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The synthesis of bioactive indolocarbazoles related to K-252a

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A range of functionalised indolocarbazoles, related to the natural product K-252a, have been prepared, starting from a readily available bridged cyclopentene. Sequences of transformations, involving initial hydroboration–oxidation to give a ketone, or by dihydroxylation and cyclic sulfate formation, enable the preparation of diverse indolocarbazole products. Issues of imide nitrogen protection for the indolocarbazole, and opportunities for asymmetric desymmetrisation of key intermediates were also explored. A novel chiral lithium amide base mediated transformation of a cyclic sulfate intermediate gave the anticipated ketone product in up to 87% ee. A number of compounds, in the form of unprotected imide substituted indolocarbazoles, were screened for biological activity and were found to be potent inhibitors of a number of kinase enzymes.

Introduction

Natural products incorporating the 1*H*-indolo[2,3-*a*]carbazole ring system have emerged as an important class of compounds due to their broad range of potent biological activities.[1] Key members of this family include staurosporine **1**,[2] K-252a **2**,[3] and rebeccamycin **3**.[4] Staurosporine **1** was the first member of this family to be identified and was isolated from *Streptomyces staurosporeus* (AM 2282), cultivated from a soil sample taken in Japan in 1977.[2] The compound has a distinctive indolocarbazole-bridged pyranose structure, and was shown to possess diverse biological activities, including antimicrobial, hypotensive, cytotoxic and kinase inhibition.[5] K-252a **2**, originally isolated from the culture broth of *Nocardiopsis* sp., has a pendant furanose, and is a highly potent inhibitor of serine/threonine and tyrosine kinases, especially protein kinase C (PKC).[6] Rebeccamycin **3** produced by *Saccharothrix aerocolonigen* possesses a doubly chlorinated heterocyclic nucleus, has only one glycosidic C–N linkage, and is known to induce topoisomerase I mediated DNA cleavage.[7]

The powerful and varied biological activities of these systems endow them with many potential therapeutic applications, particularly as anticancer agents, and several have reached the stage of clinical trials, including staurosporine.[8] Unsurprisingly, these fascinating structures have attracted substantial synthetic interest, both from the standpoint of total synthesis of the natural products themselves, and the design of simpler analogues for probing structure–activity relationships.[9] Some time ago we reported the synthesis of novel carbocyclic analogues of K-252a,[10] and more recently we described the synthesis of further related compounds by use of a cyclic sulfate as a key intermediate.[11] The purpose of this paper is to describe this work in full, including previously undisclosed chemistry and preliminary biological screening data.

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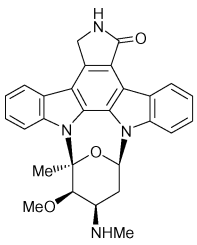
Results and discussion

(i) A rapid route to indolocarbazole-bridged cyclopentanes

Our initial efforts were directed towards establishing a rapid and efficient route to bridged structures resembling either K-252a or staurosporine. A breakthrough came with the finding that the reaction of the known indolocarbazole unit **4a** with *cis*-dibromocyclopentene **5** generated the bridged alkene **6a**, Scheme 1.

Most of our initial work was carried out using the readily available N–Bn series of compounds, but two other series of derivatives having the imide nitrogen unprotected (*i.e.* the N–H series), or protected as a *para*-methoxybenzyl (N–PMB) were also utilised. A key problem with the N–Bn compounds was the extreme difficulty of debenzylation to give the free imide compounds ultimately required for biological testing (see later). As a stopgap measure we carried out some work with the free N–H series, but this limited our synthesis options, the compounds proved extremely insoluble in most organic solvents, and the initial coupling to give **6b** was low-yielding. Eventually, we settled on the N–PMB series of compounds as a reasonable compromise in terms of availability, protecting group stability, moderate (although still less than ideal) solubility, and ease of removal. As shown in Scheme 1 each series of compounds was amenable to diastereoselective alkene hydroboration to give **7**, and oxidation to give bridged ketones **8**.



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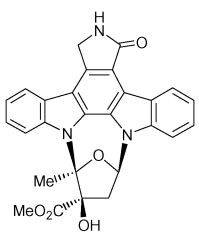

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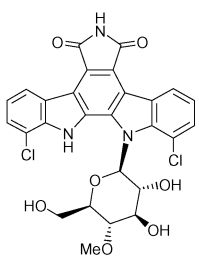

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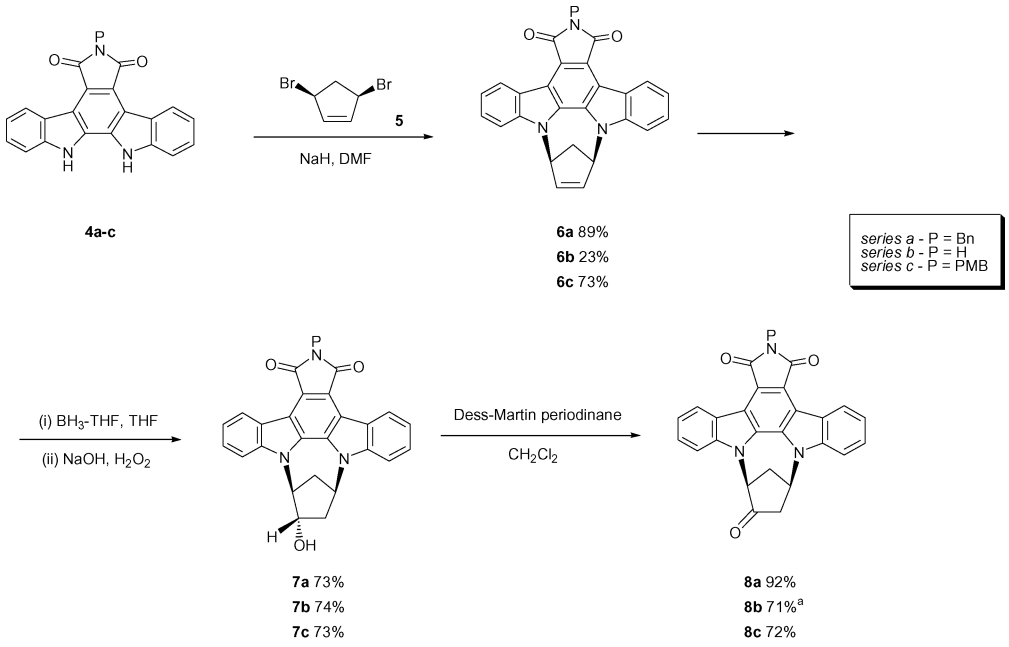
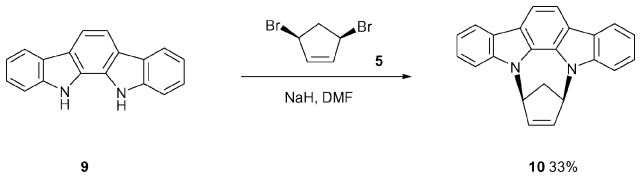


Scheme 1 [a]Overall yield for hydroboration–oxidation without alcohol purification.

The initial coupling process involving dibromide **5** was found to be more convenient and higher yielding than alternatives involving a reaction of the corresponding diacetates with palladium catalysts. Although we have not explored the scope of this reaction in detail, it is capable of supplying alternative bridged structures, for example the simpler indolocarbazole **10**, Scheme 2.



Scheme 2

The next phase of our work involved further manipulation of the ketone function present in **8a** (and subsequently **8b**) to give the type of α-hydroxyester present in K-252a. The N–Bn derivative **8a** was shown to undergo highly stereoselective addition reactions with a range of nucleophilic reagents, including borane, vinylmagnesium bromide, and a nitromethane anion, giving products **11–13**.

Alcohol **11**, the product of borane reduction, is the epimer of alkene hydroboration product **7a**, and was formed with complete stereoselectivity. It is clear that in all such reactions the indolocarbazole bridge effectively blocks one face of the ketone, leading to highly stereoselective addition reactions.

Cleavage of the alkene in **12** was seen as one possible route to the required hydroxyester grouping, but efforts to proceed directly to the corresponding hydroxyacid, by use of manganese or ruthenium based oxidants, or by ozonolysis under basic conditions, failed to give the desired products.

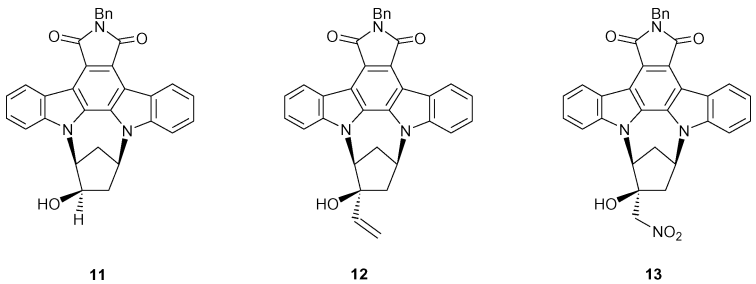
As an alternative, we prepared the cyanohydrin **14a** using the procedure described by Danishefsky,[12] which employs Me_3SiCN in the presence of catalytic quantities of 18-crown-6 and potassium cyanide, Scheme 3.

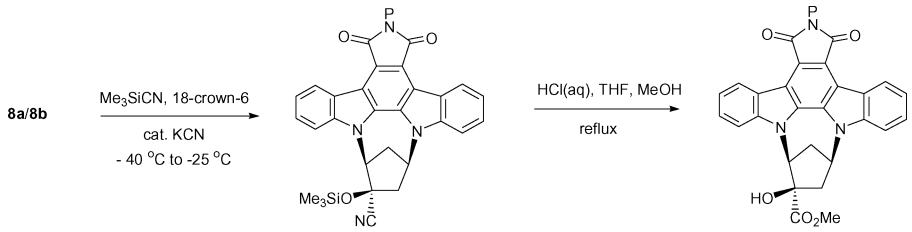
This process generated mixtures of diastereomers (presumably by equilibration) if conducted at 0 °C, but was completely diastereoselective at −25 °C. In the case of the starting ketone bearing the unprotected imide, the cyanohydrin product was isolated in the form of the N–$SiMe_3$ derivative **14b**. As shown, hydrolysis of both series of cyanohydrin under acidic conditions resulted in the formation of the desired hydroxyester derivatives **15** in good yield.

The successful series of transformations, culminating in the synthesis of K-252 model compound **15b** provided us with the first compounds suitable for biological screening (see later). We found it impossible to convert members of the N–Bn series into the N–H series, for example using conventional hydrogenation conditions, or by adopting oxidative cleavage conditions using molecular oxygen and base,[13] or by hydrolysis to an intermediate anhydride.[14] Therefore, in most subsequent chemistry, use of the N–Bn series was discontinued in favour of the corresponding N–PMB series.

(ii) Vicinally substituted products *via* a key cyclic sulfate intermediate

All of the transformations of the alkenes **6** described above rely on initial hydroboration, and so necessarily involve





14a P = Bn 96%
14b P = $SiMe_3$ 95%

15a P = Bn 87%
15b P = H 57%

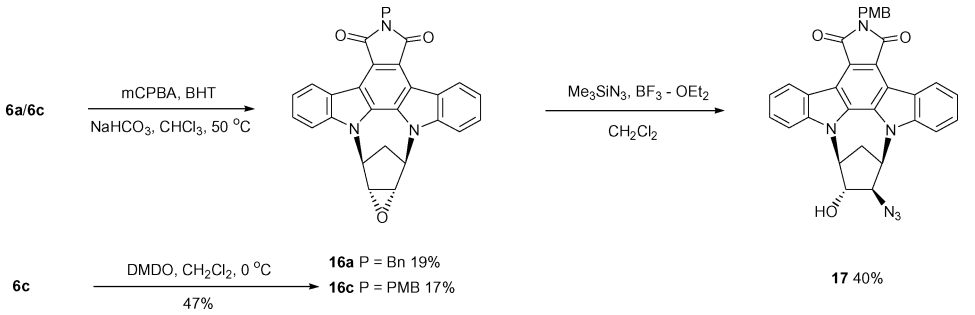
Scheme 3

reduction at one ring position. We were particularly interested in alternative processes that would enable us to generate more highly substituted systems, particularly those bearing vicinal heteroatom substituents, somewhat akin to the staurosporine glycone. Consequently, our attention became focused on the stereoselective synthesis of epoxide intermediates and their ring opening reactions. However, epoxidation of alkenes **6a** and **6c** proved to be problematic, Scheme 4.

Epoxide generation using peracids was consistently low yielding, with destruction of the material being evident, even in the presence of mild base or radical scavengers.[15] Dimethyldioxirane gave a borderline satisfactory yield with the N–PMB derivative **6c**, but the reaction proved capricious, and was not suitable for scale-up. Complementary approaches to epoxide intermediates *via* bromohydrin formation also proved ineffective.[16] To further diminish the attractiveness of epoxides **16**, experiments involving epoxide opening, using the modest supplies available from the DMDO reaction, were also discouraging, with various forms of azide (normally an excellent nucleophile for epoxide opening)[17] giving azidoalcohol products such as **17** in only very modest yield.

These problems led us to develop a complementary approach, which relied on the use of a reactive cyclic sulfate as an epoxide surrogate,[18] and which required initial alkene dihydroxylation. In contrast to the problematic epoxidation process, the corresponding dihydroxylation reaction proved efficient and totally stereoselective under standard conditions, Scheme 5.[19]

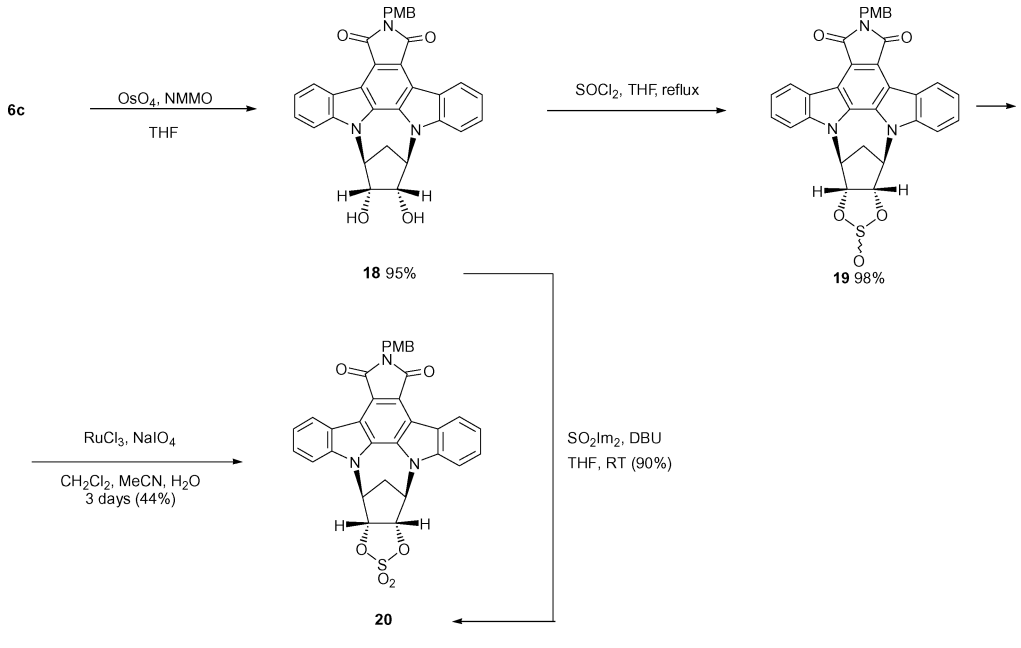
With diol **18** in hand we expected that cyclic sulfate synthesis would be routine using the standard two step procedure described by Sharpless.[20] Initial transformation to the cyclic sulfite **19**, as a mixture of diastereomers at sulfur (*ca.* 2.4 : 1), was near-quantitative using thionyl chloride, but the subsequent oxidation to the desired sulfate **20** proved exceedingly sluggish, at least in part due to the low solubility of sulfite **19** in suitable



16a P = Bn 19%
16c P = PMB 17%

17 40%

Scheme 4



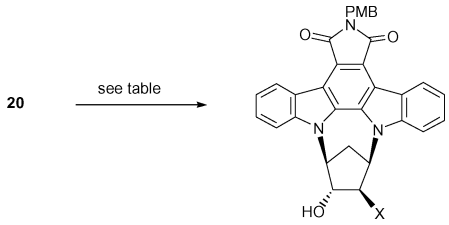
18 95%

19 98%

20

Scheme 5

Table 1



Reagent	X	Compound (yield %)
NaN_3, DMF, 80 °C	N_3	**17** (91)
Morpholine, reflux	*N*-Morpholino	**21** (36)
$PhCO_2NH_4$, DMF, 70 °C	OCOPh	**22** (88)
PhSH, NaH, THF, RT	SPh	**23** (67)
NH_4SCN, DMF, 70 °C	SCN	**24** (64)

solvents. As indicated, we found a very acceptable, and direct, alternative synthesis of the sulfate, which involved reaction of the diol **18** with sulfonyl diimidazole in THF, with DBU as base. This combination appeared uniquely suitable to this system, providing reproducibly high yields, and enabling multi-gram synthesis.[21]

Ring opening of the cyclic sulfate **20** was then carried out under various conditions to give a range of products **17**, **21–24** in which interesting vicinal functionality had been installed, Table 1.

The reaction of **20** with azide attested to the excellent activating properties of the cyclic sulfate, since the ring opening occurred in high yield under conditions which left the corresponding epoxide **16c** unreacted. However, the direct installation of amine groups still proved difficult, the modest yield obtained by reaction of **20** in neat morpholine at reflux being one of the best results.[22] Under these conditions we obtained substantial amounts of diol **18**, presumably formed by a competing nucleophilic attack at sulfur, and also quantities of ketone **8c**. The formation of this compound as a by-product stimulated further investigation of the base-mediated rearrangement of cyclic sulfates, which is described later.

In contrast to the problematic amine reactions, sulfate ring-opening with oxygen or sulfur-centred nucleophiles was relatively straightforward, leading to benzoate, thiophenyl and thiocyanate-substituted products **22–23**.

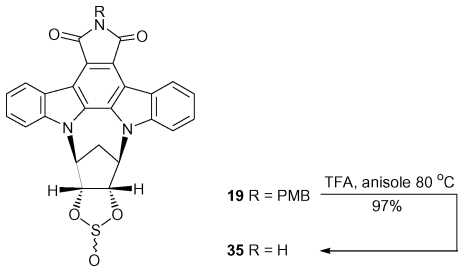
Given the apparent importance of nitrogen functionality in bioactive systems such as staurosporine, we were pleased to demonstrate that the azide function present in **17** could enable access to additional nitrogen containing products, such as **25–27** in a straightforward fashion, Scheme 6.

Thus, azide reduction to give the potentially versatile primary amine **25**, was possible under several types of typical hydrogenation conditions, the imide N–PMB being unaffected. Although amine **25** may prove useful in reductive alkylation sequences, we also gained access to diallyl amine **26** by means of the indium mediated Barbier type process described by Yadav and co-workers.[23] Azide cycloaddition using dimethyl acetylenedicarboxylate as a reaction partner, one of the processes highlighted by Sharpless in his 'click chemistry' approach,[24] was also effective, leading to triazole **27** in a very high yield.

Since a free imide N–H function was deemed a prerequisite for biological screening (see later), we next tackled the issue of PMB removal from a number of the indolocarbazole derivatives. Several protocols proved ineffective for this transformation, including hydrogenolysis at 300 psi using palladium hydroxide as a catalyst, and use of either DDQ or CAN. Ultimately, we established that the use of trifluoroacetic acid in anisole was an effective procedure, although removal of the imide protecting group was usually accompanied by trifluoroacetylation of the secondary alcohol of the cyclopentane, Table 2.

As indicated in the Table, somewhat disparate outcomes were observed in these deprotection reactions. In the case of the azide **17**, we obtained a mixture of the desired secondary alcohol and the corresponding trifluoroacetate. The morpholine adduct **21** gave the desired product **31** in 50% yield, accompanied by the trifluoroacetyl derivative of the starting N–PMB imide. In the case of thioether **23** only the trifluoroacetate **29** was isolated, whereas in the cases of thiocyanate **24** and triazole **27** we obtained only the corresponding alcohols. In the cases of the azide and thioether substituted systems, we conducted LiOH mediated hydrolysis of the initially formed trifluoroacetates **28** and **29** to generate the required secondary alcohol products.

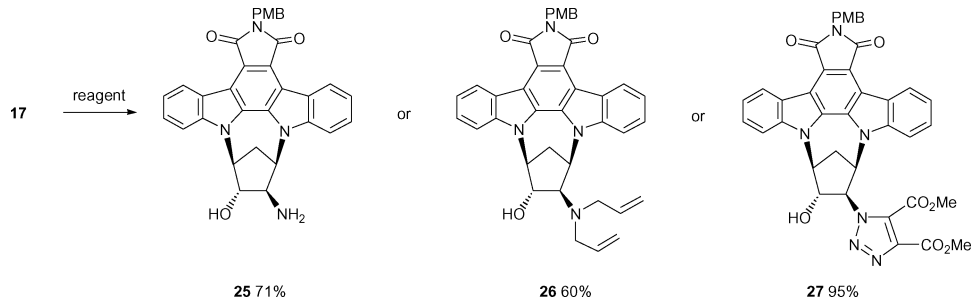
In addition, we exposed cyclic sulfite **19** to the same conditions, and were able to isolate the required product **35** (as a mixture of diastereomers at sulfur) in a very high yield, Scheme 7.



Scheme 7

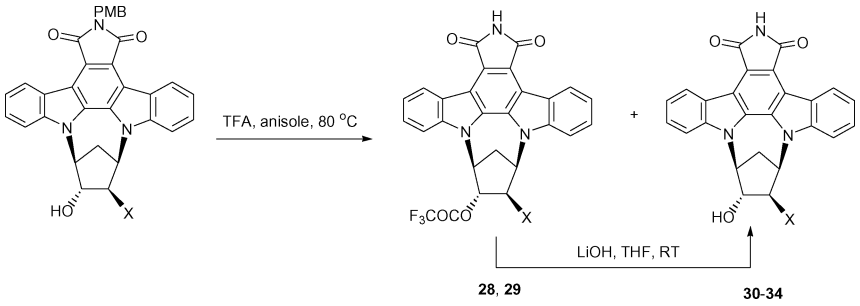
Although the cyclic sulfate ring-opening and imide deprotection sequence had been quite fruitful in delivering some attractive indolocarbazoles for biological study, we were disappointed that the chemistry did not work with carbon-centred nucleophiles. Somewhat surprisingly, we were unable to effect efficient ring opening of sulfate **20** with cyanide, using sodium or potassium cyanide under various conditions, or using Et_2AlCN.[25] A similar lack of success was seen with other carbon nucleophiles, including metal acetylides, Grignard and cuprate reagents, and with hydride ($NaBH_4$) or fluoride (TBAF).

A final transformation that was accomplished in this series was the reduction of the azidoalcohol **30** to the corresponding aminoalcohol **36**, Scheme 8.



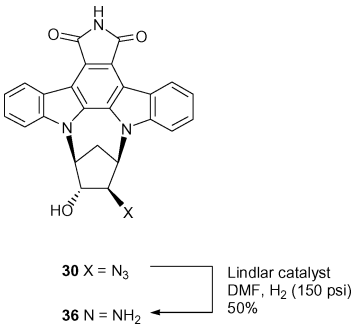
Scheme 6 *Reagents*: (**25**) Pd(C), H_2, DMF; (**26**) indium, NaI, allylbromide, DMF, 50 °C; (**27**) MeO_2C–≡–CO_2Me, DMF, 70 °C.

