed be obtained

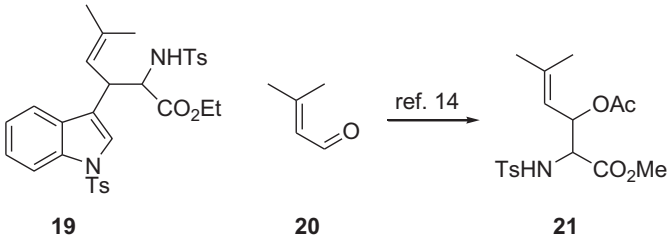


Scheme 5. An acid-catalysed cascade cyclisation.



Scheme 6. Key cascade strategy for a synthesis of α-cyclopiazonic acid **1**.

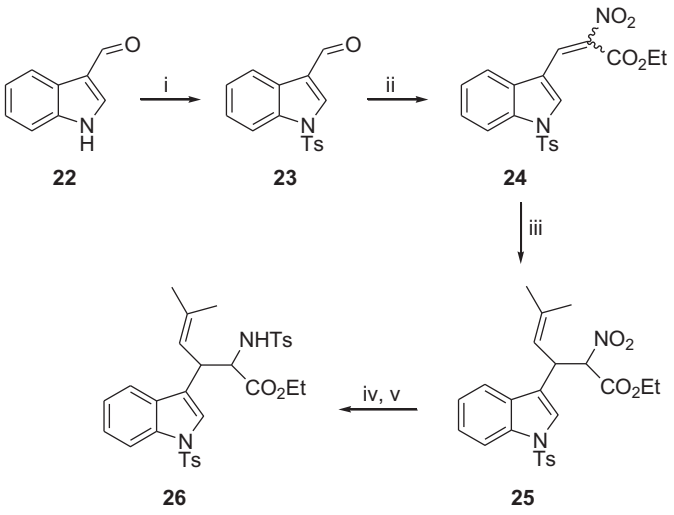
by such an acid-catalysed cyclisation in the presence of an *N*-protected indole. A suitable precursor **19** was therefore required, which we felt could be prepared from indole and the acetate **21**, which was easily obtained from senecialdehyde **20** by condensation with the dianion of methyl *N*-tosylglycinate in the presence of tin(II) chloride[14] followed by acetylation (Scheme 7). Unfortunately, all attempts to couple this electrophile with indole in the presence of various palladium catalysts[15] or lithium perchlorate[16] were unsuccessful.



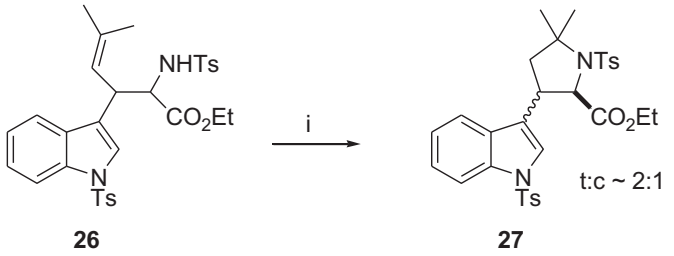
Scheme 7. Initial attempt to form model **19**.

We therefore resorted to a more conventional, linear approach, set out in Scheme 8, starting with indole-3-carboxaldehyde **22**, *N*-tosylation of which was followed by a Henry condensation of the resulting protected indole **23** with ethyl nitroacetate, triggered by titanium(IV) chloride.[17]

The resulting doubly activated alkene **24**, which was formed in a 1.5:1 ratio of geometric isomers, then underwent a smooth Michael addition of an organozinc reagent[18] to establish the required isoprene unit. The product **25** was obtained as an unassigned 3:1 mixture of two diastereoisomers, which were reduced with zinc in acetic acid, followed by *N*-tosylation of the resulting amines. The desired model precursor **26**, again isolated as a 3:1 mixture of diastereoisomers, which were not separated, was then exposed to 0.4 equiv of triflic acid in ice-cold chloroform for 0.25 h, conditions which had previously been used (Scheme 5) for generation and trapping of a tertiary carbenium ion.[12] However, this resulted in essentially no reaction. Happily, by increasing both the acid concentration and the temperature, complete conversion into the desired pyrrolidines **27** was observed (Scheme 9), which were isolated in 79% yield from a small-scale trial in a ratio of diastereoisomers of 2:1, which were not separated. We were therefore at least confident that an *N*-tosyl indole residue would survive the acidic conditions which would be necessary to induce the planned cascade cyclisation (Scheme 6).



Scheme 8. Reagents and conditions: (i) TsCl, DMAP (cat.), Et_3N, 20 °C, 4 h; (ii) $EtO_2CCH_2NO_2$, $TiCl_4$, *N*-methylmorpholine, THF, mix at 0 °C then 20 °C, 16 h; (iii) $Me_2C{=}CHMgBr$, $ZnCl_2$, THF, mix at 0 °C then 20 °C, 2 h, 88%; (iv) Zn, AcOH, EtOH, 20 °C, 2 h; (v) TsCl, DMAP (cat.), Et_3N, CH_2Cl_2, 20 °C, 16 h, 32% for two steps.



Scheme 9. Reagents and conditions: (i) TfOH (0.6 equiv), $CHCl_3$, reflux, 1 h, 79%.

^{1}H NMR coupling constant values suggested that the major product was the *trans*-isomer **28** [$J_{2,3}$=8.5 Hz]; a possible conformation is shown in Fig. 3. In contrast, the minor cis-isomer **29** showed $J_{2,3}$=4.3 Hz and in addition, an extraordinary chemical shift of the ester methyl group to δ_H=0.09. A likely explanation for this is that the ester group and the terminal methyl in particular, are positioned directly over the indole ring, as shown in conformation **29**; presumably, this conformation is favoured as it avoids any interaction with the pyrrolidine tosyl group. Natsume and Muratake noted similar effects in some advanced intermediates during their synthesis of α-cyclopiazonic acid **1**.[10]

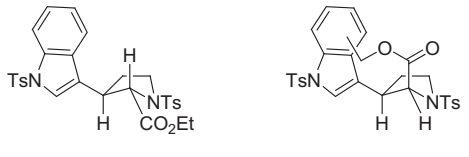
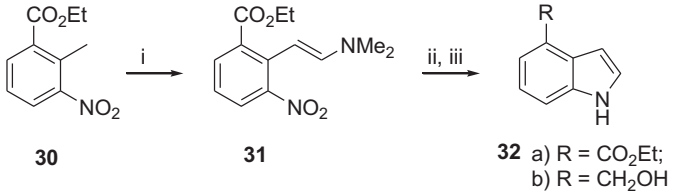


Fig. 3. Possible conformations of the *trans*- and *cis*-pyrrolidines **28** and **29**.

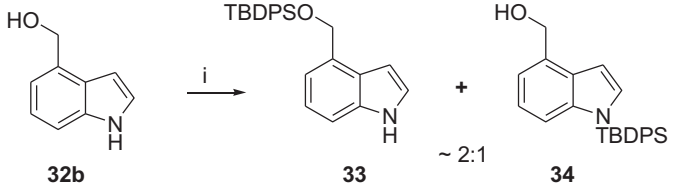
Thus encouraged, we next embarked upon the synthesis of necessary precursor(s) for the synthesis of the target **1**. Starting with the commercially available nitrobenzoate **30**, a Leimgruber–Batchko protocol was used, which proceeded via the enamine **31**, the nitro group of which was reduced using iron in ethanolic acetic acid (Scheme 10).[19] Despite a strong exotherm, during which cyclisation took place as well, this method could be used reliably on a reasonably large scale, in contrast to the

hydrogenolysis method reported by Kozikowski[20] which, in our hands, was only effective on a small scale. A second reduction of the resulting ester **32a** using Dibal-H gave a complex mixture of products, despite a report to the contrary;[20] by contrast, reduction using Red-Al[21] delivered a decent overall yield of indole-4-methanol **32b**.

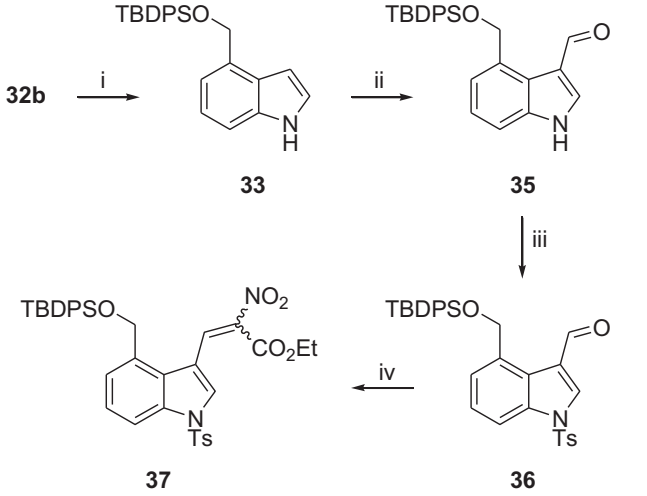


Scheme 10. Reagents and conditions: (i) DMF dimethyl acetal, DMF, reflux, 16 h, 93%; (ii) Fe, AcOH, EtOH, 50°–80 °C, then reflux, 0.5 h, 57%; (iii) Red-Al (2 M in toluene), Et_2O, 0–20 °C, 16 h, 64%.

Attempted direct Vilsmeier formylation[22] of the unprotected alcohol **32b** using $POCl_3$/DMF gave a complex mixture of products, probably because of undesired reaction(s) at the acid-sensitive benzylic alcohol site, and so we protected this function with a robust silicon-based group. While an initial attempt to achieve this (Scheme 11) led to a mixture of *O*- and *N*-silylated products **33** and **34**, using tetrahydrofuran as solvent in place of DMF delivered an excellent yield of the desired product **33** (Scheme 12).



Scheme 11. Reagents and conditions: (i) TBDPSCl, 0.1 equiv imidazole, DMF, 20 °C, 16 h. [TBDPS=*tert*-butyldiphenylsilyl].



Scheme 12. Reagents and conditions: (i) TBDPSCl, 0.1 equiv imidazole, THF, 20 °C, 16 h, 95% [TBDPS=*tert*-butyldiphenylsilyl]; (ii) $POCl_3$, pyridine, DMF 35 °C, 0.75 h then aq NaOH, 100 °C, 2 min, 82%; (iii) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 20 °C, 16 h, 85%; (iv) $EtO_2CCH_2NO_2$, $TiCl_4$, THF, 0 °C, 0.5 h then *N*-methylmorpholine, 20 °C, 16 h, 43%.

A Vilsmeier formylation was now successful when carried out in the presence of pyridine, without which extensive desilylation occurred. Subsequent *N*-tosylation of the resulting aldehyde **35** then gave the protected indole **36**, which was converted into the nitro-ester **37**, in anticipation of this undergoing Michael addition of a 2-methylpropenyl residue to complete the assembly of the required cascade precursor. Unhappily, many attempts using both methylpropenyl Grignard or the corresponding lithio reagent modified by copper(I) salts or various Lewis acids (e.g., $ZnCl_2$, $InCl_3$, $SnCl_2$) delivered none or no more than mediocre yields of the desired adduct (cf. Schemes 6 and 8), but rather desilylated material and a number of unidentified products (Fig. 4). We regarded this as a somewhat ominous indication of the excessive steric crowding at this site which, of course could have a potentially deleterious effect on the viability of any subsequent alternative schemes.

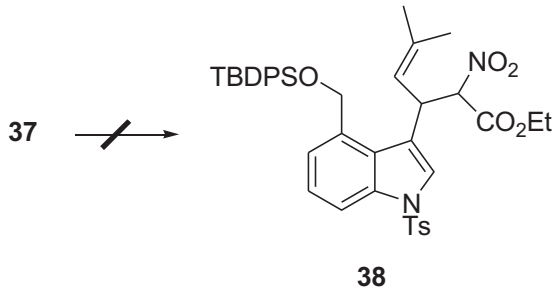
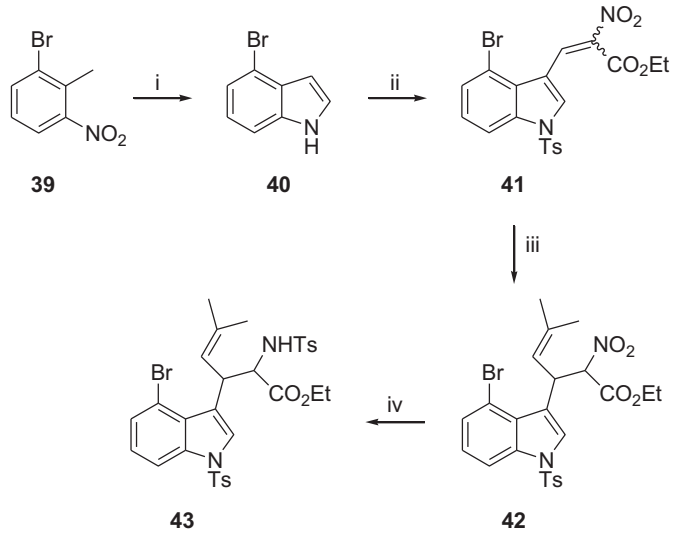


Fig. 4. Unsuccessful Michael addition.

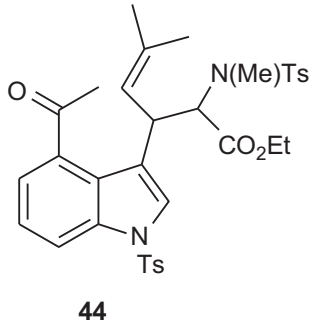
We therefore chose to use 4-bromoindole derivatives instead, with a view to introducing the 4-hydroxymethyl group at a much later stage. Using the same methodology as before, but starting with the aryl bromide **39**, the Michael acceptor **41** was prepared via 4-bromoindole **40**[23] (Scheme 13). Our views on the high level of steric hindrance around the top face of this type of molecule, such as analogue **37**, were vindicated when the latter 4-bromo derivative **41** underwent very smooth Michael addition of a propenylzinc species to deliver an excellent yield of the desired adduct **42**. A final nitro group reduction and *N*-tosylation then gave the target **43** in moderate yield, the result apparently of extreme sensitivity at the intermediate amino-ester stage, as a separable 2:1 mixture of diastereoisomers, whose exact structures were not determined.



Scheme 13. Reagents and conditions: (i) as Scheme 10, **30** to **32a**, except pyrrolidine used in place of Me_2NH (Ref. 23); (ii) as Scheme 12, **33** to **37**; (iii) $Me_2C{=}CHMgBr$, $ZnCl_2$, THF, 0 °C, 2 h, 90%; (iv) as Scheme 8, **25** to **26**, 36%.

Unfortunately, a wide range of palladium-catalysed homologation methods (Suzuki, Stille, carbonylations, low temperature halogen/metal exchange etc.) failed at this stage when applied to a mixture of isomers of the bromo derivative **43**; instead, extensive

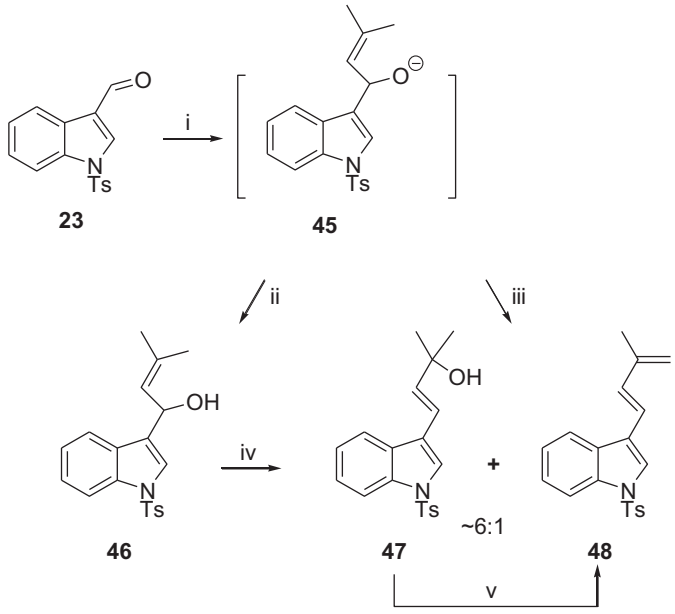
polymerisation seemed to be the primary outcome. Other metals were equally unsuccessful; the only partly successful method was a carbonylation reaction [$Co_2(CO)_8$, CO, MeLi, NaOH] reported by Miura,[24] which delivered a moderate 27% yield of the methyl ketone **44**, of possible use except that the amino group had also been methylated. This signalled another return to the planning stage (Fig. 5).



44

Fig. 5. A possibly useful carbonylation product.

As similar failures were encountered when the 'free' NH in the brominated substrate **43** was masked by a methoxycarbonyl group, this strategy overall seemed likely to be unproductive, perhaps again a victim of excessive steric crowding. We thought to reverse the order of introduction of the various functionalities in the amino-ester side chain by first forming an allylic acetate and then adding the amino-ester function by nucleophilic attack onto a π-allyl complex formed from the former.[25] Thus, the *N*-protected indole-3-carboxaldehyde **23** was homologated using a propenyl Grignard reagent with the aim of forming the allylic alcohol **46**. This proved to be unexpectedly sensitive. A standard Grignard reaction quench using aqueous ammonium chloride at ambient temperature gave instead the tertiary alcohol **47**, accompanied by small amounts of the dehydration product, the diene **48**, but in excellent overall yield (Scheme 14).

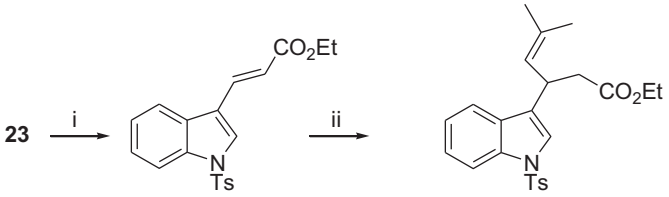


23 **45** **46** **47** **48**

Scheme 14. Reagents and conditions: (i) $Me_2C{=}CHMgBr$, THF, −78 °C, 2 h; (ii) aq NH_4Cl, −78 °C; (iii) warm to 20 °C, quench with aq NH_4Cl; (iv) 20 °C, 72 h; v) Ac_2O, pyridine, CH_2Cl_2, 0 °C or $ClCO_2Et$, pyridine, $CHCl_3$, 0 °C, 1–2 h, 81–84%.

It was only when the reaction was similarly quenched but at −78 °C that the expected secondary alcohol **46** was successfully isolated. The sensitivity of this compound was evident when it underwent smooth rearrangement to the isomeric tertiary allylic alcohol **47**, together with a lesser amount of the diene **48** after 72 h at ambient temperature; the latter was the only product when attempts were made to acylate the alcohol **47**. Halogenations, not surprisingly, were also unproductive.

We therefore altered our strategy again, this time to one in which the amino group was introduced at a much later stage. In order to assess the various methods available in the presence of a protected indole nucleus, the indole-3-propanoate **50** was synthesised from the *N*-tosyl aldehyde **23** by sequential Horner–Wadsworth–Emmons homologation[26] to give the (*E*)-alkenoate **49** and a Michael addition,[27] which delivered a good yield of this desired target, understandably after a lengthier reaction period than those required for similar additions to the more activated nitro-ester **24** and **41** (Scheme 15).

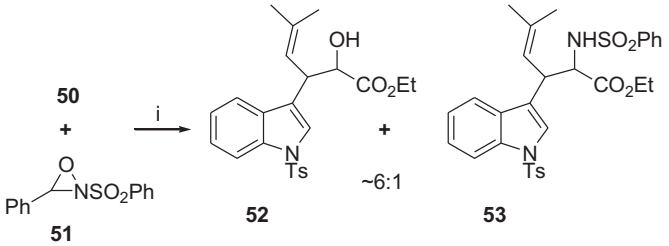


49 **50**

Scheme 15. Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, 20 °C, 2 h, 77%; (ii) $Me_2C{=}CHMgBr$, PhSCu, THF, −40 to 0 °C then −40 °C, add enoate, 20 °C, 2 h, 81%.

Our first attempt to functionalise the methylene group adjacent to the ester involved formation of its potassium enolate and reaction with the oxaziridine **51**.[28]

In the event, the reaction worked well, delivering a 76% isolated yield of the desired α-hydroxy-ester **52** along with a much smaller amount, 12%, of the readily separable amino derivative **53**, a potential final intermediate from this sequence (Scheme 16). Unfortunately, two types of Mitsunobu nucleophile **54** (Fig. 6), whose use was aimed at introducing the 4-nitrophenylsulfonylamino (nosylamino) group, which we anticipated would be more readily deprotected at the appropriate later stage,[29] failed to deliver under a range of reagent combinations and conditions.[30] The triflate **55** derived from α-hydroxy-ester **52**, while readily formed using triflic anhydride (pyridine, CH_2Cl_2, 0 °C), proved far too sensitive to elimination to give the corresponding conjugated diene to allow either purification or subsequent azide displacement.



51 **52** **53**

Scheme 16. Reagents and conditions: (i) KHMDS, THF, −78 °C, 0.75 h, 76% (**52**).

An alternative oxaziridine **56**, which has been reported as being useful for the direct amination of ester enolates[31] unfortunately reacted with the potassium enolate of the ester **50** to give an approximately equal mixture of the desired amino-ester derivative **57**

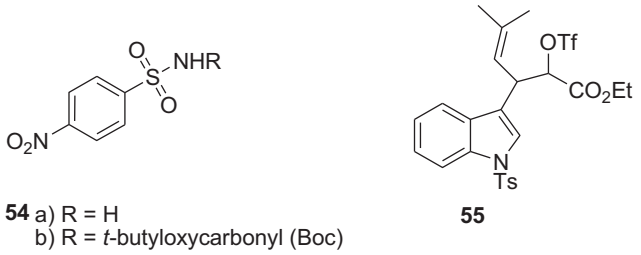
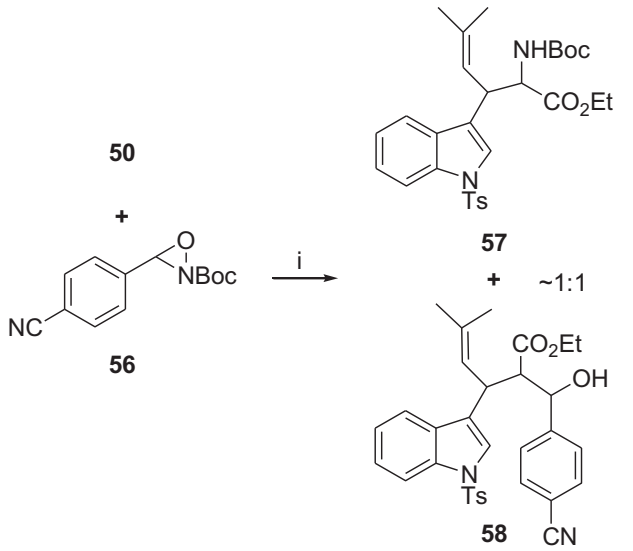


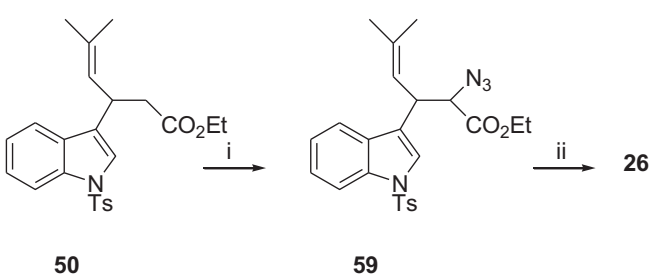
Fig. 6. More unsuccessful reagents and intermediates.

together with the adduct **58** formed from the enolate and the aldehyde released after the oxaziridine had donated its nitrogen group as desired (Scheme 17).



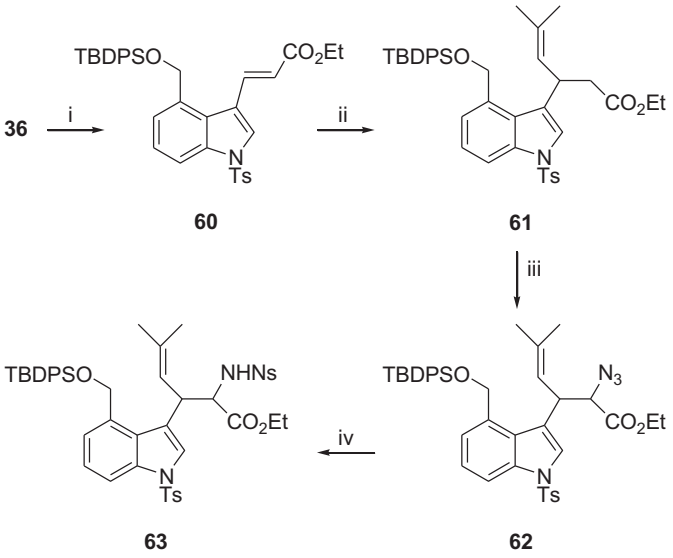
Scheme 17. Reagents and conditions: (i) KHMDS, THF, −78 °C, 0.75 h, 79% (1:1 mix).

Despite continued concerns regarding the level of steric hindrance around this reactive site, the successful introduction of a suitable nitrogen function into the unsaturated ester **50** was finally achieved using the bulky reagent 2,4,6-triisopropylbenzenesulfonyl (trisyl) azide,[32] which reacted smoothly with the same potassium enolate[33] to give a good but unoptimised yield of the α-azido-ester **59** (Scheme 18). A subsequent Staudinger reaction[34] then led to the corresponding amino-ester, which was *N*-tosylated to provide a mixture of diastereoisomers (~2:1 ratio) of the ester **26**, prepared previously for the model cyclisation methodology (Scheme 8). The identity of the two samples, except for the isomer ratio, served to confirm the validity of this method of amine group introduction.



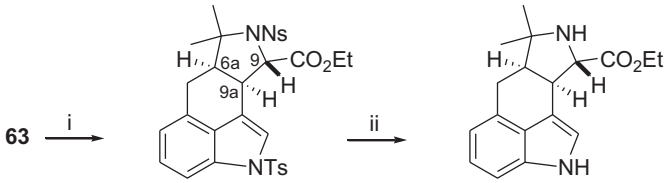
Scheme 18. Reagents and conditions: (i) KHMDS, THF/toluene, −78 °C, 0.5 h then add trisyl azide, 5 min then add AcOH and warm to 20 °C, 63%; (ii) PPh3, H2O, THF, 65 °C, 6 h then TsCl as Scheme 8, 35%.

We therefore applied this new strategy to an original a-CPA precursor **36** and were delighted to find that the chemistry continued to be viable (Scheme 19). HWE homologation smoothly provided the unsaturated ester **60** necessary for the following Michael addition, which then delivered an unoptimised yield of 53% of the propenyl homologue **61**, the potassium enolate of which reacted smoothly with trisyl azide to give the α-azide ester **62** as essentially as single diastereoisomer whose stereochemistry was not assigned. A Staudinger reaction then provided the corresponding α-amino ester, which was immediately protected as its 4-nosyl derivative **63**, in anticipation of a relatively simple deprotection step at the final stages of the synthesis, by exposure to a thiolate.[29] We have previously found that such sulfonamides participate in acid-catalysed ring closures as effectively as the related toluenesulfonamides, despite their obviously rather dissimilar electronic properties.[12] The 4-nosyl derivative **63** was isolated as a ca. 4:1 mixture of diastereoisomers which were neither separated nor structurally assigned.



Scheme 19. Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$ as Scheme 15, 62%; (ii) $Me_2C{=}CHMgBr$, PhSCu as Scheme 15, 53%; (iii) KHMDS, trisyl azide as Scheme 18, 56%; (iv) PPh_3, aq THF as Scheme 18 then 4-NsCl, pyridine, DMAP (cat.), $CHCl_3$, 0–20 °C, 16 h, 52%.

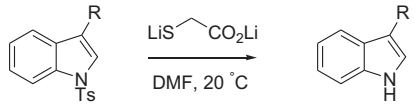
Having finally obtained a sample of a suitable intermediate **63** for the projected cascade cyclisation, we chose to first try the key step using this material directly, rather than to remove the silyl group in a separate reaction, reasoning that this could occur rapidly upon exposure to the acid or that the entire silyloxy group could leave the molecule after *O*-protonation to generate the desired benzylic carbenium ion (See Scheme 6). In the event, we were extremely pleased to observe that exposing the precursor **63** to a solution of triflic acid in chloroform at ambient temperature for 1 h resulted in smooth cascade cyclisation to give an excellent 74% isolated yield of the tetracyclic product **64** (Scheme 20). Happily, this was isolated as essentially as single diastereoisomer, which evidently possessed the required *cis*-stereochemistry at the newly created ring junction, as anticipated from molecular models (see above). A value of 4.1 Hz for $J_{6a,9a}$ led to this conclusion; a very similar derivative but one having the trans-stereochemistry across this ring junction obtained by Natsume and Muratake[10] during their synthesis of a-CPA showed $J_{6a,9a}$=12.5 Hz. The stereochemistry of the ester was assigned as *syn* to the adjacent ring junction proton on the basis of $J_{9,9a}$=9.5 Hz, also in line with a value of 10.0 Hz observed by the Japanese workers.