Table 2



Starting material (X)	Product(s) from TFA/anisole: $OCOCF_3$	Product(s) from TFA/anisole: OH	Total (%) after LiOH
17 X = N_3	**28** (*ca.* 50%)[a]	**30** (47%)	**30** (85)
21 X = morpholine	ND[b]	**31** (50%)	NA
23 X = SPh	**29** (56%)	**32** ND	**32** (45)
24 X = SCN	ND	**33** (54%)	NA
27 X = triazole unit	ND	**34** (52%)	NA

[a] Not obtained in pure form. [b] The trifluoroacetate derivative of starting PMB imide **21** was isolated in 28% yield. ND = Not detected. NA = Not applicable



Scheme 8

The reduction proved less facile than we anticipated, hydrogenation using palladium on carbon giving lower yields than Lindlar catalyst, and alternatives such as the Staudinger procedure (PPh_3, THF, H_2O), or $FeCl_3$–NaI being unproductive.[26]

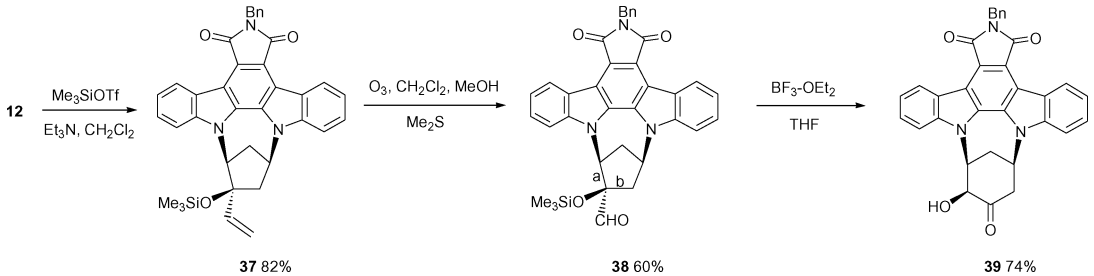
(iii) Reactions of indolocarbazole ketones: focus on cyclopentane ring-expansion

At the outset of this project it was hoped that we would be able to access staurosporine analogues in a similar fashion to the approach described above for the five membered K-252a mimics, *i.e.* combination of an indolocarbazole fragment **4** with a suitable 6-membered (electrophilic) partner. However, an alternative strategy involving ring expansion of the five-membered derivatives to give staurosporine analogues suggested itself, since Wood and co-workers had successfully accomplished such a process in their synthesis of the natural product itself.[9b]

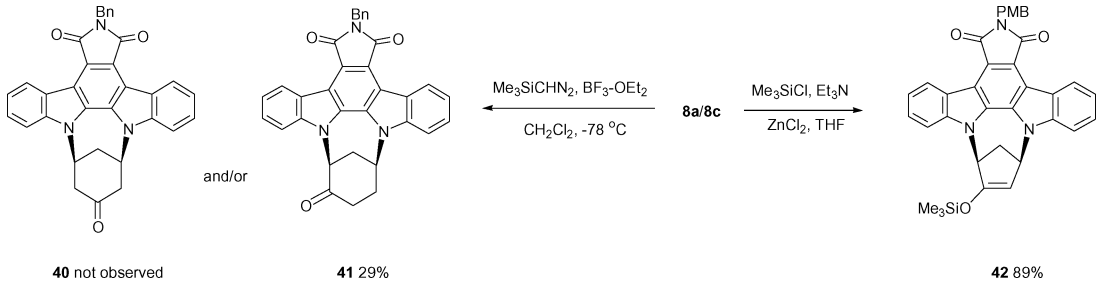
We initially considered that nitromethane adduct **13** might be useful in this regard, since reduction to a β-aminoalcohol might prelude ring expansion using diazotisation methods. However, our failure to effect nitro group reduction precluded such an investigation, and we turned instead to protocols more closely akin to those described by Wood. After some preliminary investigations, we established the synthetic sequence shown in Scheme 9.

Effective ozonolysis of **12** required prior alcohol protection, for which we installed a trimethylsilyl ether, giving **37**, and subsequently enabling access to the key aldehyde **38**. Alternative routes to this compound, either by reduction of cyanohydrin **14a**, or by redox operations on the ester **15a**, were not fruitful. Pleasingly, the type of α-ketol rearrangement described by Wood was equally effective when applied to aldehyde **38**, exposure of this compound to excess BF_3–OEt_2 leading to cyclohexanone **39**. The structure of the product was fully supported by ^1H NMR; the coupling patterns (from ^1H–^1H COSY experiments) and magnitudes of *J*-values being distinctive for the regioisomer shown (as opposed to the product from the migration of bond *b*) with the equatorial hydroxyl stereochemistry. This outcome derives from selective migration of bond *a* in **38** to the *si* face of the Lewis-acid activated aldehyde, and is exactly analogous to the result seen by Wood.

Although this approach to indolocarbazoles with six-membered bridging carbocycles provided adequate access to hydroxyketone **39**, we were also interested in a more direct route to a less functionalised cyclohexanone. In particular, the simpler cyclohexanone corresponding to **39** *without* the hydroxyl group (*i.e.* **40**, see below) was seen as an attractive intermediate, since chiral base desymmetrisation might then



Scheme 9



40 not observed **41** 29% **42** 89%

Scheme 10

enable access to diverse products in enantiomerically enriched form. We were also interested in the idea of ring expansion using the Saegusa process, which involves regioselective ring-opening of a silyloxycyclopropane using $FeCl_3$.[27] Both of these avenues were explored, Scheme 10.

In diazoalkane ring expansions of ketones, the regiochemical outcome depends upon the migratory aptitude of the two groups attached to the carbonyl in the starting ketone.[28] From the established examples we anticipated a mixture of **40** and **41** would be formed, probably with the undesired isomer **41** predominating. However, the migratory aptitudes of the groups in ketone **8a** could not be guaranteed considering the unusual features of the system. In the event, reactions using trimethylsilyldiazomethane and BF_3–OEt_2 formed only the latter ketone **41**, in rather modest yield. Substantial experimentation with the nature of the Lewis acid did not lead to any improvement or variation in regiochemistry.[29]

In the alternative approach to ring expansion that we explored, we required the enol silane **42**, which we found could be prepared in high yield from **8c** under standard conditions. Unfortunately, despite extensive experimentation, we were unable to find conditions for the cyclopropanation of this compound, which is a prerequisite for the Saegusa process.[30]

As an adjunct to this part of the work, we briefly explored alkylations of ketone **8c**. The viability of enolate chemistry was expected to be improved in the carbocyclic analogues, compared to the natural products, which would be expected to suffer β-elimination problems associated with either the ring oxygen or the carbazole nitrogen substituents. Somewhat surprisingly, we were unable to achieve meaningful alkylation results using LDA as a base, but on switching to NaH (one equivalent) we observed clean, but incomplete, transformation to the doubly alkylated products **43** and **44**, using allyl bromide and methyl iodide respectively, Scheme 11.

Both the allylation and methylation reactions proceeded to about 50% conversion, and we were unable to identify mono-alkylated product from examination of the NMR spectra of crude reaction product. The yields of **43** and **44** were about 70%, taking into consideration the recovery of about half of the starting ketone. Over-alkylation is a well known problem in ketone enolate chemistry, particularly for cyclopentanones, and under these conditions it seems that enolate equilibration leading to disubstituted products is highly favoured.[31] Although we were unable to control mono-alkylation, it did prove possible to force alkylation to give good yields of a dialkylated product, for example the dibenzylketone **45**, obtained in 71% yield, using two equivalents of base.

Although we did not explore this area further, it seems that using metal enolates derived from **8c**, or enol silane intermediates such as **42**, should provide a means to additional types of indolocarbazole, through alkylation, aldol, Mukaiyama and related processes.

(iv) Asymmetric synthesis of key indolocarbazole alcohol 7c and ketone 8c

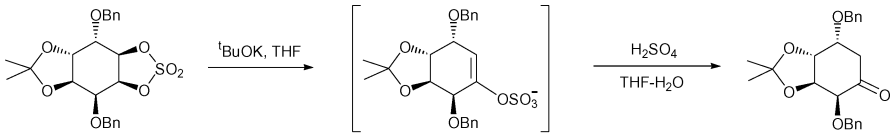
Throughout this project a key consideration had been the prospect of developing very concise routes to biologically active indolocarbazoles, which would be amenable to asymmetric modification. One idea, which would generate chiral six-membered variants, was mentioned earlier, and involved chiral base desymmetrisation of ketone **40**. Clearly, most of our chemistry involves the five-membered variants, and it would be preferable to effect the key asymmetric step on a readily available (*i.e.* early stage) intermediate. Therefore, for the five-membered systems we first considered that asymmetric hydroboration or hydrosilylation of alkene **6c** would be ideal, since the alcohol product **7c** and all subsequent materials would then be available in non-racemic form.

It was quickly established that low levels of asymmetric induction could be obtained by hydroboration of alkene **6c** using diisopinocamphenylborane (Ipc_2BH) in THF at 0 °C, to give **7c**, as shown earlier in Scheme 1.[32] Although the chemical yield for this process was good (83%) the enantiomeric excess of the material, estimated by HPLC, was a very modest 33%. This was surprising to us, since higher values (>80% ee) are established for asymmetric hydroboration of norbornene systems using this reagent.[33] The low solubility of alkene **6c** in appropriate solvents necessitated the use of rather dilute solutions, which in turn led to very slow reactions unless an excess of borane was employed. Unfortunately, this level of asymmetric induction proved optimal, since screening of the reaction with other boranes, including monoisopinocamphenylborane ($IpcBH_2$), dilongifolylborane (Lgf_2BH) or dicaranylborane (Icr_2BH) gave even less satisfactory results. As a complementary approach, we also attempted asymmetric hydrosilylation, which has given even higher levels of asymmetric induction than hydroboration, when applied to bridged systems like norbornene (96% ee).[34]

8c

43 R = allyl
44 R = methyl
45 R = benzyl

Scheme 11



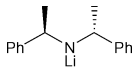
46 **47** 86%

Scheme 12

Despite extensive exploration using the Hayashi palladium catalysed process, which employs $HSiCl_3$ and the MOP binaphthyl ligand, we were unable to achieve conversion of **6c** into alcohol **7c**. Under all conditions that we could conceive, the indolocarbazole system appeared incompatible with the highly corrosive trichlorosilane reagent, and complete destruction of the substrate was observed.

In the attempted ring-opening reaction of cyclic sulfate **20** with morpholine we had noted the formation of ketone **8c** as a by-product. A literature search revealed that this type of overall transformation had been reported previously, for example the conversion of cyclitol derived cyclic sulfate **46** to give the ketone **47**, described by Fernández-Mayoralas and co-workers, Scheme 12.[35]

These authors proposed a β-elimination process to give an intermediate vinyl bisulfate, which on acidification gave the ketone product. Unfortunately, application of these conditions to our cyclic sulfate **20** gave only very modest yields (8%) of the desired ketone **8c**. Similarly, the use of LDA at low temperature also gave very modest (*ca.* 5%) yields of the desired ketone, and recovery of starting sulfate or the corresponding diol **18** predominated. Our main motivation for persisting with this transformation was the hope that an asymmetric variant might enable access to ketone **8c** in non-racemic form. Carrying out the reaction under the vigorous, high temperature, conditions involving refluxing amine, under which we had initially observed ketone formation (as a by-product), did not offer hope of asymmetric induction. Since the high-yielding literature examples used metal alkoxides, we initially probed the use of their chiral analogues, in the form of metal salts of ephedrine derivatives—but to no effect.[36] Finally, we found that chiral lithium amide base **48** provided some more encouraging preliminary results.[37] Thus, addition of cyclic sulfate **20** to a solution of (*R*,*R*)-lithium amide **48** and LiCl (4 equivalents) at −78 °C provided a 39% yield of ketone **8c**, following acidification.



48

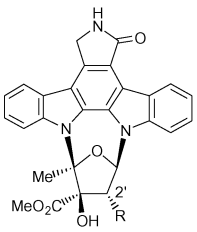
The enantiomeric excess of the ketone was established by HPLC to be 87%, and the absolute configuration was tentatively assigned as shown in Scheme 1 by correlation with material obtained from the asymmetric hydroboration reactions. Unfortunately, further screening failed to uncover conditions under which higher yields of ketone **13** can be obtained, and we have not yet been able to test additional cyclic sulfate substrates.

(v) Biological screening of indolocarbazoles

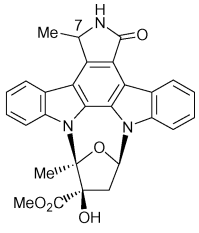
As mentioned earlier, our motivation for exploring the indolocarbazole area was to generate both new chemistry, especially involving desymmetrisation reactions, and new biologically active entities that would mimic the natural products. Both K-252a and staurosporine are potent protein kinase inhibitors, the latter compound having also been ascribed immunosuppressive activity,[38] and multidrug resistance reversal (MDR) activities.[39] We expected that the new indolocarbazoles would mimic K-252a, although some of our compounds somewhat resemble 'hybrid' systems of these two natural products. The limited biological screening carried out focused primarily on kinase inhibitory activity.

The protein kinases constitute a large family of structurally related enzymes responsible for controlling signal transduction within the cell. Inhibition of protein kinases is a well established approach for medicinal chemistry targets in a number of areas, for example, protein kinase C (PKC) is implicated in a number of key cell responses, including gene expression and cell proliferation, and established PKC inhibitors display antiproliferative activity against human tumor cell lines *in vitro*.[40]

A major obstacle blocking the potential application of kinase inhibitors in medicine is the problem of selectivity in inhibiting a particular enzyme. This arises because many inhibitors work by competing with ATP at a catalytic domain that is largely conserved across many kinase families and isoforms.[41] Although many K-252a derivatives have been prepared, the need to further probe the 'chemical space' around various regions of the molecule was identified by Wood and co-workers, who reported a number of interesting biologically active systems, including C-2′ and C-7 (either C-7 stereochemistry) modified compounds, such as **49** and **50**.[42]



49 R = Me, Et, $(CH_2)_2OH$



50

We considered that our carbocyclic analogues would enable us to further probe such effects (although with the limitations of the indolocarbazole having the symmetrical imide ring, rather than the naturally occurring lactam system).

The first group of compounds to be screened arose from our initial studies on the N-benzyl and N–H series of compounds shown in Schemes 1 and 3, Table 3.

Firstly, it should be noted that the N-benzyl series of compounds, including **6a–8a** and **15a** were inactive in these screens. This was expected, since there is usually a prerequisite for a free NH function in the indolocarbazole lactam or imide group for significant biological activity. Most likely this NH engages in hydrogen bonding to the peptide backbone of the kinase (mimicking the N-6 amino group of ATP) by analogy with the published crystal structures of staurosporine bound to CDK2 (cyclin-dependent kinase 2)[43] and PKA (cyclic AMP dependent kinase),[44] and K-252a bound to the tyrosine kinase domain of the hepatocyte growth factor receptor c-Met.[45]

Table 3 IC_{50} (nM) values for selected indolocarbazoles

Compound	PKC	p56lck	p60src	KDR	FGFr-2
K-252a **2**	23	440	809	521	447
Alkene **6b**	108	9239	>10 000	739	>10 000
Alcohol **7b**	46	838	>10 000	78	958
Ketone **8b**	66	400	3105	51	312
Ester **15b**	53	1648	>10 000	94	521

Table 4

Compound	MAPKAP-K2 (IC_{50} μM)	p38 MAPK (IC_{50} μM)	Akt (IC_{50} μM)	FGFr (IC_{50} μM)
30	63.6	14.5	0.36	0.14
31	17.2	14.7	1.20	—
32	24.1	15.0	9.70	—
33	13.0	12.0	0.29	—
34	45.5	15.8	>20	5.72
35	41.9	10.6	1.40	>20

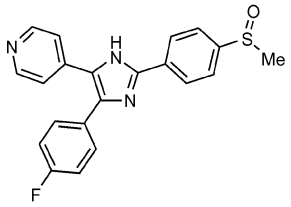
The NH series of compounds shown in Table 3 showed good PKC inhibitory activity, with alcohol **7b** and hydroxyester **15b** being the most potent, and having activities (as racemic compounds) of the same order of magnitude as K-252a. As shown, we also assayed against a number of tyrosine kinases, including p56lck, which is a T-cell specific member of the Src kinase family, p60src, FGFr-2, and recombinant Kinase Domain Receptor (KDR). Again, our new compounds showed significant levels of activity, for example ketone **8b** had an IC_{50} of 51 nM against KDR kinase, this being substantially more potent than K-252a itself. This suggests that our compounds are potential inhibitors of angiogenesis *via* their effects on VEGF receptor tyrosine kinases.[46]

On the whole, selectivity profiles for these compounds are unremarkable, although both the alcohol **7b** and the ester **15b** showed enhanced selectivity for other tyrosine kinases over p60src, compared to K-252a. In a separate screen we also established that some of the later compounds also displayed PKC and PKA inhibitory activities, including the aminoalcohol **36**, which showed an IC_{50} of 295 nM, which appears lower than the activities in Table 3 (although the values are not strictly comparable).

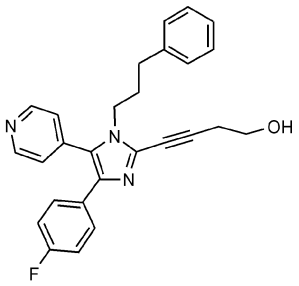
The N–H imide series of indolocarbazoles **30–35** arising from the cyclic sulfate ring opening phase of the study were also submitted to screening against the mitogen activated protein kinases MAPKAP-K2 and p38 MAPK, and against Akt and tyrosine kinase FGFr (Table 4).

Mitogen activated protein kinases are kinase enzymes which form part of the complex MAPK signalling pathway. *In vivo* (in cells), MAPAP-K2 is predominately regulated by p38 MAPK.[47] Activation of this pathway leads to the production of inflammatory cytokines like IL-1 (interleukin-1) and TNF-α (tumour necrosis factor-α). Inhibitors of either of these enzymes are expected to be of use in the control of arthritis and COPD (chronic obstructive pulmonary disease).

Micromolar inhibition was observed with all of the compounds in both the MAPKAP-K2 and p38 MAPK screens, with thiocyanate **33** being the most active against MAPKAP-K2 and sulfite **35** being the most active against p38 MAPK. Sulfite **35** and azide **30** showed a four-fold level of selectivity for p38 MAPK over MAPKAP-K2. The levels of inhibition observed in the indolocarbazole analogues are much lower than the low nanomolar p38 inhibitors SB 203580 **51** and RWJ 67657 **52**.[48]

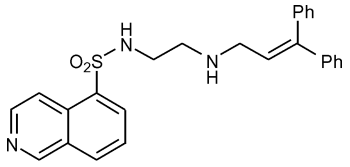


51



52

Akt, also known as protein kinase B, is an anti-apoptotic protein kinase that has strongly elevated activity in human malignancies such as breast cancer and ovarian cancer.[49] Thiocyanate **33** and azide **30** displayed the greatest level of inhibition of Akt, by an order of magnitude, with IC_{50} values of 0.29 and 0.36 μM respectively. The levels of inhibition observed compare well with those of known inhibitors, for example NL-71-101 **53**, a selective inhibitor of PKB in ovarian cancer cell lines, has an IC_{50} of 3.7 μM.[50]



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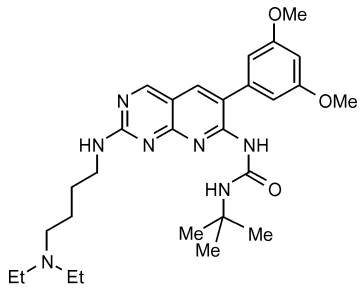
FGFr (Fibroblast Growth Factor receptor) is a receptor tyrosine kinase. The binding of FGF to FGFr results in activation of the kinase leading to the stimulation of a signalling cascade, which is implicated in the formation of blood vessels (angiogenesis). It is believed that inhibition of FGFr may cause a reduction in blood vessel growth, which would, in turn, slow tumour growth.[51] Of the three compounds tested, azide **30** displayed the greatest level of inhibition by an order of magnitude (IC_{50} = 0.14 μM). Reports on potent and selective inhibitors of receptors involved in neovascularisation, such as FGFr, are less prevalent in the literature, and the discovery of tyrosine kinase inhibitors that can inhibit angiogenesis remains a fertile area for drug discovery. However, Parke–Davis have shown that the selective FGFr inhibitor PD 173074 **54** (IC_{50} = 29 nM), currently in animal trials, is a promising candidate for use in the treatment of cancer.[52]



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Overall, the preliminary screening gave some pleasing results, with some of our new compounds showing high levels of potency and some interesting selectivities. Whether specific examples of these compounds can be further refined for clinical applications remains to be seen.

Experimental

General procedures

Melting points were obtained from a Melt Temp II machine or a Stewart Scientific SPM3 and are uncorrected. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Infrared spectra were recorded using a Perkin Elmer 1600 series FTIR spectrophotometer as sample solutions in chloroform, unless otherwise stated, and are reported in cm^{-1}. Optical rotations were recorded using a JASCO DIP370 digital polarimeter.

High resolution mass spectra were acquired on a VG Micromass LCT, VG Micron Autospec or AEI MS-902 mass spectrometer, using electrospray (ES), electron impact (EI) or fast atom bombardment (FAB), using *meta*-nitrobenzyl alcohol as the matrix.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 or Bruker DRX 500 machine. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or d_6-DMSO. Chemical shifts are given in ppm downfield from tetramethylsilane, using either TMS or a residual protic solvent as an internal standard. *J* values are recorded in Hz and quoted to the nearest 0.1. Where necessary, proton and carbon assignments were assisted with ^{1}H COSY, DEPT or NOE sequences.

Enantiomeric excesses were determined by high performance liquid chromatography (HPLC), using a Diacel Chiralpak AD column, at temperatures ranging from 20–30 °C as stated. Detection was by UV at the stated frequency and data was processed using a HP-3D Dos chemstation.

Reaction progress was monitored by thin layer chromatography (TLC), using Polygram Sil G/UV_{254} plates which were visualised using a combination of ultraviolet light, iodine and potassium permanganate. Flash column chromatography was performed using indicated solvent systems on Fluka silica gel 60 (220–240 mesh).

Organic solvents were dried as follows: THF and Et_2O (sodium-benzophenone ketyl), CH_2Cl_2 (DCM) (CaH_2), DMF (calcium sulfate), PhMe (sodium), morpholine (KOH). Petrol refers to petroleum ether (bp 40–60 °C), which was distilled before use. Brine, saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, 2N HCl and 2N NaOH were stock solutions in distilled H_2O.

A number of the indolocarbazole substrates, in particular the free imide series, do not have mass spectrometry data despite exhaustive investigations with a variety of ionisation techniques. The high melting points of the compounds, generally >250 °C, meant that CI and EI techniques were not powerful enough to volatilise the samples. The insolubility of indolocarbazole substrates in aqueous acetonitrile, the solvent system used in ES, meant that molecular ion peaks corresponding to the indolocarbazole substrates were never observed. FAB was by far the most successful technique often resulting in observation of molecular ion peaks, however, the solubility of indolocarbazole substrates in *meta*-nitrobenzyl alcohol, the matrix in FAB, was poor and in some cases compounds were insoluble, thus molecular ion peaks were not observed.

Biological assay methods

Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from either Sigma Chemical Company or Calbiochem, and we used a commercially available assay system available from Amersham International. PKC catalyses the transfer of the γ-phosphate (^{33}P) of ATP to the threonine group on a peptide specific for PKC. Phosphorylated peptide is bound to phosphocellulose paper and then quantified by scintillation counting. The other kinase assays employed kinases as GST-fusion products purified from NS0 cells.

Tyrosine kinase assays were conducted under conditions previously described.[53]

12,13-(Cyclopent-3′-ene-2′α,5′α-diyl)-6-(benzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 6a

Indolocarbazole **4a** (2.63 g, 6.33 mmol) was suspended in dry DMF (250 mL) with stirring under an N_2 atmosphere. A 60% dispersion of NaH (0.53 g, 13.30 mmol) was added in one portion and the reaction mixture was stirred for 30 minutes, before the addition of *cis*-dibromocyclopentene **5** (2.15 g, 9.50 mmol). The reaction mixture was stirred overnight before being quenched with MeOH (5 mL), concentrated *in vacuo* and partitioned between $CHCl_3$ (300 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography using a $CHCl_3$ solvent system, to give alkene **6a** as a yellow solid (2.70 g, 89%). A portion of the solid was recrystallised from acetone–water to give yellow needles: mp 309–312 °C; (found: *m/z* (FAB$^+$) M$^+$ 479.1630. $C_{32}H_{21}N_3O_2$ requires 479.1634); $\nu_{max}(CHCl_3)/cm^{-1}$ 1752, 1697, 1573, 1459, 1383, 1346, 1306; δ_H(d_6-DMSO, 500 MHz) 2.75 (1H, d, *J* 13.9, 1′-H_α), 3.18 (1H, dt, *J* 13.9, 6.4, 1′-H_β), 4.91 (s, 2H, CH_2Ph), 6.27 (2H, d, *J* 6.4, 2′-H and 5′-H), 6.46 (2H, s, 3′-H and 4′-H), 7.30 (1H, t, *J* 7.2, Ph), 7.37–7.45 (6H, m, 3-H, 9-H and Ph), 7.68 (2H, dd, *J* 8.2, 7.7, 2-H and 10-H), 8.04 (2H, d, *J* 8.2, 1-H and 11-H) and 9.08 (2H, d, *J* 8.0, 4-H and 8-H); δ_C(d_6-DMSO, 125 MHz) 40.6 (1′-CH_2), 41.6 (CH_2Ph), 59.3 (2′-CH and 5′-CH), 110.8 (CH), 117.0 (C), 119.5 (C), 121.3 (CH), 121.8 (C), 125.6 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 129.6 (CH), 129.8 (C), 136.8 (CH), 138.4 (C), 140.9 (C), 170.2 (CO); (found: C, 79.82; H, 4.40; N, 8.68. $C_{32}H_{21}N_3O_2$ requires C, 80.17; H, 4.38; N, 8.77%); *m/z* (FAB$^+$) 480 (M$^+$ + H, 15%), 479 (M$^+$, 58), 402 (4), 389 (3) and 149 (11).