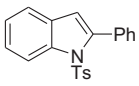
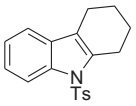
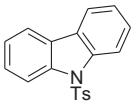
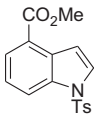


Scheme 20. Reagents and conditions: (i) 2·TfOH, $CHCl_3$, 20 °C, 1 h, 74%; (ii) 2·$HSCH_2CO_2H$, 4·LiOH, DMF, 20 °C, 4 h, 85%.

A second piece of good fortune followed immediately: during the next step, removal of the nosyl group from the pyrrolidine ring using thioglycolate,[29] the indole tosyl group was also completely removed. While cleavage of this group was not expected to be too difficult in view of the relatively low pK_a value of the indole nucleus, we had anticipated that this would require an additional step, such as warming with ethanolic hydroxide, for example.[35] Clearly this was of great benefit to the present synthesis although, as ever, the loss of so much mass in a single step was somewhat disconcerting. With the isolation of compound **65**, a new total synthesis of a-CPA had effectively been completed as this has previously served as a penultimate intermediate.[9,10] Although the stereochemistry of the ester group was that required in the natural product, this was of no concern as this centre undergoes epimerisation if necessary during the final tetramic acid ring formation (see above).

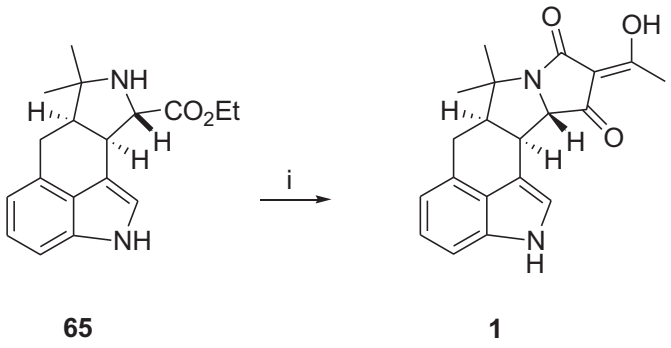
Table 1
Model indole and imidazole detosylations



Entry	R	Mp *N*-tosyl derivative °C	% Yield N–H indole
a	H	86–88[28]	86
b (=**23**)	CHO	148–150[14]	95
c	$CH2CO_2Et$	99–101	79
d (=**49**)	$CH{=}CHCO_2Et$	99–101	41
e	$C(O)CO_2Et$	105–110	0
f		108–110	87
g		93–96[29]	80
h		128–131[30]	87
i		145–147[31]	81
j		78–80[32]	92
k		127–130	88

Some of the scope and limitations of this new method for the *N*-detosylation of indoles and a few related heteroaromatic systems are presented in Table 1.[36] Simple tosylated indoles were very efficiently deprotected (entries a–c), but not surprisingly, the return from the conjugated ester (entry d) was much lower, presumably due to competing Michael addition of the thiolate. The 3-α-keto-ester (entry e) proved too sensitive for any product to be isolated. 2-Phenylindole was, not surprisingly, obtained in excellent yield (entry f) as were the two carbazole-based models (entries g and h), along with the 4-indole ester used in the present study (entry i) The success with two simple imidazole derivatives (entries j and k) suggest a generality which should be applicable to many more complex *N*-tosylated heteroaromatic systems.

Completion of the a-CPA synthesis, while mechanistically somewhat complex, in practise simply involves heating the penultimate intermediate **65** with diketene and base in dichloromethane (Scheme 21).[9,10] In our hands, this gave a decent return of a-CPA **1**, which proved to be identical in all respects, except of course for optical rotation, with a commercial sample of natural material (Tocris).



Scheme 21. Reagents and conditions: (i) Diketene, *t*-BuOK, CH_2Cl_2, 40 °C, 24 h, 79%.

In particular, the ^{1}H NMR spectra were super-imposable, even to the extent of showing around 8% of a second enol tautomer, probably involving the 1,3-dione function, in both samples. Relevant, clear and identical resonances exhibited by this tautomer were δ_H ($CDCl_3$, 400 MHz) 4.19 (d, J ~10.8 Hz) and 2.45 (s); the corresponding resonances for the main tautomer were δ_H 4.00 (d, J ~11.1 Hz) and 2.38 (s). Approximately 5% of a stereoisomer may also have been present in the synthetic sample, appearing as δ_H 4.47 (d, J ~4 Hz), suggesting the isomer with all three relevant protons cis to each other. This was not however confirmed by other obvious and assignable resonances. This may account for the slightly lower melting point (230–236 °C) to that recorded for the natural material (245–246 °C).[1a]

3. Conclusions

Overall therefore, this represents a relatively brief synthesis of α-cyclopiazonic acid **1**, which could be made better by further optimisation of some of the approach work and which also has the potential for leading to optically active material. It was good to read that this has very recently been achieved: a German group has succeeded in obtaining the advanced intermediate **63** on multigram scale using an Evans' chiral auxiliary to guide the [1.4]-propenyl group addition and then to desymmetrize the subsequent introduction of azide using an optimized version of the method we employed (Scheme 19).[37] The only place where this could now go wrong would be if the stereogenic centre α-to the ester group underwent epimerization upon exposure to acid

but prior to cyclisation, as this would be expected to give the opposite enantiomer of the natural product and hence less optically pure product, or even racemic material. This feature has yet to be tested.

4. Experimental section

4.1. General remarks

NMR spectra were recorded using a Bruker DPX spectrometer operating at 400 MHz for ^{1}H spectra and at 100.6 MHz for ^{13}C spectra, respectively. Unless stated otherwise, NMR spectra were measured using dilute solutions in deuteriochloroform. All NMR measurements were carried out at 30 °C and chemical shifts are reported as parts per million on the delta scale downfield from tetramethylsilane (TMS: δ=0.00) or relative to the resonances of $CHCl_3$ (δ_H=7.27 ppm in proton spectra and δ_C=77.0 ppm for the central line of the triplet in carbon spectra, respectively). Coupling constants (J) are reported in hertz. Infrared spectra were recorded as thin films on sodium chloride plates for liquids and as KBr disks for solids, using a Perkin–Elmer 1600 series FTIR spectrophotometer and sodium chloride plates. Low resolution mass spectra were obtained using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionization (ApcI) modes, as stated. High resolution mass spectrometric data was obtained from the EPSRC Mass Spectrometry Service, University College, Swansea, using the electrospray ionisation (ES) mode unless otherwise stated. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin–Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solutions from aqueous work-ups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. The resulting dried solutions were evaporated using a Büchi rotary evaporator under water aspirator pressure and at ambient temperature unless otherwise stated. Column chromatography was carried out using Merck Silica Gel 60 (230–400 mesh). TLC analyses were carried out using Merck silica gel 60 F_{254} pre-coated, aluminium-backed plates, which were visualized using ultraviolet light or potassium permanganate or ammonium molybdenate sprays.

Ether refers to diethyl ether and petrol to the fraction boiling 60–80 °C unless stated otherwise.

*4.1.1. Ethyl (E)- and (Z)-3-[1-(4-toluenesulfonyl)-indole-3-yl]-2-nitroacrylate **24**.* Anhydrous tetrahydrofuran (20 mL), placed in a three-necked round bottomed flask equipped with a dropping funnel, was stirred and cooled to 0 °C. Titanium(IV) chloride (2.95 mL, 26.0 mmol) was added dropwise via syringe and a bright yellow precipitate formed immediately. A mixture of 1-(4-toluenesulfonyl)-indole-3-carboxaldehyde **23** (4.00 g, 13.0 mmol; mp 148–150 °C [lit.[17,38] mp 148–150 °C]) and ethyl nitroacetate (1.48 mL, 13.0 mmol) in tetrahydrofuran (10 mL) was then added slowly from the dropping funnel. The now brown solution was stirred for 0.25 h at the same temperature before 4-methylmorpholine (5.89 mL, 52.0 mmol) was added during 0.5 h. The resulting mixture was then stirred overnight without the addition of any more coolant and finally quenched by the addition of water (50 mL). Ether (20 mL) was added and the resulting two layers separated. The aqueous layer was extracted with ether (2×50 mL) and the combined organic solutions dried, filtered and evaporated. The resulting solid was crystallised from ethyl acetate/hexanes to give the *nitroacrylate* **24** (3.70 g, 67%) as an orange solid in a ratio of (*E*)- and (*Z*)-isomers of 1.5:1. Mp 162–165 °C; [$C_{20}H_{18}N_2O_6S$: calcd C 58.0, H 4.4; N 6.8; found: C 57.8, H 4.5, N 6.6%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major) 8.17 (d, J=8.3 Hz, 1H; 7′-H), 7.94 (s, 1H; 2′-H), 7.93 (s, 1H; 3-H), 7.75 (d, J=8.2 Hz, 2H, 2× ArH), 7.58 (d, J=7.8 Hz, 1H, 4′-H), 7.35-7.31 (m, 2H, 5′- and 6′-H), 7.28 (d, J=8.2 Hz, 2H, 2× ArH), 4.33 (q, J=7.1 Hz, 2H, OCH_2), 2.33 (s, 3H; ArMe), 1.31 (t, J=7.1 Hz, 3H, CH_2CH_3); (minor) 8.17 (d, J=8.3 Hz, 1H; 7′-H), 7.95 (s, 1H; 2′-H), 7.89 (s, 1H; 3-H), 7.75 (d, J=8.2 Hz, 2H, 2× ArH), 7.59 (d, J=7.8 Hz, 1H, 4′-H), 7.35–7.31 (m, 2H, 5′- and 6′-H), 7.27 (d, J=8.2 Hz, 2H, 2× ArH), 4.43 (q, J=7.1 Hz, 2H, OCH_2), 2.34 (s, 3H; ArMe), 1.35 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major) 178.2 (CO), 159.7 (2-C), 146.5 (s), 134.7 (s), 132.4 (s), 130.7 (s), 129.0 (d), 128.9 (s), 127.8 (d), 126.5 (d), 124.8 (d), 124.3 (d), 119.2 (d), 114.2 (d), 111.6 (d), 53.9 (OCH_2), 22.1 (Me), 14.5 (Me); (minor) 176.4 (CO), 159.8 (2-C), 146.5 (s), 134.8 (s), 132.5 (s), 130.7 (s), 129.1 (d), 128.7 (s), 127.0 (d), 126.5 (d), 124.9 (d), 124.3 (d), 119.1 (d), 114.2 (d), 111.8 (d), 53.7 (OCH_2), 22.3 (Me), 16.2 (Me); IR (KBr): ν_{max}=1728, 1640, 1534, 1448, 1175 cm^{-1}; HRMS: m/z: calcd for $C_{20}H_{22}N_3O_6S$: 432.1224; found: 432.1221 $[M+NH_4]^+$.

*4.1.2. Ethyl (2RS,3RS)- and (2RS,3SR)-5-methyl-2-nitro-3-[1-(4-toluenesulfonyl)-indole-3-yl]-hex-4-enoate **25**.* 2-Methyl-1-propenylmagnesium bromide (33.6 mL of a 0.5 M solution in toluene, 17.0 mmol) was added dropwise to a suspension of zinc chloride (1.50 g, 11.0 mmol) in tetrahydrofuran (10 mL) maintained at 0 °C.[39] The resulting solution was stirred at this temperature for 0.25 h then transferred by cannula to a second flask containing the foregoing nitroacrylate **24** (1.50 g, 4.00 mmol) in dry tetrahydrofuran (20 mL) also stirred at 0 °C. The resulting mixture was stirred for 2 h without additional cooling then quenched by the addition of pH 8 buffer (40 mL) and extracted with ether (2×30 mL). The combined extracts were dried, filtered and evaporated and the crude product separated by column chromatography (70% dichloromethane/petrol) to give the *nitro-ester* **25** (1.10 g, 63%) as a 1.2:1 mixture of diastereoisomers and a pale yellow, oily solid [$C_{24}H_{26}N_2O_6S$: calcd C 61.3, H 5.6; N 6.0; found: C 61.6, H 5.5, N 5.9%], which showed: ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major) 7.88 (d, J=8.3 Hz, 1H, 7′-H), 7.70 (d, J=8.2 Hz, 2H, 2× ArH), 7.48 (d, J=7.7 Hz, 1H, 4′-H), 7.39 (s, 1H, 2′-H), 7.38-7.34 (m, 2H, 5′- and 6′-H), 7.27 (d, J=8.2 Hz, 2H, 2× ArH), 5.48–5.33 (m, 2H, 2- and 4-H), 4.76–4.73 (m, 1H, 3-H), 3.82–3.78 (m, 2H, OCH_2), 2.27 (s, 3H, ArMe), 1.72 (s, 3H, Me), 1.66 (s, 3H, Me), 1.23–1.21 (m, 3H, CH_2CH_3); (minor) 7.85 (d, J=8.3 Hz, 1H, 7′-H), 7.66 (d, J=8.2 Hz, 2H, 2× ArH), 7.45 (d, J=7.7 Hz, 1H, 4′-H), 7.43 (s, 1H, 2′-H), 7.35–7.31 (m, 2H, 5′- and 6′-H), 7.28 (d, J=8.2 Hz, 2H, 2× ArH), 5.48–5.33 (m, 2H, 2- and 4-H), 4.76–4.73 (m, 1H, 3-H), 4.18 (q, J=7.2 Hz, 2H, OCH_2), 2.26 (s, 3H, ArMe), 1.74 (s, 3H, Me), 1.65 (s, 3H, Me), 0.78 (t, 3H, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major) 172.2 (CO), 152.1 (s), 149.8 (s), 143.0 (s), 138.0 (s), 134.9 (s), 129.9 (d), 126.9 (d), 126.7 (d), 125.2 (d), 123.4 (d), 119.5 (d), 118.7 (d), 113.8 (d), 90.9 (d), 63.0 (OCH_2), 37.4 (d), 25.9 (q), 21.6 (q), 18.1 (q), 13.4 (q); (minor) 172.2 (CO), 154.3 (CO), 150.2 (s), 143.5 (s), 138.3 (s), 134.9 (s), 130.0 (d), 126.7 (d), 123.9 (d), 123.6 (d), 120.3 (d), 119.6 (d), 118.6 (d), 113.9 (d), 89.2 (d), 62.9 (OCH_2), 37.7 (d), 26.0 (q), 21.6 (q), 18.3 (q), 13.9 (q); IR ($CHCl_3$): ν_{max}=1748, 1563, 1447, 1372, 1175 cm^{-1}; HRMS [APCI]: m/z: calcd for $C_{24}H_{27}N_2O_6S$: 471.1590; found: 471.1588 $[M+H]^+$.

*4.1.3. Ethyl (2RS,3RS)- and (2RS,3SR)-5-methyl-2-(4-toluenesulfonylamino)-3-[1-(4-toluenesulfonyl)-indol-3-yl]-hex-4-enoate **26**.* The foregoing nitro-ester **25** (0.195 g, 0.41 mmol) was dissolved in glacial acetic acid (10 mL) and zinc dust (0.80 g, 12.2 mmol) added in three portions during 10 min. The resulting mixture was stirred at ambient temperature for 2 h then filtered and basified using 2 M aqueous sodium hydroxide. Dichloromethane (20 mL) was added and the resulting layers separated. The organic solution was washed with saturated aqueous sodium carbonate (10 mL) then dried, filtered and evaporated to leave

a crude amine (0.15 g, 0.34 mmol) as a yellow oil. This was immediately dissolved in dry dichloromethane (10 mL) to which was added tosyl chloride (0.40 mmol), triethylamine (0.40 mmol) and a few crystals of DMAP. The resulting mixture was stirred overnight at ambient temperature then quenched by the addition of 2 M hydrochloric acid (2 mL). The organic phase was separated and the aqueous phase extracted with dichloromethane (2×5 mL). The combined organic solutions were washed with brine then dried, filtered and evaporated. Column chromatography (dichloromethane) separated the *sulfonamide* **26** (0.08 g, 32%) as an off-white solid in a 3:1 ratio of diastereoisomers, which showed mp 126–131 °C [$C_{31}H_{34}N_2O_6S_2$: calcd C 62.6, H 5.7; N 4.7; found: C 62.6, H 5.8, N 4.7%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major) 7.80 (d, J=8.3 Hz, 1H, 7′-H), 7.67 (d, J=8.2 Hz, 2H, 2× ArH), 7.49 (s, 1H, 2′-H), 7.38–7.34 (m, 4H), 7.20–7.05 (m, 3H), 6.98 (d, J=8.2 Hz, 2H, 2× ArH), 5.26 (d, J=9.6 Hz, 1H, NH), 5.11 (d, J=9.4 Hz, 1H, 4-H), 4.15–4.10 (m, 2H, 2- and 3-H), 3.85–3.81 (m, 2H, OCH_2), 2.27 (s, 3H, ArMe), 2.25 (s, 3H, ArMe), 1.67 (s, 3H, Me), 1.48 (s, 3H, Me), 0.95 (t, J=7.2 Hz, 3H, CH_2CH_3); (minor) 7.85 (d, J=8.3 Hz, 1H, 7′-H), 7.69–7.65 (m, 4H), 7.51 (s, 1H, 2′-H), 7.38–7.34 (m, 4H), 7.20–7.05 (m, 3H), 5.24 (d, J=9.8 Hz, 1H, NH), 4.95 (d, J=9.3 Hz, 1H, 4-H), 4.15–4.10 (m, 2H, 2- and 3-H), 3.82 (q, J=7.1 Hz, 2H, OCH_2), 2.30 (s, 3H, ArMe), 2.26 (s, 3H, ArMe), 1.63 (s, 3H, Me), 1.53 (s, 3H, Me), 0.79 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major) 172.0 (CO), 152.7 (s), 149.9 (s), 146.0 (s), 136.3 (s), 135.5 (s), 133.9 (s), 132.2 (s), 130.2 (d), 129.5 (d), 126.4 (d), 125.7 (d), 123.2 (d), 122.5 (d), 121.5 (d), 120.7 (d), 119.7 (d), 111.8 (d), 59.5 (OCH_2), 58.8 (d), 42.6 (d), 25.6 (q), 21.0 (q), 20.9 (q), 19.6 (q), 18.7 (q); (minor) 171.4 (CO), 152.7 (s), 150.1 (s), 146.3 (s), 136.0 (s), 135.7 (s), 133.9 (s), 132.4 (s), 129.8 (d), 128.7 (d), 126.6 (d), 125.7 (d), 122.6 (d), 121.9 (d), 121.0 (d), 120.3 (d), 119.8 (d), 111.4 (d), 59.6 (OCH_2), 57.2 (d), 45.6 (d), 25.2 (q), 21.0 (q), 20.8 (q), 19.1 (q), 18.9 (q); IR ($CHCl_3$): ν_{max}=2966, 1750, 1640, 1441 cm^{-1}; HRMS [APCI]: m/z: calcd for $C_{31}H_{35}N_2O_6S_2$: 595.1940; found: 595.1940 $[M+H]^+$.

*4.1.4. Ethyl (2RS,3RS)- and (2RS,3SR)-5,5-dimethyl-1-(4-toluenesulfonyl)-3-[1-(4-toluenesulfonyl)indol-3-yl]-pyrrolidine-2-carboxylate **28** and **29**.* The foregoing sulfonamide **26** (30 mg, 50.0 μmol) was dissolved in dry chloroform (3 mL) containing triflic acid (45 mg, 0.60 equiv) and the resulting solution refluxed for 1 h then cooled and neutralised with saturated aqueous sodium carbonate. The two layers were separated and the aqueous layer extracted with dichloromethane (2×10 mL). The combined organic solutions were dried and filtered through a pad of silica gel and the combined filtrates and washings evaporated to leave the *pyrrolidines* **28** and **29** (25 mg, 83%) in a ca. 2:1 ratio, as a yellowish solid, mp 107–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major) 7.90 (d, J=8.4 Hz, 1H, 7′-H), 7.78 (d, J=8.2 Hz, 2H, 2× ArH), 7.65–7.60 (m, 3H), 7.32–7.08 (m, 7H), 4.43 (d, J=8.5 Hz, 1H, 2-H), 4.15–4.00 (m, 2H, OCH_2), 3.59 (td, J=8.5, 8.1 Hz, 1H, 3-H), 2.38 (s, 3H, ArMe), 2.27 (s, 3H, ArMe), 2.02–1.93 (m, 2H, 4-CH_2), 1.54 (s, 3H, 5-Me), 1.29 (s, 3H, 5-Me), 1.11 (t, J=7.1 Hz, 3H, CH_2CH_3); (minor) 7.88 (d, J=8.3 Hz, 1H, 7′-H), 7.67 (app. d, J=8.2 Hz, 4H, 4× ArH), 7.44 (d, J=8.0 Hz, 1H, 4′-H), 7.32–7.08 (m, 6H), 4.70 (d, J=4.3 Hz, 1H, 2-H), 3.63 (td, J=7.9, 4.3 Hz, 1H, 3-H), 3.09 (dq, J=10.7, 7.2 Hz, 1H, OCH_a), 2.75 (dq, J=10.7, 7.2 Hz, 1H, OCH_b), 2.32 (s, 3H, ArMe), 2.25 (s, 3H, ArMe), 2.02–1.93 (m, 2H, 4-CH_2), 1.73 (s, 3H, 5-Me), 1.59 (s, 3H, 5-Me), 0.09 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$; some resonances obscured): δ=(major) 171.3 (CO), 151.1 (s), 150.2 (s), 146.3 (s), 136.7 (s), 135.2 (s), 130.2 (d), 129.6 (d), 126.7 (d), 125.8 (d), 124.2 (d), 121.8 (d), 119.6 (d), 113.8 (d), 59.3 (OCH_2), 56.5 (2-CH), 42.5 (5-C), 42.1 (4-CH_2), 25.9 (3-CH), 25.2 (q), 24.7 (q), 21.3 (q), 21.1 (q), 17.8 (q); (minor) 169.2 (CO), 151.3 (s), 149.9 (s), 146.3 (s), 136.9 (s), 135.0 (s), 132.6 (s), 130.4 (d), 129.1 (d), 126.3 (d), 125.9 (d), 124.2 (d), 121.3 (d), 119.8 (d), 118.3 (d), 112.5 (d), 54.2 (OCH_2), 56.2 (2-CH), 43.7 (5-C), 42.6 (4-CH_2), 25.0 (3-CH), 24.9 (q), 24.3 (q), 21.2 (q), 21.1 (q), 13.6 (q); IR ($CHCl_3$): ν_{max}=1745 cm^{-1}; HRMS [APCI]: m/z: calcd for $C_{31}H_{35}N_2O_6S_2$: 595.1940; found: 595.1936 $[M+H]^+$.

*4.1.5. 4-[(tert-Butyldiphenylsilyloxy)methyl]indole **33**.* Indole-4-methanol **32b** (7.00 g, 48.0 mmol)[19,21] was dissolved in dry tetrahydrofuran (100 mL) and *tert*-butyldiphenylchlorosilane (11.4 mL, 52.0 mmol) added dropwise via syringe, followed by imidazole (0.66 g, 5.20 mmol). The resulting suspension was stirred overnight at ambient temperature then quenched by the addition of 2 M hydrochloric acid (100 mL). The resulting two layers were separated and the aqueous layer extracted with ether (2×50 mL). The combined organic solutions were dried, filtered and evaporated to leave the *silyl ether* **33** (17.41 g, 95%) as a brown oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.14 (br s, 1H, NH), 7.72–7.67 (m, 4H), 7.40–7.05 (m, 10H), 6.42 (d, J=3.2 Hz, 1H, 3-H), 5.02 (s, 2H, CH_2O), 1.03 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.2 (s), 146.0 (s), 134.4 (s), 130.3 (d), 129.0 (d), 127.2 (d), 126.1 (d), 124.4 (d), 123.8 (d), 118.9 (d), 113.8 (d), 111.2 (s), 65.6 (t), 15.3 (q), 12.9 (s); IR ($CHCl_3$): ν_{max}=3426, 2931, 2857, 1589, 1471 cm^{-1}; m/z: [APCI] 386 ($M+H^+$, 32%), 130 (100).

*4.1.6. 4-[(tert-Butyldiphenylsilyloxy)methyl]indole-3-carboxaldehyde **35**.* Phosphorus oxychloride (2.3 mL, 24.0 mmol) was added to ice-cold, stirred, dry dimethylformamide (7.8 mL, 99.0 mmol) followed by dry pyridine (2.0 mL, 26.0 mmol). A solution of the foregoing protected indole-4-methanol **33** (8.50 g, 22.0 mmol) in dimethylformamide (3 mL) was then added dropwise and the resulting solution warmed to 35 °C for 0.75 h before being poured onto ice. Sodium hydroxide (4.00 g) in water (200 mL) was added in portions and the resulting mixture boiled for 2 min then cooled and extracted with dichloromethane (3×50 mL). The combined extracts were dried, filtered and evaporated to give the *indole-3-carboxaldehyde* **35** (7.52 g, 82%) as a brown oil, which showed ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.95 (s, 1H, CHO), 9.31 (br s, 1H, NH), 7.78 (s, 1H, 2-H), 7.65–7.63 (m, 4H), 7.39–7.20 (m, 9H), 5.28 (s, 2H, CH_2O), 1.03 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=186.1 (CHO), 162.6 (s), 149.8 (s), 136.1 (s), 135.6 (d), 134.8 (d), 133.7 (s), 129.6 (d), 127.7 (d), 123.8 (d), 120.2 (d), 111.9 (d), 65.7 (CH_2O), 26.9 (q), 25.2 (s); IR ($CHCl_3$): ν_{max}=2931, 1667, 1427, 1112 cm^{-1}; m/z [APCI] 414 ($M+H^+$, 60%), 74 (100).

*4.1.7. 4-[(tert-Butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl) indole-3-carboxaldehyde **36**.* The indole-3-carboxaldehyde **35** (7.30 g, 18.0 mmol) was *N*-tosylated as described above for the preparation of the sulfonamide **26** and was purified by column chromatography to give the *N-tosyl indole-3-carboxaldehyde* **36** (8.50 g, 85%) as an off-white solid, mp 123–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H, CHO), 8.22 (s, 1H, 2-H), 7.82 (d, J=8.3 Hz, 2H, 2× ArH), 7.78 (d, J=8.3 Hz, 2H, 2× ArH), 7.58–7.54 (m, 4H), 7.40–7.10 (m, 10H), 5.14 (s, 2H, CH_2O), 2.31 (s, 3H, ArMe), 0.99 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=185.7 (CHO), 162.7 (s), 135.6 (s), 135.4 (d), 134.8 (d), 134.3 (s), 133.4 (s), 130.3 (s), 130.2 (d), 129.7 (d), 127.7 (d), 127.3 (d), 127.1 (s), 125.9 (d), 123.0 (d), 112.4 (d), 65.3 (CH_2O), 26.9 (q), 21.9 (q), 19.4 (s); IR ($CHCl_3$): ν_{max}=2931, 2856, 1748, 1562, 1427, 1373 cm^{-1}; HRMS [APCI]: m/z: calcd for $C_{33}H_{34}NO_4SSi$: 568.1972; found: 568.1968 $[M+H]^+$.

*4.1.8. Ethyl (E)- and (Z)-3-{4-[(tert-butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl)indole-3-yl}-2-nitroacrylate **37**.* Following the same method used to prepare the nitroacrylate **24**, reaction between the foregoing *N*-tosyl indole-3-carboxaldehyde **36** (3.70 g, 6.50 mmol) and ethyl nitroacetate (0.74 mL, 6.50 mmol) gave the *nitroacrylate* **37** (1.91 g, 43%) as an orange-brown solid, mp 131–135 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major isomer) 8.42 (s, 1H, 3-H), 7.89 (s, 1H, 2′-H), 7.87–7.68 (m, 3H), 7.53–7.49 (m, 4H), 7.34–7.10 (m, 10H), 4.84 (s, 2H, CH_2O), 4.26 (q, J=7.1 Hz, 2H,

OCH_2), 2.30 (s, 3H, ArMe), 1.12 (t, J=7.1 Hz, 3H, CH_2CH_3), 0.99 (s, 9H, ^{t}Bu); (minor isomer) 8.90 (s, 1H, 3-H), 8.07 (s, 1H, 2′-H), 7.87–7.68 (m, 3H), 7.53–7.49 (m, 4H), 7.34–7.10 (m, 10H), 4.84 (s, 2H, CH_2O), 4.40 (q, J=7.1 Hz, 2H, OCH_2), 2.31 (s, 3H, ArMe), 1.35 (t, J=7.1 Hz, 3H, CH_2CH_3), 0.99 (s, 9H, ^{t}Bu); m/z [APCI] 683 ($M+H^+$, 30%), 427 (M^+-TBDPSO, 100).