12,13-(Cyclopent-3′-ene-2′α,5′α-diyl)-5*H*-indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7(6*H*)-dione 6b

To a stirred solution of indolocarbazole **4b** (0.33 g, 1.0 mmol) dry DMF (30 mL), under a nitrogen atmosphere, was added 60% dispersion of NaH in mineral oil (0.126 g, 3.15 mmol), and the resulting mixture was stirred at room temperature for 45 min. Then *cis*-dibromocyclopentene **5** (0.23 g, 1.00 mmol) was added and the reaction mixture was stirred overnight before being quenched with brine (100 mL). The organic solvent was separated, the solvent removed *in vacuo*, and the residue dissolved in EtOAc (100 mL). The organic solution was washed with H_2O (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (4 : 1 $CHCl_3$–EtOAc) gave the alkene **6b** as a yellow solid (0.09 g, 23%). A portion of the solid was recrystallised from acetone–water to give yellow needles: mp 380–381 °C; (found: *m/z* (FAB$^+$) M$^+$ + H 390.1235. $C_{25}H_{15}N_3O_2$ requires 390.1243); $\nu_{max}(CHCl_3)/cm^{-1}$ 3696, 3438, 2927, 2871, 1754, 1718, 1602, 1460, 1348, 1319, 1062, 1000 and 914; δ_H(d_6-DMSO, 400 MHz) 2.71 (1H, d, *J* 14.0, 1′-H_α), 3.14 (1H, dt, *J* 14.0, 6.5, 1′-H_β), 6.23 (2H, d *J* 6.5, 2′-H and 5′-H), 6.42 (2H, s, 3′-H and 4′-H), 7.38 (2H, dd, *J* 8.0, 7.5, 3-H and 9-H), 7.63 (2H, dd, *J* 8.0, 7.5, 2-H and 10-H), 8.00 (2H, d, *J* 8.0, 1-H and 11-H), 9.07 (2H, d, *J* 8.0, 4-H and 8-H) and 11.06 (1H, s, NH); δ_C(d_6-DMSO, 126 MHz), 39.7 (1′-CH_2), 58.3 (2′- and 5′-CH), 109.8 (1-CH and 11-CH), 115.8 (C), 119.9 (C), 120.3 (3-CH and 9-CH), 121.0 (C), 124.8 (4-CH and 8-CH), 126.8 (2-CH and 10-CH), 128.9 (C), 135.9 (CH=), 139.8 (C) and 171.0 (CO); *m/z* (FAB+) 390 (M$^+$ + H, 6%), 389 (M$^+$ 8%), 329 (7), 307 (25) and 289 (14).

12,13-(Cyclopent-3′-ene-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 6c

Indolocarbazole **4c** (2.00 g, 4.49 mmol) was dissolved in dry DMF (100 mL), with stirring under N_2 and NaH (0.38 g, 9.43 mmol) was added in one portion. The reaction mixture was stirred for 0.5 h before the addition of *cis*-dibromocyclopentene **5** (1.52 g, 6.74 mmol) and then stirred overnight. TLC analysis showed consumption of starting material, MeOH (1 mL) was added to quench the reaction before concentration *in vacuo* to give a brown solid which was redissolved in $CHCl_3$ (200 mL) and washed with H_2O (200 mL) and brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid. The crude product was purified by flash column chromatography using a $CHCl_3$ solvent system to give alkene **6c** as a yellow

solid (1.66 g 73%). A portion of the solid was recrystallised from acetone–water to give **6c** as yellow needles: mp 289 °C decomp; (found: *m/z* (EI$^+$) M$^+$ 509.1712 $C_{33}H_{23}N_3O_3$ requires 509.1739); ν_{max}($CHCl_3$)/cm^{-1} 1751, 1694, 1459, 1383, 1346, 1089, 979; δ_H(d_6-DMSO, 400 MHz) 2.73 (1H, d, *J* 14.1, 1′-H$_\alpha$), 3.16 (1H, dt, *J* 14.1, 6.6, 1′-H$_\beta$), 3.72 (3H, s, OMe), 4.79 (2H, s, *CH*$_2$Ar), 6.24 (2H, d, *J* 6.6, 2′-H and 5′-H), 6.43 (2H, s, 3′-H and 4′-H), 6.92 (2H, d, *J* 8.7, PMB), 7.35–7.42 (4H, m, PMB, 3-H and 9-H), 7.65 (2H, dd, *J* 8.3, 7.3, 2-H and 10-H), 8.02 (2H, d, *J* 8.3, 1-H and 11-H), 9.06 (2H, d, *J* 7.9, 4-H and 8-H); δ_C(d_6-DMSO, 100 MHz) 40.6 (1′-CH_2), 41.1 (CH_2Ar), 56.0 (OMe), 59.3 (2′-CH and 5′-CH), 110.8 (CH), 114.9 (CH), 116.9 (C), 119.4 (C), 121.3 (CH), 121.8 (C), 125.6 (CH), 127.9 (CH), 129.8 (C), 130.0 (CH), 130.4 (C), 136.8 (CH), 140.9 (C), 159.5 (C) 170.1 (CO); (found: C, 77.33; H, 4.47; N, 8.14. $C_{33}H_{23}N_3O_3$ requires C, 77.80; H, 4.52; N, 8.25%); *m/z* (EI$^+$) 510 (M$^+$ + H, 36%), 509 (M$^+$, 100), 389 (6), 149 (5), 121 (10).

12,13-(3′β-Hydroxycyclopentan-2′α,5′α-diyl)-6-(benzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo [3,4-*c*]carbazole-5,7(6*H*)-dione 7a

To a stirred suspension of the alkene **6a** (0.70 g, 1.46 mmol) in THF (35 mL) under an N_2 atmosphere was added a 1.0 M solution of BH_3–THF (7.31 mL, 0.73 mmol), and the reaction mixture was stirred at rt. After 3 h the reaction mixture had become homogeneous and TLC analysis showed consumption of starting material. MeOH (4.0 mL) was added cautiously and the solution stirred for 15 min before the addition of 2 M NaOH (11.0 mL) and 30% H_2O_2 (2.89 mL). After 1 h, TLC analysis showed the reaction had gone to completion and most of the solvent was removed *in vacuo* to leave a crude residue. The residue was dissolved in DCM (100 mL) and the organic mixture washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product as an orange solid. Purification by flash column chromatography using a 4 : 1 DCM–EtOAc solvent system afforded alcohol **7a** as an orange solid (0.48 g, 69%): mp 306–308 °C; ν_{max}($CHCl_3$)/cm^{-1} 3696, 3606, 1751, 1696, 1602, 1573, 1384, 1351, 1315; (found: *m/z* (FAB$^+$) M$^+$ 497.1761. $C_{32}H_{23}N_3O_3$ requires 497.1739); δ_H(d_6-DMSO, 500 MHz) 2.00 (1H, dd, *J* 15.5, 6.3, 4′-H$_\alpha$), 2.41 (1H, dd, *J* 15.5, 7.7, 4′-H$_\beta$), 2.68 (1H, d, *J* 14.4, 1′-H$_\alpha$), 3.18 (1H, ddd, *J* 14.4, 7.3, 6.5, 1′-H$_\beta$), 4.24 (1H, m, 3′-H), 4.79 (2H, s, C*H*$_2$Ph), 5.35 (1H, d, *J* 6.5, 2′-H), 5.67 (1H, d, *J* 2.7, OH), 5.92 (1H, dd, *J* 7.7, 7.3, 5′-H), 7.29 (1H, t, *J* 6.9, Ph), 7.35–7.44 (6H, m, 3-H, 9-H and Ph), 7.63 (1H, dd, *J* 8.2, 7.6, 10-H), 7.68 (1H, dd, *J* 8.2, 7.5, 2-H), 7.95 (2H, app t, *J* 8.2, 1-H and 11-H), 8.99 (1H, d, *J* 7.9, 8-H), 9.04 (1H, d, *J* 7.9, 4-H); δ_C(d_6-DMSO, 125 MHz) 37.8 (1′-CH_2), 41.5 (CH_2Ph), 42.8 (4′-CH_2), 56.2 (5′-CH), 65.3 (2′-CH), 76.7 (3′-CH), 110.7 (CH), 111.0 (CH), 116.2 (C), 116.6 (C), 119.2 (C), 119.3 (C), 121.2 (CH), 121.5 (CH), 121.8 (C), 122.1 (C), 125.4 (CH), 125.5 (CH), 127.9 (CH), 127.9 (CH), 128.2 (CH), 128.9 (C), 129.5 (CH), 129.6 (C), 138.4 (C), 140.9 (C), 141.4 (C), 170.1 (CO), 170.1 (CO); *m/z* (FAB$^+$) 498 (M$^+$ + H, 20%), 497 (M$^+$, 25), 391 (4), 329 (5), 176 (13), 120 (11), 91 (21), 77 (22).

12,13-(3′β-Hydroxycyclopentan-2′α,5′α-diyl)-5*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 7b

To a stirred suspension of the alkene **6b** (0.2 g, 0.51 mmol) in dry tetrahydrofuran (20 mL) under a nitrogen atmosphere, was added a 1.0 M solution of borane in tetrahydrofuran (2.54 mL, 2.54 mmol) and the resulting mixture was stirred at room temperature. After 45 min, the mixture had become homogeneous and TLC analysis indicated that the starting material had been consumed. Methanol (3 mL) was added cautiously and the solution stirred for 15 min, before the addition of a 2 M aqueous solution of sodium hydroxide (3.82 mL, 7.34 mmol), followed by a 27% aqueous solution of hydrogen peroxide (0.96 mL, 7.34 mmol). After 30 min, TLC analysis indicated that the reaction was complete and so most of the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and the organic mixture washed with water (2 × 50 mL), 2.0 M aqueous hydrochloric acid (50 mL) and brine (50 mL). The organic extract was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to give the crude product. Purification by flash chromatography (2 : 1 $CHCl_3$–ethyl acetate), gave the product as a yellow solid (0.153 g, 74%). A portion was recrystallised from a mixture of acetone–water, to give **7b** as a yellow crystalline solid: mp 370–371 °C; (found: *m/z* (FAB$^+$) M$^+$ 407.1270. $C_{32}H_{17}N_3O_3$ requires 407.1270); ν_{max}($CHCl_3$)/cm^{-1} 3438, 2927, 1754, 1720, 1602, 1352, 1317 and 680; δ_H(d_6-DMSO, 400 MHz) 1.98 (1H, dd, *J* 15.5, 6.5, 4′-H$_\alpha$), 2.39 (1H, dd, *J* 15.5, 8.0, 4′-H$_\beta$), 2.63 (1H, d, *J* 15.0, 1′-H$_\alpha$), 3.15 (1H, ddd, *J* 15.0, 7.5, 6.5, 1′-H$_\beta$), 4.42 (1H, m, 3′-H), 5.35 (1H, d, *J* 6.5, 2′-H), 5.63 (1H, d, *J* 3.0, OH), 5.90 (1H, dd, *J* 8.0, 7.5, 5′-H), 7.35–7.43 (2H, m, 3-H and 9-H), 7.59–7.62 (2H, m, 2-H and 10-H), 7.91–7.96 (2H, m, 1-H and 11-H), 9.00–9.07 (2H, m, 4-H and 8-H) and 11.05 (1H, s, NH); δ_C(d_6-DMSO, 126 MHz) 37.0 (1′-CH_2), 41.9 (4′-CH_2), 55.3 (5′-CH), 64.4 (2′-CH), 75.8 (3′-CH), 109.8 (CH), 110.1 (CH), 115.1 (C), 115.4 (C), 119.7 (C), 119.8 (C), 120.3 (CH), 120.6 (CH), 121.1 (C), 121.4 (C), 124.6 (CH), 126.76 (CH), 126.81 (CH), 128.0 (C), 128.7 (C), 139.9 (C), 140.3 (C), 171.0 (CO) and 171.1 (CO); *m/z* (FAB$^+$) 408 (M$^+$ + H, 5%), 407 (M$^+$ 5%), 307 (27), 289 (13), 275 (11) and 176 (11).

12,13-(3′β-Hydroxycyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 7c

To a stirred suspension of the alkene **6c** (1.50 g, 2.95 mmol) in THF (150 mL) under an N_2 atmosphere was added a 1.0 M solution of BH_3·THF (14.7 mL, 14.73 mmol), and the reaction mixture was stirred at rt. After 45 min the reaction mixture had become homogeneous and TLC analysis showed consumption of starting material. MeOH (15 mL) was added cautiously and the solution stirred for 10 min before the dropwise addition of 2 M NaOH (23.4 mL) and 30% H_2O_2 (5.9 mL). After 0.5 h TLC analysis showed the reaction had gone to completion and most of the solvent was removed *in vacuo* to leave a crude residue. The residue was dissolved in DCM (200 mL) and the organic mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as an orange solid. Purification by flash column chromatography using a 2% MeOH–DCM solvent system afforded the product **7c** as an orange solid (1.13 g, 73%). A portion of the solid was recrystallised from acetone–water to give **7c** as yellow needles: mp 298–301 °C; (found: *m/z* (FAB$^+$) M$^+$ 527.1850. $C_{33}H_{25}N_3O_4$ requires 527.1845); ν_{max}($CHCl_3$)/cm^{-1} 3617, 1750, 1691, 1384, 1350, 1315; δ_H(d_6-DMSO, 400 MHz) 2.04 (1H, dd, *J* 15.4, 6.0, 4′-H$_\alpha$), 2.43 (1H, dd, *J* 15.4, 7.9, 4′-H$_\beta$), 2.78 (1H, d, *J* 14.2, 1′-H$_\alpha$), 3.21 (1H, ddd, *J* 14.2, 7.0, 6.5, 1′-H$_\beta$), 3.75 (3H, s, OMe), 4.25 (1H, d, *J* 6.0, 3′-H), 4.82 (2H, s, C*H*$_2$Ar), 5.37 (1H, d, *J* 6.5, 2′-H), 5.56 (1H, bs, OH), 5.91 (1H, dd, *J* 7.9, 7.0, 5′-H), 6.93 (2H, d, *J* 8.7, PMB), 7.38 (2H, d, *J* 8.7, PMB), 7.39 (1H, dd, *J* 8.3, 7.2, 9-H), 7.44 (1H, dd, *J* 7.8, 7.3, 3-H), 7.64 (1H, dd, *J* 8.5, 7.2, 10-H), 7.69 (1H, dd, *J* 8.2, 7.3, 2-H), 7.94 (1H, d, *J* 8.5, 11-H), 7.96 (1H, d, *J* 8.2, 1-H), 9.04 (1H, d, *J* 8.3, 8-H), 9.09 (1H, d, *J* 7.8, 4-H); δ_C(d_6-DMSO, 100 MHz) 37.8 (1′-CH_2), 41.0 (CH_2Ar), 42.8 (4′-CH_2), 56.0 (OMe), 56.2 (5′-CH), 65.3 (2′-CH), 76.7 (3′-CH), 110.7 (CH), 111.0 (CH), 114.9 (CH), 116.2 (C), 116.5 (C), 119.2 (C), 119.4 (C), 121.2 (CH), 121.5 (CH), 121.8 (C), 122.1 (C), 125.5 (CH), 127.9 (CH), 127.9 (CH), 128.9 (C), 129.6 (C), 129.8 (CH), 130.4 (C), 140.9 (C), 141.4 (C), 159.4 (C), 170.1 (CO), 170.2 (CO); *m/z* (FAB$^+$) 527 (M$^+$ 5%), 154 (18), 133 (4), 120 (5), 74 (7).

Non-racemic 7c *via* asymmetric hydroboration

$(Ipc)_2BH$ (0.56 g, 1.96 mmol) was dissolved with stirring under N_2, in freshly distilled THF (5 mL) and cooled to 0 °C. A

THF solution (10 mL) of alkene **6c** (0.10 g, 0.20 mmol) was added dropwise and the reaction mixture was stirred for 5 h. The reaction mixture was quenched by the careful addition of MeOH (2 mL) and stirred for 10 min before the dropwise addition of 2 N NaOH (3.13 mL) and 30% H_2O_2 (0.8 mL). The reaction mixture was stirred for 0.5 h before being concentrated *in vacuo*, and partitioned between DCM (100 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous Na_2SO_3 solution (2 × 100 mL), saturated aqueous $NaHCO_3$ solution (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to give a yellow solid which was purified by flash column chromatography using a 1 : 1 EtOAc–petrol solvent system. The desired alcohol was obtained as a yellow solid (86.0 mg, 83%; 33% ee, HPLC 80 : 19 : 1 hexane–^{i}PrOH–MeCN, AD column). $[\alpha]_D^{26}$ −0.70 (*c* 0.57, THF). The spectroscopic data were identical to those described above.

12,13-(3′Cyclopentan-2′α,5′α-diyl-one)-6-(benzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 8a

Alcohol **7a** (0.31 g, 0.62 mmol) was suspended in DCM (30 mL) with stirring under an N_2 atmosphere. DMP (0.52 g, 1.24 mmol) was added in one portion and the reaction mixture was stirred overnight. TLC analysis showed consumption of the starting material and the reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (25 mL). The resulting solution was stirred vigorously for 0.5 h before being partitioned between DCM (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (2 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange solid which was purified by flash column chromatography using a DCM solvent system to give ketone **8a** as a yellow solid (0.205 g, 67%): mp 315–317 °C; (found *m*/*z* (FAB$^+$) M$^+$ 495.1573. $C_{32}H_{21}N_3O_3$ requires 495.1583); $\nu_{max}(CHCl_3)/cm^{-1}$ 1755, 1698, 1603, 1573, 1460, 1384, 1349; δ_H(d$_6$-DMSO, 400 MHz) 2.50 (1H, dd, *J* 19.3, 2.9, 4′-H$_\alpha$), 3.09 (1H, dd, *J* 15.0, 2.9, 1′-H$_\alpha$), 3.26 (1H, dd, *J* 19.3, 6.8, 4′-H$_\beta$), 3.53 (1H, ddd, *J* 15.0, 8.1, 6.5, 1′-H$_\beta$), 4.80 (2H, s, C*H*$_2$Ph), 5.61 (1H, d, *J* 8.1, 2′-H), 6.17 (1H, dd, *J* 6.8, 6.5, 5′-H), 7.27–7.31 (1H, m, Ph), 7.35–7.46 (6H, m, 3-H, 9-H and Ph), 7.66 (1H, ddd, *J* 8.4, 7.2, 1.0, 10-H), 7.69 (1H, ddd, *J* 8.4, 7.2, 1.0, 2-H), 7.91 (1H, d, *J* 8.4, 11-H), 7.99 (1H, d, *J* 8.4, 1-H), 9.02 (1H, d, *J* 7.9, 8-H), 9.03 (1H, d, *J* 7.9, 4-H); δ_C(d$_6$-DMSO, 126 MHz) 37.3 (1′-CH$_2$), 41.5 (CH$_2$Ph), 45.0 (4′-CH$_2$), 54.1 (5′-CH), 58.4 (2′-CH), 110.9 (CH), 111.0 (CH), 116.6 (C), 116.9 (C), 119.3 (C), 119.9 (C), 121.7 (CH), 121.8 (CH), 121.9 (C), 125.4 (CH), 125.5 (CH), 128.2 (CH), 129.0 (C), 129.3 (C), 129.5 (CH), 138.3 (C), 141.0 (C), 141.2 (C), 170.0 (CO), 215.0 (CO); *m*/*z* (FAB$^+$) 496 (M$^+$ + H, 13%), 495 (M$^+$, 13), 154 (57), 107 (30), 92 (6), 91 (29), 77 (19).

12,13-(3′-Oxocyclopentan-2′α,5′α-diyl)-5*H*-indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7(6*H*)-dione 8b

To a stirred suspension of the alkene **6b** (0.45 g, 1.16 mmol) in dry tetrahydrofuran (40 mL) under a nitrogen atmosphere was added a 1.0 M solution of borane in tetrahydrofuran (5.8 mL, 5.8 mmol) and the stirring continued at room temperature. After 30 min, methanol (6 mL) was added and the mixture was stirred for 10 min, before the addition of a 2.0 M aqueous solution of sodium hydroxide (8.7 mL, 17.4 mmol), followed by a 27% aqueous solution of hydrogen peroxide (2.2 mL, 17.4 mmol). The reaction mixture was stirred for 20 min, then neutralised by dropwise addition of concentrated hydrochloric acid. Most of the solvent was removed *in vacuo* and the remaining residue extracted with ethyl acetate (2 × 75 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to give the crude orange alcohol **7b** (0.477 g). This alcohol was then dissolved in dry dichloromethane (150 mL) and in one portion was added Dess–Martin periodinane (1.0 g, 2.32 mmol) and the mixture was stirred for 90 min at room temperature. A saturated aqueous solution of sodium thiosulfate (20 mL) was added and the mixture was stirred for 20 min. The organic layer was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to yield the crude ketone. Purification by flash chromatography (4 : 1 CH_2Cl_2–ethyl acetate), gave the ketone **8b** as a yellow solid (0.333 g, 71%, 2 steps): mp 376–377 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 405.1115. $C_{25}H_{14}N_3O_3$ requires 405.1113); $\nu_{max}(CHCl_3)/cm^{-1}$ 3435, 2935, 1759, 1720, 1602, 1461, 1350 and 1320; δ_H(d$_6$-DMSO, 400 MHz) 2.47 (1H, dd, *J* 19.0, 2.5, 4′-H$_\alpha$), 3.04 (1H, dd, *J* 15.0, 2.5, 1′-H$_\alpha$), 3.23 (1H, dd, *J* 19.0, 6.5, 4′-H$_\beta$), 3.48 (1H, ddd, *J* 15.0, 8.0, 6.5, 1′-H$_\beta$), 5.59 (1H, d, *J* 8.0, 2′-H), 6.15 (1H, dd, *J* 6.5, 6.5, 5′-H), 7.38–7.44 (2H, m, 3-H and 9-H), 7.62–7.68 (2H, m, 2-H and 10-H), 7.90–7.98 (2H, m, 1-H and 11-H), 9.04–9.06 (2H, m, 4-H and 8-H) and 11.09 (1H, s, NH); δ_C(d$_6$-DMSO, 126 MHz) 36.6 (1′-CH$_2$), 44.3 (4′-CH$_2$), 53.4 (5′-CH), 59.9 (2′-CH), 110.1 (CH), 110.2 (CH), 115.7 (C), 116.0 (C), 120.0 (C), 120.6 (CH), 120.9 (CH), 121.0 (CH), 121.4 (C), 121.4 (C), 124.8 (CH), 124.9 (CH), 127.2 (CH), 127.4 (CH), 128.2 (C), 128.5 (C), 140.2 (C), 140.4 (C), 171.0 (CO) and 214.4 (CO); *m*/*z* (FAB$^+$) 405 (M$^+$, 27%), 307 (16), 220 (14), 219 (55) and 176 (12).

12,13-(3′-Oxocyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 8c

Alcohol **7c** (0.79 g, 1.51 mmol) was dissolved in dichloromethane (60 mL) with stirring under an N_2 atmosphere, and Dess–Martin periodinane (0.96 g, 2.26 mmol) was then added in one portion and the reaction mixture was stirred for 2 h. TLC analysis then showed consumption of the starting material and the reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (25 mL) and stirred vigorously for 30 minutes before being partitioned between dichloromethane (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (2 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange solid, which was purified by flash column chromatography (CH_2Cl_2) to yield ketone **8c** as a yellow solid (0.57 g, 72%): mp 319–321 °C; (found: *m*/*z* (EI$^+$) M$^+$ 525.1663. $C_{33}H_{23}N_3O_4$ requires 525.1689); $\nu_{max}(CHCl_3)/cm^{-1}$ 1753, 1697, 1461, 1384 and 1349; δ_H(d$_6$-DMSO, 400 MHz) 2.50 (1H, dd, *J* 19.3, 3.1, 4′-H$_\alpha$), 3.07 (1H, dd, *J* 15.0, 3.1, 1′-H$_\alpha$), 3.25 (1H, dd, *J* 19.3, 6.5, 4′-H$_\beta$), 3.52 (1H, ddd, *J* 15.0, 8.2, 6.5, 1′-H$_\beta$), 3.74 (3H, s, OMe), 4.76 (2H, s, C*H*$_2$Ar), 5.59 (1H, d, *J* 8.1, 2′-H), 6.14 (1H, app t, *J* 6.5, 5′-H), 6.92 (2H, d, *J* 8.7, PMB), 7.35 (2H, d, *J* 8.7, PMB), 7.40 (1H, dd, *J* 7.9, 7.0, 9-H), 7.44 (1H, dd, *J* 7.9, 7.0, 3-H) 7.63 (1H, dd, *J* 8.4, 7.0, 10-H), 7.68 (1H, dd, *J* 8.4, 7.0, 2-H), 7.89 (1H, d, *J* 8.4, 11-H), 7.97 (1H, d, *J* 8.4, 1-H), 9.04 (1H, d, *J* 7.9, 8-H), 9.05 (1H, d, *J* 7.9, 4-H); δ_C(d$_6$-DMSO, 100 MHz) 37.3 (1′-CH$_2$), 41.0 (CH$_2$Ar), 45.0 (4′-CH$_2$), 54.1 (5′-CH), 56.0 (OMe), 58.4 (2′-CH), 110.8 (CH), 111.0 (CH), 114.9 (CH), 116.6 (C), 116.9 (C), 119.3 (C), 119.9 (C), 121.6 (CH), 121.8 (CH), 121.9 (C), 125.4 (CH), 125.5 (CH), 128.1 (CH), 128.2 (CH), 128.9 (C), 129.2 (C), 129.9 (CH), 130.3 (C), 141.0 (C), 141.2 (C), 159.4 (C), 169.9 (CO), 215.0 (CO); (found: C, 74.89; H, 4.42; N, 7.99. $C_{33}H_{23}N_3O_4$ requires C, 75.43; H, 4.38; N, 8.00%); *m*/*z* (EI$^+$) 526 (M$^+$ + H, 11%), 525 (43), 509 (100).

Non-racemic ketone 8c by chiral base rearrangement of cyclic sulfate 20

A mixture of chiral lithium amide **48** and LiCl was prepared by treatment of a solution of the appropriate secondary amine–HCl salt (88.0 mg, 0.34 mmol) in THF (1 mL) at −78 °C under N_2 with ^{n}BuLi (1.27 M in hexanes) (0.52 mL, 0.66 mmol). The mixture was allowed to warm to room temperature for 0.5 h before being recooled to −78 °C and then a solution of cyclic sulfate **20** (50.0 mg, 0.08 mmol) in THF (15 mL) pre-cooled to −78 °C was added dropwise. After 4 h the reaction mixture was quenched with H_2O (1 mL) and 20% H_2SO_4 (3.3 mL) was added. The reaction mixture was allowed to warm to room

temperature with stirring for 18 h and was then partitioned between EtOAc (75 mL) and H_2O (75 mL). The organic layer was washed with H_2O (75 mL), saturated aqueous $NaHCO_3$ solution (75 mL), brine (75 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid which was purified by flash column chromatography using a 2–10% MeOH–CH_2Cl_2 solvent system to give firstly ketone **8c** (17.0 mg, 39%), $[a]_D^{26}$ −62.9 (*c* 0.60, $CHCl_3$), mp >280 °C, with spectroscopic data identical to those described previously. The enantiomeric excess was determined as 87% by HPLC, using a Chiralpak AD column and a solvent of MeCN–EtOH–Et_2NH (95 : 5 : 0.1), with a flow rate of 0.5 mL/min [retention times 21 min (minor) and 29 min (major)].

Diol **5** was also recovered (5.0 mg, 11%).

11,12-(Cyclopent-3′-ene-2′α,5′α-diyl)indolo[2,3-*a*]carbazole 10

To a stirred solution of indolocarbazole **9** (0.3 g, 0.78 mmol) in dry DMF (20 mL) under a nitrogen atmosphere, was added 60% dispersion of NaH in mineral oil (0.063 g, 1.6 mmol), and the resulting mixture was stirred at room temperature for 10 min. Then *cis*-dibromocyclopentene **5** (0.265 g, 1.2 mmol) was added and the reaction mixture was stirred for a further 3 h. The organic solvent was removed *in vacuo*, and the residue dissolved in $CHCl_3$ (100 mL). The organic solution was washed with H_2O (2 × 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (3 : 1 petroleum ether–ethyl acetate) gave the alkene **10** as a yellow solid (0.084 g, 33%). A portion of the solid was recrystallised from petroleum ether–ethyl acetate to give **10** as off-white needles: mp 309–310 °C; (found: *m*/*z* (EI$^+$) M$^+$ 320.1315. $C_{23}H_{16}N_2$ requires 320.1313); $\nu_{max}(CHCl_3)$/cm^{-1} 3063, 2968, 1602, 1564, 1434, 1398, 1343, 1225, 1207, 1131, 1049 and 827; δ_H($CDCl_3$, 400 MHz) 2.68 (1H, d, *J* 13.5, 1′-H_α), 3.06 (1H, dt, *J* 13.5, 6.5, 1′-H_β), 5.78 (2H, d *J* 6.5, 2′-H and 5′-H), 6.18 (2H, s, 3′-H and 4′-H), 7.17–7.23 (2H, m, 3-H and 8-H), 7.40 (2H, ddd, *J* 8.0, 7.5, 1.0, 2-H and 9-H), 7.51 (2H, d, *J* 8.0, 1-H and 10-H), 7.86 (2H, s, 5-H and 6-H) and 8.09 (2H, d, *J* 8.0, 4-H and 7-H); δ_C(d_6-acetone, 68 MHz) 40.9 (1′-CH_2), 58.6 (2′-CH and 5′-CH), 109.1 (CH), 112.0 (CH), 119.2 (CH), 120.3 (CH), 120.9 (C), 124.4 (C), 124.9 (CH), 125.1 (C), 135.9 (1′-CH and 2′-CH), 139.2 (C); *m*/*z* (EI$^+$) 320 (M$^+$, 100%), 293 (16), 255 (40) and 160 (15).

12,13-(3′α-Hydroxycyclopentan-2′α,5′α-diyl)-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 11

To a stirred suspension of the ketone **8a** (0.05 g, 0.1 mmol) in dry tetrahydrofuran (20 mL), at 0 °C under a nitrogen atmosphere, was added a 1.0 M solution of borane in tetrahydrofuran (0.3 mL, 0.3 mmol) and the stirring continued at 0 °C. After 2 h, the reaction appeared complete by TLC analysis and so water (0.5 mL), was added and the mixture was stirred for 10 min. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (30 mL). The organic layer was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield the crude product. Purification by flash chromatography (2.5% ethyl acetate in dichloromethane), gave the alcohol **11** as a yellow solid (0.047 g, 94%). A portion was recrystallised from a mixture of chloroform–dichloromethane, to give **11** as yellow needles: mp 264–265 °C; (found: *m*/*z* (FAB$^+$) 497.1727. $C_{32}H_{23}N_3O_3$ requires 497.1739); $\nu_{max}(CHCl_3)$/cm^{-1} 2928, 1750, 1697, 1574, 1462, 1385, 1351, 1097 and 908; δ_H(d_6-DMSO, 400 MHz) 1.27 (1H, dd, *J* 14.5, 7.0, 4′-H_α), 2.61 (1H, br d, *J* 15.5, 1′-H_α), 2.89–2.95 (2H, m, 1′-H_β and 4′-H_β), 4.66 (1H, m, 3′-H), 4.92–4.95 (3H, m, C*H*$_2$Ph and OH), 5.47 (1H, t, *J* 5.5, 2′-H), 5.65 (1H, t, *J* 7.0, 5′-H), 7.27 (1H, t, *J* 7.0, Ph), 7.33–7.42 (6H, m, Ar), 7.59–7.63 (2H, m, 2-H and 10-H), 7.85–7.89 (2H, m, 1-H and 11-H) and 9.02–9.08 (2H, m, 4-H and 8-H); δ_C(d_6-DMSO, 126 MHz) 37.5 (1′-CH_2), 40.4 (*C*H$_2$Ph), 41.1 (4′-CH_2), 53.9 (5′-CH), 60.0 (2′-CH), 72.5 (3′-CH), 110.2 (CH), 111.4 (CH), 116.0 (C), 116.2 (C), 118.6 (C), 118.9 (C), 120.6 (CH), 120.8 (CH), 121.5 (C), 124.7 (CH), 125.0 (CH), 127.2 (CH), 127.4 (CH), 127.8 (CH), 128.7 (C), 129.1 (CH), 130.1 (C), 138.0 (C), 140.4 (C), 143.1 (C), 169.9 (CO) and 170.0 (CO); *m*/*z* (FAB$^+$) 498 (M$^+$ + H, 17%), 497 (M$^+$, 20%), 307 (34), 289 (18), 176 (12), 120 (12) and 91 (14).

12,13-(3′α-Hydroxy-3′β-vinyl-cyclopentan-2′α,5′α-diyl)-6-(phenylmethyl)-5*H*-indolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 12

To a stirred solution of the ketone **8a** (0.05 g, 0.1 mmol) in dry tetrahydrofuran (12.5 mL) at −78 °C under a nitrogen atmosphere, was added a 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (10.5 mL, 0.5 mmo1), and the stirring continued at −78 °C. After 4 h, a saturated aqueous solution of NH_4Cl (1 mL) was added and reaction mixture was allowed to warm to room temperature. Most of the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to give the crude product. Purification by flash chromatography (1 : 1 ethyl acetate–petroleum ether), gave the allylic alcohol **12** as a yellow solid (0.028 g, 54%). A portion of the solid was recrystallised from a mixture of chloroform–petroleum ether, to give **12** as a yellow crystalline solid: mp 297–298 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 523.1896. $C_{35}H_{25}N_3O_3$ requires 523.1896); $\nu_{max}(CHCl_3)$/cm^{-1} 3577, 3445, 2940, 1750, 1694, 1574, 1494, 1462, 1385, 1351, 1111, 1068, 1021 and 943; δ_H($CDCl_3$, 400 MHz) 1.53 (1H, br s, OH), 1.95 (1H, br d, *J* 15.5, 4′-H_α), 2.71 (1H, dd, *J* 15.0, 2.0, 1′-H_α), 2.95–3.08 (2H, m, 1′-H_β and 4′-H_β), 4.78 (2H, collapsed AB, *J* 15.0, CHaHbPh), 5.15 (1H, d, *J* 6.5, 2′-H), 5.41 (1H, d, J_{cis} 10.5, CH=), 5.50–5.57 (2H, m, 5′-H and CH=), 6.37 (1H, dd, *J* 17.0, 10.5, CH=), 7.33 (3H, m, Ar), 7.34 (1H, m, Ar), 7.42 (1H, m, Ar), 7.48–7.54 (3H, m, Ar), 7.55–7.62 (3H, m, Ar), 9.15 (1H, d, *J* 8.0, 4-H or 8-H) and 9.26 (1H, d, *J* 8.0, 4-H or 8-H); δ_C($CDCl_3$, 68 MHz) 37.2 (1′-CH_2), 40.7 (CH_2Ph), 44.8 (4′-CH_2), 54.4 (5′-CH), 63.7 (2′-CH), 80.7 (3′-C), 109.8 (CH), 110.9 (CH), 112.6 (=CH_2), 115.6 (C), 115.8 (C), 118.3 (C), 120.2 (CH), 120.3 (CH), 121.1 (C), 124.2 (CH), 124.5 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 128.5 (C), 128.6 (CH), 129.7 (C), 137.5 (C), 140.0 (C), 142.5 (C), 144.3 (=CH), 169.4 (CO) and 169.5 (CO); *m*/*z* (FAB$^+$) 524 (M$^+$ + H, 25%), 523 (M$^+$, 29%), 452 (2), 413 (4), 329 (5), 207 (5), 176 (23), 120 (16), 107 (29), 91 (42), 73 (53), 69 (51), 67 (24), 57 (81) and 55 (64).

12,13-[3′α-Hydroxy-3′β-(nitromethyl)-cyclopentan-2′α,5′α-diyl]-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 13

To a stirred solution of the ketone **8a** (0.2 g, 0.4 mmol) in a mixture of dry tetrahydrofuran (40 mL) and dry nitromethane (40 mL) under a nitrogen atmosphere, was added sodium ethoxide (0.137 g, 2 mmol) and the stirring continued at room temperature. After 75 min, TLC analysis suggested that the reaction was complete and so a 2.0 M aqueous solution of hydrochloric acid (1 mL) was added to neutralise the reaction mixture. The solvent was removed *in vacuo* to yield a crude residue and water (35 mL) was added. The mixture was extracted with dichloromethane (2 × 35 mL) and the combined extracts were washed with water (35 mL), brine (35 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to yield the crude product. Recrystallisation from a mixture of acetone–water gave the product **13** as orange needles (0.168 g, 75%): mp 265–267 °C; (found: C, 70.52; H, 4.87; N, 9.07. $C_{33}H_{24}N_4O_5$ + acetone requires C, 70.33; H, 4.92; N, 9.12%); (found: *m*/*z* (FAB$^+$) M$^+$ 556.1742. $C_{33}H_{24}N_4O_5$ requires 556.1747); $\nu_{max}(CHCl_3)$/cm^{-1} 2927, 1752, 1698, 1559, 1462, 1384, 1352, 1315 and 1111; δ_H(d_6-DMSO, 400 MHz) 1.80 (1H, br d, *J* 15.0, 4′-H_α), 2.73 (1H, br d, *J* 15.0, 1′-H_α), 2.91 (1H, dd, *J* 15.5, 7.5, 4′-H_β), 3.20 (1H, m,

1′-H_β), 4.93 (2 H, s, CH_2Ph), 4.97 (1H, d, *J* 12.0, C*Ha*HbNO$_2$), 5.21 (1H, d, *J* 12.0, CHa*Hb*NO$_2$), 5.47 (1H, s, OH), 5.70 (1H, dd, *J* 7.5, 7.0, 5′-H), 5.74 (1H, d, *J* 7.0, 2′-H), 7.27 (1H, t, *J* 7.5, Ph), 7.33–7.42 (6H, m, Ar), 7.60–7.65 (2H, m, 2-H and 10-H), 7.83 (1H, d, *J* 8.5, 1-H or 11-H), 7.88 (1H, d, *J* 8.5, 1-H or 11-H) and 9.04–9.07 (2H, m, 4-H and 8-H); δ_C(d$_6$-DMSO, 68 MHz) 37.2 (1′-CH_2), 40.6 (CH_2Ph), 44.4 (4′-CH_2), 54.3 (5′-CH), 60.8 (2′-CH), 80.2 (3′-C), 82.9 (CH_2NO_2), 109.7 (CH), 110.6 (CH), 115.6 (C), 115.8 (C), 118.2 (C), 120.3 (CH), 120.4 (CH), 121.1 (C), 124.3 (CH), 124.5 (CH), 126.9 (CH), 127.0 (CH), 127.2 (CH), 128.5 (C), 128.6 (CH), 129.6 (C), 137.5 (C), 140.0 (C), 142.3 (C), 169.3 (CO) and 169.4 (CO); *m*/*z* (FAB$^+$) 557 (M$^+$ + H, 6%), 556 (M$^+$, 5%), 460 (5), 419 (4), 176 (11), 120 (11) and 91 (14).

12,13-[3′β-Cyano-3′α-(trimethylsiloxy)-cyclopentan-2′α,5′α-diyl]-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 14a

To a stirred suspension of the ketone **8a** (0.2 g, 0.4 mmol) in dry dichloromethane (40 mL) under a nitrogen atmosphere, was added a catalytic quantity of potassium cyanide (*ca.* 1 mg), followed by a catalytic quantity of 18-crown-6 (*ca.* 1 mg). The mixture was cooled to −45 °C, trimethylsilyl cyanide (0.12 mL, 0.9 mmol) was added dropwise and the stirring continued at −45 °C. After 1 h, TLC analysis indicated that the reaction was complete, so the reaction mixture was allowed to warm to 0 °C, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was stirred for 10 min. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), water (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to yield the *O*-trimethylsilylcyanohydrin **14a** as a yellow solid (0.231 g, 96%). A portion of the solid was recrystallised from a mixture of acetone–water to give **14a** as yellow needles: mp 310–311 °C; (found: C, 72.43; H, 4.98; N, 9.43. $C_{36}H_{30}N_4O_3Si$ requires C, 72.7; H, 5.09; N, 9.43%); (found: *m*/*z* (FAB$^+$) M$^+$ 594.2086. $C_{36}H_{30}N_4O_3Si$ requires 594.2087); ν_{max}($CHCl_3$)/cm^{-1} 2959, 1752, 1697, 1575, 1461, 1385, 1351, 1126, 1112, 944 and 870; δ_H($CDCl_3$, 400 MHz) −0.30 (9H, s, $SiMe_3$), 1.82 (1H, dt, *J* 15.5, 2.0, 4′-H_α), 2.86 (1 H, dd, *J* 15.5, 2.0, 1′-H_α), 3.23–3.34 (2H, m, 1′-H_β and 4′-H_β), 4.99 (2H, s, CH_2Ph), 5.61–5.65 (2H, m, 2′-H and 5′-H), 7.25–7.28 (1H, m, Ph), 7.33–7.37 (2H, m, Ar), 7.39–7.44 (2H, m, Ar), 7.51–7.63 (6H, m, Ar) and 9.22–9.25 (2H, m, 4-H and 8-H); δ_C($CDCl_3$, 68 MHz) 0.2 ($SiMe_3$), 36.8 (1′-CH_2), 41.2 (*C*H_2Ph), 46.8 (4′-CH_2), 53.6 (5′-CH), 64.4 (2′-CH), 74.9 (3′-C), 108.2 (CH), 109.5 (CH), 117.2 (C), 117.4 (C), 119.3 (C), 119.6 (C), 121.0 (CH), 121.2 (CH), 121.9 (C), 122.1 (C), 122.2 (C), 125.5 (CH), 125.9 (CH), 127.1 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH), 137.4 (C), 139.9 (C), 142.4 (C), 169.5 (CO) and 169.6 (CO); *m*/*z* (FAB$^+$) 595 (M$^+$ + H, 86%), 495 (M$^+$, 100%), 517 (8), 454 (11), 452 (13), 329 (9), 207 (10), 176 (30), 120 (16), 107 (33), 91 (54), 73 (77), 69 (26), 57 (36) and 55 (36).

12,13-[3′β-Cyano-3′α-(trimethylsilyloxy)-cyclopentan-2′α,5′α-diyl]-6-(trimethylsilyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 14b

To a stirred suspension of the ketone **8b** (0.183 g, 0.452 mmol) in dry dichloromethane (100 mL) under a nitrogen atmosphere, was added a catalytic quantity of potassium cyanide (*ca.* 1 mg), followed by a catalytic quantity of 18-crown-6 (*ca.* 1 mg). The mixture was cooled to −40 °C and trimethylsilylcyanide (0.181 mL, 1.36 mmol) was added dropwise and the stirring continued at −40 °C. After 1.5 h, TLC analysis indicated that the reaction was incomplete, so additional trimethylsilylcyanide (0.28 mL) was added and the reaction mixture was warmed to 0 °C over 4 h. Water (50 mL) was added and the mixture allowed to warm to room temperature, then stirred for 10 min. The organic layer was washed with water (4 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*, to yield *N*-trimethylsilyl-*O*-trimethylsilylcyanohydrin **14b** as a yellow solid (0.247 g, 95%); (found: *m*/*z* (FAB$^+$) M$^+$ 576.2044. $C_{32}H_{32}N_4O_3Si_2$ requires 576.2013); δ_H($CDCl_3$, 400 MHz) −0.30 (9H, s, $SiMe_3$), 0.65 (9H, s, $SiMe_3$), 1.85 (1H, br d, *J* 15.5, 4′-H_α), 2.86 (1H, dd, *J* 15.5, 2.0, 1′-H_α), 3.24–3.36 (2H, m, 1′-H_β and 4′-H_β), 5.64–5.67 (2H, m, 2′-H and 5′-H), 7.41–7.46 (2H, m, Ar), 7.52–7.62 (4H, m, Ar) and 9.24–9.28 (2H, m, 4-H and 8-H); *m*/*z* (FAB$^+$) 577 (M$^+$ + H, 3%), 576 (M$^+$, 5%), 207 (12), 147 (26), 136 (19), 133 (7), 91 (11), 90 (11), 75 (8), 74 (8), 73 (100) and 59 (8).

12,13-[3′α-Hydroxy-3′β-(methoxycarbonyl)cyc1opentan-2′α,5′α-diyl]-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 15a

A stirred solution of the *O*-trimethylsilylcyanohydrin **14a** (0.05 g, 0.1 mmol) in a mixture of tetrahydrofuran (10 mL), methanol (5 mL) and concentrated hydrochloric acid (5 mL), was heated to reflux. After 24 h, a precipitate had formed and the heating was discontinued. After cooling, the precipitate was removed by filtration and the filtrate was returned to reflux. The precipitate was washed with a minimum of methanol and left to dry. After a total time at reflux of 72 h, additional precipitate had formed, and the heating was again discontinued. This second batch of precipitate was removed by filtration and washed and dried as before. The solids were combined to give the α-hydroxymethylester **15a**, as a yellow solid (0.04 g, 87%). A portion of the product was recrystallised from a mixture of tetrahydrofuran–petroleum ether, to give **15a** as a yellow crystalline solid: mp 305–307 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 555.1788. $C_{34}H_{25}N_3O_5$ requires 555.1794); ν_{max}($CHCl_3$)/cm^{-1} 2930, 1749, 1697, 1575, 1463, 1385, 1352, 1155, 1110, 1068 and 945; δ_H(d$_6$-DMSO, 400 MHz) 1.72 (1H, br d, *J* 15.0, 4′-H_α), 2.78 (1H, dd, *J* 15.5, 2.0, 1′-H_α), 3.06 (1H, m, 1′-H_β), 3.15 (1H, dd, *J* 15.0, 7.0, 4′-H_β), 3.86 (3H, s, Me), 4.87 (2H, s, CH_2Ph), 5.55 (1H, s, OH), 5.73 (1H, d, *J* 7.0, 2′-H), 5.81 (1H, t, *J* 7.0, 5′-H), 7.26 (1H, m, Ph), 7.33–7.41 (6H, m, Ar), 7.58–7.63 (2H, m, 2-H and 10-H), 7.77 (1H, d, *J* 8.5, 1-H or 11-H), 7.88 (1H, d, *J* 8.0, 1-H or 11-H) and 9.02–9.04 (2H, m, 4-H and 8-H); δ_C(d$_6$-DMSO, 126 MHz) 39.0 (1′-CH_2), 40.8 (*C*H_2Ph), 45.6 (4′-CH_2), 52.9 (Me), 55.5 (5′-CH), 62.0 (2′-CH), 81.3 (3′-C), 110.0 (CH), 110.6 (CH), 115.8 (C), 118.4 (C), 120.5 (CH), 120.7 (CH), 121.3 (C), 121.4 (C), 124.5 (CH), 124.7 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 128.7 (C), 128.8 (CH), 129.9 (C), 137.6 (C), 140.3 (C), 142.3 (C), 169.5 (CO) and 175.5 (CO); *m*/*z* (FAB$^+$) 556 (M$^+$ + H, 8%), 555 (M$^+$, 10%), 453 (3), 452 (3), 329 (3), 123 (11), 121, (13), 107 (26) and 91 (38).