4.1.9. Ethyl (E)- and (Z)-3-[4-bromo-1-(4-toluenesulfonyl)indole-3-yl]-2-nitroacrylate ***41***. 4-Bromo-1-(4-toluenesulfonyl)indole-3-carboxaldehyde[23,40] (2.50 g, 6.50 mmol), prepared from 4-bromoindole **40**,[19,21] as described above, was condensed with ethyl nitroacetate (0.74 mL, 6.50 mmol) using titanium(IV) chloride (1.48 mL, 13.0 mmol), as described for nitroacrylate **24**, to give the *nitroacrylate* **41** (2.00 g, 63%) as an orange solid and a 1.3:1 mixture of stereoisomers, mp 112–115 °C; $C_{20}H_{17}BrN_2O_6S$: calcd C 48.7, H 3.4; N 5.7; found: C 48.5, H 3.6, N 5.6%; ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major) 8.54 (s, 1H; 3-H), 7.92 (d, J=8.7 Hz, 1H; 7′-H), 7.90 (s, 1H; 2′-H), 7.72 (d, J=8.2 Hz, 2H, 2× ArH), 7.41 (d, J=8.0 Hz, 1H, 5′-H), 7.28 (d, J=8.2 Hz, 2H, 2× ArH), 7.22 (dd, J=8.7, 8.0 Hz, 1H, 6′-H), 4.35–4.30 (m, 2H, OCH_2), 2.31 (s, 3H; ArMe), 1.35–1.30 (m, 3H, CH_2CH_3); (minor) 9.05 (s, 1H; 3-H), 8.11 (s, 1H; 2′-H), 7.93 (d, J=8.6 Hz, 1H; 7′-H), 7.73 (d, J=8.2 Hz, 2H, 2× ArH), 7.42 (d, J=8.1 Hz, 1H, 5′-H), 7.28 (d, J=8.2 Hz, 2H, 2× ArH), 7.24–7.21 (m, 1H, 6′-H), 4.35–4.30 (m, 2H, OCH_2), 2.31 (s, 3H; ArMe), 1.35–1.30 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major) 171.6 (CO), 162.3 (s), 159.8 (s), 147.3 (s), 146.7 (s), 136.0 (s), 134.8 (s), 133.2 (s), 130.8 (d), 129.3 (d), 127.6 (d), 127.4 (d), 127.0 (d), 125.5 (d), 113.4 (d), 63.5 (t), 22.1 (q), 14.4 (q); (minor; some resonances obscured or coincident with major) 172.4 (CO), 162.4 (s), 159.6 (s), 147.5 (s), 136.4 (s), 133.7 (s), 130.5 (d), 129.9 (d), 127.4 (d), 127.3 (d), 125.8 (d), 112.3 (d), 64.1 (t), 22.1 (q), 14.5 (q); IR (KBr): ν_{max}=2922, 1722, 1632, 1530, 1463, 1377 cm^{-1}; m/z [APCI] 494 (^{81}Br–M+H$^+$, 100%), 492 (^{79}Br–M+H$^+$, 100%); HRMS: m/z: calcd for $C_{20}H_{21}^{79}BrN_3O_6S$: 510.0329; found: 510.0329 $[M+NH_4]^+$.

4.1.10. Ethyl (2RS,3RS)- and (2RS,3SR)-3-[4-bromo-1-(4-toluenesulfonyl)indole-3-yl]-5-methyl-2-nitrohex-4-enoate ***42***. Zinc chloride (1.70 g, 12.1 mmol) was stirred in ice-cold tetrahydrofuran (10 mL) and 2-methyl-1-propenylmagnesium bromide (36.0 mL of a 0.5 M solution in toluene, 18.0 mmol) was added dropwise. The resulting pale yellow solution was stirred at this temperature for 0.25 h then transferred via cannula to a second flask, which contained an ice-cold, stirred solution of the foregoing nitroacrylate **41** (2.00 g, 4.10 mmol) in tetrahydrofuran (20 mL). The resulting mixture was stirred for 2 h without further cooling then quenched using aqueous pH 8 buffer and the separated aqueous layer extracted using ether (2×30 mL). The combined organic solutions were dried, filtered and evaporated and the residue separated using column chromatography (70% dichloromethane/petrol) to give the *nitroester* **42** (2.00 g, 90%) as a bright yellow oily solid and as a mixture of two diastereoisomers which showed: ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major isomer) 7.86 (d, J=8.2 Hz, 1H, 7′-H), 7.61 (d, J=8.2 Hz, 2H, 2× ArH), 7.50 (s, 1H, 2′-H), 7.35 (d, J=8.4 Hz, 1H, 5′-H), 7.19 (d, J=8.2 Hz, 2H, 2x ArH), 7.07 (dd, J=8.4, 8.1 Hz, 1H, 6′-H), 5.82–5.76 (m, 1H, 4-H), 5.59–5.48 (m, 2H, 2- and 3-H), 4.26 (q, J=7.1 Hz, 2H, OCH_2), 2.28 (s, 3H, ArMe), 1.86 (s, 3H, Me), 1.67 (s, 3H, Me), 1.29 (t, J=7.1 Hz, 3H, CH_2CH_3); (minor isomer) 7.86 (d, J=8.2 Hz, 1H, 7′-H), 7.62 (d, J=8.3Hz, 2H, 2× ArH), 7.50 (s, 1H, 2′-H), 7.35 (d, J=8.4 Hz, 1H, 5′-H), 7.17 (d, J=8.3Hz, 2H, 2x ArH), 7.07 (dd, J=8.4, 8.1 Hz, 1H, 6′-H), 5.82–5.76 (m, 1H, 4-H), 5.59–5.48 (m, 2H, 2- and 3-H), 4.13–4.06 (m, 2H, OCH_2), 2.28 (s, 3H, ArMe), 1.73 (s, 3H, Me), 1.70 (s, 3H, Me), 1.14 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major isomer) 171.3 (CO), 152.2 (s), 150.1 (s), 144.2 (s), 138.9 (s), 133.6 (s), 129.9 (d), 127.1 (d), 126.2 (d), 125.8 (d), 121.6 (d), 120.1 (d), 119.3 (d), 115.2 (s), 114.3 (d), 87.4 (d), 58.8 (OCH_2), 33.7 (d), 25.6 (q), 20.8 (q), 19.2 (q), 18.1 (q); (minor isomer) 168.8 (CO), 152.2 (s), 150.3 (s), 144.8 (s), 138.2 (s), 133.9 (s), 130.3 (d), 127.5 (d), 125.8 (d), 124.9 (d), 121.6 (d), 120.5 (d), 119.8 (d), 115.8 (s), 113.6 (d), 78.3 (d), 58.6 (OCH_2), 34.5 (d), 25.7 (q), 20.9 (q), 18.2 (q), 15.4 (q); IR ($CHCl_3$): ν_{max}=1740 cm^{-1}; m/z [APCI] 551 (^{81}Br–M+H$^+$, 100%), 549 (^{79}Br–M+H$^+$, 100%); HRMS: m/z: calcd for $C_{24}H_{26}^{79}BrN_2O_6S$: 549.0695; found: 549.0699 $[M+H]^+$.

4.1.11. Ethyl (2RS,3RS)- and (2RS,3SR)-3-[4-bromo-1-(toluenesulfonyl)indole-3-yl]-5-methyl-2-(4-toluenesulfonylamino)-hex-4-enoate ***43***. The foregoing nitro-ester **42** (1.00 g, 1.80 mmol) was dissolved in glacial acetic acid (20 mL) and zinc dust (3.61 g, 55.0 mmol) was added in portions during 10 min. The resulting mixture was stirred at ambient temperature for 1 h then filtered and basified using 2 M aqueous sodium hydroxide. Dichloromethane (50 mL) was added, the mixture shaken and the resulting two layers separated. The organic solution was washed with saturated aqueous sodium carbonate (10 mL) then dried, filtered and evaporated to leave the free amine as a pale yellow oil which was immediately tosylated as described above for the preparation of the sulfonamide **26**. The final product **43** was formed as a 2:1 mixture of diastereoisomers, which were separated by column chromatography (2:1 EtOAc/petrol) to give:

(i) The major isomer as a colourless crystalline solid, mp 145–149 °C; $[C_{31}H_{33}BrN_2O_6S_2$: calcd C 55.3, H 4.9; N 4.2; found: C 55.5, H 5.2, N 4.0%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (d, J=8.2 Hz, 1H, 7′-H), 7.69 (d, J=8.2 Hz, 2H, 2× ArH), 7.46 (s, 1H, 2′-H), 7.33 (d, J=8.2 Hz, 2H, 2× ArH), 7.28 (d, J=8.0 Hz, 1H, 5′-H), 7.23 (app. d, J=8.2 Hz, 4H, 4× ArH), 7.01 (dd, J=8.2, 8.0 Hz, 1H, 6′-H), 6.97 (d, J=8.2 Hz, 2H, 2× ArH), 5.29 (d, J=10.3 Hz, 1H, 4-H), 5.18 (d, J=10.0 Hz, 1H, NH), 5.02 (dd, J=10.3, 7.2 Hz, 1H, 3-H), 4.33 (dd, J=10.0, 7.2 Hz, 1H, 2-H), 3.98–3.90 (m, 2H, OCH_2), 2.26 (s, 3H, ArMe), 2.23 (s, 3H, ArMe), 1.68 (s, 3H, Me), 1.49 (s, 3H, Me), 1.06 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3 (CO), 145.4 (s), 143.7 (s), 137.1 (s), 136.5 (s), 135.9 (s), 134.6 (s), 130.1 (d), 129.4 (d), 128.3 (d), 128.0 (d), 127.3 (d), 127.0 (d), 125.8 (d), 125.4 (d), 121.9 (d), 120.7 (s), 114.0 (s), 112.8 (d), 61.1 (OCH_2), 60.0 (d), 29.7 (d), 26.0 (q), 21.6 (q), 21.5 (q), 18.8 (q), 13.7 (q); IR ($CHCl_3$): ν_{max}=2924, 1741, 1596, 1411, 1370, 1164 cm^{-1}; m/z [APCI] 676 (^{81}Br–M+H$^+$, 100%), 674 (^{79}Br–M+H$^+$, 100%); HRMS: m/z: calcd for $C_{31}H_{37}^{79}BrN_3O_6S_2$: 690.1307; found: 690.1305 $[M+NH_4]^+$ and

(ii) The minor isomer, also as a colourless crystalline solid, mp 138–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.82 (d, J=8.1 Hz, 1H, 7′-H), 7.66 (d, J=8.2 Hz, 2H, 2× ArH), 7.51 (d, J=8.2 Hz, 2H, 2× ArH), 7.36 (s, 1H, 2′-H), 7.29 (d, J=8.1 Hz, 1H, 5′-H), 7.16 (d, J=8.3 Hz, 2H, 2× ArH), 7.11 (d, J=8.3 Hz, 2H, 2× ArH), 7.03 (dd, J=8.1, 8.1 Hz, 1H, 6′-H), 5.27 (d, J=10.4 Hz, 1H, 4-H), 5.15 (d, J=10.0 Hz, 1H, NH), 4.90 (dd, J=10.4, 7.3 Hz, 1H, 3-H), 4.20 (dd, J=10.0, 7.3 Hz, 1H, 2-H), 4.05 (q, J=7.2 Hz, 2H, OCH_2), 2.31 (s, 3H, ArMe), 2.26 (s, 3H, ArMe), 1.68 (s, 3H, Me), 1.56 (s, 3H, Me), 0.81 (t, J=7.2 Hz, 3H, CH_2CH_3); IR ($CHCl_3$): ν_{max}=2928, 1743, 1416, 1382, 1156 cm^{-1}; m/z [APCI] 676 (^{81}Br–M+H$^+$, 100%), 674 (^{79}Br–M+H$^+$, 100%); HRMS: found: 690.1304 $[M+NH_4]^+$.

4.1.12. 3-(3-Hydroxy-3-methyl-1-buten-1-yl)-1-(4-toluenesulfonyl) indole ***47***. *N*-Tosylindole-3-carboxaldehyde **23** (3.00 g, 10.0 mmol) was dissolved in dry tetrahydrofuran (50 mL), the solution cooled to −78 °C and 2-methyl-1-propenylmagnesium bromide (40 mL of a 0.5 M solution in toluene, 20.0 mmol) added dropwise. The resulting solution was stirred overnight without further cooling then quenched by the addition of saturated aqueous ammonium chloride (100 mL) and diluted with ether (50 mL). The two layers were separated and the aqueous layer extracted with ether (2×50 mL). The combined organic solutions were dried, filtered and evaporated and the crude product separated by column chromatography (dichloromethane) to give the *alcohol* **47** (3.20 g, 90%), as a pale yellow oil which showed ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (d, J=7.1 Hz, 1H, 7-H), 7.67 (d, J=8.2 Hz, 2H, 2× ArH), 7.64 (d,

J=8.2 Hz, 1H, 4-H), 7.50 (s, 1H, 2-H), 7.24 (t, *J*=7.2 Hz, 1H, 6-H), 7.19 (t, *J*=8.2 Hz, 1H, 5-H), 7.18 (d, *J*=8.2 Hz, 2H, 2× ArH), 6.86 (d, *J*=16.2 Hz, 1H, 1′-H), 6.34 (d, *J*=16.2 Hz, 1H, 2′-H), 2.22 (s, 3H, ArMe), 1.33 (s, 6H, 2× Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.0 (s), 137.9 (s), 134.4 (s), 131.8 (s), 128.8 (d), 128.1 (s), 125.8 (d), 123.9 (d), 122.5 (d), 119.8 (d), 119.3 (d), 116.2 (d), 115.9 (d), 112.7 (d), 70.0 (s), 20.5 (q), 17.3 (q); IR ($CHCl_3$): ν_{max}=3584, 2970, 1597, 1446 cm^{-1}; *m*/*z* [APCI] 356 ($M+H^+$, 28%), 338 (M^+-OH, 100); HRMS: *m*/*z*: calcd for $C_{20}H_{22}NO_3S$: 356.1320; found: 356.1325 $[M+H]^+$.