12,13-[3′α-Hydroxy-3′β-(methoxycarbonyl)cyclopentan-2′α,5′α-diyl]-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 15b

A stirred solution of the *N*-trimethylsilyl-*O*-trimethylsilylcyanohydrin **14b** (0.05 g, 0.086 mmol) in a mixture of tetrahydrofuran (5 mL), methanol (5 mL) and concentrated hydrochloric acid (2.5 mL) was heated to reflux. After 5 d, TLC analysis suggested that the reaction was complete, so the heating was discontinued and the solvent removed *in vacuo*, furnishing a crude product. The crude mixture was purified by flash chromatography (2 : 1 $CHCl_3$–ethyl acetate), to give the α-hydroxymethylester **15b** as a yellow solid (0.023 g, 57%): mp 329–330 °C; (found: *m*/*z* (FAB$^+$) M$^+$ + H 466.1359. $C_{27}H_{20}N_{30}O_5$ requires 466.1403); ν_{max}($CHCl_3$)/cm^{-1} 3437, 2930, 2867, 1754, 1720, 1572, 1462, 1352, 1320, 1112 and 1002; δ_H(d$_6$-DMSO, 400 MHz) 1.74 (1H, d, *J* 15.0, 4′-H_α), 2.76 (1H, d, *J* 14.0, l′-H_α), 3.06 (1H, dt, *J* 14.0, 7.0, l′-H_β), 3.15 (1H, dd, *J* 15.0, 7.0, 4′-H_β), 3.86 (3H, s, Me), 5.56 (1H, s, OH), 5.74 (1H, d, *J* 7.0, 2′-H), 5.83 (1H, t, *J* 7.0, 5′-H), 7.37–7.42 (2H, m, 3-H and 9-H), 7.58–7.64 (2H, m, 2-H and 10-H), 7.77 (1H, d, *J* 8.5, 1-H or 11-H), 7.89 (1H, d, *J*, 8.0, 1-H or 11-H), 9.04–9.07 (2H, m, 4-H and 8-H) and 11.05 (1H, s, NH); δ_C(d$_6$-DMSO, 126 MHz) 39.1 (1′-CH_2), 45.6 (4′-CH_2), 52.9 (Me), 55.5 (5′-CH), 62.0 (2′-CH), 81.4 (3′-C),

110.0 (CH), 110.6 (CH), 115.6 (C), 115.7 (C), 119.8 (C), 120.5 (CH), 120.6 (CH), 121.4 (C), 121.5 (C), 124.6 (CH), 124.9 (CH), 126.9 (CH), 127.1 (CH), 128.7 (C), 129.9 (C), 140.3 (C), 142.2 (C), 171.3 (CO) and 175.5 (CO); *m/z* (FAB$^+$) 466 (M$^+$ + H, 3%), 465 (M$^+$, 3%), 329 (5), 308 (8), 307 (32), 289 (15) and 176 (11).

12,13-(3′β,4′β-Epoxycyclopentane-2′α,5α′-diyl)-6-(benzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7 (6*H*)-dione 16a

Alkene **6a** (50.0 mg, 0.11 mmol), 2,6-di-*tert*-butyl-4-methylphenol (2.0 mg, 0.01 mmol) and *m*CPBA (22.0 mg, 0.13 mmol) were dissolved in $CHCl_3$ (7 mL) and the reaction mixture was heated to reflux for 4 h. TLC analysis showed the presence of starting material so a further portion of *m*CPBA (44.0 mg) and 2,6-di-*tert*-butyl-4-methylphenol (4.0 mg) was added and the reaction mixture was returned to reflux overnight. Starting material was still present after the overnight reflux and so further equivalents of *m*CPBA (44.0 mg) were added and the mixture was heated to reflux for a further 5 h. The reaction mixture was cooled and quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), which was stirred vigorously for 30 min before being partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (50 mL), saturated aqueous $Na_2S_2O_3$ solution (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography using a DCM solvent system to give **16a** as a yellow solid (10.0 mg, 19%): mp 297–300 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2926, 2854, 1753, 1697, 1384, 1349; δ_H(d_6-DMSO, 500 MHz) 2.59 (1H, d, *J* 15.0, 1′-H$_\alpha$), 2.81 (1H, dt, *J* 15.0, 6.6, 1′-H$_\beta$), 3.83 (2H, s, 3′-H and 4′-H), 4.95 (2H, s, C*H*$_2$Ph), 5.96 (2H, d, *J* 6.6, 2′-H and 5′-H), 7.31 (1H, t, *J* 7.3, Ph), 7.39 (2H, dd, *J* 7.6, 7.3, Ph), 7.44–7.48 (4H, m, 2-H, 10-H and Ph), 7.71 (2H, dd, *J* 7.9, 7.5, 3-H and 9-H), 8.13 (2H, d, *J* 8.4, 1-H and 11-H), 9.11 (2H, d, *J* 7.9, 4-H and 8-H); δ_C(d_6-DMSO, 125 MHz) 35.0 (1′-CH_2), 41.7 (CH_2Ph), 54.8 (CH), 56.1 (CH), 111.1 (CH), 116.9 (C), 119.6 (C), 121.8 (CH), 122.0 (C), 125.5 (CH), 128.2 (CH), 129.2 (C), 129.5 (CH), 138.3 (C), 141.4 (C), 170.2 (CO).

12,13-(3′β,4′β-Epoxycyclopentane-2′α,5α′-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 16c using *m*CPBA

Alkene **6c** (50.0 mg, 0.10 mmol), 2,6-di-*tert*-butyl-4-methylphenol (2.0 mg, 0.01 mmol) and *m*CPBA (22.0 mg, 0.13 mmol) were dissolved in $CHCl_3$ (7 mL) and the reaction mixture was heated to reflux for 4 h. TLC analysis showed the presence of starting material so a further portion of *m*CPBA (44.0 mg) and 2,6-di-*tert*-butyl-4-methylphenol (4.0 mg) was added and the reaction mixture was returned to reflux overnight. Starting material was still present after the overnight reflux and so a further portion of *m*CPBA (44.0 mg) was added and the mixture heated at reflux for a further 5 h. The reaction mixture was cooled and quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), which was stirred vigorously for 30 min before being partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (50 mL), saturated aqueous $Na_2S_2O_3$ solution (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography using a DCM solvent system to give **16c** as a yellow solid (10.0 mg, 17%): mp 315–318 °C; (found: *m/z* (FAB$^+$) M$^+$ 525.1699. $C_{33}H_{23}N_3O_4$ requires 525.1689); $\nu_{max}(CHCl_3)/cm^{-1}$ 1752, 1696, 1574, 1462, 1384, 1349; δ_H(d_6-DMSO, 400 MHz) 2.55 (1H, d, *J* 14.5, 1′-H$_\alpha$), 2.80 (1H, dt, *J* 14.5, 6.8, 1′-H$_\beta$), 3.74 (3H, s, OMe), 3.82 (2H, s, 3′-H and 4′-H), 4.82 (2H, s, C*H*$_2$Ar), 5.94 (2H, d, *J* 6.8, 2′-H and 5′-H), 6.93 (2H, d, *J* 8.6, PMB), 7.37 (2H, d, *J* 8.6, PMB), 7.45 (2H, dd, *J* 7.7, 7.5, 3-H and 9-H), 7.70 (2H, dd, *J* 8.1, 7.5, 2-H and 10-H), 8.11 (2H, d, *J* 8.1, 1-H and 11-H), 9.09 (2H, d, *J* 7.7, 4-H and 8-H); δ_C(d_6-DMSO, 100 MHz) 35.0 (1′-CH_2), 41.1 (CH_2Ar), 54.8 (3′-CH and 4′-CH), 56.0 (OMe), 56.1 (2′-CH and 5′-CH), 111.0 (CH), 114.9 (CH), 116.9 (C), 119.6 (C), 121.7 (CH), 122.0 (C), 125.5 (CH), 128.2 (CH), 129.1 (C), 129.9 (CH), 130.3 (C), 141.4 (C), 159.5 (C), 170.1 (CO); *m/z* (FAB$^+$) 526 (M$^+$ + H, 3%), 525 (7), 447 (7), 307 (11), 176 (17), 155 (20), 154 (64), 136 (53), 121 (17).

Epoxidation using DMDO

Alkene **6c** (50.0 mg, 0.10 mmol) was dissolved in DCM (5 mL) and cooled to 0 °C before the addition of freshly prepared DMDO solution in acetone (~0.1 M) (4.9 mL) with stirring. The reaction mixture was stirred for 2 h at 0 °C before being allowed to warm to rt. TLC analysis showed starting material still present so the reaction mixture was recooled to 0 °C and a further 5 mL of DMDO solution were added and the reaction mixture was allowed to warm to rt overnight. TLC analysis showed consumption of starting material. The reaction mixture was concentrated *in vacuo* to give a brown solid and purified using flash column chromatography with a DCM solvent system to give epoxide **16c** as a yellow solid (24.0 mg 47%). The spectroscopic data were identical to those described above.

12,13-(3′β-Hydroxy,4′α-azidocyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 17

Epoxide **16c** (30.0 mg 0.06 mmol) was suspended in DCM (3 mL) with stirring under N_2. $TMSN_3$ (0.03 mL, 0.20 mmol) and $BF_3{\cdot}OEt_2$ (0.03 mL, 0.20 mmol) were added and the reaction was stirred for 18 h. TLC analysis showed consumption of starting material, and the reaction mixture was concentrated *in vacuo* to give a brown solid which was purified by flash column chromatography using a 2% MeOH–DCM solvent system to afford **17** as a yellow solid (0.013 g, 40%); mp 267–269 °C; (found: *m/z* (FAB$^+$) M$^+$ 568.1836. $C_{33}H_{24}N_6O_4$ requires 568.1859); $\nu_{max}(CHCl_3)/cm^{-1}$ 3449, 2930, 2108, 1750, 1695, 1385, 1350; δ_H(d_6-DMSO, 500 MHz) 2.76 (1H, d, *J* 14.8, 1′-H$_\alpha$), 3.28 (1H, ddd, *J* 14.8, 7.5, 6.5, 1′-H$_\beta$), 3.74 (3H, s, OMe), 3.87 (1H, dd, *J* 5.3, 4.8, 3′-H), 4.45 (1H, dd, *J* 5.9, 5.3, 4′-H), 4.84 (2H, s, C*H*$_2$Ar), 5.40 (1H, d, *J* 7.5, 2′-H), 5.93 (1H, dd, *J* 6.5, 5.9, 5′-H), 6.35 (1H, d, *J* 4.8, OH), 6.94 (2H, d, *J* 8.8, PMB), 7.39 (2H, d, *J* 8.8, PMB), 7.45 (2H, dd, *J* 8.4, 7.2, 3-H and 9-H), 7.70 (2H, dd, *J* 8.2, 7.2, 2-H and 10-H), 7.94 (1H, d, *J* 8.2, 11-H), 7.95 (1H, d, *J* 8.2, 1-H), 9.07 (1H, d, *J* 8.4, 8-H), 9.09 (1H, d, *J* 8.4, 4-H); δ_C(d_6-DMSO, 125 MHz) 36.3 (1′-CH_2), 41.0 (CH_2Ar), 56.0 (OMe), 59.6 (5′-CH), 63.1 (2′-CH), 72.2 (4′-CH), 83.6 (3′-CH), 111.1 (CH), 111.2 (CH), 114.9 (CH), 116.6 (C), 116.8 (C), 119.5 (C), 119.6 (C), 121.6 (CH), 121.7 (CH), 122.0 (C), 125.4 (CH), 125.5 (CH), 128.0 (CH), 128.2 (CH), 129.3 (C), 129.6 (C), 129.9 (CH), 130.4 (C), 141.0 (C), 142.6 (C), 159.5 (C), 170.1 (CO), 170.2 (CO); *m/z* (FAB$^+$) 569 (M$^+$ + H, 8%), 568 (M$^+$, 12), 419 (5), 329 (5), 289 (15), 137 (52), 108 (5), 77 (13).

Azide 17 *via* opening of cyclic sulfate 20

Cyclic sulfate **20** (0.48 g, 0.79 mmol) was dissolved in dry DMF (50 mL) with stirring under N_2. NaN_3 (0.52 g, 7.92 mmol) was added and the reaction mixture was heated to 80 °C for 5 h. TLC showed consumption of starting material. The reaction mixture was allowed to cool to rt and concentrated *in vacuo* to give a brown solid. The brown solid was redissolved in THF (20 mL), 20% H_2SO_4 (5 mL) was added and the resulting mixture was stirred vigorously for 18 h. The reaction mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL) and the organic layer was washed with H_2O (200 mL), saturated aqueous $NaHCO_3$ solution (150 mL), brine (2 × 200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude azido alcohol. Purification by flash column chromatography using a

5% MeOH–DCM solvent system yielded **17** as an orange solid (0.41 g, 91%). The spectroscopic data were identical to those described above.

12,13-(3′β,4′β-Dihydroxycyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 18

Indolocarbazole **6c** (0.37 g, 0.73 mmol) was suspended in THF (20 mL) and NMMO (0.15 g, 1.10 mmol), OsO_4 (^{t}BuOH solution, 1 mL = 0.1 mmol) (0.10 mL) and H_2O (0.1 mL) were added. The reaction mixture was stirred for 2 h before the addition of saturated aqueous $Na_2S_2O_3$ solution (15 mL) and then stirred for a further 0.5 h. The reaction mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL) and the organic layer was washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product. The crude material was purified by flash column chromatography using a 2% MeOH–DCM solvent system to afford **18** as an orange solid (0.38 g, 95%). A portion of the solid was recrystallised from acetone–water to give **18** as yellow needles: mp 260–262 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 543.1802. $C_{33}H_{25}N_3O_5$ requires 543.1794); ν_{max}($CHCl_3$)/cm^{-1} 2936, 1752, 1695, 1384, 1350, 1088; δ_H(d_6-DMSO, 500 MHz) 2.57 (1H, d, *J* 14.5, 1′-H$_\alpha$), 3.36 (1H, dt, *J* 14.5, 7.3, 1′-H$_\beta$), 3.73 (3H, s, OMe), 4.12 (2H, d, *J* 3.6, 3′-H and 4′-H), 4.76 (2H, s, C*H*$_2$Ar), 5.42 (2H, d, *J* 7.3, 2′-H and 5′-H), 5.52 (2H, d, *J* 3.6, OH), 6.92 (2H, d, *J* 8.7, PMB), 7.35 (2H, d, *J* 8.7, PMB), 7.42 (2H, dd, *J* 7.8, 7.4, 3-H and 9-H), 7.67 (2H, dd, *J* 8.2, 7.4, 2-H and 10-H), 7.86 (2H, d, *J* 8.2, 1-H and 11-H), 9.04 (2H, d, *J* 7.8, 4-H and 8-H); δ_C(d_6-DMSO, 125 MHz) 35.7 (1′-CH_2), 41.0 (CH_2Ar), 55.9 (OMe), 64.3 (2′-CH and 5′-CH), 78.1 (3′-CH and 4′-CH), 110.7 (CH), 114.9 (CH), 116.4 (C), 119.4 (C), 121.4 (CH), 122.0 (C), 125.5 (CH), 127.9 (CH), 129.6 (C), 129.8 (CH), 130.3 (C), 141.1 (C), 159.4 (C), 170.1 (CO); (found: C, 70.80; H, 5.01; N, 6.92. $C_{33}H_{25}N_3O_5\cdot H_2O$ requires C, 70.58; H, 4.81; N, 7.49%); *m*/*z* (FAB$^+$) 544 (M$^+$ +H, 17%), 543 (34), 524 (6).

12,13-((3′β,4′β)Tetrahydrocyclopenta[3′,4′,2]dioxathiole-2-oxide-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 19

Diol **18** (0.67 g, 1.24 mmol) was dissolved in THF (40 mL), $SOCl_2$ (1.35 mL, 18.56 mmol) was added and the reaction mixture was heated to reflux for 18 h. The solid yellow **19** that precipitated out of the reaction mixture was collected by filtration and washed with THF (10 mL), Et_2O (10 mL) and petrol (10 mL). The reaction mixture was partially concentrated *in vacuo* and a second crop of product was collected and washed with THF (10 mL), Et_2O (10 mL) and petrol (10 mL). The mother liquors were concentrated *in vacuo* and purified by flash column chromatography using a 2% MeOH–DCM solvent system to give cyclic sulfite **19** as a yellow solid. The batches were combined to give **19** as a 2.4 : 1 mixture of diastereoisomers (0.72 g, 98%): *major isomer* mp 340 °C decomp.; (found: *m*/*z* (FAB$^+$) M$^+$ 589.1311. $C_{33}H_{23}N_3O_6S$ requires 589.1308); ν_{max}(solid)/cm^{-1} 1691, 1386, 1242, 1213, 979, 801, 741; δ_H(d_6-DMSO, 400 MHz) 2.90 (1H, d, *J* 15.6, 1′-H$_\alpha$), 3.30 (1H, dt, *J* 15.6, 7.4, 1′-H$_\beta$), 3.74 (3H, s, OMe), 4.80 (2H, s, C*H*$_2$Ar), 5.52 (2H, d, *J* 1.6, 3′-H and 4′-H), 5.93 (2H, d, *J* 7.4, 2′-H and 5′-H), 6.94 (2H, d, *J* 8.8, PMB), 7.36 (2H, d, *J* 8.8, PMB), 7.47 (2H, dd, *J* 7.9, 7.3, 3-H and 9-H), 7.71 (2H, dd, *J* 8.4, 7.3, 2-H and 10-H), 7.96 (2H, d, *J* 8.4, 1-H and 11-H), 9.07 (2H, d, *J* 7.9, 4-H and 8-H); δ_C(d_6-DMSO, 100 MHz) 35.5 (CH_2), 41.2 (CH_2Ar), 56.0 (OMe), 61.2 (CH), 89.8 (CH), 111.0 (CH), 115.0 (CH), 117.1 (C), 119.7 (C), 122.1 (CH), 122.3 (C), 125.6 (CH), 128.5 (CH), 129.5 (C), 129.8 (CH), 130.3 (C), 141.0 (C), 159.5 (C), 170.1 (CO); (found: C, 66.67; H, 3.82; N, 7.08; S, 6.13. $C_{33}H_{23}N_3O_6S$ requires C, 67.23; H, 3.90; N, 7.13; S, 5.4%); *m*/*z* (FAB$^+$) 590 (M$^+$ + H, 11%), 589 (16). *Minor isomer* δ_H(d_6-DMSO, 400 MHz) 2.89 (1H, d, *J* 15.1, 1′-H$_\alpha$), 3.31 (1H, dt, *J* 15.1, 7.2, 1′-H$_\beta$), 3.76 (3H, s, OMe), 4.89 (2H, s, C*H*$_2$Ar), 5.38 (2H, d, *J* 1.4, 3′-H and 4′-H), 5.94 (2H, d, *J* 7.2, 2′-H and 5′-H), 6.94 (2H, d, *J* 8.8, PMB), 7.39 (2H, d, *J* 8.8, PMB), 7.50 (2H, dd, *J* 7.9, 7.2, 3-H and 9-H), 7.72 (2H, dd, *J* 8.3, 7.2, 2-H and 10-H), 8.04 (2H, d, *J* 8.3, 1-H and 11-H), 9.14 (2H, d, *J* 7.9, 4-H and 8-H).

12,13-((3′β,4′β)Tetrahydrocyclopenta[3′,4′,2]dioxathiole-2,2-dioxide-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 20

Cyclic sulfite **19** (1.00 g, 1.70 mmol) was dissolved in DCM (300 mL). MeCN (100 mL), H_2O (150 mL), $NaIO_4$ (0.726 g, 3.40 mmol) and $RuCl_3$ (0.20 g, 0.77 mmol) were added. The reaction mixture was stirred vigorously for 3 d before being partitioned between DCM (200 mL) and H_2O (200 mL). The organic layer was washed with H_2O (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid. The crude material was purified by flash column chromatography using a DCM solvent system to give cyclic sulfate **20** as a yellow solid (0.45 g, 44%): mp 275–277 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 605.1257. $C_{33}H_{23}N_3O_7S$ requires 605.1257); ν_{max}($CHCl_3$)/cm^{-1} 1754, 1698, 1384, 1350, 991; δ_H(d_6-DMSO, 400 MHz) 3.09 (1H, d, *J* 15.6, 1′-H$_\alpha$), 3.46 (1H, dt, *J* 15.6, 7.3, 1′-H$_\beta$), 3.74 (3H, s, OMe), 4.86 (2H, s, C*H*$_2$Ar), 5.73 (2H, d, *J* 1.5, 3′-H and 4′-H), 6.25 (2H, d, *J* 7.3, 2′-H and 5′-H), 6.94 (2H, d, *J* 8.8, PMB), 7.38 (2H, d *J* 8.8, PMB), 7.50 (2H, dd, *J* 7.8, 7.3, 3-H and 9-H), 7.73 (2H, dd, *J* 8.4, 7.3, 2-H and 10-H), 8.07 (2H, d, *J* 8.4, 1-H and 11-H), 9.09 (2H, d, *J* 7.8, 4-H and 8-H); δ_C(d_6-DMSO, 100 MHz) 36.1 (1′-CH_2), 41.0 (CH_2Ar), 55.8 (OMe), 60.5 (2′-CH and 5′-CH), 89.0 (3′-CH and 4′-CH), 110.9 (CH), 114.8 (CH), 117.1 (C), 119.7 (C), 122.0 (CH), 122.2 (C), 125.4 (CH), 128.2 (CH), 129.1 (C), 129.6 (CH), 130.1 (C), 140.8 (C), 159.4 (C), 167.7 (CO); (found: C, 65.03; H, 3.84; N, 6.95; S, 5.29. $C_{33}H_{23}N_3O_7S$ requires C, 65.45; H, 3.80; N, 6.94; S, 5.29%); *m*/*z* (FAB$^+$) 606 (M$^+$ + H, 8%), 605 (22), 509 (4), 137 (20), 136 (49), 121 (100), 107 (15).

Cyclic sulfate 20 by reaction of diol 18 with SO_2Im_2

Diol **18** (0.69 g, 1.26 mmol) was dissolved in THF (75 mL) with stirring under N_2 at rt. SO_2Im_2 (1.00 g, 5.05 mmol) was added in one portion and the reaction mixture was stirred for 10 min before the dropwise addition of DBU (0.76 mL, 5.05 mmol). The reaction mixture was stirred for 18 h, a yellow precipitate formed overnight and was collected by filtration. The yellow solid was washed with THF (20 mL) and dried. The organics were combined, partitioned between EtOAc (150 mL) and H_2O (150 mL) and washed with 2N HCl (150 mL), H_2O (150 mL), brine (150 mL) and concentrated *in vacuo* to give a yellow solid. The two batches were combined to give **20** as a yellow solid (0.82 g, 90%). The spectroscopic data were identical to those described above.

12,13-(3′β-Hydroxy,4′α-morpholinylcyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 21

Cyclic sulfate **20** (50.0 mg, 0.08 mmol) was dissolved in freshly distilled morpholine (4 mL), with stirring under an atmosphere of N_2 and the reaction mixture was heated to reflux for 15 h. TLC analysis showed the consumption of starting material and so the reaction mixture was cooled to rt before being partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with brine (100 mL). The aqueous washings were combined and re-extracted with EtOAc (50 mL). The organics were combined, concentrated *in vacuo*, redissolved in THF (5 mL) and 20% H_2SO_4 (5 mL) was added. The resulting mixture was stirred vigorously for 15 h. The reaction mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL). The organic layer was washed with H_2O (150 mL), saturated aqueous $NaHCO_3$ solution (2 × 150 mL), brine (200 mL), dried

($MgSO_4$), and concentrated *in vacuo* to give the crude product as an orange solid. Purification by flash column chromatography using a 10% EtOAc–DCM solvent system gave firstly ketone **8c** (15.0 mg, 28%); secondly morpholine **21** as an orange solid (R_f 0.49) (18.0 mg, 36%): mp 272–275 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3696, 3606, 2928, 2360, 1697, 1602, 1384, 1350; δ_H(d_6-DMSO, 400 MHz) 2.68 (1H, d, *J* 15.0, 1′-H_α), 3.27 (4H, dd, *J* 5.1, 4.2, NCH_2), 3.44 (1H, ddd, *J* 15.0, 7.5, 7.2, 1′-H_β), 3.61 (4H, dd, *J* 6.3, 4.2, OCH_2), 3.76 (3H, s, OMe), 4.51 (1H, dd, *J* 5.9, 5.6, 3′-H), 4.87 (2H, s, C*H*$_2$Ar), 4.99 (1H, d, *J* 5.6, 4′-H), 5.52 (1H, d, *J* 7.2, 2′-H), 5.83 (1H, d, *J* 7.5, 5′-H), 5.99 (1H, d, *J* 5.9, OH), 6.94 (2H, d, *J* 8.8, PMB), 7.39 (2H, d, *J* 8.8, PMB), 7.45 (2H, dd, *J* 8.0, 7.2, 3-H and 9-H), 7.67–7.72 (2H, m, 2-H and 10-H), 7.88 (1H, d, *J* 8.9, 1-H), 7.91 (1H, d, *J* 8.8, 11-H), 9.12 (2H, d, *J* 8.0, 4-H and 8-H); δ_C(d_6-DMSO, 100 MHz) 36.2 (1′-CH_2), 41.0 (*CH*$_2$Ar), 47.2 (NCH_2), 56.0 (OMe), 62.0 (CH), 63.8 (CH), 66.0 (OCH_2), 77.8 (CH), 86.0 (CH), 110.8 (CH), 110.9 (CH), 114.9 (CH), 116.7 (C), 116.8 (C), 119.4 (C), 119.7 (C), 121.6 (CH), 121.7 (CH), 121.9 (C), 122.1 (C), 125.4 (CH), 125.5 (CH), 128.1 (CH), 129.4 (C), 129.5 (C), 129.8 (2CH), 130.3 (C), 141.2 (C), 159.4 (C), 170.0 (2CO); and finally diol **18** (6.0 mg, 13%).

12,13-(3′β-Hydroxy-4′α-benzoatecyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 22

To a stirred solution of cyclic sulfate **20** (50.0 mg, 0.08 mmol) in DMF (5 mL) under an N_2 atmosphere was added $PhCO_2NH_4$ (0.12 g, 0.83 mmol). The reaction mixture was heated to 70 °C for 25 h. TLC analysis showed starting material was still present so a further portion of $PhCO_2NH_4$ (0.5 g) was added and the reaction mixture was stirred overnight. TLC analysis showed the reaction had gone to completion and so the reaction mixture was concentrated *in vacuo*, redissolved in THF (5 mL) and 20% H_2SO_4 (5 mL) was added. The reaction mixture was stirred vigorously overnight at rt before being partitioned between EtOAc (150 mL) and H_2O (150 mL). The organic layer was washed with H_2O (150 mL), saturated aqueous $NaHCO_3$ solution (2 × 150 mL), brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as an orange solid. Purification by flash column chromatography using a 1 : 1 EtOAc–petrol solvent system gave benzoate **22** as an orange solid (47.0 mg, 88%): mp 291–293 °C; (found: *m*/*z* (FAB$^+$) M^+ 647.2069. $C_{40}H_{29}N_3O_6$ requires 647.2056); $\nu_{max}(CHCl_3)/cm^{-1}$ 2931, 2359, 1750, 1697, 1385, 1351, 1318, 1123; δ_H(d_6-DMSO, 400 MHz) 2.92 (1H, d, *J* 15.0, 1′-H_α), 3.45 (1H, ddd, *J* 15.0, 7.0, 6.4, 1′-H_β), 3.73 (3H, s, OMe), 4.07 (1H, m, 3′-H), 4.74 (2H, s, C*H*$_2$Ar), 5.42 (1H, d, *J* 7.0, 2′-H), 5.69 (1H, dd, *J* 6.2, 3.3, 4′-H), 6.07 (1H, dd, *J* 6.4, 6.2, 5′-H), 6.22 (1H, d, *J* 5.0, OH), 6.81 (2H, d, *J* 7.5, 2″-H and 6″-H), 6.93 (2H, d, *J* 8.8, PMB), 6.98 (2H, dd, *J* 7.5, 7.3, 3″-H and 5″-H), 7.23 (1H, app t, *J* 7.8, 9-H), 7.30 (1H, t, *J* 7.3, 4″-H), 7.36 (2H, d, *J* 8.8, PMB), 7.44 (2H, app dd, *J* 7.8, 7.5, 3-H and 10-H), 7.65 (1H, d, *J* 8.0, 11-H), 7.69 (1H, dd, *J* 8.3, 7.5, 2-H), 7.95 (1H, d, *J* 8.3, 1-H), 8.88 (1H, d, *J* 7.8, 8-H), 9.05 (1H, d, *J* 7.8, 4-H); δ_C(d_6-DMSO, 100 MHz) 36.4 (1′-CH_2), 41.0 (CH_2Ar), 56.0 (OMe), 58.2 (CH), 62.8 (CH), 82.4 (CH), 110.9 (CH), 111.1 (CH), 114.9 (CH), 116.6 (C), 119.5 (C), 121.3 (CH), 121.6 (CH), 125.1 (CH), 125.5 (CH), 127.8 (CH), 128.0 (CH), 128.9 (CH), 129.1 (C), 129.3 (CH), 129.5 (C), 129.6 (C), 130.0 (CH), 130.1 (C), 130.2 (C), 130.4 (C), 134.0 (CH), 141.2 (C), 142.2 (C), 159.5 (C), 165.6 (CO), 170.0 (2CO); *m*/*z* (FAB$^+$) 647 (M^+, 3%), 322 (4), 203 (6), 137 (7), 121 (15), 107 (15), 91 (18), 83 (39) 77 (12).

12,13-(3′β-Hydroxy-4′α-phenylsulfanylcyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 23

To a stirred solution of PhSH (0.03 mL, 0.33 mmol) in THF (1 mL), under a N_2 atmosphere was added NaH (13 mg, 0.33 mmol), a gas was evolved and the reaction mixture turned milky white. The reaction mixture was stirred for 30 min at rt before the dropwise addition of a suspension of cyclic sulfate **20** (40.0 mg, 0.07 mmol) in THF (5 mL). After 7 h, H_2O (0.1 mL) was added and the reaction mixture was stirred for 5 min before the dropwise addition of 20% H_2SO_4 (5 mL); the resulting solution was stirred overnight. The reaction mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL). The organic layer was washed with H_2O (150 mL), saturated aqueous $NaHCO_3$ solution (2 × 150 mL), brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as an orange solid. Purification by flash column chromatography using a 1 : 1 EtOAc–petrol solvent system gave firstly recovered sulfate **20** (10.0 mg), followed by sulfide **23** as an orange solid (28.0 mg, 67%; 91% based on recovered starting material): mp 273–275 °C; ν_{max}(THF)/cm^{-1} 3335, 1701, 1574, 1384, 752; δ_H(d_6-DMSO, 400 MHz) 2.82 (1H, d, *J* 15.0, 1′-H_α), 3.40 (1H, ddd, *J* 15.0, 7.0, 6.8, 1′-H_β), 3.76 (3H, s, OMe), 4.01 (1H, m, 3′-H), 4.30 (1H, dd, *J* 6.7, 4.2, 4′-H), 4.89 (2H, s, C*H*$_2$Ar), 5.43 (1H, d, *J* 7.0, 2′-H), 6.13 (1H, dd, *J* 6.8, 6.7, 5′-H), 6.23 (1H, d, *J* 4.30, OH), 6.95 (2H, d, *J* 8.8, PMB), 7.12–7.23 (5H, m, Ph), 7.38 (1H, dd, *J* 8.0, 7.1, 9-H), 7.42 (2H, d, *J* 8.8, PMB), 7.46 (2H, m, 3-H, 10-H), 7.64 (1H, d, *J* 8.5, 11-H), 7.69 (1H, dd, *J* 8.5, 7.1, 2-H), 7.97 (1H, d, *J* 8.5, 1-H), 9.08 (1H, d, *J* 8.0, 8-H), 9.12 (1H, d, *J* 8.0, 4-H); δ_C(d_6-DMSO, 100 MHz) 37.8 (1′-CH_2), 41.1 (CH_2Ar), 56.0 (OMe), 58.2 (CH), 59.9 (CH), 64.6 (CH), 85.7 (CH), 111.2 (CH), 111.3 (CH), 114.9 (CH), 119.4 (C), 119.5 (C), 121.4 (CH), 121.6 (C), 121.7 (CH), 122.1 (C), 125.3 (CH), 125.5 (CH), 126.5 (CH), 127.7 (CH), 128.0 (CH), 128.6 (CH), 129.5 (C), 129.7 (C), 129.8 (CH), 130.0 (CH), 130.4 (C), 136.5 (C), 141.1 (C), 142.5 (C), 159.5 (C), 170.2 (2CO).

12,13-(3′β-Hydroxy-4′α-sulfenylcyanocyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 24

To a stirred solution of cyclic sulfate **20** (50.0 mg, 0.08 mmol) in DMF (5 mL) under an N_2 atmosphere was added NH_4SCN (63.0 mg, 0.83 mmol). The reaction mixture was heated to 70 °C for 2 h; TLC analysis showed that the reaction had gone to completion. The reaction mixture was concentrated *in vacuo*, redissolved in THF (5 mL), and 20% H_2SO_4 (5 mL) was added. The reaction mixture was stirred vigorously overnight before being partitioned between EtOAc (150 mL) and H_2O (150 mL). The organic layer was washed with H_2O (150 mL), saturated aqueous $NaHCO_3$ solution (2 × 150 mL), brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as an orange solid. Purification by flash column chromatography using a 5% MeOH–DCM solvent system gave **24** as an orange solid (28.0 mg, 64%): mp 285–288 °C; (found: *m*/*z* (FAB$^+$) M^+ 584.1500. $C_{34}H_{24}N_4O_4S$ requires 584.1518); ν_{max}(THF)/cm^{-1} 3494, 3346, 2157, 1753, 1699, 1384, 750; δ_H(d_6-DMSO, 400 MHz) 2.86 (1H, d, *J* 14.9, 1′-H_α), 3.36 (1H, ddd, *J* 14.9, 7.7, 6.0, 1′-H_β), 3.73 (3H, s, OMe), 4.10 (1H, dd, *J* 5.8, 5.2, 3′-H), 4.20 (1H, dd, *J* 6.0, 5.8, 4′-H), 4.78 (2H, s, C*H*$_2$Ar), 5.48 (1H, d, *J* 7.7, 2′-H), 6.01 (1H, app t, *J* 6.0, 5′-H), 6.61 (1H, d, *J* 5.2, OH), 6.94 (2H, d, *J* 8.8, PMB), 7.38 (2H, d, *J* 8.8, PMB), 7.45 (1H, dd, *J* 7.8, 7.2, 3-H or 9-H), 7.47 (1H, dd, *J* 7.8, 7.2, 3-H or 9-H), 7.68 (1H, dd, *J* 8.3, 7.2, 2-H or 10-H), 7.70 (1H, dd, *J* 8.3, 7.2, 2-H or 10-H), 7.94 (2H, d, *J* 8.3, 1-H and 11-H), 9.07 (2H, app t, *J* 7.8, 4-H and 8-H); δ_C(d_6-DMSO, 125 MHz) 37.6 (1′-CH_2), 41.1 (CH_2Ar), 56.0 (OMe), 58.5 (CH), 60.7 (CH), 63.8 (CH), 84.7 (CH), 111.0 (C), 111.1 (CH), 111.3 (CH), 114.9 (CH), 116.7 (C), 117.1 (C), 119.4 (C), 119.7 (C), 121.7 (CH), 121.8 (CH), 121.9 (C), 122.0 (C), 125.5 (CH), 128.0 (CH), 128.1 (CH), 129.4 (C), 129.8 (C), 130.1 (CH, CH), 130.3 (C), 140.9 (C), 142.3 (C), 159.5 (C), 170.0 (CO), 170.1 (CO); *m*/*z* (FAB$^+$) 584 (M^+ 4%), 477 (3), 325 (3), 141 (2), 137 (32), 121 (18), 107 (25), 83 (43).

12,13-(3′β-Hydroxy-4′α-aminocyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 25

Azido alcohol **17** (35.0 mg, 0.06 mmol) was dissolved in dry DMF (3 mL) and Pd/C (15.0 mg) was added. The reaction mixture was stirred under a H_2 atmosphere (300 psi) for 18 h. TLC analysis showed consumption of starting material and so the reaction mixture was filtered through celite to remove the catalyst and partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL), saturated aqueous $CaCl_2$ solution (2 × 100 mL) and brine (100 mL). The aqueous layers were re-extracted with EtOAc (2 × 50 mL) and all the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid. Purification *via* flash column chromatography using a 5% MeOH–DCM solvent system afforded amino alcohol **25** as a yellow solid (0.025 g, 71%): mp 292–296 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 542.1996. $C_{33}H_{26}N_4O_4$ requires 542.1954); ν_{max}(THF)/cm^{-1} 3383, 1751, 1698, 1572, 1385, 750; δ_H(d$_6$-DMSO, 500 MHz) 2.59 (1H, d, *J* 15.0, 1′-H$_\alpha$), 3.28 (1H, ddd, *J* 15.0, 7.3, 6.0, 1′-H$_\beta$), 3.59 (1H, m, 3′-H), 3.65 (1H, dd, *J* 5.3, 4.6, 4′-H), 3.74 (3H, s, OMe), 4.83 (2H, s, C*H*$_2$Ar), 5.28 (1H, d, *J* 7.3, 2′-H), 5.57 (1H, dd, *J* 6.0, 4.6, 5′-H), 5.79 (1H, s, OH), 6.95 (2H, d, *J* 8.6, PMB), 7.38 (2H, d, *J* 8.6, PMB), 7.43 (2H, m, 3-H and 9-H), 7.63 (1H, dd, *J* 7.9, 7.7, 10-H), 7.68 (1H, dd, *J* 7.9, 7.5, 2-H), 7.91 (1H, d, *J* 7.9, 1-H), 7.96 (1H, d, *J* 7.9, 11-H), 9.07 (1H, d, *J* 8.5, 8-H), 9.09 (1H, d, *J* 8.9, 4-H); δ_C(d$_6$-DMSO, 125 MHz) 36.6 (1′-CH$_2$), 41.1 (CH$_2$Ar), 56.0 (OMe), 61.8 (CH), 63.6 (CH), 65.6 (CH), 86.9 (CH), 111.1 (CH), 111.7 (CH), 114.9 (CH), 116.3 (C), 116.6 (C), 119.2 (C), 119.4 (C), 121.2 (CH), 121.3 (CH), 121.9 (C), 122.0 (C), 125.2 (CH), 125.4 (CH), 127.8 (CH), 129.6 (C), 129.9 (CH, CH), 130.2 (C), 130.4 (C), 140.9 (C), 143.2 (C), 159.4 (C), 170.3 (CO), 170.4 (CO); *m*/*z* (FAB$^+$) 543 (M$^+$ + H, 6%), 542 (M$^+$, 13), 435 (9), 118 (3), 107 (37).

12,13-(3′β-Hydroxy-4′α-diallylaminocyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo [2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 26

Azido alcohol **17** (50.0 mg, 0.09 mmol) was dissolved in DMF (1.5 mL) with stirring under an atmosphere of N_2 at rt. Indium powder (51.0 mg, 0.44 mmol), NaI (66.0 mg, 0.44 mmol) and allyl bromide (0.08 mL, 0.88 mmol) were added and the reaction mixture was stirred for 48 h. A yellow solid had precipitated out of solution, TLC analysis indicated no reaction had taken place and so further In (0.20 g), NaI (0.26 g) and allyl bromide (0.50 mL) were added and the reaction was heated to 50 °C. After 6 h, TLC analysis showed that no reaction had taken place. The reaction mixture was stirred overnight at 50 °C. TLC analysis showed the consumption of starting material and so the reaction mixture was cooled to rt and partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (3 × 100 mL), saturated aqueous $CaCl_2$ solution (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield an orange solid. Purification *via* flash column chromatography using a 0–2% MeOH–DCM solvent system afforded diallyl amine **26** as an orange solid (33.0 mg, 60%): mp 291–295 °C; (found: *m*/*z* (FAB$^+$) M$^+$ 622.2563. $C_{39}H_{34}N_4O_4$ requires 622.2580); ν_{max}(THF)/cm^{-1} 3356, 1752, 1699, 1573, 1384, 751; δ_H(d$_6$-DMSO, 400 MHz) 2.46 (2H, dd, *J* 14.6, 5.0, NC*H*HCH=CH$_2$), 2.59 (1H, d, *J* 14.7, 1′-H$_\alpha$), 2.74 (2H, dd, *J* 14.6, 6.4, NCH*H*CH=CH$_2$), 3.19 (1H, ddd, *J* 14.7, 7.4, 6.0, 1′-H$_\beta$), 3.68 (1H, dd, *J* 6.0, 5.7, 4′-H), 3.72 (3H, s, OMe), 4.00 (1H, dd, *J* 5.7, 5.4, 3′-H), 4.75 (2H, s, C*H*$_2$Ar), 4.79 (4H, d, *J* 8.0, C*H*$_2$=CH), 5.09–5.19 (2H, m, CH$_2$=C*H*), 5.29 (1H, d, *J* 7.4, 2′-H), 5.67 (1H, app t, *J* 6.0, 5′-H), 5.94 (1H, d, *J* 5.4, OH), 6.92 (2H, d, *J* 8.6, PMB), 7.38 (2H, d, *J* 8.6, PMB), 7.41 (2H, dd, *J* 8.0, 7.4, 3-H and 9-H), 7.65 (1H, dd, *J* 8.2, 7.4, 2-H or 10-H), 7.66 (1H, dd, *J* 8.2, 7.4, 2-H or 10-H), 7.92 (2H, d, *J* 8.2, 1-H and 11-H), 9.03 (2H, app t, *J* 8.0, 4-H and 8-H); δ_C(d$_6$-DMSO, 100 MHz) 35.9 (1′-CH$_2$), 41.1 (CH$_2$Ar), 54.8 (NCH$_2$), 56.0 (OMe), 60.3 (5′-CH), 63.9 (2′-CH), 73.3 (4′-CH), 79.2 (3′-CH), 111.2 (CH), 111.9 (CH), 114.9 (CH), 116.2 (C), 116.5 (C), 117.3 (*C*H$_2$=CH), 119.2 (C), 119.3 (C), 121.2 (CH), 121.4 (CH), 122.0 (C), 125.2 (CH), 125.4 (CH), 127.7 (CH), 127.8 (CH), 129.4 (C), 129.7 (C), 130.1 (CH), 130.4 (C), 137.2 (CH), 140.9 (C), 142.5 (C), 159.5 (C), 170.1 (CO), 170.2 (CO); *m*/*z* (FAB$^+$) 623 (M$^+$ + H, 5%), 622 (M$^+$, 10), 138 (31), 134 (4), 107 (44), 97 (14), 92 (5).

12,13-(3′β-Hydroxy-4′α-(dimethyl-1*H*-1,2,3-triazole-4,5-dicarboxylate)cyclopentan-2′α,5′α-diyl)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 27

Azido alcohol **17** (44.0 mg, 0.08 mmol) was suspended in DMF (1.5 mL) with stirring under an N_2 atmosphere. Dimethyl acetylenedicarboxylate (0.10 mL, 0.77 mmol) was added and the reaction mixture was heated to 70 °C for 15 h. TLC analysis showed consumption of starting material and so the reaction mixture was cooled to rt and partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with a saturated aqueous $CaCl_2$ solution (2 × 50 mL), brine (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification *via* flash column chromatography using a 1 : 1 EtOAc–petrol solvent system gave triazole **27** as an orange solid (0.052 g, 95%): mp 240 °C decomp; (found: *m*/*z* (FAB$^+$) M$^+$ 710.2141. $C_{39}H_{30}N_6O_8$ requires 710.2125); ν_{max}(CHCl$_3$)/cm^{-1} 3697, 3605, 2956, 1746, 1688, 1602, 1384, 1349, 1081; δ_H(d$_6$-DMSO, 400 MHz) 2.96 (1H, d, *J* 15.3, 1′-H$_\alpha$), 3.64 (1H, ddd, *J* 15.3, 7.7, 6.1, 1′-H$_\beta$), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 4.16 (3H, s, OMe), 4.84 (2H, s, C*H*$_2$Ar), 4.94 (1H, dd, *J* 5.6, 5.0, 3′-H), 5.57 (1H, d, *J* 7.7, 2′-H), 5.74 (1H, dd, *J* 5.9, 5.6, 4′-H), 6.09 (1H, dd, *J* 6.1, 5.9, 5′-H), 6.35 (1H, d, *J* 5.0, OH), 6.95 (2H, d, *J* 8.8, PMB), 7.27 (2H, app dd, *J* 8.2, 7.0, 9-H and 11-H), 7.38 (1H, ddd, *J* 8.2, 7.0, 1.3, 10-H), 7.41 (2H, d, *J* 8.8, PMB), 7.48 (1H, dd, *J* 7.8, 7.5, 3-H), 7.72 (1H, dd, *J* 8.5, 7.5, 2-H), 7.97 (1H, d, *J* 8.5, 1-H), 8.98 (1H, d, *J* 7.3, 8-H), 9.12 (1H, d, *J* 7.8, 4-H); δ_C(d$_6$-DMSO, 100 MHz) 37.1 (1′-CH$_2$), 41.0 (CH$_2$Ar), 53.5 (OMe), 55.2 (OMe), 56.0 (OMe), 60.4 (CH), 62.8 (CH), 71.7 (CH), 82.5 (CH), 109.0 (CH), 111.1 (CH), 114.9 (CH), 116.8 (C), 119.3 (C), 119.7 (C), 121.6 (CH), 121.7 (CH), 121.9 (C), 122.0 (C), 125.3 (CH), 125.5 (CH), 127.7 (CH), 128.1 (CH), 129.6 (C), 129.9 (CH), 130.3 (C), 132.7 (C), 138.6 (C), 141.0 (C), 141.5 (C), 159.5 (CO), 159.7 (C), 160.4 (CO), 170.0 (CO), 170.1 (CO); *m*/*z* (FAB$^+$) 711 (M$^+$ + H, 4%), 710 (M$^+$, 6), 603 (4), 135 (7), 121 (18), 107 (22).

12,13-(3′β-Hydroxy-4′α-azidocyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo [3,4-*c*]carbazole-5,7(6*H*)-dione 30

Azide **17** (0.10 g, 0.18 mmol) was suspended in anisole (2 mL) with stirring under N_2 and cooled to 0 °C. TFA (10 mL) was added slowly over 10 min; once the addition was complete, the reaction mixture was warmed to 70 °C for 18 h. TLC analysis showed the consumption of starting material and so the reaction mixture was cooled to rt and partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The organics were washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The addition of petrol (20 mL) resulted in precipitation of a yellow solid, which was collected by filtration and purified *via* flash column chromatography using a 5% THF–DCM solvent system to give firstly trifluoroacetate **28** (not fully pure) R_f 0.52 (65.0 mg): mp 321–325 °C; ν_{max}(THF)/cm^{-1} 3312, 2106, 1721, 1572, 749; δ_H(d$_6$-DMSO, 400 MHz) 2.92 (1H, d, *J* 15.4, 1′-H$_\alpha$), 3.26 (1H, ddd, *J* 15.4, 7.3, 6.5, 1′-H$_\beta$), 5.06–5.09 (2H, m, 3′-H and 4′-H), 6.05 (1H, d, *J* 7.3, 2′-H or 5′-H), 6.09 (1H, d, *J* 6.5, 2′-H or 5′-H), 7.47 (2H, dd, *J* 8.6, 6.5, 3-H and 9-H), 7.70 (1H, dd, *J* 7.6, 6.5, 2-H or 10-H), 7.73 (1H, dd, *J* 7.6, 6.5, 2-H or

10-H), 7.95 (2H, app t, *J* 7.6, 1-H and 11-H), 9.12 (2H, app t, *J* 8.6, 4-H and 8-H), 11.19 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 37.0 (1′-CH_2), 59.4 (CH), 59.8 (CH), 68.5 (CH), 89.0 (CH), 111.9 (CH), 111.9 (CH), 114.9 (CH), 116.9 (C), 121.1 (C), 121.8 (CH), 122.1 (2C), 122.2 (2C), 125.5 (CH), 125.7 (CH), 127.9 (CH), 128.2 (CH), 129.1 (C), 129.3 (C), 141.1 (C), 142.5 (C), 171.9 (2CO) and secondly azide **30** R_f 0.21 (37.0 mg): mp 333–336 °C; (found: *m/z* (FAB^+) M^+ 448.1272. $C_{25}H_{16}N_6O_3$ requires 448.1284); ν_{max}(THF)/cm^{-1} 3500, 3352, 2106, 1754, 1721, 1640, 1573, 749; δ_H(d_6-DMSO, 500 MHz) 2.75 (1H, d, *J* 14.8, 1′-H_α), 3.29 (1H, ddd, *J* 14.8, 7.4, 6.3, 1′-H_β), 3.88 (1H, dd, *J* 5.0, 4.8, 3′-H), 4.46 (1H, dd, *J* 5.9, 5.0, 4′-H), 5.40 (1H, d, *J* 7.4, 2′-H), 5.94 (1H, dd, *J* 6.3, 5.9, 5′-H), 6.36 (1H, d, *J* 4.8, OH), 7.46 (2H, dd, *J* 8.3, 7.3, 3-H and 9-H), 7.69 (2H, dd, *J* 8.2, 7.3, 2-H and 10-H), 7.94 (1H, d, *J* 8.2, 11-H), 7.95 (1H, d, *J* 8.2, 1-H), 9.09 (1H, d, *J* 8.3, 8-H), 9.11 (1H, d, *J* 8.3, 4-H), 11.14 (1H, s, NH); δ_C(d_6-DMSO, 125 MHz) 36.4 (1′-CH_2), 59.6 (CH), 63.2 (CH), 72.3 (CH), 83.7 (CH), 111.0 (CH), 111.1 (CH), 116.5 (C), 116.6 (C), 120.8 (C), 121.0 (C), 121.5 (C), 121.6 (CH), 122.2 (C), 125.5 (CH), 125.6 (CH), 127.9 (CH), 128.0 (CH), 129.3 (C), 129.6 (C), 140.9 (C), 142.5 (C), 171.9 (CO), 172.0 (CO); *m/z* (FAB^+) 448 (M^+, 2%), 109 (22), 85 (24).