4.1.13. 3-(1-Hydroxy-3-methyl-2-buten-1-yl)-1-(4-toluenesulfonyl) indole ***46***. The foregoing reaction was repeated on exactly the same scale but was maintained at −78 °C for only 2 h after the addition of the Grignard reagent then quenched at this temperature and worked up in exactly the same manner to give, without chromatography, the *alcohol* **46** (2.90 g, 81%) as a yellow oily solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.87 (d, *J*=8.2 Hz, 1H, 7-H), 7.64 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.52 (d, *J*=7.9 Hz, 1H, 4-H), 7.42 (s, 1H, 2-H), 7.19 (t, *J*=8.2 Hz, 1H, 6-H), 7.10 (dd, *J*=8.2, 7.9 Hz, 1H, 5-H), 7.04 (d, *J*=8.2 Hz, 2H, 2× ArH), 5.83 (d, *J*=8.8 Hz, 1H, 2′-H), 5.40 (dd, *J*=8.8, 1.3 Hz, 1H, 1′-H), 2.45 (d, *J*=1.3 Hz, 1H, OH), 2.17 (s, 3H, ArMe), 1.65 (s, 3H, Me), 1.55 (s, 3H, Me); IR ($CHCl_3$): ν_{max}=3590, 1597, 1446, 1388 cm^{-1}; *m*/*z* [APCI] 338 (M^+-OH, 100%).

The sample was contaminated with ca. 15% of the derived diene **48** (see below).

4.1.14. 3-(3-Methyl-1,3-butadien-1-yl)-1-(4-toluenesulfonyl)indole ***48***. The foregoing crude alcohol **46** (0.52 g, 1.50 mmol) was dissolved in dry pyridine (5 mL) and treated with either acetic anhydride (0.18 mL, 1.80 mmol) or ethyl chloroformate (0.17 mL, 1.80 mmol). A few crystals of DMAP were then added and the resulting solutions stirred at ambient temperature for 6 h then poured into a stirred mixture of water (10 mL) and ether (10 mL). The separated aqueous layers were extracted with ether (10 mL) and the combined organic solutions washed with saturated aqueous copper(II) sulfate (4×10 mL) then water (10 mL) before being dried and filtered through a pad of silica gel. Evaporation of the combined filtrates and washings left the *diene* **48** (0.39 g, 81% from Ac_2O and 0.41 g, 84%, from $ClCO_2Et$) as a yellow oily solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (d, *J*=8.2 Hz, 1H, 7-H), 7.66 (d, *J*=7.7 Hz, 1H, 4-H), 7.65 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.20–7.17 (m, 2H, 5- and 6-H), 7.06 (d, *J*=8.2 Hz, 2H, 2× ArH), 6.87 (d, *J*=16.3 Hz, 1H, 1′-H), 6.49 (d, *J*=16.3 Hz, 1H, 2′-H), 5.04 (app. s, 1H, 4′-H_a), 5.07 (app. s, 1H, 4′-H_b), 2.17 (s, 3H, ArMe), 1.88 (s, 3H, 3-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2 (s), 145.0 (s), 138.9 (s), 135.5 (s), 135.3 (s), 130.3 (d), 129.9 (d), 126.8 (d), 126.7 (s), 126.3 (d), 125.0 (d), 123.7 (d), 123.4 (d), 120.3 (d), 117.2 (:CH_2), 113.8 (d), 29.9 (q), 21.4 (q); IR ($CHCl_3$): ν_{max}=2855, 1597, 1447 cm^{-1}; *m*/*z* 338 ($M+H^+$, 100%); HRMS: *m*/*z*: calcd for $C_{20}H_{20}NO_2S$: 338.1205; found: 338.1209 $[M+H]^+$.

4.1.15. Ethyl (E)-3-[1-(4-toluenesulfonyl)indole-3-yl]propenoate ***49***. Lithium chloride (0.17 g, 4.00 mmol) was suspended in dry acetonitrile (10 mL), triethyl orthophosphonoacetate (0.80 mL, 4.00 mmol) was added followed by DBN (0.40 mL, 3.30 mmol) and the resulting mixture stirred at ambient temperature for 0.25 h. A solution of the indole-3-carboxaldehyde **23** (1.00 g, 3.30 mmol) in dry acetonitrile (20 mL) was then added dropwise and stirring continued at the same temperature with TLC monitoring. Upon completion of the reaction (ca. 2 h), saturated aqueous ammonium chloride (50 mL) and ether (40 mL) were added and the resulting two layers separated. The organic fraction was washed with water (2×50 mL) then dried, filtered and evaporated. Further filtration through a pad of silica gel eluted with EtOAc/petrol (1:3) separated the *enoate* **49** (0.94 g, 77%) as an off-white solid, mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (d, *J*=8.2 Hz, 1H, 7′-H), 7.85 (s, 1H, 2′-H), 7.82–7.77 (m, 4H, 2-, 4′- and 2× ArH), 7.39 (t, *J*=8.2 Hz, 1H, 6′-H), 7.32 (d, *J*=8.2 Hz, 1H, 5′-H), 7.25 (d, *J*=8.2 Hz, 2H, 2× ArH), 6.52 (d, *J*=16.2 Hz, 1H, 3-H), 4.26 (q, *J*=7.2 Hz, 2H, OCH_2), 2.35 (s, 3H, ArMe), 1.27 (t, *J*=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2 (CO), 167.1 (s), 145.6 (s), 135.6 (d), 134.7 (s), 130.3 (d), 128.5 (d), 127.3 (d), 125.5 (d), 124.1 (d), 120.7 (d), 118.3 (d), 117.9 (d), 113.8 (d), 60.6 (OCH_2), 21.6 (q), 14.4 (q); IR ($CHCl_3$): ν_{max}=1712, 1640, 1446, 1364, 1316 cm^{-1}; *m*/*z* [APCI] 369 (M^+, 100%), 86 (44); HRMS: *m*/*z*: calcd for $C_{20}H_{20}NO_4S$: 370.1105; found: 370.1108 $[M+H]^+$.

4.1.16. Ethyl (E)-5-methyl-3-[1-(4-toluenesulfonyl)indol-3-yl]hex-4-enoate ***50***. Copper(I) thiophenolate (0.24 g, 1.70 mmol) was suspended in dry tetrahydrofuran (10 mL) and the mixture stirred at −40 °C during the dropwise addition of 2-methyl-1-propenylmagnesium bromide (10 mL of a 0.5 M solution in tetrahydrofuran, 5.00 mmol) and the resulting mixture warmed to 0 °C during 1 h. The resulting green solution was re-cooled to −40 °C and a solution of the foregoing enoate **49** (0.63 g, 1.70 mmol) in dry tetrahydrofuran (20 mL) was added dropwise after which the mixture was warmed to ambient temperature and stirred for 2 h before the addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was filtered and the solid washed with ether (10 mL). The combined filtrate was separated and the aqueous portion extracted with ether (2×10 mL). The combined organic solutions were washed with saturated aqueous sodium carbonate (3×20 mL) then dried, filtered and evaporated. The crude product was filtered through silica gel eluted with dichloromethane to give the *hexenoate* **50** (0.585 g, 81%) as a pale yellow solid, mp 108–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, *J*=8.2 Hz, 1H, 7′-H), 7.66 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.43 (d, *J*=7.9 Hz, 1H, 4′-H), 7.21–7.05 (m, 5H), 5.13 (d, *J*=9.7 Hz, 1H, 4-H), 4.19–4.15 (m, 1H, 3-H), 3.99 (q, *J*=7.2 Hz, 2H, OCH_2), 2.73 (dd, *J*=14.7, 6.2 Hz, 1H, 2-H_a), 2.51 (dd, *J*=14.7, 8.8 Hz, 1H, 2-H_b), 2.27 (s, 3H, ArMe), 1.67 (s, 3H, Me), 1.63 (s, 3H, Me), 1.10 (t, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.8 (CO), 144.8 (s), 135.4 (s), 135.2 (s), 133.8 (s), 130.1 (s), 129.6 (d), 127.0 (d), 125.6 (s), 125.3 (d), 124.8 (d), 123.8 (d), 121.4 (d), 119.9 (d), 113.8 (d), 60.0 (OCH_2), 40.4 (2-CH_2), 32.5 (3-CH), 25.8 (q), 22.6 (q), 18.2 (q), 14.2 (q); IR ($CHCl_3$): ν_{max}=2980, 2924, 1762, 1447 cm^{-1}; *m*/*z* [APCI] 425 (M^+, 54%), 91 (100); HRMS: *m*/*z*: calcd for $C_{24}H_{31}N_2O_4S$: 443.1999; found: 443.1998 $[M+NH_4]^+$.

4.1.17. Ethyl (2RS,3RS)- and (2RS,3SR)-2-hydroxy-5-methyl-3-[1-(4-toluenesulfonyl)indol-3-yl]hex-4-enoate ***52***. Potassium hexamethyldisilazide (KHMDS; 0.20 mL of a 1.6 M solution in toluene, 0.30 mmol) in tetrahydrofuran (5 mL) was stirred and cooled to −78 °C before a solution of the foregoing hexenoate **50** (85 mg, 0.20 mmol) in tetrahydrofuran (1 mL) was added dropwise. The resulting orange solution was stirred for 20 min then a solution of 2-(4-toluenesulfonyl)-3-phenyloxaziridine **51** (78 mg, 0.30 mmol)[28] was added. After a further 20 min at this temperature, saturated aqueous ammonium chloride (10 mL) was added, the resulting mixture warmed to ambient temperature, the layers separated and the aqueous layer extracted with ether (2×10 mL). The combined organic solutions were dried, filtered and evaporated. Column chromatography of the residue separated the *hydroxy-ester* **52** (68 mg, 76%) as a pale yellow oily solid and a 3:1 mixture of diastereoisomers which showed: ^{1}H NMR (400 MHz, $CDCl_3$): δ=(major isomer) 7.78 (d, *J*=8.0 Hz, 1H, 7′-H), 7.55 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.40–7.36 (m, 2H, 2′- and 4′-H), 7.19 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.15–7.10 (m, 2H, 5′- and 6′-H), 5.43 (d, *J*=9.5 Hz, 1H, 4-H), 4.29 (d, *J*=3.8 Hz, 1H, 2-H), 4.08 (dd, *J*=9.5, 3.8 Hz, 1H, 3-H), 3.83–3.78 (m, 2H, OCH_2), 2.14 (s, 3H, ArMe), 1.59 (s, 3H, Me), 1.53 (s, 3H, Me), 1.11 (t, *J*=7.1 Hz, 3H, CH_2CH_3); (minor isomer) 7.79 (d, *J*=8.1 Hz, 1H, 7′-H), 7.60 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.40–7.36 (m, 2H, 2′- and 4′-H), 7.19 (d, *J*=8.2 Hz, 2H, 2× ArH), 7.15–7.10 (m, 2H, 5′- and 6′-H), 5.33 (d, *J*=9.3 Hz, 1H, 4-H), 4.36 (d, *J*=3.0 Hz, 1H, 2-H), 3.99 (dd, *J*=9.3, 3.0 Hz, 1H, 3-H), 3.83–3.78 (m, 2H, OCH_2), 2.14 (s, 3H, ArMe), 1.58 (s, 3H,

Me), 1.51 (s, 3H, Me), 0.85 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=(major isomer) 178.3 (CO), 150.4 (s), 143.8 (s), 134.8 (s), 129.9 (s), 129.8 (d), 128.8 (d), 127.0 (s), 126.7 (d), 124.7 (d), 122.3 (d), 119.6 (d), 113.7 (d), 73.7 (2-CH), 61.7 (OCH_2), 39.5 (3-CH), 25.9 (q), 21.6 (q), 18.2 (q), 13.9 (q); (minor isomer) 177.2 (CO), 149.1 (s), 143.7 (s), 134.1 (s), 129.7 (s), 129.2 (d), 128.5 (d), 127.1 (s), 126.9 (d), 124.7 (d), 122.3 (d), 119.8 (d), 115.1 (d), 73.1 (2-CH), 61.9 (OCH_2), 39.4 (3-CH), 26.0 (q), 21.6 (q), 18.3 (q), 14.1 (q) (two resonances obscured); IR ($CHCl_3$): ν_{max}=3316, 2919, 1730, 1447, 1369 cm^{-1}; m/z [APCI] 442 (M^++H, 100%); HRMS: m/z: calcd for $C_{24}H_{28}NO_5S$: 442.1683; found: 442.1685 $[M+H]^+$.

4.1.18. Ethyl (2RS,3RS)- and (2RS,3SR)-2-azido-5-methyl-3-[1-(4-toluenesulfonyl)indol-3-yl]hex-4-enoate ***59****.* A solution of the indol-3-yl hexenoate **50** (0.15 g, 0.35 mmol) in dry tetrahydrofuran (3 mL) was added to a solution of KHMDS (0.78 mL of a 0.5 M solution in toluene, 0.39 mmol) maintained at −78 °C. The resulting orange solution was stirred for 0.5 h at this temperature before a pre-cooled solution of trisyl azide (0.136 g, 0.44 mmol) in tetrahydrofuran (3 mL) was added. After a further 5 min, glacial acetic acid (0.09 mL, 1.60 mmol) was added and the mixture warmed to ambient temperature and stirred for 0.5 h then dichloromethane (20 mL) and diluted brine (40 mL) were added. The resulting two layers were separated and the aqueous fraction extracted with dichloromethane (20 mL). The combined organic solutions were washed with saturated aqueous sodium hydrogen carbonate then dried, filtered and evaporated. Column chromatography of the residue (1:3 EtOAc/petrol) separated the *azide* **59** (0.105 g, 63%) as a thick pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.79 (d, J=8.1 Hz, 1H, 7′-H), 7.67 (d, J=8.2 Hz, 2H, 2× ArH), 7.43–7.38 (m, 2H, 2′- and 4′-H), 7.24 (d, J=8.2 Hz, 2H, 2× ArH), 7.15–7.10 (m, 2H, 5′- and 6′-H), 5.18 (d, J=8.9 Hz, 1H, 4-H), 4.31 (dd, J=7.6, 4.1 Hz, 1H, 2-H), 3.70 (q, J=7.1 Hz, 2H, OCH_2), 3.56–3.60 (m, 1H, 3-H), 2.26 (s, 3H, ArMe), 1.65 (s, 3H, Me), 1.61 (s, 3H, Me), 0.92 (t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1 (CO), 150.1 (s), 143.6 (s), 144.2 (s), 135.8 (s), 134.8 (d), 131.5 (d), 129.2 (s), 128.9 (d), 128.0 (d), 125.2 (d), 124.3 (d), 113.4 (d), 66.5 (d), 59.8 (OCH_2), 35.3 (3-CH), 28.3 (q), 22.3 (q), 21.0 (q), 19.9 (q), 18.5 (q) (one sp^2-C obscured); IR ($CHCl_3$): ν_{max}=2962, 2109, 1739, 1598, 1447, 1370 cm^{-1}; m/z [APCI] 467 (M^+, 80%), 438 (M−N_2, 100).