Hydrolysis of trifluoroacetate 28 to give alcohol 30

Trifluoroacetate **28** (65.0 mg, 0.12 mmol) was dissolved in THF (1 mL) with stirring, under N_2. LiOH (29.0 mg, 1.20 mmol) was added and the reaction mixture was stirred for 0.5 h. TLC analysis showed the consumption of starting material and so the reaction mixture was partitioned between EtOAc (40 mL) and H_2O (40 mL). The organic layer was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. Purification *via* flash column chromatography using a 5% THF–DCM solvent system gave **30** as a yellow solid (30.0 mg, total yield from **17** of 85%).

12,13-(3′β-Hydroxy-4′α-morpholinylcyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 31

Morpholine derivative **21** (47.0 mg, 0.08 mmol) was suspended in anisole (0.75 mL), with stirring under an N_2 atmosphere and TFA (3.5 mL) was added dropwise. The reaction mixture was heated to 80 °C for 15 h. TLC analysis showed consumption of the starting material and so the reaction mixture was allowed to cool to rt and partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ solution (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 200 mL), H_2O (100 mL), brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown gum. The brown gum was triturated in petrol (100 mL) for 1 h to give a brown solid that was collected by filtration. Purification *via* flash column chromatography using a 5% THF–DCM solvent system gave firstly a trifluoroacetate derivative of the starting NPMB imide (R_f 0.85) as a yellow solid (15.0 mg, 28%): mp 292–294 °C; ν_{max}($CHCl_3$)/cm^{-1} 3358, 2447, 1753, 1699, 1611, 1574, 1515, 1385, 750; δ_H(d_6-DMSO, 500 MHz) 2.90 (1H, d, *J* 15.1, 1′-H_α), 3.19–3.25 (4H, m, NCH_2), 3.38 (1H, m, 1′-H_β), 3.55–3.58 (4H, m, OCH_2), 3.73 (3H, s, OMe), 4.77 (2H, s, C*H*$_2$Ar), 5.37 (1H, d, *J* 5.4, 4′-H), 5.77 (1H, d, *J* 5.4, 3′-H), 6.06 (1H, d, *J* 7.3, 2′-H), 6.13 (1H, d, *J* 7.3, 5′-H), 6.93 (2H, d, *J* 7.8, PMB), 7.35 (2H, d, *J* 7.8, PMB), 7.44–7.51 (2H, m, 3-H and 9-H), 7.70 (2H, dd, *J* 8.3, 7.8, 2-H and 10-H), 7.94 (1H, d, *J* 8.3, 1-H or 11-H), 7.97 (1H, d, *J* 8.3, 1-H or 11-H), 9.05 (2H, app t, *J* 6.9, 4-H and 8-H); δ_C(d_6-DMSO, 125 MHz) 36.9 (1′-CH_2), 41.0 (CH_2Ar), 47.2 (NCH_2), 55.8 (OMe), 60.6 (CH), 61.6 (CH), 66.0 (OCH_2), 81.2 (CH), 83.8 (CH), 111.0 (CH), 111.4 (CH), 114.9 (CH), 115.2 (q, J $^{13}C^{19}F$ = 285.7, CF_3), 117.1 (C), 117.2 (C), 119.6 (C), 119.7 (C), 121.8 (CH), 121.9 (CH), 122.0 (C), 122.1 (C), 125.4 (CH), 125.5 (CH), 128.2 (CH), 128.3 (CH), 129.4 (C), 129.6 (C), 129.8 (CH), 130.3 (C), 141.1 (C), 141.5 (C), 156.4 (q, J $^{13}C^{19}F$ = 42.3, $COCF_3$) 159.5 (C), 170.0 (2CO); and secondly alcohol **31** (R_f 0.35) as a yellow solid (16.0 mg, 50%): mp 362–365 °C; ν_{max}(THF)/cm^{-1} 3486, 1721, 1658, 1573, 1390, 750; δ_H(d_6-DMSO, 400 MHz) 2.68 (1H, d, *J* 15.1, 1′-H_α), 3.24 (4H, d, *J* 7.5, NCH_2), 3.42 (1H, ddd, *J* 15.1, 7.6, 7.0, 1′-H_β), 3.57 (4H, d, *J* 7.5, OCH_2), 4.50 (1H, dd, *J* 6.0, 5.6, 3′-H), 5.01 (1H, d, *J* 5.6, 4′-H), 5.54 (1H, d, *J* 7.6, 2′-H), 5.86 (1H, d, *J* 7.0, 5′-H), 6.22 (1H, d, *J* 6.0, OH), 7.46 (2H, dd, *J* 7.6, 7.4, 3-H and 9-H), 7.70 (1H, dd, *J* 8.2, 7.6, 2-H or 10-H), 7.71 (1H, dd, *J* 8.2, 7.6, 2-H or 10-H), 7.91 (1H, d, *J* 8.2, 1-H or 11-H), 7.92 (1H, d, *J* 8.2, 1-H or 11-H), 9.10 (2H, d, *J* 7.4, 4-H and 8-H), 11.14 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 36.3 (1′-CH_2), 47.2 (NCH_2), 62.0 (CH), 63.8 (CH), 66.0 (OCH_2), 77.9 (CH), 86.0 (CH), 110.8 (CH), 110.9 (CH), 116.6 (C), 116.7 (C), 120.9 (C), 121.1 (C), 121.6 (CH), 121.7 (CH), 122.1 (C), 122.3 (C), 125.7 (CH, CH), 128.0 (CH, CH), 129.5 (C), 129.6 (C), 141.1 (C), 141.2 (C), 171.9 (2CO).

12,13-(3′β-Hydroxy-4′α-phenylsulfanylcyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 32, *via* trifluoroacetate 29

Sulfide **23** (55.0 mg, 0.09 mmol) was suspended in anisole (1.0 mL) with stirring under an N_2 atmosphere and TFA (4.0 mL) was added dropwise. The reaction mixture was heated to 80 °C for 15 h. TLC analysis showed consumption of the starting material and so the reaction mixture was allowed to cool to rt and partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ solution (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 200 mL), H_2O (100 mL), brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown gum. The brown gum was triturated with petrol (100 mL) for 1 h to give a brown solid that was collected by filtration. The resulting solid was purified *via* flash column chromatography using a 4–10% EtOAc–DCM solvent system to give the trifluoroacetate **29** as a yellow solid (30.0 mg, 56%): mp 354–356 °C; ν_{max}($CHCl_3$)/cm^{-1} 3342, 1790, 1713, 1643, 1608, 1574, 746; δ_H(d_6-DMSO, 500 MHz) 2.98 (1H, d, *J* 15.2, 1′-H_α), 3.31 (1H, ddd, *J* 15.2, 7.3, 6.8, 1′-H_β), 4.80 (1H, dd, *J* 6.5, 4.4, 4′-H), 5.12 (1H, d, *J* 4.4, 3′-H), 6.11 (1H, d, *J* 7.3, 2′-H), 6.27 (1H, dd, *J* 6.8, 6.5, 5′-H), 7.18–7.23 (5H, m, Ph), 7.44 (1H, dd, *J* 7.8, 7.5, 9-H), 7.48 (1H, dd, *J* 7.8, 7.4, 3-H), 7.62 (1H, dd, *J* 8.2, 7.5, 10-H), 7.68 (1H, dd, *J* 8.2, 7.4, 2-H), 7.80 (1H, d, *J* 8.2, 11-H), 7.97 (1H, d, *J* 8.2, 1-H), 9.12 (1H, d, *J* 7.8, 8-H), 9.13 (1H, d, *J* 7.8, 4-H), 11.20 (1H, s, NH); δ_C(d_6-DMSO, 125 MHz) 38.5 (1′-CH_2), 56.2 (CH), 60.0 (CH), 61.1 (CH), 91.9 (CH), 111.3 (CH), 111.9 (CH), 114.9 (q, J $^{13}C^{19}F$ = 286.0, CF_3), 116.8 (C), 116.9 (C), 121.0 (C), 121.1 (C), 121.7 (CH), 121.8 (CH), 122.2 (C), 125.5 (CH), 125.6 (CH), 127.9 (CH), 128.3 (CH), 128.6 (C), 129.3 (C), 129.8 (C), 130.0 (CH), 131.6 (CH), 133.5 (C), 141.1 (C), 142.3 (C), 156.3 (q, J $^{13}C^{19}F$ = 42.3, $COCF_3$), 171.9 (2CO); *m/z* (FAB^+) 611 (M^+, 2%), 515 (M^+, 2).

Hydrolysis of 29 using LiOH

Trifluroacetate **29** (28 mg, 0.05 mmol) was dissolved in THF (1 mL) with stirring under an N_2 atmosphere. LiOH (3.0 mg. 0.14 mmol) was added and the reaction mixture was stirred for 1 h. TLC analysis showed starting material remained so a further portion of LiOH (6 mg) was added and the reaction mixture was stirred for a further 2 h. TLC analysis showed consumption of starting material and so the reaction mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification *via* flash column chromatography using a 5% THF–DCM solvent system yielded the desired product **32** as a yellow solid (19.0 mg, 81%; 45% overall from **23**): mp 371–373 °C; ν_{max}($CHCl_3$)/cm^{-1} 3352, 2076, 1719, 1644, 1573, 746; δ_H(d_6-DMSO, 400 MHz) 2.83 (1H, d, *J* 14.9, 1′-H_α), 3.39 (1H, ddd, *J* 14.9, 7.1, 7.0, 1′-H_β), 4.00 (1H, m, 3′-H), 4.30 (1H, dd, *J* 6.6, 4.2, 4′-H), 5.44 (1H, d, *J* 7.0, 2′-H), 6.18 (1H, dd, *J* 7.1, 6.6, 5′-H),

6.36 (1H, d, *J* 4.2, OH), 7.12–7.25 (5H, m, Ph), 7.38 (1H, dd, *J* 7.8, 7.2, 9-H), 7.46 (1H, dd, *J* 8.5, 7.2, 10-H), 7.49 (1H, dd, *J* 8.2, 7.1, 3-H), 7.66 (1H, d, *J* 8.5, 11-H), 7.70 (1H, dd, *J* 8.3, 7.1, 2-H), 7.99 (1H, d, *J* 8.3, 1-H), 9.08 (1H, d, *J* 7.8, 8-H), 9.11 (1H, d, *J* 8.2, 4-H), 11.13 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 37.9 (1′-CH_2), 58.2 (CH), 59.9 (CH), 64.6 (CH), 85.8 (CH), 111.1 (CH), 111.3 (CH), 116.2 (C), 116.4 (C), 120.7 (C), 120.8 (C), 121.3 (CH), 121.6 (CH), 121.7 (C), 122.3 (C), 125.4 (CH), 125.6 (CH), 126.5 (CH), 127.6 (CH), 127.8 (CH), 128.7 (CH), 129.5 (C), 129.7 (C), 129.8 (CH), 136.5 (C), 141.0 (C), 142.4 (C), 172.0 (2CO).

12,13-(3′β-Hydroxy-4′α-sulfenylcyanidecyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 33

Thiocyanate **24** (41.0 mg, 0.07 mmol) was suspended in anisole (1.0 mL) with stirring under an N_2 atmosphere and TFA (4.0 mL) was added dropwise. The reaction mixture was heated to 80 °C for 15 h. TLC analysis showed consumption of the starting material and so the reaction mixture was allowed to cool to rt and partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ solution (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 200 mL), H_2O (100 mL), brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown gum. The brown gum was triturated with petrol (100 mL) for 1 h to give a brown solid that was collected by filtration. The resulting solid was purified *via* flash column chromatography using a 10% THF–DCM solvent system to give the product **33** as a yellow solid (16.0 mg, 54%): mp 376–380 °C; ν_{max}(THF)/cm^{-1} 3472, 2157, 1754, 1721, 1644, 1574, 750; δ_H(d_6-DMSO, 400 MHz) 2.83 (1H, d, *J* 15.0, 1′-H_α), 3.36 (1H, ddd, *J* 15.0, 7.6, 6.1, 1′-H_β), 4.13 (1H, dd, *J* 5.8, 5.3, 3′-H), 4.22 (1H, dd, *J* 5.9, 5.8, 4′-H), 5.50 (1H, d, *J* 7.6, 2′-H), 6.04 (1H, dd, *J* 6.1, 5.9, 5′-H), 6.62 (1H, d, *J* 5.3, OH), 7.48 (2H, dd, *J* 8.0, 7.3, 3-H and 9-H), 7.69–7.73 (2H, m, 2-H and 10-H), 7.98 (2H, d, *J* 8.4, 1-H and 11-H), 9.12 (2H, app t, *J* 8.0, 4-H and 8-H), 11.16 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 37.7 (1′-CH_2), 58.6 (CH), 60.7 (CH), 63.8 (CH), 84.8 (CH), 111.1 (CH), 111.3 (CH), 116.5 (C), 116.9 (C), 120.8 (C), 121.1 (C), 121.7 (CH), 121.8 (CH), 122.1 (C), 122.1 (C), 125.6 (2CH, C), 127.9 (2CH), 129.5 (C), 129.8 (C), 140.8 (C), 142.3 (C), 171.9 (CO), 172.0 (CO).

12,13-(3′β-Hydroxy-4′α-(dimethyl-1*H*-1,2,3-triazole-4,5-dicarboxylate)cyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 34

Triazole **27** (63.0 mg, 0.09 mmol) was suspended in anisole (1.2 mL) with stirring under an N_2 atmosphere and TFA (6 mL) was added dropwise. The reaction mixture was heated to 80 °C for 15 h. TLC analysis showed consumption of the starting material and so the reaction mixture was allowed to cool to rt and partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ solution (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 200 mL), H_2O (100 mL), brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown gum. The brown gum was triturated in petrol (100 mL) for 1 h to give a brown solid that was collected by filtration. The resulting solid was purified *via* flash column chromatography using a 5% THF–DCM solvent system to give the desired product **34** as a yellow solid (27 mg, 52%): mp 347–350 °C; (found: *m*/*z* (ES$^+$) M^+ + Na 613.1498. $C_{31}H_{22}N_6O_7Na$ requires 613.1448); ν_{max}($CHCl_3$)/cm^{-1} 3344, 1720, 1573, 750; δ_H(d_6-DMSO, 400 MHz) 2.95 (1H, d, *J* 14.9, 1′-H_α), 3.61 (1H, ddd, *J* 14.9, 7.8, 6.0, 1′-H_β), 3.77 (3H, s, OMe), 4.16 (3H, s, OMe), 4.92 (1H, m, 3′-H), 5.60 (1H, d, *J* 7.8, 2′-H), 5.73 (1H, dd, *J* 6.0, 5.6, 4′-H), 6.10 (1H, dd, *J* 6.0, 5.6, 5′-H), 6.48 (1H, d, *J* 4.4, OH), 7.28 (2H, m, 9-H and 11-H), 7.38 (1H, dd, *J* 7.7, 7.5, 10-H), 7.49 (1H, dd, *J* 7.8, 7.5, 3-H), 7.73 (1H, dd, *J* 8.1, 7.5, 2-H), 8.01 (1H, d, *J* 8.1, 1-H), 8.97 (1H, d, *J* 8.0, 8-H), 9.12 (1H, d, *J* 7.8, 4-H), 11.19 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 37.2 (1′-CH_2), 53.5 (OMe), 55.2 (OMe), 60.4 (CH), 62.8 (CH), 71.7 (CH), 82.5 (CH), 109.1 (CH), 111.1 (CH), 116.7 (C), 120.8 (C), 121.1 (C), 121.6 (CH), 121.7 (CH), 122.1 (C), 122.2 (C), 125.5 (CH), 125.7 (CH), 127.6 (CH), 128.0 (CH), 129.7 (C), 130.0 (C), 132.8 (C), 138.6 (C), 140.9 (C), 141.4 (C), 159.7 (CO), 160.4 (CO), 171.9 (CO), 172.0 (CO); *m*/*z* (ES$^+$) 613 (M^+ + Na, 8%), 434 (5), 322 (7) 154 (13), 83 (41).

12,13-((3′β,4′β)Tetrahydrocyclopenta[3′,4′,2]dioxathiole-2-oxide-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 35

Cyclic sulfite **19** (predominantly the major diastereomer, *ca.* 12 : 1 ratio) (40.0 mg, 0.07 mmol) was suspended in anisole (1 mL) with stirring under N_2 and cooled to 0 °C. TFA (5 mL) was added dropwise over 15 min, and once the addition was complete the reaction mixture was heated to reflux for 18 h. A yellow solid formed in the reaction mixture, which was then cooled to rt and partitioned between DCM (100 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which was triturated with petrol (20 mL) for 1 h. A yellow solid precipitated out of the solution and was collected by filtration, washed with petroleum ether (3 × 20 mL) and dried to give cyclic sulfite **35**, an inseparable mixture of diastereoisomers (*ca.* 12 : 1 by NMR) (31.0 mg, 97%): mp 364 °C decomp.; ν_{max}(THF)/cm^{-1} 3494, 3188, 1754, 1722, 1643, 1573, 750; *major isomer* δ_H(d_6-DMSO, 400 MHz) 2.90 (1H, d, *J* 15.2, 1′-H_α), 3.28 (1H, dt, *J* 15.2, 7.3, 1′-H_β), 5.56 (2H, d, *J* 1.5, 3′-H and 4′-H), 5.96 (2H, d, *J* 7.3, 2′-H and 5′-H), 7.48 (2H, dd, *J* 7.8, 7.3, 3-H and 9-H), 7.71 (2H, dd, *J* 8.4, 7.3, 2-H and 10-H), 7.99 (2H, d, *J* 8.4, 1-H and 11-H), 9.09 (2H, d, *J* 7.8, 4-H and 8-H), 11.16 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 35.4 (CH_2), 61.1 (CH), 89.8 (CH), 110.8 (CH), 116.8 (C), 121.0 (C), 122.0 (CH), 122.4 (C), 125.7 (CH), 128.2 (CH), 129.4 (C), 140.8 (C), 171.7 (CO); *minor isomer* δ_H(d_6-DMSO, 400 MHz) 2.90 (1H, d, *J* 15.2, 1′-H_α), 3.28 (1H, dt, *J* 15.2, 7.3, 1′-H_β), 5.40 (2H, d, *J* 1.5, 3′-H and 4′-H), 6.09 (2H, d, *J* 7.3, 2′-H and 5′-H), 7.48 (2H, dd, *J* 7.8, 7.3, 3-H and 9-H), 7.71 (2H, dd, *J* 8.4, 7.3, 2-H and 10-H), 8.06 (2H, d, *J* 8.4, 1-H and 11-H), 9.09 (2H, d, *J* 7.8, 4-H and 8-H), 11.16 (1H, s, NH).

12,13-(3′β-Hydroxy-4′α-aminocyclopentan-2′α,5′α-diyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 36

Azido alcohol **30** (111.0 mg, 0.25 mmol) was dissolved in DMF (6 mL) and Lindlar catalyst (30.0 mg) was added. The reaction mixture was stirred under a H_2 atmosphere (150 psi) for 5 h. The reaction mixture was filtered through celite to remove the catalyst. The celite was washed with DMF (3 × 15 mL), the organics were combined and partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous $CaCl_2$ solution (3 × 100 mL), H_2O (100 mL) and brine (2 × 100 mL). The aqueous layer washings were combined and re-extracted with EtOAc (2 × 20 mL). The organics were combined and concentrated *in vacuo* to give a brown solid which was purified *via* flash column chromatography using a 5% MeOH–DCM solvent system to give **36** as a yellow solid (52.0 mg, 50%): mp 344–347 °C; ν_{max}(THF)/cm^{-1} 3478, 1753, 1720, 1640, 1570, 749; δ_H(d_6-DMSO, 400 MHz) 2.59 (1H, d, *J* 14.8, 1′-H_α), 3.20 (1H, ddd, *J* 14.8, 8.0, 5.9, 1′-H_β), 3.60 (1H, m, 3′-H), 3.65 (1H, dd, *J* 5.7, 5.4, 4′-H), 5.29 (1H, d, *J* 8.0, 2′-H), 5.58 (1H, dd, *J* 5.9, 5.4, 5′-H), 5.79 (1H, d, *J* 3.9, OH), 7.42 (1H, dd, *J* 8.2, 8.1, 9-H), 7.44 (1H, dd, *J* 8.2, 7.5, 3-H), 7.63 (1H, dd, *J* 8.7, 8.1, 10-H), 7.68 (1H, dd, *J* 8.4, 7.5, 2-H), 7.92 (1H, d, *J* 8.4, 1-H), 7.97 (1H, d, *J* 8.7, 11-H), 9.10 (2H, app t, *J* 8.2, 4-H, 8-H), 11.07 (1H, s, NH); δ_C(d_6-DMSO, 100 MHz) 39.8 (1′-CH_2), 61.8 (CH), 63.6 (CH), 65.6 (CH), 87.0 (CH), 111.0 (CH), 111.7 (CH), 116.1 (C), 116.4 (C), 120.5 (C), 120.7 (C), 121.1 (CH), 121.3 (CH), 122.0

(C), 122.1 (C), 125.4 (CH), 125.5 (CH), 127.6 (2CH), 129.6 (C), 130.2 (C), 140.8 (C), 143.2 (C), 172.1 (2CO).

12,13-[3′α-(Trimethylsilyloxy)-3′β-vinyl-cyclopentan-2′α,5′α-diyl]-6-(phenylmethyl)5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 37

To a stirred solution of the allylic alcohol **12** (0.05 g, 0.098 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere, was added triethylamine (0.04 mL, 0.3 mmol) and the mixture was cooled to 0 °C. Trimethylsilyl triflate (0.053 mL, 0.3 mmol) was added dropwise and the stirring continued. After 80 min, TLC analysis suggested that the reaction was complete, so water (10 mL) was added and the reaction mixture was stirred for 15 min. The organic layer was then washed with water (15 mL) and a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL), dried (Na_2S0_4), filtered and the solvent was removed *in vacuo* to yield the crude product. Purification by flash chromatography ($CHCl_3$) gave the allylic ether **37** as a yellow solid (0.048 g, 82%). A portion of the product was recrystallised from a mixture of acetone–water to give **37** as a yellow crystalline solid: mp 240–241 °C; (found: *m*/*z* (FAB^+) M^+ 595.2332. $C_{38}H_{33}N_{30}O_3Si$ requires 595.2291); $\nu_{max}(CHCl_3)/cm^{-1}$ 3068, 2959, 1750, 1695, 1573, 1424, 1350, 1316, 1243, 1126, 1038 and 842; $\delta_H(CDCl_3$, 400 MHz) 0.59 (9H, s, $SiMe_3$), 1.74 (1H, br d, *J* 15.0, 4′-H_α), 2.57 (1H, d, *J* 15.0, 1′-H_α), 2.91–2.98 (2H, m, 1′-H_β and 4′-H_β), 4.99 (2H, s, CH_2Ph), 5.04 (1H, d, *J* 6.0, 2′-H), 5.40 (1H, d, J_{cis} 10.5, CH_2=), 5.44–5.51 (2H, m, 5′-H and CH_2=), 6.32 (1H, dd, *J* 17.0, 10.5, CH=), 7.26 (1H, m, Ar), 7.33–7.41 (4H, m, Ar), 7.53–7.60 (6H, m, Ar) and 9.22–9.25 (2H, m, 4-H and 8-H); $\delta_C(CDCl_3$, 126 MHz) 1.1 ($SiMe_3$), 36.2 (1′-CH_2), 41.4 (CH_2Ph), 43.1 (4′-CH_2), 54.3 (5′-CH), 65.5 (2′-CH), 83.7 (3′-C), 108.2 (CH), 110.1 (CH), 114.5 (=CH_2), 116.8 (C), 117.1 (C), 119.1 (C), 119.4 (C), 120.6 (CH), 120.6 (CH), 121.9 (C), 122.2 (C), 125.5 (CH), 125.9 (CH), 126.6 (CH), 126.7 (CH), 127.5 (CH), 128.1 (C), 128.5 (CH), 128.6 (CH), 129.4 (C), 137.5 (C), 139.9 (C), 143.2 (C), 143.5 (=CH), 170.0 (CO) and 170.1 (CO); *m*/*z* (FAB^+) 596 (M^+ + H, 58%), 595 (M^+, 67%), 453 (12), 307 (5), 289 (15), 176 (16), 107 (26) and 91 (31).

12,13-[3′β-Formyl-3′α-(trimethylsilyloxy)-cyclopentan-2′α,5′α-diyl]-6-(phenylmethyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 38

A stream of ozone in oxygen was bubbled through a stirred solution of the allylic ether **37** (0.3 g, 0.5 mmol) in a mixture of dichloromethane (45 mL) and methanol (45 mL) at −78 °C. Once the reaction appeared complete by TLC analysis, the reaction mixture was purged with oxygen for 5 min, dimethyl sulfide (5 mL) was added, and the mixture was stirred at −78 °C for 20 min before being allowed to warm to room temperature. After 3 h, the solvent was removed *in vacuo* and the residue dispersed in water (50 mL). The aqueous mixture was extracted with dichloromethane (2 × 50 mL) and the combined organic extracts were washed with water (2 × 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to yield the crude product. The product was purified by flash chromatography (CH_2Cl_2) to give the aldehyde **38** as a yellow solid (0.18 g, 60%). A portion of the solid was recrystallised from a mixture of acetone–water to give **38** as yellow needles: mp 268–269 °C; (found: *m*/*z* (FAB^+) M^+ 597.2061. $C_{37}H_{31}N_3O_4Si$ requires 597.2084); $\nu_{max}(CHCl_3)/cm^{-1}$ 2958, 2808, 1750, 1730, 1697, 1574, 1462, 1384, 1351, 1124, 945 and 868; $\delta_H(CDCl_3$, 400 MHz) −0.69 (9H, s, $SiMe_3$), 1.59 (1H, d, *J* 15.0, 4′-H_α), 2.74 (1H, d, *J* 15.0, 1′-H_α), 2.84 (1H, dt, *J* 15.0, 7.0, 1′-H_β), 3.05 (1H, dd, *J* 15.0, 7.5, 4′-H_β), 4.93 (2H, s, CH_2Ph), 5.24 (1H, d, *J* 7.0, 2′-H), 5.54 (1H, dd, *J* 7.5, 7.0, 5′-H), 7.27 (1H, m, Ar), 7.34–7.39 (4H, m, Ar), 7.46–7.58 (6H, m, Ar), 9.19–9.21 (2H, m, 4-H and 8-H) and 9.92 (1H, s, CHO); $\delta_C(CDCl_3$, 126 MHz) 0.7 (Me_3Si), 36.7 (1′-CH_2), 40.4 (CH_2Ph), 41.3 (4′-CH_2), 55.2 (5′-CH), 60.3 (2′-CH), 88.0 (3′-C), 109.0 (CH), 109.1 (CH), 117.0 (C), 117.2 (C), 119.2 (C), 119.3 (C), 120.9 (CH), 122.0 (C), 122.2 (C), 125.6 (CH), 125.9 (CH), 126.9 (CH), 127.0 (CH), 127.5 (CH), 128.0 (C), 128.6 (CH), 129.3 (C), 137.5 (C), 140.0 (C), 142.5 (C), 170.0 (CO), 170.1 (CO) and 202.2 (CHO); *m*/*z* (FAB^+) 598 (M^+ + H, 26%), 597 (M^+, 30%), 452 (15), 413 (8), 391 (14), 329 (9) 307 (15), 289 (10), 176 (34) and 91 (47).

12,13-(3′α-Hydroxy-4-oxocyclohexan-2′α,6′α-diyl)-6-(phenylmethyl)-5*H*-indolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 39

To a stirred solution of the aldehyde **38** (0.05 g, 0.084 mmol) in dry tetrahydrofuran (5 mL), was added boron trifluoroetherate (0.052 mL, 0.42 mmol) and the mixture was left to stir overnight. After this period, a precipitate had formed and water (0.5 mL) was added and the mixture was stirred for 15 min. Ethyl acetate (20 mL) was then added and the organic layer was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to yield the crude product. Recrystallisation from a mixture of acetone–water gave **39** as a yellow crystalline solid (0.033 g, 74%): mp 267–269 °C; (found: *m*/*z* (FAB^+) M + H^+ 526.1746. $C_{33}H_{24}N_3O_4$ requires 526.1767); $\nu_{max}(CHCl_3)/cm^{-1}$ 3696, 3604, 2929, 2862, 1752, 1720, 1697, 1602, 1462, 1384, 1352 and 1103; δ_H(d_6-DMSO, 400 MHz) 2.62 (1H, br d, *J* 14.0, 5′-H_α), 3.03 (1H, br d, *J* 16.0, 1′-H_α), 3.45 (1H, dt, *J* 16.0, 5.0, 1′-H_β), 3.53 (1H, dd, *J* 14.0, 5.0, 5′-H_β), 4.87 (2H, s, CH_2Ph), 5.17 (1H, m, 3′-H), 5.35 (1H, d, *J* 4.0, OH), 5.91 (1H, m, 6′-H), 6.05 (1H, m, 2′-H), 7.27 (1H, t, *J* 6.5, Ph), 7.33–7.44 (6H, m, Ar), 7.57 (1H, dd, *J* 8.0, 7.0, 2-H or 10-H), 7.65 (1H, dd, *J* 8.0, 7.0, 2-H or 10-H), 7.80 (1H, d, *J* 8.0, 1-H or 11-H), 7.88 (1H, d, *J* 8.0, 1-H or 11-H) and 9.03–9.10 (2H, m, 4-H and 8H); δ_C(d_6-DMSO, 126 MHz) 31.2 (1′-CH_2), 40.7 (CH_2Ph), 47.8 (5′-CH_2), 54.5 (6′-CH), 59.9 (2′-CH), 77.2 (3′-CH), 110.0 (CH), 112.5 (CH), 115.3 (C), 116.2 (C), 118.2 (2C), 120.3 (CH), 120.7 (C), 120.9 (CH), 121.4 (C), 123.8 (CH), 124.6 (CH), 126.5 (CH), 127.3 (CH, C), 128.6 (CH), 137.4 (C), 139.5 (C), 142.8 (C), 169.2 (2CO) and 202.2 (4′-CO); *m*/*z* (FAB^+) 526 (M^+ + H, 43%), 525 (M^+, 38%), 448 (15), 391 (18), 329 (18), 307 (20), 289 (13), 242 (14), 107 (33) and 91 (37).

12,13-(3′Cyclohexan-2′α,6α′-diyl-one)-dihydro-5*H*-indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 41

Ketone **8a** (50.0 mg, 0.10 mmol) was dissolved in DCM (10 mL) with stirring under an N_2 atmosphere. $BF_3{\cdot}OEt_2$ (0.04 mL, 0.32 mmol) was added dropwise and the reaction mixture was cooled to −78 °C before the dropwise addition of $TMSCHN_2$ (0.06 mL, 0.11 mmol). The reaction mixture was stirred for 3 h before being allowed to warm to rt overnight and was quenched by the careful addition of AcOH (1 mL). The reaction mixture was partitioned between DCM (25 mL) and 2N HCl (25 mL) and the organic layer was washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL), brine (25 mL), dried ($MgSO_4$), concentrated *in vacuo* and triturated in Et_2O (10 mL) for 1 h. Purification by flash column chromatography, using a 2 : 1 EtOAc–petrol solvent system gave **41** as an orange solid (0.015 g, 29%): mp 303–305 °C; (found *m*/*z* (FAB^+) M^+ 509.1737. $C_{33}H_{23}N_3O_3$ requires 509.1739); $\nu_{max}(CHCl_3)/cm^{-1}$ 2929, 2856, 1713, 1572, 1348, 1320; $\delta_H(CDCl_3$, 400 MHz) 2.28 (1H, d, *J* 13.2, 4′-H_α), 2.44–2.59 (2H, m, 4′-H_β and 5′-H_β), 2.66 (1H, d, *J* 12.8, 5′-H_α), 3.23 (1H, ddd, *J* 15.8, 5.6, 5.2, 1′-H_α), 3.43 (1H, d, *J* 15.8, 1′-H_β), 4.92 (2H, s, CH_2Ph), 5.31–5.33 (1H, m, 6′-H), 5.36 (1 H, d, *J* 5.6, 2′-H), 7.27 (1H, t, *J* 8.0, Bn), 7.35 (2H, dd, *J* 8.0, 7.4, Bn), 7.45 (3H, app ddd, *J* 7.9, 7.4, 7.4, 3-H, 9-H and 11-H), 7.54 (2H, d, *J* 7.4, Bn), 7.62 (3H, app ddd, *J* 7.9, 7.4, 7.4, 2-H, 10-H and 1-H), 9.24 (1H, d, *J* 7.9, 8-H), 9.31 (1H, d, *J* 7.9, 4-H); $\delta_C(CDCl_3$, 125 MHz) 31.8 (CH_2), 34.2 (CH_2), 35.8 (CH_2), 41.5 (CH_2), 49.4 (CH), 60.9 (CH), 108.7 (CH), 109.8 (CH), 117.1 (C), 117.6 (C), 119.6 (C), 120.2 (C), 121.5 (CH), 122.0 (CH), 122.4 (C), 122.5 (C), 126.0 (CH), 126.3 (CH), 127.7 (CH, C), 127.9 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 130.4 (C),

137.7 (C), 140.3 (C), 140.7 (C), 169.7 (2CO), 203.5 (CO); *m/z* (FAB$^+$) 510 (M$^+$ + H, 4%), 509 (M$^+$, 3), 91 (32).

12,13-(3′Cyclopenten-2′α,5′α-diyl-oxy)(trimethyl)silane-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 42

Ketone **8c** (0.10 g, 0.19 mmol) and $ZnCl_2$ (0.10 g, 0.76 mmol) were suspended in THF (5 mL) with stirring under N_2. Freshly distilled TMSCl (0.24 mL, 1.90 mmol) and freshly distilled NEt_3 (0.05 mL, 0.38 mmol) were added and the reaction mixture was stirred for 20 min. TLC analysis showed the consumption of starting material and so the reaction mixture was concentrated *in vacuo* to give a brown solid which was redissolved in DCM (20 mL). The DCM solution was washed with saturated aqueous NH_4Cl solution (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. The crude solid was dissolved in a minimum amount of DCM and quickly filtered through a silica pad, and concentrated to give enol silane **42** was a yellow solid (0.10 g, 89%): mp 233 °C decomp.; (found: *m/z* (FAB$^+$) M$^+$ 597.2089. $C_{36}H_{31}N_3O_4Si$ requires 597.2084); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1694, 1638, 1572, 1513, 1347, 1035, 854; $\delta_H(CDCl_3$, 400 MHz) −0.31 (9H, s, $SiMe_3$), 2.63 (1H, d, *J* 13.8, 1′-H$_\alpha$), 3.26 (1H, ddd, *J* 13.8, 6.8, 6.2, 1′-H$_\beta$), 3.78 (3H, s, OMe), 4.93 (2H, s, C*H*$_2$Ar), 5.04 (1H, d, *J* 2.5, 4′-H), 5.44 (1H, d, *J* 6.8, 2′-H), 5.90 (1H, dd, *J* 6.2, 2.5, 5′-H), 6.88 (2H, d, *J* 8.5, PMB), 7.38–7.41 (2H, m, 3-H and 9-H), 7.53 (2H, d, *J* 8.5, PMB), 7.58–7.60 (3H, m, 3H, Ar), 7.65 (1H, d, *J* 8.2, Ar), 9.27 (2H, app t, *J* 7.0, 4-H and 8-H); $\delta_C(CDCl_3$, 100 MHz) −0.7 ($SiMe_3$), 38.9 (1′-CH_2), 40.9 (CH_2PMB), 55.3 (OMe), 57.4 (5′-CH), 60.0 (2′-CH), 104.8 (CH), 108.3 (CH), 108.7 (CH), 114.1 (CH), 117.2 (C), 117.3 (C), 119.5 (C), 119.8 (C), 120.5 (CH), 120.6 (CH), 122.0 (C), 122.1 (C), 125.9, (CH), 126.1 (CH), 126.8 (CH), 127.0 (CH), 129.0 (C), 129.1 (C), 129.9 (C), 130.1 (2CH), 140.1 (C), 141.0 (C), 159.1 (C), 160.0 (C), 170.0 (CO), 170.1 (CO); *m/z* (FAB$^+$) 598 (M$^+$ + H, 4%), 597 (M$^+$, 10), 137 (8), 136 (22), 121 (13), 109 (9), 107 (15), 91 (23), 75 (17).

12,13-(4′,4′-Diallyl-3′-cyclopentan-2′α,5′α-diyl-one)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 43

Ketone **8c** (30.0 mg, 0.06 mmol) was dissolved in THF (5 mL) with stirring under N_2, and was cooled to 0 °C. NaH (2.3 mg, 0.06 mmol) was added and the reaction mixture was allowed to warm to rt over 1 h before being recooled to 0 °C and allyl bromide (0.10 mL, 1.16 mmol) was added dropwise. The reaction mixture was stirred for 3 h. TLC analysis showed consumption of the starting material and so the reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid which was purified *via* flash column chromatography using a DCM solvent system to give the dialkylated product **43** as a yellow solid (12.0 mg, 71% based on *ca.* 15 mg recovered starting material): mp 331–332 °C; (found *m/z* (FAB$^+$) M$^+$ 605.2298. $C_{39}H_{31}N_3O_4$ requires 605.2315); ν_{max}(THF)/cm^{-1} 3498, 1752, 1700, 1384, 750; δ_H(d$_6$-DMSO, 400 MHz) 1.65–1.73 (2H, m, *CH*$_2$allyl$_\alpha$), 2.60 (1H, dd, *J* 14.1, 6.7, *CH*$_2$allyl$_\beta$), 2.75 (1H, dd, *J* 14.1, 7.8, *CH*$_2$allyl$_\beta$), 2.97 (1H, d, *J* 15.7, 1′-H$_\alpha$), 3.67 (1H, ddd, *J* 15.7, 8.0, 7.2, 1′-H$_\beta$), 3.76 (3H, s, OMe), 4.23 (1H, dd, *J* 17.0, 1.3, CH=*CH*$_{2\alpha}$), 4.37 (1H, dd, *J* 10.1, 1.3, CH=*CH*$_{2\alpha}$), 4.88 (2H, s, C*H*$_2$Ar), 5.07–5.16 (1H, m, C*H*=CH$_{2\alpha}$), 5.40–5.47 (2H, m, CH=*CH*$_{2\beta}$), 5.79 (1H, d, *J* 7.2, 2′-H), 5.81 (1H, d, *J* 8.0, 5′-H), 6.02–6.11 (1H, m, C*H*=CH$_{2\beta}$), 6.94 (2H, d, *J* 8.6, PMB), 7.40 (2H, d, *J* 8.6, PMB), 7.46 (1H, dd, *J* 8.1, 7.0, 3-H or 9-H), 7.48 (1H, dd, *J* 8.1, 7.0, 3-H or 9-H), 7.72 (2H, dd, *J* 8.3, 7.0, 2-H and 10-H), 7.90 (1H, d, *J* 8.3, 1-H), 7.98 (1H, d, *J* 8.3, 11-H), 9.12 (2H, 2 d, *J* 8.1, 4-H and 8-H); δ_C(d$_6$-DMSO, 100 MHz) 33.9 (CH_2), 34.8 (CH_2), 39.1 (CH_2), 40.9 (CH_2), 56.0 (OMe), 57.2 (C), 58.9 (CH), 61.2 (CH), 111.0 (CH), 111.1 (CH), 114.9 (CH), 116.6 (C), 116.9 (C), 118.4 (CH_2), 119.6 (C), 119.9 (C), 121.5 (CH_2), 121.7 (CH), 121.8 (C), 122.0 (CH), 125.5 (CH), 125.6 (CH), 128.2 (CH), 128.4 (CH), 129.6 (C), 130.0 (CH), 130.3 (C), 132.7 (CH), 133.1 (CH), 141.1 (C), 142.1 (C), 159.5 (C), 170.0 (CO), 170.1 (CO), 217.1 (CO); *m/z* (FAB$^+$) 606 (M$^+$ + H, 4%), 605 (M$^+$, 13), 498 (11).

12,13-(4′,4′-Dimethyl-3′cyclopentan-2′α,5′α-diyl-one)-6-(4-methoxybenzyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione 44

Ketone **8c** (30.0 mg, 0.06 mmol) was dissolved in THF (5 mL) with stirring under N_2, and was cooled to 0 °C. NaH (2.3 mg, 0.06 mmol) was added and the reaction mixture was allowed to warm to rt over 1 h before being recooled to 0 °C and methyl iodide (0.10 mL, 1.61 mmol) was added dropwise. The reaction mixture was stirred for 3 h. TLC analysis showed consumption of the starting material and so the reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid which was purified *via* flash column chromatography using a DCM solvent system to give the dialkylated product **44** as a yellow solid (12.0 mg, 73% based on *ca.* 14 mg recovered starting material): mp 336–338 °C; ν_{max}(THF)/cm^{-1} 3498, 1753, 1698, 1385, 750; δ_H(d$_6$-DMSO, 400 MHz) 0.44 (3H, s, Me$_\alpha$), 1.53 (3H, s, Me$_\beta$), 2.98 (1H, d, *J* 15.5, 1′-H$_\alpha$), 3.65 (1H, ddd, *J* 15.5, 8.3, 6.5, 1′-H$_\beta$), 3.75 (3H, s, OMe), 4.86 (2H, s, C*H*$_2$PMB), 5.74 (1H, d, *J* 6.5, 5′-H), 5.85 (1H, d, *J* 8.3, 5′-H), 6.94 (2H, d, *J* 8.8, PMB), 7.39 (2H, d, *J* 8.8, PMB), 7.45 (1H, dd, *J* 7.9, 7.3, 3-H), 7.47 (1H, dd, *J* 7.9, 7.3, 9-H), 7.68 (1H, dd, *J* 8.4, 7.3, 2-H), 7.71 (1H, dd, *J* 8.4, 7.3, 10-H), 7.97 (1H, d, *J* 8.4, 11-H), 8.02 (1H, d, *J* 8.4, 1-H), 9.09 (1H, d, *J* 7.9, 4-H), 9.12 (1H, d, *J* 7.9, 8-H); δ_C(d$_6$-DMSO, 100 MHz) 18.7 (Me), 25.0 (Me), 33.6 (CH_2), 41.1 (CH_2), 51.1 (C), 56.0 (OMe), 58.1 (CH), 63.4 (CH), 110.9 (CH), 111.4 (CH), 114.9 (CH), 116.7 (C), 116.9 (C), 119.6 (C), 119.9 (C), 121.6 (C), 121.7 (CH), 121.9 (CH), 122.0 (CH), 125.4 (CH), 125.5 (CH), 128.3 (CH), 128.4 (CH), 128.9 (C), 129.3 (C), 129.9 (CH), 130.3 (C), 141.2 (C), 142.4 (C), 159.5 (C), 169.9 (CO), 170.0 (CO), 219.2 (CO); *m/z* (FAB$^+$) 553 (M$^+$ 20%), 446 (30), 432 (15).

12,13-(4′,4′-Dibenzyl-3′cyclopentan-2′α,5′α-diyl-one)-6-(4-methoxybenzyl)-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7(6*H*)-dione 45

Ketone **8c** (50.0 mg, 0.10 mmol) was dissolved in THF (5 mL) with stirring under N_2, and was cooled to 0 °C. NaH (8.0 mg, 0.20 mmol) was added and the reaction mixture was allowed to warm to rt over 1 h before being recooled to 0 °C and benzyl bromide (0.11 mL, 1.00 mmol) was added dropwise. The reaction mixture was allowed to warm to rt over 18 h. TLC analysis showed consumption of the starting material and so the reaction mixture was partitioned between EtOAc (75 mL) and H_2O (75 mL). The organic layer was washed with H_2O (100 mL), brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid which was purified *via* flash column chromatography using a DCM solvent system to give the dialkylated product **45** as a yellow solid (47.0 mg, 71%): mp 335–337 °C; (found *m/z* (FAB$^+$) M$^+$ 705.2607. $C_{47}H_{35}N_3O_4$ requires 705.2628); ν_{max}(THF)/cm^{-1} 3502, 1750, 1699, 1384, 750; δ_H(d$_6$-DMSO, 400 MHz) 2.27 (1H, d, *J* 14.7, CH*H*–Ph$_\alpha$), 2.80 (1H, d, *J* 15.5, 1′-H$_\alpha$), 2.92 (1H, d, *J* 14.7, C*H*H-Ph$_\alpha$), 3.13 (1H, ddd, *J* 15.5, 7.7, 6.7, 1′-H$_\beta$), 3.26 (1H, d, *J* 13.6, C*H*$_2$Ph$_\beta$), 3.35 (1H, d, *J* 13.6, C*H*$_2$Ph$_\beta$), 3.37 (3H, s, OMe), 4.85 (2H, s, C*H*$_2$Ar), 5.61 (1H, d, *J* 7.7, 2′-H), 5.69 (2H, d, *J* 7.5, Ph$_\alpha$), 5.84 (1H, d, *J* 6.7, 5′-H), 6.10 (2H, dd, *J* 7.6, 7.5, Ph$_\alpha$), 6.31 (1H, t, *J* 7.6, Ph$_\alpha$), 6.95 (2H, d, *J* 8.7, PMB), 7.37 (2H, d, *J* 8.7, PMB), 7.39–7.60 (9H, m, 3-H, 9-H, 10-H, 11-H and Ph$_\beta$), 7.71 (1H, dd, *J* 8.3, 7.2, 2-H),

8.01 (1H, d, *J* 8.3, 1-H), 8.96 (1H, d, *J* 7.9, 8-H), 9.06 (1H, d, *J* 7.9, 4-H); δ_C(d_6-DMSO, 125 MHz) 34.1 (CH_2), 38.8 (CH_2), 41.0 (CH_2), 44.6 (CH_2), 56.0 (OMe), 60.0 (CH), 60.7 (CH), 68.0 (C), 110.1 (CH), 111.2 (CH), 114.9 (CH), 116.4 (C), 116.8 (C), 119.1 (C), 119.8 (C), 121.6 (CH), 122.0 (CH), 122.2 (C), 122.5 (C), 125.4 (CH), 125.5 (CH), 125.7 (CH), 127.1 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.9 (C), 129.6 (CH), 129.7 (CH), 130.1 (C), 130.4 (C), 131.9 (2CH), 136.0 (C), 136.9 (C), 140.8 (C), 141.9 (C), 159.5 (C), 169.9 (CO), 170.1 (CO), 216.8 (CO); *m/z* (FAB^+) 706 ($M^+ + H$, 6%), 705 (M^+, 11), 598 (6), 121 (27), 107 (26).

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