4.1.19. Ethyl (2RS,3RS)- and (2RS,3SR)-5-methyl-2-(4-toluenesulfonylamino)-3-[1-(4-toluenesulfonyl)-indol-3-yl]-hex-4-enoate ***26****.* The foregoing azide **59** (25 mg) was dissolved in tetrahydrofuran (3 mL) containing triphenylphosphine (26 mg) and water (0.03 mL) and the resulting solution refluxed for 6 h then cooled and evaporated. The crude residue was *N*-tosylated as described above for the preparation of the same sulfonamide **26** to give a sample of this sulfonamide (20 mg, 59%), which showed identical spectroscopic and analytical data, but which was isolated as a 2:1 ratio of diastereoisomers.

4.1.20. Ethyl (E)-3-{4-[(tert-butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl)indol-3-yl]}propenoate ***60****.* Following exactly the same procedure as described above for the preparation of the enoate **49**, condensation of the indole-3-carboxaldehyde **36** (3.10 g, 5.50 mmol) with triethyl *ortho*phosphonoacetate (1.5 mL, 7.00 mmol) using DBN (0.80 mL, 6.60 mmol) and finally column chromatography in dichloromethane gave the *enoate* **60** (2.20 g, 62%) as an off-white solid, mp 93–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (d, J=15.3 Hz, 1H, 3-H), 7.82 (s, 1H, 2′-H), 7.81 (d, J=8.2 Hz, 1H, 7′-H), 7.67 (d, J=8.2 Hz, 2H, 2× ArH), 7.51 (d, J=7.8 Hz, 4H, 2×2× ArH), 7.25–7.05 (m, 9H), 6.81 (d, J=7.3 Hz, 1H, 5′-H), 6.23 (d, J=15.3 Hz, 1H, 2-H), 4.87 (s, 2H, CH_2OSi), 4.12 (q, J=7.1 Hz, 2H, OCH_2), 2.17 (s, 3H, ArMe), 1.14 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.8 (CO), 149.7 (s), 149.2 (s), 144.1 (s), 137.2 (d), 136.6 (s), 135.6 (d), 134.8 (d), 133.8 (s), 133.2 (s), 132.7 (s), 129.9 (d), 129.5 (d), 128.9 (d), 127.7 (d), 127.1 (d), 124.9 (d), 124.0 (d), 119.6 (d), 113.2 (d), 64.6 (t), 60.4 (t), 28.3 (q), 21.7 (q), 19.8 (s), 14.5 (q); IR ($CHCl_3$): ν_{max}=2935, 2922, 1746, 1522, 1438 cm^{-1}; m/z [APCI] 638 (M^++H, 100%), 608 (31); HRMS: m/z: calcd for $C_{37}H_{40}NO_5SSi$: 638.2396; found: 638.2392 $[M+H]^+$.

4.1.21. Ethyl 5-methyl-3-{[4-(tert-butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl)indol-3-yl}hex-4-enoate ***61****.* Using exactly the same method as described above for the preparation of the hexenoate **50**, reaction between the foregoing enoate **60** (1.60 g, 2.50 mmol), copper(I) thiophenolate (0.36 g, 2.50 mmol) and 2-methyl-1-propenylmagnesium bromide (15.0 mL of a 0.5 M solution in tetrahydrofuran, 7.50 mmol) gave the *hexenoate* **61** (0.92 g, 53%) as a pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (d, J=8.3 Hz, 1H, 7′-H), 7.62–7.58 (m, 4H), 7.54 (d, J=8.2 Hz, 2H, 2× ArH), 7.30–7.10 (m, 11H), 5.14 (d, J=13.8 Hz, 1H, 1″-H_a), 4.99 (d, J=13.8 Hz, 1H, 1″-H_b), 4.94 (d, J=9.0 Hz, 1H, 4-H), 4.14–4.10 (m, 1H, 3-H), 3.85 (q, J=7.2 Hz, 2H, OCH_2), 2.56 (dd, J=14.9, 6.9 Hz, 1H, 2-H_a), 2.33 (dd, J=14.9, 8.2 Hz, 1H, 2-H_b), 2.27 (s, 3H, ArMe), 1.40 (s, 3H, Me), 1.21 (s, 3H, Me), 0.99 (s, 9H, ^{t}Bu), 0.98 (t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.3 (CO), 144.8 (s), 135.7 (s), 135.6 (d), 135.1 (s), 134.6 (s), 133.7 (s), 133.3 (s), 129.9 (s), 129.8 (d), 129.7 (d), 127.9 (d), 126.8 (d), 126.7 (d), 124.8 (d), 124.6 (d), 122.7 (d), 121.2 (d), 112.5 (d), 63.3 (t), 60.3 (t), 41.7 (2-CH_2), 33.2 (3-CH), 25.5 (q), 21.6 (q), 19.4 (q), 19.1 (s), 18.0 (q), 14.1 (q); IR ($CHCl_3$): ν_{max}=2946, 1748, 1535, 1477 cm^{-1}; m/z [APCI] 694 (M^++H, 32%), 437 (M−TBDPSO, 100).

4.1.22. Ethyl (2RS,3RS)- and (2RS,3SR)-2-azido-5-methyl-3-{4-[(tert-butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl)-indol-3-yl}-hex-4-enoate ***62****.* Using exactly the same procedure as described above for the synthesis of the azide **59**, reaction between the homologous hex-4-enoate derivative **61** (0.693 g, 1.00 mmol) in tetrahydrofuran (5 mL) with KHMDS (2.6 mL of a 0.5 M solution in toluene, 1.30 mol) and trisyl azide (0.34 g, 1.10 mmol) and finally chromatography in dichloromethane gave the *azide* **62** (0.48 g, 66%) as essentially a single diastereoisomer showing ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.78 (d, J=8.0 Hz, 1H, 7′-H), 7.63 (d, J=8.2 Hz, 2H, 2× ArH), 7.52–7.42 (m, 5H), 7.37 (s, 1H, 2′-H), 7.20–7.00 (m, 8H), 5.22 (d, J=9.4 Hz, 1H, 4-H), 4.97 (s, 2H, CH_2OSi), 4.26–4.22 (m, 1H, 2-H), 3.81 (q, J=7.2 Hz, 2H, OCH_2), 3.72–3.67 (m, 1H, 3-H), 2.22 (s, 3H, ArMe), 1.53(s, 3H, Me), 1.24 (s, 3H, Me), 0.99 (s, 9H, But), 0.80 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.9 (CO), 148.1 (s), 135.5 (s), 134.7 (s), 133.2 (s), 133.1 (d), 132.9 (d), 132.5 (s), 132.2 (s), 132.0 (s), 128.1 (d), 127.4 (d), 127.3 (d), 126.9 (d), 123.3 (d), 122.6 (d), 121.2 (d), 112.6 (d), 68.0 (d), 61.2 (t), 60.2 (t), 34.1 (d), 26.8 (q), 24.9 (q), 23.9 (q), 21.5 (q), 19.3 (q), 13.6 (s) (one sp^2-C obscured); IR ($CHCl_3$): ν_{max}=2965, 2108, 1743, 1432, 1287 cm^{-1}; m/z 735 (M^++H, 21%), 706 M−N_2, 100), 451 (87).

Starting material **61** (0.174 g, 25%) was also recovered.

4.1.23. Ethyl (2RS,3RS)- and (2RS,3SR)-2-(4-nitrobenzenesulfonylamino)-5-methyl-3-{4-[(tert-butyldiphenylsilyloxy)methyl]-1-(4-toluenesulfonyl)-indol-3-yl}-hex-4-enoate ***63****.* The foregoing azide **62** (0.18 g, 0.24 mmol) was dissolved in tetrahydrofuran (5 mL) containing triphenylphosphine (0.13 g, 0.48 mmol) and water (0.5 mL, 0.5 mmol). The resulting solution was refluxed for 6 h the cooled and the volatiles evaporated to leave a crude amine, IR ($CHCl_3$): ν_{max}=3438, 2959, 1732, 1435, 1372 cm^{-1} (the azide stretch at 2108 cm^{-1} was absent).

This crude material was dissolved in dry, ice-cold, stirred dichloromethane (5 mL) and treated with 4-nitrobenzenesulfonyl chloride (66 mg, 0.30 mmol), triethylamine (0.3 mL) and a crystal of DMAP. The resulting solution was stirred overnight without further cooling then evaporated and the residual paste separated directly by column chromatography (dichloromethane) to give the *N-nosyl derivative* **63** (0.12 g, 52%) as an off-white solid and a 4:1 mixture of diastereoisomers, mp 87–89 °C. The major isomer

showed ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95 (d, J=8.4 Hz, 1H, ArH), 7.87 (d, J=8.3 Hz, 2H, 2× ArH), 7.70 (d, J=8.2 Hz, 2H, 2× ArH), 7.68–7.50 (m, 7H), 7.38–7.00 (m, 10H), 5.45 (d, J=9.8 Hz, 1H, NH), 5.21 (d, J=12.4 Hz, 1H, 1″-H_a), 5.18 (d, J=10.1 Hz, 1H, 4-H), 4.97 (d, J=12.4 Hz, 1H, 1″-H_b), 4.35 (dd, J=9.7, 3.2 Hz, 1H, 2-H), 3.86 (dd, J=10.1, 3.2 Hz, 1H, 3-H), 3.80–3.70 (m, 2H, OCH_2), 2.24 (s, 3H, ArMe), 1.62 (s, 3H, Me), 1.24 (s, 3H, Me), 0.96 (s, 9H, ^{t}Bu), 0.81 (t, J=7.1 Hz, CH_2CH_3); the bulk showed IR ($CHCl_3$): ν_{max}=3290, 1740, 1610, 1435 cm^{-1}; m/z: [ES] 893 (M^+, 100%).

4.1.24. Ethyl (6aRS,9SR,9aSR)-hexahydro-7,7-dimethyl-2-(4-toluenesulfonyl)-8-(4-nitrobenzenesulfonyl)iso-indolo[4,5,6-cd]indole-9-carboxylate ***64****.* Triflic acid (20 mg) was added dropwise to a stirred, ice-cold solution of the foregoing sulfonamide **63** (60 mg) in dry chloroform (2 mL). The cooling bath was removed and stirring continued at ambient temperature for 1 h when saturated aqueous sodium carbonate (2 mL) was added and the resulting layers separated. The aqueous layer was extracted with chloroform (2×2 mL) and the combined organic solutions washed with water (2 mL) then dried, filtered and evaporated. The residue was separated using preparative TLC (1:2 EtOAc/petrol) to give the *pyrrolidine* **64** (32 mg, 74%) as a yellowish solid, mp 90–93 °C, which was essentially a single stereoisomer, ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.22 (d, J=8.3 Hz, 2H, 2× ArH), 7.95 (d, J=8.3 Hz, 2H, 2× ArH), 7.88 (d, J=8.2 Hz, 2H, 2× ArH), 7.79 (d, J=8.1 Hz, 1H, ArH), 7.65–7.55 (m, 7H), 7.45 (d, J=8.2 Hz, 2H, 2× ArH), 7.37–7.00 (m, 5H), 6.90 (dd, J=7.5, 3.3 Hz, 1H, ArH), 4.73 (d, J=9.5 Hz, 1H, 9-H), 3.86 (q, J=7.1, 2H, OCH_2), 3.57 (dd, J=9.5, 4.1 Hz, 1H, 9a-H), 2.80–2.65 (m, 2H), 2.28 (s, 3H, ArMe), 2.03 (td, J=12.2, 4.1 Hz, 1H, 6a-H), 1.60 (s, 3H, Me), 1.54 (s, 3H, Me), 0.99 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.2 (CO), 169.9 (s), 150.0 (s), 146.5 (s), 145.1 (s), 135.1 (s), 134.9 (d), 132.4 (s), 130.0 (d), 129.7 (s), 129.2 (d), 128.4 (d), 127.1 (s), 125.5 (d), 124.1 (d), 120.1 (d), 111.5 (d), 60.2 (OCH_2), 58.7 (d), 46.5 (d), 35.6 (d), 28.9 (t), 28.8 (q), 26.6 (q), 23.6 (q), 21.6 (q) (the 7-C signal was not detected with certainty); IR ($CHCl_3$): ν_{max}=1740 cm^{-1}; m/z: [ES] 637 (M^+, 12%), 618 (100).

4.1.25. Ethyl (6aRS,9SR,9aSR)-hexahydro-7,7-dimethylisoindolo[4,5,6-cd]indole-9-carboxylate ***65****.* The foregoing pyrrolidine (25 mg, 0.04 mmol) was dissolved in ice-cold dimethylformamide (2 mL) to which was then added lithium hydroxide (7.5 mg, 0.16 mmol) followed by thioglycolic acid (0.08 mL, 0.08 mmol). The resulting solution was stirred without further cooling for 4 h then diluted with ether (2 mL) and water (2 mL). The two layers were separated and the aqueous layer extracted with ether (2×2 mL). The combined organic solutions were washed with saturated aqueous sodium carbonate (3×2 mL) then dried, filtered and evaporated. Purification using preparative TLC (dichloromethane) gave the *deprotected indole* **65** (9 mg, 80%) as an off-white solid, mp 100–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (br s, 1H, NH), 7.23 (s, 1H, 1-H), 7.20–7.05 (m, 2H), 6.90–6.85 (m, 1H), 4.59 (d, J=10.3 Hz, 1H, 9-H), 3.72–3.68 (m, 2H, OCH_2), 3.50–3.47 (m, 1H, 9$_a$-H), 3.02–2.95 (m, 2H, CH_2), 2.50–2.40 (m, 1H, 6$_a$-H), 1.62 (s, 3H, Me), 1.51 (s, 3H, Me), 0.96 (t, J=7.2 Hz, 3H, CH_2CH_3); m/z [APCI] 299 ($M+H^+$, 100%), 279 (65); HRMS [APCI]: m/z: calcd for $C_{18}H_{23}N_2O_2$: 299.1764; found: 299.1768 $[M+H]^+$.

4.1.26. Preparation of N-tosylates ***66****.* An N–H indole or imidazole **67** (2.00 mmol) was dissolved in triethylamine (30 mL) and tosyl chloride (2.20 mmol) and DMAP (~20 mg) were added. The resulting solution was stirred at ambient temperature overnight then poured into a mixture of water (50 mL) and dichloromethane (100 mL). The separated organic solution was washed with 2 M hydrochloric acid (2×50 mL) and water (50 mL) then dried filtered and evaporated. The residue was usually of sufficient purity to use directly after high vacuum drying. If this were not the case, crystallisation from methanol provided pure material, generally in >85% yields after crystallisation from (aq) methanol or EtOAc/petrol. Melting point data and literature references are given in Table 1.

4.1.27. Detosylation of N-tosyl-indoles and -imidazoles—general procedure. The *N*-tosyl indole or imidazole **66** (0.50 mmol) was dissolved in DMF (2 mL). Lithium hydroxide (48 mg, 2.00 mmol) was added followed by thioglycolic acid (30 mL, 0.60 mmol). The resulting solution was stirred at ambient temperature and the reaction progress monitored by TLC. Once reaction was complete (1.5–5 h), the solution was diluted with ethyl acetate (4 mL) and water (2 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2×4 mL) and the combined organic solutions washed with saturated aqueous sodium carbonate (3×5 mL) then dried, filtered and evaporated to leave an essentially pure *N–H* indole or imidazole **67**. Each product was identified by comparisons of mp and ^{1}H NMR data with authentic material.

4.1.28. Indole ***67a****.* 1-4-(Toluenesulfonyl)indole **66a** (135 mg, 0.50 mmol) was detosylated by the general procedure during 3 h to give *indole* **67a** (50 mg, 86%) as a beige solid, mp 52–54 °C [lit.[41] mp 52–54 °C], ^{1}H NMR spectrum identical to the starting indole.

*4.1.29. Indole-3-carboxaldehyde 22 (****67b****).* 1-(4-Toluenesulfonyl)indole-3-carboxaldehyde **66b** (**23**) (150 mg, 0.50 mmol) was detosylated using the general procedure during 1.5 h to give the *aldehyde* **22** (**67b**) (69 mg, 95%) as an off-white solid, mp 197–199 °C [lit.[41] mp 195–198 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.62 (s, 1H, CHO), 8.86 (br s, 1H, NH), 8.03 (d, J=7.3 Hz, 1H), 7.97 (s, 1H), 7.34 (d, J=7.7 Hz, 1H), 7.20–6.95 (m, 2H).

Alternatively, the *N*-tosyl aldehyde **66b** (**23**) (0.50 mmol) in DMF was treated only with lithium hydroxide (48 mg, 2.00 mmol) and the resulting mixture stirred at ambient temperature for 24 h (TLC monitoring) before a similar work-up delivered an 82% yield (60 mg) of the detosylated aldehyde **22** (**67b**), which showed mp 196–198 °C.

4.1.30. Ethyl indole-3-ethanoate ***67c****.* The *N*-tosyl indole **66c** (178 mg, 0.50 mmol) was detosylated using the general procedure for 3 h to give the *indole* **67c** (80 mg, 79%) as an off-while solid, mp 42–45 °C [lit.[41] mp 44–45 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (br s, 1H, NH), 7.56 (d, J=7.9 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 7.20 (s, 2-H), 7.15–7.02 (m, 2H), 4.05 (q, J=7.1 Hz, OCH_2), 3.87 (s, 2H, 3-CH_2), 1.19 (t, J=7.1 Hz, CH_3).

4.1.31. Ethyl (E)-3-(indol-3-yl)propenoate ***67d****.* The *N*-tosyl indole **66d** (**49**) (185 mg, 0.50 mmol) was detosylated according to the general procedure during 3 h to give the *indole-4-carboxylate* **67d** (43 mg, 41%) as an off-white solid, mp 118–121 °C [lit.[42] mp 119.5–120 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.91 (br s, 1H, NH), 7.98 (d, J=16.2 Hz, 1H, 2-H), 7.92–7.78 (m, 3H), 7.45–7.42 (m, 1H), 7.25–7.21 (m, 1H), 6.47 (d, J=16.2 Hz, 1H, 3-H), 4.27 (q, J=7.2 Hz, 2H, OCH_2), 1.35 (t, J=7.2 Hz, 3H, CH_3).

4.1.32. 2-Phenylindole ***67f****.* 2-Phenyl-1-4-(toluenesulfonyl)indole **66f** (174 mg, 0.50 mmol) was detosylated by the general procedure during 3 h to give 2-*phenylindole* **67f** (85 mg, 87%) as an off-white solid, mp 187–190 °C [lit.[41] mp 188–190 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.62 (br s, 1H, NH), 7.61 (dd, J=8.2, 1.3 Hz, 2H), 7.56 (d, J=7.8 Hz, 1H), 7.40–7.33(m, 3H), 7.25–7.05 (m, 3H), 6.73 (s, 1H, 3-H).

4.1.33. Tetrahydrocarbazole ***67g****.* 1-(4-Toluenesulfonyl)tetrahydrocarbazole **66g** (163 mg, 0.50 mmol) was detosylated according to the general procedure during 3 h to give *tetrahydrocarbazole* **67g** (69 mg, 80%) as a cream solid, mp 118–120 °C [lit.[41] mp 118–120 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72 (br s, 1H, NH), 7.50 (d, J=8.1 Hz, 1H), 7.30 (d, J=8.3 Hz, 1H), 7.15–6.85 (m, 2H), 2.75 (app. t, J=5.8 Hz, 4H), 2.20–1.70 (m, 4H).

4.1.34. 1H-Carbazole ***67h****.* The carbazole **66h** (160 mg, 0.50 mmol) was detosylated according to the general procedure during 5 h to

give *carbazole* **67h** (74 mg, 87%) as a colourless solid, mp 246–248 °C [lit.[41] mp 243–246 °C] ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.03 (br s, 1H, NH), 8.08 (d, J=7.7 Hz, 2H), 7.44–7.38 (m, 4H), 7.22 (dt, J=7.7, 1.4 Hz, 2H).

4.1.35. Methyl indole-4-carboxylate ***67i***. The *N*-tosyl indole **66i** (165 mg, 0.50 mmol) was detosylated according to the general procedure to give the *indole-4-carboxylate* **67i** (70 mg, 81%) as an off-white solid, mp 64–67 °C [lit.[41] 69–71 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.36 (br s, 1H, NH), 7.86 (d, J=7.7 Hz, 1H), 7.52 (d, J=7.7 Hz, 1H), 7.25–7.19 (m, 1H), 7.17 (t, J=7.7 Hz, 1H), 7.11–7.06 (m, 1H), 3.92 (s, 3H, OMe).

4.1.36. 1H-Imidazole ***67j***. *N*-Tosylimidazole **66j** (111 mg, 0.50 mmol) was detosylated during 2 h according to the general procedure to give *imidazole* **67j** (31 mg, 92%) as a colourless solid, mp 89–92 °C [lit.[41] mp 89–91 °C].

4.1.37. 2-Phenylimidazole ***67k***. 2-Phenyl-1-tosylimidazole **66k** (150 mg, 0.50 mmol) was detosylated according to the general procedure during 2.5 h to give 2-*phenylimidazole* **67k** (65 mg, 88%) as a colourless solid, mp 147–150 °C [lit.[41] mp 144–147 °C], ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.24 (br s, 1H, NH), 7.82–7.77 (m, 2H), 7.25–7.20 (m, 3H), 7.11 (s, 2H).

4.1.38. (±)-α-Cyclopiazonic acid ***1***. The deprotected indole **65** (35 mg) was dissolved in dry dichloromethane (2 mL) containing diketene (two drops) and potassium *tert*-butoxide (a few crystals) and the resulting mixture gently refluxed for 48 h then cooled and concentrated. The crude product was purified by preparative TLC (3:2 EtOAc/petrol) to give (±)-α-*Cyclopiazonic acid* **1** (15 mg, 36%) as almost one diastereoisomer which displayed spectroscopic and analytical data [mp 230–236 °C; lit.[1a] mp 245–246 °C], which was identical to an authentic natural sample (Tocris) except for its optical rotation, including showing exactly the same relative amount of a second enol form (see discussion): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (br s, 1H, NH), 7.19 (s, 1H, 1-H), 7.18–7.05 (m, 2H), 6.85 (d, J=7.0 Hz, 1H, ArH), 4.00 (d, J=11.1 Hz, 1H, 9-H), 3.60 (dd, J=11.1, 5.8 Hz, 1H, CH), 3.02–2.95 (m, 2H, CH_2), 2.60–2.50 (m, 1H, 6_a-H), 2.38 (s, 3H, Me), 1.57(s, 3H, Me), 1.45 (s, 3H, Me); *m/z* [APCI] 337 ($M+H^+$, 100%); HRMS [APCI]: *m/z*: calcd for $C_{20}H_{21}N_2O_3$: 337.1547; found: 337.1548 $[M+H]^+$.

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References and notes

1. (a) Holzapfel, C. W. *Tetrahedron* **1968**, *24*, 2101–2119; (b) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *270*, 77–78; Harrison, J. *Trop. Sci.* **1971**, *13*, 57–63.
2. Chalmers, A. A.; Gorst-Allman, C. P.; Steyn, P. S. *J. Chem. Soc., Chem. Commun.* **1982**, 1367–1368; Schabort, J. C.; Potgiete, J. J. *Biochim. Biophys. Acta* **1971**, *250*, 329–330; Steenkam, D. J.; Schabort, J. C.; Holzapel, C. W.; Ferreira, N. P. *Biochim. Biophys. Acta* **1973**, *309*, 440–456; Neethling, D. C.; McGrath, R. M. *Can. J. Microbiol.* **1977**, *23*, 856–872.
3. For a standardised HPLC analysis method, see: Frisvad, J.; Thrane, U. *J. Chromatogr.* **1987**, *404*, 195–214.
4. El-Banna, A. A.; Pitt, J. I.; Leistner, L. *Syst. Appl. Microbiol.* **1987**, *10*, 42–46.
5. Larsen, T. O.; Gareis, M.; Frisvad, J. C. *J. Agric. Food Sci.* **2002**, *50*, 6148–6152 and references cited therein.
6. For a review of the biosynthesis of prenylated alkaloids, see: Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97–173.
7. Seidler, N. W.; Jona, I.; Vegh, M.; Martonosi, A. *J. Biol. Chem.* **1989**, *264*, 17816–17823.
8. Web of Science search for α-cyclopiazonic acid; 09/06/2011.
9. Kozikowski, A. P.; Greco, M. N.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 6873–6874.
10. Muratake, H.; Natsume, M. *Heterocycles* **1985**, *23*, 1111–1117.
11. Seshime, Y.; Juvvadi, P. R.; Tokuoka, M.; Koyama, Y.; Kitamoto, K.; Ebizuka, Y.; Fujii, I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3288–3292.
12. Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150–4166.
13. Moorthie, V. A.; McGarrigle, E. M.; Stenson, R.; Aggarwal, V. K. *ARKIVOC* **2007**, 139–151.
14. Grandel, R.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, 409–417.
15. See for example: Bush, E. J.; Jones, D. W. *Chem. Commun.* **1993**, 1200–1201; Elix, J. A.; Parker, J. L. *Aust. J. Chem.* **1987**, *40*, 187–192; Takahashi, T.; Ootake, A.; Tsuji, J.; Tachibana, K. *Tetrahedron* **1985**, *41*, 5747–5754.
16. Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 2986–2987.
17. Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528–3529.
18. Lehnert, W. *Tetrahedron* **1972**, *28*, 663–666.
19. Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 4003–4005.
20. Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 3350–3352.
21. Cannon, J. G.; Demopoulos, B. J. *J. Heterocycl. Chem.* **1982**, *19*, 1195–1199; For a recent alternative, see Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *131*, 10806–10807.
22. Bagley, M. J.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901–6904.
23. Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110.
24. Miura, M.; Akase, F.; Shinohara, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1021–1025; Ku, T. W.; Ali, F. E.; Bandinell, W. E.; Erhard, K. F.; Huffman, W. F.; Venslavaky, J. W.; Yuan, C. C.-K. *Tetrahedron Lett.* **1997**, *38*, 3131–3134.
25. See, for example Genet, J. P.; Juge, S.; Besnier, I.; Uziel, J.; Ferroud, D.; Kardos, N.; Achi, S.; Ruiz-Montes, J.; Thorimbert, S. *Bull. Soc. Chim. Fr.* **1990**, *127*, 781–786.
26. Hibino, S.; Sugino, E.; Yamochi, T.; Kuwaki, M.; Hashimoto, H. *Chem. Pharm. Bull.* **1987**, *35*, 2261–2265.
27. Behforouz, M.; Curran, T. T.; Bolan, J. L. *Tetrahedron Lett.* **1986**, *27*, 3107–3110.
28. Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087–2089; Vidal, J.; Domestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.—Eur. J.* **1997**, *3*, 1691–1709.
29. Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667–1669; Yokoshima, S.; Ueda, T.; Ayato, S.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137–2139; Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301–1303.
30. For reviews, see Mitsunobu, O. *Synthesis* **1981**, 1–28; Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.
31. Vidal, J.; Guy, L.; Stein, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791–4793.
32. Kumar, J. S.; Dupradeau, F.-Y.; Strouse, M. J.; Phelps, M. E.; Toyokuni, T. *J. Org. Chem.* **2001**, *66*, 3220–3223.
33. Evans, M. C.; Johnson, R. L. *Tetrahedron* **2000**, *56*, 9801–9808.
34. cf. He, L.; Byun, H. S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618–7626.
35. See, for example Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670–5676; Gard, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184.
36. Haskins, C. M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599–601.
37. Beyer, C.; Scherkenbeck, J.; Sondermann, F.; Figge, A. *Tetrahedron* **2010**, *66*, 7119–7123.
38. Vangveravong, S.; Nichols, D. E. *J. Org. Chem.* **1995**, *60*, 3409–3413.
39. Rodriguez, R.; Vinets, I.; Diez, A.; Rubiralta, M.; Giralt, E. *Synth. Commun.* **1996**, *26*, 3029–3059.
40. Krogsgaard-Larsen, N.; Begtrup, M.; Frydenvang, K.; Kehler, J. *Tetrahedron* **2010**, *66*, 9297–9303.
41. Aldrich Chemical Catalogue.
42. Lingens, F.; Lange, J. *Annalen* **1970**, *738*, 46–53.